Chapter 7
Acute Kidney Injury After Cardiac Surgery in Adults

Jeremiah R. Brown and Chirag R. Parikh

Objectives

- To describe definition and epidemiology of AKI
- To understand risk factors for AKI and prediction scores
- To discuss prevention and management of AKI

Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) has been recognized as a frequent adverse event following cardiac surgery [1–4]. CSA-AKI has nearly doubled over the past decade [5] and strongly associated with increased morbidity, mortality, and length of hospitalization [1–4, 6]. When AKI occurs in the hospital, the approximate additional costs in health-care expenditures amount to $7,500 [7], making AKI a costly complication and an important target for prevention.

J.R. Brown, PhD, MS (✉)
The Dartmouth Institute for Health Policy and Clinical Practice,
and the Departments of Medicine and Community and Family Medicine,
Audrey and Theodore Geisel School of Medicine at Dartmouth, HB 7505 DHMC One Medical Center Drive, Lebanon, NH 03756, USA
e-mail: jbrown@dartmouth.edu

C.R. Parikh, MD, PhD, FASN
Program of Applied Translational Research, Department of Medicine,
Yale University School of Medicine, New Haven, CT, USA
e-mail: chirag.parikh@yale.edu

C.V. Thakar, C.R. Parikh (eds.), *Perioperative Kidney Injury: Principles of Risk Assessment, Diagnosis and Treatment*, DOI 10.1007/978-1-4939-1273-5_7

AKI Epidemiology

AKI is thought to develop as a result of extended cardiopulmonary bypass pump times with paralleled hypoperfusion and reduced oxygen saturation delivery to critical organs including the brain and kidneys.

Common definitions for diagnosing AKI in cardiac surgery have included: the Society for Thoracic Surgeons (STS); the Acute Dialysis Quality Initiative Workgroup for risk, injury, failure, loss, and end-stage kidney disease (RIFLE) criteria [8]; and the Acute Kidney Injury Network (AKIN) [9] definition (Table 7.1). In addition, the duration of AKI using the AKIN definition has also been evaluated as a more sensitive and specific measure of AKI severity after general surgery [10] and cardiac surgery [2].

In cardiac surgery, even small changes in serum creatinine have been associated with poor survivorship [1] and progression of chronic kidney disease and end-stage renal disease [11]. AKI after cardiac surgery has been associated with more rapid progression to incident chronic kidney disease (CKD), progressive CKD, and renal failure (dialysis or kidney transplant) [11]. This evidence suggests that there is a direct correlation between the degree of acute injury to the kidneys during the perioperative period and long-term progression of worsening renal function.

Others have confirmed this phenomenon in other patient populations demonstrating the increase risk of progression to end-stage renal disease (ESRD) and mortality [12–14]. Therefore, patients developing perioperative AKI are at risk for progressing towards worsening renal function and should be monitored following the perioperative period to prevent unnoticed rapid progression to renal failure.

Table 7.1 Incidence of AKI following cardiovascular surgery across AKI definitions

Author	*N*	Year of study	Country	AKI definition	Incidence (%)
Brown [1]	1,391	2001	USA	Scr rise >25 %	27.8
				Scr rise>50 %	11.7
				Scr rise >100 %	4.7
Conlon [65]	2,843	1995–1997	USA	Scr rise >1 mg/dL	7.9
Lassnigg [4]	4,118	2001	Austria	Scr rise >0.5 mg/dL	4.9
Andersson [66]	2,009	1987–1990	Sweden	Scr rise>50 %	16.4
Karkouti [16]	3,500	2004	Canada	Scr rise >25 %	24
				Scr rise >25 %	37.4
Parikh [51]	1,219	2007–2009	USA	Scr rise >100 %	4.9
				Scr rise by 0.3 mg/dL or 50 %	35.2
Brown [2, 35]	4,831	2002–2007	USA	Scr rise by 0.3 or 50 %	39.3
Brown [34]	8,592	2001–2005	USA	eGFR fall by >30 %	2.7
Thakar[a][67]	22,589	1993–2000	USA	GFR fall by >50 %	4.9
Thakar[a][43]	31,677	1993–2002	USA	GFR fall by >30 %	17.4

Abbreviations: *AKI* acute kidney injury, *Scr* serum creatinine, *GFR* glomerular filtration rate, *eGFR* estimate glomerular filtration rate

[a]Patients in cohorts overlap

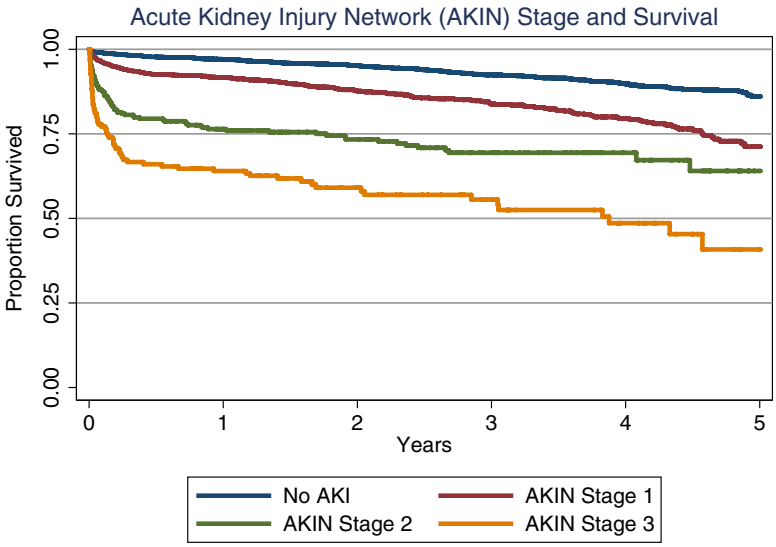

Fig. 7.1 Kaplan-Meier survival graph for cardiac surgery patients by Acute Kidney Injury Network (*AKIN*) stages: no AKI (*blue*), AKIN stage 1 (*red*), AKIN stage 2 (*green*), and AKIN stage 3 or renal failure (*yellow*) (Reprinted by permission of Oxford University Press from Brown and Parikh [68])

The Northern New England Cardiovascular Disease Study Group (NNECDSG, www.nnecdsg.org) has reported on the poor survivorship-associated perioperative changes in serum creatinine [1] and longer durations of AKI [15]. The early findings demonstrated that subtle changes in serum creatinine were directly proportional to increased 90-day mortality [1]. The association between AKIN stages of AKI and survival is consistent with the earlier reports of changes in serum creatinine (Fig. 7.1). More recently, NNECDSG AKI researchers and Translational Research Investigating Biomarker End-Points in Acute Kidney Injury (TRIBE-AKI) investigators jointly evaluated the role of the duration of AKI as a marker for AKI severity and demonstrated the proportionality associated with longer durations of AKI and worse survival (Fig. 7.2). Over 18 % of patients developed AKI for 1–2 days, 11 % for 3–6 days, and 9 % for 7 or more days. AKI duration categories were directly proportional to in-hospital dialysis rates (0.2, 0.5, and 7.2 %) as well as 5-year mortality (13.7, 17.5, and 36.9 %, respectively). These figures demonstrate the severe consequences patients face with the development of AKI and moderate or severe AKI.

Etiology Risk Factors and Prediction of AKI

AKI is postulated to result from various patient and procedural factors. Patient factors include many of the risk factors used the prediction modeling described previously (age, gender, baseline renal function, heart failure, and diabetes).

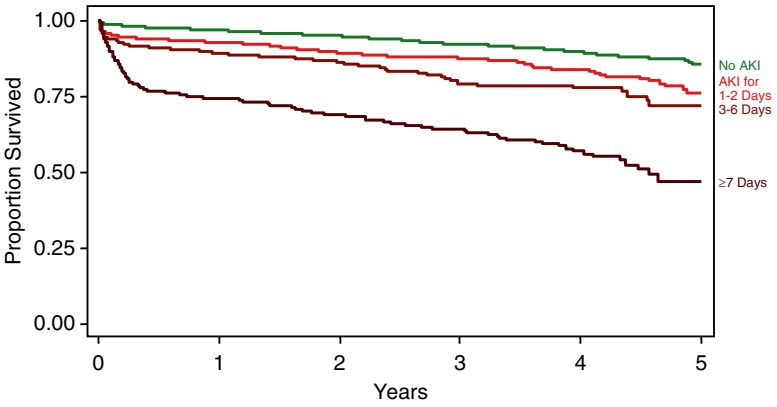

Fig. 7.2 Kaplan-Meier survival graphs by duration of acute kidney injury after cardiac surgery: no AKI, AKI lasting 1–2 days, AKI lasting 3–6 days, and AKI lasting 7 or more days (Reprinted from Brown et al. [2], copyright 2010, with permission from Elsevier)

Preoperative anemia (hemoglobin <14) has also been shown to have an inverse relationship with AKI, whereby each successive drop in hemoglobin under 14 (g/dL) increases the risk of postoperative AKI by 23 % for hemoglobin between 12 and 13.9 (g/dL), by 63 % for hemoglobin 10–11.9 (g/dL), and by 99 % for hemoglobin <10 (g/dL) [16].

Before the patient arrives to the operating room for cardiac surgery, it is most likely the patient has had a recent angiography, or cardiac catheterization. These procedures usually use small amounts of low-osmolar or iso-osmolar contrast; however, sometimes an ad hoc angioplasty (percutaneous coronary intervention, PCI) is performed and stents implanted in the coronary arteries to reestablish or sustain blood flow. During a PCI, larger, and potentially dangerous, volumes of contrast dye are injected to visualize the coronary arteries for the deployment of the devices and stents. It is during this time that patients are likely to develop contrast-induced AKI resulting from acute tubular necrosis and oxidative stress. It has been shown that there is a direct relationship between the dose of contrast and AKI [17, 18]. Others have demonstrated there is direct relationship between the timing of the cardiac catheterization and cardiac surgery, whereby the risk of AKI is higher among patients undergoing cardiac surgery within 24 h of a cardiac catheterization [19–22] with direct ties to the amount of contrast used [19, 20]. In addition, others have reported if the cardiac catheterization was conducted during the same admission as cardiac surgery (including in-patient transfers), the risk of AKI is increased by 54 % [23].

There are several operative factors that should be considered. Cardiopulmonary bypass (pump time) contributes to the development of AKI [1, 16]. Off-pump cardiac surgery has been shown to reduce the incidence of AKI [24, 25]; however, caution should be taken to only incorporate off-pump cardiac surgery as a protective measure against AKI among proficient off-pump surgeons, and the risk-benefit should be weighed against the risk of incomplete revascularization and bleeding [26]. During cardiopulmonary bypass, gaseous or particulate emboli, renal ischemia from hypoperfusion of the kidneys, and myoglobinuria and free hemoglobinuria are proposed causes of AKI [27]. It is thought that the cardiopulmonary bypass pump

may result in an imbalance in O_2 supply due to low hematocrit and the need for O_2 by the kidneys. When the O_2 is <260 mL/min/m^2, it can increase lactate levels and increase the risk of AKI. O_2 delivery can be optimized by coupling the pump flow with the hematocrit [28–30]. To counteract these causes, cardiac surgeons and perfusionists have worked together to improve cardiopulmonary bypass management through temperature and blood pressure management and development of mechanisms and filtering devices to reduce gaseous micro-emboli and optimize O_2 delivery through improving the flow rate, hemoglobin levels, and hemodilution [27].

The number of perioperative packed red blood cell (pRBCs) has a direct linear dose-response to the risk of developing AKI. Stored red blood cells have been shown to deteriorate after being frozen and stored for weeks at a lime. It has been demonstrated that these red blood cells develop specula and lose the biconcave disc shape causing inflexibility to travel through the capillaries and result in capillary damage and reduced microcirculation [31]. Others have shown that patients receiving newer blood (pRBC stored for ≤14 days) had significantly better survival and a lower incidence of renal failure than patients receiving pRBC transfusions that was stored for more than 14 days [32]. A similar effect was reported in pediatric cardiac surgery for AKI whereby AKI was reduced by 4.4 % [30].

In Table 7.2, we summarize the various etiologies of factors contributing to cardiac surgery-associated AKI in adults including patient factors, medication,

Table 7.2 Factors of cardiac surgery-associated with acute kidney injury

Patient	Medication	Prior procedures	Procedure
Advanced age	NSAIDs	Contrast dye volume	Cardiopulmonary bypass
Female gender	ACE	Contrast agent	Pump times >120 min
Diabetes	ARB	Timing from cardiac catheterization and surgery	Volume of fluids on bypass
Hypertension		Sepsis	Hypotension
Obesity		Endotoxins	Emboli
Albuminuria		Preoperative AKI	IABP
Chronic kidney disease		IABP	Low output failure
Congestive heart failure		Prior cardiac surgery	Reoperation
Peripheral vascular disease		RBC units	Return to bypass during procedure
Anemia			RBC
Inflammation			Nadir hematocrit on bypass
White blood cell count >12,000			Ultrafiltration
Rhabdomyolysis			Use of inotropes
Myoglobin			Warm cardioplegia
			Reperfusion injury
			Change in mean arterial pressure >=26 (mm Hg)
			Oxygen delivery (DO_2) <262 (mL/min/m2)

Reprinted from Huen and Parikh [48], copyright 2012 with permission from Elsevier

NSAIDs nonsteroidal antiinflammatory drugs, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blockers, *DO_2* oxygen delivery = pump flow (hemoglobin × 1.3 × O_2 saturation + 0.003 × pO_2) [1, 2, 28, 33–40]

in-hospital and prior procedural risks, as well as cardiac surgery procedural risk factors [1, 2, 28, 33–40].

Identifying risk factors for AKI and establishing prediction models are necessary to risk-stratify patients before, during, and immediately after cardiac surgery. However, most of the prediction modeling efforts have investigated the ability of patient and procedural risk factors to predict the occurrence of renal failure [41–44]. These models have also performed well for predicting severe AKI using the STS definitional of acute renal failure, defined as a 2.0 mg/dL or twofold increase in serum creatinine or new dialysis [42–45]. Yet, other investigators have developed models in predicting immediate postoperative declines in creatinine clearance (CrCl) or estimate glomerular filtration rate (eGFR) [34, 46, 47]. One example is the NNECDSG's approach to predict at least a 30 mL/min/m2 drop in eGFR among patients with normal or near-normal renal function (eGFR $\geq$60) [34]. Recent investigations have incorporated additional perioperative risk factors from the procedure and complications from the procedure as an attempt to improve the prediction of AKI and duration of AKI. There are various risk factors utilized in the prediction modeling for renal failure and AKI. Major similarities among the models include: age, gender, baseline renal function, heart failure, diabetes, use of intra-aortic balloon pump, and duration on cardiopulmonary bypass (Table 7.3) [48]. Other models to predict renal replacement therapy after cardiac surgery include the Cleveland Clinic score [43], Mehta score [42], and Simplified Renal Index score [44] with external validation [45, 49].

Another approach to predicting the severity of AKI focused on predicting the length of time, or duration, of the acute injury. The duration of AKI was modeled to predict the average projected number of days a patient may sustain AKI and is published as an online risk calculator (http://medicine.yale.edu/intmed/patr/resources/akicalc.aspx). This can be a useful way to determine a patient's risk and length, or duration, or AKI after cardiac surgery. If the duration is projected to be longer than 3 days, a nephrology consult on admission to the ICU may be helpful in preventing the onset of AKI and minimize the duration.

Novel biomarkers have the ability to improve our prediction of AKI events and provide earlier detection. Several biomarkers have been rigorously investigated including plasma cystatin C, urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin 18 (IL-18), N-acetyl-B-(D)-glucosaminidase (NAG), alpha-1 microglobulin, albuminuria, and urinary kidney injury molecule 1 (KIM-1) [50–53]. The TRIBE-AKI Consortium released evidence that supports the use of serum creatinine and cystatin C in determining risk of AKI prior to cardiac surgery; this was found to be true among all patients and more so for predicting severe AKI [53]. In cardiac surgery, TRIBE also demonstrated the clinical utility of postoperative kidney biomarkers, including plasma NGAL and urinary IL-18 and NGAL. They reported that urinary IL-18 had superior prediction for AKI over plasma or urinary NGAL [51]. A small study of 103 subjects by Liangos and colleagues reported that KIM-1, NAG, NGAL, and IL-18 significantly predicted AKI at 2 h after cardiopulmonary bypass; however, after adjustment for the preoperative Cleveland Clinic Foundation score for acute renal failure and/or cardiopulmonary bypass time, only KIM-1 remained statistically significant [50]. Albuminuria

Table 7.3 Variables included in the models

	Variable	CICSS	Cleveland	STS	SRI	McSPI	AKICS	NNECDSG
Demographics	Age			X		X	X	X
	Gender		X					X
	Race			X				
Clinical	Preoperative renal insufficiency	X	X	X	X	X	X	
	Prior heart surgery	X	X	X	X			X
	Advanced NYHA	X		X			X	
	Congestive heart failure		X			X		X
	Decreased ejection fraction		X		X			
	Cardiomegaly	X						
	Pulse pressure					X		
	Hypertension							X
	PVD/CVD	X						X
	COPD/chronic lung disease		X	X				
	Diabetes mellitus		X	X	X			X
	Preoperative capillary glucose >140						X	
	MI within last 3 weeks			X				
	Prior MI					X		
	Reoperation							
	Preoperative IABP	X	X		X			X
	Emergent surgery		X		X			
	Cardiogenic shock			X				
	Preoperative WBC >12,000							X
Surgery type	Valvular surgery	X	X	X				
	CAPG + valve		X	X			X	
	Other cardiac procedures		X		X			
Inoperative	Increased CPB time					X	X	
	>2 inotropes					X		
	Intraoperative IABP					X		
Postoperative	CVP >14 cm H_2O						X	
	Low cardiac output						X	

Adapted from Huen and Parikh [48]

AKICS acute kidney injury after cardiac surgery, *CAPG* coronary artery bypass graft, *CICSS* Continuous Improvement in Cardiac Surgery Study, *COPD* chronic obstructive pulmonary disease, *CPB* cardiopulmonary bypass, *CVD* cardiovascular disease, *CVP* central venous pressure, *IABP* intra-aortic balloon pump, *McSPI* Multicenter Study of Perioperative Ischemia, *MI* myocardial infarction, *NNECDSG* Northern New England Cardiovascular Disease Study Group, *NYHA* New York Heart Association Functional Classification, *PVD* peripheral vascular disease, *SRI* Simplified Renal Index, *WBC* white blood cell count

is a predictive marker for the development of AKI [54–58]. An increase in the ratio between urinary albumin and creatinine has been demonstrated to improve preoperative risk prediction of AKI suggesting the addition of albuminuria to preoperative risk assessment for AKI [57, 59]. KIM-1 and other markers such as L-type fatty acid-binding protein and alpha-1 microglobulin need further large-scale clinical trial investigations.

Prevention and Management of AKI

A systematic review summarized the interventions to prevent AKI that have been evaluated with mixed efficacy in cardiac surgery. Interventions have included anti-inflammatory (N-acetylcysteine, glutathione, fenoldopam, aspirin, dexamethasone, methylprednisolone, and leukodepletion), natriuretics/diuretics (nesiritide, A-type natriuretic peptide [ANP], furosemide, urodilatin, and mannitol), vasodilators (prostaglandin E1 [PGE1], diltiazem, dopexamine, dopamine [DA], mannitol, fenoldopam, angiotensin-converting enzyme (ACE) inhibitor, sodium nitroprusside, theophylline, and prostacyclin), operative techniques (mostly off pump), prophylactic continuous venovenous hemodiafiltration or renal replacement therapy, and other strategies (albumin, insulin, clonidine, and volume expansion) [25]. Park and colleagues concluded that most of the prophylactic strategies conducted prior to cardiac surgery were protective against AKI; these included ANP/nesiritide, fenoldopam, and dopamine [25].

Ischemic preconditioning prior to cardiac surgery may be an alternative prophylactic method to reduce AKI. By preconditioning a remote site in the body (arm or leg) to reduced blood flow, reperfusion injury and AKI may be prevented [60, 61]. Zimmerman and colleagues demonstrated in a small single-center randomized trial that ischemic preconditioning resulting in an absolute risk reduction of 0.27 (12 versus 28 AKI events, $p = 0.004$) and resulted in lower rates of sustained AKI at 2 or more days [61]. It is likely that simple ischemic preconditioning methods could be incorporated at the time of entry to the operating room (OR) and may not only assist in AKI event reduction but also reduce myocardial reperfusion injury.

We have summarized the clinical research that has sought to mitigate AKI in the context of cardiac surgery. Some of these interventions have demonstrated consistency in prevention, while others either need more investigation or the development of new strategies. Most of these efforts have focused around modifying or discontinuing potentially nephrotoxic medication or exposure to nephrotoxins, such as radiocontrast dye. McCoy and colleagues reported on the single-center use of a computerized medication safety tool designed for patients developing AKI. Through the use of this automated intervention tool, 52.6 % of the time potentially nephrotoxic medications were halted or modified within 24 h of an acute increase in serum creatinine qualifying as AKI, a 49 % improvement prior to the intervention [62]. Additional simple and sophisticated process tools should be developed by multidisciplinary teams to study the problem of AKI. When doing so, teams should identify

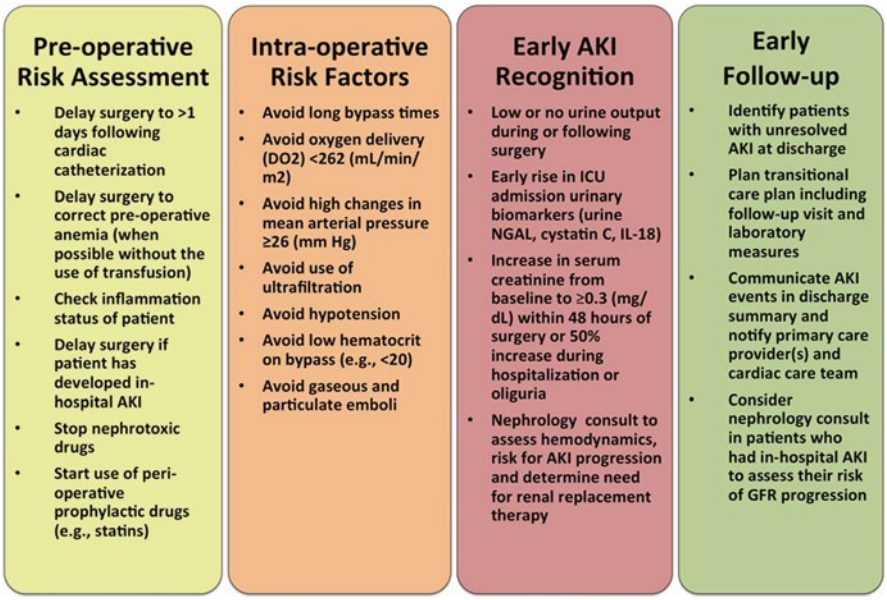

Fig. 7.3 AKI risk assessment algorithm

targets for intervention, test those interventions, evaluate their effectiveness, and redesign continually. Such microsystem-level improvement efforts are known as PDSA cycles of change (Plan-Do-Study-Act) [63, 64].

Conclusions

In this chapter, we have discussed the mortality, subsequent health-care costs, utilization, and morbidity that follow subtle changes in serum creatinine known as AKI in the perioperative setting of cardiac surgery. The field has come a long way from 10 years ago where subtle changes in serum creatinine were often ignored to the current volume of research and dedication that has identified and sought solutions for the patient safety issues surrounding cardiac surgery-associated AKI. We provide an algorithm to aid clinical care teams to identify pre- and perioperative modifiable risk factors to minimize the aid in the prevention of cardiac surgery-associated AKI and recommendations for early AKI recognition and follow-up (Fig. 7.3). Majority of the recommendations are based on epidemiologic observations or quality control protocols and require confirmation in interventional trials. In the near future, novel kidney injury biomarkers and risk tools will be available to identify early signs of AKI and acute tubular necrosis and hopefully matched with aggressive tools for medication adjustment and injury-specific interventions to mitigate AKI and its subsequent morbidity and mortality.

Key Messages

- AKI is a common adverse event following adult cardiac surgery ranging from 3 to 42 % depending on the definition used.
- Patients developing AKI are at an increased risk of in-hospital mortality, and those who are discharged face poor long-term survival and risk of end-stage renal failure.
- Prediction models for both onset and duration of AKI can assist clinical teams in therapeutic and prognostic information.
- Several modifiable strategies may be effective in preventing the risk of AKI following cardiac surgery.

References

1. Brown JR, Cochran RP, Dacey LJ, Ross CS, Kunzelman KS, Dunton RF, Braxton JH, Charlesworth DC, Clough RA, Helm RE, Leavitt BJ, Mackenzie TA, O'Connor GT. Perioperative increases in serum creatinine are predictive of increased 90-day mortality after coronary artery bypass graft surgery. Circulation. 2006;114:I409–13.
2. Brown JR, Kramer RS, Coca SG, Parikh CR. Duration of acute kidney injury impacts long-term survival after cardiac surgery. Ann Thorac Surg. 2010;90:1142–8.
3. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, Bihorac A. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation. 2009;119:2444–53.
4. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, Schmidlin D. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? Crit Care Med. 2008;36:1129–37.
5. Lenihan CR, Montez-Rath ME, Mora Mangano CT, Chertow GM, Winkelmayer WC. Trends in acute kidney injury, associated use of dialysis, and mortality after cardiac surgery, 1999 to 2008. Ann Thorac Surg. 2013;95:20–8.
6. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. Clin J Am Soc Nephrol. 2008;3:844–61.
7. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16:3365–70.
8. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (adqi) group. Crit Care (London, England). 2004;8:R204–12.
9. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care (London, England). 2007;11:R31.
10. Coca SG, King Jr JT, Rosenthal RA, Perkal MF, Parikh CR. The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. Kidney Int. 2010;78:926–33.
11. Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, Slinin Y, Ensrud KE. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. Arch Intern Med. 2011;171:226–33.

12. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. Veterans: focus on acute tubular necrosis. Kidney Int. 2009;76:1089–97.
13. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, Collins AJ. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20:223–8.
14. James MT, Ghali WA, Knudtson ML, Ravani P, Tonelli M, Faris P, Pannu N, Manns BJ, Klarenbach SW, Hemmelgarn BR. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. Circulation. 2011;123:409–16.
15. Brown JR, O'Connor GT. Coronary heart disease and prevention in the United States. N Engl J Med. 2010;362:2150–3.
16. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, Dupuis JY, Fremes SE, Kent B, Laflamme C, Lamy A, Legare JF, Mazer CD, McCluskey SA, Rubens FD, Sawchuk C, Beattie WS. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation. 2009;119:495–502.
17. Brown JR, Robb JF, Block CA, Schoolwerth AC, Kaplan AV, O'Connor GT, Solomon RJ, Malenka DJ. Does safe dosing of iodinated contrast prevent contrast-induced acute kidney injury? Circ Cardiovasc Interv. 2010;3:346–50.
18. Marenzi G, Assanelli E, Campodonico J, Lauri G, Marana I, De Metrio M, Moltrasio M, Grazi M, Rubino M, Veglia F, Fabbiocchi F, Bartorelli AL. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. Ann Intern Med. 2009;150:170–7.
19. Hennessy SA, LaPar DJ, Stukenborg GJ, Stone ML, Mlynarek RA, Kern JA, Ailawadi G, Kron IL. Cardiac catheterization within 24 hours of valve surgery is significantly associated with acute renal failure. J Thorac Cardiovasc Surg. 2010;140:1011–7.
20. Medalion B, Cohen H, Assali A, Vaknin Assa H, Farkash A, Snir E, Sharoni E, Biderman P, Milo G, Battler A, Kornowski R, Porat E. The effect of cardiac angiography timing, contrast media dose, and preoperative renal function on acute renal failure after coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2010;139:1539–44.
21. Ranucci M, Ballotta A, Kunkl A, De Benedetti D, Kandil H, Conti D, Mollichelli N, Bossone E, Mehta RH. Influence of the timing of cardiac catheterization and the amount of contrast media on acute renal failure after cardiac surgery. Am J Cardiol. 2008;101:1112–8.
22. Del Duca D, Iqbal S, Rahme E, Goldberg P, de Varennes B. Renal failure after cardiac surgery: timing of cardiac catheterization and other perioperative risk factors. Ann Thorac Surg. 2007;84:1264–71.
23. Kramer RS, Quinn RD, Groom RC, Braxton JH, Malenka DJ, Kellett MA, Brown JR. Same admission cardiac catheterization and cardiac surgery: is there an increased incidence of acute kidney injury? Ann Thorac Surg. 2010;90:1418–23; discussion 1423–4.
24. Kuss O, von Salviati B, Borgermann J. Off-pump versus on-pump coronary artery bypass grafting: a systematic review and meta-analysis of propensity score analyses. J Thorac Cardiovasc Surg. 2010;140:829–35, 835 e821–3.
25. Park M, Coca SG, Nigwekar SU, Garg AX, Garwood S, Parikh CR. Prevention and treatment of acute kidney injury in patients undergoing cardiac surgery: a systematic review. Am J Nephrol. 2010;31:408–18.
26. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ, Bailey DE, Weintraub WS, Guyton RA. Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. JAMA. 2004;291:1841–9.
27. Kaplan JA, Reich DL, Lake CL, Konstadt SN. Organ protection during cardiopulmonary bypass. In: Kaplan's cardiac anesthesia. 5th ed. Philadelphia: Saunders; 2006. p. 996–1033.
28. Ranucci M, Romitti F, Isgro G, Cotza M, Brozzi S, Boncilli A, Ditta A. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. Ann Thorac Surg. 2005;80:2213–20.
29. Ranucci M. Perioperative renal failure: hypoperfusion during cardiopulmonary bypass? Semin Cardiothorac Vasc Anesth. 2007;11:265–8.

30. Ranucci M, Isgro G, Carlucci C, De La Torre T, Enginoli S, Frigiola A. Central venous oxygen saturation and blood lactate levels during cardiopulmonary bypass are associated with outcome after pediatric cardiac surgery. Crit Care. 2010;14:R149.
31. Walter R, Mark M, Gaudenz R, Harris LG, Reinhart WH. Influence of nitrovasodilators and endothelin-1 on rheology of human blood in vitro. Br J Pharmacol. 1999;128:744–50.
32. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med. 2008;358:1229–39.
33. Benedetto U, Angeloni E, Luciani R, Refice S, Stefanelli M, Comito C, Roscitano A, Sinatra R. Acute kidney injury after coronary artery bypass grafting: does rhabdomyolysis play a role? J Thorac Cardiovasc Surg. 2010;140:464–70.
34. Brown JR, Cochran RP, Leavitt BJ, Dacey LJ, Ross CS, MacKenzie TA, Kunzelman KS, Kramer RS, Hernandez Jr F, Helm RE, Westbrook BM, Dunton RF, Malenka DJ, O'Connor GT. Multivariable prediction of renal insufficiency developing after cardiac surgery. Circulation. 2007;116:I139–43.
35. Brown JR, Kramer RS, MacKenzie TA, Coca SG, Sint K, Parikh CR. Determinants of acute kidney injury duration after cardiac surgery: an externally validated tool. Ann Thorac Surg. 2012;93:570–6.
36. de Somer F, Mulholland JW, Bryan MR, Aloisio T, Van Nooten GJ, Ranucci M. O2 delivery and co2 production during cardiopulmonary bypass as determinants of acute kidney injury: time for a goal-directed perfusion management? Crit Care (London, England). 2011;15:R192.
37. Kanji HD, Schulze CJ, Hervas-Malo M, Wang P, Ross DB, Zibdawi M, Bagshaw SM. Difference between pre-operative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury. J Cardiothorac Surg. 2010;5:71.
38. Lima RS, da Silva Junior GB, Liborio AB, Daher EF. Acute kidney injury due to rhabdomyolysis. Saudi J Kidney Dis Transpl. 2008;19:721–9.
39. Mao H, Katz N, Ariyanon W, Blanca-Martos L, Adybelli Z, Giuliani A, Danesi TH, Kim JC, Nayak A, Neri M, Virzi GM, Brocca A, Scalzotto E, Salvador L, Ronco C. Cardiac surgery-associated acute kidney injury. Cardiorenal Med. 2013;3:178–99.
40. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol. 2006;1:19–32.
41. Chertow GM, Lazarus JM, Christiansen CL, Cook EF, Hammermeister KE, Grover F, Daley J. Preoperative renal risk stratification. Circulation. 1997;95:878–84.
42. Mehta RH, Grab JD, O'Brien SM, Bridges CR, Gammie JS, Haan CK, Ferguson TB, Peterson ED. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. Circulation. 2006;114:2208–16; quiz 2208.
43. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol. 2005;16:162–8.
44. Wijeysundera DN, Karkouti K, Dupuis JY, Rao V, Chan CT, Granton JT, Beattie WS. Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. JAMA. 2007;297:1801–9.
45. Englberger L, Suri RM, Li Z, Dearani JA, Park SJ, Sundt 3rd TM, Schaff HV. Validation of clinical scores predicting severe acute kidney injury after cardiac surgery. Am J Kidney Dis. 2010;56:623–31.
46. Aronson S, Fontes ML, Miao Y, Mangano DT. Risk index for perioperative renal dysfunction/failure: critical dependence on pulse pressure hypertension. Circulation. 2007;115:733–42.
47. Palomba H, de Castro I, Neto AL, Lage S, Yu L. Acute kidney injury prediction following elective cardiac surgery: AKICS score. Kidney Int. 2007;72:624–31.
48. Huen SC, Parikh CR. Predicting acute kidney injury after cardiac surgery: a systematic review. Ann Thorac Surg. 2012;93:337–47.

49. Kiers HD, van den Boogaard M, Schoenmakers MC, van der Hoeven JG, van Swieten HA, Heemskerk S, Pickkers P. Comparison and clinical suitability of eight prediction models for cardiac surgery-related acute kidney injury. Nephrol Dial Transplant. 2013;28:345–51.
50. Liangos O, Tighiouart H, Perianayagam MC, Kolyada A, Han WK, Wald R, Bonventre JV, Jaber BL. Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. Biomarkers. 2009;14:423–31.
51. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol: JASN. 2011;22:1748–57.
52. Parikh CR, Devarajan P, Zappitelli M, Sint K, Thiessen-Philbrook H, Li S, Kim RW, Koyner JL, Coca SG, Edelstein CL, Shlipak MG, Garg AX, Krawczeski CD. Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. J Am Soc Nephrol. 2011;22:1737–47.
53. Shlipak MG, Coca SG, Wang Z, Devarajan P, Koyner JL, Patel UD, Thiessen-Philbrook H, Garg AX, Parikh CR. Presurgical serum cystatin c and risk of acute kidney injury after cardiac surgery. Am J Kidney Dis. 2011;58:366–73.
54. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. J Am Soc Nephrol. 2010;21:1757–64.
55. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int. 2008;74:101–7.
56. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, Tonelli M. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet. 2010;376:2096–103.
57. Huang TM, Wu VC, Young GH, Lin YF, Shiao CC, Wu PC, Li WY, Yu HY, Hu FC, Lin JW, Chen YS, Lin YH, Wang SS, Hsu RB, Chang FC, Chou NK, Chu TS, Yeh YC, Tsai PR, Huang JW, Lin SL, Chen YM, Ko WJ, Wu KD. Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting. J Am Soc Nephrol. 2011;22:156–63.
58. Tonelli M, Muntner P, Lloyd A, Manns BJ, James MT, Klarenbach S, Quinn RR, Wiebe N, Hemmelgarn BR. Using proteinuria and estimated glomerular filtration rate to classify risk in patients with chronic kidney disease: a cohort study. Ann Intern Med. 2011;154:12–21.
59. Coca SG, Jammalamadaka D, Sint K, Thiessen-Philbrook H, Shlipak MG, Zappitelli M, Devarajan P, Hashim S, Garg AX, Parikh CR. Preoperative proteinuria predicts acute kidney injury in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2012;143:495–502.
60. Ali ZA, Callaghan CJ, Lim E, Ali AA, Nouraei SA, Akthar AM, Boyle JR, Varty K, Kharbanda RK, Dutka DP, Gaunt ME. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. Circulation. 2007;116:I98–105.
61. Zimmerman RF, Ezeanuna PU, Kane JC, Cleland CD, Kempananjappa TJ, Lucas FL, Kramer RS. Ischemic preconditioning at a remote site prevents acute kidney injury in patients following cardiac surgery. Kidney Int. 2011;80:861–7.
62. McCoy AB, Waitman LR, Gadd CS, Danciu I, Smith JP, Lewis JB, Schildcrout JS, Peterson JF. A computerized provider order entry intervention for medication safety during acute kidney injury: a quality improvement report. Am J Kidney Dis. 2010;56:832–41.
63. Batalden PB, Nelson EC, Edwards WH, Godfrey MM, Mohr JJ. Microsystems in health care: part 9. Developing small clinical units to attain peak performance. Jt Comm J Qual Saf. 2003;29:575–85.

64. Nelson EC, Godfrey MM, Batalden PB, Berry SA, Bothe Jr AE, McKinley KE, Melin CN, Muething SE, Moore LG, Wasson JH, Nolan TW. Clinical microsystems, part 1. The building blocks of health systems. Jt Comm J Qual Patient Saf. 2008;34:367–78.
65. Conlon PJ, Stafford-Smith M, White WD, Newman MF, King S, Winn MP, Landolfo K. Acute renal failure following cardiac surgery. Nephrol Dial Transplant. 1999;14:1158–62.
66. Andersson LG, Ekroth R, Bratteby LE, Hallhagen S, Wesslen O. Acute renal failure after coronary surgery–a study of incidence and risk factors in 2009 consecutive patients. Thorac Cardiovasc Surg. 1993;41:237–41.
67. Thakar CV, Liangos O, Yared JP, Nelson DA, Hariachar S, Paganini EP. Predicting acute renal failure after cardiac surgery: validation and re-definition of a risk-stratification algorithm. Hemodial Int. 2003;7:143–7.
68. Brown JR, Parikh CR. Cardiovascular surgery and acute kidney injury. In: Turner N, editor. Textbook of clinical nephrology. London: Oxford University Press; 2014 (in press).