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AKI GUIDELINE

The Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology Clinical Practice Guidelines for the Prevention of Adult Cardiac Surgery–Associated Acute Kidney Injury

Jeremiah R. Brown, PhD, MS, Robert A. Baker, PhD, CCP, Linda Shore-Lesserson, MD, Amanda A. Fox, MD, MPH, Linda B. Mongero, CCP, Kevin W. Lobdell, MD, Scott A. LeMaire, MD, Filip M. J. J. De Somer, PhD, EBCP, Moritz Wyler von Ballmoos, MD, PhD, Viachaslau Barodka, MD, Rakesh C. Arora, MD, PhD, Scott Firestone, MS, Richard Solomon, MD, Chirag R. Parikh, MD, PhD, Kenneth G. Shann, CCP, and John Hammon, MD

Departments of Epidemiology, Biomedical Data Science, and Health Policy and Clinical Practice, Dartmouth Geisel School of Medicine, Hanover, New Hampshire; Cardiothoracic Surgery Quality and Outcomes Unit and Perfusion Service, Department of Surgery, Flinders Medical Centre and Flinders University, Adelaide, South Australia, Australia; Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas; McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, Texas; SpecialtyCare, Inc, Brentwood, Tennessee; Cardiovascular Surgery, Sanger Heart & Vascular Institute, Atrium Health, Charlotte, North Carolina; Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas; Department of Cardiac Surgery, Ghent University Hospital, Ghent, Belgium; DeBakey Heart and Vascular Center, Houston Methodist Hospital, Houston, Texas; Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland; Section of Cardiac Surgery, Department of Surgery, Max Rady College of Medicine, University of Manitoba, Manitoba, Winnipeg, Canada; The Society of Thoracic Surgeons, Chicago, Illinois; Division of Nephrology and Hypertension, University of Vermont Larner College of Medicine, Burlington, Vermont; Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, Maryland; Division of Cardiac Surgery, Massachusetts General Hospital, Boston, Massachusetts; and Department of Cardiothoracic Surgery, Wake Forest University School of Medicine, Winston-Salem, North Carolina

EXECUTIVE SUMMARY

1. In adult cardiac surgery with cardiopulmonary bypass (CPB), avoiding hyperthermic perfusion (>37 °C) is recommended to reduce the risk of cardiac surgery-associated acute kidney injury (CSA-AKI). (**Class of Recommendation: I, Level of Evidence: B-R**)
2. In adult cardiac surgery with CPB, a goal-directed oxygen delivery strategy is recommended to reduce the risk of CSA-AKI. (**Class of Recommendation: I, Level of Evidence: B-R**)
3. In adult cardiac surgery with CPB, it is reasonable to adopt the Kidney Disease Improving Global Outcomes (KDIGO) practice guidelines for patients at high risk of AKI to reduce the risk of CSA-AKI (**Class of Recommendation IIA; Level of Evidence B-R**).
4. In adult cardiac surgery with CPB, fenoldopam may be reasonable to reduce the risk of CSA-AKI, as long as hypotension is avoided (**Class of Recommendation: IIB, Level of Evidence: B-R**).
5. In adult cardiac surgery with CPB, it might be reasonable to use minimally invasive extracorporeal circulation (MiECC) techniques to reduce the risk of CSA-AKI. (**Class of Recommendation: IIB, Level of Evidence: B-R**)

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Address correspondence to Dr Lobdell, Sanger Heart & Vascular Institute-Innovation Center, 1237 Harding Pl, Charlotte, NC 28204; email: kevin.lobdell@atriumhealth.org.

Abbreviations and Acronyms

ACEi = angiotensin-converting enzyme inhibitors
ARBs = angiotensin-receptor blockers
CABG = coronary artery bypass graft
CPB = cardiopulmonary bypass
CSA-AKI = cardiac surgery–associated acute kidney injury
DO_2 = delivered oxygen
DO_{2i} = delivered oxygen index
KDIGO = Kidney Disease Improving Global Outcomes
ICU = intensive care unit
MiECC = minimally invasive extracorporeal circulation
OR = odds ratio
RCT = randomized controlled trial
RIFLE = Risk, Injury, Failure, Loss, End-Stage

6. In adult cardiac surgery with CPB, dopamine infusion alone, during CPB and the perioperative period, is not recommended to reduce the risk of CSA-AKI. (**Class of Recommendation III: No Benefit, Level of Evidence: A**)
7. In adult cardiac surgery with CPB, mannitol is not recommended to reduce the risk of CSA-AKI. (**Class of Recommendation III: No Benefit, Level of Evidence: B-R**)

Cardiac surgery-associated acute kidney injury (CSA-AKI) occurs in 15% to 50% of adults undergoing cardiac surgery and is characterized by a 0.3 mg/dL or 50% increase in serum creatinine from baseline or oliguria.[1-4] There is wide regional, national, and international variation in rates of CSA-AKI.[5,6] This is likely due to the lack of use of standardized definitions of AKI, such as the Kidney Disease Improving Global Outcomes (KDIGO),[4] the Risk, Injury, Failure, Loss, End-Stage (RIFLE), or Acute Kidney Injury Network criteria (Table 1),[7-9] and to the fact that there have been limited attempts to synthesize the current evidence for strategies to prevent and mitigate AKI after adult cardiac surgery.[10,11]

For related article, see page 11

Using a comprehensive and updated review of the literature on the prevention of CSA-AKI and other renal complications in adult cardiac surgery patients, the committee developed this joint guideline on renal protection strategies. These guidelines were created through a multispecialty partnership between The Society of Thoracic Surgeons, the Society of Cardiovascular Anesthesiologists, and the American Society of Extracorporeal Technology.

The multidisciplinary task force synthesized the evidence for renal protective strategies using the highest level of literature review and scoring consistent with other Society of Thoracic Surgeons guidelines.[12,13] Specifically, the task force synthesized and scored the evidence on pharmacologic strategies, fluid management, transfusion, cardiopulmonary bypass (CPB) management, and other more targeted strategies (eg, remote ischemic preconditioning and prophylactic dialysis).

METHODOLOGY

An initial comprehensive literature search of the MEDLINE database (National Library of Medicine) was performed in 2015, with the intent of selecting only randomized trials of adult cardiac surgery patients who underwent cardiac surgery with CPB with assessment of clinical measures of renal function as primary outcomes. The results were limited to randomized controlled trials (RCTs) and meta-analyses published in English between January 1, 2000, and March 31, 2014. This search was further expanded and updated in 2017 using a new data management tool. As a final survey of the current literature, manuscripts through March 30, 2021, were included if they met the inclusion/exclusion criteria. The strategies for conducting the 2015 and the 2017 literature searches are listed in Appendix A.

The initial literature search resulted in 365 publications that were reviewed by a team of multidisciplinary authors (R.B., J.B., K.S., and C.M.). A total of 173 studies met the inclusion criteria for full-paper review, and data for 78 were extracted into the tables (Appendix B).

The second literature search identified an additional 592 publications, from which a team of authors (R.B., J.B., K.W.L., S.L., L.M., L.S.L., A.F., F.D., and S.F.) selected 50 studies and extracted data from them into the evidence tables (Appendix B). Reference lists of identified research papers were also scanned manually to identify any additional relevant studies that might have been missed in the MEDLINE query. All relevant studies were appraised for risk of bias using a customized checklist for RCTs and meta-analyses (Appendix C).

Meta-analyses were conducted where RCT data were deemed adequate and sufficiently similar to be pooled using random-effect models requiring a minimum of 2 studies reporting comparable renal outcomes (eg, CSA-AKI, change in serum creatinine, new onset of dialysis). Only published meta-analyses are included in the main guideline document. Meta-analyses conducted by the task force are located in the supplementary materials.

Data were reviewed by all authors, and recommendations were first drafted by each subtopic author group and then refined by using a modified Delphi consensus process. The recommendations are graded

TABLE 1 Adult Cardiac Surgery–Associated Acute Kidney Injury Definitions

Variable	Serum Creatinine Diagnostic RIFLE	AKIN	KDIGO	Urine Output[a]
	No explicit criteria	≥0.3 mg/dL *or* ≥1.5× baseline within 48 hours	≥0.3 mg/dL within 48 hours *or* ≥1.5× baseline within 7 days	<0.5 mL/kg/h for ≥6 hours[b]
Staging				
Stage 1 *or* risk	≥1.5× baseline *or* eGFR decreased >25%	≥0.3 mg/dL *or* ≥1.5× to 2.0× baseline	≥0.3 mg/dL *or* ≥1.5× to 1.9× baseline	<0.5 mL/kg/h for 6 to 12 hours
Stage 2 *or* injury	≥2.0× baseline *or* eGFR decreased >50%	≥2.0× to 3.0× baseline	≥2.0 to 2.9× baseline	<0.5 mL/kg/h for ≥12 hours
Stage 3 *or* failure	≥3.0× baseline *or* increase by >0.5 mg/dL to >4.0 mg/dL *or* eGFR decreased >50%	>3.0× baseline *or* increase by >0.5 mg/dL to ≥4.0 mg/dL *or* initiation of RRT	≥3.0× baseline *or* increase by ≥0.3 mg/dL to ≥4.0 mg/dL or initiation of RRT *or* if <18 years, eGFR <35 mL/min/1.73 m^2	<0.3 mL/kg/h for >24 hours *or* anuria for ≥12 hours
Clinical outcomes				
Loss	RRT >4 weeks			
ESRD	RRT >3 months			

[a]All staging criteria for urine output match for RIFLE, AKIN, and KDIGO; [b]This criterion applies only to AKIN and KDIGO. AKIN, Acute Kidney Injury Network; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, risk, injury, failure, loss, end stage renal disease; RRT, renal replacement therapy. Data were derived from Bagshaw SM, George C, Bellomo R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol Dial Transplant*. 2008;23:1569-1574; Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by akin versus rifle using the SAPS 3 database. *Intensive Care Med*. 2009;35:1692-1702; and Acute Kidney Injury Work Group. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline for acute kidney injury. *Kidney Int*. 2012;2(suppl 1):1-138.[7-9]

according to the American College of Cardiology/American Heart Association Recommendation System,[14] included as Appendix D. A simplified list of the recommendations is included as Table 2 to aid in implementation. Additionally, a number of proposed recommendations, which were omitted due to lack of consensus or clear clinical value, are included in Appendix E.

CPB STRATEGIES

The literature summarized subsequently recommends intraoperative CPB strategies decrease the risk of developing acute renal injury after cardiac surgery. These interventions include avoiding hyperthermic perfusion (>37 °C), avoiding low delivery of oxygen (DO_2), and the adoption of minimally invasive

TABLE 2 Brief Overview of Recommendations to Prevent Acute Kidney Injury and Initiation of Dialysis by Phase of Care

Intraoperative Recommendations	
For patients undergoing cardiac surgery with CPB	Avoid hyperthermic perfusion (arterial catheter >37 °C) (Class I, Level B-R) Avoid nadir DO_2 <270 mL/min/m^2 (Class I, Level B-R) Consider minimally invasive extracorporeal circulation techniques (Class IIB, Level B-R) Consider fenoldopam infusion during CPB and perioperatively (Class IIB, Level B-R) … DO NOT USE dopamine infusion for renal protection during CPB and perioperatively (Class III: No Benefit, Level A) DO NOT USE mannitol to prime CPB for renal protection (Class III: No Benefit, Level B-R)
Postoperative Recommendations	
High AKI–risk patients: elevations in [TIMP-2]*[IGFBP7] ≥0.3	KDIGO practice guidelines can be effective: • close hemodynamic monitoring and goal directed volume resuscitation • avoidance of nephrotoxic substances • hold ACEi/ARB for 48 hours • serial serum creatinine and urine output monitoring • prevention of hyperglycemia (Class IIA, Level B-R)

ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin-receptor blocker; CPB, cardiopulmonary bypass; DO_2, oxygen delivery; IGFBP7, insulin-like growth factor-binding protein 7; KDIGO, Kidney Disease Improving Global Outcomes; TIMP2, tissue inhibitor of metalloproteinases 2.

extracorporeal circulation (MiECC) techniques. There is currently not enough evidence to *support use of* heparin-coated circuits, leukocyte filtration, pulsatile flow during CPB, intraoperative hemofiltration and ultrafiltration, *relative hypertension* during CPB, or multipass hemoconcentration (vs centrifugation of residual CPB blood) to decrease acute renal injury after cardiac surgery. These strategies may be beneficial for other outcomes.

Class I

1. In adult cardiac surgery with CPB, avoiding hyperthermic perfusion (>37 °C) is recommended to reduce the risk of CSA-AKI. **(Level of Evidence: B-R)**
2. In adult cardiac surgery with CPB, a goal-directed DO_2 strategy is recommended to reduce the risk of CSA-AKI. **(Level of Evidence: B-R)**

Class IIB

1. In adult cardiac surgery with CPB, the use of MiECC techniques to minimize the risk of CSA-AKI might be reasonable. **(Level of Evidence: B-R)**

TEMPERATURE MANAGEMENT. A randomized trial by Boodhwani and colleagues[15] of 223 low-risk coronary artery bypass graft (CABG) surgery patients found that rewarming on CPB from 32 °C to a nasopharyngeal target of 37 °C vs 34 °C resulted in significantly higher postoperative serum creatinine values. The authors identified rewarming as an independent risk factor for renal dysfunction, suggesting differential rewarming and potential hyperthermia as proposed mechanisms for this difference.[15]

Newland and colleagues[16] performed a single-center retrospective cohort study of 1393 consecutive adult patients undergoing valve, CABG, or combined CABG and valve surgery and found that increased number of minutes on CPB with arterial outlet temperature >37 °C and higher postoperative intensive care unit (ICU) arrival temperatures were associated with a significantly increased incidence of CSA-AKI (CPB hyperthermia odds ratio [OR], 1.03 per minutes increase, 95% CI, 1.01-1.05; ICU admission temperature OR, 1.44 per degree increase, 95% CI 1.13-1.85). This finding was reproduced in a multicenter study of 8407 patients that found in both cohort and propensity-matched studies that duration of rewarming temperature >37 °C (hyperthermic perfusion) was independently associated with RIFLE risk classification or greater (OR, 1.42; 95% CI, 1.09-1.77; $P = .012$) and injury classification or greater AKI (OR, 1.52; 95% CI, 1.09-1.97; $P = .016$) in the entire cohort, and injury classification or greater AKI (OR, 1.51; 95% CI, 1.15-1.90; $P = .006$) in propensity-matched patients.[17]

DO_2 STRATEGY. Ranucci and colleagues[18] (2005) demonstrated in a single-center prospective observational study of 1048 individuals that the minimum DO_2 index (DO_{2i}) during CPB was independently associated with CSA-AKI requiring renal replacement therapy, with an optimal diagnostic threshold for DO_{2i} identified as 272 mL/min/m^2. Newland and Baker (2017)[19] supported this finding in an observational study of 210 patients in which they suggested that the integral of the amount and time for DO_2 below a critical threshold was an independent predictor of AKI. They reported a DO_{2i} threshold of 270 mL/min/m^2.[19] Mukaida and associates[20] reported that increased time <300 mL/min/m^2 was significantly associated with increased AKI. A small propensity-matched study demonstrated that when targeted DO_2 (>300 mL/min/m^2) was included as part of a multifaceted goal-directed strategy, CSA-AKI was reduced.[20]

In 2018, Ranucci and investigators[21] published a multicenter RCT in which goal-directed perfusion aimed to avoid a CPB nadir DO_{2i} of <280 mL/min/m^2 resulted in significantly lower AKI stage 1. The goal-directed perfusion intervention aimed to maintain DO_{2i} at ≥280 mL/min/m^2 by adjusting arterial flow according to hematocrit value to maintain DO_2 above the prespecified threshold (280 mL/min/m^2). When low hematocrit resulted in an inability to achieve the desired threshold, red blood cells were transfused to increase DO_2.[21] In 2019, the Australian and New Zealand Collaborative Perfusion Registry group published findings from >19 000 adult cardiac surgery patients and reported that nadir DO_{2i} <270 mL/min/m^2 was associated with significantly increased odds of developing AKI by 52% (OR, 1.52; 95% CI, 1.29-1.77; $P <$ .001).[22]

The goal-directed perfusion investigations include a range of temperatures and target DO_{2i}, thereby limiting precise specification of goals. Despite these limitations, goal-directed perfusion correlates with a reduction in CSA-AKI and is recommended.

MINIMALLY INVASIVE EXTRACORPOREAL CIRCULATION. MiECC is a strategy that requires coordinated efforts between surgeons, anesthesiologists, and perfusionists and has been proposed as an alternative approach to undertaking cardiac surgery using standard CPB.[23] The Minimal invasive Extra-Corporeal Technologies International Society defined that in addition to core components for CPB (membrane oxygenator, heat exchanger, cardioplegia system), an MiECC system should include a closed system, biologically inert (coated) circuit coating, have reduced priming volume, use a centrifugal pump, contain a venous bubble trap/venous air removal device, and incorporate a shed blood management system. Additional features and components, such as vents and reservoirs, may be included.

The results of randomized trials using MiECC circuits have been conflicting. The literature is limited by the heterogeneity in the techniques reported for both the intervention (MiECC techniques) and the control arm (CPB) of the trials reported. Two meta-analyses have reported on the impact of MiECC on the renal outcome of cardiac surgery with CPB, with conflicting findings. Sun and associates[24] (2015) reported no difference in acute renal failure in 6 studies, with a relative risk of 0.922 (95% CI, 0.388-1.01; $P = .854$; $I^2 = 11.9\%$); however, a more recent meta-analysis reported MiECC reduced the odds of CSA-AKI by >50% compared with conventional CPB (OR, 0.47; 95% credibility interval, 0.24-0.89).[25] More recent RCTs have not reported CSA-AKI outcomes.

PHARMACOLOGIC STRATEGIES

Recommendations:

Class IIB

1. In adult cardiac surgery with CPB, fenoldopam may be reasonable to reduce the risk of CSA-AKI, as long as hypotension is avoided (**Level of Evidence: B-R**).

Class III: No Benefit

1. In adult cardiac surgery with CPB, dopamine infusion alone, during CPB and the perioperative period, is not recommended to reduce the risk of CSA-AKI. (**Class of Recommendation III: No Benefit, Level of Evidence: A**)
2. In adult cardiac surgery with CPB, mannitol is not recommended to provide protection against CSA-AKI. (**Level of Evidence: B-R**)

DIURETICS. Dopamine is a widely studied diuretic.[26] At low doses (0.3-5 μg/kg/min), dopamine has been purported to increase renal blood flow and promote natriuresis and diuresis. Consequently, there has been substantial interest in using a "renal-dose" dopamine infusion to improve kidney perfusion and prevent acute renal injury in patients undergoing CPB. Most of the single-center randomized clinical trials[27-34] have not demonstrated benefit with dopamine infusion to prevent AKI.

Two other diuretic agents, mannitol and furosemide, have been studied in randomized trials and consistently demonstrated no benefit.[28,31,35-37] Further, one trial raises concerns that furosemide infusion may have deleterious effects on postoperative renal function.[28]

In a randomized clinical trial involving patients with normal preoperative renal function, patients who received a dopamine infusion (2 μg/kg/min) during the cardiac operation and in the early postoperative period had similar postoperative renal function and clinical outcomes as those who received placebo treatment.[30] Most of the other trials investigating low-dose dopamine infusion during CPB have relied on urinary biomarkers to determine whether dopamine reduced subclinical levels of renal injury. The findings of biomarker studies have been inconsistent; overall, they have not yielded evidence supporting a renal-protective effect of dopamine.

In a randomized clinical trial involving patients with normal preoperative renal function, those who received a dopamine infusion (2.5 μg/kg/min) during cardiac surgery and in the early postoperative period had significantly lower levels of urinary retinol-binding protein on postoperative day 1, but not on days 2 or 5, compared with patients who received placebo; however, there were no significant differences in clinical outcomes or in other biomarker levels.[31]

A study focused on patients at high risk for postoperative renal dysfunction found that patients who received a dopamine infusion (3 μg/kg/min) during their cardiac operations and during the early postoperative period had a significantly more negative fluid balance than those who received placebo, but there were no significant differences in clinical outcomes or biomarkers, including urinary retinol-binding protein, during the 6 days after surgery.[32]

In a trial comparing treatment strategies in patients with normal preoperative renal and cardiac function who were undergoing elective CABG with CPB, patients were randomly assigned to receive or not receive a dopamine infusion (2 μg/kg/min) during the perioperative period.[33] The authors reported that the dopamine infusion was associated with significantly higher urinary β_2-microglobulin excretion—an indicator of renal tubular injury—on postoperative day 3 compared with controls; there were no significant differences in clinical outcomes or other biomarkers.

Similarly, in the randomized clinical trial by Carcoana and colleagues,[28] the authors compared 4 treatment strategies—dopamine infusion (2 μg/kg/min) throughout the CPB period, mannitol (1 g/kg) added to the pump prime, both dopamine infusion and mannitol, or placebo—in patients with normal preoperative renal function who were undergoing CABG with CPB. Although there were no differences in renal function indicators or clinical outcomes, the infusion of dopamine (alone or in combination with mannitol) was associated with significantly higher β_2-microglobulin excretion at 1 hour after CPB compared with placebo; this difference did not persist at 6 or 24 hours after CPB. Logistic regression analysis revealed that the dopamine infusion was associated with up to a 7.7-fold increase in the odds of an increased β_2-microglobulin excretion rate at 1 hour after CPB.[28]

No studies have demonstrated that dopamine reduces the incidence of clinical AKI or renal replacement

therapy. In fact, few studies include major clinical end points. In the meta-analysis performed by Patel and colleagues,[27] only 4 of the 11 randomized clinical trials focusing on dopamine reported clinical outcomes. Although the analysis revealed that dopamine infusion was associated with a small decline in renal function as measured by creatinine clearance, the effect size was small and was not evident when low-quality studies were excluded.

One small clinical trial among 60 patients with normal preoperative renal function who were undergoing CABG with CPB evaluated dopamine with diltiazem. Patients were assigned to receive 1 of 4 treatments during the perioperative period: dopamine infusion (2 μg/kg/min), diltiazem infusion (2 μg/kg/min), both dopamine and diltiazem infusion, or neither infusion (controls). Importantly, patients who received dopamine alone or diltiazem alone exhibited significantly higher urinary β_2-microglobulin levels at 24 hours than controls; in contrast, patients who received combined dopamine and diltiazem infusion had urinary β_2-microglobulin levels that were similar to controls. Further, compared with the other groups, the patients who received the combined dopamine and diltiazem infusion exhibited significantly higher creatinine clearance and osmotic clearance 24 hours after surgery and significantly higher free water clearance at 24 and 72 hours after surgery.[34]

Two randomized clinical trials focusing on the impact of mannitol in providing renal protection in 2 different patient populations were reported. In the first study, 40 patients with normal preoperative renal function were randomized to have mannitol (500 mg/kg) or Hartmann solution added to the CPB prime during elective cardiac operations.[37] Compared with the control group, the use of mannitol was not associated with differences in postoperative renal function or in urinary retinol-binding protein or microalbumin levels. In the second study, 47 patients with preoperative renal dysfunction (serum creatinine 130-250 μmol/L) undergoing elective cardiac operations were randomized to the same 2 groups, and the use of mannitol was not associated with differences in postoperative renal function compared with controls.[36]

Another single-center randomized clinical trial compared treatment strategies in patients with normal preoperative renal function who were undergoing CABG with CPB.[28] Patients were assigned to receive mannitol (1 g/kg) added to the pump prime, dopamine infusion (2 μg/kg/min) throughout the CPB period, both dopamine infusion and mannitol, or placebo. Compared with placebo, the use of mannitol without dopamine was not associated with any differences in β_2-microglobulin excretion, renal function variables, or clinical end points, including major postoperative events and ICU and hospital lengths of stay. The group that received both dopamine and mannitol exhibited significantly higher β_2-microglobulin excretion 1 hour after CPB compared with placebo. Logistic regression analysis revealed that the combination of mannitol and dopamine infusion was associated with a 5.3-fold increase in the odds of an increased β_2-microglobulin excretion rate ($P = .008$).[28]

Lassnigg and colleagues[30] (2000) observed no significant differences between the placebo and diuretic treatments of dopamine and furosemide, specifically in length of stay in the ICU or hospital mortality. Significance for other clinical outcomes was not measured, but for groups undergoing furosemide treatments, 2 died of myocardial infarction and 2 underwent renal replacement therapy.

When testing dopexamine, Dehne and colleagues[29] observed no significant clinical complications in their cohort regarding death or renal replacement therapy; other key clinical outcomes were not measured. Sumeray and colleagues[31] made no conclusions about clinical outcomes after dopamine infusion in their study. Woo and coworkers[32] observed no significant differences between placebo and dopamine treatments for postoperative renal replacement therapy or ICU length of stay. Yavuz and colleagues[34] (2002) recorded no patients with clinical complications, including in-hospital mortality, cardiac complications, respiratory issues, or renal dysfunction, during their dopamine trial, which was consistent with a follow-up study by Yavuz and colleagues[34] published in the same year. Carcoana and coworkers[28] observed nonsignificant differences in clinical outcomes, including ICU length of stay, among the treatment groups for dopamine or for furosemide.

VASODILATORS. Several different types of vasodilators have been studied to determine whether they provide renal protection during CPB. There is some clinical evidence suggesting that the use of several agents—including fenoldopam, nitroprusside, diltiazem combined with dopamine, and prostaglandin I_2 analogues—may improve renal outcomes.[27,34,38-46] Clinical evidence in support of using angiotensin-receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEi), or nifedipine is lacking.[47-49] Importantly, although some studies have indicated that the use of vasodilators may improve various indicators of postoperative renal function, very few have demonstrated that vasodilators reduce the incidence of acute renal failure after CPB.

Of the various vasodilators, the most frequently studied has been fenoldopam, a selective dopamine

TABLE 3 Standard of Care and Kidney Disease Improving Global Outcomes Bundle Intervention

Control	Intervention KDIGO Bundle
Standard care	Discontinuation of all nephrotoxic agents if possible
ACEi and ARBs continued according to ACC recommendations	Discontinuation of ACE inhibitors and ARBs for the first 2 days after surgery
MAP will be kept >65 mm Hg	Close monitoring of serum creatinine and urinary output
CVP between 8 and 10 mm Hg	Avoidance of hyperglycemia by close monitoring
	Consideration of alternatives to radio contrast agents
	Hemodynamic monitoring and optimization according to a hemodynamic algorithm

ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CVP, central venous pressure; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, mean arterial pressure. Adapted from Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery–associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med*. 2017;43:1551-1561; and Acute Kidney Injury Work Group. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline for acute kidney injury. *Kidney Int*. 2012;2(suppl 1):1-138.[8,11]

receptor D_1 agonist. Three principal trials yielded differing results. One single-center randomized clinical trial comparing perioperative fenoldopam (0.05 μg/kg/min) vs dopamine (2.5 μg/kg/min) infusion in high-risk patients undergoing cardiac surgery found no differences in renal outcomes between the groups.[39] This study was interrupted by the safety monitoring board because of "the documented lack of efficacy of fenoldopam in improving renal outcome, the significant increased incidence of hypotension during CPB, and the suggestive intraoperative trend toward the use of vasoconstrictors." [39]

In a double-blind randomized clinical trial that compared complex cardiac surgery patients who received perioperative fenoldopam infusion (0.1 μg/kg/min) vs placebo, the difference in the incidence of AKI did not reach statistical significance (0 of 38 in the fenoldopam group vs 4 of 40 in controls; $P = .1$).[44] Interestingly, in the subgroup analysis of patients who received inotropic support to treat low cardiac output syndrome immediately after surgery, the patients who received fenoldopam had a significantly lower incidence of AKI than those who received placebo (0 of 11 vs 4 of 6; $P = .006$).

Cogliati and colleagues[40] published the largest randomized clinical trial regarding the use of fenoldopam during cardiac operations. This double-blind randomized clinical trial compared perioperative fenoldopam infusion (0.1 μg/kg/min for 24 hours) vs placebo in patients who underwent elective CABG and/or valve operations with CPB. Cogliati and colleagues[40] found that fenoldopam administration significantly reduced the incidence of AKI (12 of 95 vs 27 of 98; $P = .02$) and renal replacement therapy (0 of 95 vs 8 of 98; $P = .007$). The patients who received fenoldopam also had a shorter mean ICU stay than controls (2.3 ± 1.1 days vs 4.2 ± 3.1 days; $P < .0005$). No drug-related episodes of hypotension were noted during the study.

In 2019, a meta-analysis of 7 trials using trial sequential analysis to reduce random error also demonstrated a benefit of fenoldopam with respect to renal insufficiency but documented an increased occurrence of hypotension.[50] Sun and colleagues[50] did not confirm an association between fenoldopam use and reduced incidence of renal replacement therapy after cardiac operations, suggesting that most studies were small and variable and that there is not enough evidence to support it.

However, a benefit has been reported in cohort studies and in 3 other meta-analyses.[27,43,45-46,51] Roasio and colleagues[46] found a similar decrease in need for dialysis in patients treated with fenoldopam (17% vs 39%; $P = .037$) but did not find ICU stay to be significantly different. In the systematic review by Patel and colleagues,[27] fenoldopam was not found to significantly reduce mortality (OR, 1.36; 95% CI, 0.29-6.36; P value not published) but did reduce the need for postoperative dialysis (OR, 0.35; 95% CI, 0.13-0.96; P value not published).[27]

Although the previously described results support the potential benefit of using fenoldopam during CPB, the 3 principal studies had substantial differences in patient populations, fenoldopam dosage, infusion timing, study design, and control group treatment. The impact of fenoldopam appears positive in the cardiac surgery literature, but the marked heterogeneity of the studies weakens the strength of the collective evidence and precludes a recommendation stronger than IIb. The KDIGO recommendation to not use fenoldopam to prevent or treat AKI (2C) may seem inconsistent with our recommendation. The preponderance of data in cardiac surgery does show benefit in reducing AKI and renal replacement therapy, presuming hypotension can be avoided. Analysis of the totality of the literature, including studies in contrast-induced nephropathy and critically ill patients, have not shown universal benefit and most likely contribute to the KDIGO 2C recommendation.

TARGETED THERAPIES

Recommendations:

Class IIA

1. In adult cardiac surgery with CPB, it is reasonable to adopt the KDIGO practice guidelines for patients

at high risk of AKI to reduce the incidence of AKI (**Level of Evidence B-R**).

KDIGO GUIDELINE IMPLEMENTATION. In patients at high risk of AKI, the use of the KDIGO guideline recommendations in practice can be useful to reduce the incidence of AKI.[9,11] The PrevAKI (Prevention of Cardiac-Surgery Associated Acute Kidney Injury by Implementing the KDIGO Guidelines in High-Risk Patients Identified by Biomarkers) trial is a single-center trial that randomized patients at 4 hours after surgery found to be at high risk of AKI to receive either the KDIGO surgical bundle or to control. The KDIGO bundle includes close monitoring to optimize volume status and hemodynamics, avoidance of nephrotoxic drugs, stopping ACEi and ARBs for 48 hours, measurement of serum creatinine and urine output, prevention of hyperglycemia for 72 hours, and use of alternatives to constant agents.[11] Controls received standard of care in addition to specifications to maintain mean arterial pressure >65 mm Hg and central venous pressure between 8 and 10 mm Hg, with ACEi and ARBs continued according to American College of Cardiology recommendations (Table 3).[9,11]

The PrevAKI trial demonstrated a statistically significant reduction in AKI overall (55.1% intervention vs 71.7% control; OR, 0.48; 95% CI, 0.29-0.80; $P = .004$) significant reductions in moderate to severe AKI as well (29.7% vs 44.9%; $P = .009$). However, there were no differences in the need for renal replacement therapy, 90-day mortality, ICU length of stay, or major adverse kidney events end points.[11] A retrospective, bundled approach by Engelman and colleagues[52] demonstrated that hemodynamic monitoring, a liberal transfusion threshold, and avoidance of nephrotoxic drugs used in high-risk cardiac surgery patients (identified with AKI biomarkers) mitigated the risk of AKI. These efforts were coordinated through a multidisciplinary acute kidney response team and demonstrated a relative risk reduction of 89% for stage 2/3 CSA-AKI. Magruder and colleagues[53] reported a small retrospective propensity-matched study in which a goal-directed perfusion initiative to reduce CSA-AKI demonstrated a significant reduction in AKI (8 of 88 vs 21 of 88) and reduced creatinine increase after cardiac surgery.

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