Title

Society of Cardiovascular Anesthesiologists Clinical Practice Update for Management of Acute Kidney Injury Associated With Cardiac Surgery

Journal

Anesthesia & Analgesia, 135(4)

ISSN

0003-2999

Authors

Peng, Ke
McIlroy, David R
Bollen, Bruce A
et al.

Publication Date

2022-10-01

DOI

10.1213/ane.0000000000006068

Peer reviewed

SYSTEMATIC REVIEW ARTICLE

Society of Cardiovascular Anesthesiologists Clinical Practice Update for Management of Acute Kidney Injury Associated With Cardiac Surgery

Ke Peng, MD, PhD,*† David R. McIlroy, MBBS,‡ Bruce A. Bollen, MD,§ Frederic T. Billings IV, MD,‡ Alexander Zarbock, MD,‖ Wanda M. Popescu, MD,¶ Amanda A. Fox, MD, MPH,# Linda Shore-Lesserson, MD,** Shaofeng Zhou, MD,†† Mariya A. Geube, MD, ‡‡ Fuhai Ji, MD, PhD,† Meena Bhatia, MD,§§ Nanette M. Schwann, MD,‖‖ Andrew D. Shaw, MB, FCCM, FFICM, FRCA,¶¶ and Hong Liu, MD, FASE*

Cardiac surgery-associated acute kidney injury (CS-AKI) is common and is associated with increased risk for postoperative morbidity and mortality. Our recent survey of the Society of Cardiovascular Anesthesiologists (SCA) membership showed 6 potentially renoprotective strategies for which clinicians would most value an evidence-based review (ie, intraoperative target blood pressure, choice of specific vasopressor agent, erythrocyte transfusion threshold, use of alpha-2 agonists, goal-directed oxygen delivery on cardiopulmonary bypass [CPB], and the "Kidney Disease Improving Global Outcomes [KDIGO] bundle of care"). Thus, the SCA's Continuing Practice Improvement Acute Kidney Injury Working Group aimed to provide a practice update for each of these strategies in cardiac surgical patients based on the evidence from randomized controlled trials (RCTs). PubMed, EMBASE, and Cochrane library databases were comprehensively searched for eligible studies from inception through February 2021, with search results updated in August 2021. A total of 15 RCTs investigating the effects of the above-mentioned strategies on CS-AKI were included for meta-analysis. For each strategy, the level of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. Across the 6 potentially renoprotective strategies evaluated, current evidence for their use was rated as "moderate," "low," or "very low." Based on eligible RCTs, our analysis suggested using goal-directed oxygen delivery on CPB and the "KDIGO bundle of care" in high-risk patients to prevent CS-AKI (moderate level of GRADE evidence). Our results suggested considering the use of vasopressin in vasoplegic shock patients to reduce CS-AKI (low level of GRADE evidence). The decision to use a restrictive versus liberal strategy for perioperative red cell transfusion should not be based on concerns for renal protection (a moderate level of GRADE evidence). In addition, targeting a higher mean arterial pressure during CPB, perioperative use of dopamine, and use of dexmedetomidine did not reduce CS-AKI (a low or very low level of GRADE evidence). This review will help clinicians provide evidence-based care, targeting improved renal outcomes in adult patients undergoing cardiac surgery. (Anesth Analg 2022;00:00–00)

GLOSSARY

AKI = acute kidney injury; **CVP** = central venous pressure; **AKIN** = acute kidney injury network; **ARR** = absolute risk reduction; **CABG** = coronary artery bypass grafting; **CI** = confidence interval; **CPB** = cardiopulmonary bypass; **CPI** = continuing practice improvement; **CS-AKI** = cardiac surgery-associated acute kidney injury; **DECADE** = Dexmedetomidine for Reduction of Atrial Fibrillation and Delirium After Cardiac Surgery; **GRADE** = Grading of Recommendations, Assessment, Development and Evaluation; **Hb** = hemoglobin; **Hct** = hematocrit; **ICU** = intensive care unit; **KDIGO** = Kidney Disease Improving Global Outcomes; **MAP** = mean arterial pressure; **M-H** = Mantel-Haenszel; **PICCO** = pulse index continuous cardiac output; **RCT** = randomized controlled trial; **RIFLE** = Risk-Injury-Failure-Loss-End-stage renal disease; **RR** = risk ratio; **RRT** = renal replacement therapy; **SCA** = Society of Cardiovascular Anesthesiologists; **sCr**, serum creatinine

From the *Department of Anesthesiology and Pain Medicine, University of California Davis Health, Sacramento, California; †First Affiliated Hospital of Soochow University, Suzhou, China; ‡Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee; §Department of Anesthesiology, The International Heart Institute of Montana, Missoula, Montana; ‖Department of Anesthesiology and Intensive Care Medicine, University Hospital of Muenster, Muenster, Germany; ¶Department of Anesthesiology, Yale University School of Medicine, Easton, Connecticut; #Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas; **Department of Anesthesiology, Northwell Health, Manhasset, New York; ††Department of Anesthesiology, University of Texas Medical School, Sugar Land, Texas; ‡‡Department of Cardiothoracic Anesthesiology, Cleveland Clinic, Cleveland, Ohio; §§Department of Anesthesiology, University of North Carolina, Chapel Hill, North Carolina; ‖‖Department of Anesthesiology, Lehigh Valley Health Network, Allentown, Pennsylvania; and ¶¶Department of Intensive Care and Resuscitation, Cleveland Clinic, Cleveland, Ohio.

DOI: 10.1213/ANE.0000000000006068

Accepted for publication March 30, 2022.

Funding: None.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Reprints will not be available from the authors.

Address correspondence to Hong Liu, MD, FASE, Department of Anesthesiology and Pain Medicine, University of California Davis Health, 4150 V St, Suite 1200, Sacramento, CA 95817. Address e-mail to hualiu@ucdavis.edu.

Worldwide, >2 million cardiac surgical procedures are performed each year.[1] Acute kidney injury (AKI) is the most frequent perioperative complication for patients undergoing cardiac surgery, with the reported incidence ranging from 5% to 42% depending on the definition of AKI used and type of surgery.[2] Cardiac surgery-associated acute kidney injury (CS-AKI) is independently associated with an increased risk for chronic kidney disease, a higher postoperative mortality, and increased health care cost.[1,2] The development of consensus criteria for AKI definition has enhanced our awareness of this possibly underdiagnosed complication after cardiac surgery. These criteria include Risk-Injury-Failure-Loss-End-stage renal disease (RIFLE), acute kidney injury network (AKIN), and kidney disease improving global outcomes (KDIGO), which are used to define AKI based on increase in serum creatinine and/or reduced urinary output.[3–5] However, there is no effective prophylactic or therapeutic treatment for patients with CS-AKI, and renal replacement therapy (RRT) is the only option to treat severe cases.

The etiology underlying CS-AKI remains incompletely understood and probably multifactorial, involving renal ischemia-reperfusion injury, oxidative stress, inflammation, hemolysis, and toxins.[6] Based on the results of our recent survey of Society of Cardiovascular Anesthesiologists (SCA) members, there were 6 potentially renoprotective strategies, for which clinicians were most interested in an evidence-based review.[7] These strategies include intraoperative target blood pressure, choice of specific vasopressor agent, erythrocyte transfusion threshold, use of alpha-2 agonists, goal-directed oxygen delivery on cardiopulmonary bypass (CPB), and the "KDIGO bundle of care." In this context, the SCA's Continuing Practice Improvement (CPI) Acute Kidney Injury Working Group aimed to provide a practice update on these 6 topics to support decision-making in the prevention of CS-AKI through a comprehensive search of randomized controlled trials (RCTs), data pooling using meta-analysis, and a rigorous assessment of the levels of evidence for each interventional strategy.

METHODS

Working Group

The SCA's CPI Acute Kidney Injury Working Group includes members from the United States and international experts. The working group systematically searched the most recent literature to identify eligible RCTs that investigated potentially renoprotective strategies based on our recent survey of clinicians. A consensus within the working group was achieved to complete this clinical practice update. Informed by a recent survey of SCA members,[7] discussions were conducted and group consensus achieved to define our database search criteria, coordinate evaluation of included manuscripts, and develop a timeline for this project, through telephone calls, emails, and a CPI-AKI working group meeting.

Literature Search and Trial Selection

The PubMed, EMBASE, and Cochrane library databases were comprehensively searched for relevant publications from inception to February 2021, and updated in August 2021, using medical subject heading terms combined with text words (Supplemental Digital Content, Table, http://links.lww.com/AA/D952). The reference lists of relevant publications were also checked manually for additional studies.

The working group predefined eligibility criteria for this systematic review. To be included in the review, studies had to meet the following inclusion criteria: (1) study design: RCT, (2) patients: adults undergoing cardiac surgery, (3) outcome measure: postoperative AKI, (4) interventions: intraoperative target blood pressure, choice of specific vasopressor agent, erythrocyte transfusion threshold, use of alpha-2 agonists, goal-directed oxygen delivery on CPB, or the "KDIGO bundle of care," (5) total sample size: n ≥80 for final analysis, and (6) published in major journals, defined as journals with Impact Factor ≥1.0 in Journal Citation Reports 2020. Studies that did not meet these criteria were excluded. Any discrepancy over trial selection was resolved by reevaluation of the full-text study and a consensus within the working group.

Data Synthesis

Data synthesis was performed using meta-analysis with the RevMan software (version 5.3; Cochrane Collaboration). For each potentially renoprotective strategy, the effect size of the intervention compared with control for the outcome of postoperative AKI was estimated and reported as the risk ratio (RR) with 95% confidence interval (CI). A random-effects model was applied for data synthesis.[8] The heterogeneity among studies was evaluated using the $I2$ method, with I^2 >50% indicating a significant heterogeneity.[9] A 2-sided P value <.05 indicated a statistically significant difference.

Level of Evidence Assessment

The quality of each included study was assessed in 5 domains, including risk of bias, inconsistency, indirectness, imprecision, and other considerations. Thereafter, the level of evidence for each interventional strategy was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology (GRADEpro GDT software, available online: https://gdt.gradepro.org).[10] The absolute effect with 95% CI was estimated.

The level of evidence was rated as high, moderate, low, or very low based on the quality assessment in each domain. An assessment of "serious" in each domain downgrades the certainty by 1 score and a "very serious" downgrades the certainty by 2 scores. As CS-AKI is a frequent complication that leads to increased postoperative chronic kidney disease and mortality, the importance of this topic was judged as "critical." Any discrepancy over the level of evidence assessment was resolved by reevaluation of the full-text studies and a consensus within the working group.

RESULTS

Literature Search

The flow diagram of literature search is shown in Figure 1. A total of 569 publications were initially identified through database search. Of these, 70 duplicate records and 484 ineligible articles were excluded. Finally, a total of 15 RCTs were included in this systematic review.[11–25]

Study Characteristics

Table 1 shows the characteristics of the 15 RCTs, including region, procedure type, sample size, intervention and control treatments, main findings on CS-AKI, definitions of AKI, and journal (Impact Factor). The most performed procedures were coronary artery bypass grafting (CABG) and/or valve surgery. The definitions of AKI included RIFLE, AKIN, KDIGO, and specific changes in serum creatinine. Three RCTs (n = 579) investigated target blood pressure during CPB,[11–13] 1 RCT (n = 123) observed perioperative use of dopamine,[14] 1 RCT (n = 300) compared vasopressin with norepinephrine for vasoplegic shock after surgery,[15] 2 RCTs with 5033 patients assessed intraoperative erythrocyte transfusion threshold,[16,17] 4 RCTs with 1387 patients evaluated perioperative use of dexmedetomidine,[18–21] 2 RCTs (n = 601) explored the goal-directed oxygen delivery on CPB,[22,23] and 2 RCTs (n = 554) utilized the "KDIGO bundle of care" in high-risk cardiac patients.[24,25]

Summary of Outcomes

The effects of each interventional strategy versus control on the incidence of CS-AKI are presented in Table 2. For the use of dopamine and vasopressin, only 1 study was included for each outcome, and thus, data synthesis using meta-analysis could not be done.

Figure 2 shows the results of meta-analysis. A higher target for mean arterial pressure (MAP) during CPB did not reduce the incidence of CS-AKI (18.3% vs 14.6%; RR, 1.28; 95% CI, 0.76–2.14; $P = .35$; I^2,

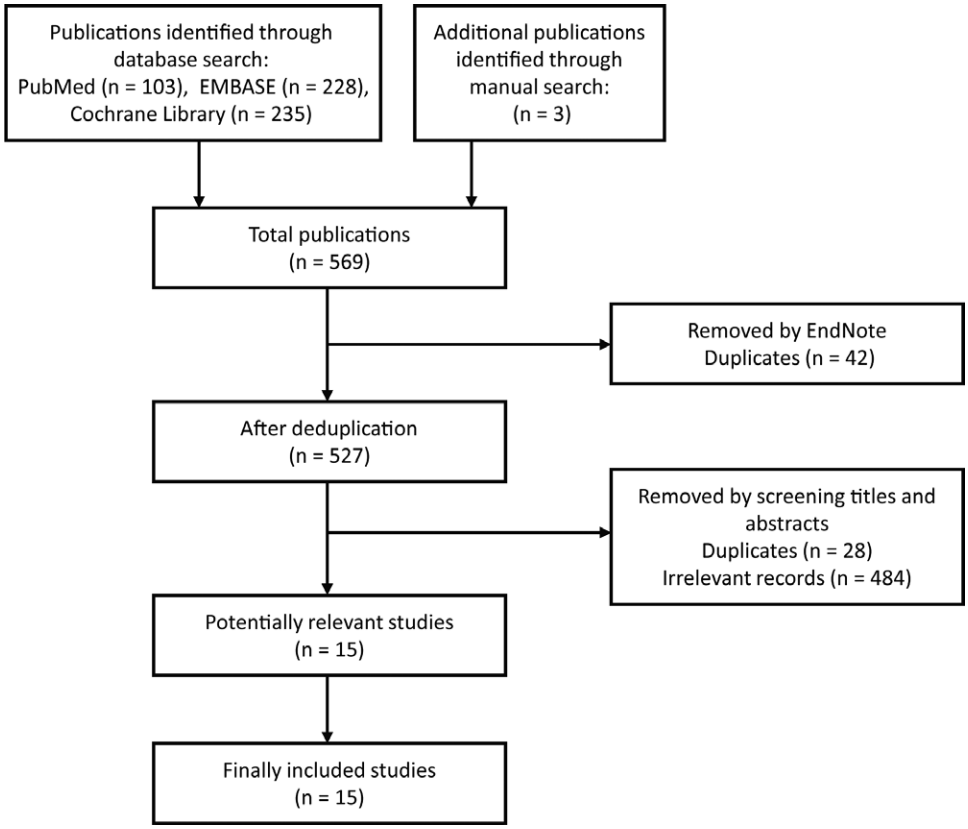

Figure 1. Flow diagram of literature search.

Table 1. Study Characteristics

Study	Region	Procedure	N	Interventional and control treatments, and main findings on CS-AKI	AKI definition	Journal (IF2020)
Intraoperative target blood pressure						
Azau et al 2014[11]	France	CABG, valve, or aorta, with CPB	292	A high level of MAP (75–85 mm Hg) versus control (MAP, 50–60 mm Hg) during normothermic CPB did not reduce the risk of AKI.	30% rise in sCr	*Perfusion* (1.97)
Kandler et al 2019[12]	Denmark	CABG + valve, with CPB	90	Arterial pressure >60 mmHg versus control (MAP, 47 mm Hg) during CPB did not reduce the incidence of AKI or chronic kidney injury at postoperative 4 mo.	RIFLE	*J Cardiothorac Sur* (1.64)
Vedel et al 2018[13]	Denmark	CABG and/or valve, with CPB	197	A higher MAP (70–80 mm Hg) versus control (MAP, 40–50 mm Hg) increased the number of patients with postoperative doubling of sCr.	sCr ≥2 times of baseline	*Circulation* (29.7)
Choice of specific vasopressor agent						
Lassnigg et al 2000[14]	Austria	CABG and/or valve, with CPB	123	Renal-dose dopamine (2 μg/kg/min) versus control (normal saline placebo) is ineffective for preventing AKI.	$\Delta Crea_{max} > 0 > 0.5$ mg/dL	*J Am Soc Nephrol* (10.12)
Hajjar et al 2017[15]	Brazil	CABG and/or valve, with CPB	300	For vasoplegic shock after surgery, vasopressin versus control (norepinephrine) titrated to maintain MAP ≥65 mm Hg reduced AKI when compared to norepinephrine.	AKIN	*Anesthesiology* (7.89)
Erythrocyte transfusion threshold						
Garg et al 2019[16]	73 centers in 19 countries	CABG and/or valve, or other, with CPB	4531	A restrictive threshold for transfusion (Hb < 7.5 g/dL) versus control (a liberal strategy; 9.5 g/dL in the operating room or ICU, or 8.5 g/dL on the ward) reduced erythrocyte transfusion without increasing AKI risk.	ΔsCr ≥0.3 mg/dL within 48 h or ≥50% within 7 d	*J Am Soc Nephrol* (10.12)
Hajjar et al 2010[17]	Brazil	CABG and/or valve, with CPB	502	A restrictive transfusion (to maintain Hct ≥24%) versus control (a liberal strategy of Hct ≥30%) led to noninferior rates of 30-d mortality and severe morbidity, including AKI.	RIFLE	*JAMA* (56.27)
Use of dexmedetomidine						
Cho et al 2016[18]	Korea	Valve with CPB	200	Dexmedetomidine 0.4 μg/kg/h for 24 h versus control (normal saline placebo) starting after anesthesia induction reduced the incidence and severity of AKI.	AKIN	*Kidney Int* (10.61)
Li et al 2017[19]	Two centers in China	CABG and/or valve, 57%–58% with CPB	285	Dexmedetomidine (0.6 μg/kg for 10 min, 0.4 μg/kg/h until the end of surgery, and 0.1 μg/kg/h until the end of mechanical ventilation)versus control (normal saline placebo) did not affect the incidence of AKI.	KDIGO	*PLoS One* (3.24)
Soh et al 2020[20]	Korea	Aorta with CPB	108	Dexmedetomidine 0.4 μg/kg/h for 24 h versus control (normal saline placebo) starting after induction reduced the incidence of AKI.	KDIGO	*Br J Anaesth* (9.17)

(*Continued*)

Table 1. Continued

Study	Region	Procedure	N	Interventional and control treatments, and main findings on CS-AKI	AKI definition	Journal (IF2020)
Turan et al 2020[21]	Six centers in the United States	CABG and/or valve, aorta with CPB	794	Dexmedetomidine versus control (normal saline placebo) initiated at anesthetic induction and continued for 24 h did not decrease atrial arrhythmias, delirium, or AKI.	AKIN	*Lancet* (79.32)
Goal-directed oxygen delivery on CPB						
Ranucci et al 2018[22]	Nine centers in 7 countries	CABG and/or valve, aorta with CPB	326	A goal-directed perfusion strategy of maintaining oxygen delivery ≥280 mL/min/m^2 versus control (a conventional perfusion strategy of target pump flow 2.4 L/min/m^2) during CPB is effective for reducing AKI.	AKIN	*J Thorac Cardiovasc Surg* (5.21)
Mukaida et al 2021[23]	Japan	CABG and/or valve, or other, with CPB	275	Maintaining an oxygen delivery index value >300 mL/min/m^2 versus control (a conventional strategy of target pump flow 2.6 L/min/m^2) during CPB reduced the incidence of AKI.	KDIGO	*J Thorac Cardiovasc Surg* (5.21)
The "KDIGO bundle of care"						
Meersch et al 2017[24]	Germany	CABG and/or valve, other	276	A "KDIGO bundle of care" (volume and hemodynamic optimization, avoidance of nephrotoxic drugs, and preventing hyperglycemia) versus control (a standard care including MAP >65 mm Hg and CVP 8–10 mm Hg) reduced the incidence and severity of AKI in high-risk cardiac patients.	KDIGO	*Intensive Care Med* (17.44)
Zarbock et al 2021[25]	12 centers in Europe	CABG and/or valve, or other, with CPB	278	A KDIGO bundle (volume and hemodynamic optimization, functional hemodynamic monitoring, avoidance of nephrotoxic drugs, and prevention of hyperglycemia) versus control (a standard care including MAP >65 mm Hg and CVP 8–10 mm Hg) did not reduce all types of AKI, but reduced the occurrence of moderate and severe AKI in high-risk patients.	KDIGO	*Anesth Analg* (5.11)

Abbreviations: AKI, acute kidney injury; AKIN, acute kidney injury network; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; CS-AKI, cardiac surgery-associated acute kidney injury; CVP, central venous pressure; ICU, intensive care unit; IF, Impact Factor in Journal Citation Reports 2020; KDIGO, Kidney Disease Improving Global Outcomes; MAP, mean arterial pressure; RIFLE, Risk-Injury-Failure-Loss-End-stage renal disease.

Table 2. Summary of Outcomes

Interventions on AKI incidence	Intervention group no./total	Control group no./total	Risk ratio (95% CI)	*P* value	I^2 (%)
A high target blood pressure during CPB	53/289 (18.3%)	42/288 (14.6%)	1.28 (0.76–2.14)	.35	42
Perioperative use of dopamine	1/42 (2.4%)	0/40 (0%)	2.86 (0.12–68.23)	.52	NA
Postoperative use of vasopressin in vasoplegic shock patients	50/149 (33.6%)	95/151 (62.9%)	0.53 (0.41–0.69)	<.00001	NA
A restrictive transfusion threshold	634/2500 (25.4%)	649/2533 (25.6%)	0.99 (0.90–1.09)	.84	0
Perioperative use of dexmedetomidine	99/685 (14.5%)	124/686 (18.1%)	0.71 (0.41–1.21)	.21	77
Goal-directed oxygen delivery on CPB	44/293 (15%)	84/308 (27.3%)	0.55 (0.40–0.76)	.0004	0
Use of "KDIGO bundle of care" in high-risk patients	139/274 (50.7%)	158/280 (56.4%)	0.91 (0.63–1.32)	.63	81
Use of "KDIGO bundle of care" in high-risk patients (stage 2/3 AKI)	60/274 (21.9%)	96/280 (34.3%)	0.64 (0.49–0.84)	.001	0

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CPB, cardiopulmonary bypass; KDIGO, Kidney Disease Improving Global Outcomes.

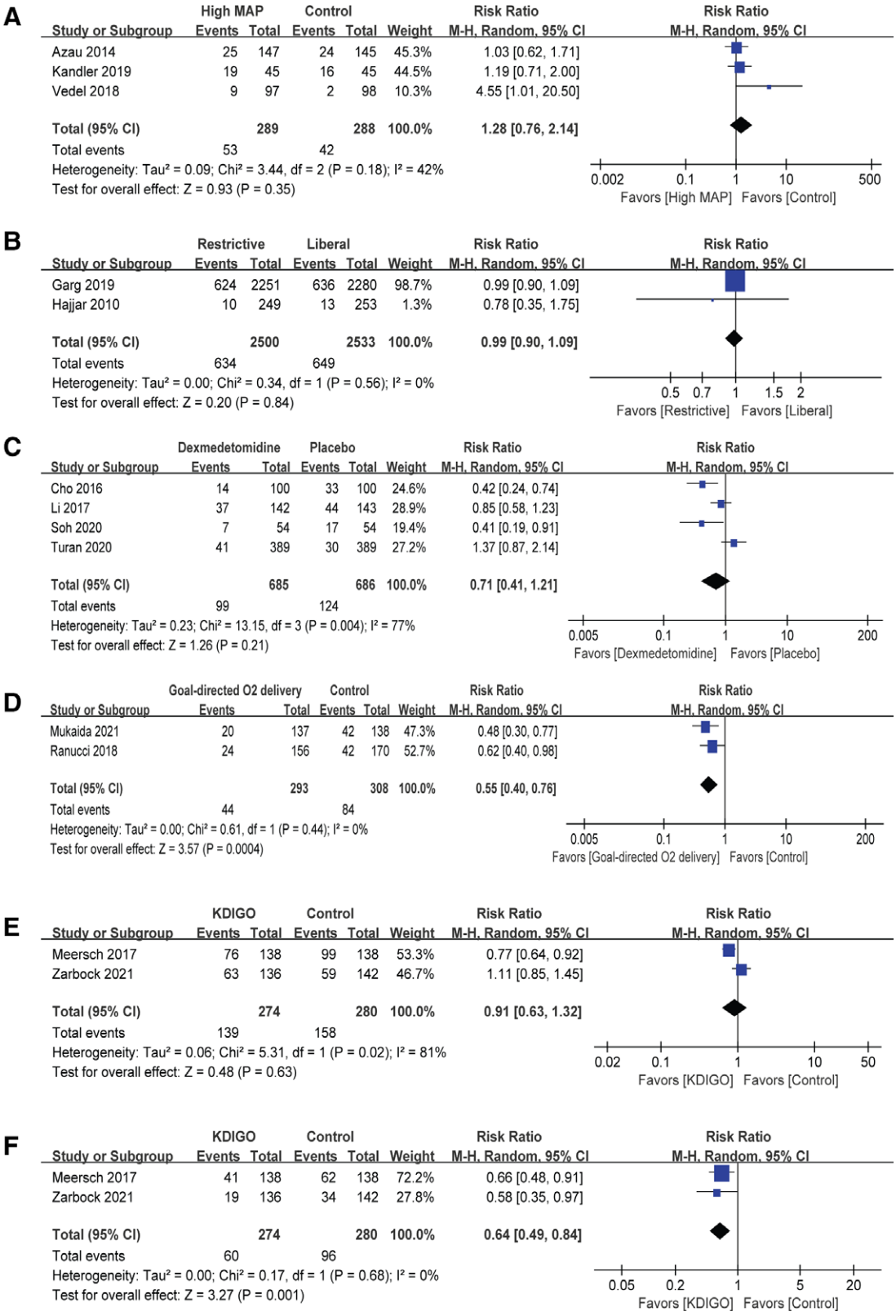

Figure 2. Pooling data using meta-analysis. A, Target MAP during CPB. B, Threshold for transfusion. C, Use of dexmedetomidine. D, Goal-directed oxygen delivery on CPB. E, Use of "KDIGO bundle of care" in high-risk patients. F, Use of "KDIGO bundle of care" in high-risk patients to prevent stage 2/3 AKI. CI indicates confidence interval; CPB, cardiopulmonary bypass; KDIGO, Kidney Disease Improving Global Outcomes; MAP, mean arterial pressure; M-H, Mantel-Haenszel.

42%) (Figure 2A). The use of a restrictive transfusion threshold did not influence CS-AKI (25.4% vs 25.6%; RR, 0.99; 95% CI, 0.90–1.09; $P = .84$; I^2, 0%) (Figure 2B). Perioperative dexmedetomidine use did not reduce the incidence of CS-AKI (14.5% vs 18.1%; RR, 0.71; 95% CI, 0.41–1.21; $P = .21$; I^2, 77%) (Figure 2C). A goal-directed oxygen delivery strategy on CPB reduced the incidence of CS-AKI (15% vs 27.3%; RR, 0.55; 95% CI, 0.40–0.76; $P = .0004$; I^2, 0%) (Figure 2D). In high-risk patients, use of the "KDIGO bundle of care" did not reduce the over-all incidence of CS-AKI (50.7% vs 56.4%; RR, 0.91; 95% CI, 0.63–1.32; $P = .63$; I^2, 81%) (Figure 2E), but did reduce moderate to severe (stages 2 and 3) AKI (21.9% vs 34.3%; RR, 0.64; 95% CI, 0.49–0.84; $P = .001$; I^2, 0%) (Figure 2F, based on the same 2 RCTs as in Figure 2E).

GRADE Evidence Profile

The levels of GRADE evidence are shown in Table 3. Targeting a higher blood pressure during CPB did not reduce CS-AKI, with a low level of GRADE evidence due to serious risk of bias and serious imprecision. Perioperative use of dopamine did not decrease CS-AKI, with a very low level of GRADE evidence due to very serious imprecision and other considerations (only 1 RCT included). Postoperative use of vasopressin in patients with vasoplegic shock led to a decrease in CS-AKI, with a low level of GRADE evidence due to only 1 RCT included. A restrictive threshold for intraoperative erythrocyte transfusion did not influence CS-AKI, with a moderate level of GRADE evidence due to serious other considerations (only 2 RCTs included). Perioperative use of dexmedetomidine did not lead to decreased CS-AKI, with a low level of GRADE evidence due to very serious inconsistency. The goal-directed oxygen delivery on CPB reduced CS-AKI, with a moderate level of GRADE evidence due to only 2 RCTs included. The use of the "KDIGO bundle of care" in high-risk patients did not reduce CS-AKI overall (a very low level of GRADE evidence due to very serious inconsistency and only 2 RCTs included), but did reduce stage 2/3 AKI (a moderate level of GRADE evidence due to only 2 RCTs included).

DISCUSSION

This systematic review and meta-analysis suggest that (1) goal-directed oxygen delivery on CPB may reduce the incidence of CS-AKI; (2) implementing the "KDIGO bundle of care" in high-risk patients may reduce moderate-to-severe AKI; and (3) the use of vasopressin in patients with vasoplegic shock may reduce CS-AKI. The risk for CS-AKI was not altered by any of: a restrictive versus liberal transfusion strategy, a higher versus conventional MAP target during CPB, and perioperative dopamine administration or dexmedetomidine administration.

Intraoperative Target Blood Pressure

A recent retrospective study showed that MAP <65 mm Hg for 10 minutes or more after CPB was associated with an increased risk of new postoperative RRT.[26] However, there was no association between hypotension before and during CPB with RRT in this study.[26] In addition, the association between intraoperative hypotension and AKI was not strong, when compared with preexisting and procedure-related factors, such as obesity, anemia, renal insufficiency, heart failure, and complex or emergent surgery. Thus, whether there is a causal link between the intraoperative level of MAP and CS-AKI remains unknown.

In 2 RCTs, the authors hypothesized that a higher target MAP during CPB would reduce the incidence of CS-AKI.[11,12] While the range for renal autoregulation is 75 to 160 mm Hg in normal conditions,[27] MAP during CPB is typically below the lower limit of this range, and increasing the level of blood pressure during this period would represent a readily achievable renoprotective strategy, if demonstrated effective. However, Azau et al[11] found no difference in the incidence of AKI when targeting an MAP of 75 to 80 mm Hg compared to an MAP of 50 to 60 mm Hg during normothermic CPB in patients undergoing CABG, valve, or aorta surgical procedures. A further study demonstrated that targeting an MAP >60 mm Hg during CPB compared to a control group with no specific target pressure during CPB did not reduce the incidence of AKI or chronic kidney injury at 4 months postoperatively.[12] In addition, Vedel et al[13] hypothesized that, when compared to a target MAP of 40 to 50 mm Hg during CPB, a target MAP of 70 to 80 mm Hg during CPB would reduce brain injury after cardiac surgery. However, they found that the number of patients with postoperative doubling of serum creatinine was higher in the high-target MAP group than in the low-target MAP group. Our pooled analysis did not find a reduction in the risk of CS-AKI by targeting a higher MAP during CPB (a low level of GRADE evidence).

Intraoperative Choice of Specific Vasopressors

Intravenous catecholamines (norepinephrine and epinephrine), vasopressin, dopamine, and angiotensin II all increase systemic vascular resistance and can be used to increase blood pressure during surgery. Some studies have reported the effect of the use of different agents during cardiac surgery on postoperative AKI, and we can also extrapolate some results from intensive care unit (ICU) cardiac surgery patient studies to inform intraoperative use of different agents.

Table 3. GRADE Evidence Profile

Certainty assessment							No. of patients		Effect			
No.of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
A high target blood pressure during CPB												
3	RCT	Serious [a]	Not serious	Not serious	Serious[b]	None	53/289 (18.3%)	42/288 (14.6%)	RR 1.28 (0.76–2.14)	41 more per 1000 (from 35 fewer to 166 more)	⨁⨁◯◯ LOW	CRITICAL
Perioperative use of dopamine												
1	RCT	Not serious	Not serious	Not serious	Very serious [c]	Very serious [d]	1/42 (2.4%)	0/40 (0.0%)	RR 2.86 (0.12–68.23)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Postoperative use of vasopressin in vasoplegic shock patients												
1	RCT	Not serious	Not serious	Not serious	Not serious	Very serious [d]	50/149 (33.6%)	95/151 (62.9%)	RR 0.53 (0.41–0.96)	296 fewer per 1000 (from 371 fewer to 195 fewer)	⨁⨁◯◯ LOW	CRITICAL
A restrictive transfusion threshold												
2	RCT	Not serious	Not serious	Not serious	Not serious	Serious [e]	634/2500 (25.4%)	649/2533 (25.6%)	RR 0.99 (0.90–1.09)	3 fewer per 1000 (from 26 fewer to 23 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Perioperative use of dexmedetomidine												
4	RCT	Not serious	Very serious [f]	Not serious	Not serious	none	99/685 (14.5%)	124/686 (18.1%)	RR 0.71 (0.41–1.21)	52 fewer per 1000 (from 107 fewer to 38 more)	⨁⨁◯◯ LOW	CRITICAL
Goal-directed oxygen delivery on CPB												
2	RCT	Not serious	Not serious	Not serious	Not serious	Serious [e]	44/293 (15.0%)	84/308 (27.3%)	RR 0.55 (0.40–0.76)	123 fewer per 1000 (from 164 fewer to 65 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Use of "KDIGO bundle of care" in high-risk patients												
2	RCT	Not serious	Very serious [g]	Not serious	Not serious	Serious [e]	139/274 (50.7%)	158/280 (56.4%)	RR 0.91 (0.63–1.32)	51 fewer per 1000 (from 209 fewer to 181 more)	⨁◯◯◯ VERY LOW	CRITICAL
Use of "KDIGO bundle of care" in high-risk patients (stage 2/3 AKI)												
2	RCT	Not serious	Not serious	Not serious	Not serious	Serious [e]	60/274 (21.9%)	96/280 (34.3%)	RR 0.64 (0.49–0.84)	123 fewer per 1000 (from 175 fewer to 55 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CPB, cardiopulmonary bypass; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; KDIGO, Kidney Disease Improving Global Outcomes; RCT, randomized controlled trial; RR, risk ratio.

[a]Azau 2014[11] was judged to be at unclear risk of performance bias.

[b]RR of 1.28 with a relatively wide 95% CI of (0.76–2.14).

[c]RR of 2.86 with a very wide 95% CI of (0.12–68.23).

[d]Based on 1 trial only.

[e]Based on 2 trials.

[f]Heterogeneity: $I^2 = 77\%$.

[g]Heterogeneity: $I^2 = 81\%$.

There is one study evaluating the effect of intraoperative dopamine on renal outcomes. Lassnigg et al[14] reported that 2-μg/kg/min dopamine may even increase the occurrence of AKI in patients who underwent CABG and/or valve surgical procedures. Our results showed that perioperative use of dopamine did not prevent CS-AKI (a very low level of GRADE evidence).

In patients with postcardiac surgery vasoplegic shock (defined as MAP <65 mm Hg, resistant to fluid challenge, and cardiac index >2.2 L/min2/m^2), Hajjar et al[15] showed that vasopressin reduced the odds of acute renal failure by 74% (10.3% vs 35.8%; $P < .0001$) when compared to norepinephrine. Some potentially important differences between study groups and methodologic irregularities around altering the primary end point and intention to treat analysis have been raised,[28] but these data suggest that it is reasonable to use vasopressin as a first-line vasoactive agent to treat vasoplegia after cardiac surgery. However, in 2018, the Acute Kidney Quality Group recommended using norepinephrine as a first choice over vasopressin to treat vasoplegia during cardiac and vascular surgeries.[29] Their summary table stated that more research was needed before recommending vasopressin as equal choice to norepinephrine. This decision was made after considering Hajjar's article and the methodological concerns related to the study. Angiotensin II may be a promising agent to treat vasodilatory shock.[30] Nonetheless, angiotensin II is not widely used in cardiac surgery cohorts, and its role in the management of hypotension in cardiac surgery patients remains to be determined.

Taken together, it appears reasonable to use norepinephrine as a first-line agent, add vasopressin if hypotension is refractory to norepinephrine, if patients have pulmonary hypertension, or patients have moderate-severe right ventricular dysfunction, and consider additional catecholamine-sparing agents such as hydroxocobalamin, methylene blue, or high-dose ascorbate only as rescue agents. Their benefit has not been confirmed in rigorous clinical trials. Therefore, our study suggests considering the use of vasopressin in vasoplegic shock patients to reduce CS-AKI (a low level of GRADE evidence).

Intraoperative Erythrocyte Transfusion Threshold

The optimal threshold for intraoperative erythrocyte transfusion is of great importance, because both anemia and erythrocyte transfusion are independently associated with CS-AKI.[31,32] In the substudy of a large randomized noninferiority trial with 4531 cardiac surgical patients, Garg et al[16] demonstrated that a restrictive threshold for transfusion (hemoglobin [Hb] <7.5 g/dL, intraoperatively and postoperatively), compared with a liberal one (9.5 g/dL in the operating room or ICU or 8.5 g/dL in the nonintensive care ward), reduced erythrocyte transfusions without increasing the risk for AKI. In addition, a restrictive transfusion (to maintain a hematocrit [Hct] ≥24%) compared with a liberal one (Hct ≥30%) led to noninferior postoperative outcomes, including 30-day mortality and renal complications.[17]

A recent meta-analysis also supports the use of a restrictive erythrocyte transfusion threshold in adults undergoing cardiac surgery, with noninferior outcomes including acute myocardial infarction, cerebrovascular accidents, pulmonary morbidity, AKI, postoperative infection, and 30-day mortality.[33] Thus, the results of our analysis based on RCTs suggest that the decision to use a restrictive versus liberal strategy for perioperative red cell transfusion should not be based on renal protection (a moderate level of GRADE evidence).

Intraoperative Dexmedetomidine (Alpha-2 Agonists)

The existing evidence for the effects of dexmedetomidine on CS-AKI is inconsistent. In 2 RCTs, dexmedetomidine infusion at a rate of 0.4 μg/kg/h for 24 hours initiated after anesthesia induction reduced the incidence of AKI in patients undergoing valve or aortic surgical procedures.[18,20] However, Li et al[19] found that dexmedetomidine (0.6 μg/kg for 10 minutes, 0.4 μg/kg/h until the end of surgery, and 0.1 μg/kg/h until the end of mechanical ventilation) did not affect the incidence of AKI in patients undergoing CABG and/or valve surgery. In the recent DECADE (Dexmedetomidine for Reduction of Atrial Fibrillation and Delirium After Cardiac Surgery) study, the authors showed that dexmedetomidine infusion, at a stepwise increased infusion rate of 0.1 to 0.4 μg/kg/h from anesthetic induction until postoperative 24 hours, even worsened delirium and AKI after cardiac surgery, although not by a significant amount.[21] More clinically, important hypotension events occurred in patients receiving dexmedetomidine, and the authors suggested that dexmedetomidine should be used cautiously in patients undergoing cardiac surgery.

Two recent meta-analyses showed that perioperative dexmedetomidine use helped to reduce the incidence of CS-AKI, especially when dexmedetomidine was started right after anesthesia induction and infused intraoperatively in elderly patients.[8,34] However, these previous meta-analyses did not include the most recent DECADE study. Including results of the DECADE study into our pooled analysis, the perioperative use of dexmedetomidine did not reduce the incidence of CS-AKI. There is a substantial heterogeneity ($I^2 = 77\%$) among the included studies, which downgrades the GRADE evidence to a low level. Our results do not support using dexmedetomidine for the purpose of reducing CS-AKI (a low level of GRADE evidence).

Goal-Directed Oxygen Delivery on CPB

Observational studies have identified nadir oxygen delivery while on CPB as a potentially modifiable risk factor for the development of AKI.[35–37] The concept of goal-directed perfusion is to maintain oxygen delivery on CPB above a critical value, suggested to be in the range of 260 to 272 mL/min/m^2 during moderately hypothermic CPB.[36] Ranucci et al[22] performed an RCT to test the hypothesis that a goal-directed oxygen delivery approach on CPB would reduce CS-AKI. Patients in the interventional group received a specific intervention that aimed to maintain oxygen delivery ≥280 mL/min/m^2 during CPB based on adjustment of the arterial pump flow and Hct. If the oxygen delivery was still below the threshold after increasing the pump flow, 1 unit of red blood cells was transfused to maintain venous oxygen saturation >68% and the oxygen extraction rate <40%. Patients in the control group received arterial pump flow at a target value of 2.4 L/min/m^2 at normothermia. Goal-directed oxygen delivery on CPB reduced the incidence of AKI, especially AKIN stage 1 AKI (18/156 [11.5%] vs 38/170 [22.4%]). Later, Mukaida et al[23] confirmed that maintaining an oxygen delivery index value >300 mL/min/m^2 during CPB reduced the incidence of AKI. Both of these trials report an approximate 50% reduction in rates of AKI with goal-directed oxygen delivery on CPB. However, the sample size, quality, variation in intervention protocol, and other limitations of these trials suggest that effect estimates for the renoprotective effect of goal-directed perfusion are likely to change with further evidence. Thus, the level of GRADE evidence was rated as moderate for this strategy. Further studies are needed to better characterize the effect of this intervention and any potentially associated adverse effects. It should also be noted that maintaining a high or low fraction of delivered oxygen during CPB, irrespective of flow and oxygen delivery, has not been shown to impact AKI.[38] Based on these studies, together with the relative ease of implementation of the strategy and little evidence of adverse effects, the use of goal-directed oxygen delivery on CPB to prevent CS-AKI appears reasonable (a moderate level of GRADE evidence).

The "KDIGO Bundle of Care"

The complex pathophysiology of CS-AKI makes it unlikely that significant renoprotection will be achieved through a single pharmacological or nonpharmacological intervention. Targeted care, involving the implementation of a bundle of interventions based on a consensus management guideline in patients at risk for AKI, might be expected to provide more potent beneficial effects on renal outcomes. Meersch et al[24] investigated whether implementation of a "bundle of care" in strict accordance with the KDIGO guidelines could prevent CS-AKI in high-risk patients. These high-risk patients were identified by AKI biomarkers. The "KDIGO bundle of care" consists of optimization of hemodynamic and volume status by close monitoring using a pulse index continuous cardiac output (PICCO) catheter, avoidance of nephrotoxic agents (such as radiocontrast agents, aminoglycosides, aprotinin, and so on), prevention of hyperglycemia for the first 72 hours postoperatively, discontinuation of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for the first postoperative 48 hours, and close monitoring of serum creatinine and urine output. In high-risk patients for CS-AKI, this "KDIGO bundle of care" strategy significantly reduced the incidence (76/138 [55.1%] vs 99/138 [71.7%]; absolute risk reduction [ARR], 16.6%; 95% CI, 5.5–27.9; P = .004) and severity of AKI (moderate and severe AKI, 41/138 [29.7%] vs 62/138 [44.9%]; ARR, 15.2%; 95% CI, 4.0–26.5; P = .009) after cardiac surgery.

A recently published multicenter RCT investigated the feasibility of implementing a bundle of supportive measures based on the KDIGO guideline in high-risk patients undergoing cardiac surgery.[25] The study included 278 patients, and it was demonstrated that 65.4% of patients in the intervention group received the complete bundle as compared to 4.2% in the control group (ARR, 61.2%; 95% CI, 52.6–69.9; P < .001). The incidence of moderate and severe AKI (ie, stage 2 and 3 AKI) was significantly lower in the intervention group than in the control group (14.0% vs 23.9%; ARR, 10.0%; 95% CI, 0.9–19.1; P = .034). In line with these results, Engelman et al[39] also demonstrated, in a quality improvement initiative, that implementation of the KDIGO-bundle in high-risk patients significantly reduced the incidence of stage 2 or 3 AKI.

Our pooled analysis found that the use of the "KDIGO bundle of care" did not reduce the overall incidence of AKI in high-risk patients (a very low level of GRADE evidence), but significantly reduced the incidence of stage 2 or 3 AKI (a moderate level of GRADE evidence). While a larger definitive trial is still needed, this working group suggests considering the use of the "KDIGO bundle of care" strategy in patients at high risk for AKI to prevent CS-AKI.

Other Possible Renoprotective Strategies

A recent meta-analysis included 228 trials enrolling 56,047 patients to evaluate pharmacological interventions for renoprotection in patients undergoing surgery.[40] The authors found that the use of atrial natriuretic peptides (14 trials; n = 2207) reduced 30-day mortality (RR, 0.63; 95% CI, 0.41–0.97) and AKI events (RR, 0.43; 95% CI, 0.33–0.56), and that these effects were consistent across the subgroups of cardiac surgery and vascular surgery. In addition, the

use of inodilators (13 trials; n = 2941) reduced mortality (RR, 0.71; 95% CI, 0.53–0.94) and AKI events (RR, 0.65; 95% CI, 0.50–0.85) in cardiac surgery patients.

Strengths and Limitations

Our study has several important strengths and limitations. The systematic review and meta-analysis, with structured application of GRADE methodology to evaluate the level of evidence for each potential strategy, ensured objective and reproducible results. Including only those RCTs with ≥80 participants and published in major journals may have excluded otherwise eligible trials and observational studies. Our goal, however, was to provide clinicians with a succinct summary of the current evidence to aid their clinical decision-making. Inclusion of nonrandomized and small studies would have resulted in further downgrading our assessment of the quality of evidence for any given strategy. Instead, we chose to focus the analysis on higher quality studies with more stable estimates for an intervention's effect size and, although arbitrary, this was based on previously used criteria.[41] The limited number of high-quality, randomized trials addressing each strategy was insufficient to support making specific recommendations but, importantly, serves to highlight the ongoing uncertainty around the true renal effects of these strategies and need for additional research. Moreover, the heterogeneity in observed incidence of AKI across included studies (13.6%–56.4%) also highlights the uncertainty regarding the generalizability of results from the included studies to other populations. Our review focused on only 6 potential renoprotective strategies for patients undergoing cardiac surgery. While other strategies such as atrial natriuretic peptide, inodilators, and remote ischemic preconditioning were not included in our review, the included strategies were based on our recent survey of the SCA membership to reflect those strategies for which the membership most wanted an evidence-based, expert review.[7]

CONCLUSIONS

CS-AKI is common and is associated with increased risk for postoperative morbidity and mortality. In this practice update of the SCA's CPI Acute Kidney Injury Working Group, a total of 15 RCTs involving 6 potentially renoprotective strategies were systematically reviewed (Figure 3). Based on a moderate level of GRADE evidence, the authors believe that the current evidence supports potential renoprotective benefit from goal-directed oxygen delivery on CPB (maintaining oxygen delivery at ≥280–300 mL/min/m^2) and the "KDIGO bundle of care" (optimization of hemodynamic and volume, functional hemodynamic monitoring, avoidance of nephrotoxic drugs, and prevention of hyperglycemia) in patients at high risk for AKI undergoing cardiac surgery. In addition, we believe that the use of vasopressin in vasoplegic shock patients might potentially reduce CS-AKI. Our

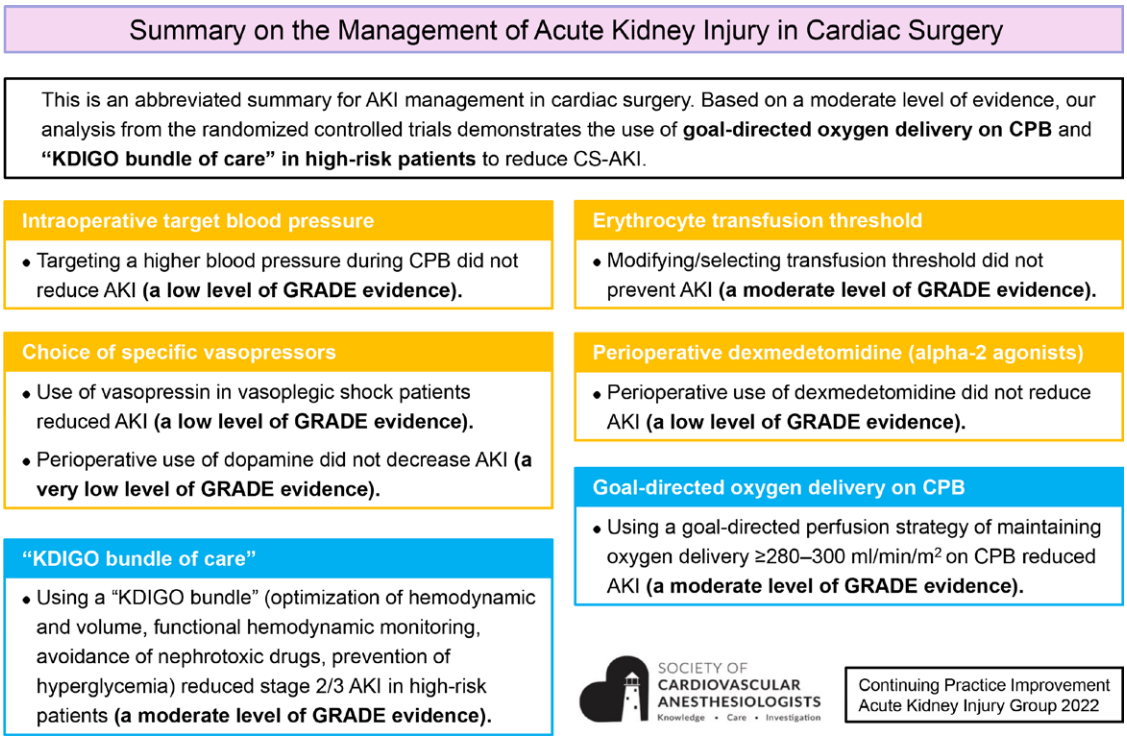

Figure 3. Summary on the management of CS-AKI. CPB indicates cardiopulmonary bypass; CS-AKI, cardiac surgery-associated acute kidney injury; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; KDIGO, Kidney Disease Improving Global Outcomes.

results do not support modifying/selecting transfusion threshold, targeting a higher MAP during CPB, or using dopamine or dexmedetomidine for the purpose of reducing CS-AKI. ■

DISCLOSURES

Name: Ke Peng, MD, PhD.
Contribution: This author helped in manuscript writing, data search, statistical analysis, interpretation of data, and revision of the manuscript, and read and approved the final version.
Name: David R. McIlroy, MBBS.
Contribution: This author helped in study design, manuscript writing, interpretation of data, and revision of the manuscript, and read and approved the final version.
Name: Bruce A. Bollen, MD.
Contribution: This author helped in study design, manuscript writing, interpretation of data, and revision of the manuscript, and read and approved the final version.
Name: Frederic T. Billings IV, MD.
Contribution: This author helped in study design, manuscript writing, interpretation of data, and revision of the manuscript, and read and approved the final version.
Name: Alexander Zarbock, MD.
Contribution: This author helped in study design, interpretation of data, manuscript writing, and revision of the manuscript, and read and approved the final version.
Name: Wanda M. Popescu, MD.
Contribution: This author helped in interpretation of data and revision of the manuscript, and read and approved the final version.
Name: Amanda A. Fox, MD, MPH.
Contribution: This author helped in study design, interpretation of data, and revision of the manuscript, and read and approved the final version.
Name: Linda Shore-Lesserson, MD.
Contribution: This author helped in study design, interpretation of data, and revision of the manuscript, and read and approved the final version.
Name: Shaofeng Zhou, MD.
Contribution: This author helped in interpretation of data, manuscript preparation, and revision of the manuscript, and read and approved the final version.
Name: Mariya A. Geube, MD.
Contribution: This author helped in study design, interpretation of data, manuscript writing, and revision of the manuscript, and read and approved the final version.
Name: Fuhai Ji, MD, PhD.
Contribution: This author helped in manuscript writing, data search, statistical analysis, interpretation of data, and revision of the manuscript, and read and approved the final version.
Name: Meena Bhatia, MD.
Contribution: This author helped in study design, interpretation of data, manuscript writing, and revision of the manuscript, and read and approved the final version.
Name: Nanette M. Schwann, MD.
Contribution: This author helped in study design, interpretation of data, and revision of the manuscript, and read and approved the final version.
Name: Andrew D. Shaw, MB, FCCM, FFICM, FRCA.
Contribution: This author helped in study design, interpretation of data, manuscript writing, and revision of the manuscript, and read and approved the final version.
Name: Hong Liu, MD, FASE.
Contribution: This author helped in study design, statistical analysis, interpretation of data, manuscript writing, and revision of the manuscript, and read and approved the final version.
This manuscript was handled by: Stefan G. De Hert, MD.

REFERENCES

1. Meersch M, Zarbock A. Prevention of cardiac surgery-associated acute kidney injury. *Curr Opin Anaesthesiol*. 2017;30:76–83.
2. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. *Nat Rev Nephrol*. 2017;13:697–711.
3. Ricci Z, Cruz DN, Ronco C. Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. *Nat Rev Nephrol*. 2011;7:201–208.
4. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int*. 2015;87:62–73.
5. Sutherland L, Hittesdorf E, Yoh N, Lai T, Mechling A, Wagener G. Acute kidney injury after cardiac surgery: a comparison of different definitions. *Nephrology (Carlton)*. 2020;25:212–218.
6. Massoth C, Zarbock A, Meersch M. Risk stratification for targeted AKI prevention after surgery: biomarkers and bundled interventions. *Semin Nephrol*. 2019;39:454–461.
7. McIlroy DR, Roman B, Billings FT IV, et al. Potential renoprotective strategies in adult cardiac surgery: a survey of Society of Cardiovascular Anesthesiologists members to explore the rationale and beliefs driving current clinical decision-making. *J Cardiothorac Vasc Anesth*. 2021;35:2043–2051.
8. Peng K, Li D, Applegate RL II, Lubarsky DA, Ji FH, Liu H. Effect of dexmedetomidine on cardiac surgery-associated acute kidney injury: a meta-analysis with trial sequential analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth*. 2020;34:603–613.
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
10. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.
11. Azau A, Markowicz P, Corbeau JJ, et al. Increasing mean arterial pressure during cardiac surgery does not reduce the rate of postoperative acute kidney injury. *Perfusion*. 2014;29:496–504.
12. Kandler K, Nilsson JC, Oturai P, et al. Higher arterial pressure during cardiopulmonary bypass may not reduce the risk of acute kidney injury. *J Cardiothorac Surg*. 2019;14:107.
13. Vedel AG, Holmgaard F, Rasmussen LS, et al. High-target versus low-target blood pressure management during cardiopulmonary bypass to prevent cerebral injury in cardiac surgery patients: a randomized controlled trial. *Circulation*. 2018;137:1770–1780.
14. Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml W, Hiesmayr M. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol*. 2000;11:97–104.
15. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al. Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: the VANCS randomized controlled trial. *Anesthesiology*. 2017;126:85–93.
16. Garg AX, Badner N, Bagshaw SM, et al; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Safety of a restrictive versus liberal approach to red blood cell transfusion on the outcome of AKI in patients undergoing cardiac surgery: a randomized clinical trial. *J Am Soc Nephrol*. 2019;30:1294–1304.
17. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA*. 2010;304:1559–1567.
18. Cho JS, Shim JK, Soh S, Kim MK, Kwak YL. Perioperative dexmedetomidine reduces the incidence and severity

of acute kidney injury following valvular heart surgery. *Kidney Int*. 2016;89:693–700.
19. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: a randomized controlled trial. *PLoS One*. 2017;12:e0170757.
20. Soh S, Shim JK, Song JW, et al. Effect of dexmedetomidine on acute kidney injury after aortic surgery: a single-centre, placebo-controlled, randomised controlled trial. *Br J Anaesth*. 2020; S0007-0912(20)30001-5. doi:10.1016/j.bja.2019.12.036.
21. Turan A, Duncan A, Leung S, et al; DECADE Study Group. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet*. 2020;396:177–185.
22. Ranucci M, Johnson I, Willcox T, et al. Goal-directed perfusion to reduce acute kidney injury: a randomized trial. *J Thorac Cardiovasc Surg*. 2018;156:1918–1927.e2.
23. Mukaida H, Matsushita S, Yamamoto T, et al. Oxygen delivery-guided perfusion for the prevention of acute kidney injury: a randomized controlled trial. *J Thorac Cardiovasc Surg*. 2021;S0022-5223(21)00511-0. doi:10.1016/j.jtcvs.2021.03.032.
24. 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.
25. Zarbock A, Küllmar M, Ostermann M, et al. Prevention of cardiac surgery-associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: the PrevAKI-multicenter randomized controlled trial. *Anesth Analg*. 2021;133:292–302.
26. Ngu JMC, Jabagi H, Chung AM, et al. Defining an intraoperative hypotension threshold in association with de novo renal replacement therapy after cardiac surgery. *Anesthesiology*. 2020;132:1447–1457.
27. Guyton AC, Hall JE. *Textbook of Medical Physiology*. Elsevier Saunders, 2006:323.
28. James A, Amour J. Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: a discussion of the level of evidence. *Anesthesiology*. 2018;128:228.
29. Nadim MK, Forni LG, Bihorac A, et al. Cardiac and vascular surgery-associated acute kidney injury: the 20th International Consensus Conference of the ADQI (Acute Disease Quality Initiative) Group. *J Am Heart Assoc*. 2018;7:e008834.
30. Khanna A, English SW, Wang XS, et al; ATHOS-3 Investigators. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med*. 2017;377:419–430.
31. Delaney M, Wendel S, Bercovitz RS, et al; Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet*. 2016;388:2825–2836.
32. Miceli A, Romeo F, Glauber M, de Siena PM, Caputo M, Angelini GD. Preoperative anemia increases mortality and postoperative morbidity after cardiac surgery. *J Cardiothorac Surg*. 2014;9:137.
33. Chen QH, Wang HL, Liu L, Shao J, Yu J, Zheng RQ. Effects of restrictive red blood cell transfusion on the prognoses of adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Crit Care*. 2018;22:142.
34. Liu Y, Sheng B, Wang S, Lu F, Zhen J, Chen W. Dexmedetomidine prevents acute kidney injury after adult cardiac surgery: a meta-analysis of randomized controlled trials. *BMC Anesthesiol*. 2018;18:7.
35. Magruder JT, Dungan SP, Grimm JC, et al. Nadir oxygen delivery on bypass and hypotension increase acute kidney injury risk after cardiac operations. *Ann Thorac Surg*. 2015;100:1697–1703.
36. Ranucci M, Romitti F, Isgrò G, et al. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. *Ann Thorac Surg*. 2005;80:2213–2220.
37. de Somer F, Mulholland JW, Bryan MR, Aloisio T, Van Nooten GJ, Ranucci M. O_2 delivery and CO_2 production during cardiopulmonary bypass as determinants of acute kidney injury: time for a goal-directed perfusion management? *Crit Care*. 2011;15:R192.
38. McGuinness SP, Parke RL, Drummond K, et al; SO-COOL investigators. A multicenter, randomized, controlled phase IIb trial of avoidance of hyperoxemia during cardiopulmonary bypass. *Anesthesiology*. 2016;125:465–473.
39. Engelman DT, Lother S, George I, et al; Society of Thoracic Surgeons COVID-19 Task Force. Adult cardiac surgery and the COVID-19 pandemic: aggressive infection mitigation strategies are necessary in the operating room and surgical recovery. *J Thorac Cardiovasc Surg*. 2020;160:447–451.
40. Pathak S, Olivieri G, Mohamed W, et al. Pharmacological interventions for the prevention of renal injury in surgical patients: a systematic literature review and meta-analysis. *Br J Anaesth*. 2021;126:131–138.
41. McIlroy DR, Bellomo R, Billings FT IV, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: renal endpoints. *Br J Anaesth*. 2018;121:1013–1024.