

# Strategies to Prevent Acute Kidney Injury after Pediatric Cardiac Surgery

## A Network Meta-Analysis

Jef Van den Eynde <sup>1,2</sup>, Nicolas Cloet,<sup>2</sup> Robin Van Lerberghe,<sup>2</sup> Michel Pompeu B.O. Sá <sup>3</sup>, Dirk Vlasselaers,<sup>4</sup> Jaan Toelen,<sup>5,6</sup> Jan Y. Verbakel,<sup>7,8</sup> Werner Budts,<sup>2,9</sup> Marc Gewillig,<sup>2,10</sup> Shelby Kutty,<sup>1</sup> Hans Pottel,<sup>11</sup> and Djalila Mekahli<sup>12,13</sup>

### Abstract

**Background and objectives** AKI is a common complication after pediatric cardiac surgery and has been associated with higher morbidity and mortality. We aimed to compare the efficacy of available pharmacologic and nonpharmacologic strategies to prevent AKI after pediatric cardiac surgery.

**Design, setting, participants, & measurements** PubMed/MEDLINE, Embase, Cochrane Controlled Trials Register, and reference lists of relevant articles were searched for randomized controlled trials from inception until August 2020. Random effects traditional pairwise, Bayesian network meta-analyses, and trial sequential analyses were performed.

**Results** Twenty randomized controlled trials including 2339 patients and 11 preventive strategies met the eligibility criteria. No overall significant differences were observed compared with control for corticosteroids, fenoldopam, hydroxyethyl starch, or remote ischemic preconditioning in traditional pairwise meta-analysis. In contrast, trial sequential analysis suggested a 80% relative risk reduction with dexmedetomidine and evidence of <57% relative risk reduction with remote ischemic preconditioning. Nonetheless, the network meta-analysis was unable to demonstrate any significant differences among the examined treatments, including also acetaminophen, aminophylline, levosimendan, milrinone, and normothermic cardiopulmonary bypass. Surface under the cumulative ranking curve probabilities showed that milrinone (76%) was most likely to result in the lowest risk of AKI, followed by dexmedetomidine (70%), levosimendan (70%), aminophylline (59%), normothermic cardiopulmonary bypass (57%), and remote ischemic preconditioning (55%), although all showing important overlap.

**Conclusions** Current evidence from randomized controlled trials does not support the efficacy of most strategies to prevent AKI in the pediatric population, apart from limited evidence for dexmedetomidine and remote ischemic preconditioning.

CJASN 16: 1480–1490, 2021. doi: <https://doi.org/10.2215/CJN.05800421>

### Introduction

AKI is the most common severe complication following pediatric cardiac surgery (1). The incidence varies but may be up to 36% (2). In addition, AKI is associated with a nine-fold higher risk of developing CKD and a three-fold higher risk of developing kidney failure (3). The etiology of AKI can be renal, extrarenal, or combined (4). Because of their younger age and lower body weight, as well as hemodynamic instability, children with congenital heart disease carry a high risk for cardiac surgery–related AKI (5).

Because AKI is associated with important morbidity and mortality, there is a need for effective preventive measures (6). Several pharmacologic and nonpharmacologic strategies have been tested in randomized controlled trials (RCTs) over the past 2 decades, with variable success. Here, we aimed to summarize current evidence for the efficacy of strategies to prevent AKI after pediatric cardiac surgery.

### Materials and Methods

#### Search Strategy

This systematic review was designed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (7). PubMed/MEDLINE, Embase, Cochrane Controlled Trials Register, and reference lists of relevant articles were searched for articles published by August 5, 2020. The detailed search terms that were used for this search are given in Supplemental Material.

#### Eligibility Criteria

Using the Population, Interventions, Comparison, Outcome and Study design strategy, studies were included if

- (1) the population comprised pediatric patients undergoing cardiac surgery;

Due to the number of contributing authors, the affiliations are listed at the end of this article.

#### Correspondence:

Mr. Jef Van den Eynde, Department of Cardiovascular Diseases, University Hospitals Leuven, KU Leuven, Herestraat 49, 3000 Leuven, Belgium. Email: jef.vandeneynde@student.kuleuven.be

- (2) the study assessed the effectiveness of pharmacologic or nonpharmacologic strategies to prevent AKI after cardiac surgery;
- (3) outcomes studied included incidence of postoperative AKI; and
- (4) studies were RCTs.

### Study Selection

The following steps were taken: (1) identification of titles of records through databases search, (2) removal of duplicates, (3) screening and selection of abstracts, (4) assessment for eligibility through full-text articles, and (5) final inclusion in the study. Studies were selected (both at the title and the abstract and full-text stages) by two independent reviewers (N.C. and R.V.L.). In case of disagreement, a third reviewer made the decision (J.V.d.E.).

### Data Items

Two independent reviewers extracted the data (N.C. and R.V.L.). In case of disagreement, a third reviewer checked the data and made the final decision (J.V.d.E.). The extracted data included the first author's name, publication year, country, intervention, population, total number of participants, median or mean age, weight, boys, cardiopulmonary bypass duration, types of cardiac surgery, number of participants with or without AKI, and definition of AKI. The outcome of interest was incidence of AKI after cardiac surgery. Three main definitions for AKI currently exist (Table 1); these are explained in detail in Supplemental Material.

### Risk of Bias in Individual Studies

Using the RoB 2 tool (8), the RCTs included were assessed for biases. Two independent reviewers (N.C. and R.V.L.) assessed risk of bias. In the case of disagreement, a third reviewer (J.V.d.E.) checked the data to arrive at the final decision.

### Direct Pairwise Meta-Analysis

Prior to performing the network meta-analysis, we conducted traditional pairwise meta-analysis on direct comparisons that contained at least two RCTs. The chi-squared test and the  $I^2$  test were performed for assessment of statistical heterogeneity (9). The odds ratios (ORs) and 95% confidence intervals (95% CIs) were combined across the studies using a DerSimonian–Laird random effects model. Forest plots represent the estimated effect sizes for incidence of AKI. Funnel plots were not appropriate for detecting publication bias because there were fewer than ten studies (10). Analyses were performed using the “metafor” package of R Statistical Software (version 4.0.2 2020–06–22; Foundation for Statistical Computing, Vienna, Austria). A two-tailed  $P=0.05$  was considered statistically significant.

### Trial Sequential Analyses

To assess whether effectiveness or futility of each intervention had already sufficiently been demonstrated in identified RCTs, trial sequential analysis was performed using TSA software version 0.9.5.10 (The Copenhagen Trial Unit) (11). All preventive strategies that were compared

with placebo in at least one RCT were considered. The O'Brien–Fleming  $\alpha$ -spending function was implemented, permitting adjustment of the desired statistical significance level. The risk for type I error was set at 5%, and statistical power was set at 80%. The cumulative Z curve, along with the two-sided 5% symmetrical significance boundaries, was plotted. During the analysis, it was also evaluated whether the total event size reached the required limit to ensure sufficient power. Futility boundaries were plotted to indicate whether the desired effect could be achievable when the required sample would be reached.

### Network Meta-Analysis

Network meta-analysis compares multiple interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies (12). Direct evidence refers to evidence obtained from RCTs, whereas indirect evidence refers to the evidence obtained through one or more common comparators. For example, in the absence of RCTs that directly evaluate interventions A and B, interventions A and B can be compared indirectly if both have been compared with intervention C in RCTs. The results of a network meta-analysis are thus estimates of the relative effects between any pair of interventions in the network, which are considered to be more precise estimates than a single direct or indirect estimate. The network meta-analysis was conducted using a random effects model and a Bayesian method using the “BUGSnet” package of R software. We specified a burn-in period of 50,000 iterations followed by 100,000 iterations with 10,000 adaptations in the `nma.run()` function. Higher event rate was defined to imply a worse treatment.

In addition, we used Bayesian Markov chain Monte Carlo modeling to rank the treatments according to the surface under the cumulative ranking curve (SUCRA) probabilities. Ranking is performed by probability ( $P$ ) scores on the basis of the point estimates and SEMs of the network estimates. They measure the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments. Rank 1 is considered as the best and leads to the greatest reduction in the relevant outcome, whereas rank  $N$  is the worst and is associated with higher rates of the outcome. A league heat plot and a forest plot were constructed to demonstrate the estimated relative effect sizes for all preventive strategies. League heat plots present the comparative effectiveness of all treatments within the network. The estimate (OR; 95% CI) is located at the intersection of the row defining index treatment and the column defining comparison treatment. Loop inconsistency is an analysis that assesses the difference between direct and indirect estimates for the same comparison, thus highlighting hot spots where the network does not exactly fit the data; this could not be evaluated because no closed triangles were available in this network (13).

## Results

### Study Selection

A total of 3453 citations were identified, of which 30 studies were potentially relevant and retrieved as full text.

**Table 1. Classifications for the diagnosis of AKI**

RIFLE (7)		Pediatric RIFLE (8)		AKI Network (9)		Kidney Disease Improving Global Outcomes (10)		Urine Output <sup>a</sup>
Criteria	Creatinine Definition	Criteria	Creatinine Definition	Criteria	Creatinine Definition	Criteria	Creatinine Definition	
Risk	≥1.5-fold increase from baseline SCr or decrease in GFR≥25%	Risk	Decrease in eCrCl≥25%	Stage 1	≥0.3-mg/dl increase or ≥1.5-fold increase from baseline SCr within 48 h	Stage 1	≥0.3 mg/dl increase within 48 h or 1.5–1.9 times baseline SCr within 7 d	<0.5 ml/kg per hour for >6 h
Injury	≥2-fold increase from baseline SCr or decrease in GFR≥50%	Injury	Decrease in eCrCl≥50%	Stage 2	≥2-fold increase from baseline SCr	Stage 2	2.0–2.9 times baseline SCr within 7 d	<0.5 ml/kg per hour for 12 h
Failure	≥3-fold increase from baseline SCr or increase to ≥4 mg/dl or decrease in GFR≥75%	Failure	Decrease in eCrCl≥75% or <35 ml/min per 1.73 m <sup>2</sup>	Stage 3	≥3-fold increase from baseline SCr or increase to ≥4 mg/dl with an acute increase of >0.5 mg/dl or initiation of KRT <sup>b</sup>	Stage 3	≥3 times baseline within 7 d or increase to ≥4 mg/dl with an acute increase of >0.5 mg/dl or initiation of KRT <sup>b</sup>	<0.3 ml/kg per hour for 24 h or anuria for >12 h

SCr, serum creatinine; eCrCl, estimated creatinine clearance.  
<sup>a</sup>Urine output criteria are common to all three definitions.  
<sup>b</sup>KRT is often left out of the definition for neonates and infants.

Twenty publications (14–33) fulfilled our eligibility criteria (Figure 1).

### Study Characteristics

Characteristics of each study and their participants are shown in Table 2. Additional information on interventions and operations is given in Supplemental Table 1. A total of 2339 patients were included from 20 two-armed RCTs published from 2000 to 2020. Most studies consisted of patients with mean age of 17.2 months (20 studies, 2339 patients) who were mostly boys (54%; 17 studies, 2145 patients). Kidney Disease Improving Global Outcomes (KDIGO) guidelines (34) were applied in four studies, whereas one study used the RIFLE criteria (35), four studies used the pediatric RIFLE (pRIFLE) criteria (36), and three used the AKI Network (AKIN) criteria (37). AKI was detected with various creatinine-based criteria in the rest of the studies. The overall internal validity was considered low risk of bias (Supplemental Table 2).

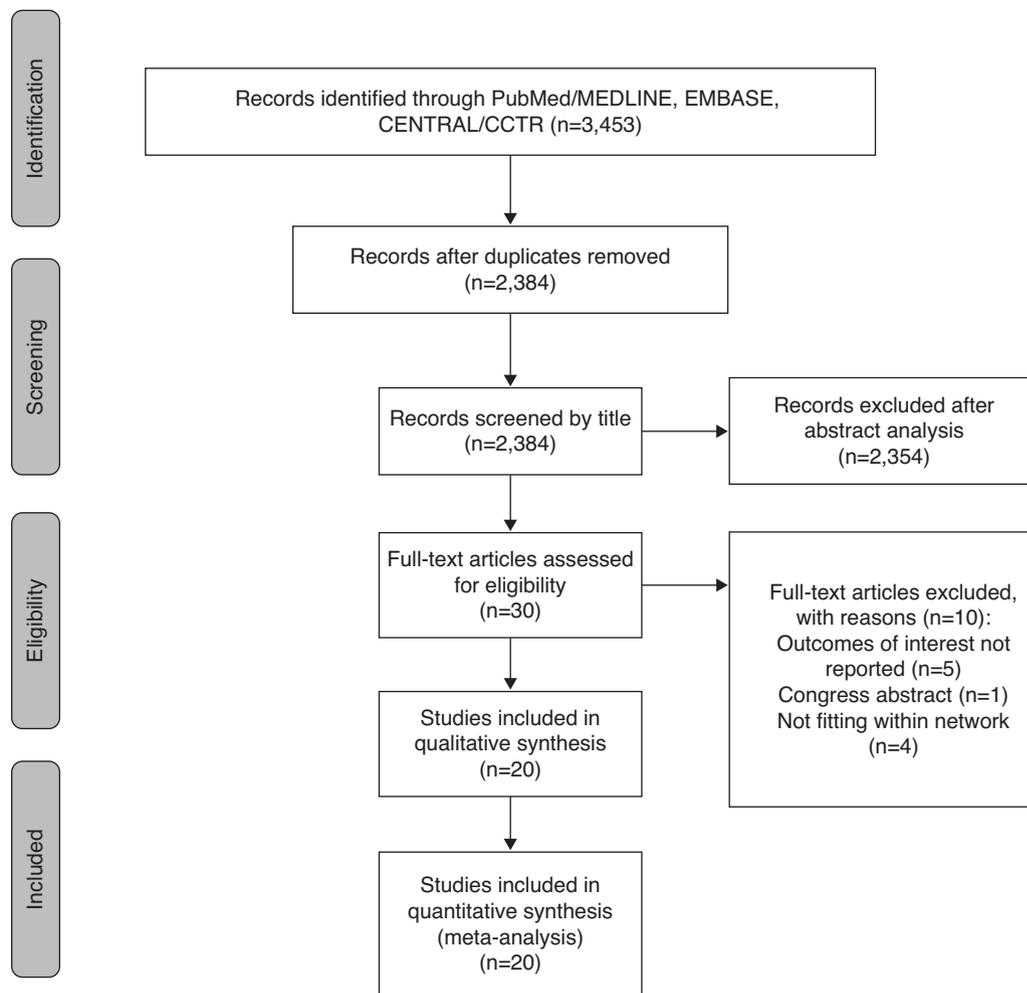
Eleven strategies were represented in the RCT arms: acetaminophen (one study, 15 patients), aminophylline (one study, 72 patients), corticosteroids (seven studies, 399 patients), dexmedetomidine (one study, 15 patients), fenoldopam (two studies, 60 patients), hydroxyethyl starch (HES; two studies, 110 patients), levosimendan (two studies, 126 patients), milrinone (one study, 38 patients), normothermic cardiopulmonary bypass (one study, 28 patients), remote ischemic preconditioning (RIPC; three studies, 309 patients), and control/placebo (19 studies, 1167 patients). Control/placebo referred either to the inactive substance in case of pharmacologic strategies or to the standard management in case of nonpharmacologic strategies.

### Synthesis of Results

The results of the direct pairwise meta-analyses are presented in Figure 2. The ORs for postoperative AKI showed no significant difference compared with control for corticosteroids (OR, 0.84; 95% CI, 0.43 to 1.67;  $P=0.57$ ), fenoldopam (OR, 0.47; 95% CI, 0.01 to 32.05;  $P=0.27$ ), HES (OR, 1.47; 95% CI, 0.39 to 5.54;  $P=0.17$ ), or RIPC (OR, 0.43; 95% CI, 0.13 to 1.49;  $P=0.10$ ). In contrast, a trial (28) investigating dexmedetomidine showed a significant advantage of this strategy compared with control (OR, 0.20; 95% CI, 0.04 to 0.98;  $P=0.04$ ).

Trial sequential analysis revealed that only the Z curve for dexmedetomidine had surpassed both conventional boundaries for benefit and trial sequential monitoring boundaries for benefit, which makes it likely that the assumed effect is in fact true (Supplemental Figure 1A). Conventional boundaries were only crossed after reaching the required information size for RIPC, suggesting evidence of <57% relative risk reduction (Supplemental Figure 1B). Such effect of RIPC might indeed be true under certain conditions, given the strongly significant findings in the study by Kang *et al.* (25) (OR, 0.27; 95% CI, 0.13 to 0.42;  $P<0.001$ ). For all other interventions, boundaries for benefit were not crossed, although the required information size was not yet reached (Supplemental Figures 2–5).

Figure 3A shows the network plot on which the random effects Bayesian network meta-analysis is based, and Figure 3B demonstrates the estimated effect sizes of all preventive strategies compared with control. In addition, Figure 3C shows the comparative effectiveness of the various preventive strategies. The network was unable to demonstrate any significant differences among the examined treatments.



**Figure 1.** | Flow diagram of the literature search depicting the number of included and excluded studies throughout the process. CENTRAL/CCTR, Cochrane Controlled Trials Register.

Figure 4 presents the SUCRA plot. SUCRA rankings revealed that milrinone (SUCRA probability: 76%) was most likely to result in the lowest risk of AKI, followed by dexmedetomidine (70%), levosimendan (70%), aminophylline (59%), normothermic cardiopulmonary bypass (57%), and RIPC (55%), although all showed important overlap. On the other hand, fenoldopam (47%), corticosteroids (42%), acetaminophen (32%), control (23%), and HES (20%) appeared less attractive.

## Discussion

In this study, we assessed the efficacy of 11 strategies to minimize the risk of AKI in a pediatric population following cardiac surgery. Traditional pairwise meta-analysis revealed no overall significant differences compared with control for corticosteroids, fenoldopam, HES, or RIPC. In contrast, trial sequential analysis suggested 80% relative risk reduction with dexmedetomidine and evidence of <57% relative risk reduction with RIPC. Nonetheless, the network meta-analysis was unable to demonstrate any significant differences among the examined treatments, including also acetaminophen, aminophylline, levosimendan, milrinone, and normothermic cardiopulmonary bypass. SUCRA

probabilities showed that milrinone (76%) was most likely to result in the lowest risk of AKI, followed by dexmedetomidine (70%), levosimendan (70%), aminophylline (59%), normothermic cardiopulmonary bypass (57%), and RIPC (55%), although all showed important overlap. In summary, our analyses highlight that, despite 2 decades of research, no effective strategies have been established for the prevention of AKI in children undergoing cardiac surgery.

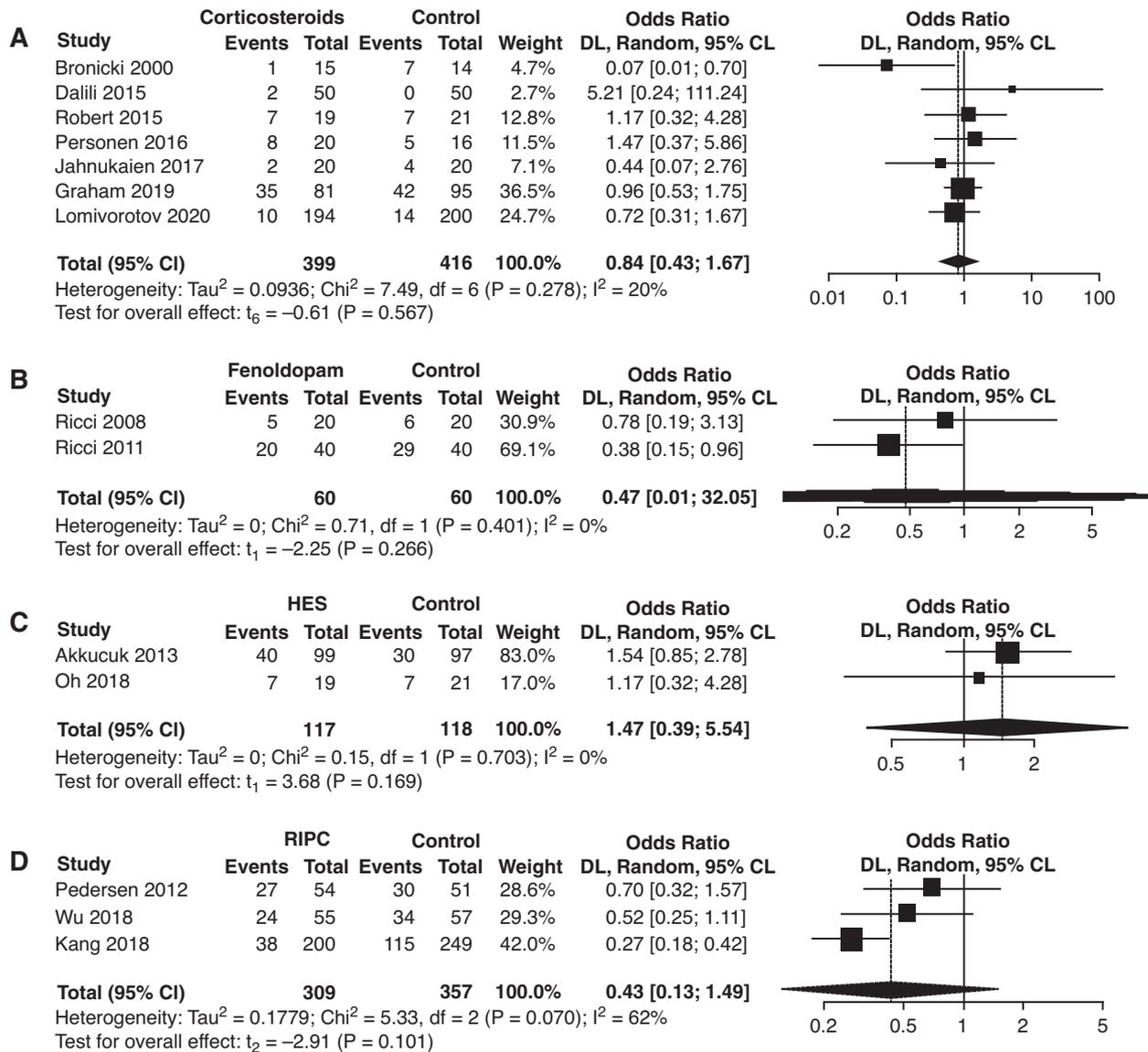
The results of a network meta-analysis should be interpreted carefully. First of all, the ORs reported by a network meta-analysis consist of pooling both direct comparisons of two therapies within RCTs and indirect inferences from the network about the relative effects of those therapies. The network of RCTs itself adds information to individual comparisons. As a result, the effect estimates in our network meta-analysis are different from those derived from direct pairwise meta-analysis.

Second, ranking measures such as SUCRA probabilities cannot be used as a substitute for relative treatment effects. SUCRAs are dependent on which treatments are selected and, thus, might be subject to chance if a different subset of these treatments was to be selected. Furthermore, a highly ranking treatment might not be clinically relevant if its

Table 2. Study and participant characteristics

Study	Country	Total No. of Participants	Population	Age	Weight	Boys	Cardiopulmonary Bypass Duration	AKI	AKI Definition
Simpson <i>et al.</i> (14)	United States	Acetaminophen: 15, control: 15	Infants + children	Acetaminophen: 33.1±9.2 mo, control: 34.1±8.9 mo	Acetaminophen: 14.5±2.6 kg, control: 15.9±3.8 kg	Acetaminophen: 53%, control: 47%	Acetaminophen: 80.2±13 min, control: 77.1±7.9 min	Aminophylline: 53%, control: 53%	AKIN
Axelrod <i>et al.</i> (15)	United States	Aminophylline: 72, control: 72	Infants + children	Aminophylline: 430±212 d, control: 257±98.7 d	Aminophylline: 7.4±1.63 kg, control: 6.58±1.12 kg	Aminophylline: 58%, control: 54%	Aminophylline: 155±21.2 min, control: 138±19.5 min	Aminophylline: 1%, control: 1%	KDIGO
Bronicki <i>et al.</i> (27)	United States	Dexamethasone: 15, control: 14	Infants + children	Dexamethasone: 28±33 mo, control: 25±35 mo	ND	ND	Dexamethasone: 111±41 min, control: 135±37 min	Dexamethasone: 7%, control: 50%	Creatinine increase ≥0.2 mg/dl of preoperative value
Lomivorotov <i>et al.</i> (26)	China, Brazil, and Russia	Dexamethasone: 194, control: 200	Neonates + infants	Dexamethasone: 6.6±0.9 mo, control: 6.1±0.9 mo	Dexamethasone: 6.4±0.4 kg, control: 6.3±0.43 kg	Dexamethasone: 48%, control: 47%	Dexamethasone: 52.3±7.2 min, control: 49.3±6.5 min	Dexamethasone: 5%, control: 7%	pRIFLE
Robert <i>et al.</i> (33)	United Kingdom	Hydrocortisone: 19, control: 21	Neonates	Hydrocortisone: 5.3±0.5 d, control: 7±1 d	Hydrocortisone: 3.2±0.1 kg, control: 3±0.1 kg	ND	Hydrocortisone: 130±8.5 min, control: 133±9.7 min	Hydrocortisone: 37%, control: 33%	Serum creatinine increase ≥50% of preoperative value
Dalili <i>et al.</i> (21)	Iran	Methylprednisolone: 50, control: 50	Infants + children	Methylprednisolone: 39.8±24.7 mo, control: 38.2±19.8 mo	Methylprednisolone: 12.9±4.3 kg, control: 12.7±3.7 kg	Methylprednisolone: 54%, control: 54%	Methylprednisolone: 106±27.8 min, control: 111±31.8 min	Methylprednisolone: 4%, control: 0%	Creatinine clearance <10 ml/min per 1.73 m <sup>2</sup>
Pesonen <i>et al.</i> (20)	Finland	Methylprednisolone: 20, control: 16	Neonates	Methylprednisolone: 9.9±7 d, control: 11±7.2 d	Methylprednisolone: 3.6±0.4 kg, control: 3.5±0.6 kg	Methylprednisolone: 60%, control: 55%	Methylprednisolone: 168±43 min, control: 198±85 min	Methylprednisolone: 40%, control: 31%	Serum creatinine increase ≥50% of preoperative value during 3 first postoperative days
Jahnukainen <i>et al.</i> (18)	Finland	Methylprednisolone: 20, control: 20	Neonates	Methylprednisolone: 8.1±2.6 d, control: 8.2±4.7 d	Methylprednisolone: 3.4±0.5 kg, control: 3.5±0.6 kg	Methylprednisolone: 65%, control: 70%	Methylprednisolone: 181±47 min, control: 162±61.7 min	Methylprednisolone: 10%, control: 20%	KDIGO
Graham <i>et al.</i> (19)	United States	Methylprednisolone: 81, control: 90	Neonates	Methylprednisolone: 9.1±5.6 d, control: 8.2±5.6 d	Methylprednisolone: 3.2±0.5 kg, control: 3.4±0.5 kg	Methylprednisolone: 57%, control: 64%	Methylprednisolone: 185±64 min, control: 176±64 min	Methylprednisolone: 43%, control: 44%	AKIN
Jo <i>et al.</i> (28)	South Korea	Dexametomidine: 15, control: 14	Children	Dexametomidine: 31±14 mo, control: 32±19 mo	Dexametomidine: 11.8±2.2 kg, control: 11.1±3.2 kg	Dexametomidine: 60%, control: 64%	Dexametomidine: 107±39 min, control: 106±34 min	Dexametomidine: 27%, control: 64%	AKIN
Ricci <i>et al.</i> (29)	Italy	Fenoldopam: 20, control: 20	Neonates	Fenoldopam: 14.5±2.3 d, control: 17.8±3.2 d	Fenoldopam: 3.2±0.1 kg, control: 3.5±0.2 kg	ND	Fenoldopam: 198±27.3 min, control: 183±20.8 min	Fenoldopam: 25%, control: 30%	pRIFLE
Ricci <i>et al.</i> (30)	Italy	Fenoldopam: 40, control: 40	Neonates + infants	Fenoldopam: 14.5±156 d, control: 139±130 d	Fenoldopam: 5.1±2.2 kg, control: 5±2.2 kg	ND	Fenoldopam: 212±70 min, control: 217±74 min	Fenoldopam: 50%, control: 73%	pRIFLE
Akkucak <i>et al.</i> (31)	Turkey	HES: 12, control: 12	Children	HES: 3.9±1.7 yr, control: 5.1±3.7 yr	HES: 13.5±4.5 kg, control: 16.2±8.8 kg	HES: 50%, control: 58%	HES: 65.6±29.2 min, control: 73.8±40.9 min	HES: 0%, control: 0%	At least one of the following criteria: increase in serum creatinine ≥50% above baseline, absolute increase in serum creatinine of ≥0.3 mg/dl, and/or urine output <0.5 ml/kg per hour for at least 6 h
Oh <i>et al.</i> (32)	South Korea	HES: 98, control: 97	Neonates + infants + children	HES: 0.8±0.3 yr, control: 0.6±0.2 yr	ND	HES: 54%, control: 55%	HES: 140±56 min, control: 145±56.2 min	HES: 41%, control: 31%	pRIFLE
Wang <i>et al.</i> (16)	China	Levosimendan: 94, control: 93	Infants + children	Levosimendan: 5.8±1.5 mo, control: 8±2.3 mo	ND	Levosimendan: 55%, control: 56%	Levosimendan: 81±34 min, control: 84±30 min	Levosimendan: 1%, control: 2%	ND
Thorlacius <i>et al.</i> (17)	Finland and Sweden	Levosimendan: 32, milrinone: 38	Infants	Levosimendan: 5.9±2.9 mo, Milrinone: 5.6±2.7 mo	Levosimendan: 6.4±2 kg, Milrinone: 6.2±1.5 kg	Levosimendan: 50%, milrinone: 47%	Levosimendan: 90±33 min, Milrinone: 93±45 min	Levosimendan: 47%, milrinone: 40%	KDIGO
Caputo <i>et al.</i> (22)	United Kingdom	Normothermic CPB: 28, hypothermic CPB (control): 31	Children	Normothermic CPB: 87.5±14.2 mo, Hypothermic CPB (control): 67±18.7 mo	ND	Normothermic CPB: 32%, hypothermic CPB (control): 52%	Normothermic CPB: 50.5±4.5 min, Hypothermic CPB (control): 62.5±5.3 min	Normothermic CPB: 4%, hypothermic CPB (control): 3%	Serum creatinine increase ≥50% of preoperative value
Pedersen <i>et al.</i> (23)	Denmark	RIPC: 54, control: 51	Neonates + infants + children	RIPC: 2.1±1 yr, control: 1.8±0.8 yr	ND	RIPC: 46%, control: 65%	RIPC: 133±11.3 min, control: 134±12.3 yr	RIPC: 50%, control: 59%	RIFLE
Wu <i>et al.</i> (24)	China	RIPC: 35, control: 57	Infants + children	RIPC: 10.5±6.7 mo, control: 11.2±6.2 mo	RIPC: 8.9±2.9 kg, control: 9.1±2.8 kg	RIPC: 55%, control: 56%	RIPC: 108±20.7 min, control: 109±20.2 min	RIPC: 44%, control: 60%	ND
Kang <i>et al.</i> (25)	China	RIPC: 200, control: 249	Infants + children	RIPC: 41.5±33 mo, control: 31.5±22.2 mo	ND	RIPC: 57%, control: 52%	RIPC: 69.6±49.5 min, control: 60.2±30 min	RIPC: 19%, control: 46%	KDIGO

Data are presented as mean ± SD. AKIN, AKI Network; KDIGO, Kidney Disease Improving Global Outcomes; ND, not determined; pRIFLE, pediatric RIFLE; HES, hydroxyethyl starch; CPB, cardiopulmonary bypass; RIPC, remote ischemic preconditioning.

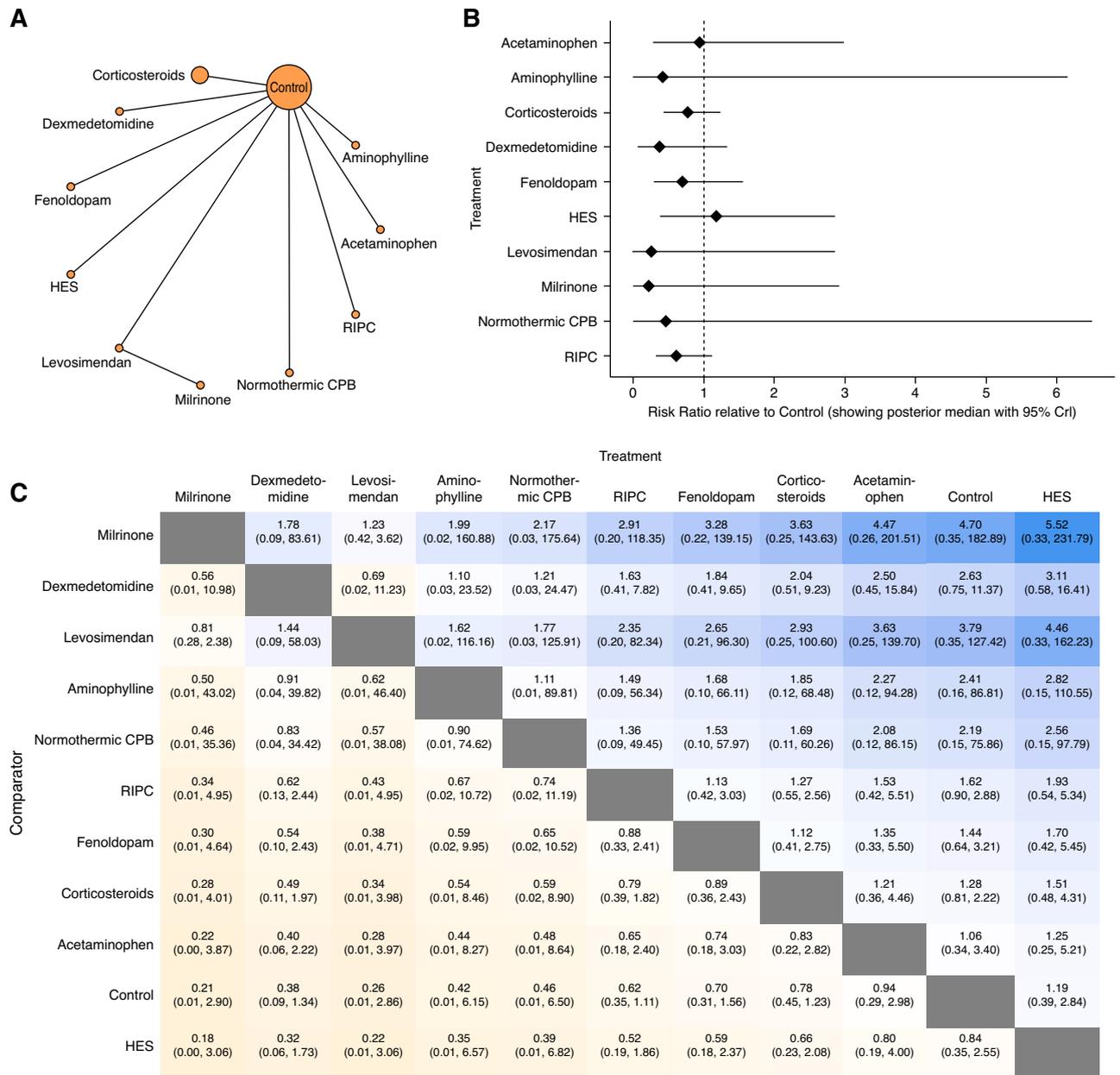


**Figure 2.** | Direct pairwise meta-analysis. Forest plots showing no effects of either (A) corticosteroids, (B) fenoldopam, (C) hydroxyethyl starch (HES), or (D) remote ischemic preconditioning (RIPC) on AKI after pediatric cardiac surgery. Pooled odds ratio and conclusions plots. 95% CI, 95% confidence interval;  $\text{df}$ , degrees of freedom; DL, DerSimonian-Lairds.

relative treatment effect compared with control is not significant (*i.e.*, if the efficacy of this therapy could not be confirmed). In our study, milrinone was suggested as the best-ranking strategy on the basis of SUCRA probability, yet its comparison with control did not reach statistical significance.

Bellos *et al.* (38) conducted a network meta-analysis of 2625 pediatric patients from 14 studies, including both RCTs and observational studies. They found that both dexmedetomidine (OR, 0.49; 95% CI, 0.28 to 0.87) and acetaminophen (OR, 0.43; 95% CI, 0.28 to 0.67) significantly reduced AKI, whereas no difference was observed in patients receiving corticosteroids, fenoldopam, or aminophylline. In their analyses, dexmedetomidine was found to be the best-ranking therapy, although showing overlap with the other therapies.

Our study differs in several aspects. First, Bellos *et al.* (38) designed their search to identify all studies related to five predefined pharmacologic therapies. In contrast, we ran a broad search to detect any preventive strategies that have been used to reduce the incidence of AKI in the setting of pediatric cardiac surgery. As such, we included ten interventions apart from control, including two nonpharmacologic strategies. Nine studies (14,15,18,20,21,27–30) overlapped between our study and the study by Bellos *et al.* (38), whereas 11 of the studies included in our analysis had not been identified by Bellos *et al.* (38). Furthermore, we considered only RCTs to exclude the effect of confounding in observational studies. Lastly but importantly, we applied random effects meta-analyses, which are considered to be more appropriate given the clinical heterogeneity of the included populations.

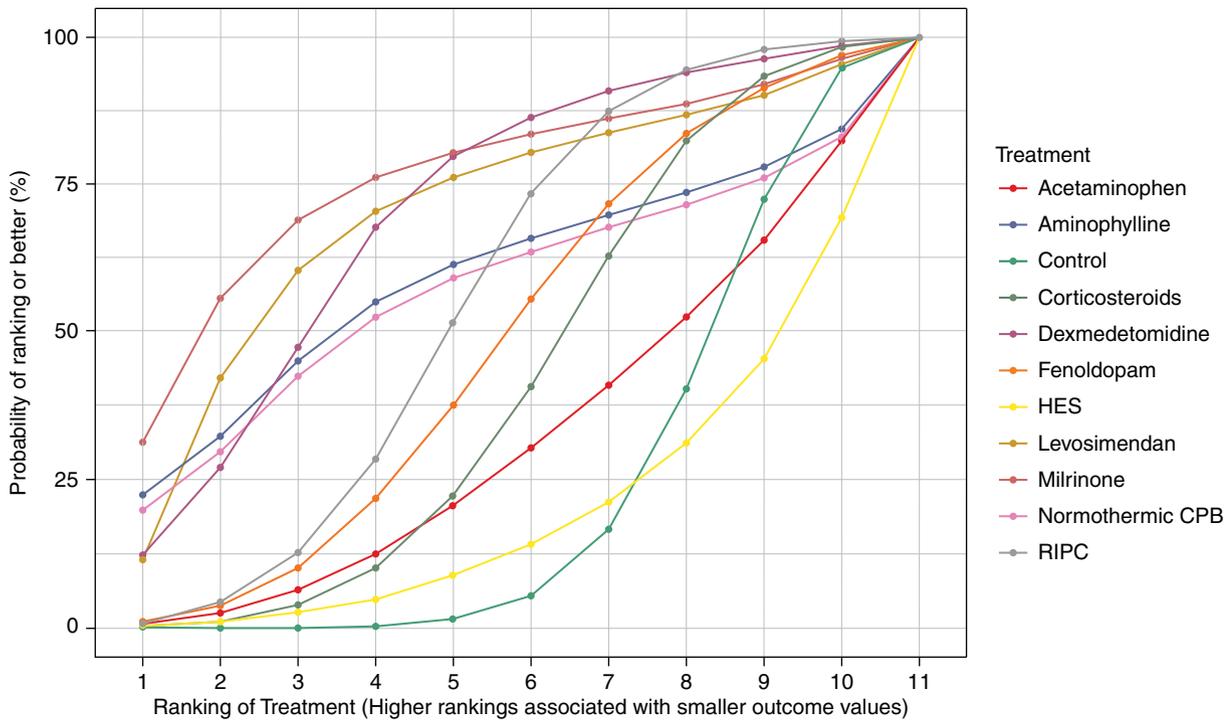


**Figure 3. | Network meta-analysis.** (A) Network plot showing the preventive strategies that have been tested in randomized controlled trials for their efficacy in preventing AKI. Circles are weighted according to the number of studies including the intervention, and lines are weighted according to the number of studies comparing the two connected interventions. (B) Forest plots showing that none of the strategies could effectively prevent AKI. The relative effects of preventive strategies compared with control, as estimated from both direct and indirect estimates in the network, are shown. (C) League heat plot showing no differences in the comparative efficacy of preventive strategies included in the network meta-analysis. The estimate (odds ratio; 95% confidence interval) is located at the intersection of the row defining index treatment and the column defining comparison treatment. CPB, cardiopulmonary bypass; CrI, credible interval; HES, hydroxyethyl starch; RIPC, remote ischemic preconditioning.

In this study, we could not confirm the findings from the network meta-analysis by Bellos *et al.* (38). In fact, only limited evidence from RCTs existed for dexmedetomidine and RIPC, whereas our network meta-analysis could not support the superiority of any of the examined strategies over the others. On the other hand, the results for milrinone, levosimendan, aminophylline, and normothermic cardiopulmonary bypass appeared promising, whereas the trial sequential futility boundaries were not yet reached;

therefore, more RCTs are warranted to reach definitive conclusions about the efficacy of these strategies. Furthermore, the current lack of convincing data encourages data sharing for prospective studies and individual patient data meta-analyses.

The use of different criteria to define AKI is a fundamental issue that complicates comparison between studies, as was also observed in this review. Currently, three main definitions for AKI exist, in addition to several versions



**Figure 4.** | Surface under the cumulative ranking curve (SUCRA) plot showing that milrinone had the highest probability of being ranked first, although showing important overlap with the other preventive strategies. For each preventive strategy, the cumulative probability of being ranked 1st through 11th is displayed. The more the curve for a certain strategy is located toward the upper left corner, the higher its SUCRA value and the greater its performance.

customized by researchers themselves. Definitions differ on whether they are on the basis of a 48-hour rolling window or on a 7-day window of observation, whether they consider GFR or not, and whether they assess serum creatinine (SCr) in terms of relative or absolute changes. The choice of criteria might thus be very influential on the incidence of AKI.

This issue is even more pertinent in the pediatric setting. First, all three main definitions have initially been designed for adults. Even the pRIFLE classification is on the basis of a small cohort of 150 patients aged >1 year and extrapolation from adult data (36). Furthermore, SCr in children increases with age (or height, as a surrogate for muscle mass), and kidney maturation only occurs at the age of 2–3 years (39). Therefore, an absolute change in SCr is different for a very young child compared with an older child. As most studies included in these analyses consisted of patients with mean age of 17.2 months, baseline creatinine would be expected around 0.25–0.30 mg/dl. An absolute change of 0.30 mg/dl would thus be equivalent to doubling the SCr, which is much more severe than a relative increase of 1.5 times the baseline value. It might, therefore, be problematic in the pediatric setting that KDIGO treats an absolute increase in SCr of 0.30 mg/dl over 48 hours as equivalent to a 1.5-fold relative increase in SCr over 7 days.

In a large prospective cohort of 1489 consecutive neonates and infants undergoing cardiac operations, Lex *et al.* (40) compared the three main definitions for AKI. They found that, particularly in this age group, the pRIFLE system had superior sensitivity compared with AKIN and KDIGO in the early detection of AKI requiring KRT. Interestingly, about 5% of patients (74 of 1489) were detected

only by pRIFLE. This can be explained by the fact that a 25% decrease in the estimated creatinine clearance (as in pRIFLE) in neonates and infants is less severe than a 1.5-fold increase in SCr (as in AKIN and KDIGO). These observations warrant further assessment and careful selection of the appropriate definition of AKI.

For the purposes of this meta-analysis, it is important to note that within all included studies, the same definition of AKI was applied in both the intervention and placebo arms. It can, therefore, be assumed that the effect of the definition affected all patients within each study equally, such that the observed treatment effect would be expected to remain relatively unaffected. The main question, however, remains whether currently existing definitions of AKI may be enough to make decisions on the efficacy of interventions to prevent AKI. Therefore, novel biomarkers that allow for early detection of AKI are much needed.

The pathophysiology of postoperative AKI is complex, and multiple risk factors have been described (4). Even though developments have been made in the supportive care for patients with AKI, survival remains poor (41). In the light of our findings, it is likely that not a single therapy but, rather, multiple preventive measures will provide optimal protection against AKI. As specific combinations of preventive strategies might have additive, synergistic, or antagonistic effects, dedicated studies would need to be set up to discover which combinations hold the most promise. Eventually, the knowledge obtained from these studies might help design the ideal perioperative protocol. However, such an approach on the basis of a trial and error design is limited by its time-consuming and expensive

nature. Furthermore, children undergoing cardiac surgery constitute a heterogeneous population. As a result, certain combinations of preventive strategies might be more effective than others in different subgroups of patients depending on demographics and setting. Recent developments in machine learning allow for individual prediction of therapy response, including treatment recommendation functions (42,43). The application of such analysis techniques on large databases might potentially substitute time and cost-intensive RCTs in the future.

Another important challenge is the limited capacity of conventional markers of kidney function, such as SCr, to detect early loss of function. As a result, AKI is often detected late, attenuating the opportunity for early successful intervention and leading to worse outcomes (44). Again, machine learning has emerged as a promising tool, allowing for the early prediction of AKI and having been shown to outperform human predictive performance (45). On the basis of the risk for the development of AKI calculated by these models, appropriate and effective treatments can be initiated in an early stage to prevent progression. In addition, more exhaustive and expensive tests that would otherwise yield high false-positive rates could be omitted (41). Other avenues might be the investigation of biomarkers, including cystatin C, kidney injury molecule 1, neutrophil gelatinase-associated lipocalin, tissue inhibitor of metalloproteinases-2, and IGF-binding protein 7, all of which have been reported to appear before increases in creatinine can be observed (46,47).

There are some points that merit consideration when interpreting these findings. First, the interpretation of outcomes is limited by statistical heterogeneity. As highlighted above, this might be due to differences in definitions of AKI. Furthermore, other sources might exist, including age, underlying congenital heart defect, cardiopulmonary bypass time, anesthesia protocol, admission to intensive care unit, definition of AKI, or timing and dose of the intervention. A formal clustered analysis according to these sources of heterogeneity was deferred because of lack of individual patient data, but random effects models were used in all analyses to account for clinical heterogeneity. These models assume that the true effect sizes may differ across studies, while still allowing us to assess the net relative efficacy of two or more treatments. Of interest, a dosing effect might have played a role in the meta-analyses for fenoldopam. The study by Ricci *et al.* (29) from 2008 found no significant effect of an intravenous dose of fenoldopam 0.1 µg/kg per minute, whereas a study from 2011 by Ricci *et al.* (30) showed a 62% relative risk reduction with a dose of 1 µg/kg per minute (OR, 0.38; 95% CI, 0.15 to 0.96). The latter dose of fenoldopam might thus in fact prove effective in further RCTs. Second, no direct comparisons of the investigated strategies were available, except for one study comparing levosimendan and milrinone (17). As a result, our network did not contain any closed triangle or quadratic loops. Chance may explain any apparent difference between treatments, especially given the limited number of direct comparisons. Moreover, many treatments were compared with placebo in only a single trial, such that only four could be considered for direct pairwise meta-analysis. Third, although most management cardiopulmonary bypass protocols use a combination of therapies, our

analysis did not allow us to estimate any additive or synergistic effects that might exist among the investigated treatments. Lastly, we only considered the effect of these therapies on AKI incidence; a treatment that performs best in this outcome might, however, be the worst in another outcome (for example, a harm outcome).

The results of this network meta-analysis, on the basis of current evidence from RCTs, do not support the efficacy of most strategies to prevent AKI in the pediatric population, apart from limited evidence for dexmedetomidine and RIPC. Further investigations are needed to define an optimal protocol for prevention of AKI after pediatric cardiac surgery. We identified an unmet need for more sensitive biomarkers for the definition of AKI.

#### Disclosures

W. Budts reports consultancy agreements with Abbott, Medtronic, and Occlutech; serving as a scientific advisor or member of Abbott, Medtronic, and Occlutech; and speakers bureaus for Abbott, Medtronic, and Occlutech. M. Gewillig is proctor for Edwards and Medtronic. S. Kutty reports consultancy agreements with GE Healthcare. D. Mekahli reports consultancy agreements with Otsuka (all paid to her institution KU Leuven); receiving research funding from Galapagos and Otsuka (all paid to KU Leuven); and serving as a scientific advisor or member of Galapagos, Otsuka, and Sanofi (all paid to KU Leuven). All remaining authors have nothing to disclose.

#### Funding

None.

#### Acknowledgments

J. Van den Eynde was supported by a fellowship of the Belgian American Educational Foundation.

Prof. W. Budts, Mr. N. Cloet, Prof. M. Gewillig, Prof. S. Kutty, Prof. D. Mekahli, Prof. H. Pottel, Prof. M.O. Sá, Prof. J. Toelen, Mr. J. Van den Eynde, Mr. R. Van Lerberghe, Prof. J.Y. Verbakel, and Prof. D. Vlasselaers conceptualized the study; Mr. N. Cloet, Mr. J. Van den Eynde, and Mr. R. Van Lerberghe were responsible for data curation; Prof. W. Budts, Mr. N. Cloet, Prof. M. Gewillig, Prof. S. Kutty, Prof. D. Mekahli, Prof. H. Pottel, Prof. M.O. Sá, Prof. J. Toelen, Mr. J. Van den Eynde, Mr. R. Van Lerberghe, Prof. J.Y. Verbakel, and Prof. D. Vlasselaers were responsible for investigation; Mr. J. Van den Eynde was responsible for formal analysis; Mr. J. Van den Eynde was responsible for methodology; Mr. J. Van den Eynde was responsible for project administration; Mr. J. Van den Eynde was responsible for software; Mr. J. Van den Eynde was responsible for validation; Mr. J. Van den Eynde was responsible for visualization; Prof. W. Budts, Prof. M. Gewillig, Prof. S. Kutty, Prof. D. Mekahli, Prof. H. Pottel, Prof. M.O. Sá, Prof. J. Toelen, Prof. J.Y. Verbakel, and Prof. D. Vlasselaers provided supervision; Mr. N. Cloet, Mr. J. Van den Eynde, and Mr. R. Van Lerberghe wrote the original draft; and Prof. W. Budts, Prof. N. Cloet, Prof. M. Gewillig, Prof. S. Kutty, Prof. D. Mekahli, Prof. H. Pottel, Prof. M.O. Sá, Prof. J. Toelen, Mr. J. Van den Eynde, Mr. R. Van Lerberghe, Prof. J.Y. Verbakel, and Prof. D. Vlasselaers reviewed and edited the manuscript.

#### Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.05800421/-/DCSupplemental>.

Supplemental Material. Search strategy and definitions of AKI.

Supplemental Table 1. Interventions and operations per study.

Supplemental Table 2. Bias assessment of RCTs (RoB 2 tool).

Supplemental Figure 1. Trial sequential analysis for (A) RIPC and (B) dexmedetomidine.

Supplemental Figure 2. Trial sequential analysis for (A) fenoldopam and (B) corticosteroids.

Supplemental Figure 3. Trial sequential analysis for HES.

Supplemental Figure 4. Trial sequential analysis for (A) acetaminophen and (B) aminophylline.

Supplemental Figure 5. Trial sequential analysis for (A) levosimendan and (B) normothermic CPB.

## References

- Van den Eynde J, Rotbi H, Gewillig M, Kutty S, Allegaert K, Mekahli D: In-hospital outcomes of acute kidney injury after pediatric cardiac surgery: A meta-analysis. *Front Pediatr* 9: 733–744, 2021
- Zappitelli M, Bernier PL, Saczkowski RS, Tchervenkov CI, Gottesman R, Dancea A, Hyder A, Alkandari O: A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. *Kidney Int* 76: 885–892, 2009
- Morgan C, Al-Aklabi M, Garcia Guerra G: Chronic kidney disease in congenital heart disease patients: A narrative review of evidence. *Can J Kidney Health Dis* 2: 27, 2015
- Lee SH, Kim SJ, Kim HJ, Son JS, Lee R, Yoon TG: Acute kidney injury following cardiopulmonary bypass in children – Risk factors and outcomes. *Circ J* 81: 1522–1527, 2017
- Yuan S-M: Acute kidney injury after pediatric cardiac surgery. *Pediatr Neonatol* 60: 3–11, 2019
- Selewski DT, Askenazi DJ, Kashani K, Basu RK, Gist KM, Harer MW, Jetton JG, Sutherland SM, Zappitelli M, Ronco C, Goldstein SL, Mottes TA: Quality improvement goals for pediatric acute kidney injury: Pediatric applications of the 22nd Acute Disease Quality Initiative (ADQI) conference. *Pediatr Nephrol* 36: 733–746, 2021
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 151: 264–269, W64, 2009
- Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT; RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 366: l4898, 2019
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. *BMJ* 327: 557–560, 2003
- Macaskill P, Walter SD, Irwig L: A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 20: 641–654, 2001
- Wetterslev J, Thorlund K, Brok J, Gluud C: Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 61: 64–75, 2008
- Chaimani A, Caldwell D, Li T, Higgins J, Salanti G: Chapter 11: Undertaking network meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions*, edited by Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, 2021. Available at: [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook)
- Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR: Consistency and inconsistency in network meta-analysis: Concepts and models for multi-arm studies. *Res Synth Methods* 3: 98–110, 2012
- Simpson SA, Zaccagni H, Bichell DP, Christian KG, Mettler BA, Donahue BS, Roberts LJ 2nd, Pretorius M: Acetaminophen attenuates lipid peroxidation in children undergoing cardiopulmonary bypass. *Pediatr Crit Care Med* 15: 503–510, 2014
- Axelrod DM, Sutherland SM, Anglemyer A, Grimm PC, Roth SJ: A double-blinded, randomized, placebo-controlled clinical trial of aminophylline to prevent acute kidney injury in children following congenital heart surgery with cardiopulmonary bypass. *Pediatr Crit Care Med* 17: 135–143, 2016
- Wang A, Cui C, Fan Y, Zi J, Zhang J, Wang G, Wang F, Wang J, Tan Q: Prophylactic use of levosimendan in pediatric patients undergoing cardiac surgery: A prospective randomized controlled trial. *Crit Care* 23: 428, 2019
- Thorlacius EM, Suominen PK, Wählander H, Keski-Nisula J, Vistnes M, Ricksten SE, Synnergren M, Romlin BS, Castellheim A: The effect of levosimendan versus milrinone on the occurrence rate of acute kidney injury following congenital heart surgery in infants: A randomized clinical trial. *Pediatr Crit Care Med* 20: 947–956, 2019
- Jahnukainen T, Keski-Nisula J, Tainio J, Valkonen H, Pätälä T, Jalanko H, Suominen P: Efficacy of corticosteroids in prevention of acute kidney injury in neonates undergoing cardiac surgery—A randomized controlled trial. *Acta Anaesthesiol Scand* 62: 1072–1079, 2018
- Graham EM, Martin RH, Buckley JR, Zyblewski SC, Kavarana MN, Bradley SM, Alsoufi B, Mahle WT, Hassid M, Atz AM: Corticosteroid therapy in neonates undergoing cardiopulmonary bypass: Randomized controlled trial. *J Am Coll Cardiol* 74: 659–668, 2019
- Pesonen EJ, Suominen PK, Keski-Nisula J, Mattila IP, Rautiainen P, Jahnukainen T: The effect of methylprednisolone on plasma concentrations of neutrophil gelatinase-associated lipocalin in pediatric heart surgery. *Pediatr Crit Care Med* 17: 121–127, 2016
- Dalili M, Vesal A, Tabib A, Khani-Tafti L, Hosseini S, Totonchi Z: Single dose corticosteroid therapy after surgical repair of Fallot's tetralogy: A randomized controlled clinical trial. *Res Cardiovasc Med* 4: e25500, 2015
- Caputo M, Patel N, Angelini GD, de Siena P, Stoica S, Parry AJ, Rogers CA: Effect of normothermic cardiopulmonary bypass on renal injury in pediatric cardiac surgery: A randomized controlled trial. *J Thorac Cardiovasc Surg* 142: 1114–1121, 2011
- Pedersen KR, Ravn HB, Povlsen JV, Schmidt MR, Erlandsen EJ, Hjortdal VE: Failure of remote ischemic preconditioning to reduce the risk of postoperative acute kidney injury in children undergoing operation for complex congenital heart disease: A randomized single-center study. *J Thorac Cardiovasc Surg* 143: 576–583, 2012
- Wu Q, Wang T, Chen S, Zhou Q, Li H, Hu N, Feng Y, Dong N, Yao S, Xia Z: Cardiac protective effects of remote ischaemic preconditioning in children undergoing tetralogy of fallot repair surgery: A randomized controlled trial. *Eur Heart J* 39: 1028–1037, 2018
- Kang Z, Li Z, Huang P, Luo J, Liu P, Wang Y, Xia T, Zhou Y: Remote ischemic preconditioning upregulates microRNA-21 to protect the kidney in children with congenital heart disease undergoing cardiopulmonary bypass. *Pediatr Nephrol* 33: 911–919, 2018
- Lomivorotov V, Kornilov I, Boboshko V, Shmyrev V, Bondarenko I, Soyrov I, Voytov A, Polyanskiy S, Strunin O, Bogachev-Prokophiev A, Landoni G, Nigro Neto C, Oliveira Nicolau G, Saurith Izquierdo L, Nogueira Nascimento V, Wen Z, Renjie H, Haibo Z, Bazylev V, Evdokimov M, Sulejmanov S, Chernogrivov A, Ponomarev D: Effect of intraoperative dexmethasone on major complications and mortality among infants undergoing cardiac surgery: The DECISION Randomized Clinical Trial. *JAMA* 323: 2485–2492, 2020
- Bronicki RA, Backer CL, Baden HP, Mavroudis C, Crawford SE, Green TP: Dexmethasone reduces the inflammatory response to cardiopulmonary bypass in children. *Ann Thorac Surg* 69: 1490–1495, 2000
- Jo YY, Kim JY, Lee JY, Choi CH, Chang YJ, Kwak HJ: The effect of intraoperative dexmedetomidine on acute kidney injury after pediatric congenital heart surgery: A prospective randomized trial. *Medicine (Baltimore)* 96: e7480, 2017
- Ricci Z, Stazi GV, Di Chiara L, Morelli S, Vitale V, Giorni C, Ronco C, Picardo S: Fenoldopam in newborn patients undergoing cardiopulmonary bypass: Controlled clinical trial. *Interact Cardiovasc Thorac Surg* 7: 1049–1053, 2008
- Ricci Z, Luciano R, Favia I, Garisto C, Muraca M, Morelli S, Di Chiara L, Cogo P, Picardo S: High-dose fenoldopam reduces postoperative neutrophil gelatinase-associated lipocalin and

- cystatin C levels in pediatric cardiac surgery. *Crit Care* 15: R160, 2011
31. Akkucuk FG, Kanbak M, Ayhan B, Celebioglu B, Aypar U: The effect of HES (130/0.4) usage as the priming solution on renal function in children undergoing cardiac surgery. *Ren Fail* 35: 210–215, 2013
  32. Oh HW, Lee JH, Kim HC, Kim EH, Song IK, Kim HS, Kim JT: The effect of 6% hydroxyethyl starch (130/0.4) on acute kidney injury in paediatric cardiac surgery: A prospective, randomised trial. *Anaesthesia* 73: 205–215, 2018
  33. Robert SM, Borasino S, Dabal RJ, Cleveland DC, Hock KM, Alten JA: Postoperative hydrocortisone infusion reduces the prevalence of low cardiac output syndrome after neonatal cardiopulmonary bypass. *Pediatr Crit Care Med* 16: 629–636, 2015
  34. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. Available at: <https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf>. Accessed June 21, 2021
  35. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative Workgroup: 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* 8: R204–R212, 2004
  36. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL: Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 71: 1028–1035, 2007
  37. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 11: R31, 2007
  38. Bellos I, Iliopoulos DC, Perrea DN: Pharmacological interventions for the prevention of acute kidney injury after pediatric cardiac surgery: A network meta-analysis. *Clin Exp Nephrol* 23: 782–791, 2019
  39. Springate JE, Christensen SL, Feld LG: Serum creatinine level and renal function in children. *Am J Dis Child* 146: 1232–1235, 1992
  40. Lex DJ, Tóth R, Cserép Z, Alexander SI, Breuer T, Sári E, Szatmári A, Székely E, Gál J, Székely A: A comparison of the systems for the identification of postoperative acute kidney injury in pediatric cardiac patients. *Ann Thorac Surg* 97: 202–210, 2014
  41. Hodgson LE, Selby N, Huang TM, Forni LG: The role of risk prediction models in prevention and management of AKI. *Semin Nephrol* 39: 421–430, 2019
  42. Hosseini MM, Zargoush M, Alemi F, Kheirbek RE: Leveraging machine learning and big data for optimizing medication prescriptions in complex diseases: A case study in diabetes management. *J Big Data* 7: 26, 2020
  43. Katzman JL, Shaham U, Cloninger A, Bates J, Jiang T, Kluger Y: DeepSurv: Personalized treatment recommender system using a Cox proportional hazards deep neural network. *BMC Med Res Methodol* 18: 24, 2018
  44. Balasubramanian G, Al-Aly Z, Moiz A, Rauchman M, Zhang Z, Gopalakrishnan R, Balasubramanian S, El-Achkar TM: Early nephrologist involvement in hospital-acquired acute kidney injury: A pilot study. *Am J Kidney Dis* 57: 228–234, 2011
  45. Rank N, Pfahringer B, Kempfert J, Stamm C, Kühne T, Schoenrath F, Falk V, Eickhoff C, Meyer A: Deep-learning-based real-time prediction of acute kidney injury outperforms human predictive performance. *NPJ Digit Med* 3: 1–12, 2020
  46. Shi S, Fan J, Shu Q: Early prediction of acute kidney injury in neonates with cardiac surgery. *World J Pediatr Surg* 3: e000107, 2020
  47. Desanti De Oliveira B, Xu K, Shen TH, Callahan M, Kiryluk K, D'Agati VD, Tatonetti NP, Barasch J, Devarajan P: Molecular nephrology: Types of acute tubular injury. *Nat Rev Nephrol* 15: 599–612, 2019

**Received:** April 28, 2021 **Accepted:** July 30, 2021

Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).

See related editorial, “Prevention of Acute Kidney Injury after Cardiac Surgery: When Fixing Broken Hearts, Is Breaking Kidneys Avoidable?” on pages 1459–1461.

## AFFILIATIONS

<sup>1</sup>Helen B. Taussig Heart Center, The Johns Hopkins Hospital and School of Medicine, Baltimore, Maryland

<sup>2</sup>Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

<sup>3</sup>Division of Cardiovascular Surgery of Pronto Socorro Cardiológico de Pernambuco–PROCAPE, University of Pernambuco–UPE, Recife, Brazil

<sup>4</sup>Department of Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium

<sup>5</sup>Division of Woman and Child, Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

<sup>6</sup>Department of Development and Regeneration, KU Leuven, Leuven, Belgium

<sup>7</sup>Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

<sup>8</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom

<sup>9</sup>Congenital and Structural Cardiology, University Hospitals Leuven, Leuven, Belgium

<sup>10</sup>Pediatric Cardiology, University Hospitals Leuven, Leuven, Belgium

<sup>11</sup>Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium

<sup>12</sup>Department of Pediatric Nephrology, University Hospitals of Leuven, Leuven, Belgium

<sup>13</sup>PKD Research Group, GPURE, Department of Development and Regeneration, KU Leuven, Leuven, Belgium