Dexmedetomidine prevents acute kidney injury after adult cardiac surgery: a meta-analysis of randomized controlled trials

Yang Liu, Bo Sheng, Suozhu Wang, Feiping Lu, Jie Zhen and Wei Chen*

Abstract

Background: Dexmedetomidine has been shown to confer direct renoprotection by stabilizing the sympathetic system, exerting anti-inflammatory effects and attenuating ischemia/reperfusion (I/R) injury in preclinical studies. Results from clinical trials of dexmedetomidine on acute kidney injury (AKI) following adult cardiac surgery are controversial.

Methods: We searched EMBASE, PubMed, and Cochrane CENTRAL databases for randomized controlled trials (RCTs) comparing the renal effect of dexmedetomidine versus placebo or other anesthetic drugs in adult patients undergoing cardiac surgery. The primary outcome was the incidence of AKI. The secondary outcomes were mechanical ventilation (MV) duration, intensive care unit (ICU) stay and hospital length of stay (LOS), and postoperative mortality (in-hospital or within 30 days).

Results: Ten trials with a total of 1575 study patients were selected. Compared with controls, dexmedetomidine significantly reduced the incidence of postoperative AKI (68/788 vs 97/787; odds ratio (OR), 0.65; 95% confidence interval (CI), 0.45–0.92; \( P = 0.02 \); \( I^2 = 0.0\% \)), and there was no difference between groups in postoperative mortality (4/487 vs 11/483; OR, 0.43; 95% CI, 0.14–1.28; \( P = 0.13 \); \( I^2 = 0.0\% \)), MV duration (in days; \( n = 1229 \); weighted mean difference (WMD), −0.22; 95% CI, −2.04 to 1.70; \( P = 0.81 \)), ICU stay (in days; \( n = 1363 \); WMD, −0.85; 95% CI, −2.14 to 0.45; \( P = 0.20 \)), and hospital LOS (in days; \( n = 878 \); WMD, −0.24; 95% CI, −0.71 to 0.23; \( P = 0.32 \)).

Conclusions: Perioperative administration of dexmedetomidine in adult patients undergoing cardiac surgery may reduce the incidence of postoperative AKI. Future trials are needed to determine the dose and timing of dexmedetomidine in improving outcomes, especially in patients with decreased baseline kidney function.

Keywords: Dexmedetomidine, Acute kidney injury, Cardiac surgery, Meta-analysis

Background

Acute kidney injury (AKI) following cardiac surgery is a widely recognized complication in association with high mortality risk [1, 2]. AKI is tightly interrelated with hemodynamic status, inflammatory and nephrotoxic components [3]. Both hemodynamic instability and sympathetic activity during surgery are harmful for renal function [4]. Almost half of these patients need mechanical ventilation (MV) support and are related with prolonged intensive care unit (ICU) stay [5, 6]. Moreover, along with the increasing high-risk population including advanced age, diabetes mellitus, severe cardiac failure, especially in association with cardiopulmonary bypass, AKI after cardiac surgery has become an interesting and challenge issue in clinical practice [7]. As yet, there is no definite strategy for preventing AKI after cardiac surgery [8].

Dexmedetomidine, a highly selective \( \alpha_2 \) adrenergic receptor agonist, induces sedation, analgesia, hemodynamic stabilization, anti-inflammation, as well as diuresis [9], and has theoretical advantage for reducing renal injury in animal studies [10, 11]. Several single-center randomized controlled trials (RCTs) with relatively small sample size have addressed this question and the results are controversial [12–14]. Whether perioperative dexmedetomidine could reduce the risk for AKI in adult patients undergoing cardiac surgery remains unclear. In addition, there has been no systematic review that comprehensively focuses on the potential renal effect of dexmedetomidine in adult cardiac surgery. Therefore, we...
conducted a meta-analysis to evaluate the effect of peri-operative dexmedetomidine (compared to placebo or other drugs) on the risk for AKI and mortality.

**Methods**

**Search strategy and study criteria**

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [15] and approved by the Institutional Review Board in Beijing Shijitan Hospital, Capital Medical University. We did a systematic search in PubMed (1999 to March 2017), EMBASE (1999 to March 2017), and Cochrane Library (1999 to March 2017) using the keywords “dexmedetomidine,” “cardiac surgery,” “heart surgery,” “kidney,” and “renal.” English-published RCTs concerning adult patients were included. Exclusion criteria were as follows: emergency surgery, or studies without reporting AKI incidence.

**Literature review and data extraction**

The literature review and data extraction were independently completed by 2 investigators (BS and SZW). In case of duplicate records pertaining to a single study, we considered the PubMed database to take precedence. Disagreements were handled by discussion for consensus. Quality assessment was completed using the Cochrane risk of bias tool and Jadad scale. Data extraction included patient characteristics (age, proportion of males, proportion with diabetes, proportion with history of myocardial infarction, proportion with hypertension, baseline left ventricular ejection fraction, baseline creatinine levels, β-blocker use, and statin use), as well as dexmedetomidine dosage.

**Postoperative outcomes**

The primary end point was incidence of AKI (defined as RIFLE, AKIN, KDIGO within 7 days after cardiac surgery). Secondary outcomes included all-cause mortality (in-hospital or within 30 days), mechanical ventilation (MV) duration, ICU length of stay, and hospital length of stay (LOS).

**Statistical analysis**

For dichotomous outcomes (reported with incidence), we calculated the odds ratio (OR) with 95% confidence interval (CI). For continuous outcomes (reported as mean ± standard deviation, median and interquartile range, or median and range), we calculated mean differences for each study according to the statistical method of Hozo et al. [16] and used weight (the inverse variance of the estimate) to pool the estimate (weighted mean difference, WMD) with 95% CI. We used the random-effect model to pool all the data for the potential clinical inconsistency. Heterogeneity was assessed with the inconsistency statistic (I²). Publication bias was assessed by Begg’s test and Egger’s test. \( P < 0.05 \) (2 sided) was considered to be statistically significant for hypothesis testing.

![Flow diagram of studies included into meta-analysis](Fig. 1)
| Study               | Country | Surgery            | Dexmedetomidine Dose | Control  | Time and Duration of intervention or Control | No. of Patients | Clinical End Point | AKI Definition                          | Follow-Up          |
|---------------------|---------|--------------------|----------------------|----------|---------------------------------------------|----------------|-------------------|----------------------------------------|--------------------|
| Balkanay 2015 I [17]| Turkey  | On-PUMP CABG       | 0.04 μg/kg/h - 0.05 μg/kg/h | placebo  | Start preCPB and last for 24 h             | 31 vs 28        | AKI, MV duration; ICU stay; RIFE         | In hospital          |
| Balkanay 2015 II [17]| Turkey  | On-PUMP CABG       | 0.04 μg/kg/h - 0.05 μg/kg/h | placebo  | Start preCPB and last for 24 h             | 29 vs 28        | AKI, MV duration; ICU stay; RIFE         | In hospital          |
| Cho 2015 [12]       | Korea   | Combined           | 0.04 μg/kg/h          | placebo  | Start immediately after anesthetic induction and last for 24 h | 100 vs 100      | AKI, Mortality; ICU stay; AKIN          | In hospital          |
| Djaiani 2016 [18]   | Canada  | Combined           | 0.4 μg/kg 0.2 - 0.7 μg/kg/h | propofol | Start postsurgery and last for 24 h        | 91 vs 92        | AKI, MV duration; ICU stay; RIFE         | In hospital          |
| Leino 2011 [19]     | Finland | On-PUMP CABG       | 0.6 ng/ml             | placebo  | Start immediately after anesthetic induction and last for 4 h arrive ICU | 35 vs 31        | AKI, MV duration; RIFE                   | In hospital          |
| Li 2017 [14]        | China   | Combined           | 0.1 μg/kg/h - 0.6 μg/kg/h | placebo  | Start preCPB and last until the end of MV   | 142 vs 143      | AKI, MV duration; ICU stay; KDIGO        | 30 days after surgery|
| Liu 2016 [20]       | China   | Combined           | <1.5 μg/kg/h          | propofol | Start after surgery and last until the end of MV | 44 vs 44        | AKI, MV duration; ICU stay; RIFE         | In hospital          |
| Park 2014 [13]      | Korea   | Combined           | 0.5 μg/kg 0.2 - 0.8 μg/kg/h | remifentanil | Start after surgery and last until extubation | 67 vs 75        | AKI, MV duration; ICU stay; hospital stay| In hospital          |
| Shehabi 2009 [21]   | Australia| Combined           | 0.1 - 0.7 μg/kg/ml    | morphine | Start within 1 h of admission to OCU until the removal of chest drains | 152 vs 147      | AKI, Mortality; ICU stay; Hospital stay; Cr > 100% above baseline or new dialysis need | In hospital          |
| Ammar 2016 [22]     | Egypt   | Combined           | 1 μg/kg over 15 min, followed by 0.5 μg/kg/h | placebo  | Start preCPB and last until 6 h after surgery | 25 vs 25        | AKI, Mortality; ICU stay; hospital stay; Cr > 115 μmol/L | In hospital          |
| Soliman 2016 [23]   | Egypt   | Aortic vascular surgery | 1 μg/kg 0.3 μg/kg/h | placebo  | Start 15 min before induction maintained to the end of surgery | 75 vs 75        | AKI, Mortality; Cr > 115 μmol/L         | In hospital          |

Abbreviations: AKI Acute kidney injury, CABG Coronary artery bypass graft, CPB Cardiopulmonary bypass, ICU Intensive care unit, CICU Cardiac intensive care unit, MV Mechanical ventilation, NA Not available, Cr Creatinine, RIFE Risk–Injury–Failure–Loss–End-stage renal disease, AKIN Acute Kidney Injury Network, KDIGO Kidney Disease Improving Global Outcomes
Table 2: Summarized patient characteristic of the included randomized trials

| Study            | Age    | Male (%) | DM (%) | HP (%) | PreMI (%) | LVEF (%) | CPB duration (min) | Anesthetics | Baseline Serum Creatinine | β-blocker (%) | Statins (%) |
|------------------|--------|----------|--------|--------|-----------|----------|--------------------|-------------|---------------------------|---------------|-------------|
| Balkanay 2015 I [17] | NA    | NA       | NA     | NA     | NA        | NA       | NA                 | NA          | NA                        | NA            | NA          |
| Balkanay 2015 II [17] | NA    | NA       | NA     | NA     | NA        | NA       | NA                 | NA          | NA                        | NA            | NA          |
| Cho 2015 [12]     | 63     | 48       | 19.5   | 45.5   | NA        | 61.5     | 131                | Sevoflurane  | NA                        | 33            | NA          |
| Djaiani 2016 [18] | 72.55  | 75.4     | 21.9   | 75.4   | 16.4      | NA       | 98.99              | Isoflurane   | 53                        | 68.85         | 72.55       |
| Leino 2011 [19]   | 60.86  | 89.4     | NA     | NA     | NA        | NA       | NA                 | Isoflurane   | NA                        | NA            | 60.86       |
| Li 2017 [14]      | 67.18  | 69.1     | 32.3   | 63.2   | 98        | NA       | 102.99             | Sevoflurane  | 69.73                     | 48.42         | 67.18       |
| Liu 2016 [20]     | 54.75  | 39.8     | 12.5   | 29.5   | NA        | 65       | 71.15              | Sevoflurane  | NA                        | NA            | 54.75       |
| Park 2014 [13]    | 53.81  | 55.6     | 9.15   | 27.5   | NA        | 61.87    | 166.75             | Sevoflurane  | NA                        | NA            | 53.81       |
| Shehabi 2009 [21] | 71.25  | 75.3     | 29.5   | 80.1   | 36.6      | NA       | 98.98              | Sevoflurane  | NA                        | NA            | 71.25       |
| Ammar 2016 [22]   | 57.25  | 76       | 68     | 82     | NA        | 66.2     | Isoflurane         | 94          | 56                        | 57.25         |             |
| Soliman 2016 [23] | 58.1   | 50       | 30.7   | 48.7   | 8.6       | 529      | NA                 | NA          | 36.67                     | NA            | 58.1        |

Abbreviations: DM Diabetes mellitus, HP Hypertension, PreMI Previous myocardial infarction, LVEF Left ventricular ejection fraction, CPB Cardiopulmonary bypass, NA Not available

Values are given as means unless otherwise specified.
| Study                  | Random sequence generation | Allocation Concealment | Blinding of participants and personnel | Blinding of outcome assessment | Attrition bias | Selective reporting | Jadad scale |
|-----------------------|-----------------------------|-------------------------|----------------------------------------|-------------------------------|----------------|---------------------|-------------|
| Balkanay 2015 I [17]  | Yes                         | Unclear                 | Yes                                    | Yes                           | Unclear        | Unclear             | 4           |
| Balkanay 2015 II [17] | Yes                         | Unclear                 | Yes                                    | Yes                           | Unclear        | Unclear             | 4           |
| Cho 2015 [12]         | Yes                         | Sealed envelopes        | Blinding of personnel                  | Yes                           | Unclear        | Unclear             | 4           |
| Djaiani G 2016 [18]   | Yes                         | Sealed envelopes        | Blinding of personnel                  | No                            | Yes            | Unclear             | 3           |
| Leino 2011 [19]       | Yes                         | Sealed envelopes        | No                                     | Yes                           | Yes            | Unclear             | 5           |
| Li 2017 [14]          | Yes                         | Sealed envelopes        | Yes                                    | No                            | Yes            | Unclear             | 5           |
| Liu 2016 [20]         | Yes                         | Unclear                 | Unclear                                | Unclear                       | Unclear        | Unclear             | 1           |
| Park 2014 [13]        | Yes                         | Unclear                 | Unclear                                | Unclear                       | Unclear        | Unclear             | 1           |
| Shehabi 2009 [21]     | Yes                         | Unclear                 | Yes                                    | No                            | Yes            | Unclear             | 5           |
| Ammar 2016 [22]       | Yes                         | Unclear                 | Yes                                    | Yes                           | Unclear        | Unclear             | 4           |
| Soliman 2016 [23]     | Yes                         | Unclear                 | Yes                                    | No                            | Unclear        | Unclear             | 4           |
testing. All statistical analyses were performed in REV-
MAN (version 5.0; Cochrane Collaboration, Oxford, UK)
and Stata (version 9.0; StataCorp LP).

Results

Study characteristics

Figure 1 shows the PRISMA flow chart for the RCTs
screening and selection process for inclusion in this
study. Ten trials enrolling 1575 study subjects ultim-
ately met our criteria (Fig. 1). Two studies were for
coronary artery bypass grafting (CABG) [17, 19],
seven were for combined cardiac surgery [12–
14, 18, 20–22] and 1 was for aortic vascular surgery [23].
Six trials used placebo as control [12, 14, 17, 19, 22,
23], whereas two used propofol [18, 20], one used
morphine [21] or remifentanil [13]. Dexmedetomi-
dine was continuously infused at a rate of 0.2 to
0.8 μg/kg/h for 24 h after a loading dose (0.4–1μg/kg)
in 4 studies [13, 18, 22, 23] or infused at a rate of
0.04 to 1.5μg/kg/h without a loading dose in 6 [12,
14, 17, 19–21].

For postoperative outcomes, AKI incidence was
reported in 9 trials [12–14, 17, 19–23], need for dialysis in
1 [18], mortality in 6 [12, 18, 20–23], mechanical ventila-
tion duration in 8 [13, 14, 17–22], ICU stay in 8 [12–14,
17, 18, 20–22], and hospital stay in 6 [13, 17, 18, 20–22].

Study design and patient characteristics were summa-
rized in Tables 1 and 2. The quality assessment was
listed in Table 3.

| Study or Subgroup | Dex | Control | Odd Ratio | M.H. | Random | 95% CI |
|-------------------|-----|---------|-----------|------|--------|--------|
| Ammar 2014        | 0   | 25      | 0         | 25   | Not estimable |
| Balkanay 2015     | 1   | 29      | 1         | 28   | 1.6%   | 0.96 [0.08, 16.21] |
| Balkanay 2015     | 1   | 31      | 1         | 28   | 1.6%   | 0.90 [0.05, 15.10] |
| Cho 2015          | 14  | 100     | 33        | 100  | 25.5%  | 0.33 [0.16, 0.67] |
| Dziaian 2016      | 0   | 91      | 2         | 92   | 1.4%   | 0.20 [0.01, 4.18] |
| Leino 2011        | 0   | 35      | 0         | 31   | Not estimable |
| Li 2017           | 37  | 142     | 44        | 143  | 47.2%  | 0.76 [0.47, 1.33] |
| Liu 2016          | 5   | 44      | 3         | 44   | 5.6%   | 1.75 [0.39, 7.83] |
| Park 2014         | 2   | 67      | 1         | 75   | 2.1%   | 2.28 [0.20, 25.69] |
| Shehab 2009       | 4   | 149     | 6         | 146  | 7.6%   | 0.64 [0.18, 2.33] |
| Soliman 2015      | 4   | 75      | 6         | 75   | 7.4%   | 0.65 [0.18, 2.40] |
| Total (95% CI)    | 788 | 787     | 100.0%    | 0.65 [0.45, 0.92] |
| Total events      | 68  | 97      | 100.0%    | 0.65 [0.45, 0.92] |

Fig. 2 Dexmedetomidine (Dex) reduced the incidence of acute kidney injury

Effect of Dexmedetomidine on incidence of AKI, and
mortality

The outcome of AKI was reported in 1575 study par-
ticipants, and the overall incidence was 10.48% (dex-
medetomidine group, 68/788; control group, 97/7787).
The postoperative incidence of AKI was significantly
reduced by dexmedetomidine (10 studies with 11 compari-
sion; OR, 0.65; 95% CI, 0.45–0.92; P = 0.02; I² = 0.0%; Fig. 2). Different analysis method (Mantel-
Haenszel or Inverse Variance) or different summary
statistics (RR vs OR vs RD) was listed in Table 4. There
was no evidence of significant publication bias (Begg’s
test, P = 0.22; Egger’s test, P = 0.32; Fig. 3).

Subgroup analyses for the potential sources of hetero-
genocity were listed in Table 5. We divided study partici-
ants into 11 groups according to different characteristics
such as age(year, ≥60 versus <60), proportion of male
(≥60% versus <60%), proportion with diabetes (≥25% ver-
sus <25%), CPB duration(min, ≥100 versus <100), statin
use(≥60% versus <60%), loading dose (use or not), con-
tinuous infusion dosing (low versus high), controlled type
(placebo versus nonplacebo), administration timing (pre/
intraoperative versus postoperative), surgical type (CABG
only versus combined) surgery, JADAD score (≥3 versus
<3). Overall, no significant differences existed in the inci-
dence of AKI (Table 5).

Sensitivity analysis excluding each included study at
a time revealed that the Cho 2015 study was incon-
sistent with the direction and size of the overall AKI-
reducing effect of dexmedetomidine (P = 0.34),and the

Table 4 Different analysis method and summary statistics for the incidence of acute kidney injury

| Analysis method | OR  | 95%CI | I² | P   | RD  | 95%CI | I² | P   | RR  | 95%CI | I² | P   |
|-----------------|-----|-------|----|-----|-----|-------|----|-----|-----|-------|----|-----|
| Mantel-Haenszel | 0.65| 0.45,0.92 | 0% | 0.02| -0.02| -0.04,0.01| 46% | 0.28| 0.72| 0.54,0.95 | 0% | 0.02|
| Inverse Variance| 0.65| 0.45,0.92 | 0% | 0.02| -0.01| -0.04,0.01| 21% | 0.22| 0.72| 0.54,0.95 | 0% | 0.02|

Abbreviations: OR Odds ratio, RR Risk ratio, RD Risk difference, CI Confidence interval
other studies were consistent with the direction and size of the overall AKI-reducing effect of dexmedetomidine (P for all <0.04).

The outcome of mortality was reported in 970 study participants, and the overall incidence was 1.5% (dexmedetomidine group, 4/487; control group, 11/483). There were no statistically significant reduction for mortality owing to perioperative dexmedetomidine (6 studies; OR, 0.43; 95% CI, 0.14–1.28; P = 0.13; I² = 0.0%; Fig. 4).

**Effect of Dexmedetomidine on MV duration, ICU stay and hospital stay**

A trend toward reduction of postoperative MV duration (8 studies; WMD, −0.22; 95%CI, −2.04 to 1.70; P = 0.81; I² = 68%; Fig. 5), ICU stay (8 studies; WMD, −0.85; 95%CI, −2.14 to 0.45; P = 0.20; I² = 0%; Fig. 6) and hospital stay (6 studies; WMD, −0.24; 95%CI, −0.71 to 0.23; P = 0.32; I² = 55%; Fig. 7) by dexmedetomidine was observed, although there were not statistically significant.

**Discussion**

In this meta-analysis of 10 RCTs involving 1575 adult patients undergoing cardiac surgery, we found that perioperative dexmedetomidine use was associated with a decrease in postoperative AKI risk. However, postoperative parameters including MV duration, ICU stay and hospital LOS appeared to be no significant decrease as a result of the dexmedetomidine use. To the best of our knowledge, this is the first meta-analysis evaluating the safety and efficacy of dexmedetomidine for the prevention of cardiac surgery associated AKI.

AKI is a common complication with an estimated incidence about 7% to 45% in adult cardiac surgery [24]. Small increases in postoperative serum creatinine levels after cardiac surgery have been reported to be associated with increased morbidity and mortality even if the renal function has returned to normal at discharge [25]. For this reason, strategies to lower the incidence of postoperative AKI are of high interest to clinicians.

Dexmedetomidine is widely used for perioperative anesthesia/analgesia, and may have a more profound renal protection by stabilizing the sympathetic system, exerting anti-inflammatory effects and attenuating ischemia/reperfusion (I/R) injury [10, 26]. In this meta-analysis, positive renoprotective effects were shown in 3 studies [12, 17, 22] and only 1 [12] study showed the prevention for the AKI. However, there were also controversial or negative studies pertaining to the effect of dexmedetomidine. Our analysis combining all these positive and negative studies showed a reduced incidence of AKI in association with the dexmedetomidine use. In view of the definition for AKI using conventional tests such as the blood urea nitrogen, serum creatinine levels, urine output quantity and creatinine clearance rate, it may result in delay in the timely detection of kidney injury and can lead to false-negative results, and dexmedetomidine for the prevention of AKI may be more effective than the current results.

In the included trials, dexmedetomidine was used with a loading dose (0.4 μg/kg-1μg/kg) and continuous infusion (0.04–0.6 μg/kg/h). Balkanay enrolled adult patients undergoing CABG found a significant difference between high dose group (8 μg/kg) and low dose group (4 μg/kg) for the 24th postoperative hour in the mean values of neutrophil gelatinase-associated lipocalin (NGAL) [17], indicating that dexmedetomidine had marked effects on renoprotection in a dose-dependent fashion. Our subgroup analyses showed that dexmedetomidine infusion without loading dose at low
### Table 5 Subgroup analyses for the potential sources of heterogeneity

| Subgroup | Endpoint | No. of Comparisons | OR WMD | 95% CI | Z Value | P Value | I² | P Heterogeneity Value |
|----------|----------|--------------------|--------|-------|---------|---------|----|-----------------------|
| 1. Age(years) | AKI | 9 | 0.64 | 0.41–1.01 | 0.06 | 43.8% | 0.18 |
| ≥ 60 | 5 | 0.54 | 0.31–0.94 | 0.03 | 32% |
| < 60 | 4 | 1.12 | 0.45–2.79 | 0.81 | 0% |
| 2. Gender(Male%) | AKI | 9 | 0.64 | 0.41–1.01 | 0.06 | 0% | 0.91 |
| ≥ 60 | 4 | 0.70 | 0.28–1.74 | 0.45 | 47% |
| < 60 | 5 | 0.75 | 0.46–1.20 | 0.22 | 0.0% |
| 3. Previous DM (%) | AKI | 8 | 0.64 | 0.41–1.01 | 0.22 | 0% |
| ≥ 25 | 4 | 0.75 | 0.48–1.18 | 0.22 | 0% |
| < 25 | 4 | 0.68 | 0.21–2.14 | 0.51 | 49% |
| 4. CPB duration(minutes) | AKI | 7 | 0.65 | 0.38–1.14 | 0.13 | 0% | 0.59 |
| ≥ 100 | 3 | 0.61 | 0.27–1.36 | 0.22 | 60% |
| < 100 | 4 | 0.85 | 0.34–2.15 | 0.73 | 0% |
| 5. Statin (%) | AKI | 9 | 0.64 | 0.41–1.01 | 0.06 | 43.8% | 0.18 |
| ≥ 60 | 5 | 0.54 | 0.31–0.94 | 0.03 | 32% |
| < 60 | 4 | 1.12 | 0.45–2.79 | 0.81 | 0% |
| 6. Loading dose use | AKI | 10 | 0.65 | 0.45–0.92 | 0.02 | 0% | 0.86 |
| Yes | 4 | 0.72 | 0.24–2.10 | 0.54 | 0% |
| No | 6 | 0.64 | 0.40–1.02 | 0.06 | 16% |
| 7. Continuous infusion | AKI | 9 | 0.61 | 0.42–0.88 | 0.008 | 68.3% | 0.08 |
| ≥ 0.1 μg/kg/h | 6 | 0.76 | 0.49–1.18 | 0.22 | 0% |
| < 0.1 μg/kg/h | 3 | 0.37 | 0.19–0.72 | 0.003 | 0% |
| 8. Control drugs | AKI | 11 | 0.65 | 0.45–0.92 | 0.02 | 0% | 0.33 |
| Placebo | 7 | 0.60 | 0.40–0.89 | 0.01 | 2% |
| Others | 4 | 0.96 | 0.40–2.29 | 0.93 | 0% |
| 9. Dex administration | AKI | 11 | 0.65 | 0.45–0.92 | 0.02 | 0% | 0.21 |
| Pre/Intraoperation | 8 | 0.59 | 0.40–0.87 | 0.007 | 0% |
| Postoperation | 3 | 1.11 | 0.45–2.74 | 0.83 | 0% |
| 10. Surgical procedures | AKI | 11 | 0.65 | 0.45–0.92 | 0.02 | 0% | 0.87 |
| CABG or Aortic surgery | 4 | 0.72 | 0.24–2.16 | 0.56 | 0% |
| Combined | 7 | 0.65 | 0.38–1.14 | 0.13 | 33% |
| 11. JADAD score | AKI | 11 | 0.65 | 0.45–0.92 | 0.02 | 0% | 0.21 |
| ≥ 3 | 9 | 0.59 | 0.41–0.86 | 0.006 | 0% |
| < 3 | 2 | 1.88 | 0.53–6.73 | 0.33 | 0% |

**Abbreviations:** AKI: Acute kidney injury, OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus, CPB: Cardiopulmonary bypass, Dex: Dexmedetomidine, CABG: Coronary artery bypass graft.
continuous dose appeared to be safe and potentially efficacious by avoiding undesirable haemodynamic effects and was possibly more effective for renal-protection, although there was no significant difference ($P = 0.86$ and $P = 0.08$). To date, the optimal dose of dexmedetomidine to improve kidney function after cardiac surgery is unclear. The optimal dose of dexmedetomidine on postoperative renal events can’t be drew because of the lack of detailed patient data. Future large and well-designed randomized trails should explore the more appropriate dose of dexmedetomidine to maximize its renal protective effect with less side effects affecting prognosis.

The timing of dexmedetomidine administration in relation to cardiac surgery is emerging as an important consideration. In 6 of 10 included trials [12, 14, 17, 19, 22, 23], dexmedetomidine was used in a preemptive strategy, and early intervention of dexmedetomidine before the cardiopulmonary bypass seems to be critical for its organ-protective effect against I/R injury [27]. Dexmedetomidine pretreatment attenuated the I/R injury by reducing inflammatory response mediated by toll-like receptor4 expression [28, 29]. Our subgroup analyses indicated that dexmedetomidine was possibly more effective for renal-protection with pre/intraoperative administration compared with postoperative administration, but there was no significant difference ($P = 0.21$). Our findings do not provide a strong guidance on this question, and it merits further investigation. Future trials in this area would most likely be of greatest benefit.

Two recent expert consensus articles on postoperative AKI have been recently published, which discussed also new possible therapies/preventive measures [30, 31]. Our results was in keeping with one of the article conducted by M. Joannidis and colleagues, which showed dexmedetomidine was promising to reduce the rate of AKI, although no recommendation can be given on the basis of current data. Our subgroup analyses showed that dexmedetomidine was possibly effective for renal-protection compared with placebo but not against other treatments ($P = 0.33$). The advantages of dexmedetomidine compared with other anesthetics still call for further research.

Our analysis has several disadvantages. First, AKI in cardiac surgery is common and may have several different causes. It is difficult to establish a protective role for dexmedetomidine. We were unable to access...
individual patient data, so the influences of age, sex, and other confounding factors may be underestimated. Second, the definition of AKI was not uniform in the included trials. Third, sample size in each study is relatively low, so future large clinical studies were needed. Fourth, the exclusion of non-English studies may be inappropriate, however, the assessment of publication bias did not show statistical significance. Fifth, Bland [32] and Kwon & Reis [33] have argued that the statistical method of Hozo et al. may have limited their statistical ability to detect differences. When samples are not normally distributed. So the effect of dexmedetomidine may be overestimation, especially for negative findings. Last, perioperative dexmedetomidine might be of most benefit for certain patients who are at different stage of AKI, but most of the included study did not report the existed renal impairment before surgery.

Conclusion
In summary, available evidence from the present meta-analysis suggests that perioperative administration of dexmedetomidine in adult cardiac surgery might reduce the incidence of AKI. Future trials are needed to be much larger and ascertain the optimal dose and, more importantly, the time of the dose, especially in patients with decreased kidney function at baseline.

Abbreviations
AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; CI: Confidence interval; I/R: Ischemia/reperfusion; ICU: Intensive care unit; KDIGO: Kidney Disease Improving Global Outcomes; OR: Odds ratio; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; RCTs: Randomized controlled trials; RIFLE: Risk–Injury–Failure–Loss–End-stage renal disease; WMD: Weighted mean difference

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The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
Study design: YL; data acquisition: BS and SZW; data analysis/interpretation: YL, FPL and JZ; supervision or mentorship: WC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. YL and WC take responsibility that this study has been reported honestly, accurately, and transparently. All authors approved the final manuscript.

Ethics approval and consent to participate
This meta-analysis was approved by the Institutional Review Board in Shijitan Hospital, Capital Medical University, Beijing.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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