Meta-Analysis: Shouldn’t Prophylactic Corticosteroids be Administered During Cardiac Surgery with Cardiopulmonary Bypass?

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Background: Corticosteroids can effectively inhibit systemic inflammation induced by cardiopulmonary bypass. Recently clinical trials and meta-analyses and current guidelines for cardiac surgery do not support corticosteroids prophylaxis during cardiac surgery because of an increase in myocardial infarction and no benefit for patients. The aim of this study is to determine whether specific corticosteroids dose ranges might provide clinical benefits without increasing myocardial infarction.

Methods: The PubMed, Web of Science, Embase, Clinical Trials, and Cochrane databases were searched for randomized controlled trials (RCTs) published before August 1, 2021.

Results: 88 RCTs with 18,416 patients (17,067 adults and 1,349 children) were identified. Relative to placebo and high-dose corticosteroids, low-dose corticosteroids (≤20 mg/kg hydrocortisone) during adult cardiac surgery did not increase the risks of myocardial infarction (odds ratio [OR]: 0.96, 95% confidence interval [CI]: 0.43–2.17; \( p = 0.93 \)). However, low-dose corticosteroids were associated with lower risks of atrial fibrillation (OR: 0.58, 95% CI: 0.44–0.76; \( p < 0.0001 \)) and kidney injury (OR: 0.29, 95% CI: 0.09–0.96; \( p = 0.04 \)). Furthermore, low-dose corticosteroids significantly shortened the mechanical ventilation times (mean difference [MD]: −2.74 h, 95% CI: −4.14, −1.33; \( p = 0.0001 \)), intensive care unit (ICU) stay (MD: −1.48 days, 95% CI: −2.73, −0.22; \( p = 0.02 \)), and hospital stay (MD: −2.29 days, 95% CI: −4.51, −0.07; \( p = 0.04 \)).

Abbreviations: CPB, cardiopulmonary bypass; RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval; MD, mean difference; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; ECMO, extracorporeal membrane oxygenation; LOS, length of stay; CRP, C-reactive protein.
INTRODUCTION

Cardiopulmonary bypass (CPB) is used during most cardiac surgeries, although CPB often induces systemic inflammatory response syndrome (SIRS) (1). The development of SIRS involves activation of complement, platelets, neutrophils, monocytes, macrophages, and cascade reactions, which leads to increased endothelial permeability, blood vessel damage, and parenchymal cell damage (2–4). These events are associated with single and multiple organ dysfunction, myocardial injury and infarction, respiratory failure, and ultimately death (5–7).

Corticosteroids are inexpensive drugs that can effectively inhibit inflammation, limit systemic capillary leak syndrome, and reduce organ damage, which provides a theoretical basis for their use during CPB (8–10). However, corticosteroids can cause side effects, including hyperglycemia, which is associated with immunosuppression and poor wound healing (11, 12). In addition, high-dose corticosteroids are associated with an increased risk of gastrointestinal bleeding and myocardial infarction (11, 12). Thus, the benefits of corticosteroids treatment are controversial for patients undergoing cardiac surgery with CPB (13–15).

Three meta-analyses of small RCTs revealed that prophylactic corticosteroids could reduce the risk of atrial fibrillation after adult cardiac surgery, also caused some side effects (5–7). Two large multi-center RCTs subsequently revealed that corticosteroids therapy provided no benefits and increased the risk of myocardial infarction in adult patients (13, 14). Thus, the adult cardiac surgery guidelines do not recommend routine prophylactic use of corticosteroids during cardiac surgery (16), although there are no specific guidelines regarding corticosteroids use during pediatric cardiac surgery. We hypothesized that the specific corticosteroids dose range might influence the risks and benefits during cardiac surgery with CPB. Therefore, this systematic review and meta-analysis aimed to evaluate the dose-dependent benefits and risks of prophylactic corticosteroids for adults and children undergoing cardiac surgery with CPB.

METHODS

Ethical Statement

This study was a meta-analysis of the results of published randomized controlled trials, and ethical approval and informed consent of patients were not required.

Search Strategy and Selection Criteria

Two authors (XJY and MYT) searched the PubMed, Web of Science, Embase, ClinicalTrials, and Cochrane Central Register of Controlled Trials databases for relevant RCTs that were published in any language before August 1, 2021. The reference lists of relevant articles were also manually checked. The study protocol followed the PRISMA-P guidelines (https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42020193658). The search terms were: ("corticosteroids" OR "dexamethasone" OR "prednisolone" OR "prednisone" OR "methylprednisolone" OR "hydrocortisone") AND ("cardiopulmonary bypass" OR "cardiac surgery") AND ("randomized controlled trials") (Supplementary Table S1).

The meta-analysis only included RCTs that compared corticosteroids with a placebo used before or at the beginning of CPB. Patients undergoing surgery with CPB for heart and/or valvar diseases were included. And the studies were excluded if they used different concomitant medications or evaluated corticosteroids during off-pump heart surgery.

Two authors (TCC and XHZ) independently determined whether the identified articles fulfilled the inclusion criteria. The two authors also independently used pre-designed data extraction forms to record information regarding trial characteristics, clinical outcomes, randomization methods, application of blinding, allocation concealment, inclusion criteria, and exclusion criteria. There were no instances of disagreement regarding the extracted data.

Data Analysis

Study characteristics included first author, publication date, country, study size, study design, randomization, blinding, follow-up duration, patient withdrawals, and study duration. Patient characteristics included age, sex, surgery type, blood pressure, history of diabetes, history of smoking, renal status, and fulfillment of the inclusion criteria. The interventions included the corticosteroids type, dose, timing, and route of administration during CPB.

The primary outcomes included myocardial infarction, insulin use, mortality, new atrial fibrillation, lengths of ICU and hospital stays, acute kidney injury, mechanical ventilation time. The secondary outcomes included postoperative bleeding, re-intubation, duration of CPB and procedure, pulmonary complications (pulmonary edema), postoperative infection, neurological complications (stroke), delirium, gastrointestinal bleeding, extracorporeal membrane oxygenation (ECMO) use, vasoactive medication use, re-thoracotomy, inotropic score, blood transfusion, and and blood concentrations of glucose, lactate, C-reactive protein (CRP), tumor necrosis factor-α(TNF-α), interleukin (IL)-6, IL-8, and IL-10 at 24 h after CPB.

The Cochrane Handbook for Systematic Reviews of Interventions and Jadad score were used to assess the risk of bias

Conclusion: Low-dose corticosteroids prophylaxis during cardiac surgery provided significant benefits for adult patients, without increasing the risks of myocardial infarction and other complications.

Keywords: corticosteroids prophylaxis, cardiac surgery, cardiopulmonary bypass, myocardial infarction, randomized controlled trial
RESULTS

This study identified 88 RCTs from 27 countries that included 18,416 patients (Figure 1). The trials considered adult patients (73 trials and 17,067 patients) or pediatric patients (15 trials and 1,349 patients). The corticosteroids treatments included dexamethasone, betamethasone, methylprednisolone, hydrocortisone, and prednisolone, with a broad range of total doses (1–900 mg/kg hydrocortisone equivalent). Table 1 shows the characteristics of the included studies, Table 2 shows the GRADE summary of the findings and Table 3 summarizes the impact of corticosteroids on adults and pediatric.

During adult cardiac surgery with CPB, corticosteroids prophylaxis was associated with increased risks of myocardial infarction (OR: 1.19, 95% CI: 1.05–1.35; p = 0.008, I² = 0%) (Figure 2) and insulin infusion (OR: 1.91, 95% CI: 1.18–3.11; p = 0.009, I² = 46%) (Supplementary Figure S1), with no obvious improvement in mortality (OR: 0.86, 95% CI: 0.71–1.03; p = 0.10, I² = 0%) (Figure 3). However, corticosteroids prophylaxis reduced the risk of postoperative atrial fibrillation (OR: 0.68, 95% CI: 0.57–0.82; p < 0.0001, I² = 48%) (Figure 4), shortened the ICU stay (MD: −0.27 days. 95% CI: −0.34, −0.19 days; p < 0.001, I² = 93%), and shortened the hospital stay (MD: −0.66 days, 95% CI: −1.03, −0.30 days; p = 0.0003, I² = 95%) (Supplementary Figures S2, S3). In addition, corticosteroids prophylaxis was associated with reduced postoperative bleeding and a reduced risk of re-intubation (Table 3 and Supplementary Figures S4, S5).

Corticosteroids prophylaxis also reduced the blood concentrations of some inflammatory markers in adult patients, which included IL-6, TNF-α, and IL-8 (Table 3 and Supplementary Figures S6–S8). Among children, corticosteroids prophylaxis was associated with a significantly lower peak CRP concentration, a significantly lower IL-6 concentration, and a significantly higher IL-10 concentration (Table 3 and Supplementary Figures S9–S11).

Relative to the placebo group, corticosteroids prophylaxis was not associated with significant improvements in terms of kidney injury, pulmonary complications, stroke, gastrointestinal bleeding, postoperative infection or mechanical ventilation time (Table 3 and Figure 5, Supplementary Figures S12–S17).

Subgroup analysis that the benefits were largely attributable to the prophylactic use of low-dose corticosteroids (≤20 mg/kg hydrocortisone), and these benefits were not observed at higher corticosteroids doses (Table 2). Low-dose corticosteroids prophylaxis was associated with a significantly reduced mechanical ventilation time (MD: −2.74 h, 95% CI: −4.14, −1.33 h; p = 0.0001, I² = 92%) (Figure 5), without increased risks of myocardial infarction (OR: 0.96, 95% CI: 0.43–2.17; p = 0.93, I² = 0%) (Figure 2) or insulin infusion (OR: 1.72, 95% CI: 0.83–3.55; p = 0.15, I² = 36%) (Supplementary Figure S7). Pooled analysis with meta-regression revealed that corticosteroids dose was significantly related to the variation in the mechanical ventilation time (exp: 1.004, 95% CI: 1.002–1.006; p < 0.0001), but not the variation in the other clinical outcomes (Supplementary Figures S18–S26). Funnel plots failed to reveal evidence of publication bias regarding mortality, myocardial infarction, pulmonary complications, kidney injury, postoperative infection, and neurological complications (stroke) (Supplementary Figures S27–S32). However, the funnel plots suggested that there might be some publication bias regarding new atrial fibrillation, mechanical ventilation time, and hyperglycemia requiring insulin infusion (Supplementary Figures S33–S35). Thus, we used the trim and fill method to adjust the analysis, which did not significantly alter the findings.

During pediatric cardiac surgery with CPB, corticosteroids prophylaxis was associated with a decreased CPB time (MD: −11.54 min, 95% CI: −14.32, −8.75 min; p < 0.001, I² = 5%) and an increased insulin infusion (OR: 3.68, 95% CI: 1.53–8.84; p = 0.004, I² = 48%), but did not significantly influence mortality, kidney injury, ECMO use, postoperative infection, mechanical ventilation time, and ICU length of stay [LOS] (Tables 2, 3 and Supplementary Figures S36–S43). Relative to placebo and higher dose corticosteroids (>50 mg/kg hydrocortisone), corticosteroids prophylaxis (≤50 mg/kg hydrocortisone) significantly reduced the risk of kidney injury (OR: 0.29, 95% CI: 0.09–0.96; p = 0.04, I² = 49%) (Table 2 and Supplementary Figure S39). Meta-regression revealed that corticosteroids dose was not related to the variations in mortality (exp: 0.998, 95% CI: 0.981–1.015; p = 0.734) or the duration of CPB (exp: 1.000, 95% CI: 0.993–1.008; p = 0.89) (Supplementary Figures S44, S45). The funnel plots failed to reveal evidence of publication bias regarding mechanical ventilation time and CPB duration (Supplementary Figures S50–S51). Thus, we used the trim and fill method to adjust the analysis, which did not significantly alter the findings.

DISCUSSION

This meta-analysis revealed that corticosteroids prophylaxis during cardiac surgery with CPB was associated with significantly decreased blood inflammatory factor concentrations of CRP, TNF-α, IL-6, and IL-8. During adult cardiac surgery, corticosteroids prophylaxis reduced the risks of postoperative atrial fibrillation and re-intubation, shortened
the ICU and hospital LOSs, and reduced postoperative bleeding, although it was associated with increased risks of myocardial infarction and hyperglycemia requiring insulin infusion. Interestingly, the benefits among adult patients were largely attributable to low-dose corticosteroids use (≤20 mg/kg hydrocortisone), as the benefits were not observed among patients who received higher corticosteroids doses. In addition, low-dose corticosteroids significantly reduced the mechanical ventilation time without increasing the risks of myocardial infarction and insulin infusion, while high-dose corticosteroids were associated with increased risks of myocardial infarction and prolonged mechanical ventilation. During pediatric cardiac surgery, corticosteroids prophylaxis was associated with a shortened CPB time, an increased risk of insulin infusion, and no substantial changes in terms of mortality, ECMO use, postoperative infection, mechanical ventilation time, and ICU LOS. Moreover, corticosteroids prophylaxis (≤50 mg/kg hydrocortisone) significantly reduced the risk of kidney injury in pediatric patients.

The SIRS plays a vital role in the development of complications after cardiac surgery with CPB (1). Corticosteroids can effectively inhibit SIRS and reduce inflammatory factor concentrations, which provides a theoretical basis for prophylactic administration during cardiac surgery with CPB (2-10). However, several RCTs have indicated that corticosteroids prophylaxis did not provide significant benefits to patients undergoing cardiac surgery with CPB, and was instead associated with an increased risk of myocardial infarction and prolonged mechanical ventilation (10, 13, 14, 19). Thus, the adult cardiac surgery guidelines, as well as routine practice for adult and pediatric cardiac surgery with CPB, involve limited or no prophylactic corticosteroids.
| Country | Population 0000 size (n) | Patient population | Age group | Study design | Blinding | Follow-up | Steroid | Hydrocortisone equivalent dose (mg/kg) | Time of administration | Quality* |
|---------|-------------------------|--------------------|-----------|--------------|----------|-----------|---------|---------------------------------------|------------------------|---------|
| Abbaszadeh et al. (2012) (24) Iran 185 CABG Adults RCT Y 3 days Dexamethasone 4.6 Post induction and surgery High (7) |
| Abd El-Hakeem et al. (2003a) (25) Egypt 20 Valve Adults RCT Y ICU stay Dexamethasone 38 Pre CPB High (7) |
| Abd El-Hakeem et al. (2003b) (25) Egypt 20 Valve Adults RCT Y ICU stay Dexamethasone 38 Pre CPB High (7) |
| Al-Shawabkeh et al. (2016) (26) Jordan 340 CABG or valve Adults RCT Y 96 h Methylprednisolone and hydrocortisone 84 Pre CPB and last for 3 days High (7) |
| Amanullah et al. (2016) (27) Pakistan 129 Cardiac surgery Children RCT Y Hospital stay Dexamethasone 80 Pre CPB and post surgery High (7) |
| Andersen et al. (1989) (28) Denmark 16 CABG Adults RCT N 7 days Methylprednisolone 150 Pre CPB Low (1) |
| Ando et al. (2005) (29) Japan 20 Cardiac surgery Children RCT Y Hospital stay Hydrocortisone 17.71 Post CPB High (6) |
| Bingol et al. (2005) (30) Turkey 40 CABG Adults RCT Y 3 months Prednisolone 11 Pre induction and post surgery High (6) |
| Boscoe et al. (1983) (31) UK 34 CABG or valve Adults or complex RCT Unclear 24 h Methylprednisolone 300 Pre CPB Low (3) |
| Bourbon et al. (2004) (32) France 36 CABG Adults RCT N 24 h Methylprednisolone 25/50 Pre CPB Low (2) |
| Brettner et al. (2019) (33) Germany 30 Cardiac surgery Adults RCT Y 28 days Hydrocortisone 1 Pre surgery High (4) |
| Bronicki et al. (2000) (34) US 29 Cardiac surgery Children RCT Y Hospital stay Dexamethasone 26.67 Pre CPB High (6) |
| Butler et al. (1996) (35) UK 18 Cardiac surgery Children RCT Y Hospital stay Methylprednisolone 50 During initiation of CPB High (6) |
| Cavarocchi et al. (1986) (36) US 61 CABG or valve Adults or complex RCT N 24 h Methylprednisolone 150 Pre CPB Low (2) |
| Celik et al. (2004) (37) Turkey 60 CABG Adults RCT Y Hospital stay Methylprednisolone 900 Pre surgery High (4) |
| Chaney et al. (1998/1999) (38, 39) US 60 CABG Adults RCT Y Hospital stay Methylprednisolone 300 During sternotomy and pre CPB High (4) |
| Chaney et al. (2001) (40) US 90 CABG Adults RCT Y Hospital stay Methylprednisolone 300/150 During sternotomy and initiation of CPB High (4) |
| Cecchia et al. (2003) (41) US 28 Cardiac surgery Children RCT Y Hospital stay Dexamethasone 26.67 Pre CPB High (6) |
| Coedt et al. (1977) (42) US 150 CABG Adults RCT Unclear 5 days Methylprednisolone 143 Pre CPB Low (3) |
| Coetzee et al. (1996) (43) South Africa 295 Cardiac surgery Adults RCT Unclear 30 days Methylprednisolone 150 Pre CPB High (5) |
| Danielson et al. (2018) (44) Sweden 30 CABG or valve Adults RCT Y Hospital stay Methylprednisolone 75 Post induction High (5) |
| Demir et al. (2009) (45) Turkey 30 CABG Adults RCT Unclear Hospital stay Methylprednisolone 143 Pre CPB Low (3) |
| Demir et al. (2015) (46) Turkey 40 CABG Adults RCT Y Unclear Methylprednisolone 71 Pre CPB Low (3) |

(continued)
| Country            | Population size (n) | Patient population | Age group | Study design | Blinding | Follow-up | Steroid | Hydrocortisone equivalent dose (mg/kg) | Time of administration | Quality |
|-------------------|---------------------|--------------------|-----------|--------------|----------|-----------|---------|----------------------------------------|------------------------|---------|
| Dieleman et al. (2012) (13) | Netherlands 4494   | CABG or valve or complex | Adults    | RCT          | Y        | 12 months | Dexamethasone | 27                        | Pre CPB               | High (7) |
| El Azab et al. (2002) (47) | Netherlands 18     | CABG               | Adults    | RCT          | Y        | Hospital stay | Dexamethasone | 38                        | Pre surgery            | High (5) |
| Enc et al. (2006) (48)    | Turkey 40          | CABG               | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone | 125                        | Pre CPB               | High (6) |
| Engelman et al. (1995) (49) | US 19             | CABG               | Adults    | RCT          | Y        | Hospital stay | Dexamethasone and Methylprednisolone | 78                        | Pre CPB and post surgery | High (4) |
| Fecht et al. (1978) (50)  | US 50              | CABG               | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone | 286                        | Pre CPB               | High (4) |
| Ferries et al. (1984/1987) (51) | US 80            | CABG or valve or complex | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone | 150                        | Pre CPB               | High (5) |
| Fillinger et al. (2002) (52) | US 50             | CABG               | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone | 81                        | Pre incision and post surgery | High (7) |
| Giomarelli et al. (2003) (53) | Italy 20          | CABG               | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone | 116                        | Pre surgery and post CPB | High (7) |
| Gomez et al. (2018) (54)   | Spain 104         | CABG or valve or complex | Adults    | RCT          | Y        | Unclear | Methylprednisolone and Dexamethasone | 40                        | Post induction and surgery | High (4) |
| Graham et al. (2019) (55)  | US 176            | Cardiac surgery    | Children  | RCT          | Y        | 90 days   | Methylprednisolone | 150                        | Post induction            | High (7) |
| Halonen et al. (2007) (56) | Finland 241       | CABG or valve or complex | Adults    | RCT          | Y        | ICU stay | Hydrocortisone | 14                        | Pre surgery            | High (7) |
| Halvorsen et al. (2003) (57) | US 300           | CABG               | Adults    | RCT          | Y        | ICU stay | Dexamethasone | 3                         | Post induction            | High (6) |
| Hao et al. (2019) (58)     | China 36          | Valve              | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone | 36                        | During initiation of CPB | Low (3)  |
| Harig et al. (1999/2001) (59, 60) | Germany 40       | CABG               | Adults    | RCT          | N        | 30 days   | Prednisolone | 29                        | Pre induction and post surgery | Low (2)  |
| Heying et al. (2012) (61)  | Germany 20        | Cardiac surgery    | Children  | RCT          | Y        | Hospital stay | Dexamethasone | 26.67                       | Pre CPB               | High (6) |
| Jansen et al. (1991) (62)  | Netherlands 25     | CABG               | Adults    | RCT          | Y        | Hospital stay | Dexamethasone | 27                        | Pre CPB               | High (4) |
| Keski-Nisula et al. (2013) (15) | Finland 40      | Cardiac surgery    | Children  | RCT          | Y        | Hospital stay | Methylprednisolone | 150                       | Post induction            | High (6) |
| Keski-Nisula et al. (2015) (63) | Finland 45       | Cardiac surgery    | Children  | RCT          | Y        | Hospital stay | Methylprednisolone | 150                       | During induction and initiation of CPB | High (6) |
| Keski-Nisula et al. (2020) (64) | Finland 29       | Cardiac surgery    | Children  | RCT          | Y        | Hospital stay | Methylprednisolone | 150                       | During induction            | High (6) |
| Kilger Schelling et al. (2003/2004) (65, 66) | Germany 91      | CABG or valve or complex | Adults    | RCT          | N        | 6 months | Hydrocortisone | 8                         | Pre induction and last for 3 days | Low (3)  |
| Killickan et al. (2008) (67) | Turkey 60         | CABG               | Adults    | RCT          | N        | Hospital stay | Methylprednisolone | 75                        | Pre induction            | Low (3)  |
| Liakopoulos et al. (2007) (68) | Germany 78       | CABG               | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone | 75                        | Pre CPB               | High (4) |
| Lindberg et al. (2003) (69) | Sweden 40         | Cardiac surgery    | Children  | RCT          | Y        | Hospital stay | Dexamethasone | 26.67                       | During surgery            | High (6) |
| Loej et al. (2004) (4)     | Netherlands 20     | CABG               | Adults    | RCT          | Y        | Hospital stay | Dexamethasone | 40                        | Pre induction and post surgery | High (4) |

(continued)
| Country          | Population size (n) | Patient population | Age group | Study design | Blinding | Follow-up | Steroid | Hydrocortisone equivalent dose (mg/kg) | Time of administration | Quality a |
|------------------|---------------------|--------------------|-----------|--------------|----------|-----------|---------|---------------------------------------|------------------------|-----------|
| Russia           | 50                  | CABG               | Adults    | RCT          | Y        | 24 h      | Methylprednisolone                   | 100                    | Post induction | High (4) |
| Russia           | 394                 | Cardiac surgery    | Children  | RCT          | Y        | 30 days   | Dexamethasone                         | 26.67                  | Post induction | High (7) |
| Iran             | 110                 | CABG or valve      | Adults    | RCT          | Unclear  | Unclear   | Dexamethasone                         | 30                     | Pre and post surgery | Low (3) |
| Japan            | 24                  | Valve              | Adults    | RCT          | Y        | 7 days    | Methylprednisolone                   | 200                    | Pre and post CPB | High (4) |
| Ireland          | 35                  | CABG               | Adults    | RCT          | N        | 72 h      | Methylprednisolone                   | 150                    | Pre induction | Low (1) |
| Netherlands      | 20                  | CABG               | Adults    | RCT          | Y        | Hospital stay | Dexamethasone                    | 40                     | Pre induction and post surgery | High (5) |
| US               | 95                  | CABG               | Adults    | RCT          | Y        | 30 days   | Methylprednisolone                   | 150                    | Pre induction | High (6) |
| US               | 246                 | Cardiac surgery    | Children  | RCT          | Y        | 30 days   | Methylprednisolone                   | 25                     | Pre incision and post surgery | High (7) |
| US               | 109                 | CABG or valve      | Adults    | RCT          | Y        | Hospital stay | Dexamethasone                   | 6                      | During induction and initiation of CPB | High (7) |
| US               | 90                  | CABG               | Adults    | RCT          | Y        | 9 days    | Methylprednisolone or dexamethasone  | 150/160                | During sternotomy | High (7) |
| US               | 125                 | CABG or valve      | Adults    | RCT          | Y        | ICU stay  | Methylprednisolone                   | 78                     | Pre induction and post surgery | High (4) |
| Canada           | 86                  | CABG               | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone and dexamethasone | 78                     | Pre induction and post surgery | High (7) |
| US               | 150                 | CABG               | Adults    | RCT          | Unclear  | Hospital stay | Methylprednisolone                   | 71                     | Pre CPB | Low (3) |
| Canada           | 68                  | CABG               | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone                   | 71                     | Pre CPB | High (7) |
| US               | 13                  | CABG               | Adults    | RCT          | N        | 6 months  | Methylprednisolone                   | 71                     | During induction | Low (1) |
| Japan            | 28                  | CABG or valve      | Adults    | RCT          | N        | 7 days    | Hydrocortisone                       | 100                    | Pre and post CPB | Low (3) |
| Japan            | 60                  | CABG or valve      | Adults    | RCT          | N        | Hospital stay | Hydrocortisone                      | 100                    | Pre and post CPB | Low (3) |
| Switzerland      | 50                  | CABG               | Adults    | RCT          | N        | Hospital stay | Methylprednisolone                   | 50                     | Pre surgery | Low (3) |
| US               | 28                  | CABG               | Adults    | RCT          | Y        | 72 h      | Dexamethasone                         | 38                     | Pre CPB | High (4) |
| Israel           | 60                  | CABG               | Adults    | RCT          | N        | 2 weeks   | Betamethasone                        | 3                      | Pre surgery | Low (2) |
| Finland          | 40                  | Cardiac surgery    | Children  | RCT          | Y        | Hospital stay | Methylprednisolone and hydrocortisone | 25.6                   | Post induction and last for 5 High (7) days | |
| Slovenia         | 76                  | CABG or valve      | Adults or complex | RCT          | Y        | 30 days   | Methylprednisolone                   | 71                     | During CPB | High (7) |
| Germany          | 52                  | CABG               | Adults    | RCT          | Y        | Hospital stay | Methylprednisolone                   | 71                     | Pre CPB | High (7) |
| Canada           | 25                  | CABG               | Adults    | RCT          | N        | Hospital stay | Methylprednisolone                   | 18                     | Pre induction | Low (3) |
| Denmark          | 16                  | Cardiac surgery    | Adults    | RCT          | N        | Hospital stay | Methylprednisolone                   | 150                    | During induction | Low (3) |

(continued)
| Country                  | Population 0000 size | Patient population | Age group | Study design | Blinding | Follow-up       | Steroid               | Hydrocortisone equivalent dose (mg/kg) | Time of administration | Qualitya |
|-------------------------|----------------------|--------------------|-----------|--------------|----------|----------------|-----------------------|----------------------------------------|------------------------|----------|
| Toledo-Pereyra et al. (1980) (94) | US 95               | Cardiac surgery    | Children  | RCT          | Y        | Hospital stay  | Methylprednisolone    | 150                                    | Pre CPB                | Low (3)  |
| Turkoz et al. (2001) (95)             | Turkey 30           | CABG Adults        | RCT       | N            | 24 h     | Methylprednisolone | 150                                 | Pre CPB                | Low (3)  |
| Vallejo et al. (1977) (96)            | Spain 100           | CABG Adults        | RCT       | N            | Hospital stay | Methylprednisolone | 150                                | Pre CPB                | Low (2)  |
| Volk et al. (2001) (97)               | Germany 39          | CABG Adults        | RCT       | Y            | Hospital stay | Methylprednisolone | 75                                  | Pre CPB                | High (4) |
| Volk et al. (2003) (98)               | Germany 36          | CABG Adults        | RCT       | Y            | Hospital stay | Methylprednisolone | 75                                  | Pre CPB                | High (4) |
| Von Spiegel et al. (2001/2002) (99, 100) | Germany 20         | CABG Adults        | RCT       | Y            | 24 h     | Dexamethasone   | 27                                   | Post induction          | High (5) |
| Vukovic et al. (2011) (101)           | Serbia 57           | CABG Adults        | RCT       | Y            | Hospital stay | Methylprednisolone | 50                                  | Post induction          | High (4) |
| Wan et al. (1999) (102)               | Belgium 20          | CABG or valve Adults | RCT     | Y            | Hospital stay | Methylprednisolone | 150                                | During induction        | High (4) |
| Weis et al. (2006) (103)              | Switzerland 36      | High risk CPB Adults | RCT     | Y            | Hospital stay | Hydrocortisone    | 8                                   | Pre induction and last for 3 days   | High (5) |
| Weis et al. (2009) (104)              | Germany 36          | High risk CPB Adults | RCT     | Y            | 28 days     | Hydrocortisone   | 8                                   | Pre induction and last for 2 days    | High (6) |
| Whitlock et al. (2008) (14)           | Canada 60           | CABG or valve Adults or complex | RCT | Y | Hospital stay | Methylprednisolone | 21                                | During induction and initiation of CPB | High (4) |
| Whitlock et al. (2015) (105)          | Canada 7507         | CABG or valve Adults or complex | RCT | Y | 6 months    | Methylprednisolone | 36                                | During induction and initiation of CPB | High (7) |
| Yared et al. (1998/2000) (106, 107)   | US 236              | CABG or valve Adults or complex | RCT | Y | Hospital stay | Dexamethasone   | 16                                 | Post induction            | Low (3)  |
| Yared et al. (2007) (108)             | US 71               | CABG or valve Adults | RCT     | Y            | Hospital stay | Dexamethasone   | 16                                 | Post induction            | High (4) |
| Yasser et al. (2009) (109)            | Egypt 100           | CABG Adults        | RCT       | Unclear      | Hospital stay | Dexamethasone   | 40                                 | During induction and surgery         | Low (3)  |
| Yilmaz et al. (1999) (110)            | Turkey 20           | CABG Adults        | RCT       | Y            | Hospital stay | Methylprednisolone | 5                                  | During CPB               | High (5) |

CABG, coronary artery bypass grafting. RCT, randomized controlled trial. CPB, cardiopulmonary bypass.

*aJadad score (18).*
### TABLE 2 | GRADE summary of findings.

Corticosteroids compared to placebo or saline for cardiopulmonary bypass

| Outcomes                         | No. of participants (studies) | Anticipated absolute effectsa (95% CI) | Relative effect (95% CI) | Test for overall effect (p) | Certainty of the evidence (GRADE) |
|----------------------------------|-------------------------------|----------------------------------------|--------------------------|-----------------------------|----------------------------------|
|                                  | Risk with placebo or saline  | Risk with corticosteroids              |                          |                             |                                  |
| Adult                            |                               |                                        |                          |                             |                                  |
| Mortality                        | 15780 (47 RCTs)               | 32 per 1,000 (23 to 33)                | 28 per 1,000             | OR 0.86 (0.71 to 1.03)      | 1.66 (0.10) ⊕⊕⊕⊕ HIGH           |
| ≤20 mg/kg hydrocortisone         | 1312 (10 RCTs)                | 20 per 1,000 (5 to 26)                 | 12 per 1,000             | OR 0.57 (0.25 to 1.31)      | 1.32 (0.19) ⊕⊕⊕⊕ HIGH           |
| 20–40 mg/kg hydrocortisone       | 12317 (11 RCTs)               | 34 per 1,000 (25 to 37)                | 30 per 1,000             | OR 0.87 (0.71 to 1.07)      | 1.32 (0.19) ⊕⊕⊕⊕ HIGH           |
| 40–100 mg/kg hydrocortisone      | 1025 (11 RCTs)                | 14 per 1,000 (5 to 36)                 | 14 per 1,000             | OR 0.99 (0.37 to 2.69)      | 0.01 (0.99) ⊕⊕⊕⊕ HIGH           |
| >100 mg/kg hydrocortisone        | 1126 (15 RCTs)                | 40 per 1,000 (19 to 61)                | 35 per 1,000             | OR 0.85 (0.47 to 1.55)      | 0.53 (0.60) ⊕⊕⊕⊕ HIGH           |
| New atrial fibrillation          | 14745 (33 RCTs)               | 284 per 1,000 (185 to 246)            | 213 per 1,000            | OR 0.68 (0.57 to 0.82)      | 4.15 (<0.0001) ⊕⊕⊕⊕ HIGH         |
| ≤20 mg/kg hydrocortisone         | 1279 (10 RCTs)                | 371 per 1,000 (206 to 309)            | 255 per 1,000            | OR 0.58 (0.44 to 0.76)      | 3.90 (<0.0001) ⊕⊕⊕⊕ HIGH         |
| 20–40 mg/kg hydrocortisone       | 12394 (8 RCTs)                | 272 per 1,000 (243 to 274)            | 258 per 1,000            | OR 0.93 (0.86 to 1.01)      | 1.83 (0.07) ⊕⊕⊕⊕ HIGH           |
| 40–100 mg/kg hydrocortisone      | 775 (9 RCTs)                  | 351 per 1,000 (167 to 443)            | 286 per 1,000            | OR 0.74 (0.37 to 1.47)      | 0.87 (0.39) ⊕⊕⊕⊕ HIGH           |
| >100 mg/kg hydrocortisone        | 297 (6 RCTs)                  | 264 per 1,000 (144 to 331)            | 225 per 1,000            | OR 0.81 (0.47 to 1.38)      | 0.78 (0.43) ⊕⊕⊕⊕ HIGH           |
| Myocardial infarction            | 14669 (25 RCTs)               | 65 per 1,000 (68 to 86)                | 77 per 1,000             | OR 1.19 (1.05 to 1.35)      | 2.66 (0.008) ⊕⊕⊕⊕ HIGH          |
| ≤20 mg/kg hydrocortisone         | 1115 (6 RCTs)                 | 20 per 1,000 (9 to 42)                 | 19 per 1,000             | OR 0.96 (0.43 to 2.17)      | 0.09 (0.93) ⊕⊕⊕⊕ HIGH           |
| 20–40 mg/kg hydrocortisone       | 12242 (5 RCTs)                | 72 per 1,000 (76 to 97)                | 86 per 1,000             | OR 1.21 (1.06 to 1.38)      | 2.79 (0.005) ⊕⊕⊕⊕ HIGH          |
| 40–100 mg/kg hydrocortisone      | 780 (6 RCTs)                  | 33 per 1,000 (13 to 61)                | 28 per 1,000             | OR 0.85 (0.38 to 1.88)      | 0.41 (0.68) ⊕⊕⊕⊕ HIGH           |
| >100 mg/kg hydrocortisone        | 532 (8 RCTs)                  | 49 per 1,000 (28 to 111)               | 56 per 1,000             | OR 1.15 (0.55 to 2.43)      | 0.37 (0.71) ⊕⊕⊕⊕ HIGH           |

(continued)
| Outcomes                        | No. of participants (studies) | Anticipated absolute effects (95% CI) | Risk with placebo or saline | Risk with corticosteroids | Relative effect (95% CI) | Test for overall effect (p) | Certainty of the evidence (GRADE) |
|---------------------------------|------------------------------|---------------------------------------|-----------------------------|---------------------------|--------------------------|---------------------------|-----------------------------|
| Pulmonary complications         | 8932 (17 RCTs)               | 92 per 1,000                          | 85 per 1,000                | OR 0.91                   | (0.78 to 1.05)           | 1.30 (0.20)                | ⬤⬤⬤⬤ HIGH                  |
| ≤20 mg/kg hydrocortisone       | 822 (8 RCTs)                 | 42 per 1,000                          | 41 per 1,000                | OR 0.97                   | (0.48 to 1.93)           | 0.10 (0.92)                | ⬤⬤⬤⬤ HIGH                  |
| 20–40 mg/kg hydrocortisone     | 7567 (2 RCTs)                | 99 per 1,000                          | 91 per 1,000                | OR 0.91                   | (0.78 to 1.06)           | 1.22 (0.22)                | ⬤⬤⬤⬤ HIGH                  |
| 40–100 mg/kg hydrocortisone    | 433 (5 RCTs)                 | 65 per 1,000                          | 56 per 1,000                | OR 0.86                   | (0.40 to 1.88)           | 0.37 (0.71)                | ⬤⬤⬤⬤ HIGH                  |
| >100 mg/kg hydrocortisone      | 110 (2 RCTs)                 | 73 per 1,000                          | 56 per 1,000                | OR 0.76                   | (0.18 to 3.24)           | 0.37 (0.71)                | ⬤⬤⬤⬤ HIGH                  |
| Kidney injury                  | 12826 (13 RCTs)              | 34 per 1,000                          | 28 per 1,000                | OR 0.83                   | (0.68 to 1.01)           | 1.68 (0.06)                | ⬤⬤⬤⬤ HIGH                  |
| ≤20 mg/kg hydrocortisone       | 520 (6 RCTs)                 | 43 per 1,000                          | 17 per 1,000                | OR 0.38                   | (0.13 to 1.11)           | 1.77 (0.08)                | ⬤⬤⬤⬤ HIGH                  |
| 20–40 mg/kg hydrocortisone     | 12142 (4 RCTs)               | 33 per 1,000                          | 28 per 1,000                | OR 0.84                   | (0.68 to 1.03)           | 1.66 (0.10)                | ⬤⬤⬤⬤ HIGH                  |
| 40–100 mg/kg hydrocortisone    | 164 (2 RCTs)                 | 49 per 1,000                          | 72 per 1,000                | OR 1.49                   | (0.40 to 5.58)           | 0.59 (0.55)                | ⬤⬤⬤⬤ HIGH                  |
| >100 mg/kg hydrocortisone      | 1 (RCT)                      | 0 per 1,000                           | 0 per 1,000                 | not estimable             |                          | -                          | ⬤⬤⬤⬤ HIGH                  |
| Postoperative infection         | 14880 (37 RCTs)              | 81 per 1,000                          | 77 per 1,000                | OR 0.95                   | (0.84 to 1.07)           | 0.84 (0.40)                | ⬤⬤⬤⬤ HIGH                  |
| ≤20 mg/kg hydrocortisone       | 1299 (11 RCTs)               | 67 per 1,000                          | 57 per 1,000                | OR 0.84                   | (0.52 to 1.33)           | 0.75 (0.45)                | ⬤⬤⬤⬤ HIGH                  |
| 20–40 mg/kg hydrocortisone     | 12295 (7 RCTs)               | 86 per 1,000                          | 82 per 1,000                | OR 0.95                   | (0.84 to 1.08)           | 0.76 (0.45)                | ⬤⬤⬤⬤ HIGH                  |
| 40–100 mg/kg hydrocortisone    | 612 (10 RCTs)                | 56 per 1,000                          | 59 per 1,000                | OR 1.06                   | (0.54 to 2.09)           | 0.17 (0.87)                | ⬤⬤⬤⬤ HIGH                  |
| >100 mg/kg hydrocortisone      | 674 (9 RCTs)                 | 39 per 1,000                          | 41 per 1,000                | OR 1.07                   | (0.51 to 2.26)           | 0.18 (0.86)                | ⬤⬤⬤⬤ HIGH                  |
| Neurological complications (strok) | 13439 (18 RCTs)              | 21 per 1,000                          | 18 per 1,000                | OR 0.85                   | (0.66 to 1.08)           | 1.33 (0.18)                | ⬤⬤⬤⬤ HIGH                  |
| ≤20 mg/kg hydrocortisone       | 626 (4 RCTs)                 | 19 per 1,000                          | 16 per 1,000                | OR 0.85                   | (0.25 to 2.82)           | 0.27 (0.79)                | ⬤⬤⬤⬤ HIGH                  |

(continued)
### Table 2: Corticosteroids compared to placebo or saline for cardiopulmonary bypass

| Outcomes                                      | No. of participants (studies) | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | Test for overall effect (p) | Certainty of the evidence (GRADE) |
|-----------------------------------------------|------------------------------|---------------------------------------|--------------------------|-----------------------------|----------------------------------|
| Patient or population: cardiopulmonary bypass |                              |                                       |                          |                             |                                  |
| Intervention: corticosteroids                 |                              |                                       |                          |                             |                                  |
| Comparison: placebo or saline                 |                              |                                       |                          |                             |                                  |
| Anticipated absolute effects (95% CI)         | Risk with placebo or saline  | Risk with corticosteroids             |                          |                             |                                  |
| Test for overall effect (p)                   |                              |                                       |                          |                             |                                  |
| Certainty of the evidence (GRADE)            |                              |                                       |                          |                             |                                  |
| Risk with placebo or saline                  | 19 per 1,000                 | 17 per 1,000                          | OR 0.89                  | 0.86 (0.39)                 | @@@@ HIGH                       |
| (4 RCTs)                                      |                              | (13 to 22)                            | (0.68 to 1.16)           |                             |                                  |
| Risk with corticosteroids                     | 20–40 mg/kg hydrocortisone   | 52 per 1,000                          | OR 0.48                  | 1.52 (0.13)                 | @@@@ HIGH                       |
| (6 RCTs)                                      | 26 per 1,000                 | (10 to 64)                            | (0.18 to 1.24)           |                             |                                  |
| Risk with corticosteroids                     | >100 mg/kg hydrocortisone    | 56 per 1,000                          | OR 0.83                  | 0.31 (0.76)                 | @@@@ HIGH                       |
| (4 RCTs)                                      | 47 per 1,000                 | (15 to 135)                           | (0.26 to 2.66)           |                             |                                  |
| Risk with corticosteroids                     | Gastro-intestinal bleeding   | 10 per 1,000                          | OR 1.22                  | 1.17 (0.24)                 | @@@@ HIGH                       |
| (6 RCTs)                                      | 12 per 1,000                 | (9 to 17)                             | (0.88 to 1.69)           |                             |                                  |
| Risk with placebo or saline                  | 20–40 mg/kg hydrocortisone   | 19 per 1,000                          | OR 0.89                  | 0.86 (0.39)                 | @@@@ HIGH                       |
| (6 RCTs)                                      | 17 per 1,000                 | (13 to 22)                            | (0.68 to 1.16)           |                             |                                  |
| Risk with corticosteroids                     | >100 mg/kg hydrocortisone    | 52 per 1,000                          | OR 0.48                  | 1.52 (0.13)                 | @@@@ HIGH                       |
| (6 RCTs)                                      | 26 per 1,000                 | (10 to 64)                            | (0.18 to 1.24)           |                             |                                  |
| Risk with corticosteroids                     | Mechanical ventilation time (hours) | The mean mechanical ventilation time (hours) was 8.39 | MD 0.48 lower | 1.66 (0.10) | @@@@ HIGH |
| (7 RCTs)                                      | (1.04 lower to 0.09 higher)  |                                       |                          |                             |                                  |
| Risk with placebo or saline                  | ≤20 mg/kg hydrocortisone     | 20–40 mg/kg hydrocortisone            | MD 0.53 lower            | 1.23 (0.22)                 | @@@@ HIGH                       |
| (11 RCTs)                                     | The mean mechanical ventilation time (hours) was 9.82 | (4.14 lower to 1.33 lower) | 1.20 (0.23) | 1.23 (0.22) | @@@@ HIGH |
| Risk with corticosteroids                     | >100 mg/kg hydrocortisone    | 639 per 1,000                         | OR 0.94 lower            | 1.23 (0.22)                 | @@@@ HIGH                       |
| (12 RCTs)                                     | The mean mechanical ventilation time (hours) was 12.15 | (1.39 lower to 0.34 higher) | 1.20 (0.23) | 1.23 (0.22) | @@@@ HIGH |
| Risk with corticosteroids                     | ≥100 mg/kg hydrocortisone    | 301 per 1,000                         | OR 3.82 higher           | 2.45 (0.01)                 | @@@@ HIGH                       |
| (7 RCTs)                                      | The mean mechanical ventilation time (hours) was 10.91 | (0.76 higher to 6.87 higher) | 1.23 (0.22) | 2.45 (0.01) | @@@@ HIGH |
| Risk with placebo or saline                  | Hyperglycemia requiring insulin infusion | 8316 per 1,000                     | OR 1.91                  | 2.61 (0.009)                | @@@@ HIGH                       |
| (14 RCTs)                                     | 196 per 1,000                | (131 to 284)                          | (1.18 to 3.11)           |                             |                                  |
| Risk with corticosteroids                     | ≤20 mg/kg hydrocortisone     | 421 per 1,000                         | OR 1.72                  | 1.46 (0.15)                 | @@@@ HIGH                       |
| (4 RCTs)                                      | 233 per 1,000                | (201 to 518)                          | (0.83 to 3.55)           |                             |                                  |
| Risk with corticosteroids                     | >100 mg/kg hydrocortisone    | 7547 per 1,000                        | OR 4.41                  | 1.46 (0.14)                 | @@@@ HIGH                       |
| (3 RCTs)                                      | 335 per 1,000                | (64 to 786)                           | (0.60 to 32.10)          |                             |                                  |
| Risk with corticosteroids                     | Mechanical ventilation time (hours) | The mean mechanical ventilation time (hours) was 7.44 | MD 0.53 lower | 1.20 (0.23) | @@@@ HIGH |
| (12 RCTs)                                     | (1.39 lower to 0.34 higher)  |                                       |                          |                             |                                  |
| Risk with placebo or saline                  | ≥100 mg/kg hydrocortisone    | 120 per 1,000                         | OR 11.88                 | 2.28 (0.02)                 | @@@@ HIGH                       |
| (2 RCTs)                                      | 417 per 1,000                | (502 to 986)                          | (1.41 to 100.00)         |                             |                                  |
| Risk with corticosteroids                     | Delirium                     | 228 per 1,000                         | OR 1.53                  | 0.98 (0.33)                 | @@@@ HIGH                       |
| (5 RCTs)                                      | 88 per 1,000                 | (59 to 258)                           | (0.65 to 3.59)           |                             |                                  |
| Risk with placebo or saline                  | LOS in ICU (days)            | 12181 per 1,000                       | OR 0.89                  | 1.78 (0.08)                 | @@@@ HIGH                       |
| (6 RCTs)                                      | The mean LOS ICU (days) was 1.69 | (74 to 93)                           | (0.79 to 1.01)           |                             |                                  |
| Risk with corticosteroids                     | ≤20 mg/kg hydrocortisone     | 641 per 1,000                         | OR 1.48 lower            | 2.31 (0.02)                 | @@@@ HIGH                       |
| (9 RCTs)                                      | The mean LOS ICU (days) was 2.55 | (2.73 lower to 0.22 lower) | 2.31 (0.02) | 2.31 (0.02) | @@@@ HIGH |

(continued)
| Outcomes                          | No. of participants (studies) | Anticipated absolute effects 95% CI | Relative effect 95% CI | Test for overall effect (p) | Certainty of the evidence (GRADE) |
|----------------------------------|-------------------------------|-------------------------------------|------------------------|-----------------------------|----------------------------------|
|                                  | Risk with placebo or saline  | Risk with corticosteroids           |                        |                             |                                  |
| **LOS in hospital (days)**       |                               |                                     |                        |                             |                                  |
| ≤20 mg/kg hydrocortisone         | 1445 (7 RCTs)                 | The mean LOS hospital (days) was 9.07 | MD 0.66 lower (1.03 lower to 0.3 lower) | -                           | ⚫⚫⚫⚫ HIGH                        |
| >20–40 mg/kg hydrocortisone      | 12432 (13 RCTs)               | The mean LOS hospital (days) was 11.02 | MD 0.94 higher (0.69 lower to 2.56 higher) | -                           | ⚫⚫⚫⚫ HIGH                        |
| >40–100 mg/kg hydrocortisone     | 4519 (3 RCTs)                 | The mean LOS hospital (days) was 199.30 | MD 3.73 higher (1.72 lower to 9.19 higher) | -                           | ⚫⚫⚫⚫ HIGH                        |
| >100 mg/kg hydrocortisone        | 219 (4 RCTs)                  | The mean LOS hospital (days) was 214.37 | MD 11.78 higher (1.08 lower to 33.74 higher) | -                           | ⚫⚫⚫⚫ HIGH                        |
| Duration of CPB (minutes)        |                               |                                     |                        |                             |                                  |
| ≤20 mg/kg hydrocortisone         | 1445 (7 RCTs)                 | The mean duration of CPB (minutes) was 111.02 | MD 0.94 higher (0.69 lower to 2.56 higher) | -                           | ⚫⚫⚫⚫ HIGH                        |
| >20–40 mg/kg hydrocortisone      | 12432 (13 RCTs)               | The mean duration of CPB (minutes) was 114.87 | MD 0.89 higher (3.36 lower to 5.15 higher) | -                           | ⚫⚫⚫⚫ HIGH                        |
| >40–100 mg/kg hydrocortisone     | 4519 (3 RCTs)                 | The mean duration of CPB (minutes) was 241.88 | MD 9.64 higher (8.92 lower to 28.2 higher) | -                           | ⚫⚫⚫⚫ HIGH                        |
| >100 mg/kg hydrocortisone        | 219 (4 RCTs)                  | The mean duration of CPB (minutes) was 214.37 | MD 11.78 higher (1.08 lower to 33.74 higher) | -                           | ⚫⚫⚫⚫ HIGH                        |

TABLE 2 | Continued
TABLE 2 | Continued
Corticosteroids compared to placebo or saline for cardiopulmonary bypass

| Outcomes                             | No. of participants (studies) | Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Test for overall effect (p) | Certainty of the evidence (GRADE) |
|--------------------------------------|------------------------------|---------------------------------------|--------------------------|-----------------------------|-----------------------------------|
| >100 mg/kg hydrocortisone            | 200 (6 RCTs)                 | The mean duration of procedure (minutes) was 289.88 MD 14.03 higher (10.19 lower to 38.25 higher) | –                        | 1.14 (0.26)                  | @@@@@    |
| Postoperative bleeding (mL)          | 1084 (13 RCTs)               | The mean postoperative bleeding (mL) was 763.32 MD 99.73 lower (169.45 lower to 30 lower) | –                        | 2.80 (0.005)                 | @@@@@    |
| ≤20 mg/kg hydrocortisone            | 569 (3 RCTs)                 | The mean postoperative bleeding (mL) was 666.99 MD 20.83 lower (56.43 lower to 14.78 higher) | –                        | 1.15 (0.25)                  | @@@@@    |
| 20–40 mg/kg hydrocortisone          | 100 (3 RCTs)                 | The mean postoperative bleeding (mL) was 847.00 MD 66.96 lower (192.33 lower to 58.41 higher) | –                        | 1.05 (0.30)                  | @@@@@    |
| 40–100 mg/kg hydrocortisone         | 295 (4 RCTs)                 | The mean postoperative bleeding (mL) was 919.53 MD 194.85 lower (302.08 lower to 87.61 lower) | –                        | 3.56 (0.0004)                | @@@@@    |
| >100 mg/kg hydrocortisone           | 120 (3 RCTs)                 | The mean postoperative bleeding (mL) was 758.50 MD 83.82 lower (130.62 lower to 37.03 lower) | –                        | 3.51 (0.0004)                | @@@@@    |
| Vaso-active medication use           | 1405 (20 RCTs)               | 272 per 1,000 OR 1.01 (0.69 to 1.47) | –                        | 0.03 (0.98)                  | @@@@@    |
| ≤20 mg/kg hydrocortisone            | 639 (4 RCTs)                 | 177 per 1,000 OR 0.91 (0.58 to 1.45) | –                        | 0.38 (0.70)                  | @@@@@    |
| 20–40 mg/kg hydrocortisone          | 183 (6 RCTs)                 | 462 per 1,000 OR 0.43 (0.12 to 1.51) | –                        | 1.32 (0.19)                  | @@@@@    |
| 40–100 mg/kg hydrocortisone         | 80 (2 RCTs)                  | 293 per 1,000 OR 1.05 (0.23 to 4.81) | –                        | 0.06 (0.95)                  | @@@@@    |
| >100 mg/kg hydrocortisone           | 503 (8 RCTs)                 | 320 per 1,000 OR 1.50 (0.96 to 2.35) | –                        | 1.78 (0.08)                  | @@@@@    |
| IL-6 concentrations at 24 h (pg/mL) | 506 (14 RCTs)                | The mean IL-6 concentrations at 24 h (pg/mL) was 310.89 MD 139.77 lower (161.56 lower to 117.97 lower) | –                        | 12.57 (<0.00001)          | @@@@@    |
| CRP concentrations at 24 h (µg/mL)  | 631 (4 RCTs)                 | The mean CRP concentrations at 24 h (µg/mL) was 139.04 MD 8.98 lower (20.41 lower to 2.45 higher) | –                        | 1.54 (0.12)                  | @@@@@    |
| TNF-α concentrations at 24 h (pg/mL)| 199 (6 RCTs)                 | The mean TNF-α concentrations at 24 h (pg/mL) was 16.73 MD 4.23 lower (6.85 lower to 1.6 lower) | –                        | 3.16 (0.002)                 | @@@@@    |
| IL-8 concentrations at 24 h (pg/mL) | 199 (6 RCTs)                 | The mean IL-8 concentrations at 24 h (pg/mL) was 15.01 MD 5.81 lower (10.96 lower to 0.66 lower) | –                        | 2.21 (0.03)                  | @@@@@    |
| Outcomes                          | No. of participants (studies) | Risk with placebo or saline | Risk with corticosteroids | Anticipated absolute effects (95% CI) | Relative effect (95% CI) | Test for overall effect (p) | Certainty of the evidence (GRADE) |
|----------------------------------|------------------------------|----------------------------|---------------------------|---------------------------------------|--------------------------|---------------------------|---------------------------------|
| IL-10 concentrations at 24 h (pg/mL) | 109 (3 RCTs)                | The mean IL-10 concentrations at 24 h (pg/mL) was 14.34 (2.93 lower to 15.19 higher) | MD 6.13 higher – 1.33 (0.19) |
| Re-intubation                    | 258 (5 RCTs)                | 102 per 1,000               | 38 per 1,000              | OR 0.35 (0.13 to 0.95)                | 2.06 (0.04)               | ⊕⊕⊕⊕                               |
| Re-thoracotomy                   | 935 (9 RCTs)                | 27 per 1,000                | 32 per 1,000              | OR 1.17 (0.57 to 2.40)                | 0.44 (0.66)               | ⊕⊕⊕⊕                               |
| Pediatric                         |                              |                            |                           |                                       |                          |                          |                                 |
| Mortality                        | 931 (12 RCTs)               | 48 per 1,000                | 28 per 1,000              | OR 0.57 (0.30 to 1.11)                | 1.64 (0.10)               | ⊕⊕⊕⊕                               |
| ≤50 mg/kg hydrocortisone         | 531 (6 RCTs)                | 22 per 1,000                | 16 per 1,000              | OR 0.71 (0.23 to 2.19)                | 0.59 (0.55)               | ⊕⊕⊕⊕                               |
| >50 mg/kg hydrocortisone         | 400 (6 RCTs)                | 82 per 1,000                | 44 per 1,000              | OR 0.51 (0.23 to 1.17)                | 1.59 (0.11)               | ⊕⊕⊕⊕                               |
| Kidney injury                    | 659 (5 RCTs)                | 236 per 1,000               | 127 per 1,000             | OR 0.47 (0.22 to 1.01)                | 1.94 (0.05)               | ⊕⊕⊕⊕                               |
| ≤50 mg/kg hydrocortisone         | 483 (4 RCTs)                | 127 per 1,000               | 40 per 1,000              | OR 0.29 (0.09 to 0.96)                | 2.02 (0.04)               | ⊕⊕⊕⊕                               |
| >50 mg/kg hydrocortisone         | 176 (1 RCT)                 | 516 per 1,000               | 457 per 1,000             | OR 0.79 (0.44 to 1.43)                | 0.78 (0.44)               | ⊕⊕⊕⊕                               |
| ECMO                             | 570 (2 RCTs)                | 47 per 1,000                | 19 per 1,000              | OR 0.38 (0.13 to 1.10)                | 1.79 (0.07)               | ⊕⊕⊕⊕                               |
| Postoperative infection           | 304 (5 RCTs)                | 70 per 1,000                | 48 per 1,000              | OR 0.68 (0.25 to 1.85)                | 0.75 (0.45)               | ⊕⊕⊕⊕                               |
| Hyperglycemia requiring insulin  | 256 (3 RCTs)                | 67 per 1,000                | 208 per 1,000             | OR 3.68 (1.53 to 8.84)                | 2.91 (0.004)              | ⊕⊕⊕⊕                               |
| Mechanical ventilation time (hours) | 505 (8 RCTs)                | The mean mechanical ventilation time (hours) was 80.35 (15.53 lower to 0.79 higher) | MD 7.37 lower – 1.77 (0.08) |
| ≤50 mg/kg hydrocortisone         | 100 (3 RCTs)                | The mean mechanical ventilation time (hours) was 103.04 (73.47 lower to 17.01 higher) | MD 28.23 lower – 1.22 (0.22) |
| >50 mg/kg hydrocortisone         | 405 (5 RCTs)                | The mean mechanical ventilation time (hours) was 74.94 (19.89 lower to 4.95 higher) | MD 7.47 lower – 1.18 (0.24) |
| Duration of CPB (minutes)        | 875 (14 RCTs)               | The mean duration of CPB (minutes) was 132.73 (14.32 lower to 8.75 lower) | MD 11.54 lower – 8.12 (<0.00001) |

(continued)
### TABLE 2 | Continued

Corticosteroids compared to placebo or saline for cardiopulmonary bypass

| Outcomes and Context | No. of participants (studies) | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | Test for overall effect (p) | Certainty of the evidence (GRADE) |
|----------------------|------------------------------|----------------------------------------|-------------------------|---------------------------|----------------------------------|
| **≤50 mg/kg hydrocortisone** | 441 (8 RCTs) | The mean duration of CPB (minutes) was 129.29 MD 12.06 lower (15.19 lower to 8.94 lower) | – | 7.56 (<0.00001) | ⊕⊕⊕⊕ HIGH |
| **>50 mg/kg hydrocortisone** | 434 (6 RCTs) | The mean duration of CPB (minutes) was 136.04 MD 9.52 lower (15.63 lower to 3.41 lower) | – | 3.05 (0.02) | ⊕⊕⊕⊕ HIGH |
| **LOS ICU (days)** | 405 (8 RCTs) | The mean LOS ICU (days) was 8.08 MD 7.56 lower (0.12 lower to 0.11 higher) | – | 0.05 (0.96) | ⊕⊕⊕⊕ HIGH |
| **≤50 mg/kg hydrocortisone** | 100 (3 RCTs) | The mean LOS ICU (days) was 7.52 MD 1.06 lower (3.08 lower to 0.96 higher) | – | 1.03 (0.30) | ⊕⊕⊕⊕ HIGH |
| **>50 mg/kg hydrocortisone** | 305 (5 RCTs) | The mean LOS ICU (days) was 8.25 MD 0.03 lower (0.34 lower to 0.39 higher) | – | 0.14 (0.89) | ⊕⊕⊕⊕ HIGH |
| **Inotropic score** | 454 (7 RCTs) | The mean inotropic score was 12.88 MD 0.99 lower (0.39 lower to 0.22 higher) | – | 0.56 (0.58) | ⊕⊕⊕⊕ HIGH |
| **Highest/24 h temperature (°C)** | 216 (7 RCTs) | The mean highest/24 h temperature (°C) was 37.63 MD 0.07 lower (0.43 lower to 0.29 higher) | – | 0.40 (0.69) | ⊕⊕⊕⊕ HIGH |
| **≤50 mg/kg hydrocortisone** | 87 (3 RCTs) | The mean highest/24 h temperature (°C) was 37.38 MD 0.28 lower (0.08 lower to 0.63 higher) | – | 1.54 (0.12) | ⊕⊕⊕⊕ HIGH |
| **>50 mg/kg hydrocortisone** | 129 (4 RCTs) | The mean highest/24 h temperature (°C) was 37.80 MD 0.26 lower (0.61 lower to 0.1 higher) | – | 1.42 (0.16) | ⊕⊕⊕⊕ HIGH |
| **Highest/24 h glucose concentrations (mg/dl)** | 236 (3 RCTs) | The mean highest/24 h glucose concentrations (mg/dl) was 138.50 MD 17.94 higher (0.17 lower to 36.06 higher) | – | 1.94 (0.05) | ⊕⊕⊕⊕ HIGH |
| **Highest/24 h lactate concentrations (mmol/l)** | 305 (5 RCTs) | The mean highest/24 h lactate concentrations (mmol/l) was 3.04 MD 0.66 lower (0.17 lower to 0.05 higher) | – | 1.07 (0.28) | ⊕⊕⊕⊕ HIGH |
| **Highest/24 h CRP concentrations (µg/mL)** | 98 (3 RCTs) | The mean highest/24 h CRP concentrations (µg/mL) was 50.58 MD 20.12 lower (28.68 lower to 11.55 lower) | – | 4.60 (<0.00001) | ⊕⊕⊕⊕ HIGH |
| **(≤50 mg/kg hydrocortisone)** | 316 (8 RCTs) | The mean highest/24 h IL-6 concentrations (pg/mL) was 211.77 MD 108.6 lower (206.02 lower to 11.18 lower) | – | 2.18 (0.03) | ⊕⊕⊕⊕ HIGH |
| **≤50 mg/kg hydrocortisone** | 98 (4 RCTs) | The mean highest/24 h IL-6 concentrations (pg/mL) was 386.84 MD 102.67 lower (185.42 lower to 19.93 lower) | – | 2.43 (0.02) | ⊕⊕⊕⊕ HIGH |
| **>50 mg/kg hydrocortisone** | 218 (4 RCTs) | The mean highest/24 h IL-6 concentrations (pg/mL) was 133.07 MD 85.72 lower (308.08 lower to 136.64 higher) | – | 0.76 (0.45) | ⊕⊕⊕⊕ HIGH |
| Outcomes                  | No. of participants (studies) | Anticipated absolute effectsa (95% CI) | Relative effect (95% CI) | Test for overall effect (p) | Certainty of the evidence (GRADE) |
|--------------------------|------------------------------|--------------------------------------|-------------------------|----------------------------|----------------------------------|
| Highest/24 h IL-10 concentrations (pg/mL) | 258 (5 RCTs) | The mean highest/24 h IL-10 concentrations (pg/mL) was 298.04 (169.67 higher to 285.03 higher) | MD 227.35 higher (169.67 higher to 285.03 higher) | 7.73 (<0.00001) | ⊕⊕⊕⊕ HIGH |
| ≤50 mg/kg hydrocortisone | 40 (1 RCT) | The mean highest/24 h IL-10 concentrations (pg/mL) was 48.1 (99.29 higher to 542.91 higher) | MD 321.1 higher (99.29 higher to 542.91 higher) | 2.84 (0.005) | ⊕⊕⊕⊕ HIGH |
| >50 mg/kg hydrocortisone | 218 (4 RCTs) | The mean highest/24 h IL-10 concentrations (pg/mL) was 343.91 (160.82 higher to 280.28 higher) | MD 220.55 higher (160.82 higher to 280.28 higher) | 7.24 (<0.00001) | ⊕⊕⊕⊕ HIGH |

CI, Confidence interval; OR, odds ratio; MD, mean difference.

GRADE Working Group grades of evidence
- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
TABLE 3 | Summary of corticosteroids impact on adults and pediatric.

| Group                      | Outcome                          | OR      | CI       | p        | I²       | Impact        |
|----------------------------|----------------------------------|---------|----------|----------|----------|---------------|
| Adult                      | Myocardial infarction            | 1.19    | 1.05–1.35| 0.008    | 0%       | Increased     |
|                            | Insulin infusion                 | 1.91    | 1.18–3.11| 0.009    | 46%      | Increased     |
|                            | Mortality                        | 0.86    | 0.71–1.03| 0.1      | 0%       | Unaffected    |
|                            | Postoperative atrial fibrillation| 0.68    | 0.57–0.82| <0.0001  | 48%      | Reduced       |
|                            | ICU stay                         | −0.27   | −0.34–−0.19| <0.0001  | 93%      | Reduced       |
|                            | Hospital stay                    | −0.66   | −1.03–−0.30| 0.0003  | 95%      | Reduced       |
|                            | Postoperative bleeding           | −0.73   | −169.45–−30.00| 0.005  | 84%      | Reduced       |
|                            | Re-intubation                    | 0.35    | 0.13–0.95| 0.004    | 6%       | Reduced       |
|                            | IL-6                             | −139.77 | −161.56–−117.97| <0.001  | 99%      | Reduced       |
|                            | TNF-α                            | −4.23   | −6.85–−1.60| 0.002   | 88%      | Reduced       |
|                            | IL-8                             | −5.81   | −10.96–−0.66| 0.003   | 97%      | Reduced       |
|                            | Kidney injury                    | 0.83    | 0.68–1.01| 0.06     | 0%       | Unaffected    |
|                            | Pulmonary complications           | 0.91    | 0.78–1.05| 0.2      | 0%       | Unaffected    |
|                            | Stroke                           | 0.85    | 0.66–1.08| 0.18     | 0%       | Unaffected    |
|                            | Gastrointestinal bleeding        | 1.22    | 0.88–1.69| 0.24     | 0%       | Unaffected    |
|                            | Postoperative infection          | 0.95    | 0.84–1.07| 0.4      | 0%       | Unaffected    |
|                            | Delirium                         | 0.89    | 0.79–1.01| 0.08     | 45%      | Unaffected    |
|                            | Mechanical ventilation time      | −0.48   | −1.04–0.09| 0.1     | 94%      | Unaffected    |
| Pediatric                  | Myocardial infarction            | 0.96    | 0.43–2.17| 0.93     | 0%       | Unaffected    |
| ≤20 mg/kg hydrocortisone   | Insulin infusion                 | 1.72    | 0.83–3.55| 0.15     | 36%      | Unaffected    |
|                            | Mortality                        | 0.57    | 0.25–1.31| 0.19     | 0%       | Unaffected    |
|                            | Postoperative atrial fibrillation| 0.58    | 0.44–0.76| <0.0001  | 13%      | Reduced       |
|                            | ICU stay                         | −1.48   | −2.73–−0.22| <0.0001  | 96%      | Reduced       |
|                            | Hospital stay                    | −2.29   | −4.51–−0.07| <0.0001  | 96%      | Reduced       |
|                            | Mechanical ventilation time      | −2.74   | −4.14–1.33| 0.0001  | 92%      | Reduced       |
|                            | Postoperative bleeding           | −20.83  | −56.43–14.78| 0.25   | 0%       | Unaffected    |
|                            | Kidney injury                    | 0.38    | 0.13–1.11| 0.08     | 0%       | Unaffected    |
|                            | Pulmonary complications          | 0.97    | 0.48–1.93| 0.92     | 0%       | Unaffected    |
|                            | Stroke                           | 0.85    | 0.25–2.82| 0.79     | 0%       | Unaffected    |
|                            | Postoperative infection          | 0.84    | 0.52–1.33| 0.45     | 0%       | Unaffected    |
| Pediatric                  | Reduced CRP                      | −20.12  | −28.68–−11.55| <0.001  | 42%      | Reduced       |
| ≤50 mg/kg hydrocortisone   | Reduced IL-6                     | −108.60 | −206.02–−11.18| 0.03   | 95%      | Reduced       |
|                            | Increased IL-10                  | 227.35  | 169.67–285.03| <0.001  | 40%      | Increased     |
|                            | Decreased CPB time               | −11.54  | −14.32–−8.75| <0.001  | 5%       | Reduced       |
|                            | Increased insulin infusion       | 3.68    | 1.53–8.84| 0.004    | 48%      | Increased     |
|                            | mortality                        | 0.57    | 0.30–1.11| 0.1      | 0%       | Unaffected    |
|                            | kidney injury                    | 0.47    | 0.22–1.01| 0.05     | 46%      | Unaffected    |
|                            | ECMO use                         | 0.38    | 0.13–1.10| 0.07     | 0%       | Unaffected    |
|                            | postoperative infection          | 0.68    | 0.25–1.85| 0.45     | 0%       | Unaffected    |
|                            | mechanical ventilation time      | −7.37   | −15.53–0.79| 0.08   | 83%      | Unaffected    |
|                            | ICU length of stay               | −0.00   | −0.12–0.11| 0.96     | 0%       | Unaffected    |
| Pediatric                  | Reduced IL-6                     | −102.67 | −185.42–−19.93| 0.02   | 78%      | Reduced       |
| ≤50 mg/kg hydrocortisone   | Decreased CPB time               | −12.06  | −15.19–−8.94| <0.001  | 3%       | Reduced       |
|                            | kidney injury                    | 0.29    | 0.09–0.96| 0.04     | 49%      | Reduced       |
|                            | mortality                        | 0.71    | 0.23–2.19| 0.55     | 0%       | Unaffected    |
|                            | mechanical ventilation time      | −28.23  | −73.47–17.01| 0.22   | 65%      | Unaffected    |
|                            | ICU length of stay               | −1.06   | −3.08–0.96| 0.3      | 51%      | Unaffected    |

(16). However, corticosteroids exert dose-dependent anti-inflammatory effects and clinical side effects (3, 4, 7). Thus, we hypothesized that an appropriate dosage range might effectively inhibit SIRS and provide clinical benefits without major side effects, as the optimal corticosteroids dose would protect cardiomyocytes rather than damage them.

Our results revealed that corticosteroids prophylaxis reduced the blood concentrations of various inflammatory markers after cardiac surgery, including CRP, TNF-α, IL-6, and IL-8. These findings support the prophylactic administration of corticosteroids to prevent SIRS after cardiac surgery with CPB (8–10). However, we did not detect any significant change in mortality, which is consistent with the results of previous studies (5–7, 13, 14, 19). This may be related to advanced cardiac surgery management and active treatment of complications in the current era.

The SIRS trial and Ho et al.’s meta-analysis of 50 small RCTs revealed that corticosteroids prophylaxis in adults significantly increased the risks of myocardial infarction and hyperglycemia requiring insulin infusion (6, 14). In this context, high doses of corticosteroids can rapidly and significantly induce insulin resistance, reduce cellular utilization of glucose, and cause hyperglycemia (20). Hyperglycemia downregulates glyoxalase 1 and glyoxalase 2, which inhibits the post-injury repair of
cardiomyocytes (21). This may be the main mechanism through which high-dose corticosteroids induce myocardial infarction. We found that corticosteroids (>20 mg/kg hydrocortisone), but not low-dose corticosteroids, increased the risk of myocardial infarction and hyperglycemia requiring insulin infusion in adults. This may be because low-dose corticosteroids inhibit SIRS and protect cardiomyocytes, without substantially impairing glucose utilization. We did not observe a substantial change in this relationship when we re-analyzed data from 18 high-quality RCTs (Jadad score of ≥4, 18/25 trials), which all adopted the general definition of myocardial infarction and used cardiac biomarkers to predict its occurrence. In children, corticosteroids increased the use of insulin but did not significantly influence the risk of myocardial infarction, which may be related to neonatal cardiomyocytes having increased glucose uptake and utilization (22).

The DECS trial (13) and the SIRS trial (14) revealed that corticosteroids prophylaxis did not reduce the risk of atrial fibrillation in adult patients after cardiac surgery. However, meta-analyses by Ho et al. (6) and Ng et al. (7) revealed that corticosteroids prophylaxis could significantly reduce the incidence of atrial fibrillation. Ho et al. (6) reported that both low-dose and high-dose corticosteroids could significantly reduce the risk of atrial fibrillation. Ng et al.’s meta-analysis included the DECS and SIRS trials, but did not include a stratified dose analysis (7). Interestingly, we found that only

### TABLE 1

| Corticosteroids | Control | Odds Ratio | Odds Ratio |
|----------------|---------|------------|------------|
| Abbassazadeh 2012 | 4 92 | 6 92 1.3% | 0.65 [0.18, 2.39] |
| Halonen 2007 | 1 120 | 1 121 0.2% | 1.01 [0.06, 16.31] |
| Hlawatsch 2003 | 3 147 | 1 147 0.2% | 3.04 [0.31, 29.58] |
| Murphy 2011 | 2 60 | 2 49 0.5% | 0.81 [0.11, 5.97] |
| Yared 1998/2000 | 0 106 | 1 110 0.3% | 0.34 [0.01, 8.51] |
| Yared 2007 | 1 37 | 0 34 0.1% | 2.84 [0.11, 71.99] |
| Subtotal (95% CI) | 562 | 553 2.8% | 0.96 [0.43, 2.17] |

**FIGURE 2** Impact of corticosteroids on myocardial infarction (adult).
### FIGURE 3 | Impact of corticosteroids on mortality (adult).

#### Corticosteroids

| Study or Subgroup | Events | Total | Odds Ratio | Odds Ratio |
|-------------------|--------|-------|------------|------------|
|                    |        |       | M-H. Fixed 95% CI |            |
|                    |        |       |            | M-H. Fixed 95% CI |            |
| 1.1.1 ≤ 20mg/kg hydrocortisone |        |       |            |            |
| Abbaszadeh 2012  | 0      | 92    | 0.6% | 0.33 [0.01, 8.20] |            |
| Bingol 2005      | 0      | 20    | 20% | 0.18 [0.01, 4.01] |            |
| Brethner 2019     | 0      | 15    | 15% | Not estimable |            |
| Halonen 2007    | 1      | 120   | 0.2% | 3.05 [0.12, 75.62] |            |
| Halvorsen 2003  | 1      | 147   | 0.4% | 1.00 [0.06, 16.14] |            |
| Kilger Schelling 2003/2004 | 2      | 48    | 43% | 0.27 [0.05, 1.41] |            |
| Murphy 2011      | 0      | 60    | 0% | Not estimable |            |
| Weis 2009        | 0      | 19    | 17% | Not estimable |            |
| Yared 1998/2000  | 2      | 106   | 110% | 0.69 [0.11, 4.19] |            |
| Yared 2007      | 0      | 37    | 0% | 2.64 [0.11, 71.99] |            |
| Subtotal (95% CI) | 664    | 648   | 9.9% | 0.57 [0.23, 1.31] |            |
| Total events     | 7      | 13    |            |            |

Heterogeneity: Chi² = 3.63, df = 6 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)

#### 1.1.2 20–40mg/kg hydrocortisone

| Study or Subgroup | Events | Total | Odds Ratio | Odds Ratio |
|-------------------|--------|-------|------------|------------|
| Abd El-Hakeem 2003a | 0      | 23    | 23% | Not estimable |            |
| Bourbon 2004a     | 0      | 12    | 12% | Not estimable |            |
| Deiterman 2012    | 31     | 2235  | 13.3% | 0.92 [0.59, 1.44] |            |
| El Azab 2002      | 0      | 9     | 8% | Not estimable |            |
| Hang 1999/2001    | 0      | 10    | 10% | 0.30 [0.01, 8.33] |            |
| Mardani 2012      | 0      | 43    | 50% | Not estimable |            |
| Moraru 2005       | 0      | 10    | 10% | Not estimable |            |
| Sobieski 2008     | 0      | 13    | 15% | Not estimable |            |
| VonSpiegel 2001/2002 | 0   | 10    | 10% | Not estimable |            |
| Whitleck 2006     | 154    | 3755  | 67.7% | 0.98 [0.69, 1.08] |            |
| Whitleck 2015     | 1      | 30    | 0% | 3.10 [0.12, 79.23] |            |
| Subtotal (95% CI) | 6150   | 6167  | 81.7% | 0.87 [0.71, 1.07] |            |
| Total events      | 186    | 212   |            |            |

Heterogeneity: Chi² = 1.03, df = 3 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)

#### 1.1.3 40–100mg/kg hydrocortisone

| Study or Subgroup | Events | Total | Odds Ratio | Odds Ratio |
|-------------------|--------|-------|------------|------------|
| Al-Shawabih 2016  | 2      | 170   | 0.8% | 1.00 [0.14, 7.18] |            |
| Bourbon 2004b     | 0      | 12    | 12% | Not estimable |            |
| Liakopoulos 2007  | 1      | 40    | 0% | 2.92 [0.12, 74.01] |            |
| Lommrothov 2013  | 2      | 22    | 22% | 2.10 [0.18, 20.01] |            |
| Oliver 2004       | 0      | 62    | 63% | Not estimable |            |
| Prasongsukarn 2005 | 0    | 43    | 43% | Not estimable |            |
| Rao 1977          | 2      | 75    | 3% | 0.69 [0.11, 4.05] |            |
| Rubens 2005       | 0      | 34    | 34% | 0.32 [0.01, 8.23] |            |
| Rumalla 2001      | 0      | 6     | 7% | Not estimable |            |
| Taleska 2020      | 0      | 20    | 20% | Not estimable |            |
| Vukovic 2011      | 0      | 29    | 28% | Not estimable |            |
| Subtotal (95% CI) | 913    | 912   | 3.1% | 0.99 [0.37, 2.69] |            |
| Total events      | 7      | 7     |            |            |

Heterogeneity: Chi² = 1.44, df = 4 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)

#### 1.1.4 > 100mg/kg hydrocortisone

| Study or Subgroup | Events | Total | Odds Ratio | Odds Ratio |
|-------------------|--------|-------|------------|------------|
| Andersen 1989     | 1      | 8     | 8% | 3.40 [0.12, 96.70] |            |
| Boscoe 1983       | 3      | 17    | 17% | 0.2% | 8.45 [0.40, 177.29] |            |
| Celik 2004        | 1      | 30    | 30% | 0.8% | 0.48 [0.04, 5.63] |            |
| Chaney 1998/1999  | 1      | 30    | 30% | 0.8% | 0.48 [0.04, 5.63] |            |
| Chaney 2001a      | 0      | 29    | 29% | 0.6% | 0.32 [0.01, 8.24] |            |
| Chaney 2001b      | 0      | 30    | 30% | 0.6% | 0.31 [0.01, 7.90] |            |
| Codd 1977         | 1      | 75    | 75% | 0.2% | 3.04 [0.12, 75.83] |            |
| Cweitzer 1996     | 7      | 165   | 130% | 2.1% | 1.11 [0.34, 3.57] |            |
| Fich 1978         | 0      | 25    | 25% | Not estimable |            |
| Fierres 1964/1987 | 0      | 40    | 40% | Not estimable |            |
| Mayumi 1997       | 0      | 12    | 12% | Not estimable |            |
| Niazi 1979a       | 0      | 30    | 30% | Not estimable |            |
| Niazi 1979b       | 0      | 30    | 30% | Not estimable |            |
| Villepe 1977      | 6      | 50    | 50% | 3.9% | 0.48 [0.16, 1.43] |            |
| Wain 1959         | 0      | 10    | 10% | Not estimable |            |
| Subtotal (95% CI) | 581    | 545   | 9.2% | 0.85 [0.47, 1.53] |            |
| Total events      | 20     | 22    |            |            |

Heterogeneity: Chi² = 5.81, df = 8 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)

Total (95% CI) 7908 7872 100.0% 0.86 [0.71, 1.03]
Total events 220 254

Heterogeneity: Chi² = 12.78, df = 24 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)
Test for subgroups differences: Chi² = 1.04, df = 3 (P = 0.76); I² = 0%
low-dose corticosteroids (≤20 mg/kg hydrocortisone) were effective for reducing the risk of atrial fibrillation, with no positive effects observed at a slightly higher dose (20–40 mg/kg hydrocortisone), a high dose (40–100 mg/kg hydrocortisone), or an ultra-high dose (>100 mg/kg hydrocortisone). These findings were not noticeably different when we re-analyzed 27 high-quality RCTs (27/33 RCTs), with low heterogeneity and no detectable publication bias. Unfortunately, the relevant molecular mechanisms are not clear, although the SIRS can induce atrial fibrillation (23). Thus, we speculate that low-dose corticosteroids might inhibition SIRS without increasing cardiomyocyte damage, which would reduce the incidence of atrial fibrillation. In contrast, high-dose corticosteroids might reduce SIRS but increase cardiomyocyte damage, which would not reduce the risk of atrial fibrillation.

The SIRS can cause systemic multi-organ damage, which often involves kidney damage (5–7). Prophylactic administration of corticosteroids protects the tissues and prevents the further development of organ damage. This can be confirmed in Fig. 4, where corticosteroids significantly reduce the incidence of atrial fibrillation in high-risk patients.

![Figure 4](https://example.com/figure4.png)

**FIGURE 4** Impact of corticosteroids on postoperative new atrial fibrillation (adult).
organisms by inhibiting SIRS and thus reduces complications (8–10). We failed to identify significant effects of corticosteroids prophylaxis on the risks of pulmonary complications, neurological complications (stroke), gastrointestinal bleeding, and delirium, which might be related to the low incidences of those outcomes. However, prophylactic corticosteroids (≤50 mg/kg hydrocortisone) significantly reduced the risk of kidney injury in pediatric patients, and low-dose corticosteroids (≤20 mg/kg hydrocortisone) might reduce the risk of kidney injury in adult patients. While corticosteroids suppress the normal immune response and may increase the risk of postoperative infection (7), our results and those from previous studies suggest that corticosteroids prophylaxis did not influence the risk of postoperative infection (6, 13, 14). Ho et al. (6) reported that corticosteroids prophylaxis was closely associated with prolonged mechanical ventilation, and we found that low-dose corticosteroids (≤20 mg/kg hydrocortisone) significantly shortened the mechanical

![FIGURE 5](image-url)
ventilation duration for adult patients, while high doses (>100 mg/kg hydrocortisone) significantly prolonged the mechanical ventilation duration. We also found that low-dose corticosteroids significantly reduced the ICU and hospital LOSs for adult patients, which might be related to accelerated recovery that was caused by suppression of the SIRS and reduced tissue and organ damage. Therefore, corticosteroids may be a cost-effective prophylactic treatment (generally <$5/patient) that can help reduce the burden on patients and hospitals by decreasing the risks of complications and shortening the ICU and hospital LOSs. Furthermore, the lower risk of complications may improve patients’ perioperative quality of life.

Our meta-analysis considered the dose-dependent benefits and risks of prophylactic corticosteroids during adult and pediatric cardiac surgery based on 29 clinical outcomes. Our findings conflict with the lack of support for corticosteroids prophylaxis during cardiac surgery in previous studies (5–7, 13, 14) and the guidelines for adult cardiac surgery (16). Our results suggest that low-dose corticosteroids (≤20 mg/kg hydrocortisone) were not associated with a significant reduction in mortality, but might substantially benefit adult patients by inhibiting SIRS and reducing complications. Therefore, we recommend prophylactic administration of low-dose corticosteroids (≤20 mg/kg hydrocortisone) during adult cardiac surgery. However, the optimal dose range for corticosteroids prophylaxis during pediatric cardiac surgery is unclear, as we only identified a small number of related RCTs. Nevertheless, our results indicate that high-dose glucocorticoids did not provide any benefits and significantly increased insulin use, which may increase the risk of hyperglycemia and related complications.

The evidence from our study was judged to be high based on the GRADE system. The low-dose subgroup for adult cardiac surgery (≤20 mg/kg hydrocortisone) only included 14 small RCTs, although 10 of these RCTs were considered high-quality based on the Jadad scores. Thus, large multi-center RCTs are needed as an additional source of evidence to clarify efficacy and optimal dose range for low-dose prophylactic corticosteroids during adult and pediatric cardiac surgery with CPB.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS
LWC, TCC, XHZ, and ZHQ designed the study. XJY, ZHQ, and MYT completed the literature search. All authors screened the results, extracted the data, and assessed the risk of bias. LWC, TCC, and XJY performed the statistical analyses. TCC and XHZ wrote the report. All authors participated in evaluating
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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/article/10.3389/fsurg.2022.832205/full#supplementary-material.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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