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REVIEW

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The efficacy and safety of prophylactic corticosteroids for the prevention of adverse outcomes in patients undergoing heart surgery using cardiopulmonary bypass: a systematic review and meta-analysis of randomized controlled trials

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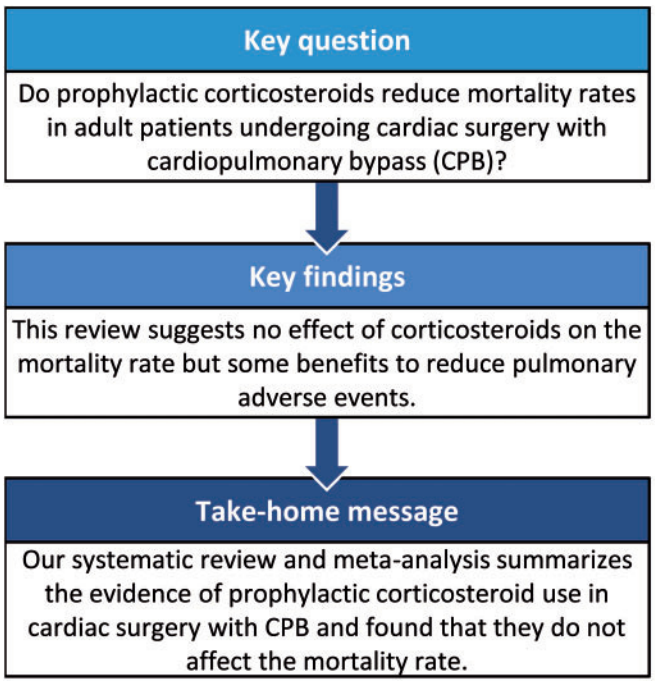

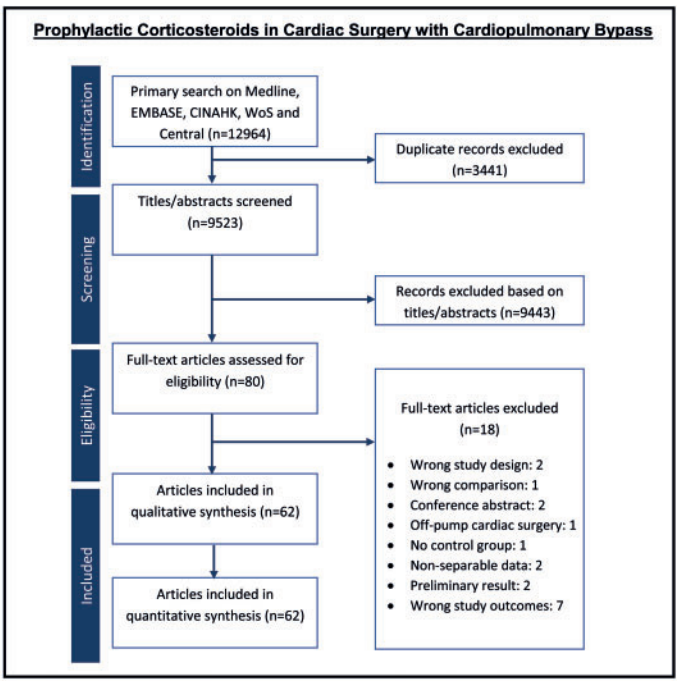

Summary

Corticosteroids are often administered prophylactically to attenuate the inflammatory response associated with cardiac surgery using cardiopulmonary bypass (CPB). However, the efficacy and safety profile of corticosteroids remain uncertain. The primary aim of this

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systematic review and meta-analysis was to investigate the effect of corticosteroids on mortality in adult cardiac surgery using CPB. Secondary aims were to examine the effect of corticosteroids on myocardial adverse events, pulmonary adverse events, atrial fibrillation, surgical site infection, gastrointestinal bleeding and duration of stay in the intensive care unit and hospital. Randomized controlled trials (RCTs) were systematically searched in electronic databases (MEDLINE, EMBASE, CINAHL, CENTRAL and Web of Science) from their inception until March 2019. Observational studies, case reports, case series and literature reviews were excluded. Sixty-two studies ($n = 16\,457$ patients) were included in this meta-analysis. There was no significant difference in mortality between the corticosteroid and placebo groups [odds ratio (OR) 0.96, 95% confidence interval (CI) 0.81–1.14; $P = 0.65$, participants = 14 693, studies = 24, evidence of certainty: moderate]. Compared to those receiving a placebo, patients who were given corticosteroids had a significantly higher incidence of myocardial adverse events (OR 1.17, 95% CI 1.03–1.33; $P = 0.01$, participants = 14 512, studies = 23) and a lower incidence of pulmonary adverse events (OR 0.86, 95% CI 0.75–0.98; $P = 0.02$, participants = 13 426, studies = 17). The incidences of atrial fibrillation (OR 0.87, 95% CI 0.81–0.94; $P < 0.001$, participants = 14 148, studies = 24) and surgical site infection (OR 0.81, 95% CI 0.73–0.90; $P < 0.001$, participants = 13 946; studies = 22) were all lower in patients who were given corticosteroids. In the present meta-analysis of 62 RCTs (16 457 patients), including the 2 major RCTs (SIRS and DECS trials: 12 001 patients), we found that prophylactic corticosteroids in cardiac surgery did not reduce mortality. The clinical significance of an increase in myocardial adverse events remains unclear as the definition of a relevant myocardial end point following cardiac surgery varied greatly between RCTs.

Keywords: Atrial fibrillation • Corticosteroids • Cardiopulmonary bypass • Cardiac surgery • Mortality • Surgical site infection

ABBREVIATIONS

CABG	Coronary artery bypass grafting
CI	Confidence interval
CPB	Cardiopulmonary bypass
DECS	The Dexamethasone for Cardiac Surgery trial
ICU	Intensive care unit
OR	Odds ratio
RCTs	Randomized controlled trials
SIRS	The Steroids in Cardiac Surgery trial

INTRODUCTION

Based on data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, ∼292 500 patients underwent myocardial revascularization and/or heart valve replacement in 2017 [1]. The introduction of cardiopulmonary bypass (CPB) in the early 1950s revolutionized heart surgery [2, 3]. However, CPB often induces a systemic inflammatory response syndrome (SIRS) where at least 2 or more systemic inflammatory response syndrome criteria were met by nearly 95% of patients within the first day after cardiac surgery [4–8]. Systemic inflammatory response syndrome involves complement activation, along with activation of platelets, neutrophils, monocytes and macrophages [5, 9]. As a result, coagulation and fibrinolytic cascades are initiated [6, 9]. The ensuing systemic inflammatory response is associated with fever, impaired alveolar gas exchange, vasodilatation, myocardial stunning, renal insufficiency and multi-organ dysfunction [4, 10–12]. Adverse outcomes from heart surgery including myocardial infarction, pulmonary dysfunction, renal impairment and death are associated with systemic inflammatory response syndrome [13–15].

Corticosteroids are potent anti-inflammatory agents, which inactivate inflammatory genes and inhibit synthesis of anti-inflammatory proteins during the process of inflammation [5, 16]. They inhibit the release of biochemical inflammatory markers, minimizing the CPB-induced inflammatory response [5, 16]. In addition, generic corticosteroids are low-cost drugs, and as such more likely to be cost-effective if their use is associated with reduced incidences of adverse events after heart surgery with CPB. However, corticosteroids may have their own adverse effects. They commonly cause hyperglycaemia, which has been associated with immunosuppression and poor wound healing [5, 17, 18]. In addition, high-dose corticosteroids use have been associated with an increased risk of gastrointestinal bleeding [5, 17]. Whilst the anti-inflammatory effects of corticosteroids seem desirable, robust analysis on the evidence of efficacy and safety of corticosteroids is required before recommendations on the use of corticosteroids in heart surgery with CPB can be made.

A previous systematic review and meta-analysis published in 2011 found that corticosteroids were not associated with any significant reduction in clinically important adverse outcomes from heart surgery [19]. Since that review was published, 8 randomized controlled trials (RCTs) including 2 trials [20, 21] with large population sample sizes have been published [20–27]. Thus, an updated systematic review and meta-analysis is warranted to summarize the current understanding of the use of corticosteroids in patients undergoing heart surgery with CPB.

The primary aim of this review was to determine the effect of prophylactic corticosteroids on mortality in adult cardiac surgery with CPB. Secondary aims were to examine the effect of corticosteroids on complications of adult cardiac surgery, such as myocardial adverse events (including fatal and non-fatal myocardial infarction), pulmonary adverse events (including pulmonary oedema, infection or prolonged postoperative ventilation for respiratory failure), atrial fibrillation, surgical site infection, gastrointestinal bleeding and duration of stay in the intensive care unit (ICU) and hospital.

METHODS

This review paper was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [28]. The research questions were formulated using a population-intervention-comparison-outcomes approach (Supplementary Material, eTable 1).

Literature search

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (OvidSP), Embase (OvidSP), CINAHL (EBSCO), Science Citation Index Expanded (SCI-EXPANDED), Social Science Citation Index (SSCI) and Web of Science (Thomson Reuters) were searched (Supplementary Material, eTable 2), from their

inceptions until 31 March 2019, for RCTs comparing corticosteroids with either placebo or no treatment in adults undergoing heart surgery with CPB. The ClinicalTrials.gov (www.CLINICALTRIals.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/) databases were searched for any ongoing or unpublished trials. No restrictions on language of publication were applied. Reference lists from retrieved RCTs and systematic reviews and meta-analyses were hand-searched to identify any additional trials. Study authors were contacted for any missing or incomplete data when required.

Studies reporting parallel-arm RCTs were included in this review. There were no restrictions with regard to the duration of the study follow-up period. Studies comprising only off-pump coronary artery bypass grafting (CABG) surgery were excluded. However, studies that included both heart surgery with/and without CPB were included if data for those patients who underwent heart surgery with CPB, were reported separately. Studies involving paediatric populations were also excluded in this review because the harmful biological effects of CPB are more prominent in infants and newborns than the adult population, which may introduce a type II statistical error.

Outcomes

The primary outcome for this meta-analysis was mortality, where the data of the longest duration of follow-up were used for analysis. Secondary outcomes included postoperative myocardial adverse events (myocardial infarction based on either electrocardiography diagnosis, troponin-I, creatinine kinase-muscle/brain or lactate dehydrogenase), pulmonary adverse events (including pulmonary oedema, pleural effusion, pneumonia, pulmonary embolism and respiratory failure), surgical site infection (wound infection or mediastinitis), atrial fibrillation, gastrointestinal bleeding (ulcer, bleeding or perforation), resternotomy, stroke, author-defined acute kidney injury (increased creatinine level, oliguria or requiring dialysis), author-defined use of positive inotropes/vasopressor intraoperatively, requirement for blood transfusion and postoperative blood glucose level. Data from all available time points were recorded and for data analysis, the longest reported time-point was used for each study. Process outcomes that were evaluated included the duration of ICU stay (hours), duration of hospital stay (days) and quality of life (The Assessment of Quality of Life Scales, 5-Level EuroQol Health Survey, 36-Item Short-Form Health Survey).

Study selection

Selection of studies was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [29]. Two review authors (C.L. and D.P.S.) independently screened titles and abstracts for eligibility. Studies were coded as 'retrieve' (eligible or potentially eligible) or 'do not retrieve' (not eligible). Any disagreements at this stage were resolved by a third author (K.T.N.). The full-text study reports of potentially eligible studies were retrieved. Two review authors (C.L. and D.P.S.) independently screened the full-texts, identified those studies for inclusion and recorded reasons for the exclusion of ineligible studies. Any disagreements were resolved through consultation with a third author (K.T.N.). Duplicates were excluded and multiple reports of the same study were collated so that each study rather than each report was the unit of interest in this review.

Data extraction

Data were extracted from the full-text article of each included study by 2 authors independently (C.L. and D.P.S.) using a standardized data-extraction form. Disagreements between the data extractors were resolved by involving a third author (K.T.N.). One review author (K.T.N.) transcribed the data into the Review Manager file and ensured that data had been entered correctly by comparing the extracted data with that in the study reports. A second review author (D.P.S.) spot-checked study characteristics for accuracy.

Risk of bias assessment

Two review authors (C.L. and D.P.S.) independently assessed the risk of bias for each study using the Cochrane Collaboration's Risk of Bias tool [28]. Disagreements were resolved through discussion with a third author (K.T.N.). Each potential source of bias was graded as low, high or unclear. The risk of bias for each domain was summarized across all the included studies.

Statistical analysis

Review Manager version 5.3 was used for statistical analyses [30]. A 2-sided ρ-value of <0.05 was considered as statistical significance. For continuous variables, the weighted mean difference was calculated according to the inverse of the square of standard error. In view of the low event rates in all the measured outcomes, the Peto odds ratio (OR) was used for binary outcomes as it is a robust model for sparse outcome meta-analysis without extreme group imbalances [31], as was the case in the present meta-analysis. Due to variations in study-patient groups, clinical settings, concomitant care and differences in treatment, clinical heterogeneity was expected. The I^2 statistic was used to assess the statistical heterogeneity [28]. Boundaries of <40%, 40–60% and >60% were used to define low, moderate and substantial levels of heterogeneity, respectively. If no substantial heterogeneity was noted, a fixed effects model analysis was used to pool estimates. If substantial heterogeneity ($I^2 \geq 60\%$) was observed, a random effects model analysis was used.

Subgroup analyses and sensitivity analysis

A funnel plot was created to explore the possibility of publication bias for the primary outcome. Subgroup analyses were performed on the major outcomes (mortality, myocardial adverse events, pulmonary adverse events, atrial fibrillation and surgical site infection), by stratifying dose of steroids into high-dose (total administered dose >1 g of hydrocortisone-equivalent) and low-dose (total administered dose ≤1 g of hydrocortisone-equivalent) (equivalent anti-inflammatory doses of corticosteroids: prednisolone 5 mg = betamethasone 750 μg; deflazacort 6 mg; dexamethasone 750 μg; hydrocortisone 20 mg; methylprednisolone 4 mg; prednisone 5 mg; triamcinolone 4 mg) [32]. To assess the robustness of our primary outcome (mortality), we also performed a sensitivity analysis by including only studies of low risk of bias.

Certainty of evidence assessment

The GRADE assessments of the evidence and summary of findings were independently performed by 2 authors (D.P.S. and C.L.) using the GRADEpro/GDT software [31]. Based on the Cochrane handbook, we downgraded a starting rating of 'high quality' evidence of RCT based on the 5 criteria (risk of bias, inconsistency, indirectness, imprecision and publication bias) by 1 level for serious concern or by 2 levels for very serious concerns. Any disagreements were resolved by a third author (K.T.N.).

Trial sequential analysis

Trial sequential analysis was performed on the primary outcome (mortality) to assess the risk of random error and multiplicity phenomenon due to repeated significant testing in meta-analyses [33]. The required meta-analysis information size and adjusted significance thresholds were calculated based on a 2-sided sequential analysis-adjusted fixed effects model with 5% risk of type 1 error and power of 80%.

RESULTS

Trial selection

Searching of the databases found 9523 non-duplicate citations for titles and/or abstracts screening. Eighty relevant articles were retrieved for full-text assessment. Of these, a total of 62 studies (16 457 patients) were included in this present systematic review (Supplementary Material, eFig. 1). The clinical characteristics of all included studies are illustrated in Supplementary Material, eTable 3. Searching of clinical trials registers identified 2 relevant ongoing studies (Supplementary Material, eTable 4) [34, 35].

Study characteristics

Of the included 62 studies, 8 were published since 2010, 36 were in the 2000s, 11 in the 1990s, 4 in the 1980s and 3 in the 1970s. Altogether, 16 457 patients were included from 62 trials with a mean age of 65 years and a predominance of male participants (66.3%). Only 7 studies included specifically 'high-risk' surgical patients with all other study-populations consisting of 'low-risk' or 'unspecified-risk' CABG, heart valve or other heart surgery. In the majority of the studies, the sample sizes were small (median number of patients per study = 50). The type of corticosteroids [hydrocortisone ($n = 7$), methylprednisolone ($n = 53$), dexamethasone ($n = 15$), prednisone ($n = 2$), betamethasone ($n = 1$), combination of hydrocortisone and methylprednisolone ($n = 1$), combination of methylprednisolone and prednisone ($n = 3$)], period of treatment and dosage of corticosteroids administered varied widely between studies.

Risk of bias assessment

The summary risk of bias assessment was 'Low' for 19 studies, 'Unclear' for 27 studies and 'High' for 16 studies (Supplementary Material, eFigs 2 and 3). The greatest source of bias across the studies was lack of blinding. The summary of findings/quality of evidence is displayed in Supplementary Material, eTable 5. Results of the meta-analyses for all primary and secondary outcomes are outlined in Supplementary Material, eTable 6.

Primary outcome

The use of corticosteroids in heart surgery did not reduce mortality [Peto OR 0.96, 95% confidence interval (CI) 0.81–1.14; participants = 14 693; studies = 24; certainty of the evidence: moderate]. Statistical heterogeneity was low ($I^2 = 0\%$). The funnel plots for mortality did not reveal substantial asymmetry, suggesting a low risk of publication bias. Sensitivity analysis of low-risk bias trials demonstrated similar results (Peto OR 0.95, 95% CI 0.79–1.13). The trial sequential analysis of a diversity-adjusted required information size for mortality was 17 248 patients (Fig. 1). With 14 693 patients, only 85.2% of the required information size was available to detect or reject a relative risk reduction of 20%, based on a 5% risk of type 1 error (2-sided), a power of 80%, and an incidence in the control arm of 3.95% with a model variance-based heterogeneity correction.

Secondary outcomes

The risk of myocardial adverse events was significantly increased in patients receiving corticosteroids (Peto OR 1.17, 95% CI 1.03–1.33; participants = 14 512, studies = 23, the certainty of the evidence: very low). The definition of myocardial adverse events used in the Steroids in Cardiac Surgery trial [20] differed from the other studies as it was based only on a rise in the cardiac enzyme (creatinine kinase-muscle/brain), which led to a very high incidence of myocardial adverse events (13% in corticosteroids group, 11% in the placebo group) [20]. The combination of *post-hoc* analysis on the incidence of myocardial infarction (defined as the presence of new Q-waves on the postoperative electrocardiograph) in the SIRS trial [20] and sub-analysis of the remaining studies showed no significant difference in myocardial adverse events between the corticosteroid and placebo groups (Peto OR 0.90, 95% CI 0.70–1.16; participants = 14 512, studies = 23; certainty of the evidence: very low), indicating the introduction of bias as a result of including the SIRS trial in this measured outcome. By removing the SIRS trial in the sensitivity analysis, the difference in the incidence of the myocardial adverse events became non-significant and the effect changed direction (Peto OR 0.91, 95% CI 0.68–1.20; participants = 7005, studies = 22).

Corticosteroids significantly reduced the incidence of pulmonary adverse outcomes (Peto OR 0.86, 95% CI 0.75–0.98; participants = 13 426; studies = 17 studies, $I^2 = 0\%$, the certainty of the evidence: low). In comparison to the placebo, the incidence of atrial fibrillation (Peto OR 0.87, 95% CI 0.81–0.94; participants = 14 148, studies = 24, certainty of the evidence: very low) and surgical site infections (Peto OR 0.81, 95% CI 0.73–0.90; participants = 13 946, studies = 22, certainty of the evidence: low) were significantly lower in the corticosteroids group. The duration of ICU stay was shorter in patients who received corticosteroids compared to a placebo (mean difference -4.41 h, 95% CI −6.13 to −2.70; participants = 13 490, studies = 31) as was the duration of hospital stay (mean difference −0.54 days, 95% CI -1.05 to -0.02; participants = 13 196, studies = 21). There were no significant differences between patients who received corticosteroids compared to placebo in the incidence of gastrointestinal bleeding (Peto OR 1.29, 95% CI 0.70–2.39; participants = 5026,

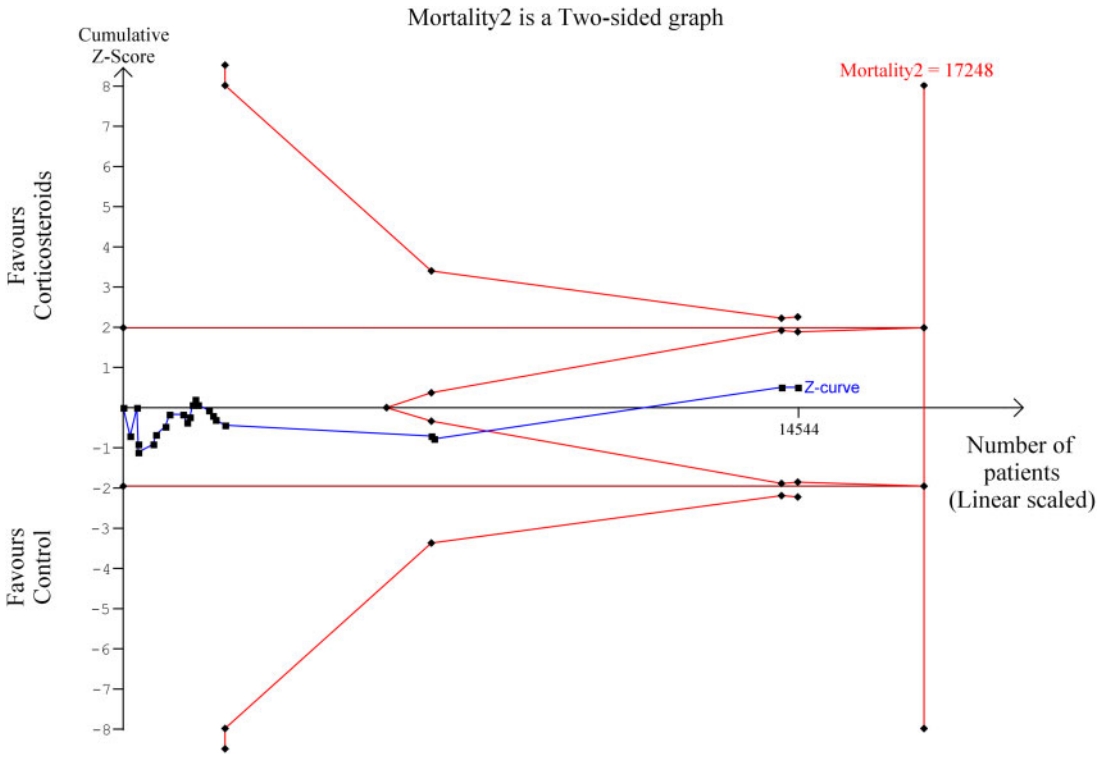

Figure 1: Trial sequential analysis of mortality.

studies = 5), author-defined acute kidney injury (Peto OR 0.84, 95% CI 0.68–1.02; participants = 12 734, studies = 12), resternotomy (Peto OR 1.12, 95% CI 0.47–2.65; participants = 818, studies = 7), stroke (Peto OR 0.84, 95% CI 0.66–1.06; participants = 13 218; studies = 14), use of positive inotropes (Peto OR 0.98, 95% CI 0.74–1.30; participants = 1390, studies = 19) or required for packed red cell transfusion (Peto OR 0.96, 95% CI 0.88–1.05; participants = 8127, studies = 7).

There was no standardization on the reporting of postoperative blood glucose levels across all the included studies. Three studies recorded the highest postoperative blood glucose level [9, 21, 36], another 4 trials [20, 23, 37, 38] reported the number of patients with postoperative hyperglycaemia and 10 [18, 25–27, 39–44] reported different time-points of blood glucose level between the corticosteroid and placebo groups. Thus, a meta-analysis of postoperative blood glucose levels was not performed due to significant variation in the interpretation of glucose level across studies.

Subgroup analyses

Eleven studies [22, 27, 37, 38, 45–51] used low-dose corticosteroids with the remaining 51 studies administered high-dose corticosteroids. There was no significant interaction between high- and low-dose corticosteroid and the incidences of myocardial or pulmonary adverse events and surgical site infection. However, there was significant interaction ($P = 0.001$) with the incidence of atrial fibrillation, with the treatment effect favouring low- over high-dose corticosteroids. Covariate distribution occurred in this subgroup analysis due to an inadequate number of trials (6) and sample size ($n = 924$) with moderate heterogeneity in the low-dose corticosteroid subgroup.

Quality of life

Since the earlier review, only 2 studies [21, 32] investigated quality of life outcomes. In the Dexamethasone for Cardiac Surgery trial, using the SF-36 (physical and mental components), there was no clear difference between the corticosteroid and placebo groups [21]. The outcomes of EQ-5D also remained similar between the 2 groups [21]. One sub-study of SIRS trial utilized the Postoperative Quality of Recovery Scale to assess the quality of recovery after heart surgery [32]. In 482 patients available for the recovery analysis, there were no differences between the corticosteroid and placebo groups for overall recovery and individual recovery domains [32].

DISCUSSIONS

In this updated systematic review and meta-analysis of the use of prophylactic corticosteroids in heart surgery with CPB, no effect on mortality could be demonstrated. This finding supports the recommendation of the 2017 EACTS Guidelines on Perioperative Medication in Adult Cardiac Surgery where the routine use of prophylactic corticosteroids is not indicated for adults undergoing cardiac surgery (Class of recommendation III and Level of Evidence A) [52]. The present study includes 2 recent RCTs (DECS and SIRS trials), which both have very much larger sample sizes compared to earlier published RCTs [20, 21]. Both trials included mainly 'high-risk' patients for heart surgery. As these 2 trials dominate the results of the meta-analysis, the evidence from the present systematic review and meta-analysis can be considered generalizable to the current population undergoing heart surgery, which commonly consists of elderly patients with multiple comorbidities.

In the subgroup analysis of the DECS trial based on the treatment-by-age interaction of corticosteroids on mortality events, it suggested that a younger patient age (<65 years) was associated with a lower risk of mortality than older age (≥65 years) when receiving corticosteroids [21]. It is possible that younger patients have a more intense inflammatory response than elderly patients where suppression of this effect with corticosteroids may contribute to a benefit in young patients [52]. However, such treatment-by-age interaction was not observed in the SIRS trial [20]. The sex-based subgroup differences of corticosteroids on mortality were not significant in both the DECS and SIRS trials [20, 21]. Given that the mortality risk after cardiac surgery was small (∼4%), we would need a trial with a large population sample size to prove an effect on mortality from corticosteroids. The present meta-analysis did not achieve the required population sample size to detect a 20% reduction in mortality based on a 5% risk of type 1 error (2-sided) and 80% power. Thus, the findings of this meta-analysis cannot reliably exclude that corticosteroids may influence mortality in patients undergoing heart surgery with CPB.

The higher incidence of myocardial adverse events in patients receiving corticosteroid needs to be interpreted with caution as different definitions of myocardial infarction were used across different RCTs. The majority of cases of myocardial complications came from the SIRS trial [20]. In this study, the myocardial injury was defined as a rise in creatinine kinase-muscle/brain levels above a predefined threshold and/or presence of new Q-waves on the postoperative electrocardiography due to limited access to troponin measurement in some centres [20]. This may have contributed to the high levels of heterogeneity found in the analysis of myocardial adverse outcomes. Sensitivity analysis following the removal of data from the SIRS trial resulted in a major change in the direction of the effect and magnitude of the statistical finding. By including the reported incidence of myocardial infarction based on the *post-hoc* analysis of the SIRS [20], the finding corresponded to the aforementioned sensitivity analysis that corticosteroids did not increase the risk of myocardial infarction. Despite a statistically significant increase in the incidence of myocardial adverse events in patients receiving corticosteroids in the present meta-analysis, the clinical significance of this finding is unclear as it was not associated with an increase in mortality. Heart surgery is associated with myocyte trauma from cardioplegia and surgical trespass of the myocardium, so biological markers will be released but will not always be associated with clinically relevant adverse myocardial outcomes. Therefore, defining what clinically relevant myocardial adverse events following heart surgery are, is challenging.

In the present systematic review and meta-analysis, the reduction of pulmonary complications, atrial fibrillation and surgical site infections along with shorter durations of ICU and hospital stay in patients receiving corticosteroids may indicate the limited value of mortality as an outcome where the disease-specific benefit is likely to be in other clinical outcomes [53]. There remains scope for further investigation of patient recovery outcomes and inflammation-specific outcomes in future trials. Thus, an ongoing RCT (DECS-II study, NCT03002259) has been designed to examine the patient-centred outcomes, which focusses on enhanced recovery and earlier hospital discharge in adult patients after high-dose corticosteroids in heart surgery with CPB (single-dose administration of 1 mg/kg, maximal dose of 100 mg of dexamethasone before CPB) [35].

Given that the majority of sample size for incidences of atrial fibrillation and surgical site infection were contributed by two high quality large trials (DECS and SIRS), it is likely reflective of the true effect of prophylactic corticosteroids on the aforementioned outcomes [20, 21]. The positive effect of corticosteroids in reducing the incidence of atrial fibrillation and surgical site infection found in the present meta-analysis could be skewed by many of the previous RCTs with a small population sample size with a high risk of study bias and substantial heterogeneity. Thus, we confirmed that corticosteroids did not reduce the incidence of atrial fibrillation and surgical site infection based on the negative findings of the 2 robust large RCTs [20, 21]. However, patients with chronic steroid therapy should continue their usual dose of corticosteroids on the day of operation [52, 54]. Additional preoperative stress–dose corticosteroids may be appropriate but is not evidence-based [54]. The potential benefits of corticosteroids on these secondary outcomes warrant future adequately powered RCTs to establish the true effect on these postoperative outcomes.

The present systematic review and meta-analysis are incomparable with those undertaken prior to publication of the DECS and SIRS trials [14, 15], because the sample sizes of these 2 trials are so much larger than all the previously published trials. The benefits of corticosteroids reducing mortality found in meta-analyses undertaken prior to these 2 large RCTs may have had false-positive signals due to small sample sizes and so the potential for a type I error. Another systematic review and meta-analysis have been published recently which included both recent large RCTs [20, 21]. It included 56 studies between 1977 and 2015 and concluded that corticosteroids had an unclear impact on mortality with an increased risk of myocardial injury [55]. In the present systematic review, we have updated our literature search up to 2019 and included 11 studies [23–25, 43, 48, 56–61] that were not included by Dvirnik et al.'s review [55]. Moreover, 5 of the 56 studies were excluded from our review due to lack of randomization [62, 63], the inclusion of children in the study population [64], the inclusion of patients undergoing non-heart surgery [65] or non-compatible study design [66]. There were also some slight differences in our search strategy which may have led to different search outcomes between the 2 meta-analyses. In contrast to the latest meta-analysis [55], our findings suggest that the risk of myocardial adverse events may be overestimated and indeed, there may be some benefits on secondary outcomes, namely postoperative pulmonary complication and length of ICU/hospital stay from the use of corticosteroids that require future RCTs to confirm the certainty of evidence.

Limitations

There are several important qualitative limitations of the RCTs that were used in the present meta-analysis, which will have influenced the interpretation of our findings. Firstly, the risk of bias of most of the included RCTs was classified as either 'Unclear' or 'High' (43/62). Secondly, in many of the included RCTs, the primary end points were either surrogate markers of inflammation or ventilator parameters, and reporting of clinical outcomes did not form part of the study protocol. Non-standardized collection of clinical outcomes carries a high risk of observer bias, particularly when

outcome adjudication is not blinded. Furthermore, the duration of follow-up periods were short and heterogeneous in the majority of RCTs, so inflating the risk of under-reporting of adverse outcomes. Thirdly, DECS and SIRS trials that contributed 12 001/16 457 patients and resulted in >80% of the pooled effects on the primary outcome [20, 21]. Therefore, these 2 RCTs [20, 21] will have heavily influenced both the mortality outcome and the risk of bias for this meta-analysis. As these 2 RCTs [20, 21] were of high quality and had well-defined clinical outcomes as primary end points, as well as long periods of follow-up, some qualitative limitations discussed earlier will clearly be of less importance in this updated meta-analysis. Furthermore, 62 RCTs spanned across 4 decades, from the mid-1970s until 2017. During this time, many aspects of anaesthesia, surgical and perioperative care have greatly changed. The type of cardiac surgery, study protocols and definitions of myocardial or pulmonary adverse events that were used, varied across all the included studies, which may have introduced variance into our findings. In this review, the very low to moderate level of evidence as a result of the risk of bias, inconsistency, imprecision and publication bias, limits any recommendations on the prophylactic use of corticosteroids in cardiac surgery with CPB.

CONCLUSION

In conclusion, in the present meta-analysis of 62 RCTs (16 457 patients), including of the 2 major RCTs (SIRS and DECS; 12 001 patients), prophylactic corticosteroids in cardiac surgery did not reduce mortality. The clinical significance of an increase in myocardial adverse events remains unclear as defining a relevant myocardial end point following cardiac surgery is challenging.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Author contributions

Ka Ting Ng: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Writing–original draft; Writing–review & editing. **Judith Van Paassen:** Conceptualization; Formal analysis; Supervision; Writing–review & editing. **Clare Langan:** Conceptualization; Data curation; Writing–review & editing. **Deep Pramod Sarode:** Conceptualization; Data curation; Formal analysis; Writing–original draft; Writing–review & editing. **M. Sesmu Arbous:** Conceptualization; Data curation; Writing–review & editing. **R Peter Alston:** Conceptualization; Data curation; Formal analysis; Project administration; Supervision; Writing–original draft; Writing–review & editing. **Olaf M. Dekkers:** Conceptualization; Formal analysis; Supervision; Writing–review & editing.

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