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REVIEW

Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: a meta-analysis of randomized trials

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We sought to establish the efficacy and safety of prophylactic steroids in adult patients undergoing cardiopulmonary bypass (CPB). We performed a meta-analysis of randomized trials reporting the effects of prophylactic steroids on clinical outcomes after CPB. Outcomes examined were mortality, myocardial infarction, neurological events, new onset atrial fibrillation, transfusion requirements, postoperative bleeding, duration of ventilation, intensive care unit (ICU) stay, hospital stay, wound complications, gastrointestinal complications, and infectious complications. We included 44 trials randomizing 3205 patients. Steroids reduced new onset atrial fibrillation [relative risk (RR) 0.71, 95% confidence interval (CI) 0.59 to 0.87], postoperative bleeding [weighted mean difference (WMD) −99.6 mL, 95% CI −149.8 to −49.3], and duration of ICU stay (WMD −0.23 days, 95% CI −0.40 to −0.07). Length of hospital stay was also reduced (WMD −0.59 days, 95% CI −1.17 to −0.02), but this result was less robust. A trend towards reduction in mortality was observed (RR 0.73, 95% CI 0.45 to 1.18). Randomized trials suggest that perioperative steroids have significant clinical benefit in CPB patients by decreasing the risk of new onset atrial fibrillation, while results are encouraging for reducing bleeding, length of stay, and mortality. These data do not raise major safety concerns, however, a sufficiently powered trial is warranted to confirm or refute these findings.

Keywords Steroids • Cardiac surgery • Meta-analysis • Cardiopulmonary bypass • Inflammatory response • Clinical outcomes

Introduction

Cardiopulmonary bypass (CPB) exposes the body to foreign surfaces and non-physiologic blood flow. This initiates a systematic inflammatory response that is intensified by the ischaemia-reperfusion injury that can occur when weaning from CPB.[1–3] The increased endothelial permeability and free radical damage to vessels and parenchyma that results is due to a complex interplay between platelets, neutrophils, monocytes, macrophages, coagulation, fibrinolytic cascades, and kallikrein cascades.[1–5] This inflammatory reaction may contribute to postoperative complications including ventricular dysfunction and multiorgan failure.

Studies demonstrate steroids are effective in attenuating the inflammation secondary to CPB.[5] Despite this, many surgeons remain unenthusiastic about the routine use of perioperative steroids in patients undergoing CPB. This may be because many of the existing studies are underpowered to assess clinically important outcomes, focusing on surrogate outcomes such as markers of inflammation. Further, physicians fear potential adverse effects associated with their use.

Accurate understanding of the impact of steroid therapy in patients undergoing CPB requires a systematic, comprehensive, and unbiased accumulation and summary of the available evidence. We therefore undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to address the following question: What is the efficacy and safety of perioperative steroids in patients undergoing CPB?

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Methods

A protocol was prospectively developed outlining the criteria for trial selection, outcomes of interest, approach to assessing trial quality, and the statistical methodology.

Eligibility criteria

We included RCTs that compared perioperative steroid treatment with a control group (i.e. standard care or placebo) among adults undergoing CPB reporting at least one of the a priori defined outcomes, having at least one event occur in the treatment or control group. RCTs were eligible regardless of their primary objective or language of publication. We excluded trials only published in abstract forms.

Trial identification

We undertook an electronic search of Embase, Medline, Cochrane, CINAHL, and OVID using the search terms cardiac surgery, cardiac surgical procedure, open heart surgery, coronary artery bypass, mitral valve, aortic valve, heart valve, cardiopulmonary bypass, extracorporeal circulation, preoperative, and prophylactic, in combination with generic and trade names of steroid preparations. We handsearched the reference lists from eligible trials. Finally, we used the 'see related articles' feature for key publications in Pubmed.

Trial selection

All title and abstracts from the electronic search were uploaded into TrialStat SRS version 3.0 and were evaluated by two independent investigators ($\kappa = 0.96$). The consensus process to resolve disagreements required researchers to discuss the decision; in all cases one person recognized an error.

Data extraction and quality assessment

We abstracted descriptive data (e.g. patient population, intervention) and markers of validity (e.g. blinding) from all trials. Outcomes of interest were mortality, myocardial infarction (MI), neurological events, new onset atrial fibrillation, transfusion requirements, postoperative bleeding, duration of ventilation, intensive care unit (ICU) stay, and hospital stay, wound, gastrointestinal (GI), and infectious complications. We accepted the authors' definitions for clinical outcomes. Postoperative bleeding was defined as 24 h chest tube output or total chest tube output, which ever was reported.

Two independent investigators abstracted data and resolved differences using the consensus process mentioned earlier. We attempted to obtain all missing data from the corresponding author. We used the Jadad criteria to evaluate the trials included in our meta-analysis ($\geq$3 points was considered high quality).[6]

Statistical analysis

For each trial we calculated the relative risk (RR) of each binary outcome and the weighted mean difference (WMD) for continuous variables and their 95% confidence intervals (CI), comparing patients receiving perioperative steroid therapy with patients receiving control therapy. We pooled the effect estimate of the outcomes using the DerSimonian and Liard random effects model.

The I^2 value was calculated as a measure of heterogeneity for each outcome analysis. An I^2 of $<$25% was considered low.[7] A priori hypotheses related to blinding status, surgery type [i.e. isolated coronary artery bypass graft (CABG) surgery vs. other (valve or combined)], steroid used (i.e. methylprednisolone vs. other), and steroid dose (i.e. (1.5 gm methylprednisolone or equivalent in 24 h or repeated dosing for $>$24 h vs. $<$1.5 gm in 24 h) were explored to explain potential heterogeneity (I^2 value (25%).

In studies reporting the median and quartiles, the median was assumed to most accurately represent the central tendency and was treated as the mean. The distribution was assumed to be normal with a z-value of $\pm$0.68 corresponding to the reported 25th and 75th percentiles. In this manner, the standard deviation was calculated. The variances for three data points were imputed by using the mean of the other studies. In studies reporting multiple steroid treatment groups, the results of the groups were pooled.

We conducted a sensitivity analysis to examine the robustness of the results. The analyses were repeated after (i) removing those studies with imputed data and (ii) including only the high-quality studies. To evaluate potential publication bias we constructed a funnel plot for the outcomes and visually inspected it for asymmetry. All statistical calculations were performed using RevMan 4.2.8 (Cochrane Collaboration, Oxford).

The sample size required for a meta-analysis is at least as large as that of a single optimally powered RCT and can be determined using the heterogeneity-corrected optimal information size. If the meta-analysis does not surpass its heterogeneity-corrected optimal information size then it is essentially similar to an interim analysis of a single RCT. Because statistically significant findings in this situation are prone to false positive findings, we used methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis to assess the reliability and conclusiveness of the available evidence. We used the optimal information size to construct a Lan DeMets sequential monitoring boundary, analogous to interim monitoring in an RCT.[8] The sequential ordering of the studies was based on the publication date of the manuscript. In this way, we assessed whether the evidence for significant outcomes that had not surpassed their optimal information size were reliable and conclusive.

Results

Selection of included studies

The process of trial selection is presented in *Figure 1*. Forty-four RCTs published between the years 1977 and 2007 fulfilled our eligibility criteria. *Table 1* summarizes the characteristics of the included trials. The median sample size of the RCTs was 51 patients (range 13–295). Twenty-eight trials focused on isolated CABG patients, three on isolated valve patients, seven on CABG and valve patients, and six on all CPB patients. Treatment protocols varied in duration and formulation including dexamethasone, methylprednisolone, hydrocortisone, and prednisolone.

Quality assessment

Twenty-nine of the trials reported a double-blind design. Twenty-six of the trials were of high quality by the criteria of Jadad *et al.* (score $\geq$3). The mean Jadad score for all the trials was 2.7 $\pm$ 1.4. The Jadad scores are presented in *Table 1*.

Outcomes

Table 2 presents the results of the meta-analysis for each outcome. There were few events reported for most outcomes, limiting inferences possible about whether steroids affect outcomes.

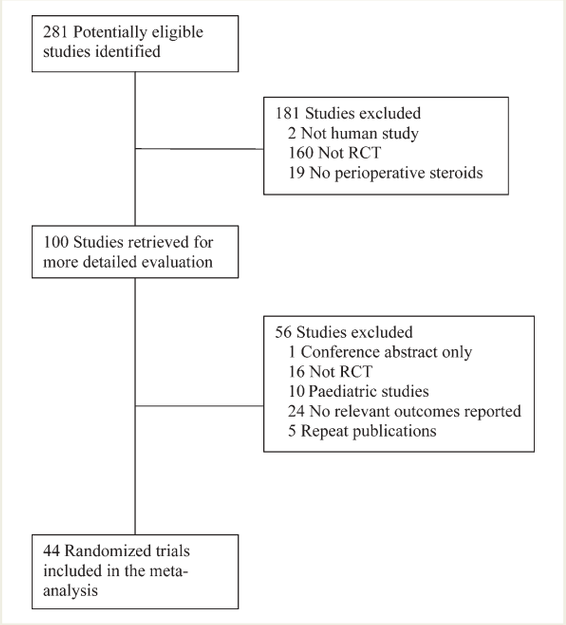

Figure 1 Process of trial selection.

Mortality

The overall mortality rate from the data was 3.2% (65 of 2038 patients). There was a trend towards a reduction in mortality with steroid therapy (RR 0.73, 95% CI 0.45 to 1.18, $P = 0.20$, $I^2 = 0\%$) (*Figure 2*).

Myocardial infarction

The pooled results showed no significant decrease in MI with steroid treatment compared with no steroid or placebo (RR 0.99, $P = 0.98$). There were a small number of MIs within these trials (54 in 1288 patients, 4.2%).

Neurological events

The pooled results showed no significant decrease in neurological events with steroid treatment compared with no steroid or placebo (RR 0.85, $P = 0.77$). There was a small number of neurological events reported (27 in 1103 patients, 2.4%).

New onset atrial fibrillation

There were 178 patients who developed new onset atrial fibrillation among the 719 patients (24.7%) randomized to steroid therapy compared with 246 patients who developed new onset atrial fibrillation among the 693 patients (35.5%) randomized to placebo or standard care (RR 0.71, 95% CI 0.59 to 0.87, $P = 0.001$, $I^2 = 21\%$) (*Figure 3*).

Postoperative bleeding and homologous red blood cell requirements

Although steroid treatment resulted in a small but significant reduction in postoperative bleeding (WMD −100 mL, $P < 0.0001$), there was no difference in the number of homologous RBCs administered (WMD −0.33, $P = 0.41$). Only four of the included studies reported transfusion requirements and these results were heterogeneous ($I^2 = 76\%$) (*Figure 4*).

Duration of mechanical ventilation

The pooled results showed no significant difference in the duration of mechanical ventilation in hours between the treatment groups (WMD −0.25, $P = 0.59$).

Duration of intensive care unit stay

Steroid treatment resulted in a significant reduction in the number of days spent in the ICU compared with control therapy (WMD −0.23, $P = 0.006$) (*Figure 5*).

Duration of hospital stay

Steroid treatment resulted in a significant reduction in the number of days spent in the hospital compared with no steroid or placebo (WMD −0.59, $P = 0.04$).

Postoperative wound, gastrointestinal and infectious complications

Relatively few studies reported on these three outcomes. In the pooled analyses, no significant difference was observed in GI complications (three studies available), wound complications (three studies available), or infectious complications (13 studies available).

Exploring heterogeneity and subgroup analyses

Significant heterogeneity was observed in the outcomes of length of ICU stay, length of hospital stay, length of ventilation, postoperative bleeding, and transfusion requirements. Only for duration of mechanical ventilation did an a priori hypothesis help explain the observed heterogeneity. There was a difference in the effect of steroids on duration of mechanical ventilation between the CABG studies ($n = 13$ studies, 95% CI −0.21 to 2.51 h) and the other surgery studies ($n = 10$ studies, 95% CI −1.28 to −0.40 h).

Sensitivity analysis

Repeating the analyses including only those trials scored as high quality did not alter the significance of any of the results. Funnel plots of those outcomes with sufficient number of included trials displayed no asymmetry to suggest publication bias.

In the sensitivity analysis for imputed/calculated data, five trials were excluded from analyses examining 'duration of hospital stay', one trial in each of 'postoperative bleeding' and 'transfusion requirements', three trials in 'duration of ventilation', and two trials in 'duration of ICU stay'. Sensitivity analyses resulted in similar results in terms of significance and direction of effect except for 'duration of hospital stay'. The total *n* for 'length of hospital stay' decreased from 1285 to 1021 patients, the 95% CI widened, and the new WMD was −0.49 days, $P = 0.16$.

Reliability and conclusiveness of new onset atrial fibrillation outcome

To determine the optimal information size we assumed a 33% control event rate (the control event rate in our meta-analysis for new atrial fibrillation) and a 25% RR reduction (most

Table 1 Characteristics of trials included in systematic review

Trials	*N*	Patient population	Steroid	Primary outcome	Blinding	Quality[a]
Abd El-Hakeem and El-Minshawy[12]	20	Valve	Dexamethasone	Biochemical	Double-blind	High (4)
Andersen *et al.*[13]	16	CABG	Methylprednisolone	Biochemical	Open label	Low (1)
Bourbon *et al.*[14]	36	CABG	Methylprednisolone	Biochemical	Open label	Low (1)
Celik *et al.*[15]	60	CABG	Methylprednisolone	Biochemical	Double-blind	High (3)
Chaney *et al.*[16]	60	CABG	Methylprednisolone	Clinical	Double-blind	High (3)
Chaney *et al.*[17]	88	CABG	Methylprednisolone	Clinical	Double-blind	High (4)
Coetzer *et al.*[18]	295	All CPB patients	Methylprednisolone	Clinical	Open label	Low (2)
Codd *et al.*[19]	150	CABG	Methylprenisolone	Biochemical	Open label	Low (0)
Enc *et al.*[20]	40	CABG	Methylprednisolone	Biochemical	Double-blind	High (3)
El Azab *et al.*[21]	18	All CPB patients	Dexamethasone	Biochemical	Double-blind	High (4)
Fecht *et al.*[22]	50	CABG	Methylprednisolone	Clinical	Double-blind	Low (2)
Ferries *et al.*[23]	80	All CPB patients	Methylprednisolone	Biochemical	Open label	Low (2)
Fillinger *et al.*[24]	30	CABG	Methylpredisolone	Biochemical	Double-blind	High (3)
Giomarelli *et al.*[25]	20	CABG	Methylprednisolone	Biochemical	Double-blind	High (4)
Halvorsen *et al.*[26]	294	CABG	Dexamethasone	Clinical	Double-blind	High (5)
Halonen *et al.*[27]	241	CABG or valve	Hydrocortisone	Clinical	Double-blind	High (5)
Harig *et al.*[28]	20	CABG	Prednisolone	Biochemical	Open label	Low (1)
Jansen *et al.*[29]	25	CABG	Dexamethasone	Biochemical	Double-blind	High (4)
Kilger *et al.*[30]	91	CABG and valve	Hydrocortisone	Biochemical	Open label	Low (1)
Loef *et al.*[31]	20	CABG	Dexamethasone	Biochemical	Double-blind	High (3)
Liakopolous *et al.*[32]	78	CABG	Methylprednisolone	Clinical	Open label	High (3)
Mayumi *et al.*[33]	24	Valve	Methylprednisolone	Biochemical	Double-blind	High (5)
McBride *et al.*[34]	35	CABG	Methylprednisolone	Biochemical	Double-blind	High (3)
Morton *et al.*[35]	95	CABG	Methylprednisolone	Clinical	Double-blind	High (3)
Niazi *et al.*[36]	90	CABG	Methylprednisolone	Biochemical	Double-blind	Low (2)
Oliver *et al.*[37]	125	CABG and valve	Methylprednisolone	Clinical	Double-blind	High (4)
Prasongsukarn *et al.*[38]	86	CABG	Methylprednisolone	Clinical	Double-blind	High (3)
Rao *et al.*[39]	150	CABG	Methylprednisolone	Clinical	Open label	Low (1)
Rubens *et al.*[40]	68	CABG	Methylprednisolone	Biochemical	Double-blind	High (5)
Rumalla *et al.*[41]	13	CABG	Methylprednisolone	Biochemical	Open label	Low (1)
Sano *et al.*[42]	60	CABG or valve	Hydrocortisone	Clinical	Open label	Low (1)
Schurr *et al.*[43]	50	CABG	Methylprednisolone	Biochemical	Open label	Low (1)
Tassani *et al.*[44]	52	CABG	Methylprednisolone	Biochemical	Double-blind	High (3)
Toft *et al.*[45]	16	All CPB patients	Methylprednisolone	Biochemical	Open label	Low (1)
Turkoz *et al.*[46]	20	CABG	Methylprednisolone	Biochemical	Double-blind	Low (1)
Vallejo *et al.*[47]	100	Valve	Methylprednisolone	Clinical	Open label	Low (2)
Volk *et al.*[48]	38	CABG	Methylprednisolone	Biochemical	Double-blind	High (4)
Volk *et al.*[49]	36	CABG	Methylprednisolone	Biochemical	Double-blind	Low (1)
Wan *et al.*[50]	20	CABG and valve	Methyprednisolone	Biochemical	Open label	Low (1)
Weis *et al.*[51]	28	All CPB patients	Hydrocortisone	Clinical	Double-blind	High (5)
Whitlock *et al.*[11]	60	All CPB Patients	Methylprednisolone	Biochemical	Double-blind	High (5)
Yared *et al.*[52]	216	CABG and valve	Dexamethasone	Clinical	Double-blind	High (4)
Yared *et al.*[53]	71	CABG and valve	Dexamethasone	Clinical	Double-blind	High (4)
Yilmaz *et al.*[54]	20	CABG	Methylprednisolone	Biochemical	Double-blind	High (4)

[a]By Jadad score.[6]

cardiovascular treatment effects are moderate) with 80% power and two sided $\alpha = 0.01$. The data were heterogeneous, reflected in an $I^2 = 20.9\%$. Our calculations indicated that the heterogeneity-corrected optimal information size needed to detect a plausible treatment effect is 1431 patients. Currently, 1412 patients have been randomized to steroids in the RCTs reporting new atrial fibrillation as an outcome. We used the optimal information size to help construct a Lan DeMets sequential monitoring boundary (*Figure 6*). The sequential monitoring boundary has been crossed, indicating that the cumulative evidence is reliable and conclusive.

Table 2 Summary of effect of steroid treatment on clinical outcomes

Outcome and trials (number of studies)	Steroid groups	Control groups	Relative risk	95% Confidence interval	I^2 (%)
Dichotomous variables					
Mortality (16)	28/1049	37/989	0.73	0.45 to 1.18	0
Myocardial infarction (10)	22/554	24/493	0.99	0.57 to 1.72	0
Neurological events (10)	10/442	15/420	0.85	0.38 to 1.88	0
New atrial fibrillation (14)	178/719	246/693	0.71	0.59 to 0.87	20.9
Wound complications (3)	4/220	3/220	1.16	0.27 to 4.89	0
Infectious complications (13)	44/726	39/731	1.14	0.75 to 1.72	0
Gastrointestinal complications (3)	8/103	5/103	1.57	0.52 to 4.76	0
Outcome and trials	Number of studies (Total *N*)	Weighted mean difference	95% Confidence interval	I^2 (%)	
Continuous variables					
Length of hospital stay (days)	20 (1285)	−0.59	−1.17 to −0.02	46.7	
Length of ICU stay (days)	22 (1268)	−0.23	−0.40 to −0.07	92.8	
Length of mechanical ventilation (h)	47 (3001)	−0.25	−1.18 to 0.67	87.5	
Postoperative bleeding (mL)	11 (880)	−99.55	−149.82 to −49.29	31.8	
Homologous RBC transfusion requirements (units)	4 (223)	−0.33	−1.13 to 0.46	76.3	

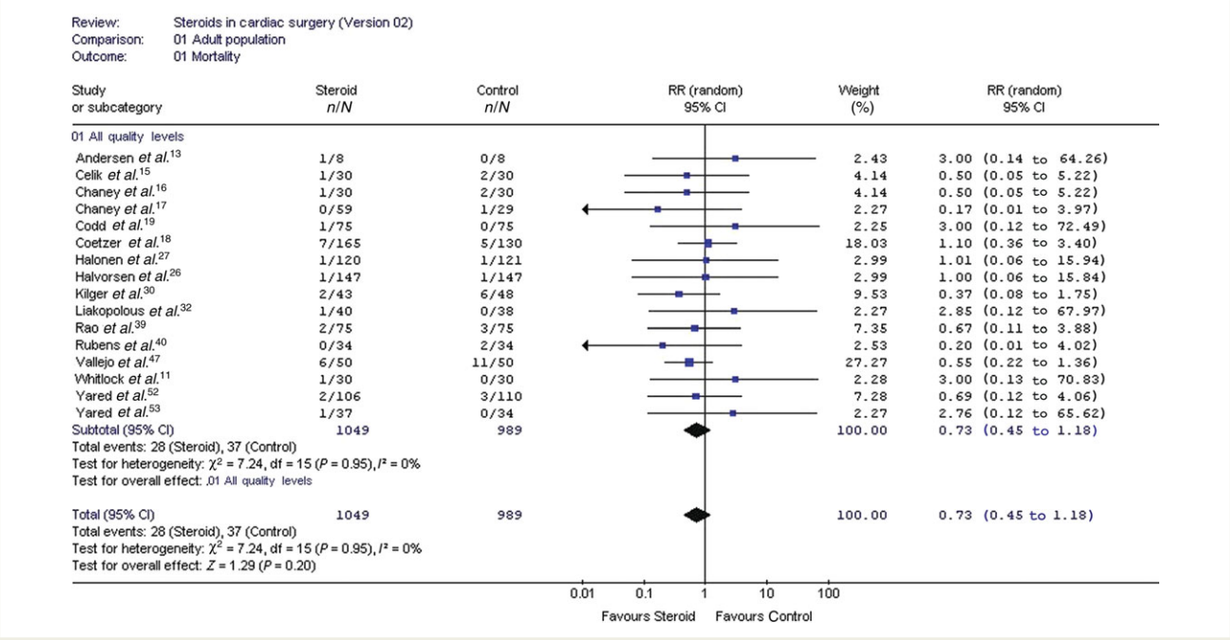

Figure 2 Impact of steroids on in-hospital mortality.

Discussion

The standards of a meta-analysis should be no less vigorous that those for a single RCT. Based on the sequential monitoring boundary generated, the current evidence for clinical benefit of perioperative steroids on postoperative new onset atrial fibrillation appears reliable and conclusive. Further, our results suggest that perioperative steroid treatment may decrease postoperative bleeding and shorten the duration of ICU and hospital stay. We found a trend towards reduced risk of death in patients receiving

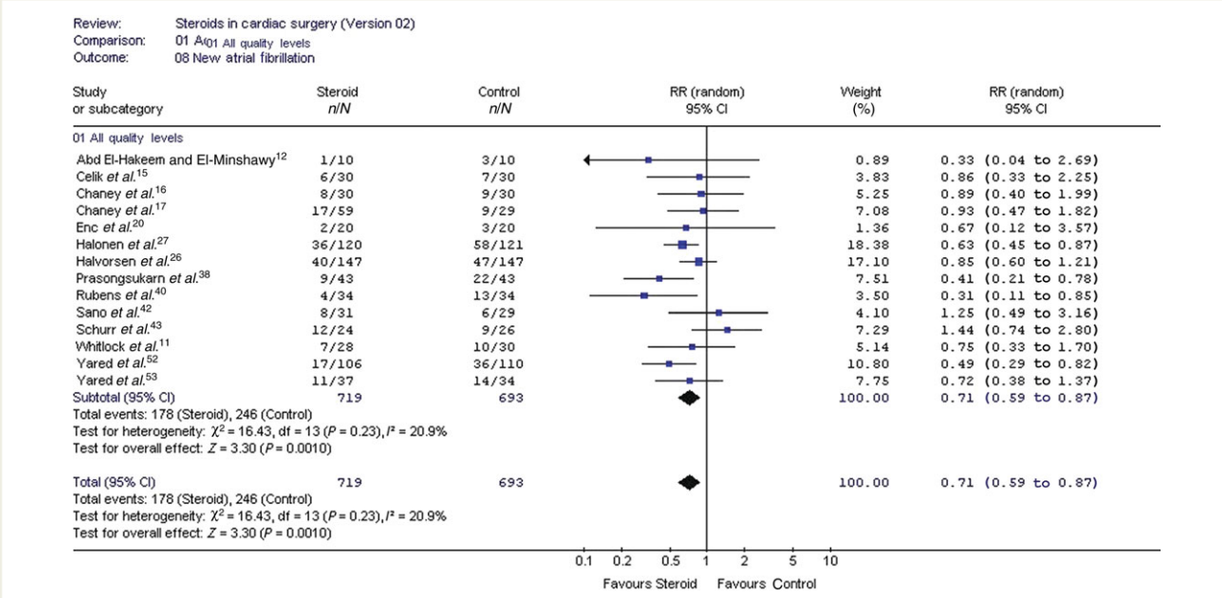

Figure 3 Impact of steroids on new atrial fibrillation.

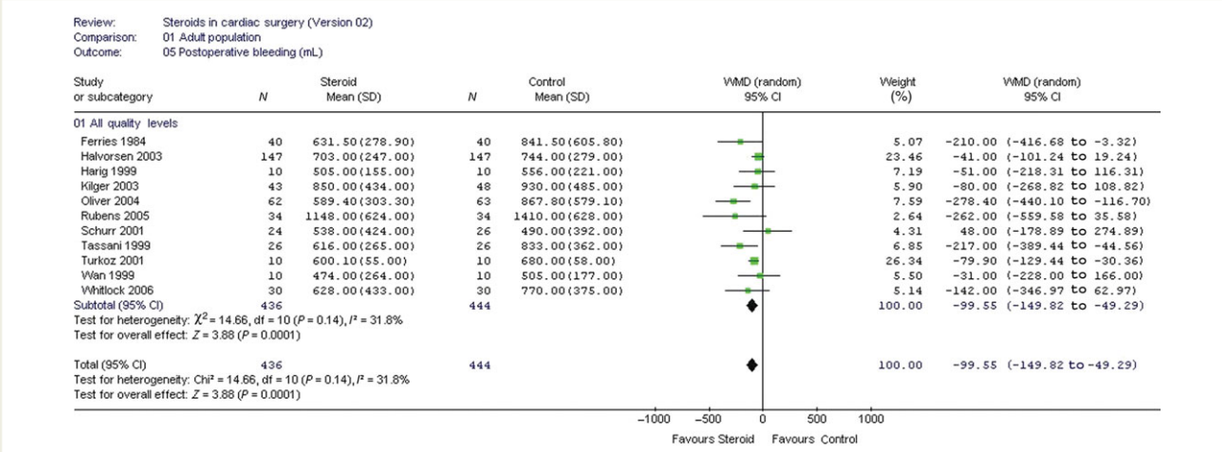

Figure 4 Impact of steroids on postoperative bleeding (mL).

steroid treatment, although the meta-analysis is underpowered for this outcome, and ~10 000 patients need to be studied to conclusively demonstrate this apparent mortality benefit. There was no increase in wound, gastrointestinal, or infectious complications in the steroid groups, but the event rates were low with few trials reporting these outcomes.

Strengths and weaknesses

Our meta-analysis has several strengths. The methodology was rigorous, with a comprehensive search to identify relevant RCTs including non-English literature. Eligibility decisions and abstraction was performed in duplicate with a high degree of agreement. Finally, the results were demonstrated to be robust.

On the other hand, the majority of the trials focused on low risk patients (70% isolated CABG), which is a poor reflection of the population currently undergoing cardiovascular surgery. Further, the majority of the trials focused on biochemical markers of inflammation and the tracking of secondary clinical outcomes was often poorly described (*Table 1*). Without clear definitions, tracking events such as MI after cardiac surgery risks under-reporting. The MI event rate observed (4.2%) is much lower than what would be expected for all CPB patients today with appropriate tracking. Two large well-designed trials [pexelizumab for the

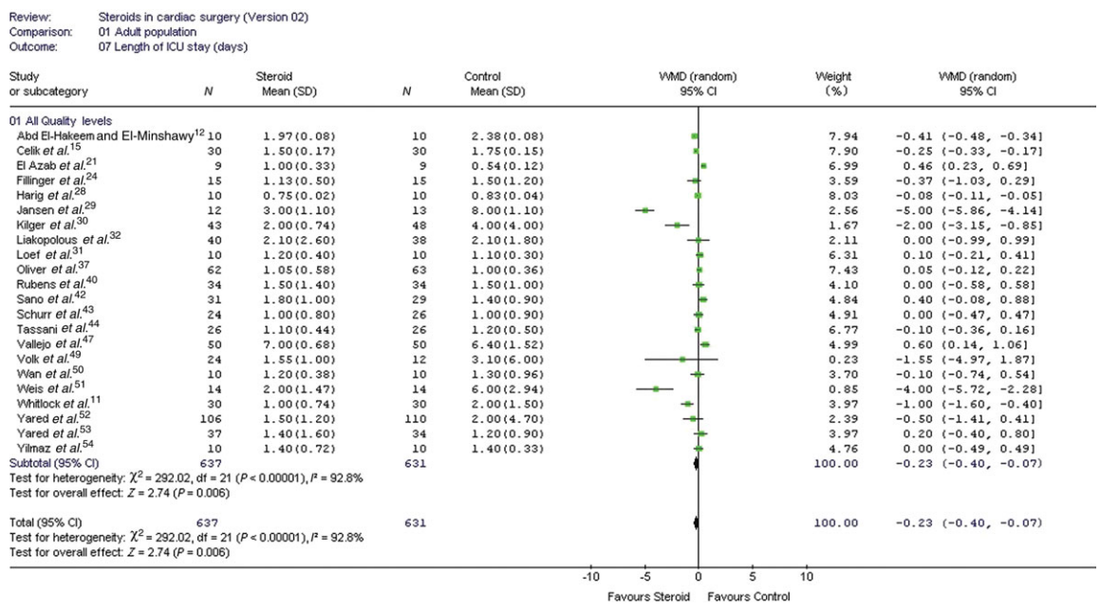

Figure 5 Impact of steroids on length of intensive care unit (ICU) stay (days).

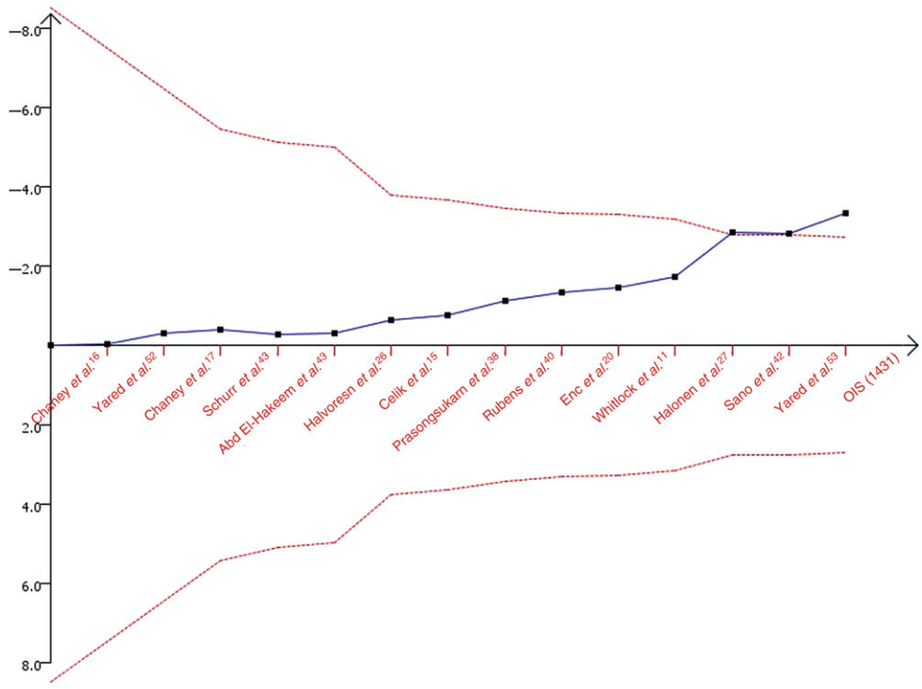

Figure 6 Cumulative meta-analysis assessing the impact of steroids on new atrial fibrillation.

reduction of infarction and mortality in CABG (PRIMO CABG) and MC-1 to eliminate necrosis and damage in CABG (MEND CABG)] recently reported a 30-day incidence of MI in the placebo groups of 12.0 and 14.4%, respectively.[9,10] The low event rates for the outcomes of wound, gastrointestinal, and infectious complications and transfusion requirements also hindered our ability to draw firm conclusions about the effect of steroids. We also had to assume a normal distribution for the continuous variables known to be

skewed (e.g. duration of ventilation, ICU stay, and hospital stay). Finally, although the amount of missing data was minimal, it was necessary for us to impute a small number of values. Nevertheless, examining these assumptions and imputations within a sensitivity analysis suggested that our methods were robust.

The trials also focused on patient groups of differing complexity (e.g. isolated CABG vs. valve and combined cases), and examined different steroid protocols. Thus, there was both clinical (patient type) and methodological (steroid type and dosing) diversity within this meta-analysis. The subgroup analysis suggests that patients undergoing more complicated surgery (valve or combined surgery) may derive greater benefit on length of mechanical ventilation from steroids. The included studies also span >2 decades. Clinical practice in cardiovascular surgery changed significantly over this time, as did the patient demographics. Changes have included CPB technology (especially bubble vs. membrane oxygenators), myocardial protection, and anti-fibrinolytic therapies. These variables are not accounted for within the subgroup analyses and may limit the generalizability of our results to the current cardiac surgery population.

This meta-analysis presents the most thorough quantitative review of perioperative steroids in CPB patients. From it, we can make several conclusions. First, the available literature remains insufficient to make conclusive statements on the major safety questions regarding steroid use around CPB. However, no trend exists within the data to raise major concerns. Secondly, the optimal steroid type, dose, and frequency are not well established. Adverse effects are dose dependent. Prasongsukarn *et al*., although suppressing atrial fibrillation, demonstrated increase in GI complications with their high dose regimen. We have published two studies demonstrating efficacy of a low dose protocol in inflammatory suppression.[2,11] If steroid benefit is derived through the suppression of this cascade, high doses with a prolonged duration is not necessary. Finally, no adequately powered RCT has been performed examining the effect of steroids on clinical outcomes in CPB patients. There is continued interest in steroid use for CPB demonstrated by the ongoing publication of small studies of surrogate outcomes. This meta-analysis supports the need for a sufficiently powered trial to end the debate about the clinical benefit of steroids. The pharmaceutical industry is now exploring a variety of new anti-inflammatory modalities that carry significant cost. Steroids are generic, inexpensive, and widely accessible.

Our group is now recruiting patients into the Steroids In caRdiac Surgery study (SIRS) examining methylprednisolone (Clinicaltrials.com identifier NCT00427388), while Dieleman *et al*. are examining a dexamethasone protocol (NCT00293592). Together, these trials aim to recruit >14 000 patients. Clear evidence establishing the role of steroids in patients having cardiac surgery with CPB awaits the results of such trials.

Conflict of interest: the authors declare no conflicts of interest.

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