

# Corticosteroid use in cardiac surgery: a systematic review and meta-analysis

## ORIGINAL RESEARCH

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### ABSTRACT

**Background:** This systematic review and meta-analysis seeks to determine whether corticosteroids are of beneficial use in cardiac surgery.

**Methods:** A database search was conducted using PubMed and EMBASE for randomised controlled trials (RCTs) comparing steroid use with a placebo in adults undergoing cardiac surgery, between 1990–2018. The quality of each study was assessed using the Jadad scoring system, and only double-blind studies with a score  $\geq 3$  were included. 53 RCTs were identified, and 14 were considered suitable for analysis.

**Results:** The corticosteroids used in the studies were methylprednisolone (57.1%), dexamethasone (35.7%), and hydrocortisone (7.1%). Steroid use significantly reduced incidence of infection [relative risk (RR) 0.83; 95% confidence interval (CI) 0.84–1.06;  $P < 0.0001$ ;  $I^2 = 75\%$ ] and length of hospital stay [mean difference  $-0.36$ ; 95% CI  $-0.5 - -0.21$ ;  $P < 0.00001$ ;  $I^2 = 88\%$ ]. Incidence of new atrial fibrillation was significantly reduced [RR 0.94; 95% CI 0.89–1.06;  $P = 0.03$ ;  $I^2 = 0\%$ ], but this outcome was no longer significant when only large studies were included [RR 0.96; 95% CI 0.90–1.01;  $P = 0.13$ ;  $I^2 = 0\%$ ]. Myocardial infarction was more frequent with steroid administration [RR 1.17; 95% CI 1.07–1.38;  $P = 0.008$ ;  $I^2 = 0\%$ ], and there was no significant difference in mortality [RR 0.87; 95% CI 0.70–1.07;  $P = 0.14$ ;  $I^2 = 0\%$ ].

**Conclusions:** After analysing the data from RCTs of 12,999 patients, perioperative corticosteroid administration was found to significantly reduce the risk of postoperative infection and length of hospital stay but increased the risk of myocardial infarction. More large trials need to be conducted in order to adequately assess the potential benefits of corticosteroid use in cardiac surgery.

## INTRODUCTION

Cardiac surgery is a common surgical procedure, with an average of 49 coronary artery bypass grafts alone per 100,000 people in the EU each year, (1) and cardiopulmonary bypass (CPB) is utilised in most cardiac surgery procedures. CPB use producing a systemic inflammatory response has been thoroughly reported in the literature, and the mechanism has been linked to the exposure of blood to hypothermia, non-physiological flow, and foreign surfaces, (2) resulting in the activation of platelets, neutrophils, and cytokine cascades. (3) This inflammatory reaction is exacerbated by ischaemia-reperfusion injury when removing the patient from CPB. (3) This systemic inflammatory response may contribute to postoperative complications of cardiac surgery including atrial fibrillation, (3) myocardial dysfunction, (4) multiple organ dysfunction, (5) and mortality. This is because inflammatory mediators are known to have cardiodepressive effects. (6)

Steroids have been shown to reduce the body's inflammatory response to CPB, (2,7) but their effect on clinical outcomes is not yet clear. The 2017 EACTS guidelines (32) on the use of steroids indicate that a previous 2008 meta-analysis has shown that steroids reduced postoperative atrial fibrillation, postoperative bleeding, and duration of hospital stay, but produced an increased rate of myocardial infarction. More recently, two larger trials have been carried out, the Steroids In caRdiac Surgery (SIRS) trial (7) and the Dexamethasone in Cardiac Surgery (DECS) study, (8) and thus the author thought it relevant to the field, and a good exercise as a medical student, to revisit the data.

As such, this systematic review and meta-analysis aims to determine whether prophylactic corticosteroid administration is effective in reducing morbidity and mortality in patients undergoing on-pump cardiac surgery.

## METHODS

### RCT identification

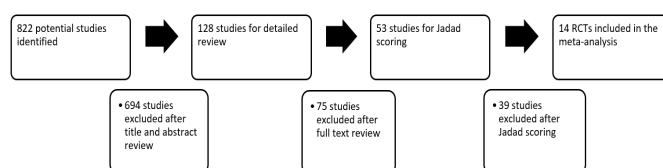
A database search was conducted for published randomised controlled trials (RCTs) comparing corticosteroid use with a placebo in adults undergoing cardiac surgery involving CPB, between 1990-2018. PubMed and EMBASE databases were searched. The search terms included: 'cardiac surgery, open heart surgery, coronary artery bypass graft, CABG, valve surgery, aortic valve, mitral valve, heart valve, CPB, cardiopulmonary bypass, pre-operative, intraoperative, and prophylactic', in combination with 'steroid, corticosteroid, glucocorticoid, hydrocortisone, dexamethasone, and methylprednisolone'. The references of included studies were then reviewed for other potentially relevant studies.

### RCT selection

Exclusion criteria were then applied to the identified RCTs, and trials were excluded if: 1) there was a lack of a randomised double-

blind trial design, 2) there was a lack of data regarding clinical outcomes, 3) there was a lack of a placebo group, or 4) if there were other treatments confounding the corticosteroids. This meant that 53 RCTs were selected from those initially identified.

The quality of each study was then assessed using the Jadad scoring system, (9) mainly focussing on patient randomisation and adequacy of follow-up. As previously advised in the literature, (10) only studies with a score of at least 3 were included. Following this, 14 studies fulfilled the criteria and were included in this meta-analysis. The search strategy is shown in Figure 1.



**Figure 1**

Flow diagram of trial selection

## Study Design

Summary characteristics of the RCTs that were included in this meta-analysis are shown in Table 1.

	Number of RCTs (%)	Number of patients (%)
<b>Total</b>	14	12,999
<b>Decades</b>		
1990-1999	1 (7.1)	60 (0.4)
2000-2009	9 (64.2)	661 (5.1)
2010-2018	4 (28.5)	12,278 (94.5)
<b>Jadad score</b>		
3	7 (50.0)	336 (2.6)
4	2 (14.3)	272 (2.1)
5	5 (35.7)	12,391 (95.3)
<b>Sample size</b>		
<60	5 (35.7)	159 (1.2)
60-100	5 (35.7)	361 (2.8)
>100	4 (28.5)	12,479 (96.0)

**Table 1**

Summary characteristics of included RCTs

Ten trials included patients undergoing isolated coronary artery bypass graft, (8,11-17,19,21) and four trials included all patients undergoing CPB. (7,18,20,22) The vast majority (96.0%) of patients belonged to four trials. (13,19,20,22) All trials involved steroids being administered preoperatively or intraoperatively, and the steroids used in the trials were methylprednisolone, (7,8,11,12,14,15,17,22) dexamethasone, (13,16,19-21) or hydrocortisone (18) (Table 2). Differing doses of corticosteroids were given in each trial, as there is no effective guideline for dosage in preoperative or intraoperative steroid administration, and these are outlined below.

Included study	N (patients)	Steroid used	Steroid dosage	Administration (intra/pre-op)
Chaney 1998	88	Methylprednisolone	60 mg.kg <sup>-1</sup>	Intra-op
Chaney 2001	295	Methylprednisolone	60 mg.kg <sup>-1</sup>	Intra-op
Fillinger 2002	30	Methylprednisolone	15 mg.kg <sup>-1</sup>	Pre-op
Halvorsen 2003	294	Dexamethasone	8 mg	Intra-op
Celik 2004	60	Methylprednisolone	60 mg.kg <sup>-1</sup>	Intra-op
McBride 2004	35	Methylprednisolone	30 mg.kg <sup>-1</sup>	Pre-op
Whitlock 2006	60	Methylprednisolone	500 mg	Intra-op
Sobieski 2008	28	Dexamethasone	100 mg	Intra-op
Demir 2009	30	Methylprednisolone	1 g	Pre-op
Weis 2009	36	Hydrocortisone	100 mg	Pre-op
Abbaszadeh 2012	185	Dexamethasone	12 mg	Intra-op
Dieleman 2012	4494	Dexamethasone	1 mg.kg <sup>-1</sup>	Intra-op
Mardani 2013	93	Dexamethasone	8 mg	Pre-op
Whitlock 2015	7507	Methylprednisolone	500 mg	Intra-op

**Table 2**

Comparison of steroids and dosages in included RCTs

Eleven studies looked at mortality, (7,8,11,13,14,16-20,22) nine at the incidence of myocardial infarction (MI), (7,8,11,13,14,19-22) twelve at the hospital length of stay, (7,8,11,12,14-18,20-22) ten at the incidence of new-onset AF, (7,8,11,14,16,18-22) and seven at the incidence of infection. (7,16,17,19-22)

### Definitions

Mortality was considered as all-cause mortality occurring before hospital discharge, or up to thirty days postoperatively. Infection was considered as relevant if it occurred before hospital discharge, or up to thirty days postoperatively. MI or new-onset AF were considered if it occurred before hospital discharge, or up to thirty days postoperatively. Length of hospital stay was measured in days.

### Statistical analysis

Clinical outcome data were extracted from each trial, and the outcomes for the patients receiving steroids were compared with patients in the control groups. Discrete outcomes, i.e. mortality, infection, AF and MI, were reported as relative risks (RRs) with a 95% CI. Continuous outcomes, i.e. length of hospital stay, were reported as a mean difference (MD) with a 95% CI. The outcomes were compared using the fixed-effects model. The software used to perform the statistical calculations was RevMan (version 5.3, Cochrane Collaboration, Oxford). The I<sup>2</sup> test was used to assess statistical heterogeneity, and a I<sup>2</sup> >25 was considered as significant heterogeneity. A sensitivity analysis was conducted using only large trials (>1000 patients), to assess the validity of the results.

## RESULTS

### Outcomes

Mortality in the steroid group was 189 out of 6425 patients (2.9%) compared to 218 out of 6404 patients (3.4%) in the control group, which indicates no significant difference [RR 0.87; 95% CI 0.70-1.07; p=0.14; I<sup>2</sup>=0%] (Figure 2).

Myocardial infarction incidence in the steroid group was 532 out of 6421 patients (8.3%) compared to 452 out of 6407 patients (7%) in the control group, which is a significant increase in the steroid group [RR 1.17; 95% CI 1.07-1.38; p=0.008; I<sup>2</sup>=0%] (Figure 3).

New-onset atrial fibrillation incidence in the steroid group was 1671 out of 6451 patients (25.9%) compared to 1778 out of 6439 patients (27.6%) in the control group, which represents a significant reduction in the steroid group [RR 0.94; 95% CI 0.89-1.06; p=0.03; I<sup>2</sup>=0%] (Figure 4).

The incidence of infection in the steroid group was 686 out of 6183 patients (11.1%) compared to 832 out of 6201 patients (13.4%) in the control group, which represents a significant reduction with steroid use [RR 0.83; 95% CI 0.84-1.06; p<0.0001; I<sup>2</sup>=75%] (Figure 5).

There was statistically significant decrease in length of hospital stay in the steroid group compared with the control group of 0.36 days [MD -0.36; 95% CI -0.5 - -0.21; p<0.00001; I<sup>2</sup>=88%] (Figure 6).

### Sensitivity analysis

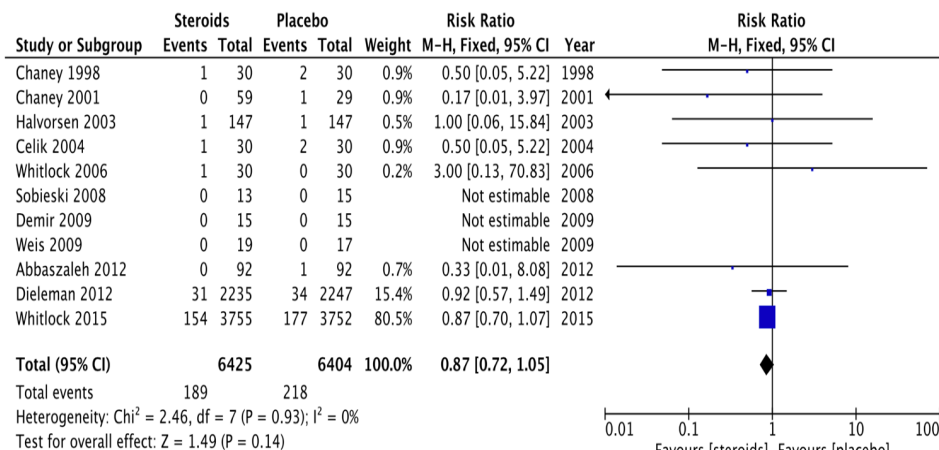
When the sensitivity analysis was carried out, including only large trials (>1000 patients), only the outcome of new-onset atrial fibrillation was changed, with the effect of steroids becoming non-significant when compared to the control group [RR 0.96; 95% CI 0.90-1.01; p=0.13; I<sup>2</sup>=0%] (Figure 7). All statistical analysis of the outcomes was heavily influenced by the largest trial in the analysis (21), with the weighting ranging from 47.6% for new-onset AF to 88.0% for MI.

### Heterogeneity analysis

Significant heterogeneity (I<sup>2</sup> >25) was encountered for length of hospital stay and incidence of infection. Surgery type did not affect the outcomes.

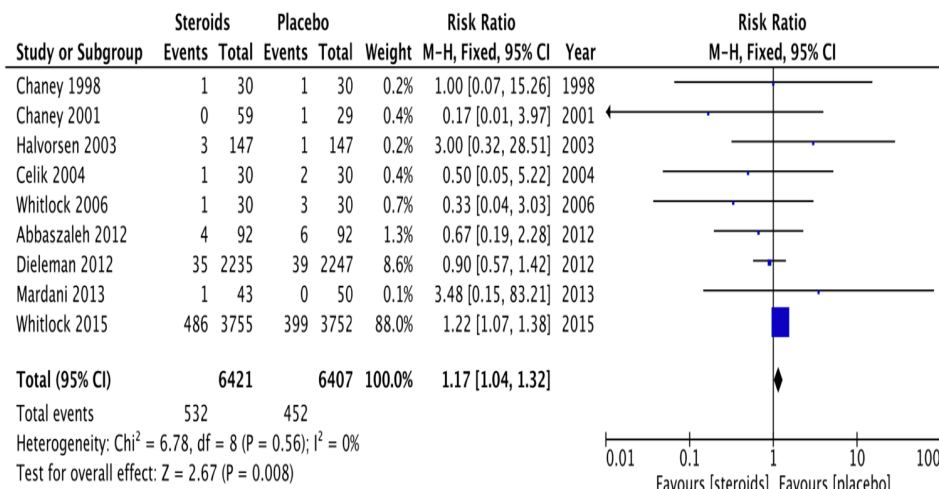
**Figure 2**

Forest plot for mortality - the size of the box correlates with the weight of the study estimate



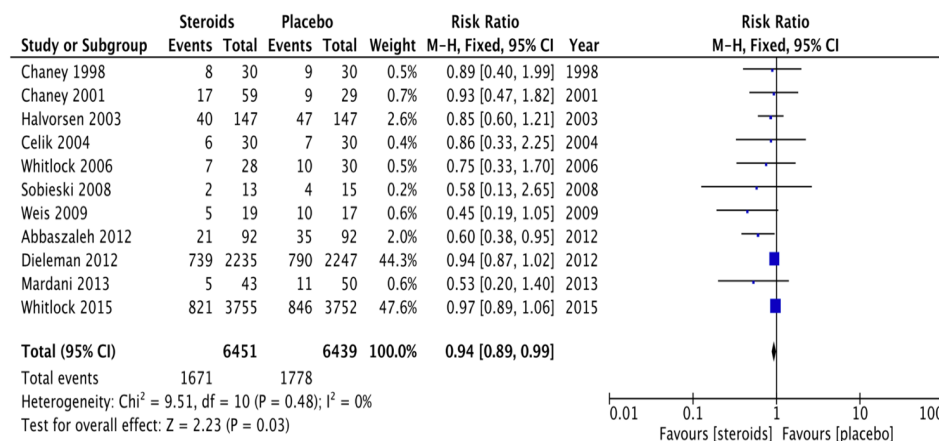
**Figure 3**

Forest plot for myocardial infarction - the size of the box correlates with the weight of the study estimate



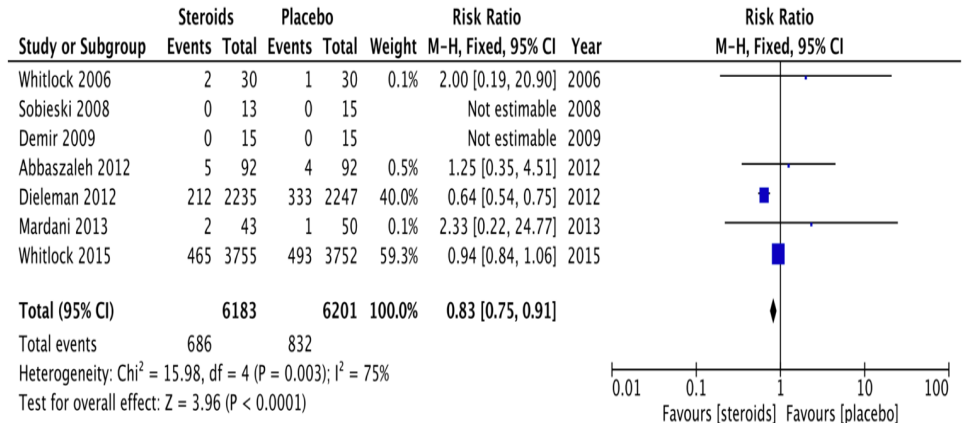
**Figure 4**

Forest plot for atrial fibrillation - the size of the box correlates with the weight of the study estimate



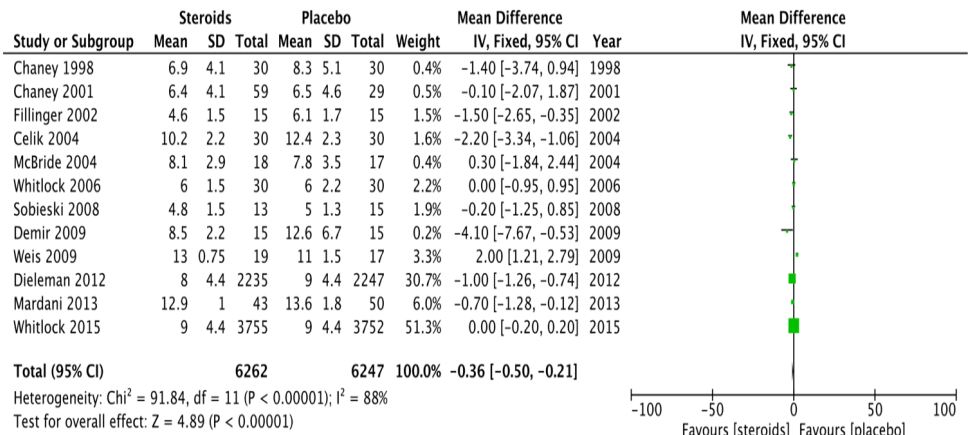
**Figure 5**

Forest plot for incidence of infection – the size of the box correlates with the weight of the study estimate



**Figure 6**

Forest plot for length of hospital stay – the size of the box correlates with the weight of the study estimate



**Figure 7**

Forest plot for atrial fibrillation: only including large trials (>1000 patients) – the size of the box correlates with the weight of the study estimate





## DISCUSSION

This systematic review and meta-analysis suggests that preoperative or intraoperative administration of corticosteroids results in a significant reduction in the incidence of infection and the length of hospital stay after cardiac surgery, although these results were associated with significant heterogeneity. The reduced incidence of infection following corticosteroid administration is counter-intuitive, as steroid-induced immune suppression is widely considered to potentially increase the risk of postoperative infection. Thus, this outcome may be a result of spurious diagnosis of systemic inflammatory response as opposed to infection, or vice versa. However, several studies have noted a correlation between preoperative C-reactive protein concentration (and thus inflammatory status) and incidence of postoperative infection, (23,24) with a possible mechanism being that rate of bacterial growth has been shown to increase in the presence of proinflammatory cytokines *in vitro*. (25)

Although length of hospital stay was significantly decreased in the steroid group, this author questions whether a reduction in length of stay of 0.36 days is of clinical significance.

These data also suggest that prophylactic steroid administration does not significantly affect mortality when compared to control groups but is associated with an increased incidence of myocardial infarction. This increase in myocardial infarction may possibly be due to the effect of increased insulin resistance afforded by corticosteroids, blocking glucose from entering cardiac myocytes and furthering ischaemic injury.

The increase in rates of myocardial infarction is difficult to align with no increase in mortality, as this is a patient population in which myocardial injury is associated with poorer clinical outcomes. This discrepancy may be due to the difficulty in defining myocardial injury after cardiac surgery, as all patients experience release of cardiac biomarkers. Evidence for the thresholds of clinically significant cardiac biomarkers following cardiac surgery is not available, and therefore a robust and well-defined approach needs to be taken. Whitlock et al (22) used systematic monitoring of CK-MB to diagnose myocardial injury, and consequently found an increase in both myocardial infarction and associated mortality, suggesting that the discrepancy in these rates may be due to study design.

The data show a statistically significant decrease in new-onset atrial fibrillation, but this significance disappears when only larger trials are included in the analysis, suggesting that the smaller studies are producing this result. Inflammation of myocardial tissue following CPB and cardiac surgery has been theorised to be the cause of new-onset AF postoperatively, (26,27) hence the rationale for the inclusion of new-onset AF in the RCTs in this analysis. However, when only large trials were included, this meta-analysis demonstrated that prophylactic steroid administration has no effect on the incidence of new-onset AF, suggesting that the pathogenesis of AF following CPB is more complex than a result of myocardial inflammation.

## Strengths and weaknesses

Previous meta-analyses have been conducted on the use of steroids in cardiac surgery, (28,29) but this is the first to include only high quality RCTs (as demonstrated by the Jadad scoring system). As a result, this meta-analysis had a reduced number of RCTs included, but the quality of the analysis and resulting outcomes was higher with a mean Jadad score of 3.9.

An additional strength of this systematic review and meta-analysis is the diligent methodology of trial identification, data extraction, and outcome analysis, resulting in a high degree of confidence in the results. The search was comprehensive, utilising two large trial databases for published data, and the vast majority of patient groups included in the RCTs represented all CPB procedures (93.1%), leading to a high degree of generalisability of outcomes.

This systematic review and meta-analysis does, however, have several limitations. The majority of the data came from four individual RCTs, meaning they had a very significant effect weighting on the outcomes measured. A greater number of large trials to draw data from would improve the reliability of these results. Furthermore, there was significant heterogeneity and variability between trials regarding the steroids and dosages used, meaning that clinical and methodological variability was introduced into the results. A subgroup analysis was conducted that found there was no statistical significance in results between different types of steroid ( $p=0.16$ ), and thus a fixed-effects model was suitable for the analysis. A random-effects model could have been used to address the heterogeneity in dosage between studies, but as all dosages were within therapeutic range, the author felt that this was not suitable. Were a benefit to be found in corticosteroid administration during this review, a random-effects model could have been used to determine if steroid dosage affected the clinical outcomes.

Additionally, this meta-analysis was carried out by a medical student and began as a training review before being adapted into a full systematic review. As such, this work was not able to be prospectively registered with the PROSPERO register of systematic reviews, (30) and did not benefit from the presence of additional reviewers, against standard PRISMA-P guidelines. (31) The author acknowledges the possibility of introducing methodological errors, unnecessary bias, and a reduction in transparency that these decisions afford this work. However, the author believes that the robustness of the protocols and validity of the analysis warrant consideration of the results. Were similar work to be repeated, the author would ensure the PRISMA-P protocols for systematic review were adhered to.

## CONCLUSION

This systematic review represents a thorough and comprehensive assessment of the safety and efficacy of prophylactic corticosteroid use in cardiac surgery. This review suggests that steroid use decreases the incidence of postoperative infection, reduces the length of hospital stay, increases the risk of myocardial infarction, has no statistically significant effect on postoperative mortality, and significantly reduces the incidence of new-onset AF (although this result should be taken with caution, as analysis of large trials showed no significant difference). Two large RCTs accounted for the majority weighting of these results, and further large trials are needed in order to confirm or refute these findings with greater certainty.

Given the increased risk of myocardial infarction, the dubious result of reduction in postoperative infection, and the trivial reduction in length of hospital stay, this meta-analysis has found that the EACTS guidance that routine use of prophylactic steroids is not indicated for patients undergoing cardiac surgery remains true and prudent advice.

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