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Protective effects of corticosteroids in coronary artery bypass graft surgery alone or combined with valvular surgery: an updated and comprehensive meta-analysis and systematic review

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Abstract

This systematic review with meta-analysis sought to determine the protective effects of corticosteroids on clinical outcomes following coronary artery bypass grafting (CABG). Medline, Embase, Elsevier and Sciences online database as well as Google scholar literature were used for selecting appropriate studies with randomized controlled design. The effect sizes measured were odds ratio (OR) for categorical variables and weighted mean difference with 95% confidence interval (CI) for calculating differences between mean values of duration of hospitalization in intervention and control groups. Values of $P < 0.1$ for Q-test or $I^2 > 50\%$ indicated significant heterogeneity between the studies. The literature search of all major databases retrieved 3735 studies. After screening, a total of 45 trials were identified that reported outcomes. Pooled analysis was performed on incidence of atrial fibrillation (OR of 0.71; 95% CI: 0.59–0.86; $P = 0.000$), stroke (OR of 1.61; 95% CI: 0.63–4.1; $P = 0.3$), infection (OR of 1.03; 95% CI: 0.68–1.5; $P = 0.8$), re-infarction (OR of 0.88; 95% CI: 0.47–1.63; $P = 0.6$), length of ventilation time [weighted mean difference (WMD) of 0.257; 95% CI: 0.10–0.41; $P = 0.00$], length of hospital stay (WMD of −0.48; 95% CI: −0.66 to −0.3; $P = 0.000$), amount of blood loss (WMD of −124.05; 95% CI: −147.72 to −100.38; $P = 0.00$), re-exploration (OR of 1.25; 95% CI: 0.66–2.35; $P = 0.4$) and mortality (OR of 0.87; 95% CI: 0.46–1.64; $P = 0.6$). Overall, steroid prophylaxis in patients undergoing CABG could significantly reduce complications such as atrial fibrillation and length of hospital stay, but slightly increased the length of ventilation time. On the other hand, no significant impact on the incidence of infection was observed compared with the placebo.

Keywords: Coronary artery bypass graft • Cardiopulmonary bypass • Complication • Clinical outcome • Atrial fibrillation

INTRODUCTION

Coronary artery bypass grafting (CABG) and cardiopulmonary bypass (CPB) induce a systemic inflammatory response characterized by leucocytes and complement activation, and elevated levels of inflammatory mediators that may contribute to postoperative complications including atrial fibrillation (AF), infections, organ dysfunction, blood loss, prolonged duration of intensive care unit (ICU) and hospital stay, as well as increase in costs of therapy [1, 2]. AF is the most frequent complication after cardiac surgery. Incidence of AF has been reported in 20–50% of patients following CABG and is even higher after combined CABG and valve surgery. Factors predictive of postoperative AF (POAF) include advanced age, male sex, body mass index >30, atrial dilatation, prolonged aortic cross-clamp times, preoperative leucocytosis and increased postoperative plasma levels of proinflammatory markers [3, 4]. POAF may increase stroke rates, trigger haemodynamic instability with heart failure and increase risk of thromboembolic complications [3, 4]. Corticosteroids (CSs) have been recommended during CABG surgery to prevent haemodynamic instability and inhibit the inflammatory process [5]. However, there is still controversy in terms of their protective effects [5]. They also have several side effects, such as hyperglycemia, gastrointestinal disturbances and postoperative infections [5].

Various studies have reported on the influence of corticosteroids on complications after cardiac surgery. However, data from randomized controlled trials (RCTs) are limited, and so far largely inconclusive. This systematic review with meta-analysis sought to determine the strength of evidence for the effects of steroids on hospital mortality, incidence of AF, infection, length of mechanical ventilation, ICU and hospital stay, postoperative blood loss and re-exploration for bleeding after CABG.

[†]Both authors contributed equally.

METHODS AND MATERIALS

Literature search

A comprehensive literature search was conducted in major electronic databases (Medline/Pubmed, Embase, Elsevier, Sciences online database and Google scholar) from their inception through 30 July 2014 to identify the RCTs reporting the effects of corticosteroids on the complications following cardiac surgery. Predefined search terms included 'glucocorticoid', 'steroid', 'hydrocortisone', 'dexamethasone', 'methylprednisolone' and 'cardiac surgery', 'cardiothoracic surgery', 'heart surgery', 'cardiopulmonary bypass', 'CPB', 'coronary artery bypass grafting', 'CABG', 'CAB'. No language restrictions were applied. All retrieved references of the included RCTs were also reviewed to determine additional studies not indexed in the common databases. Studies were included into the analysis when they met the following criteria: (i) RCTs about comparison of steroids with a control group, (ii) adult patients undergoing CABG surgery (off-pump or on-pump) alone or combined with valvular surgery and [3] reporting data on the incidence of postoperative complications according to our review-checklist. In addition, abstracts without peer-review publications of manuscripts were not included.

Data extraction and outcome measures

Two investigators (Sadegh Ali-Hassan-Sayegh and Fatemeh Haddad) extracted the data independently, and discrepancies were resolved via a consensus standardized abstraction checklist used for recording data in each study. Data retrieved from the trials included author's name, type of surgery (CABG alone or CABG combined with valvular surgery), type of CABG surgery (on-pump or off-pump), study design, type of controls (placebo or not), type of blinding (double-blinded or not), details of therapeutic regimens, sample size, mean age and gender. The incidence of postoperative AF, stroke, renal disease, infection, myocardial infarction, length of ventilation time, ICU and hospital stay, amount of bleeding, re-exploration for bleeding and mortality were recorded for each group. The primary effect measure was the incidence rate of POAF during hospital stay or over follow-up. For exploration of heterogeneity among trials, a subgroup analysis of disparities in the patients' characteristics was performed for (i) average age (<65 years vs ≥65 years), (ii) percentage of males (<80% vs ≥80%), (iii) hypertension (≤70% vs >70%), (iv) diabetes (≤30% vs >30%), (v) dose of steroids (low, medium and high), (vi) type of surgery (CABG alone vs CABG combined valvular surgery) and (vii) type of CABG (on-pump vs off-pump).

Definitions

The following end-points were defined: new onset AF was considered when it occurred before hospital discharge. Postoperative mortality was considered as all-cause mortality occurring up to 30 days postoperatively or before hospital discharge. The length of mechanical ventilation support was measured in hours, and hospital stay was measured in days. Postoperative infections include any type of infection occurring after surgery. Postoperative chest tube drainage was measured in millilitres (ml). We defined total CS use <1000 mg hydrocortisone or equivalent as low dose, the total CS use >10 000 mg hydrocortisone or equivalent as high dose and the total CS use between 1000 and 10 000 mg hydrocortisone or equivalent as medium dose.

Statistical analysis, publication bias and quality assessment

Data were analysed by STATA version 11.0 utilizing METAN and METABIAS modules. The effect sizes measured were odds ratio (OR) with 95% confidence interval (CI) for categorical variables. For non-categorical data, the standard mean difference with 95% CI was used for calculating differences between intervention and control groups. OR <1 favoured CS and OR >1 favoured control. RCTs with no events in the two arms were discarded from pooled analysis. Forest plots were created for each outcome. A value of $P < 0.1$ for Q-test or $I^2 > 50\%$ indicated significant heterogeneity among the studies. Sample weighting assigned studies with larger sample sizes and more weight, and reduced the effect of sampling error because sampling error generally decreases as the sample size increases. Heterogeneity among trials was addressed by applying a random effect model when indicated. The presence of publication bias was evaluated using the Begg and Egger tests. Quality assessment of RCTs was performed using the Jadad score. The Jadad score assesses three items including randomization (0–2 points), blinding of study (0–2 points) and withdrawals and drop-outs (0–1 points). Higher scores indicate better reporting ('high' quality: 5; 'good' quality: 3–4; 'poor' quality: 0–2). Results were considered statistically significant at P-values <0.05.

RESULTS

Literature search strategy and included trials

Literature search retrieved 3735 studies from screened databases of which 3231 (86.5%) were excluded after initial review. Of 504 primary included studies, 459 were excluded after detailed evaluation due to insufficient reporting of end-points of interest. The final analysis included 45 RCTs. Details of demographic characteristics have been presented in Table 1.

STUDY CHARACTERISTICS, EFFECT MEASURES AND CLINICAL OUTCOMES

Postoperative atrial fibrillation

A total of 2451 patients were included from 24 RCTs, which reported data on POAF. Patient population of RCTs ranged from 20 to 305. Of 2451 patients, 1271 cases were allocated to CS, and 1180 cases to the control group (Table 2). The overall incidence of POAF was 24.7% ranging from 6.4 to 43.9%. POAF occurred in 21.5% in the CS group, and 28.09% in the control group. Pooled treatment effect analysis revealed that CS therapy significantly reduced the incidence of POAF with an OR of 0.71 (95% CI: 0.59–0.86; $P = 0.000$) using a random model (Fig. 1). Significant heterogeneity was observed among the RCTs ($\chi^2 = 35.57$, $I^2 = 35.3$, $P = 0.04$). Subgroup analysis showed that CS had anti-arrhythmic effects in ages above and below 65 years, male and female, diabetic and non-diabetic patients (Supplementary material, Table S1). A subgroup analysis of the steroid dosage revealed that medium dose of CS significantly reduced the incidence of POAF with an OR of 0.59 (CI: 0.43–0.78; $P = 0.000$), whereas low and high doses of CS

Table 1: Demographic characteristics of randomized controlled trials

Study	Year/country	Regimen	*n*		Mean age (years)		Male (%)		Type of CABG	Study design	Jadad score
			CS	C	CS	C	CS	C			
Halonen *et al.* [15]	2007/Finland	100 mg per 2 ml of hydrocortisone sodium succinate into polyethylene infusion (first dose: in the evening of the operation day, and second dose: 1 dose every 8 h during the next 3 days)	120	127	64.4 ± 8.4	66.1 ± 9.5	80	73.6	On-pump CABG combined valvular surgery	RCT	4
Halvorsen *et al.* [16]	2003/Norway	4 mg dexamethasone at 2 doses (total 8 mg IV). First initiating maintenance of anaesthesia, and second dose on the morning of the first POD	147	147	63 ± 11	64 ± 10	77.5	81.6	On-pump CABG	RCT	5
Fillinger *et al.* [17]	2002/Lebanon	15 mg/kg at 1 h before surgery, followed by 0.3 mg/kg every 6 h for 4 doses beginning 2 h after completion of surgery	15	15	60.5 ± 2.4	69.9 ± 1.7	N.D	N.D	On-pump CABG	RCT	4
Engelman *et al.* [18]	1995/USA	1 g methyl prednisolone (MP) before CPB. Every 6 h at 4 doses (4 mg × 4) in the 24 after surgery	10	9	68.2 ± 2.1	58.8 ± 3.5	70	77.8	On-pump CABG	RCT	3
Enc *et al.* [19]	2006/Turkey	25 mg/kg MP at 1 h before CPB	20	20	60.1 ± 9.9	56.6 ± 9.9	100	100	On-pump CABG	RCT	3
Azab *et al.* [20]	2002/Netherlands	100 mg dexamethasone on the morning of the surgery	9	8	63 ± 10	63 ± 7	77.7	75	On-pump CABG	RCT	3
Demir *et al.* [21]	2009/Turkey	1 g MP before CPB	15	15	61.6 ± 9.9	61.6 ± 9.5	53.3	80	On-pump CABG	RCT	3
Channey	1998/USA	30 mg/kg MP at 2 doses, first dose during the sternotomy, second dose during CPB	30	30	66 ± 10	67 ± 10	73.3	76.6	On-pump CABG	RCT	4
Channey	2001/USA	15 mg/kg MP at 2 doses or 30 mg/kg MP at 2 doses, first dose during the sternotomy, second dose during CPB	59	29	64.5 ± 10.5	67 ± 10	77.9	75.8	On-pump CABG	RCT	4
Celik *et al.* [22]	2004/Turkey	30 mg/kg MP at 6 times, 10 min before CPB, immediately after CPB, every 6 h for the next 24 h in ICU	30	30	60 ± 8	62 ± 7	N.D	N.D	On-pump CABG	RCT	4
Bourbon *et al.* [23]	2004/France	5 mg/kg MP or 10 mg/kg during CPB	24	12	61 ± 13.9	62 ± 7.4	N.D	N.D	On-pump CABG	RCT	2
Bingol *et al.* [24]	2005/Turkey	20 mg prednisolone daily: 10 days before surgery, during postoperative period the dosage was reduced to half of initial dose every 3 days and withdrawal at the POD7	20	20	63.7 ± 6.2	63.8 ± 6.6	80	75	On-pump CABG	RCT	4
Abbaszadeh *et al.* [25]	2012/Iran	6 mg/kg dexamethasone at 2 times, first dose after induction of anaesthesia, second dose on the morning after surgery	92	92	60.7 ± 8.7	59.4 ± 10	51.2	48.8	On-pump CABG	RCT	4
Yilmaz *et al.* [26]	1999/Turkey	1 mg/kg MP in the pump prime solution	10	10	46.6 ± 8.8	55.1 ± 6	80	80	On-pump CABG	RCT	2
Amr *et al.* [27]	2009/Egypt	1 mg/kg at induction of anaesthesia and 0.5 mg/kg at 8 h later	50	50	68 ± 14	67 ± 12	70	72	On-pump CABG	RCT	2
Yared *et al.* [28]	2007/USA	0.6 mg/kg dexamethasone intravenously after induction of anaesthesia	37	34	N.D	N.D	83.8	73.5	On-pump CABG combined valvular surgery	RCT	4
Yared *et al.* [29]	2000/USA	0.6 mg/kg dexamethasone intravenously after induction of anaesthesia	106	110	62.6 ± 11.4	63.2 ± 11.3	84.9	80	On-pump CABG combined valvular surgery	RCT	3
Whitlock *et al.* [30]	2006/Canada	250 mg MP at 2 times, first dose during anaesthetic induction and second dose during CPB	30	30	67 ± 10	66 ± 11	70	76.6	On-pump CABG combined valvular surgery	RCT	4

Continued

Table 1: (*Continued*)

Study	Year/country	Regimen	*n*		Mean age (years)		Male (%)		Type of CABG	Study design	Jadad score
			CS	C	CS	C	CS	C			
Weis *et al.* [31]	2006/Germany	100 mg over 10 min before induction of anaesthesia, continuous infusion of 10 mg/h for 24 h at POD1, 5 mg/h infusion over 24 h at POD2, 20 mg intravenously at 3 times at POD3 and 10 mg intravenously at 3 times at POD4	14	14	68 (63–72)	69(63–73)	71.4	64.2	On-pump CABG combined valvular surgery	RCT	4
Wan *et al.* [32]	1999/China	3 mg/kg MP during induction of anaesthesia	10	10	65 ± 10	65 ± 5	70	70	On-pump CABG combined valvular surgery	RCT	2
von Spiegel *et al.* [33]	2002/Germany	1 mg/kg dexamethasone intravenously after induction of anaesthesia	10	10	62.5 ± 9.5	66.8 ± 3.7	90	60	On-pump CABG	RCT	3
Volk *et al.* [34]	2003/Germany	15 mg/kg MP at 1.5 h before extracorporeal circulation	12	12	65 ± 1	60 ± 3	83.3	91.6	On-pump CABG	RCT	2
Volk *et al.* [35]	2001/Germany	15 mg/kg MP at 1.5 h before extracorporeal circulation	12	13	64.8 ± 5	60.7 ± 9.1	83.3	92.3	On-pump CABG	RCT	4
Tassani *et al.* [36]	1999/Germany	1 g MP at 30 min before CPB	26	26	N.D	N.D	N.D	N.D	On-pump CABG	RCT	3
Suezawa *et al.* [37]	2013/Japan	1000 mg MP during induction of anaesthesia	15	15	66 ± 11	71 ± 7	80	73.3	Off-pump CABG	RCT	3
Sobieski *et al.* [38]	2008/USA	100 mg dexamethasone after general anaesthesia	13	15	62 ± 6.6	64.5 ± 9.9	84.6	80	On-pump CABG	RCT	3
Schurr *et al.* [39]	2001/Switzerland	10 mg/kg MP intravenously at 4 h before surgery	24	26	64.9 ± 9	60.8 ± 8.9	87.5	84.6	On-pump CABG	RCT	2
Sauër *et al.* [40]	2014/Netherlands	1 mg/kg dexamethasone intravenously at the time of induction of anaesthesia	367	370	67 ± 12	66 ± 12	70	69	On-pump CABG combined valvular surgery	RCT	4
Sano *et al.* [41]	2006/Japan	50 mg/kg hydrocortisone before and after CPB	31	29	63.5 ± 10.1	61.4 ± 10.7	54.8	48.2	On-pump CABG combined valvular surgery	RCT	2
Rubens *et al.* [42]	2005/Canada	1 g MP intravenously before CPB	17	17	56 ± 5	54 ± 9	88	76	On-pump CABG	RCT	4
Liakopoulos *et al.* [43]	2007/Germany	15 mg/kg MP 30 min before CPB	40	38	66.8 ± 8.2	65.6 ± 7.2	75	66	On-pump CABG	RCT	3
Prasongsukarn *et al.* [44]	2005/Canada	1 g MP before CPB, followed by 4 mg dexamethasone every 6 h for 4 doses in POD1	43	43	67.2 (64.5–70)	61.7 (58.6–64.8)	76.7	76.7	On-pump CABG	RCT	4
Mirhosseini *et al.* [45]	2011/Iran	5 mg/kg MP intravenously after induction of anaesthesia	60	60	63 ± 11	61 ± 13	73.3	68.3	Off-pump CABG	RCT	3
Oliver *et al.* [46]	2004/USA	1 g MP immediately before induction of anaesthesia, followed by 4 mg dexamethasone every 6 h for 4 doses in POD1	62	63	63.7 ± 10.7	62.1 ± 11.8	87.1	82.5	On-pump CABG combined valvular surgery	RCT	3
Murphy *et al.* [47]	2011/USA	8 mg dexamethasone at 2 times, first dose at 45 min before surgical incision, and second dose the initiation of CPB	60	49	63.2 ± 13.1	63.1 ± 12.4	68.3	73.5	On-pump CABG combined valvular surgery	RCT	5
Morariu *et al.* 48]	2005/Netherlands	1 mg/kg dexamethasone before induction of anaesthesia and 0.5 mg/kg 8 h later	10	10	67.8 (63.4–72.1)	59.5 (53.4–65.5)	80	90	On-pump CABG	RCT	3
McBride *et al.* [49]	2004/Ireland	30 mg/kg MP before induction of anaesthesia	18	17	62.7 ± 6.4	60.1 ± 5.6	100	94.1	On-pump CABG	RCT	3
Mayumi *et al.* [50]	1997/Japan	20 mg/kg MP intravenously 5–10 min before and after CPB	12	12	53.1 ± 10.5	53.7 ± 8.4	66.6	58.3	On-pump CABG combined valvular surgery	RCT	3

Mardani *et al.* [51]	2013/Iran	8 mg dexamethasone before induction of anaesthesia, followed by 8 mg dexamethasone every 8 h for 3 days	43	50	64.5 ± 11.1	60 ± 12.7	83.7	88	On-pump CABG combined valvular surgery	RCT	4
Lomivorotov *et al.* [52]	2013/Russia	20 mg/kg MP immediately after induction of anaesthesia	22	22	57.8 ± 7.7	57.3 ± 6.8	72.7	95.4	On-pump CABG	RCT	5
Loef *et al.* [53]	2004/Netherlands	1 mg/kg dexamethasone before induction of anaesthesia and 0.5 mg/kg 8 h later	10	10	67.7 (58–76)	59.6 (47–76)	90	80	On-pump CABG	RCT	2
Jansen *et al.* [54]	1991/Netherlands	30 mg/kg MP or 1 mg/kg dexamethasone or 1 mg/kg prednisolone after induction of anaesthesia	36	12	59.3 ± 3	61 ± 3	N.D	N.D	On-pump CABG	RCT	2
Giomarelli *et al.* [55]	2003/Italy	1 g MP preoperatively, 125 mg at the end of CPB, 125 mg in the ICU every 6 h for 4 times	10	10	70	60	N.D	N.D	On-pump CABG	RCT	4
Kilger *et al.* [57]	2011/Germany	Stress dose of hydrocortisone	183	122	N.D	N.D	N.D	N.D	Off-pump CABG	RCT	2
Kilickan *et al.* [56]	2008/Turkey	15 mg/kg MP intravenously 60 min before induction of anaesthesia	15	15	N.D	N.D	N.D	N.D	On-pump CABG	RCT	3

CABG: coronary artery bypass grafting; CS: corticosteroid; RCT: randomized controlled trial; IV: intravenously; CPB: cardiopulmonary bypass; ICU: intensive care unit; MP: methyl prednisolone; N.D: no data; POD: post operative day.

could not reduce incidence of POAF (Supplementary material, Table S1). Begg and Egger tests showed that there was no potential publication bias among the included RCTs (Begg test, $P = 0.346$; Egger test, $P = 0.346$).

Postoperative stroke

A total of 1423 patients were included from 8 RCTs, which reported data on postoperative stroke (Table 2). After removing RCTs with no events in two arms, a total of 1256 patients from 5 studies were enrolled in the present meta-analysis. Patient population of RCTs ranged from 60 to 737. From 1256 patients, 622 cases were allocated to CS and 634 to the control group. The overall incidence of stroke was 1.4% ranging from 0.8 to 4.3%. Stroke occurred in 1.7% of the cases in the CS group and 1.1% in the control group. Pooled treatment effect analysis revealed that CS therapy could not reduce incidence of stroke after surgery with an OR of 1.61 (95% CI: 0.63–4.1; $P = 0.3$) using a fixed model (Supplementary material, Fig. S1). No significant heterogeneity was observed among the RCTs ($\chi^2 = 2.91$, $I^2 = 0.0\%$, $P = 0.5$). A subgroup analysis showed that CS did not have anti-stroke effects in ages above and below 65 years, male and female, diabetic and non-diabetic patients (Supplementary material, Table S1). All doses of CS (low, medium and high) did not have preventing effects on stroke after surgery (Supplementary material, Table S1). Begg and Egger tests showed no potential publication bias among the included RCTs (Begg test, $P = 0.805$; Egger test, $P = 0.805$).

Postoperative infection

A total of 2060 patients were included from 23 RCTs, which reported data on postoperative infection (Table 2). After removing RCTs with no events in two arms, a total of 1749 patients from 15 studies were enrolled in the meta-analysis. Patient population of RCTs ranged from 34 to 294 patients. From 1749 patients, 874 cases were allocated to the CS group and 875 to the control group. The overall incidence of infection was 5.43% ranging from 0.9 to 14.1%. Infections occurred in 5.4% of the cases in the CS group and 5.3% in the control group. Pooled treatment effect analysis revealed that CS therapy did not increase incidence of postoperative infection with an OR of 1.03 (95% CI: 0.68–1.5; $P = 0.8$) using a fixed model (Fig. 2). No significant heterogeneity was observed among the RCTs ($\chi^2 = 6.71$, $I^2 = 0.0\%$, $P = 0.9$). A subgroup analysis showed that CS did not increase incidence of infection in ages above and below 65 years, male and female, diabetic and non-diabetic patients (Supplementary material, Table S1). All doses of CS (low, medium and high) did not have increasing effects on infection after surgery (Supplementary material, Table S1). Begg and Egger tests showed no potential publication bias among the included RCTs (Begg test, $P = 0.369$; Egger test, $P = 0.369$).

Postoperative myocardial infarction

A total of 1258 patients were included from 12 RCTs, which reported data on postoperative myocardial infarction (MI) (Table 2). After removing one single RCT with two zero-columns, a total of 1234 patients from 11 studies were enrolled in our analysis. Patient population of RCTs ranged from 20 to 294. From 1234 patients, 628 cases were allocated to CS and 606 to the control group. The overall incidence of MI was 3.07% ranging from 0.68 to 6.6%. MI occurred in 2.8% of the cases in the CS group and 3.3% in the control group.

Table 2: Reports of postoperative clinical outcomes of randomized controlled trials

Study	POAF		Stroke		Re-MI		Infection		Ventilation time (h)	
	CS	C	CS	C	CS	C	CS	C	CS	C
Halonen *et al.* [15]	44	62	1	1	6	2	17	7	N.D	N.D
Halvorsen *et al.* [16]	40	47	N.D	N.D	1	1	3	2	2.4 ± 1.15	2.4 ± 1.11
Fillinger *et al.* [17]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	9.9 ± 1.4	15.6 ± 6.5
Engelman *et al.* [18]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	13.1 ± 2.2	10.5 ± 1
Enc *et al.* [19]	2	3	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Azab *et al.* [20]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	11 ± 2	13 ± 3
Demir *et al.* [21]	N.D	N.D	N.D	N.D	N.D	N.D	0	0	9.5 ± 4.9	8.2 ± 4.3
Channey	8	9	N.D	N.D	1	1	N.D	N.D	12.8 ± 4.9	10 ± 5.2
Channey	17	9	N.D	N.D	0	1	N.D	N.D	15.6 ± 36.7	7.6 ± 5.1
Celik *et al.* [22]	6	7	N.D	N.D	N.D	N.D	N.D	N.D	10.7 ± 0.9	8.5 ± 0.6
Bourbon *et al.* [23]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	12.7 ± 5.5	11.2 ± 4.5
Bingol *et al.* [24]	1	3	N.D	N.D	N.D	N.D	0	2	N.D	N.D
Abbaszadeh *et al.* [25]	32	19	N.D	N.D	4	6	5	4	10.3 ± 2.4	10.4 ± 1.6
Yilmaz *et al.* [26]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	13.4 ± 11.05	11.7 ± 3.56
Amr *et al.* [27]	7	8	N.D	N.D	2	2	4	3	N.D	N.D
Yared *et al.* [28]	11	14	N.D	N.D	N.D	N.D	0	0	6.4 ± 6.6	8.3 ± 4.7
Yared *et al.* [29]	17	36	N.D	N.D	N.D	N.D	1	2	11.6 ± 11.9	13.1 ± 13.8
Whitlock *et al.* [30]	7	10	1	1	1	3	2	1	7.7 ± 4.1	10.7 ± 4.6
Weis *et al.* [31]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	11 ± 3	14 ± 7
Wan *et al.* [32]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	14 ± 7	18 ± 10
von Spiegel *et al.* [33]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Volk *et al.* [34]	N.D	N.D	N.D	N.D	0	0	N.D	N.D	N.D	N.D
Volk *et al.* [35]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Tassani *et al.* [36]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	8.1 ± 0.7	9.2 ± 0.8
Suezawa *et al.* [37]	1	7	0	0	N.D	N.D	0	0	8.1 ± 6.9	9.7 ± 7
Sobieski *et al.* [38]	2	4	0	0	N.D	N.D	0	0	8 ± 2.7	9 ± 4.1
Schurr *et al.* [39]	12	9	N.D	N.D	N.D	N.D	2	2	N.D	N.D
Sauër *et al.* [40]	N.D	N.D	7	2	N.D	N.D	N.D	N.D	8 ± 3	8 ± 3
Sano *et al.* [41]	N.D	N.D	N.D	N.D	N.D	N.D	0	0	22 ± 12	20.4 ± 19.4
Rubens *et al.* [42]	1	8	N.D	N.D	N.D	N.D	1	1	N.D	N.D
Liakopoulos *et al.* [43]	2	3	N.D	N.D	N.D	N.D	3	2	14 ± 8.8	11.4 ± 6.9
Prasongsukarn *et al.* [44]	9	22	N.D	N.D	N.D	N.D	4	2	N.D	N.D
Mirhosseini *et al.* [45]	10	13	N.D	N.D	N.D	N.D	1	5	N.D	N.D
Oliver *et al.* [46]	N.D	N.D	1	0	N.D	N.D	N.D	N.D	8.6 ± 4.9	10.3 ± 6.7
Murphy *et al.* [47]	11	10	0	0	N.D	N.D	0	1	6.3 ± 16.2	7 ± 15.7
Morariu *et al.* [48]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	18.8 ± 1.3	15 ± 0.9
McBride *et al.* [49]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Mayumi *et al.* [50]	N.D	N.D	N.D	N.D	N.D	N.D	0	0	34 ± 15.3	31.2 ± 11
Mardani *et al.* [51]	5	11	1	3	1	0	3	2	9.1 ± 2.4	10.5 ± 3.8
Lomivorotov *et al.* [52]	5	2	N.D	N.D	N.D	N.D	2	1	6.7 ± 1.9	5.7 ± 1.7
Loef *et al.* [53]	1	0	N.D	N.D	1	0	N.D	N.D	N.D	N.D
Jansen *et al.* [54]	N.D	N.D	N.D	N.D	N.D	N.D	0	0	N.D	N.D
Giomarelli *et al.* [55]	N.D	N.D	N.D	N.D	N.D	N.D	0	0	12.5 ± 2.7	11.8 ± 3
Kilger *et al.* [57]	23	15	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Kiliçkan *et al.* [56]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	187.2 ± 18.9	172.8 ± 15.6
	ICU stay		Hospital stay		Bleeding		Death		Re-explore	
	CS	C	CS	C	CS	C	CS	C	CS	C
Halonen *et al.* [15]	N.D	N.D	N.D	N.D	N.D	N.D	1	1	5	3
Halvorsen *et al.* [16]	N.D	N.D	N.D	N.D	703 ± 247	744 ± 279	1	1	1	1
Fillinger *et al.* [17]	27 ± 0.3	36 ± 7.4	4.6 ± 0.3	6.1 ± 0.45	N.D	N.D	N.D	N.D	N.D	N.D
Engelman *et al.* [18]	28.8 ± 2.4	50.4 ± 7.2	6.5 ± 1.1	5.2 ± 0.4	N.D	N.D	N.D	N.D	N.D	N.D
Enc *et al.* [19]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Azab *et al.* [20]	24 ± 8	52	32	N.D	N.D	N.D	0	0	N.D	N.D
Demir *et al.* [21]	55.9 ± 14.6	83 ± 75.6	8.5 ± 2.1	12.6 ± 6.7	N.D	N.D	N.D	N.D	N.D	N.D
Channey	N.D	N.D	6.9 ± 4.1	8.3 ± 5.1	N.D	N.D	1	2	N.D	N.D
Channey	N.D	N.D	6.4 ± 4.1	6.5 ± 4.6	N.D	N.D	0	1	N.D	N.D
Celik *et al.* [22]	36.2 ± 4.7	42.1 ± 3.7	10.2 ± 2.2	12.4 ± 2.3	N.D	N.D	1	2	N.D	N.D
Bourbon *et al.* [23]	N.D	N.D	N.D	N.D	N.D	N.D	0	0	N.D	N.D
Bingol *et al.* [24]	33.6 ± 16.3	124.8 ± 78	8.3 ± 1.1	12.9 ± .9	N.D	N.D	0	2	N.D	N.D
Abbaszadeh *et al.* [25]	N.D	N.D	N.D	N.D	415 ± 154	421 ± 166	0	1	N.D	N.D
Yilmaz *et al.* [26]	33.7 ± 17.3	34.2 ± 7.8	6.6 ± 0.9	9.2 ± 8.7	N.D	N.D	N.D	N.D	N.D	N.D
Amr *et al.* [27]	64.8 ± 19.2	67.2 ± 16.8	15 ± 1	14 ± 2	N.D	N.D	N.D	N.D	N.D	N.D
Yared *et al.* [28]	34 ± 43	29 ± 13	6 ± 4	8 ± 2	N.D	N.D	1	0	N.D	N.D
Yared *et al.* [29]	36.8 ± 28	47.9 ± 113.6	7 ± 5.2	7.3 ± 5.3	N.D	N.D	2	3	N.D	N.D

Continued

Table 2: (*Continued*)

	ICU stay		Hospital stay		Bleeding		Death		Re-explore	
	CS	C	CS	C	CS	C	CS	C	CS	C
Whitlock *et al.* [30]	N.D	N.D	6 ± 1	6 ± 2	505 ± 197	690 ± 368	1	0	N.D	N.D
Weis *et al.* [31]	48 ± 24	144 ± 48	5 ± 7	18 ± 9	N.D	N.D	N.D	N.D	N.D	N.D
Wan *et al.* [32]	29 ± 9	32 ± 23	N.D	N.D	474 ± 264	505 ± 177	0	0	0	0
von Spiegel *et al.* [33]	N.D	N.D	N.D	N.D	1599 ± 713	1369 ± 357	N.D	N.D	N.D	N.D
Volk *et al.* [34]	36 ± 7.2	38.4 ± 7.2	N.D	N.D	N.D	N.D	0	0	N.D	N.D
Volk *et al.* [35]	36 ± 28.8	74.4 ± 158.4	14.6 ± 16.1	8.7 ± 6.8	N.D	N.D	0	0	N.D	N.D
Tassani *et al.* [36]	27 ± 2.1	28 ± 2.2	13.3 ± 0.9	10.5 ± 1.2	616 ± 52	833 ± 71	N.D	N.D	N.D	N.D
Suezawa *et al.* [37]	45.6 ± 16.8	50.4 ± 40.8	14 ± 7	18 ± 9	N.D	N.D	0	0	0	0
Sobieski *et al.* [38]	23.7 ± 2.6	24.6 ± 12.3	4.8 ± 1.5	5 ± 1.3	568 ± 432	671 ± 340	0	0	0	0
Schurr *et al.* [39]	24 ± 19.2	24 ± 21.6	11 ± 2	11 ± 1.6	538 ± 424	490 ± 392	N.D	N.D	1	0
Sauër *et al.* [40]	23 ± 3	22 ± 2	N.D	N.D	N.D	N.D	4	2	7	6
Sano *et al.* [41]	43.2 ± 24	33.6 ± 21.6	1.8 ± 1	1.4 ± 0.9	N.D	N.D	N.D	N.D	N.D	N.D
Rubens *et al.* [42]	43.2 ± 48	36 ± 21.6	5.4 ± 1.9	6.5 ± 2.8	N.D	N.D	0	1	N.D	N.D
Liakopoulos *et al.* [43]	50.4 ± 62.4	50.4 ± 43.2	13.1 ± 5.2	12.3 ± 2.3	N.D	N.D	1	0	N.D	N.D
Prasongsukarn *et al.* [44]	N.D	N.D	N.D	N.D	N.D	N.D	0	0	N.D	N.D
Mirhosseini *et al.* [45]	57.6 ± 19.2	72.2 ± 24.2	5.9 ± 1.2	7.4 ± 2.08	N.D	N.D	1	2	N.D	N.D
Oliver *et al.* [46]	25.2 ± 14	23.9 ± 8.7	N.D	N.D	589.4 ± 303.3	867 ± 579.1	0	0	0	4
Murphy *et al.* [47]	24.7 ± 308.5	25.7 ± 237	6 ± 21	6 ± 13	N.D	N.D	N.D	N.D	N.D	N.D
Morariu *et al.* [48]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
McBride *et al.* [49]	N.D	N.D	8 ± 2.9	7.7 ± 3.5	N.D	N.D	N.D	N.D	N.D	N.D
Mayumi *et al.* [50]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	3	2
Mardani *et al.* [51]	68.6 ± 31.2	88.3 ± 31.9	12.9 ± 1	13.6 ± 1.7	807 ± 506	748 ± 496	N.D	N.D	2	1
Lomivorotov *et al.* [52]	N.D	N.D	N.D	N.D	N.D	N.D	2	1	N.D	N.D
Loef *et al.* [53]	28.8 ± 9.6	26.4 ± 7.2	N.D	N.D	N.D	N.D	N.D	N.D	2	0
Jansen *et al.* [54]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Giomarelli *et al.* [55]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Kilger *et al.* [57]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Kiliçkan *et al.* [56]	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D

CS: corticosteroid; POAF: postoperative atrial fibrillation; N.D: no data; MI: myocardial infarction.

Pooled treatment effect analysis revealed that CS therapy did not have ability for reducing the incidence of MI after surgery with an OR of 0.88 (95% CI: 0.47–1.63; $P = 0.6$) using a fixed model (Supplementary material, Fig. S2). No significant heterogeneity was observed among the RCTs ($\chi^2 = 7.02$, $I^2 = 0.0\%$, $P = 0.7$). All doses of CS (low, medium and high) could not decrease MI after surgery (Supplementary material, Table S1). Begg and Egger tests showed that there was no potential publication bias among the included RCTs (Begg test, $P = 0.6$; Egger test, $P = 0.681$).

Postoperative duration of ventilation

A total of 2653 patients were included from 29 RCTs, which reported data on postoperative duration of ventilation time (Table 2). Mean duration for all trials was 11.55 ± 5.93 h with 11.63 ± 6.36 for CS and 11.47 ± 5.51 for the control group. Applying a random effect model, pooled analysis revealed that CS therapy succeeded significantly in reducing duration of ventilation with a WMD of 0.257 (95% CI: 0.10–0.41; $P = 0.00$) (Supplementary material, Fig. S3). There was significant heterogeneity among the studies ($\chi^2 = 257.6$, $I^2 = 98.1\%$, $P = 0.000$). A subgroup analysis is presented in Supplementary material, Table S1.

Postoperative length of hospital stay

Mean length of hospital stay (LHS) for 35 trials (1536 patients) was 9.7 ± 4 days with 9.4 ± 4.13 for the CS group and 10 ± 3.99 for the control group. Pooled analysis revealed that CS therapy could significantly reduce LHS with a WMD of −0.48 (95% CI: −0.66 to −0.3; $P = 0.000$) using a random effect model (Fig. 3). Significant heterogeneity was observed among the RCTs ($\chi^2 = 288.9$, $I^2 = 91.7\%$, $P = 0.000$).

Postoperative blood loss

Mean amount of bleeding for all trials was 707.66 ± 325.87 ml with 681.44 ± 329.23 ml for CS and 733.88 ± 322.51 ml for the control group. Applying a random effect model, pooled analysis revealed that CS therapy succeeded strongly in reducing blood loss with a WMD of −124.05 (95% CI: −147.72 to −100.38; $P = 0.00$) (Fig. 4). There was significant heterogeneity among the studies ($\chi^2 = 73.5$, $I^2 = 87.8\%$, $P = 0.00$). A subgroup analysis is presented in Supplementary material, Table S1.

Postoperative re-exploration

Eleven RCTs reported data on postoperative re-exploration (Table 2). Overall incidence of re-exploration was 2.28%, 2.55% in the CS group and 2.02% in the control group. In fact, 3 of 11 comparisons did not present any postoperative re-exploration events in two comparative arms; therefore, the remaining 8 RCTs (1584 patients) were used to perform the meta-analysis. Pooled treatment effect analysis revealed that CS therapy could not reduce incidence of postoperative re-exploration with an OR of 1.25 (95% CI: 0.66–2.35; $P = 0.4$) using a fixed model (Supplementary

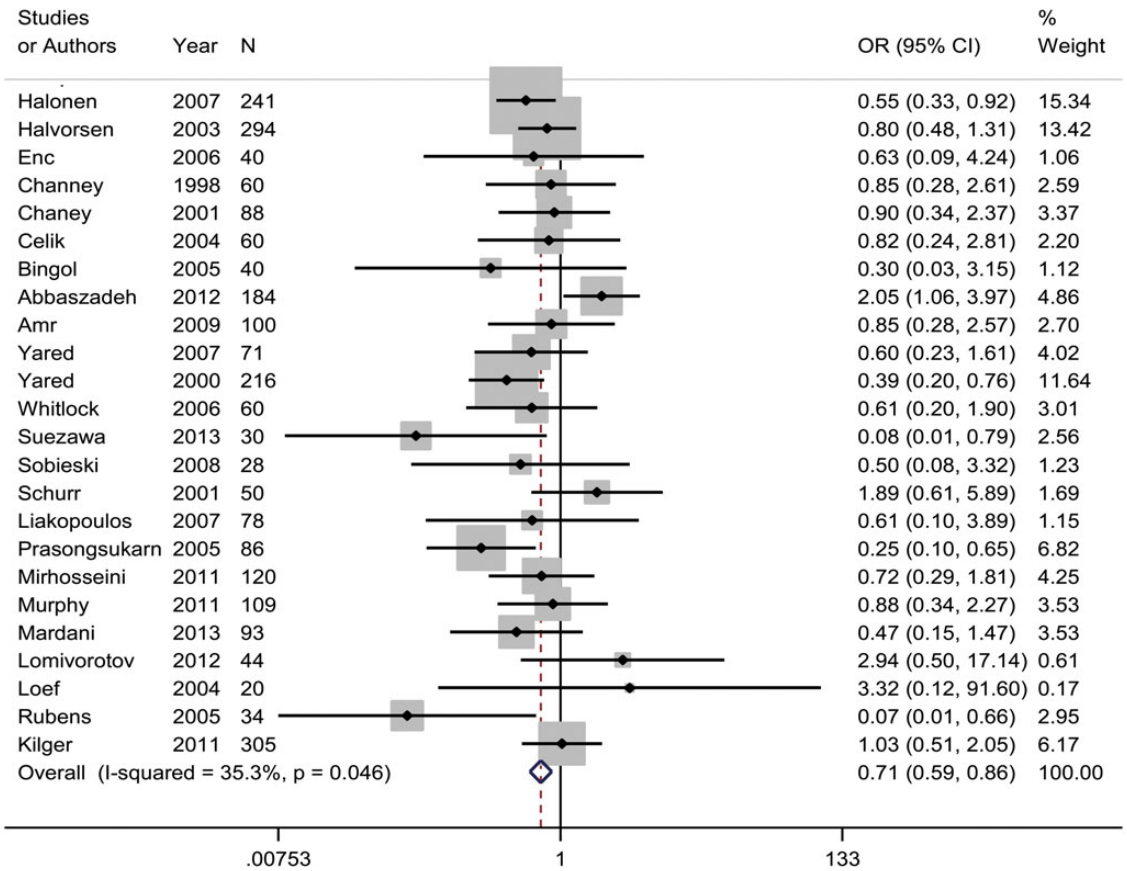

Figure 1: Forest plot of odds ratio (OR) for treatment with CS on incidence of postoperative atrial fibrillation.

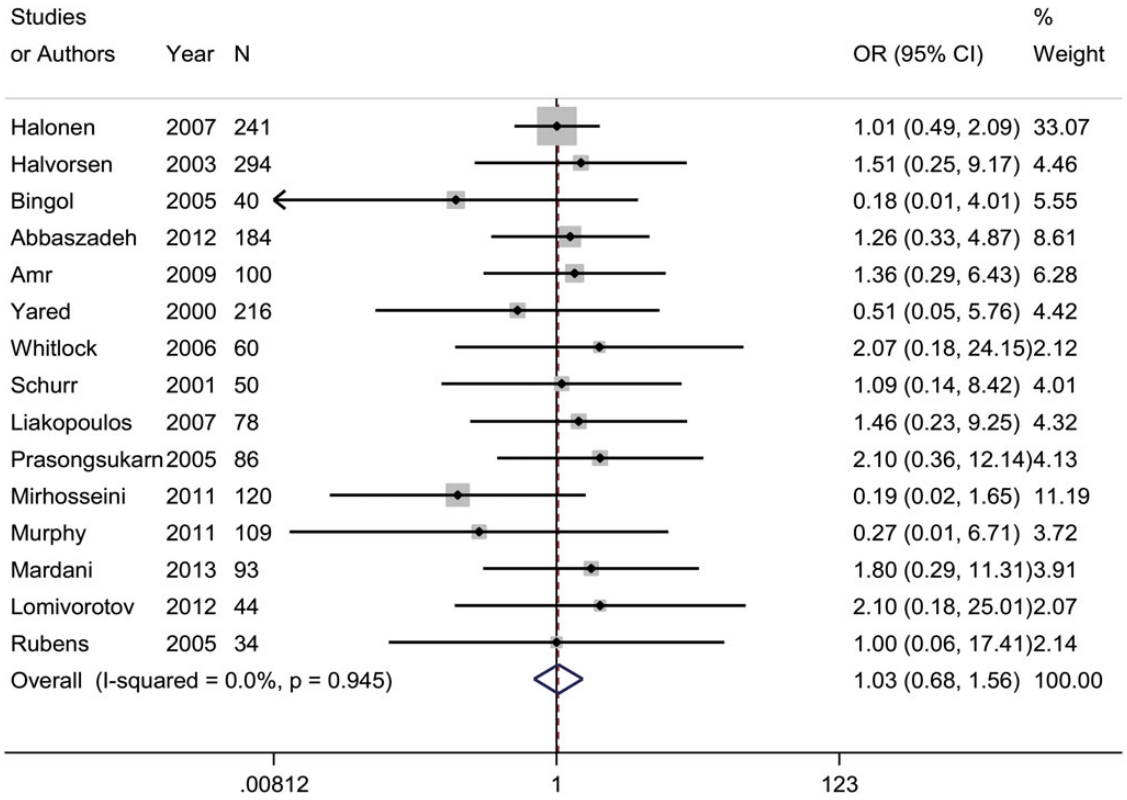

Figure 2: Forest plot of odds ratio (OR) for treatment with CS on incidence of postoperative infection.

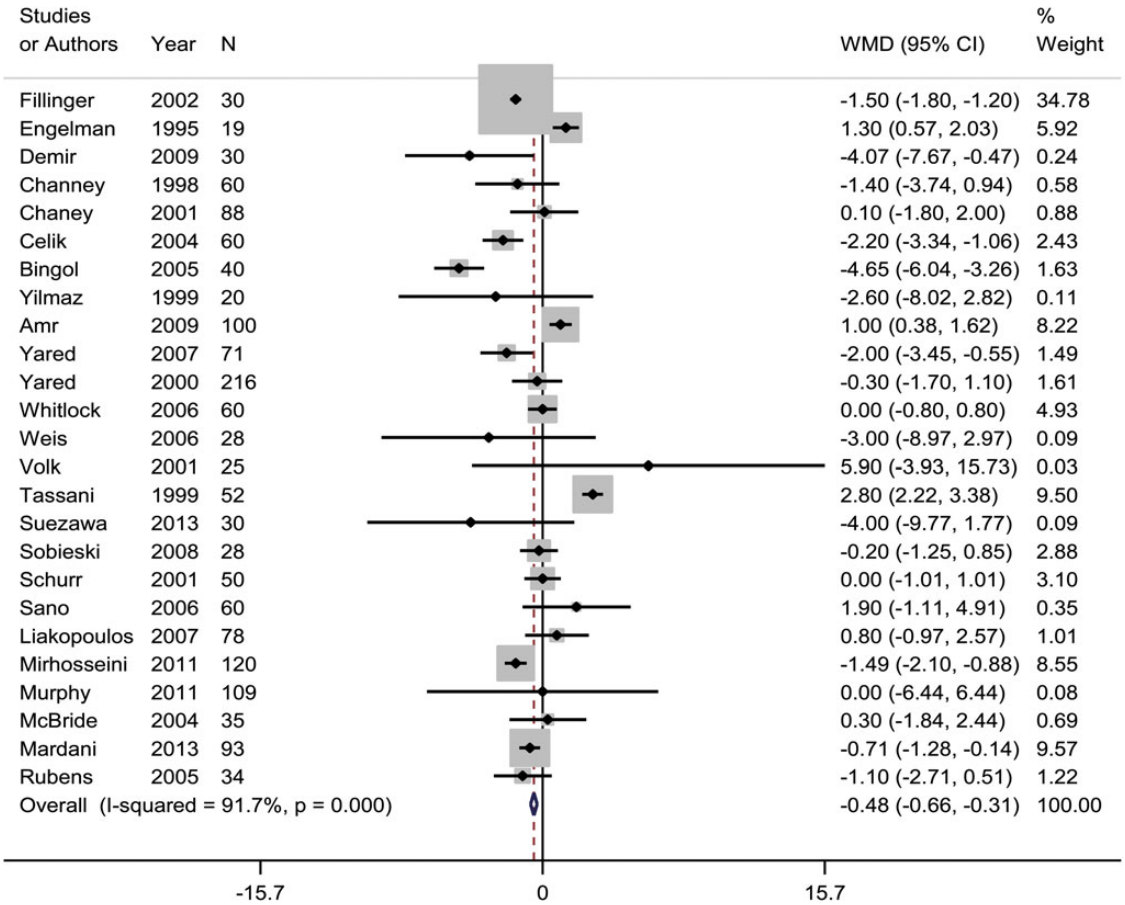

Figure 3: Forest plot of weighted mean differences (WMD) for treatment with corticosteroids on length of hospital stay.

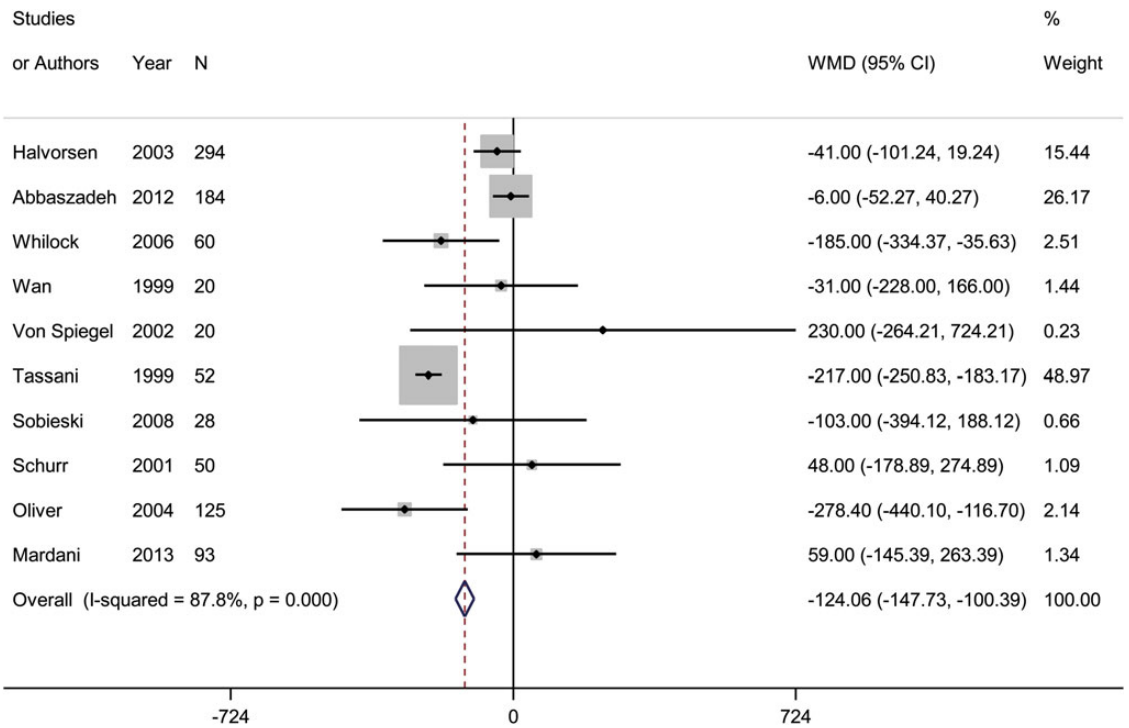

Figure 4: Forest plot of weighted mean differences (WMD) for treatment with corticosteroids on amount of blood loss.

material, Fig. S4). No significant heterogeneity was observed among the RCTs ($\chi^2 = 6.37$, $I^2 = 0.0\%$, $P = 0.7$).

Postoperative mortality

Twenty-three RCTs reported data on postoperative death (Table 2). Mortality occurred in 1.11% of the cases in the CS group and 1.29% in the control group. In fact, 9 of 23 comparisons did not present any postoperative death event in two comparative arms; therefore, the remaining 14 RCTs (2267 patients) were used to perform the meta-analysis. Pooled treatment effect analysis revealed that CS therapy could not reduce incidence of postoperative mortality with an OR of 0.87 (95% CI: 0.46–1.64; $P = 0.6$) using a fixed model (Supplementary material, Fig. S5). No significant heterogeneity was observed among the RCTs ($\chi^2 = 6.37$, $I^2 = 0.0\%$, $P = 0.9$). A subgroup analysis showed that CS did not decrease the incidence of mortality in ages above and below 65 years, male and female, diabetic and non-diabetic patients (Supplementary material, Table S1). All doses of CS (low, medium and high) did not have decreasing effects on death (Supplementary material, Table S1).

DISCUSSION

Nowadays, increasing incidence of coronary artery disease highlights the importance of CABG [1]. Despite its notable complications, CABG surgery is considered an elective treatment for patients with several significant stenoses of coronary arteries [2]. POAF is one of the main complications associated with increased morbidity and mortality [6]. AF occurs in 30% of patients following CABG, and rises up to 40–50% in combined CABG and valve surgery [6]. POAF can increase the incidence of stroke, thromboembolic events, and haemodynamic instability and, as a result, LHS [6]. Inflammatory responses after cardiac surgery are known to contribute to the pathogenesis of POAF [6]. Therefore, an increase in acute phase proteins, such as C-reactive protein and tumor necrosis factor, may be a predictor of new onset POAF [7]. Glucocorticoids as anti-inflammatory drugs are widely used in the treatment of inflammatory diseases [7, 8]. As the activated inflammatory processes in cardiac procedure can predispose the incidence of other complications, administration of corticosteroids for prophylaxis and their effects on clinical outcomes have always been taken into account [9].

Our meta-analysis revealed that in general steroids were able to dramatically reduce the incidence of POAF. Interestingly, CSs in low and high doses were unable to reduce AF, whereas administration of a medium dose of CSs was associated with a great anti-arrhythmic effect. A possible explanation for this might be that fewer studies on low and high doses of CS have been performed and, as a result, in this study CSs in low and high doses did not have prophylactic effects on AF. Also, it can be related to the AF response to CS therapy, which is in normal distribution (bell curve) where the optimum effective dose is the medium. According to pharmacology, anti-inflammatory effects of CS are dose-dependent [10]. This fact was confirmed in our meta-analysis in a way that optimum dose was the medium one, and higher doses did not have more significant effects. Moreover, Liu *et al.* pointed out that CS prophylaxis in high dose had more anti-arrhythmic effects than in low dose. This finding suggests that high doses of corticosteroids may alter the phospholipid cell membrane, causing potassium flux across the cell membrane [10].

Stroke is an important neurological complication after cardiac surgery occurring in ∼3% of cases [11, 58]. Predisposing factors for stroke are as follows: age >50 years, urgent or emergency surgery, aortic valve disease, history of AF prior to surgery, previous stroke and CPB time of more than 110 min [11, 58]. As CSs have anti-arrhythmic effects, and can prevent the incidence of POAF, we investigated whether there is an effect of CS on stroke as well. The findings of our study revealed that CS was unable to reduce postoperative stroke statistically.

One of the possible downsides of applying CS perioperatively is that steroid-induced suppression could significantly increase the risk of infection [5]. For that reason, physicians avoid administering CS prior to high-risk surgical interventions [5, 10]. Also, one of the reasons why administration of CS is contraindicated in diabetic patients is that this category of patients are more susceptible to postoperative infections compared with non-diabetic patients and CS might worsen their condition [5]. The findings of our study indicated that administration of steroids did not increase the risk of infection at all. No study had investigated the effect of high dose of CS on infection; however, low and medium doses did not increase the incidence of infection. Furthermore, according to our subgroup analysis, the incidence of infection after administration of CS did not differ significantly in diabetic and non-diabetic patients. The findings of our study showed that CS resulted in a statistical increase in length of ventilation compared with the placebo group, implying that administration of steroids could lead to pulmonary functional disorders. Chaney *et al.* [12, 13] claimed that steroids could possibly increase the need for respiratory support through increasing pulmonary shunt and alveolar-arterial oxygen gradient. This rationalization is consistent with our findings. A subgroup analysis showed that length of ventilation following low and medium doses of CS was not significantly different compared with placebo group. However, if high doses of steroids were administered, mechanical ventilation time would intensely increase. Therefore, it can be summarized that when using high doses of steroids, pulmonary function of the patient should be thoroughly assessed, and taken into account. There is a relationship between inflammation and coagulation: that is, in inflammation process, coagulation system might get involved through three mechanisms: (i) activation of coagulation, (ii) down-regulation of natural anticoagulation, (iii) suppression of fibrinolysis. Since the activation of inflammatory and coagulation systems presents similar pathways, a better presentation of coagulation system with reduced thrombin generation may be the cause of reduced blood loss in therapy-based anti-inflammation [14].

The findings of our study demonstrated that CS receivers had statistically less bleeding compared with the control group; however, the clinical significance for this effect is questionable. Nevertheless, there might be a slight relationship between inflammation and coagulation systems. Interestingly, our subgroup analysis showed that medium dose had a more prophylactic effect on haemorrhage than low dose. The current meta-analysis also stated that steroid prophylaxis had no effect on the incidence of MI, re-exploration and mortality in patients undergoing CABG. Factors leading to increase in LHS and postoperative clinical costs are as follows: incidence of POAF, major haemorrhage, nosocomial infections and increase in length of need for mechanical ventilation. The current study claimed that CS was able to remarkably decrease LHS, which indeed depends on reduction of surgical complications and improvement in clinical outcomes after CABG. In agreement with our study, Cappabianca *et al.* [5] also reported that steroids could reduce morbidity, surgical complications and

LHS. As the number of patients analysed for several end-points, such as stroke and bleeding, was low, though statistically correct, the clinical conclusion regarding these end-points may be limited. Concluding steroid prophylaxis in patients undergoing CABG could significantly reduce complications such as AF, and LHS and increase length of ventilation time statistically. On the other hand, it did not increase the incidence of infection compared with the placebo. Steroids are able to improve clinical outcomes, and thus can be used as an effective safe treatment in CABG.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Conflict of interest: none declared.

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