Benefits and Risks of Corticosteroid Prophylaxis in Adult Cardiac Surgery: A Dose-Response Meta-Analysis

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Benefits and Risks of Corticosteroid Prophylaxis in Adult Cardiac Surgery

A Dose-Response Meta-Analysis

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Background—Cardiopulmonary bypass and cardiac surgery are associated with a significant systemic inflammatory response that may increase postoperative complications. This meta-analysis assessed whether the benefits and risks of corticosteroid use were dose dependent in adult cardiac surgery.

Methods and Results—Randomized controlled trials of the use of corticosteroid prophylaxis in adult cardiac surgery (>18 years of age) requiring cardiopulmonary bypass were selected from MEDLINE (1966 to August 1, 2008), EMBASE (1988 to August 1, 2008), and the Cochrane controlled trials register without any language restrictions. A total of 3323 patients from 50 randomized controlled trials were identified and subject to meta-analysis. Corticosteroid prophylaxis reduced the risk of atrial fibrillation (25.1% versus 35.1%; number needed to treat, 10; relative risk, 0.74; 95% confidence interval [CI], 0.63 to 0.86; $P<0.01$) and length of stay in the intensive care unit (weighted mean difference, −0.37 days; 95% CI, −0.21 to −0.52; $P<0.01$) and hospital (weighted mean difference, −0.66 days; 95% CI, −0.77 to −1.25; $P=0.03$) compared with placebo. The use of corticosteroid was not associated with an increased risk of all-cause infection (relative risk, 0.93; 95% CI, 0.61 to 1.41; $P=0.73$), but hyperglycemia requiring insulin infusion after corticosteroid prophylaxis was common (28.2%; relative risk, 1.49; 95% CI, 1.11 to 2.01; $P<0.01$). No additional benefits were found on all outcomes beyond a total dose of 1000 mg hydrocortisone, and very high doses of corticosteroid were associated with prolonged mechanical ventilation.

Conclusions—Evidence suggests that low-dose corticosteroid is as effective as high-dose corticosteroid in reducing the risk of atrial fibrillation and duration of mechanical ventilation but with fewer potential side effects in adult cardiac surgery. (***Circulation*. 2009;119:1853-1866.)**

Key Words: arrhythmia ■ cardiopulmonary bypass ■ coronary disease ■ inflammation ■ steroid ■ surgery

Cardiopulmonary bypass and ischemia/reperfusion injury in cardiac surgery are associated with significant activation of complement, platelets, neutrophils, monocytes, and macrophages.[1] Sequestration of neutrophils and activation of coagulation, fibrinolysis, and kallikrein cascades may occur, resulting in a systemic inflammatory response syndrome.[1] This systemic inflammatory response syndrome is characterized by elevated concentrations of tumor necrosis factor, C-reactive protein (CRP), interleukin (IL)-6, and IL-8 within the first few days after cardiac surgery.[1–3]

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Atrial fibrillation after cardiac surgery is very common and is associated with significant morbidities, including prolonged intensive care unit (ICU) and hospital stay.[4] Both systemic inflammatory response and local inflammation of the atrium are believed to contribute to the pathogenesis of atrial fibrillation after cardiac surgery.[3,5] The link between inflammation and atrial fibrillation after cardiac surgery is further strengthened by studies that showed that corticosteroid prophylaxis can reduce the occurrence of atrial fibrillation after cardiac surgery.[4,6] Apart from atrial fibrillation, excessive systemic inflammatory response also may induce myocardial, respiratory, renal, hepatic, and intestinal injury.[1,6]

Corticosteroid prophylaxis in cardiac surgery has been studied extensively for >30 years,[1,2,4,6] but its potential benefits and risks remain controversial and inconclusive. Small sample sizes, a wide range of doses, and different preparations of corticosteroid used in different studies are the major confounders affecting the interpretation of these studies. Although a meta-analysis on this topic exists,[7] the wide range of doses of corticosteroid in the included studies was not considered.

We hypothesized that corticosteroid prophylaxis may have a dose-dependent effect on outcomes after cardiac surgery and performed a dose-response meta-analysis to assess the

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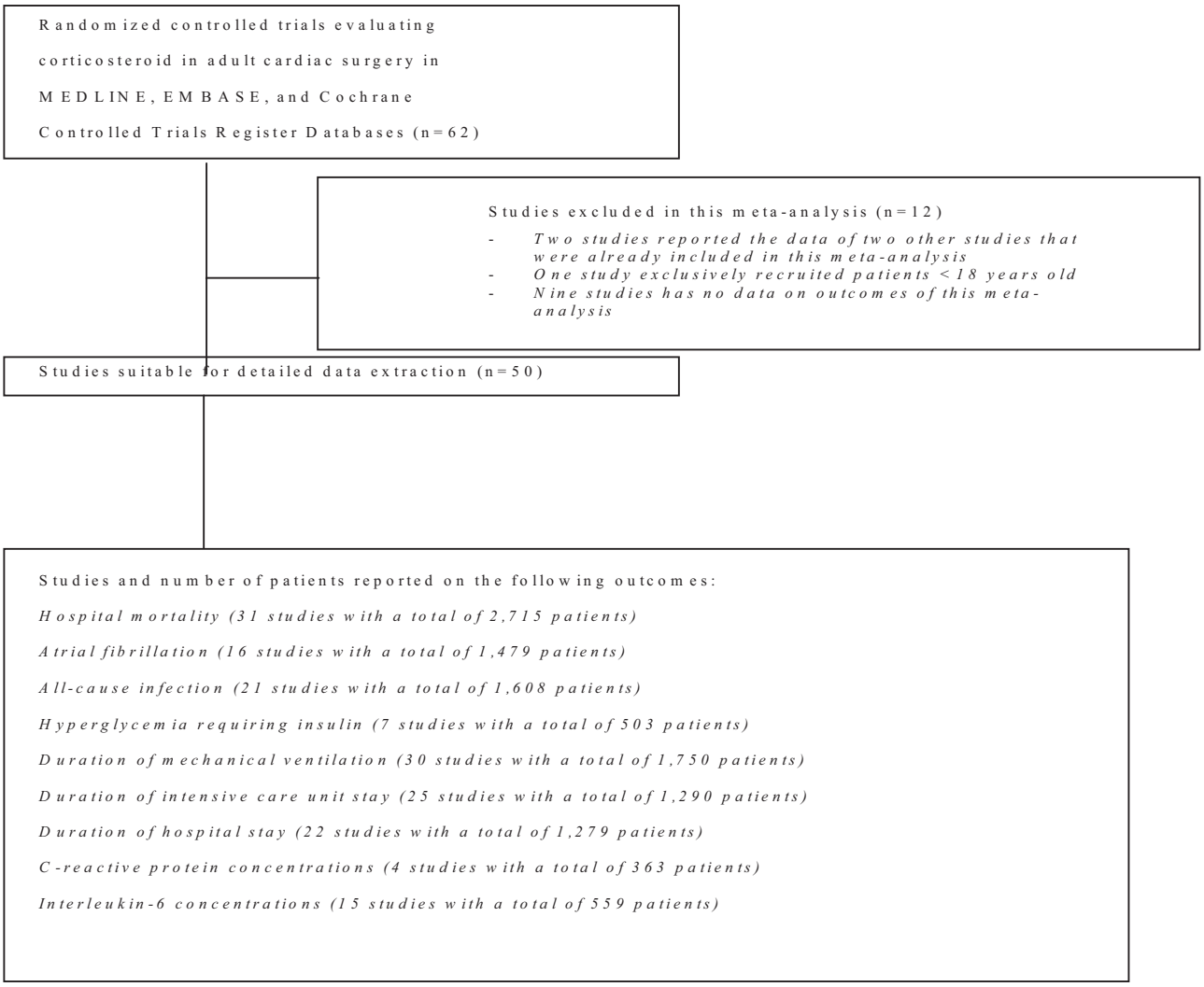

Figure 1. Flow chart showing study inclusion and exclusion in this meta-analysis.

clinical benefits and risks of corticosteroid use in adult cardiac surgery.

Methods

Search Strategy

Two researchers searched the Cochrane controlled trials register (2008, issue 2) and the EMBASE (January 1988 to August 1, 2008) and MEDLINE (1966 to August 1, 2008) databases independently. During the electronic database search, the following exploded Medical Subject Heading (MeSH) terms were used: "steroid," "corticosteroid," "glucocorticoid," "dexamethasone," "prednisolone," "prednisone," "methylprednisolone," "hydrocortisone" with "cardiac surgery," "cardiopulmonary bypass," or "heart surgery." The search was limited to clinical trials, letters, editorial, reviews, or randomized controlled trials. The reference lists of related editorials, reviews, and original articles identified were searched for relevant trials. Finally, the Websites of the International Network of Agencies of Health Technology Assessment and International Society of Technology Assessment in Health Care were searched to ensure that all suitable trials were included. No language restrictions existed for inclusion in this meta-analysis.

Selection Criteria and Validity Assessment

Only randomized controlled clinical trials comparing corticosteroid with placebo or equal volume of normal saline, initiated either before or at the time of cardiopulmonary bypass, in adult (>18 years of age) cardiac surgery were included. Studies that used unequal concurrent medical therapies or studies that evaluated corticosteroid in off-pump cardiac surgery were excluded. Two independent reviewers examined all identified trials to confirm that they fulfilled the inclusion criteria. They examined and recorded the trial characteristics and outcomes independently using a predesigned data abstraction form. This abstraction form was used to record information regarding the quality of the trial such as allocation concealment, randomization method, blinding of treatment, and inclusion and exclusion criteria. The grading of allocation concealment was based on the Cochrane approach, ie, adequate, uncertain, or clearly inadequate. The 2 independent reviewers had no disagreements on the data extracted.

Outcomes of Interest

The proportion of patients with new-onset atrial fibrillation in the postoperative period was chosen as the main outcome of interest because atrial fibrillation is common and associated with other significant morbidities after cardiac surgery.[4] The other outcomes assessed included the proportion of patients who developed infections after cardiac surgery, hyperglycemia requiring insulin infusion, hospital mortality, CRP/IL-6/IL-8 concentrations at 24 hours after cardiopulmonary bypass or surgery, duration of mechanical ventilation, and length of ICU and hospital stay.

Table. Characteristics of the Included Studies

Study, Country of Origin, Year of Publication	Inclusion (Mean Age of Participants) and Exclusion Criteria	Interventions and No. of Patients Analyzed	Outcomes	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Rao et al,[6] US, 1977	Inclusion: CABG; exclusion: not described	1g IV methylprednisolone (n=75) or control (n=75) before bypass	Mortality and proportion of patients with infection	Allocation concealment unclear, no blinding, analysis not by intention to treat, 1.3% did not complete the study
Codd et al,[16] US, 1977	Inclusion: elective CABG (mean age, 52 y); exclusion: patients with valve replacement or aneurysmectomy	2 g IV methylprednisolone (n=75) or control (n=75) before bypass	Mortality	Allocation concealment inadequate, no blinding, analysis by intention to treat, all completed the study
Vallejo et al,[17] Spain, 1977	Inclusion: elective valve surgery (mean age, 36 y)	30 mg/kg IV methylprednisolone (n=50) or control (n=50) before cross-clamp	Mortality and infection postoperatively	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Fecht et al,[18] US, 1978	Inclusion: elective CABG (with 1 patient with aneurysm resection) (mean age, not reported); exclusion: patients with infection	1 g IV methylprednisolone twice (n=25) or control (n=25) before cross-clamp of the aorta and after release of the cross-clamp	Mortality	Allocation concealment unclear, double blinded, analysis by intention to treat, all completed the study
Niazi et al,[19] US, 1979	Inclusion: CABG required ≥2 grafts (mean age, 57 y); exclusion: patients required left ventricular resection or valvular replacement	30 mg/kg IV methylprednisolone (n=30), 6 mg/kg IV dexamethasone (n=30), or identical-looking placebo (n=30) during sternotomy	Mortality	Allocation concealment unclear, double blinded, analysis by intention to treat, all completed the study
Ferries et al,[20] US, 1984	Inclusion: elective CABG, atrial septal repair, or valve surgery (mean age, 59 y); exclusion: after the first 2 patients of the operating day, emergency surgery, patient refusal	30 mg/kg IV methylprednisolone with membrane (n=20) or bubble oxygenator (n=20) or control with membrane (n=20) or bubble (n=20) oxygenator	Mortality	Allocation concealment adequate, double blinded, analysis by intention to treat, all completed the study
Andersen et al,[21] Denmark, 1989	Inclusion: elective CABG (mean age, 58 y); exclusion: patients with infection	30 mg/kg IV methylprednisolone (n=8) or control (n=8) during the induction of anesthesia	Mortality	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Jansen et al,[22] Netherlands, 1991	Inclusion: elective CABG (mean age, 63 y); exclusion: insulin-dependent DM, preoperative steroid, chronic obstructive lung disease, bypass >180 min, use of IABP	1 mg/kg IV dexamethasone (n=12) or normal saline (n=10) after induction of anesthesia	Length of ICU stay (mean and SD)	Allocation concealment unclear, double blinded, analysis not by intention to treat, 12% did not complete the study
Teoh et al,[2] Canada, 1995	Inclusion: elective CABG (mean age, 58 y); exclusion: DM, steroid dependent	250 mg IV methylprednisolone (n=16) or control (n=9) before anesthesia induction	IL-6 and IL-8 at 24 h after surgery, proportion of patients required insulin postoperatively	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Engelman et al,[23] US, 1995	Inclusion: elective CABG with ≥3 grafts and bypass time >90 min (mean age, 64 y); exclusion: not described	1 g IV methylprednisolone followed by 4 mg IV dexamethasone every 6 h for 24 h (n=10) or control (n=9) before anesthesia induction	IL-8 at 24 h after surgery, duration of intubation, length of ICU and hospital stay (mean and SD)	Allocation concealment unclear, not blinded (except the blood tests results), analysis by intention to treat, all completed the study
Coetzer et al,[24] South Africa, 1996	Inclusion: cardiac surgery required bypass (mean age not reported); exclusion: patients <18 y of age, with steroid treatment	30 mg/kg IV methylprednisolone (n=165) or control (n=130) 1 h before bypass	Mortality	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Mayumi et al,[25] Japan, 1997	Inclusion: elective valvular replacement (mean age, 53 y); exclusion: end-stage valvular heart disease	20 mg/kg IV methylprednisolone (n=12) or normal saline (n=12) 5 to 10 min before and also after bypass	Mortality, intubation time (mean and SD), infection, CRP concentrations 24 h after surgery	Allocation concealment inadequate, double blinded, analysis not by intention to treat, 11% did not complete the study
Toft et al,[26] Denmark, 1997	Inclusion: elective cardiac surgery (mean age, 63 y); exclusion: unstable cardiovascular patients or surgical problems were expected	30 mg/kg IV methylprednisolone at induction of anesthesia (n=8) or control (n=8)	Proportion of patients required insulin or with infection	Allocation concealment unclear, no blinding, intention to treat analysis, all completed the study

(*Continued*)

Table. Continued

Study, Country of Origin, Year of Publication	Inclusion (Mean Age of Participants) and Exclusion Criteria	Interventions and No. of Patients Analyzed	Outcomes	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Chaney et al,[14] US, 1998	Inclusion: elective CABG (mean age, 66 y); exclusion: reoperation, EF <40%, preoperative steroid or inotrope or IABP, previous lung surgery	30 mg/kg IV methylprednisolone during sternotomy and 30 mg/kg methylprednisolone during initiation of bypass (n=30) or normal saline (n=30)	Mortality, proportion of patients with AF, proportion of patients with gastrointestinal bleeding or perforation, intubation time, length of hospital stay (mean and SD)	Allocation concealment unclear, double blinded, analysis by intention to treat, all completed the study
Wan et al,[27] Belgium, 1999	Inclusion: elective CABG or valve surgery (mean age, 65 y); exclusion: patients with infection, steroid treatment, emergency surgery, redo, <3 grafts	30 mg/kg IV methylprednisolone (n=10) or control (n=10) during the induction of anesthesia	Mortality, intubation time, length of ICU stay (mean and SD)	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Tassani et al,[28] Germany, 1999	Inclusion: elective CABG; exclusion: reoperation, age >75 y, body weight >50% over ideal body weight, EF <40%, valvular heart disease, renal or liver failure	1g IV methylprednisolone 30 min before bypass (n=26) or control (n=26)	IL-6 and IL-8 at 24 h after surgery, intubation time, length of ICU and hospital stay (mean and SD), proportion of patients required insulin postoperatively	Allocation concealment adequate, double blinded, analysis by intention to treat, all completed the study
Yilmaz et al,[29] Turkey, 1999	Inclusion: elective CABG (mean age, 53 y); exclusion: reoperation, concurrent steroid, aspirin, dipyridamole or anticoagulant treatment, COPD, insulin dependent DM, congestive heart failure, peptic ulcer disease, recent myocardial infarction	1 mg/kg IV methylprednisolone (n=10) or placebo (n=10) into the pump prime solution	IL-6 and IL-8 at 24 h after surgery, intubation time, length of ICU and hospital stay (mean and SD), proportion of patients with infection postoperatively	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Harig et al,[30] Germany, 1999	Inclusion: elective CABG (mean age, 62 y); exclusion: EF <55%, renal or hepatic insufficiency	250 mg oral prednisolone preoperatively and postoperatively (n=10) or placebo (n=10)	Mortality, intubation time (mean and range)	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Yared et al,[31] US, 2000	Inclusion: elective CABG or valvular surgery (mean age, 53 y); exclusion: DM, concurrent steroid treatment, received aprotinin, hypersensitive to dexamethasone	0.6 mg/kg IV dexamethasone (n=106) or normal saline (n=110) after induction of anesthesia before skin incision	Mortality; proportion of patients with infection, with AF, and required insulin; intubation time; length of hospital and ICU stay (mean and SD)	Allocation concealment unclear, no blinding, analysis not by intention to treat, 8.5% did not complete the study
Chaney et al,[13] US, 2001	Inclusion: elective CABG (mean age, 65 y); exclusion: reoperation, EF <40%, preoperative steroid, inotrope, or IABP, previous lung surgery	30 mg/kg IV methylprednisolone during sternotomy and initiation of bypass (n=30), 15 mg/kg IV methylprednisolone during sternotomy and during initiation of bypass (n=30), or normal saline (n=30)	Mortality, proportion of patients with AF, intubation time, and length of hospital stay (mean and SD)	Allocation concealment unclear, double blinded, analysis not by intention to treat, 2.2% did not complete the study
Volk et al,[32] Germany, 2001	Inclusion: elective CABG (mean age, 63 y); exclusion: EF <40%, infection, on steroid, renal or liver dysfunction, insulin-dependent DM	15 mg/kg IV methylprednisolone (n=13) or placebo (n=13) within 1.5 h before bypass	Length of ICU and hospital stay (mean and SD)	Allocation concealment unclear, no blinding, analysis by intention to treat, 3.8% did not complete the study
Rumalla et al,[33] US, 2001	Inclusion: elective CABG (mean age, 62 y); exclusion: steroid treatment or with immunodeficiency	1 g IV methylprednisolone (n=6) or placebo (n=7) before induction of anesthesia	Mortality and infections	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Schurr et al,[34] Switzerland, 2001	Inclusion: primary isolated CABG (mean age, 64 y); exclusion: peptic ulcer history, immunologic deficiency, renal or liver insufficiency, insulin-dependent DM	10 mg/kg methylprednisolone IV (n=24) or placebo (n=26) 4 h before induction of anesthesia	IL-6 at 24 h after surgery, proportion of patients with AF, infection, intubation time, length of ICU and hospital stay (mean and SD)	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study

(*Continued*)

Table. Continued

Study, Country of Origin, Year of Publication	Inclusion (Mean Age of Participants) and Exclusion Criteria	Interventions and No. of Patients Analyzed	Outcomes	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Turkoz et al,[35] Turkey, 2001	Inclusion: elective CABG (mean age, 61 y); exclusion: reoperation, on steroid, recent myocardial infarction, systemic disease, DM	15 mg/kg IV methylprednisolone (n=10) or placebo (n=10) before induction of anesthesia	IL-6 and IL-8 at 24 h after surgery	Allocation concealment unclear, no blinding, analysis not by intention to treat, 6.3% did not complete the study
El Azab et al,[36] Netherlands, 2002	Inclusion: elective CABG (mean age, 63 y); exclusion: EF <40%, infection, on steroid, myocardial infarction, systemic disease, insulin-dependent DM	100 mg IV dexamethasone (n=9) or placebo (n=9) before induction of anesthesia	IL-6 and IL-8 at 24 h after surgery, mortality, intubation time, length of ICU stay (mean and SD)	Allocation concealment unclear, double blinded, analysis not by intention to treat, 5.6% did not complete the study
Fillinger et al,[37] US, 2002	Inclusion: elective CABG (mean age, 65 y); exclusion: reoperation, preoperative infection, on steroid	15 mg/kg IV methylprednisolone before surgical incision followed by 0.3 mg/kg IV methylprednisolone started 2 h after surgery every 0.6 h for 24 h (n=15) or normal saline (n=15)	IL-6 at 24 h after surgery, intubation time, length of ICU and hospital stay (mean and SD)	Allocation concealment adequate, double blinded, analysis by intention to treat, all completed the study
Giomarelli et al,[38] Italy, 2003	Inclusion: elective CABG (mean age, 64 y); exclusion: EF <35%, previous heart surgery, on steroid, myocardial infarction, systemic disease, insulin-dependent DM	1g IV methylprednisolone preoperatively, then 125 mg IV methylprednisolone at the end of bypass, then 4 more doses of 125 mg every 6 h in ICU (n=10) or placebo (n=10)	IL-6 and IL-8 at 24 h after surgery, infections, intubation time (mean and SD)	Allocation concealment adequate, double blinded, analysis not by intention to treat, all completed the study
Kilger et al,[39] Germany, 2003	Inclusion: elective CABG with ≥4 grafts, CABG with valvular surgery, EF <40% (mean age, 69 y); exclusion: preoperative infection, on steroid, insulin-dependent DM, renal or liver failure, HIV positive	100 mg IV hydrocortisone before induction of anesthesia, then 10 mg/h for 24 h, then 5 mg/h for 24 h, then 20 mg IV 3 times a day, then 10 mg IV 3 times a day (n=48) or control (n=43)	Mortality, intubation time, length of ICU and hospital stay (median and IQR)	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Volk et al,[40] Germany, 2003	Inclusion: elective CABG (mean age, 63 y); exclusion: EF <40%, preoperative infection or on steroid, insulin-dependent DM, renal or liver insufficiency	15 mg/kg IV methylprednisolone (n=12) or normal saline (n=12) within 1.5 h before bypass	Length of ICU stay (mean and SD)	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Halvorsen et al,[41] US, 2003	Inclusion: elective CABG (mean age, 63 y); exclusion: preoperative on steroid, insulin, history AF or other cardiac arrhythmias	8 mg IV dexamethasone (n=147) or normal saline (n=147)	Mortality, proportion of patients with AF or infection	Allocation concealment adequate, double blinded, analysis not by intention to treat, 2% did not complete the study
Abd El-Hakeem et al,[42] Egypt, 2003	Inclusion: elective aortic or mitral valve replacement (mean age, 35 y); exclusion: preoperative on steroid, uncontrolled rapid AF, poorly controlled DM, EF <50%	100 mg dexamethasone (n=10) before induction of anesthesia or control (n=10)	IL-6 and IL-8 at 24 h after surgery, length of ICU stay, intubation time (mean and SD), proportion of patients with AF	Allocation concealment adequate, double blinded, analysis by intention to treat, all completed the study
Abd El-Hakeem et al,[43] Egypt, 2003	Inclusion: elective aortic or mitral valve replacement (mean age, 36 y); exclusion: preoperative on steroid, uncontrolled rapid AF, poorly controlled DM, EF <50%	100 mg dexamethasone (n=23) before induction of anesthesia or control (n=23)	Length of ICU stay, intubation time (mean and SD), mortality	Allocation concealment adequate, double blinded, analysis by intention to treat, all completed the study
McBride et al,[44] Ireland, 2004	Inclusion: elective CABG (mean age, 61 y); exclusion: preoperative on steroid, myocardial infarction, insulin-dependent DM, renal, heart or liver failure	30 mg/kg methylprednisolone (n=18) before induction of anesthesia or control (n=17)	IL-8 at 24 h after surgery, length of hospital stay (mean and SD), proportion of patients required insulin	Allocation concealment unclear, double blinded, analysis not by intention to treat, 2.8% did not complete the study
Loef et al,[45] Netherlands, 2004	Inclusion: elective CABG with normal renal failure (mean age, 64 y); exclusion: EF <45%, reoperation, preoperative on steroid, myocardial infarction, DM	1 mg/kg dexamethasone before induction of anesthesia and 0.5 mg/kg 8 h later (n=10) or placebo (n=10)	Proportion of patients required insulin, length of ICU stay (mean and SD)	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study

(*Continued*)

Table. Continued

Study, Country of Origin, Year of Publication	Inclusion (Mean Age of Participants) and Exclusion Criteria	Interventions and No. of Patients Analyzed	Outcomes	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Bourbon et al,[46] France, 2004	Inclusion: elective CABG with normal renal failure (mean age, 64 y); exclusion: EF <45%, reoperation, preoperative on steroid, myocardial infarction, DM	5 mg /kg IV methylprednisolone (n=12) or 10 mg/kg IV methylprednisolone (n=12) or control (n=12) before bypass	IL-6 at 24 h after surgery, mortality, intubation time (mean and SD)	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Celik et al,[47] Turkey, 2004	Inclusion: elective CABG (mean age, 61 y); exclusion: EF <40%, pulmonary, on steroid, severe systemic disease, insulin-dependent DM	30 mg/kg IV methylprednisolone (n=30) or placebo (n=30) before and also after bypass (total of 6 doses of methylprednisolone or placebo)	IL-6 and IL-8 at 24 h after surgery, AF, mortality, intubation time, length of ICU and hospital stay (mean and SD)	Allocation concealment unclear, double blinded, analysis by intention to treat, all completed the study
Oliver et al,[48] US, 2004	Inclusion: elective CABG or valvular surgery (mean age, 62 y); exclusion: congenital heart disease, EF <35%, reoperation, preoperative on steroid, insulin-dependent DM, renal impairment, end-stage pulmonary disease	1g IV methylprednisolone before induction of anesthesia followed by 4 mg IV dexamethasone every 6 h for 24 h (n=62) or normal saline (n=63)	Mortality, intubation time, length of ICU stay (mean and SD)	Allocation concealment unclear, double blinded, intention to treat, 1.6% did not complete the study
Rubens et al,[49] Canada, 2005	Inclusion: elective CABG (mean age, 55 y); exclusion: reoperation, Fev_1 <1.5 L, reoperation, peptic ulcer disease, preoperative on steroid or warfarin, insulin-dependent DM, renal impairment, end-stage pulmonary disease	1g IV methylprednisolone before bypass with (n=17) and also without using a modified bypass circuit (n=17) or placebo with a modified bypass circuit (n=17) and without a modified bypass circuit (n=17)	IL-6 and IL-8 at 24 h after surgery, mortality, proportion of patients on insulin, with infection or, with AF, length of ICU and hospital stay (mean and SD)	Allocation concealment adequate, double blinded, analysis by intention to treat, all completed the study
Bingol et al,[50] Turkey, 2005	Inclusion: elective CABG with diagnosis of COPD but not asthma (mean age, 64 y); exclusion: reoperation or off-pump CABG, insulin-dependent DM, EF <35%, familial atopy	20 mg oral prednisolone daily for 10 d before operation and continue until discharge (n=20) or placebo (n=20)	Mortality, proportion of patients with AF and infection, intubation time, length of ICU and hospital stay (mean and SD)	Allocation concealment adequate, double blinded, analysis by intention to treat, all completed the study
Morariu et al,[1] Netherlands, 2005	Inclusion: elective CABG (mean age, 64 y); exclusion: reoperation, abnormal renal or liver function, EF <45%, DM, recent radiocontrast or steroid	1 mg/kg IV dexamethasone at induction of anesthesia and 0.5 mg/kg 8 h later (n=10) or placebo (n=10)	IL-6, IL-8, CRP at 24 h after surgery, mortality, intubation time (mean and SD)	Allocation concealment unclear, double blinded, analysis by intention to treat, all completed the study
Prasongsukarn et al,[51] Canada, 2005	Inclusion: elective CABG (mean age, 64 y); exclusion: reoperation, history of arrhythmias or heart block, steroid dependency or allergy	1g IV methylprednisolone before bypass and 4 mg IV dexamethasone every 6 h for a total of 24 h (n=43) or placebo (n=43)	IL-6 at 24 h after surgery, mortality, proportion of patients with AF or infection	Allocation concealment adequate, double blinded, analysis not by intention to treat, 2.3% did not complete the study
Weis et al,[52] Switzerland, 2006	Inclusion: elective cardiac surgery requiring bypass >97 min or with preoperative EF <35% (mean age, 68 y); exclusion: pregnancy, renal dysfunction, insulin-dependent DM, steroid treatment, HIV positive	100 mg IV hydrocortisone before induction of anesthesia, 10 mg/h for 24 h, 5 mg/h for 24 h, 20 mg IV 3 times a day and then 10 mg IV 3 times a day (n=14) or placebo (n=14)	Intubation time, length of ICU and hospital stay (median and IQR)	Allocation concealment adequate, double blinded, analysis not by intention to treat, 22% did not complete the study
Enc et al,[53] Turkey, 2006	Inclusion: male, elective CABG (mean age, 58 y); exclusion: reoperation, DM	25 mg/kg IV methylprednisolone (n=20) or normal saline (n=20) 1 h before bypass	Proportion of patients with infection or AF, length of hospital stay	Allocation concealment unclear, double blinded, analysis by intention to treat, all completed the study
Whitlock et al,[15] Canada, 2006	Inclusion: >18 y of age requiring cardiopulmonary bypass (mean age, 67 y); exclusion: preoperative on steroid, infection within 30 d, steroid intolerance	250 mg methylprednisolone (n=30) on induction of anesthesia and another 250 mg methylprednisolone before cardiopulmonary bypass or control (n=30)	Mortality, length of ICU and hospital stay, intubation time (mean and SD), proportion of patients with AF and infection	Allocation concealment adequate, triple blinded, analysis by intention to treat, all completed the study

(*Continued*)

Table. Continued

Study, Country of Origin, Year of Publication	Inclusion (Mean Age of Participants) and Exclusion Criteria	Interventions and No. of Patients Analyzed	Outcomes	Allocation Concealment, Blinding, Intention to Treat, Lost to Follow-Up
Sano et al,[54] Japan, 2006	Inclusion: elective cardiac surgery (mean age, 62 y); exclusion: kidney or liver dysfunction	50 mg/kg IV hydrocortisone (n=31) or normal saline (n=29) before and also after bypass	Proportion of patients with infection, atrial flutter, intubation time, length of ICU and hospital stay (mean and SD)	Allocation concealment adequate, no blinding, analysis by intention to treat, all completed the study
Liakopoulos et al,[12] Germany, 2007	Inclusion: elective CABG (mean age, 66 y); exclusion: >80 y, EF <30%, infection, renal or liver dysfunction, aprotinin treatment, recent myocardial infarction, antiinflammatory treatment	15 mg/kg IVmethylprednisolone (n=40) or placebo (n=38) before bypass	IL-6, IL-8, and CRP at 24 h after surgery, mortality, proportion of patients with infection, intubation time, length of ICU and hospital stay (mean and SD)	Allocation concealment adequate, no blinding, analysis not by intention to treat, 2.5% did not complete the study
Yared et al,[55] US, 2007	Inclusion: elective combined CABG and valvular surgery (mean age, 72 y); exclusion: aprotinin, amiodarone, or steroid treatment, history of AF	0.6 mg/kg IV dexamethasone (n=37) or placebo (n=34) before induction of anesthesia	Mortality, proportion of patients with AF, required insulin, or with infection, intubation time, length of ICU and hospital length of stay (median and IQR)	Allocation concealment adequate, no blinding, analysis not by intention to treat, 8.9% did not complete the study
Halonen et al,[4] Finland, 2007	Inclusion: elective CABG, aortic valve replacement, combined CABG and aortic valve replacement (mean age, 65 y); exclusion: reoperation, AF, DM, infection, psychotic mental disorder, herpes simplex keratitis, renal failure, peptic ulcer	100 mg IV hydrocortisone every 8 h for 3 d started in the evening of operative day (n=120) or normal saline (n=121)	CRP at 24 h after surgery, mortality, proportion of patients with AF<infection	Allocation concealment adequate, double blinded, analysis not by intention to treat, 0.4% did not complete the study
Kilickan et al,[56] Turkey, 2008	Inclusion: elective CABG (mean age, 62 y); exclusion: EF <40%, DM, preoperative steroid, chronic inflammatory disease, contraindications to epidural technique	15 mg/kg IV methylprednisolone 60 min before induction of anesthesia (with [n=15] or without [n=15] thoracic epidural) or placebo (with [n=15] or without [n=15] thoracic epidural)	Intubation time, length of hospital stay (mean and SD)	Allocation concealment unclear, no blinding, analysis by intention to treat, all completed the study
Sobieski et al,[57] US, 2008	Inclusion: elective CABG and <80 y (mean age, 63 y); exclusion: recent myocardial infarction, significant organ failure, steroid treatment or IABP before surgery	100 mg IV dexamethasone (n=13) or normal saline (n=15) after induction of anesthesia	Mortality, proportion of patients with AF or infection, intubation time, length of ICU and hospital stay (mean and SD)	Allocation concealment adequate, double blinded, intention to treat analysis, all completed the study

CABG indicates coronary artery bypass graft; DM, diabetes mellitus; IABP, intra-aortic balloon pump; EF, ejection fraction; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; and IRQ, interquartile range.

Statistical Analysis

The differences in categorical outcomes were reported as relative risk (RR) with 95% confidence interval (CI) using a random-effects model. The differences in continuous outcomes were reported as weighted mean difference (WMD) also using a random-effects model.

The dose response of corticosteroid was assessed by two methods. First, the trials were stratified into 3 broad dose strata. They were classified as low dose if the total dose of corticosteroid used was <1000 mg hydrocortisone or equivalent, as medium dose if the total dose used was between 1000 and 10 000 mg hydrocortisone or equivalent, and as high dose if the total dose used was >10 000 mg hydrocortisone or equivalent. These cut points were chosen so that the doses of corticosteroid used in high-dose stratum were at least 10 times higher than those in the low-dose stratum. For studies that used prednisolone/prednisone, methylprednisolone, or dexamethasone, the total dose of corticosteroid used was converted to an equivalent dose of hydrocortisone with similar glucocorticoid effect. The dose conversion factors for prednisolone/prednisone, methylprednisolone, and dexamethasone to hydrocortisone were 4, 5, and 26.7, respectively (http://www.globalrph.com/steroid.cgi). To interpret subtle dose-response pattern, individual studies were listed sequentially according to the total dose of corticosteroid used in all forest plots, with the studies using the smallest dose of corticosteroid at the top. The interactions among the 3 dose strata were then tested by ratio of RRs for categorical outcomes and mean difference for continuous outcomes.[8,9] Second, the dose of corticosteroid was used as a continuous "predictor" in meta-regression to assess whether the dose of corticosteroid affected the RRs of atrial fibrillation between the studies.

The presence of heterogeneity between trials was assessed by the χ^2 statistics, and the extent of inconsistency was assessed using I^2 statistics.[10] An I^2>40% was regarded as significant heterogeneity in this study. Sensitivity analyses were conducted by restricting the analysis to trials that were double blinded and with adequate allocation concealment, were published after 1997, did not use routine postoperative β-blockers, or included only coronary artery bypass graft surgery. Publication bias was assessed by funnel plot

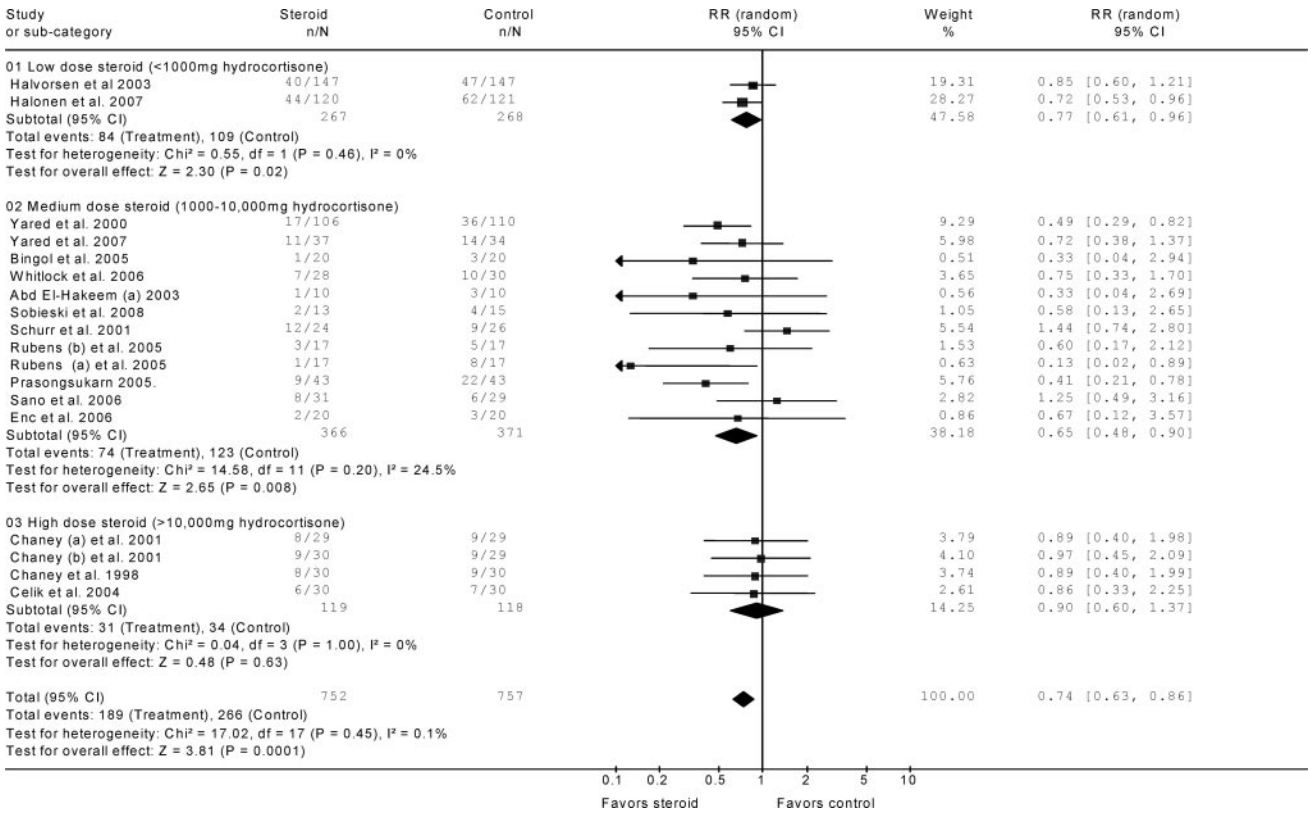

Figure 2. The effect of corticosteroid prophylaxis on risk of atrial fibrillation in adult cardiac surgery.

with the risk of atrial fibrillation used as an end point. The "trim and fill" method was used to adjust for any potential publication bias.[11] Data were analyzed by Review Manager (version 4.2.6 for Windows, The Cochrane Collaboration, Oxford, UK, 2003), and meta-regression and trim and fill adjustment were performed by Comprehensive Meta Analysis (version 2.2.034, 2006; Biostat). A value of $P<0.05$ was regarded as significant in this meta-analysis.

The authors have full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Characteristics of the Included Studies

A total of 3323 patients from 50 randomized controlled trials in 16 countries were identified and subject to meta-analysis (Figure 1).[1,2,4,6,12–57] All studies except 1 were published in English.[17] The total dose of corticosteroid used was quite variable and ranged between 214 and 72 000 mg hydrocortisone. Routine postoperative β-blocker therapy to prevent atrial fibrillation was used in only 2 studies.[4,51] Seventeen studies had adequate allocation concealment; 26 studies used double or triple blinding; and 14 studies had both adequate allocation concealment and double blinding.[4,15,20,28,37,38,41–43,49–52,57] The characteristics of the included trial are described in the Table.

Effects of Corticosteroid Prophylaxis on Inflammatory Markers

Corticosteroid prophylaxis was associated with a reduction in concentrations of some inflammatory markers 24 hours after surgery. CRP concentrations (WMD, −44.2 mg/L; 95% CI, −15.4 to −72.9; $P<0.01$; $I^2=90.7\%$) and IL-6 concentrations (WMD, −148.0 pg/mL; 95% CI, −114.8 to −181.1; $P<0.01$; $I^2=98.1\%$) were significantly reduced after corticosteroid prophylaxis. Also, a suggestion was found that IL-8 was mildly reduced after corticosteroid (WMD, −8.2 pg/mL; 95% CI, −17.0 to 0.60; $P=0.07$; $I^2=97.0\%$). Significant heterogeneity was present in the concentrations of these inflammatory markers between the included studies, but no significant differences between different dose strata were observed.

Effects of Corticosteroid Prophylaxis on Atrial Fibrillation, Mortality, All-Cause Infection, and Hyperglycemia

Corticosteroid prophylaxis was associated with a significant reduction in the risk of atrial fibrillation (25.1% versus 35.1%; number needed to treat, 10; 95% CI, 7 to 19; RR, 0.74; 95% CI, 0.63 to 0.86; $P<0.01$; $I^2=0.1\%$; Figure 2). Meta-regression showed that the doses of corticosteroid were not significantly related to the variations in the RR of atrial fibrillation in the pooled studies (Figure 3). The RR ratios between the low-dose or moderate-dose stratum and the high-dose stratum were 0.86 (95% CI, 0.53 to 1.37) and 0.72 (95% CI, 0.43 to 1.21), respectively, suggesting that the RR reduction in atrial fibrillation was not significantly different between the 3 dose strata.

Hyperglycemia requiring insulin infusion was common (28.2%) after corticosteroid prophylaxis (RR, 1.49; 95% CI, 1.11 to 2.01; $P<0.01$; $I^2=36.1\%$; Figure 4), but corticosteroid did not appear to increase the risk of all-cause infection (RR, 0.93; 95% CI, 0.61 to 1.41; $P=0.73$; $I^2=0\%$; Figure 5) or mortality (RR, 0.72; 95% CI, 0.45 to 1.14; $P=0.16$; $I^2=0$;

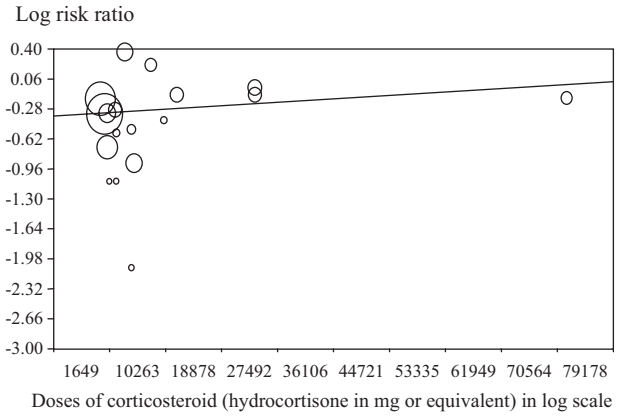

Figure 3. Meta-regression using doses of corticosteroid as a predictor of risk of atrial fibrillation in adult cardiac surgery (slope of the regression line, 1.00; 95% CI, 0.99 to 1.01; $P=0.47$).

Figure 6). Meta-regression showed that the doses of corticosteroid were not significantly related to the variations in the RR of infections in the pooled studies (slope of the regression line, 1.00; 95% CI, 0.99 to 1.01; $P=0.89$). No significant heterogeneity in these clinical outcomes was found between the studies.

Effects of Corticosteroid Prophylaxis on Duration of Mechanical Ventilation, Length of ICU, and Hospital Stay

Corticosteroid prophylaxis was associated with a reduction in duration of mechanical ventilation when all trials were pooled together (WMD, −0.68 hours; 95% CI, −0.03 to −1.33; $P=0.04$; Figure 7). However, the effect of high-dose corticosteroid on duration of mechanical ventilation was very different from the effect of lower doses of corticosteroid. The high-dose stratum was associated with an increased duration of mechanical ventilation without significant heterogeneity (WMD, 2.1 hours; 95% CI, 1.76 to 2.52; $P<0.01$; $I^2=0\%$). Further analysis of this dose-response relationship showed that the effect of high-dose corticosteroid was significantly different from either the low-dose (mean difference, 4.9 hours; 95% CI, 0.59 to 9.25; $P=0.03$) or medium-dose (mean difference, 3.09 hours; 95% CI, 2.17 to 3.92; $P<0.01$) corticosteroid stratum. No significant difference was found, however, between the low- and medium-dose strata in this outcome.

Corticosteroid prophylaxis was associated with a reduction in length of ICU (WMD, −0.37 days; 95% CI, −0.21 to −0.52; $P<0.01$; $I^2=89.1\%$) and hospital stay (WMD, −0.66 days; 95% CI, −0.77 to −1.25; $P=0.03$; $I^2=77.2\%$) with no significant difference between the dose strata. Heterogeneity in these 2 outcomes between the pooled studies was significant.

Sensitivity Analyses and Publication Bias

After the analysis was restricted to studies that both were double blinded and had adequate allocation concealment, the effect of corticosteroid on atrial fibrillation remained unchanged (RR, 0.69; 95% CI, 0.57 to 0.84; $P<0.01$; $I^2=0\%$). Restricting the analysis to studies that did not use routine postoperative β-blocker therapy, were published after 1997, or recruited only coronary artery bypass graft surgery also did not change the effects of corticosteroid on risk of atrial fibrillation and all-cause infection. The funnel plot suggested the possibility of a small publication bias (Figure 8). With the trim and fill method, the adjusted effect of corticosteroid on

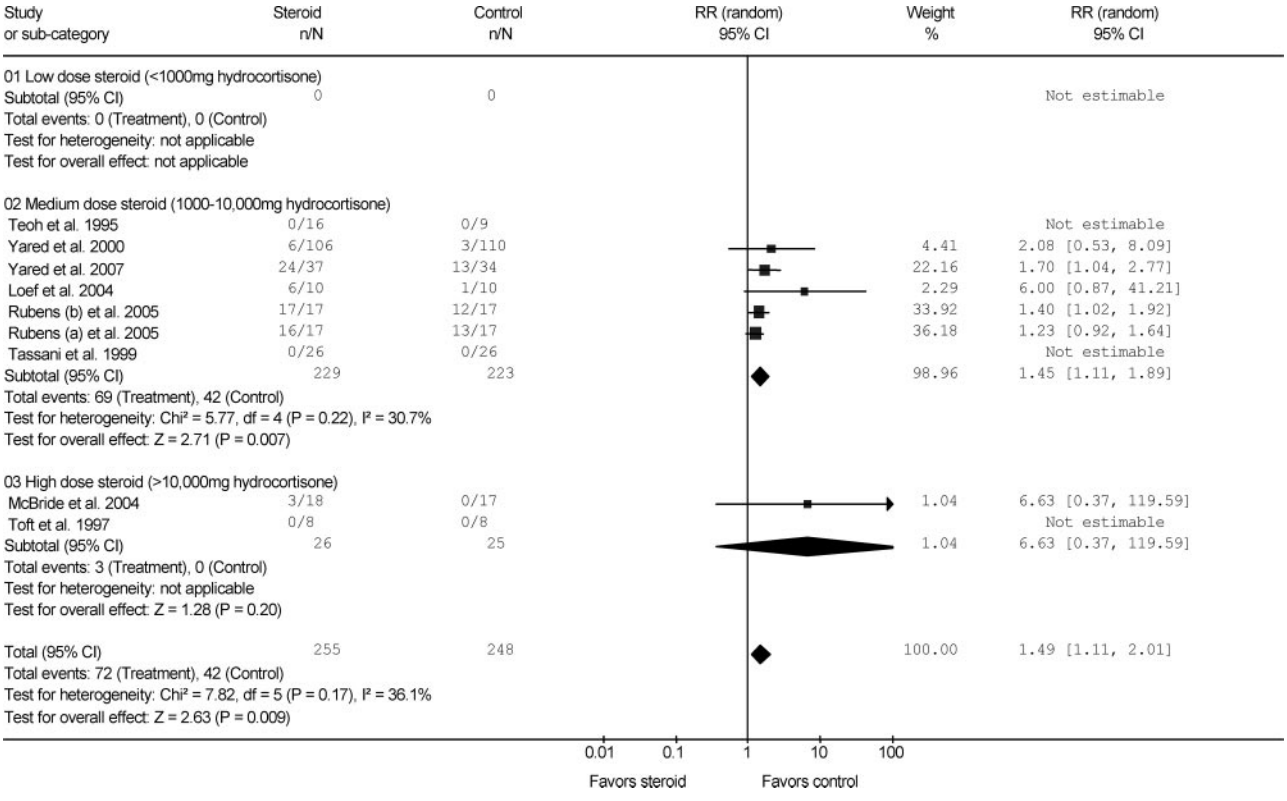

Figure 4. The effect of corticosteroid prophylaxis on risk of hyperglycemia requiring insulin infusion in adult cardiac surgery.

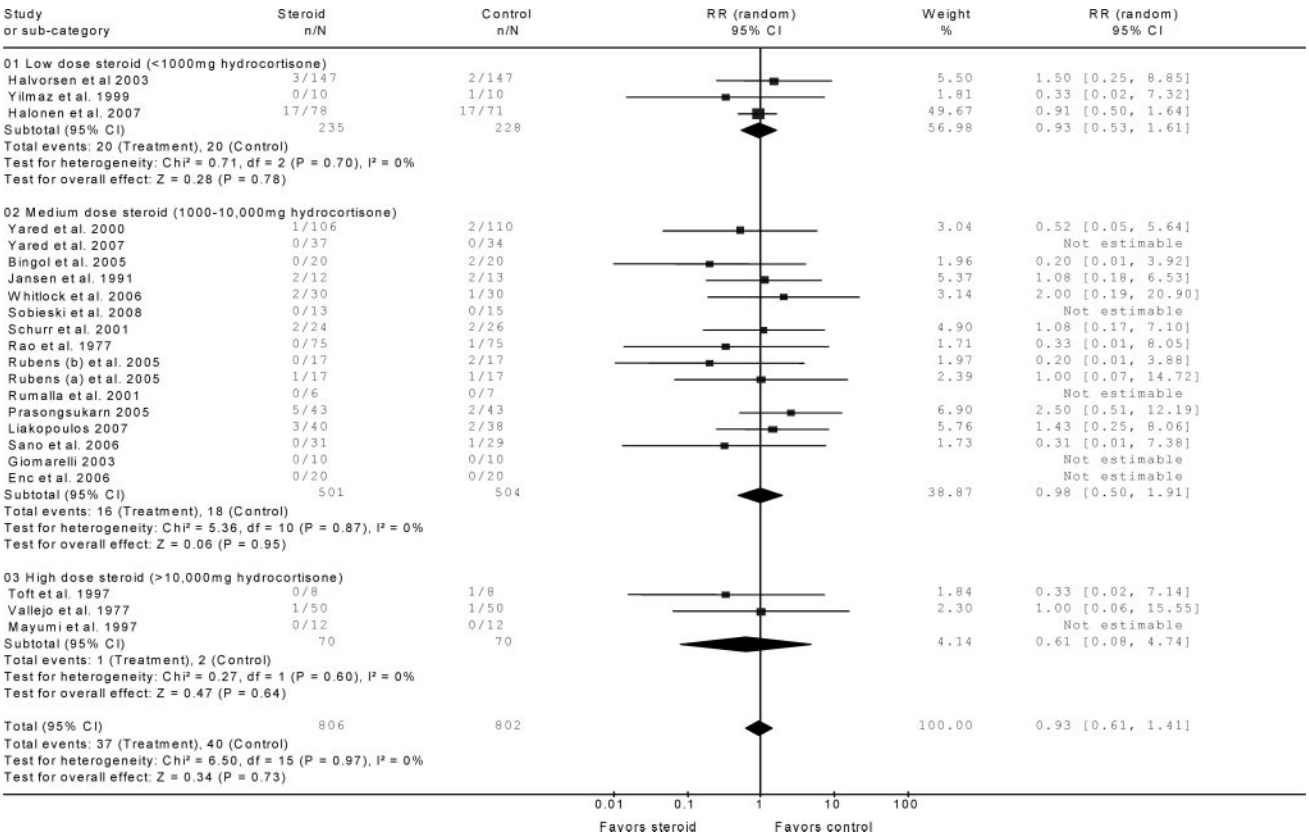

Figure 5. The effect of corticosteroid prophylaxis on risk of all-cause infection in adult cardiac surgery.

atrial fibrillation was slightly more conservative but remained significant (RR, 0.75; 95% CI, 0.63 to 0.89; $P<0.01$).

Discussion

This meta-analysis showed that corticosteroid prophylaxis was effective in reducing the risk of atrial fibrillation and that this benefit was not significantly different between different doses of corticosteroid. Corticosteroid prophylaxis was associated with an increased risk of hyperglycemia requiring insulin infusion, and at high doses (equivalent to >10 000 mg hydrocortisone), it was also associated with an increased duration of mechanical ventilation.

The systemic inflammatory response after cardiopulmonary bypass and cardiac surgery is usually short-lived, but it can be severe and prolonged in some patients.[1] The clinical effects of corticosteroid are known to be dose dependent; thus, different doses are often used for different medical conditions and titrated to the magnitude of antiinflammatory action required. Although corticosteroid prophylaxis in adult cardiac surgery has been studied extensively for >30 years, its role remains controversial, and the optimal dose remains uncertain. To the best of our knowledge, this is the first meta-analysis that assessed the dose-response relationship of corticosteroid in adult cardiac surgery. Our results showed that corticosteroid had no adverse effect on mortality and was effective in reducing atrial fibrillation. This latter beneficial effect of corticosteroid was not significantly different between different doses. Previous studies have shown that corticosteroid prophylaxis may offer some beneficial effects to patients who require cardiopulmonary bypass through a number of different mechanisms. These may include an improvement in myocardial or pulmonary cell integrity, a reduction in the expression of endothelial adhesion molecules, complement activation, and cytokine release.[58] It is highly possible that only low doses of corticosteroid are required to activate these protective mechanisms to attenuate the systemic and atrial inflammation associated with cardiopulmonary bypass. Our results also showed that very high doses of corticosteroid did not offer any additional benefits and might hinder weaning of mechanical ventilation after surgery. The potential adverse effects of high-dose corticosteroid on sodium and water clearance, risk of respiratory tract infections, and intrapulmonary shunt may explain our results.[12,13]

Corticosteroid can induce hyperglycemia, and our results confirmed that corticosteroid prophylaxis was associated with an increased risk of hyperglycemia requiring insulin infusion. None of the studies in the low-dose stratum reported this outcome; thus, whether lower doses of corticosteroid (<1000 mg hydrocortisone) will have less adverse effect on glucose hemostasis remains uncertain. Recent evidence suggests that tight blood glucose control by an insulin clamp technique can have significant antiinflammatory effect during cardiopulmonary bypass.[59] Whether the benefits of corticosteroid can be further enhanced with this new technique remains uncertain but merits further investigation.

Corticosteroid can suppress the normal immune response and may potentially increase the risk of infection after surgery.[54] Our results are reassuring, albeit still limited, that

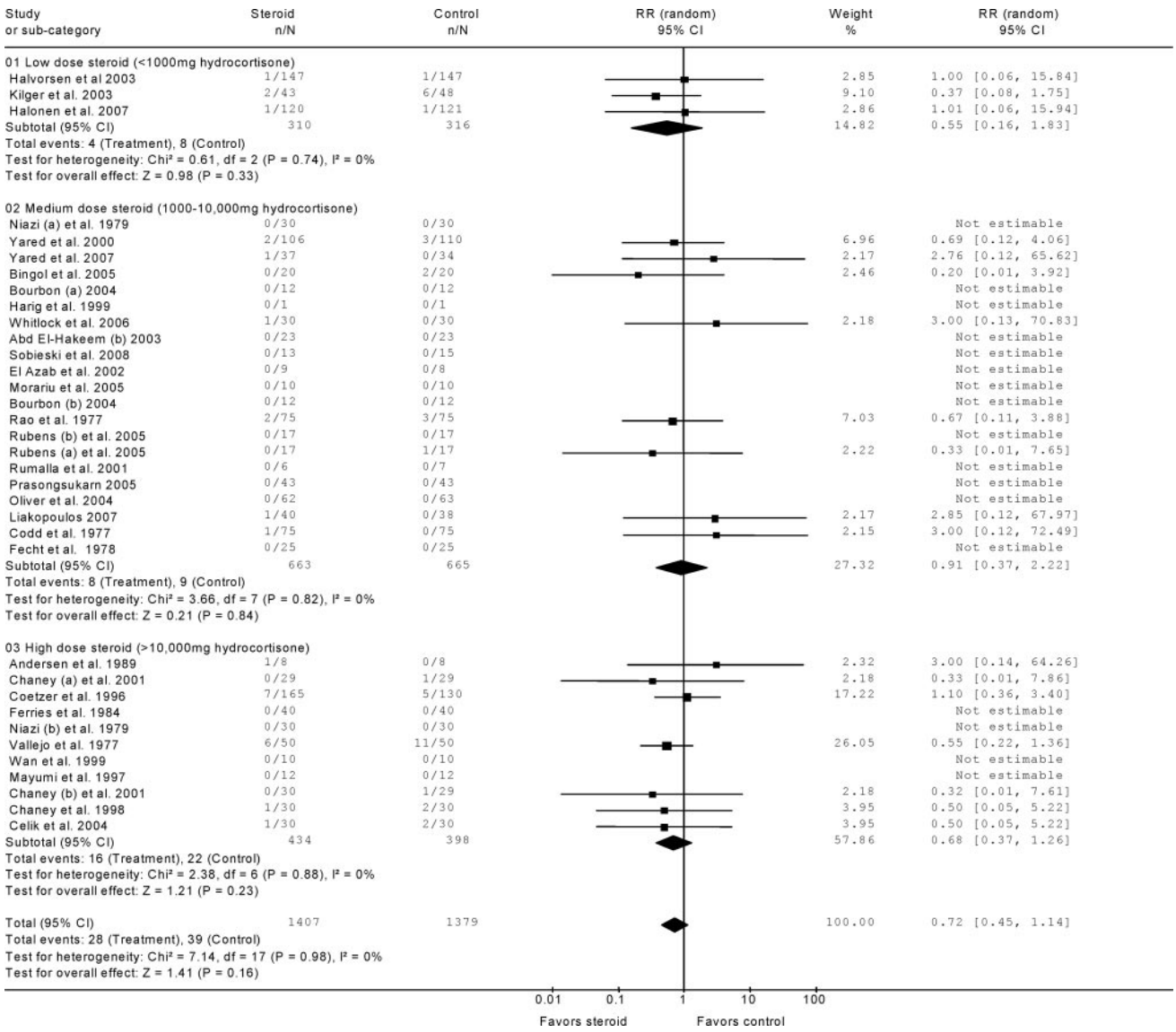

Figure 6. The effect of corticosteroid prophylaxis on mortality of adult cardiac surgery.

a short course of corticosteroid prophylaxis (<24 to 72 hours) did not appear to increase the risk of perioperative infection. However, the sample size of our data on this outcome (n=1608) has a power of only 80% to exclude a 3.5% absolute increase in risk of all-cause infections if the baseline infection rate of the control group is 5%.

If corticosteroid prophylaxis is truly effective in reducing complications related to the inflammatory response of cardiopulmonary bypass, corticosteroid prophylaxis may in fact represent a very cost-effective preventive strategy in adult cardiac surgery. Because low-dose corticosteroid was less likely to have an adverse effect on the duration of mechanical ventilation than higher doses, low-dose corticosteroid (<1000 mg hydrocortisone or equivalent) is likely to be the most cost-effective option. Intravenous hydrocortisone is inexpensive (US $2 per 100 mg), and the estimated cost of preventing 1 atrial fibrillation is less than US $200 if we use less than a total dose of 1000 mg hydrocortisone. Accurate cost-effective analysis from our data, however, is not possible because of the significant heterogeneity in the duration of mechanical ventilation and length of ICU and hospital stay among the pooled trials.

This study has some limitations. First, meta-analysis is prone to bias inherited from the original studies and to publication bias. However, the direction and magnitude of our results were not significantly different after we restricted the analysis to higher-quality studies (n=14) and adjusted for the potential publication bias with the trim and fill method. Second, different studies used different doses, preparations, and durations of corticosteroid prophylaxis during the perioperative period. Although we have adjusted for the different doses of corticosteroid between the studies, the optimal duration of therapy remains uncertain. Furthermore, the variable duration of follow-up and incomplete monitoring for atrial fibrillation in some of the pooled studies may have affected the accuracy of the incidence of atrial fibrillation reported in this study. Third, significant heterogeneity limits the generalizability of the effects of corticosteroid on duration

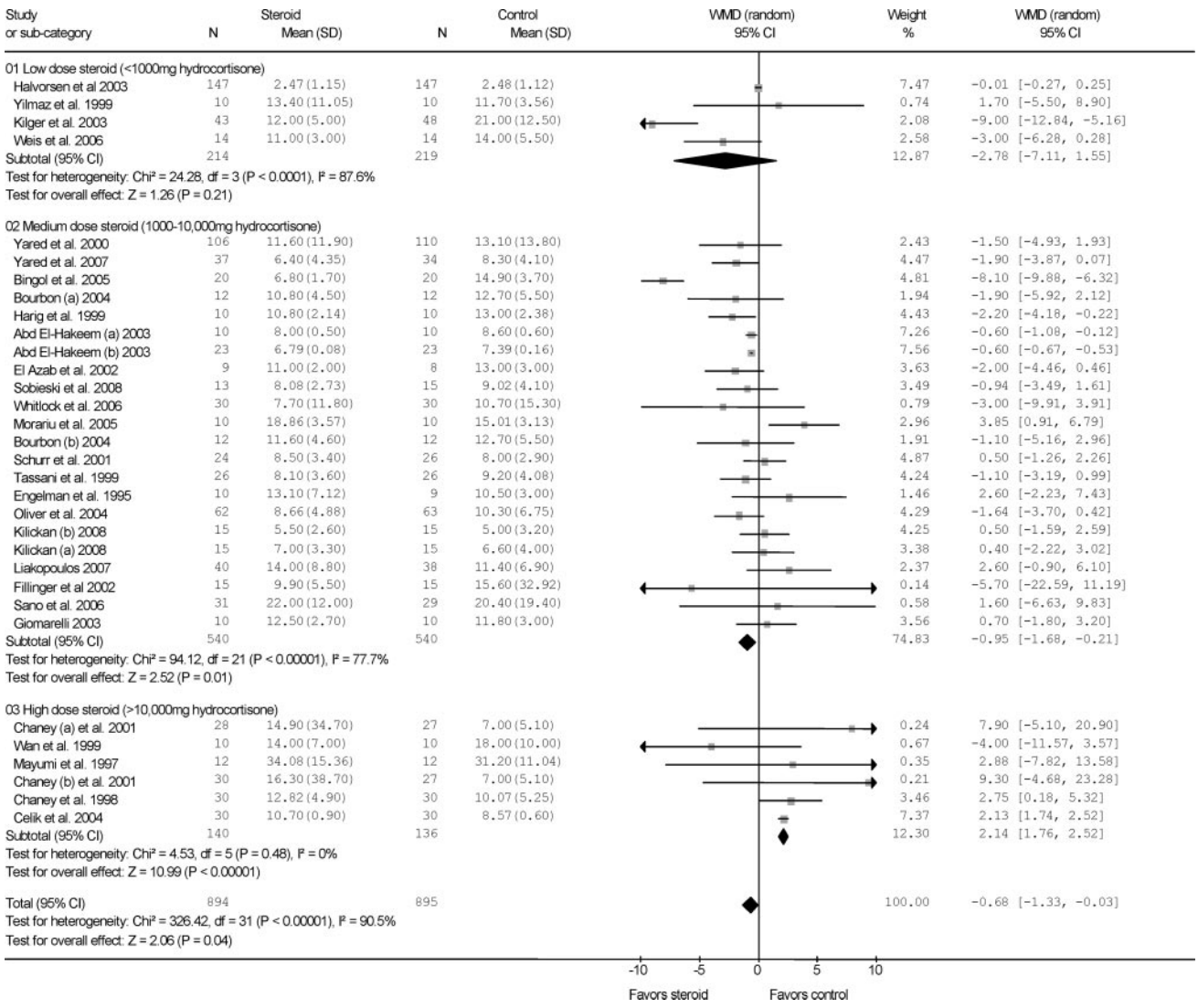

Figure 7. The effect of corticosteroid prophylaxis on duration of mechanical ventilation (in hours) in adult cardiac surgery.

of ICU and hospital stay reported in this meta-analysis. Fourth, detailed cost-effectiveness was not reported in any of the pooled studies. Corticosteroid is inexpensive, but accurate cost-effective analysis should also include other indirect costs such as insulin for hyperglycemia, stress ulcer prophylaxis, use of amiodarone for atrial fibrillation, blood glucose monitoring, and other adverse outcomes, including bleeding, stroke, and altered mental function. Evidence suggests that

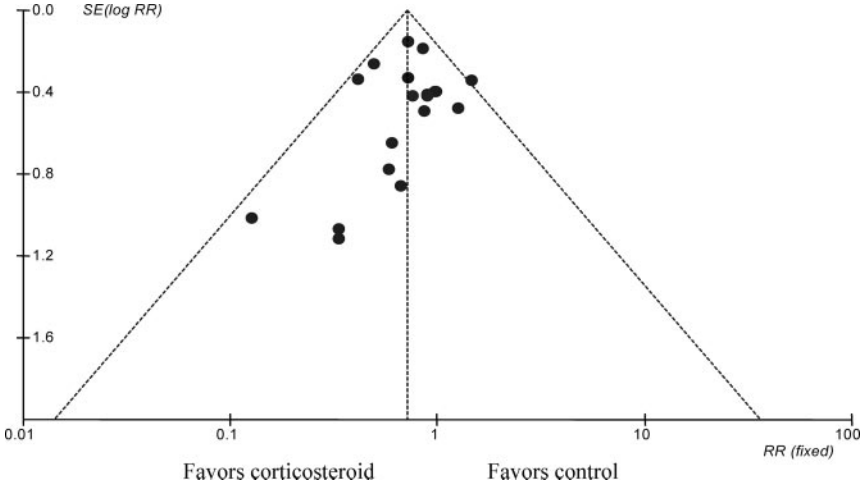

Figure 8. Using risk of atrial fibrillation as an end point, the funnel plot shows the possibility of a small publication bias.

corticosteroid also may offer some benefits on these patient-centered outcomes.[7,52] Finally, almost all the pooled studies excluded patients undergoing emergency cardiac surgery and patients with diabetes mellitus or other organ failure. Thus, the benefits and risks of corticosteroid prophylaxis reported in this study may not be generalizable to these patients.

Conclusions

Current evidence suggests that low-dose corticosteroid is as effective as high-dose corticosteroid in reducing the risk of atrial fibrillation but with fewer potential side effects in adult cardiac surgery. Large randomized controlled trials are needed to confirm the cost-effectiveness of low-dose corticosteroid prophylaxis in adult cardiac surgery.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Corticosteroid prophylaxis in cardiac surgery has been studied extensively for >30 years, but its potential benefits and risks remain inconclusive. Small sample sizes and a wide range of doses of corticosteroid used in different studies are the major confounders affecting the interpretation of these studies. We assessed the dose-response relationship of corticosteroid in adult on-pump cardiac surgery by meta-analyzing a total of 3323 patients from 50 randomized controlled trials. Corticosteroid prophylaxis was effective in reducing serum inflammatory markers, atrial fibrillation, and length of stay in the intensive care unit and hospital compared with placebo. The number of patients needed to treat to prevent 1 atrial fibrillation was estimated to be 10. No additional benefits were found on all outcomes beyond a total dose of 1000 mg hydrocortisone or equivalent. The use of corticosteroid prophylaxis was not associated with a change in hospital mortality or an increased risk of all-cause infection. The sample size of this meta-analysis has a power of 80% to exclude a 3.5% increase in infection risk if the infection rate of the control group is 5%. Hyperglycemia requiring insulin infusion, however, was common after corticosteroid prophylaxis, and very high doses of corticosteroid (>10 000 mg hydrocortisone or equivalent) were associated with prolonged mechanical ventilation. The current evidence suggests that low-dose corticosteroid, <1000 mg hydrocortisone, is safe and effective in reducing the risk of atrial fibrillation after on-pump adult cardiac surgery. Large randomized controlled studies are needed to confirm the cost-effectiveness of corticosteroid in adult cardiac surgery.