Prophylactic corticosteroids for cardiopulmonary bypass in adults (Review)

Dieleman JM, van Paassen J, van Dijk D, Arbous MS, Kalkman CJ, Vandenbroucke JP, van der Heijden GJ, Dekkers OM

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[Intervention Review]

Prophylactic corticosteroids for cardiopulmonary bypass in adults

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ABSTRACT

Background

High-dose prophylactic corticosteroids are often administered during cardiac surgery. Their use, however, remains controversial, as no trials are available that have been sufficiently powered to draw conclusions on their effect on major clinical outcomes.

Objectives

The objective of this meta-analysis was to estimate the effect of prophylactic corticosteroids in cardiac surgery on mortality, cardiac and pulmonary complications.

Search methods

Major medical databases (CENTRAL, MEDLINE, EMBASE, CINAHL and Web of Science) were systematically searched for randomised studies assessing the effect of corticosteroids in adult cardiac surgery. Database were searched for the full period covered, up to December 2009. No language restrictions were applied.

Selection criteria

Randomised controlled trials comparing corticosteroid treatment to either placebo treatment or no treatment in adult cardiac surgery were selected. There were no restrictions with respect to length of the follow-up period. All selected studies qualified for pooling of results for one or more end-points.

Data collection and analysis

The processes of searching and selection for inclusion eligibility were performed independently by two authors. Also, quality assessment and data-extraction of selected studies were independently performed by two authors. The primary endpoints were mortality, cardiac and pulmonary complications. The main effect measure was the Peto odds ratio comparing corticosteroids to no treatment/placebo.

Main results

Fifty-four randomised studies, mostly of limited quality, were included. Altogether, 3615 patients were included in these studies. The pooled odds ratio for mortality was 1.12 (95% CI 0.65 to 1.92), showing no mortality reduction in patients treated with corticosteroids. The odds ratios for myocardial and pulmonary complications were 0.95, (95% CI 0.57 to 1.60) and 0.83 (95% CI 0.49 to 1.40), respectively. The use of a random effects model did not substantially influence study results. Analyses of secondary endpoints showed a reduction of atrial fibrillation and an increase in gastrointestinal bleeding in the corticosteroids group.

Authors' conclusions

This meta-analysis showed no beneficial effect of corticosteroid use on mortality, cardiac and pulmonary complications in cardiac surgery patients.

PLAIN LANGUAGE SUMMARY

High-dose corticosteroids in heart surgery

During heart surgery, high doses of corticosteroids aiming to reduce inflammation are often administered. This practice, however, is controversial since there is no evidence available to show clear benefits. Moreover, corticosteroids have the potential of important side-effects. The aim of this meta-analysis was to summarize (pool) data from studies on this subject and to estimate the effect of corticosteroid administration on the risk of major complications (death, heart infarction, lung problems) following heart surgery.

Major databases of medical literature were searched for publications of studies that randomly assigned adult patient undergoing heart surgery to receive either corticosteroid treatment compared to no treatment or placebo. A total of 54 publications were selected for the analysis. The quality of most of these publications was rather poor, thereby limiting the value of the pooled risk estimate. For none of the major complications (death, heart infarction, lung problems), a change of risk by corticosteroid administration could be demonstrated. Only the risk of (often encountered) heart rhythm disturbances (atrial fibrillation) was clearly shown to be reduced (around 40% less).

The authors therefore conclude that no beneficial effects of high-dose corticosteroids could be shown on the risk of major complications following heart surgery, although this conclusion is limited to low quality of the data available. For a more definitive conclusion, studies with much larger numbers of patients need to be performed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Comparison outcome	Number of studies	Participants	Peto OR (Fixed) [95 % CI]	Heterogeneity (I^2%)	Mantel-Haenszel OR (random) [95% CI]	Heterogeneity (I^2%)
Primary endpoints						
Mortality	49	3213	1.06 [0.58, 1.95]	1	1.00 [0.55, 1.82]	0
Myocardial complications	26	2103	0.95 [0.57, 1.60]	4	0.95 [0.55, 1.64]	0
Pulmonary complications	21	1340	0.83 [0.49, 1.40]	5	0.90 [0.51, 1.58]	0
Secondary endpoints						
Atrial fibrillation	17	1399	0.60 [0.46, 0.78]	11	0.61 [0.45, 0.82]	10
Infections	16	1517	0.86 [0.56, 1.31]	0	0.88[0.57, 1.36]	0
Gastro-intestinal complications	4	304	2.84 [0.40, 20.36]	36	1.86 [0.30, 11.68]	0
Re-thoracotomy	9	866	1.12 [0.47, 2.65]	34	1.28 [0.51, 3.22]	0
Neurological complications	14	1171	0.70 [0.33, 1.48]	16	0.87 [0.38, 1.96]	0
Renal failure	13	825	1.00 [0.45, 2.19]	26	1.02 [0.44, 2.36]	0
Inotrope y/n	17	1237	0.91 [0.67, 1.23]	49	0.92 [0.58, 1.45]	39
Bloodtransfusion y/n	6	535	0.87 [0.54, 1.39]	0	0.87 [0.54, 1.40]	0
			WMD (fixed) [95% CI]		**WMD (random) [95% CI]**	

Number of bloodtransfusions	4	122	-0.19 [-0.44, 0.06]	0	-0.19 [-0.44, 0.06]	0
Time to extubation (min)	23	1351	-1.81 [-11.46, 7.83]	93	-46.87 [-100.25, 6.25]	93
ICU stay (hours)	25	1215	-2.32 [-2.84, -1.81]	87	-5.47 [-8.13, -2.82]	87
Hospital stay (days)	15	635	-0.59 [-0.84, -0.34]	96	-0.97 [-2.42, 0.47]	96

OR: Odds Ratio, CI: Confidence interval, WMD: weighted medan difference.
An OR < 1 or a WMD < 0 indicates a benefit of corticosteroids treatment

BACKGROUND

Description of the condition

Cardiovascular diseases have a high incidence in western society, affecting one in every three persons (Lloyd-Jones 1999) and are currently the leading cause of death, with coronary heart disease being responsible for around 20% of annual deaths in the United States (AHA 2009). Millions of cardiac interventions are performed every year worldwide (AHA 2009). Currently, 30-40% of these procedures comprise cardiac surgery, mainly for revascularization or treatment of valve defects (AHA 2009) .

The development of cardiopulmonary bypass in the early 1950's has been a breakthrough in cardiac surgery (Hill 1982; Pastuszko 2004). The possibility of temporary suppression of cardiac activity while maintaining systemic circulation with a heart-lung machine, made surgery on a non-beating heart possible (Gibbon 1954). Patients with coronary vessel or heart valve disease could from then on be treated with an effective relief of symptoms and prolonged life expectancy (Lee 1976; Hunt 2000; Rahimtoola 1993; Thompson 1999). However, extracorporeal circulation often induces a systemic inflammatory response syndrome, a sepsis like condition (Asimakopoulos 1999; Chaney 2002; Kirklin 1983; McGuinness 2008; Wan 1997a). This response involves complement activation, along with activation of platelets, neutrophils, monocytes, and macrophages (Chaney 2002; Loef 2004). As a result, coagulation and fibrinolytic cascades are initiated (Kirklin 1983; Loef 2004; Whitlock 2005). The ensuing systemic inflammatory response syndrome is associated with fever, impaired alveolar gas exchange, vasodilatation, myocardial stunning, renal insufficiency and even multiorgan dysfunction (Asimakopoulos 1999; Moat 1993; Roach 1996; Zanardo 1994). It is conceivable that the systemic inflammatory response syndrome contributes to the incidence of major complications after heart surgery, including death, myocardial infarction, pulmonary dysfunction and loss of renal function (Hill 1995b; Ho 2009; Talmor 1999; Whitlock 2008). In the past decades, several studies have explored the association between the systemic inflammatory response syndrome and major complications after heart surgery. These studies have shown very variable results, with often conflicting conclusions. However, generally due to a lack of statistical power, no clear associations with important clinical outcomes have been established so far (Fillinger 2002; Kilger 2003a; McBride 2004; Tassani 1999; Toft 1997; Turkoz 2001).

Description of the intervention

Due to the potential associations between the systemic inflammatory response syndrome and a variety of ensuing clinical symptoms, it may appear beneficial to attenuate this response with anti-inflammatory agents (Hall 1997; Whitlock 2008). The proper timing and duration of administration of corticosteroids are incompletely resolved; there is evidence that early corticosteroid prophylaxis in advance of an insult is more efficacious (Lasser 1987). The guidelines of the American Heart Association advocate liberal prophylactic use (AHA 2004; Hall 1997), and frequently, one or two doses of dexamethasone or methylprednisolone are injected intravenously before commencing cardiopulmonary bypass (Chaney 2002; Ho 2009; Whitlock 2008). Corticosteroids are potent anti-inflammatory agents that possess multi-inhibitory effects on numerous components of the inflammatory response (Chaney 2002; Hill 1998; Wan 1997a). Moreover, corticosteroids are low-cost, generic drugs, and potentially cost-effective if any reduction in major complications (and a subsequent improvement of quality of life) can be achieved by their administration.

However, the use of corticosteroids has important potential disadvantages. Almost all patients experience higher mean and peak blood-glucose levels (Chaney 2002; Mayumi 1997; Tassani 1999), which is associated with increased morbidity and mortality (Van den Berghe 2001). Furthermore, it has been demonstrated that the use of corticosteroids is associated with higher lactate levels, a higher sensitivity to infectious agents, impaired wound healing and gastrointestinal blood loss (Chaney 2002; Mayumi 1997), but all studies were too small to demonstrate significant effects. Moreover corticosteroids-use has been associated with a prolonged ventilation time (longer than twelve hours) in some studies (Chaney 1998; Chaney 1999; Chaney 2001). Some of these complications could lead to prolonged intensive care stay and increased morbidity and mortality (Chaney 2002; Van den Berghe 2001).

Why it is important to do this review

To date, the use of corticosteroids in heart surgery is almost standard care in several European countries (Van Dijk 2005), while in the United States very few centres for cardiac surgery use corticosteroids in the perioperative period (personal communications, data not published). However, there is no convincing evidence that potential benefits of corticosteroid use outweigh their possible disadvantages in adult cardiac surgery (Chaney 2002).

A substantial number of trials have been conducted comparing outcome following heart surgery with and without corticosteroid use. Most trials focused on intermediate, non-clinical end-points like serum markers and pulmonary water content, demonstrating a significant suppression of inflammation (Andersen 1989; Anic 2004; Boldt 1986; Boscoe 1983; Celik 2004; Corbi 2001; El Busto Osacar 1979; Engelman 1995; Ferries 1984; Fosse 1987; Harig 1999; Hill 1994; Jansen 1991a; Jorens 1993; Karlstad 1993; Kawamura 1995; Kawamura 1999; Loubser 1997; Mayumi 1997; Nuutinen 1976; Tabardel 1996; Tassani 1999; Tennenberg 1986; Toft 1997; Wan 1997b; Wan 1999). Of the trials which evaluated clinical end-points after corticosteroid administration, the results were unequivocal (Chaney 1998; Chaney 1999; Chaney 2001; Coffin 1975; Fecht 1978; Fillinger 2002; Heikkinen 1985; Kilger

2003a; Loef 2004; Mangos 1995; Miranda 1982; Morton 1976; Niazi 1979; Oliver 2004; Rao 1977; Toft 1997; Toledo-Pereyra 1980; von Spiegel 2001; Yared 1998).

Two meta-analyses have been conducted recently in the last three years (Ho 2009; Whitlock 2008). Both meta-analyses claimed positive effects in cardiac surgery patients treated with corticosteroids. However, the conclusions of these meta-analyses are not completely convincing for reasons outlined below:

Firstly, Whitlock 2008 showed a non-significant reduction of in hospital mortality (RR 0.73, 95% CI 0.45 to 1.18), but overall no increased number of adverse effects. Importantly, the positive effect on mortality was largely accounted for by the study from Vallejo 1977. This study showed a reduction in mortality (relative risk 0.55) in patients given corticosteroids and accounted for 27% of the weight in the meta-analysis. Vallejo 1977 was designated by Whitlock 2008 as "low quality". It is also uncertain whether the randomisation was truly concealed. More substantially, mortality in the non-steroid group was 22%. Even considering the state of the art for cardiac surgical care 30 years ago, this is a surprisingly high mortality. We therefore conclude that the possible mortality benefit in steroids that was reported by Whitlock 2008 is mainly due to the inclusion of one single low quality trial in which the mortality in the non-steroid group was an outlier.

Secondly, the meta-analysis from Ho 2009 did not include outcomes on cardiac and pulmonary outcomes and focused on the effects of corticosteroids on atrial fibrillation (RR 0.74, 95 % CI 0.63 to 0.86). The interpretation of this positive effect must not be overstretched, mainly because atrial fibrillation post-operative is self-limiting (Banach 2010) and because drugs with less potential side effects than corticosteroids, such as amiodarone and beta-blockers, have shown to be effective in the prevention and treatment of atrial fibrillation (Crystal 2004).

A new meta-analysis on corticosteroids in adult cardiac surgery could overcome the outlined limitations. Firstly, the study from Vallejo 1977 will be excluded from our analysis since children were included. Secondly, the aim of a meta-analysis should be on mortality, cardiac ischemia and pulmonary complications in stead of self-limiting conditions as atrial fibrillation. A third advantage is that the search strategy is more up-to-date, with two respectively three additional years of inclusion. Finally, it is expected that in the next few years this review can be updated with data from several ongoing studies (DECS trial; SIRS trial) that will, based on their large size, probably importantly impact the results of this meta-analysis.

OBJECTIVES

To estimate the effect of corticosteroid use for cardiopulmonary bypass on:

a) a composite end-point of mortality, myocardial infarction and pulmonary complications (including pulmonary edema and/or infection);

b) other relevant outcomes such as other complications, including prolonged mechanical ventilation and stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials in human adults, complying with the Participants-Interventions-Comparisons-Outcomes (PICO) parameters described below (Moher 2009). There were no restrictions with respect to length of the follow-up period.

Types of participants

Adults (18 years or older):

- diagnosed with coronary artery disease or coronary valve disease;
- undergoing cardiac surgery with the use of cardiopulmonary bypass.

Types of interventions

Cardiac surgery with cardiopulmonary bypass with or without prophylactic corticosteroid administration. For comparator study arms, trials with concomitant study arms on other interventions were not excluded, as long as patients in the comparator arm received the same treatment as the corticosteroid arm except for corticosteroid administration.

Types of outcome measures

Primary outcomes

Composite end-point, consisting of the following:

- all-cause mortality (in-hospital);
- fatal and non-fatal myocardial infarction (defined as: ECG changes, echocardiological changes, disproportionate elevation of troponines);
- pulmonary complications (including pulmonary edema and/or infection).

Secondary outcomes

- infectious complications
- gastro-intestinal bleeding
- occurrence of atrial fibrillation
- re-thoracotomy
- neurological complications
- renal failure
- inotropic use
- blood transfusion
- time to extubation
- length of ICU stay
- length of hospital stay

Although in the published protocol an analysis of the secondary outcomes "Quality of life" and "Cost effectiveness" was initially planned, these outcomes have not been included in this final review due to a lack of available data.

Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL) (1898 to 31 December 2009; Issue 4, 2009) on *The Cochrane Library*, MEDLINE (PubMed) (1809 to 31 December 2009), EMBASE (1980 to 31 December 2009), CINAHL (1982 to 31 December 2009) and Web of Science (Science Citations Index (SCI) and Social Science Citations Index (SSCI)) (1945 to 31 December 2009) were all searched on 14 February 2010. Furthermore, trial registers were also searched to identify unpublished and ongoing studies (metaRegister of Controlled trials on www.controlled-trials.com/mrct/, WHO ICTRP (http://apps.who.int/trialsearch/). Search strategies are displayed in Appendix 1. No language restrictions were applied; native speakers were contacted for translation of articles in languages other than English, Dutch, German, French, Spanish or Italian.
Reference lists from retrieved randomised trials, meta-analyses and systematic reviews were screened to identify additional trials. 'Related Articles' identified by PubMed were screened.

Data collection and analysis

Selection of studies

The selection of studies was done in three different phases:

- First phase: judging of each title found by two independent authors (JMD, JvP). If both were certain that a study was unsuitable, based on the title, this study was excluded. The abstracts of all studies that were considered suitable based on the title by at least one author, were printed.
- Second phase: judging of the remaining studies based on the abstract by the two independent authors (JMD and JvP) If both were certain that a study was unsuitable, based on its abstract, this study was excluded. The complete text of all other studies that were considered suitable based on the abstract by at least one author, was printed.
- Third phase: judging of the remaining studies based on the complete article by two independent authors (JMD and JvP). If both were certain that a study was unsuitable, this study was excluded. The exclusion was motivated briefly on the selection form. If their opinion was split, the article was discussed until consensus was achieved, if necessary with help of a third author (DvD).

After completion of retrieval and selection of full-text articles, results from both search strategies were combined. Discrepancies were discussed by both authors (JMD and JvP); selection of articles was based on consensus between the reviewers. When disagreement persisted, a third author (DvD) decided on selection of articles.
For each title, abstract or full-text article a standardised selection form was used to assess study eligibility (Appendix 2) The authors were not blinded to authors' names or journal names.
The flow of studies was reported according the PRISMA guidelines (Moher 2009).

Data extraction and management

Data was extracted from the full-text article of every included study by two authors independently (JMD and JvP) using a standardised data-extraction form (Appendix 3). Additional data on major events, if missing in the published studies data, was requested from corresponding authors. The primary outcomes for both the intervention and placebo groups of the present analysis were mortality, cardiac and pulmonary complications. Cardiac complications were defined as evidence for myocardial infarction (ECG changes, echocardiographic changes, disproportionate elevation of cardiac enzymes). Pulmonary complications were defined more variably, including edema and pulmonary infection. When authors stated explicitly "no major complications" occurred in the study, this was interpreted as no deaths, and no cardiac or pulmonary complications for that specific study.
We aimed to perform a pooled analysis for a composite endpoint consisting of the three major endpoints: death, cardiac and pulmonary complications, as well as on each of these outcomes separately. Furthermore, data on infectious complications, gastro-intestinal bleeding, atrial fibrillation, re-thoracotomy, neurological complications, renal failure, inotropic use, blood transfusion, time to extubation, length of intensive care stay and length of hospital stay was extracted and analysed. We did not perform subgroup analyses according to age and sex, since effect measure modification was not a priori expected for these variables.

Assessment of risk of bias in included studies

The following criteria were used to assess the risk of bias of the included studies (see Appendix 3, items 2, 3, 5, 7, 8 and 10)

according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011):

- concealed allocation,
- Intention to treat analysis
- blinding during pre-, peri- and postoperative care,
- blinded data-collection and analysis,
- blinded adjudication of endpoints,
- standardised pre-, peri- and post-surgical care,
- completeness of (follow-up) data.

Quality score adjusted analysis were not performed, because they are known to be of limited added value (Juni 1999).

Unit of analysis issues

The odds were calculated per treatment group for all binary outcomes. The Peto odds ratio was used as the pooled measure of effect. For continuous variables, weighted means were calculated according to the inverse of the squared standard error.

We expected the meta-analysis to be on sparse outcome data. The best model as well as the appropriate continuity correction for sparse outcome meta-analysis is still under debate (Shuster 2007; Sweeting 2004). The use of the Peto odds ratio has two advantages: at first, no continuity correction is needed when one study arm has zero events, and secondly, the Peto odds ratio has been shown to be a robust model for sparse outcome meta-analysis without extreme group imbalances (Sweeting 2004), as was the case in the present meta-analysis. Trials with zero events in both arms do not contribute to the weighted average of the Peto odds ratio, as they do not contribute to the treatment effect of ratio measures in general.

Assessment of heterogeneity

Due to variations in study-patient groups, clinical settings, concomitant care, and differences in treatment, clinical heterogeneity was to be expected. However, the power from conventional statistical methods to detect heterogeneity is low in case of a small number of included studies or in case of sparse outcome data (Ioannidis 2007). To deal with expected heterogeneity, we performed a random effects model, besides the Peto odds ratio, for all outcomes. We added 0.5 events to each cell for trials with zero events in one treatment arm. The disadvantage of this continuity correction is that the added 0.5 'events' can bias the results, especially when treatment groups are imbalanced. To check the robustness of this correction we also calculated the pooled estimate of the primary outcomes by adding the reciprocal of the opposite treatment arm size (Sweeting 2004). This calculation of the odds ratio enabled inclusion of trials with zero events in both arms. Moreover, we planned to perform sensitivity analyses to explore heterogeneity for the primary outcomes in case of considerable heterogeneity (I^2>40%). Since the included trials were published over a period of four decades, we decided to perform a sensitivity analysis according to the publication date. Stratified analyses were performed for the primary endpoints, using the year 1995 as a cut off between "old" and "new" studies. The choice of this cut off date was rather arbitrary. The year 1995 is in the middle of our study period and mainly based on the "natural gap" in publications, that was present in the mid 1990's. After a period of a very low frequency of publications on the subject of this review, we observed that a renewed interest seems to be present in the second half of that century, given the sharp increase in the number of new publications on the subject.

Publication bias was assessed for the three primary outcomes by both graphical inspection of the funnel plot and statistical testing of plot asymmetry, using a 95% confidence interval. We assessed statistical heterogeneity of trial data by using the I-square test (Higgins 2002).

RESULTS

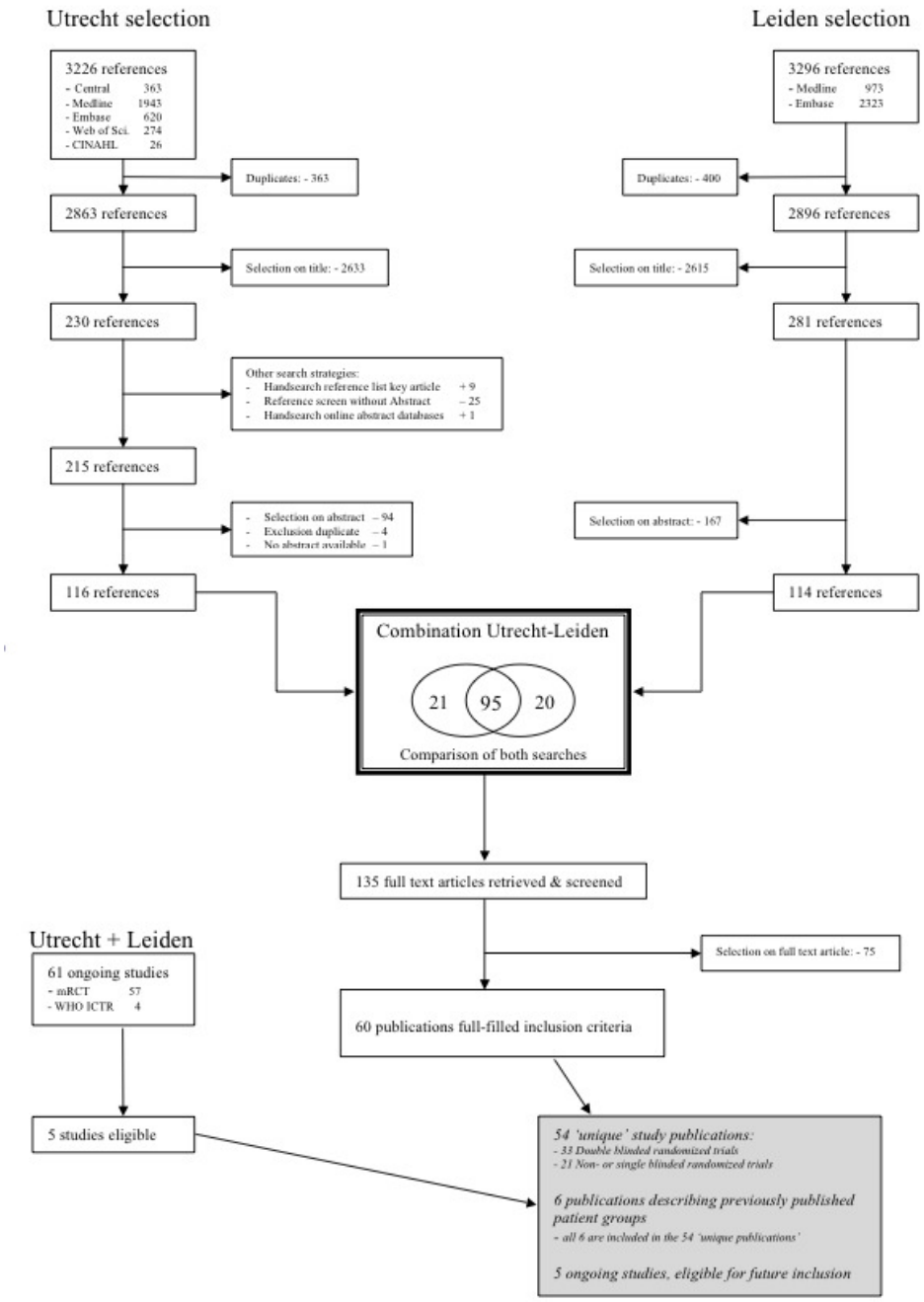
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

By search of CENTRAL, MEDLINE (PubMed), EMBASE, CINAHL and Web of Science (SCI/SSCI) 6522 studies were identified in the two separate search arms; 3226 studies in the Utrecht group and 3296 studies the Leiden group (Figure 1). After screening of title and abstracts 116 potentially relevant articles were retrieved for detailed assessment by the Utrecht group and 114 articles by the Leiden group. Of these 230 articles, 94 articles were duplicates, which left 136 articles for assessment based on the full-text paper. Of these resulting 136 potentially relevant articles, 75 were excluded because they reported the results of animal experiments, did not report relevant endpoints, or because of lack of randomisation. Thus, a total of 54 studies (60 references) were finally included for the present meta-analysis.

Figure 1. Study selection chart



Searching the clinical trials registers identified five relevant ongoing studies (Characteristics of ongoing studies).

Of the included studies, 36/54 were published in the last 10 years (2000 or later), 11/54 in the 1990s, 4/54 in the 1980s and 3/54 in the 1970s. The majority of studies were conducted in Europe (35/54) and North America (14/54). Altogether, 3615 patients were included in these 54 trials, with a mean age of 60 years and a predominance of male patients (71.9%). Only five studies included high risk surgery patients (Ferries 1984; Kilger 2003a; Weis 2006; Weis 2009; Whitlock 2006). All other study-populations consisted of low risk CABG or valve surgery. Follow-up time was relatively short in most of the studies (duration of hospital stay or shorter in 47 of the 54 studies) (Appendix 4). None of the studies reported industry funding.

Risk of bias in included studies

The study demographics are shown in Characteristics of included studies and Appendix 4. For all the studies a low risk of bias was unlikely, since no study scored positively on all items of the risk of bias criteria (Figure 2; Figure 3). In addition some general remarks regarding the quality of studies can be made. The type, frequency and dosage of corticosteroids administered varied largely between studies. In the majority of the studies, the study population was relatively small (median number of patients: 40 per group). Significant heterogeneity was present in the duration of the postoperative stay in both the intensive care and the hospital. This heterogeneity was apparently dictated by a great variation in 'routine' duration of stay both over time (i.e. much longer in the earlier studies) and between hospitals.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

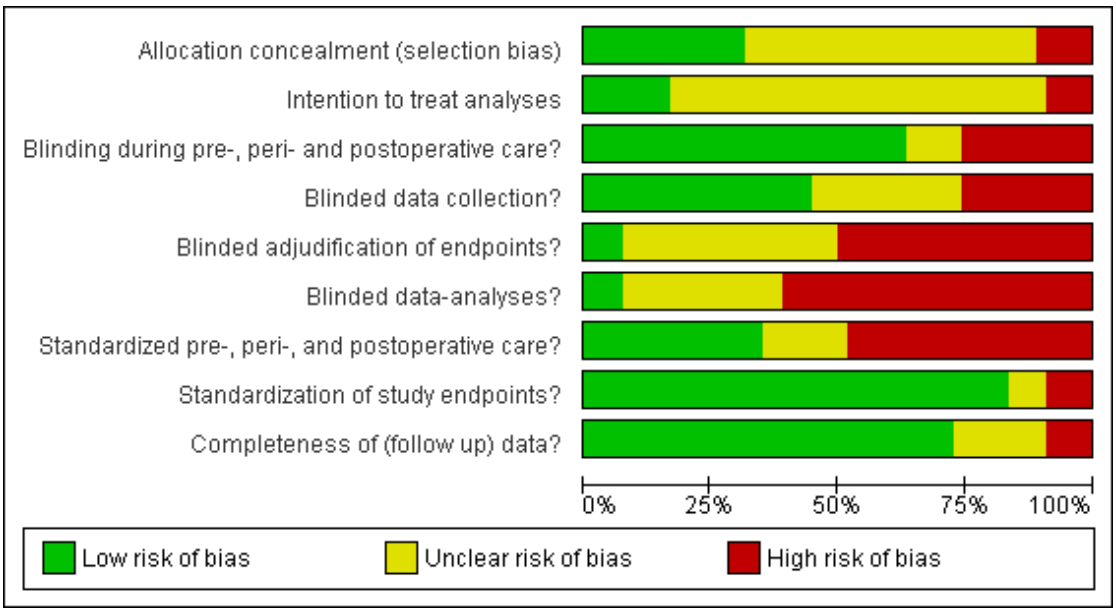
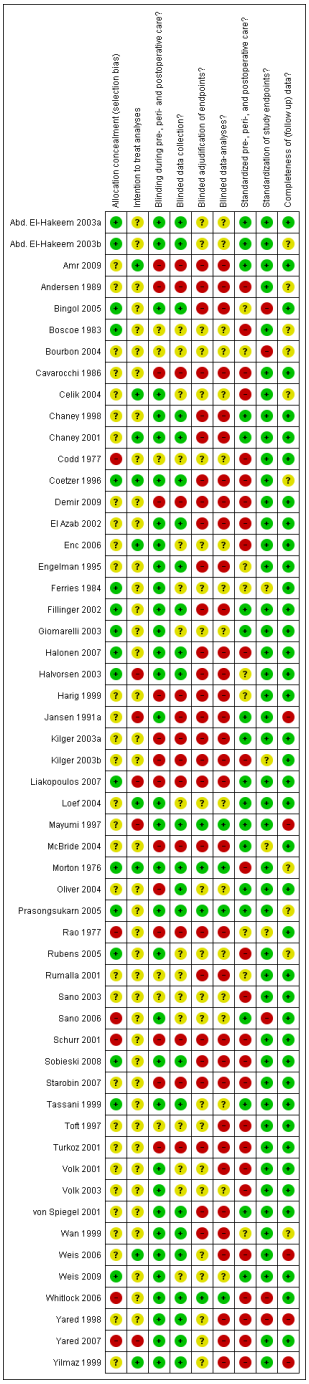


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Adequate concealment of allocation was present in only 31% of the trials (Figure 3). Out of all the fifty-five randomized trials, only seventeen studies reported concealment of allocation. In six trials concealment of allocation was inadequate, and in the remainder of twenty-one studies randomization or allocation procedures were not specified.

Blinding

Overall, only 34 studies could be classified as blinded. We judged these studies on blinding in several stages: pre- peri- and post-operative care, data-collection. adjudication to endpoints. Besides blinded care and data-collection, only four studies carried out triple blinding and blinded data-analyses (Mayumi 1997; Morton 1976; Prasongsukarn 2005, Whitlock 2006)

Incomplete outcome data

The follow-up period was variable (ranging from only a few hours to six months), but was mostly short and restricted to hospital stay or ICU stay.A mean follow up period could not be calculated due to the unspecified reporting of follow up period in 33 of the 54 studies (intensive care stay, or hospital stay) *(*Appendix 4*).* Most primary endpoints were standardized and complete. In ten studies patients were excluded from analyses when major complications occurred (Chaney 1998; Chaney 2001; Jansen 1991a; Mayumi 1997; Rubens 2005; von Spiegel 2001; Wan 1999; Weis 2006; Yared 1998; Yilmaz 1999). More importantly, data regarding serious complications, such as mortality, cardiac and pulmonary complications, often appeared to be reported only incidentally, instead of having been subject to a proper follow-up and blinded adjudication for these outcomes according to a study protocol.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings for primary and secondary endpoints. OR with fixed and random effects model and with opposite reciprocal correction; **Summary of findings 2** Dose dependant analyses

Mortality, cardiac and pulmonary complications

Only five studies reported all three elements of a composite endpoint: mortality, cardiac complications and pulmonary complications (Appendix 5) (Giomarelli 2003; Halvorsen 2003; Rao 1977; Whitlock 2006; Yared 2007). In order to prevent double counting of patients and consequently overestimation of the actual number of events, the three accounting endpoints need to be reported on an individual patient-level. Since none of these five studies reported outcome on the individual patient level, we did not perform a pooled analysis of the composite endpoint.

Separate analyses of mortality, myocardial complications and pulmonary complications were performed using the Peto odds ratio. For these separate analyses, all fifty-four studies were taken into account when at least data regarding one of the primary endpoints were available. Data on the number of included studies, as well as on the number of included patients for each of the primary endpoints, are shown in Summary of findings for the main comparison. The use of corticosteroids in coronary bypass surgery did not reduce mortality (odds ratio = 1.12, 95% CI 0.65 to 1.92; 17 studies, 2012 patients, Analysis 1.1), nor cardiac complications (odds ratio = 0.95, 95% CI 0.57 to 1.60; 16 studies, 1778 patients, Analysis 1.2), nor pulmonary complications (odds ratio = 0.83, 95% 0.49 to 1.49); 12 studies, 1076 patients, Analysis 1.3) significantly.

The I^2 for the primary endpoints were 0% (mortality), 4% (cardiac complications) and 5% (pulmonary complications). Comparing the older studies (published before 1995) with the recent ones (published after 1995) in stratified sensitivity analyse (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.5; Analysis 4.6) did not reveal differences in Peto odds ratio for mortality, cardiac complications or pulmonary complications over the years. The funnel plots for mortality, cardiac and pulmonary complications did not reveal important asymmetry (Figure 4, Figure 5, Figure 6, respectively). The use of a random effects model did not materially influence the results and showed odds ratios similar to the Peto odds ratio and confidence intervals including 1 (Summary of findings for the main comparison).The use of a continuity correction according to the reciprocal of the opposite treatment arm size did also show similar results (data not shown).

Figure 4. Funnel plot of mortality.

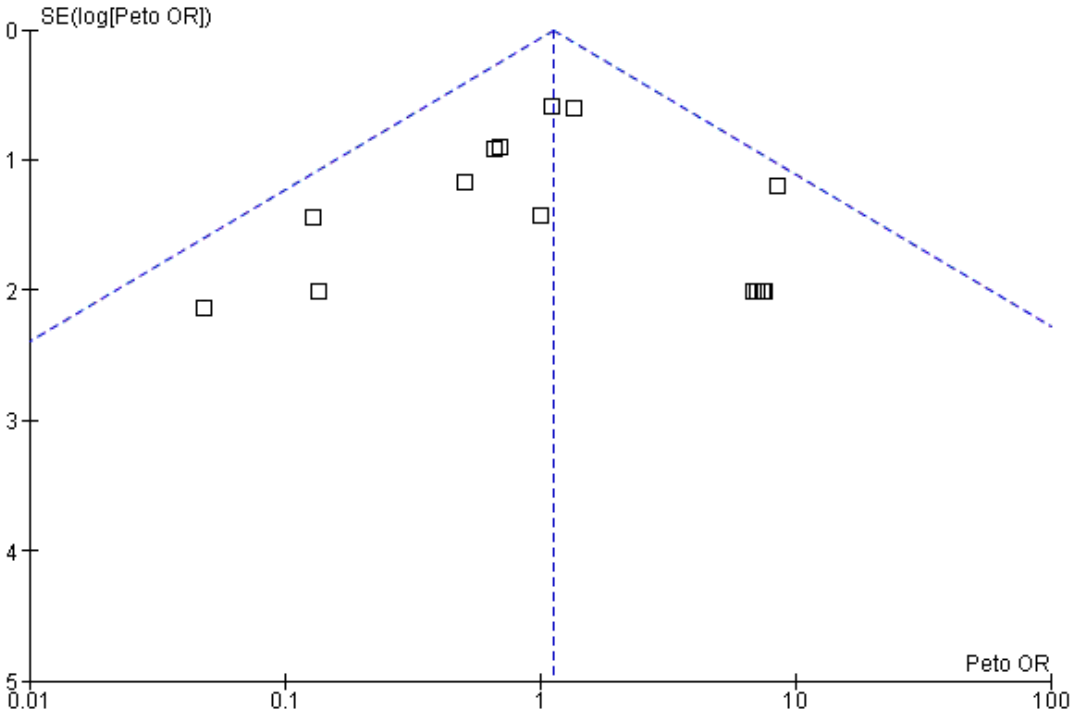


Figure 5. Funnel plot of cardiac complications.

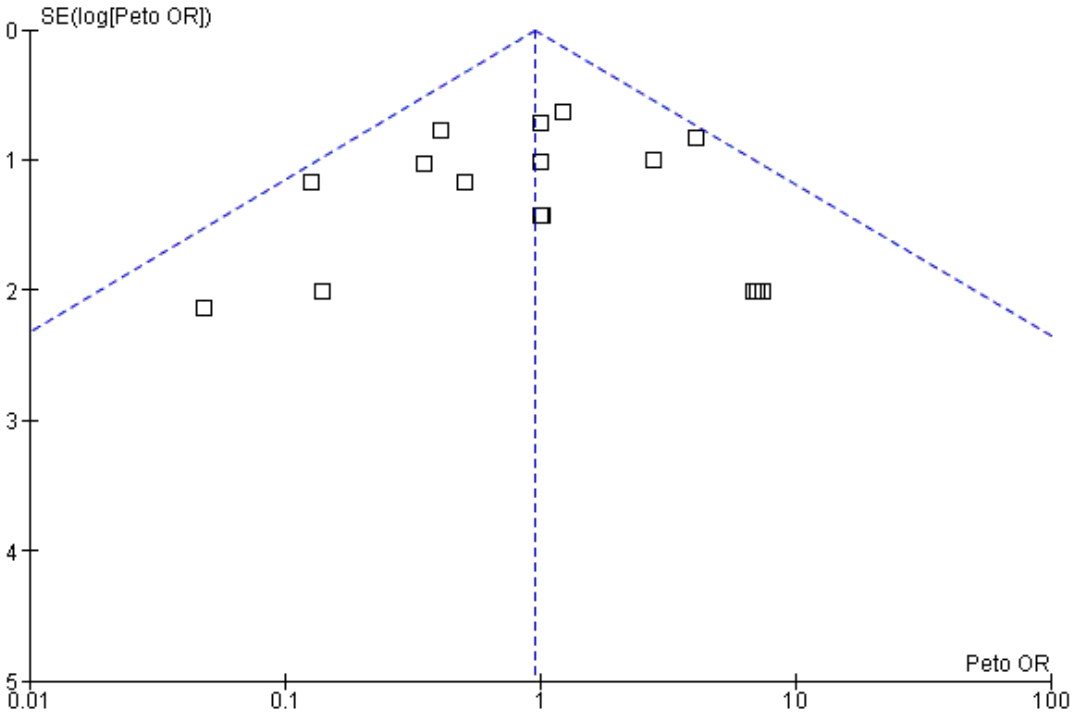
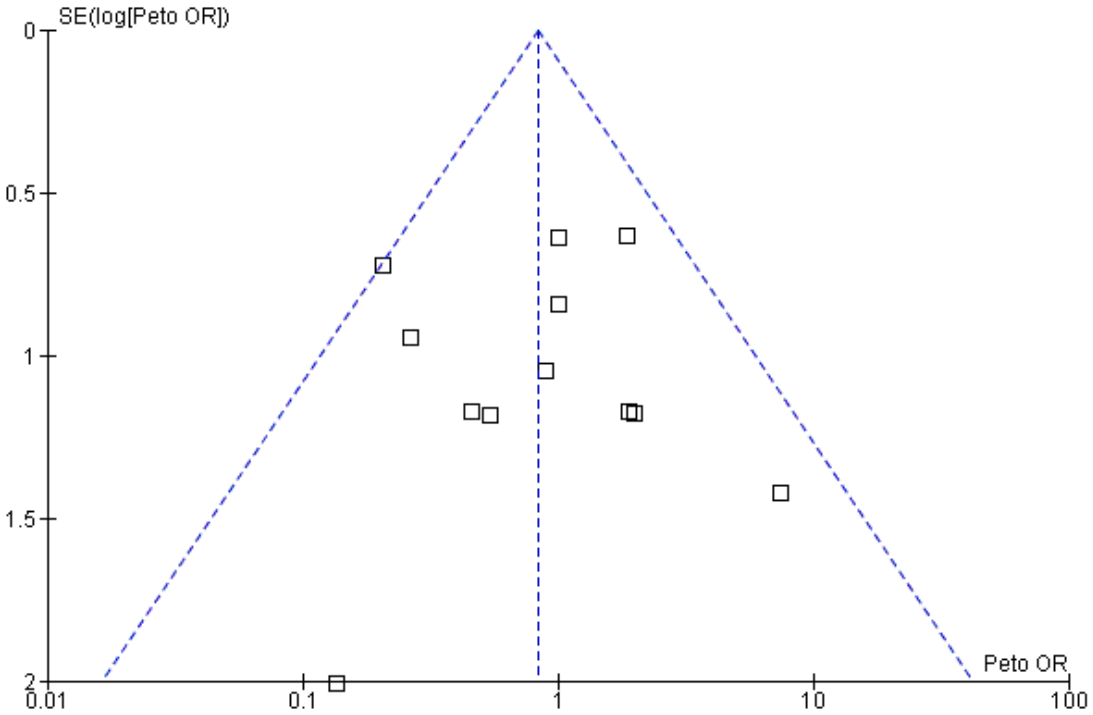


Figure 6. Funnel plot of pulmonary complications.



Secondary outcomes

We analysed potential complications of the use of corticosteroids: gastro-intestinal ulceration or bleeding and (wound) infections. Also, other outcomes that were reported in two or more studies were analysed, including some outcomes that were not planned for analysis in the review protocol. For all secondary outcomes, the number of included studies, the number of patients, the Peto odds ratios, the random effects odds ratios and the I^2 are shown in the Summary of findings for the main comparison.

Hyperglycaemia is a well known side-effect of corticosteroids administration (because of insulin resistance). Glucose regulation reports (regarding levels of serum glucose and insulin administration) were available in as many as 21 studies. Eight studies reported on insulin therapy, without clear definitions with respect to glucose levels that would dictate administration of insulin (Amr 2009; Loef 2004; McBride 2004; Rubens 2005; Tassani 1999; Toft 1997; Yared 1998; Yared 2007). Two studies mentioned the insulin dose necessary to maintain "normal" glucose levels (Liakopoulos 2007; Sano 2006). Finally, in fourteen studies, glucose levels after corticosteroid administration were reported. In four of these studies quantitative data were shown (Amr 2009; Chaney 2001; Tassani 1999; Yared 1998) while in the other ten studies only qualitative data were available ("higher levels or no significantly different levels") (Celik 2004; Fillinger 2002; Giomarelli 2003; Halvorsen 2003; Jansen 1991a; Kilger 2003a; Mayumi 1997; Oliver 2004; Sano 2006; Toft 1997). Overall, sixteen out of 21 studies reported either more often insulin therapy or higher glucose levels in the corticosteroids group (Amr 2009; Amr 2009; Chaney 2001; Fillinger 2002; Jansen 1991a; Liakopoulos 2007; Loef 2004; Mayumi 1997; McBride 2004; Oliver 2004; Rubens 2005; Sano 2006; Tassani 1999; Yared 1998; Yared 1998; Yared 2007). The remaining five studies could not show any difference in insulin therapy or glucose levels (Celik 2004; Giomarelli 2003; Halvorsen 2003; Kilger 2003a; Toft 1997). Due to the heterogeneity of the available data, no further analyses could be performed for the association between glucocorticosteroids and hyperglycaemia.

Another well known side effect of corticosteroids administration is the occurrence of gastrointestinal complications. Only four studies, comprising a total of 304 patients, explicitly reported on gastrointestinal complications (both bleeding and ulceration). The odds ratio was 2.84 (95% CI 0.40 to 20.36) Analysis 2.3.

Moreover, the incidence of atrial fibrillation was reduced in the corticosteroids group (odds ratio 0.60, 95% CI 0.46 to 0.78,17 studies, 1389 patients, Analysis 2.1). The length of intensive care

stay was slightly shorter in the corticosteroids group (2.32 hours, 95 % CI -2.84 to -1.81; 25 studies, 1215 patients, Analysis 2.5). For all other secondary endpoints neither advantage nor disadvantage could be demonstrated for the use of corticosteroids in cardiac surgery. (Infectious complications (Odds ratio 0.89, 95% CI 0.89 to 1.38; 15 studies, 1487 patients, Analysis 2.2). Time to extubation (hours) (Odds ratio -1.81, 95% CI -11.46 to 7.83; 23 studies, 1351 patients, Analysis 2.4). Length of hospital stay (days) (Odds ratio -0.40, 95% CI -0.65 to -0.15; 15 studies, 625 patients, Analysis 2.6). Renal failure (Odds ratio1.00, 95% CI 0.45 to 2.19; 9 studies, 677 patients, Analysis 2.7). Re-thoracotomy [Odds ratio 1.12, 95% CI 0.47 to 2.65; 7 studies, 818 patients, Analysis 2.8). Neurological complications (Odds ratio 0.7, 95% CI 0.33 to 1.48; 10 studies, 1052 patients, Analysis 2.10). Vasoactive medication (Odds ratio 0.91, 95% CI 0.67 to 1.23; 17 studies, 1237 patients, Analysis 2.11). Blood transfusion (yes/no) (Odds ratio 0.87, 95% CI 0.54 to 1.39; 5 studies, 511 patients, Analysis 2.12])

Analysis according to corticosteroid dose

We categorized the included studies into high-dose (total administered dose > 1000 mg hydrocortisone equivalents) and low-dose (total administered dose (≤ 1000 mg hydrocortisone equivalents) studies and performed a stratified meta analysis (Summary of findings 2). More detailed stratification and/or dose-response analyses were limited due to sparsity of data. In only nine studies, a hydrocortisone equivalent of 1000 mg or lower was administered (Halonen 2007; Halvorsen 2003; Harig 1999; Kilger 2003a; Kilger 2003b; Starobin 2007; Weis 2006; Weis 2009; Yilmaz 1999). Eight of these "low-dose" studies reported on mortality, two on cardiac complications, three on pulmonary complications and none reported on gastrointestinal bleeding. No statistically significant dose dependent difference in major outcomes could be demonstrated, but concomitant confidence intervals were wide (Summary of findings 2). The only one exception was atrial fibrillation, which was reduced in both the low- and high-dose groups.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Comparison outcome	corticosteroid dose	studies	participants	PetoOR (fixed) [95% CI]
Mortality	low	8	726	1.96 [0.20, 18.85]
	high	41	2423	1.01 [0.51, 1.79]
Cardiac complications	low	2	535	1.96 [0.39, 9.80]
	high	24	1568	0.88 [0.51, 1.52]
Pulmonary complications	low	3	390	1.26 [0.46, 3.42]
	high	18	950	0.71 [0.38, 1.31]
Gastro-intestinal bleeding	low	0	0	not estimable
	high	4	304	2.84 [0.40, 20.36]
Infections	low	5	651	0.89 [0.52, 1.52]
	high	11	866	0.81 [0.40, 1.62]
Atrial fibrillation	low	4	631	0.61 [0.40, 0.94]
	high	13	748	0.60 [0.43, 0.83]

Low dose: </=1000 mg Hydrocortisone equivalent, High dose: > 1000 mg hydrocortisone equivalent.
OR: Odds ratio, CI: Confidence interval

DISCUSSION

Summary of main results

In this meta-analysis on the effects of prophylactic corticosteroid use in adult cardiac surgical patients, there was no beneficial effect on mortality, cardiac and pulmonary complications. Also, an increased risk of potential side effects of corticosteroids, such as infection, impaired wound healing, gastro-intestinal ulceration or bleeding, could not be demonstrated. Of other, secondary endpoints, only the risk for atrial fibrillation and length of ICU stay were found to be reduced. Moreover, no dose dependent effects of corticosteroids for any outcome could be demonstrated, although this conclusion is limited due to the imprecise estimation of the effects.

Overall completeness and applicability of evidence

Both the quality and the completeness of this review have, in our view, been improved by combining the efforts of two research groups in the Netherlands, that were coincidently working on very similar systematic review projects. Although the search results with the two different (but robust) search strings reached quite comparable results with respect to the most important studies, as many as 4229 references were part of the results of only one of both strategies. Thus, parallel but separate searching can be a valuable method to improve at least the completeness of future systematic reviews.

The data presented in this systematic review provide no convincing evidence for a beneficial effect of the use of corticosteroids on important outcomes in patients undergoing cardiac surgery with cardiopulmonary bypass, with odds ratios for mortality, cardiac and pulmonary complications that were all close to unity. However, while drawing this conclusion, one should keep in mind the study's important qualitative limitations which are discussed in detail below. Moreover, applicability of the results may be limited because most studies included in this meta-analysis were performed in low-risk patient populations (Dekkers 2010).

A risk-reduction for postoperative atrial fibrillation seems to be one of the few clinical advantages of corticosteroid administration

that has been demonstrated repeatedly (Halonen 2007; Whitlock 2006). The mechanism of this effect is not entirely clear, although several studies have shown an association between higher levels of inflammatory markers and the incidence of atrial fibrillation (Halonen 2007; Whitlock 2006). Atrial fibrillation following cardiac surgery is associated with an increased hospital length of stay, increased rate of post-operative stroke and increased surgical costs, which can be prevented effectively with anti-arrhythmic drugs, such as beta-blockers or amiodarone (Crystal 2004). However, based on the data of the meta-analysis the reduced risk for atrial fibrillation did not translate into a mortality reduction. Moreover, since especially beta-blockers are associated with fewer side-effects than corticosteroids, the sole reduction of atrial fibrillation is not an indication for the use of corticosteroids.

Quality of the evidence

There are several important qualitative limitations for this set of published randomised studies on corticosteroids in adult cardiac surgery. These limitations may influence the quality of the evidence and must lead to caution in the interpretation of the results. First, based on well-established criteria for conduction and reporting of clinical trials, the quality of the included studies was mostly scored as being low. Secondly, in many of the included studies the primary focus was on intermediate endpoints such as markers of inflammation and ventilatory parameters, while reporting of clinical endpoints was not part of the study protocol. Non-standardized collection of clinical outcomes carries a high risk of observer bias, particularly when the endpoint adjudication is not blinded. Furthermore, due to the short follow-up period in the majority of studies, the risk of underreporting of endpoints is also present. Third, the individual studies included in this meta-analysis appeared clinically very heterogeneous. They range over three decades, from the mid 1970s until 2009, a period over which the quality of the surgical, anaesthesiological and postoperative care has dramatically improved. Moreover, the use of perioperative medication has changed over time (aspirin, beta-blockers, aprotinin). Finally, the definitions of cardiac and pulmonary complications that were used across the studies were not uniform (Appendix 5). Although in many studies cardiac complications were defined as ischaemic events, the definitions that were employed for pulmonary complications were far more variable.

Agreements and disagreements with other studies or reviews

Recently, two other meta-analyses were published on the same topic by Whitlock 2008 and Ho 2009. The meta-analysis from Whitlock 2008 included 44 trials, 41 of which identical to those in our meta-analysis. We did not include three studies that were included in this particular review, for reasons of inclusion of children (Vallejo 1977), no randomisation (Fecht 1978) and no information regarding randomisation (Niazi 1979). Moreover, we retrieved and included 14 more studies (Abd. El-Hakeem 2003a; Amr 2009; Bingol 2005; Boscoe 1983; Cavarocchi 1986; Demir 2009; Engelman 1995; Kilger 2003b; Sano 2003; von Spiegel 2001; Weis 2009; Sobieski 2008; Starobin 2007). Our results differ in particular with respect to mortality. Whereas Whitlock 2008 found a trend towards a reduction in mortality (relative risk 0.73, 95% CI 0.45 to 1.18), no clear mortality benefit was found in our study (Peto odds ratio 1.12, 95% CI 0.65 to 1.92, Analysis 1.1). This difference in point estimates is largely accounted for by the study from Vallejo 1977. This study showed a reduction in mortality (relative risk 0.55) in patients receiving steroids and accounted for 27% of the weight of the mortality point estimate in the meta-analysis by Whitlock 2008. However, the study from Vallejo 1977 was published in 1977 and was designated by Whitlock 2008 as "low quality". It is also uncertain whether the randomisation was truly concealed. We decided not to include this particular study because of the inclusion of patients under the age of 18 years in the study population. However, and even more importantly, the mortality rate in the non-steroid group was 22%: by far the highest mortality rate of all included studies. Even considering the state of the art for cardiac surgical care 30 years ago, this rate is surprisingly high. We therefore conclude that the possible mortality benefit in steroids that was reported by Whitlock *et al.* is mainly due to the inclusion of one single low quality trial, in which the mortality in the non-steroid group was an outlier. Similar to Whitlock 2008 (relative risk 0.99, 95% CI 0.57-1.72), we found no reduction in cardiac complications (Peto odds ratio 0.95, 95% CI 0.57 to 1.60, Analysis 1.2). Pulmonary complications were not studied by Whitlock 2008.

The meta-analysis from Ho 2009 included 50 trials, 45 of which are identical to those in our meta-analysis. Besides Vallejo 1977, Niazi 1979 and Fecht 1978, as discussed here above, we excluded both Teoh 1995 (missing description of randomisation procedure) and Kilickan 2008 (deficient data on primary outcome measures). Moreover, twelve more studies were included in our meta-analysis (Amr 2009; Boscoe 1983; Cavarocchi 1986; Demir 2009; Kilger 2003b; Liakopoulos 2007; Morton 1976; Sano 2003; Starobin 2007; von Spiegel 2001; Yared 1998; Weis 2009), accounting for 680 patients. The inclusion of the study of Vallejo 1977 in this review resulted in a relative risk estimate for mortality that was similar to that in the study of Whitlock 2008, with the limitations that have been addressed in the previous paragraph. Apart from the difference in the relative risk for mortality, the results of the meta-analysis of Ho 2009 were largely similar to our results with respect to the effect on other major clinical endpoints, atrial fibrillation and length of intensive care stay.

AUTHORS' CONCLUSIONS

Implications for practice

The use of corticosteroids in cardiac surgery has been advocated because of the ability of corticosteroids to inhibit the systemic inflammatory response (Chaney 2002; Whitlock 2005). In the present meta-analysis, we were not able to demonstrate that this concept results in important clinical benefits, as there was no positive effect on major clinical outcomes in cardiac surgical patients receiving corticosteroids. Only a beneficial effect on the occurrence of postoperative atrial fibrillation could be demonstrated.

In the absence of substantial beneficial effects, also other possible adverse effects of corticosteroids, such as gastrointestinal complications, glucose imbalance, and possibly an increased number of (wound) infections, must be taken into account when considering the use of corticosteroids in cardiopulmonary bypass. However, no increased risk on these side effects could be demonstrated.

Therefore, the liberal use of corticosteroids, as advocated by the guidelines of the American Heart Association AHA 2009, cannot be supported by this meta-analysis as a potentially effective treatment to reduce major complications following cardiac surgery.

Implications for research

The studies included in this systematic review were clinically heterogeneous and carried a high risk of bias. Moreover, the confidence intervals of the point estimates of the meta-analysis were broad. Given these important limitations, larger clinical trials are required to determine a precise estimate of the effect sizes. Ideally, these trials would be randomized, blinded, placebo controlled trials of frequently used corticosteroid treatment protocols (i.e. high dose methylprednisolone or dexamethasone). These studies should focus on serious complications (mortality, myocardial infarction and organ failure) as the primary endpoint, which will require a very large number of patients (several thousands) for sufficient statistical power.

As far as we are informed, two major randomized clinical trials evaluating corticosteroid administration in cardiac surgery are currently underway: the SIRS trial (NCT00427388) and the DECS trial (NCT00293592), including 10,000 and 4,500 patients, respectively. The results from these trials are expected in the period 2011-2013.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abd. El-Hakeem 2003a

Methods	Randomized placebo-controlled, double blinded trial
Participants	46 elective valve surgery (aortic or mitral)
Interventions	100 mg Dexamethasone, pre-CPB
Outcomes	mortality, time to extubation, ICU-stay, vaso-active medication, blood transfusions y/n "no major complications"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was by using the sealed envelope method so that there would be equal number of patients in the two groups"
Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "Randomized double-blind placebo controlled study. This was performed by an anaesthesiologist not involved with the patients perioperative care."
Blinded data collection?	Low risk	Quote: "Randomized double-blind placebo controlled study. This was performed by an anaesthesiologist not involved with the patients perioperative care. " Comment: probably blinded data-collection
Blinded adjudification of endpoints?	Unclear risk	Quote: "Randomized double-blind placebo controlled study. This was performed by an anaesthesiologist not involved with the patients perioperative care." Comment: unclear whether ad-

Abd. El-Hakeem 2003a (*Continued*)

		judification of endpoints were blinded
Blinded data-analyses?	Unclear risk	Quote: "Randomized double-blind placebo controlled study. This was performed by an anaesthesiologist not involved with the patients perioperative care. " Comment: unclear whether data-analyses were blinded
Standardized pre-, peri-, and postoperative care?	Low risk	Quote: "All patients were pre-medicated with..." Quote: "A standard Anaesthetic technique for a patients was performed" Quote: "While the patients were in the ICU, standard care and processes were followed until discharge"
Standardization of study endpoints?	Low risk	Shivering score after Holtzclaw and secondary endpoints were stated in the Methods section
Completeness of (follow up) data?	Low risk	Follow-up: ICU-stay. 0% loss to follow up.

Abd. El-Hakeem 2003b

Methods	Randomized placebo-controlled, double blinded trial
Participants	20 elective valve surgery (aortic or mitral)
Interventions	100 mg Dexamethasone, pre-CPB
Outcomes	mortality, time to extubation, ICU-stay, atrial fibrillation, vaso-active medication, number of blood transfusion, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was done by using the sealed envelope method so that there would be equal number of patients in the two groups"
Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic,

Abd. El-Hakeem 2003b (*Continued*)

		given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "Randomized double-blind placebo controlled study. This was performed by an anaesthesiologist not involved with the patients perioperative care."
Blinded data collection?	Low risk	Quote: "Randomized double-blind placebo controlled study. This was performed by an anaesthesiologist not involved with the patients perioperative care." Comment: probably blinded data-collection
Blinded adjudification of endpoints?	Unclear risk	Quote: "Randomized double-blind placebo controlled study. This was performed by an anaesthesiologist not involved with the patients perioperative care." Comment: unclear whether adjudication of endpoints or data-analyses were blinded
Blinded data-analyses?	Unclear risk	Quote: "Randomized double-blind placebo controlled study. This was performed by an anaesthesiologist not involved with the patients perioperative care." Comment: unclear whether adjudication of endpoints or data-analyses were blinded
Standardized pre-, peri-, and postoperative care?	Low risk	Quote: "All patients were pre-medicated with..." Quote: "A standard Anaesthetic technique for a patients was performed" Quote: "While the patients were in the ICU, standard care and processes were followed until discharge"
Standardization of study endpoints?	Low risk	In sections "Study-design and measurements", "calculation of shunt fraction", "laboratory methods" all endpoints were specified
Completeness of (follow up) data?	Unclear risk	Follow-up: ICU-stay. 0% loss to follow up.

Amr 2009

Methods	Randomized placebo-controlled trial
Participants	100 elective CABG
Interventions	dexamethasone 1 mg/kg pre-CPB, 0,5 mg/kg after 8 hr
Outcomes	mortality, cardiac complications, ICU-stay, hospital stay, atrial fibrillation, gastro-intestinal complications, infections
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information on randomisation or allocation concealment was available
Intention to treat analyses All outcomes	Low risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Quote: "Randomized placebo controlled trial", implicates an unblinded study
Blinded data collection?	High risk	Quote: "Randomized placebo controlled trial", implicates an unblinded study
Blinded adjudification of endpoints?	High risk	Quote: "Randomized placebo controlled trial", implicates an unblinded study
Blinded data-analyses?	High risk	Quote: "Randomized placebo controlled trial", implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	Low risk	Quote: "In addition to patients' regular cardiovascular medications, all patients were premedicated with..." Quote: "The surgical techniques were standardized in all cases" Comment: Specified anaesthesiological care and Cardiopulmonary bypass management was described as well Quote: "After completion of the operation, patients were transferred to the ICU, where postoperative care was standardized as follows:... "

Amr 2009 (*Continued*)

Standardization of study endpoints?	Low risk	In sections "pulmonary measurements", "renal measurements", and "specimen collection" all endpoints were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Andersen 1989

Methods	Randomized, placebo-controlled trial
Participants	16 elective CABG
Interventions	30 mg/kg Methylprednisolone, pre-CPB
Outcomes	mortality, cardiac complications, infections, biomarker "no major complications"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information on randomisation or allocation concealment was available
Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Quote: "Randomized placebo controlled trial", implicates an unblinded study
Blinded data collection?	High risk	Quote: "Randomized placebo controlled trial", implicates an unblinded study
Blinded adjudification of endpoints?	High risk	Quote: "Randomized placebo controlled trial", implicates an unblinded study
Blinded data-analyses?	High risk	Quote: "Randomized placebo controlled trial", implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	High risk	Surgical and anaesthesiological procedures and cardiopulmonary bypass management were described in detail, but there was no information regarding the ICU-care

Andersen 1989 (*Continued*)

Standardization of study endpoints?	Low risk	Timing of blood specimens, types of markers, correction for haemodilution and laboratory methods were specified
Completeness of (follow up) data?	Unclear risk	Follow-up: seven days. 0% loss to follow up.

Bingol 2005

Methods	Randomized, placebo-controlled, double-blind trial
Participants	40 elective CABG-patients with a history of COPD
Interventions	17 days (10 pre op, 7 postop) oral prednisolon (20 mg/day in a single dose) or placebo
Outcomes	Postoperative pulmonary function and pulmonary complications
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "These patients were divided into two groups randomly by using random numbers on the computer"
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "Our study-team, the patients and the spirometry technician were blind to the study whereas the pharmacist and the statistical data analysts were not blind to the coding of the groups"
Blinded data collection?	Low risk	Quote: "Our study-team, the patients and the spirometry technician were blind to the study whereas the pharmacist and the statistical data analysts were not blind to the coding of the groups"
Blinded adjudification of endpoints?	High risk	Quote: "Our study-team, the patients and the spirometry technician were blind to the study whereas the pharmacist and the statistical data analysts were not blind to the

Bingol 2005 (*Continued*)

		coding of the groups"
Blinded data-analyses?	High risk	Quote: "Our study-team, the patients and the spirometry technician were blind to the study whereas the pharmacist and the statistical data analysts were not blind to the coding of the groups"
Standardized pre-, peri-, and postoperative care?	Unclear risk	No information regarding anaesthesiological techniques was specified
Standardization of study endpoints?	High risk	Spirometry measurement techniques were not specified
Completeness of (follow up) data?	Low risk	Follow-up: 3 months. 0% loss to follow up.

Boscoe 1983

Methods	Randomized, placebo-controlled trial
Participants	44 elective CABG and/or valve surgery (17 steroids, 17 placebo, 10 pulsatile flow) - 34 included in meta-analysis
Interventions	2 x 30 mg/kg Methylprednisolone, pre-CPB
Outcomes	mortality, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "consecutive patients were selected by random number allocation for one or two groups"
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Unclear risk	Quote: "group 2 received in addition 30 mg/kg methylprednisolon", Comment: Placebo medication was not mentioned. Probably unblinded

Boscoe 1983 (*Continued*)

Blinded data collection?	Unclear risk	Quote: "group 2 received in addition 30 mg/kg methylprednisolon", Comment: Placebo medication was not mentioned. Probably unblinded
Blinded adjudification of endpoints?	Unclear risk	Quote: "group 2 received in addition 30 mg/kg methylprednisolon", Comment: Placebo medication was not mentioned. Probably unblinded
Blinded data-analyses?	Unclear risk	Quote: "group 2 received in addition 30 mg/kg methylprednisolon", Comment: Placebo medication was not mentioned. Probably unblinded
Standardized pre-, peri-, and postoperative care?	High risk	Anaestesiologic management was conducted "as appropriate". No surgical management, ICU-care management was specified
Standardization of study endpoints?	Low risk	Timing of blood specimen sampling, laboratory management and interpretation were specified
Completeness of (follow up) data?	Unclear risk	Follow-up: 24 hours. 0% loss to follow up.

Bourbon 2004

Methods	Randomized, placebo-controlled trial
Participants	36 elective CABG
Interventions	high dose (10 mg/kg), low dose (5 mg/kg) Methylprednisolone, pre-CPB
Outcomes	mortality, time to extubation (not included in meta-analyses; separate outcomes in high- and low dose group), biomarker "no major complications"
Notes	no dose dependant analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomised equally to one of the three following groups"

Bourbon 2004 (*Continued*)

Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Unclear risk	No information regarding blinding was available
Blinded data collection?	Unclear risk	No information regarding blinding was available
Blinded adjudification of endpoints?	Unclear risk	No information regarding blinding was available
Blinded data-analyses?	Unclear risk	No information regarding blinding was available
Standardized pre-, peri-, and postoperative care?	Unclear risk	No information regarding standardization of study endpoints available
Standardization of study endpoints?	High risk	Only cardiopulmonary bypass management was specified.
Completeness of (follow up) data?	Unclear risk	Follow-up: 24 hours. 0% loss to follow up.

Cavarocchi 1986

Methods	Randomized, placebo-controlled trial
Participants	91 elective CABG and/or valve surgery 30 excluded: different type of oxygenator (membrane in stead of bubble)
Interventions	30 mg/kg Solumedrol, pre-CPB different types of oxygenators
Outcomes	mortality, time to extubation (not included in meta-analysis; stratified analyses), vasoactive medication, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information regarding Randomization procedure or allocation concealment was available

Cavarocchi 1986 (*Continued*)

Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Comment: Study was designed to evaluate the effect of different types of oxygenators, which makes blinding impossible
Blinded data collection?	High risk	Comment: Study was designed to evaluate the effect of different types of oxygenators, which makes blinding impossible
Blinded adjudification of endpoints?	High risk	Comment: Study was designed to evaluate the effect of different types of oxygenators, which making blinding impossible
Blinded data-analyses?	High risk	Comment: Study was designed to evaluate the effect of different types of oxygenators, which makes blinding impossible
Standardized pre-, peri-, and postoperative care?	High risk	Anaestesiologic management and ICU care not specified
Standardization of study endpoints?	Low risk	Blood specimen sampling and handling in the laboratories were specified
Completeness of (follow up) data?	Low risk	Follow-up: 24 hours. 0% loss to follow up.

Celik 2004

Methods	Randomized placebo-controlled, double blinded trial	
Participants	60 elective CABG	
Interventions	6 x 30 mg/kg Methylprednisolone, peri-operatively	
Outcomes	mortality, cardiac complications, re-intubation, time to extubation, ICU-stay, atrial fibrillation, vaso-active medication, number of blood transfusions, biomarker	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Celik 2004 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information regarding the exact randomisation method or concealment of allocation was available
Intention to treat analyses All outcomes	Low risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of solution that were administered" Quote: "Therefore, all physicians and nursing staff caring for the patients were blinded to the treatment group."
Blinded data collection?	Unclear risk	Comment: It was not specified whether data-collection, adjunction of endpoints or analyses were blinded
Blinded adjudification of endpoints?	Unclear risk	Comment: It was not specified whether data-collection, adjudication of endpoints or analyses were blinded
Blinded data-analyses?	Unclear risk	Comment: It was not specified whether data-collection, adjudication of endpoints or analyses were blinded
Standardized pre-, peri-, and postoperative care?	High risk	Anaesthesia technique and surgical procedure was specified. Extubation algorithm was specified, further ICU-care was unspecified
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling was specified. Definitions of major clinical complications were specified
Completeness of (follow up) data?	Unclear risk	Follow-up: hospital stay. 0% loss to follow up.

Chaney 1998

Methods	Randomized placebo-controlled, double blinded trial
Participants	60 elective CABG
Interventions	2 x 30 mg/kg Methylprednisolone, sternotomy and at initiation of CPB
Outcomes	mortality, cardiac complications, time to extubation, hospital stay, neurological complications, atrial fibrillation, gastro-intestinal complications, vaso-active medication, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information regarding the exact randomisation procedure or concealment of allocation was available
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of blinded solution that were administered. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group"
Blinded data collection?	Low risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of blinded solution that were administered. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group"
Blinded adjudification of endpoints?	High risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of blinded solution that were administered. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group" Comment: Adjudication of endpoints or analyses were not specified; probably unblinded

Chaney 1998 (*Continued*)

Blinded data-analyses?	High risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of blinded solution that were administered. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group" Comment: Adjudication of endpoints or analyses were not specified; probably unblinded
Standardized pre-, peri-, and postoperative care?	Low risk	Anesthesia technique, cardiopulmonary bypass managing, specimen sampling and laboratory handling, post-operative monitoring and care were specified
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling, post-operative haemodynamic monitoring, complication definition and monitoring were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Chaney 2001

Methods	Randomized placebo-controlled, double blinded trial
Participants	90 elective CABG
Interventions	high dose (2 x 30 mg/kg), low dose (2 x 15 mg/kg) Methylprednisolone, sternotomy and at initiation of CPB
Outcomes	mortality, cardiac complications, time to extubation, neurological complications, vasoactive medication "no major complications"
Notes	2 patients excluded; study-violation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information regarding the exact randomisation method or concealment of allocation was available

Intention to treat analyses All outcomes	Low risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of blinded solution that were administered. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group"
Blinded data collection?	Low risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of blinded solution that were administered. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group"
Blinded adjudification of endpoints?	High risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of blinded solution that were administered. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group"
Blinded data-analyses?	High risk	Quote: "An anaesthesia research nurse performed the randomisation and prepared the two syringes of blinded solution that were administered. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group"
Standardized pre-, peri-, and postoperative care?	Low risk	Quote: "the anaesthetic technique was standardized" Comment: cardiopulmonary bypass managing was specified in detail. Quote: "postoperative care was standardized"
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling, post-operative haemodynamic and pulmonary monitoring, and complication definition and monitoring were specified in detail
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up. Two patients excluded: study violation

Codd 1977

Methods	Randomized placebo-controlled trial
Participants	150 elective CABG
Interventions	1000 mg Methylprednisolone, half an hour before initiation of CPB
Outcomes	mortality, cardiac complications, vasoactive medication "no major complications"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Quote: "Randomization by hospital number". Concealment not guaranteed
Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Unclear risk	Quote: "randomized placebo-controlled trial" implicates an unblinded study
Blinded data collection?	Unclear risk	Quote: "randomized placebo-controlled trial" implicates an unblinded study
Blinded adjudification of endpoints?	Unclear risk	Quote: "randomized placebo-controlled trial" implicates an unblinded study
Blinded data-analyses?	Unclear risk	Quote: "randomized placebo-controlled trial" implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	High risk	Comment: Only surgical technique was specified
Standardization of study endpoints?	Low risk	Definition of myocardial infarction, timing of electrocardiogram, serum samples and laboratory investigations were specified
Completeness of (follow up) data?	Low risk	Follow-up: five days. 0% loss to follow up.

Coetzer 1996

Methods	Randomized placebo-controlled trial
Participants	295 cardiac surgery, not further specified
Interventions	30 mg/kg Methylprednisolone, before initiation of CPB
Outcomes	mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote": "Patients were allocated by random card draw to on of the groups". Concealment of allocation was not specified
Intention to treat analyses All outcomes	Low risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "The first author of the study was blinded"
Blinded data collection?	Low risk	Quote: "the first author of the study was blinded" Comment: it was assumed that this first author did the data collection, but adjudication of endpoints and further analyses are probably done together with the unblinded co-authors
Blinded adjudification of endpoints?	High risk	Quote: "the first author of the study was blinded" Comment: it was assumed that this first author did the data collection, but adjudication or endpoints and further analyses are probably done together with the unblinded co-authors
Blinded data-analyses?	High risk	Quote: "the first author of the study was blinded" Comment: it was assumed that this first author did the data collection, but adjudication or endpoints and further analyses are probably done together with the unblinded co-authors

Coetzer 1996 (*Continued*)

Standardized pre-, peri-, and postoperative care?	High risk	Anaestetia technique, cardiopulmonary bypass managing, post operative care was not standardized
Standardization of study endpoints?	Low risk	Clinical outcome measurements and relevant calculations were specified
Completeness of (follow up) data?	Unclear risk	Follow-up: unclear, at least > 30 days with completeness of data

Demir 2009

Methods	Randomized placebo-controlled trial
Participants	30 elective CABG
Interventions	1000 mg methylprednisolone before CPB
Outcomes	mortality, time to extubation, ICU-stay, hospital stay, renal failure, neurological complications, infections, vasoactive medication, number of blood-transfusions, "no major complications"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	no information with regard to randomization method or concealment of allocation was available
Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	No information regarding blinding was present
Blinded data collection?	High risk	No information regarding blinding was present
Blinded adjudification of endpoints?	High risk	No information regarding blinding was present
Blinded data-analyses?	High risk	No information regarding blinding was present

Demir 2009 (*Continued*)

Standardized pre-, peri-, and postoperative care?	High risk	Postoperative management was not standardized
Standardization of study endpoints?	Low risk	Blood specimen sampling and handling in the laboratory was specified in detail
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

El Azab 2002

Methods	Randomized placebo-controlled, double blinded trial	
Participants	18 elective CABG	
Interventions	100 mg Dexamethasone, pre-surgery	
Outcomes	mortality, time to extubation, ICU-stay, vaso-active medication, biomarker "no major complications"	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information regarding the exact randomization procedure or concealment of allocation was available
Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "This dosage was masked"
Blinded data collection?	Low risk	Quote: "This dosage was masked"
Blinded adjudification of endpoints?	High risk	Quote: "This dosage was masked" Comment: Since no information on adjudification or analyses was provided, this was assumed to be unblinded
Blinded data-analyses?	High risk	Quote: "This dosage was masked" Comment: Since no information on adjudification or analyses was provided, this was

El Azab 2002 (*Continued*)

		assumed to be unblinded
Standardized pre-, peri-, and postoperative care?	High risk	Comment: Only post-operative care was standardized
Standardization of study endpoints?	Low risk	Blood specimen sampling and handling in the laboratory were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Enc 2006

Methods	Randomized placebo-controlled, double blinded trial
Participants	40, elective CABG
Interventions	25 mg/kg Methylprednisolone, 1 hour before initiation of CPB
Outcomes	hospital-stay, renal failure, neurological complications, atrial fibrillation "no major complications"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information regarding randomization procedure or allocation concealment was available
Intention to treat analyses All outcomes	Low risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "double blind, randomized prospective study"
Blinded data collection?	Unclear risk	Quote: "double blind, randomized prospective study" Comment: whether data-collection was blinded was not specified

Enc 2006 (*Continued*)

Blinded adjudification of endpoints?	Unclear risk	Quote: "double blind, randomized prospective study" Comment: whether analyses were blinded was not specified
Blinded data-analyses?	Unclear risk	Quote: "double blind, randomized prospective study" Comment: whether adjudification of endpoints was blinded was not specified
Standardized pre-, peri-, and postoperative care?	High risk	Only anaesthesia technique was standardized
Standardization of study endpoints?	Low risk	Blood specimen sampling and handling in the laboratory were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Engelman 1995

Methods	Randomized placebo-controlled, double blinded trial
Participants	19 elective CABG
Interventions	1 x 1000 mg Methylprednisolone before CPB, 4 x 4 mg Dexamethasone after surgery
Outcomes	mortality, time to extubation, ICU-stay, Hospital-stay, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No specified randomization method or concealment of allocation was specified
Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "the blood study was carried out in a blinded fashion as to the steroid/no steroid group"

Engelman 1995 (*Continued*)

Blinded data collection?	Low risk	Quote: "the blood study was carried out in a blinded fashion as to the steroid/no steroid group"
Blinded adjudification of endpoints?	High risk	Quote: "the blood study was carried out in a blinded fashion as to the steroid/no steroid group". Comment:"The blood study" refers to data-collection and not to data-analysis; we assumed unblinded analyses
Blinded data-analyses?	High risk	Quote: "the blood study was carried out in a blinded fashion as to the steroid/no steroid group". Comment:"The blood study" refers to data-collection and not to data-analysis; we assumed unblinded adjudification of endpoints
Standardized pre-, peri-, and postoperative care?	Unclear risk	Quote: "all patients were treated similarly in a manner described as fast track" Intensive care management was not specified
Standardization of study endpoints?	Low risk	Blood specimen sampling, storage and handling in the laboratory were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Ferries 1984

Methods	Randomized placebo-controlled, double blinded trial	
Participants	80 CABG and/or valve surgery and/or ASD surgery	
Interventions	30 mg/kg Methylprednisolone Membrane versus bubble oxygenator	
Outcomes	mortality, biomarker "no major complications"	
Notes	same study-population as Ferries 1987	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ferries 1984 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "the randomization was planned so as to create four groups of 20 patients by random number allocation using a standard table of random numbers"
Intention to treat analyses All outcomes	Unclear risk	Comment: Study-medication was single-dose and no cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "Neither surgeon, perfusionist nor laboratory technician knew which patient was in which group"
Blinded data collection?	Unclear risk	No information available
Blinded adjudification of endpoints?	Unclear risk	No information available
Blinded data-analyses?	Unclear risk	No information available
Standardized pre-, peri-, and postoperative care?	Unclear risk	Sugical management of post-operative care was not specified
Standardization of study endpoints?	Unclear risk	Blood specimen sampling and handling in the laboratory handling were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Fillinger 2002

Methods	Randomized placebo-controlled, double blinded trial
Participants	50 elective CABG (15 steroids, 15 placebo, 14 etomidate, 6 healthy volunteered) - 30 included in meta-analysis
Interventions	15 mg/kg Methylprednisolone 60 minutes before surgical incision, 4 x 0,3 mg/kg Methylprednisolone after surgery. Etomidate
Outcomes	time to extubation, ICU-stay, hospital-stay, biomarker
Notes	
Risk of bias	

Fillinger 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by the hospital pharmacy with prepared syringes of solution administered by the anaesthesiologist intraoperatively and by the cardiothoracic intensive care unit nurses" Comment: the exact manner of randomization was not described
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "study patients, investigators, and other physicians and nurses caring for the patient perioperatively were blinded to the treatment group"
Blinded data collection?	Low risk	Investigators were blinded; probably blinded data collection
Blinded adjudification of endpoints?	High risk	Although investigators were blinded, it was not stated that adjudification of endpoints was blinded as well
Blinded data-analyses?	High risk	Although investigators were blinded, it was not stated that analyses were blinded as well
Standardized pre-, peri-, and postoperative care?	Low risk	Quote: "After surgery, all patients were transferred to the ICU, where postoperative care was at the discretion of a perioperative care team who followed standard clinical protocol for treatment of cardiopulmonary function, including decisions about tracheal extubations." Comment: together with standardized anaesthesiologic and cardiopulmonary bypass managing, the whole care was judged as "standardized"
Standardization of study endpoints?	Low risk	Blood specimen sampling and handling in the laboratory was specified in detail
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Giomarelli 2003

Methods	Randomized placebo-controlled, double blinded trial
Participants	20 elective CABG
Interventions	1000 mg Methylprednisolon pre-operatively, 5 x 125 mg Methylprednisolone after CPB and at ICU
Outcomes	mortality, cardiac complications, pulmonary complications, time to extubation, ICU-stay, hospital-stay, renal failure, neurological complications, atrial fibrillation, vasoactive medication, blood transfusion Y/N, biomarker
Notes	outcome retrieved after correspondence with author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized according to a computer-generated sequence and assigned either to the standard care..."
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "an anaesthesia nurse performed the randomisation and prepared the syringes of blinded solution that were administered by the anaesthesiologist managing the case. All physicians and nursing staff caring for the patient perioperatively were unaware of the treatment groups."
Blinded data collection?	Unclear risk	No information available
Blinded adjudification of endpoints?	Unclear risk	No information available
Blinded data-analyses?	Unclear risk	No information available
Standardized pre-, peri-, and postoperative care?	Low risk	Anesthesia technique, cardiopulmonary bypass, myocardial protection and post-operative care at the ICU were specified
Standardization of study endpoints?	Low risk	Blood specimen sampling and handling in the laboratory were specified

Giomarelli 2003 (*Continued*)

Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Halonen 2007

Methods	Randomized placebo-controlled, double blinded trial
Participants	241 CABG and/or aortic valve surgery
Interventions	10 x 100 mg Hydrocortisone; first in the evening pre-surgery, repeated eight hourly
Outcomes	mortality, cardiac complications, neurological complications, atrial fibrillation, infections, re-thoracotomy "no major complications"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "Randomization lists were produced by a biostatistician. The groups were block-randomized with block sizes of 6, separately in each hospital"
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "The study group remained unknown to all caring nurses and physicians. The randomization codes were opened after the end of the study. It was unnecessary to break the code for any of the patients, so blinding was ensured"
Blinded data collection?	Low risk	Quote: "The randomization codes were opened after the end of the study"
Blinded adjudification of endpoints?	High risk	Quote: "The randomization codes were opened after the end of the study." Comment: this implicates unblinded adjudification of endpoints

Blinded data-analyses?	High risk	Quote: "The randomization codes were opened after the end of the study." Comment: this implicates unblinded data-analyses
Standardized pre-, peri-, and postoperative care?	High risk	Anesthesia technique was not standardized.
Standardization of study endpoints?	Low risk	Endopoints 'acute myocardial infarction' and 'stroke' were pre-defined. Infection was not specified, but there was a thorough follow up to check for any major complication
Completeness of (follow up) data?	Low risk	Follow-up: ICU stay. 0% loss to follow up.

Halvorsen 2003

Methods	Randomized, placebo-controlled, double blinded trial
Participants	300 elective CABG 6 excluded from analysis (abdominal complications, anaphylaxis, study violation)
Interventions	8 mg/kg Dexamethasone after induction
Outcomes	mortality, cardiac complications, pulmonary complications, time to extubation, ICU-stay, atrial fibrillation, gastro-intestinal complications, infections, vasoactive medication, blood transfusion Y/N, re-thoracotomy
Notes	6 excluded from analysis (abdominal complications, anaphylaxis, study violation)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "a block randomization schema was used with 20 patients allocated to each block". "The sealed envelope..."
Intention to treat analyses All outcomes	High risk	Quote: "Six patients were excluded from the efficacy analysis because of anaphylactoid reaction, development of acute abdominal complications, a perforated ventricular ulcus and protocol violation"
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "to maintain the double blinded study design, the sealed envelope was

Halvorsen 2003 (*Continued*)

		opened immediately before surgery, and the study drug was prepared in identical appearing syringes by a nurse who did nog participate in the treatment of the study patients"
Blinded data collection?	Low risk	Comment: "by a nurse who dit not participate in the treatment" implicates blinding during hospital care period, during which data was collected
Blinded adjudification of endpoints?	High risk	Comment: "by a nurse who dit not participate in the treatment" implicates blinding during hospital care period, during which data was collected
Blinded data-analyses?	High risk	Comment: "by a nurse who dit not participate in the treatment" implicates blinding during hospital care period, during which data was collected
Standardized pre-, peri-, and postoperative care?	Unclear risk	Quote: "all patients were tracheally extubated in the ICU when they were judged to be haemodynamically stable with adequate spontaneous ventilatory function" Comment: no further specification was described, which makes it unclear whether ICU care was standardized
Standardization of study endpoints?	Low risk	a verbal five points verbal rating scale was applied to assess pain and nausea/vomiting
Completeness of (follow up) data?	Low risk	Follow-up: ICU stay. 0% loss to follow up.

Harig 1999

Methods	Randomized, placebo-controlled trial
Participants	40 elective CABG (10 steroids, 10 placebo, 10 aprotinine, 10 heparine coated system), 20 included in meta-analysis
Interventions	2 x 250 mg Prednisolone pre-and postoperatively
Outcomes	mortality, time to extubation, ICU-stay, re-thoracotomy, biomarker
Notes	

Harig 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Quote: "Cohorts of 10 patients were randomized independently" Comment: Concealment of allocation was unclear
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Comment: The absence of information regarding blinding implicates an unblinded study
Blinded data collection?	High risk	Comment: The absence of information regarding blinding implicates an unblinded study
Blinded adjudification of endpoints?	High risk	Comment: The absence of information regarding blinding implicates an unblinded study
Blinded data-analyses?	High risk	Comment: The absence of information regarding blinding implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	Unclear risk	No information regarding standardization of ICU-care was provided
Standardization of study endpoints?	Low risk	In section "blood sampling and biochemical measurements" study-endpoints are specified
Completeness of (follow up) data?	Low risk	Follow-up: 30 days. 0% loss to follow up.

Jansen 1991a

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	25 elective CABG
Interventions	1 mg/kg Dexamethasone
Outcomes	mortality, ICU-stay, infections, biomarker
Notes	3 excluded, study-violation
Risk of bias	

Jansen 1991a (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No randomization method, nor concealment of allocation was described
Intention to treat analyses All outcomes	High risk	Quote: "After evaluation of the data, three patients in the placebo group were excluded from the postoperative study because they required dexamethasone treatment in the intensive care unit."
Blinding during pre-, peri- and postoperative care?	Low risk	Comment: The study is qualified as a "Randomized, double-blind trial", but no blinding-method was not specified
Blinded data collection?	High risk	Comment: The study is qualified as a "Randomized, double-blind trial", but no blinding-method or duration was not specified
Blinded adjudification of endpoints?	High risk	Comment: The study is qualified as a "Randomized, double-blind trial", but no blinding-method or duration was not specified
Blinded data-analyses?	High risk	Comment: The study is qualified as a "Randomized, double-blind trial", but no blinding-method or duration was specified in detail
Standardized pre-, peri-, and postoperative care?	Low risk	In section "Technique of CPB, technique of anaesthesia and postoperative care" treatment were specified
Standardization of study endpoints?	Low risk	In section "hematology" blood specimen sampling and laboratory handling were specified
Completeness of (follow up) data?	High risk	Follow-up: hospital stay. 0% loss to follow up. 3 patients excluded in placebo-group, due to corticosteroids use

Kilger 2003a

Methods	Randomized, placebo-controlled trial
Participants	91 high risk cardiac surgery

Kilger 2003a (*Continued*)

Interventions	Hydrocortisone, 1x 100 mg before induction, followed by 240 mg/day, 120 mg/day, 60 mg/day, 30 mg/day
Outcomes	mortality, time to extubation, ICU-stay, hospital-stay, number of blood transfusions, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were allocated randomly to two groups" Comment: allocation procedure was not described
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Quote: "one limitation of this study is that is was performed only in a randomized controlled, but not in a double-blind manner."
Blinded data collection?	High risk	Quote: "one limitation of this study is that is was performed only in a randomized controlled, but not in a double-blind manner."
Blinded adjudification of endpoints?	High risk	Quote: "one limitation of this study is that is was performed only in a randomized controlled, but not in a double-blind manner."
Blinded data-analyses?	High risk	Quote: "one limitation of this study is that is was performed only in a randomized controlled, but not in a double-blind manner."
Standardized pre-, peri-, and postoperative care?	Low risk	Anesthesia technique, Cardio pulmonary bypass management and postoperative care were specified
Standardization of study endpoints?	Low risk	Both primary and secondary endpoints were specified
Completeness of (follow up) data?	Low risk	Follow-up: six months. 0% loss to follow up.

Kilger 2003b

Methods	Randomized, placebo-controlled trial
Participants	80 high risk cardiac surgery
Interventions	Hydrocortisone, 1x 100 mg before induction, followed by 240 mg/day, 120 mg/day, 60 mg/day, 30 mg/day
Outcomes	time to extubation, ICU-stay, hospital-stay, number of blood transfusions, biomarker
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	no information on Randomization procedure or concealment of allocation was available
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Quote: "die patienten erhielten randomisiert vor narkoseeinleitung" Comment: absence of blinding manners implies no blinding.
Blinded data collection?	High risk	Quote: "die patienten erhielten randomisiert vor narkoseeinleitung" Comment: absence of blinding manners implies no blinding.
Blinded adjudification of endpoints?	High risk	Quote: "die patienten erhielten randomisiert vor narkoseeinleitung" Comment: absence of blinding manners implies no blinding.
Blinded data-analyses?	High risk	Quote: "die patienten erhielten randomisiert vor narkoseeinleitung" Comment: absence of blinding manners implies no blinding.
Standardized pre-, peri-, and postoperative care?	High risk	pre-peri- and postoperative care was not specified
Standardization of study endpoints?	Unclear risk	There were no details regarding study-endpoints

Kilger 2003b (*Continued*)

Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Liakopoulos 2007

Methods	Randomized, placebo-controlled trial
Participants	80 elective CABG
Interventions	15 mg/kg Methylprednisolone pre-CPB
Outcomes	mortality, pulmonary complications, re-intubation, time to extubation, ICU-stay, hospital-stay, renal failure, infections, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "Following a computer-generated sequence, patients were randomly assigned to receive either a ..."
Intention to treat analyses All outcomes	High risk	Two patients were excluded from the study because of post-operative bleeding
Blinding during pre-, peri- and postoperative care?	High risk	qualifying the study as "prospective placebo-controlled randomized trial" implies an unblinded study
Blinded data collection?	High risk	qualifying the study as "prospective placebo-controlled randomized trial" implies an unblinded study
Blinded adjudification of endpoints?	High risk	qualifying the study as "prospective placebo-controlled randomized trial" implies an unblinded study
Blinded data-analyses?	High risk	qualifying the study as "prospective placebo-controlled randomized trial" implies an unblinded study
Standardized pre-, peri-, and postoperative care?	Low risk	In section "peri-operative management" all relevant care was specified

Liakopoulos 2007 (*Continued*)

Standardization of study endpoints?	Low risk	In section "data-collection" blood specimen sampling and laboratory handling and relevant information on clinical outcome measures were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Loef 2004

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	20 elective CABG
Interventions	Dexamethasone, 1 mg/kg before induction, 0,5 mg/kg after 8 hours
Outcomes	mortality, time to extubation, ICU-stay, vasoactive medication, number of blood transfusions, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information on randomization procedure or concealment of allocation was provided
Intention to treat analyses All outcomes	Low risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "patients were randomized in a double-blind fashion" Comment: No further information regarding blinding procedures was available
Blinded data collection?	Unclear risk	Quote: "patients were randomized in a double-blind fashion" Comment: No further information regarding blinding procedures was available
Blinded adjudification of endpoints?	Unclear risk	Quote: "patients were randomized in a double-blind fashion" Comment: No further information regarding blinding procedures was available

Loef 2004 (*Continued*)

Blinded data-analyses?	Unclear risk	Quote: "patients were randomized in a double-blind fashion" Comment: No further information regarding blinding procedures was available
Standardized pre-, peri-, and postoperative care?	Low risk	In section "anaesthetic management" pre-peri- and postoperative care were specified
Standardization of study endpoints?	Low risk	Quote:"the injury to glomerular and tubular structure was assessed by measurement of sensitive markers of glomerular and tubular dysfunction and damage" Comment: in section "renal markers" and "laboratory methods" detailed description on plasma and urinary specimen sampling and laboratory handling was provided
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Mayumi 1997

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	24 elective valve replacement surgery
Interventions	2 x 20 mg/kg Methylprednisolone, before and after bypass
Outcomes	mortality, time to extubation, infection, transfusion Y/N, biomarker
Notes	3 patients excluded; 1x IABP - 2x Bloodtransfusion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Quote: "a chief anaesthesiologist, who was not directly involved in the present study, was responsible for opening an envelope indicating the drug" Comment: this quote indicates a sealed envelope method used for randomization and allocation concealment
Intention to treat analyses All outcomes	High risk	Quote: "but patients who underwent intra-aortic balloon pumping or allogeneic blood transfusion were excluded from this study"

Mayumi 1997 (*Continued*)

Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "a chief anaesthesiologist, who was not directly involved in the present study, was responsible for opening an envelope indicating the drug"
Blinded data collection?	Low risk	Quote: "The patient names, but not drug names, included in the two groups were told by the anaesthesiologist to the senior author at the end of study"
Blinded adjudification of endpoints?	Low risk	Quote: "After the statistical analysis was completed, the used drug for each group and the used dose of the steroid in each patient were disclosed to the senior author"
Blinded data-analyses?	Low risk	Quote: "After the statistical analysis was completed, the used drug for each group and the used dose of the steroid in each patient were disclosed to the senior author"
Standardized pre-, peri-, and postoperative care?	Low risk	In sections "technique of cardiopulmonary bypass", "technique of anaesthesia and operation" and "postoperative care" pre-peri- and postoperative care was specified
Standardization of study endpoints?	Low risk	In section "hematology" and "Hemodynamics metabolism and blood gas" detailed information regarding data-collection for pre-defined endpoints was provided
Completeness of (follow up) data?	High risk	Follow-up: 7 days, 12,5% loss to follow up. 3 patients excluded: IABP (1), and Bloodtransfusion (2)

McBride 2004

Methods	Randomized, placebo-controlled trial
Participants	36 elective CABG
Interventions	30 mg/kg Methylprednisolone, before induction
Outcomes	mortality, cardiac complications, time to extubation, hospital-stay, vasoactive medication, re-thoracotomy, biomarker
Notes	

Risk of bias

McBride 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No information available regarding randomization procedure or allocation concealment was provided
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Quote: "Ethical consideration required that the peri-operative physician was aware of the randomisation group"
Blinded data collection?	High risk	Quote: "Ethical consideration required that the peri-operative physician was aware of the randomisation group"
Blinded adjudification of endpoints?	High risk	Quote: "Ethical consideration required that the peri-operative physician was aware of the randomisation group"
Blinded data-analyses?	High risk	Quote: "Ethical consideration required that the peri-operative physician was aware of the randomisation group"
Standardized pre-, peri-, and postoperative care?	Low risk	Management procedures with regard to cardiopulmonary bypass, haemodynamic support or extubation timing were not specified
Standardization of study endpoints?	Unclear risk	Blood specimen sampling and handling in the laboratory were specified
Completeness of (follow up) data?	Low risk	Follow-up: 72 hours. 0% loss to follow up.

Morton 1976

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	95 elective CABG
Interventions	30 mg/kg or 2000 mg Methylprednisolone, before induction
Outcomes	mortality, cardiac complications, pulmonary complications
Notes	

Morton 1976 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "The drug and placebo were supplied, packaged and randomly coded by the upjohn company"
Intention to treat analyses All outcomes	Low risk	Comment: Single-dose study medication. No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "The code was not revealed until the study was completed and all the data had been collected and interpreted"
Blinded data collection?	Low risk	Quote: "The code was not revealed until the study was completed and all the data had been collected and interpreted"
Blinded adjudification of endpoints?	Low risk	Quote: "The code was not revealed until the study was completed and all the data had been collected and interpreted"
Blinded data-analyses?	Low risk	Quote: "The code was not revealed until the study was completed and all the data had been collected and interpreted"
Standardized pre-, peri-, and postoperative care?	High risk	Only information regarding surgical procedure was available.
Standardization of study endpoints?	Low risk	Main outcome: myocardia preservation was assessed by laboratory investigation (LDH and CK), ECG-judgement by a cardiologist,
Completeness of (follow up) data?	Unclear risk	Follow-up: unclear, at least 30 days 0% loss to follow up

Oliver 2004

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	189 cardiac surgery requiring CPB (62 steroids, 63 placebo, 64 hemofiltration), 125 included in meta-analysis
Interventions	1000 mg Methylprednisolone, before induction, 4 x 4 mg Dexamethasone 6 hourly
Outcomes	mortality, cardiac complications, pulmonary complications, time to extubation, ICU-stay, neurological complications, transfusion Y/N, re-thoracotomy
Notes	3 exclusions; study-violation (lateral thoracotomy, retrosternal mass, surgery cancelled)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information on randomization procedure or allocation concealment
Intention to treat analyses All outcomes	Unclear risk	Three patients were excluded (lateral thoracotomy, retrosternal mass, surgery cancelled)
Blinding during pre-, peri- and postoperative care?	High risk	Quote: "Perfusionists were aware of subjects assigned to hemofil, but no other study assignment. All remaining operating room and intensive care unit personnel were blinded to group identity"
Blinded data collection?	Low risk	Quote: "Perfusionists were aware of subjects assigned to hemofil, but no other study assignment. All remaining operating room and intensive care unit personnel were blinded to group identity"
Blinded adjudification of endpoints?	Unclear risk	Quote: "Perfusionists were aware of subjects assigned to hemofil, but no other study assignment. All remaining operating room and intensive care unit personnel were blinded to group identity"
Blinded data-analyses?	Unclear risk	Quote: "Perfusionists were aware of subjects assigned to hemofil, but no other study assignment. All remaining operating room and intensive care unit personnel were blinded to group identity"

Oliver 2004 (*Continued*)

Standardized pre-, peri-, and postoperative care?	Low risk	Anesthesia technique, Cardiopulmonary bypass managing, blood transfusions and ICU care were specified
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling, post-operative haemodynamic monitoring, complication definition and monitoring were specified
Completeness of (follow up) data?	Low risk	Follow-up: ICU stay. 0% loss to follow up. 3 patients excluded, because they didn't met inclusion criteria

Prasongsukarn 2005

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	86 elective CABG
Interventions	1000 mg Methylprednisolone, before induction, 4 x 4 mg Dexamethasone 6 hourly
Outcomes	mortality, renal failure, neurological complications, atrial fibrillation, gastro-intestinal complications, infections, biomarker
Notes	2 patients excluded; off pump

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "All vials of the steroid and placebo medication were prepared and randomized by the hospital pharmacy. The steroid and placebo solution were visually indistinguishable"
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "A planned interim analyses was performed after 50 % enrolment...Therefore, study enrolment was terminated on February 29, 2001 and the code was broken."

Prasongsukarn 2005 (*Continued*)

Blinded data collection?	Low risk	Quote: "A planned interim analyses was performed after 50 % enrolment...Therefore, study enrolment was terminated on February 29, 2001 and the code was broken"
Blinded adjudification of endpoints?	Low risk	Quote: "A planned interim analyses was performed after 50 % enrolment...Therefore, study enrolment was terminated on February 29, 2001 and the code was broken"
Blinded data-analyses?	Low risk	Quote: "A planned interim analyses was performed after 50 % enrolment...Therefore, study enrolment was terminated on February 29, 2001 and the code was broken"
Standardized pre-, peri-, and postoperative care?	Low risk	Quote: "Standatdized anaesthesia and surgical protocols were applied in all cases" postoperative care was specified in section "haemodynamic measurement and monitoring"
Standardization of study endpoints?	Low risk	Atrial fibrillation monitoring, occurrence (including study definitions of atrial fibrillation) and treatment were specified Blood specimen sampling and laboratory handling were specified
Completeness of (follow up) data?	Unclear risk	Follow-up: hospital stay. 0% loss to follow up. 2 patients excluded, because they didn't met inclusion criteria

Rao 1977

Methods	Randomized, placebo-controlled trial
Participants	150 elective CABG
Interventions	1000 mg Methylprednisolone before CPB
Outcomes	mortality, cardiac complications, pulmonary complications, neurological complications, infections,
Notes	

Rao 1977 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	No randomization procedure, concealment of allocation or blinding was described
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	The study was classified as a "prospective randomized study". This implicates an unblinded study
Blinded data collection?	High risk	The study was classified as a "prospective randomized study". This implicates an unblinded study
Blinded adjudification of endpoints?	High risk	The study was classified as a "prospective randomized study". This implicates an unblinded study
Blinded data-analyses?	High risk	The study was classified as a "prospective randomized study". This implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	Unclear risk	Only Cardiopulmonary bypass technique was standardized, other care was not specified
Standardization of study endpoints?	Unclear risk	Quote: "observations were made regarding: acidoses during CPB, Need for supportive therapy; incidence and management of cardiac arrhythmias immediately post-operatively and during the rest of the hospital course; incidence and management of pulmonary complications; consumption of oxygen by the body tissues during cardiopulmonary bypass using the A-V flux formula" Comment: Endpoints were no further specified or standardized
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Rubens 2005

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	68 elective CABG
Interventions	1000 mg Methylprednisolone, before CPB Surface Modifiing additive - CPB
Outcomes	mortality, cardiac complications, ICU-stay, hospital-stay, atrial fibrillation, infections, biomarker
Notes	3 excluded before surgery started

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "The perfusionist performed the treatment assignment immediately pre-operatively by opening a sealed numbered envelope. Randomization was in blocks of four generated using SAS version 8.2" Quote: "all syringes containing the MPSS or the Placebo were prepared in the hospital pharmacy and labelled with a code"
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "all the members of the surgical and anaesthetic teams were blinded to the use of MPSS
Blinded data collection?	Unclear risk	It is unclear when allocation was disclosed
Blinded adjudification of endpoints?	Unclear risk	It is unclear when allocation was disclosed
Blinded data-analyses?	Unclear risk	It is unclear when allocation was disclosed
Standardized pre-, peri-, and postoperative care?	High risk	Comment: Post-operative care was not specified and probably unstandardized
Standardization of study endpoints?	Low risk	In sections "primary outcome variables" and "secondary outcome variables" endpoints were specified

Completeness of (follow up) data?	Unclear risk	Follow-up: hospital stay. 0% loss to follow up. 3 excluded before surgery started

Rumalla 2001

Methods	Randomized, placebo-controlled trial
Participants	13 elective CABG
Interventions	1000 mg Methylprednisolone, at induction
Outcomes	mortality, neurological complications, infections, re-thoracotomy, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomization procedure was not specified, probably no concealment of allocation
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Unclear risk	Study was classified as a "randomized control study". This implicates an unblinded study
Blinded data collection?	Unclear risk	Study was classified as a "randomized control study". This implicates an unblinded study
Blinded adjudification of endpoints?	High risk	Study was classified as a "randomized control study". This implicates an unblinded study
Blinded data-analyses?	High risk	Study was classified as a "randomized control study". This implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	Unclear risk	Pre-peri- and postoperative care was not specified
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling were specified
Completeness of (follow up) data?	Low risk	Follow-up: 6 months. 0% loss to follow up.

Sano 2003

Methods	Randomized, placebo-controlled trial
Participants	28 elective CABG (10 steroids, 10 placebo, 10 off pump), 20 included in meta-analysis
Interventions	2 x 50 mg/kg Hydrocortisone, before and after CPB
Outcomes	mortality, pulmonary complications, blood transfusion Y/N, biomarker "no major complications"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomization procedure was not specified. Probably no concealment of allocation
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Unclear risk	Quote: "these patients were randomly divided into two groups" Comment: no remark concerning blinding implicates an unblinded study
Blinded data collection?	Unclear risk	Quote: "these patients were randomly divided into two groups" Comment: no remark concerning blinding implicates an unblinded study
Blinded adjudification of endpoints?	Unclear risk	Quote: "these patients were randomly divided into two groups" Comment: no remark concerning blinding implicates an unblinded study
Blinded data-analyses?	Unclear risk	Quote: "these patients were randomly divided into two groups" Comment: no remark concerning blinding implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	High risk	In section "intraoperative patient management" anaesthetic techniques and CPB management is described. There is no information regarding postoperative management

Sano 2003 (*Continued*)

Standardization of study endpoints?	Low risk	In section "blood sampling", "analysis of T cell response to PPD antigen" and "cross-stimulation system" endpoints are specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up

Sano 2006

Methods	Randomized, placebo-controlled, double-blinded trial	
Participants	60 elective CABG	
Interventions	50 mg/kg Hydrocortisone, before and after CPB	
Outcomes	pulmonary complications, time to extubation, ICU-stay, renal failure, atrial fibrillation, infections "no major complications"	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Quote: "Were prospectively randomized into two groups by our operation-registry staff who were not involved in this study"
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "Were prospectively randomized into two groups by our operation-registry staff who were not involved in this study"
Blinded data collection?	Unclear risk	Quote: "Were prospectively randomized into two groups by our operation-registry staff who were not involved in this study" Comment: whether data collection, adjudification of endpoints or analyses were blinded was not specified
Blinded adjudification of endpoints?	Unclear risk	Quote: "Were prospectively randomized into two groups by our operation-registry staff who were not involved in this study"

Sano 2006 (*Continued*)

		Comment: whether data collection, adjudification of endpoints or analyses were blinded was not specified
Blinded data-analyses?	Unclear risk	Quote: "Were prospectively randomized into two groups by our operation-registry staff who were not involved in this study" Comment: whether data collection, adjudification of endpoints or analyses were blinded was not specified
Standardized pre-, peri-, and postoperative care?	Low risk	Anethesia Technique, Cardiopulmonary bypass managing, Surgery techniques and ICU care were specified
Standardization of study endpoints?	High risk	Quote: "Aim: to investigate whether this retardation of recovery of adaptive immunity induced by steroid administration would increase the risk of infection after open heart surgery" Comment: retardation of adaptive immunity and infection was not pre-defined
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Schurr 2001

Methods	Randomized, placebo-controlled trial	
Participants	50 elective CABG	
Interventions	10 mg/kg Methylprednisolone, 4 hours before surgery	
Outcomes	time to extubation, ICU-stay, hospital-stay, atrial fibrillation, vasoactive medication, rethoracotomy, biomarker "no major complications"	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Comment: Study was unblinded, allocation concealment was not done

Schurr 2001 (*Continued*)

Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Study was qualified as: "prospective randomized" Comment: absence of blinding manner implies an unblinded study
Blinded data collection?	High risk	Study was qualified as: "prospective randomized" Comment: no remark regarding blinding implicates an unblinded study
Blinded adjudification of endpoints?	High risk	Study was qualified as: "prospective randomized" Comment: no remark regarding blinding implicates an unblinded study
Blinded data-analyses?	High risk	Study was qualified as: "prospective randomized" Comment: no remark regarding blinding implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	High risk	Quote: "the peri-operative anaesthesia management and medication treatment were identical in both groups" Comment: further care was not specified
Standardization of study endpoints?	Low risk	Detailed endpoint specifications were present In sections "blood sampling and analyses" and "clinical variables"
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Sobieski 2008

Methods	Randomized placebo-controlled double-blinded trial
Participants	28 elective CABG
Interventions	100 mg dexamethasone pre-CPB
Outcomes	mortality, time to extubation, ICU-stay, hospital stay, renal failure, neurological complications, atrial fibrillation, re-thoracotomy
Notes	

Sobieski 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "On the day of surgery, patient enrolled in the study were randomized by the pharmacy."
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "At the completion of the study, the pharmacy unblinded all the patient treatment groups"
Blinded data collection?	Low risk	Quote: "At the completion of the study, the pharmacy unblinded all the patient treatment groups"
Blinded adjudification of endpoints?	High risk	Quote: "At the completion of the study, the pharmacy unblinded all the patient treatment groups"
Blinded data-analyses?	High risk	Quote: "At the completion of the study, the pharmacy unblinded all the patient treatment groups"
Standardized pre-, peri-, and postoperative care?	High risk	Post-operative care was not specified
Standardization of study endpoints?	Low risk	In sections "Sample collection and clinical variables" and "Cytokine, complement, and plama norepinephrine assays" all endpoints were specified
Completeness of (follow up) data?	Low risk	Follow-up: 72 hours. 0% loss to follow up.

Starobin 2007

Methods	Randomized placebo-controlled trial
Participants	60 elective CABG
Interventions	5 mg betamethasone slow release, 2 mg betamethasone rapid-release 2-3 weeks prior to surgery

Starobin 2007 (*Continued*)

Outcomes	mortality, pulmonary complications, time to extubation, ICU-stay, hospital stay, renal failure, neurological complications, atrial fibrillation, infections, re-thoracotomy
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	No information on randomization procedure or concealment of allocation
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	Study was classified as a "prospective open randomized trial"
Blinded data collection?	High risk	Study was classified as a "prospective open randomized trial"
Blinded adjudification of endpoints?	High risk	Study was classified as a "prospective open randomized trial"
Blinded data-analyses?	High risk	Study was classified as a "prospective open randomized trial"
Standardized pre-, peri-, and postoperative care?	High risk	Anesthetic technique, Cardiopulmonary bypass managing, surgery and post-operative care at ICU were not specified
Standardization of study endpoints?	Low risk	In section "study-endpoints" are both primary and secondary endpoints specified
Completeness of (follow up) data?	Low risk	Follow-up: 72 hours. 0% loss to follow up.

Tassani 1999

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	52 elective CABG
Interventions	1000 mg Methylprednisolone, half an hour before CPB
Outcomes	time to extubation, ICU-stay, hospital-stay, blood transfusion Y/N, biomarker "no major complications"

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "The study drug or placebo was prepared in the morning at the hospital pharmacy."
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "the study was performed double-blinded"
Blinded data collection?	Low risk	Quote: "the study was performed double-blinded"
Blinded adjudification of endpoints?	Unclear risk	Quote: "the study was performed double-blinded" Comment: it is unclear when allocation was disclosed
Blinded data-analyses?	Unclear risk	Quote: "the study was performed double-blinded" Comment: it is unclear when allocation was disclosed
Standardized pre-, peri-, and postoperative care?	Low risk	Anesthetic Technique, Cardiopulmonary bypass managing, surgery and Post-operative care at the ICU were specified
Standardization of study endpoints?	Low risk	Blood specimen sampling, laboratory handling, monitoring of relevant clinical, haemodynamic and respiratory parameters and formula's tor calculations were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Toft 1997

Methods	Randomized, placebo-controlled trial
Participants	16 low risk cardiac surgery with CPB
Interventions	30 mg/kg Methylprednisolone at induction
Outcomes	mortality, pulmonary complications, renal failure, infections, biomarker
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No randomization procedure or concealment of allocation was described
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Unclear risk	Probably an unblinded study, since blinding is not mentioned
Blinded data collection?	Unclear risk	Probably an unblinded study, since blinding is not mentioned
Blinded adjudification of endpoints?	Unclear risk	Probably an unblinded study, since blinding is not mentioned
Blinded data-analyses?	High risk	Probably an unblinded study, since blinding is not mentioned
Standardized pre-, peri-, and postoperative care?	High risk	Only anaesthetic technique and Cardiopulmonary bypass were described
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling were specified in detail
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Turkoz 2001

Methods	Randomized, placebo-controlled trial
Participants	30 elective CABG (10 steroids, 10 placebo, 10 aprotinine), 20 included in meta-analysis
Interventions	30 mg/kg Methylprednisolone, before CPB
Outcomes	number of transfusions, biomarker "no major complications"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomization procedure and concealment of allocation was not described
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	High risk	The study was classified as a prospective randomized study, which implicates an unblinded study
Blinded data collection?	High risk	The study was classified as a prospective randomized study, which implicates an unblinded study
Blinded adjudification of endpoints?	High risk	The study was classified as a prospective randomized study, which implicates an unblinded study
Blinded data-analyses?	High risk	The study was classified as a prospective randomized study, which implicates an unblinded study
Standardized pre-, peri-, and postoperative care?	High risk	Post-operative care was not specified
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling were specified
Completeness of (follow up) data?	Low risk	Follow-up: 24 hours. 0% loss to follow up.

Volk 2001

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	39 elective CABG (13 steroids, 13 placebo, 13 tirilazad mesylate) 26 included in meta-analysis
Interventions	15 mg/kg Methylprednisolone, one and a half hour before CPB
Outcomes	mortality, ICU-stay, hospital-stay, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomization procedure and concealment of allocation were not specified
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	The study was classified as a "randomized, controlled, double-blind, prospective trial"
Blinded data collection?	Unclear risk	The study was classified as a "randomized, controlled, double-blind prospective trial". , but it is unclear when allocation was disclosed
Blinded adjudification of endpoints?	Unclear risk	The study was classified as a "randomized, controlled, double-blind prospective trial". , but it is unclear when allocation was disclosed
Blinded data-analyses?	High risk	Quote: "one patient received both TM and MP and had to be excluded from data-analyses" Comment: This implies breaking of the code before data-analyses
Standardized pre-, peri-, and postoperative care?	High risk	Post-operative care at the ICu was not described
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling were specified

Volk 2001 (*Continued*)

Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Volk 2003

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	36 elective CABG (12 steroids, 12 placebo, 12 tirilazad mesylate) 24 included in meta-analysis
Interventions	15 mg/kg Methylprednisolone, one and a half hour before CPB
Outcomes	mortality, cardiac complications, ICU-stay, number of blood transfusions
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Qote: "Patients were randomized to receive..." No randomization procedure or concealment of allocation was described
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	The study was classified as a "randomized controlled blinded prospective trial"
Blinded data collection?	Unclear risk	The study was classified as a "randomized controlled blinded prospective trial", but it is unclear when allocation was disclosed
Blinded adjudification of endpoints?	Unclear risk	The study was classified as a "randomized controlled blinded prospective trial", but it is unclear when allocation was disclosed
Blinded data-analyses?	Unclear risk	The study was classified as a "randomized controlled blinded prospective trial", but it is unclear when allocation was disclosed
Standardized pre-, peri-, and postoperative care?	High risk	Post-operative care at the ICU was not described

Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling were specified
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

von Spiegel 2001

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	20 elective CABG
Interventions	1 mg/kg Dexamethasone, after induction
Outcomes	mortality, vasoactive medication
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Quote: "individuals were randomized into two groups under controlled, double-blind conditions"
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "Throughout the entire study, the care of the patients was managed by anaesthesiologists and intensivists who were not involved in the study"
Blinded data collection?	Low risk	Quote: "Throughout the entire study, the care of the patients was managed by anaesthesiologists and intensivists who were not involved in the study"
Blinded adjudification of endpoints?	High risk	Quote: "Throughout the entire study, the care of the patients was managed by anaesthesiologists and intensivists who were not involved in the study"

von Spiegel 2001 (*Continued*)

Blinded data-analyses?	High risk	Quote: "Throughout the entire study, the care of the patients was managed by anaesthesiologists and intensivists who were not involved in the study"
Standardized pre-, peri-, and postoperative care?	Low risk	Quote: "Peri-operative care was standardized according to our clinical routine, with the following guidelines"
Standardization of study endpoints?	Low risk	Endpoints and various relevant calculations were described in section "fluid balances" and "double indicator dilution"
Completeness of (follow up) data?	Low risk	Follow-up: 20 hours. 0% loss to follow up.

Wan 1999

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	20 elective CABG or valve
Interventions	30 mg/kg Methylprednisolone, during induction
Outcomes	mortality, time to extubation, ICU-stay, biomarker
Notes	77 eligible patients were excluded from the final study because they didn't met inclusion criteria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomization procedure and concealment of allocation were not specified
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "The ICU staff was blinded as to the pretreatment of steroids"
Blinded data collection?	Low risk	Quote: "The ICU staff was blinded as to the pretreatment of steroids"

Wan 1999 (*Continued*)

Blinded adjudification of endpoints?	High risk	Quote: "The ICU staff was blinded as to the pretreatment of steroids"
Blinded data-analyses?	High risk	Quote: "The ICU staff was blinded as to the pretreatment of steroids"
Standardized pre-, peri-, and postoperative care?	Unclear risk	Post-operatieve care is not specified
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling were specified
Completeness of (follow up) data?	Unclear risk	Follow-up: hospital stay. 0% loss to follow up. 77 patients excluded because of a very long CPB time, which was defined as an exclusion criterion

Weis 2006

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	36 high risk CPB-patients (8 lost to follow up) 28 included in meta-analysis
Interventions	Hydrocortisone, 1x 100 mg before induction, followed by 240 mg/day, 120 mg/day, 60 mg/day, 30 mg/day
Outcomes	mortality, time to intubation, ICU-stay, hospital stay, post-traumatic stress, health related quality of life
Notes	8 patients lost to follow up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Quote: "... in identical vials in a double-blind fashion. The vials were prepared by a study nurse who was not involved in the care of patients participating in the trial" Comment: randomization procedure is not specified
Intention to treat analyses All outcomes	Low risk	Comment: no cross overs were mentioned.

Weis 2006 (*Continued*)

Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "... in identical vials in a double-blind fashion. The vials were prepared by a study nurse who was not involved in the care of patients participating in the trial"
Blinded data collection?	Low risk	Quote: "... in identical vials in a double-blind fashion. The vials were prepared by a study nurse who was not involved in the care of patients participating in the trial"
Blinded adjudification of endpoints?	Unclear risk	Quote: "... In identical vials in a double-blind fashion. The vials were prepared by a study nurse who was not involved in the care of patients participating in the trial" Comment: It is unclear when allocation was disclosed
Blinded data-analyses?	High risk	Quote: "... In identical vials in a double-blind fashion. The vials were prepared by a study nurse who was not involved in the care of patients participating in the trial" Comment: It is unclear when allocation was disclosed
Standardized pre-, peri-, and postoperative care?	High risk	Anesthetic technique, cardiopulmonary bypass managing, Surgery, post operative care at the ICU were not specified
Standardization of study endpoints?	Low risk	Post-traumatic stress and Health related quality of life were assessed by validated scoring systems
Completeness of (follow up) data?	High risk	Follow-up: hospital stay. 22% loss to follow up.

Weis 2009

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	36 high-risk CPB patients
Interventions	Hydrocortisone, 1x 100 mg before induction, followed by 240 mg/day, 120 mg/day, 60 mg/day, 30 mg/day
Outcomes	mortality, pulmonary complications, intubation time, ICU-stay, hospital stay, renal failure, atrial fibrillation, infections, number of blood-transfusions, biomarker
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomly allocated to two groups by block randomization"
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols Quote: "No other steroids were given during the study period"
Blinding during pre-, peri- and postoperative care?	Low risk	Study was classified as prospective, randomized, double-blinded, placebo controlled" Comment: when concealment of allocation was disclosed is unclear
Blinded data collection?	Unclear risk	Study was classified as prospective, randomized, double-blinded, placebo controlled" Comment: when concealment of allocation was disclosed is unclear
Blinded adjudification of endpoints?	Unclear risk	Study was classified as prospective, randomized, double-blinded, placebo controlled" Comment: when concealment of allocation was disclosed is unclear
Blinded data-analyses?	Unclear risk	Study was classified as prospective, randomized, double-blinded, placebo controlled" Comment: when concealment of allocation was disclosed is unclear
Standardized pre-, peri-, and postoperative care?	Low risk	In section "Patient management" all details were specified
Standardization of study endpoints?	Low risk	Blood specimen sampling and laboratory handling were specified
Completeness of (follow up) data?	Low risk	Follow-up: 28 days. 0% loss to follow up.

Whitlock 2006

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	60 all types of cardiac surgery with CPB
Interventions	2 x 150 mg Methylprednisolone, at induction and at start CPB
Outcomes	mortality, cardiac complications, pulmonary complications, time to extubation, ICU stay, hospital stay, renal failure, neurological complications, atrial fibrillation, gastro-intestinal complications, infections, vasoactive medication, number of blood transfusions, biomarker
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Quote: "Block randomization via a computer-generated sequence was performed on the day of surgery by the local hospital pharmacy" Comment: Adequate randomization, bu no information about concealment after randomization
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Quote: "all patients, clinicians, and statisticians were blinded until the completion of data analyses by group"
Blinded data collection?	Low risk	Quote: "all patients, clinicians, and statisticians were blinded until the completion of data analyses by group"
Blinded adjudification of endpoints?	Low risk	Quote: "all patients, clinicians, and statisticians were blinded until the completion of data analyses by group"
Blinded data-analyses?	Low risk	Quote: "all patients, clinicians, and statisticians were blinded until the completion of data analyses by group"
Standardized pre-, peri-, and postoperative care?	High risk	Quote: "Neither operative technique nor anaesthesia was standardized to maintain generalizablility of the study" "Likewise the

Whitlock 2006 (*Continued*)

		postoperative ICU-care was not standardized"
Standardization of study endpoints?	High risk	In section "measurements" all relevant details were described
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0% loss to follow up.

Yared 1998

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	236 elective CABG or valve surgery
Interventions	0,6 mg/kg Dexamethasone, after induction
Outcomes	mortality, cardiac complications, time to extubation, ICU-stay, renal failure, neurological complications, infections, vasoactive medication, shivering
Notes	20 exclusions (no study-medication (10), bleeding (3), aprotinine (1), Additive steroids (6))

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Randomization procedure and concealment of allocation were not specified
Intention to treat analyses All outcomes	Unclear risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Blinded data collection?	Low risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation

Yared 1998 (*Continued*)

Blinded adjudification of endpoints?	Unclear risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Blinded data-analyses?	High risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Standardized pre-, peri-, and postoperative care?	High risk	Quote: "patients were weaned to CPAP and extubated according to ICU routine"
Standardization of study endpoints?	High risk	Primary endpoint was shivering, but no definition of shivering was provided
Completeness of (follow up) data?	High risk	Follow-up: hospital stay. 8,5% loss to follow up. 20 exclusions (no study-medication (10) , bleeding (3), Aprotinine (1), Additive steroids(6))

Yared 2007

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	78 elective combined CABG and valve surgery (7 excluded) 71 included in meta-analysis
Interventions	0,6 mg/kg Dexamethasone, after induction
Outcomes	mortality, cardiac complications, pulmonary complications, time to extubation, ICU-stay, renal failure, neurological complications, atrial fibrillation, infections, biomarker "no major complications"
Notes	7 exclusions (change in surgical plan (5), aprotinine (1), additives steroids (1))

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Quote: "A computer-generated random table was used"

		Comment: adequate randomization, but no description of concealment after randomization
Intention to treat analyses All outcomes	High risk	Patients receiving additional steroids were excluded from the trial
Blinding during pre-, peri- and postoperative care?	Low risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Blinded data collection?	Low risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Blinded adjudification of endpoints?	Unclear risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Blinded data-analyses?	High risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Standardized pre-, peri-, and postoperative care?	High risk	There is no description of peri- or post operative care
Standardization of study endpoints?	Low risk	In section "materials and methods" all relevant information was available
Completeness of (follow up) data?	Low risk	Follow-up: hospital stay. 0 % loss to follow up.

Yilmaz 1999

Methods	Randomized, placebo-controlled, double-blinded trial
Participants	20 elective CABG
Interventions	1 mg/kg Methylprednisolone in pump prime solution
Outcomes	time to extubation, ICU-stay, hospital stay, infections, vasoactive medication, biomarker
Notes	pump-prime solution!! 5 patients excluded: (2x glucose dysregulation, transfusion need 3x)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Quote: "Twenty patients were randomly divided in two groups" Comment: no information on randomization procedure or concealment
Intention to treat analyses All outcomes	Low risk	Comment: No cross-overs were mentioned. This absence of cross-overs seems realistic, given the very short duration of the treatment protocols
Blinding during pre-, peri- and postoperative care?	Low risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Blinded data collection?	Low risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Blinded adjudification of endpoints?	Unclear risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study" Comment: there is no information available with regard to the timing of disclosure of allocation
Blinded data-analyses?	High risk	Study was classified as " a prospective, randomized, double-blind, placebo-controlled study"

Yilmaz 1999 (*Continued*)

		Comment: there is no information available with regard to the timing of disclosure of allocation
Standardized pre-, peri-, and postoperative care?	High risk	Post-operative care was not described
Standardization of study endpoints?	Low risk	In section "blood sampling", "assay technique" and "follow up" details are described
Completeness of (follow up) data?	High risk	Follow-up: hospital stay. 25 % loss to follow up. 5 patients excluded (2x glucose dysregulation, 3x transfusion need)

Abbreviations are explained in full in Table 1.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anic 2004	No clinical endpoints reported
Augoustides 2007	Comment on another study in letter to the editor. No randomized controlled trial
Baker 2007	Review article
Baraka 1995	No clinical endpoints reported
Biagioli 1981	No clinical endpoints reported
Boldt 1986	No clinical endpoints reported
Chaney 1999	Review article
Coffin 1975	No randomization (consecutive patients)
Coraim 1987	No clinical endpoints reported
Corbi 2001	Comment on another study in letter to the editor. No randomized controlled trial
Dernek 1999	No randomization
Diego 1997	No clinical endpoints reported

(*Continued*)

El Busto Osacar 1977	No randomization
El Busto Osacar 1979	No clinical outcomes reported
Enderby 1987	No randomization
Erel 1994	No clinical endpoints reported
Fecht 1978	No randomization
Fosse 1987	No randomization
Giannaris 1997	No clinical endpoints reported
Gott 1998	No untreated control group
Gupta 1998	No clinical endpoints reported
Halonen 2008	Review article
Hill 1994	No clinical endpoints reported
Hill 1995a	No clinical endpoints reported
Hill 1995b	No clinical endpoints reported
Hoche 1995	No clinical endpoints reported
Hoche 1997	No clinical endpoints reported
Husedzinovic 1998	No clinical endpoints reported
Inaba 1994	No randomization reported
Jahangiri 2008	Review article
Janower 2007	Review article
Jansen 1991b	No clinical endpoints reported
Jorens 1993	No clinical endpoints reported
Juneja 2000	Unsufficient data in abstract (only publication about this study); no additional data received upon request
Karlstad 1993	No clinical endpoints reported
Kawamura 1995	No clinical endpoints reported

(*Continued*)

Kawamura 1999	No clinical endpoints reported
Kilger 2007	Review article
Kilickan 2008	No data regarding major clinical outcomes available
Kirsh 1979	Steroids in cardioplegic solution only
Kito 1980	No clinical endpoints reported
Kobayashi 1996	No clinical endpoints reported
Launo 1990	No cardiac surgical patient (general thoracic surgery)
Lee 2005	Administration only postoperatively (not prophylactic)
Levinsky 1979	Steroids in cardioplegic solution only
Loubser 1997	No clinical endpoints reported
Medonca-Filho 2004	Observational prospective study. It was listed two times in our database under names Medonca 2004 and Filho 2004
Ming 2001	No clinical endpoints reported
Miranda 1982	No clinical endpoints reported
Niazi 1979	Not randomized (consecutive patients)
Oh 2007	Comment on another study in letter to the editor. No randomized controlled trial
Ohe 1993	Not randomized
Raff 1987	No clinical endpoints reported
Ranucci 1994	No clinical endpoints reported
Santarpino 2009a	No untreated control group
Santarpino 2009b	No untreated control group
Schelling 2006	Review article
Schmartz 1996	No clinical endpoints reported
Tabardel 1996	No clinical endpoints reported

(*Continued*)

Teoh 1995	No data regarding major clinical outcomes available, unclear randomization procedure
Thompson 1980	No clinical endpoints reported
Thompson 1982	No clinical endpoints reported
Toledo-Pereyra 1980	Study in children
Turkoz 2000	No clinical endpoints reported
Us 2001	No clinical endpoints reported
Vallejo 1977	Study in children
Van Overveld 1994	No clinical endpoints reported
Vogelzang 2007	No control group
Wan 1997b	No clinical endpoints reported
Weis 2007	Review article
Whitlock 2005	Review (debate article)
Wu 2001	Not randomized
Yaeger 2005	No clinical endpoints reported
Yasser 2009	This study was listed two times in our database under names Yasser 2009 and Amr 2009. First author's name was Yasser Mohamed Amr. This study was included under name Amr 2009. And Yasser 2009 was excluded.
Yasuura 1977	No clinical endpoints reported

Compared to other recent meta-analyses (Ho 2009; Whitlock 2008), some discrepancies were present regarding study-inclusion; only these discrepancies were mentioned in this table. Many other eligible trials were aimed at intermediate endpoints only and in spite of several attempts to reach the authors, no information regarding major clinical endpoints could be gathered and all these studies were excluded.

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00490828

Methods	Randomized, placebo-controlled, blinded trial
Participants	92 high risk cardiac surgery patients
Interventions	hydrocortisone
Outcomes	Immunologic markers, health care related quality of life, PTSD one and a half year No
Notes	status: completed, but not yet published

Characteristics of ongoing studies *[ordered by study ID]*

DECS trial

Trial name or title	Dexamethasone for Cardiac Surgery trials
Methods	Multicentre, randomized, placebo-controlled, double blind trial
Participants	
Interventions	Dexamethasone
Outcomes	Occurrence of major complications at 30 days
Starting date	May 2006
Contact information	s.dieleman@umcutrecht.nl
Notes	sub-project DECS-PNAF (post-operative new-onset atrial fibrillation)

NCT00879931

Trial name or title	Influence of Corticoids on Renal Function in Cardiac Surgery
Methods	Randomized, Placebo-controlled double blind trial
Participants	Estimated enrolment: 80 patients
Interventions	Methylprednisolone
Outcomes	Renal dysfunction and renal failure postoperatively in cardiac surgery within 48 hours after cardiac surgery
Starting date	September 2010

NCT00879931 (*Continued*)

Contact information	Stefaan.Bouchez@Ugent.be
Notes	

SIRS trial

Trial name or title	Phase 3 study of perioperative steroids' effects on death or myocardial infarction in patients undergoing cardiac surgery requiring cardiopulmonary bypass
Methods	Randomized, placebo-controlled, double blind trial
Participants	Target sample size 10.000
Interventions	Methylprednisolon
Outcomes	Composite death or Myocardial infarction at 30 days
Starting date	June 2007
Contact information	Rwhitlock1@cogeco.ca
Notes	

STRESS trial

Trial name or title	Reduction of the cardiac proapoptotic stress response by dexamethasone in patients undergoing coronary artery bypass grafting
Methods	Randomized, placebo-controlled, single blinded trial
Participants	Target sample size: 96
Interventions	Dexamethasone
Outcomes	Expression of p38 in cultured cells and cardiac tissue
Starting date	December 2008, recruiting
Contact information	Dr. Christa Boer, VU Medical Center, Amsterdam, The Netherlands. C.Boer@vumc.nl
Notes	

DATA AND ANALYSES

Comparison 1. Primary outcome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality, including "no major complications"	17	2012	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.65, 1.92]
2 Cardiac complications, including "no major complications"	16	1778	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.57, 1.60]
3 Pulmonary complications, including "no major complications"	12	1076	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.49, 1.40]

Comparison 2. Secondary outcome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Atrial fibrillation	17	1389	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.46, 0.78]
2 Infections	15	1487	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.56, 1.31]
3 Gastro-intestinal bleeding	3	204	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.84 [0.40, 20.36]
4 Mechanical ventilation time (minutes)	23	1351	Mean Difference (IV, Fixed, 95% CI)	-1.81 [-11.46, 7.83]
5 ICU-stay (hours)	25	1215	Mean Difference (IV, Fixed, 95% CI)	-2.32 [-2.84, -1.81]
6 Hospital stay (days)	15	625	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.65, -0.15]
7 Renal failure	9	677	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.45, 2.19]
8 Re-thoracotomy	7	818	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.47, 2.65]
9 Re-intubation	3	178	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.12, 1.49]
10 Neurological complication (stroke)	10	1052	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.33, 1.48]
11 Vaso-active medication Y/N	17	1237	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.67, 1.23]
12 Bloodtransfusion Y/N	5	511	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.54, 1.39]
13 Number of bloodtransfusions	4	122	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.44, 0.06]

Comparison 3. Dose-dependant analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality, high dose	14	1386	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.54, 1.90]
2 Mortality, low dose	3	626	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [0.52, 4.14]
3 Cardiac complications, high dose	14	1243	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.51, 1.52]
4 Cardiac complications, low dose	2	535	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.39, 9.80]
5 Pulmonary complications, high dose	9	686	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.38, 1.31]
6 Pulmonary complications, low dose	3	390	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.46, 3.42]
7 Gastro-intestinal complications, high dose	3	204	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.84 [0.40, 20.36]
8 Infections, high dose	10	836	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.40, 1.62]
9 Infections, low dose	5	651	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.52, 1.52]
10 Atrial fibrillation, high dose	13	758	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.43, 0.83]
11 Atrial fibrillation, low dose	4	631	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.40, 0.94]

Comparison 4. sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality, trials before 1995	4	350	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.28 [0.65, 8.05]
2 Mortality, trials after 1995	13	1662	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.53, 1.73]
3 Cardiac complications, trials before 1995	4	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.43, 2.00]
4 Cardiac complications, trials after 1995	12	1418	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.48, 1.98]
5 Pulmonary complications, trials before 1995	2	246	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.14, 1.19]
6 Pulmonary complications, trials after 195	10	830	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.57, 1.89]

ADDITIONAL TABLES

Table 1. Glossary of abbreviations used in the tables

ASD	Atrial septum defect
CABG	Coronary artery bypass grafting
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
IABP	Intra aortic balloon pump
ICU	Intensive care unit
MPSS	Methylprednisolon sodium succinate

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 5, 2011

CONTRIBUTIONS OF AUTHORS

Drs Dieleman

Participated in writing and amending of the protocol. He will participate screening of search results, retrieving papers, data collection, analysis and interpretation, and in writing of the main text. Together with Drs Van Paassen, Drs Dieleman will be the guarantor of the review.

Drs van Paassen

Participated in writing and amending of the protocol. She will participate in screening of search results, retrieving papers, data collection, analysis and interpretation, and in writing of the main text. Together with Drs Dieleman, Drs Van Paassen will be the guarantor of the review.

Dr Van Dijk

Participated in the coordination and writing of the protocol. He has participated in screening of search results, and assisted in data collection, analysis and interpretation, and in writing of the main text.

Dr Arbous

Participated in amending of the protocol. She assisted in analysis and interpretation of the data and participated in writing of the main text.

Prof Dr Kalkman

Participated in the coordination, writing and amending of the protocol. He assisted in data collection, analysis and interpretation, and coordinated writing of the main text.

Prof Dr Vandenbroucke

Participated in amending the protocol. He assisted in analysis and interpretation of data, and coordinated writing of the main text.

Dr Van der Heijden

Participated in the coordination, writing and amending of the protocol. He assisted in data collection, analysis and interpretation, and in writing of the main text.

Dr Dekkers

Participated in amending the protocol. He assisted in data collection, analysis and interpretation, and in writing of the main text.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Perioperative Care and Emergency Medicine, University Medical Center Utrecht, Netherlands.
- Department of Intensive Care Medicine, University Medical Center, Leiden, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Many of the selected studies reported clinical outcomes sparsely. Most often, the reported clinical outcomes were only secondary endpoints in studies looking primarily at intermediate endpoints like, for example, cytokine levels or parameters of mechanical ventilation. As a result, we have not been able to extract data for every outcome listed in the 'Objectives' section. This has lead to a discrepancy between the outcomes that were described in the protocol of this review and the outcomes that we have been able to analyse. More specifically, this applies to the secondary outcomes "Quality of life" and "Cost effectiveness".

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects; *therapeutic use]; Anti-Inflammatory Agents [adverse effects; *therapeutic use]; Atrial Fibrillation [prevention & control]; Cardiac Surgical Procedures [methods]; Cardiopulmonary Bypass [*adverse effects; mortality]; Gastrointestinal Hemorrhage [chemically induced]; Heart Diseases [etiology; surgery]; Lung Diseases [etiology]; Randomized Controlled Trials as Topic; Systemic Inflammatory Response Syndrome [*prevention & control]

MeSH check words

Adult; Humans