Corticosteroids for cardiac surgery: a continuing controversy

Jan M. Dieleman

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PhD thesis, Utrecht University, The Netherlands

Research in this thesis was financially supported by grants from the Netherlands Organization for Health Research and Development (ZonMw) and from the Dutch Heart Foundation.

ISBN: 978-9-46-228683-2

Cover design by Proefschriftmaken.nl II Uitgeverij BOXPress
Printed & Lay Out by Proefschriftmaken.nl II Uitgeverij BOXPress
Published by Uitgeverij BOXPress, 's-Hertogenbosch

Corticosteroids for cardiac surgery: a continuing controversy

Corticosteroïden in de hartchirurgie: een aanhoudende controverse

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van de Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
dinsdag 29 september 2015 des morgens te 10.30 uur

door

Jan Marinus Dieleman
geboren op 1 november 1977 te Terneuzen

Promotoren: Prof.dr. D. van Dijk
Prof.dr. C.J. Kalkman
Prof.dr. K.G.M. Moons

The research described in this thesis was supported by a grant of the Dutch Heart Foundation (DHF-2007B125)

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Chapter 1

General introduction

Open heart surgery is among the most commonly performed surgical procedures.[1] For most patients these expensive, high volume procedures lead to significant improvements in symptoms of acquired cardiac disease and quality of life. However, despite important improvements in surgical techniques, anaesthesia management, and postoperative care, cardiac surgery is still associated with a substantial risk of major adverse events, including mortality, stroke, myocardial infarction and postoperative organ failure.[1-3] These perioperative adverse events contribute considerably to postoperative disability.[4]

The perioperative inflammatory response associated with cardiac surgery likely plays a role in the development of several of these adverse outcomes, either as the primary triggering mechanism or an important contributing factor.[5,6] Cardiopulmonary bypass induces a complex acute phase response, characterized by both cell and protein activation, which may be further intensified by the surgical trauma, ischemia-reperfusion injury, and endotoxaemia. As a result, a postoperative systemic inflammatory response syndrome (SIRS) develops in almost every cardiac surgical patient, although the severity varies substantially between individuals.[7] SIRS following cardiac surgery is typically characterized by fever and leucocytosis, combined with variable degrees of haemodynamic instability, respiratory compromise and organ dysfunction. More severe SIRS increases the risk of perioperative multisystem organ failure and mortality.[7,8]

Given the undesirable effects of excessive systemic inflammation, multiple strategies have been developed that aim to prevent, or at least attenuate, the inflammatory activation associated with cardiac surgery.[9] Improvements in surgical techniques, myocardial preservation and cardiopulmonary bypass have reduced the number and the intensity of triggers that drive the perioperative immune response.[10-12] As a result, these technical improvements have reduced the inflammatory response to a more manageable level – a response that does little harm in the majority of cardiac surgery patients, yet is intense enough to aid in the recovery of the trauma associated with the cardiac surgical procedure. However, in a considerable number of patients, moderate to severe SIRS still affects postoperative recovery.

In order to attenuate the inflammatory response, prophylactic pharmacologic treatment options have often been included in perioperative anaesthetic regimens. For many decades, corticosteroids have been routinely used for this purpose on a large scale. Besides steroids, other strategies have also been used clinically[13], while some more experimental therapeutics, such as the monoclonal complement inhibitor pexelizumab[14,15], have only been tested in late-phase clinical trials. Corticosteroids are low-cost and potent anti-inflammatory agents that possess multi-inhibitory effects on numerous components of the inflammatory response. Together with the extensive experience with corticosteroids in clinical practice and their availability for a broad range of indications, corticosteroids represent an appealing option for both

prophylaxis and treatment in this scenario. As such, high-dose corticosteroids are still routinely used during cardiac surgery in many centres around the world.

Multiple studies, both non-randomised and randomised, have assessed the effects of corticosteroids on a large number of inflammatory mediators, as well as on measures of organ function in the perioperative period of cardiac surgery. The majority of these investigations have shown that corticosteroids are able to reliably attenuate the activation of the complement pathways associated with cardiopulmonary bypass[16,17], and as such alter the balance between pro- and anti-inflammatory mediators toward a more anti-inflammatory state.[16,18] Corticosteroid administration was also consistently associated with more severe postoperative hyperglycaemia. However, the results of studies on the effects of corticosteroids on clinical measures of organ function have been much more variable. While in some studies corticosteroids improved pulmonary gas exchange, lung compliance, cardiac index and fluid balance, other studies have demonstrated no or even opposite effects.[16]

The effects of corticosteroids on major clinical outcomes have been studied in multiple small studies over the last decades, usually as secondary endpoints in mechanistic studies with a relatively small number of patients.[19,20] Also, the potential adverse effects of high-dose steroids, such as increased risk of infection and gastrointestinal complications, had only been reported incidentally. Appropriately sized studies on important clinical outcomes and safety aspects, however, were lacking when the projects leading to this thesis were initiated around 2005. As a result of this evidence gap, corticosteroid administration during cardiac surgery has remained controversial. In many hospitals in Europe, Asia and New Zealand it is part of routine care, whereas steroid use is far less common in North American cardiac surgical centres.[18]

The overall aim of the research projects in this thesis is to provide a significant contribution to the body of evidence around the clinical effects of routine corticosteroid prophylaxis in cardiac surgery. Chapter 2 includes the results of a Cochrane systematic review of the effects of corticosteroids in cardiac surgery on clinical outcomes. In Chapter 3, the primary results of the DExamethasone for Cardiac Surgery (DECS) study are presented. Chapter 4 represents the results of a long-term follow-up, and also includes a formal economic analysis of the trial. Chapters, 5 and 6 contain the results of subsequent focussed sub studies on hemodynamic effects and on re-interventions, respectively. Chapter 7 represents an explanatory study into the effects of patient age on the early C-reactive protein response following cardiac surgery. Finally, Chapter 8 includes the results of a separate large study that focuses on clinical determinants of postoperative clinical SIRS. Multiple other sub studies of the DECS study that could not be part of this thesis, are listed in the List of publications.

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Chapter 2

Prophylactic corticosteroids for cardiopulmonary bypass in adults

Jan M. Dieleman[1], Judith van Paassen[2], Diederik van Dijk[1], M. Sesmu Arbous[2], Cor J. Kalkman[1], Jan P. Vandenbroucke[2], Geert J. van der Heijden[1], Olaf M. Dekkers[2]

[1] University Medical Center Utrecht, The Netherlands
[2] Leiden University Medical Center, The Netherlands

Published in:
The Cochrane Database of Systematic Reviews 2011; 5

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. Databases 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 endpoints.

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.

Background

Description of the condition

Cardiovascular diseases have a high incidence in western society, affecting one in every three persons[1] and are currently the leading cause of death, with coronary heart disease being responsible for around 20% of annual deaths in the United States.[2] Millions of cardiac interventions are performed every year worldwide.[2] Currently, 30-40% of these procedures comprise cardiac surgery, mainly for revascularization or treatment of valve defects.[2]

The development of cardiopulmonary bypass in the early 1950's has been a breakthrough in cardiac surgery. [3,4] 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.[5] Patients with coronary vessel or heart valve disease could from then on be treated with an effective relief of symptoms and prolonged life expectancy. [6-9] However, extracorporeal circulation often induces a systemic inflammatory response syndrome, a sepsis like condition.[10-14] This response involves complement activation, along with activation of platelets, neutrophils, monocytes, and macrophages.[11,15] As a result, coagulation and fibrinolytic cascades are initiated.[12,15,16] The ensuing systemic inflammatory response syndrome is associated with fever, impaired alveolar gas exchange, vasodilatation, myocardial stunning, renal insufficiency and even multi-organ dysfunction.[10,17-19] 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.[20-23] 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.[24-29]

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.[23,30] 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.[31] The guidelines of the American Heart Association advocate liberal prophylactic use[30,32], and frequently, one or two doses of dexamethasone or methylprednisolone are injected intravenously before commencing cardiopulmonary bypass.[11,23,33] Corticosteroids are potent anti-inflammatory agents that possess multi-inhibitory effects on numerous components of the inflammatory response.[11,14,34]

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[11,27,35], which is associated with increased morbidity and mortality.[36] 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[11,35], 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.[37-39] Some of these complications could lead to prolonged intensive care stay and increased morbidity and mortality.[11,36]

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[40], 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.[11]

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 endpoints like serum markers and pulmonary water content, demonstrating a significant suppression of inflammation.[14,27,28,35,41-62] Of the trials which evaluated clinical end-points after corticosteroid administration, the results were unequivocal.[15,24,25,28,37,38,63-75]

Two meta-analyses have been conducted recently in the last three years.[21,76] 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[76] 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.[77] 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[77] was designated by Whitlock 2008[76] 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[76] 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[21] 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[78] 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.[79]

A new meta-analysis on corticosteroids in adult cardiac surgery could overcome the outlined limitations. Firstly, the study from Vallejo 1977[77] 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 instead 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[80,81] 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 oedema 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.[82] 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, echocardiographic changes, disproportionate elevation of troponines);
- pulmonary complications (including pulmonary oedema 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. The authors were not blinded to authors' names or journal names.The flow of studies was reported according the PRISMA guidelines.[82]

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. 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 oedema 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 according to the Cochrane Handbook for Systematic Reviews of Interventions[83]:

- 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.[84]

Unit of analysis issues

The odds were calculated per treatment group for all binary out- comes. 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.[85,86] 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[86], 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.[87] 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.[86] 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.[88]

Results

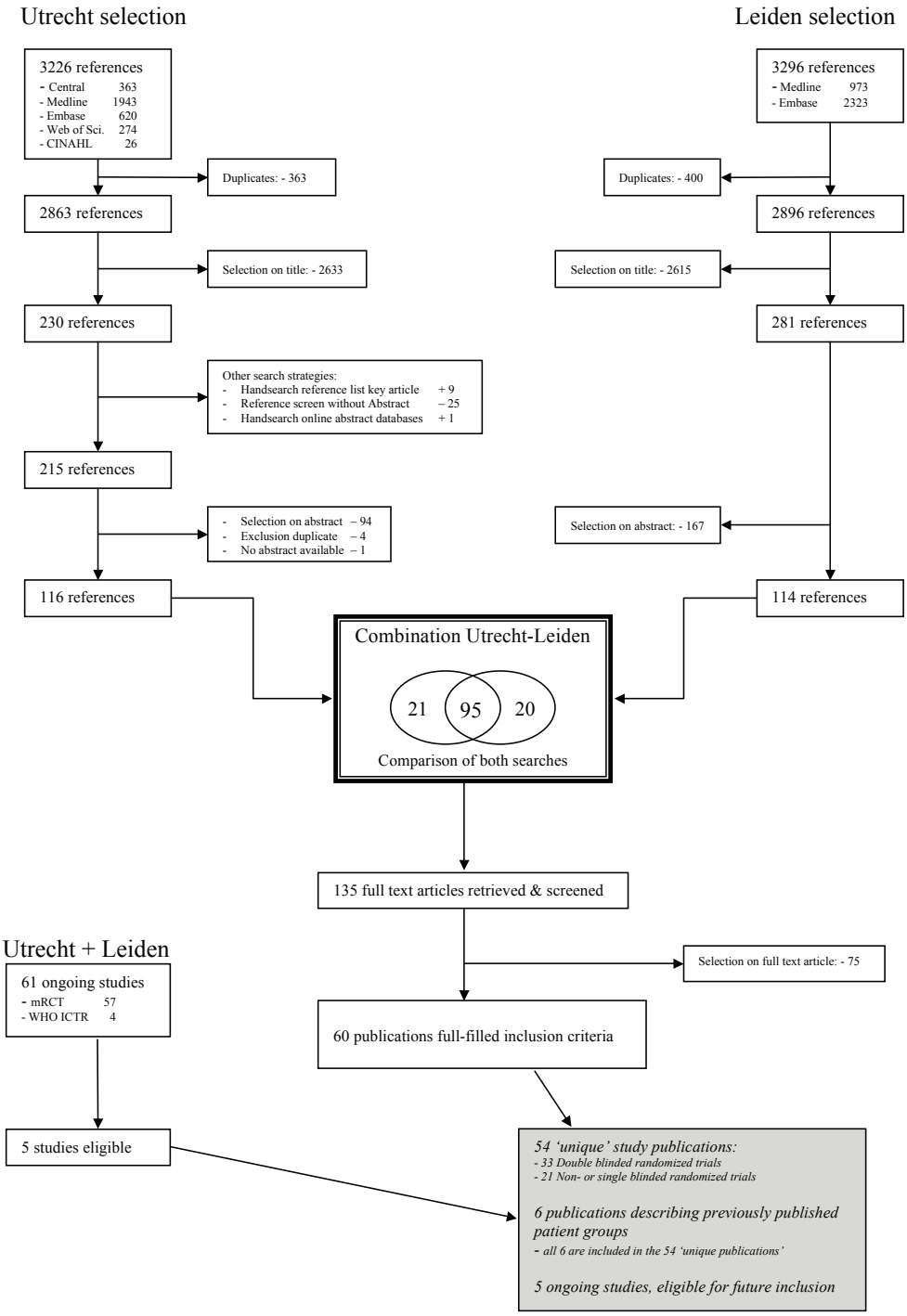
Description of studies

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

Figure 1: Study selection chart



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.

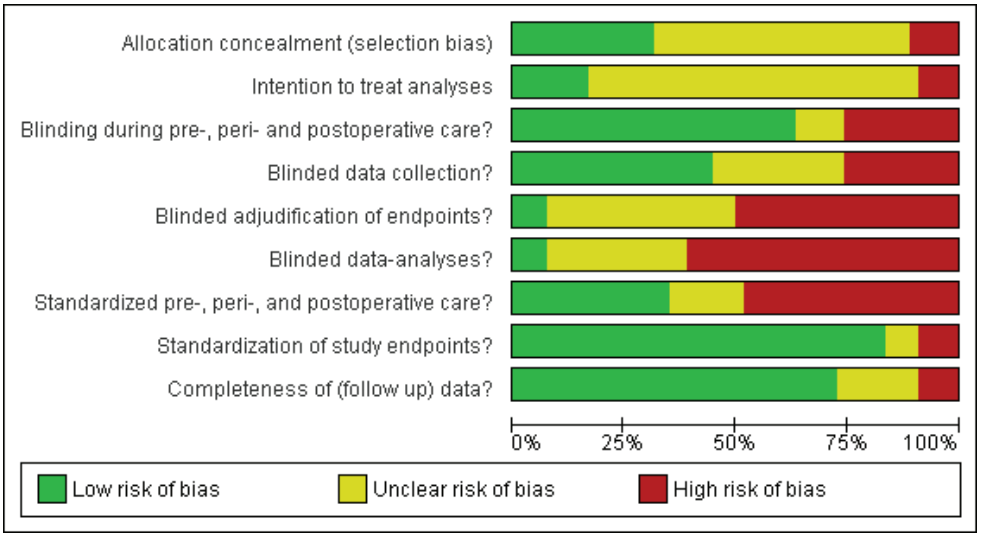
Searching the clinical trials registers identified five relevant ongoing studies (Characteristics of ongoing studies).Of the included studies, 36/54 were published in the last 10 years (2000 or later), 11/54 in the 1990s, 4/54 in the 1980s and 3/54 in the 1970s. The majority of studies were conducted 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.[25,49,89-91]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). 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 2. 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

Figure 2: Risk of bias graph

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



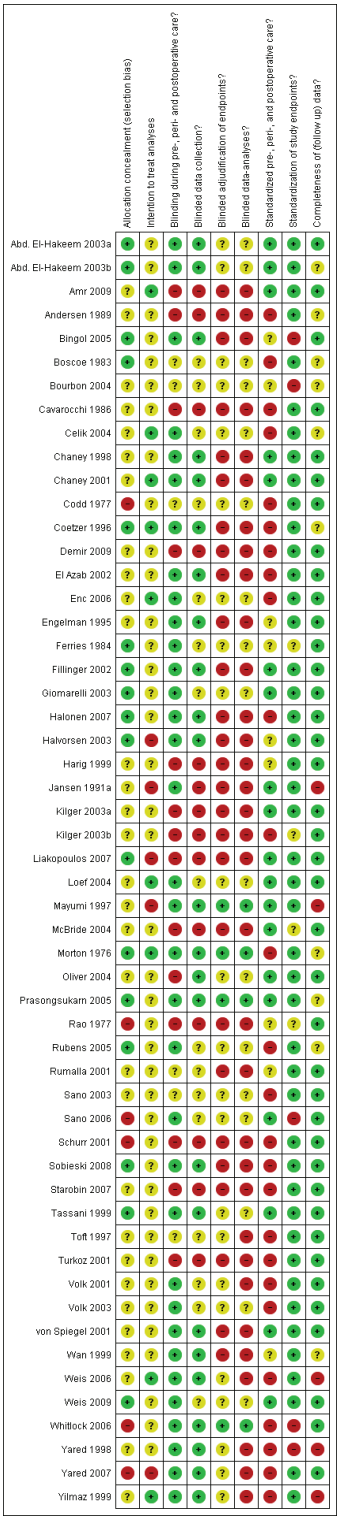


Figure 3: Risk of bias summary

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

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.

Allocation

Adequate concealment of allocation was present in only 31% of the trials (Figure 3). Out of all the fifty-five randomised trials, only seventeen studies reported concealment of allocation. In six trials concealment of allocation was inadequate, and in the remainder of twenty-one studies randomisation 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 postoperative care, data-collection, and adjudication to endpoints. Besides blinded care and data-collection, only four studies carried out triple blinding and blinded data-analyses. [35,69,91,92]

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). Most primary endpoints were standardized and complete. In ten studies patients were excluded from analyses when major complications occurred.[35,37,39,62,74,75,90,93-95] 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 (Table 1): Summary of findings for primary and secondary endpoints. OR with fixed and random effects model and with opposite reciprocal correction; Summary of findings (Table 1) and Analyses 1.1 – 1.3 (Figure 4).

Mortality, cardiac and pulmonary complications

Only five studies reported all three elements of a composite endpoint: mortality, cardiac complications and pulmonary complications (Appendix 3).[72,91,96-98] 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 per- form a pooled analysis of the composite endpoint.

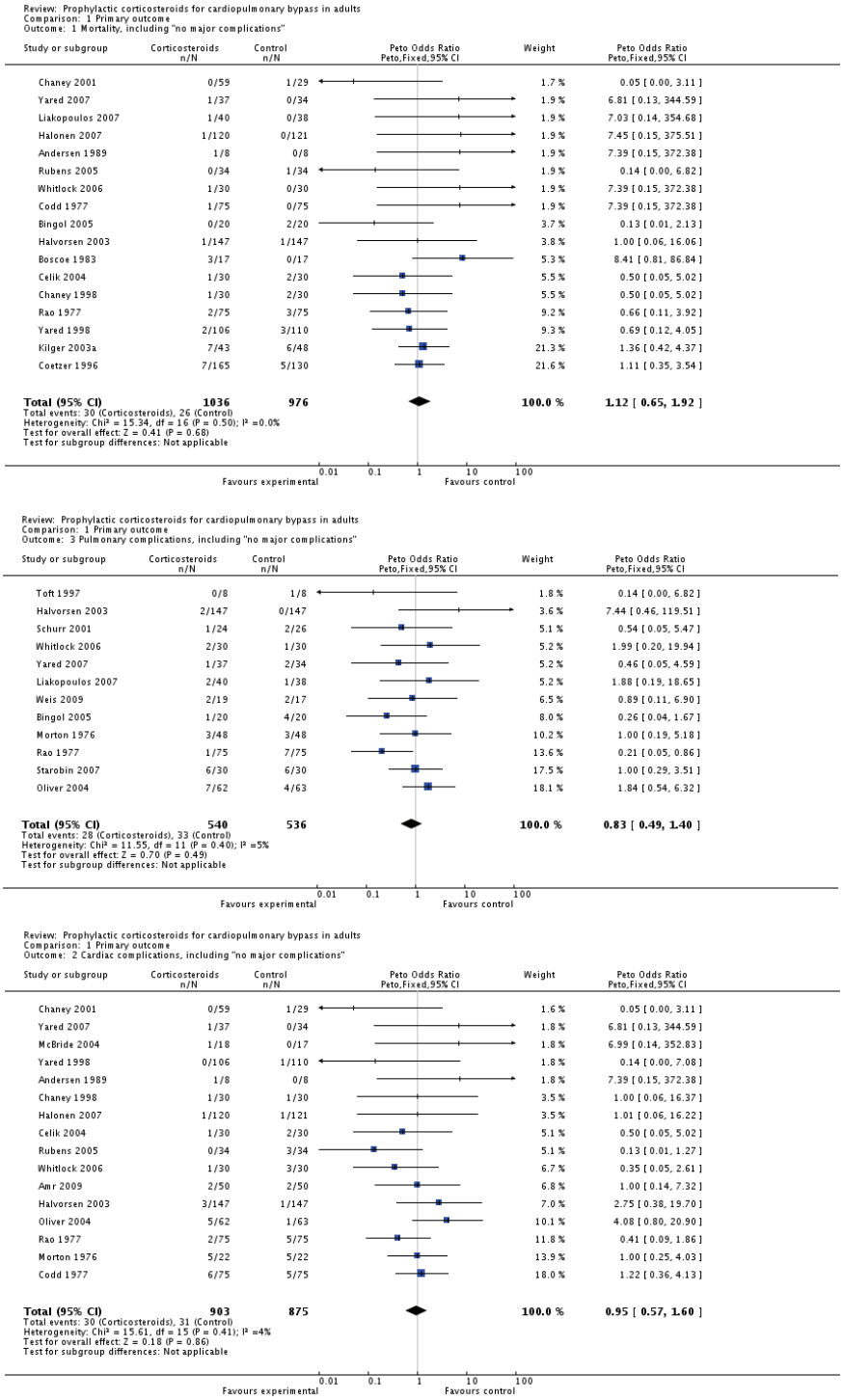
Separate analyses of mortality, myocardial complications and pulmonary complications were performed using the Peto odds ratio. For these separate analyses, all fifty-four studies were taken into account when at least data regarding one of the primary endpoints were available. Data on the number of included 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 (Table 1). The use of corticosteroids in coronary bypass surgery did not reduce mortality (odds ratio = 1.12, 95% CI 0.65

Table 1

Comparison outcome	Number of studies	Partici-pants	Peto OR (Fixed) [95% CI]	Hetero-geneity (I^2%)	M-H OR (random) [95% CI]	Hetero-geneity (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	17	1237	0.91 [0.67, 1.23]	49	0.92 [0.58, 1.45]	39
Bloodtransfusion	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 blood transfusions	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 [-100.3, 6.25]	93
ICU stay (hours)	25	1215	-2.32 [-2.84, -1.81]	87	-5.47 [-8.13, -2.82]	87
Hospital stay (d)	15	635	-0.59 [-0.84, -0.34]	96	-0.97 [-2.42, 0.47]	96

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

Figure 4: Analysis 1: Main comparisons



to 1.92; 17 studies, 2012 patients, Figure 4, Analysis 1.1), nor cardiac complications (odds ratio = 0.95, 95% CI 0.57 to 1.60; 16 studies, 1778 patients, Figure 4, Analysis 1.2), nor pulmonary complications (odds ratio = 0.83, 95% 0.49 to 1.49); 12 studies, 1076 patients, Figure 4, Analysis 1.3) significantly.

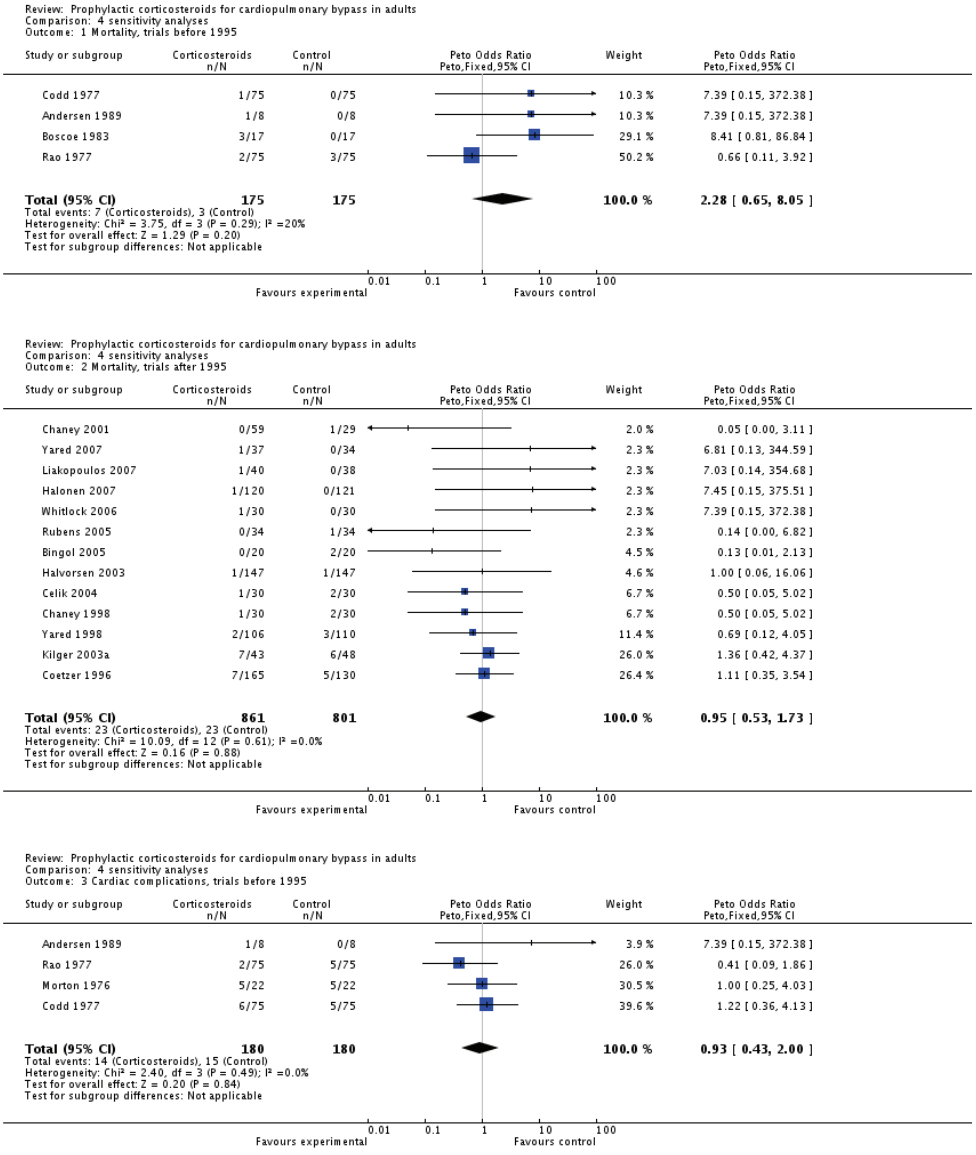
The I^2 for the primary endpoints were 0% (mortality), 4% (cardiac complications) and 5% (pulmonary complications). Comparing the older studies (published before 1995) with the recent ones (published after 1995) in stratified sensitivity analyses (Figure 5; Analysis 4.1 - 4.6) did not reveal differences 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 6, Figure 7, Figure 8, 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; Table 1). The use of a continuity correction according to the reciprocal of the opposite treatment arm size did also show similar results (data not shown).

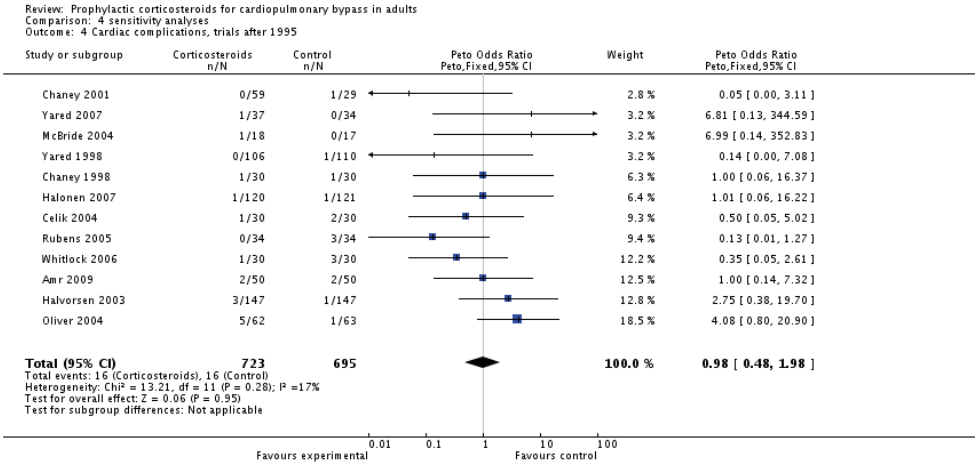
Secondary outcomes

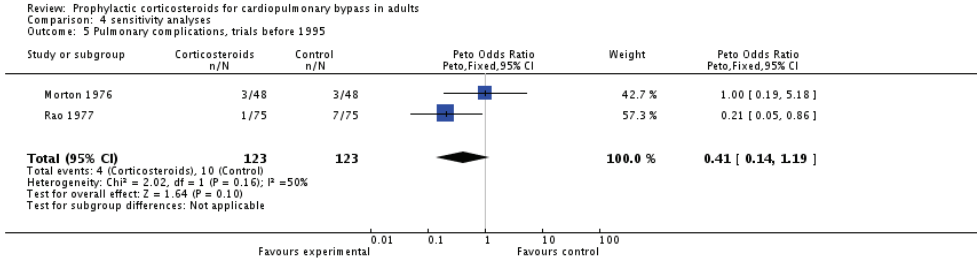
We analysed potential complications of the use of corticosteroids: gastro-intestinal ulceration or bleeding and (wound) infections. Also, other outcomes that were reported in two or more studies were analysed, including some outcomes that were not planned for analysis in the review protocol. For all 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.[15,26-28,75,94,98,99] Two studies mentioned the insulin dose necessary to maintain “normal” glucose levels.[100,101] Finally, in fourteen studies, glucose levels after corticosteroid administration were reported. In four of these studies quantitative data were shown[27,39,75,99] while in the other ten studies only qualitative data were available (“higher levels or no significantly different levels”).[24,25,28,35,45,53,71,96,97] Overall, sixteen out of 21 studies reported either more often insulin therapy or higher glucose levels in the corticosteroids group.[15,24,26,27,35,39,71,75,93,94,98-101] The remaining five studies could not show any difference in insulin therapy or glucose levels.[25,28,45,96,97] Due to the heterogeneity of the available data, no further analyses could be performed for the association between glucocorticoids 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,

Figure 5: Stratified sensitivity analyses (Analysis 4)




Review: Prophylactic corticosteroids for cardiopulmonary bypass in adults
Comparison: 4 sensitivity analyses
Outcome: 4 Cardiac complications, trials after 1995
Study or subgroup
Corticosteroids n/N
Control n/N
Peto Odds Ratio Peto,Fixed,95% CI
Weight
Peto Odds Ratio Peto,Fixed,95% CI
Chaney 2001 0/59 1/29 2.8 % 0.05 [0.00, 3.11]
Yared 2007 1/37 0/34 3.2 % 6.81 [0.13, 344.59]
McBride 2004 1/18 0/17 3.2 % 6.99 [0.14, 352.83]
Yared 1998 0/106 1/110 3.2 % 0.14 [0.00, 7.08]
Chaney 1998 1/30 1/30 6.3 % 1.00 [0.06, 16.37]
Halonen 2007 1/120 1/121 6.4 % 1.01 [0.06, 16.22]
Celik 2004 1/30 2/30 9.3 % 0.50 [0.05, 5.02]
Rubens 2005 0/34 3/34 9.4 % 0.13 [0.01, 1.27]
Whitlock 2006 1/30 3/30 12.2 % 0.35 [0.05, 2.61]
Amr 2009 2/50 2/50 12.5 % 1.00 [0.14, 7.32]
Halvorsen 2003 3/147 1/147 12.8 % 2.75 [0.38, 19.70]
Oliver 2004 5/62 1/63 18.5 % 4.08 [0.80, 20.90]
Total (95% CI) 723 695 100.0 % 0.98 [0.48, 1.98]
Total events: 16 (Corticosteroids), 16 (Control)
Heterogeneity: Chi² = 13.21, df = 11 (P = 0.28); I² =17%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control


Review: Prophylactic corticosteroids for cardiopulmonary bypass in adults
Comparison: 4 sensitivity analyses
Outcome: 5 Pulmonary complications, trials before 1995
Study or subgroup
Corticosteroids n/N
Control n/N
Peto Odds Ratio Peto,Fixed,95% CI
Weight
Peto Odds Ratio Peto,Fixed,95% CI
Morton 1976 3/48 3/48 42.7 % 1.00 [0.19, 5.18]
Rao 1977 1/75 7/75 57.3 % 0.21 [0.05, 0.86]
Total (95% CI) 123 123 100.0 % 0.41 [0.14, 1.19]
Total events: 4 (Corticosteroids), 10 (Control)
Heterogeneity: Chi² = 2.02, df = 1 (P = 0.16); I² =50%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control

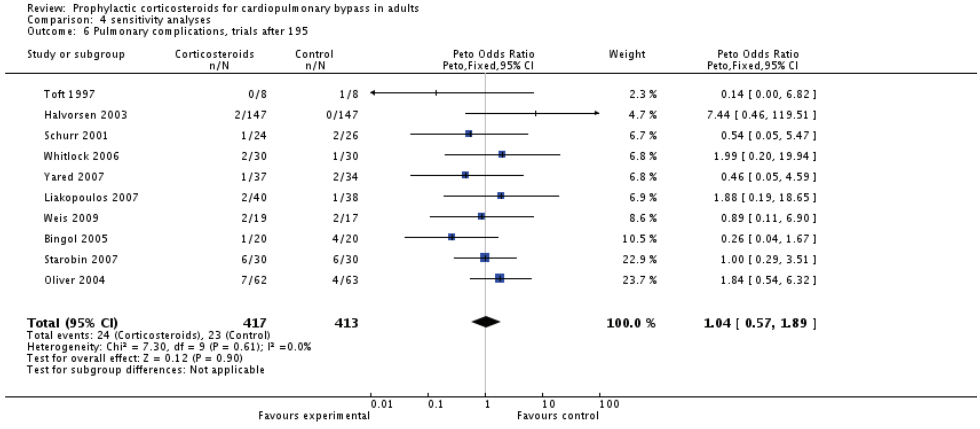

Review: Prophylactic corticosteroids for cardiopulmonary bypass in adults
Comparison: 4 sensitivity analyses
Outcome: 6 Pulmonary complications, trials after 195
Study or subgroup
Corticosteroids n/N
Control n/N
Peto Odds Ratio Peto,Fixed,95% CI
Weight
Peto Odds Ratio Peto,Fixed,95% CI
Toft 1997 0/8 1/8 2.3 % 0.14 [0.00, 6.82]
Halvorsen 2003 2/147 0/147 4.7 % 7.44 [0.46, 119.51]
Schurr 2001 1/24 2/26 6.7 % 0.54 [0.05, 5.47]
Whitlock 2006 2/30 1/30 6.8 % 1.99 [0.20, 19.94]
Yared 2007 1/37 2/34 6.8 % 0.46 [0.05, 4.59]
Liakopoulos 2007 2/40 1/38 6.9 % 1.88 [0.19, 18.65]
Weis 2009 2/19 2/17 8.6 % 0.89 [0.11, 6.90]
Bingol 2005 1/20 4/20 10.5 % 0.26 [0.04, 1.67]
Starobin 2007 6/30 6/30 22.9 % 1.00 [0.29, 3.51]
Oliver 2004 7/62 4/63 23.7 % 1.84 [0.54, 6.32]
Total (95% CI) 417 413 100.0 % 1.04 [0.57, 1.89]
Total events: 24 (Corticosteroids), 23 (Control)
Heterogeneity: Chi² = 7.30, df = 9 (P = 0.61); I² =0.0%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control

Figure 6: Funnel plot of mortality

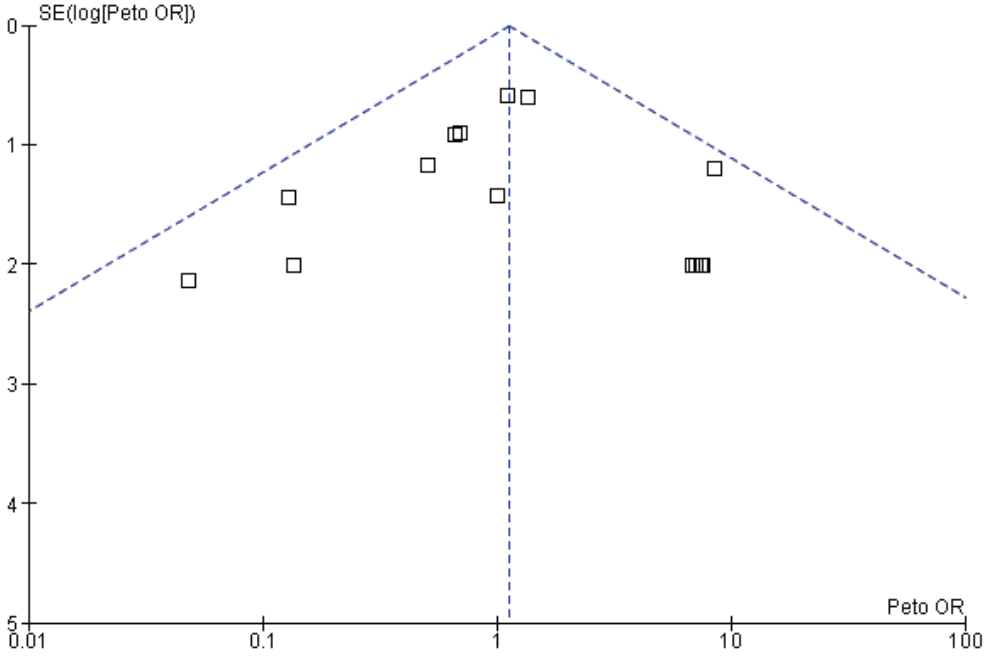


Figure 7: Funnel plot of cardiac complications

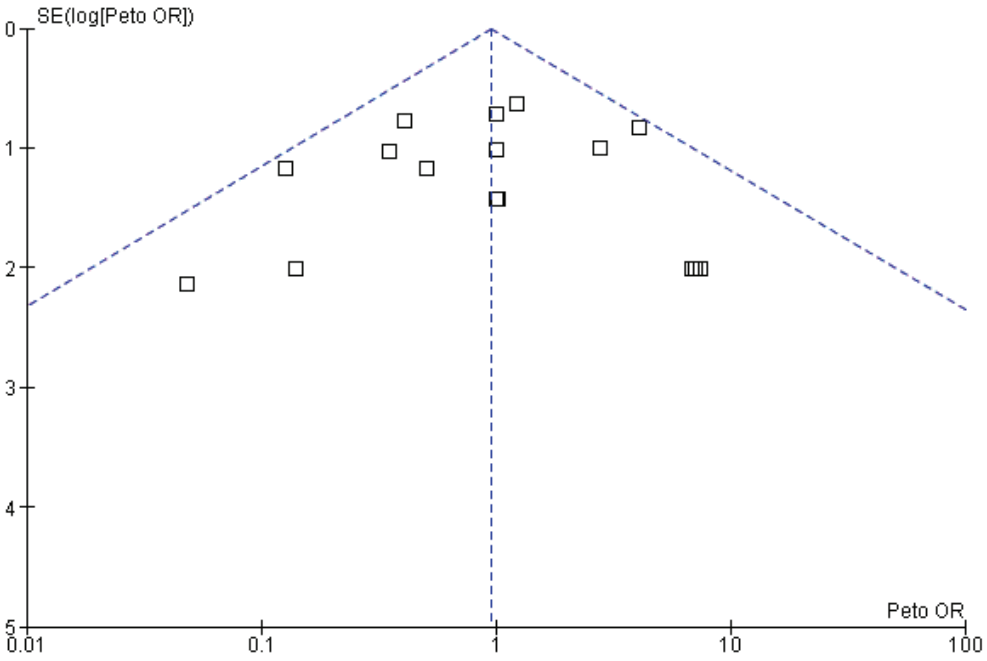
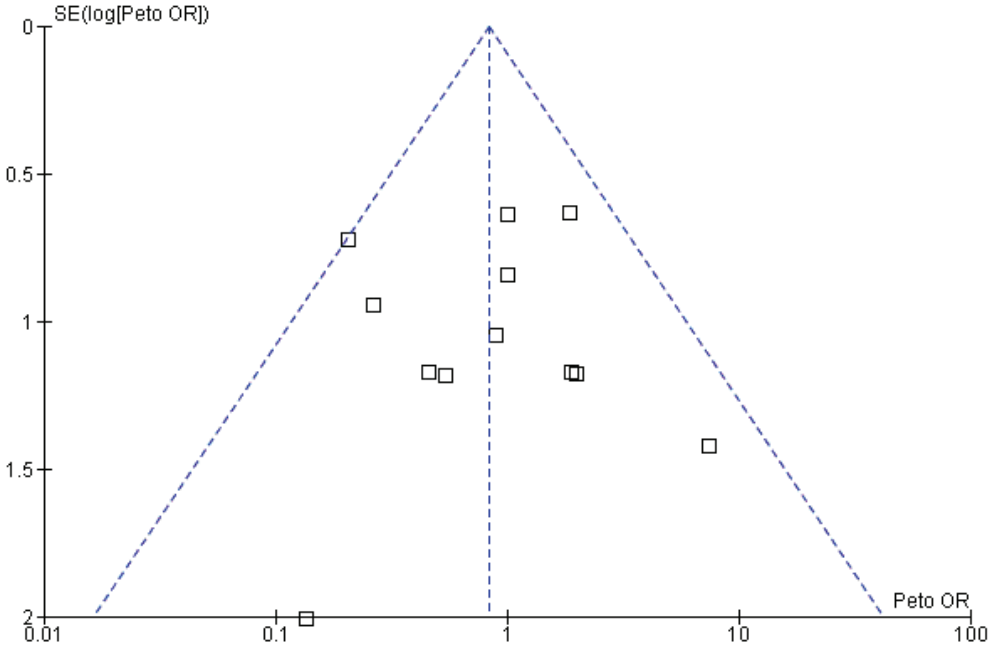


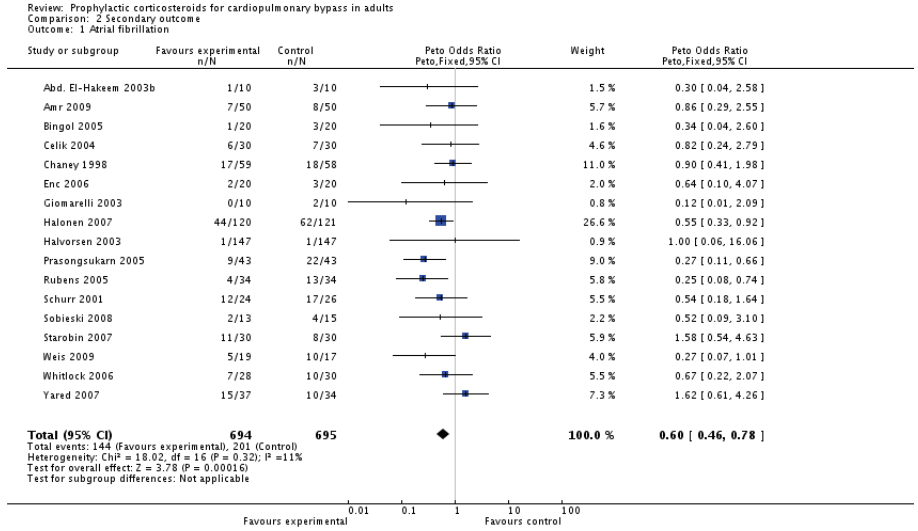
Figure 8: Funnel plot of pulmonary complications

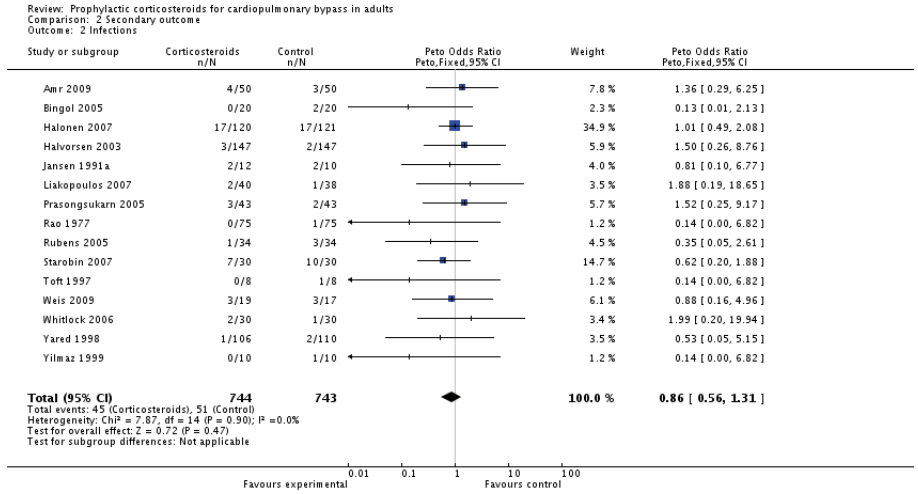


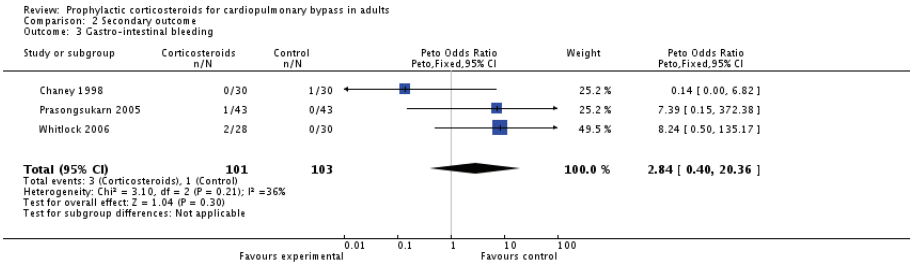
explicitly reported on gastrointestinal complications (both bleeding and ulceration). The odds ratio was 2.84 (95% CI 0.40 to 20.36, Figure 9, Analysis 2.3).

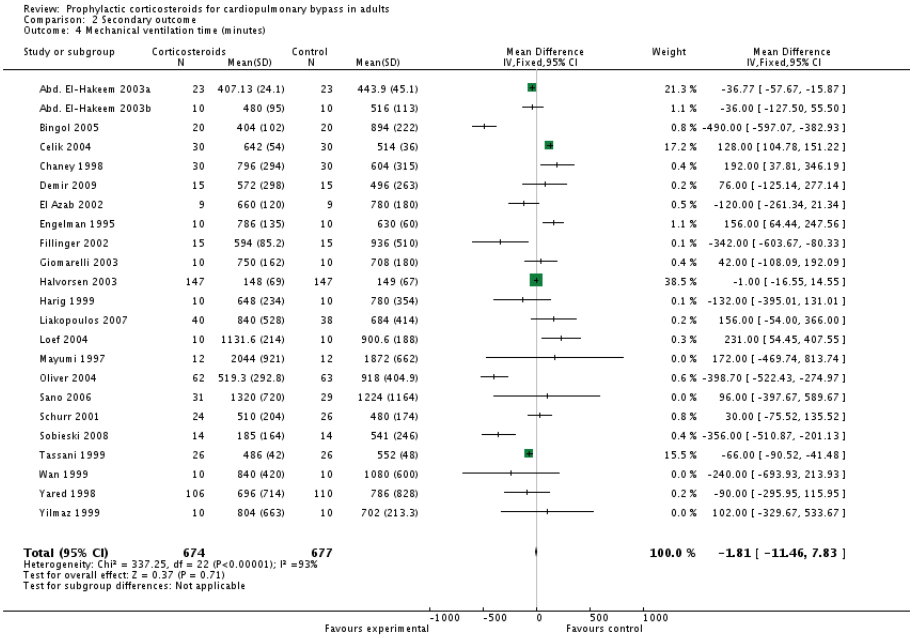
Moreover, the incidence of atrial fibrillation was reduced in the corticosteroids group (odds ratio 0.60, 95% CI 0.46 to 0.78, 17 studies, 1389 patients, Figure 9, Analysis 2.1). The length of intensive care stay was slightly shorter in the corticosteroids group (2.32 hours, 95 % CI -2.84 to -1.81; 25 studies, 1215 patients, Figure 9, 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, Figure 9, Analysis 2.2). Time to extubation (hours) (Odds ratio -1.81, 95% CI -11.46 to 7.83; 23 studies, 1351 patients, Figure 9, Analysis 2.4). Length of hospital stay (days) (Odds ratio -0.40, 95% CI -0.65 to -0.15; 15 studies, 625 patients, Figure 9, Analysis 2.6). Renal failure (Odds ratio1.00, 95% CI 0.45 to 2.19; 9 studies, 677 patients, Figure 9, Analysis 2.7). Re-thoracotomy [Odds ratio 1.12, 95% CI 0.47 to 2.65; 7 studies, 818 patients, Figure 9, Analysis 2.8). Neurological complications (Odds ratio 0.7, 95% CI 0.33 to 1.48; 10 studies, 1052 patients, Figure 9, Analysis 2.10). Vasoactive medication (Odds ratio 0.91, 95% CI 0.67 to 1.23; 17 studies, 1237 patients, Figure 9, Analysis 2.11). Blood transfusion (yes/no) (Odds ratio 0.87, 95% CI 0.54 to 1.39; 5 studies, 511 patients, Figure 9, Analysis 2.12]).

Figure 9: Analysis 2: Secondary outcomes









Analysis according to corticosteroid dose

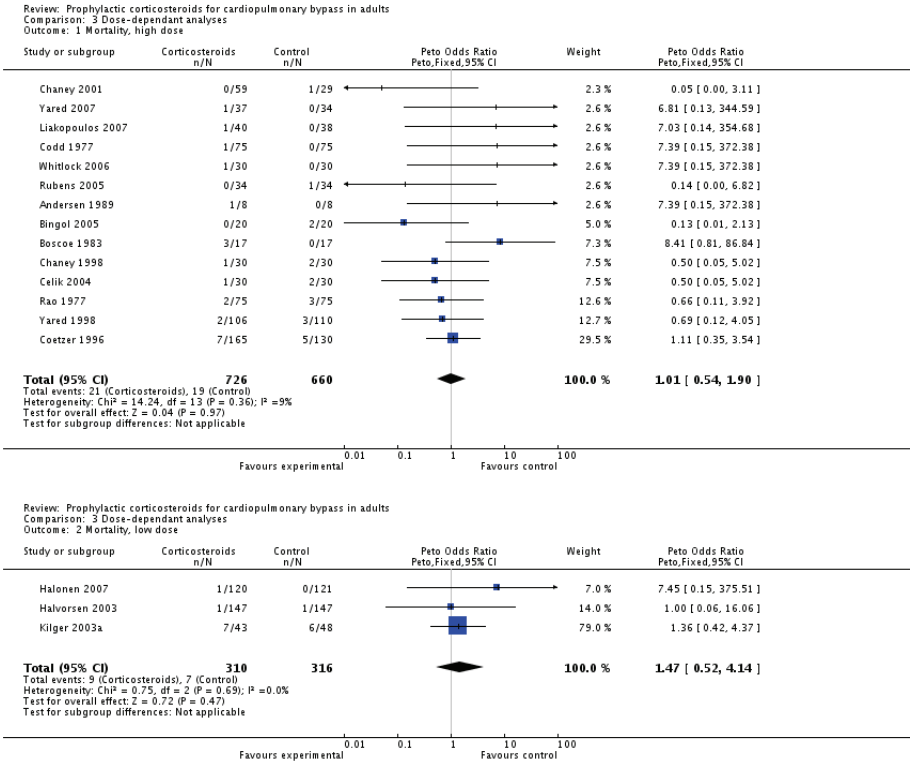
We categorized the included studies into high-dose (total administered dose >1000 mg hydrocortisone equivalents) and low-dose (total administered dose (<1000 mg hydrocortisone equivalents) studies and performed a stratified meta-analysis (Summary of findings 2, Table 2). More detailed stratification and/or dose-response analyses were limited due to scarcity of data. In only nine studies, a hydrocortisone equivalent of 1000 mg or lower was administered.[25,51,90,95,97,102-104] 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, Table 2). The only one exception was atrial fibrillation, which was reduced in both the low- and high-dose groups.

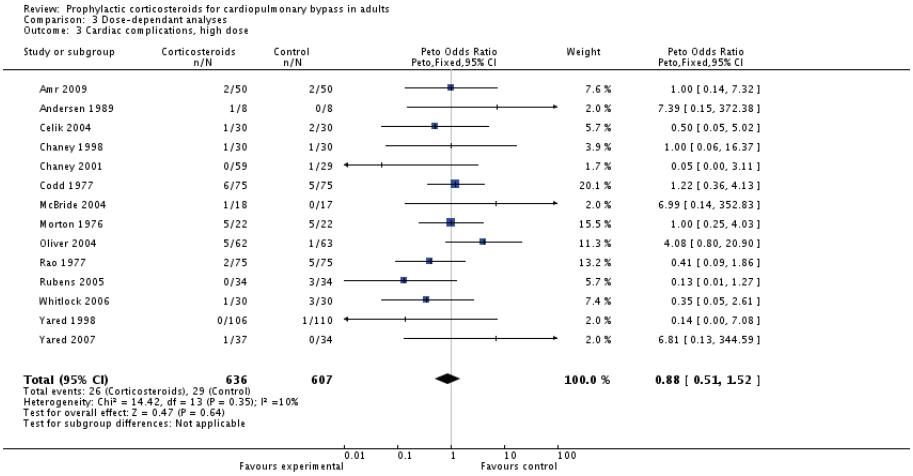
Table 2

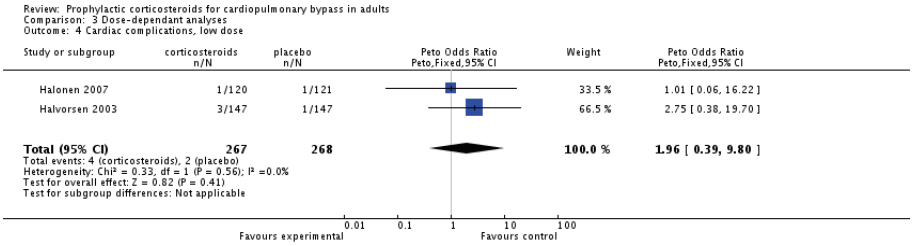
Comparison outcome	Corticosteroid dose	Studies	Participants	Peto OR (fixed) [95% CI]
Mortality	Low	8	726	1.96 [0.20, 18.85]
	High	41	2423	1.01 [0.51, 1.79]
Cardiac complications	Low	2	535	1.96 [0.39, 9.80]
	High	24	1568	0.88 [0.51, 1.52]
Pulmonary complications	Low	3	390	1.26 [0.46, 3.42]
	High	18	950	0.71 [0.38, 1.31]

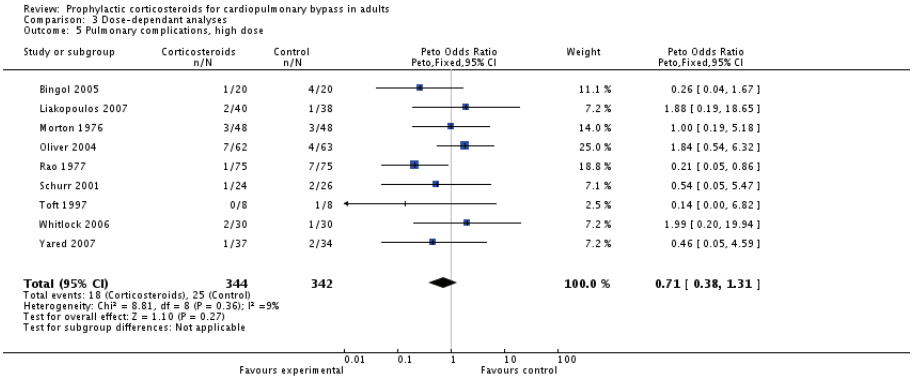
Low dose: ≤1000 mg Hydrocortisone equivalent; High dose: > 1000 mg hydrocortisone equivalent. OR: Odds ratio, CI: Confidence interval

Figure 10: Dose dependent analyses (Analysis 3)




Review: Prophylactic corticosteroids for cardiopulmonary bypass in adults
Comparison: 3 Dose-dependant analyses
Outcome: 3 Cardiac complications, high dose
Study or subgroup
Corticosteroids n/N
Control n/N
Peto Odds Ratio Peto,Fixed,95% CI
Weight
Peto Odds Ratio Peto,Fixed,95% CI
Amr 2009 2/50 2/50 7.6 % 1.00 [0.14, 7.32]
Andersen 1989 1/8 0/8 2.0 % 7.39 [0.15, 372.38]
Celik 2004 1/30 2/30 5.7 % 0.50 [0.05, 5.02]
Chaney 1998 1/30 1/30 3.9 % 1.00 [0.06, 16.37]
Chaney 2001 0/59 1/29 1.7 % 0.05 [0.00, 3.11]
Codd 1977 6/75 5/75 20.1 % 1.22 [0.36, 4.13]
McBride 2004 1/18 0/17 2.0 % 6.99 [0.14, 352.83]
Morton 1976 5/22 5/22 15.5 % 1.00 [0.25, 4.03]
Oliver 2004 5/62 1/63 11.3 % 4.08 [0.80, 20.90]
Rao 1977 2/75 5/75 13.2 % 0.41 [0.09, 1.86]
Rubens 2005 0/34 3/34 5.7 % 0.13 [0.01, 1.27]
Whitlock 2006 1/30 3/30 7.4 % 0.35 [0.05, 2.61]
Yared 1998 0/106 1/110 2.0 % 0.14 [0.00, 7.08]
Yared 2007 1/37 0/34 2.0 % 6.81 [0.13, 344.59]
Total (95% CI) 636 607 100.0 % 0.88 [0.51, 1.52]
Total events: 26 (Corticosteroids), 29 (Control)
Heterogeneity: Chi² = 14.42, df = 13 (P = 0.35); I² =10%
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control


Review: Prophylactic corticosteroids for cardiopulmonary bypass in adults
Comparison: 3 Dose-dependant analyses
Outcome: 4 Cardiac complications, low dose
Study or subgroup
corticosteroids n/N
placebo n/N
Peto Odds Ratio Peto,Fixed,95% CI
Weight
Peto Odds Ratio Peto,Fixed,95% CI
Halonen 2007 1/120 1/121 33.5 % 1.01 [0.06, 16.22]
Halvorsen 2003 3/147 1/147 66.5 % 2.75 [0.38, 19.70]
Total (95% CI) 267 268 100.0 % 1.96 [0.39, 9.80]
Total events: 4 (corticosteroids), 2 (placebo)
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.56); I² =0.0%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control


Review: Prophylactic corticosteroids for cardiopulmonary bypass in adults
Comparison: 3 Dose-dependant analyses
Outcome: 5 Pulmonary complications, high dose
Study or subgroup
Corticosteroids n/N
Control n/N
Peto Odds Ratio Peto,Fixed,95% CI
Weight
Peto Odds Ratio Peto,Fixed,95% CI
Bingol 2005 1/20 4/20 11.1 % 0.26 [0.04, 1.67]
Liakopoulos 2007 2/40 1/38 7.2 % 1.88 [0.19, 18.65]
Morton 1976 3/48 3/48 14.0 % 1.00 [0.19, 5.18]
Oliver 2004 7/62 4/63 25.0 % 1.84 [0.54, 6.32]
Rao 1977 1/75 7/75 18.8 % 0.21 [0.05, 0.86]
Schurr 2001 1/24 2/26 7.1 % 0.54 [0.05, 5.47]
Toft 1997 0/8 1/8 2.5 % 0.14 [0.00, 6.82]
Whitlock 2006 2/30 1/30 7.2 % 1.99 [0.20, 19.94]
Yared 2007 1/37 2/34 7.2 % 0.46 [0.05, 4.59]
Total (95% CI) 344 342 100.0 % 0.71 [0.38, 1.31]
Total events: 18 (Corticosteroids), 25 (Control)
Heterogeneity: Chi² = 8.81, df = 8 (P = 0.36); I² =9%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control

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 end- points, 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.[105]

A risk-reduction for postoperative atrial fibrillation seems to be one of the few clinical advantages of corticosteroid administration that has been demonstrated repeatedly.[91,102] 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.[91,102] 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.[79] 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 3). 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[23] and Ho 2009.[33] 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[77]), no randomisation (Fecht 1978[65]) and no in- formation regarding randomisation (Niazi 1979[70]). Moreover, we retrieved and included 14 more studies.[44,48,74,89,99,104,106-112] Our results differ in particular with respect to mortality. Whereas Whitlock 2008[23] 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.[113] 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.[23] However, the study from Vallejo 1977[113] was published in 1977 and was designated by Whitlock 2008[23] 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)[23], 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.[23]

The meta-analysis from Ho 2009[33] included 50 trials, 45 of which are identical to those in our meta-analysis. Besides Vallejo 1977[113], Niazi 1979[70] and Fecht 1978[65], as discussed here above, we excluded both Teoh 1995[114] (missing description of randomisation procedure) and Kilickan 2008[115] (deficient data on primary outcome measures). Moreover, twelve more studies were included in our meta-analys is[44,69,74,75,89,99,100,104,109,111], accounting for 680 patients. The inclusion of the study of Vallejo 1977[77] in this review resulted in a relative risk estimate for mortality that was similar to that in the study of Whitlock 2008[23], 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[33] 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. [11,16,116] 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[32], 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 randomised, 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 randomised clinical trials evaluating corticosteroid administration in cardiac surgery are currently underway: the SIRS trial (NCT00427388)[81] and the DECS trial (NCT00293592)[80], including 10,000 and 4500 patients, respectively. The results from these trials are expected in the period 2011-2013.

Acknowledgements

We thank J.W. Schoones, library consultant in the Leiden university centre, for his major contribution in developing our search strategy. We further acknowledge Dr. Scoletta for providing additional data for the analysis of his article Giomarelli 2003.[96]

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Appendix 1: Search strategies

CENTRAL

#1 MeSH descriptor steroids this term only
#2 MeSH descriptor Anti-Inflammatory Agents this term only
#3 steroid* in All Text
#4 dexamethasone in All Text
#5 predniso* in All Text
#6 methylpredniso* in All Text
#7 glucocortico* in All Text
#8 hydrocortiso* in All Text
#9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)
#10 MeSH descriptor Extracorporeal Circulation explode all trees
#11 cardiopulmonary next bypass in All Text
#12 extracorporeal next circulation in All Text
#13 MeSH descriptor Heart-Lung Machine this term only
#14 heart next lung next machine in All Text
#15 cpb in All Text
#16 MeSH descriptor Cardiac Surgical Procedures explode all trees
#17 (coronary in All Text near/6 bypass in All Text)
#18 heart next bypass in All Text
#19 (heart in All Text near/6 bypass in All Text)
#20 cardiac next bypass in All Text
#21 (cardiac in All Text near/6 bypass in All Text)
#22 cardiac next surgery in All Text
#23 heart next surgery in All Text
#24 open next heart in All Text
#25 (#10 or #11 or #12 or #13 or #14 or #15)
#26 (#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)
#27 (#25 or #26)
#28 (#9 and #27)

MEDLINE (PubMed)

LUMC:

("Extracorporeal Circulation"[MeSH:NoExp] OR "extracorporeal circulation"[tw] OR "Cardiopulmonary Bypass"[MeSH] OR "Cardiopul- monary Bypass"[tw] OR "Heart Bypass, Left"[MeSH] OR "Heart-Lung Machine"[MeSH] OR "heart lung machine" OR "heart lung ma- chines" OR "Cardiac Surgical Procedures"[MeSH:NoExp] OR "Cardiomyoplasty"[mesh] OR "Heart Arrest, Induced"[mesh] OR "Heart By- pass, Right"[mesh] OR "Heart Valve Prosthesis Implantation"[Mesh] OR "Myocardial Revascularization"[Mesh:NoExp] OR "Coronary Artery Bypass"[Mesh] OR "Pericardial Window Techniques"[Mesh] OR "Cardiomyoplasty" OR "Induced Heart Arrest" OR "Deep Hypothermia Induced Circulatory Arrest" OR "Right Heart Bypass" OR "Fontan Procedure" OR "Heart Valve Prosthesis Implantation" OR "Myocardial Revascularization" OR "coronary atherectomy" OR "Coronary Artery Bypass" OR "Pericardial Window" OR "Heart/surgery"[MeSH] OR ((dor OR suma) AND reconstruction) OR "cardiac bypass" OR "heart bypass" OR "cardiac surgery" OR "heart surgery" OR "open heart") AND (glucocorticoids OR steroids[ti] OR Dexamethasone OR Methylprednisolone OR Prednisolone OR Prednisone OR Dexamethaso OR Methylprednisolo* OR Predniso* OR hydrocortisone OR hydrocortiso* OR glucocortico* OR "Anti-Inflammatory Agents"[MeSH:NoExp]) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospective* [tw] OR volunteer* [tw] OR randomised controlled trial OR randomised controlled trials)*

UMCU:

(\Steroids"[mh:noexp] OR \Adrenal Cortex Hormones"[mh:noexp] OR \Anti-Inflammatory Agents"[mh]) OR (steroid [tiab] OR steriod* [tiab] OR predniso* [tiab] OR methylpredniso* [tiab] OR dexamethasone*

[tiab] OR glucocortico [tiab] OR hydrocortiso* [tiab]) AND ((\Cardiac surgical procedures"[mh] OR \ coronary artery bypass"[tiab] OR \cardiac surgery"[tiab] OR \thoracic surgery"[tiab]) OR (\Ex- tracorporeal Circulation"[mh] OR \Heart-Lung Machine"[mh] OR \cardiopulmonary bypass"[tiab] OR \extracorporeal circulation"[tiab] OR \heart-lung machine"[tiab] OR \heart lung machine"[tiab] OR \cpb"[tiab])) AND (((((meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])))))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti])))) BUTNOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt]) OR (randomised controlled trial[PTYP] OR randomised controlled trials OR controlled clinical trial[PTYP] OR clinical trial[PTYP] OR clinical trials OR (clinical AND trial) OR random allocation OR random* OR double blind method OR single blind method OR (singl* OR doubl* OR trebl* OR tripl*) OR blind* OR mask* OR placebo* OR placebos OR research design OR comparative study OR evaluation studies OR follow up studies OR prospective studies OR control OR controlled OR prospectiv* OR volunteer*)) OR (random* OR randomised controlled trial* OR Randomised Controlled Trial [PT]) NOT (letter [pt] OR editorial [pt] OR comment [pt] OR in vitro [mh]) OR (randomised controlled trial [PTYP] OR drug therapy [SH] OR therapeutic use [SH:NOEXP] OR random* [WORD])))) NOT (\animals"[MeSH Terms] NOT (\ humans"[MeSH Terms] OR \hominidae"[MeSH Terms]))*

EMBASE

LUMC:

(exp extracorporeal circulation/ OR extracorporeal circulation.mp OR cardiopulmonary bypass.mp OR exp coronary artery surgery/ OR exp Heart Lung Machine/ OR heart lung machine$.mp OR heart surgery/ OR exp heart valve surgery/ OR cardiomyoplasty/ OR heart aneurysmectomy/ OR heart ventricle remodeling/ OR minimally invasive cardiac surgery/ OR mustard operation/ OR norwood procedure/ OR open heart surgery/ OR induced heart arrest.mp OR right heart bypass.mp OR Cardiomyoplasty.mp OR Deep Hypothermia Induced Circulatory Arrest.mp OR Right Heart Bypass.mp OR Fontan Procedure.mp OR Heart Valve Prosthesis Implantation.mp OR Myocardial Revascularization.mp OR coronary atherectomy. mp OR Coronary Artery Bypass.mp OR (Dor operation OR dor technique OR suma operation OR suma technique).mp OR cardiac bypass.mp OR heart bypass.mp OR cardiac surgery.mp OR heart surgery.mp OR open heart.mp) AND (exp Glucocorticoid/ OR (steroids OR Dexamethaso$ OR Methylprednisolo$ OR Predniso$ OR hydrocortisone OR hydrocortiso$ OR glucocortico$).ti)

UMCU:

'human'/exp AND ('corticosteroid'/exp OR 'antiinflammatory agent'/exp OR 'steroid':ti,ab OR 'steroids':ti,ab OR 'dexamethasone':ti,ab OR 'prednisone':ti,ab OR 'prednisolone':ti,ab OR 'methylprednisolone':ti,ab OR 'steriod':ti,ab OR 'steriods':ti,ab) AND (('heart surgery'/exp OR 'heart surgery':ti,ab OR 'heart-surgery':ti,ab OR 'open heart surgery':ti,ab OR 'coronary surgery':ti,ab OR 'coronary artery surgery':ti,ab OR 'coronary artery bypass surgery':ti,ab OR 'cabg':ti,ab OR 'coronary artery bypass graft':ti,ab OR 'coronary bypass graft':ti,ab OR 'coronary bypass graft surgery':ti,ab OR 'heart valve surgery':ti,ab) OR ('extracorporeal circulation'/exp OR 'cardiopulmonary bypass':ti,ab OR 'cpb':ti,ab OR 'extracorporeal circulation':ti,ab OR 'ecc':ti,ab)) AND (random$:ti,ab OR factorial$:ti,ab OR (crossover$ or cross over$ or cross-over$):ti,ab OR placebo$:ti,ab OR (doubl$ adj blind$):ti,ab OR (singl$ adj blind$):ti,ab OR assign$:ti,ab OR allocat$:ti,ab OR volunteer$:ti,ab OR (CROSSOVER PROCEDURE):sh OR (DOUBLE-BLIND PROCEDURE):sh OR (RANDOMISED CONTROLLED TRIAL):sh OR (SINGLE-BLIND PROCEDURE):sh)

ISI Web of Science

UMCU:

TS=(steroid OR corticosteroid* OR dexamethasone OR prednisone OR prednisolone OR methylprednisolone OR steriod* OR antiinflammatory agent) AND TS=((cardiopulmonary bypass OR cpb OR extracorporeal circulation OR ecc) OR (heart surgery OR heart-surgery OR open heart surgery OR coronary surgery OR coronary artery surgery OR coronary artery bypass surgery OR cabg OR coronary artery bypass graft OR coronary bypass graft OR coronary bypass graft surgery OR heart valve surgery)) AND TS=(metaanalysis OR meta-analysis OR review OR consensus OR guideline OR random* OR trial* OR control* OR ((singl* OR doubl* OR trebl* OR tripl*) AND (blind* OR mask*)))*

CINAHL

UMCU:

((explode \Steroids-" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) OR ((steroid OR corticosteroid* OR dexam- ethasone OR prednisone OR prednisolone OR methylprednisolone OR steriod* OR antiinflammatory agent) in de,ti,ab)) AND (((explode \Extracorporeal-Circulation" / allTOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE)) OR ((cardiopulmonary bypass OR cpb OR extracorporeal circulation OR ecc) in de,ti,ab)) AND ((\Heart-Surgery" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) OR ((heart surgery OR heart-surgery OR open heart surgery OR coronary surgery OR coronary artery surgery OR coronary artery bypass surgery OR cabg OR coronary artery bypass graft OR coronary bypass graft OR coronary bypass graft surgery OR heart valve surgery) in de,ti,ab)) AND ((explode \Clinical-Trials" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) OR ((Randomised controlled trial OR clinical trial* OR clinical-trial* OR control* OR prospectiv* OR volunteer* OR ((singl* OR doubl* OR trebl* OR tripl*) AND (blind* OR mask*)) OR placebo* OR random* OR evaluation studies OR prospective study) in de,ti,ab))*

Metaregister of Controlled Trials (mRCT)

UMCU – LUMC:

(glucocorticoids OR steroids OR steroid OR Dexamethasone OR Methylprednisolone OR Prednisolone OR Prednisone OR Dexamethaso OR Methylprednisolo* OR Predniso* OR hydrocortisone OR hydrocortiso* OR glucocortico*) AND cardiac surgery*

WHO international Clinical Trials Registry Platform

UMCU-LUMC:

(Steroids AND Cardiac Surgery)Footnote:Two teams (UMCU and LUMC) will run searches.

Appendix 2: Detailed Study Characteristics

Author	Year of publication	Enrolment	Blinding	Study size (number of patients)	Type of corticosteroid	HC equivalent dosage (total administered amount)	Total HC equivalent dose given, considering average weight70 kg	Period of treatment	Time to follow up	Mean Age (steroids/placebo)	Surgery type CABG (C), Valve (V) or complex	Remarks
Weis	2009	Unclear	Y	36	HC	550 mg	550 mg	4 days	28 days	67/69	High risk	
Sobiesky	2008	Unclear	Y	28	DX	2667 mg	2667 mg	once	72 hr	62/65	C	
Halonen	2007	08/05-06/06	Y	241	HC	400 mg	400 mg	3 days	ICU-stay	64/66	C and/or V	
Yared	2007	10/00-07/01	Y	71	DX	16 mg/kg	1120 mg	once	Hosp-stay	69/74	C and/or V	
Sano	2006	Unclear	Y	60	HC	100 mg/kg	7000 mg	surgery	Hosp-stay	64/61	C or V	
Enc	2006	Unclear	Y	40	MP	125 mg/kg	8750 mg	once	Hosp-stay	60/57	C (3VD)	
Whitlock	2006	04/04-02/05	Y	60	MP	2500 mg	2500 mg	surgery	Hosp-stay	67/66	C/V/complex	
Weis	2006	09/02-09/03	Y	36	HC	550 mg	550 mg	4 days	Hosp-stay	68/69	High risk	8 lost to Follow up
Prasongsukam	2005	08/00-02/01	Y	86	MP/DX	5427 mg	5427 mg	24 hr	Hosp-stay	67/62	C	
Bingol	2005	01/00-01/03	Y	40	P	1600 mg	1600 mg	>10 days	3 months	64/64	C + other	COPD-patients
Rubens	2005	Unclear	Y	68	MP	5000 mg	5000 mg	once	Hosp-stay	56/54	C	3 excl
Loef	2005		Y	20	DX	40 mg/kg	2800 mg	surgery	Hosp-stay	68/60	C	
Morariu	2004											
Celik	2004	Unclear	Y	60	MP	900 mg/kg	63,000 mg	24 hr	Hosp-stay	60/62	C	
Oliver	2004	Unclear	Y	125	MP/DX	5427 mg	5427 mg	24 hr	ICU-stay	64/62	C and/or V	3 excl
Volk	2003	Unclear	Y	24	MP	75 mg/kg	5250 mg	once	Hosp-stay	65/60	C	
Halvorsen	2003	Unclear	Y	300	DX	213 mg	213 mg	once	ICU-stay	63/64	C	
Giomarelli	2003	01/02-04/02	Y	20	MP	3750 mg	3750 mg	24 hr	Hosp-stay	63/65	C	
Abd. El-Hakeem	2003	Unclear	Y	46	DX	2667 mg	2667 mg	once	ICU-stay	36/35	V	
Abd. El-Hakeem	2003	Unclear	Y	20	DX	2667 mg	2667 mg	once	ICU stay	35/36	V	
El Azab	2002	Unclear	Y	18	DX	2667 mg	2667 mg	once	Hosp-stay	63/63	C	
Fillinger	2002	Unclear	Y	30	MP	81 mg/kg	5670 mg	24 hr	Hosp-stay	61/70	C	
Von Spiegel	2002	Unclear	Y	20	DX	27 mg/kg	1867 mg	once	20 hr	63/67	C	
Von Spiegel	2001											
Chaney	2001	Unclear	Y	90	MP	300 mg/kg 150 mg/kg	21,000 mg 10,500 mg	surgery	Hosp-stay	67-62 / 67	C	2 excl
Volk	2001	Unclear	Y	26	MP	75 mg/kg	5250 mg	once	Hosp-stay	65/61	C	

(continued)

Yared	2000	Unclear	Y	236	DX	16 mg/kg	1120 mg	once	Hosp-stay	63/63	C and/or V	20 excl
Yared	1998											
Tassani	1999	Unclear	Y	52	MP	5000 mg	5000 mg	once	Hosp-stay	unclear	C	
Wan	1999	Unclear	Y	20	MP	150 mg/kg	10,500 mg	once	Hosp-stay	65/65	C and/or V	65 excl
Yilmaz	1999	Unclear	Y	20	MP	5 mg/kg	350 mg	once	Hosp-stay	50/55	C	5 excl
Chaney	1999	Unclear	Y	60	MP	150 mg/kg	10,500 mg	once	Hosp-stay	66/67	C	
Chaney	1998											
Mayumi	1997	12/93-07/94	Y	24	MP	100 mg/kg	70,000 mg	once	7 days	53/54	V	3 excl
Engelman	1995	Unclear	Y	19	MP/DX	5427 mg	5427 mg	24 hr	Hosp-stay	60/68	C	
Jansen	1991	Unclear	Y	25	DX	27 mg/kg	1867 mg	once	Hosp-stay	64/61	C	3 excl
Ferries	1987	Unclear	Y	80	MP	150 mg/kg	10,500 mg	once	24 hr	60/60	C/V/complex	
	1984									58/58		
Morton	1976	Unclear	Y	95	MP	150 mg/kg	10,500 mg	once	> 30 days	unclear	C	
Amr	2009	Unclear	N	100	DX	40 mg/kg	2800 mg	24 hr	Hosp-stay	68/67	C	
Demir	2009	Unclear	N	30	MP	5000 mg	5000 mg	once	Hosp-stay	62/62	C	
Starobin	2007	02/04-01/05	N	90	BetaM	215 mg	215 mg	2-6 weeks	2 weeks	68/66	C	COPD-patients
Liakopoulos	2007	11/03-07/04	N	78	MP	75 mg/kg	5250 mg	once	Hosp-stay	67/66	C	
McBride	2004	Unclear	N	36	MP	150 mg/kg	10,500 mg	once	72 hr	63/30	C	
Bourbon	2004	Unclear	N	49	MP	25 mg/kg	1750 mg	once	24 hr	62-60 / 62	C	
						50 mg/kg	3500 mg					
Kilger	2004	12/99-12/00	N	91	HC	550 mg	550 mg	4 days	6 months	70/69	C and/or V	
Schelling	2003											
Kilger	2003	Unclear	N	80	HC	550 mg	550 mg	4 days	Hosp-stay	unclear	High risk	
Sano	2003	Unclear	N	20	HC	50 mg/kg	3500 mg	once	7 days	64/61	C and/or V	
Turkoz	2001	Unclear	N	20	MP	150 mg/kg	10,500 mg	once	24 hr	58/64	C	
Schurr	2001	08/99-11/00	N	50	MP	50 mg/kg	3500 mg	once	Hosp-stay	64/61	C	
Rumalla	2001	Unclear	N	13	MP	5000 mg	5000 mg	once	6 months	63/61	C	
Harig	2001	Unclear	N	40	PR	1000 mg	1000 mg	surgery	30 days	63/61	C	
Harig	1999					500 mg	500 mg	once		65/61		
Toft	1997	Unclear	N	16	MP	150 mg/kg	10,500 mg	once	Hosp-stay	63/64	C	
Coetzer	1996	Unclear	N	295	MP	150 mg/kg	10,500 mg	once	> 30 days	unclear	Unclear	
Andersen	1989	Unclear	N	16	MP	150 mg/kg	10,500 mg	once	7 days	58 all	C	
Cavarocchi	1986	Unclear	N	61	MP	150 mg/kg	10,500 mg	once	24 hr	62/64	Unclear	
Boscoe	1983	Unclear	N	34	MP	300 mg/kg	21,000 mg	surgery	24 hr	41-75 / 38-71	C or V	
Codd	1977	Unclear	N	150	MP	10000 mg	10,000 mg	once	5 days	53/51	C	

Appendix 3: Reported study endpoints

Author	Year of publication	Mortality	Cardiac complications	Pulmonary complications	Re-intubation	Intubation time	LOS ICU	LOS hospital	Renal failure	Neurologic complications	Atrial fibrillation	Gastro-intedstinal complications	Infections	Inotrope use	Transfusion	Re-thoracotomy	Biomarker	No major complications
Weis	2009	X		X		X*	X*	X*	X		X		X		X*c		X	
Sobiesky	2008	X				X	X	X	X	X	X					X		
Halonen	2007	X	X							X	X		X			X		X
Yared	2007	X	X	X		X*	X		X	X	X		X				X	X
Sano	2006			X		X	X		X		X							X
Enc	2006							X	X	X	X							X
Whitlock	2006	X	X	X		X*	X*	X	X	X	X	X	X	X	Xc		X	
Weis	2006	X				X*	X*	X*										
Prasongsukam	2005	X							X		X	X	X				X	
Bingol	2005	X		X	X	X	X	X			X		X					
Rubens	2005	X	X				X	X*			X		X				X	
Loef	2005	X				X	X							X	Xc		X	
Morariu	2004																	
Celik	2004	X	X		X	X	X				X			X	Xc		X	
Oliver	2004	X	X	X		X	X			X					X	X		
Volk	2003	X	X				X								Xc			
Halvorsen	2003	X	X	X		X	X*				X	X	X	X	X	X		
Giomarelli	2003	X	X	X		X	X	X	X	X	X			X	X		X	
Abd. El-Hakeem	2003	X				X	X							X	X			X
Abd. El-Hakeem	2003	X				X	X				X			X	Xc		X	
El Azab	2002	X				X	X							X			X	X
Fillinger	2002					X	X	X									X	
Von Spiegel	2002	X												X				
Von Spiegel	2001																	
Chaney	2001	X	X			X				X				X				X
Volk	2001	X					X	X									X	

(continued)

Yared	2000	X	X			X	X*		X	X			X	X				X	
Yared	1998																		
Tassani	1999					X	X	X								X		X	X
Wan	1999	X				X	X											X	
Yilmaz	1999					X	X	X					X	X				X	
Chaney	1999	X	X			X		X		X	X	X		X				X	
Chaney	1998																		
Mayumi	1997	X				X							X		X			X	
Engelman	1995	X				X	X	X										X	
Jansen	1991	X					X						X					X	
Ferries	1987	X																X	X
	1984																		
Morton	1976	X	X	X															
Amr	2009	X	X				X	X			X	X	X						
Demir	2009	X				X	X	X	X	X			X	X	X*c				X
Starobin	2007	X		X		X*	X*	X*	X	X	X		X			X			
Liakopoulos	2007	X		X	X	X	X	X	X				X					X	
McBride	2004	X	X			X*		X						X		X		X	
Bourbon	2004	X				X*												X	X
Kilger	2004	X				X*	X*	X*							Xc			X	
Schelling	2003																		
Kilger	2003					X*	X*	X*							Xc				
Sano-2	2003	X		X											X			X	X
Turkoz	2001														Xc			X	X
Schurr	2001					X	X	X			X			X		X	X	X	X
Rumalla	2001	X								X			X			X		X	
Harig	2001	X				X	X									X		X	
Harig	1999																		
Toft	1997	X		X					X				X					X	
Coetzer	1996	X																	
Andersen	1989	X											X					X	X
Cavarocchi	1986	X				X*								X					
Boscoe	1983	X																X	
Codd	1977	X	X											X					X

X: Only Median or Ranges are mentioned; these studies were not included in analysis. Xc: Number of transfusions, continuous variable.*

Chapter 3

Intraoperative high-dose dexamethasone for cardiac surgery: a randomised controlled trial

Jan M. Dieleman[1], Arno P. Nierich[2], Peter M. Rosseel[3], Joost M. van der Maaten[4], Jan Hofland[5], Jan C. Diephuis[6], Ronald M. Schepp[7], Christa Boer[8], Karel G. Moons[1], Lex A. van Herwerden[1], Jan G. Tijssen[9], Sandra C. Numan[1], Cor J. Kalkman[1], Diederik van Dijk[1]. *For the Dexamethasone for Cardiac Surgery (DECS) Study Group.*

[1] University Medical Center Utrecht, The Netherlands
[2] Isala Klinieken, Zwolle, The Netherlands
[3] Amphia Ziekenhuis, Breda, The Netherlands
[4] University Medical Center Groningen, The Netherlands
[5] Erasmus Medical Center, Rotterdam, The Netherlands
[6] Medisch Spectrum Twente, Enschede, The Netherlands
[7] Medical Center Leeuwarden, The Netherlands
[8] Vrije Universiteit Medical Center, Amsterdam, The Netherlands
[9] Academic Medical Center, University of Amsterdam, The Netherlands

Published in:
Journal of the American Medical Association 2012; 308:1761-1767

Abstract

Context

Prophylactic corticosteroids are often administered during cardiac surgery to attenuate the inflammatory response to cardiopulmonary bypass and surgical trauma; however, evidence that routine corticosteroid use can prevent major adverse events is lacking.

Objective

To quantify the effect of intraoperative high-dose dexamethasone on the incidence of major adverse events in patients undergoing cardiac surgery.

Design, Setting, and Participants

A multicentre, randomised, double-blind, placebo-controlled trial of 4494 patients aged 18 years or older undergoing cardiac surgery with cardiopulmonary bypass at 8 cardiac surgical centres in the Netherlands enrolled between April 13, 2006, and November 23, 2011.

Intervention

Patients were randomly assigned to receive a single intraoperative dose of 1 mg/kg dexamethasone (n=2239) or placebo (n=2255).

Main Outcome Measures

A composite of death, myocardial infarction, stroke, renal failure, or respiratory failure, within 30 days of randomisation.

Results

Of the 4494 patients who underwent randomisation, 4482 (99.7%) could be evaluated for the primary outcome. A total of 157 patients (7.0%) in the dexamethasone group and 191 patients (8.5%) in the placebo group reached the primary study end point (relative risk, 0.83; 95% CI, 0.67-1.01; absolute risk reduction, –1.5%; 95% CI, –3.0% to 0.1%; p=0.07). Dexamethasone was associated with reductions in postoperative infection, duration of postoperative mechanical ventilation, and lengths of intensive care unit and hospital stays. In contrast, dexamethasone was associated with higher postoperative glucose levels.

Conclusion

In our trial of adults undergoing cardiac surgery, the use of intraoperative dexamethasone did not reduce the 30-day incidence of major adverse events compared with placebo.

Trial Registration

Clinicaltrials.gov Identifier: NCT00293592

Introduction

Cardiac surgery is among the most commonly performed surgical procedures.[1] Despite important improvements in surgical technique, anaesthesia management, and postoperative care, cardiac surgery is still associated with a substantial risk of major adverse events.[1-3]

Cardiopulmonary bypass (CPB) may play a role in the development of many of these adverse outcomes.[4,5] Cardiopulmonary bypass induces a complex acute phase response, characterized by both cell and protein activation, which may further be intensified by the surgical trauma, ischemia-reperfusion injury, and endotoxaemia. In a significant number of patients, a postoperative systemic inflammatory response syndrome develops, characterized by fever, organ dysfunction, and even multisystem organ failure. It therefore seems reasonable to try to attenuate the inflammatory response, which is part of routine care in many cardiac surgical centres. Often, this is accomplished with long-acting corticosteroids, typically by administering a high dose of intravenous methylprednisolone or dexamethasone during the surgery. These drugs are low-cost, potent anti-inflammatory agents and therefore represent an appealing treatment option in this scenario.[6,7] However, concerns about potential adverse effects, including inadequate serum glucose control, infectious complications, poor wound healing, and gastrointestinal bleeding, have precluded their widespread adoption in cardiac surgical practice.[8,9] In contrast with several European countries, corticosteroids are not routinely used during cardiac surgery in most centres in the United States.[10]

Previous studies have shown that corticosteroids attenuate the increase of se- rum inflammatory markers and may improve pulmonary gas exchange and reduce the need for postoperative inotropic support.[7] However, appropriately sized studies on important clinical outcomes are lacking. Also, recent meta-analyses did not generate sufficient statistical power to allow conclusions on the effectiveness of corticosteroids in the reduction of major adverse events.[11-13] As a result, corticosteroid administration during cardiac surgery is still controversial - in many European hospitals it is part of routine care, whereas this is not the case in most North American cardiac surgical centers.[14]

We conducted a large randomised clinical trial to quantify the effect of a single intraoperative dose of dexamethasone on the incidence of major adverse events in patients undergoing cardiac surgery.

Methods

Study Design and Participants

The Dexamethasone for Cardiac Surgery (DECS) study is a multicentre, randomised, double blind, placebo-controlled study comparing high-dose intravenous dexamethasone with placebo treatment in patients undergoing cardiac surgery. Between April 13, 2006, and November 23, 2011, we recruited patients in 8 cardiac surgical centres in the Netherlands. Patients aged 18 years or older who were scheduled for any type of elective or urgent cardiac surgical procedure requiring CPB were considered eligible. Exclusion criteria included an emergent or off-pump procedure and a life expectancy of less than 6 months.
The study protocol was designed by the academic authors, in collaboration with the members of the DECS Study Group. The study was conducted in accordance with Good Clinical Practice principles and applicable national regulations. The research ethics committee at each participating centre approved the protocol. All patients were required to provide written informed consent before randomisation.

Randomisation and Masking

After providing written informed consent, patients were randomised to receive either dexamethasone or placebo treatment. Dexamethasone (1 mg/kg of body weight, with a 100 mg maximum) or placebo was administered as a single intravenous injection after induction of anaesthesia, but before initiation of CPB. The study drug was supplied in packaged ampoules, each assigned to a unique study number. Packages and ampoules of dexamethasone and placebo were identical and contained an equal volume (5 mL) of a 20 mg/mL dexamethasone solution or normal saline, respectively. An independent statistician created a computer-generated 1:1 randomisation scheme, which was stratified to participating centre and in blocks of 40. The research pharmacist of the University Medical Center Utrecht, Utrecht, the Netherlands, prepared and delivered batches of 40 ampoules to each centre. When a consenting patient arrived in the operating department, a packaged ampoule was taken from the batch. When the ampoule had been opened and the study drug was administered, the patient was considered randomised and the corresponding study number was assigned to that patient. Patients, caregivers, and researchers were unaware of study group assignment.

Procedures

Anaesthesia and surgical treatment were performed according to the standard procedures of each participating centre. Surgical access to the heart was achieved via midline sternotomy. The anaesthetic technique was based on either total intravenous anaesthesia or a combination of intravenous opioids and muscle relaxants in combination with volatile anaesthetics. Techniques for cardioplegia, myocardial protection, and CPB, as well as use of inotropic support, antifibrinolytic

therapy, and cell saving techniques, were left at the discretion of the attending team. Use of corticosteroid-containing solutions for cardioplegia or bypass circuit prime was not allowed. When indicated, patients taking preoperative systemic corticosteroids received a perioperative corticosteroid stress regimen.

After surgery, patients were transferred to the intensive care unit (ICU) and weaned from mechanical ventilation when there was no excessive ongoing blood loss and patients were cooperative and haemodynamically stable. Perioperative serum glucose was regulated according to local sliding scale protocols.

Statistical Analysis

The primary study end point of major adverse events was a composite of death, myocardial infarction (MI), stroke, renal failure, or respiratory failure, occurring within 30 days of randomisation. Perioperative MI was defined as the presence of new Q waves or a new left bundle branch block on the electrocardiogram, combined with a biomarker (creatine kinase-MB or troponin) elevation of more than 5 times the upper reference limit. Data from routine cardiac biomarker surveillance were used to detect possible perioperative MI. The specific type of biomarker used was dictated by the local protocol in each centre, rather than by the study protocol. Post-discharge MI was defined according to the criteria of the Universal Definition of Myocardial Infarction.[15] Stroke was defined as a neurologic deficit lasting more than 24 hours, with increased invalidity (increase on Rankin scale[16] of ≥1 point) and signs of a new ischemic cerebral infarction on computed tomography or magnetic resonance imaging scan. Renal failure in patients not previously receiving dialysis was defined according to the RIFLE criteria as an increase in postoperative serum creatinine of at least 3 times the preoperative value, or a serum creatinine level of more than 4 mg/dL (to convert to micromoles per litre, multiply by 88.4) associated with an acute increase of serum creatinine of at least 0.5 mg/dL.[17] Respiratory failure was defined as postoperative mechanical ventilation or reinstitution of mechanical respiratory support via an orotracheal tube or tracheostomy for an uninterrupted period of at least 48 hours.

An exploratory analysis of prospectively defined secondary outcomes included each separate component of the primary end point (i.e., death, MI, stroke, renal failure, or respiratory failure, within the first 30 days); postoperative infections; postoperative atrial fibrillation; highest serum glucose concentration in the ICU; highest body temperature in the ICU; postoperative delirium (defined as the postoperative indication for treatment with neuroleptic drugs); time to weaning from postoperative mechanical ventilation; and time to discharge from the ICU and from the hospital.

An independent, blinded critical event adjudication committee reviewed all cases of death, possible MI, and possible stroke. Cases of possible MI or stroke were either confirmed or revoked according to the study definitions of these events.

We hypothesized that dexamethasone administration would reduce the incidence of the primary study outcome. Based on the Society of Thoracic Surgeons database,[18] the incidence of the primary outcome in the placebo group was estimated to be 6%. To detect an absolute difference of 2% (from 6% to 4%) with a power of 80% at a 2-sided 0.05 significance level, 1962 patients would be required in each study group. To compensate for possible losses to follow-up, we planned to include 2250 patients per study group.

During the study, 3 pre-planned interim analyses on the primary study end point were performed when 1000, 2000, and 3250 patients, respectively, had been enrolled. Interim analyses were performed by the independent data and safety monitoring board, which consisted of an epidemiologist, a cardiac surgeon, and a cardiac anaesthesiologist not involved in the study. These blinded analyses were adjusted according to an O'Brien and Fleming type I error spending function,[19] using an overall 0.05 significance level. As a result of these interim analyses, the threshold for significance of the primary study end point in the final analysis was 0.044.

Patient follow-up for secondary outcomes was until 1 year from randomisation by study protocol. Herein, we report the primary study end point together with exploratory analyses of other outcomes in the first 30 days after randomisation. Analyses were conducted according to randomisation (intention-to-treat analyses). Baseline characteristics in the 2 study groups were evaluated using frequency distributions.

We also performed pre-planned subgroup analyses for the primary out- come and its separate components, which included 4 age groups (<65, 65- 74, 75-79, and ≥80 years), sex, diabetes, chronic obstructive pulmonary disease, higher (≥5) vs low (≤4) EuroScore preoperative risk estimate[20] (cut-off value based on the median EuroScore of the study population), and prolonged CPB duration (defined as >150 minutes).

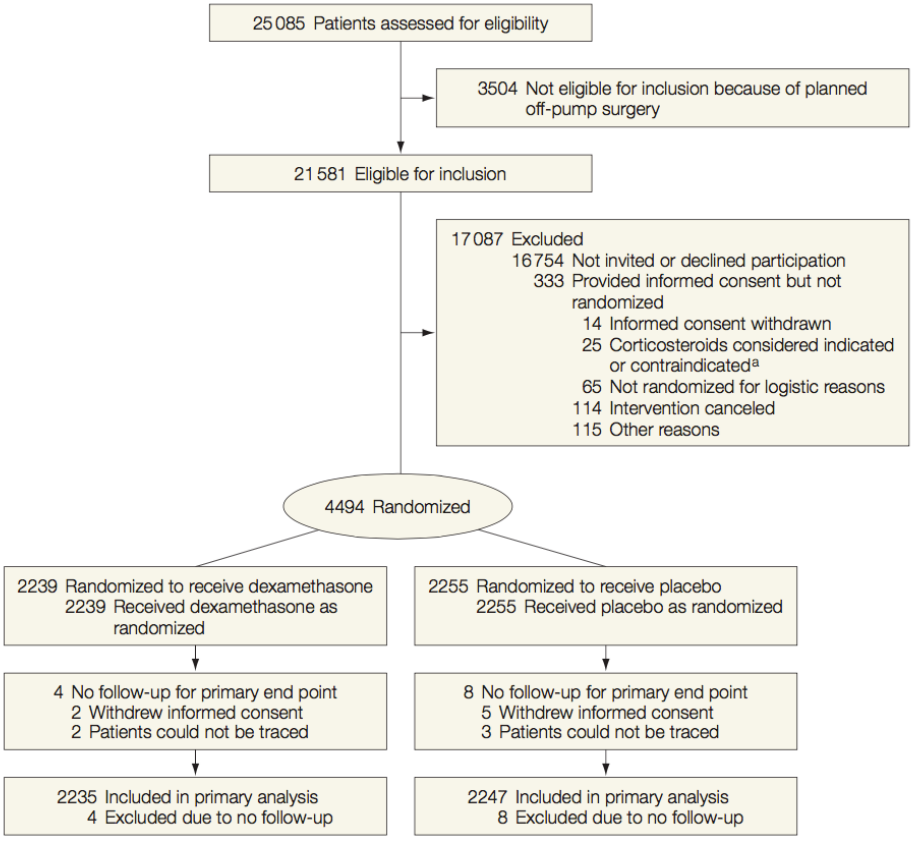
For the comparison of the proportions of patients with primary and secondary outcomes, we used the $\mathbf{X}^2$ test. Absolute risk reduction or relative risk (RR) with 95% CIs was calculated for each dichotomous outcome measure. Logistic regression was used for assessing heterogeneity in the subgroup analyses, with a 0.10 threshold for significance. For comparison of mean and median values of the continuous secondary outcome measures, we used Student *t* test or Mann-Whitney U test, as appropriate. IBM SPSS version 19 (SPSS Inc) was used for all analyses.

Results

Study Population

An estimated 25,085 patients scheduled to undergo elective or urgent cardiac surgery were screened, of whom 21,581 were eligible for inclusion. Of the 4827 patients who provided written informed consent, 4494 eventually underwent randomisation (Figure 1). Two patients who were unintentionally randomised without having provided informed consent were excluded from the analysis. Of the 4494 randomised patients, 2239 (49.8%) were randomised to dexamethasone treatment and 2255 (50.2%) to placebo treatment. Two patients (0.1%) in the dexamethasone group and 5 patients (0.2%) in the placebo group withdrew consent; therefore, their primary outcome could not be assessed. We were unable to obtain 30-day outcome

Figure 1: Enrolment flowchart



Data on the number of patients that were not invited to participate, or that declined participation, were not consistently logged in all centres and are therefore not sufficiently accurate to be reported in detail. a Indication or contraindication dictated by either the treating medical team or the clinical situation during the start of the procedure in the operating department.

Table 1: Demographic, clinical, and surgical characteristics of the dexamethasone and placebo groupsa

Characteristics, no. (%) of patients	Dexamethasone (n=2235)	Placebo (n=2247)
Demographics		
Age, mean (SD), y	66.2 (11.0)	66.1 (10.7)
Male sex	1622 (72.6)	1628 (72.5)
Weight, mean (SD), kg	82.4 (14.3)	82.0 (14.4)
Height, mean (SD), cm	174 (9.1)	173 (9.2)
Coexisting medical conditions		
Hypertension	1179 (54.7)	1180 (54.8)
Diabetes mellitus		
Insulin dependent	106 (4.8)	125 (5.8)
Non-insulin dependent	309 (13.9)	311 (13.9)
Treatment for pulmonary disease	243 (10.9)	266 (11.9)
Previous cerebrovascular event		
Stroke	86 (3.9)	78 (3.5)
Transient ischemic attack	107 (4.8)	103 (4.6)
Peripheral vascular disease	191 (8.6)	192 (8.6)
Preoperative creatinine, mean (SD), mg/dL	1.04 (0.38)	1.07 (0.57)
Chronic renal dysfunction	17 (0.8)	29 (1.3)
Cardiac status		
Recent myocardial infarction (<90 d)	195 (8.7)	176 (7.8)
Left ventricular function[b]		
Moderate	503 (22.6)	534 (23.9)
Poor	103 (4.6)	117 (5.2)
EuroScore (IQR)[c]	5 (3-7)	5 (3-7)
Preoperative medication		
Beta-blocker	1485 (68.4)	1479 (68.2)
Statin	836 (58.0)	771 (53.8)
Corticosteroid	130 (7.2)	98 (5.4)
Surgical		
Type of surgery		
Isolated CABG	873 (39.1)	895 (39.8)
CABG plus valve surgery	360 (16.1)	388 (17.3)
Single valve surgery	575 (25.7)	558 (24.8)
Surgery on multiple valves	82 (3.7)	99 (4.4)
Other procedures	336 (15.0)	295 (13.1)
Repeat surgery	140 (6.3)	147 (6.6)
Duration of procedure, mean (SD), min	244 (102)	242 (93)
Duration of extracorporeal circulation, mean (SD), min	125 (68)	124 (64)
Duration of aortic cross-clamping, mean (SD), min	87 (47)	85 (44)
Deep hypothermic circulatory arrest	15 (0.7)	23 (1.0)
Use of cell saving device	1151 (51.8)	1104 (49.4)
Use of anti-fibrinolytic drug		
Tranexamic acid	1834 (82.4)	1835 (81.8)
Other anti-fibrinolytic drug	10 (0.4)	18 (0.8)

Abbreviations: CABG, coronary artery bypass graft; IQR, interquartile range. SI conversion: To convert creatinine to µmol/L, multiply by 88.4.a Data are shown as No. (%) unless otherwise indicated.b Definition of left ventricular function classes[20]: moderate, ejection fraction of 30% to 50%; and poor, ejection fraction of less than 30%. c Higher EuroScores present increased risk of perioperative mortality.[20]

information in 2 patients (0.1%) in the dexamethasone group and 3 patients (0.1%) in the placebo group after hospital discharge. Thus, the analysed population consisted of 4482 patients (99.7%). Patients in the study groups were similar with respect to baseline demographic, clinical, and surgical characteristics (Table 1).

Primary Study End Point

In total, 348 patients (7.8%) reached the composite primary study end point of death, MI, stroke, renal failure, or respiratory failure, within 30 days after randomisation (Table 2). The primary study end point occurred in 157 of the 2235 patients (7.0%) randomised to dexamethasone and in 191 of the 2247 patients (8.5%) randomised to placebo (RR, 0.83; 95% CI, 0.67- 1.01; absolute risk reduction, –1.5%; 95% CI, –3.0% to 0.1%; p=0.07).

Exploratory Analysis of the Combined End Point Components

The rate of death, MI, stroke, and renal failure was similar in both groups. In the dexamethasone group, 67 patients (3.0%) experienced respiratory failure compared with 97 patients (4.3%) in the placebo group (RR, 0.69; 95% CI, 0.51-0.94; p=0.02) (Table 2). The RR for a composite end point without the respiratory failure component, consisting of only mortality, MI, stroke, and renal failure, was 0.84 (95% CI, 0.66-1.08; p=0.18).

Table 2: Primary study endpoint and components of the primary study endpoint in the dexamethasone and placebo Groups

Outcomes, no. (%) of patients	**Dexamethasone** (n=2235)	**Placebo** (n=2247)	**Relative risk** [95% CI]
Primary study endpoint[a]	157 (7.0%)	191 (8.5%)	0.83 [0.67, 1.01]
Components of the primary study endpoint			
Death	31 (1.4%)	34 (1.5%)	0.92 [0.57, 1.49]
Myocardial infarction	35 (1.6%)	39 (1.7%)	0.90 [0.57, 1.42]
Stroke	29 (1.3%)	32 (1.4%)	0.91 [0.55, 1.50]
Renal failure	28 (1.3%)	40 (1.8%)	0.70 [0.44, 1.14]
Respiratory failure	67 (3.0%)	97 (4.3%)	0.69 [0.51, 0.94]

a Primary study end point was a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure, within 30 days after surgery.

Secondary End Points

The median (interquartile range [IQR]) time to weaning from mechanical ventilation was 7.0 (4.7-10.0) hours (mean, 11.0 hours) in the dexamethasone group and 7.0

(5.0-11.0) hours (mean, 14.3 hours) in the placebo group (p<0.001) (Table 3). The median (IQR) time to discharge from the ICU was 22.0 (19.0-24.0) hours (mean, 34.2 hours) in the dexamethasone group and 22.0 (19.0-25.0) hours (mean, 43.6 hours) in the placebo group (p<0.001). The low p values for both comparisons despite similar median values are the result of a higher proportion of patients requiring prolonged ventilation times and prolonged ICU stay in the placebo group. For example, the proportion of patients requiring more than 24 hours of postoperative mechanical ventilation was 3.4% in the dexamethasone group compared with 4.9% in the placebo group. Similarly, the proportion of patients requiring more than 48 hours of ICU stay was lower in the dexamethasone group than in the placebo group (10.2% vs 14.0%, respectively). The median (IQR) time to discharge from the hospital in the dexamethasone group was 8 (7-13) days (mean, 11.3 days) vs 9 (7-13) days (mean, 11.7 days) in the placebo group (p=0.009).

The risk of developing a postoperative infection was lower in the dexamethasone group than in the placebo group (9.5% vs 14.8%, respectively; RR, 0.64; 95% CI, 0.54-0.75; p<0.001) (Table 3). This protective effect was primarily related to a decreased incidence of pneumonia in the dexamethasone group (6.0% vs 10.6% in

Table 3: Secondary endpoints in the dexamethasone and placebo groups

Outcomes	**Dexamethasone** (n=2235)	**Placebo** (n=2247)	**Relative Risk** [95% CI]	**P-value**[a]
(median (IQR))				
Duration of postoperative mechanical ventilation (hours)	7.0 (4.7-10.0)	7.0 (5.0-11.0)	N/A	<0.001
Length of stay in the intensive care unit (hours)	22.0 (19.0-24.0)	22.0 (19.0-25.0)	N/A	<0.001
Length of hospital stay (days)	8 (7-13)	9 (7-13)	N/A	0.009
(mean (SD))				
Highest serum glucose concentration in the ICU, mg/dL	195 (50)	177 (59)	N/A	<0.001
(no. (%))				
Body temperature in the intensive care unit > 38 ºC	132 (5.9)	564 (25.2)	0.23 [0.20, 0.27]	<0.001
Atrial fibrillation	739 (33.1)	790 (35.2)	0.94 [0.87, 1.02]	0.14
Delirium	205 (9.2)	262 (11.7)	0.79 [0.66, 0.94]	0.006
Gastrointestinal bleeding	13 (0.6)	11 (0.5)	1.19 [0.53, 2.65]	0.67
Any postoperative infection	212 (9.5)	333 (14.8)	0.64 [0.54, 0.75]	<0.001
Pneumonia	133 (6.0)	238 (10.6)	0.56 [0.46, 0.69]	<0.001
Urinary tract infection	50 (2.2)	60 (2.7)	0.84 [0.58, 1.21]	0.35
Wound infection	34 (1.5)	32 (1.4)	1.07 [0.66, 1.72]	0.79
Catheter related infection	6 (0.3)	21 (0.9)	0.29 [0.12, 0.71]	0.004
Sepsis	18 (0.8)	26 (1.2)	0.70 [0.38, 1.27]	0.23

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NA, not applicable.
SI conversion: To convert glucose to mmol/L, multiply by 0.0555.
a For parametric and nonparametric comparisons of continuous data.

the placebo group; RR, 0.56; 95% CI, 0.46- 0.69; p<0.001). In contrast, the mean highest serum glucose concentration was higher in the dexamethasone group and the incidence of postoperative fever was higher in the placebo group (Table 3).

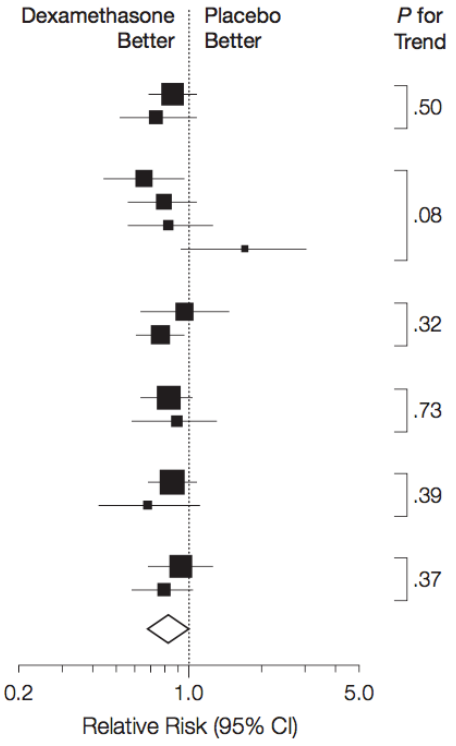
Subgroup Analysis

The pre-planned subgroup analyses suggested an age-dependent effect of dexamethasone on the primary study end point (p for heterogeneity=0.08) (Figure 2). In patients younger than 65 years, dexamethasone was associated with lower likelihood for the primary end point (RR, 0.65; 95% CI, 0.44-0.96; p=0.03), whereas in patients aged 80 years or older, the RR was 1.69 (95% CI, 0.92-3.10; p=0.09). There was no differential treatment effect in the subgroup analyses on sex, diabetes, chronic obstructive pulmonary disease, EuroScore, or prolonged CPB duration.

The bidirectional effect of dexamethasone across the 4 age groups appeared to be predominantly caused by the mortality component of the primary study end point, which showed significant heterogeneity (p=0.05). In patients younger than 65 years, the RR for mortality was 0.42 (95% CI, 0.13-1.34; p=0.13), but it gradually increased with age to 3.87 (95% CI, 1.10-13.6; p=0.02) in patients aged 80 years or older.

Figure 2: Forest plot of subgroup analyses

Subgroup	No. of Patients		No. of Events		Relative Risk (95% CI)	*P* for Trend
	Dexamethasone	Placebo	Dexamethasone	Placebo		
Sex						
Male	1622	1628	112	130	0.86 (0.68-1.10)	.50
Female	613	619	45	61	0.74 (0.52-1.08)	
Age, y						
<65	913	962	38	62	0.65 (0.44-0.96)	.08
65-74	818	781	57	70	0.78 (0.56-1.09)	
75-79	344	336	38	44	0.84 (0.56-1.27)	
≥80	159	168	24	15	1.69 (0.92-3.10)	
EuroScore						
0-4	1025	1060	43	46	0.97 (0.64-1.45)	.32
≥5	1180	1147	113	142	0.77 (0.61-0.98)	
Diabetes						
No	1816	1805	115	142	0.81 (0.64-1.02)	.73
Yes	415	436	41	49	0.88 (0.59-1.30)	
COPD						
No	1987	1978	133	153	0.87 (0.69-1.08)	.39
Yes	243	266	24	38	0.69 (0.43-1.12)	
Prolonged CPB						
No	1674	1659	85	92	0.92 (0.69-1.22)	.37
Yes	536	563	71	96	0.78 (0.59-1.03)	
Total	2235	2247	157	191	0.83 (0.67-1.01)	



COPD indicates chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass. The effect estimates for the primary study end point in the subgroup analyses are shown. The size of each data marker correlates with the total number of patients in that subgroup.

Comment

Our randomised study of 4494 patients undergoing cardiac surgery failed to show a statistically significant benefit of intraoperative administration of dexamethasone on the incidence of the composite primary study end point of major adverse events (p=0.07). In an exploratory analysis of secondary end points, a reduced incidence of respiratory failure was found, which was accompanied by an overall reduced time to weaning from mechanical ventilation, a lower risk of pneumonia, and a reduction in ICU and hospital stay.

The DECS trial is the first large randomised controlled trial to our knowledge on the controversial topic of routine corticosteroid use during cardiac surgery in adults. The numerous small randomised studies published in the last decades had conflicting results[13] and provided only limited guidance for selection of components for the composite primary end point of our study. No significant benefit from dexamethasone treatment was observed on the composite primary end point, which was largely cardiovascular. However, further exploration of the study data suggested a consistent pattern of improved pulmonary condition, manifested as a lower risk of postoperative respiratory failure, shorter times to weaning from the ventilator, and reduced risk of pneumonia during post- operative hospitalization in the dexamethasone group. This improved respiratory condition was accompanied by earlier discharge from both the ICU and the hospital. It might be argued that the beneficial effect of dexamethasone on these multiple secondary outcomes was only a coincident finding. However, also at a more conservative cut-off value for statistical significance of 0.0025 - to correct for testing a total of 19 secondary outcomes using a Bonferroni approach - most of the effects found remained significant. These effects may actually be interrelated and explained by attenuation of the perioperative systemic inflammatory response syndrome, which is the pathophysiologic goal of the single high-dose corticosteroid treatment.[11-14] Thus, although the effect of dexamethasone on the primary end point was negative, there is the possibility that a clinically significant effect was missed. Therefore, a new prospective study focusing on pulmonary outcomes seems a logical next step to further explore the secondary findings of our trial. Such a study should also consider patient selection for the therapy as we found a larger beneficial effect in younger patients and no apparent benefit in those aged 80 years or older.

Our study failed to confirm that corticosteroids reduce the incidence of postoperative atrial fibrillation, as demonstrated in a previous study.[21] The 241 patients in that particular trial received moderate-dose hydrocortisone 3 days postoperatively, instead of the single intraoperative high dose of dexamethasone in our study.

The reduced risk of postoperative infections, in particular pulmonary infections, in the dexamethasone group was unexpected, and contrary to existing knowledge that corticosteroids increase the risk of infections.[7] However, this adverse effect is mainly related to chronic corticosteroid use, rather than to a single prophylactic

pulse dose in circumstances wherein the activation of the immune system could be detrimental.[11-14] The reduced infection risk persisted when patients with respiratory failure were excluded from the analysis, suggesting that the observation is not the result of shorter exposure to mechanical ventilation.

A pooled analysis of this study with the results of our previous meta-analysis of 56 studies on prophylactic corticosteroids in cardiac surgery, which was recently published,[13] showed no effect of corticosteroids for mortality or cardiac complications. However, corticosteroid treatment reduced respiratory complications (Peto odds ratio, 0.59; 95% CI, 0.49-0.71; p<0.001) (eMethods and eFigure, available at http://www.jama.com).

A limitation of our trial is that we studied a high-dose dexamethasone regimen, which is often used during cardiac surgery in several European countries. In North America, however, methylprednisolone is usually preferred when corticosteroids are administered during cardiac surgery. The effect of high-dose methylprednisolone for cardiac surgery is being studied in an on-going large study (Steroids In cardiac Surgery [SIRS] trial, NCT00427388). A strength of our study is that blinding for treatment was well maintained during the perioperative period. The small differences in serum glucose and postoperative body temperature are unlikely to have caused awareness of randomisation. It is thus unlikely that such aware- ness, if any, could have influenced clinical management to a degree that could have produced the present effects on pulmonary outcome and duration of ICU and hospital stay.

In conclusion, in our trial of adults undergoing cardiac surgery, the use of intraoperative dexamethasone did not reduce the 30-day incidence of major adverse events compared with placebo.

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Chapter 4

Long-term outcomes and cost-effectiveness of high-dose dexamethasone for cardiac surgery: a randomised trial

Jan M. Dieleman[1], G. Ardine de Wit[1], Arno P. Nierich[2], Peter M. Rosseel[3], Joost M. van der Maaten[4], Jan Hofland[5], Jan C. Diephuis[6], Fellery de Lange[7], Christa Boer[8], Rabin E. Neslo[1], Karel G. Moons[1], Lex A. van Herwerden[1], Jan G. Tijssen[9], Cornelis J. Kalkman[1], Diederik van Dijk[1], *for the DExamethasone for Cardiac Surgery (DECS) Study Group*

[1] University Medical Center Utrecht, The Netherlands
[2] Isala Klinieken, Zwolle, The Netherlands
[3] Amphia Ziekenhuis, Breda, The Netherlands
[4] University Medical Center Groningen, The Netherlands
[5] Erasmus Medical Center, Rotterdam, The Netherlands
[6] Medisch Spectrum Twente, Enschede, The Netherlands
[7] Medical Center Leeuwarden, The Netherlands
[8] Vrije Universiteit Medical Center, Amsterdam, The Netherlands
[9] Academic Medical Center, University of Amsterdam, The Netherlands

Submitted for publication

Abstract

Background

Prophylactic intraoperative administration of dexamethasone may improve short-term clinical outcomes in cardiac surgical patients. The goal of this study was to evaluate long-term clinical outcomes and cost-effectiveness of dexamethasone *versus* placebo.

Methods

Patients included in the multicentre, randomised, double blind, placebo-controlled DExamethasone for Cardiac Surgery (DECS) trial were followed up for 12 months after their cardiac surgical procedure. In the DECS trial, patients received a single intraoperative dose of dexamethasone 1 mg/kg (n=2239) or placebo (n=2255). The effects on the incidence of major postoperative complications, survival and event-free survival were evaluated. Also, overall costs for the 12 months postoperative period and cost-effectiveness were compared between groups.

Results

Of 4494 randomised patients, 4457 patients (99%) were followed up until 12 months after surgery. There was no difference in either survival (hazard ratio (HR) 1.08; 95% CI 0.80–1.45; p=0.63), or event-free survival (HR 0.85; 95% CI 0.70–1.03; P=0.09). Treatment with dexamethasone reduced costs per patient with €1084 (95% CI €-1968 to €-161), mainly through reduction of postoperative respiratory failure and duration of postoperative hospital stay. The probability of dexamethasone being cost-effective compared to placebo was 97% at a threshold value of €20,000 per quality-adjusted life year.

Conclusions

Intraoperative high-dose dexamethasone did not have an effect on survival or major adverse events at 12 months after cardiac surgery, but was associated with a reduction in costs. Routine dexamethasone administration is expected to be cost-effective at commonly accepted threshold levels for cost-effectiveness.

Introduction

Cardiac surgery is among the most common surgical interventions, with over two million procedures performed worldwide each year.[1] Despite considerable improvements over the last decades, cardiac surgery still carries a substantial risk of complications with significant associated costs.[1-3]
The intense, multimodal inflammatory response associated with cardiac surgery and cardiopulmonary bypass has the potential to increase the risk of organ dysfunction and postoperative complications.[4,5] Several strategies can be employed in attempts to reduce inflammatory activation, and thus improve outcomes.
Routine administration of intraoperative high-dose corticosteroids is a controversial but often used strategy. Solid evidence of its beneficial effects on clinical outcomes, as well as on potential adverse drug effects is scarce.[6,7] Recently, we published the short-term outcomes of the DECS trial, a randomised trial of high-dose dexamethasone *versus* placebo in 4494 patients undergoing cardiac surgery with cardiopulmonary bypass.[8] No significant benefit of dexamethasone on the primary composite outcome of major adverse events in the first 30 days after surgery could be demonstrated. However, pre-specified secondary outcomes analyses indicated that high-dose dexamethasone was associated with less respiratory complications and a reduced postoperative length of stay in the hospital.
We here report on the results of the 12 months follow-up of the patients in the DECS trial, including a cost-effectiveness analysis.

Materials & Methods

The DECS trial was conducted in accordance with Good Clinical Practice principles and applicable national regulations. The research ethics committee at each participating center approved the protocol. All patients provided written informed consent before randomisation. The study was registered prior to patient enrolment at ClinicalTrials.gov, under registration number NCT00293592.

Study design and patients

The DECS trial was a double-blinded randomised multicentre study in The Netherlands, comparing high-dose dexamethasone versus placebo in patients undergoing cardiac surgery. The design and primary study results have been described in detail.[8] Briefly, 4494 patients were randomised to receive a single intravenous dose of either 1 mg/kg of dexamethasone or placebo following the induction of anaesthesia for cardiac surgery. Patients aged 18 or over, who were referred for elective cardiac surgery requiring cardiopulmonary bypass, were eligible for inclusion.

Endpoints

We report the long-term (12 months) effects of intraoperative dexamethasone on major adverse events, survival, and event-free survival, and on health-related quality

of life at 30 days and 12 months postoperatively. We also report the results of a cost-effectiveness analysis of the intervention.

The predefined major adverse events during the first 12 months of follow-up were mortality, MI, stroke, renal failure and respiratory failure. Perioperative MI was defined as presence of new Q-waves or a new left bundle-branch block on the electrocardiogram, combined with elevated biomarkers (CK-MB or troponin) of more than five times the upper reference limit. MI occurring post-discharge or >30 days postoperatively was defined according to the criteria of the Universal Definition of Myocardial Infarction.[9] Stroke was defined as neurologic deficit lasting more than 24 hours, with increased invalidity (≥1 point increase on the Rankin scale[10]) and signs of new ischemic cerebral infarction on computed tomography or magnetic resonance imaging. Renal failure in patients not previously receiving dialysis was defined according to the RIFLE criteria, as an increase in serum creatinine of at least 3 times the preoperative value, or a serum creatinine level >4 mg/dL (>354 µmol/L) associated with an acute increase of serum creatinine ≥0.5 mg/dL (≥44 µmol/L).[11] Respiratory failure was defined as postoperative mechanical ventilation or reinstitution of mechanical ventilation via an orotracheal tube or tracheostomy for an uninterrupted period of at least 48 hours.
An independent, blinded critical event adjudication committee reviewed all cases of death, possible MI, and possible stroke. Cases of possible MI or stroke were either confirmed or revoked according to the study definitions.

Health-related quality of life after 30 days and 12 months was assessed using two generic, self-administered questionnaires. The SF-36 comprises 8 domains and a physical and mental component summary score, all 0-100, where higher scores indicate higher levels of functioning or well-being.[12] The EQ-5D questionnaire covers 5 domains of quality of life, each with 3 levels reflecting severity of problems.[13] We applied the Dutch value set to calculate utility values for each of the 243 (3^5) health states derived from the this questionnaire.[14]

Analysis of health care resources use & costs

Healthcare costs were collected during 12 months of postoperative follow-up and analysed from a healthcare perspective. The cost of the study intervention consisted of fixed costs of the drug and its administration. Data on resource use during immediate postoperative hospitalization were collected from study case report forms, administrative hospital databases, and surgical discharge letters. Data on number and length of hospital readmissions following initial postoperative hospital discharge were collected through information from patient questionnaires at 30 days and 12 months, and from discharge letters of hospital readmissions.
Data on resources use consisted of hospitalizations, diagnostic and therapeutic procedures related to complications of surgery, and medication use. Hospitalization included primary postoperative hospitalization, postoperative transfer to other

hospitals, and hospital readmission. Days in hospital were divided into ward days and days in intensive care unit, and valued according to Dutch guidelines for costing research in healthcare.[15] Medication use was registered via patient questionnaires. Medication costs were retrieved from the Dutch formulary and included a pharmacist fee for every 3-months prescription.[15] It was assumed that patients used a Daily Defined Dose as reflected in the Formulary. Costs of diagnostic and surgical procedures were retrieved from an online database of Diagnosis Related Groups[16], or adapted from estimates in literature. The cost of a rethoracotomy was estimated in a bottom-up manner (i.e. valuing staff involvement and surgery time based on real use of time and resources). As the study takes a healthcare perspective, we did not monetarily value productivity losses of patients. The most relevant cost estimates are displayed in Table 3. Costs of surgery were omitted from the analysis as these costs are expected to be identical in both study arms. A comprehensive overview of all cost estimates used is provided in Table 1 of the Appendix.

Statistics

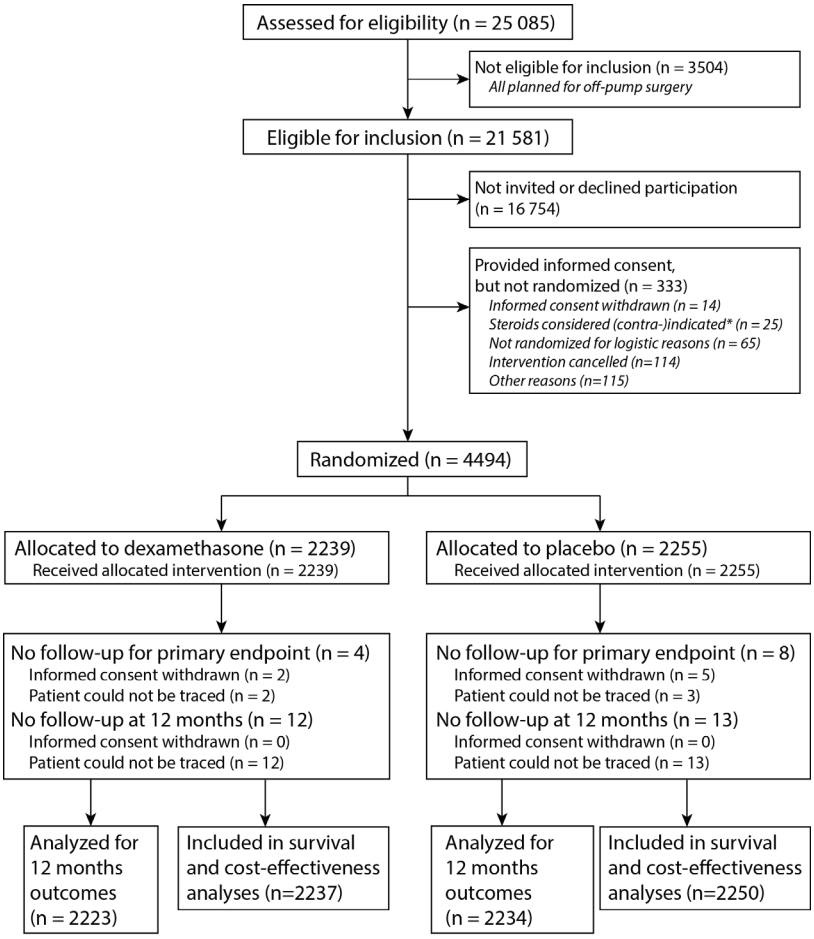
All data were analysed according to the intention-to-treat principle. The incidence of major adverse events within 12 months postoperatively between both groups was compared and presented as relative risk (RR) with a corresponding 95% confidence interval (95% CI). Dichotomous data were compared using the chi-square statistic. Continuous values are expressed as mean ± standard deviation (SD) and were compared using the two-sample t-test. Continuous variables that were not distributed normally were compared using Mann–Whitney tests. Survival and event-free survival were compared using Kaplan–Meier curves, and Cox regression was used to calculate hazard ratios (HR) with 95% CIs. All reported P-values are two-sided.

Using age and Euroscore[17], we employed multiple imputation to account for missing data in the healthcare utilization measures and the EQ-5D.[18,19] Next, we calculated the total costs for each patient by multiplying healthcare resources used by their unit costs (Table 1 of the Appendix). Quality-Adjusted Life Years (QALY) were calculated for each patient, using an area under the curve approach with linear interpolation of EQ-5D utility values as reported at 30 days and 12 months. Using the mean total costs and effects for both the dexamethasone and placebo groups, we divided the cost difference between groups by the difference in QALY, to obtain the Incremental Cost-Effectiveness Ratios (ICER). Bootstrapping (1000 iterations) was used to estimate uncertainty around the ICER. The bootstrapped pairs of costs and effects were plotted in a cost-effectiveness plane. Furthermore, a Cost-Effectiveness Acceptability Curve (CEAC) for a plausible spectrum of different amounts of money society would be willing to pay for an additional QALY was drawn. In The Netherlands, amounts between €20,000 and €80,000 are regarded acceptable threshold values. As our time frame was limited to 12 months, discounting of costs and effects was not necessary. We employed a sensitivity analysis using complete cases.

Results

An estimated 25,085 patients were screened, of whom 21,581 were eligible for inclusion. Of the 4827 patients who consented for participation, 4494 eventually underwent randomisation (Figure 1). Of these, 2239 (49.8%) were randomised to dexamethasone and 2255 (50.2%) to placebo treatment.
Of the 4482 patients for whom 30 days follow-up was completed[8], 31 (0.7%) were unavailable for follow-up at 12 months. Of these 31 patients, 6 had experienced one or more major adverse events in the first 30 days, and were as such accounted for

Figure 1: Inclusion flow chart



Overview of patient enrolment, randomisation, and follow-up.
** Indication or contra-indication dictated by either the treating medical team or the clinical situation during the start of the procedure in the operating room.*
Note: Data on the number of patients that were not invited to participate, or that declined participation were not consistently logged in all centres, and are therefore not sufficiently accurate to be reported in detail.

Table 1: Characteristics of the patients

Characteristic, no. (%) of patients	Dexamethasone (n=2223)	Placebo (n=2234)	% missing data
Demographics			
Age (yrs)	66.2 ± 11.0	66.1 ± 10.7	0%
Male sex	1614 (72.6%)	1616 (72.3%)	0%
Weight (kg)	82.4 ± 14.2	82.0 ± 14.4	0.3%
Height (cm)	174 ± 9.0	173 ± 9.2	0.4%
Coexisting Medical Conditions			
Hypertension	1176 (54.9%)	1174 (54.8%)	3.8%
Diabetes mellitus			0.2%
Insulin dependent	106 (4.8%)	124 (5.6%)	
Non-insulin dependent	305 (13.7%)	309 (13.8%)	
Treatment for pulmonary disease	241 (10.9%)	265 (11.9%)	0.2%
Cerebrovascular disease			0.3%
Stroke	85 (3.8%)	78 (3.5%)	
Transient ischemic attack	107 (4.8%)	103 (4.6%)	
Peripheral vascular disease	188 (8.5%)	190 (8.5%)	0.2%
Preoperative creatinine, mg/dL	1.04 ± 0.38	1.07 ± 0.57	0.2%
Chronic renal dysfunction	17 (0.8%)	29 (1.3%)	0.2%
Cardiac status			
Recent myocardial infarction <90 days	194 (8.7%)	173 (7.8%)	0.2%
Left ventricular function			0.5%
Moderate	498 (22.5%)	530 (23.8%)	
Poor	103 (4.7%)	117 (5.3%)	
EuroScore	5 (3-7)	5 (3-7)	1.4%
Preoperative medication			
Beta-blocker	1480 (68.5%)	1472 (68.2%)	3.1%
Statin	831 (57.9%)	766 (53.7%)	35.8%
Corticosteroid	129 (7.2%)	98 (5.4%)	19.2%
Operative characteristics			
Surgery type			0%
Isolated CABG	883 (39.9%)	891 (40.2%)	
CABG plus valve surgery	372 (16.8%)	361 (16.3%)	
Single valve surgery	574 (25.9%)	561 (25.3%)	
Surgery on multiple valves	86 (3.9%)	92 (4.2%)	
Other procedures	298 (13.5%)	310 (14.0%)	
Repeat surgery	137 (6.2%)	147 (6.6%)	0.2%
Duration of procedure (min)	244 ± 102	242 ± 93	2.2%
Duration of extracorporeal circulation (min)	125 ± 68	124 ± 64	0.7%
Duration of aortic cross-clamping (min)	87 ± 47	86 ± 44	1.1%
Deep hypothermic circulatory arrest	15 (0.7%)	23 (1.0%)	1.6%
Use of cell saving device	1143 (51.7%)	1099 (49.5%)	0.5%
Use of tranexamic acid	1822 (82.3%)	1824 (81.8%)	0.3%
Use of other anti-fibrinolytic drug	10 (0.4%)	18 (0.8%)	

Values for binary and categorical variables represent the number of patients (percentage). Values for continuous variables are means ± standard deviations. Definition of left ventricular function classes17: moderate = ejection fraction 30-50%; poor = ejection fraction <30%. EuroScores are presented as medians with interquartile range; higher EuroScores present increased risk of perioperative mortality.17 CABG denotes coronary artery bypass grafting.

in the 12 months analysis. Thus, the analysed population consisted of 4457 patients for the comparative analyses. However, for the survival analyses and the cost-effectiveness analyses, data from all 4487 patients with an active informed consent were used: patients who were lost to follow-up after 30 days were censored in the survival analyses.
Patients in both study groups did not differ with respect to demographic and baseline characteristics (Table 1).

Adverse events at 12 months

In the dexamethasone group, 208 (9.4%) of 2223 patients had a major adverse event, compared to 242 (10.8%) of 2234 patients in the placebo group (RR 0.86; 95% CI 0.72 – 1.03; p=0.10) (Table 2).
The incidences of mortality, myocardial infarction, stroke and renal failure were comparable between the treatment groups. The incidence of respiratory failure was significantly less in the dexamethasone group, but all the respiratory failure events occurred in the first 30 days.[8]
The effects of dexamethasone on pre-defined secondary outcomes during the early postoperative period have been reported.[8] Rethoracotomy (for any cause) was not specified as a secondary outcome measure, but was included in the cost effectiveness analysis. This complication occurred in 9.7% of the patients randomised to dexamethasone and in 7.3% of the patients randomised to placebo (RR 1.32; 95% CI 1.09 – 1.61; p=0.005). This difference between the groups was mainly due to an increased incidence of late re-thoracotomies (>24 hours) in the dexamethasone group (6.1%, versus 4.2% in the placebo group; p=0.005), whereas the incidences of re-thoracotomy within 24 hours were comparable between the groups (3.6% versus 3.1%, respectively; p=0.35).

Table 2: Outcomes: major adverse events after 12 months

Outcome, no. (%) of patients	**Dexamethasone** (n=2223)	**Placebo** (n=2234)	**Relative risk** [95% CI]	**P-value**
Mortality	90 (4.0%)	83 (3.7%)	1.09 [0.81, 1.46]	0.56
Myocardial infarction	46 (2.1%)	50 (2.2%)	0.92 [0.62, 1.37]	0.70
Perioperative new Q-wave	34 (1.5%)	37 (1.7%)		
Perioperative new LBBB	2 (0.1%)	2 (0.1%)		
Myocardial infarction >30 days after randomisation	10 (0.4%)	11 (0.5%)		
Stroke	41 (1.8%)	49 (2.2%)	0.84 [0.56, 1.27]	0.41
Renal failure	28 (1.3%)	41 (1.8%)	0.69 [0.43, 1.10]	0.10
Respiratory failure	67 (3.0%)	97 (4.3%)	0.69 [0.51, 0.94]	0.02
Postoperative MV >48 hours	57 (2.6%)	35 (1.6%)		
Re-intubation >48h MV	42 (1.9%)	35 (1.6%)		
Any re-intubation	54 (2.4%)	48 (2.2%)		
Any major adverse event	208 (9.4%)	242 (10.8%)	0.86 [0.72, 1.03]	0.10

LBBB: left bundle branch block

Table 3: Cost data: unit costs, number of patients involved, mean resources use and mean costs per patient over 12 months

		Dexamethasone (n=2237)				**Placebo** (n=225)			
Cost item	**Unit cost (Euro)/unit**	**n**	**Number of units**	**Mean; SD**	**Mean total costs (SD) (Euro)**	**n**	**Number of units**	**Mean; SD**	**Mean total costs (SD) (Euro)**
Intervention	***7.60***		***1***		***7.60***				***0***
Hospitalization									
Hospital days, ICU	2270.98	2227	3925	1.75; 3.69	3985 (8371)	2238	4790	2.13; 4.95	4835 (11,240)
Hospital days, ward	485.42	2215	30,453	13.61;17.4	6608 (8458)	2224	31,446	13.98; 21.55	6784 (10,462)
Blood products and cell saver device									
Packed red cells	213.50	711	2659	1.19; 11.78	254 (2515)	763	2209	0.98; 2.18	210 (466)
Fresh frozen plasma	183.76	434	1407	0.63; 1.68	116 (308)	459	1491	0.66; 1.60	122 (295)
Thrombocytes	515.17	359	619	0.28; 1.03	143 (528)	397	694	0.31; 0.96	159 (492)
Use of Cell Saver	164.00	1151	1151	0.51; 0.50	84 (82)	1104	1104	0.49; 0.50	80 (82)
Complications, excluding hospitalization									
Myocardial infarction	See Table S1	46	46	0.02; 0.14	226 (2593)	50	50	0.02; 0.15	192 (1307)
Stroke	1782.24	41	41	0.02; 0.13	33 (239)	49	49	0.02; 0.15	39 (260)
Renal failure	See Table S1	28	28	0.01; 0.11	10 (383)	41	41	0.02; 0.13	106 (2157)
Atrial fibrillation	See Table S1	739	739	0.33; 0.47	34 (93)	790	790	0.35; 0.48	36 (96)
Rethoracotomy	1885.00	207	207	0.09; 0.29	206 (626)	160	160	0.07; 0.26	161 (615)
Infections	See Table S1	241	241	0.11; 0.35	11 (39)	377	377	0.17; 0.43	19 (51)
Medication during follow-up									
Drug use*	See Table S1				631 (339)				624 (327)
Total costs					**12,364 (13,964)**				**13,448 (17,353)**

*ICU: Intensive Care Unit; *including dispensation charges*

Kaplan-Meier curves for both survival and event-free survival are displayed in Figure 1 of the Appendix. The HR for survival at 12 months was 1.08 (95% CI 0.80 – 1.45; p=0.63). For event-free survival at 12 months, the HR was 0.85 (95% CI 0.71 – 1.03; p=0.09).

Health care resources use & costs

Mean costs per patient were lower in patients randomised to dexamethasone as compared to those randomised to placebo (Table 3). Mean healthcare costs were €12,364 (SD €13,964) and €13,448 (SD €17,353), respectively. Hospitalization comprised the largest part of costs, as patients were on average hospitalized for 15.4 (dexamethasone) and 16.1 (placebo) days during 12 months follow-up.

Health-related quality of life

Quality of life data were available for 3558 (79.4%) patients at 30 days, and for 3449 (77.4%) patients at 12 months. The quality of life scores improved significantly between 30 days and 12 months follow-up. However, there was no difference between the treatment groups in any of the 8 domains (not shown) or component summary scores of the SF-36. Also, average scores on the EQ-5D were similar between the treatment groups (Table 2 of the Appendix).

Cost-effectiveness analysis

Bootstrapping showed costs in the dexamethasone group to be €1084 lower than in the placebo group (95% CI €-1968 to €-161), with a QALY difference of -0.0042 (95% CI -0.0160 to 0.0067) (Table 3 of the Appendix). The cost-effectiveness plane (Figure 2A) resulting from the probabilistic sensitivity analyses shows that healthcare costs of the dexamethasone group are lower than those of the placebo group. Compared to placebo, treatment with dexamethasone is associated with a small loss of QALYs. The CEAC (Figure 2B) demonstrates that at a willingness-to-pay (WTP) of €20,000, the probability of cost-effectiveness was 97%, while it was 84% at a threshold value of €80,000. Sensitivity analyses (Table 3 of the Appendix) did not alter these conclusions.

Figure 2: Cost-effectiveness plane and cost-effectiveness acceptability curve

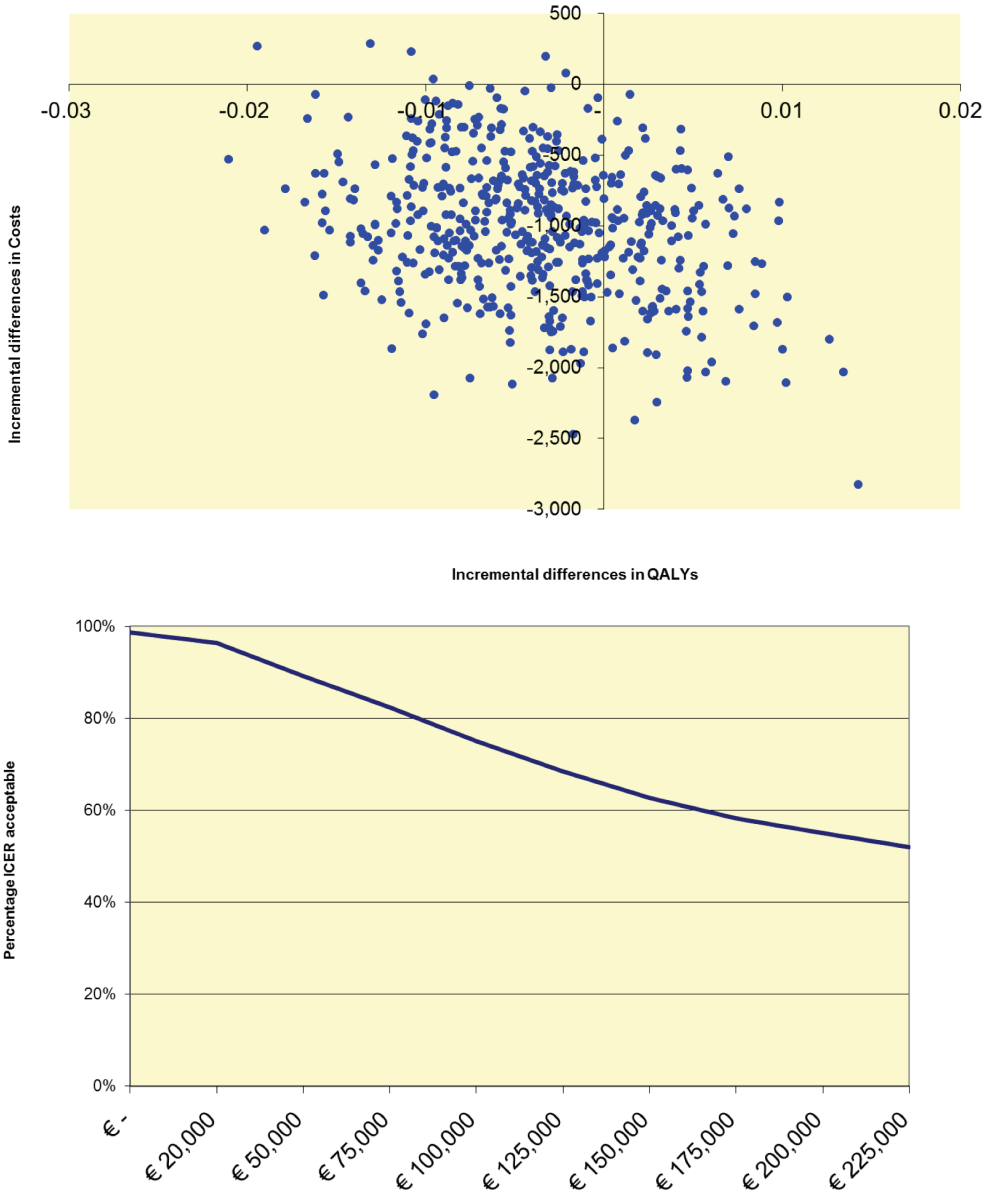


Figure 2A: Cost-effectiveness plane, showing the distribution of 1000 bootstrap replications of differences in costs (y-axis) and effects (x-axis), for dexamethasone compared to placebo.
Figure 2B: Cost-effectiveness acceptability curve, depicting the probability that dexamethasone is most cost-effective (y-axis), depending on the willingness-to-pay per quality-adjusted life year (QALY, x-axis)

Discussion

This randomised, placebo-controlled trial of high-dose intraoperative dexamethasone in cardiac surgery, showed no statistically significant difference in either survival or the incidence of major adverse events after 12 months. By decreasing the incidence of postoperative respiratory failure and by reducing the length of postoperative hospitalization, treatment with dexamethasone significantly reduced cost with on average €1084 per patient. The probability that prophylactic high dose dexamethasone is cost-effective compared to placebo is high.

The DECS study is one of the largest studies on the efficacy of intraoperative, prophylactic high-dose dexamethasone in cardiac surgery. Although no statistically significant effect of dexamethasone on the primary composite endpoint of major adverse events at 30 days could be demonstrated, beneficial effects on short-term secondary endpoints were observed. In the immediate postoperative period, the patients treated with dexamethasone had a reduced incidence of respiratory failure necessitating prolonged mechanical ventilation.[8] Despite previous concerns about a possible higher risk of infections, the incidence of pneumonia decreased from 10.6% in the placebo group to 6.0% dexamethasone group. The risk of wound infection was similar across the two groups, as was the risk of gastrointestinal bleeding. However, there was an unexpected increased incidence of rethoracotomy. The net result of these effects was a shorter postoperative ICU and hospital stay in patients treated with dexamethasone. Combined with the low costs of this generic drug, this reduction in ICU and hospital utilization is the principal reason for the substantial cost benefit of dexamethasone found in this study. Considering the large number of cardiac surgical procedures performed in Western countries, prophylactic use of dexamethasone may generate substantial savings in healthcare costs.

The risk of rethoracotomy was not specified as a secondary outcome measure, but was included in the cost effectiveness analysis for apparent reasons. This complication appeared to occur more frequently in the patients randomised to dexamethasone. We have no plausible explanation for this unexpected but important observation. As far as we know, the effect of steroids on the risk of rethoracotomy has not been reported before.[6,7]

Another large randomised study (Steroids In caRdiac Surgery [SIRS] trial, NCT00427388)[6,20] that has recently finished recruitment, has looked at the effects of intraoperative high-dose methylprednisolone. Similar to the results of the DECS study, the 30 days results of the SIRS trial did not show a difference on the co-primary endpoints of both mortality and a composite of major adverse events.[21] However, administration of methylprednisolone in the SIRS trial was associated with an increased risk of non-Q wave myocardial infarction, which demonstrates another potential side effect of corticosteroids during cardiac surgery.

There were no significant long-term effects of dexamethasone on major adverse events. Given the nature of the intervention, it was to be expected that the effects of dexamethasone on clinical outcomes in this study, if any, would be present shortly after the surgical procedure rather than in the longer term. However, since full clinical recovery from cardiac surgery in most patients takes much longer than the 30 days of the primary study endpoint[23], we believe it is important to have assessed outcomes up to 12 months.

A limitation is that only the effect of a single injection of high-dose dexamethasone was evaluated. Other treatment regimens, which may include lower doses, multiple administrations or different types of corticosteroids, are often used for the same indication.[6,7] In the design of the DECS study, a single high-dose of dexamethasone was the regimen of choice because this represents the most commonly used anti-inflammatory treatment during cardiac surgery in The Netherlands, and several other countries around the world.[6,7]
Strengths of our study include the well maintained blinding and a very low number of patients that could not be followed up to 12 months (0.8%). Although we cannot entirely exclude that there has been selective loss to follow-up, the characteristics of these patients were well balanced between the two treatment groups.

In conclusion, high-dose dexamethasone during cardiac surgery did not have an effect on survival or major adverse events at 12 months. The use of dexamethasone was associated with a reduction of the average cost per patient, mainly through a reduction in the risk of respiratory failure and a reduced length of postoperative hospital stay. Routine dexamethasone administration is expected to be cost-effective at common threshold levels for cost-effectiveness.

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Appendix to Chapter 4

Appendix Table 1: Overview of all cost-estimates and their sources

Resource used	Assumptions made (if any)	2012 Cost (€)	Source
Dexamethasone		7.60	*
Hospital day, ICU †	-	2270.98	Hakkaart[1]
Hospital day, ward †	-	485.42	Hakkaart[1]
MI, follow-up costs year 1 ‡		7699.92	Thurston[2]
ECG, diagnostic	1 per MI, 2 for atrial fibrillation	36.94	Tan[3]
Diagnostic angiography		1455.35	Tan[3]
MI – PCI treatment ‡		3906.00	NZA[4]
MI – IABP treatment ‡		6861.00	NZA[4]
MI – VAD treatment ‡	Once-only	84,127.00	Neyt[5]
MI – VAD treatment ‡	Per month	1261.00	Neyt[5]
Stroke, follow-up costs year 1, ‡		1782.24	Thurston[2]
Atrial fibrillation – ECV ‡		683.00	Knackstedt[6]
Renal failure, acute	ICU, per day	317.45	NZA[4]
Renal failure, permanent	Per year #	86,086.00	Mazairac[7]
Cell-saver		164.00	So-Osman[8]
Packed red cells, per unit		213.50	Hakkaart[1]
Fresh frozen plasma, per unit		183.76	Hakkaart[1]
Thrombocytes, per unit		515.16	Hakkaart[1]
Lower respiratory tract infection ‡	2 thorax X-ray + laboratory	148.60	*
Urinary tract infection ‡	Laboratory	34.44	*
Sepsis ‡	Laboratory	62.35	Van Rijen[9]
Catheter related infection ‡	Laboratory	93.52	*
Wound infection ‡	Laboratory	62.35	Van Rijen[9]
Rethoracotomy ‡		1885.00	*
Medication	Per DDD		Medicijn-kosten[10]

** financial administration of University Medical Center Utrecht; † = including medication during hospitalization, weighted average for academic and non-academic hospitals; ‡ = excluding hospitalization. ICU = intensive care unit; MI = myocardial infarction; PCI = percutaneous coronary intervention; IABP = intra-aortic balloon pump; VAD = ventricular assist device; ECV = electro-cardioversion; DDD = daily defined dose.*

Appendix Table 2: Quality of life

Measure		Dexamethasone	Placebo	*P value*
SF-36 *Physical Component Summary score*	30 days	56.5	56.8	0.72
	12 months	71.5	71.7	0.85
SF-36 *Mental Component Summary score*	30 days	66.3	66.2	0.84
	12 months	75.5	75.4	0.92
EQ-5D *Overall score*	Baseline (estimated)	0.69	0.69	0.70
	30 days	0.78	0.78	0.77
	12 months	0.85	0.85	0.27

All values are observed values, except for the baseline EQ-5D values.

Appendix Table 3: Results of the cost-effectiveness analysis: dexamethasone group compared to placebo group

	Δ Cost (€) [95% CI]	**Δ Effect [95% CI]**	**Distribution cost effectiveness plane (quadrant)**				
Analysis			***North East****	***South East**†*	***South West**‡*	***North West**x*	**Percentage (%) cost-effective at WTP of € 20,000**
Base case analysis							
Healthcare perspective, imputed data, adjusted QALYs	-1084 [-1968 to -161]	- 0.0042 [-0.0160, 0.0067]	0.00	0.24	0.75	0.01	97%
Sensitivity analyses							
Healthcare perspective, imputed data, unadjusted QALYs	-1084 [-1941 to -154]	- 0.00297 [-0.0119 to 0.0055]	0.00	0.26	0.73	0.01	98%
Healthcare perspective, unadjusted QALYs	-1084 [-1945 to -226]	-0.00298 [-0.0111 to 0.0054]	0.00	0.26	0.73	0.01	98%
Complete cases only	-932 [-1846 to -90]	-0.00503 [-0.0160 to 0.0071]	0.00	0.19	0.80	0.01	96%

*D Cost is the mean difference in the costs of 1000 bootstrapped samples. D Effect is the mean difference in the effect of 1000 bootstrapped samples. The distribution on the cost-effectiveness plane reflects the percentage of 1000 bootstrapped ICERs (with each bootstrapped ICER calculated on an individual cost and effect difference) that lies in one of the four quadrants of the cost-effectiveness plane: * = additional costs & additional effects; †= cost savings & additional effects; ‡ = cost savings & less effects; x = additional costs & less effects. QALY = quality-adjusted life year; WTP = willingness-to-pay.*

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Chapter 5

The effects of intraoperative dexamethasone on haemodynamic stability early after cardiopulmonary bypass: a sub study of the DExamethasone for Cardiac Surgery randomised controlled trial

Jan M. Dieleman, Wietze Pasma, Wilton A. van Klei, Diederik van Dijk. *For the DExamethasone for Cardiac Surgery (DECS) Study Group*

All from the University Medical Center Utrecht, The Netherlands.

Submitted for publication

Abstract

Background

Corticosteroids are used in cardiac surgery for prophylaxis of severe systemic inflammation, and are often claimed to improve perioperative haemodynamic stability. We hypothesized that intraoperative use of high-dose dexamethasone in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) would improve haemodynamic stability early after CPB.

Methods

This was a single-centre post-hoc sub study within a randomised trial of high-dose dexamethasone (1 mg/kg) versus placebo in cardiac surgery. Perioperative blood pressure variability was assessed using 3 different standardization algorithms, during three time intervals: the intraoperative period, between 2 and 3 hours, and between 5 and 6 hours after weaning from CPB, respectively. Additionally, use of vasoactive medication and fluid balance were analysed during the postoperative intensive care (ICU) stay.

Results

The analysis included 1254 patients. In patients randomised to dexamethasone, blood pressure variability was significantly less up to 2 hours after CPB compared to placebo patients, but mean blood pressure was also less. Fluid balance was more positive after 8 and 16 hours of ICU stay in the dexamethasone group (absolute difference 3 ml/kg), which was mainly accounted for by less urinary output in this group. No differences in use of vasoactive medication could be demonstrated between the groups.

Conclusions

High-dose dexamethasone reduced blood pressure variability in the first hours after cardiopulmonary bypass, at the cost of a slightly lower blood pressure and a more positive fluid balance. There were no differences in haemodynamic support. We therefore cannot recommend the use of corticosteroids to improve haemodynamic stability after CPB.

Introduction

Cardiac surgery and cardiopulmonary bypass are associated with an intense, multimodal inflammatory response. The surgical trauma generates a systemic stress response, while cardiopulmonary bypass (CPB) exposes blood to large surface areas of synthetic materials, which triggers the production and release of numerous chemotactic and vasoactive substances.[1] The increased blood levels of various cytokines and endotoxins lead to increasing endothelial cell permeability and, after migrating into tissues, activated leukocytes cause additional vascular and parenchymal damage via the release of local proteases and elastase.[1]

The effects of this systemic inflammatory response can complicate the postoperative period by causing a systemic inflammatory response syndrome (SIRS), which is characterized by vasodilatation and increased capillary permeability resulting in extravascular leakage of fluids and proteins. Clinically, this physiological response is often associated with hypotension and the potential for organ hypoperfusion, leading to increased requirements for intravascular volume administration and the use of vasoactive medication to support the circulation. SIRS has the potential to increase the risk of organ dysfunction and postoperative complications. [2,3] Several strategies to reduce inflammatory activation in attempts to improve postoperative outcomes have been reported. A controversial, but often-used strategy to reduce systemic inflammation is the routine administration of intraoperative high-dose corticosteroids, typically 1 mg/kg of dexamethasone, or 15-30 mg/kg of methylprednisolone.[4,5] These steroids are potent anti-inflammatory drugs that have been demonstrated to reliably suppress the inflammatory response after cardiac surgery.[6] In the experience of clinicians who routine use corticosteroids, the some of the most important arguments have been that use of corticosteroids improves postoperative haemodynamic stability[7], reduces the risk of respiratory complications, and thus enhances postoperative recovery.[8,9] In fact, some studies have reported that corticosteroids reduce length of postoperative stay in both the intensive care unit (ICU) and the hospital.[4,5] However, the potential clinical benefits of corticosteroids that contribute to this improved postoperative recovery have not been well studied.

The aim of this study was to investigate the effect of corticosteroids on perioperative haemodynamic parameters, as a possible mediator of faster postoperative recovery in patients receiving steroids. We hypothesized that the intraoperative administration of high-dose dexamethasone in patients undergoing cardiac surgery with CPB would decrease postoperative blood pressure variability and transfusion requirements as compared to patients not receiving corticosteroids.

Methods

This was a single-centre post-hoc study of the larger, multicentre placebo controlled randomised Dexamethasone for Cardiac Surgery (DECS) trial. The design and primary outcomes of the DECS trial have been published in detail elsewhere.[2] Briefly, patients 18 years or older undergoing cardiac surgery with CPB were randomised, in a double-blind fashion, to receive a single 1 mg/kg intravenous injection of dexamethasone or placebo at the time of induction of anaesthesia. Patients who required emergency surgery, those who were scheduled for a procedure using an off-pump technique, and patients with a life expectancy ≤6 months, were not eligible for inclusion. For the current study, we used data only from patients who were recruited at the University Medical Center (UMC) Utrecht, The Netherlands. The Institutional Review Board of the UMC Utrecht approved the use of routine care data for this post hoc study.

The primary outcome of interest in this study was the variability of mean arterial blood pressure in the period after CPB, as a measure of haemodynamic stability. Other outcomes were the use of vasoactive medication in the first hours after CPB and the fluid balance in the first hours of ICU admission after surgery. Each outcome was compared between patients who were randomised to receive dexamethasone and patients who were randomised to receive placebo.

Blood pressure measurements

Data of invasive blood pressure measurements were obtained from the databases of the automated monitoring data storage systems in the operating room (Anstat, an in-house developed anaesthesia information management system (AIMS), storing data from AS5 Monitors, General Electric) of the UMC Utrecht. Each minute, this system automatically stores the median of the measurements during the preceding minute in the database.[10]
Data of invasive blood pressure measurements during ICU admission were obtained from the database of the ICU electronic health record system (Metavision, IMD-soft, 5.45.0.6202), which also stores data every minute.

Calculation of blood pressure variability

Mean blood pressure readings <20 mmHg or >200 mmHg were considered to be invalid measurements and as such excluded from the analysis. The variability of mean blood pressure after CPB was quantified using three methods: one using absolute blood pressure differences, one utilizing a running standard deviation, and one using the overall standard deviation of all mean blood pressure measurements.

In the absolute blood pressure differences method, an absolute difference (delta) was calculated for each pair of subsequent blood pressure measurements. The

mean of these deltas over the period of interest was calculated and divided by the mean of all valid post CPB blood pressure measurements. In the method utilizing the running standard deviation method, a standard deviation of a series of 10 subsequent minutes (epoch) of mean blood pressure measurements was calculated. The next epoch started on the next minute: the epochs thus overlapped each other by nine minutes. The amount of calculated epochs per patient equals the time in minutes from the first blood pressure measurement after weaning from CPB until the time of disconnection from the blood pressure monitor, minus nine. In each epoch the coefficient of variance (CV_{epoch}) was calculated. The mean CV_{epoch} over all epochs was then used for the analysis. Finally, we calculated the standard deviation of all mean blood pressure measurements. This standard deviation was then divided by the mean of all valid post CPB blood pressure measurements to get a coefficient of variance (CV_{SD}). The result of each of the methods of mean blood pressure variability quantification was normalized using a natural logarithm transformation. Normal distribution was confirmed by a Kolmogornov-Smirnov test.
All calculations were performed for the entire post-bypass period in the OR, and for two periods during the early postoperative ICU phase, i.e. the period between 2 hours and 3 hours after CPB and the period between 5 and 6 hours after CPB. Patients who were not admitted to the ICU or not connected to a blood pressure monitor during these one-hour periods were excluded from the corresponding analysis.

Medication use

Requirements for vasoactive medication in the post-bypass period and in the postoperative ICU were analysed. The decision to use vasopressor and/or inotropic support in the post-bypass period was made on an individual patient basis at the discretion of the attending anaesthetist (i.e. there is no routine use). The routinely used vasoactive drugs in our hospital were noradrenaline, dobutamine, and milrinone. The data were extracted from the AIMS and ICU databases, where the administered dose is automatically registered with each dose change.
The requirement for each of these medications after CPB and during the early ICU admission was compared between the treatment groups. The number of patients who required medication, the total dosage of medication administered, and the time until the last administration, were compared. Since patients could not be discharged from the ICU with vasoactive medication, patients who had record of vasoactive medication in the ICU database at the end of their ICU stay had their last administration at ICU discharge.

Fluid balance

Fluid balance was calculated at 8 and 16 hours after first arrival in the ICU. Detailed input and output fluid data during the ICU stay were extracted from the ICU electronic patient data management system. Fluid input consisted of intravenous fluids (including blood products), medications, and oral intake and was registered

continuously. Fluid output consisted of urine, drain fluids, and other outputs, and registered on an hourly basis. When the time points of interest (i.e., 8 and 16 hours) did not match an output registration time (usually a fixed time point, i.e. on the hour), output until the specific time point was calculated using linear interpolation.
The fluid balance from end of surgery until each of the time points was calculated by subtracting total output from total input. When total input exceeded total output, this was referred to as a positive balance, while with a negative fluid balance output exceeded input. Finally, resulting balance parameters were divided by the preoperative weight of the patient.
In addition, an analysis was performed to explore differences in fluid balance in more detail. In this analysis, the components of input and output were analysed separately from one another. For this, input was divided into three groups (crystalloids, colloids and blood products) and output was divided in two groups (chest drain production and urine production).
Since values of fluid balance, fluid input and output did not follow a normal distribution, and could not be normalized using a logarithmic transformation, each of these parameters was left untransformed for non-parametric analysis.

Statistics

Blood pressure variability quantifications were analysed using a repeated measures analysis of variance (ANOVA). Post-hoc analyses of statistical differences from the initial repeated measures ANOVA, as well as the comparisons of requirements for vasoactive medication between the dexamethasone and placebo groups, were performed using a Student's t-test or chi-square test, where appropriate. Fluid balance and intravenous fluid or blood product input were analysed using a Mann-Witney U test. If differences between the groups in baseline variables existed ($p<0.05$), multivariable linear regression analysis was applied to adjust for these differences in the pairwise comparisons with each of the variability quantification methods, incorporating treatment group and only those baseline variables with a difference into the regression model.

With the number of patients available for the analysis, post CPB relative differences of 4.4% in the mean absolute difference, of 7.2% in the CV_{epoch}, and of 13.0% in the CV_{SD}, respectively, could be detected with a statistical power of at least 90%.

Since each of these analyses contained multiple comparisons, P-value cut-off levels for statistical significance were determined separately for each analysis through a Bonferroni correction (using a=0.05 and the number of comparisons per analysis). All statistical analyses were done using R statistical software (version 2.15.2, http://www.R-project.org/).

Results

The multicentre DECS trial cohort consists of 4494 patients.[2] Our current study was executed in the consecutive 1300 patients who were included at the UMC Utrecht after 1 December 2007, when the current electronic patient data management systems in the OR and ICU were fully implemented. Of these, 1254 patients (96%) were used in the final analysis (Figure 1). Of all the patients included in the current study, 2 were discharged before 8 hours of ICU stay, and 31 were discharged between 8 and 16 hours of ICU stay. These 33 patients were, however, included in the analyses. For these patients, fluid balance at 16 hours was linearly extrapolated from the fluid balance at discharge. The baseline characteristics of the study population are summarized in Table 1.

First, blood pressure variability was analysed using absolute differences and a running standard deviation. These parameters were well correlated (Pearson's correlation coefficient 0.90; p<0.001). After this, the simplified running standard deviation was calculated. This method correlated well with both the running standard deviation method (correlation coefficient of 0.84; p<0.001) and the mean delta (Pearson's correlation coefficient 0.76 (p<0.001, OR data).

Table 1: Study cohort characteristics

Characteristics	**Dexamethasone** (n=630)	**Placebo** (n=624)
Age, mean (SD)	65.8 (12.0)	65.4 (11.6)
Male, n (%)	445 (70.6)	429 (68.8)
EuroScore, median (IQR)	5 (3-7)	4 (3-6)
Repeat surgery, n (%)	38 (6.0)	28 (4.5)
Type of surgery, n (%)		
Isolated CABG	262 (42.0)	274 (43.9)
CABG plus valve	104 (16.7)	86 (13.8)
Single valve	151 (24.2)	154 (24.7)
Surgery on multiple valves	28 (4.5)	26 (4.2)
Other procedures	85 (13.6)	84 (13.5)
Duration of procedure, minutes, mean (SD)	207 (106)	202 (75)
Duration of CPB, minutes, mean (SD)	118 (63)	116 (61)
Duration of aortic cross-clamp, minutes, mean (SD)	90 (50)	87 (48)
Deep hypothermic circulatory arrest, n (%)	4 (0.6)	3 (0.5)
Maximum blood glucose, mmol/L, mean (SD) [1]	10.7 (2.2)	8.8 (2.0)

A higher EuroScore[11] indicates a higher risk of perioperative mortality. SD denotes standard deviation, IQR interquartile range, CPB cardiopulmonary bypass. To convert blood glucose concentrations from mmol/L to mg/dL, multiply by the constant 18. [1] Measured over first 8 hours of ICU stay; P<0.001

With each of the quantification methods used, blood pressure variability was significantly less in patients randomised to dexamethasone (p=0.001 for the mean absolute difference, p=0.027 for the CV_{epoch}, and p<0.001 for the CV_{SD}, respectively). In the post-hoc analyses, there were significant differences during the post-bypass period in the operating room and also in the period between 2 hours and 3 hours post-bypass (Table 2). The absolute blood pressure was slightly less than in the placebo group. At five hours post-bypass, the previous significant differences in blood pressure variability had disappeared (on any of the quantification methods, Table 2). Also, there was no difference in absolute blood pressure at five hours post-bypass.

Because of the baseline difference in EuroScore, a commonly used stratification tool to predict perioperative mortality risk in patients who undergo cardiac surgery[11], between the groups (Table 1), we performed a multivariable linear regression analysis for each of the quantification methods (the primary outcome of interest) with EuroScore. In this analysis, all differences in the immediate post-bypass period

Table 2: Blood pressure variability

	Dexamethasone	**Placebo**	**Uni-variable p-value**	**Multi-variable p-value**
Variability after bypass in OR, n	630	624		
CV_{epoch}, mean [CI]	0.080 [0.078, 0.082]	0.087 [0.084, 0.089]	<0.001 *	<0.001*
CV_{SD}, mean [CI]	0.126 [0.123, 0.129]	0.135 [0.131, 0.138]	0.001 *	<0.001*
Mean Delta, mean [CI]	0.045 [0.044, 0.046]	0.050 [0.048, 0.051]	<0.001 *	<0.001*
Mean BP, mm Hg, mean [CI]	60.7 [60.2, 61.1]	61.8 [61.2, 62.1]	0.005	0.01
Variability 2 hours after bypass on ICU, n	581	577		
CV_{epoch}, mean [CI]	0.041 [0.039, 0.042]	0.046 [0.044, 0.048]	<0.001 *	0.08
CV_{SD}, mean [CI]	0.080 [0.076, 0.083]	0.087 [0.083, 0.090]	0.01	0.28
Mean Delta, mean [CI]	0.029 [0.028, 0.030]	0.033 [0.032, 0.034]	<0.001*	0.004 *
Mean BP, mm Hg, mean [CI]	78.1 [77.1, 78.9]	81.7 [80.7, 82.4]	<0.001 *	<0.001*
Variability 5 hours after bypass on ICU, n	591	587		
CV_{epoch}, mean [CI]	0.051 [0.049, 0.053]	0.053 [0.051, 0.055]	0.21	0.21
CV_{SD}, mean [CI]	0.082 [0.078, 0.085]	0.084 [0.080, 0.087]	0.39	0.51
Mean Delta, mean [CI]	0.042 [0.040, 0.043]	0.042 [0.041, 0.044]	0.61	0.98
Mean BP, mm Hg, mean [CI]	75.0 [74.1, 75.7]	74.7 [73.9, 75.4]	0.70	0.58

*OR denotes operating room, ICU intensive care unit, BP blood pressure, CI 95% confidence interval. Values that were normalized (logarithmic) are back-transformed in this Table. CV_{epoch} Method of variability quantification using 10 minute epochs (see methods). CV_{SD} Coefficient of Variance (see methods). * Statistically significant difference. P-value cut-off levels for statistical significance were determined using a Bonferroni correction to adjust for multiple testing (α=0.05, 12 comparisons)[13]*

persisted. However, in the period between 2 and 3 hours post-bypass, only the differences between the groups in mean delta and mean absolute blood pressure remained significantly different (Table 2).

In the ICU period, there was no significant difference in vasopressor and inotropic medication use between the treatment groups (Table 3). Fluid balance at both 8 and 16 hours after ICU admission differed significantly between the treatment groups. At both time points, the fluid balance was slightly more positive in the dexamethasone group (absolute difference 3 ml/kg) compared to the placebo group (p=0.001 and p=0.002, respectively, Table 4).
Based on these findings, we performed a post-hoc analysis to explore the difference in fluid balance in more detail, the results of which are shown in Table 4. Urine output was significantly different between the treatments groups. At both 8 and 16 hours after ICU admission, urine output was significantly less in the dexamethasone group (p<0.001). This difference in urine output accounted for the increased overall fluid balance in the dexamethasone group at both time points. During surgery there was no significant difference in fluid input.

Table 3: Use of vasopressor and inotropic medication

	Dexamethasone (n=630)	**Placebo** (n=624)	**P-value**
Nor-epinephrine			
n (%)	248 (39.4)	233 (37.3)	0.50
Time until weaning, hours [CI]	4.6 [3.0, 6.4]	3.6 [2.3, 6.2]	0.83
Total dose, mg [CI]	1.0 [0.8, 1.2]	0.9 [0.7, 1.1]	0.62
Dobutamine			
n (%)	120 (19.0)	122 (19.6)	0.88
Time until weaning, hours [CI]	23.5 [19.9, 47.9]	24.0 [22.0, 60.5]	0.87
Total dose, mg [CI]	161 [120, 200]	167 [119, 213]	0.88
Milrinone			
n (%)	49 (7.8)	47 (7.5)	0.95
Time until weaning, hours [CI]	18.8 [17.5, 22.0]	17.2 [16.1, 22.1]	0.84
Total dose, mg [CI]	11.1 [7.6, 14.6]	9.6 [6.2, 13.3)	0.62
Dopamine			
n (%)	53 (8.4)	55 (8.8)	0.88
Time until weaning, hours (CI)	32.7 [21.4, 54]	19.1 [NA]	0.14
Total dose, mg (CI)	144.7 [93.7, 199]	98.7 [63.7, 136]	0.23
Any vasoactive medication			
n (%)	315 (50.0)	307 949.2)	0.82
Time until weaning, hours [CI]	13.3 [9.9, 17.4]	15.5 [11.8, 18.2]	0.83

CI denotes 95% Confidence interval, NA not available

Table 4: Fluid balance

Fluid balance & components, mean [CI]	**Dexamethasone** (n=630)	**Placebo** (n=624)	**P-value**
Total input during OR, ml/kg	37.7 [28.1, 49.7]	36.2 [27, 48.1]	0.15
Fluid input during OR, after bypass, ml/kg	20.1 [12.1, 28.2]	18.1 [10.9, 27.5]	0.09
Balance at 8 hours ICU stay, ml/kg	3.8 [-4.3, 13.3]	0.5 [-7.3, 10.5]	<0.001 *
Input, ml/kg	20.0 [11.6, 30.7]	18.4 [9.7, 30.8]	0.24
crystalloids, ml/kg	16.1 [8.1, 24.4]	14.8 [7.8, 23.6]	0.28
blood products			0.74
received, n (%)	153 (24.3)	158 (25.3)	
dose if received (ml/kg)	7.7 [4.1, 11.7]	7.1 [4.1, 11.9]	
colloids			0.63
received, n (%)	191 (30.3)	180 (28.8)	
dose if received (ml/kg)	6.9 [5.7, 9.4]	6.8 [5.9, 10.0]	
Output	15.3 [11.7, 20.8]	17.8 [13.3, 23.8]	<0.001 *
urine, ml/kg	10.0 [7.3, 13.8]	11.6 [8.8, 16.2]	<0.001 *
drains, ml/kg	4.4 [2.7, 7.3]	4.7 [3.1, 7.4]	0.02
Balance 16 hours ICU stay ml/kg	6.2 [-3.1, 16.9]	2.9 [-7.5, 15.4]	<0.001 *
Input	30.7 [20.1, 43.7]	29.7 [19.2, 44.7]	0.68
crystalloids, ml/kg	24.3 [14.8, 34.4]	23.5 [14.6, 35.1]	0.70
blood products			0.80
received, n (%)	161 (25.6)	165 (26.4)	
dose if received (ml/kg)	8.2 [4.0, 12.2]	7.3 [3.9, 12.3]	
colloids			0.94
received, n (%)	225 (35.7)	224 (35.9)	
dose if received (ml/kg	7.5 [6.0, 12.7]	7.1 [6.2, 12.2]	
Output	23.4 [18, 30]	26.1 [20.4, 34.5]	<0.001 *
urine, ml/kg	16.1 [12.1, 20.8]	17.6 [13.6, 23.5]	<0.001 *
drains, ml/kg	5.6 [3.8, 9.4]	6.4 [4.5, 9.9]	<0.001 *

** Statistically significant difference. P-value cut-off levels for statistical significance were determined using a Bonferroni correction to adjust for multiple testing (α=0.05, 18 comparisons)[13]*

Discussion

In this single centre sub study within the DExamethasone for Cardiac Surgery (DECS) trial, we have demonstrated that up to three hours after CPB blood pressure variability was significantly reduced in patients receiving dexamethasone. However, this improved blood pressure stability did not translate into a decreased use of vasoactive medication or less fluid transfusion in the ICU. Moreover, absolute blood pressure was slightly less in the dexamethasone group, and the fluid balance was more positive, as compared to the placebo patients.

For those cardiac anaesthetists who routinely use high-dose corticosteroids, increased postoperative haemodynamic stability after cardiac surgery has been a dominant clinical argument.[5] As significant systemic inflammation may provoke vasodilatation, decreased vascular resistance, and increased vascular permeability,

prophylaxis of inflammatory activation with steroids could potentially increase cardiovascular stability.

This randomised study has been the first to evaluate the effects of dexamethasone on blood pressure variability. The reduction in variability of mean blood pressure in the first hours after CPB in patients treated with dexamethasone was significant and consistent, even when approaching this parameter in various different ways. As illustrated in the boxplots in Appendix Figure 1, fewer patients in the dexamethasone group were in the upper extreme of the distribution of blood pressure variability compared to the placebo group. Reduction of the number of these unstable patients is responsible for the difference found in this study, and may correspond to the clinical experience of improved postoperative stability with dexamethasone after cardiac surgery.[7,8] Yet, we were unable to associate this increased haemodynamic stability with a reduction in the clinical need for haemodynamic support. Apparently, the clinical relevance of this improved stability is relatively minor or even absent.
Nonetheless, blood pressure variability previously has been reported to have an impact on mortality in cardiac surgery patients in an analysis of data of the ECLIPSE trials.[12] However, the aim of the ECLIPSE trials analysis was to study the ability to reach a certain target blood pressure, rather than the blood pressure fluctuations we have looked at in our study. This makes comparing the results of the two studies complicated, if not impossible. Furthermore, it was not our aim to study at clinical outcomes, since our study population was too small to have sufficient statistical power to look at the effects of blood pressure variability on short-term mortality.

Several hours after CPB, the effect of dexamethasone on blood pressure fluctuation seemed to disappear. It is unlikely that this has been a result of a decreasing effect of the inflammatory response, which will usually persist for many days.[13] The same is true for the pharmacological effects of dexamethasone, although the non-genomic mechanisms of action[14] of a very high dose could have accounted for effects that were present only for a few hours. Most arguably, the main reason for the disappearance of the effect seems that at 5 hours post-bypass many patients had been stabilized and sedation was weaned, and some even had their tracheal tubes removed.
The difference in postoperative urinary output between the 2 groups was an unexpected finding. One could speculate that at supra-therapeutic doses of dexamethasone, some minimal mineralocorticoid action may have had clinical effects through sodium and volume retention. Another possible explanation could be that this small absolute difference in urinary output is related to the reduced mean absolute blood pressure in the dexamethasone group during the first hours after CPB.

When we compare our results with those of previous studies looking at the effects of steroids on haemodynamic parameters after cardiopulmonary bypass, there are some differences. Improved haemodynamics in patients treated with corticosteroids have also been reported in several small studies, although more advanced

parameters were used compared to our study.[7,15] In contrast, in another study by the same group of investigators this effect was not observed.[16] Consistent with our findings, no difference in the use of vasoactive medication was demonstrated in a pooled analysis of the results of 17 small studies in a recent Cochrane meta-analysis.[5]

One of the strengths of our study is that we used a high-resolution, automated registration of haemodynamic data. These data were used to calculate blood pressure variability using three different methods, which ensured that any differences could be considered consistent. Other strengths of the study include its blinded design, and the large sample size.
A potential shortcoming of our study is the limited number of available parameters to quantify the haemodynamic stability. For example, direct measures of cardiac output were not routinely available. Although we could have missed subtle differences in these more advanced cardiac performance parameters such as cardiac output or vascular resistance, any clinically important differences would likely have affected the postoperative use of fluids or vasoactive medication. Another limitation of this study is that no reliable data were available on fluid balance in the intraoperative period. Therefore, only fluid balance data during the ICU period could be analysed, by which we could have missed a very early intraoperative effect of dexamethasone on volume requirement. Also, extrapolation of missing fluid balance data of patients who were discharged from the ICU before 16 hours postoperatively could potentially have influenced our results. Finally, we have only been able to look at the macro-circulatory effects of dexamethasone, while on a micro-circulatory level differences may have been much more pronounced.

In conclusion, we have shown that a high-dose dexamethasone reduced blood pressure variability in the first hours after cardiopulmonary bypass, at the cost of a slightly lower blood pressure and a more positive fluid balance. There were no differences in perioperative haemodynamic support. We therefore cannot recommend the use of corticosteroids to improve haemodynamic stability after CPB.

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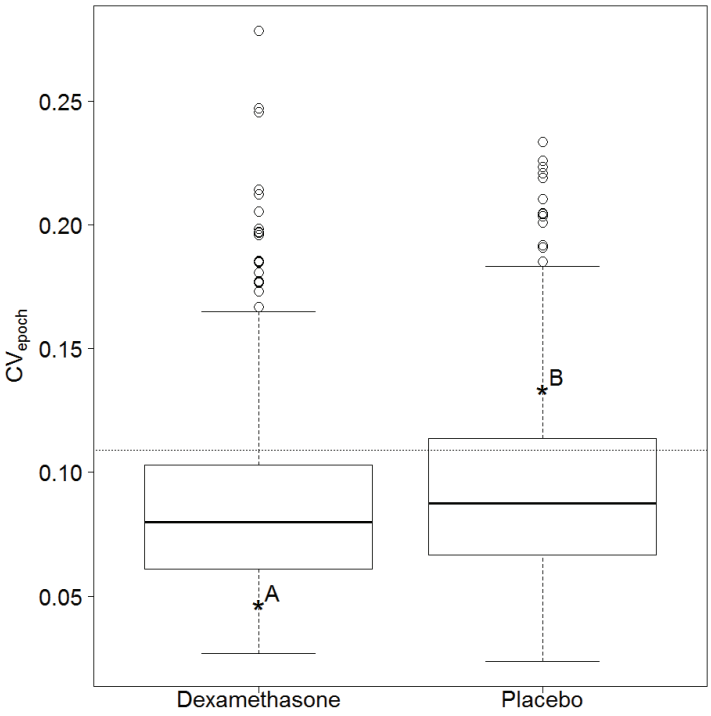
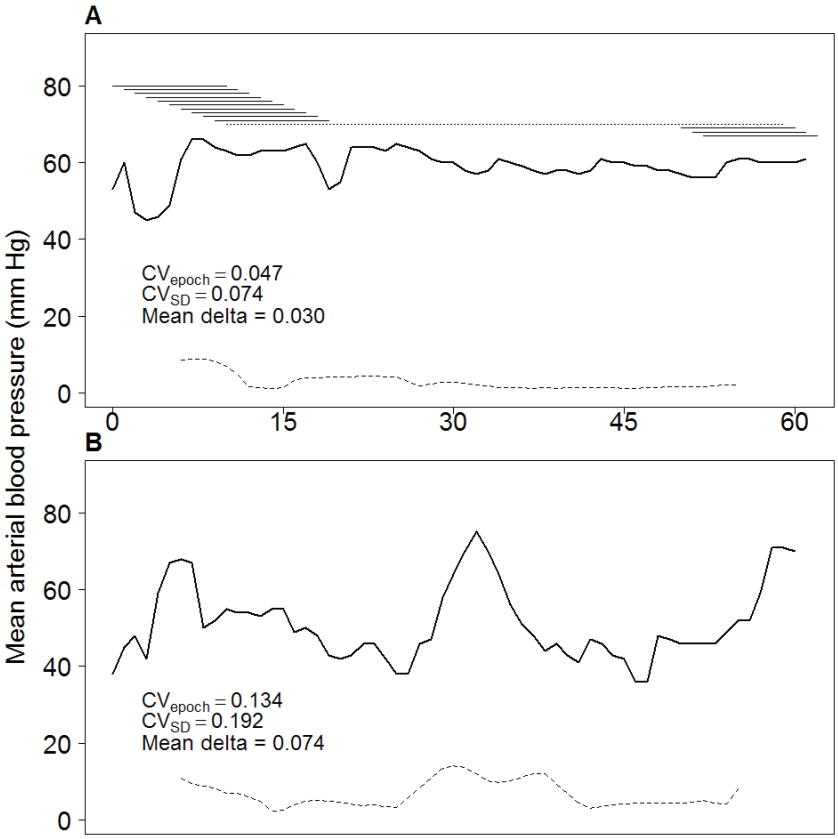
Appendix to Chapter 5

Appendix figure 1: Boxplots illustrating inter-individual spread of blood pressure variability (CV_{epoch}) in each treatment arm



The horizontal dotted line represents the 75th percentile of the CV_{epoch} calculated over the entire study population. Subject A and B are plotted in Figure 2.

Appendix figure 2: Illustration of blood pressure variability measurements.



Typical blood pressure curves of two patients randomised for the trial. One illustrating high (A) blood pressure variability, and one illustrating low (B) blood pressure variability. The Figure includes the actual values of the coefficient of variance (CoV) and the mean delta.
The solid line represents the actual blood pressure. In panel A, the horizontal lines above the blood pressure curve represent the 10 minutes epochs that were used for the analysis. For each line (epoch) a standard deviation (dotted line) and a CV_{epoch} were calculated.

Chapter 6

Intraoperative high-dose dexamethasone in cardiac surgery and the risk of rethoracotomy

Dirk van Osch[1], Jan M. Dieleman[1], Hendrik M. Nathoe[1], Marc P. Boasson[1], Jolanda Kluin[1], Jeroen J.H. Bunge[2], Arno P. Nierich[3], Peter M. Rosseel[4], Joost M. van der Maaten[5], Jan Hofland[2], Jan C. Diephuis[6], Fellery de Lange[7], Christa Boer[8], Diederik van Dijk[1], *for the Dexamethasone for Cardiac Surgery (DECS) study group*

[1] University Medical Center Utrecht, The Netherlands
[2] Erasmus Medical Center, Rotterdam, The Netherlands
[3] Isala Klinieken, Zwolle, The Netherlands
[4] Amphia Ziekenhuis, Breda, The Netherlands
[5] University Medical Center Groningen, The Netherlands
[6] Medisch Spectrum Twente, Enschede, The Netherlands
[7] Medical Center Leeuwarden, The Netherlands
[8] Vrije Universiteit Medical Center, Amsterdam, The Netherlands

Accepted for publication in The Annals of Thoracic Surgery

Abstract

Background

Cardiac surgery with use of cardiopulmonary bypass (CPB) is associated with a systemic inflammatory response. Intraoperative corticosteroids are administered to attenuate this inflammatory response. The recent DExamethasone for Cardiac Surgery (DECS) trial could not demonstrate a beneficial effect of dexamethasone on major adverse events in cardiac surgical patients. Previous studies suggest that corticosteroids may affect postoperative coagulation and blood loss and therefore could influence the risk of surgical reinterventions. We investigated the effects of prophylactic intraoperative dexamethasone treatment on the rate of rethoracotomy after cardiac surgery.

Methods

We performed a post-hoc additional data collection and analysis in the DECS trial. A total of 4494 adult patients undergoing cardiac surgery with use of CPB were randomised to intravenous dexamethasone (1.0 mg/kg) or placebo. The primary endpoint for the present study was the incidence of any rethoracotomy within the first 30 postoperative days. Secondary endpoints included the reason for rethoracotomy, and the incidence of perioperative transfusion of blood products.

Results

In the dexamethasone group 217 (9.7%) patients underwent a rethoracotomy, and in the placebo group 165 (7.3%) patients (RR 1.32; 95% CI 1.09-1.61; p=0.005). The most common reason for rethoracotomy was tamponade: 3.9% versus 2.1%, respectively (RR 1.84, 95% CI 1.30-2.61, $p<0.001$).

Conclusion

Intraoperative high-dose dexamethasone administration in cardiac surgery was associated with an increased rethoracotomy risk.

Introduction

Cardiac surgery with use of cardiopulmonary bypass (CPB) is associated with intense activation of the immune system, leading to a postoperative systemic inflammatory response syndrome (SIRS) in many patients.[1-3] SIRS may lead to postoperative organ dysfunction, and even multi-organ failure.[1-5] Also, through parallel activation of the coagulation system via tissue factor and NF-κB, the systemic inflammatory response may induce perioperative coagulation disorders that commonly occur after cardiac surgery.

Corticosteroids can be administered during cardiac surgery to attenuate systemic inflammatory activation, typically as a high dose of dexamethasone or methylprednisolone.[6] The use of high-dose dexamethasone has been shown to reduce the incidence of postoperative respiratory complications as well as the length of postoperative stay in the intensive care unit (ICU) and the hospital.[7]

The effect of prophylactic corticosteroid administration on bleeding-related complications has not been studied extensively. Meta-analyses of multiple small randomised studies that reported outcomes related to bleeding, have not shown a clinically important effect of corticosteroids on rethoracotomy or blood transfusions between patients receiving corticosteroids or placebo treatment.[6,8] However, in one meta-analysis postoperative chest tube output was reduced in patients receiving corticosteroids.[8]

We recently conducted the DExamethasone for Cardiac Surgery (DECS) trial. The trial did not demonstrate a beneficial effect of dexamethasone on major adverse events in cardiac surgical patients, but found less postoperative infections and a shorter hospitalization in patients randomised to dexamethasone. Rethoracotomy was not part of the predefined study outcomes. To explore the hypothesis that high-dose dexamethasone may reduce the risk of rethoracotomy, we conducted a post-hoc study in all 4494 patients who were included in the DECS trial.

Patients and methods

Study design and population

The present study was a post-hoc analysis of both existing and additionally collected data of patients who were included in the DECS trial, which has been described in detail elsewhere.[7] Briefly, this trial was a multicentre, double-blind, randomised, placebo-controlled study, comparing high-dose intravenous dexamethasone with placebo treatment in 4494 patients undergoing cardiac surgery between April 2006 and November 2011. Adult patients (18 years or older) undergoing elective or urgent on-pump cardiac surgery were eligible for inclusion in this trial. Patients needing an emergency operation, or patients with a life expectancy of less than 6 months, were excluded. The primary outcome of the study was a composite of major adverse events in the first 30 days.

In the present study, we retrospectively analysed the incidence of rethoracotomy. In the main study, all patients provided written informed consent before randomisation. The research ethics committee at each participating centre approved the protocol.

Intervention

Patients were randomised to receive an intravenous injection of dexamethasone (1 mg/kg, with a maximum of 100 mg) or placebo, after induction of anaesthesia, but before initiation of CPB.

Outcome

The primary outcome of interest for the present analysis was the incidence of any rethoracotomy within the first 30 postoperative days.
Secondary study endpoints included the primary reason for rethoracotomy (categorized as bleeding, tamponade, wound or sternal problems, and other reasons), early versus late rethoracotomy (<24 hours vs ≥24 hours), freedom of surgical reinterventions, the incidence of transcutaneous interventions (pericardial or pleural puncture), and the exposure to transfusion of blood products during the operation and during the ICU stay.

Data collection

For the present study, we used data from the DECS study database, as well as additionally collected data from the patients' charts. The prospectively collected data registered in the case record forms of the trial included baseline characteristics, intraoperative characteristics, and use of blood products in the operation room and intensive care unit. Reoperations were reported as in the case record form, but not a predefined endpoint of the DECS trial and were therefore possibly underreported. Therefore, discharge letters, readmission letters, letters from referring centres and surgical reports of all patients included in the DECS trail were retrospectively retrieved and checked (DvO and MB) for rethoracotomies, subxyphoidal incisions and pericardial and pleural punctures. Causes and timing of rethoracotomies and punctures were recorded on a dedicated form. After data collection, all reports were independently assessed by a cardiothoracic surgeon (JK). Discrepant assessments were discussed and scored after consensus was reached. All assessors were blinded for the treatment allocation of the patients during data collection and scoring.

Statistical analyses

Data analyses were performed according to the intention to treat principle. Continuous variables are expressed as mean +/- standard deviation (SD), or as median and interquartile range (IQR) where applicable. Dichotomous variables are expressed as the absolute number of cases followed by a percentage (n, (%)). For the comparison of dichotomous variables, relative risks (RRs) with 95% confidence intervals (CIs)

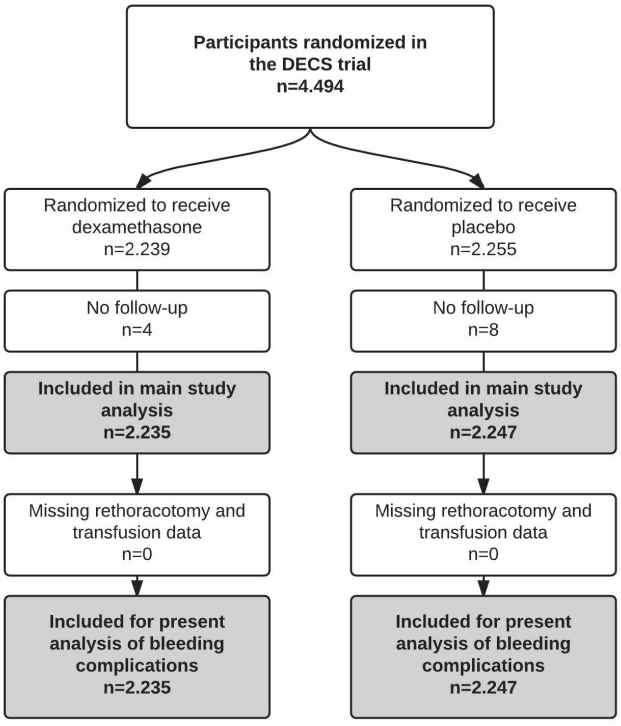
were calculated and analysed using the chi-square test. For comparison of mean and median values of continuous variables, the Student *t* test or the Mann-Whitney U test where used, as appropriate. Freedom of reinterventions was compared using Kaplan-Meier survival analysis using the log-rank analysis. Hazard ratios (HRs) with 95% CIs were calculated using Cox-regression analysis. A value of $p<0.05$ was considered to show statistical significance. IBM SPSS version 20 (SPSS Inc.) was used for all analyses.

Results

Study population

Of 4494 randomised patients, 4482 (99.9%) completed 30 days follow-up. Data concerning reinterventions and transfusions were available for these 4482 patients. A flow diagram of the study is given in Figure 1. Baseline characteristics of the study population are listed in Table 1. There were no differences in baseline characteristics between the two treatment groups.

Figure 1: Study flowchart



DECS: DExamethasone for Cardiac Surgery

Table 1: Baseline characteristics

Characteristic	Dexamethasone (n=2235)	Placebo (n=2247)	P-value
Patient characteristics			
Age (mean±SD), years	66.2 (11.0)	66.1 (10.7)	0.69
Male sex, n (%)	1622 (72.6)	1628 (72.5)	0.93
EuroScore[a], median (IQR)	5 (3-7)	5 (3-7)	0.65
Medical history, n (%)			
Hypertension	1179 (54.7)	1180 (54.8)	0.98
Diabetes	415 (18.6)	436 (19.4)	0.47
Preoperative use of: n (%)			
Corticosteroids	130 (7.2)	98 (5.4)	0.03
Aspirin	1292 (59.5)	1256 (57.8)	0.26
LMWH/Warfarin	537 (24.6)	554 (25.4)	0.57
Intraoperative parameters			
CPB time (mean±SD), minutes	125 (68)	124 (64)	0.54
AoX time (mean±SD), minutes	87 (47)	85 (44)	0.16
Use of cell-saving device, n (%)	1151 (51.8)	1104 (49.4)	0.12
Use of tranexamic acid[b], n (%)	1834 (82.4)	1835 (81.8)	0.64

Abbreviations: CABG: Coronary Artery Bypass Grafting; CPB: Cardiopulmonary Bypass; AoX: Aortic Cross-clamp; EF: ejection fraction; IQR: interquartile range; LMWH: Low Molecular Weight Heparin; SD: standard deviation. [a]EuroScore preoperative risk estimate. [b]The typical tranexamic acid dose was 6.25 mg/kg/hour after a loading dose of 12.5 mg/kg. Dowd NP, Anesthesiology 2002, Aug;97(2):390-9. The baseline characteristics of the main study have been published earlier[7]

Outcomes

The incidence of rethoracotomy for any reason was 9.7% in the dexamethasone treated group, versus 7.3% in the placebo group (RR 1.32, 95% CI 1.09-1.61, p=0.005)(Table 2).

There was a significantly higher incidence of rethoracotomy for tamponade in the dexamethasone treated group compared to the placebo group; 3.9% versus 2.1% respectively (RR 1.84, 95% CI 1.30-2.61, p<0.001).

There were more late rethoracotomies (≥24 hours postoperative) in the dexamethasone group; 6.1% vs 4.3% respectively (RR 1.44, 95% CI 1.12-1.86, p=0.005). Incidences of rethoracotomies for postoperative bleeding or wound problems, as well as early rethoracotomies (<24 hours postoperative) were comparable between the groups (Table 2). Survival analysis showed a significantly lower freedom of surgical

reinterventions in the dexamethasone group (Figure 2), with a hazard ratio of 1.34 (95% CI 1.09-1.64, p=0.005).
Of the transcutaneous interventions, there was no difference in pericardial punctures; 1.1% vs. 0.9% respectively (RR 1.26, 95% CI 0.70-2.26, p=0.44). However, the incidence of pleural puncture was higher in de dexamethasone treated group compared to the placebo group: respectively 5.1% versus 3.6% (RR 1.40, 95% CI 1.06-1.85, p=0.017).

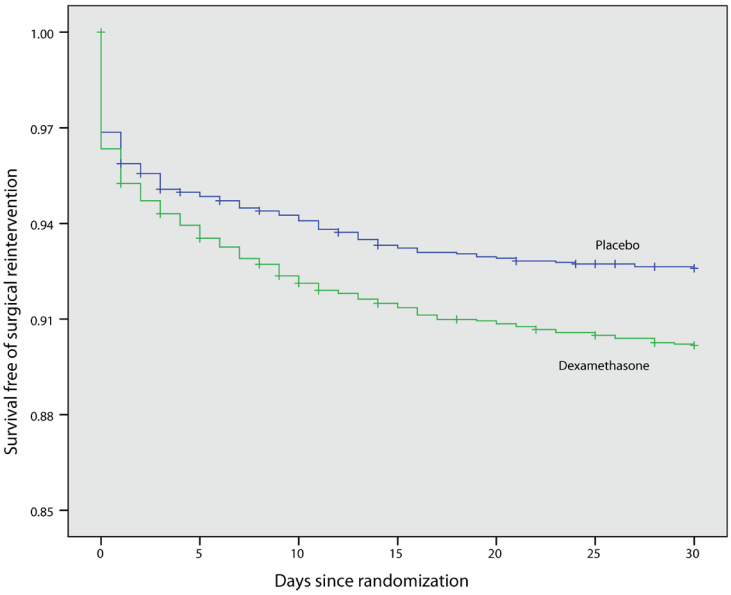
Table 2: Primary and secondary study endpoints

Outcome, n (%)	Dexamethasone (n=2235)	Placebo (n=2247)	Relative Risk [95% CI]	P-value
Primary study endpoint				
Rethoracotomy	217 (9.7)	165 (7.3)	1.32 [1.09-1.61]	<0.01
Secondary study endpoints				
Reason for rethoracotomy[a]				
Tamponade	88 (3.9)	48 (2.1)	1.84 [1.30, 2.61]	<0.01
Rebleed	89 (4.0)	80 (3.6)	1.12 [0.83, 1.50]	0.46
Wound problems	20 (0.9)	18 (0.8)	1.12 [0.59, 2.11]	0.73
Other	20 (0.9)	19 (0.8)	1.06 [0.57, 1.98]	0.86
Rethoracotomy ≤24 hours	81 (3.6)	70 (3.1)	1.16 [0.85, 1.59]	0.35
Rethoracotomy >24 hours	136 (6.1)	95 (4.2)	1.44 [1.12, 1.86]	<0.01
Pericardial puncture	25 (1.1)	20 (0.9)	1.26 [0.70, 2.26]	0.44
Pleural puncture	113 (5.1)	81 (3.6)	1.40 [1.06, 1.85]	0.02
Any blood product transfusion	871 (39.0)	946 (42.1)	0.93 [0.86, 0.99]	0.03
Any packed red cells	711 (31.8)	763 (34.0)	0.94 [0.86, 1.02]	0.13
Any platelets	359 (16.1)	397 (17.7)	0.91 [0.80, 1.04]	0.15
Any fresh frozen plasma	434 (19.4)	459 (20.4)	0.95 [0.85, 1.07]	0.40

All the study endpoints were measured within 30 days after cardiac surgery. [a] In case of multiple (>1) rethoracotomies, the reason for the first rethoracotomy was used as the primary reason.

Of the 2235 dexamethasone patients, 1364 (61.0%) remained free of transfusion of blood products, as compared to 1301/2247 patients (57.9%) in the placebo group (absolute risk reduction (ARR) 3.1%; 95% CI 0.3 to 6.0%; p=0.03).
There was no difference in the number of transfused blood products (fresh frozen plasma, thrombocytes or erythrocytes). The median number of transfused blood products was 3 (IQR 2-6) in the placebo group compared to 3 (IQR 1-6) in the dexamethasone group (p=0.44).

Figure 2: Survival curves of surgical reintervention.



Comment

This study aimed to quantify the effect of intraoperative high-dose dexamethasone administration in cardiac surgery on the risk of rethoracotomy. We found a significant increase in the incidence of rethoracotomy in patients who received dexamethasone, particularly late interventions for tamponade.
This has been the first study with sufficient statistical power to examine the effect of high-dose dexamethasone on rethoracotomy after cardiac surgery. A few very small studies on corticosteroids in cardiac surgery have reported these outcomes previously. Meta-analyses of these studies have not been able to show any effect of corticosteroid administration on these complications, although there was a significant reduction in blood loss in the steroid treated group (mean difference -204.2 mL; 95% CI -287.4 mL to -121 mL; $p<0.0001$).[9] The latter is consistent with our finding of an increased proportion of patients who remained free of perioperative transfusion in the dexamethasone group.[6,8,9]

There are several potential mechanisms that may explain the increased rethoracotomy risk caused by dexamethasone. One possible mechanism could be an increased bleeding tendency caused by dexamethasone. In multiple pre-clinical studies the effects of dexamethasone on coagulation were investigated. These studies found varying effects of dexamethasone on different components of coagulation (platelet aggregation, fibrinogen, factor VIII, von Willebrand Factor, soluble P-selectin), indicating both an increased as well as a decreased bleeding risk.[10-13]

There are also several clinical studies available that have specifically looked at the effects of dexamethasone on coagulation parameters and on postoperative bleeding after surgical procedures.[9,11,14-16] Most of these studies have been performed in non-cardiac surgery. The effects of corticosteroids in these studies have also been variable, with an increased bleeding risk in some patients, and a decreased bleeding risk in others, depending on the circumstances and parameters measured.
Another explanation for the increased incidence of need for (late) reinterventions in the dexamethasone group may relate to impaired recovery as a result of an actual lack of inflammatory response. As some level of inflammation is probably required to aid recovery from the major trauma of cardiac surgery, 'over-suppression' may delay recovery and thereby increase the risk of complications, such as impaired wound healing. This concept of over-suppression is also consistent with the differential effects of corticosteroids that have been demonstrated between younger and elderly patients after cardiac surgery[7], which may be based on the same principle of over-suppression of a relatively senescent immune system in the elderly. In several studies, corticosteroids have been shown to impair the healing of surgical skin wounds, which may relate to a similar mechanism.[17,18] However, an important difference is that these effects have mainly been demonstrated for chronic use of steroids, rather than for a single dose as it was used in our study.[17,19,20]

Our other finding of an increased proportion of patients remaining free of perioperative transfusion of blood products in the dexamethasone group, needs some consideration as well. Although administered to improve oxygen transport capacity or to treat coagulopathy, transfusion of blood products carries substantial adverse risks. Multiple studies have shown that transfusion of allogeneic blood is independently associated with an increased risk of infections, and even with a higher long-term mortality.[21,22] A limitation of the study is that we only recorded the use of blood products during the operation and the ICU admission, but not after ICU discharge. This might explain the unexpected combination of a lower rate of transfusion and a higher rate of rethoracotomy in the dexamethasone group. The survival curves (Figure 2) show that the higher rate of rethoracotomy in the dexamethasone group develops after the first postoperative day and gradually increases during the first postoperative weeks. It is conceivable that a decreased transfusion rate during operation and ICU stay, and an increase in late rethoracotomies reflect separate mechanisms. At 30 day follow-up, the difference in blood transfusion favouring dexamethasone may have disappeared, or even changed in direction, because the rethoracotomies after ICU discharge were probably associated with additional, but unrecorded transfusions of blood products. Furthermore, despite the increased proportion of patients remaining free of perioperative transfusions in the dexamethasone group, the number of transfused blood products did not differ statistically significant between the two groups.

There is always the possibility that the statistically significant differences in either the incidence of rethoracotomy or the reduced transfusion rate have been a play of

chance. Evaluating several secondary outcome measures, may potentially lead to false positive results. The Steroids In caRdiac Surgery (SIRS) trial, which evaluated the effect of high-dose methylprednisolone in 7507 cardiac surgical patients found no effect of corticosteroids on transfusions.[23]

Strengths and limitations

One of the strengths of our study is that it has a very large sample size, representing a broad selection of patients undergoing any form of elective on-pump cardiac surgery. The randomised design of this study ensures an equal distribution of factors that could possibly influence the outcome, while the blinding minimized the risk of observer bias.

An important limitation of the present study is that this was a post-hoc analysis. Rethoracotomy data were based on information obtained from discharge letters and surgical reports. Reporting of rethoracotomies, pericardial punctures and pleural punctures (and their respective reasons) in discharge letters were not standardized. Furthermore, the distinction between bleeding and tamponade in the early postoperative phase is difficult to make. Another limitation is the lack of transfusion data beyond the initial postoperative ICU admission.

Conclusion

Intraoperative high-dose dexamethasone administration in cardiac surgery was associated with an increased rethoracotomy risk.

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Chapter 7

The effect of age on the early C-reactive protein response following cardiac surgery

Jan M. Dieleman[1], Arno P. Nierich[2], Erik C. Hack[1], Cor J. Kalkman[1], Diederik van Dijk[1]

[1] University Medical Center, Utrecht, The Netherlands
[2] Isala Clinics, Zwolle, The Netherlands

Submitted for publication

Abstract

Background

The intensity of the systemic inflammatory response to cardiac surgery is known to vary substantially between individual patients. We studied the hypothesis that magnitude of the early C-reactive protein response to cardiac surgery is inversely correlated with patient age.

Methods

This was a single-centre cohort study in 453 patients undergoing elective cardiac surgery. The primary objective was to analyse the effects of patient age on the magnitude of the early C-reactive protein (CRP) response, defined as the absolute difference between the preoperative and postoperative day 1 CRP levels. Secondary objectives included the analysis of the CRP response in the different age groups during the first postoperative week, and the effects of age on extremes of the CRP response distribution.

Results

There was a statistically significant correlation between increasing age and a reduced early CRP response, which persisted after correction for potential confounders ($r=0.24$; $p=0.001$). Increasing age was also significantly associated with a lower risk of developing an extreme early CRP response (odds ratio 0.95 per year, 95% CI 0.92 – 0.97; $p<0.001$). There was no difference between the age groups in the overall CRP response during the first postoperative week ($p=0.37$).

Conclusion

The magnitude of the early postoperative C-reactive protein response in cardiac surgical patients is inversely related to patient age. Also, the risk of developing an extreme (high) early CRP response is lower in patients with increasing age.

Introduction

The magnitude of the systemic inflammatory response to cardiac and major non-cardiac surgery varies substantially between individual patients. While in the majority of patients this response is relatively mild, a proportion of patients develops more severe systemic inflammation, characterized by fever, organ dysfunction, and even multisystem organ failure.[1,2] This may complicate the postoperative course, and may eventually contribute to adverse outcomes. The underlying causes for this variability are likely multifactorial, and probably result from both patient susceptibility and the intensity of external stimuli that activate the innate immune response.

In two recent large randomised studies in cardiac surgery, the clinical effects of corticosteroids for inflammatory prophylaxis were heterogeneous throughout the study populations. [3,4] While some patient subgroups seemed to derive benefit of prophylactic corticosteroids, others had no benefit at all, or were even harmed. Of particular interest, predefined subgroup analyses in both studies indicated a benefit on mortality in patients <65 years, but potential harm in patients >80 years. A comparable effect across age groups was present for the primary composite endpoint of the DECS study as well.

Several authors speculated that these differential effects may be related to a decreased intensity of the innate immune response with advancing age, a phenomenon also known as immune senescence.[5,6] In line with this hypothesis, it has also been speculated that administration of high-dose steroids in the context of such a senescent systemic immune response may thus lead to an increased risk of complications associated with postoperative immunosuppression.

The aim of this study was to explore age-related variability in the early systemic C-reactive protein response in patients undergoing cardiac surgery.

Methods

Study population

This was a post-hoc single-centre cohort study of patients included in the larger, multicentre placebo controlled randomised Dexamethasone for Cardiac Surgery (DECS) trial. The design and primary outcomes of the DECS trial have been published in detail elsewhere.[3] Briefly, patients 18 years or older undergoing cardiac surgery with CPB were randomised, in a double-blind fashion, to receive a single 1 mg/kg intravenous injection of dexamethasone or placebo at the time of induction of anaesthesia. Patients who required emergency surgery, those who were scheduled for a procedure using an off-pump technique, and patients with a life expectancy ≤6 months, were not eligible for inclusion. For the current study, we used data only from patients who were recruited at the Isala Clinics, Zwolle, The Netherlands. In the

Isala Clinics, a total of 985 patients were included in the DECS trial from May 2008 until November 2011. Of these patients, 495 were randomised to the placebo group, and 490 were randomised to the dexamethasone group. The principal analyses of the current study were carried out in the patients who were randomised to receive placebo. Institutional Review Board approved the use of routine care data and data from the DECS trial database for this study.

Study outcomes

The primary objective of this study was to analyse the effects of patient age on the early C-reactive protein (CRP) response in the patients who had received placebo. The early CRP response was defined as the absolute difference between the preoperative CRP level and the CRP level on postoperative day 1. We also analysed the effect of age on the incidence of extreme (high) early CRP responses. To study the possible effects of high-dose exogenous steroids on the age-dependent CRP response, we performed comparable analyses in patients who had been randomised to dexamethasone treatment. Finally, in a subset of patients who had CRP measured beyond day 1, we compared the postoperative CRP response pattern between pre-defined age groups during the first week both in placebo patients as well as in patients receiving dexamethasone.

Data collection

Demographic data, baseline patient characteristics and perioperative data, were all obtained from the DECS trial database. CRP levels were measured routinely in all patients on the day before surgery and on the morning of postoperative day 1, as per the perioperative care protocol for patients undergoing cardiac surgery in the Isala Clinics. A large proportion of the patients with an uncomplicated course were transferred to their referring hospital after 3 or 4 postoperative days. For the patients included from May 2008 until January 2010, who were not discharged before day 6 after surgery, routine CRP measurements at postoperative days 3 and 6 were also available. After January 2010, routine measurement of CRP at these time points was removed from the perioperative care protocol. CRP was quantified on a Roche Modular Analyser using commercially available reagents (Roche Diagnostics, Almere, The Netherlands of Roche Diagnostics International AG, RotKreuz, Switzerland). CRP data were extracted from the laboratory data management system of the Isala Clinics after the DECS trial data collection was completed. If more than one CRP level was measured on a single day, the highest value was used for the analyses.

Statistical analysis

In analyses of the early CRP response, age was included as a continuous variable. However, in order to illustrate the distribution of baseline variables and outcomes across patients of different ages, data were presented as four separate age groups defined based on the grouping that was used in the initial analyses of both the DECS

trial and the SIRS trial, as <65, 65-74, 75-80 and >80 years. [3,4] This grouping was also used to analyse the perioperative CRP trends.

The effect of age on the early CRP response, was initially analysed in both groups using simple linear regression analysis, and thereafter corrected for potential confounders (all in table 1, with the exception of EuroScore) using multivariable linear regression analysis. These potential confounders were all prospectively recorded in the DECS trial database, and were selected based on their possible relationship with either age or the outcome of the study. EuroScore was not included as a potential confounder, since the majority of the components of this risk score were accounted for by the other potential confounders.

Table 1a: Baseline characteristics of the placebo patients, by age group

Characteristic	**<65** (n=212)	**65-75** (n=170)	**75-80** (n=70)	**>80** (n=43)
Age (years; mean, SD)*	57.1 (6.4)	69.7 (2.8)	77.3 (1.5)	82.2 (1.8)
Male gender*	189 (89.2)	127 (74.7)	47 (67.1)	31 (72.1)
Hypertension*	93 (44.1)	83 (49.1)	34 (48.6)	26 (60.5)
Diabetes*				
Insulin dependent	12 (5.7)	7 (4.1)	4 (5.9)	1 (2.4)
Non-insulin dependent	27 (12.9)	29 (17.2)	7 (10.3)	13 (31.0)
COPD*	30 (14.2)	27 (16.0)	17 (24.3)	5 (11.6)
Peripheral artery disease*	15 (7.1)	27 (16.0)	10 (14.3)	9 (20.9)
Preoperative creatinine (mcmol/l) (median, IQR)*	84 (74-94)	84 (71-100)	91 (75-102)	95 (78-110)
Recent^ myocardial infarction*	23 (10.9)	9 (5.3)	7 (10.0)	0
Left ventricular function*				
Moderate	69 (32.7)	51 (30.4)	18 (25.7)	14 (32.6)
Poor	18 (8.5)	12 (7.1)	1 (1.4)	3 (7.0)
EuroScore (median, IQR)	2 (1-4)	5 (4-7)	7 (6-9)	8 (7-10)
Type of surgery*				
CABG	123 (58.6)	72 (43.1)	25 (36.2)	12 (28.6)
CABG + valve	14 (6.7)	30 (18.0)	20 (29.0)	7 (16.7)
Single valve	25 (11.9)	27 (16.2)	6 (8.7)	13 (31.0)
Multiple valves	1 (0.5)	3 (1.8)	0	2 (4.8)
Other	47 (22.4)	35 (21.0)	18 (26.1)	8 (19.0)
Repeat surgery*	12 (5.7)	15 (8.9)	6 (8.6)	6 (14.0)
Preoperative CRP (mg/l) (median, IQR)	2 (1-5)	3 (1-6)	3 (1-8)	3 (1-8)
Duration of CPB (minutes) (median, IQR)*	114 (88-160)	113 (84-164)	141 (98-173)	129 (103-169)
Duration of AoX (minutes) (median, IQR)*	78 (56-103)	76 (56-102)	89 (60-119)	91 (69-116)

*Baseline characteristics of the placebo patients, by age group as previously defined in the DECS trial[3] and the SIRS trial.[4] Values are number (% within age group), unless otherwise indicated. ^within 90 days before surgery. EuroScore - preoperative mortality risk according to the EuroScore-I system[17]; SD – standard deviation; IQR – interquartile range; COPD – chronic obstructive pulmonary disease; CABG - coronary artery bypass surgery; CRP – C-reactive protein; CPB – cardiopulmonary bypass; AoX – aortic cross-clamp. * denotes that variable was included in multivariable analysis.*

Table 1b: Baseline characteristics of the dexamethasone patients, by age group

Characteristic	<65 (n=220)	65-75 (n=174)	75-80 (n=62)	>80 (n=34)
Age (years; mean, SD)*	56.4 (6.5)	69.8 (2.8)	77.3 (1.4)	82.9 (2.1)
Male gender*	192 (87.3)	136 (78.2)	42 (67.7)	17 (50.0)
Hypertension*	97 (44.1)	101 (58.0)	38 (61.3)	17 (50.0)
Diabetes*	7 (3.2)	9 (5.2)	7 (11.3)	0
Insulin dependent	25 (11.4)	29 (16.8)	8 (12.9)	4 (12.1)
Non-insulin dependent	8 (3.6)	26 (14.9)	8 (12.9)	8 (23.5)
COPD*	10 (4.5)	18 (10.3)	8 (12.9)	4 (11.8)
Peripheral artery disease*	84 (74-95)	86 (73-100)	82 (71-109)	89 (73-106)
Preoperative creatinine (mcmol/l) (median, IQR)*	18 (8.2)	15 (8.6)	1 (1.6)	0
Recent^ myocardial infarction*	47 (21.5)	45 (26.0)	17 (27.9)	9 (26.5)
Left ventricular function*	14 (6.4)	11 (6.4)	2 (3.3)	2 (5.9)
Moderate	2 (1-3)	5 (4-7)	6 (5-7)	8 (7-9)
Poor	56.4 (6.5)	69.8 (2.8)	77.3 (1.4)	82.9 (2.1)
EuroScore (median, IQR)	192 (87.3)	136 (78.2)	42 (67.7)	17 (50.0)
Type of surgery*				
CABG	109 (49.8)	79 (45.7)	28 (45.9)	10 (29.4)
CABG + valve	12 (5.5)	24 (13.9)	9 (14.8)	9 (26.5)
Single valve	46 (21.0)	26 (15.0)	13 (21.3)	7 (20.6)
Multiple valves	4 (1.8)	2 (1.2)	1 (1.6)	3 (8.8)
Other	48 (21.9)	42 (24.3)	10 (16.4	5 (14.7)
Repeat surgery*	9 (4.1)	15 (8.6)	2 (3.2)	0
Preoperative CRP (mg/l) (median, IQR)	1 (1-4)	2 (1-6)	2 (1-6)	3 (1-4)
Duration of CPB (minutes) (median, IQR)*	115 (87-158)	122 (82-171)	128 (86-168)	130 (93-170)
Duration of AoX (minutes) (median, IQR)*	76 (60-106)	86 (61-109)	84 (57-109)	96 (65-117)

Baseline characteristics of the dexamethasone patients, by age group as previously defined in the DECS trial[3] and the SIRS trial.[4] Values are number (% within age group), unless otherwise indicated. ^within 90 days before surgery. EuroScore - preoperative mortality risk according to the EuroScore-I system[17]; SD – standard deviation; IQR – interquartile range; COPD – chronic obstructive pulmonary disease; CABG - coronary artery bypass surgery; CRP – C-reactive protein; CPB – cardiopulmonary bypass; AoX – aortic cross-clamp.

To compare the prevalence of extreme (high) CRP values - as markers of an exaggerated early inflammatory response - among the different age groups (as defined earlier), we arbitrarily selected the upper 15th percentile of the early CRP response distribution in both study groups. Multivariable logistic regression was used to analyse the effects of age on developing an extreme early response, while correcting for the same potential confounders as in the primary analysis.

For the patients who were not discharged early and who were recruited before January 2010, we compared the trend of perioperative CRP up to day 6 after surgery across the age groups using a repeated measures analysis of variance (ANOVA).

As a sensitivity analysis, we repeated the primary analysis limited to placebo patients who had a normal preoperative CRP (defined as a baseline CRP <10 mg/l), in order to exclude the effects of an acute preoperative pro-inflammatory state.

Results

Baseline characteristics for each age group are shown in Tables 1a and 1b for the placebo group and the dexamethasone group, respectively. CRP data to define the early CRP response were available from 889 of the 985 randomised patients: 453 (91.5%) patients randomised to placebo, and 436 (89.0%) patients randomised to dexamethasone. In patients included until January 2010, CRP data up to postoperative day 6 were available in 114 (46.0%) of the 248 patients in the placebo group, and in 119 (50.6%) of the 235 patients in the dexamethasone group.

Simple linear regression analysis showed a weak, statistically significant correlation between increasing age and a reduced early CRP response (r=0.19; p<0.001). This correlation persisted after correction for potential confounders (r=0.25; p=0.001; Table

Table 2: Components of the multivariable linear regression model

Variable	Beta coefficient [95% CI]	P-value
Age (per year)	-0.58 [-0.87, -0.29]	<0.001
Gender	-2.11 [-9.08, 4.86]	0.55
Hypertension	3.44 [-2.03 to 8.90]	0.22
Diabetes	3.95 [-2.83 to 10.73]	0.25
COPD	-2.53 [-9.93 to 4.88]	0.50
Cerebrovascular disease	6.13 [-3.97 to 16.23]	0.23
Peripheral artery disease	1.61 [-7.27 to 10.50]	0.72
Preoperative creatinine level (per mcmol/l)	-0.007 [-0.06 to 0.05]	0.82
Recent^ myocardial infarction	-6.55 [-16.45 to 3.35]	0.19
Left ventricular function	1.27 [-3.37 to 5.91]	0.59
Reoperation	-2.41 [-13.55 to 8.74]	0.67
Total cardiopulmonary bypass time (per minute)	0.01 [-0.08 to 0.10]	0.83
Total aortic cross-clamping time (per minute)	-0.01 [-0.15 to 0.13]	0.88
Model constant	90.84 [69.44 to 112.24]	<0.001

Variables included in the multivariable linear regression model. ^ within 90 days before surgery. CI – confidence interval; COPD – chronic obstructive pulmonary disease; CPB – cardiopulmonary bypass; AoX – aortic cross-clamp.

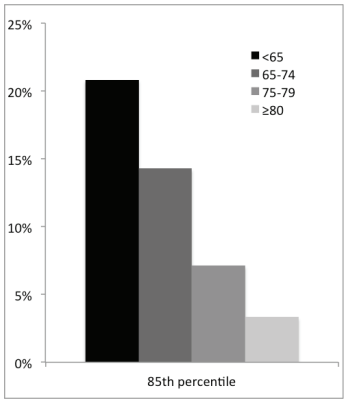
2). The sensitivity analysis restricted to placebo patients with a normal preoperative CRP yielded comparable results.

Based on the 85th percentile CRP cut-off value (86 mg/l), 67 placebo patients were categorized as having developed an extreme (high) early response. In the age groups of <65, 65-74, 75-79, and >80, these patients accounted for 18.7%, 14.3%, 4.3%, and 2.7% of patients, respectively (Figure 1). In logistic multivariable regression analysis, increasing age was significantly associated with a lower risk of developing extreme inflammation (odds ratio [OR] 0.95 per year, 95% CI 0.92 – 0.97; p<0.001).

In the dexamethasone group, there was no statistically significant correlation between age and the early CRP response (r=0.17, p=0.06). Using a cut-off for an extreme (high) response of 38 mg/l (85th percentile), also in the dexamethasone group the risk of developing a 'high' CRP response was reduced in patients of increasing age (OR 0.96 per year, 95% CI 0.96 – 0.99; p=0.003).

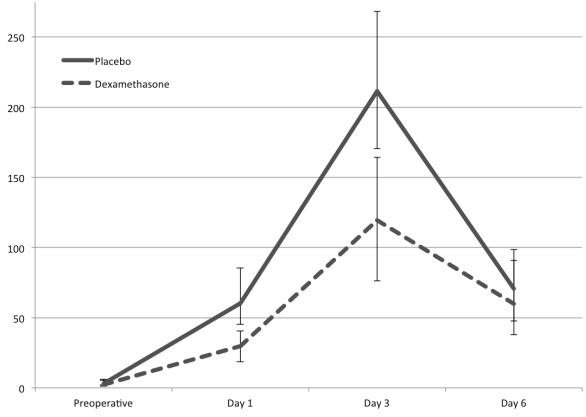
In patients with CRP data up to postoperative day 6, the postoperative CRP response was significantly lower in the dexamethasone group compared to the placebo group (p<0.001 for between-subjects effects; Figure 2). Also, for each of the age groups separately, the CRP response was lower in the dexamethasone group (p≤0.001 for each of the comparisons).
The comparison of the postoperative CRP response pattern up to day 6 between the different age groups in each of the study groups did not show a statistically significant

Figure 1: Incidence of an 'extreme' early C-reactive protein response by age group



Proportion of patients with an early CRP response exceeding the 85th percentile of the entire placebo group (i.e., >86 mg/l), by age group.

Figure 2: Perioperative C-reactive protein response in the placebo and dexamethasone groups



Perioperative CRP response in patients in the placebo and dexamethasone groups. Values on the Y-axis are median CRP values (mg/l); error bars denote the interquartile ranges.

difference in either the placebo group (p=0.37 for between-subjects effects), or the dexamethasone group (p=0.48 for between-subjects effects).

Discussion

An intense systemic inflammatory response can complicate the postoperative course following surgery, and may increase the risk of adverse outcomes. The ability to predict which patients will develop such an excessive response may aid in a more precise selection of those patients who may receive benefit from perioperative anti-inflammatory prophylaxis and avoid the use of prophylaxis on patients who will not benefit or may suffer adverse effects.

In this study, we evaluated the effects of patient age on the early postoperative inflammatory response in patients undergoing cardiac surgery. We demonstrated that the early C-reactive protein (CRP) response was inversely related to increasing patient age. In particular, the risk of developing an extreme early CRP response was considerably lower in older patients.

The rationale for this study emerged after observing contrasting effects of high-dose dexamethasone on mortality and major adverse outcomes in different age groups. In the DECS trial, in which 4494 cardiac surgery patients were randomised to dexamethasone or placebo, younger patients seemed to benefit from the intervention, but older patients were harmed.[3] A similar pattern was observed in the international SIRS trial (n=7507) where cardiac surgery patients were randomised to high-dose methylprednisolone or placebo.[4] These age-dependent divergent results in are important, because the goal of routine steroid prophylaxis in cardiac surgery is to improve outcome by reducing the pro-inflammatory response to surgery and cardiopulmonary bypass. The typical practice in heart centres that use high-dose dexamethasone or methylprednisolone for prophylactic suppression of the inflammatory response is to administer the drug in every cardiac surgery patient, in the hope of preventing inflammatory complications in the subgroup of patients who are prone to developing an exaggerated systemic inflammatory response.[7-9] Based on the results of the two aforementioned trials, it can be speculated that younger patients, as compared to older patients, are at a much higher risk of developing such an exaggerated immune response.

In recent years, the effects of ageing on the immune system have been extensively investigated. In this context, the concept of ‘inflammaging’ has been increasingly well established.[10] Inflammaging is characterized by a persistent low-grade innate immune activation with increasing age and believed to be a consequence of a cumulative lifetime exposure to antigenic load caused by both clinical and subclinical infections as well as exposure to non-infective antigens.[11] Also, it is increasingly recognized that parallel to inflammaging, the potential of the human immune system to generate an acute systemic inflammatory response to new antigens becomes

impaired with increasing age, a phenomenon known as 'immune senescence'.[5,6] Immune senescence of the innate immune response is thought to be the net result of a complex combination of diminished pro-inflammatory responses, and age-associated immune hyperreactivity.[12] The underlying causes leading to these changes are likely multifactorial, including a diminished ability of monocytes to produce cytokines, impaired neutrophil function, reduced natural killer cell cytotoxicity, and an overall loss of regenerative capacity of the bone marrow.[13,14] The mechanisms leading to these changes are still unclear, but may involve age-associated changes on a genetic and epigenetic level, which ultimately results in altered gene expression.[14] However, also effects of ageing on other systems than the immune system may play a role, such as changes in the hypothalamic–pituitary–adrenal axis[15], leading to an unbalanced response to surgical and oxidative stress.

As a result of these changes, the immune system of an older patient (>75 years) may - on average - not be able to generate the same 'potent' innate inflammatory response to surgery as a younger patient. In contrast, younger patients – especially those with an innate tendency for an exaggerated immune response to surgical trauma - might receive benefit from perioperative anti-inflammatory prophylaxis. The results of the present study are consistent with the proposed concept that there is an age-related decline in the early immune response to surgery. Moreover, they show that the incidence of an extreme early response is not equally distributed across different age groups. However, these results and hypotheses must be confirmed in prospective studies that will need to be much larger to achieve sufficient statistical power. These studies should be designed to specifically focus on the (upper) extreme of the phenotype of the systemic inflammatory response, in order to identify those mechanisms that form the basis for an exaggerated systemic inflammatory response.

One of the strengths of the current study is the relatively large number of patients with available pre- and postoperative CRP data. This provided us with the opportunity to look at a broad range of ages, as well as investigating a subset of patients with extreme (high) early CRP responses, all with sufficient statistical power. This also made it possible to correct for a number of potential confounders in a multivariable regression model. Another strength is that there is a low risk that selection bias, or confounding by indication influenced the results. Patient inclusion in the parent DECS study was prospective, patient allocation to the placebo group was random and well-concealed[3], and the CRP data that we have used were collected as part of routine perioperative care in the hospital.

Limitations of this study include its post-hoc nature, and the fact that this was only a single-centre sub study within a multicentre randomised trial cohort. Furthermore, changes in the routine care protocol during the conduct of the study led to the unavailability of CRP data from postoperative days 3 and 6 in a large group of patients. Since these missing data were not missing at random, correction by multiple

imputation was not considered justified, and we had to resort to an analysis of only complete cases for most of the secondary outcomes of this study.[16]
Another potential limitation is that C-reactive protein may not be the optimal outcome measure to describe the very complex nature of the early innate and adaptive immune responses. In addition, CRP typically peaks around postoperative day 3, while we had complete CRP data only for postoperative day 1. However, the design of the current study was prompted by the unexpected finding of a heterogeneous dexamethasone effect on both the primary composite endpoint of the DECS study and on 30 day mortality, in a predefined age subgroups analysis. In order to better understand these results, we sought to explore the hypothesis that younger patients have an increased likelihood to develop an 'exaggerated' (or deranged) pro-inflammatory response. In the current single centre subpopulation of the DECS study, C-reactive protein was the best available measure of the perioperative inflammatory response. Very few centres routinely measured perioperative CRP while the DECS study was recruiting patients. In order to avoid effects on CRP of between-centre differences in perioperative practice, we have chosen to use data from only one centre in the study that had included a relatively large number of patients.

In conclusion, we have demonstrated that the magnitude of the early postoperative C-reactive protein response in cardiac surgical patients in inversely related to patient age. Also, the risk of developing a more extreme early CRP response was lower in patients with increasing age.

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Chapter 8

Age and other pre- and intraoperative risk factors of a systemic inflammatory response syndrome (SIRS) after cardiac surgery

Jan M. Dieleman[1,2], Tim G. Coulson[1], Linda M. Peelen[2], Paul S. Myles[1], David Pilcher[1,3]

[1] Alfred Hospital and Monash University, Melbourne, Victoria, Australia
[2] University Medical Center, Utrecht, The Netherlands
[3] ANZICS Centre for Outcome and Resource Evaluation, Melbourne, Australia

Submitted for publication

Abstract

Introduction

The inflammatory response to cardiac and major non-cardiac surgery is known to vary considerably between individual patients. Several recent studies have suggested that patient age may be a substantial factor in this variability.

Objectives

To examine the association of patient age with the occurrence of a systemic inflammatory response syndrome (SIRS) during the first 24 hours after cardiac surgery.

Methods

The Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) database and Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database were linked. The association between age and postoperative SIRS was analysed using Poisson regression, both before and after including other pre- and intraoperative risk factors. Restricted cubic splines were used to assess linearity of the influence of age and to determine relevant age categories. Results are expressed as risk ratios (RR) with 95% confidence intervals (CI). The *c*-statistic was calculated to estimate the extent to which the set of risk factors could identify patients at increased risk of postoperative SIRS.

Results

Data from 25,095 patients were used in the analyses. In both univariable and multivariable models, increasing patient age was strongly associated with a decreasing incidence of SIRS. Using ≤43 years as the reference category, the RR (95% CI) for the age categories were 0.86 (0.80-0.92) for 44-63 years, 0.75 (0.70-0.80) for 64-72 years, 0.70 (0.65-0.75) for 73-83 years, and 0.73 (0.65-0.81) for >83 years, respectively. The predictive value of the final model for the occurrence of SIRS, however, was only moderate (*c*-statistic: 0.61 [95% CI 0.61-0.62]).

Conclusion

We have demonstrated that advancing patient age is associated with a decreased risk of postoperative SIRS, where patients aged over 72 years had the lowest risk. However, age and other routinely available clinical perioperative data can only to a limited extent predict the occurrence of SIRS following cardiac surgery.

Introduction

The systemic inflammatory response to cardiac and major non-cardiac surgery is known to vary substantially between individual patients, both at a clinical and biochemical level.[1,2] Patients who develop a more severe systemic inflammatory response that has the potential to derange and complicate the postoperative course, are likely to have an increased risk of adverse outcomes.[3,4] The underlying causes for this variation are likely multifactorial, and are probably a resultant of both patient genetic and other susceptibility, and the degree of intensity of perioperative stimuli that activate the systemic immune response.

For many decades, multiple strategies have been used and investigated to prevent and treat excessive systemic inflammation following surgery and trauma, as well as during sepsis. Despite promising clinical experiences with many of these strategies, results of clinical evaluation studies have thus far been largely disappointing.[5-9] In recent large randomised studies of corticosteroids for inflammatory prophylaxis in cardiac surgery, the clinical effects of treatment were heterogeneous throughout the study populations.[5,6] While certain patient subgroups received benefit from prophylaxis, particularly with respect to respiratory outcomes, others received no benefit at all. Of particular interest, a predefined subgroup analysis on the effects of steroids on mortality in different age groups indicated benefit in patients <65 years, but potential harm in patients >80 years. It has been speculated that this differential effect may be a result of changes in the intensity of the immune response related to advancing age.[10,11] Younger patients may be able to generate a more intense inflammatory response to surgery compared to elderly patients, and as such receive more benefit from anti-inflammatory prophylaxis. This concept of the potential benefits of more targeted treatment of patients who develop a more severe inflammatory response, is further supported by recent findings from studies in severe community-acquired pneumonia.[12,13] It is therefore increasingly recognised that, in order to achieve an objectively demonstrable benefit of prophylactic treatment to prevent an exaggerated inflammatory response, tools are needed that allow clinicians to more precisely target treatment to only those patient groups who are at the highest risk of developing a severe, clinically important SIRS phenotype.[5,14] The setting of elective surgery and perioperative medicine provides favourable clinical circumstances for the application of such targeted strategies for anti-inflammatory prophylaxis and treatment. Within the relatively controlled perioperative setting, the triggering insults of the inflammatory response are often short lasting, and timing is entirely predictable in elective surgery.

In the current study, we have used data from a large population of patients undergoing cardiac surgery. The main objective of this study was to examine the association of patient age with the occurrence of a systemic inflammatory response syndrome (SIRS) during the first 24 hours after cardiac surgery.

Methods

Study cohort

The analyses were carried out using a linked patient dataset from the Australian and New Zealand Intensive Care Society Adult ICU Patient Database (ANZICS-APD), and the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) Database, which has been previously described.[15]

The Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgical Database (ANZSCTS-CSD) was developed in 2001 and includes data from public and private hospitals in both countries. For all cardiac surgical procedures occurring at the participating hospitals demographic data; pre-, intra-, and postoperative data; outcomes; and derived scores are recorded. The ANZICS-APD is one of four registries run by the ANZICS Centre for Outcome and Resource Evaluation. The ANZICS-APD contains de-identified patient data on >1.4 million intensive care unit (ICU) admissions from 85% of ICUs in Australia and New Zealand. It contains demographic, diagnostic, and physiologic data from the first 24 hours of ICU admission for calculation of severity of illness scores such as the Acute Physiological and Chronic Health Evaluation (APACHE) III score.[16] It can therefore provide information on the immediate postoperative period. Both databases are structurally audited to assess reliability of submitted data.[17-19]

For the current analysis, we included all patients from the linked dataset who underwent surgery for coronary artery bypass grafting and/or valve replacement or -repair in the period from 2008 to 2013, and whom had data recorded in both databases (Figure 1). Only data from centres that contributed >400 patients to the combined database were used. Furthermore, patients younger than 18 years, as well as patients with unreliable values for body mass index (BMI) (<14 kg/m^2), height (<135 cm), or weight (<30 kg), were excluded from the analysis.

Outcome definition

For this study, postoperative SIRS was defined as the presence of any two (or more) criteria of the original SIRS definition[20], with the exception of the hypothermia criterion, in the first 24 hours after cardiac surgery (Appendix Table 1). We adapted the temperature criterion by using hyperthermia only, as hypothermia in the immediate postoperative period is likely a result of intraoperative cooling during cardiopulmonary bypass and body heat loss after decannulation, rather than a sign of SIRS.

Risk factors

Potential risk factors for postoperative SIRS were selected from the linked study database. Their selection for the analysis was based either on a known association between a risk factor and postoperative SIRS, or on pathophysiologic plausibility of a risk factor's effect on postoperative SIRS (i.e., generally accepted effects).

We were primarily interested in the association of age with postoperative SIRS. We expected this association to be non-linear; hence the shape and strength of the multivariable relation between age and SIRS were evaluated using a flexible model-fitting approach involving restricted cubic spline functions (by visual inspection of plots and assessment of model fit) and fractional polynomials. Based on the observed knots in these functions, 5 age categories were defined for the final modelling approach.
Besides patient age, other preoperative risk factors included gender, BMI, smoking history, hypertension, diabetes, preoperative kidney function (KDIGO classification[21]), dialysis, peripheral vascular disease, respiratory disease, use of immunosuppressive medication, history of chronic heart failure, previous myocardial infarction, previous cardiac surgery, left ventricular impairment, number of diseased coronary systems, planned coronary artery bypass grafting, planned valve surgery, and planned use of cardiopulmonary bypass. Additional intraoperative risk factors included cardiopulmonary bypass time (with category ranges based on the quartiles of the distribution), the use of cardioplegia, intraoperative use of an intra-aortic balloon pump (IABP), and the intraoperative transfusion of blood products.

Statistical analysis

The incidences of all risk factors described above were summarized. Regression modelling was used to investigate associations between these risk factors and the outcome of SIRS, and to correct for relevant interactions between risk factors. We used Poisson regression analysis, as we expected the incidence of SIRS to be considerably larger than 10%, in which case odds ratios (OR) resulting from logistic regression analysis would considerably overestimate the risk ratios (RR).[22] Associations between risk factors and the presence of SIRS were expressed as RRs, with their accompanying 95% confidence intervals (95% CI).
To assess to which extent the models could be used to identify patients at increased risk to develop postoperative SIRS, we assessed the discriminative performance of final model (i.e., to which extent does the model distinguish between patients who do and who do not develop SIRS in the postoperative period). Discrimination was expressed in terms of the *c*-statistic, which in this case amounts to the area under the receiver operating characteristic curve (AUROC) with its accompanying 95% confidence interval.[23]

Sensitivity analyses

In order to assess the robustness of the outcome of SIRS (according to the original cut-off of two criteria) in a cardiac surgical population, we repeated the modelling process as described above for cut-off values of 3 and 4 criteria.

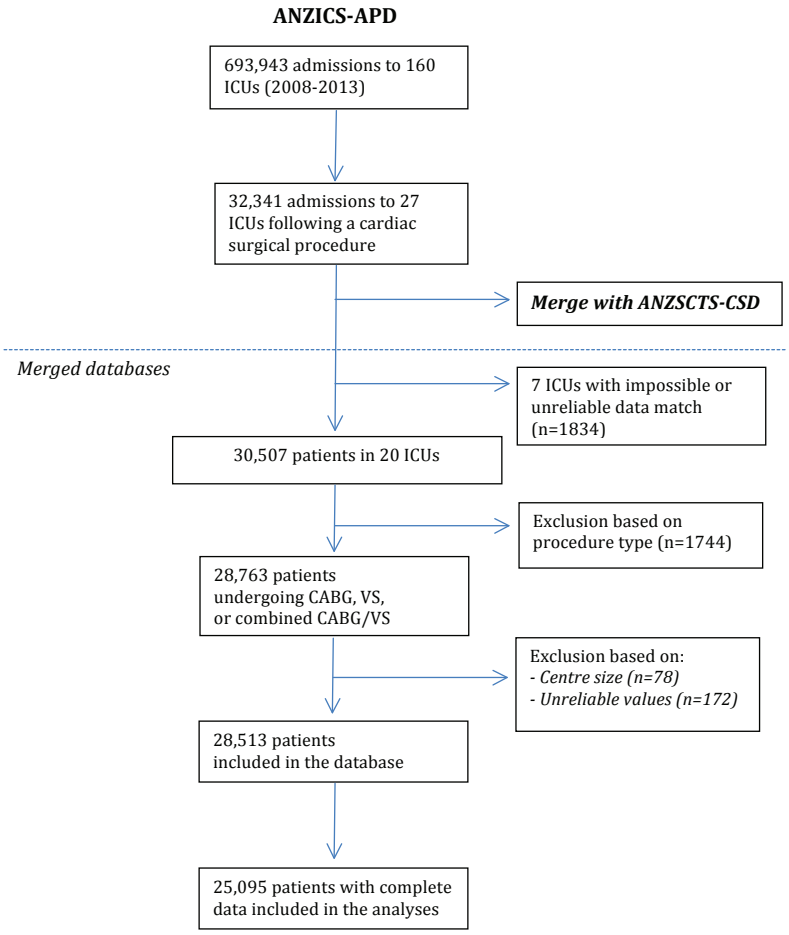
Throughout the analyses we used a level of significance of 0.05. Analyses were carried out in SPSS Statistics v21.0 (IBM, New York, NY) and R statistical software

(v3.2) using the mice library for multiple imputation, splines library to fit restricted cubic spline functions, and the fracpoly function for inclusion of fractional polynomials.

Results

Data from 28,763 patients from a total of 20 centres were available after linking the ANZICS-APD and ANZSCTS-CSD. After exclusion of patients from centres contributing <400 patients (1 centre, 78 patients) and of patients with preoperative values that were considered unreliable (172 patients in total), data from 28,513 patients were included in the analyses (Figure 1). The incidence of missing data was

Figure 1: CONSORT flow diagram



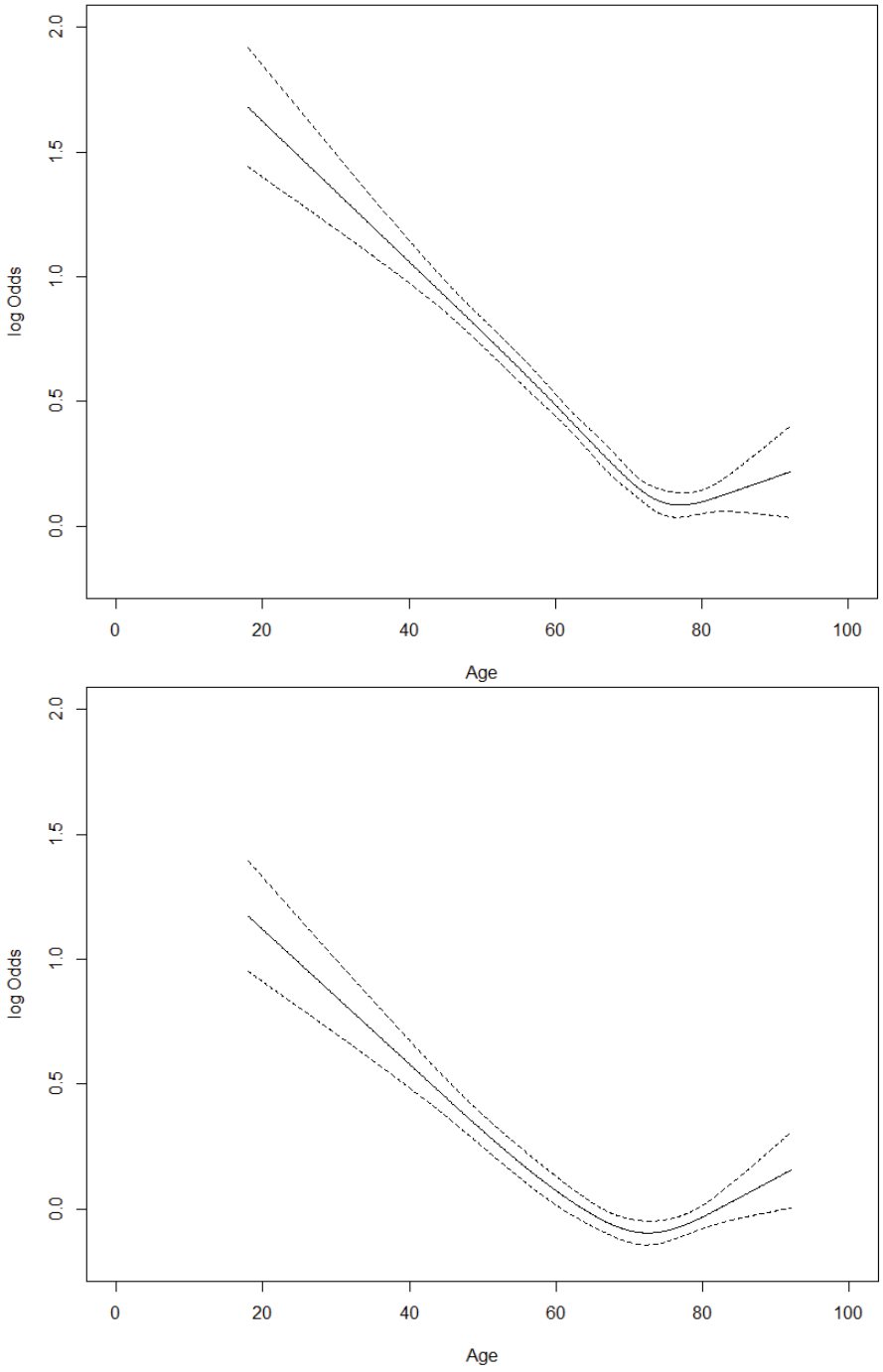
CONSORT flow diagram showing original databases and final merged database. ANZICS-APD, Australian and New Zealand Intensive Care Society Adult Patient Database; ICUs, intensive care units; ANZSCTS-CSD, Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database; CABG, coronary artery bypass graft; VR, valve repair/replacement.

Table 1: Pre- and intraoperative characteristics of the study cohort and proportions of missing values

Variables, no. (%)		SIRS (n=14,735)	No SIRS (n=10,360)	% missing values*
Age	≤43	956 (6.5)	315 (3.0)	0.2
	44-63	5249 (35.6)	2895 (27.9)	
	64-72	4074 (27.6)	3148 (30.4)	
	73-83	3928 (26.7)	3562 (34.4)	
	≥84	528 (3.6)	440 (4.2)	
Preoperative variables				
Male gender		10,928 (74.2)	7504 (72.4)	<0.1
BMI	<18.5	182 (1.2)	109 (1.1)	<0.1
	18.5 to <25	3385 (23.0)	2756 (26.6)	
	25 to <30	5659 (38.4)	4245 (41.0)	
	30 to <35	3545 (24.1)	2328 (22.5)	
	35 to <40	1332 (9.0)	689 (6.7)	
	≥40	632 (4.3)	233 (2.2)	
Smoking history	Never	5397 (36.6)	4141 (40.0)	0.5
	Past	6914 (46.9)	4953 (47.8)	
	Current	2424 (16.5)	1266 (12.2)	
Hypertension		10,874 (73.8)	7893 (76.2)	0.2
Diabetes	IDDM	1357 (9.2)	713 (6.9)	<0.1
	NIDDM	3457 (23.5)	2222 (21.4)	
Kidney function (KDIGO classification[21])	G1	6513 (44.2)	3504 (33.8)	0.3
	G2	4817 (32.7)	3974 (38.4)	
	G3a	1915 (13.0)	1671 (16.1)	
	G3b	1005 (6.8)	886 (8.6)	
	G4	336 (2.3)	232 (2.2)	
	G5	149 (1.0)	93 (0.9)	
Preoperative dialysis		269 (1.8)	136 (1.3)	0.2
Peripheral vascular disease		1388 (9.4)	953 (9.2)	0.2
Respiratory disease	Mild	1444 (9.8)	988 (9.5)	0.2
	Moderate	511 (3.5)	293 (2.8)	
	Severe	90 (0.6)	41 (0.4)	
Immunosuppressive rx		446 (3.0)	315 (3.0)	<0.1
History of CHF		3160 (21.4)	2030 (19.6)	0.2
Recent MI	≤21 days	3555 (24.1)	1892 (18.3)	0.3
	>21 days	2573 (17.5)	1759 (17.0)	
Previous cardiac surgery		2741 (18.6)	1926 (18.6)	0.1
Left ventricular impairment	Mild	4330 (29.4)	2897 (28.0)	1.9
	Moderate	2044 (13.9)	1210 (11.7)	
	Severe	669 (4.5)	274 (2.6)	
# of diseased coronary systems	1	1108 (7.5)	880 (8.5)	0.6
	2	2601 (17.7)	1890 (18.2)	
	3	7259 (49.3)	4728 (45.6)	
CABG		10,797 (73.3)	7357 (71.0)	<0.1
Valve surgery	No	8831 (59.9)	5875 (56.7)	3.3
	1 valve	5334 (36.2)	4132 (39.9)	
	≥2 valves	570 (3.9)	353 (3.4)	
CPB use		14,683 (99.6)	10,328 (99.7)	<0.1
Intraoperative variables				
CPB time (if used)	<74 mins	3269 (22.2)	2215 (21.4)	0.3
	74-98 mins	3954 (26.8)	2756 (26.6)	
	99-131 mins	3850 (26.1)	2805 (27.1)	
	>131 mins	3662 (24.9)	2584 (24.9)	
Cardioplegia use (if CPB used)		14,425 (97.9)	10,177 (98.2)	0.1
Intraoperative IABP		824 (5.6)	338 (3.3)	0.2
Any intraoperative transfusion		6966 (47.3)	5067 (48.9)	0.3

*Values are numbers (%). BMI: body mass index; IDDM: insulin dependent diabetes mellitus; NIDDM: non-insulin dependent diabetes mellitus; CHF: chronic heart failure; MI: myocardial infarction; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump. *Percentage of missing values per variable in the full database of 28,513 patients.*

Figure 2: Spline functions for age versus SIRS



Spline functions for patient age versus the log odds of SIRS (defined as ≥2 criteria). The upper panel represents the spline function for the univariable analysis, the lower panel represents the spline functions of the adjusted multivariable analysis.

Table 2: Predictors in the univariable and multivariable models

Predictors		Univariable model RR	[95% CI]	Multivariable model RR	[95% CI]
Age	≤43	*Ref*		*Ref*	
	44-63	0.86	[0.80, 0.92]	0.83	[0.77, 0.90]
	64-72	0.75	[0.70, 0.80]	0.75	[0.70, 0.82]
	73-83	0.70	[0.65, 0.75]	0.73	[0.67, 0.79]
	≥84	0.73	[0.65, 0.81]	0.77	[0.69, 0.87]
Preoperative variables					
Male gender				1.01	[0.97, 1.05]
BMI	<18.5			1.10	[0.95, 1.28]
	18.5 to <25			*Ref*	
	25 to <30			1.03	[0.99, 1.08]
	30 to <35			1.07	[1.02, 1.13]
	35 to <40			1.13	[1.06, 1.22]
	≥40			1.23	[1.12, 1.34]
Smoking history	Never			*Ref*	
	Past			1.01	[0.97, 1.05]
	Current			1.05	[0.99, 1.11]
Hypertension				0.97	[0.93, 1.01]
Diabetes	IDDM			1.09	[1.03, 1.16]
	NIDDM			1.06	[1.02, 1.10]
Kidney function (KDIGO classification[21])	G1			*Ref*	
	G2			0.93	[0.89, 0.97]
	G3a			0.91	[0.86, 0.97]
	G3b			0.91	[0.84, 0.98]
	G4			0.95	[0.83, 1.09]
	G5			1.00	[0.71, 1.42]
Preoperative dialysis				0.94	[0.63, 1.39]
Peripheral vascular disease				1.01	[0.96, 1.07]
Respiratory disease	Mild			1.04	[0.94, 1.16]
	Moderate			1.17	[0.97, 1.40]
	Severe			1.11	[0.65, 1.87]
Immunosuppressive rx				1.02	[0.93, 1.12]
History of CHF				1.03	[0.99, 1.08]
Recent MI	≤21 days			1.12	[1.07, 1.17]
	>21 days			1.03	[0.98, 1.08]
Previous cardiac surgery				0.97	[0.93, 1.02]
Left ventricular impairment	Mild			1.05	[1.01, 1.09]
	Moderate			1.06	[1.01, 1.12]
	Severe			1.16	[1.06, 1.26]
# of diseased coronary systems	1			1.02	[0.91, 1.13]
	2			1.03	[0.93, 1.15]
	3			1.07	[0.96, 1.19]
CABG				1.02	[0.91, 1.13]
Valve surgery	No			*Ref*	
	1 valve			0.97	[0.44, 2.17]
	≥2 valves			1.05	[0.47, 2.34]
CPB use				0.93	[0.71, 1.23]
Intraoperative variables					
CPB time (minutes)	<74			*Ref*	
	74-98			0.98	[0.94, 1.03]
	99-131			0.96	[0.91, 1.01]
	>131			0.96	[0.91, 1.01]
Cardioplegia use (if CPB used)				0.96	[0.85, 1.07]
Intraoperative IABP				1.12	[1.04, 1.21]
Any intraoperative transfusion				0.99	[0.96, 1.03]
Intercept of full model				0.73	[0.55, 0.99]
C-statistic of full model				0.61	[0.61, 0.62]

BMI: body mass index; IDDM: insulin dependent diabetes mellitus; NIDDM: non-insulin dependent diabetes mellitus; CHF: chronic heart failure; MI: myocardial infarction; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump; Ref: reference category. Included interaction terms: [kidney function x dialysis]; [smoking x respiratory disease]; [CABG x valve surgery]

relatively low for each of the individual variables, ranging from 0% to 3.3% (Table 1). In our complete case analysis of the data we included 25,095 patients.

The overall incidence of the outcome of SIRS according to the original SIRS criteria (i.e., 2 or more criteria present) was 58.7%. Following the restricted cubic splines analysis of the multivariable association between age and SIRS (Figure 2), age categories were defined as ≤43, 44-63, 64-72, 73-83, and >83 years. The incidence of SIRS decreased with increasing patient age, although in the highest age category the incidence slightly increased again compared to the preceding age category (73-83 years). The respective RR and 95% CI for the age categories (using ≤43 years as the reference category) were 0.86 (0.80-0.92), 0.75 (0.70-0.80), 0.70 (0.65-0.75), and 0.73 (0.65-0.81) (Table 2; all p-values <0.001).

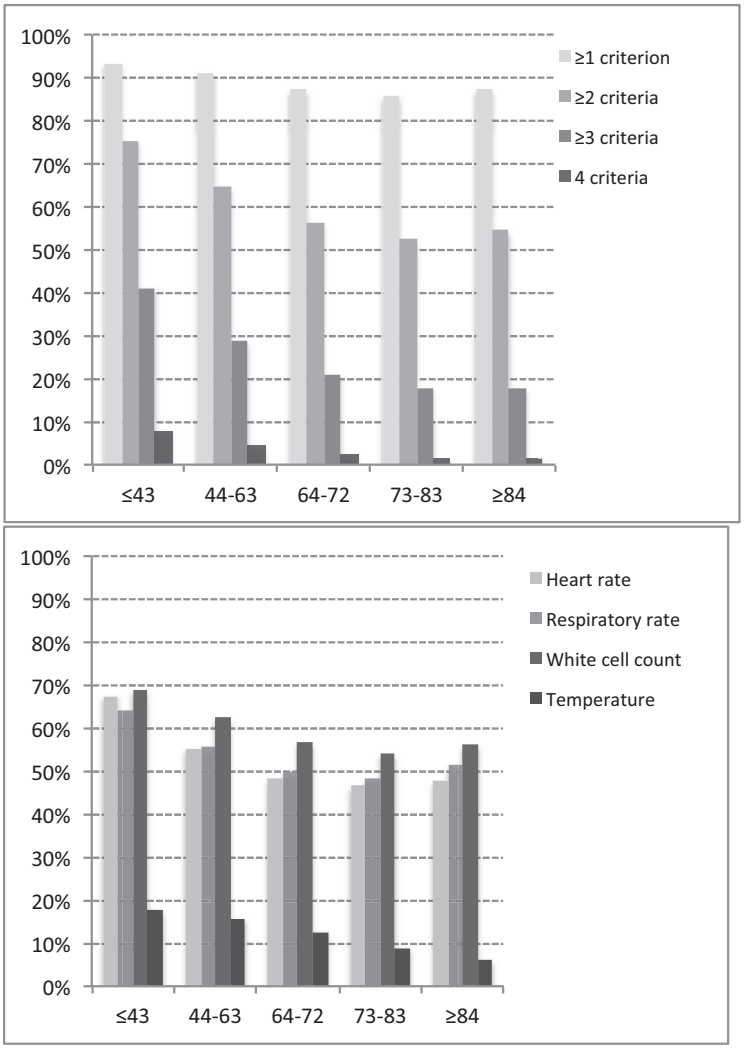
Increasing patient age remained strongly associated with a decreasing incidence of SIRS after correction for other risk factors and relevant interactions (Table 2, Appendix Table 2). Other risk factors that were associated with SIRS were a BMI>30, diabetes, a recent myocardial infarction (<21 days before surgery), left ventricular impairment, and the intraoperative use of an IABP. When using the final model to

Table 3: Multivariable effect estimates of the relative risk of SIRS in different age groups in the sensitivity analyses*

		≤43	44-63	64-72	73-83	>83	C-statistic
SIRS cut-off value	≥2 criteria	*Ref*	0.83 [0.77, 0.89]	0.75 [0.69, 0.81]	0.72 [0.66, 0.78]	0.78 [0.69, 0.88]	0.61 [0.61, 0.62]
	≥3 criteria	*Ref*	0.63 [0.57, 0.70]	0.49 [0.43, 0.55]	0.45 [0.40, 0.51]	0.50 [0.41, 0.61]	0.63 [0.63, 0.64]
	4 criteria	*Ref*	0.48 [0.37, 0.61]	0.31 [0.23, 0.41]	0.20 [0.15, 0.29]	0.25 [0.13, 0.47]	0.71 [0.69, 0.73]
Separate criteria	Temperature	*Ref*	0.78 [0.67, 0.92]	0.65 [0.55, 0.77]	0.49 [0.41, 0.59]	0.42 [0.31, 0.58]	0.65 [0.64, 0.66]
	White cell count	*Ref*	0.92 [0.85, 0.99]	0.86 [0.79, 0.93]	0.83 [0.76, 0.91]	0.86 [0.77, 0.98]	0.61 [0.61, 0.62]
	Heart rate	*Ref*	0.78 [0.72, 0.84]	0.69 [0.64, 0.76]	0.69 [0.63, 0.75]	0.72 [0.64, 0.82]	0.61 [0.60, 0.61]
	Respiratory rate	*Ref*	0.81 [0.75, 0.88]	0.75 [0.69, 0.81]	0.75 [0.68, 0.82]	0.83 [0.73, 0.94]	0.58 [0.57, 0.59]

*Values are RR (95% CI) for each age category. C-statistic represents the AUROC (95% CI). Ref: reference category. * For the sensitivity analyses, only data from patients with complete data for each of the separate criteria were used (n=24,232). To aid comparability between the models, the effect estimates for the initial model (i.e., ≥2 criteria) have been recalculated using this same dataset of 24,232 patients.*

Figure 1: CONSORT flow diagram



CONSORT flow diagram showing original databases and final merged database. ANZICS-APD, Australian and New Zealand Intensive Care Society Adult Patient Database; ICUs, intensive care units; ANZSCTS-CSD, Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database; CABG, coronary artery bypass graft; VR, valve repair/replacement.

predict SIRS, model performance was only moderate, with a C-statistic of 0.61 (95% CI 0.61-0.62).

Sensitivity analyses

In the analyses of the association between age and SIRS with a stricter SIRS cut-off (i.e., ≥3 or 4 SIRS criteria), increasing age remained associated with a decreasing

incidence of postoperative SIRS (Table 3, and Figure 3, upper panel). Differences in effect sizes were generally larger between the age categories, and predictive performance of the models improved (Table 3).
When the associations between age and each of the individual SIRS criteria were analysed separately, each of the models showed a decrease of their incidence with increasing patient age (Table 3, and Figure 3, lower panel). However, the effect of age on SIRS in the model with the temperature criterion was the most similar to that in the models with cumulative SIRS criteria.

Discussion

In this study, we used data from a large, well-validated binational ICU database to study the association of patient age with the occurrence of a postoperative systemic inflammatory response syndrome (SIRS) following cardiac surgery. We demonstrated that increasing patient age was associated with a decreasing incidence of postoperative SIRS (according to established criteria), whereby patients aged over 72 years had the lowest risk. However, based on age and other routinely collected clinical variables, the multivariable model had only moderate discriminatory value for predicting which patients are at risk of developing postoperative SIRS.

The inverse association between patient age and the incidence of postoperative SIRS that was demonstrated in this study is consistent with our hypothesis that ageing patients have an overall reduced ability of the immune to generate an acute immune response. This phenomenon is increasingly recognised, and more generally known as immunosenescense.[10,24] The clinical effects of ageing on the immune system have mainly been studied in chronic disease and in the context of minor stressors such as vaccination.[25] However, very few studies have looked at the association between age and the immune response after major stressors, such as major surgery or trauma. Most of the work around this topic published so far has been performed in trauma patients, although these studies are relatively small. In this setting, the inflammatory response in the elderly was found to be increasingly variable and, on average, less pronounced compared to younger patients.[26,27]

Our finding of a relatively increased acute inflammatory response in younger patients is also consistent with the results of two recent large trials of anti-inflammatory prophylaxis with corticosteroids in cardiac surgery[5,6]. In these studies, most treatment benefit was observed in the younger age groups. With an on average increased immune response in younger patients, the likelihood of an exaggerated inflammatory response may increase as well. Such an exaggerated response can set the stage for an on-going deregulated systemic immune and inflammatory cascade, with an associated risk of complications and adverse outcomes. Younger patients may therefore be more likely to receive benefit from anti-inflammatory therapy.

Pre- and intraoperative estimation of the postoperative inflammatory response that can be expected in individual cardiac surgical patients is a first and important step towards a more targeted approach to SIRS prophylaxis. The results of this study do suggest that postoperative SIRS is indeed associated with several clinical variables that are known already before cardiac surgery. Most of these factors, such as diabetes and obesity, are disease states that are typically associated with chronic low-grade inflammation. However, the final multivariable model including these factors had only moderate performance when using it to predict SIRS, which may have several reasons. First, despite a relatively large number of variables and interactions that were included in the model, there is always the risk of having missed out on important risk factors that could not be accounted for in the analysis. Most of the variables that were available in the linked database are commonly collected variables in populations of cardiovascular and critically ill patients. However, many patient characteristics that predispose to inflammatory syndromes, such as environmental or genetic factors, may be even more important determinants.[28-30] These variables, in particular in the perioperative setting, are still not well defined, and as such not routinely collected.
Another reason for the moderate predictive value of our models may be that the SIRS criteria are not the most appropriate outcome measure for a clinically important systemic inflammatory response following cardiac surgery. Standardized criteria for a SIRS were described more than two decades ago[20], with the aim of specifically classifying patients with sepsis based on signs that form part of a clinically important inflammatory syndrome. Ever since, these criteria have been widely adopted throughout clinical practice and research in critical care. However, the high incidence of SIRS in this study demonstrates that the clinical relevance of the use of the original SIRS criteria in the setting of the early postoperative period following cardiac surgery may be limited. Besides systemic inflammation, other clinical syndromes may have manifested with SIRS criteria, such as tachycardia due to bleeding or postoperative pain. Also, SIRS criteria may have been present in some patients before surgery, for example in patients undergoing valve replacement for endocarditis. In addition, the sensitivity analyses in this study demonstrate that of the four SIRS criteria, only the component that is likely most specific for early, acute inflammation (i.e., hyperthermia) had the strongest association with patient age. Only when we used stricter SIRS cut-off values, and as such had a higher proportion of patients with SIRS who fulfilled the hyperthermia criterion, the predictive value of the model increased. Likewise, several other recent studies have shown the limitations of the SIRS criteria. In a recent study of 2764 patients who were admitted to the ICU following cardiac surgery, 96% of patients met two or more SIRS criteria during the first 24 hours of their admission.[2] And even in the setting of sepsis, the presence of signs meeting two or more SIRS criteria was shown to be common in all patients in the ICU, and to have rather poor discriminative value for severe sepsis.[16]

A strength of this study is that the population that we have used for developing the prediction model in this study, forms part of large intensive care and cardiac surgery databases from the ANZICS Adult ICU Patient Database, and the ANZSCTS Database,

respectively. Both databases contain prospectively collected, well-validated data[17-19], and are increasingly used for research purposes.[15,16,31] This underlines the excellent quality of these databases and, at least in part, compensates for the retrospective nature of this study. However, the resolution of the available data in both databases was limited to only the highest and lowest values of the first 24 hours postoperatively in the ICU. Future prospective studies are needed that collect more phenotypic and genomic detail around the perioperative inflammatory response, in order to be able to more precisely predict an individual patient's predisposition to inflame.
Another limitation of this study is that, despite the fact that the incidence of missing values in individual variables was low, only 88% of the cases had complete data for all variables and could as such be used in the final multivariable model. The decision to use a complete case analysis, which was based on a pre-planned imputation threshold of >5% missing data in individual variables, could theoretically have introduced selection bias.[32,33] Also, additional selection bias may have occurred due to the fact that not all patients from the two databases could be linked.[15] Furthermore, the age categories that we have used are different from commonly used risk categories in cardiac surgery. However, since the quantitative effects of age on the inflammatory response are still largely unknown, we have decided to use restricted cubic splines based on the data to determine these age ranges rather then just choosing 'arbitrary' categories.

In conclusion, we have demonstrated that advancing patient age is associated with a decreasing risk of postoperative SIRS, whereby patients aged over 72 years had the lowest risk. However, age and other routinely available clinical perioperative data can predict the occurrence of SIRS following cardiac surgery only to a limited extent.

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Appendix to Chapter 8

Appendix Table 1: Overview of the criteria used in our analyses to define a systemic inflammatory response syndrome (SIRS; adapted from original SIRS criteria, defined by Bone, et al[20])

Criterion	Cut-off values
Temperature*	>38.0 °C
White cell count	>12 $\cdot 10^9$ cells/L, *or* <4 $\cdot 10^9$ cells/L
Tachycardia	Heart rate >90 beats/min
Tachypnea	Respiratory rate >20/min, *or* P_aCO_2 <32 mm Hg

** The low-temperature (<36.0 °C) criterion for the original SIRS criteria was excluded as a contributing criterion for the outcome of this study, since hypothermia in the immediate postoperative period is likely a result of intraoperative cooling during cardiopulmonary and body heat loss after decannulation, rather than a sign of SIRS.*

Appendix Table 2: Additional models: model 2 (only preoperative variables, without interaction terms) and model 3 (pre- and intraoperative variables, without interaction terms)

Predictors		Model 2 RR	[95% CI]	Model 3 RR	[95% CI]
Age	≤43	*Ref*		*Ref*	
	44-63	0.83	[0.77, 0.89]	0.83	[0.77, 0.90]
	64-72	0.75	[0.69, 0.81]	0.75	[0.70, 0.81]
	73-83	0.73	[0.67, 0.79]	0.73	[0.67, 0.79]
	≥84	0.78	[0.69, 0.88]	0.78	[0.69, 0.88]
Preoperative variables					
Male gender		1.00	[0.96, 1.04]	1.00	[0.97, 1.05]
BMI	<18.5	1.10	[0.95, 1.28]	1.10	[0.95, 1.28]
	18.5 to <25	*Ref*		*Ref*	
	25 to <30	1.03	[0.99, 1.08]	1.03	[0.99, 1.08]
	30 to <35	1.07	[1.02, 1.13]	1.07	[1.02, 1.13]
	35 to <40	1.13	[1.06, 1.21]	1.14	[1.06, 1.22]
	≥40	1.23	[1.12, 1.34]	1.23	[1.12, 1.34]
Smoking history	Never	*Ref*		*Ref*	
	Past	1.01	[0.97, 1.05]	1.01	[0.97, 1.05]
	Current	1.04	[0.99, 1.10]	1.04	[0.99, 1.10]
Hypertension		0.97	[0.93, 1.00]	0.97	[0.93, 1.01]
Diabetes	IDDM	1.09	[1.03, 1.16]	1.09	[1.03, 1.16]
	NIDDM	1.06	[1.01, 1.10]	1.06	[1.02, 1.10]
Kidney function (KDIGO classification[21])	G1	*Ref*		*Ref*	
	G2	0.92	[0.89, 0.97]	0.93	[0.89, 0.97]
	G3a	0.91	[0.86, 0.97]	0.92	[0.86, 0.97]
	G3b	0.90	[0.84, 0.98]	0.91	[0.84, 0.98]
	G4	0.94	[0.83, 1.06]	0.94	[0.83, 1.06]
	G5	0.88	[0.71, 1.09]	0.88	[0.71, 1.09]
Preoperative dialysis		1.10	[0.94, 1.29]	1.10	[0.94, 1.29]
Peripheral vascular disease		1.01	[0.96, 1.07]	1.01	[0.96, 1.07]
Respiratory disease	Mild	1.02	[0.96, 1.08]	1.02	[0.96, 1.08]
	Moderate	1.08	[0.99, 1.18]	1.08	[0.99, 1.18]
	Severe	1.19	[0.97, 1.46]	1.19	[0.97, 1.46]
Immunosuppressive rx		1.02	[0.93, 1.12]	1.02	[0.93, 1.13]
History of CHF		1.04	[0.99, 1.08]	1.03	[0.99, 1.08]
Recent MI	≤21 days	1.12	[1.07, 1.18]	1.12	[1.07, 1.17]
	>21 days	1.03	[0.98, 1.08]	1.03	[0.98, 1.08]
Previous cardiac surgery		0.97	[0.93, 1.02]	0.97	[0.93, 1.02]
Left ventricular impairment	Mild	1.05	[1.01, 1.09]	1.05	[1.01, 1.09]
	Moderate	1.07	[1.02, 1.13]	1.06	[1.01, 1.12]
	Severe	1.19	[1.09, 1.29]	1.15	[1.06, 1.26]
# of diseased coronary systems	1	1.02	[0.92, 1.13]	1.02	[0.91, 1.13]
	2	1.04	[0.93, 1.15]	1.03	[0.93, 1.15]
	3	1.06	[0.95, 1.18]	1.07	[0.96, 1.19]
CABG		1.01	[0.91, 1.12]	1.02	[0.91, 1.13]
Valve surgery	No	*Ref*		*Ref*	
	1 valve	0.97	[0.43, 2.16]	0.97	[0.44, 2.17]
	≥2 valves	1.03	[0.46, 2.30]	1.04	[0.47, 2.34]
CPB use		0.91	[0.69, 1.20]	0.93	[0.70, 1.22]
Intraoperative variables					
CPB time (minutes)	<74			*Ref*	
	74-98			0.98	[0.94, 1.03]
	99-131			0.96	[0.91, 1.01]
	>131			0.96	[0.91, 1.01]
Cardioplegia use (if CPB used)				0.96	[0.85, 1.07]
Intraoperative IABP				1.12	[1.04, 1.21]
Any intraoperative transfusion				0.99	[0.96, 1.03]

BMI: body mass index; IDDM: insulin dependent diabetes mellitus; NIDDM: non-insulin dependent diabetes mellitus; CHF: chronic heart failure; MI: myocardial infarction; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump; Ref: reference category

Chapter 9

General discussion

Steroids in cardiac surgery: an eminence-based routine

The use of high-dose corticosteroid drugs ('steroids') for prophylaxis of perioperative systemic inflammation in cardiac surgery is a topic of increasing controversy. With severe SIRS gradually becoming less of an issue for the every-day cardiac surgical patient, it is now increasingly recognised that the scientific evidence necessary to justify the routine use of perioperative high-dose steroids – especially regarding the effects on clinical outcomes and safety – was largely lacking.[1-4] With this evidence gap, local experience and subjective 'belief' have essentially been the driving forces that determined practice of corticosteroid prophylaxis in most places, resulting in large global variation. This practice variability formed the ideal basis for a definitive, large pragmatic study - the DExamethasone for Cardiac Surgery (DECS) study, described in this thesis. The DECS study randomised between two widely accepted routines and focussed on the effects of steroids on important patient outcomes.

Inherent weaknesses of the available evidence

As part of the design and preparation process for this study, we first performed a systematic review and meta-analysis of all randomised studies of corticosteroids in cardiac surgery that were available until 2009.[4] Around the same time our (Cochrane) review was published, three other independent meta-analyses around the exact same topic appeared.[3,5,6] However, as a result of inherent qualitative limitations of the available evidence, the results of each of these four meta-analyses remain of limited value. The main reason for this is that important methodological issues arise when using data from a large number of relatively small studies, most of which had a primary focus on intermediate endpoints, rather than on relevant patient effects.[7,8] Furthermore, the available studies were very heterogeneous, spanning a 35-year period of dramatic improvements in the quality of surgical techniques, cardiopulmonary bypass and perioperative care[9-11], and a subsequent decreased perioperative risk. A pooled analysis of such data is likely to be dominated by results from the earlier studies with the highest incidence of adverse outcomes, but which are least relevant for current clinical practice.

A large randomised trial to study important clinical outcomes

Our DECS study[12,13] was designed as a large pragmatic randomised clinical trial in a broad cardiac surgical population, with the aim to provide definitive evidence whether or not routine corticosteroids have benefit on relevant patient outcomes .[14] Previous large trials in cardiac surgery and interventional cardiology have traditionally used death and major adverse cardiovascular events in the perioperative period as their primary outcomes.[13,15-18] However, for the composite primary endpoint of the DECS study, it was considered important to also include events related to non-cardiovascular organ failure commonly associated with severe SIRS, such as respiratory and acute renal failure.

Combining these adverse events, however, led to an instinctive discrepancy between the severity of each of the endpoint components. Yet, an increasing body of evidence shows that even acute, transient organ failure in the perioperative period is strongly associated with worse long-term outcomes, including mortality.[19-21] The relative importance of components of a composite outcome is therefore not easy to determine, unless the long-term implications are known.

DECS study results: benefit and harm

Our DECS study did not demonstrate a statistically significant difference on the primary composite endpoint between the two treatment arms. As a consequence, there is no evidence to suggest that cardiac surgery patients have an overall benefit from corticosteroids and should therefore receive routine dexamethasone prophylaxis. However, further analysis of pre-planned secondary endpoints and subgroups did show some substantial treatment effects, which formed an interesting but complex blend of potential benefit[13,22], absence of anticipated clinical effects[23-25], and also possible harm.[26,27]

Of the 'secondary' effects of dexamethasone, its overall pulmonary benefit was probably the most marked effect, which was demonstrable on multiple levels. The most prominent effect was a 31% reduction of the incidence of respiratory failure, associated with a reduced duration of postoperative mechanical ventilation, and a reduced length of postoperative stay in the ICU and the hospital. Each of these effects contributed to the € 1084 cost benefit per patient, that was demonstrated in the formal cost-effectiveness analysis of the DECS study. The observed pulmonary benefits in the DECS study may be the result of an improved pulmonary condition due to less inflammatory effects on the lung tissue, and are consistent with results from previous smaller studies.[28,29] Also, the incidence of postoperative pneumonia was reduced in the dexamethasone group. This effect was contrary to our expectations, since the potential for an increased risk of infections as a result of immunosuppression was one of the major safety concerns associated with the use of high-dose corticosteroids.[30] Interestingly, similar effects of steroids on infectious complications have been observed in several recent studies in ICU patients with trauma or sepsis.[31,32]

The DECS study also generated data that indicated the potential for harm from dexamethasone treatment. Increased postoperative hyperglycaemia, with markedly higher insulin requirements[26], confirmed the well-known steroids side-effect of increased insulin-resistance. Although the jury is still out on whether or not hyperglycaemia is associated with adverse outcomes in cardiac surgical patients, it should be considered a significant downside of routine steroid prophylaxis, in particular in patients who are unlikely to benefit otherwise. It has even been suggested that increased postoperative hyperglycaemia following dexamethasone administration may have contributed to a possible negative effect on postoperative cognitive

function, that was observed in one of the sub studies of the DECS study.[27] Moreover, in the report on the results of the large international Corticosteroid Randomisation after Significant Head Injury (CRASH) trial[33], the authors hypothesise that steroid-associated hyperglycaemia was the driving mechanism behind the negative effect of methylprednisolone on neurological outcomes in their study.
An unanticipated finding in our DECS study was the increased rate of late surgical re-interventions in patients randomised to dexamethasone. Although the mechanisms of this effect are not clear, it is possible that suppression of the inflammatory response has resulted in a delayed resolution of the sterile pericarditis that is present in many cardiac surgical patients, resulting in increased pericardial fluid accumulation. As such, steroid prophylaxis may have the potential to impair postoperative recovery in otherwise uncomplicated cases.

Another key finding was an apparent difference in the effects of dexamethasone between age groups. Dexamethasone reduced the incidence of both the primary endpoint and mortality in relatively young patients (up until the age of 75), but in patients older than 80 years the incidence of these adverse outcomes was actually increased. We hypothesise that these differential effects of corticosteroids on patient outcomes between the different age groups may be based on a decreasing magnitude of the systemic inflammatory response phenotype with advancing age. In other words, this variability may result from age-related, *a priori* differences in the susceptibility of individual patients to develop a severe systemic inflammatory response, when exposed to the stimuli associated with cardiac surgery. We have further explored this proposed concept in two additional explanatory studies around the effect of patient age on the inflammatory response to cardiac surgery. In both studies, we demonstrated an association between advanced age and a decreased early (clinical) immune response. These findings support the hypothesis that changes that occur with increasing age, are important contributing factors in the variability of the perioperative inflammatory response phenotype.
A similar bidirectional pattern of the effect of steroids on mortality in different age groups was subsequently found in the large Steroids In caRdiac Surgery (SIRS) study, which makes it highly likely that this is indeed a true effect. In the SIRS study, which will be published shortly, 7507 patients undergoing cardiac surgery were randomised between high-dose methylprednisolone or placebo.[34,35] The SIRS trial did not show a significant effect of methylprednisolone on a comparable composite primary endpoint of major adverse events, with a relative risk close to 1. However, this effect was a combination of a roughly 10% reduction by methylprednisolone of the incidence of 4 out of the 5 components of the composite endpoint (mortality, stroke, renal failure, and respiratory failure), and a 20% increase in the incidence of myocardial infarction. So, similar to the DECS study, also in the SIRS study the effects of high-dose steroid prophylaxis seem to be heterogeneous, showing both potential benefit and possible harm.

Despite the large number of patients included, we must conclude that the DECS study has not been able to provide the much needed 'definitive' evidence to either support or advise against routine corticosteroid administration in all patients undergoing cardiac surgery. The recent SIRS study has not been able to provide this evidence either. However, although these two large randomised trials failed to demonstrate a benefit of steroids on their primary endpoints, substantial benefits in terms of costs, pulmonary and renal outcomes have been observed, especially in the DECS study. Also, both trials indicate that the effects of steroids vary markedly across different age groups. Lacking a clear answer, perioperative corticosteroid prophylaxis therefore continues, unfortunately, to be a topic of great controversy. As such, the effects of the results the DECS study on clinical practice have been very variable up till now, and much dependent on local practices. In centres where steroids were already routinely used, their use is still common, although clinicians are now more reluctant to administer dexamethasone to elderly patients. Yet, in most centres where steroids were not used routinely, the results of the DECS study did not change practice (personal communication).

Considering all these findings from our DECS study, combined with some comparable results of the SIRS study[34,35], there are legitimate reasons to further explore the possible beneficial effects of steroids in cardiac surgery. Based on the findings of both trials, the aim of a next study should be to develop strategies for more precise targeting of anti-inflammatory prophylaxis with corticosteroids, selectively at those patient groups who are likely to develop an excessive, potentially harmful perioperative inflammatory response.

Heterogeneity in clinical trials of anti-inflammatory therapy

The inter-individual variability of the perioperative systemic inflammatory response phenotype is a challenge that researchers will have to face when designing and performing clinical studies to evaluate anti-inflammatory treatment options. The same is true for studies in comparable conditions in other environments, such as studies of sepsis in the intensive care unit.[36] One of the fundamental problems of these acute inflammatory conditions is the lack of our ability to predict, in an early phase, which patients are likely to develop the clinical phenotype that is to be targeted by the treatment under evaluation. While in other specialties (e.g. oncology), models for prediction of 'the next stage' clinical phenotype - and the response to therapy - are reasonably well developed[37], such prediction models are virtually non-existent for the phenotype of systemic inflammation in the field of perioperative and critical care medicine. Although several well-validated prediction models for end-stage adverse clinical outcomes like mortality or myocardial infarction are available in the perioperative and critical care arena[38-42], these models are non-specific for predicting the occurrence of these adverse outcomes occurring as a result of a severe perioperative SIRS. Consequently, these models are of little value for targeting patients for anti-inflammatory interventions.

Because of this limited ability to select patients based on *a priori* inflammatory risk, studies of anti-inflammatory therapy in cardiac surgery have often been designed to include either patients at an increased risk of one or more serious adverse end-stage outcomes, or just 'all-comers'.[13,16-18] This has frequently resulted in the inclusion of a relatively large proportion of patients who received little or no benefit - or even harm - from the intervention, thereby diluting the therapeutic signal and significantly reducing a potential benefit from the therapy that may have occurred in specific subgroups. This dilution effect may in part explain the lack of actionable evidence from some recent large clinical trials in perioperative medicine.[13,43,44] As steroid therapy is a 'double-edged sword', it is also understandable that all-comers approaches can also harm specific subpopulations of patients, particularly those with a pre-existing impaired inflammatory response.

The four largest randomised studies into the effects of perioperative anti-inflammatory therapy for cardiac surgery that have been published over the last 10 years[13,16,17,35], are a good example of such all-comers approaches. Each of these studies used broad inclusion criteria, with an increased *a priori* risk for 30 days mortality as the only restriction in 2 studies.[17,35] Without exception, these studies have been negative on their primary endpoints of mortality or major adverse outcomes. However, in each of these trials, treatment benefit was demonstrable in one or more relevant subgroups. Most importantly, the two largest studies both demonstrated an overall benefit in younger patients but also harm in elderly patients.

The clinical spectrum of the perioperative inflammatory response

The phenotype of perioperative systemic inflammation likely embraces a broad, clinically heterogeneous spectrum of responses, rather than a single disorder that complicates surgery.[45] Most cardiac surgical patients develop a systemic inflammatory response that is in the milder range of the spectrum. Such a response serves as a supportive response for wound healing and recovery, and has a low probability of having significant negative clinical impact.[46,47] As suggested by the results of the DECS study and some of its sub studies, suppression of the inflammatory response is harmful in certain patients.[13,26,27] However, at the more extreme end of this spectrum are patients who develop a severe phenotype of systemic inflammation, which has the potential to complicate their postoperative course, and which puts them at an increased risk of postoperative morbidity, and possibly even mortality.[48]
When considering this inter-individual variability in the inflammatory response phenotype, it is not surprising that the effects of anti-inflammatory therapy could vary between patients too. Such variable effects of therapy may well account for the mixed results found in the recent large trials. In other words, suppression of inflammation in subgroups of patients with an exaggerated response may be beneficial, whereas suppression in patients with a much more controlled, or even senescent[49], inflammatory response could impair its purpose of recovery from the surgical trauma, and as such contribute to adverse outcomes.

The concept of broad-spectrum inter-individual variability of immune responses is, of course, not unique for the perioperative setting, but is increasingly recognized in several other medical areas as well. For example, patients suffering from major trauma often develop an exaggerated systemic inflammatory response, but the severity is also large variable between individuals.[50] Several recent studies in this field have demonstrated that in those patients, a more excessive early inflammatory response is associated with an increased risk of organ failure and mortality.[50-53]

Determinants of immune response heterogeneity

The phenotypic heterogeneity of the inflammatory response arises at multiple levels, and is formed by a complex interaction between the individual and external stimuli. These include patient-associated factors, but also factors related to the perioperative environment.[54] Patient-associated factors that define individual susceptibility include predefined (genetic) make-up on the one hand, and acquired co-morbidities (and associated medications) on the other. It has been generally accepted that genetic make-up has a significant role in determining the way in which we respond to our environment. However, the results of studies linking variations in 'fixed' genetic predisposition (single nucleotide polymorphisms) to inflammation severity have not been able to explain a large part of the variability in the perioperative inflammatory response phenotype so far, thereby limiting the clinical applicability of the results.[55] Similarly, while genetic variation in many candidate genes has been implicated in sepsis susceptibility, it has thus far not been possible to establish predictive links to clinical outcomes.[56] As such, the importance of the variability of gene expression, rather than genetic makeup per se, has been recognized in recent years. Gene expression is controlled by epigenetic mechanisms (including DNA methylation) in a way that is stably propagated over multiple cell divisions, but that is also flexible enough to respond to environmental influences.[54,57] This intermediate position between stability and plasticity may explain how we interact with our environment at the genetic level, and is potentially of great importance in understanding the relationship between gene expression and complex diseases, including the perioperative inflammatory response. Differences between patients in methylation of genes involved in the inflammatory response are determined by multiple factors, such as age, co-morbidities and environment.[58-60] These differences result in differential expression of an otherwise fixed genetic sequence; a subsequent variable transcription of inflammatory proteins that drive the innate and adaptive components of the immune response; and finally a clinically variable phenotype of systemic inflammation.[59,61,62] This variability results in differences in individual susceptibility for developing a more severe inflammatory response, and may have been a key determinant of the differential effects of dexamethasone between different age groups that were found in the DECS study and the SIRS study.

Combined with individual susceptibility, environmental factors in the perioperative period further shape the systemic inflammatory response phenotype that ultimately

develops in a patient undergoing cardiac surgery. The type of procedure performed[63], the duration of exposure to cardiopulmonary bypass, the extent of ischemia-reperfusion injury[64], perioperative medications, and the type of anaesthetic used, are just a few examples of the factors that contribute to this process.

Precision medicine: selecting the right patient for the right therapy

The challenge in developing effective prophylactic strategies for those individual patients who may suffer from harmful perioperative inflammation, lies in achieving optimal preoperative characterization of both the inflammatory response and the response to anti-inflammatory treatment that can be expected. Only in this way will it be possible to better define patient populations that receive benefit from anti-inflammatory treatment, and concurrently recognise other patient groups that should not receive treatment. This should allow to more selectively target anti-inflammatory prophylaxis and treatment at the personalised level.

The next steps in research into perioperative anti-inflammatory therapy

To accomplish the goal of personalised perioperative anti-inflammatory therapy, comparative studies are needed that allow to address effects on relevant patient outcomes, as well as the pathophysiological mechanisms that form the basis of these effects.[36] Such studies should therefore not only be large[14], but should also collect an appropriate amount of phenotypic detail, appreciating both the phenotypes of inflammation[65] and the pharmacological treatment effects.
Furthermore, in a contemporary study design, there should be a focus on longer-term patient-centred outcomes rather than just on perioperative major adverse events.[66-68] That is, not just survival or freedom of perioperative complications, but also the relief of symptoms, the avoidance of long-term disability, and a sense of well-being, that are likely to be the most important and highly valued outcomes for patients undergoing major surgery.[69-71]

Based on the results discussed in this thesis, we have designed a next study with dexamethasone in cardiac surgery: the Corticosteroid Effects on inflammation, Long-term disability and Survival in patients Undergoing cardiac Surgery (CELSUS) study. The CELSUS study addresses two types of questions. Primarily, the clinical effectiveness of prophylaxis with dexamethasone will be tested at the highest possible quality level, in a placebo-controlled, randomised trial in a well-defined cardiac surgical population that is most likely to benefit. But equally important, a full-scale bio-repository around the systemic inflammatory response will be established in the population of the CELSUS study. This bio-repository will contain high-quality clinical and phenotypic data, as well as stored, pre-processed inflammatory tissue. With this stored tissue it will be possible to selectively generate genetic, epigenetic, transcriptomic and biomarker data, which will allow multiple explanatory sub studies to be performed with significant statistical power. In these studies, it will be possible

to identify patients with increased susceptibility for an excessive inflammatory response, and to further explore the effects of corticosteroids in these specific patient subgroups.

Such a parallel study, combining the feasibility and quality of a pragmatic, routine care based randomised trial design[72] with the explanatory potential and flexibility of a large-scale bio-repository, greatly enhances study efficiency. With adequate statistical power for combining phenotypic data with important clinical outcomes, this study will simultaneously provide high-level clinical evidence for the effects of corticosteroids in cardiac surgery, as well as detailed guidance towards more precisely targeted therapy for perioperative inflammation. Also, since this study will be performed as an intercontinental collaborative project, including sites throughout Europe, Australasia and North America, the results can be extrapolated to a broad range of cardiac surgical populations around the world.

Cardiopulmonary bypass as a unique model of inflammation in humans

Within the relatively controlled setting of elective surgery, the insults triggering an inflammatory response are usually short lasting (hours, rather than days), and timing is almost entirely predictable. These characteristics make the perioperative setting particularly suitable for investigating well-targeted treatment strategies. More specific for the systemic inflammatory response, the perioperative environment could potentially provide a good model for research into more precisely targeted treatment approaches for complex inflammatory conditions such as sepsis and severe trauma.

Conclusion

In the multicentre DECS study, the use of intraoperative dexamethasone did not reduce the overall incidence of major adverse events. However, multiple important effects of dexamethasone were present in analyses of pre-planned secondary outcomes and subgroups, and also in several smaller sub studies of the trial. Effects were variable in terms of benefit and harm, and different between patient subgroups. These heterogeneous effects are likely based on substantial inter-individual variability in the severity of the systemic inflammatory response to cardiac surgery. As a result of this variability, benefit from corticosteroid treatment may only be present in subgroups of patients who develop an excessive, potentially harmful inflammatory response. We therefore need to aim at more precisely targeting anti-inflammatory prophylaxis, as planned in the CELSUS study. With the results of this study, one may better identify those individual patients who are more susceptible to develop an excessive inflammatory response, and who will as such receive most benefit from anti-inflammatory prophylaxis.

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Appendix

Members of the DECS Study Group (the Netherlands)

University Medical Center, Utrecht

Jaap J. Bredée, Wolfgang F. Buhre, Jan M. Dieleman, Diederik van Dijk, Lex A. van Herwerden, Cor J. Kalkman, Jan van Klarenbosch, Karel G. Moons, Hendrik M. Nathoe, Sandra C. Numan, Thomas H. Ottens, Kit C. Roes, Anne-Mette C. Sauer, Arjen J. Slooter

Isala Klinieken, Zwolle

Arno P. Nierich, Jacob J. Ennema

Amphia Ziekenhuis, Breda

Peter M. Rosseel, Nardo J. van der Meer

University Medical Center, Groningen

Joost M. van der Maaten, Vlado Cernak

Erasmus Medical Center, Rotterdam

Jan Hofland, Robert J. van Thiel

Medisch Spectrum Twente, Enschede

Jan C. Diephuis

Medical Center, Leeuwarden

Ronald M. Schepp, Jo Haenen, Fellery de Lange

Vrije Universiteit Medical Center, Amsterdam

Christa Boer, Jan R. de Jong

Academic Medical Center, Amsterdam

Jan G. Tijssen

DECS Study Steering Committee

Jan M. Dieleman, Jan C. Diephuis, Diederik van Dijk, Lex A. van Herwerden, Jan Hofland, Jan R. de Jong, Cor J. Kalkman, Jan van Klarenbosch, Joost M. van der Maaten, Karel G. Moons, Arno P. Nierich, Peter M. Rosseel, Ronald M. Schepp

DECS Study Data and Safety Monitoring Board

Peter Bruins, Bas A. de Mol, Jan G. Tijssen

DECS Study Critical Event Adjudication Committee

Jaap J. Bredée, Hendrik M. Nathoe, Arjen J. Slooter

Summary

Open heart surgery is among the most commonly performed surgical procedures, leading to significant improvements in symptoms of acquired cardiac disease and a better quality of life. However, despite important progress in surgical techniques, anaesthesia management and postoperative care, cardiac surgery is still associated with a substantial risk of major adverse events and postoperative disability. The perioperative inflammatory response associated with cardiac surgery often results in a systemic inflammatory response syndrome (SIRS), and may play a role in the development of several of these adverse outcomes, either as the primary triggering mechanism or as an important contributing factor. In order to prevent a SIRS, high-dose corticosteroids ('steroids') have been routinely used during cardiac surgery for several decades in many centres around the world. However, until recently, appropriately sized studies on the effect of corticosteroids on important clinical outcomes and safety aspects were lacking.

We aimed to establish a more evidence-based approach to steroids prophylaxis in cardiac surgery. The first step was to conduct a systematic review and meta-analysis of the available evidence. The results of this Cochrane review are presented in **Chapter 2**. This review demonstrated that the existing evidence around corticosteroid effects in cardiac surgery was based on a large number of very small studies, and was therefore inherently very weak. Although a formal pooled analysis of the data was done as part of this review, the most important conclusion was that there was an urgent need for an appropriately sized clinical trial to investigate the effects of steroids on important clinical outcomes.

Such a clinical trial, the DExamethasone for Cardiac Surgery (DECS) study, was subsequently performed between 2006 and 2011, in eight centres in The Netherlands. In the DECS study, 4494 cardiac surgical patients were randomised to receive either intraoperative high-dose dexamethasone or placebo, and followed up for one year after their surgery. The principal results of the DECS study are presented in **Chapter 3**. No statistically significant effect of dexamethasone could be demonstrated on the primary outcome of major adverse events at 30 days after surgery, although a trend towards benefit of dexamethasone was present (relative risk (RR) 0.83; 0.67-1.01; p=0.07). Of the secondary endpoints, the overall pulmonary benefit in patients receiving dexamethasone was probably the most marked effect, which was demonstrable on multiple levels. The incidence of respiratory failure was reduced by 31%, and was associated with a reduced duration of postoperative mechanical ventilation, and a reduced length of postoperative stay in both the ICU and the hospital. The incidence of postoperative pneumonia was also reduced. In a pre-planned subgroup analysis, younger patients (up to 75 years) had most benefit from dexamethasone treatment, with a reduced incidence of both the primary endpoint and 30-day mortality. On the contrary, in patients aged >80 years there was a signal of a possible harmful effect of dexamethasone.

In **Chapter 4**, the results of the analysis of the longer-term outcomes at 1 year are presented. In this analysis, no effects of dexamethasone past its effects in the immediate postoperative period were demonstrable. There was no difference between the groups in either survival (hazard ratio (HR) 1.08; 0.80–1.45), or event-free survival (HR 0.85; 0.70–1.03). However, in the formal cost-effectiveness analysis that was included in the long-term analyses, the early effects of dexamethasone treatment on pulmonary outcomes and length of stay contributed significantly to an estimated € 1084 per patient cost benefit.

In the experience of many clinicians steroids improve postoperative haemodynamic stability, and thereby enhance postoperative recovery. We investigated the effect of dexamethasone on perioperative haemodynamic parameters, as a possible mediator of faster postoperative recovery. The results of this single-centre analysis of the DECS study are reported in **Chapter 5**. In this study, blood pressure variability in the early post-cardiopulmonary bypass period was used as the primary measure for haemodynamic stability. Although blood pressure variability during the first hours after cardiopulmonary bypass was lower in the dexamethasone group compared to the placebo group, there was no demonstrable effect on clinical therapeutic measures used to treat this reduced haemodynamic stability, such as vasopressors and fluids. Moreover, the mean blood pressure was slightly lower in the dexamethasone group. We therefore concluded that the statistical difference in blood pressure variability is not of clinical significance, and that dexamethasone does not improve postoperative haemodynamic stability.

An unexpected finding in the DECS study was the increased rate of rethoracotomy in the dexamethasone group, with a relative risk of 1.32 (95% CI 1.09-1.61). The study in **Chapter 6** represents a detailed analysis of the re-interventions, and also of the use of blood products, in the DECS study population. In patients receiving dexamethasone, the risk of surgical re-interventions for late cardiac tamponade was increased (RR 1.84; 95% CI 1.30-2.61). The fact that this difference was primarily determined by cases of late tamponade, combined with the finding that a significantly higher proportion of patients in the dexamethasone group actually remained free of any blood transfusion (61.0%, versus 57.9% in the placebo group), suggests that the higher rate of rethoracotomy was not a result of an increased bleeding tendency in the dexamethasone group. We hypothesized that patients receiving dexamethasone may have had 'over-suppression' of their inflammatory response, resulting in delayed resolution and prolonged postoperative accumulation of reactive pericardial fluid.

The final two studies that are reported in this thesis were designed to improve our understanding of the finding of differential steroid effects across age groups on several important outcomes in the DECS study. A similar effect on mortality was also observed in a recent large randomised study of high-dose methylprednisolone in cardiac surgery, the Steroids In caRdiac Surgery (SIRS) trial. This consistent finding of a beneficial effect of corticosteroids in younger patients, led us to hypothesize

that the phenotype of the perioperative inflammatory response may be different between these age groups. As a result of this variability in the phenotype, the risk of developing deregulated SIRS, which is the extreme form of the phenotype that corticosteroid prophylaxis aims to prevent, may be different as well. This variability may have lead to the differential steroid effects across age groups, that were found in both the DECS study and the SIRS trial.

In **Chapter 7**, the effects of patient age on the early C-reactive protein response were studied in 985 patients who were randomised in one of the centres of the DECS study. We demonstrated a significant correlation between increasing age and a reduced early CRP response ($r=0.24$; $p<0.001$). Also, increasing age was associated with a lower risk of developing a high early CRP response (OR 0.95 per year; 0.92 – 0.97).

In **Chapter 8**, the association between patient age and the occurrence of a postoperative clinical SIRS was studied in a cohort of 25,095 cardiac surgical patients from Australia and New Zealand. In this study we showed that advancing patient age is indeed associated with a decreasing risk of postoperative SIRS (according to established criteria), whereby patients aged over 72 years had the lowest risk. However, based on age and other routinely collected clinical variables, the multivariable model had only moderate discriminatory value for predicting which patients are at risk of developing postoperative SIRS.

Given the apparent variability in the phenotype of perioperative inflammation, prediction of the likelihood that an individual patient will develop a clinically important deregulated inflammatory response, is a crucially important next step towards developing more precise strategies for SIRS prophylaxis. In the General Discussion in **Chapter 9**, the design of a next randomised study of corticosteroids in cardiac surgery, the CELSUS study, is discussed. The CELSUS study focuses on a patient population with a higher risk of developing deregulated SIRS. However, equally important, a focused bio-repository around perioperative inflammation will be established, in which inflammatory tissue from all 4000 patients included in the study will be stored. With this tissue, it will be possible to selectively generate genomic, epigenetic, transcriptomic and biomarker data, to allow multiple well-powered explanatory sub studies around the phenotype of perioperative inflammation. Based on these studies, it will be possible to better identify those patients who have an increased susceptibility for a deregulated inflammatory response. This may eventually lead to a more personalised approach where corticosteroids are only used in patients with a high risk of such an intense inflammatory response, whereas their use can be avoided in other patients.

Samenvatting in het Nederlands

Open hartchirurgie is één van de meest uitgevoerde chirurgische procedures. Hartchirurgie leidt tot vermindering van symptomen van hartziekten, en tot een verbeterde kwaliteit van leven. Ondanks een aanzienlijke verbetering van chirurgische technieken, anesthesiologische praktijk, en postoperatieve zorg in de afgelopen decennia, is er nog steeds een substantieel risico op ernstige postoperatieve complicaties. De perioperatieve inflammatoire respons die optreedt bij hartchirurgie leidt vaak tot een 'systemic inflammatory response syndrome', ofwel SIRS. Het optreden van een SIRS heeft waarschijnlijk een belangrijke rol in het ontstaan van diverse van deze postoperatieve complicaties; ofwel als de primaire oorzaak, of als een belangrijke bijdragende factor aan de ernst van andere complicaties. Ter voorkoming van een SIRS is het in veel ziekenhuizen gebruikelijk om tijdens hartchirurgie routinematig een hoge dosis corticosteroïden aan de patiënt toe te dienen. Echter, tot een aantal jaren geleden was er geen goede evidence voor de klinische effecten en de veiligheid van corticosteroïden in de hartchirurgie.

Een eerste stap naar een meer evidence-based benadering van het gebruik van steroïden in hartchirurgie, was een systematische review en meta-analyse van de beschikbare gerandomiseerde klinische studies rondom dit onderwerp. De resultaten van deze Cochrane review zijn te vinden in **Hoofdstuk 2**. Deze review liet zien dat de bestaande evidence rondom de effecten van steroïden was gebaseerd op een groot aantal zeer kleine studies, en dat deze daarmee zwak was. Een formele meta-analyse van de data werd nog wel uitgevoerd als onderdeel van deze review, maar de belangrijkste conclusie was toch dat om de effecten van steroïden op klinische uitkomsten te kunnen onderzoeken, er een noodzaak was voor een grote klinische trial.

Een dergelijke klinische trial was de DExamethasone for Cardiac Surgery (DECS) studie, die tussen 2006 en 2011 werd uitgevoerd in een aantal Nederlandse hartcentra. In de DECS studie werden 4494 hartchirurgische patiënten gerandomiseerd tussen een intra-operatieve hoge dosis dexamethason of placebo, en vervolgens gedurende een jaar na de operatie gevolgd. De primaire resultaten van de DECS studie zijn te vinden in **Hoofdstuk 3**. Er was geen statistisch significant verschil aantoonbaar in het primaire eindpunt van ernstige complicaties binnen 30 dagen na de operatie, al was er wel een duidelijke trend van voordeel in de dexamethason groep (relatief risico (RR) 0.83; 0.67-1.01; p=0.07). Van de effecten van dexamethason op secundaire eindpunten was het effect op respiratoire uitkomsten het meest uitgesproken. De incidentie van respiratoir falen was 31% lager, en was geassocieerd met een kortere duur van postoperatieve beademing, en een kortere postoperatieve ligduur op zowel de intensive care als in het ziekenhuis. Bovendien was de incidentie van postoperatieve pneumonie fors lager in de dexamethason groep. In een vooraf geplande subgroep analyse hadden jongere patiënten (tot 75 jaar) het meeste voordeel van behandeling met dexamethason, met een verminderde incidentie van zowel het primaire eindpunt als mortaliteit na 30 dagen. Daarentegen was er in

patiënten van ouder dan 80 jaar een signaal van een mogelijk schadelijk effect van dexamethason.

In **Hoofdstuk 4** zijn de resultaten van de analyse van lange-termijn uitkomsten na 1 jaar weergegeven. In deze studie waren er geen effecten van dexamethason aantoonbaar bovenop de effecten in de directe postoperatieve periode. Er was geen verschil tussen de groepen in overleving (hazard ratio (HR) 1.08; 0.80-1.45), of overleving zonder ernstige complicaties (HR 0.85; 0.70-1.03). Desondanks was er in de formele kosten-effectiviteitsanalyse die onderdeel uitmaakte van deze studie, een geschat kostenvoordeel van € 1084 per patiënt in de dexamethason groep. Dit effect werd grotendeels bepaald door de vroege effecten van dexamethason op respiratoire uitkomsten en ligduur.

In de ervaring van veel clinici zijn patiënten die corticosteroïden hebben gekregen in de postoperatieve fase hemodynamisch stabieler, wat zou kunnen bijdragen aan een sneller herstel. In een sub studie binnen de patiënten uit één van de centra van de DECS studie (**Hoofdstuk 5** van dit proefschrift) hebben we gekeken naar het effect van dexamethason op perioperatieve hemodynamische parameters, als één van de mogelijke determinanten van de kortere ligduur die in de DECS studie werd gevonden. In deze studie werd bloeddruk variabiliteit gebruikt als de primaire maat voor hemodynamische stabiliteit. Ondanks dat de bloeddruk variabiliteit in de dexamethason groep was lager gedurende de eerste uren na het gebruik van de hart-longmachine, was er geen aantoonbaar effect op het gebruik klinische interventies voor behandeling van verminderde hemodynamische stabiliteit, zoals vasopressoren en ‘vulling’. Bovendien was de gemiddelde bloeddruk zelfs iets lager in de dexamethason groep. We concludeerden daarom dat dit statistische verschil in bloeddruk variabiliteit waarschijnlijk niet van klinisch belang is, en dat dexamethason daarom niet leidt tot een verbeterde hemodynamische stabiliteit.

Een onverwachte bevinding van de DECS studie was het verhoogde risico op een rethoracotomie in de dexamethason groep, met een relatief risico of 1.32 (95% CI 1.09-1.61). De studie in **Hoofdstuk 6** bevat een gedetailleerde analyse van de re-interventies in de DECS studiepopulatie, alsmede van het gebruik van bloedproducten. In patiënten die waren behandeld met dexamethason was het risico op een chirurgische behandeling voor late tamponade hoger (RR 1.84; 95% CI 1.30-2.61). Het feit dat dit verschil primair was bepaald door laat optredende tamponades, gecombineerd met de bevinding dat er in een groter deel van de patiënten in de dexamethason groep geen transfusie van bloedproducten nodig was (61.0%, tegen 57.9% in de placebo groep), suggereert dat het verhoogde risico op rethoracotomieën niet het gevolg was van een toegenomen bloedingsneiging. Een mogelijke verklaring voor dit effect zou kunnen zijn dat patiënten die dexamethason kregen een ‘over-suppressie’ van hun inflammatoire response hebben gehad, wat heeft geresulteerd in het vertraagd oplossen, en daardoor een langduriger ophoping, van postoperatief reactief pericardvocht.

De laatste twee studies in dit proefschrift waren ontworpen om beter te begrijpen waarom corticosteroïden in verschillende leeftijdsgroepen een variabel effect hadden op belangrijke complicaties en uitkomsten. Een vergelijkbaar effect is ook gevonden in een recentere grote gerandomiseerde studie met methylprednisolon in hartchirurgie, de Steroids In caRdiac Surgery (SIRS) trial. Een mogelijke verklaring voor deze consistente bevinding van een voordeel van corticosteroïden in met name jongere patiënten, zou kunnen zijn dat het fenotype van de perioperatieve inflammatoire respons verschilt tussen de verschillende leeftijdsgroepen. Als gevolg van deze variabiliteit in het fenotype is dan het risico op het ontwikkelen van een ontregelde SIRS, wat de extreme vorm van het fenotype is waar steroïden-profylaxe op is gericht, eveneens verschillend. Deze variabiliteit heeft mogelijk geleid tot de verschillende effecten van profylaxe met steroïden die werden gevonden in zowel de DECS studie als de SIRS trial.

Hoofdstuk 7 beschrijft een sub studie in 985 patiënten uit één van de centra van de DECS studie, naar het effect van leeftijd op de vroege postoperatieve C-reactive protein (CRP) respons. In deze studie werd een significante correlatie gevonden tussen toenemende leeftijd en een afnemende vroege CRP respons ($r=0.24$; $p<0.001$). Daarnaast was een hogere leeftijd ook geassocieerd met een lager risico op het ontwikkelen van een hoge vroege CRP respons (OR 0.95 per jaar; 0.92-0.97).

In **Hoofdstuk 8** wordt een studie beschreven in een cohort van 25,095 hartchirurgische patiënten uit Australië en Nieuw Zeeland, waarin het verband werd onderzocht tussen leeftijd en het optreden van een postoperatieve klinische SIRS. In deze studie toonden we aan dat toenemende leeftijd inderdaad is geassocieerd met een verminderd risico op een postoperatieve SIRS (gedefinieerd volgens algemeen geaccepteerde criteria), waarbij patiënten ouder dan 72 jaar het laagste risico hadden. Desondanks had het multivariabele model, met daarin leeftijd en andere routinematig verzamelde klinische parameters, slechts een matige discriminatieve waarde voor het voorspellen van welke patiënten een verhoogd risico hebben op het ontwikkelen van een postoperatieve SIRS.

Het voorspellen van de kans van een individuele patiënt op het ontwikkelen van een klinisch belangrijke ontregelde inflammatoire respons, is een cruciale volgende stap op weg naar een meer gerichte manier van SIRS profylaxe, gegeven de duidelijke variabiliteit in het fenotype van perioperatieve inflammatie. In de Algemene Discussie in **Hoofdstuk 9** wordt het ontwerp van een volgende gerandomiseerde studie met corticosteroïden in hartchirurgie, de CELSUS studie, besproken. De CELSUS studie richt zich op een patiënten populatie met een verhoogd risico op het ontwikkelen van een ontregelde SIRS. Maar een minimaal zo belangrijk onderdeel van de studie is het opzetten van een gefocuste bio-bank rondom perioperatieve inflammatie, met weefsel van alle 4000 patiënten die in de studie worden geïncludeerd. Met dit opgeslagen weefsel zal het mogelijk zijn om selectief data te genereren op genetisch, epigenetisch, transcriptie en bio marker niveau. Hiermee is het mogelijk

om met voldoende statistische power explanatoire sub studies uit te voeren rondom het fenotype van perioperatieve inflammatie. Op basis van deze studies zal het uiteindelijk mogelijk moeten worden om patiënten met een verhoogd risico op een ontregelde inflammatoire respons beter te identificeren. Dit kan dan vervolgens leiden tot een meer gepersonaliseerde behandeling, waarbij corticosteroïden alleen worden gebruikt in patiënten met een hoog risico op zo'n intense inflammatoire response, terwijl het gebruik in andere patiënten juist kan worden vermeden.

Curriculum vitae

Stefan Jan Marinus Dieleman was born on 1 November 1977, and grew up in Middelburg, The Netherlands. In 1996, he graduated from the Christelijke Scholengemeenschap Walcheren in Middelburg. Starting in 1996, he studied Medical Biology at the Utrecht University. From 1998, he also studied Medicine at the same University.

From 2001-2003, he performed several research projects with a preclinical model of cognitive decline after cardiopulmonary bypass, at the Department of Anesthesiology at the University Medical Center Utrecht. After obtaining his medical degree in 2005, he started a formal PhD project under the supervision of prof. Cor Kalkman, prof. Carl Moons, and prof. Diederik van Dijk. This project was designed around the subject of 'The clinical effects of corticosteroid prophylaxis in cardiac surgery', and has resulted in this thesis. The basis of this project was formed by the DExamethasone for Cardiac Surgery (DECS) trial. Stefan was actively involved in writing the study protocol, obtaining two large grants, executing the study in 8 Dutch cardiac surgical centres (between 2006 and 2011), and publishing the study results.

In 2007, he completed his Medical Biology training, by mastering in Clinical Epidemiology. Also in 2007, he commenced his training in anaesthesia under the supervision of prof. Hans Knape, which he completed in 2012. From 2012 to 2014, he worked in Melbourne, Australia as a clinical fellow in adult cardiac anaesthesia (The Alfred Hospital) and paediatric cardiac anaesthesia (The Royal Children's Hospital), and also as a clinical research fellow (Monash University, prof. Paul Myles). Since September 2014, he has been appointed as a staff cardiac anaesthetist at the University Medical Center Utrecht.

Stefan and his partner Judith van Abeelen have 3 children: Lucas, Jinte and Ravie.

List of additional publications

(not included in this thesis)

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Dankwoord

Nou, het is af... Als je me ruim tien jaar geleden had gevraagd of ik voor een project wilde tekenen waarbij ik pas in 2015 zou promoveren, dan had ik daar misschien nog wel eens een paar keer over nagedacht. Gelukkig was ik toen naïef genoeg, en heb ik vrijwel meteen ja gezegd toen ik deze kans kreeg. En geen haar op mijn hoofd die er spijt van heeft! Maar is dit nu echt af? Ik vrees van niet… ☺

Als allereerste wil ik alle patiënten bedanken die hebben bijgedragen aan dit proefschrift. Alleen door uw beslissing om deel te nemen aan onderzoek, en door het keer op keer weer geduldig beantwoorden van onze vragen tijdens de jaren na de operatie, kunnen wij doen wat we doen. En dat doen we uiteindelijk voor u.

Geachte professor Kalkman, beste Cor, mentor van het eerste uur: ruim 14 jaar geleden stond ik voor het eerst bij je op de stoep, voor een vermeend studentenproject wat toen al lang niet meer bestond. Maar ik had geen betere stoep kunnen uitkiezen. Toen ik na een paar fantastische jaren in het lab had besloten om proefdieren te willen verruilen voor klinisch onderzoek, bood je me een promotie-plek aan voor een nog te ontwerpen onderzoek met dexamethason, waarvan je niet zeker wist of het wel haalbaar zou zijn. Nou, het is toch gelukt. Dank voor je vertrouwen en support, je schier eindeloze geduld met dit project (“komt goed Stefan, het komt écht goed”), je immer kritische blik, en natuurlijk voor de regelmatige aanvoer van verse scharreleieren!

Geachte professor Van Dijk, beste Diederik: Als geen ander heb jij mij geleerd om zaken ‘lean’ en eenvoudig te houden, en om problemen vooral niet moeilijker te maken dan ze zijn. En die problemen waren er toch nog zat in deze ‘large, simple trial’: te vaak heb ik jouw gewicht in de strijd moeten gooien omdat iemand het weer eens onbegrijpelijk vond dat ik zo’n grote studie coördineerde. Maar dat deed je onvermoeibaar, en altijd met een de nodige dosis humor en sarcasme: ik had me geen betere begeleider kunnen bedenken! Ondertussen ben je hooggeleerd en druk, maar ik hoop van harte dat je net zo nuchter kunt blijven als altijd.

Geachte professor Moons, beste Carl: Als mijn promotor vanuit het Julius Centrum was jij een belangrijke schakel naar vele elementen die de DECS studie uiteindelijke tot een succes hebben gemaakt. Je grote talent voor het schrijven van subsidieaanvragen met ronkende passages heeft ongetwijfeld bijgedragen tot de twee grote subsidies die we hebben binnengehaald. Maar ook bij het verfijnen van het design van de studie, en bij het vormgeven van zaken als datamanagement, quality control en de uiteindelijke data-analyse, was je rol als epidemiologische promotor onmisbaar.

Dear Paul: thank you so much for being a great mentor in the last few years. You have provided me with many fantastic opportunities in my professional development, both as a clinician and as a clinical researcher. Our new CELSUS project is exciting, and will hopefully secure many years of future collaborative work.

To all the people in Melbourne who have made our two years out there such an unforgettable experience: a massive Thank You! Of all the friends we have made there, I would especially like to thank Nigel and Kellie, Chris and Tania, and Ben and Anna, for making it so enjoyable. Dave, thank you for the 'season tickets' to your beach house on the Peninsula. And all the cardiac anaesthetists at The Alfred: thanks for your patience with the Dutchie, and for giving me a truly unique cardiac anaesthesia experience.

Leden van de DECS study group: jullie bijdrage aan de DECS studie was van onschatbare waarde. De motivatie van ieder van jullie om dit project met cardio-anesthesiologisch Nederland voor elkaar te boksen, was een cruciaal element in het succesvol afronden van de DECS studie. Ik hoop van harte dat we zoiets in de nabije toekomst nog eens voor elkaar kunnen krijgen.

Allen die een bijdrage hebben geleverd aan de DECS trial vanuit de Isala Klinieken, het Amphia Ziekenhuis, het Erasmus MC, het UMC Groningen, het Medische Spectrum Twente, het Medische Centrum Leeuwarden, en het VU Medisch Centrum. Dit zijn teveel mensen om hier allemaal te kunnen noemen. Ongelofelijk bedankt voor al jullie inspanningen, en voor het ondergaan van mijn opdringerigheid! Ik hoop dat de taarten en kerstpakketjes dat in ieder geval een beetje hebben goedgemaakt.

Beste Sandra, Ada, Margaret, Marcel, Selma, Karin, Joanne, Gea, Marianne en José; ofwel Het Trialbureau. Zonder jullie was de DECS studie nooit gelukt. Punt uit. Jullie eindeloze geduld en volharding bij de inclusie, bij het notoir onvoorspelbare cardio-chirurgische OK-programma, en bij de follow-up van die duizenden patiënten uit alle centra, zijn bewonderenswaardig. En een follow-up die bijna 100% compleet was: een topprestatie!

Jilles, Teus, Suzanne, Suleyman, Lidwien, Kim en Judith: de andere promovendi van 'boven de ambulance-sluis'. Onze bijna verborgen locatie (tweehoog, voorbij het kleine deurtje achterin de sluis) was een fantastische 'hang-out' voor jonge onderzoekers, die heeft bijgedragen aan vele vruchtbare discussies. Dank voor deze experience, en voor al jullie hulp en input bij het succesvol maken van dit project!

De andere 'DECS promovendi': Thomas, Anne-Mette, Kirolos en Dirk. Gelukkig ben ik toch nog de eerste DECS-er die promoveert, want een aantal van jullie was hard op weg om me rechts in te halen. Jullie enorme bijdrage aan het project maakte mijn leven regelmatig een stuk gemakkelijker. Als ik af en toe verschijnselen van DECS-moeheid begon te vertonen, of soms net iets meer tijd nodig had voor mijn gezin of de kliniek, dan pakten jullie nieuwe projecten en achterstallige klussen met vers enthousiasme op en klaarden die dan meestal in een mum van tijd! Enorm bedankt voor alle inzet, en succes met jullie eigen 'laatste loodjes'.

Collega's van de Divisie Vitale Functies: hartelijk dank voor alle medewerking, steun, geduld, en vooral enorm leuke samenwerking in de afgelopen jaren. Na ruim twee jaar weg te zijn geweest voelde terugkomen enorm als thuis komen: dat zegt genoeg!

Mijn paranimfen, Fellery de Lange en Sandra Numan. Met jullie hulp voor en op de promotie-dag moet het allemaal wel goedkomen. Maar dat gold eigenlijk al voor de afgelopen jaren. Fellery, onze jaren in het lab waren in één woord geweldig. Ik heb enorm veel geleerd van jouw ongekende doorzettingsvermogen en toewijding. We zijn goede vrienden geworden, en ik hoop dat we de trend van de inmiddels ontelbare tripjes en sportwedstrijden in binnen- en buitenland nog lang kunnen voortzetten. En daarnaast kunnen we hopelijk ook nog lang samenwerken op onderzoeksgebied. Sandra: jij was mijn rechterhand als het ging om het uitvoeren van de DECS studie. Een kort mailtje of telefoontje was vaak voldoende om geregeld te krijgen wat er geregeld moest worden, of om het zoveelste probleem op te lossen. En als het niet zo gemakkelijk op te lossen viel kwamen we er meestal ook wel uit, al was het alleen maar doordat we even ons hart konden luchten. En dankzij Menno natuurlijk. Ik hoop dat we nog vele jaren kunnen samenwerken; als het een beetje meezit in een nieuw, nog groter project.

Lieve familie en vrienden. Dank dat jullie er voor mij (en mijn gezin) waren in de afgelopen jaren. Jullie vriendschap, gezelschap, hulp en begrip zijn van onschatbare waarde geweest. Niks was teveel als het hier weer eens spaak liep. En twee jaar aan de andere kant van de wereld heeft daar niets aan afgedaan: een flink aantal van jullie is ons zelfs komen opzoeken! Ik hoop dat dit nog lang zo blijft, waar we ook heen gaan.

Mijn lieve ouders: door jullie kon het uiteindelijk allemaal. Jullie hebben me alle kansen van de wereld gegeven. En me door dik en dun gesteund, ook als ik weer eens iets geks in mijn hoofd haalde. Daar leerde ik toch vast iets van, vonden jullie dan. Het is niet in woorden te vatten hoe dankbaar ik jullie ben!

Lieve Lucas, Jinte en Ravie, my little mates! Uiteindelijk draait het natuurlijk allemaal om jullie. Want boven alles ben ik jullie papa. Ik zal voortaan nog iets minder werken als ik thuis ben, OK? ☺

Lieve, lieve Judith. Onze afgelopen 10 jaar waren 'tropenjaren'. Maar ik had ze voor geen goud willen missen. Drie prachtige kinderen, jouw drukke baan, mijn opleiding en promotie, twee jaar op avontuur aan de andere kant van de wereld. Met jou waren ze elke seconde waard. You're the best. Love you! XX