# Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial

*Richard P Whitlock, P J Devereaux, Kevin H Teoh, Andre Lamy, Jessica Vincent, Janice Pogue, Domenico Paparella, Daniel I Sessler, Ganesan Karthikeyan, Juan Carlos Villar, Yunxia Zuo, Álvaro Avezum, Mackenzie Quantz, Georgios I Tagarakis, Pallav J Shah, Seyed Hesameddin Abbasi, Hong Zheng, Shirley Pettit, Susan Chrolavicius, Salim Yusuf, for the SIRS Investigators**

## Summary

**Background** Cardiopulmonary bypass initiates a systemic inflammatory response syndrome that is associated with postoperative morbidity and mortality. Steroids suppress inflammatory responses and might improve outcomes in patients at high risk of morbidity and mortality undergoing cardiopulmonary bypass. We aimed to assess the effects of steroids in patients at high risk of morbidity and mortality undergoing cardiopulmonary bypass.

**Methods** The Steroids In caRdiac Surgery (SIRS) study is a double-blind, randomised, controlled trial. We used a central computerised phone or interactive web system to randomly assign (1:1) patients at high risk of morbidity and mortality from 80 hospital or cardiac surgery centres in 18 countries undergoing cardiac surgery with the use of cardiopulmonary bypass to receive either methylprednisolone (250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass) or placebo. Patients were assigned with block randomisation with random block sizes of 2, 4, or 6 and stratified by centre. Patients aged 18 years or older were eligible if they had a European System for Cardiac Operative Risk Evaluation of at least 6. Patients were excluded if they were taking or expected to receive systemic steroids in the immediate postoperative period or had a history of bacterial or fungal infection in the preceding 30 days. Patients, caregivers, and those assessing outcomes were masked to allocation. The primary outcomes were 30-day mortality and a composite of death and major morbidity (ie, myocardial injury, stroke, renal failure, or respiratory failure) within 30 days, both analysed by intention to treat. Safety outcomes were also analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00427388.

**Findings** Patients were recruited between June 21, 2007, and Dec 19, 2013. Complete 30-day data was available for all 7507 patients randomly assigned to methylprednisolone (n=3755) and to placebo (n=3752). Methylprednisolone, compared with placebo, did not reduce the risk of death at 30 days (154 [4%] *vs* 177 [5%] patients; relative risk [RR] 0·87, 95% CI 0·70–1·07, p=0·19) or the risk of death or major morbidity (909 [24%] *vs* 885 [24%]; RR 1·03, 95% CI 0·95–1·11, p=0·52). The most common safety outcomes in the methylprednisolone and placebo group were infection (465 [12%] *vs* 493 [13%]), surgical site infection (151 [4%] *vs* 151 [4%]), and delirium (295 [8%] *vs* 289 [8%]).

**Interpretation** Methylprednisolone did not have a significant effect on mortality or major morbidity after cardiac surgery with cardiopulmonary bypass. The SIRS trial does not support the routine use of methylprednisolone for patients undergoing cardiopulmonary bypass.

**Funding** Canadian Institutes of Health Research.

## Introduction

Cardiac surgery is a common surgical procedure and cardiopulmonary bypass is used in most procedures.[1] Cardiopulmonary bypass initiates a systemic inflammatory response syndrome, which is associated with adverse clinical outcomes.[2] Inflammatory responses include activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein),[3–5] which results in increased endothelial permeability and vascular and parenchymal damage.[6–9] These inflammatory responses are associated with the development of postoperative complications including myocardial injury and infarction, respiratory failure, renal and neurological dysfunction, excessive bleeding, altered liver function, multiple organ failure, and death.[10–15]

Steroids attenuate the inflammatory response to cardiopulmonary bypass,[16] but their effect on clinical outcomes is uncertain. Meta-analyses[17] of small trials suggest that steroids decrease perioperative atrial fibrillation and possibly mortality, but definitive evidence is not available. After this meta-analysis was published,[17] the Dexamethasone for Cardiac Surgery (DECS) trial[18] did not show a benefit of dexamethasone for patients undergoing cardiopulmonary bypass, but suggested that steroids might benefit patients at high risk of morbidity and mortality undergoing cardiopulmonary bypass.

We aimed to assess whether prophylactic steroids benefit patients at high risk of morbidity and mortality undergoing cardiac surgery with cardiopulmonary bypass.

*Lancet* 2015; 386: 1243–53

See Editorial page 1212

See Comment page 1215

*Members listed in the appendix

**Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada** (R P Whitlock MD, Prof P J Devereaux MD, A Lamy MD, J Vincent MSc, J Pogue PhD, S Pettit RN, S Chrolavicius BA, Prof S Yusuf DPhil); **Department of Surgery** (R P Whitlock, A Lamy), **Department of Clinical Epidemiology and Biostatistics** (R P Whitlock, Prof P J Devereaux, A Lamy), **and Department of Medicine** (Prof P J Devereaux, Prof S Yusuf), **McMaster University, Hamilton, ON, Canada; Department of Surgery, Southlake Regional Health Centre, Newmarket, ON, Canada** (K H Teoh MD); **University of Bari Aldo Moro, Bari, Italy** (D Paparella MD); **Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA** (Prof D I Sessler MD); **All India Institute of Medical Sciences, New Delhi, India** (G Karthikeyan MD); **Fundación Cardio Infantil—Instituto de Cardiología, Bogotá, Colombia** (J C Villar MD); **Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China** (Prof Y Zuo MD); **Divisão de Pesquisa, Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil** (Prof Á Avezum MD); **London Health Sciences Centre, London, ON, Canada** (M Quantz MD); **Department of Cardiovascular and Thoracic Surgery, University of Thessaly, Larissa, Greece** (G I Tagarakis MD); **Princess Alexandra Hospital, Woolloongabba, Brisbane, QLD, Australia** (P J Shah FRACS);

**Tehran Heart Centre, Tehran University of Medical Sciences, Tehran, Iran** (S H Abbasi MD); **and First Teaching Hospital of Xinjiang Medical University, Urumqi, China** (Prof H Zheng MD)

Correspondence to: Dr Richard Whitlock, Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON L8L 2X2, Canada
**richard.whitlock@phri.ca**

See Online for appendix

## Research in context

### Evidence before this study

In 2008, we published a systematic review and meta-analysis of 44 randomised trials assessing the effect of a steroid in patients undergoing cardiopulmonary bypass. These trials were identified through a search of Embase, MEDLINE, Cochrane, CINAHL, and OVID between 1977 and October, 2007, using the search terms "cardiac surgery", "cardiac surgical procedure", "open heart surgery", "coronary artery bypass", "mitral valve", "aortic valve", "heart valve", "cardiopulmonary bypass", "extracorporeal circulation", and "preoperative" and "prophylactic" in combination with generic and trade names of steroid preparations. We hand searched the reference lists from eligible trials. Trials were eligible irrespective of their primary objective or language of publication. This meta-analysis showed a non-significant reduction in mortality with the use of steroids (relative risk [RR] 0·73, 95% CI 0·45–1·18) that, if real, would be clinically important. This meta-analysis result was based on few events (n=65 deaths) and the results were inconclusive.

Subsequently, the Dexamethasone for Cardiac Surgery (DECS) trial of 4494 patients did not show a reduction in mortality (RR 0·92, 0·57–1·49) or a significant reduction in the primary outcome of death, myocardial infarction, stroke, renal failure, or respiratory failure within 30 days (RR 0·83, 0·67–1·01). A subgroup analysis suggested the possibility that the steroid was beneficial in patients at higher risk of morbidity and mortality (EuroSCORE ≥5; RR 0·77, 0·61–0·98).

### Added value of this study

The SIRS trial included 7500 patients with a EuroSCORE of at least 6. In the SIRS trial, methylprednisolone compared with placebo had no effect on mortality (154 deaths *vs* 177; RR 0·87, 0·70–1·07). An updated meta-analysis that included 14 027 patients showed no effect of steroids on mortality (RR 0·85, 0·71–1·02). SIRS identified a significant increase in myocardial injury based on raised cardiac enzymes.

### Implications of all the available evidence

The collective data from all trials suggests no benefit to perioperative steroids but an increased risk of myocardial injury with routine use of steroids in patients undergoing cardiac surgery; therefore, the routine use of steroids for cardiopulmonary bypass is cautioned. Future studies should elucidate the mechanism of myocardial injury associated with the administration of steroids at the time of cardiac surgery with cardiopulmonary bypass.

## Methods

### Study design and participants

The Steroids In caRdiac Surgery (SIRS) trial was an international, multicentre, parallel-group, double-blind, randomised, placebo-controlled trial of adult patients at high risk of morbidity and mortality undergoing cardiopulmonary bypass. Patients were recruited from 80 hospital-based cardiac surgery practices in 18 countries by dedicated local research teams. Patients aged 18 years or older were eligible if they had a European System for Cardiac Operative Risk Evaluation (EuroSCORE) of at least 6 and provided written informed consent. At the time of initiation of SIRS, EuroSCORE was a widely used and validated risk prediction index.[19] We needed patients to have a EuroSCORE of at least 6 because previous research[20] identified that patients with this score were at high risk of mortality and would have an expected mortality rate of at least 6%. From July 5, 2011, in China and India, we allowed inclusion of patients with a EuroSCORE of at least 4 if the patient was undergoing valvular surgery because research[21,22] showed that patients from China and India with these lower EuroSCOREs had higher than expected mortality rates (ie, observed mortality rates of 4·9% with EuroSCORE predicted mortality rates of 3·0%). Patients were excluded if they were taking or expected to receive systemic steroids in the immediate postoperative period, had a history of bacterial or fungal infection in the preceding 30 days, had an allergy or intolerance to steroids, were expected to receive aprotinin, or had previously participated in SIRS. The protocol has already been published.[23] All participating sites obtained institutional ethics approval.

### Randomisation and masking

Patients were randomly assigned (1:1) by the local study team using a central computerised phone or interactive web system to receive either intravenous methylprednisolone 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass or placebo. Patients were assigned by block randomisation with random block sizes of 2, 4, or 6, stratified by centre. Methylprednisolone was obtained from the centre's local pharmacy, and the study drug was prepared and masked by the local pharmacy following procedures described in a provided study manual. Patients, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation.

### Procedures

In previous trials[24] of patients undergoing cardiopulmonary bypass, the most common methylprednisolone dose was 30 mg/kg (ie, >2 g for a 70 kg patient). We decided, however, to use a cumulative dose of 500 mg of methylprednisolone given intraoperatively for the following reasons: data for surrogate endpoints from the SIRS pilot study[16] showed that this lower dose was

effective in abolishing the inflammatory response to cardiopulmonary bypass across a broad array of measured mediators; a meta-analysis by Ho and Tan[24] suggested that low-dose and moderate-dose corticosteroids are as effective as high-dose corticosteroids in improving clinical outcomes; and data from this meta-analysis[24] also suggested that higher doses of steroids might be associated with adverse outcomes such as prolonged ventilation. Therefore, the dose of 500 mg of methylprednisolone seemed to strike the optimum balance between potential efficacy and safety.

Electrocardiograms were done preoperatively, at 24 h postoperatively, and at hospital discharge or on postoperative day 4, whichever was earlier. Creatine kinase myocardial band (CK-MB) was measured preoperatively, and at 8 h and 24 h after surgery. Creatinine was measured preoperatively. Study personnel collected all in-hospital creatinine measurements until 14 days after surgery, peak blood glucose measurement until 24 h after surgery, and the Confusion Assessment Method (CAM) delirium score on postoperative day 3. After randomisation, patients were followed up for 30 days for all outcomes and for 6 months for vital status.

### Outcomes

Primary outcomes were mortality at 30 days after randomisation and a composite of death, myocardial injury, stroke, renal failure (stage 3 acute kidney injury, 2012 Kidney Disease Improving Global Outcomes [KDIGO] guidelines), or respiratory failure (uninterrupted postoperative mechanical ventilation for more than 48 h) at 30 days after randomisation. 30-day secondary outcomes included individual components of the primary composite outcome, myocardial injury or mortality, new atrial fibrillation, chest drain output during the first 24 h after surgery, the number of patients with transfusions during the first 24 h after surgery, the duration of mechanical ventilation, duration of intensive care unit stay, and length of hospital stay. Safety outcomes included infection, stroke, wound complications (superficial or deep surgical site infection, or sterile wound dehiscence), gastrointestinal haemorrhage, gastrointestinal perforation within 30 days, delirium on postoperative day 3, and postoperative insulin use and peak blood glucose during the first 24 h after surgery. We also assessed mortality at 6 months.

Few data inform the diagnostic criteria for early myocardial injury after cardiac surgery (ie, within 72 h of surgery), particularly after non-coronary-artery-bypass-graft surgery. In this study, we established a prognostically relevant postoperative CK-MB threshold for the protocol diagnostic criteria of early myocardial injury. We decided to use CK-MB instead of troponin for the following reasons. First, some centres participating in SIRS did not have access to troponin measurements, whereas all centres were able to measure CK-MB. Second, at the time of starting the SIRS trial, substantially more data were available for CK-MB, suggesting CK-MB was a prognostically important measure of myocardial injury after cardiopulmonary bypass compared with troponin measurements. Third, although we recognised that we would have to assess two CK-MB assays (ie, mass and activity), determination of the optimum thresholds for troponin would be more challenging and we would probably have had insufficient power because in addition to troponin T and several troponin I assays, we would also encounter both non-high-sensitive and high-sensitive troponin assays for both troponin T and I assays. Therefore, from a masked analysis of the first 7000 patients included in SIRS, we used a modification of the method developed by Mazumdar and colleagues[25,26] to identify the lowest CK-MB threshold that had an independent hazard ratio (HR) of more than 2 for 30-day mortality after adjustment for patients' EuroSCORE values. Thresholds were established for CK-MB measured by mass assay and by activity assay, as well as separately for patients who had isolated coronary artery bypass and for those having other cardiac surgeries. On the basis of these analyses, the SIRS protocol diagnostic criterion of early myocardial injury was any one of the following: for the mass assay, a CK-MB measurement at least six times the upper limit of normal in patients who had isolated coronary artery bypass or at least 15 times the upper limit of normal in patients who had other cardiac surgery; for the activity assay, a CK-MB activity measurement of at least 40 U/L in patients who had isolated coronary artery bypass or at least 120 U/L in patients who had other cardiac surgery; angiographic graft occlusion or new native coronary artery occlusion; or imaging evidence of new loss of viable myocardium.

In patients with a CK-MB greater than the upper limit of normal before randomisation, an absolute increase in a patient's CK-MB measurement based on our stated definition was needed. For example, if a patient undergoing isolated coronary artery bypass surgery had a myocardial injury before cardiac surgery and had a peak CK-MB activity assay value of 60 U/L 2 days before surgery, this patient would need a CK-MB activity assay measurement of at least 100 U/L during the first 72 h after surgery to fulfil the diagnostic criterion of myocardial injury.

Outcome definitions are described in more detail in the appendix. An adjudication committee whose members were unaware of study group assignments assessed all deaths and myocardial injuries and their decisions were used in the analyses.

### Statistical analysis

We planned to enrol 7500 patients to have more than 80% power to detect a 25% relative risk (RR) reduction for the first primary outcome of death at 30 days with an

α of 0·041 (two-sided), anticipating a 6% mortality rate in the control group. The study had more than 99·9% power to detect a 20% RR reduction for the second primary outcome of death, myocardial injury, stroke, renal failure, or respiratory failure at 30 days with an α of 0·01 (two-sided), anticipating a 25% rate in the control group.

For the analysis of the two primary efficacy outcomes, the overall type I error was partitioned. We tested the first primary outcome of death at a 0·041 level of significance and the second primary outcome at a level of 0·01. This maintained the overall type I error rate for both primary comparisons at 5%, under the assumption that the overlap between the two outcomes was at least 15%. The non-additivity of the type I error rates shows the correlation between these two outcomes, estimated from 10 million simulations with the Mantel-Haenszel statistic.

All analyses were based on the intention-to-treat principle. We compared the proportions of patients developing the primary outcomes using the Pearson $\chi^2$ test. The RR was calculated along with its 95% CIs associated with methylprednisolone. We compared all secondary outcomes with a $\chi^2$ test or a *t* test (or a non-parametric test if data were not normally distributed) where appropriate.

We did subgroup analyses based on sex, diabetes, EuroSCORE, cardiopulmonary bypass duration, age, and surgery type by stratified analyses through logistic regression or Cox proportional hazards models, as appropriate. A priori, we stated the expected direction of effects in the subgroups. The test of interaction between each subgroup factor and the treatment group was done by including a product term in the model already containing treatment and the subgroup factor, designated as significant at $p<0·05$. An independent data and safety monitoring board reviewed the interim analyses when 50% and 75% of the 30-day follow-up data were available. SAS version 9.1 was used for all analyses.

This study is registered with ClinicalTrials.gov, number NCT00427388.

## Role of the funding source

The Population Health Research Institute designed and coordinated the trial and was responsible for the

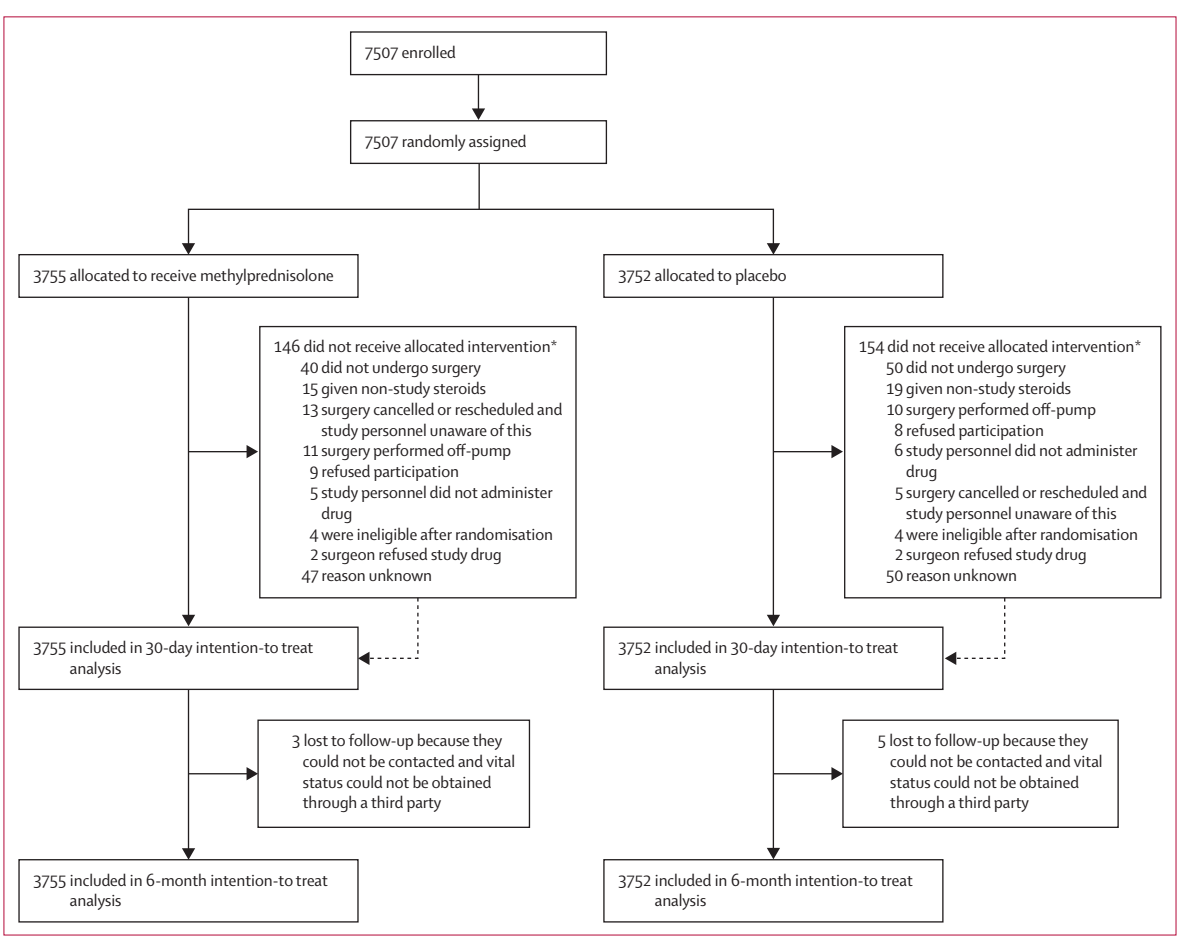


***Figure 1:*** **Trial profile**
*Data were not collected for the first 490 patients in the pilot study.

| | Methylprednisolone (n=3755) | Placebo (n=3752) |
|---|---|---|
| Age | | |
| Mean (years) | 67·5 (13·6) | 67·3 (13·8) |
| <65 years | 1175 (31%) | 1213 (32%) |
| 65–80 years | 1972 (52·5%) | 1925 (51%) |
| >80 years | 483 (13%) | 500 (13%) |
| Sex | | |
| Male | 2257 (60%) | 2280 (61%) |
| Female | 1498 (40%) | 1472 (39%) |
| Body-mass index* | 26·7 (5·8) | 26·6 (5·4) |
| Coexisting medical conditions | | |
| Diabetes | 984 (26%) | 991 (26%) |
| Current smoker | 462 (12%) | 485 (13%) |
| Former smoker | 1339 (36%) | 1347 (36%) |
| Hypertension | 2494 (66%) | 2473 (66%) |
| Previous myocardial infarction | 981 (26%) | 918 (24%) |
| Congestive heart failure | 1005 (27%) | 1021 (27%) |
| Previous stroke | 305 (8%) | 317 (8%) |
| Peripheral arterial disease† | 368 (10%) | 414 (11%) |
| Preoperative atrial fibrillation | 839 (22%) | 870 (23%) |
| Chronic renal failure | 260 (7%) | 277 (7%) |
| Dialysis | 45 (1%) | 52 (1%) |
| Preoperative creatinine in patients not on dialysis | 90·8 (31·1) | 90·9 (31·0) |
| Chronic obstructive pulmonary disease | 348 (9%) | 391 (10%) |
| Peptic ulcer disease | 166 (4%) | 160 (4%) |
| Previous gastrointestinal haemorrhage | 99 (3%) | 110 (3%) |
| EuroSCORE | | |
| Mean | 7·1 (2·0) | 7·1 (2·0) |
| 4–5 | 518 (14%) | 504 (13%) |
| 6–8 | 2454 (65%) | 2495 (66%) |
| >8 | 400 (11%) | 398 (11%) |
| Increased CK-MB preoperatively | 371 (10%) | 383 (10%) |
| Cardiac status | | |
| Left ventricular grade I‡ | 2339 (62%) | 2376 (63%) |
| Coronary stenosis >50% | | |
| Left main | 450 (12%) | 459 (12%) |
| Left anterior descending | 1601 (43%) | 1523 (41%) |
| Circumflex | 1315 (35%) | 1232 (33%) |
| Right | 1422 (38%) | 1328 (35%) |
| Valvular heart disease | 3015 (80%) | 3068 (82%) |
| Preoperative medications within 7 days | | |
| ACE/ARB§¶ | 2069 (55%) | 2043 (54%) |
| β blocker | 2197 (59%) | 2169 (58%) |
| Statin¶ | 1963 (56%) | 1933 (55%) |
| Aspirin | 1736 (46%) | 1690 (45%) |
| Other antiplatelet drugs** | 330 (9%) | 329 (9%) |
| Vitamin K antagonists | 319 (8%) | 308 (8%) |
| Dabigatran¶ | 22 (<1%) | 27 (<1%) |
| H2 antagonist or proton-pump inhibitor | 1422 (38%) | 1381 (37%) |
| Insulin | 439 (12%) | 385 (10%) |
| Oral hypoglycaemic drugs¶ | 444 (13%) | 469 (13%) |
| Operative characteristics | | |
| Repeat cardiac surgery | 588 (16%) | 569 (15%) |
| Procedure | | |
| Any cardiac valve | 2651 (71%) | 2724 (73%) |
| Any coronary artery bypass | 1837 (49%) | 1796 (48%) |
| Isolated cardiac valve | 1209 (32%) | 1228 (33%) |
| Isolated coronary artery bypass | 825 (22%) | 762 (20%) |
| Bypass time (min) | 108 (82–144) | 110 (84–142) |
| Cross-clamp time (min) | 77 (54–105) | 76 (55–104) |
| Hypothermic arrest | 96 (3%) | 55 (1%) |
| Hypothermic arrest time (min) | 18 (13–36) | 20 (12–39) |
| Coated circuit | 1733 (46%) | 1753 (47%) |
| Antifibrinolytic drugs | 2568 (68%) | 2617 (70%) |
| Preoperative inotropes, vasopressors, intra-aortic balloon pump, or ventricular assist device | 333 (9%) | 353 (9%) |
| Received at least one dose of study drug or placebo ¶ | 3364 (96%) | 3353 (96%) |
| Non-study postoperative steroids ¶ | 75 (2%) | 85 (2%) |

Data are mean (SD), n (%), or median (IQR). CK-MB=creatine kinase myocardial band. ACE=angiotensin converting enzyme inhibitor. ARB=angiotensin II receptor blocker. *The body-mass index is the weight (kg) divided by the square of the height (m). †Diagnosis of any one of intermittent claudication, vascular surgery for atherosclerotic disease, ankle to arm systolic ratio of at least 0·90 in either leg at rest, angiographic, or Doppler study showing at least 70% stenosis in a non-cardiac artery. ‡From ejection fraction or reported. §Angiotensin converting enzyme inhibitor or angiotensin II receptor blocker. ¶Data for these variables were not collected in the pilot phase of the first 490 patients, thus the denominator is slightly lower. **Thienopyridine, ticagrelor, glycoprotein IIb, or glycoprotein IIIa inhibitor.

***Table 1:*** **Baseline characteristics**

randomisation scheme, database, data validation, and analyses. The Operations Committee designed the trial, prespecified the statistical analysis plan, and were responsible for the data and analyses. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between June 21, 2007, and Dec 19, 2013, we recruited 7507 patients to this study (figure 1). The 30-day

| | Methylprednisolone (n=3755) | Placebo (n=3752) | Relative risk (95% CI) | p value |
|---|---|---|---|---|
| **Primary outcomes** | | | | |
| Death | 154 (4%) | 177 (5%) | 0·87 (0·70–1·07) | 0·19 |
| Death, myocardial injury, stroke, new renal failure, or respiratory failure | 909 (24%) | 885 (24%) | 1·03 (0·95–1·11) | 0·53 |
| **Components of composite primary outcome** | | | | |
| Myocardial injury | 486 (13%) | 399 (11%) | 1·22 (1·07–1·38) | 0·002 |
| Stroke | 71 (2%) | 79 (2%) | 0·90 (0·65–1·23) | 0·51 |
| New renal failure | 139 (4%) | 160 (4%) | 0·87 (0·69–1·08) | 0·21 |
| Respiratory failure | 343 (9%) | 375 (10%) | 0·91 (0·79–1·05) | 0·21 |
| **Secondary outcomes** | | | | |
| Death or myocardial injury | 605 (16%) | 530 (14%) | 1·14 (1·02–1·27) | 0·02 |
| New atrial fibrillation | 821 (22%) | 846 (23%) | 0·97(0·89–1·06) | 0·48 |
| Transfusions | 1832 (49%) | 1865 (50%) | 0·98 (0·94–1·03) | 0·43 |
| Chest drain output (mL) | 440 (280–720) | 480 (300–760) | .. | 0·0007 |
| Length of ICU stay (h) | 46·0 (23·0–90·0) | 47·0 (24·0–91·0) | .. | 0·05 |
| Length of hospital stay (days) | 9·0 (7·0–13·0) | 9·0 (7·0–13·0) | .. | 0·06 |
| **Safety outcomes** | | | | |
| Infection | 465 (12%) | 493 (13%) | 0·94 (0·84–1·06) | 0·33 |
| Surgical site infection | 151 (4%) | 151 (4%) | 1·00 (0·80–1·25) | 0·99 |
| Delirium | 295 (8%) | 289 (8%) | 1·02 (0·87–1·19) | 0·80 |
| Gastrointestinal perforation or haemorrhage | 55 (1%) | 46 (1%) | 1·19 (0·81–1·76) | 0·37 |
| Peak blood glucose (mmol/L) | 12·7 (7·2) | 12·1 (18·7) | .. | 0·04 |
| Postoperative insulin (units) | 50·3 (66·3) | 32·6 (52·9) | .. | <0·0001 |

Data are n (%), median (IQR), or mean (SD), unless otherwise specified. ICU=intensive care unit.

***Table 2:*** **Effects of methylprednisolone on outcomes**

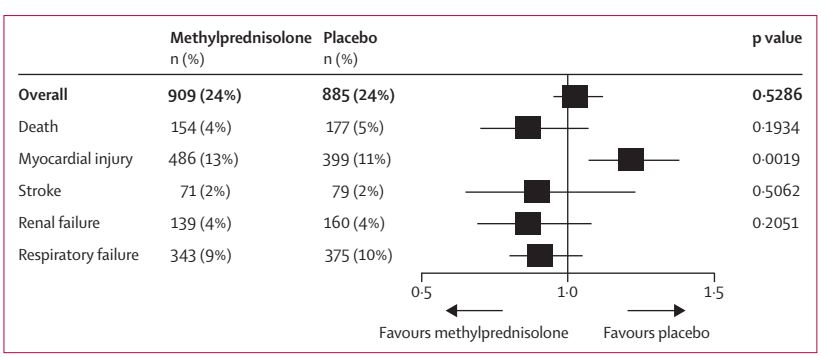


***Figure 2:*** **Relative risk of the composite primary outcome and its components**
The horizontal lines represent the 95% CI.

follow-up was complete in 7507 patients (100%) and the 6-month follow-up was complete in 7499 patients (99·9%). All 7507 patients were included in the 30-day and 6-month intention-to-treat analyses.

The baseline characteristics were similar in the methylprednisolone and placebo groups (table 1). Of 7507 patients, the mean age was 67·4 years (SD 13·7), 1587 (21%) underwent isolated coronary artery bypass surgery, 2437 (32%) underwent isolated valvular surgery, 3379 (45%) underwent combined or other surgery, and the average EuroSCORE was 7·1 (SD 2·0). 96% of patients received at least one dose of the study drug (table 1).

The primary outcome of death at 30 days occurred in 154 patients (4%) allocated to methylprednisolone and in 177 patients (5%) allocated to placebo (RR for the methylprednisolone group 0·87, 95% CI 0·70–1·07, p=0·19; table 2). The primary outcome of death, myocardial injury, stroke, new renal failure, or respiratory failure at 30 days occurred in 909 patients (24%) allocated to methylprednisolone and in 885 patients (24%) allocated to placebo (RR 1·03, 95% CI 0·95–1·11; figure 2).

Secondary outcomes of stage 3 renal failure, stroke, new atrial fibrillation, transfusion requirements, infection, gastrointestinal complications, delirium, respiratory failure, length of intensive care unit stay, or length of hospital stay did not differ between the methylprednisolone and placebo groups. The most common adverse events in both groups were infection, surgical site infection, and delirium (table 2). Methylprednisolone reduced the chest drain output during the first 24 h after surgery (table 2). The peak postoperative serum glucose and the postoperative insulin requirements in the first 24 h after surgery were both increased by methylprednisolone (table 2).

The effects of methylprednisolone on the primary outcomes did not vary significantly across the prespecified subgroups (figure 3). The Kaplan-Meier

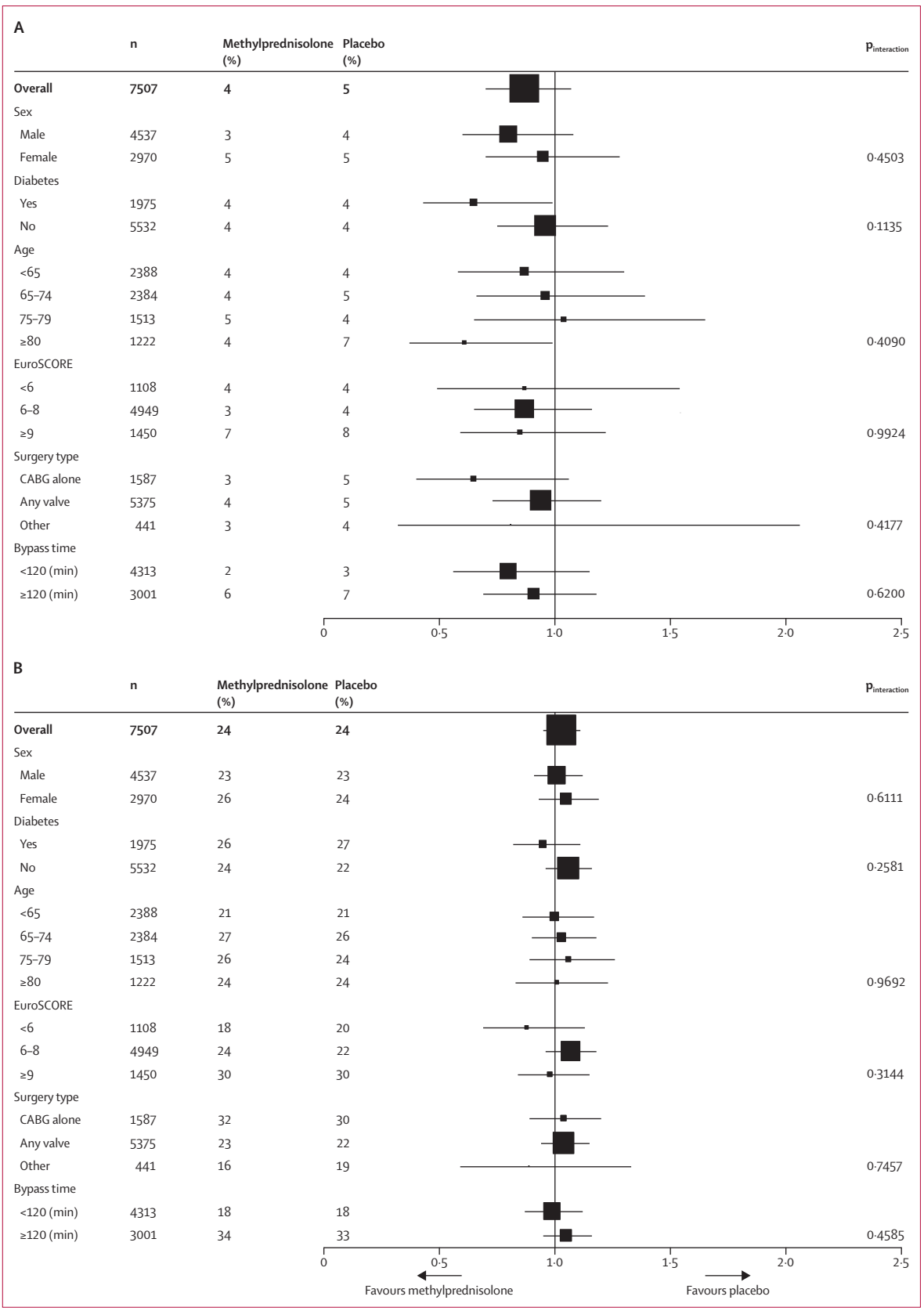


***Figure 3:*** **Primary outcome of death (A) and primary composite outcome (B) by prespecified subgroups**
The size of the black box is proportional to the weight and the horizontal lines represent the 95% CI. CABG=coronary artery bypass grafting.

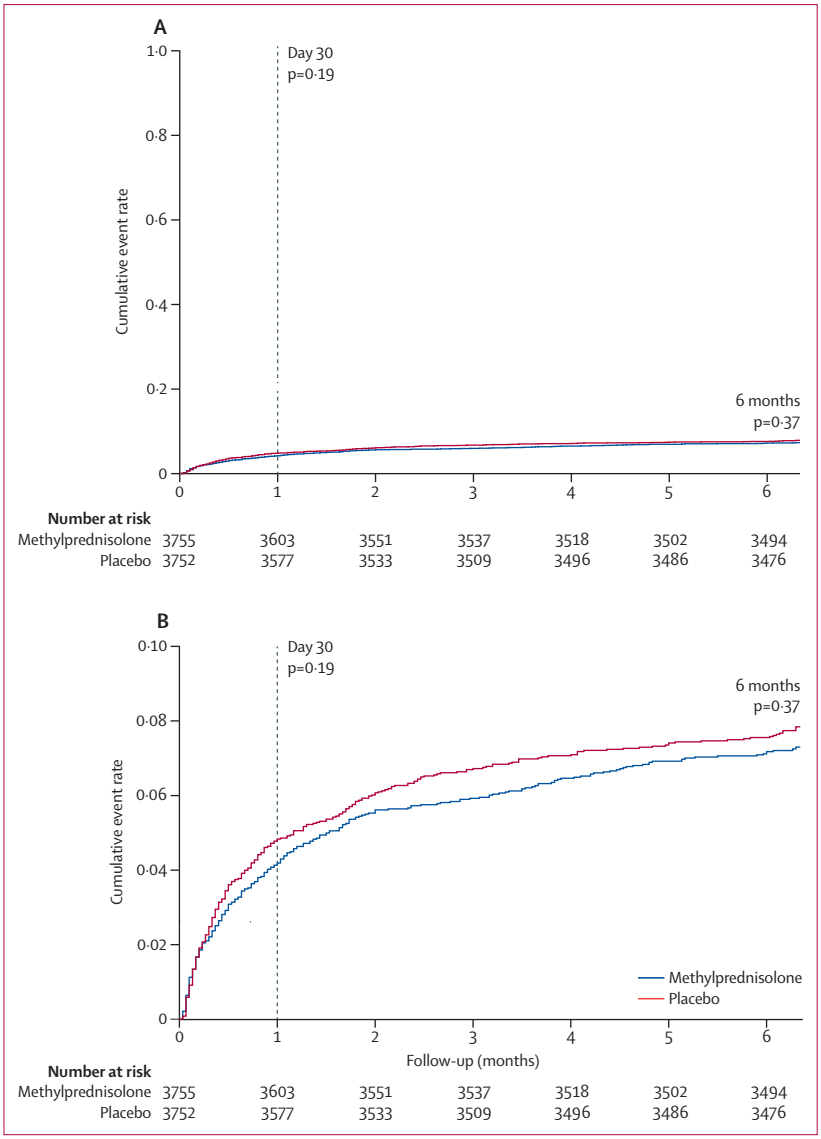


*Figure 4:* **Effects of methylprednisolone versus placebo on mortality at 30 days and 6 months shown on a scale from 0 to 1·0 (A) and expanded scale from 0 to 0·1(B)**

curve for 6-month mortality by treatment group shows no effect of methylprednisolone on mortality (figure 4).

Methylprednisolone increased the risk of myocardial injury (as defined in our protocol) compared with placebo (table 2). A post-hoc analysis showed that the risk of Q-wave myocardial infarction did not differ between patients allocated to methylprednisolone (21 patients [<1%]) and those allocated to placebo (24 patients [<1%]; RR 0·87, 95% CI 0·49–1·57). The increase in myocardial injury with methylprednisolone was reported in early events that were non Q-wave (RR 1·24, 1·09–1·41). This early myocardial injury increased the RR of death at 30 days compared with those without myocardial injury (RR 2·3, 1·8–2·9). Furthermore, myocardial injury increased mortality in both the methylprednisolone and placebo treatment groups ($p_{interaction}$=0·07; appendix). With the high use of statin therapy in this population, we assessed whether an interaction between methylprednisolone and myocardial injury existed because both can induce myopathy. The excess in enzymatic evidence of myocardial injury was similar in those receiving and not receiving a statin ($p_{interaction}$=0·75). Finally, we did a post-hoc analysis to assess the effect of methylprednisolone on the primary outcomes by geographical region and identified no significant interaction (appendix).

## Discussion

In patients at high risk of morbidity and mortality undergoing cardiac surgery with the use of cardiopulmonary bypass, administration of perioperative methylprednisolone did not decrease the risk of death, or the composite risk of death, myocardial injury, stroke, renal failure, and respiratory failure at 30 days. Perioperative methylprednisolone did, however, significantly increase the risk of myocardial injury (as defined by the SIRS protocol; RR 1·22, 95% CI 1·07–1·38).

Our previously published systematic review[17] that included 44 randomised controlled trials of 3205 patients suggested that perioperative steroids reduced the risk of new postoperative atrial fibrillation (424 total events; RR 0·71, 95% CI 0·59–0·87), postoperative bleeding (weighted mean difference –100 mL, 95% CI –150 to –59), length of intensive care unit stay (weighted mean difference –0·23 days, –0·40 to –0·07), and length of hospital stay (weighted mean difference, –0·59 days; –1·17 to –0·02). The RR for the effect of steroids on mortality was 0·73 (95% CI 0·45–1·18), but this was based on only 65 deaths, indicating substantial uncertainty.

The DECS trial[18] randomly assigned 4494 patients to receive one intraoperative dose of dexamethasone 1 mg/kg or placebo. The primary outcome was a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure within 30 days, which was one of the primary outcomes in our study. In the DECS trial, 7% of patients had the primary outcome in the dexamethasone group versus 8% in the placebo group (RR 0·83, 95% CI 0·67–1·01, p=0·07). A statistically significant benefit of dexamethasone was reported in a prespecified subgroup of patients with a EuroSCORE of at least 5 (RR 0·77, 95% CI 0·61–0·98); however, the test for interaction was not significant ($p_{interaction}$=0·32). Dexamethasone also significantly reduced infection (212 patients [9%] *vs* 333 patients [15%]; RR 0·64, 0·54–0·75), delirium (RR 0·79, 0·66–0·94), and respiratory failure (RR 0·69, 0·51–0·94).

Our study did not show a benefit of perioperative steroids on death or major morbidity in patients at high

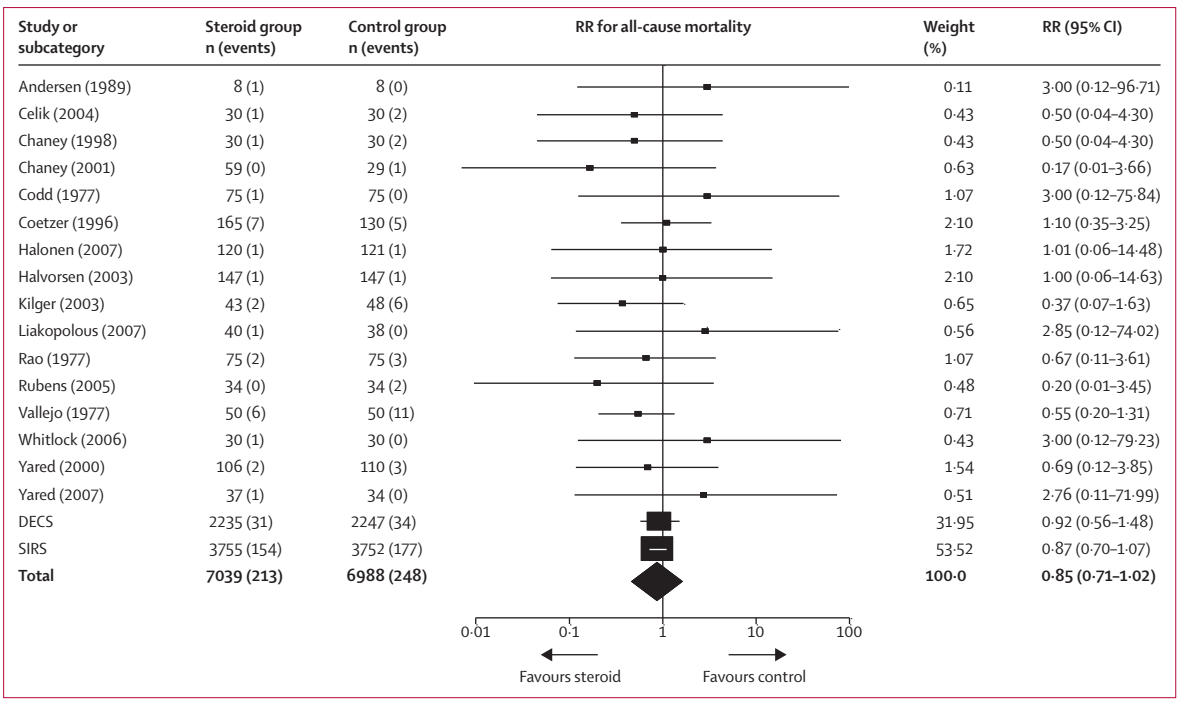


***Figure 5:*** **2008 meta-analysis updated with data from SIRS and DECS trials**
RR=relative risk.

risk of morbidity and mortality as suggested in the DECS trial. We have updated our 2008 meta-analysis[17] with the SIRS and DECS mortality data (figure 5). This meta-analysis includes data for 14 027 patients and does not show a significant reduction in mortality with steroids (RR 0·84, 95% CI 0·71–1·02, p=0·08). This finding suggests that the potential benefits, if any, are likely to be much smaller than previously postulated. Both the DECS trial and SIRS identified no reduction in new postoperative atrial fibrillation that was suggested by our previous meta-analysis.[17] SIRS did show a statistically significant reduction in bleeding in the first 24 h after surgery; however, we noted no effect on transfusion needs, suggesting that the small difference between the median chest drain output (40 mL) was not clinically important.

The increase in myocardial injury noted with methylprednisolone in this study was not reported in DECS or previous trials. The DECS trial did not, however, mandate the measurement of postoperative biomarkers, and probably did not detect some prognostically important asymptomatic myocardial injuries that were masked by analgesic medications early after surgery. Furthermore, the DECS trial used the Universal Definition of Myocardial Infarction, which the Joint Task Force indicated was based on arbitrary biomarker thresholds.[27] Therefore, a significant number of clinically important myocardial injuries were probably missed in the DECS trial (ie, only 74 myocardial infarctions were reported, with an incidence of 2%), whereas in SIRS, we used systematic monitoring of CK-MB and identified 885 myocardial injuries (12%). Another trial in cardiac surgery that mandated collection of CK-MB reported an incidence of myocardial injury of 11% with a similar definition to the SIRS definition.[20] Perioperative myocardial injury based on biomarker increase alone is associated with an increase in short-term and long-term mortality and therefore the excess myocardial injury reported in our trial is probably clinically important.[28]

Although the mechanism of the increase in CK-MB with steroids is not clear, we have generated several hypotheses. First, steroids might impair metabolic modulation of the ischaemic insult. After ischaemia, glucose entry into the myocyte is essential for its recovery of contractile function. Steroids induce insulin resistance, as shown by the higher peak serum glucose measurements and the increased need for insulin use in the methylprednisolone group. This insulin resistance might block glucose from entering the myocyte and thereby worsen ischaemic injury. Second, steroids might alter CK-MB release or its clearance; for example, through a mechanism of steroid-induced myositis in which an increased release of skeletal CK-MB might occur. However, we could not find any supportive evidence for this possibility. Roberts and colleagues[29] showed that methylprednisolone had no direct effect on creatine phosphokinase concentrations or the kinetics of its release. Furthermore, the increase in CK-MB

concentrations in our study was associated with a doubling of risk of death at 30 days in the methylprednisolone group, suggesting that its increase probably has adverse prognostic consequences. Third, inflammation after myocardial injury has been shown to be a prerequisite of healing, and steroids might interfere with this process.[30] Early studies of steroids after acute myocardial infarction increased infarct size.[29] Therefore, the suppression of inflammation after cardiac injury might inhibit necessary processes of myocardial repair, specifically, neutrophil and macrophage recruitment.[31,32] Although the exact mechanism is not clear, the highly significant association with increased mortality in such patients should urge substantial caution in using steroids in patients undergoing cardiac surgery.

The definition of myocardial injury after cardiac surgery is challenging in that all patients have cardiac biomarker release by the very nature of the surgery. Robust evidence to determine thresholds of biomarkers to define clinically important myocardial injury is not available, particularly for non-coronary artery bypass cardiac surgery. However, our approach to defining myocardial injury in SIRS was objective, defined a priori, and was associated with increased mortality, suggesting that the approach we used is clinically relevant. However, if this finding is an epiphenomenon rather than a clinically relevant effect, it does not alter the fact that we did not show a benefit in important outcomes with methylprednisolone.

We did not measure inflammatory markers in this study. However, we used the same dosing regimen in this study that we used in the SIRS pilot study that showed our dosing regimen was effective to prevent the inflammatory response to cardiopulmonary bypass.[16]

The SIRS trial does not support the routine use of methylprednisolone for patients undergoing cardiopulmonary bypass, but does suggest an increased risk of myocardial injury. The routine use of steroids for cardiopulmonary bypass is cautioned. Further research should elucidate the mechanism by which methylprednisolone led to an increased risk of myocardial injury.

#### Contributors

RPW, KHT, and SY initiated the study. RPW and SY wrote the first and final drafts of the report. JP analysed the data. PJD, KHT, AL, JV, DP, DIS, GK, JCV, YZ, AA, MQ, GIT, PJS, SHA, HZ, SP, and SC contributed to each draft of the report. All authors were international leads, members of the International Steering Committee of the SIRS trial, or members of the central coordinating office.

#### Declaration of interests

We declare no competing interests.

#### Acknowledgments

SIRS was funded by the Canadian Institutes of Health Research and the Canadian Network and Centre for Trials Internationally.

#### References

1 Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation* 2012; **125:** e2–220.
2 Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. *Eur J Cardiothorac Surg* 2002; **21:** 232–44.
3 Asimakopoulos G, Smith PL, Ratnatunga CP, Taylor KM. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. *Ann Thorac Surg* 1999; **68:** 1107–15.
4 Boyle EM, Pohlman TH Jr, Johnson MC, Verrier ED. Endothelial cell injury in cardiovascular surgery: the systemic inflammatory response. *Ann Thorac Surg* 1997; **63:** 277–84.
5 Mojcik CF, Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. *Ann Thorac Surg* 2001; **71:** 745–54.
6 Chaney MA. Corticosteroids and cardiopulmonary bypass: a review of clinical investigations. *Chest* 2002; **121:** 921–31.
7 Kirklin JK, McGiffin DC. Early complications following cardiac surgery. *Cardiovasc Clin* 1987; **17:** 321–43.
8 Teoh KH, Bradley CA, Gauldie J, Burrows H. Steroid inhibition of cytokine-mediated vasodilation after warm heart surgery. *Circulation* 1995; **92** (suppl 9)**:** II347–53.
9 Vincent JL, Wan S, Yim AP. Steroids in cardiopulmonary bypass. *Crit Care Med* 2000; **28:** 3373–74.
10 Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1983; **86:** 845–57.
11 Levi M, Cromheecke ME, de Jonge E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; **354:** 1940–47.
12 Royston D. Preventing the inflammatory response to open-heart surgery: the role of aprotinin and other protease inhibitors. *Int J Cardiol* 1996; **53** (suppl)**:** S11–37.
13 Rubens FD, Mesana T. The inflammatory response to cardiopulmonary bypass: a therapeutic overview. *Perfusion* 2004; **19** (suppl 1)**:** S5–12.
14 Wan S, LeClerc JL, Schmartz D, et al. Hepatic release of interleukin-10 during cardiopulmonary bypass in steroid-pretreated patients. *Am Heart J* 1997; **133:** 335–39.
15 Whitlock RP, Rubens FD, Young E, Teoh KH. Pro: steroids should be used for cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2005; **19:** 250–54.
16 Whitlock RP, Young E, Noora J, Farrokhyar F, Blackall M, Teoh KH. Pulse low dose steroids attenuate post-cardiopulmonary bypass SIRS; SIRS I. *J Surg Res* 2006; **132:** 188–94.
17 Whitlock RP, Chan S, Devereaux PJ, et al. Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: a meta-analysis of randomized trials. *Eur Heart J* 2008; **29:** 2592–600.
18 Dieleman JM, Nierich AP, Rosseel PM, et al. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA* 2012; **308:** 1761–67.
19 Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999; **16:** 9–13.
20 Verrier ED, Shernan SK, Taylor KM, et al. Terminal complement blockade with pexelizumab during coronary artery bypass graft surgery requiring cardiopulmonary bypass: a randomized trial. *JAMA* 2004; **291:** 2319–27.
21 Wang C, Yao F, Han L, Zhu J, Xu ZY. Validation of the European system for cardiac operative risk evaluation (EuroSCORE) in Chinese heart valve surgery patients. *J Heart Valve Dis* 2010; **19:** 21–27.
22 Malik M, Chauhan S, Malik V, Gharde P, Kiran U, Pandey RM. Is EuroSCORE applicable to Indian patients undergoing cardiac surgery? *Ann Card Anaesth* 2010; **13:** 241–45.
23 Whitlock R, Teoh K, Vincent J, et al. Rationale and design of the steroids in cardiac surgery trial. *Am Heart J* 2014; **167:** 660–65.
24 Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. *Circulation* 2009; **119:** 1853–66.
25 Mazumdar M, Smith A, Bacik J. Methods for categorizing a prognostic variable in a multivariable setting. *Stat Med* 2003; **22:** 559–71.

26 Mazumdar M, Glassman JR. Categorizing a prognostic variable: review of methods, code for easy implementation and applications to decision-making about cancer treatments. *Stat Med* 2000; **19:** 113–32.

27 Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation* 2007; **116:** 2634–53.

28 Domanski MJ, Mahaffey K, Hasselblad V, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. *JAMA* 2011; **305:** 585–91.

29 Roberts R, DeMello V, Sobel BE. Deleterious effects of methylprednisolone in patients with myocardial infarction. *Circulation* 1976; **53:** 1204–06.

30 Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. *Cardiovasc Res* 2002; **53:** 31–47.

31 Hammerman H, Kloner RA, Hale S, Schoen FJ, Braunwald E. Dose-dependent effects of short-term methylprednisolone on myocardial infarct extent, scar formation, and ventricular function. *Circulation* 1983; **68:** 446–52.

32 Bulkley BH, Roberts WC. Steroid therapy during acute myocardial infarction. A cause of delayed healing and of ventricular aneurysm. *Am J Med* 1974; **56:** 244–50.