



**Steroids in cardiac surgery (SIRS) trial: Acute kidney injury
substudy protocol of an international randomised controlled
trial**

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Complete List of Authors:	Garg, Amit; University of Western Ontario Vincent, Jessica; Population Health Research Institute, Cuerden, Meaghan; University of Waterloo, Department of Statistics and Actuarial Science Parikh, Chirag; Yale University School of Medicine Devereaux, P.J.; McMaster University, Medicine Teoh, Kevin; Population Health Research Institute, Yusuf, Salim; McMaster University, Medicine Hildebrand, Ainslie; Western University, Medicine (Nephrology) Lamy, Andre; McMaster University, Surgery Zuo, Yunxia; West China Hospital / Sichuan University, Sessler, Daniel; Cleveland Clinic, Shah, Pallav; Princess Alexandra Hospital, Abbasi, Seyed Hesameddin; Tehran Heart Center, Quantz, Mackenzie; Western University, Surgery Yared, Jean-Pierre; Cleveland Clinic, Noiseux, Nicolas; Universite de Montreal, Cardiac Surgery Tagarakis, Georgios; University of Thessaly, Rochon, Antoine; Montreal Heart Institute, Pogue, Janice; Population Health Research Institute, Walsh, Michael; McMaster University, Surgery Chan, MTV; The Chinese University of Hong Kong, Anesthesia and Intensive Care Lamontagne, Francoise; Universite de Sherbrooke, Salehiomran, Abbas; Tehran Heart Center, Whitlock, Richard; McMaster University, Surgery
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Steroids in cardiac surgery (SIRS) trial: Acute kidney injury substudy protocol of an international randomised controlled trial

Amit X. Garg amit.garg@lhsc.on.ca¹, Jessica Vincent jessica.vincent@phri.ca²,
Meaghan Cuerden meaghan.cuerden@gmail.com³, Chirag Parikh chirag.parikh@yale.edu⁴,
P.J. Devereaux philipi@mcmaster.ca¹, Kevin Teoh kteoh@southlakeregional.org¹,
Salim Yusuf Salim.Yusuf@phri.ca¹, Ainslie Hildebrand ainsliehildebrand@gmail.com⁶,
Andre Lamy alamy1@mac.com¹ Yunxia Zuo zuoyunxia666@gmail.com⁵,
Daniel I. Sessler ds@or.org⁶, Pallav Shah pallavshah@ozemail.com.au⁷,
Seyed Hesameddin Abbasi abbasi.hesam@gmail.com⁸, Mackenzie Quantz maquantz@gmail.com¹,
Jean-Pierre Yared YAREDJ@ccf.org⁶, Nicolas Noiseux noiseuxn@videotron.ca⁹,
Georgios Tagarakis gtagarakis@gmail.com¹⁰, Antoine Rochon antoine.rochon@icm-mhi.org¹¹,
Janice Pogue Janice.Pogue@phri.ca¹, Michael Walsh lastwalsh1975@gmail.com¹,
Matthew T.V. Chan mtvchan@cuhk.edu.hk¹², Francois Lamontagne Francois.Lamontagne@usherbrooke.ca¹³,
Abbas Salehiomran abbasomran@yahoo.com⁸, Richard Whitlock richard.whitlock@phri.ca¹,
on behalf of the SIRS Investigators

1. Western University, London, Canada
2. Population Health Research Institute / McMaster University / Hamilton Health Sciences, Hamilton, Canada
3. University of Waterloo, Waterloo, Canada
4. Yale University, Connecticut, United States of America
5. West China Hospital / Sichuan University, Chengdu, China
6. Department of Outcomes Research / Cleveland Clinic, Cleveland, United States of America
7. Princess Alexandra Hospital, Woolloongabba, Australia
8. Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran
9. Centre Hospitalier de l'Université de Montréal, Montréal, Canada
10. University of Thessaly, Larissa, Greece
11. Montreal Heart Institute, Montréal, Canada
12. The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China
13. Université de Sherbrooke, Sherbrooke, Canada

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ABSTRACT

Introduction: SIRS is a large international randomised controlled trial of methylprednisolone or placebo in patients undergoing cardiac surgery with the use of a cardiopulmonary bypass pump. At the time of surgery, compared to placebo, methylprednisolone divided into two intravenous doses of 250 mg each may reduce the risk of post-operative acute kidney injury (AKI).

Methods and analysis: With respect to the study schedule, the last of over 7000 substudy eligible patients from 81 centres in 18 countries were randomised in December 2013. The authors will use a logistic regression to estimate the adjusted odds ratio of methylprednisolone versus placebo on the primary outcome of AKI in the 14 days following surgery (a post-operative increase in serum creatinine of $\geq 50\%$, or $\geq 26.5 \mu\text{mol/L}$, from the pre-operative value). The stage of AKI will also be considered, as will the outcome of AKI in those with and without pre-operative CKD. After receipt of grant funding, the authors began to record additional peri-operative serum creatinine measurements in consecutive patients enrolled at substudy participating centres, and patients were invited to enroll in a 6-month serum creatinine collection. In these trial subpopulations the authors will consider the outcome of AKI defined in alternate ways, and the outcome of a 6-month change in kidney function from the pre-operative value.

Ethics and dissemination: The authors were competitively awarded a grant from the Canadian Institutes of Health Research for this SIRS AKI substudy. Ethics approval was obtained for additional serum creatinine recordings in consecutive patients enrolled at participating centres. The additional kidney data collection first began for patients enrolled after March 1 2012. In patients who provided consent, the last 6-month kidney outcome data will be collected in 2014. The results will be reported no later than 2015.

Clinical Trial Registration Number: NCT00427388

ARTICLE SUMMARY

Article focus

- SIRS is a large international randomised controlled trial of methylprednisolone or placebo in patients undergoing cardiac surgery with the use of cardiopulmonary bypass pump.
- Compared to placebo, we hypothesize that methylprednisolone will reduce the risk of post-operative AKI.
- Secondary analyses will examine whether results are consistent across alternate definitions of AKI, whether effects are similar in patients with and without pre-operative chronic kidney disease, and the effect of methylprednisolone at the time of surgery on kidney function 6-months after surgery.

Key messages

- Presented is this pre-specified SIRS AKI analytic protocol.
- Data collection will be completed in 2014.
- If methylprednisolone reduces the risk of AKI, the finding will support inflammation as an important modifiable mechanism of AKI in cardiac surgery. Such a finding will also support the need for trials of corticosteroids in other settings to prevent AKI.

Strengths and limitations of this study

- International recruitment across 81 centres in 18 countries will provide generalizable estimates of the treatment effect.
- The kidney data collection schedule in this large international trial is feasible and efficient. Additional studies of the effects of methylprednisolone in cardiac surgery can consider multiple measures of kidney function over time, both before and far after AKI, examine trajectories of kidney function loss, and new markers of kidney function or injury.

BACKGROUND

Worldwide, about 2 million cardiac surgeries are performed each year, and most surgeries use a cardiopulmonary bypass pump. About a third of patients undergoing such procedures develop acute kidney injury (AKI) (defined by an acute rise in serum creatinine of 50% or more or an acute rise of 26 $\mu\text{mol/L}$ or more), and 1% receive acute dialysis. This means there are several hundred thousand cases of AKI attributed to cardiac surgery worldwide each year with about 20,000 cases receiving acute dialysis. When AKI occurs (compared to when it does not) it associates with increased mortality, a longer hospital length of stay, and higher healthcare costs.¹⁻³

The major mechanism of AKI in cardiac surgery is impaired kidney perfusion causing an initial hypoxic insult followed by activation of inflammatory pathways during reperfusion (schematic depicted in Figure 1).⁴ In animal models of kidney ischemia-reperfusion injury, an elaboration of proinflammatory cytokines, reactive oxygen species and interstitial inflammation all result in AKI.⁴

In this setting, an inexpensive drug that attenuates the inflammatory response and related consequences could have a worldwide impact. Corticosteroids are an inexpensive, generic class of anti-inflammatory agents. We provide four lines of evidence to support the hypothesis that they reduce the risk of AKI from cardiac surgery with cardiopulmonary bypass.⁴⁻⁷ The mechanisms for AKI prevention are presented in Figure 1.

First, corticosteroid use may mitigate peri-operative cardiac events. This may occur through a few processes including the inhibition of cytokines released during cardiopulmonary bypass (Figure 1). Many studies of corticosteroid use report post-operative improvements in the cardiac index and mean arterial pressure, with less use of inotropic support. A meta-analysis demonstrates that peri-operative corticosteroid use clearly reduces the risk of post-operative atrial fibrillation (44 studies).⁸ Acute cardiac events are inextricably linked to AKI events; both events often co-occur in the non-operative setting. The process may include hypotension as a primary inciting event or from the cardiac injury itself, or from the aggressive use of diuretics used to treat acute heart failure.

Second, corticosteroid use targets the key pathologic mechanisms for the development of AKI (displayed in Figure 1 along with where steroids act to prevent AKI). This involves reducing the systemic inflammatory response syndrome from cardiopulmonary bypass surgery, with reductions in inflammatory mediators, cytokines, complement, transcription factors, and adhesion molecules.

Third, in the largest multi-centre randomised trial of dexamethasone in cardiac surgery with a cardiopulmonary bypass pump, 4494 adult patients from the Netherlands were randomly assigned to receive dexamethasone (1 mg/kg of body weight with a 100 kg maximum) or placebo administered as a single intravenous injection after the induction of anesthesia before the initiation of cardiopulmonary bypass.⁷ An outcome of acute renal failure defined by the study investigators was an increase in postoperative serum creatinine of at least three times the preoperative value, or a serum creatinine more than 350 $\mu\text{mol/L}$ associated with an acute increase of serum creatinine of at least 44 $\mu\text{mol/L}$, within 30 days of surgery. This outcome of acute renal failure was one of five components of the primary composite outcome. Dexamethasone versus placebo resulted in trends in the reduction of the primary outcome and the acute renal failure outcome that were non-significant (primary outcome: 157

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3 patients of 2235 with dexamethasone [7.0%] vs 191 patients of 2247 with placebo [8.5%]; relative risk
4 reduction 17% (95% CI -1% to 33%); acute renal failure outcome 28 patients of 2235 with
5 dexamethasone [1.3%] vs. 40 patients of 2247 with placebo [1.8%], relative risk reduction 30%
6 (95% CI -14 to 56%).
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9 Two of the four existing small randomised controlled trials raise the possibility that corticosteroids may
10 prevent AKI in cardiopulmonary surgery. In one trial 29 children were randomised to receive either
11 intravenous dexamethasone (1 mg / kg) or saline one hour prior to cardiopulmonary bypass surgery.⁵ In
12 the dexamethasone group, 1 of 15 (7%) children demonstrated AKI vs. 7 of 14 (50%) children in the
13 saline group; $p = 0.014$ (AKI defined by $\geq 18 \mu\text{mol/L}$ increase in serum creatinine compared to the pre-
14 operative value). Another trial randomised 236 adults undergoing elective valvular or coronary artery
15 bypass surgery to intravenous dexamethasone (0.6 mg/kg) or placebo soon after the induction of
16 anesthesia.⁶ Three of 110 (2.7%) patients with placebo versus none of the 110 patients with
17 dexamethasone developed AKI (where AKI was defined by use of hemodialysis or oliguria). The results
18 were statistically non-significant, recognising there were only three events, $p=0.24$. A non-statistically
19 significant reduction in the risk AKI was observed in the other two randomised trials (enrolled 86 and 20
20 patients respectively, with the former also limited by a small number of events (2 episodes of AKI
21 (undefined), 1/43 in steroid group vs. 1/43 in placebo group)).^{9;10}
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27 Fourth, intravenous corticosteroids are a mainstay of therapy for many acute processes that involve
28 kidney inflammation: acute glomerulonephritis, vasculitis, lupus, and resistant forms of acute allergic
29 interstitial nephritis. It is rational to hypothesize similar benefits in cardiopulmonary bypass.
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31 We are conducting the Steroids In caRdiac Surgery trial (acronym SIRS). The rationale and design of this
32 large, international, randomised placebo controlled trial are described elsewhere.¹¹ In brief, adults at
33 high risk of post-operative complications who are undergoing cardiac surgery with a cardiopulmonary
34 bypass pump are randomly allocated to receive either methylprednisolone divided into two intravenous
35 250 mg doses (one dose at the start of anaesthesia and the other at the start of the cardiopulmonary
36 bypass pump) or matching placebo. Allocation is done by a central randomisation service and is
37 stratified by centre. Patients, health care providers, data collectors, and outcome adjudicators are
38 blinded to treatment allocation. This trial is funded by the Canadian Institutes of Health Research. With
39 respect to the study schedule, the last of over 7500 patients from 82 centres in 19 countries was
40 randomised on December 20, 2013. The primary outcome is 30-day all-cause mortality. The most
41 important secondary outcome is a 30-day composite outcome of death, myocardial infarction, stroke,
42 renal failure or respiratory failure. Renal failure is defined using thresholds of stage III AKI described in
43 recent guidelines.¹² Secondary safety outcomes include post-operative infection, wound complications,
44 gastrointestinal hemorrhage, delirium and insulin use.
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50 In addition to the primary outcome, SIRS is uniquely positioned to determine the effects of
51 corticosteroids on various stages and alternate definitions of AKI (and whether the treatment effect is
52 homogeneous across these stages), to consider whether the treatment effect differs in those with and
53 without pre-operative chronic kidney disease (CKD), and to investigate the effect of corticosteroids at
54 the time of surgery on kidney function 6 months later. We were competitively awarded an additional
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grant from the Canadian Institutes of Health Research to examine these issues in a SIRS AKI substudy. The questions detailed in this grant are presented below followed by a pre-specified analytic plan.

Primary questions

1. In patient undergoing cardiac surgery with a cardiopulmonary bypass pump, does the use of intravenous methylprednisolone at the time of surgery compared with placebo alter the risk of post-operative AKI? Is the treatment effect (the observed relative risk reduction) statistically homogeneous across multiple alternate stages and definitions of AKI? Hypothesis: Corticosteroids reduce the risk of post-operative AKI, with a similar treatment effect across alternate definitions of AKI.

Secondary questions

2. Does the presence of pre-operative CKD modify the effect of treatment (methylprednisolone versus placebo) on AKI? Hypothesis: A greater relative risk reduction will be observed in patients with pre-operative CKD than those without CKD (as we demonstrated in another setting - a large international randomised trial of coronary artery bypass surgery performed either with or without a bypass pump).

3. Does methylprednisolone versus placebo at the time of surgery alter kidney function 6-months after surgery? Hypothesis: We will be unable to demonstrate corticosteroids improve this outcome (due either to the study methods, or the limited impact of any observed AKI risk reduction on 6-month kidney function).

KIDNEY DATA COLLECTION AND ANALYTIC PLAN

SIRS enrollment began in 2007. To refine the analytic plan we reviewed SIRS data as of November 2013 (without knowledge of the treatment allocation and recognizing SIRS data is actively being adjudicated and data discrepancies reconciled).

SIRS kidney data collection

Kidney data collection in all SIRS patients: A pre-operative serum creatinine is measured and recorded in the 30 days prior to surgery. The date of surgery (and not the date of randomisation) will be used to identify the start of follow-up in this protocol; the median (interquartile range (IQR)) number of days between the date of randomisation and the date of surgery is 1 day (0 to 1), and the < 2% of randomised patients expected not to receive surgery will be excluded from analysis (see section Patient selection). A single peak serum creatinine in the 14 days following surgery is recorded along with the date of this measurement. At the start of our study, two weeks was felt to be a reasonable period in which any AKI related the surgery would manifest (either from the initial insult during surgery, and/or related to a second insult that occurred soon after surgery). Since the launch of SIRS, international AKI guidelines were published in 2012 which define AKI by an increase in serum creatinine of ≥ 26.5 $\mu\text{mol/L}$ within 48 hours, or an increase in serum creatinine of $\geq 50\%$ known or presumed to have occurred within the prior 7 days.¹² Currently, for all SIRS participants the single peak post-operative serum creatinine is recorded a median of 1 day after surgery (IQR 2 to 4 days). Approximately 60% of patients have this peak measurement recorded within 2 days of surgery, and 70%, 80%, and 83% of patients have this

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3 measurement recorded within 3, 4 and 5 days of surgery, respectively. Less than 1.5% of patients die in
4 the operating room or in the 48 hours after surgery (which may influence serum creatinine
5 measurement). Less than 2% of patients are expected to have a missing peak serum creatinine value
6 within 14 days of surgery, and in such cases in the absence of receipt of acute dialysis, we will carry
7 forward the pre-randomisation serum creatinine value for all analyses (which means the patient will not
8 have developed AKI; see analysis section). No urine output data has been collected in SIRS, given
9 difficulties with its accurate measurement in the setting of international data collection. Receipt of new
10 dialysis for kidney failure is recorded at hospital discharge and at 30 days after surgery.

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12 Additional peri-operative kidney data recordings in consecutive patients: After receipt of grant funding
13 for this substudy, additional peri-operative serum creatinine data began to be recorded in consecutive
14 patients enrolled at substudy participating centres (earliest centre to start this process began in March
15 2012). The data collection includes all serum creatinine values done as a part of routine care (and the
16 time of measurement) within the 14 days after surgery. If a patient is still in hospital beyond 14 days, the
17 most recent serum creatinine value done in routine care prior to the hospital discharge is also recorded.

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19 6-month kidney function data: After receipt of grant funding, in substudy participating centres, patients
20 have been invited to enroll at the time of randomisation to record a single 6-month serum creatinine
21 value (with instructions that a value is acceptable provided it is collected anytime between 3 to 8
22 months after surgery when a patient is not acutely ill).

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24 The additional serum creatinine collection (particularly the 6-month creatinine measurement) was
25 added to the patient consent requests and received ethical approval at each of the AKI substudy
26 participating sites.

27 28 29 **Patient selection**

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31 All SIRS randomised patients will be included in the AKI substudy except for the following three reasons:
32 (1) Those with end-stage renal disease prior to randomisation (expected < 2% of patients), as the
33 assessment of AKI is no longer relevant (estimated glomerular filtration rate (eGFR) < 15 mL/min per
34 1.73 m² as determined by the CKD-Epi equation¹³, receipt of chronic dialysis or a prior kidney transplant,
35 or a baseline serum creatinine > 327 µmol/L; the last exclusion also enables retained patients to have
36 their new onset AKI staged according to most recent guidelines)¹², (2) Those missing a pre-
37 randomisation serum creatinine value, or missing age or sex (expected in < 1% of patients) as this is
38 needed to define AKI or baseline CKD, (3) Those who never underwent cardiac surgery (expected in < 2%
39 of patients) as they won't have the opportunity to have any post-operative serum creatinine
40 measurements. When we publish the final results, these exclusions will be reported separately in each
41 of the methylprednisolone and placebo groups. We expect over 7000 SIRS patients will be eligible for
42 the AKI substudy from 81 centres in 18 countries.

43 44 45 **Intention to treat**

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47 The intention to treat principle will guide all primary analyses, irrespective of whether there is a
48 deviation from the randomly allocated therapy or not (methylprednisolone or matching placebo).
49 Currently, approximately 3% of patients did not receive the study medication, 2.4% of patients received
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3 non-study corticosteroids in the operating room, and 4.4% of patients received non-study
4 corticosteroids after surgery. At the time of final analysis these results will be reported by treatment
5 group.
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8 9 **Primary Definition of Acute Kidney Injury**

10 We will use a mixed effects logistic regression model to obtain an estimate of the odds ratio of AKI
11 comparing methylprednisolone to placebo (after testing model assumptions). While logistic regression
12 models will be used for hypothesis testing, at the time of final analysis we will preferentially report
13 relative risk reductions of methylprednisolone versus placebo as this metric is easier to interpret by a
14 clinical audience (and hence we use relative risk reduction nomenclature throughout the protocol
15 appreciating the logistic regression model produces an odds ratio; the method to derive a relative risk
16 reduction from an odds ratio is described elsewhere¹⁴). In SIRS this AKI outcome will use most recent
17 consensus criteria and will be defined as any of the following two criteria¹²: (1) $\geq 50\%$ percent change in
18 the post-operative serum creatinine value from the pre-operative value [$((\text{peak post-operative serum}$
19 $\text{creatinine} - \text{pre-operative serum creatinine})/\text{pre-operative serum creatinine}) \times 100$], (2) $\geq 26.5 \mu\text{mol/L}$
20 increase in serum creatinine after surgery from the pre-operative value. Given the nature of SIRS data
21 collection this peak post-operative serum creatinine value is assessed in the 14 days following surgery
22 (recognizing greater than 80% of peak values are currently evident within 5 days of surgery), thus the
23 timing in this SIRS AKI definition is slightly modified than what is presented in the AKI consensus
24 definition.¹² For the primary analysis we will treat centre as a random effect, and will adjust for the
25 following baseline characteristics: age (per year), sex, left ventricular function ($\geq 50\%$, 35-49%, 20-34%,
26 $< 20\%$), diabetes, pre-randomisation ACE inhibitor or angiotensin receptor blocker use, pre-
27 randomisation statin use, pre-randomisation diuretic use, pre-operative eGFR category (≥ 60
28 ml/min/1.73m^2 , $< 60 \text{ ml/min/1.73m}^2$), surgery type (CABG, valve, CABG and valve), and evidence of non-
29 elective surgery (defined by either pre-operative use of inotropes or vasopressors, pre-operative use of
30 an intraaortic balloon pump or ventricular assist device, or history of a myocardial infarction within the
31 30 days prior to surgery). In patients who underwent surgery but are missing a post-operative serum
32 creatinine value (expected in $< 2\%$ of patients), we will carry the pre-randomisation serum creatinine
33 value forward which should provide a more conservative estimate of the intervention effect than the
34 alternative of removing such patients. For patients missing a left ventricular ejection fraction
35 measurement (at present $< 1.5\%$ missing), we will impute a value of 50%. If required, for each remaining
36 covariate we will include a missing data indicator variable (at present $< 0.1\%$ data is missing for each
37 variable).¹⁵ We will report the 95% confidence interval (CI) for the adjusted RRR, and a two-tailed p-
38 value of ≤ 0.05 will be considered statistically significant. We will have over 90% power to detect at least
39 a 10% RRR in AKI with methylprednisolone versus placebo should it exist (anticipated incidence of AKI in
40 the placebo group in SIRS, which has enrolled a group at high risk of post-operative complications, is
41 about 38%, two-tailed $\alpha 0.05$, χ^2 test; Table 1). For completeness in the setting of a significant adjusted
42 RRR, we will also report the unadjusted RRR (with 95% CI) and the unadjusted absolute risk difference
43 (with 95% CI). A significant unadjusted absolute risk difference will also be expressed as the 'number
44 needed to treat (NNT)' ($1/\text{absolute risk difference}$; a measure which indicates how many patients need
45 to receive methylprednisolone to prevent one patient from developing AKI who otherwise would
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develop AKI if they receive placebo; a lower number indicating a greater benefit of methylprednisolone). The 95% CI of the NNT is the inverse of the Wald CI for the absolute risk difference.^{16;17}

Alternate Definitions of Acute Kidney Injury

To determine how robust the AKI results are, we will examine the effect of methylprednisolone versus placebo on alternate definitions of AKI, including definitions examined in subpopulations of SIRS patients with additional serum creatinine measurements. A p value ≤ 0.05 will be considered statistically significant in all these analyses if results are concordant with the primary SIRS AKI definition. The statistical power to detect a 20% RRR in each of these outcomes (for all SIRS patients) is presented in Table 1, and for a subpopulation with multiple post-operative serum creatinine values in Table 2. As seen there is inadequate statistical power to detect a clinically important difference in some outcomes (such as the outcome of receipt of acute dialysis); however these outcomes will be reported given their clinical significance and we will visually compare the point estimates and 95% CI of the RRR for each outcome. As well, in an additional analysis we will test for statistical homogeneity of the RRR across the various alternate definitions of AKI.¹⁸

In all SIRS patients:

- **Stage 2 AKI or more (a SIRS definition):** Defined by any of the following three criteria: (1) post-operative percent change in serum creatinine $\geq 100\%$, (2) increase in post-operative serum creatinine to an absolute value $\geq 353.6 \mu\text{mol/L}$, or (3) receipt of acute dialysis. This outcome uses the peak serum creatinine recorded within 14 days of surgery, or receipt of acute dialysis within 30 days of surgery.
- **Stage 3 AKI (a SIRS definition):** Defined by any of the following three criteria: (1) post-operative percent change in serum creatinine $\geq 200\%$, (2) increase in post-operative serum creatinine to an absolute value $\geq 353.6 \mu\text{mol/L}$, or (3) receipt of acute dialysis. This outcome uses the peak serum creatinine recorded within 14 days of surgery, or receipt of acute dialysis within 30 days of surgery. This is the definition of renal failure that will be reported in the overall (non-renal SIRS) report, where renal failure is a component of a composite key secondary outcome in the trial (this composite aligns with the reporting of another prominent trial in the field).⁷
- **Receipt of acute dialysis:** Receipt of acute dialysis within 30 days of surgery.
- **Primary definition of AKI (a SIRS definition) or death.** A composite outcome of either the primary AKI definition or death within 48 hours of surgery. This is to account for the potential impact early deaths may have on the ascertainment of AKI.

In addition to dichotomous outcomes, we will use a linear regression model to compare the groups in the outcome of percent change in serum creatinine ((peak post-operative serum creatinine (within 14 days of surgery) – pre-operative serum creatinine)/pre-operative serum creatinine), adjusting for the variables described in the primary outcome analysis (assuming model assumptions are not violated¹⁹). We will report the result as the average difference in percent change in serum creatinine between the two treatment groups with 95% CI.

In subpopulation of SIRS patients with multiple post-operative serum creatinine recordings:

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3 We expect over 4200 patients (a subpopulation of SIRS patients) will be consecutively enrolled at each
4 participating centre in the protocol to record multiple post-operative serum creatinine measurements.
5 The AKI outcomes to be examined in this subpopulation are presented in Table 2, and are:
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- 7 • AKI (a guideline definition¹²): Defined as any of the following 2 criteria: (1) an increase in serum
8 creatinine ≥ 26.5 $\mu\text{mol/L}$ within 48 hours of surgery, or (2) increase in serum creatinine $\geq 50\%$ from
9 baseline within 7 days of surgery.
- 10 • AKI for at least 2 days (or at least 3 days): Defined by evidence of either post-operative increase in
11 serum creatinine $\geq 50\%$ from the pre-operative value, or a serum creatinine ≥ 26.5 $\mu\text{mol/L}$ from
12 the pre-operative value, evident on at least 2 separate days (or at least 3 separate days) within
13 the 7 days of surgery. While the magnitude of the peak change in serum creatinine defines the
14 stage of AKI in recent guidelines, a longer duration of AKI is also associated with poorer
15 outcomes.²⁰
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20 21 **Subgroup analyses: presence of pre-operative chronic kidney disease**

22 To statistically test whether the effect of treatment (methylprednisolone versus placebo) on our primary
23 definition of AKI differs in those with and without CKD, we will use an interaction term in a mixed effects
24 logistic regression model where centre is treated as a random effect (assuming model assumptions are
25 not violated). With 7000 patients we will have over 80% power to detect a 25% lower odds ratio of AKI
26 with treatment for patients with and without CKD (an estimate derived from our simulations; in another
27 recent large trial of coronary artery bypass graft surgery performed with and without a bypass pump,
28 the observed percent decrease in the odds ratio of AKI was 40% lower in patients with CKD compared to
29 those without CKD (p-value for interaction 0.01)).
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34 35 **Additional Analyses**

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37 Kidney function loss 6 months after surgery: This analysis will focus on those patients who at the time of
38 surgery consent to the collection of a single 6-month serum creatinine measurement. For our main
39 analysis, we will compare the absolute change in eGFR between the methylprednisolone and placebo
40 groups, reporting the mean and 95% CI. We will carry forward the pre-randomisation serum creatinine
41 value for any patient missing the longer term serum creatinine measurement after surgery (for reasons
42 of death or missing measurement) and will impute an eGFR value of 5 mL/min/1.73 m² for the long term
43 measurement for any patient who developed end-stage renal disease (≥ 3 months of continuous
44 dialysis), or who died shortly after receipt of acute dialysis for severe acute kidney injury. We expect
45 over 800 patients will consent to participate in this longer term creatinine measurement. A sample of
46 800 patients will allow a minimum 10 mL/min per 1.73 m² or more difference to be detected between
47 the groups, with over 80% statistical power (two-tailed alpha 0.05, independent samples t-test,
48 expected standard deviation 50). Even in the scenario where we demonstrate corticosteroids versus
49 placebo reduces the risk of post-operative AKI, we do not expect to demonstrate peri-operative
50 corticosteroids versus placebo alters this 6 month outcome (which may relate to our study methods or
51 the limited impact of the AKI risk reduction on longer term kidney function).
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Post-operative Cardiac Events: Acute cardiac events are inextricably linked to AKI events and both events often co-occur in the non-operative setting. In the setting where methylprednisolone reduces the risk of AKI, we will also examine cardiac events, and report how frequently both co-occur.

Post-operative Infection Events: If we observe methylprednisolone versus placebo increases the risk of AKI, then we examine infection events and report how frequently both co-occur.

RECOGNIZED LIMITATIONS

This protocol has some limitations.

Post-operative serum creatinine collection: In SIRS post-operative in hospital serum creatinine measurements are recorded as done in routine care in each participating site (in the subpopulation with serial serum creatinine measurements the median (IQR) number of measurements is 5 (3 to 7)). Most patients routinely have their serum creatinine measured as a part of routine care for many days after cardiac surgery, so the potential of ascertainment bias is low (i.e. where methylprednisolone versus placebo alters the incidence of another event such as myocardial infarction or infection, which in turn influences the likelihood of serum creatinine measurement). At the time of final analysis we will examine the number of measurements by treatment group, and also look at the length of hospital stay in each group to consider whether there is the potential for differential ascertainment of AKI in the two treatment groups.

Errors with serum creatinine as a measure of kidney function: In SIRS the pre-operative serum creatinine is only recorded once in the 30 days prior to cardiac surgery (where patients may be undergoing elective, urgent or emergent surgery). It would be preferably to have at least two baseline serum creatinine values on all SIRS patients, separated by at least 3 months, to more accurately define the presence of CKD. Also in SIRS there is no knowledge of potential serum creatinine changes close to the time of surgery (particularly in the case of emergency surgery, poor perfusion or recent contrast) which may mean the pre-operative serum creatinine value is not in a steady state (although this characteristic should be equally balanced in the methylprednisolone and placebo groups). All of these considerations increase 'noise' related to the baseline serum creatinine measurement, and reduce the ability to detect post-operative changes in the serum creatinine. To partly address this concern we are adjusting for a definition of urgent surgery in the primary statistical models, and can also repeat the analysis excluding patients who meet the definition of urgent surgery.

Worldwide over the last decade there have been efforts to better standardize the serum creatinine assay. It seems likely (although not documented in SIRS) that most pre-operative and post-operative serum creatinine measurements prior to hospital discharge would be done in the same laboratory, with most measurements within a given patient done within two months of each other. This reduces concerns about interlaboratory and intralaboratory variability (drift) in the serum creatinine measurement. However, the same cannot be said for the 6-month measurement. Serial measures of serum creatinine assayed at a central laboratory 6 months after surgery (and longer) were desired, but not possible to obtain in SIRS. Also SIRS has no measures of baseline or follow-up proteinuria, which are now featured in more recent CKD staging systems.

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3 If corticosteroids decrease creatinine production, this in theory could blunt any rise in serum creatinine
4 after surgery and result in less patients meeting our definitions of AKI. However, in other settings such
5 as rheumatoid arthritis, high dose intravenous glucocorticoid (equivalent to 1000 mg of
6 methylprednisolone) did not reduce the amount of creatinine in subsequent urine measurements
7 (which would have declined if creatinine production had declined).²¹
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10 Limited statistical power for the most clinically important kidney outcomes. Stage III AKI with receipt of
11 dialysis, and long-term end-stage renal disease are the most clinically important kidney outcomes.
12 However, there will be too few events for adequate statistical power to reliably determine the effect of
13 our intervention on these outcomes. We focus on mild to moderate AKI (defined by accepted thresholds
14 of changes in serum creatinine).¹² While mild to moderate AKI is the outcome used in virtually all AKI
15 prevention trials, we recognize that it is a surrogate outcome that may not directly impact how a patient
16 feels, functions or survives. Similarly, the longer term outcome of between group difference in change in
17 eGFR is also a surrogate outcome, and concerns about its validity as a measure of kidney disease
18 progression have been raised.²² For this reason the overall SIRS trial results (which focus primarily on
19 non-kidney outcomes) rather than the results of this AKI protocol, should be the primary information
20 used to inform decisions about whether or not intravenous methylprednisolone should be adopted as a
21 standard of care in cardiac surgery with a cardiopulmonary bypass pump.
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27 **CONCLUSIONS**

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29 The sample of SIRS AKI substudy far exceeds the cumulative number of patients enrolled across 70
30 different randomised controlled trials, which tested strategies to prevent or treat AKI in cardiac
31 surgery.²³ Strengths of this protocol and the overall SIRS trial are generalizable estimates derived from
32 patients recruited in 81 centres in 18 countries and rigorous randomised trial methodology (e.g.
33 concealed allocation, placebo-controlled trial, blinded central adjudication of the outcomes). In this
34 report, we have judiciously pre-specified the main questions and analytic protocol that will be used to
35 test relevant AKI hypotheses in SIRS. We have done so to minimise the chance of spurious post-hoc
36 assertions of effect, so that the AKI results from this large international are robust and believable.
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Table 1. SIRS patients meeting definitions of Acute Kidney Injury using peak serum creatinine in the 14 days following surgery

	All patients (n=6598) *	Patients with a pre-operative eGFR ≥ 60 ml/min/1.73 m ² (n=4668)	Patients with a pre-operative eGFR <60 ml/min/1.73 m ² (n=1930)	Statistical Power to detect a 20% Relative Risk Reduction (7000 patients) †
Primary Definition				
AKI (a SIRS definition)	2557 (38.8%)	1678 (36.0%)	879 (45.5%)	99%
Alternate Definitions				
AKI stage 2 or more (a SIRS definition)	614 (9.3%)	395 (8.5%)	219 (11.3%)	79%
AKI stage 3 or more (a SIRS definition)	265 (4.0%)	132 (2.8%)	133 (6.9%)	44%
Receipt of acute dialysis within 30 days	164 (2.5%)	71 (1.5%)	93 (4.8%)	29%
AKI (a SIRS definition) or death	2625 (39.8%)	1721 (36.9%)	904 (46.8%)	99%

AKI, Acute kidney injury

*Number of SIRS patients with data as of November 2013. We expect over 7000 patients will meet criteria for the primary AKI analysis.

† two-tailed α 0.05, χ^2 test, assumes that the incidence observed in all patients (n=6598), will be the incidence observed in the placebo group.

Table 2. Subpopulation of SIRS patients meeting definitions of Acute Kidney Injury using multiple post-operative creatinine measurements

	All patients (n=4231) *	Patients with a pre-operative eGFR ≥ 60 ml/min/1.73 m ² (n=3016)	Patients with a pre-operative eGFR < 60 ml/min/1.73 m ² (n=1215)	Statistical Power to detect a 20% Relative Risk Reduction (4200 patients) †
AKI (a guideline definition)	1386 (32.8%)	935 (31.0%)	451 (37.1%)	99%
AKI for at least 2 days	903 (21.3%)	549 (18.2%)	354 (29.1%)	94%
AKI for at least 3 days	575 (13.6%)	324 (10.7%)	251 (20.7%)	78%

AKI, Acute kidney injury

*Number of SIRS patients with multiple post-operative creatinine data as of November 2013 (raw data). At the time of final analysis we expect over 4200 patients will meet criteria for the primary AKI analysis.

† two-tailed α 0.05, χ^2 test, assumes that the incidence observed in all patients (n=4231), will be the incidence observed in the placebo group.

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Figure legend

Figure 1 Inflammation in cardiac surgery with a cardiopulmonary bypass pump, and mechanism by which acute kidney injury may be prevented by peri-operative corticosteroids. Figure modified from Rosner and Okusa, and reproduced with permission.⁴

Contributorship

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Dr. Garg and the SIRS Publications Committee take responsibility for the integrity of any data and the accuracy of the analysis. All authors who are listed meet ICMJE criteria for authorship.

Competing Interests

Conflict of interest disclosures: As per the ICMJE form, no disclosures were reported by any of the authors that are relevant to the current protocol.

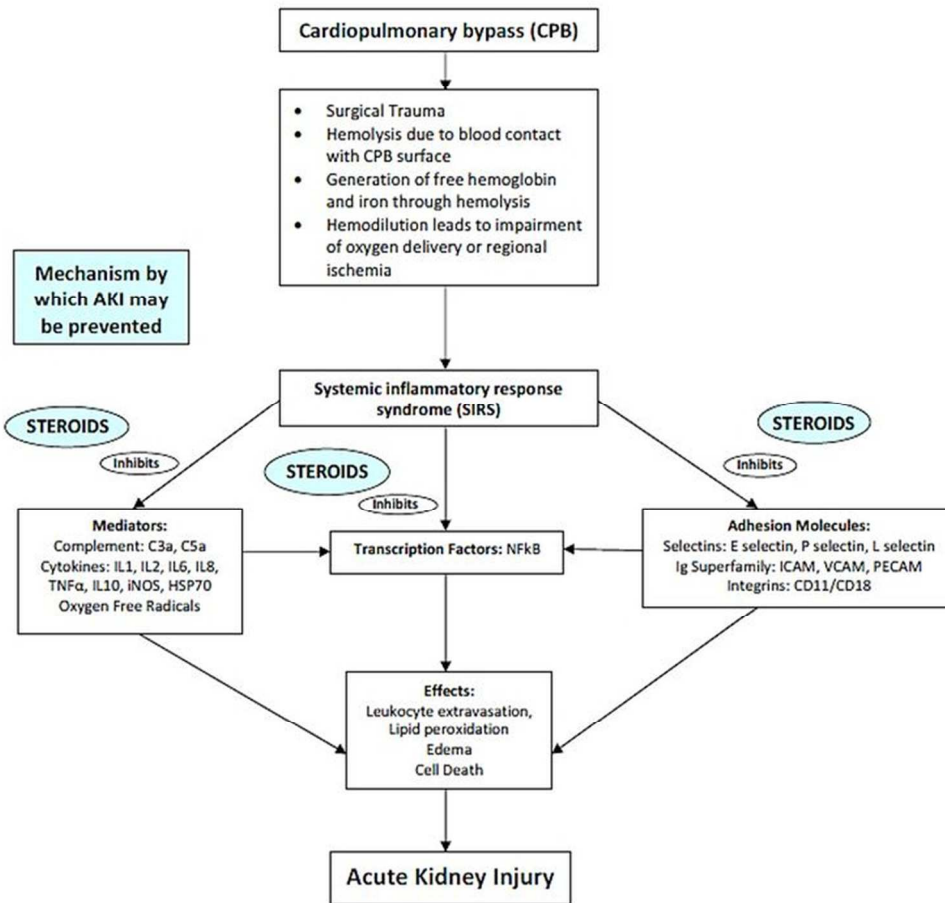
Role of the Sponsor: The sponsor of SIRS and the SIRS AKI substudy has no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of any manuscripts; or decisions to submit manuscripts for publication.

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