A bout 20% of the 4 million cardiopulmonary bypass surgeries performed worldwide each year are complicated by acute kidney injury, defined as a sudden reduction in kidney function. Acute kidney injury is associated with longer hospital stays, higher health care costs and death. In the most severe cases, dialysis is needed to sustain life. An intervention that can reduce the risk of acute kidney injury has, to date, proven elusive.

Cardiopulmonary bypass can initiate a systemic inflammatory response, which is associated with adverse clinical outcomes including acute kidney injury. Several lines of evidence support testing whether corticosteroids can mitigate perioperative inflammation and acute kidney injury. Corticosteroids can attenuate the systemic inflammatory response to cardiopulmonary bypass by reducing inflammatory mediators, cytokines, transcription factors and adhesion molecules. Physicians commonly use intravenous corticosteroids to treat acute conditions that involve renal inflammation, including glomerulonephritis and vasculitis. In a post-hoc analysis of the Dexamethasone for Cardiac Surgery Trial, use of intravenous dexamethasone (a corticosteroid) was associated with a significant relative risk (RR) reduction for dialysis use during the hospital stay (although there were few outcome events and all occurred in patients with chronic kidney disease).

We conducted a prespecified substudy of the Steroids in Cardiac Surgery (SIRS) trial to test the effect of intraoperative...
methylprednisolone versus placebo on acute kidney injury after cardiopulmonary bypass surgery. The protocol and outcomes for this substudy were prespecified and published before the results of the main trial were known, and the substudy received separate grant funding from the Canadian Institutes of Health Research. We hypothesized that methylprednisolone would reduce the risk of acute kidney injury, and that the RR reduction would be greater in patients with preoperative chronic kidney disease.

**Methods**

**Design and setting**

This was a parallel-group (1:1) randomized controlled trial that evaluated intraoperative intravenous methylprednisolone versus placebo in 7507 patients (including 490 pilot patients enrolled between June 19, 2007, and Sept. 10, 2010) from 18 countries who had cardiac surgery with cardiopulmonary bypass (2007-2014). Eligible patients were aged 18 years and older with a moderate-to-high risk for perioperative death (based on a preoperative score of ≥6 on the European System for Cardiac Operative Risk Evaluation I [patients from China and India were eligible if their score was ≥4 and they were having valvular surgery]), were not taking or expecting to take aprotinin or systemic steroids in the immediate postoperative period, had no history of bacterial or fungal infection in the last 30 days, and had no intolerance or allergy to steroids. The primary results are reported elsewhere; briefly, methylprednisolone did not alter the risk of 30-day mortality, myocardial injury, stroke, renal failure or respiratory failure.

**Acute kidney injury substudy**

The original protocol for this substudy was published previously (minor changes are summarized in Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181644/-/DC1). The following patients (<3%) were excluded from this substudy: those with prerandomization end-stage kidney disease (i.e., patients with an estimated glomerular filtration rate of <15 ml/min/1.73 m² [calculated using the Chronic Kidney Disease Epidemiology Collaboration equation] or patients receiving dialysis), those missing a prerandomization serum creatinine measurement (which is needed to define acute kidney injury) and those who did not undergo surgery.

**Interventions**

Patients were randomly assigned to receive either intravenous methylprednisolone (250 mg at anesthetic induction and 250 mg at initiation of cardiopulmonary bypass) or matching placebo. Prior randomized trials suggested that this steroid regimen, compared with placebo, decreased plasma concentrations of inflammatory biomarkers, improved hemodynamic stability, and reduced the need for vasopressors in patients having cardiac surgery with cardiopulmonary bypass.

**Data sources**

Research personnel at each site collected patient data from medical charts, hospital discharge notes and patient interviews. Preoperative serum creatinine levels were recorded in the 30-day period before surgery and the peak postoperative serum creatinine level was recorded in the 14-day period after surgery. Beginning on Mar. 1, 2012 (after receipt of substudy grant funding), centres began recording all postoperative serum creatinine measurements taken in routine care in the 14-day period after surgery for eligible patients. No data on urine output were collected given difficulties with the accurate measurement of urine output in the setting of international data collection.

**Substudy outcomes**

The primary outcome of postoperative acute kidney injury (prespecified when enrolment began in 2007) was defined as an increase in the serum creatinine concentration (from the preoperative value) of 0.3 mg/dL or greater (≥26.5 μmol/L) or 50% or greater within 14 days after surgery, or receipt of dialysis within 30 days after surgery.

**Prespecified secondary definitions of acute kidney injury**

To determine whether the primary results were robust, we examined 6 secondary definitions of acute kidney injury (comparing the peak postoperative serum creatinine concentration in the 14-day period after surgery to the preoperative value).

1. **The primary definition of acute kidney injury or death within 48 hours after surgery (to account for the potential impact of early deaths on outcome ascertainment).**

2. **Stage 2 acute kidney injury or higher, defined as an increase in postoperative serum creatinine of 100% or greater, or an increase to an absolute value of 4.0 mg/dL or greater (≥353.6 μmol/L) (while meeting the primary definition), or receipt of dialysis within 30 days after surgery.**

3. **Stage 3 acute kidney injury, defined as an increase in postoperative serum creatinine of 200% or greater, or an increase to an absolute value of 4.0 mg/dL or greater (≥353.6 μmol/L) (while meeting the primary definition), or receipt of dialysis within 30 days after surgery.**

4. **Receipt of dialysis within 30 days after surgery.**

5. **Percentage change in serum creatinine, defined as ((peak postoperative serum creatinine – preoperative serum creatinine)/preoperative serum creatinine) × 100.**

6. **Absolute change in serum creatinine defined as peak postoperative serum creatinine – preoperative serum creatinine.**

In 2012, Kidney Disease Improving Global Outcomes published a guideline defining acute kidney injury with an increase in serum creatinine of 0.3 mg/dL or greater (≥26.5 μmol/L) within 48 hours, or an increase of 50% or greater within 7 days. We examined this definition in a subsample of patients who were randomly assigned on or after Mar. 1, 2012 (when the study began recording all serum creatinine values measured during routine care). Acute kidney injury that was present on (i) at least 2 days and (ii) at least 3 days within 7 days after surgery was also examined in this subsample.
Sample size
We anticipated that at least 7000 patients enrolled in the main trial would be eligible for the kidney substudy, providing at least 90% power to detect a 10% RR reduction for the primary outcome of acute kidney injury (2-sided \( \alpha = 0.05 \)), assuming an incidence of 38% in the placebo group. With the inclusion of 7286 patients (97% of 7507 randomly assigned in the main trial), this substudy had 94% power to detect a 10% RR reduction in the primary outcome.

Statistical analysis
We conducted analyses using the intention-to-treat principle. Data were analyzed using SAS version 9.2. A modified Poisson regression model (accounting for centre) was used to estimate the RR and 95% confidence interval (CI) for acute kidney injury in patients randomly assigned to methylprednisolone versus placebo; a sandwich variance estimator was used to account for the effect of centre and to incorporate a robust error estimator in the modified Poisson regression approach for a binary response variable.\(^{16,17}\)

We determined unadjusted and adjusted estimates. The adjusted models included 10 prespecified covariates: age, sex, left ventricular function less than 50%, diabetes, prerandomization medication use, estimated glomerular filtration rate less than 60 mL/min/1.73m\(^2\), surgery type and evidence of nonelective surgery. We used multiple imputation to impute missing data on left ventricular ejection fraction (a covariate; missing for 0.9%) and in a sensitivity analysis of acute kidney injury (missing for 0.8%); further details are provided in Appendices 2 and 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181644/-/DC1. We estimated the adjusted percent-change and absolute change in postoperative serum creatinine using linear regression models. The risk of acute kidney injury in patients with preoperative chronic kidney disease (defined by an estimated glomerular filtration rate of < 60 mL/min/1.73 m\(^2\)) was examined by including an interaction term in the model.

We conducted 3 other prespecified analyses. First, the between-group difference in adherence was examined, where adherence was defined as the percentage of patients receiving the treatment as randomly assigned, and the percentage using nonstudy corticosteroids in the operating room and in the first 3 days after surgery. Second, the possibility of differential outcome ascertainment was assessed in the subgroup of patients who had multiple serum creatinine measurements within 7 days of surgery (those randomly assigned on or after Mar. 1, 2012). Third, the primary analyses were repeated after excluding patients who underwent emergent or urgent surgery (defined based on preoperative use of inotropes, vasopressors, an intra-aortic balloon pump, or a ventricular assist device, or evidence of myocardial infarction in the 30 days before surgery).

Ethics approval
Ethics approval to conduct the trial was obtained at all participating centres, and all participants provided written informed consent before enrolment; SIRS was centrally coordinated at the Population Health Research Institute at McMaster University and Hamilton Health Sciences, Hamilton, Ontario. In some countries with more than 3 centres recruiting, a national coordinating office was responsible for obtaining the national regulatory approvals and coordinating research ethics application at each site.\(^{11,12}\)

![Figure 1: Flow diagram of patient enrolment, allocation, follow-up and analysis. Note: SIRS = Steroids in Cardiac Surgery.](image-url)
Results

Trial enrolment began on June 19, 2007, and the last patient was randomly assigned on Dec. 19, 2013. Of 7507 patients randomly assigned in the main trial, 7286 met the eligibility criteria for this substudy (3647 methylprednisolone and 3639 placebo) (Figure 1). The median time from the prerandomization serum creatinine assessment to surgery was 2 (interquartile range [IQR] 1–7) days. The median time from randomization to surgery was 1.0 (IQR 0.0–1.0) day in the methylprednisolone group and 1.0 (IQR 0.0–1.0) day in the placebo group. The lowest prerandomization estimated glomerular filtration rate was 15 mL/min/1.73m². Surgeries were completed between June 2007 and January 2014, and the last day of follow-up was Mar. 21, 2014. Baseline characteristics are shown in Table 1. Both groups had a mean age of 68 (standard deviation [SD] 14) years and a mean prerandomization estimated glomerular filtration rate of 73 (SD 22) mL/min/1.73m².

The flow of patients in the subsample with serial postoperative serum creatinine assessments is shown in Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181644/-/DC1. Differences in baseline characteristics between patients in the main trial, the kidney substudy and the subsample with serial postoperative creatinine assessments are shown in Appendix 5, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181644/-/DC1.

Postoperative acute kidney injury

Postoperative acute kidney injury occurred in 1479 of 3647 patients (40.6%) in the methylprednisolone group and in 1426 of 3639 patients (39.2%) in the placebo group (unadjusted RR 1.03, 95% CI 0.98 to 1.09; adjusted RR 1.04, 95% CI 0.96 to 1.11) (Table 2). Results were consistent across 4 other categorical definitions of acute kidney injury (Table 2) and in sensitivity analyses using different methods to handle missing outcome data (Appendix 6, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181644/-/DC1). The adjusted mean difference in the percentage change in serum creatinine was 0.02% (95% CI –3.7% to 3.7%), and the adjusted mean difference in the absolute change was –0.01 mg/dL (0.6 µmol/L), 95% CI –0.04 to 0.02 (Table 3). The RR of acute kidney injury did not differ significantly in patients with and without preoperative chronic kidney disease (Figure 2 and Table 4).
Table 1 (part 2 of 2): Baseline characteristics of 7286 patients in the SIRS kidney substudy,*† by treatment group

| Characteristic | Methylprednisolone (n = 3647) | Placebo (n = 3639) |
|----------------|--------------------------------|-------------------|
| eGFR††† | 73 ± 22 | 73 ± 22 |
| eGFR < 60 mL/min/1.73m² | 72563 (70.3) | 2589 (71.2) |
| eGFR > 60 mL/min/1.73m² | 84 ± 17 | 83 ± 17 |
| Mean ± SD, mL/min/1.73m² | 1084 (29.7) | 1050 (28.9) |
| Mean ± SD, mL/min/1.73m² | 47 ± 10 | 47 ± 10 |
| eGFR < 60 mL/min/1.73m² | 395 (10.8) | 393 (10.8) |
| eGFR ≥ 60 mL/min/1.73m² | 81 (2.2) | 80 (2.2) |

Pre-randomization medication use

| Medication | Methylprednisolone (n = 3647) | Placebo (n = 3639) |
|------------|--------------------------------|-------------------|
| Statin | 2058 (56.4) | 2018 (55.5) |
| ACE inhibitor or ARB | 2016 (55.3) | 1983 (54.5) |
| Diuretic | 2016 (55.3) | 2007 (55.2) |
| Acetylsalicylic acid | 1681 (46.1) | 1623 (44.6) |

Surgery

| Operation | Methylprednisolone (n = 3647) | Placebo (n = 3639) |
|-----------|--------------------------------|-------------------|
| Isolated CABG | 797 (21.9) | 737 (20.3) |
| Isolated valve | 1195 (32.8) | 1216 (33.4) |
| CABG and valve | 878 (24.1) | 913 (25.1) |
| Other†† | 777 (21.3) | 773 (21.2) |

Note: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CABG = coronary artery bypass graft, eGFR = estimated glomerular filtration rate, IABP = intra-aortic balloon pump, MI = myocardial infarction, SD = standard deviation, SIRS = Steroids in Cardiac Surgery, VAD = ventricular assist device.

*All baseline characteristics (except surgical data) were assessed before randomization (surgical data [i.e., preoperative use of inotropes or vasopressors, or IABP or VAD, and surgery type] were assessed at the time of surgery; the median time from randomization to surgery was 17 [interquartile range 3–26] hours; time of randomization was missing for all 483 pilot patients; time of surgery was missing for 2 patients from the main study).

†(All patients in the pilot study [methylprednisolone (n = 243) and placebo (n = 240)] were missing data on pretreatment body mass index, ethnicity, and prerandomization use of ACE inhibitors or ARBs; however, information on combined ACE/ARB use was available). Data on left ventricular ejection fraction were missing in 68 patients (methylprednisolone [n = 29], placebo [n = 39]). Data on the remaining variables were missing for < 2% of patients. Missing data on categorical variables, the condition/medication/procedure was considered absent; for calculating eGFR, patients missing ethnicity were assumed to be white. Pilot patients who answered “yes” to taking a statin or a nonstatin lipid-lowering agent were assumed to be taking a statin. UNless stated otherwise.

Data on self-reported ethnic origin were collected and recorded by a research assistant using prespecified categories (black or white ethnic origin is needed for the calculation of eGFR).

°Calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation).14

**Evidence of nonelective surgery was defined by preoperative use of inotropes, vasopressors, an IABP or a VAD, or history of an MI in the 30 days before surgery. T1Surgery type “other” includes patients who had an aorta surgery (patch enlargement, Bentall procedure, ascending aortic replacement, arch replacement, and/or descending thoracic aortic replacement) or cardiac ablation surgery, or some type of “other cardiac procedure.” Patients in this category may have had one of CABG or valve surgery, but not both; if a patient had both CABG and valve as well as aorta surgery and/or cardiac ablation surgery, they are included in the “CABG and valve” category.
To understand the effect of corticosteroids on acute kidney injury better, we updated a previous meta-analysis of placebo-controlled trials involving adult patients undergoing cardiac surgery.7 In these trials, acute kidney injury was usually defined as a 50% or greater increase in serum creatinine from the preoperative value or receipt of dialysis. The updated forest plot is shown in Appendix 9, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181644/-/DC1. The pooled RR of acute kidney injury (steroids [1564 events] v. placebo [1533 events]) was 0.93 (95% CI 0.68 to 1.28). The lack of evidence of a protective effect of steroids combined with some adverse effects suggests that prophylactic use of steroids during cardiopulmonary bypass surgery is not warranted.11,19

### Table 2: Effect of methylprednisolone versus placebo on the risk of acute kidney injury in 7286 patients undergoing cardiopulmonary bypass surgery

| Variable                                                                 | No. (% of events) | Relative risk (95% CI) |
|--------------------------------------------------------------------------|-------------------|------------------------|
|                                                                           | Methylprednisolone | Placebo                |
|                                                                           |                   |                        |
| Acute kidney injury (primary definition)$                               | 1479 (40.6)       | 1426 (39.2)            |
|                                                                           | 1.03 (0.98 to 1.09) | 1.04 (0.96 to 1.11)    |
| Secondary definitions                                                    |                   |                        |
| Acute kidney injury or death¶                                            | 1512 (41.5)       | 1459 (40.1)            |
|                                                                           | 1.03 (0.98 to 1.09) | 1.03 (0.96 to 1.11)    |
| Stage 2 or higher acute kidney injury**                                   | 360 (9.9)         | 356 (9.8)              |
|                                                                           | 1.01 (0.88 to 1.16) | 1.01 (0.87 to 1.17)    |
| Stage 3 acute kidney injury††                                             | 145 (4.0)         | 161 (4.4)              |
|                                                                           | 0.90 (0.72 to 1.12) | 0.89 (0.71 to 1.12)    |
| Acute dialysis within 30 d of surgery‡‡                                   | 95 (2.6)          | 88 (2.4)               |
|                                                                           | 1.08 (0.81 to 1.43) | 1.07 (0.80 to 1.43)    |

Note: CAGB = coronary artery bypass grafting, CI = confidence interval.
*A peak postoperative serum creatinine measurement was available for 99.1% of patients. Of 62 patients missing a peak postoperative value (31 in the methylprednisolone group and 31 in the placebo group), 2 received dialysis in the 30-day period after surgery and were coded as having acute kidney injury (1 in the methylprednisolone group and 1 in the placebo group). The remaining 60 patients were assumed to not have acute kidney injury; of these 60 patients, 50 (83.3%) died on the day of surgery or on day 1 or 2 after surgery (27/30 [90.0%] in the methylprednisolone group and 23/30 [76.7%] in the placebo group).
†Adjusted for 10 prespecified covariates using a generalized estimating equation approach accounting for centre: age (yr); sex; left ventricular function < 50%; diabetes; preoperative estimated glomerular filtration rate < 60 mL/min/1.73m²; prerenalization use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins or diuretics; surgery type (isolated valve [referent], isolated CAGB, CAGB and valve, or other); and evidence of nonelective surgery (defined as preoperative use of inotropes or vasopressors, preoperative use of an intra-aortic balloon pump or ventricular assist device, or evidence of myocardial infarction in the 30 days before surgery).
‡‡Receipt of dialysis in the 30 days after surgery. In patients who received acute dialysis, the median increase in serum creatinine concentration from the preoperative value was 1.7 (interquartile range 1.1–3.0) mg/dL (153 [interquartile range 97–268] µmol/L).

### Table 3: Percentage change* and absolute change† in serum creatinine concentration: methylprednisolone versus placebo

| Variable                                                                 | Median (IQR) | Mean ± SD | Median (IQR) | Mean ± SD | Adjusted‡ mean difference (95% CI) |
|--------------------------------------------------------------------------|--------------|-----------|--------------|-----------|----------------------------------|
|                                                                           | Methylprednisolone | Placebo |               |           |                                  |
|                                                                           | n = 3647     | n = 3639  |               |           |                                  |
| Percentage change in serum creatinine*                                   | 22 (4 to 46) | 38 ± 78   | 20 (1 to 46) | 38 ± 82  | 0.02 (–3.7 to 3.7)               |
| Absolute change in serum creatinine, mg/dL†                              | 0.20 (0.03 to 0.44) | 0.35 ± 0.60 | 0.20 (0.01 to 0.44) | 0.36 ± 0.65 | –0.01 (–0.04 to 0.02)           |

Note: CI = confidence interval, IQR = interquartile range (25th, 75th percentiles), SD = standard deviation.
*Percentage change in serum creatinine: ([peak postoperative serum creatinine within 14 days after surgery – prerenadization serum creatinine]/ prerenadization serum creatinine) × 100%.
†Absolute change in serum creatinine: peak postoperative serum creatinine within 14 days after surgery – prerenadization serum creatinine.
‡Adjusted for 10 prespecified covariates: age (yr); sex; left ventricular function < 50%; diabetes; preoperative estimated glomerular filtration rate < 60 mL/min/1.73m²; prerenalization use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, statins, or diuretics; surgery type (isolated valve [referent], isolated coronary artery bypass grafting [CAGB], CAGB and valve, or other); and evidence of nonelective surgery (defined as preoperative use of inotropes or vasopressors, preoperative use of an intra-aortic balloon pump or ventricular assist device, or evidence of myocardial infarction in the 30 days before surgery).
Effect of methylprednisolone versus placebo on the risk of acute kidney injury: subgroup analysis by preoperative chronic kidney disease.

Note: CI = confidence interval, RR = relative risk. *Adjusted for 9 prespecified covariates: age (years); sex; left ventricular function < 50%; diabetes; pre-randomization use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, or diuretics; surgery type (isolated valve [referent], isolated coronary artery bypass grafting [CABG], CABG and valve, or other); and evidence of nonelective surgery (defined as preoperative use of inotropes or vasopressors, preoperative use of an intra-aortic balloon pump or ventricular assist device, or evidence of myocardial infarction in the 30 days before surgery). †Chronic kidney disease was defined as a preoperative estimated glomerular filtration rate < 60 mL/min/1.73m². The RR of acute kidney injury with methylprednisolone versus placebo was not statistically significantly different in those with versus without preoperative chronic kidney disease (p = 0.3 for interaction).

Table 4: Subgroup analysis by pre-existing chronic kidney disease: effect of methylprednisolone versus placebo on the risk of acute kidney injury (4 secondary definitions)

| Variable | Methylprednisolone | Placebo | Adjusted relative risk (95% CI)* | p value (interaction)* |
|----------|--------------------|--------|---------------------------------|------------------------|
| Acute kidney injury or death† | | | | |
| Chronic kidney disease‡ | Yes | 521/1084 (48.1) | 507/1050 (48.3) | 1.00 (0.88 to 1.13) | 0.5 |
| No | 991/2563 (38.7) | 952/2589 (36.8) | 1.06 (0.97 to 1.16) | 0.5 |
| Stage 2 or higher acute kidney injury§ | | | | |
| Chronic kidney disease‡ | Yes | 119/1084 (11.0) | 134/1050 (12.8) | 0.87 (0.68 to 1.11) | 0.1 |
| No | 241/2563 (9.4) | 222/2589 (8.6) | 1.10 (0.92 to 1.33) | 0.1 |
| Stage 3 acute kidney injury¶ | | | | |
| Chronic kidney disease‡ | Yes | 71/1084 (6.6) | 83/1050 (7.9) | 0.83 (0.60 to 1.14) | 0.5 |
| No | 74/2563 (2.9) | 78/2589 (3.0) | 0.96 (0.70 to 1.32) | 0.5 |
| Acute dialysis within 30 days of surgery | | | | |
| Chronic kidney disease‡ | Yes | 54/1084 (5.0) | 48/1050 (4.6) | 1.09 (0.74 to 1.62) | 0.9 |
| No | 45/2563 (1.6) | 40/2589 (1.5) | 1.03 (0.67 to 1.60) | 0.9 |

Note: CI = confidence interval. *Analyzed using modified Poisson regression; models were adjusted for 9 prespecified covariates: age (yr); sex; left ventricular function < 50%; diabetes; pre-randomization use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, or diuretics; surgery type (isolated valve [referent], isolated coronary artery bypass grafting [CABG], CABG and valve, or other); and evidence of nonelective surgery (defined as preoperative use of inotropes or vasopressors, preoperative use of an intra-aortic balloon pump or ventricular assist device, or evidence of myocardial infarction in the 30 days before surgery). †Met the primary definition of acute kidney injury (i.e., an increase in serum creatinine concentration of ≥ 0.3 mg/dL [≥ 26.5 µmol/L] or ≥ 50% from the preoperative value) within 14 days of surgery, or receipt of dialysis within 30 days of surgery) or died within 48 hours of surgery. ‡Chronic kidney disease was defined as a preoperative estimated glomerular filtration rate < 60 mL/min/1.73m², calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation). §Defined as (i) a postoperative percentage increase in serum creatinine concentration of 100% or more (from the preoperative value) within 14 days of surgery, (ii) an increase in postoperative serum creatinine concentration to an absolute value of ≥ 4.0 mg/dL (≥ 353.6 µmol/L) within 14 days of surgery, or (iii) receipt of dialysis within 30 days of surgery. ¶Defined as (i) a postoperative percentage increase in serum creatinine concentration of ≥ 200% from the preoperative value within 14 days of surgery, (ii) an increase in postoperative serum creatinine concentration of ≥ 0.3 mg/dL (≥ 26.5 µmol/L) to an absolute value of ≥ 4.0 mg/dL (≥ 353.6 µmol/L) within 14 days of surgery, or (iii) receipt of dialysis within 30 days of surgery.
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Table 5: Effect of methylprednisolone versus placebo on the risk of acute kidney injury in a subsample of patients with serial postoperative serum creatinine assessments (restricted to the 4824 patients who were randomly assigned on or after Mar. 1, 2012)

| Variable                                      | Methylprednisolone n = 2405 | Placebo n = 2419 | Unadjusted† | Adjusted‡ |
|-----------------------------------------------|-----------------------------|------------------|-------------|-----------|
| Acute kidney injury (KDIGO guideline definition)§15 | 832 (34.6)                  | 819 (33.9)       | 1.02 (0.94 to 1.10) | 1.02 (0.92 to 1.12) |
| Acute kidney injury for ≥ 2 days¶            | 538 (22.4)                  | 549 (22.7)       | 0.99 (0.89 to 1.09) | 0.98 (0.87 to 1.10) |
| Acute kidney injury for ≥ 3 days**           | 358 (14.9)                  | 363 (15.0)       | 0.99 (0.87 to 1.13) | 0.98 (0.85 to 1.14) |

Note: CI = confidence interval, KDIGO = Kidney Disease Improving Global Outcomes.
*At least 1 postoperative serum creatinine measurement in the first 7 days after surgery was available for 98.2% of patients. Patients with no serum creatinine measurements in the 7-day period after surgery (and who did not receive dialysis within 30 days of surgery) were assumed to not have acute kidney injury (n = 89; 43 [2.0%] in the methylprednisolone group and 46 [1.7%] in the placebo group). Of these 89 patients, 43 (48.3%) died within 0, 1 or 2 days after surgery (22 [46.9%] in the methylprednisolone group and 21 [50.0%] in the placebo group).

†Adjusted for 10 prespecified covariates: age (yr); sex; left ventricular function < 50%; diabetes; preoperative estimated glomerular filtration rate < 60 mL/min/1.73m²; prerandomization use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, or diuretics; surgery type (isolated valve [referent], isolated coronary artery bypass grafting [CABG], CABG and valve, or other); and evidence of noninfective surgery (defined as preoperative use of intrapleural or vaspessors, preoperative use of an intra-aortic balloon pump or ventricular assist device, or evidence of myocardial infarction in the 30 days before surgery).

∥Defined as an increase in serum creatinine concentration (from the preoperative value) of ≥ 0.3 mg/dL [≥ 26.5 µmol/L] or ≥ 50%, evident on at least 2 separate days within 7 days of surgery, or receipt of dialysis within 30 days after surgery. Results were similar in a sensitivity analyses that imputed missing postoperative creatinine data with a peak value obtained in the first 14 days after surgery (available for 50 of the 89 patients missing outcome data for the KDIGO guideline definition): adjusted relative risk 1.02 (95% CI 0.93 to 1.12).§Defined as an increase in serum creatinine concentration (from the preoperative value) of ≥ 0.3 mg/dL [≥ 26.5 µmol/L] or ≥ 50%, evident on at least 2 separate days within 7 days of surgery, or receipt of dialysis within 30 days after surgery.

Limitations

Although serum creatinine measurement is part of routine care after cardiac surgery, sole reliance on routine measures could introduce ascertainment bias. For example, if methylprednisolone altered the incidence of myocardial infarction or other events, this could alter the frequency of serum creatinine assessment and influence the detection of acute kidney injury. Also, multiple measures of serum creatinine are preferred for the accurate assessment of kidney function. To address these concerns, we examined several definitions of acute kidney injury, and we collected multiple postoperative serum creatinine measurements in a subsample of 4824 patients (66%). Results were consistent across all sensitivity analyses, and no between-group differences in the frequency of serum creatinine measurements were observed. Results were also consistent after excluding patients having urgent surgery (baseline concentrations of serum creatinine may have been unstable in these patients).

Conclusion

Prophylactic intravenous steroids administered in the operating room did not alter the risk of acute kidney injury in patients with a moderate-to-high risk of perioperative death who had cardiac surgery with cardiopulmonary bypass. Strategies focusing on other noninflammatory contributors of perioperative acute kidney injury, such as improving renal perfusion and decreasing hemolysis warrant future consideration.

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Affiliations: Division of Nephrology (Garg, Cuerden, Sonthrop), Department of Medicine, London Health Sciences Centre, London, Ont.; Department of Anaesthesia and Intensive Care (Chan), The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China; Departments of Health Research Methods, Evidence, and Impact, and Medicine (Devereaux, Walsh), McMaster University, Hamilton, Ont.; Tehran Heart Center (Abbas), Tehran University of Medical Sciences, Tehran, Iran; Division of Nephrology (Hildebrand), Department of Medicine, University of Alberta, Edmonton, Alta.; Département de médecine (Lamontagne), Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Que.; Department of Surgery (Lamy) McMaster University, Hamilton, Ont.; Department of Cardiac Surgery (Noisieux), Université de Montréal, Montréal, Que.; Division of Nephrology, Johns Hopkins School of Medicine (Parikh), Baltimore, Md.; The George Institute for Global Health (Perkovic), Sydney, Australia; Division of Cardiac Surgery (Quantz), London Health Sciences Centre, University Hospital, London, Ont.; Montreal Heart Institute (Rochon), Université de Montréal, Montréal, Que.; Department of Surgery (Roysse), University of Melbourne, Melbourne, Australia; Department of Outcomes Research (Sessler), Cleveland Clinic, Cleveland, Ohio; Department of Cardiac Surgery (Shah), Princess Alexandra Hospital, Brisbane, Australia; Department of Cardiovascular and Thoracic Surgery (Tagarakis), Aristotle University of Thessaloniki, Thessaloniki, Greece; Division of Cardiac Surgery (Teoh), Southlake Regional Health Centre, Newmarket, Ont.; Population Health Research Institute (Vincent, Whitlock), Hamilton, Ont.; Department of Cardiothoracic Anaesthesiology (Yared), Cleveland Clinic, Cleveland, Ohio; Division of Cardiology (Yusuf), Department of Medicine, McMaster University, Hamilton, Ont.

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SIRS Investigators: The following list includes investigators who participated in acute kidney injury substudy of SIRS by country: Canada — Hamilton Health Sciences: R. Whitlock, A. Lamy, L. Semelhago, V. Chu, A. Dyub, I. Cybulsky, R. Van Ooosteen, G. Cordova; London Health Sciences Centre: M.A. Quantz, F.N. McKenzie, S. Fox, L. Chase; Centre Hospitalier de l’Université de Montréal: N. Noiseux, L.M. Stevens, I. Prieto, F. Basile; University of Alberta Hospital: B.A. Finegan, C. Bryden, S. Meyer, A. Chappell; St. Michael’s Hospital: C.D. Mazier, J. Dixon, S. Vagnik, C. Crescini, S. Verma; Queen Elizabeth II Health Sciences Centre: J.F. Legaré; Centre hospitalier universitaire de Sherbrooke: F. Lamontagne, D. Greentree, M. Coutu, J. Teijeira; Southlake Regional Health Centre: K.H. Teoh, W. Wiley, C. Peniston, C. Teng; Montreal Heart Institute: A.G. Rochon, Y. Lamarche, A. Deschamps; Institut universitaire de cardiologie et de pneumologie de Québec: P. Voisine, F. Dagenais; St. Boniface General Hospital: R.K. Singal; New Brunswick Heart Centre: C.D. Brown; Foothills Medical Centre: T.M. Kieser, R. Robinson; Sunnybrook Health Sciences Centre: S.E. Fremes, G.T. Christakis; Eastern Health: K.N. Melvin, M. Parsons; China — First Teaching Hospital of Xinjiang Medical University: H. Zheng, J. Yu, W. Xu, Q. Zhang, C. Chen; West China Hospital, Sichuan University: H. Yu, J. Zeng, Y. Zuo, J. Liu; General Hospital of Shenyang Military Command: T. Zhang, Y. Sun, D. Song; Xijing Hospital: H. Dong, M. Chen, J. Zhao; Wuhan Asia Heart Hospital: L. Tao, W. Huang, Y. Cheng; Union Hospital: Y.S. Long, W. Lei; First Affiliated Hospital of Zhengzhou University: W. Zhang; Shanghai Thoracic Hospital: M.Y. Xu; Anzhen Hospital, Beijing: E. Qing; Third Military Medical University: Y.B. Xiao; India — See Chitra Tirunal Institute for Medical Sciences and Technology: J. Karunakan, V.V. Pillai, P.B. Reddy, S. Kundan; SAL Hospital and Medical Institute: A.R. Jain, S.S. Mallya, C.B. Mehta; Christian Medical College: V. Shukla, K. Kuruvilla; All India Institute of
Medical Sciences: G. Karthikeyan, V. Devagourou, M.P. Hote, B. Airan; G. Kuppuswamy Naidu Memorial Hospital: C. Padmanabhan, M. Srinivasan; Sanjay Gandhi Postgraduate Institute of Medical Sciences: S.K. Agarwal, S. Pande; Sri Jayadeva Institute of Cardiovascular Sciences and Research: P. Simha Mohan Rao, R. Math; Frontier Lifeline Hospital: B.P.R. Shankar, P.H. Vajjyanath; Amrita Institute of Medical Sciences: S.K. Nair; Nizam’s Institute of Medical Sciences: D.R. Ayapati; United States — Cleveland Clinic: J.P. Yared, A. Kurz, A. Awais, K. Panjasawatwong, B.K. Kashy; University of Virginia Health System: J.L. Huffmyer, D.C. Scalzo, A. Kazemi; St. John’s Medical Research/Mercy Hospital: K.F. Huang, S.V. Parvathaneni; Wake Forest University Health Sciences: J.C. Gardner; Hillcrest Hospital: M.R. Malik, Y. Eshraghi; Maine Medical Center: R.S. Kramer; The Ohio State University: M.K. Essandoh, J. Portillo; Fairview Hospital: S.S. Ayad, Z. Akhtar; Georgia Regents University: M.R. Castresana; Texas Heart Institute/CHI Baylor St. Luke’s Medical Center: C.D. Collard; University of Miami: Y.F. Rodriguez-Blanco; University of Rochester: M.P. Eaton; Colombia — Fundación Cardiofetil Instituto de Cardiología: J.C. Villar, J.P. Umaña, C.L. Domínguez, P.A. Alvarado, D. Zuluaga; Fundación Clínica Shaio: M. Abello, T. Sarquis, E. Vaquiro, C.A. Oliveros; Instituto del Corazón de Bucaramanga: E.J. Manrique, S. Vasquez, L.M. Ortiz; Australia — Princess Alexandra Hospital: P.J. Shah, J. Holliday, R. Griffin; Royal Melbourne Hospital: A.G. Royse, C.F. Royse, Z. Williams; Italy — Università degli Studi Aldo Moro di Bari: D. Paparella, C. Rotunno, M. De Palo, V. Margari; San Raffaele University Hospital: O. Alfieri, D. Ferrara, D. Schiavi; Centro Cardiologico Monzino IRCCS: A. Parolari, V.A. Myasoedova, A. Daprazi; University of Bologna: R. Di Bartolomeo, D. Pacini; Azienda Ospedaliera Città della Salute e della Scienza: M. Ribezzo; Iran — Tehran Heart Center: S.H. Abbasi, A. Karimi, A. Salehiomran, A. Hajighasemi, P. Bina; Czech Republic — Hospital Universitario de la Princesa: M. Orts Rodríguez; Brazil — Instituto Dante Pazzanese de Cardiologia: M. Issa, D.C. Vila Nova; Fundação Faculdade de Medicina de São José do Rio: L.N. Maia, M.A. Nakazone; Real e Benemérita Associação Portuguesa de Beneficência: G.V. Lico e Cividanes; Instituto do Câncer do Estado de São Paulo: L.A. Haji; Cardioclínica Paulista: V. Ávila Neto; São Francisco Hospital: F.A. Lucchese; Unidade de Doenças Torácicas Stolf SA Ltda: N.A. Stolf; Austria — Medical University of Vienna: D. Hutschala, K. Ruetzler, B. Sima; Belgium — ZNA Middelheim: S. Engelen, S. Borms; University Hospital Leuven: M. Van de Velde, S. Rex; Ghent University Hospital: S.G. De Hert; Hong Kong — The Chinese University of Hong Kong: A.M.H. Ho, M.T.V. Chan, M.J. Underwood; Argentina — Sociedad Italiana de Beneficencia en Buenos Aires: D. Deluca Bisurgi; Chile — Clinica Santa Maria: D. Torres; Ireland — Mater Misericordiae University Hospital: D.J. Buggy.

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Correspondence to: Amit Garg, amit.garg@lhsc.on.ca