RESEARCH

Effect of methylprednisolone on acute kidney injury in patients undergoing cardiac surgery with a cardiopulmonary bypass pump: a randomized controlled trial

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ABSTRACT

BACKGROUND: Perioperative corticosteroid use may reduce acute kidney injury. We sought to test whether methylprednisolone reduces the risk of acute kidney injury after cardiac surgery.

METHODS: We conducted a prespecified substudy of a randomized controlled trial involving patients undergoing cardiac surgery with cardiopulmonary bypass (2007–2014); patients were recruited from 79 centres in 18 countries. Eligibility criteria included a moderate-to-high risk of perioperative death based on a preoperative score of 6 or greater on the European System for Cardiac Operative Risk Evaluation I. Patients (n = 7286) were randomly assigned (1:1) to receive intravenous methylprednisolone (250 mg at anesthetic induction and 250 mg at initiation of cardiopulmonary bypass) or placebo. Patients, caregivers, data collectors and outcome adjudicators were unaware of the assigned intervention. The primary outcome was postoperative acute kidney injury, 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 in the 14-day period after surgery, or use of dialysis within 30 days after surgery.

RESULTS: Acute kidney injury occurred in 1479/3647 patients (40.6%) in the methylprednisolone group and in 1426/3639 patients (39.2%) in the placebo group (adjusted relative risk 1.04, 95% confidence interval 0.96 to 1.11). Results were consistent across several definitions of acute kidney injury and in patients with preoperative chronic kidney disease.

INTERPRETATION: Intraoperative corticosteroid use did not reduce the risk of acute kidney injury in patients with a moderate-to-high risk of perioperative death who had cardiac surgery with cardiopulmonary bypass. Our results do not support the prophylactic use of steroids during cardiopulmonary bypass surgery. **Trial registration:** ClinicalTrials.gov, no. NCT00427388

About 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.[1] Acute kidney injury is associated with longer hospital stays, higher health care costs and death.[2,3] 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.[1] Several lines of evidence support testing whether corticosteroids can mitigate perioperative inflammation and acute kidney injury.[1,4] Corticosteroids can attenuate the systemic inflammatory response to cardiopulmonary bypass by reducing inflammatory mediators, cytokines, transcription factors and adhesion molecules.[3,5–8] Physicians commonly use intravenous corticosteroids to treat acute conditions that involve renal inflammation, including glomerulonephritis and vasculitis.[9] 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).[5,10]

We conducted a prespecified substudy of the Steroids in Cardiac Surgery (SIRS) trial[11] 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,[4] 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).[11,12] 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]),[13] 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.[11]

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).[4] 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 m^2 [calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[14]] 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.[8]

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.[4]

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[15] 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.[4]

Randomization procedures

Patients were randomly assigned (1:1) using a central 24-hour computerized randomization system. Patients were assigned to either intravenous methylprednisolone or placebo by block randomization with random block sizes of 2, 4 or 6, stratified by centre. The study drug was prepared and masked by local pharmacies at the study centres. Patients, health care providers, data collectors and outcome adjudicators were unaware of treatment allocation.

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 percentage 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]

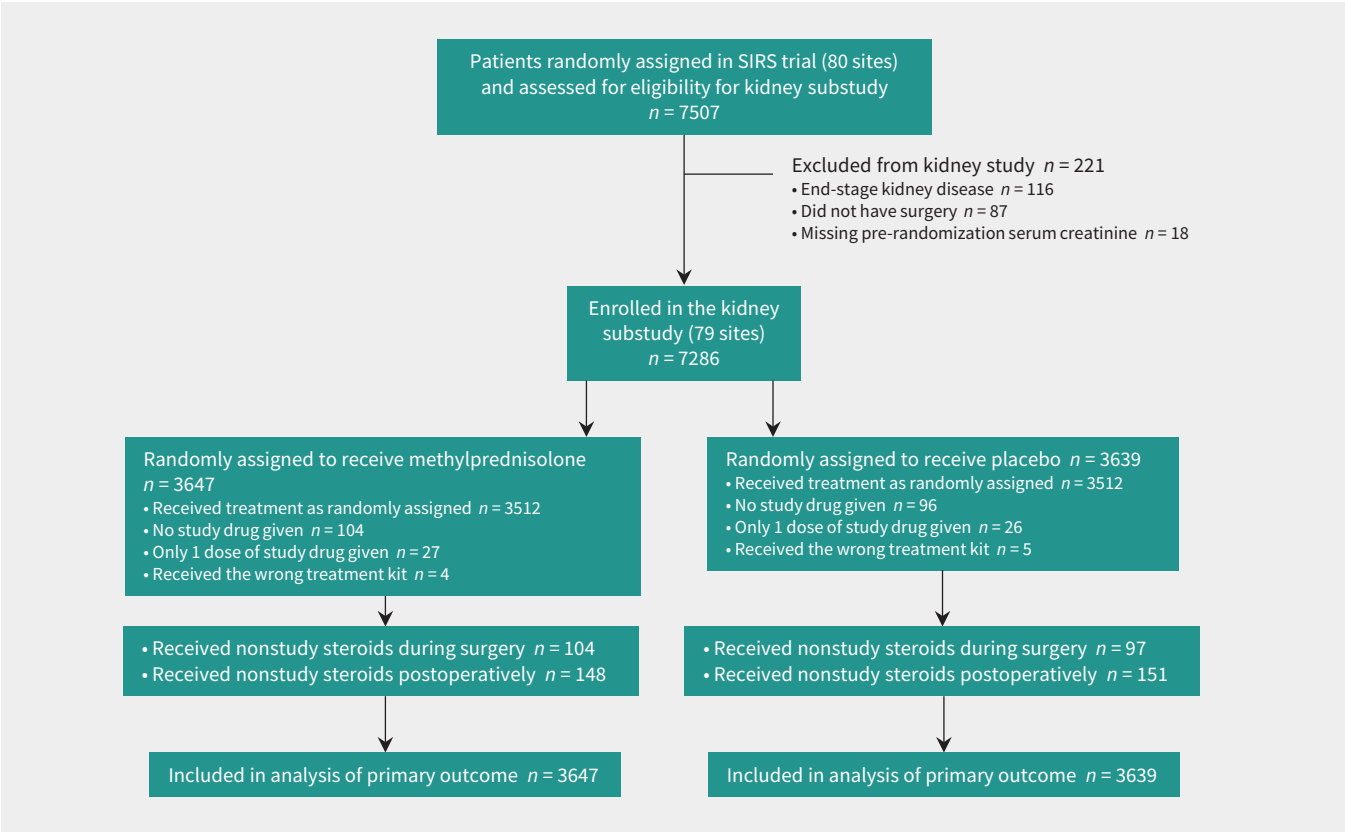

Figure 1: Flow diagram of patient enrolment, allocation, follow-up and analysis. Note: SIRS = Steroids in Cardiac Surgery.

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 eligibly 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/1.73m^2. 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/1.73m^2.

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). In the subsample of 4824 patients with serial postoperative serum creatinine assessments, postoperative acute kidney injury (serum creatinine threshold defined according to guidance from Kidney Disease Improving Global Outcomes) occurred in 832/2405 patients (35%) in the methylprednisolone group and in 819/2419 patients (34%) in the

Table 1 (part 1 of 2): Baseline characteristics of 7286 patients in the SIRS kidney substudy,*† by treatment group

Characteristic	No. (%) of patients‡ Methylprednisolone *n* = 3647	Placebo *n* = 3639
Age, yr, mean ± SD	68 ± 14	68 ± 14
Sex, female	1461 (40.1)	1423 (39.1)
Body mass index, mean ± SD	27 (6)	27 (5)
Ethnic origin†§	*n* = 3404	*n* = 3399
White	2097 (61.6)	2070 (60.9)
Asian (including South Asian)	904 (26.6)	894 (26.3)
Hispanic	233 (6.8)	235 (6.9)
Middle Eastern	144 (4.2)	156 (4.6)
African	21 (0.6)	39 (1.2)
Aboriginal	5 (0.2)	5 (0.2)
Year of randomization		
2007–2010	293 (8.0)	298 (8.2)
2011	735 (20.2)	709 (19.5)
2012	1426 (39.1)	1438 (39.5)
2013	1193 (32.7)	1194 (32.8)
Location		
North America	1617 (44.3)	1603 (44.1)
Asia	882 (24.2)	878 (24.1)
Europe	511 (14.0)	511 (14.0)
South America	282 (7.7)	282 (7.8)
Australia	220 (6.0)	222 (6.1)
Middle East	135 (3.7)	143 (3.9)
Medical history		
Hypertension	2408 (66.0)	2385 (65.5)
Congestive heart failure	970 (26.6)	993 (27.3)
Diabetes	932 (25.6)	939 (25.8)
Atrial fibrillation	816 (22.4)	848 (23.3)
Previous cardiac surgery	579 (15.9)	550 (15.1)
CABG	195 (5.4)	188 (5.2)
Valve	340 (9.3)	313 (8.6)
Other	110 (3.0)	118 (3.2)
Peripheral artery disease	352 (9.7)	392 (10.8)
Smoking (within 12 mo)	453 (12.4)	466 (12.8)
Stroke	292 (8.0)	301 (8.3)
Left ventricular ejection fraction†	*n* = 3618	*n* = 3600
≥ 50%	2281 (63.0)	2313 (64.3)
< 50%	1337 (37.0)	1287 (35.8)

Table 1 (part 2 of 2): Baseline characteristics of 7286 patients in the SIRS kidney substudy,*† by treatment group

Characteristic	No. (%) of patients‡	
	Methylprednisolone *n* = 3647	Placebo *n* = 3639
eGFR¶		
eGFR, mL/min/1.73m^2, mean ± SD	73 ± 22	73 ± 22
eGFR ≥ 60 mL/min/1.73m^2	2563 (70.3)	2589 (71.2)
Mean ± SD, mL/min/1.73m^2	84 ± 17	83 ± 17
eGFR < 60 mL/min/1.73m^2	1084 (29.7)	1050 (28.9)
Mean ± SD, mL/min/1.73m^2	47 ± 10	47 ± 10
eGFR ≤ 45 mL/min/1.73m^2	395 (10.8)	393 (10.8)
eGFR ≤ 30 mL/min/1.73m^2	81 (2.2)	80 (2.2)
Pre-randomization medication use		
Statin	2058 (56.4)	2018 (55.5)
ACE inhibitor or ARB	2016 (55.3)	1983 (54.5)
ACE inhibitor†	*n* = 3404 1341 (39.4)	*n* = 3399 1304 (38.4)
ARB†	*n* = 3404 593 (17.4)	*n* = 3399 594 (17.5)
Diuretic	2016 (55.3)	2007 (55.2)
Acetylsalicylic acid	1681 (46.1)	1623 (44.6)
Surgery		
Evidence of non-elective surgery**	711 (19.5)	693 (19.0)
Preoperative use of inotropes or vasopressors	300 (8.2)	308 (8.5)
Preoperative use of IABP or VAD	53 (1.5)	69 (1.9)
Previous MI within 30 d of surgery	439 (12.0)	395 (10.9)
Surgery type		
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 prerandomization 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. For 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.
††Surgery 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.

placebo group; adjusted RR, 1.02 (95% CI 0.92 to 1.12) (Table 5).

The treatment was received as assigned for 96% in each group. Nonstudy corticosteroids were received in the operating room by 2.9% and 2.7% in the methylprednisolone versus placebo group, respectively, and by 4.1% in each group in the first 3 days after surgery. In the subsample of patients with serial postoperative serum creatinine measurements, 98% of each group had at least 1 measurement, and each group had a median of 5 (IQR 3–6) measurements (Appendix 7, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181644/-/DC1). The primary results were consistent when patients who underwent emergent or urgent surgery were excluded from the analysis (Appendix 8, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.181644/-/DC1).

Interpretation

In this randomized controlled trial involving patients who underwent cardiopulmonary bypass surgery, allocation to perioperative methylprednisolone did not alter the risk of acute kidney injury. Results were consistent across several definitions of acute kidney injury, and in patients with preoperative chronic kidney disease.

This study provides reliable, generalizable effect estimates from a sample of more than 7000 patients recruited from 79 centres in 18 countries. The lower bound of the 95% CI of the treatment estimates suggests that clinically important benefits of perioperative steroids on the risk of acute kidney injury are unlikely. Although inflammatory markers were not measured in this study, we used the same steroid regimen that was used in the pilot study that resulted in decreased plasma concentrations of inflammatory biomarkers, improved hemodynamic stability and a reduced need for vasopressors.[8]

Our findings are discordant with a post-hoc analysis of a similar but smaller trial (*n* = 4465) in which dexamethasone (1 mg/kg, maximum 100 mg) versus placebo significantly reduced the risk of in-hospital dialysis (10/2229 [0.4%] v. 23/2236 [1.0%], RR 0.44, 95% CI 0.19 to 0.96).[5,10] However, the wide CI and low number of dialysis events (33 v. 183 in our study) means this result is statistically fragile (i.e., the result would be statistically nonsignificant if 1 more event occurred in the intervention group).[18]

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

	No. (%) of events*		Relative risk (95% CI)	
Variable	Methylprednisolone *n* = 3647	Placebo *n* = 3639	Unadjusted†	Adjusted‡
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: CABG = 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).
†A modified Poisson regression model was used without adjustment for covariates or accounting for centre.
‡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/1.73m^2; prerandomization use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins or diuretics; surgery type (isolated valve [referent], isolated 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).
§Defined as an increase in serum creatinine concentration (from the preoperative value) of 0.3 mg/dL or more (≥ 26.5 µmol/L) or 50% or more in the 14-day period after surgery, or receipt of dialysis in the 30-day period after surgery.
¶Met the primary definition of acute kidney injury or died within 48 hours of surgery. This was examined to account for the potential impact of early deaths on the ascertainment of acute kidney injury; early deaths occurred in 48 (1.3%) patients in the methylprednisolone group and in 47 (1.3%) patients in the placebo group.
**Defined as an increase in postoperative serum creatinine of 100% or more from the preoperative value or an increase to an absolute value of 4.0 mg/dL or more (≥ 353.6 µmol/L) (while meeting the primary definition) within 14 days of surgery, or (iii) receipt of dialysis within 30 days of surgery.
††Defined as an increase in postoperative serum creatinine of 200% or more from the preoperative value or an increase to an absolute value of 4.0 mg/dL or more (≥ 353.6 µmol/L) (while meeting the primary definition) within 14 days of surgery, or receipt of dialysis within 30 days of 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 to the postoperative 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

	Methylprednisolone *n* = 3647		Placebo *n* = 3639		
Variable	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Adjusted‡ mean difference (95% CI)
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 – prerandomization serum creatinine)/prerandomization serum creatinine] × 100%.
†Absolute change in serum creatinine: peak postoperative serum creatinine within 14 days after surgery – prerandomization serum creatinine.
‡Adjusted for 10 prespecified covariates: age (yr); sex; left ventricular function < 50%; diabetes; preoperative estimated glomerular filtration rate < 60 mL/min/1.73m^2; 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 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).

Source	Acute kidney injury events among at-risk patients, no./total (%)		Unadjusted RR (95% CI)	Adjusted RR (95% CI)*
	Methylprednisolone	Placebo		
Overall	1479/3647 (40.6)	1426/3639 (39.2)	1.03 (0.98 to 1.09)	1.04 (0.96 to 1.11)
Chronic kidney disease†				
Yes	507/1084 (46.8)	497/1050 (47.3)	0.99 (0.90 to 1.08)	0.99 (0.87 to 1.12)
No	972/2563 (37.9)	929/2589 (35.9)	1.06 (0.98 to 1.14)	1.06 (0.97 to 1.16)

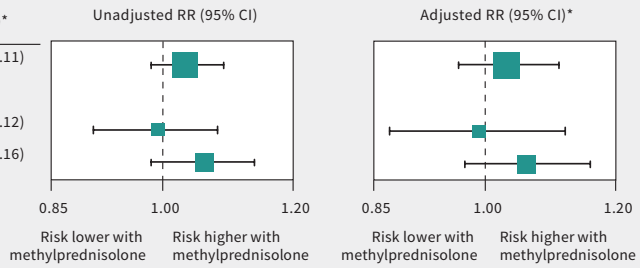

Figure 2: Effect of methylprednisolone versus placebo on the risk of acute kidney injury: subgroup analysis by preoperative chronic kidney disease. Note: CI = confidence interval, RR = relative risk. *Adjusted for 9 prespecified covariates: age (years); sex; left ventricular function < 50%; diabetes; 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 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/1.73m^2. 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	No. of events/no. of patients (%)		Adjusted relative risk (95% CI)*	*p* value (interaction)*
	Methylprednisolone	Placebo		
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	41/2563 (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; 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 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/1.73m^2, calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation).[14]
§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) (while meeting the primary definition) 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) (while meeting the primary definition) within 14 days of surgery, or (iii) receipt of dialysis within 30 days of surgery.

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	No. (%) of events*		Relative risk (95% CI)	
	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; 49 [2.0%] in the methylprednisolone group and 40 [1.7%] in the placebo group). Of these 89 patients, 43 (48.3%) died within 0, 1 or 2 days after surgery (23 [46.9%] in the methylprednisolone group and 20 [50.0%] in the placebo group).
†A modified Poisson regression model was used without adjustment for covariates or accounting for centre.
‡Adjusted for 10 prespecified covariates: age (yr); sex; left ventricular function < 50%; diabetes; preoperative estimated glomerular filtration rate < 60 mL/min/1.73m^2; 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 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).
§Defined as an increase in the serum creatinine concentration (from the preoperative value) of ≥ 0.3 mg/dL [≥ 26.5 µmol/L] within 48 hours of surgery, or ≥ 50% 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 KIDIGO 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.
**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 3 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[20] warrant future consideration.

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