Background Steroids may improve outcomes in high-risk patients undergoing cardiac surgery with the use of cardiopulmonary bypass (CBP). There is a need for a large randomized controlled trial to clarify the effect of steroids in such patients.

Methods We plan to randomize 7,500 patients with elevated European System for Cardiac Operative Risk Evaluation who are undergoing cardiac surgery with the use of CBP to methylprednisolone or placebo. The first co-primary outcome is 30-day all-cause mortality, and the second co-primary outcome is a composite of death, MI, stroke, renal failure, or respiratory failure within 30 days. Other outcomes include a composite of MI or mortality at 30 days, new onset atrial fibrillation, bleeding and transfusion requirements, length of intensive care unit stay and hospital stay, infection, stroke, wound complications, gastrointestinal complications, delirium, postoperative insulin use and peak blood glucose, and all-cause mortality at 6 months.

Results As of October 22, 2013, 7,034 patients have been recruited into SIRS in 82 centers from 18 countries. Patient’s mean age is 67.3 years, and 60.4% are male. The average European System for Cardiac Operative Risk Evaluation is 7.0 with 22.1% having an isolated coronary artery bypass graft procedure, and 66.1% having a valve procedure.

Conclusions SIRS will lead to a better understanding of the safety and efficacy of prophylactic steroids for cardiac surgery requiring CBP. (Am Heart J 2014;167:660-5.)

Background

Worldwide, >2 million patients undergo cardiac surgery annually. Most cardiac surgeries use cardiopulmonary bypass (CBP). Although CPB serves an important role, it initiates a systemic inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein),1–4 which results in increased endothelial permeability and vascular and parenchymal damage.5–8 These inflammatory responses are associated with the development of postoperative complications including myocardial injury and infarction, respiratory failure, renal and neurologic dysfunction, excessive bleeding, altered liver function, multiple organ failure, and death.9–14 (See Table.)

In an attempt to minimize the deleterious effects of CPB, investigators have explored various strategies ranging from the complete avoidance of CPB for some coronary bypass procedures,15–17 to the use of biocompatible circuits12 and pharmacologic agents to mitigate the systemic response. None of these interventions is, however, accepted to improve clinical outcomes.3,7,12,18–23 A cheap drug that attenuates the SIRS response, and its related consequences could have substantial clinical potential. Steroids are one such generic class of agents that are antiinflammatory and cheap.7,8,14,18,19,24–53

Existing trials provide encouraging evidence that steroids may impact clinically important outcomes in patients going...
on CPB. The DECS trial by Dieleman et al is the largest published trial on this topic. The DECS trial included 4,494 patients requiring CPB in 8 surgical hospitals in the Netherlands. Patients were randomized to a single intraoperative dose of dexamethasone 1 mg/kg or placebo. The primary outcome was a composite of death, myocardial infarction (MI), stroke, renal failure, or respiratory failure within 30 days. Overall, 7% of patients reached the primary outcome in the dexamethasone arm versus 8.5% in the placebo group (relative risk [RR] 0.83; 95% CI 0.67-1.01; \( P = .07 \)). Although in the overall trial, population dexamethasone did not demonstrate a statistically significant effect on the primary outcome, a prespecified subgroup analysis focused on patients with a cally significant effect on the primary outcome, a population dexamethasone did not demonstrate a statistically significant effect on the primary outcome, a prespecified subgroup analysis focused on patients with a

### Patient population

Study personnel will consider patients undergoing elective, urgent, or emergent cardiac surgery for enrollment. All consenting patients (men and women of any ethnicity) age >18 years undergoing CPB for any cardiac surgical procedure (such as coronary artery bypass graft [CABG], valve, aorta, or combined procedures) with a European System for Cardiac Operative Risk Evaluation (EuroSCORE)\(^{55} \geq 6\) are eligible. Patients are excluded if they are taking systemic steroids or will undergo planned systemic steroid therapy in the immediate postoperative period, have a history of bacterial or fungal infection in the last 30 days before enrolment, have an allergy or intolerance to corticosteroids, will receive aprotinin, or have previously participated in SIRS.

On June 5, 2011, we altered the inclusion criteria in India and China. For these 2 countries, the EuroSCORE inclusion criteria was lowered to >4 for patients undergoing cardiac valvular surgery; however, for patients undergoing a nonvalvular cardiac surgery, the EuroSCORE requirement remained >6. We made this change because China and India serve populations whose dominant cardiac pathology is rheumatic valvular disease. A study by Wang et al demonstrated that Chinese cardiac valvular surgery patients with a EuroSCORE of 3 to 5 had a higher observed mortality (4.9%) compared with the EuroSCORE predicted mortality rate (3.0%). A study in India suggested similar findings.

### Randomization

Randomization occurs before surgery for all eligible patients for whom informed consent is obtained. Research personnel randomize patients via a 24-hour computerized randomization phone service or interactive web randomization system maintained by the coordinating center at the Population Health Research Institution, which is part of the Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada. The randomization process uses block randomization stratified by center. Study center personnel are not aware of the block size.

### Trial drug

Patients in the SIRS trial receive 500 mg of methylprednisolone or placebo divided into 2 intravenous doses of 250 mg each, one during anesthetic induction and the other on CPB initiation. Numerous types and doses of steroids have been evaluated in the CPB population. The most commonly reported steroid regimen is 60 mg/kg of methylprednisolone given in 2 divided doses (approximately 4 grams for a 70-kg patient). We chose 500 mg of methylprednisolone because (a) data on surrogate end points from the SIRS pilot demonstrated that this lower dose was effective in abolishing the inflammatory

### Table. Characteristics of the first 6970 patients randomized in SIRS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SIRS n = 6970</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>67.3 y (13.8)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>32.1%</td>
</tr>
<tr>
<td>65-80 y</td>
<td>54.8%</td>
</tr>
<tr>
<td>&gt;80 y</td>
<td>13.1%</td>
</tr>
<tr>
<td>EuroSCORE (SD)</td>
<td>7.0 (2.0)</td>
</tr>
<tr>
<td>Male</td>
<td>60.4%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26.3%</td>
</tr>
<tr>
<td>Isolated CABG</td>
<td>22.0%</td>
</tr>
<tr>
<td>Any valve procedure</td>
<td>71.3%</td>
</tr>
<tr>
<td>Any other procedure*</td>
<td>6.7%</td>
</tr>
<tr>
<td>CBP time (SD)</td>
<td>119 min (56)</td>
</tr>
<tr>
<td>Continent recruited</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>44.4%</td>
</tr>
<tr>
<td>Asia</td>
<td>27.8%</td>
</tr>
<tr>
<td>Europe</td>
<td>13.8%</td>
</tr>
<tr>
<td>South America</td>
<td>8.0%</td>
</tr>
<tr>
<td>Australia</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

* Any procedure that did not include isolated CABG or a valve procedure.
response to CPB across a broad array of mediators (interleukin 2 [IL2], IL4, IL6, IL8, interferon γ, tumor necrosis factor α, monocyte chemotactic protein-1 [MCP-1] and epidermal growth factor [EGF], and unpublished data from SIRS I) in all patients with promising clinical results and no obvious increase in adverse effects. (b) a meta-analysis by Ho and Tan suggested that low-dose corticosteroids are as effective as high-dose protocols in improving clinical outcomes; and (c) data from that meta-analysis suggest that higher dose steroid protocol may be associated with adverse outcomes such as prolonged ventilation. Therefore, the dose of 500 mg of methylprednisolone appears to strike the optimal balance between potential efficacy and safety.

**Patient follow-up**

Key baseline patient characteristics (cardiac history, cardiovascular anatomy, and comorbidities) as well as patient’s eligibility criteria are collected. Electrocardiograms (ECGs) are performed preoperatively, at 24 hours postoperatively, and just before hospital discharge or on postoperative day 4 whichever comes first. Creatinine kinase (CK)-MB measurement is mandated preoperatively, at 8 hours, and at 24 hours postoperatively. Creatinine is measured (in micromoles per liter) preoperatively and peak postoperative inhospital creatinine (within 14 days of surgery will be recorded). Peak blood glucose will be measured within 24 hours postoperatively. Confusion Assessment Method is used to assess delirium on postoperative day 3. Patients are followed up to day 30 for outcome events and are followed up to 6 months postoperatively for vital status. This final follow-up visit is completed by telephone.

**Study outcomes**

The first coprimary outcome is all-cause mortality at 30 days after randomization. The secondary coprimary outcome is a composite of death, MI, stroke, renal failure (stage III acute kidney injury; 2012 Kidney Disease Improving Global Outcomes guidelines), or respiratory failure (uninterrupted postoperative mechanical ventilation for >48 hours) within 30 days. Additional secondary outcomes include (1) a composite of significant MI or mortality at 30 days, (2) new onset atrial fibrillation at 30 days, (3) 24-hour chest tube output, (4) 24-hour transfusion requirements, (5) duration of mechanical ventilation, and (6) length of intensive care unit (ICU) stay and hospital stay. The secondary safety outcomes include infection, stroke, wound complications (superficial surgical site infection, deep surgical site infection, or sterile wound dehiscence), gastrointestinal hemorrhage, gastrointestinal perforation within 30 days, delirium at postoperative day 3, and postoperative insulin use and peak blood glucose during the first 24 hours after surgery. Our intermediate-term outcome is all-cause mortality at 6 months.

The coprimary outcomes at 30 days were selected due to available evidence suggesting that corticosteroids attenuate the inflammatory response to CPB, which is felt to contribute to morbidity and mortality in cardiac surgery patients. We decided to use total mortality rather than cardiovascular mortality as our primary outcome as the exact cause of mortality is often difficult to pinpoint in cardiac patients who develop multiple organ failure. The meta-analysis of the literature demonstrates a trend toward reduced risk of death in patients receiving steroid treatment, RR of 0.73, CI of 0.45 to 1.18, which, if real, would have substantial global impact. Furthermore, the important signal was observed in the DECS trial suggesting benefit of steroids in higher risk patients in the second coprimary outcome.

Our definition of early perioperative MI (within 72 hours of surgery) is defined as fulfilling any one of the following criteria:

**CK-MB mass assay patients**

In patients with normal baseline CK-MB, (1) a CK-MB measurement ≥6 times the upper limit of normal (ULN) (in isolated CABG patients) or ≥15 times the ULN (in all other cardiac surgery patients), (2) angiographic evidence of graft occlusion or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium.

In patients with elevated baseline CK-MB (greater than reported ULN), (1) an absolute increase in CK-MB measurement to the increment of ≥6 times the ULN (in isolated CABG patients) or ≥15 times the ULN (in all other cardiac surgery patients), (2) angiographic evidence of graft occlusion or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium.

**CK-MB activity assay patients**

In patients with normal baseline CK-MB activity, (1) a CK-MB activity measurement ≥40 U/L (in isolated CABG patients) or ≥120 U/L (in all other cardiac surgery patients), (2) angiographic evidence of graft occlusion or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium.

In patients with elevated baseline CK-MB activity (greater than reported ULN), (1) an absolute increase in CK-MB measurement to the increment of ≥40 U/L (in isolated CABG patients) or ≥120 U/L (in all other cardiac surgery patients), (2) angiographic evidence of graft occlusion or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium.

As planned in the protocol, we determined the CK-MB thresholds from a blinded analysis of the first 7,000 patients included in SIRS. We used a modification of the method developed by Mazumdar et al to identify the lowest CK-MB threshold that had an independent hazard ratio >2 for 30-day mortality after adjustment for the EuroSCORE.
Late perioperative MI (later than 72 hours after surgery) is defined in all patients as ECG changes consistent with MI (new significant Q waves in 2 contiguous leads) or evolving ST-segment or T-wave changes in 2 contiguous leads signifying ischemia or new left bundle branch block or ST-segment elevation and elevated cardiac markers (troponins or CK-MB) in the necrosis range. Myocardial infarction occurring after a percutaneous coronary intervention (PCI) are included in the late perioperative MI group but are defined as elevation of cardiac markers ≥3 times ULN within 24 hours of PCI or characteristic evolution of new ECG changes.

Outcome adjudication

The events adjudication committee evaluates all reported deaths, strokes, and myocardial injuries using standardized definitions, along with supporting documentation. Members of the events adjudication committee were chosen based on their clinical expertise. All event adjudication is blinded to treatment group.

Statistical considerations

Sample size

The sample size for the study is 3,750 patients per group, for a total of 7,500 patients. The study has >80% power to detect a 25 relative risk reductions for the first coprimary outcome of death at 30 days with an α = 0.0409 (2 sided), anticipating a 6% mortality rate in the control arm.

The study has >99.9% power to detect a 20% relative risk reductions for the most important secondary outcome of death, MI, stroke, renal failure, or respiratory failure at 30 days with an α of .01 (2 sides), anticipating a 25% rate in the control arm.

Data analysis

The intention-to-treat principle, in which all participants will be included in their assigned treatment groups regardless of adherence, will guide all analyses. The proportion of patients developing the coprimary outcome will be compared at 30 days using Pearson χ² test. We will control the overall type 1 error rate at 5% between the first coprimary outcome and the second coprimary outcome. The type 1 error rate was fixed at 1% for the most important secondary, and the remaining α of 4.09% determined by simulation is to be used for the first coprimary.

All other outcomes will be compared via a t test or χ² test where appropriate. The length of hospital stay and length of intensive care unit/cardiac care unit (ICU/CCU) stay will be compared using a nonparametric test because these data are not normally distributed. The relative and absolute risk reductions will be calculated and the associated 95% CI for the outcomes with methylprednisolone. An events adjudication committee (blinded to the treatment allocation) will centrally review all suspected major outcomes listed above.

Subgroup analyses

The effect of the following treatment among different subgroups: (1) gender (females derive greater benefit), (2) diabetes (equivalent benefit with no increased wound complications), (3) EuroSCORE (more benefit with higher EuroSCORE), (4) CPB duration (patients with longer CPB time may derive greater benefit), (5) age (older patients derive less benefit), and (6) surgery type (isolated CABG versus other; other derives greater benefit) will be conducted by stratified analysis through a logistic regression or Cox proportional hazards model, as appropriate. The test of interaction between each subgroup factor and the treatment group will be done by including a product term in the model already containing treatment and the subgroup factor. Heterogeneity based on geographic diversity will be explored within the stratified analysis. Heterogeneity will be considered significant at a P < .05.

Interim analyses

The independent data safety monitoring board will ensure patient safety, receive and review interim analyses of efficacy data, provide feedback to the steering committee, and ensure the study follows the highest standards of ethics. Two formal interim analyses for safety and efficacy will be undertaken when 50% and 75% of the 30-day follow-up data are available. Conservative statistical guidelines for data monitoring have been developed and will follow the modified Haybittle-Peto rule. For efficacy, reductions in events with a Z value ≥−4 (P < .00003) at the first interim analysis and a Z value ≥−3 (P < .00135) at the second interim analysis are required to consider the findings statistically significant at these interim analyses. For safety, increase in the rates of the primary outcome require a Z value ≥3 (first interim analysis) and a Z value ≥2.5 (second interim analysis) to trigger a discussion of early stopping.

Trial organization and funding

SIRS is coordinated at the Population Health Research Institute at McMaster University and Hamilton Health Sciences, Hamilton, Canada. In some countries with ≥3 centers recruiting, there is a National Coordinating Office headed by an expert in cardiovascular disease and/or clinical trials. These units are responsible for obtaining the national regulatory approvals, coordination of research ethics application at each site, organization of training and follow-up meetings, dealing with other issues related to recruitment, data quality, and ensuring high rates of follow-up. All the national coordinators along with the operations committee serve on the study steering committee. The steering committee is consulted regarding major decisions about the study.
Current status of trial

We are recruiting patients in 82 centers from 18 countries. As of October 22, 2013, 7,034 patients have been recruited into SIRS. We expect to complete recruitment by December 2013 with results on the 30-day outcomes being available in the spring of 2014. The baseline and surgical characteristics for selected parameters is shown in the Table. The average EuroSCORE of the included patients to date is 7.0. The average age of the recruited patients is 67.3 years, and 60.4% are male. Twenty-two point one percent has undergone isolated CABG, 66.1% had a valve procedure, and 8.8% had other surgery.

Discussion

Many small trials examining the impact of corticosteroids on surrogate outcomes such as inflammatory mediators have been published on the field of cardiac surgery. However, these trials have had insufficient power to detect moderate but important differences in clinical events. This changed with the recent publication of the DECS trial, which demonstrates that administration of inexpensive corticosteroids yields reduction of infections, pulmonary failure, and length of ICU and hospital stay. Importantly, there is a strong signal that the higher risk patients may derive greater benefit for corticosteroid prophylaxis. This led to the SIRS steering committee altering the primary outcome of the trial to the coprimary outcome described. The SIRS trial seeks to answer whether the mitigation of the inflammatory response to CPB via corticosteroids results in improved mortality and morbidity for these higher risk patients. More than 2 million people annually undergo cardiac surgery requiring CPB, and approximately 100,000 will not survive. Because corticosteroids are both accessible and inexpensive, if SIRS demonstrates benefit, the practice would have very fast uptake globally and have tremendous impact.

Disclosures

SIRS is registered with Clinical trial registration: ClinicalTrials.gov no. NCT00427388 and is completely funded by the Canadian Institutes of Health Research. The authors are solely responsible for the design and conduct of this study, the study analyses, the drafting and editing of the manuscript, and its final contents.

References
