Rationale and design of the PeriOperative ISchemic Evaluation-2 (POISE-2) trial: An international 2 × 2 factorial randomized controlled trial of acetyl-salicylic acid vs placebo and clonidine vs placebo in patients undergoing noncardiac surgery

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Background  Worldwide, 200 million adults undergo major noncardiac surgery annually, and 10 million of these patients will have a major vascular complication. Low-dose clonidine and low-dose acetyl-salicylic acid (ASA) may prevent major perioperative vascular complications. We therefore initiated the POISE-2 trial to establish the perioperative effects of these 2 interventions.

Methods  The POISE-2 trial is a 2 × 2 factorial randomized controlled trial of low-dose ASA vs placebo and low-dose clonidine vs placebo in 10,000 patients at risk for a perioperative cardiovascular event who are undergoing noncardiac surgery. Both study drugs are initiated prior to surgery (goal 2-4 hours) and are continued after surgery. Patients, health care providers, data collectors, and outcome adjudicators are blinded to treatment allocation. The primary outcome is a composite of mortality and nonfatal myocardial infarction at 30 days after randomization.

Results  To date, the POISE-2 trial has recruited more than 9,000 patients from 135 centers in 23 countries. Among the first 7,500 patients recruited, patients' mean age was 68.2 years, 53.4% were male, 34.0% had a history of vascular disease, and 38.3% had diabetes that was treated. Participants had orthopedic (38.1%), general (27.0%), urologic or gynecologic (17.2%), vascular (6.6%), thoracic (5.7%), and other (5.4%) surgery.

Conclusions  POISE-2 is a large international trial that will rigorously evaluate the effects of low-dose clonidine and ASA in patients having noncardiac surgery. (Am Heart J 2014;167:804-809.e4.)

Globally, more than 200 million adults have major noncardiac surgery annually, and 10 million of these patients have a major vascular complication within 30 days of surgery. Despite the magnitude of this problem, there is no proven effective and safe intervention to prevent major perioperative vascular complications.

Myocardial infarction is the most common major perioperative vascular complication. In the placebo group of the POISE trial (a 8,351-patient international perioperative β-blocker trial), 1.4% of the patients had a vascular death, 0.5% had a stroke, 0.5% had a nonfatal cardiac arrest, and 5.7% had a myocardial infarction in the first 30 days after surgery. Perioperative myocardial infarction portends a poor prognosis. In POISE, 11.6% of patients with a perioperative myocardial infarction died within the first 30 days compared with only 2.2% of patients who did not have a myocardial infarction. There remains uncertainty regarding the pathophysiology of perioperative myocardial infarction; however, it is likely that both supply-demand mismatch and coronary thrombus account for a portion of the myocardial infarctions that occur in the first 30 days after noncardiac surgery. A perioperative prevention strategy would ideally impact both proposed mechanisms to provide the greatest potential for benefit.

During surgery and in the next few days thereafter, there is marked activation of the sympathetic system. Clonidine, an α-2 agonist, blunts central sympathetic outflow and has other effects (eg, analgesic, anxiolytic, antishivering, anti-inflammatory) that may prevent perioperative vascular complications. Randomized controlled trials (RCTs) demonstrate that low-dose perioperative clonidine reduces myocardial ischemia without inducing hemodynamic instability, and suggest that clonidine may prevent death and myocardial infarction.
Surgery also increases platelet activation.\textsuperscript{15} Acute withdrawal of chronic acetylsalicylic acid (ASA) may result in a prothrombotic state (ie, increased thromboxane A\textsubscript{2} and decreased fibrinolyis).\textsuperscript{16,17} Given these physiological changes, ASA initiation or, for chronic users, ASA continuation—and the associated inhibition of platelet aggregation—may prevent major perioperative vascular events through impeding thrombus formation.\textsuperscript{18} Large RCTs have demonstrated that ASA prevents vascular events in the nonoperative setting.\textsuperscript{19} Although perioperative RCTs suggest that ASA may prevent vascular death,\textsuperscript{20} the effect of ASA on myocardial infarction is unclear,\textsuperscript{21} and there are concerns that the increased risk of bleeding may outweigh the benefits.\textsuperscript{22,23} This uncertainty has led to great variability in clinical practice.\textsuperscript{24}

We initiated the POISE-2 trial to determine the impact of low-dose ASA and low-dose clonidine on the 30-day risk of mortality and nonfatal myocardial infarction in patients having noncardiac surgery.

**Methods**

**Trial design**

POISE-2 is an international RCT of 10,000 patients with, or at risk for, atherosclerotic disease who are undergoing noncardiac surgery. Using a 2 × 2 factorial design, POISE-2 will determine the effect of low-dose clonidine vs placebo and low-dose ASA vs placebo in the perioperative setting. Patients, health care providers, data collectors, and outcome adjudicators are blinded to treatment allocation.

**Trial population**

Study personnel consider patients undergoing elective and urgent/emergent noncardiac surgery for enrollment. Tables I and II report the POISE-2 inclusion and exclusion criteria, respectively. We enroll patients in 1 of 2 ASA strata. The ASA Continuation Stratum involves patients who are taking ASA chronically. The ASA Starting Stratum involves patients who are not taking ASA chronically. We consider patients who report having taken ASA daily for at least 1 month within a 6-week period prior to surgery to be on ASA chronically, and we enroll these patients in the ASA Continuation Stratum.

**Randomization**

Randomization occurs prior to surgery for all eligible patients for whom written informed consent is obtained. Research personnel randomize patients via a 24-hour computerized randomization telephone service or interactive Web randomization system maintained by the coordinating center at the Population Health Research Institute at the University, Hamilton, Ontario, Canada. The randomization process uses block randomization stratified by center and ASA stratum; block size is undisclosed to research personnel. We randomize patients in a 1:1:1:1 allocation to receive clonidine/ASA, clonidine/ASA placebo, clonidine/placebo/ASA, or clonidine placebo/ASA. Patients in the ASA Continuation Stratum and ASA Starting Stratum are evenly assigned to each of the 4 randomization groups.

**Trial drug administration**

Prior to surgery (goal 2-4 hours), patients fulfilling hemodynamic requirements (ie, systolic blood pressure ≥105 mm Hg and a heart rate ≥55 beats/min) receive 0.2 mg of oral clonidine or matching placebo and have a transdermal clonidine (0.2 mg/d) or placebo patch applied to their upper arm or chest. The clonidine patch releases clonidine at a constant rate (0.2 mg/d), and the patch is removed at 72 hours after surgery. No cases of clonidine withdrawal hypertension have been reported with transdermal clonidine\textsuperscript{25}; therefore, we do not use a tapering process. Research personnel telephone patients discharged before 72 hours after surgery to remind them to remove the patch at 72 hours after surgery.

Patients in both ASA strata receive the same trial ASA intervention (ie, either ASA 100 mg or matching placebo). For the first dose prior to surgery (goal 2-4 hours), they take 2 tablets orally. Starting on the day after surgery, patients take 1 tablet daily for 30 days in the Starting Stratum and 7 days in the Continuation Stratum, after which they resume their regular ASA.

**Monitoring for and approach to potential problems**

Patients have monitoring of blood pressure and heart rate prior to study drug administration, 1 hour after administration, and every 4 hours for the first 96 hours after surgery. Decisions regarding holding or discontinuing either study drug rest with the attending physician. For patients developing clinically important hypotension or bradycardia, study personnel encourage the attending physician to consider fluid resuscitation, administering an inotrope or vasopressor, withholding nonstudy antihypertensive medication(s), or changing epidural prescriptions or infusion.
Table II. Exclusion criteria of the POISE-2 trial

We will exclude patients meeting any of the following criteria:
1. consumption of ASA within 72 h prior to surgery;
2. hypersensitivity or known allergy to ASA or clonidine;
3. systolic blood pressure <105 mm Hg;
4. heart rate <55 beats/min in a patient who does not have a permanent pacemaker;
5. second- or third-degree heart block without a permanent pacemaker;
6. active peptic ulcer disease or gastrointestinal bleeding within previous 6 wk;
7. intracranial hemorrhage in the 6 mo prior to randomization;
8. subarachnoid hemorrhage or epidural hematoma unless the event occurred >6 mo prior to randomization and the offending aneurysm or arterial lesion has been repaired;
9. drug-eluting coronary stent <1 y prior to randomization;
10. bare-metal coronary stent <6 wk prior to randomization;
11. P2Y12 inhibitor within 72 h prior to surgery or intent to start during the first 7 d after surgery; or currently taking an α-2 agonist, α-methyldopa, monoamine oxidase inhibitors, or reserpine;
12. planned use of therapeutic dose anticoagulation during the first three d after surgery;
13. undergoing intracranial surgery, carotid endarterectomy, or retinal surgery;
14. not consenting to participate in POISE-2 prior to surgery; or
15. previously enrolled in the POISE-2 trial.

rates. When clinically important hypotension or bradycardia persists, or the patient requires ongoing inotrope or vasopressor administration, study personnel encourage removal of the clonidine patch.

For patients experiencing a life-threatening or major bleed, study personnel recommend that patients have their ASA trial medication held until the bleeding is stabilized and the attending physician believes it is safe to restart the ASA trial medication. Medical management, including any drug therapy, is at the discretion of the attending physician.

Patient follow-up

Patients have a troponin measurement (or creatine kinase-myocardial band if troponin is not available) drawn 6 to 12 hours after surgery and on the first, second, and third days after surgery. Patients have electrocardiography (ECG) immediately after an elevated troponin is detected. Research personnel follow up patients throughout their hospital stay and contact patients at 30 days and 1 year after randomization to determine if a patient has experienced a trial outcome.

Trial outcomes

The overall primary outcome of the POISE-2 trial is a composite of mortality and nonfatal myocardial infarction at 30 days after randomization. The secondary outcome is a composite of mortality, nonfatal myocardial infarction, and nonfatal stroke at 30 days after randomization. Online Appendix A reports the individual tertiary outcomes at 30 days after randomization.

In each ASA stratum and in the ASA group overall, we will also assess a composite outcome of mortality, nonfatal myocardial infarction, cardiac revascularization procedure, nonfatal pulmonary embolism, and nonfatal deep venous thrombosis at 30 days after randomization. The safety outcomes for ASA are stroke, clinically important hypotension, congestive heart failure, life-threatening bleeding, and major bleeding at 30 days after randomization. The safety outcomes for clonidine are stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure at 30 days after randomization.

For the 1-year follow-up, our primary outcome is mortality and nonfatal myocardial infarction. Online Appendix A reports the 1-year secondary outcomes. Online Appendix B provides definitions for all outcomes.

Outcome adjudication

Outcome adjudicators, who are blinded to treatment allocation, are adjudicating the following outcomes: death (vascular vs nonvascular), myocardial infarction, nonfatal cardiac arrest, pulmonary embolism, deep venous thrombosis, stroke, life-threatening bleeding, major bleeding, and peripheral arterial thrombosis. We will use the decisions of the outcome adjudicators for all statistical analyses.

Statistical considerations

Sample size. We assumed that each of clonidine and ASA will result in a hazard ratio (HR) of 0.75 for the primary outcome (mortality or nonfatal myocardial infarction). We used the control event rate for mortality and nonfatal myocardial infarction in POISE and adjusted this event rate accounting for the factorial design, and this suggests a placebo event rate of 6.1%. POISE-2 will include 10,000 patients because this will provide 84% power if our event rate is 6.1% and 81% power if our event rate is 5.6% (2sided α = .05).

Data analysis

We will analyze patients in the treatment group to which they are allocated, according to the intention-to-treat principle. We will compare patients allocated to clonidine with patients allocated to clonidine placebo, and we will compare patients allocated to ASA with patients allocated to ASA placebo.

Main analysis. We will present the time-to-the first occurrence of one of the components of the primary outcome using the Kaplan-Meier estimator. We will use Cox proportional hazards models to estimate the effect of each individual study drug on the HR for the primary and secondary outcomes, with stratification according to whether treatment included the other agent. We will calculate the HRs and their associated 95% CIs. We will infer statistical significance if the computed 2-sided P value is <.05. We anticipate that the treatment effect of clonidine and ASA, if present, will act independently; we will, however, evaluate the possibility of synergism or antagonism by formally testing the interaction term in a Cox model.
Subgroup analyses. Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the clonidine subgroup analyses (ie, neuraxial blockade, vascular surgery, β-blocker usage in the 24 hours preceding surgery, and baseline risk according to the revised cardiac risk index) and the ASA subgroup analyses (ie, ASA stratum and baseline risk according to the revised cardiac risk index). We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at \( P < .05 \).

Interim analyses. Three interim efficacy analyses based on the primary outcome occurred when 25%, 50%, and 75% of the 30-day data were available. The External Safety and Efficacy and Monitoring Committee (ESEMC) used the modified Haybittle-Peto rule of 4 SDs (\( \alpha = .0001 \)) for analyses in the first half of the trial and 3 SDs (\( \alpha = .0047 \)) for all analyses in the second half. For a finding of 1 or both active treatments to be considered significant, these predefined boundaries had to be exceeded in at least 2 consecutive analyses, 3 or more months apart. The \( \alpha \) level for the final analysis will remain the conventional \( \alpha = .05 \), given the infrequent interim analyses, their extremely low \( \alpha \) levels, and the requirement for confirmation with subsequent analyses. The ESEMC monitored for an adverse impact of clonidine on stroke or mortality and ASA on stroke, life-threatening bleeding, or mortality. For these analyses, a 3-SD excess in the first half and a 2.6-SD excess in the second half of the trial would have triggered discussions about stopping for harm.

Trial organization

The Population Health Research Institute is the coordinating center for this study worldwide and is primarily responsible for the organization of the trial, development of the randomization scheme, the study database, data consistency checks, data analysis, and coordination of the study centers. The trial structure includes the following groups: the Project Office Operations Committee, National Coordinators, Investigators, Coordinating Center, International Operations Committee, Steering Committee, Adjudication Committee, and the ESEMC. Online Appendix C lists the group members.

Current status of the trial and funding

The POISE-2 trial is currently recruiting patients in 135 centers within 23 countries and has randomized more than 9,000 patients as of October 2013. Tables III and IV present baseline characteristics and type of surgery and anesthesia/analgesia, respectively. These data demonstrate that among the first 7,500 patient randomized, patients’ mean age was 68.2 years, 53.4% were male, 34.0% had a history of vascular disease, and 38.3% were treated for diabetes. Participants underwent orthopedic (38.1%), general (27.0%), urologic or gynecologic (17.2%), vascular (6.6%), thoracic (5.7%), or other (5.4%) surgery; 23.9% of the patients received a β-blocker within 24 hours preceding surgery, and 56.8% of patients received a general anesthesia and 43.2% received neuraxial anesthesia or a nerve block. After the 3 interim analyses, the ESEMC was unanimous in recommending that the POISE-2 trial continue.

Grants from the Canadian Institutes of Health Research, the Commonwealth Government of Australia’s National Health and Medical Research Council, and the Spanish Ministry of Health and Social Policy fund POISE-2. Boehringer Ingelheim provided the clonidine study drug and some funding, and Bayer Pharma AG provided the ASA study drug. The authors are solely responsible for the design and conduct of this trial, all trial analyses, the drafting and editing of the manuscript, and its final contents.

Discussion

Patients undergoing noncardiac surgery frequently experience major perioperative vascular complications. There exists encouraging but inconclusive evidence that clonidine and ASA may prevent perioperative cardiovascular events.

Oral clonidine is absorbed rapidly and reaches peak serum concentrations within 2 to 4 hours and demonstrates physiological effects within 1 hour; these effects persist for 24 hours. Transdermal clonidine reaches peak serum concentrations at 48 hours after application and demonstrates physiological effects at 24 hours; after removal of the clonidine patch serum concentrations, physiological effects can persist for 2 to 3 days. Administering oral clonidine 2 to 4 hours before surgery allows us to achieve physiological effects before surgery, and these effects will persist for 24 hours. Applying the transdermal patch 2 to 4 hours before surgery allows us to achieve physiological effects starting around the time the effects of the oral clonidine dose are resolving. This

### Table III. Baseline characteristics (n = 7500)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>68.2 (10.4)</td>
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<tr>
<td>Gender (female)</td>
<td>46.6%</td>
</tr>
<tr>
<td>Prerandomization heart rate (beats/min), mean (SD)</td>
<td>76.4 (12.6)</td>
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<tr>
<td>Prerandomization systolic blood pressure (mm Hg), mean (SD)</td>
<td>141.1 (20.0)</td>
</tr>
<tr>
<td>Percentage of patients fulfilling eligibility criterion</td>
<td></td>
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<tr>
<td>History of coronary artery disease</td>
<td>23.5</td>
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<tr>
<td>History of peripheral arterial disease</td>
<td>9.1</td>
</tr>
<tr>
<td>History of stroke</td>
<td>5.5</td>
</tr>
<tr>
<td>History of vascular disease (ie, any of above)</td>
<td>34.0</td>
</tr>
<tr>
<td>Undergoing major vascular surgery</td>
<td>5.5</td>
</tr>
<tr>
<td>3 of 9 risk criteria</td>
<td>82.1</td>
</tr>
<tr>
<td>Undergoing major surgery</td>
<td>76.9</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>3.7</td>
</tr>
<tr>
<td>History of a transient ischemic attack</td>
<td>3.8</td>
</tr>
<tr>
<td>Diabetes and currently on an oral hypoglycemic agent or insulin</td>
<td>38.3</td>
</tr>
<tr>
<td>Age ≥70 y</td>
<td>50.4</td>
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<tr>
<td>Hypertension</td>
<td>86.0</td>
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<tr>
<td>Preoperative serum creatinine &gt;175 μmol/L (≥2.0 mg/dL)</td>
<td>3.4</td>
</tr>
<tr>
<td>History of smoking within 2 y of surgery</td>
<td>25.7</td>
</tr>
<tr>
<td>Emergent/Urgent surgery</td>
<td>7.3</td>
</tr>
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</table>


The CURRENT OASIS-7 trial evaluated 2 doses of ASA. This trial randomized 25,087 patients with acute coronary syndrome to ASA 75 to 100 mg/d vs ASA 300 to 325 mg/d. At 30-day follow-up, there was no difference between the groups regarding major cardiovascular outcomes. The Antithrombotic Trialists’ Collaboration meta-analysis of RCTs evaluating the effects of initiating antiplatelet therapy demonstrated that low-dose ASA (75-150 mg daily) was as effective but less gastrotoxic than higher doses; however, in acute settings, an initial loading dose of 160 mg of ASA (which is sufficient to provide rapid and complete inhibition of thromboxane A2-mediated platelet aggregation) may be required.

Our decision to allow patients to participate in the Continuation Stratum even if they have taken their ASA no less than 72 hours prior to surgery was based upon the following 2 considerations. First, the mean life span of human platelets is approximately 8 to 10 days, and about 12% of circulating platelets are replaced every 24 hours. O’Brien demonstrated that abnormal platelet aggregation after ingestion of ASA can be corrected ex vivo by 10% normal platelet-rich plasma. Furthermore, it has been reported that if as little as 20% of platelets have normal COX-1 activity, hemostasis is unimpaired. Therefore, stopping ASA for 72 hours is likely to ensure substantial (if not complete) recovery of platelet function. Second, investigators of the ISIS-2 trial that randomized 17,187 patients to ASA or placebo in the acute myocardial infarction setting included patients who were taking ASA chronically even if they took ASA on the day of their myocardial infarction. There were 2,266 patients in this subgroup, and ASA demonstrated a statistically significant reduction in vascular death, consistent with the overall finding.

POISE-2 is a large factorial RCT designed to determine if clonidine, and separately if ASA, can prevent mortality and nonfatal myocardial infarction at 30 days of follow-up. To date, the POISE-2 trial has randomized more than 9,000 patients. POISE-2 will answer 2 crucial management questions and influence future perioperative practices around the world.

Disclosures

Competing interests: Boehringer Ingelheim has provided the clonidine study drug and some funding, and Bayer Pharma AG has provided the acetyl-salicylic acid study drug. Dr Devereaux has received a grant from Boehringer Ingelheim to conduct an investigator-initiated trial of
dabigatran in patients with myocardial injury after noncardiac surgery, and many of the POISE-2 investigators are participating in this trial.

References


Appendix A. Individual tertiary outcomes at 30 days and secondary 1-year outcomes

Individual tertiary outcomes at 30 days after randomization include: total mortality, vascular mortality, myocardial infarction, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary embolism, deep venous thrombosis, new clinically important atrial fibrillation, amputation, peripheral arterial thrombosis, infection, sepsis, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit/cardiac care unit stay, and new acute renal failure requiring dialysis.

A secondary outcome includes the composite of mortality, nonfatal myocardial infarction, and nonfatal stroke at 1 year after randomization. Individual secondary 1-year follow-up outcomes include all-cause mortality, vascular mortality, myocardial infarction, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary embolism, deep venous thrombosis, amputation, peripheral arterial thrombosis, new diagnosis of cancer, diagnosis of recurrent cancer, rehospitalization for vascular reason, and chronic incisional pain. Online Appendix B provides definitions for all outcomes.
## Appendix B. Outcome definitions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Myocardial infarction</td>
<td>The diagnosis of myocardial infarction requires any one of the following criterion: 1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post surgery in a patient without a documented alternative explanation for an elevated troponin (eg, pulmonary embolism) OR a rapid rise and fall of creatine kinase–myocardial band. This criterion also requires that 1 of the following must also exist: A. ischemic signs or symptoms (ie, chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); B. development of pathologic Q waves present in any 2 contiguous leads that are ≥30 ms; C. ECG changes indicative of ischemia (ie, ST segment elevation [≥2 mm in leads V1, V2, or V3 OR ≥1 mm in the other leads], ST segment depression [≤1 mm], or symmetric inversion of T waves ≥1 mm) in at least 2 contiguous leads; D. coronary artery intervention (ie, PCI or CABG surgery); or E. new or presumed new fixed defect on radionuclide imaging 2. Pathologic findings of an acute or healing myocardial infarction; or 3. Development of new pathologic Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event</td>
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<tr>
<td>Nonfatal cardiac arrest</td>
<td>Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.</td>
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<tr>
<td>Cardiac revascularization procedure</td>
<td>Cardiac revascularization procedure is defined as PCI or CABG surgery.</td>
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<tr>
<td>Stroke</td>
<td>Stroke is defined as a new focal neurologic deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.</td>
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<td>Pulmonary embolism</td>
<td>The diagnosis of pulmonary embolism requires any one of the following: 1. A high probability ventilation/perfusion lung scan; 2. An intraluminal filling defect of segmental or larger artery on a helical computed tomographic scan; 3. An intraluminal filling defect on pulmonary angiography; or 4. A positive diagnostic test for deep venous thrombosis (eg, positive compression ultrasound) and one of the following: A. nondiagnostic (ie, low or intermediate probability) ventilation/perfusion lung scan; or B. nondiagnostic (ie, subsegmental defects or technically inadequate study) helical computed tomographic scan.</td>
</tr>
<tr>
<td>Deep venous thrombosis of leg or arm</td>
<td>The diagnosis of deep venous thrombosis requires any one of the following: 1. A persistent intraluminal filling defect on contrast venography; 2. Noncompressibility of one or more venous segments on B mode compression ultrasonography; or 3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography.</td>
</tr>
<tr>
<td>New clinically important atrial fibrillation</td>
<td>New clinically important atrial fibrillation is defined as new atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.</td>
</tr>
<tr>
<td>Rehospitalization for vascular reasons</td>
<td>Rehospitalization for vascular reasons is defined as rehospitalization for myocardial infarction, cardiac arrest, stroke, congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, cardiac arrhythmia, cardiac revascularization procedure, deep venous thrombosis, pulmonary embolus, any vascular surgery, or bleeding.</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>Life-threatening bleeding is bleeding that is fatal, or leads to significant hypotension that requires inotrope or vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Major bleeding is defined as bleeding that is not specified under “life-threatening bleeding” above and results in any one of the following: 1. a hemoglobin level ≤70 g/L and the patient receives a transfusion of ≥2 units of red blood cells; 2. a hemoglobin drop of ≤50 g/L and the patient receives a transfusion of ≥2 units of red blood cells; 3. the patient receives a transfusion of ≥4 units of red blood cells within a 24-h period; 4. any one of the following interventions (ie, embolization, superficial vascular repair, nasal packing); or 5. retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging) bleeding.</td>
</tr>
</tbody>
</table>
Clinically important hypotension is defined as a systolic blood pressure <90 mm Hg requiring fluid resuscitation, intra-aortic balloon pump, an inotropic or vasopressor agent, or study drug discontinuation.

Clinically important bradycardia is defined as a heart rate <55 beats/min requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation.

The definition of congestive heart failure requires at least one of the following clinical signs (ie, any of the following signs: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following radiographic findings (ie, vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

Dialysis is defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.

We will consider a peripheral arterial thrombosis to have occurred where there is clear evidence of abrupt occlusion of a peripheral artery (ie, not a stroke, myocardial infarction, or pulmonary embolism) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition, we require at least one of the following objective findings of peripheral arterial thrombosis:

1. Surgical report indicating evidence of arterial thrombosis/peripheral arterial embolism;
2. Pathological specimen demonstrating arterial thrombosis/peripheral arterial embolism;
3. Imaging evidence consistent with arterial thrombosis/peripheral arterial embolism; or
4. Autopsy reports documenting arterial thrombosis/peripheral arterial embolism.

Infection/sepsis is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms. Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Systemic inflammatory response requires 2 or more of the following factors: core temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min; white blood cell count >12 x 10^9/L or <4 x 10^9 L.

Defined as a patient with a new diagnosis of cancer (ie, the patient has no prior history of this cancer) within the first 12 mo after their initial surgery for which they were enrolled in POISE-2. This outcome is for all cancers except nonmelanoma skin cancers.

Defined as patients with any diagnosis of recurrent cancer (ie, a recurrence of a previous cancer for which the patient received curative treatment) within the 12 mo after their initial surgery for which they were enrolled in POISE-2. Recurrent cancer does not include nonmelanoma skin cancers.

Appendix C. Trial groups


National Coordinators: Argentina—F. Botto and R. Díaz; Australia/New Zealand—K. Leslie; Austria—E. Fleischmann; Belgium—P.Forget; Brazil—O. Berwanger; Canada—P.J. Devereaux, M. Mrkobrada; Chile—D. Torres; Colombia—J.C. Villar, O.L.Cortés; Denmark—C. Meyhoff, J. Wetterslev; France—P. Alfonsi; Germany—A. Hoeft, M. Wittmann; Hong Kong—M. Chan; India—A. Sigamani, D. Xavier; Italy—G. Landoni; Malaysia—C. Y. Wang; Pakistan—O. Ishitaq; Peru—G. Malaga; South Africa—B. Biccard; Spain—P. Alonso-Coello; Switzerland—D. Conen; United Kingdom—P. Balaji; United States—A. Kurz.


Population Health Research Institute Coordinating Center: A. Robinson (Trial Coordinator), T. Sovereign, L. Blake, J. Sephton, A. Serra, M. Lawrence, P. Gao, S. Chrolavicius (Project Manager).


ESEMC: L. Friedman (chairperson), D. Cheng, D. Johnstone, E. Lowenstein, R. Roberts.