**One-year results of a factorial randomized trial of aspirin versus placebo and clonidine versus placebo in patients having noncardiac surgery**

Supplementary appendix

**Supplemental Table 1. Eligibility criteria for POISE-2**

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| Inclusion criteria – patients >45 years of age undergoing in-hospital noncardiac surgery had to fulfill 1 or more of the following 5 inclusion criteria: |
| 1. history of coronary artery disease, |
| 1. history of peripheral arterial disease, |
| 1. history of stroke, |
| 1. undergoing major vascular surgery, OR |
| 1. any 3 of 9 risk criteria 2. age ≥70 years; 3. undergoing major surgery defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery; 4. history of congestive heart failure 5. history of transient ischemic attack; 6. diabetes and currently taking an oral hypoglycemic agent or insulin; 7. history of hypertension; 8. preoperative serum creatinine >175 μmol/L (>2.0 mg/dl); 9. smoking within 2 years of surgery; or 10. undergoing emergent/urgent surgery |
| Exclusion criteria – patients fulfilling any of the following criteria were excluded: |
| 1. hypersensitivity or known allergy to aspirin or clonidine; |
| 1. consumption of aspirin within 72 hours prior to surgery; |
| 1. systolic blood pressure <105 mm Hg; |
| 1. heart rate <55 beats per minute or second or third degree heart block in a patient who did not have a permanent pacemaker; |
| 1. active peptic ulcer disease or gastrointestinal bleeding within 6 weeks before surgery; |
| 1. intracranial hemorrhage in the 6 months before surgery; |
| 1. subarachnoid hemorrhage or epidural hematoma unless the event occurred more than 6 months before surgery and the abnormality was repaired; |
| 1. drug-eluting coronary stent <1 year before surgery; |
| 1. bare-metal coronary stent <6 weeks before surgery; |
| 1. taking a thienopyridine or ticagrelor within 72 hours before surgery or intent to use one of these drugs during the first 7 days after surgery; |
| 1. taking an alpha-2 agonist, alpha methyldopa, monoamine oxidase inhibitors, or reserpine before surgery; |
| 1. planned use of therapeutic dose anticoagulation during the first 3 days after surgery; |
| 1. undergoing intracranial surgery, carotid endarterectomy, or retinal surgery; |
| 1. not consenting to participate in POISE-2 before surgery; OR |
| 1. previously enrolled in POISE-2 |

**Supplemental Table 2. Definition of outcomes**

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| **Outcome** | **Definition** |
| **Sub classification of death** | Judicial outcome assessors will classify all deaths as either vascular or non-vascular. Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (e.g. trauma, infection, malignancy). |
| **Myocardial infarction** | The diagnosis of myocardial infarction requires any one of the following criteria:  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 (e.g., pulmonary embolism) OR a rapid rise and fall of CK-MB. This criterion also requires that 1 of the following must also exist:  A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);  B. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds;  C. ECG changes indicative of ischemia (i.e., 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 two contiguous leads;  D. coronary artery intervention (i.e., PCI or CABG surgery); or  E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging;  2. Pathologic findings of an acute or healing myocardial infarction; or  3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event. |
| **Nonfatal cardiac arrest** | 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. |
| **Cardiac revascularization procedure** | Cardiac revascularization procedure is defined as PCI or CABG surgery. |
| **Stroke** | Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death. |
| **Pulmonary embolism** | 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 CT scan;  3. An intraluminal filling defect on pulmonary angiography; or  4. A positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) and one of the following:  A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan; or  B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan. |
| **Deep venous thrombosis of leg or arm** | 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. |
| **New clinically important atrial fibrillation** | 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. |
| **Re-hospitalization for vascular reasons** | Re-hospitalization for vascular reasons is defined as re-hospitalization 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. |
| **Congestive heart failure** | The definition of congestive heart failure requires at least one of the following clinical signs (i.e., 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 (i.e., vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema). |
| **New acute renal failure requiring dialysis** | Dialysis is defined as the use of a hemodialysis machine or peritoneal dialysis apparatus. |
| **Amputation** | Amputation is defined as an amputation procedure subsequent to the initial surgery. |
| **Peripheral arterial thrombosis** | We will consider a peripheral arterial thrombosis to have occurred where there is clear evidence of abrupt occlusion of a peripheral artery (i.e., 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. |
| **New diagnosis of cancer since surgery** | Defined as a patient with a new diagnosis of cancer (i.e., the patient has no prior history of this cancer) within the first 12 months after their initial surgery for which they were enrolled in POISE-2. This outcome is for all cancers except non-melanoma skin cancers. |
| **Diagnosis of recurrent cancer since surgery** | Defined as patients with any diagnosis of recurrent cancer (i.e., a recurrence of a previous cancer for which the patient received curative treatment) within the 12 months after their initial surgery for which they were enrolled in POISE-2. Recurrent cancer does not include non-melanoma skin cancers. |
| **Chronic incisional pain** | This refers to whether the patient has pain at his/her surgical site 1 year after surgery, and this relates to the initial surgical site for which the patient was enrolled in POISE-2. |

**Supplemental Table 3**

|  | | Aspirin versus placebo | | |
| --- | --- | --- | --- | --- |
| Hazard ratio | 95% confidence interval | P value |
| Mortality | Overall | 0.97 | 0.83-1.14 | 0.75 |
| No PCI | 0.99 | 0.84-1.16 | 0.91 |
| PCI | 0.69 | 0.31-1.55 | 0.37 |
| P interaction | . | . | 0.33 |
| Non-fatal myocardial infarction | Overall | 1.00 | 0.86-1.16 | 0.97 |
| No PCI | 1.04 | 0.89-1.21 | 0.64 |
| PCI | 0.54 | 0.30-0.98 | 0.04 |
| P interaction | . | . | 0.07 |

**Supplemental Figure 1: Trial flow diagram**

1. **Aspirin factorial**

Analyzed by intention to treat (n=5012)

Analyzed by intention to treat (n=4998)

Allocated to placebo (n=5012)

Starting Stratum (n=2821)

Continuation Stratum (n=2191)

Allocated to aspirin (n=4998)

Starting Stratum (n=2807)

Continuation Stratum (n=2191)

Randomized (n=10,010)

Eligible patients (n=33,509)

Eligible patients not randomized (n=23,499)

Patient did not consent (n=10,329)

Patient not identified prior to surgery (n=4735)

Physician declined to participate (n=3569)

Other reason (n=4866)

Withdrew from trial (n=1)

Lost to follow-up (n=24)

Starting Stratum (n=12)

Continuation Stratum (n=12)

Withdrew from trial (n=2) Lost to follow-up (n=20)

Starting Stratum (n=11)

Continuation Stratum (n=9)

1. **Clonidine factorial**

Randomized (n=10,010)

Eligible patients (n=33,509)

Eligible patients not randomized (n=23,499)

Patient did not consent (n=10,329)

Patient not identified prior to surgery (n=4735)

Physician declined to participate (n=3569)

Other reason (n=4864)

Withdrew from trial (n=2)

Lost to follow-up (n=21)

Analyzed by intention to treat (n=5001)

Analyzed by intention to treat (n=5009)

Withdrew from trial (n=1)

Lost to follow-up (n=23)

Allocated to clonidine (n=5009)

Allocated to placebo (n=5001)