PeriOperative ISchemic Evaluation-2 (POISE-2) Trial

**LONG-TERM STATISTICAL ANALYSIS PLAN**

**POPULATION HEALTH RESEARCH INSTITUTE**

**June 7, 2015**

**1. TRIAL OBJECTIVES**

**Primary Efficacy Objective:**

1. To determine the impact of perioperative administration of low-dose clonidine versus placebo and separately low-dose ASA versus placebo on the 1-year risk of mortality or nonfatal myocardial infarction (MI) in patients with, or at risk of, atherosclerotic disease who underwent noncardiac surgery.

**Secondary Efficacy Objectives:**

1. To determine the impact of perioperative administration of low-dose clonidine versus placebo and separately low-dose ASA versus placebo on the 1-year risk of a composite of mortality, nonfatal MI, and nonfatal stroke in patients with, or at risk of, atherosclerotic disease who underwent noncardiac surgery.

2. To determine the impact of perioperative administration of low-dose clonidine versus placebo and separately low-dose ASA versus placebo on the 1-year risk of a composite of new diagnosis of cancer and diagnosis of recurrent cancer in patients with, or at risk of, atherosclerotic disease who underwent noncardiac surgery.

3. To determine the impact of perioperative administration of low-dose clonidine versus placebo and separately low-dose ASA versus placebo on the 1-year risk of each of the following individual secondary outcomes: chronic incisional pain, new diagnosis of cancer, and diagnosis of recurrent cancer in patients with, or at risk of, atherosclerotic disease who underwent noncardiac surgery..

4. To determine among all the ASA versus placebo patients the impact on the 1-year risk of a composite outcome of mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis and whether the effects differ from each other in each ASA stratum, in patients with, or at risk of, atherosclerotic disease who underwent noncardiac surgery.

**Tertiary Efficacy Objectives:**

1. To determine the impact of perioperative administration of low-dose clonidine versus placebo and separately low-dose ASA versus placebo on the 1-year risk of each of the following individual tertiary outcomes: mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary embolism, deep venous thrombosis, new clinically important atrial fibrillation, amputation, peripheral arterial thrombosis, rehospitalization for vascular reasons, congestive heart failure, and new acute renal failure requiring dialysis, in patients with, or at risk of, atherosclerotic disease who underwent noncardiac surgery.

**2. TRIAL OUTCOME EVENTS**

**Primary Efficacy Outcome for Clonidine and ASA**

1. The primary efficacy outcome for clonidine and ASA is the first occurrence of any component of the following composite up to 1 year after randomization: mortality or nonfatal MI.

**Secondary Efficacy Outcomes**

1. A secondary efficacy outcome for clonidine and ASA is the first occurrence of any component of the following composite up to 1 year after randomization: mortality, nonfatal MI, or nonfatal stroke.

2. A secondary efficacy outcome for clonidine and ASA is the following composite outcome up to 1 year after randomization: new diagnosis of cancer and diagnosis of recurrent cancer.

3. A secondary efficacy outcome for clonidine and ASA is each of the following individual outcomes up to 1 year after randomization: chronic incisional pain, new diagnosis of cancer, and diagnosis of recurrent cancer.

4. A secondary efficacy outcome among all the ASA patients (and whether the effects differ in each of the two ASA strata on the outcome) is the first occurrence of any component of the following composite up to 1 year after randomization: mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, or nonfatal deep venous thrombosis.

**Tertiary Efficacy Outcomes up to 1 year after Randomization for Clonidine and ASA**

1. Mortality

2. Vascular mortality

3. MI

4. Nonfatal cardiac arrest

5. Cardiac revascularization procedure

6. Pulmonary embolism

7. Deep venous thrombosis

8. New clinically important atrial fibrillation

9. Amputation

10. Peripheral arterial thrombosis

11. Rehospitalization for vascular reasons

12. Congestive heart failure

13. New acute renal failure requiring dialysis

**3. STATISTICAL AND ANALYTICAL METHODS**

**Analysis population**

All efficacy analyses will include all randomized patients. We will analyze patients in the treatment group to which they were originally allocated. There is no intention to define a per protocol population. We will include all events that centres have reported and the adjudication committee has not refuted.

**Efficacy analysis**

**Primary efficacy analyses**

The primary efficacy variable is the first occurrence of mortality or nonfatal myocardial infarction up to 1 year after randomization. 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. Patients lost to follow-up before 1 year after randomization with no primary outcome event reported will be censored at the last day the patient had a complete evaluation of the primary efficacy variable.

The primary efficacy variable will be analyzed using a stratified (by the opposite component of the factorial design and ASA starting/continuing strata) Cox proportional hazards model. All follow up will be censored at 1 year or their outcome day, whichever occurs first. We will address the clonidine objective of superiority through the following hypotheses:

**H0: Hazard ratio of clonidine versus placebo (at 1 year after randomization) = 1**

**Ha: Hazard ratio of clonidine versus placebo (at 1 year after randomization) ≠ 1**

We will consider clonidine superior to placebo if the upper limit of the two-sided 95% confidence interval of the hazard ratio remains below 1.

We will address the ASA objective of superiority through the following hypotheses:

**H0: Hazard ratio of ASA versus placebo (at 1 year after randomization) = 1**

**Ha: Hazard ratio of ASA versus placebo (at 1 year after randomization) ≠ 1**

We will consider ASA superior to placebo if the upper limit of the two-sided 95% confidence interval of the hazard ratio remains below 1.

Estimates of the hazard ratios and two-sided 95% confidence intervals will be calculated using the Cox proportional hazards model. If the validity of the proportional hazards assumption is not acceptable, we will compare the proportion of patients with a primary outcome at 1 year after randomization between the two treatment groups, controlling for the same stratification factors. We will also summarize the primary outcome event with Kaplan-Meier curves by treatment group.

**Primary subgroup analyses on the primary efficacy parameter**

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the following clonidine subgroup analyses: 1.neuraxial blockade versus no neuraxial blockade (i.e., we expect clonidine to have a greater beneficial effect in patients who did not receive neuraxial blockade compared to patients who did receive neuraxial blockade); 2. vascular surgery versus no vascular surgery (i.e., we expect clonidine to have a greater beneficial effect in patients who underwent vascular surgery compared to patients who did not undergo vascular surgery); 3. beta-blocker usage in the 24 hours preceding surgery versus no beta-blocker usage in the 24 hours preceding surgery (we expect clonidine to have a greater beneficial effect in patients who did not receive a beta-blocker in the 24 hours prior to surgery compared to patients who did receive a beta-blocker in the 24 hours before surgery) and 4. baseline risk according to number of Revised Cardiac Risk Index (RCRI) criteria (i.e., we expect clonidine to have a greater beneficial effect in patients with more RCRI criteria compared to patients with less RCRI criteria).

For the subgroup analyses based on the number of RCRI criteria, we will examine if treatment effect varies across the number of RCRI criteria between the two treatment groups. The RCRI criteria consist of the following variables.

1. history of coronary artery disease

2. history of congestive heart failure

3. history of stroke or transient ischemic attack

4. diabetes and preoperative treatment with insulin or an oral hypoglycemic agent

5. preoperative serum creatinine >175 μmol/L [>2.0 mg/dl]

6. high-risk surgery defined as major vascular, major thoracic, or major general surgery

The analysis will consist, for each number of eligibility criteria (i.e., 0, 1, 2, 3, or ≥4), of a stratified Cox proportional hazards model, incorporating terms for treatment group, the individual number of RCRI criteria, and the treatment group by subgroup interaction.

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the following ASA subgroup analyses: 1. ASA continuation stratum versus ASA starting stratum (i.e., we expect ASA to have a greater beneficial effect in patients in the ASA continuation stratum compared to patients in the ASA starting stratum); 2. vascular surgery versus no vascular surgery (i.e., we expect ASA to have a greater beneficial effect in patients who underwent vascular surgery compared to patients who did not undergo vascular surgery); 3. baseline risk according to number of RCRI criteria (i.e., we expect ASA to have a greater beneficial effect in patients with more RCRI criteria compared to patients with less eligibility criteria); and 4. vascular disease versus no vascular disease (i.e., we expect ASA to have a greater beneficial effect in patients with vascular disease). The subgroup analyses based on the number of RCRI criteria for ASA will follow the same approach as outlined for clonidine.

The number of patients with outcomes, estimated hazard ratios, and associated two-sided 95% CIs will be calculated within each of the subgroups generated by these analyses. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at p<0.05.

**Analyses of secondary and tertiary efficacy parameters**

The first occurrence of the secondary composite outcomes will be analyzed up to 1 year after randomization using the same analytical approach as for the primary efficacy variable. The only exception to this approach is that we will analyze the outcome chronic incisional pain using a Chi-square test, because it is only assessed as present 1 year after surgery. The first occurrence of each individual tertiary outcome will be analyzed at 30 days after randomization using the same analytical approach as for the primary efficacy variable. For new acute renal failure requiring dialysis we did not collect the date that dialysis was initiated after randomization, and we will therefore use a log-rank test.

**Primary subgroup analyses on the secondary efficacy parameter**

We will undertake one subgroup analysis for our secondary outcome of the first occurrence of any component of the following composite up to 1 year after randomization: mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, or nonfatal deep venous thrombosis. Cox proportional hazards models assessing this secondary outcome will provide the basis for evaluating the following ASA subgroup analysis: ASA continuation stratum versus ASA starting stratum (i.e., we expect ASA to have a greater beneficial effect in patients in the ASA continuation stratum compared to patients in the ASA starting stratum). For this subgroup analysis, we will remove the ASA continuation/starting factor as a strata within the Cox regression.

The number of patients with outcomes, estimated hazard ratios, and associated two-sided 95% CIs will be calculated within each of the subgroups generated by these analyses. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at p<0.05.