POISE-2 Trial

PeriOperative ISchemic Evaluation-2 Trial

A large, international, placebo-controlled, factorial trial to assess the impact of clonidine and acetyl-salicylic acid (ASA) in patients undergoing noncardiac surgery who are at risk of a perioperative cardiovascular event

An International Collaborative Initiative

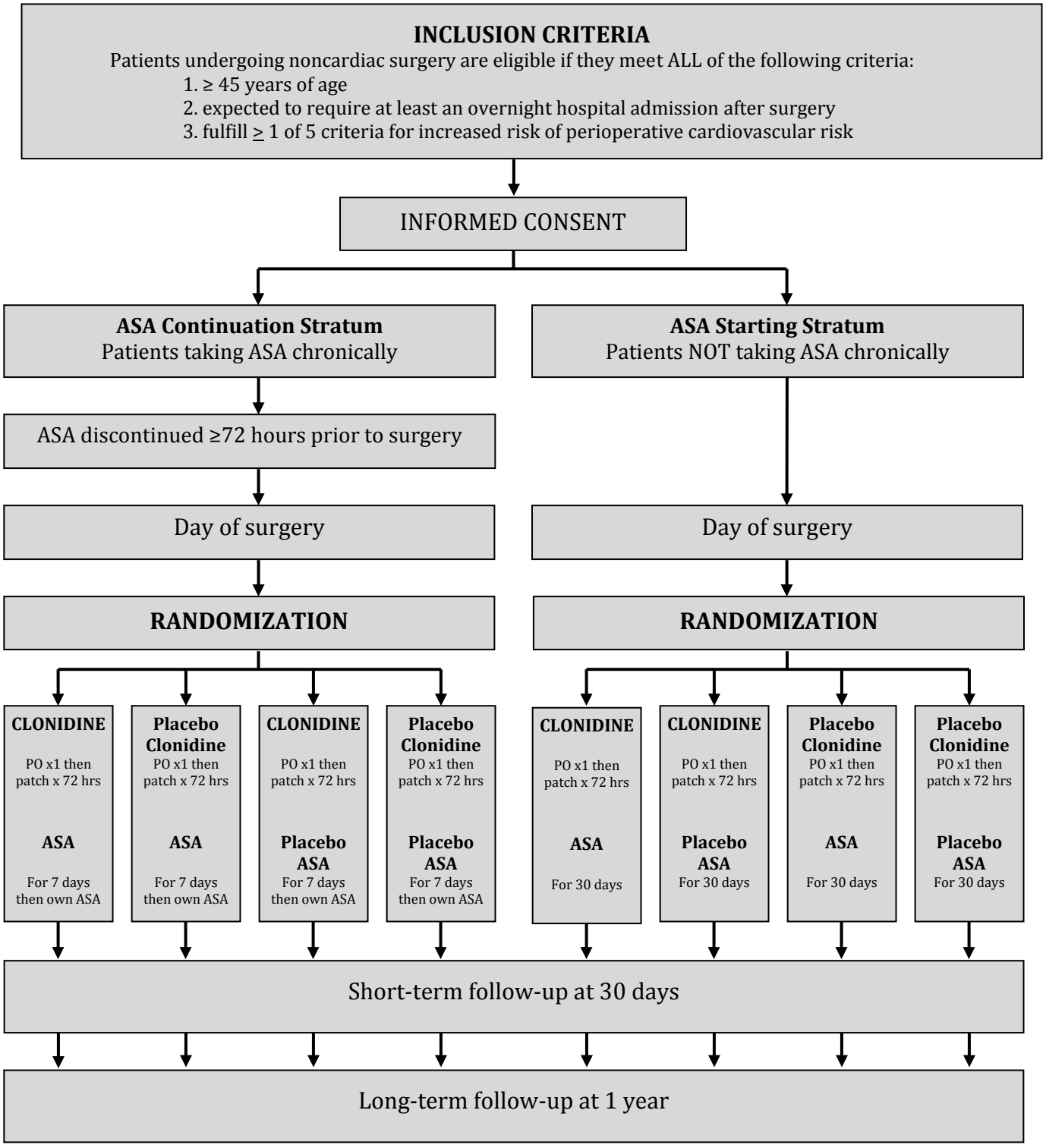
Study Coordinating Group and Central Address:

POISE-2 Project Office
Population Health Research Institute
Hamilton General Hospital Campus, DBCVSRI
237 Barton Street East, Room C1-239
Hamilton, Ontario, Canada L8L 2X2
poise2@phri.ca

Tel: 905-527-4322 ext. 40473
Fax: 905-297-3779

Version Date: March 1, 2010

Study Flow Chart



Title	**The PeriOperative Ischemic Evaluation-2 (POISE-2) Trial**
Project Office	POISE-2 Project Office Population Health Research Institute Hamilton General Hospital Campus, DBCVSRI 237 Barton Street East, Room C1-239 Hamilton, Ontario, Canada L8L 2X2
Study Size	10,000 patients
Study Design	Multicentre, international, blinded, 2x2 factorial randomized controlled trial of acetyl-salicylic acid (ASA) and clonidine.
Primary Objective	To determine the impact of clonidine versus placebo and ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery.
Secondary Objective	To determine the impact of clonidine and ASA on cardiovascular events at 30 days and 1 year after surgery.
Inclusion Criteria	Patients undergoing noncardiac surgery are eligible if they: 1. are ≥ 45 years of age; 2. are expected to require at least an overnight hospital admission after surgery; AND 3. fulfill one or more of the following 5 criteria A. history of coronary artery disease; B. history of peripheral vascular disease; C. history of stroke; D. undergoing major vascular surgery; OR E. any 3 of the following 9 criteria: undergoing major surgery (i.e. intraperitoneal, intrathoracic, or major orthopedic surgery), history of congestive heart failure, transient ischemic attack, diabetes and currently taking an oral hypoglycemic agent or insulin, age ≥ 70 years, hypertension, serum creatinine > 175 μmol/L (> 2.0 mg/dl), history of smoking within 2 years of surgery, undergoing urgent/emergent surgery
Treatment Regimen	**Clonidine:** 2-4 hours prior to surgery, patients will take 0.2 mg of oral clonidine or matching placebo and will have a transdermal clonidine (0.2 mg/day) or placebo patch applied to their upper arm or chest. The patch will be removed at 72 hours after surgery. **ASA Continuation Stratum (patients taking ASA chronically):** Patients will be randomized to continue ASA or withdraw ASA and take a placebo starting on the day of surgery. Patients will continue taking the ASA trial intervention until 7 days after surgery after which patients will restart taking their regular ASA. **ASA Starting Stratum (patients not taking ASA chronically):** Patients will be randomized to start ASA or placebo on the day of surgery and will continue taking the ASA trial intervention until 30 days after surgery.

TABLE OF CONTENTS

1.0 INTRODUCTION AND RATIONALE

During the last few decades, substantial advances in noncardiac surgery have improved disease treatment and patients' quality of life. As a result, the number of patients undergoing noncardiac surgery is growing. A recent study that used surgical data from 56 countries suggests that 200 million major noncardiac surgical procedures are undertaken annually around the world.[1,2]

Noncardiac surgery is associated with major vascular complications (i.e., vascular death, nonfatal myocardial infarction [MI], nonfatal cardiac arrest, and nonfatal stroke). Worldwide, approximately 3-5 million adult patients annually suffer a major perioperative vascular complication in the first 30 days after surgery,[2] a number similar to the annual global incidence of new patients acquiring human immunodeficiency virus (HIV).[3] There is not a single established effective and safe intervention to prevent major perioperative vascular complications.[4] The striking absence of prophylactic interventions reflects the paucity of large randomized controlled trials (RCTs) evaluating perioperative interventions. Major perioperative vascular complications are therefore a major neglected public health problem.

We recently completed the largest RCT focused on cardiovascular complications in noncardiac surgery (the PeriOperative ISchemic Evaluation-1 [POISE-1] Trial).[5] In POISE-1, we randomized 8,351 patients with, or at risk of, atherosclerotic disease from 190 hospitals in 23 countries to receive extended-release metoprolol succinate (metoprolol CR) or placebo starting 2-4 hours prior to surgery and continuing for 30 days. Metoprolol decreased the 30-day risk of MI (hazard ratio [HR], 0.73; 95% CI, 0.60-0.89) but increased the risk of death (HR, 1.33; 95% CI, 1.03-1.74) and stroke (HR, 2.17; 95% CI, 1.26-3.74). These harmful consequences, unanticipated prior to POISE-1, have influenced thinking in this area and highlight the importance and need for large RCTs in perioperative medicine.

There are encouraging laboratory, physiology, operative and non-operative data suggesting that perioperative low-dose clonidine and low-dose acetyl-salicylic acid (ASA) may prevent all-cause mortality and nonfatal MI without excessive risk of major bleeding and clinically important hypotension. We will undertake a large international factorial RCT to establish the effects of these 2 interventions in patients undergoing noncardiac surgery. We call this RCT the POISE-2 Trial.

1.1 Principal Research Question

What is the effect of low-dose clonidine versus placebo and low-dose ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery?

1.2 Need for POISE-2 Trial

1.2.1 Pathophysiology of perioperative MI

MI is the most common major perioperative vascular complication. In the placebo group of the POISE-1 Trial 1.4% of the patients suffered a vascular death, 0.5% suffered a stroke, 0.5% suffered a nonfatal cardiac arrest, and 5.7% suffered an MI in the first 30 days.[5] Perioperative MI carries a poor prognosis. In the POISE-1 Trial 11.6% of the patients suffering a perioperative MI died within the first 30 days, and both asymptomatic and symptomatic perioperative MIs were powerful independent predictors of death at 30 days (odds ratio [OR] 3.45; 95% CI, 2.20-5.41 and OR 3.31; 95% CI, 1.78-6.15, respectively).[5] Further, a meta-analysis of noncardiac surgery studies suggests that an elevated troponin after surgery is a strong independent predictor of mortality up to 1 year after surgery (OR 6.7; 95% CI, 4.1-10.9).[6] Insights from the pathophysiology of perioperative MI may inform the type of intervention that will prevent this event.

Rupture of atherosclerotic plaque with superimposed arterial thrombosis constitutes the underlying pathophysiology in the majority of non-operative MIs.[7] Among patients suffering a non-operative MI, 64-100% have coronary artery plaque fissuring and 65-95% have an acute luminal thrombus.[8-13]

1.2.1.1 Potential role of supply-demand mismatch in the pathophysiology of perioperative MI

In contrast to non-operative MI, myocardial oxygen supply-demand mismatch represents a commonly proposed mechanism of perioperative MI.[14] Patients undergoing major noncardiac surgery experience an increase in sympathetic output and hence a rise in catecholamines[15-17] that result in an increase in heart rate and hence myocardial oxygen demand.[15 16] Noncardiac surgery is also associated with hypothermia that leads to shivering, which increases myocardial oxygen demand and is associated with myocardial ischemia.[18] In a coronary artery with a high grade stenosis, the supply response is limited, and can result in supply-demand mismatch MI when myocardial oxygen demand increases.

Consistent with this hypothesis, two small retrospective autopsy studies (<70 patients in total) reported that two-thirds of the patients who suffered a fatal perioperative MI had significant left main or 3 vessel coronary artery disease.[19 20] Most patients did not exhibit plaque fissuring and only about one-third had an intracoronary thrombus. Although the timing of the autopsies relative to the MIs may have allowed resolution of intracoronary thrombus, these data suggest that some fatal perioperative MIs are secondary to supply-demand mismatch.

1.2.1.2 Potential role of coronary thrombus in the pathophysiology of perioperative MI

An alternative mechanism of perioperative MI is that the acute stress of surgery and mechanical tissue injury induce a hypercoagulable-inflammatory state that increases the risk of coronary thrombus formation. The sympathetic hyperactivity associated with surgery promotes hypercoagulability by up-regulating coagulation and platelets and down-regulating fibrinolysis.[21-23] The increase in perioperative catecholamines is also associated with an increase in coronary shear stress, which may trigger plaque fissuring and acute coronary thrombosis.[24] Noncardiac surgery also results in inflammation (e.g., an increase in tumor necrosis factor α [TNF-α], interleukin [IL] -6, and IL-8) that may have a direct role in initiating plaque fissuring and acute coronary thrombosis.[25]

A small study of 21 patients who suffered a perioperative MI who had undergone a coronary angiography prior to vascular surgery revealed that the majority of nonfatal perioperative MIs occurred in arteries without a high-grade stenosis, suggesting that these events may have resulted from an acute coronary artery thrombosis.[26] Further evidence to support the thrombosis hypothesis comes from the Coronary Artery Revascularization Prophylaxis (CARP) Trial.[27] This trial randomized 510 patients undergoing elective vascular surgery who had at least one coronary artery with a $\geq$ 70% stenosis that was suitable for revascularization to receive coronary artery revascularization or no coronary artery revascularization before vascular surgery. This trial failed to demonstrate a significant reduction in the risk of perioperative MI in the patients randomized to undergo coronary revascularization. If supply-demand mismatch is the cause of perioperative MI, one would expect the risk of perioperative MI to decrease with coronary revascularization prior to noncardiac surgery.

Given the limitations of the evidence, it is not possible to draw firm conclusions regarding the pathophysiology of perioperative MI. It is likely that both mechanisms of perioperative MI (i.e., supply-demand mismatch and coronary thrombus) account for a portion of the perioperative MIs. Figure 1 summarizes the physiological changes that occur with surgery and how they may result in an MI. A perioperative prevention trial would ideally impact both proposed mechanisms to provide the greatest potential for benefit.

1.2.2 Laboratory and physiology evidence suggests clonidine may prevent death and nonfatal MIs in patients undergoing noncardiac surgery

Like beta-blockers, alpha-2 agonists (e.g., clonidine) attenuate the perioperative stress response, but they do so through a different mechanism. Alpha-2 agonists act on central and presynaptic receptors to inhibit the release of norepinephrine leading to a reduction in central sympathetic outflow.[28 29] Clonidine, the most available alpha-2 agonist, has a number of attributes that make it attractive as a potential agent to prevent perioperative MI and death. Perioperative clonidine induces sympatholysis,[30 31] has analgesic[32-34] and anti-shivering effects,[35] reduces myocardial oxygen uptake,[36] and reduces TNF-α, IL-6, and IL-8.[37 38] A meta-analysis of 2 noncardiac surgery clonidine RCTs (total 358 patients)

found a reduction in myocardial ischemia (based upon Holter recordings) with clonidine, without an increased risk of hemodynamic instability.[39] Perioperative clonidine trials have also demonstrated that clonidine decreases the average heart rate during the perioperative period.[30 31 40] Given these physiological changes, which may minimize the risk of supply-demand mismatch (i.e., sympatholytic, analgesic, and anti-shivering effects) and thrombus formation (i.e., sympatholytic, analgesic, and anti-inflammatory effects), clonidine may prevent major perioperative vascular events without incurring an increased risk of events mediated through hemodynamic instability, particularly stroke.

1.2.3 Experimental evidence and relevant systematic reviews evaluating the effects of alpha-2 agonists and clonidine in patients undergoing noncardiac surgery

1.2.3.1 Alpha-2 agonist data

A meta-analysis of alpha-2 agonists (clonidine, dexmedetomidine, mivazerol) included 12 noncardiac surgery RCTs.[41] The authors of this systematic review reported separately the results for patients who had vascular surgery and patients who had nonvascular noncardiac surgery. The meta-analysis demonstrated a statistically significant reduction in both death (39 events; relative risk [RR] 0.47; 95% CI, 0.25-0.90) and MI (110 events; RR 0.66; 95% CI 0.46-0.94) with alpha-2 agonist therapy among the vascular surgery patients. The investigators found no effect on mortality (31 events; RR 1.09; 95% CI 0.52-2.09) and MI (62 events; RR 1.25; 95% CI 0.83-2.21) among the nonvascular noncardiac surgery patients. The 6 trials that reported hypotension did not suggest an increase in hypotension with an alpha-2 agonist (RR 1.03; 95% CI 0.89-1.21).

The likelihood of a true subgroup effect is low.[42] Although there were 12 RCTs included in this meta-analysis, a single trial of mivazerol accounted for 80% of the deaths and 91% of the MIs.[43] While this trial randomized 2854 patients, the published report excludes 957 of these patients at high risk of coronary artery disease in whom an interim analysis demonstrated a lower than expected event rate.[43] The investigators reported on the remaining 1897 patients with established coronary artery disease among whom 91 (9.5%) assigned mivazerol and 100 (10.6%) assigned placebo suffered a death or nonfatal MI (risk ratio 0.89; 95% CI, 0.67-1.18). The authors reported a statistically significant reduction in this composite outcome with mivazerol only for the subgroup of vascular surgery patients, but there was no interaction P value reported and no prior hypothesis for a subgroup effect.

1.2.3.2 POISE-2 Pilot Trial

Since this prior meta-analysis, we have conducted the POISE-2 Pilot. We report here the data on the first 60 patients included in this pilot, Table 1. In the POISE-2 Pilot 6 of 30 clonidine patients versus 10 of 30 placebo patients developed clinically important hypotension. Although the POISE-2 Pilot is small these results are encouraging and suggest that the POISE-2 clonidine regimen may allow us to obtain the benefits we demonstrated in POISE-1 while mitigating the risks that appeared to have primarily occurred through clinically important hypotension.

1.2.3.3 Updated perioperative clonidine meta-analysis

The outdated perioperative clonidine meta-analysis mentioned above (section 1.2.2) included only 2 noncardiac surgery clonidine trials.[39] We therefore conducted a systematic review and meta-analysis of clonidine given to patients undergoing noncardiac surgery, which also includes the POISE-2 Pilot data. Thirty-two RCTs met our eligibility criteria.[30 31 33 36 37 40 44-68]

Table 2 reports the perioperative clonidine meta-analysis results. There was a statistically significant reduction in mortality with clonidine (RR 0.27; 95% CI, 0.07-0.99), but there were only 10 deaths in total making this result unreliable. The MI, stroke, and congestive heart failure results are also encouraging but limited by few events. Myocardial ischemia was less common among the patients randomized to clonidine (19.3%) compared to control (31.0%) (RR 0.66; 95% CI, 0.49-0.89).

Table 3 reports the clinically important hypotension results. The results demonstrate a significant increase in clinically important hypotension with clonidine (RR 1.51; 95% CI, 1.20-1.91), but there was moderate heterogeneity (I^2 31%). Our a priori hypothesis for heterogeneity based upon low-

dose clonidine (daily effective dose < 0.3 mg) versus high-dose clonidine (daily effective dose ≥ 0.3mg) explained this heterogeneity. The trials evaluating high-dose clonidine, but not those evaluating low-dose clonidine, demonstrated a significant increase in clinically important hypotension (P value for the test of interaction between these subgroups was < 0.01). Importantly, the low-dose clonidine trials showed the same positive trends as the high-dose clonidine trials regarding the other outcomes (e.g., mortality). Since clinically important hypotension had the largest population-attributable risk for stroke in POISE-1, the results suggest we will not find an increased risk of stroke with low-dose clonidine.

A meta-analysis of the low-dose clonidine RCTs demonstrates that low-dose clonidine reduces heart rate (mean difference = -5.94; 95% CI, -9.61, -2.27). No trials reported any rebound hypertension after discontinuation of the short courses of perioperative clonidine.

1.2.4 Perioperative clonidine may reduce intermediate-term mortality

An elevated troponin measurement after surgery is an independent predictor of death at 1 year. It has been hypothesized that perioperative ischemia results in unstable coronary plaques that are prone to fissuring weeks to months later, resulting in cardiac events.[69] This hypothesis, if correct, would explain how clonidine (which prevents perioperative myocardial ischemia) might, even after its discontinuation, affect intermediate-term (i.e., 1 year) vascular events.

Wallace and colleagues undertook an RCT evaluating the effect of 4 days of perioperative clonidine in patients undergoing noncardiac surgery.[31] Clonidine demonstrated an absolute risk reduction (ARR) of 5.4% for mortality at 30 days (total of 5 deaths, p=0.048) and demonstrated an ARR of 14% for mortality at 2 years (total of 38 deaths, p=0.035). These encouraging but limited data (Wallace is the only clonidine trial that reported following patients beyond 30 days) highlight the need for further RCTs to examine whether perioperative clonidine reduces intermediate-term mortality.

1.2.5 Current perioperative clonidine practices and feasibility of a perioperative clonidine RCT

We are currently conducting a 40,000 patient prospective cohort study (i.e., VISION) in 10 centres in 7 countries. VISION is evaluating a representative sample of patients ≥ 45 years of age who are undergoing noncardiac surgery. Of the first 6000 patients included in VISION, 2839 fulfilled the POISE-2 eligibility criteria and only 1.2% of these patients received an alpha-2 agonist sometime during the perioperative period. These data demonstrate that clonidine is used infrequently in the perioperative setting; indicating that the available information on clonidine has not impacted clinical practice. These data also indicate that it should not be difficult to recruit patients into a perioperative clonidine trial, as confirmed by our POISE-2 pilot where 3 centres enrolled 60 patients, and each centre recruited on average > 3 patients per week. The infrequent routine use of perioperative clonidine and our rapid recruitment rate in the POISE-2 Pilot demonstrate the feasibility of the POISE-2 Trial.

1.2.6 Observational and experimental evidence regarding the effects of initiating and withdrawing ASA in the <u>non-operative</u> setting

The Antithrombotic Trialists' Collaboration undertook a meta-analysis of RCTs evaluating the effects of initiating anti-platelet therapy. This non-operative meta-analysis included 195 trials involving 135,640 patients and 17,207 major vascular events. This meta-analysis demonstrated that ASA reduced nonfatal MI by one third, nonfatal stroke by one quarter, and mortality by one sixth in patients with or at high risk of atherosclerotic disease.[70] This meta-analysis also demonstrated that low-dose ASA (75-150 mg daily) was as effective but less gastrotoxic than higher doses, but in acute settings an initial loading dose of 160 mg of ASA (which is sufficient to provide rapid and complete inhibition of TXA_2 mediated platelet aggregation)[71] may be required.[72]

A recent meta-analysis of 3 prospective cohort studies that included 34,344 patients evaluated the effects of discontinuing ASA in the non-operative setting.[73] ASA discontinuation was associated with an increased risk for thrombotic events (RR 1.82; 95% CI, 1.52-2.18; $I^2 = 0\%$).

1.2.7 Laboratory and physiology evidence that suggests ASA may prevent vascular death and nonfatal myocardial infarctions in patients undergoing noncardiac surgery

Immediately after noncardiac surgery, patients experience a rise in circulating platelet release products.[74] Platelet surface catalyzing coagulation reactions facilitate thrombin generation and these events may promote thrombus formation and lead to arterial occlusion in the perioperative setting.[25] Acute withdrawal of chronic ASA results in a pro-thrombotic state (i.e., increased thromboxane A_2 [TXA_2] and decreased fibrinolysis).[75 76] 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 inhibition of thrombus formation.[77]

1.2.8 Experimental evidence and relevant systematic reviews evaluating the effects of ASA in patients undergoing noncardiac surgery

We have undertaken a systematic review and meta-analysis of perioperative ASA trials that included patients undergoing any type of noncardiac surgery. Fifteen RCTs fulfilled eligibility criteria and are included in our systematic review.[78-92]

Table 4 reports our perioperative ASA meta-analysis results. Both all-cause mortality (RR 0.85; 95% CI, 0.63-1.14) and vascular mortality (RR 0.59; 95% CI, 0.28-1.25) show trends towards benefit from perioperative ASA. In contrast, 58 of 9069 patients assigned ASA and 43 of 9037 patients assigned control suffered a nonfatal MI (RR 1.31; 95% CI, 0.88-1.94). This trend towards harm was identified in trials that did not routinely monitor daily cardiac biomarkers after surgery, except for the POISE-2 Pilot, and in total there were only a moderate number of nonfatal MIs. The meta-analysis did not demonstrate an impact on nonfatal stroke with perioperative ASA (total 125 events; RR 0.91; 95% CI 0.64-1.29), and suggested a trend towards fewer nonfatal pulmonary emboli with ASA (total 91 events; RR 0.74; 95% CI, 0.49-1.11). Perioperative ASA demonstrated an increase in major bleeding (total 357 events; RR 1.47; 95% CI, 1.19-1.80).

Although there were 19 trials in our ASA meta-analyses the Pulmonary Embolism Prevention (PEP) Trial dominated contributing the majority of patients and events.[85] PEP was a trial of hip fractures focused on pulmonary emboli, and they did not monitor for perioperative MI with daily troponin measurements. PEP provides important information, but there is a need for a large perioperative ASA trial that includes the majority of noncardiac surgeries and actively monitors for perioperative MIs.

1.2.9 Low versus high-dose ASA

The only surgical trial that has compared low versus high-dose ASA randomized patients undergoing carotid endarterectomy to low-dose ASA (i.e., 709 patients assigned 81 mg/day and 708 patients assigned 325 mg/day) and they had a lower risk (i.e., 6.2%) of the primary outcome (i.e., a composite of death, nonfatal MI, and nonfatal stroke at 3 months) than the patients randomized to high-dose ASA (i.e., 715 patients assigned 650 mg/day and 717 patients assigned 1300 mg/day) of which 8.4% suffered the primary outcome, P 0.03.[93] Recently the CURRENT OASIS-7 Trial was presented at the European Society of Cardiology 2009 Congress. This trial of 2 low-doses of ASA randomized 25,087 patients suffering an acute coronary syndrome to ASA 75-100 mg per day versus ASA 300-325 mg per day. At 30 day follow-up there was no difference between the groups regarding major cardiovascular outcomes (i.e., cardiovascular death, myocardial infarction, and stroke). Given this evidence we will evaluate low-dose ASA 100mg per day in POISE-2.

1.2.10 Current perioperative ASA practices and feasibility of a perioperative ASA trial

In POISE-1, 36.1% of the participants took ASA sometime in the week prior to surgery, and 39.7% took ASA sometime during their hospital admission. Because 84% of the patients in POISE-1 underwent general, orthopedic, or vascular surgery, we conducted a cross-sectional survey of all practicing Canadian general, orthopedic, and vascular surgeons.[94] Our survey demonstrated marked variations among surgeons regarding the starting and holding of ASA around the time of surgery. A majority of respondents also reported a willingness to have their patients participate in a perioperative ASA trial. Our survey identified the need for, and support of, a large randomized trial of perioperative ASA

among patients undergoing noncardiac surgery. Our recruitment rate in the POISE-2 Pilot demonstrates the feasibility of recruiting patients into a perioperative ASA trial.

1.2.11 Summary of why POISE-2 is needed now

Laboratory and physiology evidence suggests clonidine may minimize the risk of supply-demand mismatch and thrombus formation; perioperative trial evidence demonstrates clonidine prevents myocardial ischemia and suggests clonidine may prevent MI and mortality in both the short and intermediate-term. Perioperative trials also suggest low-dose clonidine does not result in hemodynamic instability, making an increase in stroke less likely. Despite this evidence, clonidine is uncommonly used in the perioperative setting. The need for a large adequately powered perioperative low-dose clonidine trial to settle the issue in a clear way that will drive subsequent practice is compelling.

Laboratory and physiological evidence suggests that ASA initiation or, for chronic users, ASA continuation may prevent major perioperative vascular events. The perioperative trial evidence suggests ASA may prevent mortality, but the effect on MI is unclear and the increased risk of bleeding is imprecise. There is overwhelming RCT evidence in the non-operative setting that ASA prevents death, MI, and, stroke. Observational data suggest that ASA discontinuation in the non-operative setting results in adverse thrombotic events. A perioperative carotid endarterectomy RCT of 2849 patients demonstrated improved outcomes with low-dose ASA compared to high-dose ASA. Our national survey demonstrates that perioperative ASA usage is variable, identifying the need for, and community interest in, a large perioperative low-dose ASA trial.

2.0 PLAN OF INVESTIGATION

2.1 Trial Objectives

2.1.1 Primary efficacy objectives

To determine the impact of low-dose clonidine versus placebo and low-dose ASA versus placebo on the 30-day risk of all-cause mortality or nonfatal MI in patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery.

2.1.2 Secondary efficacy objectives

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes at 30 days after randomization: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis.

2. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 30 days after randomization.

3. To determine in each ASA stratum the impact on a composite outcome of all-cause mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis at 30 days after randomization.

2.1.3 Safety objectives

1. To determine the impact of perioperative low-dose clonidine on each of the following individual outcomes at 30 days after randomization: stroke, clinically important hypotension, clinically important bradycardia, and congestive heart failure.

2. To determine the impact of perioperative low-dose ASA on each of the following individual outcomes at 30 days after randomization: stroke, life-threatening bleeding, and major bleeding.

2.1.4 One year follow-up objectives

1. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on all-cause mortality and nonfatal MI at 1 year after randomization.

2. To determine the impact of perioperative administration of low-dose clonidine and separately

low-dose ASA on the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 1 year after randomization.

3. To determine the impact of perioperative administration of low-dose clonidine and separately low-dose ASA on each of the following individual secondary outcomes at 1 year after randomization: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, and rehospitalization for vascular reason.

2.2 Trial Design

POISE-2 is an international RCT of 10,000 patients with, or at risk of, atherosclerotic disease who are undergoing noncardiac surgery. Utilizing a 2X2 factorial design, POISE-2 will determine the effect of low-dose clonidine versus placebo and low-dose ASA versus placebo in the perioperative setting. Patients, health care providers, data collectors, and outcome adjudicators will be blind to treatment allocation.

2.3 Sample Size

Our perioperative meta-analysis suggested that clonidine had an RR of 0.27 for mortality and 0.45 for MI, but the confidence intervals were wide. Given the multitude of pathogenic mechanisms associated with perioperative MI, it is only realistic to expect a moderate relative treatment effect[95] (as was the case in POISE-1).[5] Therefore, we assume clonidine will result in a HR of 0.75 for the primary outcome (all-cause mortality or nonfatal MI). Our perioperative meta-analysis suggested ASA had a RR of 0.85 for all-cause mortality and 1.31 for nonfatal MI, but the confidence intervals were wide. The MI data are inconsistent with the overwhelming evidence in the non-operative setting in which ASA results in a RR of 0.70 for MI.[70] Further, the observational ASA withdrawal data suggest an increased risk of thrombotic events with ASA discontinuation.[73] Therefore, we believe it is more probable that ASA will result in a moderate treatment effect consistent with a HR of 0.75 for the primary outcome.

Table 5 presents our sample size calculations. We used the control event rate for all-cause mortality and nonfatal MI in POISE-1 and adjusted this event rate accounting for the factorial design (i.e., both interventions will have a HR of 0.75), and this suggests a placebo event rate of 6.1%. Our sample size calculation also takes into account patients discontinuing their study drug. We will undertake a trial of at least 10,000 patients as this will provide 84% power if our event rate is 6.1% and 81% power if our event rate is 5.6% (2-sided alpha = 0.05).

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Patients are eligible if they:

1. are undergoing noncardiac surgery;
2. are ≥ 45 years of age;
3. are expected to require at least an overnight hospital admission after surgery; AND
4. fulfill ≥ 1 of the following 5 criteria:

A. history of coronary artery disease as defined by any one of the following 6 criteria

i. history of angina

ii. history of a myocardial infarction or acute coronary syndrome

iii. history of a segmental cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging

iv. history of a positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia

v. history of a coronary angiographic or CT coronary angiographic evidence of atherosclerotic stenosis ≥ 50% of the diameter of any coronary artery

vi. ECG with pathological Q waves in two contiguous leads

B. history of peripheral vascular disease as defined by a physician diagnosis of a current or prior history of any one of the following 4 criteria

i. intermittent claudication
ii. vascular surgery for atherosclerotic disease
iii. an ankle/arm systolic blood pressure ratio $\leq$ 0.90 in either leg at rest
iv. angiographic or doppler study demonstrating $\geq$ 70% stenosis in a noncardiac artery

C. history of stroke as defined by any one of the following 2 criteria
i. a physician diagnosis of stroke
ii. CT or MRI evidence of a prior stroke

D. undergoing major vascular surgery defined as all vascular surgery except arteriovenous shunt, vein stripping procedures, and carotid endarterectomies; OR

E. any 3 of 9 risk criteria
i. undergoing major surgery defined as intraperitoneal, intrathoracic, or major orthopedic surgery (i.e., hip arthroplasty, internal fixation of hip or femur, pelvic arthroplasty, knee arthroplasty, above-knee amputation or amputation below the knee but above the foot)
ii. history of congestive heart failure defined as a physician diagnosis of a current or prior episode of congestive heart failure OR prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema
iii. history of a transient ischemic attack;
iv. diabetes and currently taking an oral hypoglycemic agent or insulin;
v. age $\geq$ 70 years;
vi. hypertension;
vii. serum creatinine > 175 μmol/L (> 2.0 mg/dl);
viii. history of smoking within 2 years of surgery;
ix. undergoing emergent/urgent surgery defined as surgery that a surgeon schedules to go to the operating room within 48 hours of an acute presentation to the hospital

3.2 Exclusion Criteria

We will exclude patients meeting any of the following criteria:

1. consumption of ASA within 72 hours prior to surgery;
2. hypersensitivity or known allergy to ASA or clonidine;
3. systolic blood pressure < 105 mm Hg;
4. heart rate < 55 beats per minute 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 weeks;
7. intracranial hemorrhage (including subdural hematoma and parenchymal hematoma as a complication of primary ischemic stroke) documented by neuro-imaging, in the 6 months prior to randomization. This does not include petechial hemorrhagic transformation of a primary ischemic stroke;
8. subarachnoid hemorrhage or epidural hematoma unless the event occurred more than 6 months prior to randomization and the offending aneurysm or arterial lesion has been repaired;
9. drug-eluting coronary stent in the year prior to randomization;[96]
10. bare-metal coronary stent in the 6 weeks prior to randomization;[96]
11. currently taking an alpha-2 agonist, alpha methyldopa, reserpine, ticagrelor, or thienopyridine (e.g., clopidogrel, ticlopidine, prasugrel);
12. planned use – during the first 3 days after surgery – therapeutic dose anticoagulation (e.g., warfarin with a target INR $\geq$ 2.0, dabigatran > 250 mg/day, or rivaroxaban > 10 mg/day) or a therapeutic subcutaneous or intravenous antithrombotic agent (defined as full dose unfractionated heparin [i.e., > 15, 000 u/24hrs], low molecular weight heparin [i.e., > 6,000 u/24hrs or enoxaparin: > 60 mg/24hrs], or fondaparinux [i.e., > 2.5mg/24hrs];
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 POISE-2 Trial

4.0 PATIENT RECRUITMENT AND INFORMED CONSENT

We will utilize efficient recruitment strategies we developed in POISE-1. In the majority of centres, research personnel will screen the patient list in the preoperative assessment clinic to identify eligible patients. Research personnel will use a variety of screening approaches to capture patients who do not attend the preoperative assessment clinic, including screening: the daily surgical list in the operating room, patients on surgical wards and intensive care units, and patients in the preoperative holding area. Centres will also use all potential patient sources including asking the services of anesthesia, surgery, and medicine to page the study personnel regarding all surgical admissions through the emergency department and consultations for ward patients requiring surgery. Research personnel will approach all eligible patients to obtain informed consent. POISE-2 will enroll patients from approximately 150 centres in 16 countries.

5.0 RANDOMIZATION

Randomization will occur 2-4 hours prior to surgery for all eligible patients for whom informed consent is obtained. Research personnel will randomize patients via a 24-hour computerized randomization phone service at the coordinating centre at the Population Health Research Institution (PHRI) at the Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada. The randomization process will use block randomization stratified by centre. Study centre personnel will not know the block size. We will randomize patients in a 1:1:1:1 fashion to receive clonidine/ASA, clonidine/ASA placebo, clonidine placebo/ASA, or clonidine placebo/ ASA placebo. Patients in the ASA Continuation Stratum and ASA Starting Stratum will be evenly assigned to each of the 4 randomization groups. Approximately half the POISE-2 patients will come from each ASA stratum (i.e., we will ensure that each ASA stratum constitutes as least 45% of the overall trial population, as we were able to achieve in the POISE-2 Pilot).

6.0 ADMINISTRATION OF STUDY MEDICATION

Medical orders will include all drug administration protocols.

6.1 Clonidine or Placebo

Prior to surgery (goal 2-4 hours) patients fulfilling hemodynamic requirements (i.e., systolic blood pressure $\geq$ 105 mm Hg and a heart rate $\geq$ 55 bpm) will take 0.2 mg of oral clonidine or matching placebo and will have a transdermal clonidine (0.2 mg/day) or placebo patch applied to their upper arm or chest. The clonidine patch releases clonidine at a constant rate (0.2 mg/day) for 7 days. Patients will have the patch removed at 72 hours after surgery. No cases of clonidine withdrawal hypertension have been reported with transdermal clonidine, therefore we do not require a tapering process.[97]

Oral clonidine is absorbed rapidly and reaches peak serum concentrations within 2-4 hours and demonstrates physiological effects (e.g., a decrease in heart rate) within 1 hour; these effects persist for 24 hours.[98 99] Transdermal clonidine reaches peak serum concentrations at 48 hours after application, demonstrates physiological effects at 24 hours; after removal of the clonidine patch serum concentrations and physiological effects can persist for 2 -3 days.[100] Giving oral clonidine 2-4 hours before surgery will allow us to achieve physiological effects before surgery and these effects will persist for 24 hours. Applying the transdermal patch 2-4 hours before surgery will allow us to achieve physiological effects starting around the time the effects of the oral clonidine dose are resolving. This dosing regimen is consistent with a low-dose clonidine regimen (i.e., an effective dose < 0.3 mg/day).

6.2 ASA or Placebo

We will enrol patients in 1 of 2 ASA strata. The ASA Continuation Stratum will involve patients who are taking ASA chronically; we will randomize these patients to continue ASA or withdraw ASA and take a placebo. The ASA Starting Stratum will involve patients who are not taking ASA chronically; we will randomize these patients to start ASA or placebo. All patients will be randomized

on the day of surgery, and approximately half the POISE-2 patients will come from each ASA stratum, as supported by our prior research (i.e., POISE-2 Pilot). Patients in both ASA strata will receive the same trial ASA intervention (i.e., either ASA 100 mg or matching placebo). For the first dose prior to surgery (goal 2-4 hours) they will take 2 tablets orally. After the first dose, patients will take 1 tablet daily for 30 days in the Starting Stratum and 7 days in the Continuation Stratum, after which they will resume their regular ASA. Patients who are not able to take ASA orally will receive it rectally.

We will consider patients who have taken ASA daily for at least 1 month within a 6 week period prior to surgery to be on ASA chronically, and we will enrol these patients in the ASA Continuation Stratum. In this stratum, we will include patients who have had their ASA withheld sometime in the 2 weeks before surgery. No ASA is allowed for 72 hours prior to surgery (outside of the study drug), and if a patient has taken ASA in the 72 hours before surgery they are ineligible.

Our decision to allow patients to participate in the Continuation Stratum even if they have taken their ASA 73 hours prior to surgery was based upon the following 2 points. 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.[101 102] In patients treated with ASA it may take 10 days for the total platelet population to be renewed, and thus restore normal COX-1 activity. O'Brien has demonstrated, however, that abnormal platelet aggregation after ingestion of aspirin can be corrected ex vivo by 10% normal platelet rich plasma.[102] Further, it has been reported that if as little as 20% of platelets have normal COX-1 activity, hemostasis is normal.[103 104] Therefore stopping ASA for 72 hours is likely to ensure substantial (if not complete) recovery of platelet function. Second, in the ISIS-2 Trial that randomized 17,187 patients to ASA or placebo in the acute MI setting, they included patients who were taking ASA chronically even if they took ASA on the day of their MI.[72] There were 2266 patients in this subgroup, and it demonstrated a statistically significant reduction in vascular death, consistent with the overall finding.[72]

7.0 PLAN TO MINIMIZE RISKS AND MONITORING FOR AND APPROACH TO POTENTIAL PROBLEMS

Perioperative ASA may increase the risk of major bleeding. To minimize this risk, we are excluding patients with active peptic ulcer disease and patients undergoing intracranial or retinal surgery. Further, we are using low-dose ASA in POISE-2.

Multivariable analyses suggested that clinically important hypotension primarily caused the negative outcomes of death and stroke in POISE-1. Perioperative clonidine may result in clinically important hypotension, but we have incorporated many design features into POISE-2 to minimize this risk. In POISE-2 we require patients to have a SBP $\geq$ 105 mm Hg and a heart rate $\geq$ 55 beats per minute (bpm) to be eligible for the trial and to receive the clonidine study drug, whereas in POISE-1 patients received the study drug if they had a SBP $\geq$ 100 mm Hg and their heart rate was $\geq$ 50 bpm. We have also mandated more frequent monitoring of blood pressure and heart rate in POISE-2 (i.e., prior to study drug administration, 1 hour after administration, and Q 4 hours for the first 96 hours after surgery) compared to POISE-1 (i.e., we only required monitoring prior to and during administration of metoprolol). In POISE-2 we are using low-dose clonidine (i.e., < 0.3 mg/day) starting 2-4 hours prior to surgery and continuing for 72 hours after surgery. The POISE-2 Pilot and our systematic review provide encouraging evidence that low-dose clonidine does not induce clinically important hypotension.

Because non-study antihypertensive medications can also exacerbate the risk of clinically important hypotension we encourage the following approach for all POISE-2 patients:

1. Study personnel will tell POISE-2 patients who are taking an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) to not take any of these medications on the day of surgery. We have conducted a meta-analysis of the 3 RCTs that have randomized patients to either hold or continue their ACE-I or ARB on the day of surgery, Table 6.[105-107] Patients taking their ACE-I or ARB on the day of surgery demonstrated a higher risk of hypotension (RR 7.7; 95% CI, 3.4-17.2, I^2 0%).

2. Study personnel will tell POISE-2 patients who are taking any other anti-hypertensive medications to not take these medications on the morning of surgery but to take these medications to the preoperative surgical holding area.
3. In the preoperative surgical holding area (goal 2-4 hours prior to surgery) study personnel will check the patient's vital signs. Study personnel will convey the patient's hemodynamics to the anesthesiologist or surgeon managing the case and ask if they want the patient to receive any of their non-ACE-I/ARB anti-hypertensive medications and if yes at what dose.

Decisions regarding holding or discontinuing either study drug rest with the attending physician. If a patient develops clinically important hypotension or bradycardia, study personnel will encourage the attending physician to consider fluid resuscitation, administering an inotrope or vasopressor, withholding the patient's non-study antihypertensive medication(s), or if applicable changing the patient's epidural infusion rate. If the patient's clinically important hypotension or bradycardia persists despite these measures or if the patient requires ongoing inotrope or vasopressor administration, study personnel will encourage removal of the patient's clonidine patch. If a patient without a pacemaker develops asystole or a second or third degree heart block that does not quickly resolve and for which there is not a likely alternative explanation (e.g., metabolic abnormality) then study personnel will recommend that removal of the patient's clonidine patch.

If a patient experiences a life-threatening or major bleed, study personnel will recommend that the patient have their ASA trial medication held until the bleeding is stabilized. After the bleeding episode has resolved study personnel will ask the attending physician if they feel it is safe to restart the ASA trial medication.

8.0 OTHER MANAGEMENT AT THE DISCRETION OF THE ATTENDING PHYSICIAN

All aspects of the patient's management are at the discretion of the attending physician. This includes all decisions on antiplatelet, anticoagulation, and anti-ischemic therapies. We will encourage physicians not to prescribe an alpha-2 agonist during the first 4 days after surgery while the clonidine trial medication is likely having an effect (i.e., the first 3 days during administration of the clonidine patch and the 24 hours after removal of the patch when physiological effects are likely to persist). We will also encourage physicians not to prescribe antiplatelet therapy during the initial 7 days after surgery to patients in the ASA Continuation Stratum and for the initial 30 days after surgery to patients in the ASA Starting Stratum (i.e., periods when the patients will receive the ASA trial medication). If specific indications for an alpha-2 agonist or antiplatelet drug arise, the relevant trial medication can be stopped while an open label alpha-2 agonist or ASA is administered. Study personnel will document any open label usage of an alpha-2 agonist or ASA during the first 30 days after surgery.

9.0 FOLLOW-UP

Patient's will have a troponin (or CK-MB if troponin is not available) drawn 6 to 12 hours after surgery and on the first, second, and third days after surgery. Standard orders will dictate these tests are drawn. Standard orders will also ensure patients have an electrocardiogram (ECG) immediately after an elevated troponin is detected. Study personnel will recommend and attempt to obtain an echocardiogram on patients with an elevated troponin but no ECG changes, ischemic symptoms, or pulmonary edema.

Research personnel will follow patients throughout their time in hospital evaluating the patients and reviewing their medical records ensuring trial orders are followed and noting any outcomes. The research personnel will contact patients by phone at 30 days and 1 year after randomization. If patients indicate that they have experienced an outcome, study personnel will obtain the appropriate documentation.

10.0 TRIAL OUTCOMES

The overall primary outcome of the POISE-2 Trial is a composite of all-cause mortality and nonfatal MI at 30 days after randomization. A secondary outcome includes the composite of all-cause

mortality, nonfatal MI, and nonfatal stroke at 30 days after randomization. Individual secondary outcomes at 30 days after randomization include: all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, rehospitalization for vascular reasons, length of hospital stay, length of intensive care unit / cardiac care unit (ICU/CCU) stay, and new acute renal failure requiring dialysis. In each ASA stratum, we will also assess a composite outcome of all-cause mortality, nonfatal MI, cardiac revascularization procedure, nonfatal pulmonary emboli, and nonfatal deep venous thrombosis at 30 days after randomization. The safety outcomes in the ASA trial are stroke, congestive heart failure, life-threatening bleeding, and major bleeding at 30 days after randomization. The safety outcomes in the clonidine trial 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 all-cause mortality and nonfatal MI. A secondary outcome includes the composite of all-cause mortality, nonfatal MI, and nonfatal stroke at 1-year after randomization. Secondary 1-year follow-up outcomes include each of the following individual outcomes: all cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, stroke, pulmonary emboli, deep venous thrombosis, and rehospitalization for vascular reason. Appendix provides definitions for all outcomes.

11.0 ADJUDICATION OF TRIAL OUTCOMES

Outcome adjudicators (a committee of clinicians with expertise in perioperative outcomes) who are blinded to treatment allocation will adjudicate the following outcomes: death (vascular versus non-vascular), MI, nonfatal cardiac arrest, pulmonary emboli, deep venous thrombosis, stroke, life-threatening bleeding, and major bleeding. We will use the decisions of the outcome adjudicators for all statistical analyses of these events. Drs. Gordon Guyatt and Ganesan Karthikeyan will Co-chair the Adjudication Committee.

12.0 DATA ANALYSES

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.

12.1 Main Analyses

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 log-rank tests to compare the rate of occurrence of the primary outcome between the ASA versus ASA placebo group and separately the clonidine versus the clonidine placebo group. We will use Cox proportional hazards models to estimate the effect of clonidine, and of ASA, on the hazard ratio for the primary and secondary outcomes (with stratification according to whether treatment included the other agent). We will calculate the hazard ratios and their associated 95% confidence intervals. We will infer statistical significance if the computed 2-sided p-value is < 0.05. We anticipate that the treatment effect of clonidine and ASA, if present, will act independently, but we will, however, evaluate the possibility of synergism or antagonism by formally testing the interaction term in a Cox model.

12.2 Subgroup Analyses

Cox proportional hazards models assessing the primary outcome will provide the basis for evaluating the clonidine subgroup analyses (i.e. neuro-axial blockade, vascular surgery, and baseline risk according to number of eligibility criteria) and the ASA subgroup analyses (i.e. ASA stratum, diabetes, creatinine > 175 μmol/L, and baseline risk according to number of eligibility criteria). We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant at $P < 0.05$.

12.3 Interim Analyses

Three interim efficacy analyses based on the primary outcome will occur when 25%, 50% and

75% of the 30-day data are available. The External Safety and Efficacy and Monitoring Committee (ESEMC) will employ the modified Haybittle-Peto rule of 4 standard deviations (SDs) ($\alpha = 0.0001$) for analyses in the first half of the trial and 3 SDs ($\alpha = 0.00047$) for all analyses in the second half.[108 109] For a finding in favor of 1 or both active treatments to be considered significant, these predefined boundaries will have to be exceeded in at least 2 consecutive analyses, 3 or more months apart. The α-level for the final analysis will remain the conventional $\alpha = 0.05$ given the infrequent interim analyses, their extremely low α levels, and the requirement for confirmation with subsequent analyses.

The ESEMC will monitor for an adverse impact of clonidine on stroke or mortality, or ASA on stroke, life-threatening bleeding, or mortality. For these analyses, a 3 SDs excess in the first half and a 2.6 SDs excess in the second half of the trial would trigger discussions about stopping for harm.

At any time during the trial if safety concerns arise the ESEMC chairperson will assemble a formal meeting of the full committee. The ESEMC will make their recommendations to the Operations Committee after considering all the available data and any external data from relevant studies. If a recommendation for termination is being considered the ESEMC will invite the Operations Committee to explore all possibilities before a decision is made.

13.0 REPORTING SERIOUS ADVERSE EVENTS

We define serious adverse events (SAEs) as those which are fatal, life threatening or fulfill a definition of being clinically important. Efficacy or safety outcomes will not be considered as SAEs, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition. All events considered as part of the primary, secondary, or safety events (as outlined in section 10.0), should be reported on the appropriate page(s) in the case report forms (CRFs) but not as an SAE, unless considered exceptional in this medical condition.

In this trial, the following events (all-cause mortality, vascular mortality, MI, nonfatal cardiac arrest, cardiac revascularization procedure, pulmonary emboli, deep venous thrombosis, clinically important atrial fibrillation, congestive heart failure, stroke, rehospitalization for vascular reasons, life-threatening bleeding, major bleeding, clinically important hypotension, and clinically important bradycardia are considered related to the underlying cardiovascular disease and are not considered an SAE. These events will not be considered unexpected unless their course, severity or other specific features are such that the investigator, according to his/her best medical judgment, considers these events as exceptional in the context of the patient's medical condition.

Only unexpected and not previously described serious adverse events that are believed with a reasonable level of certainty to be associated with the trial medication need to be reported immediately (i.e. within 24 hours of knowledge of the event) to the Central Coordinating Office. For such events research personnel should complete an SAE CRF and immediately enter it into the iDatafax Database System or fax it to the Project Office, who will then inform the sponsor and the regulatory bodies.

14.0 TRIAL MANAGEMENT

14.1 What are the Arrangements for the Day to Day Management of the Trial?

Figure 2 illustrates the organizational structure of POISE-2 and Table 7 describes the trial timetable. The Population Health Research Institute (PHRI) Project Office, McMaster University, Hamilton, Canada is the coordinating center for this trial and is primarily responsible for the development of the trial protocol, organization of the trial, development of the randomization scheme, the trial database, data internal consistency checks, data analyses, and coordination of the trial centres. The POISE-2 Principal Investigator, Project Officer, Project Manager, and Coordinator are responsible for the activities of the Project Office. Dr. P.J. Devereaux is the Principal Investigator (PI), and he is responsible for the overall supervision of the trial. Dr. Devereaux was the Co-PI of the largest perioperative cardiac RCT (POISE-1), and he is the PI of the largest international perioperative vascular complications prospective cohort study (VISION). Dr. Marko Mrkobrada is the Project Officer, and he

is responsible for providing clinical support to the trial and providing guidance to the Trial Coordinator.

The Project Manager (Ms. Susan Chrolavicius) has extensive experience running large cardiovascular trials, and she will oversee the Trial Coordinator (Ms. Andrea Robinson) who has experience in large international trials. The POISE-2 Trial Coordinator is responsible for the daily conduct of the trial including supervising the data management assistant (who is responsible for data validation and quality); supplying centres with POISE-2 posters, pocket cards, and a detailed Manual of Operations that will outline each step of the protocol; producing and presenting to the Principal Investigator, Project Officer, and Project Manager: monthly reports on screening, patient follow-up, data transmission, consistency and thoroughness of data collection, and event rates; transmitting these reports to sites; develop and transmit to all trial investigators and research personnel weekly enrolment reports; monitoring and contacting any centres with high rates of eligible but not enrolled patients to discuss procedures and establish solutions to problems; communication with investigators and research personnel regarding protocol and other procedural questions; answer the project office's toll free phone number that investigators and trial personnel can call to resolve any problems or questions that arise; coordination of supplying study drug and aids; writing and distributing quarterly trial newsletters; maintenance of required documentation for regulatory agencies; review of all events prior to adjudication, compilation of all the records required for the adjudication process, coordination of the adjudication process, maintenance of the adjudication database; preparation of presentations to the trial committees; organization of Investigator Meetings, Project Office Operations Committee meetings, International Operations Committee meetings, Steering Committee meetings, Adjudication Committee meetings, External Safety and Efficacy and Monitoring Committee, Sub-study and Publications Committee meetings, and weekly project office meetings with the Principal Investigator and Project Officer.

14.2 Project Office Operations Committee and International Operations Committee

The project office is responsible for the day-to-day trial management and will report directly to the Project Office Operations Committee. This committee will consist of P.J. Devereaux, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Salim Yusuf, Gordon Guyatt, Janice Pogue, Dan Sessler, and Kristian Thorlund. The Project Office Operations Committee will meet monthly to review trial progress and all pertinent issues related to the conduct of POISE-2. The Project Office Operations Committee will report directly to the International Operations Committee. This committee will include broad international representation, and we may add members as the trial progresses. At the initiation of the POISE-2 Trial the International Operations Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, Kristian Thorlund, Ganesan Karthikeyan, Pablo Alonso-Coello, Colin Baigent, Otavio Berwanger, Bruce Biccard, Matthew Chan, Clara Chow, Christian Gluud, Claes Held, Michael Jacka, Giovanni Landoni, Kate Leslie, German Malaga, Paul Myles, Martin O'Donnell, Prem Pais, Dan Sessler, Wojciech Szczeklik, Juan Carlos Villar, Chew Wang, Jorn Wetterslev, and Denis Xavier. The International Operations Committee will hold confererence calls biannually and will review the progress of the trial, international POISE-2 issues, and strategies to ensure the successful conduct and completion of POISE-2.

14.3 The Steering Committee and National Principal Investigators

The International Operations Committee will report to the Steering Committee. We will hold an on-site meeting of the Steering Committee twice during the trial and annual conference calls. At these meetings the International Operations Committee will report to the Steering Committee regarding the overall progress of the trial and plans to ensure successful conduct and completion of POISE-2. For each participating country in POISE-2, the Project Office Operations Committee will appoint a member of the Steering Committee to act as the National Principal Investigator. At the Steering Committee Meetings each National Principal Investigator will provide a brief report to the Steering Committee

regarding the country's progress in POISE-2, goals for the coming year, and any issues that require input. The Steering Committee will include a broad international representation, and we may add members as the trial progresses. At the initiation of the POISE-2 Trial the Steering Committee consists of the following individuals: P.J. Devereaux, Salim Yusuf, Gordon Guyatt, Marko Mrkobrada, Susan Chrolavicius, Andrea Robinson, Janice Pogue, Kristian Thorlund, Ganesan Karthikeyan, Pablo Alonso-Coello, Sonia Anand, Andrew Auerbach, Colin Baigent, Scott Beattie, Otavio Berwanger, Mohit Bhandari, Bruce Biccard, Norm Buckley, Matthew Chan, Clara Chow, David Conen, Deborah Cook, Jim Douketis, John Eikelboom, Jim Eisenach, Amit Garg, Bill Ghali, Christian Gluud, Michelle Graham, Robert Hart, Claes Held, Michael Hill, Michael Jacka, Eric Jacobsohn, Clive Kearon, Andre Lamy, Giovanni Landoni, Kate Leslie, German Malaga, Finlay McAlister, Paul Myles, Peter Nagele, Martin O'Donnell, Prem Pais, Joel Parlow, Dan Sessler, Thomas Schricker, Marko Simunovic, Sadeesh Srinathan, Wojciech Szczeklik, Kevin Teoh, David Torres Perez, Gerard Urrutia, Juan Carlos Villar, Michael Walsh, Chew Wang, Jørn Wetterslev, Richard Whitlock, Duminda Wijeysundera, Denis Xavier, and Homer Yang.

14.4 Centre Principal Investigators

All participating centres will have a Centre Principal Investigator, and this individual is responsible for: (1) obtaining ethics approval from the institutional review board or the ethics board and forwarding this to the Project Office; (2) ensuring study approval is obtained before recruitment starts; (3) ensuring the protocol is followed; (4) ensuring all physicians and nurses involved in the perioperative care of patients undergoing non-cardiac surgery are aware and informed about the POISE-2 Trial (this will involve organizing and presenting educational in-services about the trial and distributing posters and pocket protocols); (5) ensuring that all surgical patients are screened for the trial; (6) ensuring that all enrolled patients have their troponins obtained and ECGs and echocardiograms when appropriate; (7) ensuring that all enrolled patients are followed appropriately; (8) ensuring that all Case Report Forms (CRFs) are promptly and accurately completed and submitted to the Project Office, and that all inquiries from the Project Office regarding patient forms or other matters are addressed promptly; (9) ensuring that a simple screening log is kept of all eligible noncardiac surgery patients who are not enrolled in the POISE-2 Trial and the primary reason they were not enrolled; (10) ensuring they maintain for at least 10 years after the publication of the main results, the list of patient identification numbers and patient names to enable identification of hospital records at a later date.

14.5 Sub-study and Publication Committee

The Project Office Operations Committee will appoint members to a Sub-study and Publication Committee. This committee will create guidelines for sub-studies and publications related to POISE-2. We will publish the main POISE-2 manuscript under group authorship, with the roles of all investigators acknowledged in an appendix. Subsequent publications will be authored by specific individuals on behalf of the POISE-2 Investigators. Individuals selected to lead the writing of these subsequent publications will depend on their role in and contribution to POISE-2, scientific interest, and scientific expertise.

15.0 OTHER CONSIDERATIONS

15.1 Ensuring Data Quality

Several procedures will ensure data quality including: 1) all research personnel will undergo a training session prior to trial commencement to ensure consistency in trial procedures including data collection and reporting; 2) all centres will have a detailed trial Manual of Operations that will outline each step of the protocol; 3) investigators can use a toll free phone number to a help line at the project office to resolve any problems or questions that arise; 4) the project office personnel will evaluate all data as soon as it is received and quality control checks will identify any errors or omissions; then the project office personnel will notify the sender of any such issues via secure internet, email, telephone, or visit if necessary; 5) the project office personnel will review detailed monthly reports on screening,

enrollment, patient follow-up, data transmission, consistency, thoroughness, and completeness of data collection (e.g., troponin measurements), and event rates, and they will immediately address any identified issues; and 6) the programmer will create internal validity and range checks using the Clinical iDataFax Database System which will identify any errors or omissions and notify the sender and data management assistants of any such issues; 7) the data management assistants will undertake multi-level data validation of the trial Case Report Forms; 8) the Trial Coordinator will (A) send investigators regular quality control reports; (B) obtain from the trial statistician and present to the principal investigator bi-monthly reports on internal validity and range checks using the iDataFax Database System; 9) the study statistician will undertake statistical monitoring every 6 months to identify outliers through (A) comparing centre and data collector variables (e.g., rates of reported primary outcomes), and (B) multivariate tests to examine associations of patient variables across hospitals and data collectors, and 10) we will undertake on-site monitoring at sites based upon the number of patients recruited and for any sites that stand out on statistical monitoring and an experienced monitor will audit a random selection of trial patients with and without a submitted primary outcome case report form.

15.2 Confidentiality and Blinding

All patient information will be stored on a high security computer system and kept strictly confidential. Only the ESEMC and the study statistician who reports to the ESEMC will be aware of the unblinded data until the trial is completed or a recommendation is made to terminate the trial.

15.3 Unblinding

Legitimate situations such as a large overdose of the study drug may require unblinding. We will avoid unblinding when appropriate through use of the following strategy. Prior to unblinding the attending physician will have to complete a detailed checklist to document the reason for unblinding and whether alternatives have been explored. Frequently stopping the study medication, skipping a dose, or giving open label medication will be adequate for the management of most situations. We recommend that all unblinding decisions be made jointly with the Project Office. If after these steps the local study investigator believes emergency unblinding is essential for the patient's management then it can be undertaken.

15.4 Patients Stopping Their Study Medication(s)

Patients can choose to stop their study medication(s) at any time during the course of the trial. Study Personnel will follow patients who make this decision in the same way that they follow all other trial participants. If a patient stops their study medication(s), the Centre Principal Investigator will discuss this decision with the patient. If after this discussion the trial participant decides they want to resume the trial medication(s) the Centre Principal Investigator will re-initiate the study medication(s) if they feel the study medication(s) can be safely restarted.

16.0 POTENTIAL SIGNIFICANCE OF POISE-2

Over 200 million adults annually undergo major noncardiac surgery and 3-5 million will suffer a major vascular complication. POISE-2 will answer two crucial management questions and influence future perioperative practices around the world.

17.0 REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008;372(9633):139-44.
2. Devereaux PJ, Chan M, Eikelboom J. Major vascular complications in patients undergoing noncardiac surgery: The magnitude of the problem, risk prediction, surveillance, and prevention. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. *Evidence based Cardiology*. 3rd ed. London, England: BMJ Books, 2009.
3. The Global HIV/AIDS pandemic, 2006. *MMWR Morb Mortal Wkly Rep* 2006;55(31):841-4.
4. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. *CMAJ* 2005;173(7):779-88.
5. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;371(9627):1839-47.
6. Levy M, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, et al. The prognostic value of post operative troponin and CK-MB measurements in patients undergoing noncardiac surgery: A systematic review and meta-analysis. *Submitted* 2009.
7. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92(3):657-71.
8. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J* 1983;50(2):127-34.
9. Horie T, Sekiguchi M, Hirosawa K. Coronary thrombosis in pathogenesis of acute myocardial infarction. Histopathological study of coronary arteries in 108 necropsied cases using serial section. *Br Heart J* 1978;40(2):153-61.
10. Sinapius D. [Relationship between coronary-artery thrombosis and myocardial infarction]. *Dtsch Med Wochenschr* 1972;97(12):443-8.
11. Chapman I. Relationships of recent coronary artery occlusion and acute myocardial infarction. *J Mt Sinai Hosp N Y* 1968;35(2):149-54.
12. Spain D. Pathologic spectrum of myocardial infarction. In: Likoff W, Segal B, Insull W, al. e, editors. *Atherosclerosis and Coronary Heart Disease*. New York: Grune & Stratton, 1972:133-139.
13. Davies MJ, Woolf N, Robertson WB. Pathology of acute myocardial infarction with particular reference to occulsive coronary thrombi. *British Heart Journal* 1976;38:659-664.
14. Landesberg G. The pathophysiology of perioperative myocardial infarction: facts and perspectives. *J Cardiothorac Vasc Anesth* 2003;17(1):90-100.
15. Chernow B, Alexander HR, Smallridge RC, Thompson WR, Cook D, Beardsley D, et al. Hormonal responses to graded surgical stress. *Arch Intern Med* 1987;147(7):1273-8.
16. Udelsman R, Norton JA, Jelenich SE, Goldstein DS, Linehan WM, Loriaux DL, et al. Responses of the hypothalamic-pituitary-adrenal and renin-angiotensin axes and the sympathetic system during controlled surgical and anesthetic stress. *J Clin Endocrinol Metab* 1987;64(5):986-94.
17. Clarke RS, Johnston H, Sheridan B. The influence of anaesthesia and surgery on plasma cortisol, insulin and free fatty acids. *Br J Anaesth* 1970;42(4):295-9.
18. Frank SM, Beattie C, Christopherson R, Norris EJ, Perler BA, Williams GM, et al. Unintentional hypothermia is associated with postoperative myocardial ischemia. The Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology* 1993;78(3):468-76.
19. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. *Int J Cardiol* 1996;57(1):37-44.

20. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol* 1999;8(3):133-9.
21. von Kanel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. *Eur J Haematol* 2000;65(6):357-69.
22. von Kanel R, Mills PJ, Ziegler MG, Dimsdale JE. Effect of beta2-adrenergic receptor functioning and increased norepinephrine on the hypercoagulable state with mental stress. *Am Heart J* 2002;144(1):68-72.
23. Yun AJ, Lee PY, Bazar KA. Can thromboembolism be the result, rather than the inciting cause, of acute vascular events such as stroke, pulmonary embolism, mesenteric ischemia, and venous thrombosis?: a maladaptation of the prehistoric trauma response. *Med Hypotheses* 2005;64(4):706-16.
24. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. *Br J Anaesth* 2004;93(1):9-20.
25. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005;173(6):627-34.
26. Ellis SG, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. *Am J Cardiol* 1996;77(12):1126-8.
27. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004;351(27):2795-804.
28. Muzi M, Goff DR, Kampine JP, Roerig DL, Ebert TJ. Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. *Anesthesiology* 1992;77(5):864-71.
29. Dorman T, Clarkson K, Rosenfeld BA, Shanholtz C, Lipsett PA, Breslow MJ. Effects of clonidine on prolonged postoperative sympathetic response. *Crit Care Med* 1997;25(7):1147-52.
30. Ellis JE, Drijvers G, Pedlow S, Laff SP, Sorrentino MJ, Foss JF, et al. Premedication with oral and transdermal clonidine provides safe and efficacious postoperative sympatholysis. *Anesth Analg* 1994;79(6):1133-40.
31. Wallace AW, Galindez D, Salahieh A, Layug EL, Lazo EA, Haratonik KA, et al. Effect of clonidine on cardiovascular morbidity and mortality after noncardiac surgery. *Anesthesiology* 2004;101(2):284-93.
32. Hidalgo MP, Auzani JA, Rumpel LC, Moreira NL, Jr., Cursino AW, Caumo W. The clinical effect of small oral clonidine doses on perioperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg* 2005;100(3):795-802, table of contents.
33. Quintin L, Bouilloc X, Butin E, Bayon MC, Brudon JR, Levron JC, et al. Clonidine for major vascular surgery in hypertensive patients: a double-blind, controlled, randomized study. *Anesth Analg* 1996;83(4):687-95.
34. Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987;67(1):3-10.
35. Kranke P, Eberhart LH, Roewer N, Tramer MR. Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002;94(2):453-60, table of contents.
36. Quintin L, Viale JP, Annat G, Hoen JP, Butin E, Cottet-Emard JM, et al. Oxygen uptake after major abdominal surgery: effect of clonidine. *Anesthesiology* 1991;74(2):236-41.
37. Nader ND, Ignatowski TA, Kurek CJ, Knight PR, Spengler RN. Clonidine suppresses plasma and cerebrospinal fluid concentrations of TNF-alpha during the perioperative period. *Anesth Analg* 2001;93(2):363-9 , 3rd contents page.
38. Wu CT, Jao SW, Borel CO, Yeh CC, Li CY, Lu CH, et al. The effect of epidural clonidine on perioperative cytokine response, postoperative pain, and bowel function in patients undergoing colorectal surgery. *Anesth Analg* 2004;99(2):502-9, table of contents.

39. Nishina K, Mikawa K, Uesugi T, Obara H, Maekawa M, Kamae I, et al. Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature. *Anesthesiology* 2002;96(2):323-9.
40. Pluskwa F, Bonnet F, Saada M, Macquin-Mavier I, Becquemin JP, Catoire P. Effects of clonidine on variation of arterial blood pressure and heart rate during carotid artery surgery. *J Cardiothorac Vasc Anesth* 1991;5(5):431-6.
41. Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. *Am J Med* 2003;114(9):742-52.
42. Guyatt G, Wyer P, Ioannidis J. Advanced topics in systematic reviews: When to believe a subgroup analysis. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. *Users' guides to the medical literature: A manual for evidence-based clinical practice*. 2nd ed. United States of America: The McGraw Hill Companies, Inc., 2008:571-593.
43. Oliver MF, Goldman L, Julian DG, Holme I. Effect of mivazerol on perioperative cardiac complications during non-cardiac surgery in patients with coronary heart disease: the European Mivazerol Trial (EMIT). *Anesthesiology* 1999;91(4):951-61.
44. Lemes ET, Van Der Fritz F, Homrich PHP, Stolz AP, De Freitas JCM, Felix Fortis EA. Preoperative intravenous clonidine in the surgical treatment of cataract: Evaluation of the clinical benefits. [Portuguese, English]. Revista Brasileira de Anestesiologia. *Sociedade Brasileira de Anestesiologia* 2008;58:342-353.
45. Mayson KV, Gofton EA, Chambers KG. Premedication with low dose oral clonidine does not enhance postoperative analgesia of intrathecal morphine. *Can J Anaesth* 2000;47(8):752-7.
46. Morris J, Acheson M, Reeves M, Myles PS. Effect of clonidine pre-medication on propofol requirements during lower extremity vascular surgery: a randomized controlled trial. *Br J Anaesth* 2005;95(2):183-8.
47. Sia S. I.v. clonidine prevents post-extradural shivering. *Br J Anaesth* 1998;81(2):145-6.
48. Stapelfeldt C, Lobo EP, Brown R, Talke PO. Intraoperative clonidine administration to neurosurgical patients. *Anesth Analg* 2005;100(1):226-32.
49. Owen MD, Fibuch EE, McQuillan R, Millington WR. Postoperative analgesia using a low-dose, oral-transdermal clonidine combination: lack of clinical efficacy. *J Clin Anesth* 1997;9(1):8-14.
50. Park J, Forrest J, Kolesar R, Bhola D, Beattie S, Chu C. Oral clonidine reduces postoperative PCA morphine requirements. *Can J Anaesth* 1996;43(9):900-6.
51. Parlow JL, Begou G, Sagnard P, Cottet-Emard JM, Levron JC, Annat G, et al. Cardiac baroreflex during the postoperative period in patients with hypertension: effect of clonidine. *Anesthesiology* 1999;90(3):681-92.
52. Takahashi H, Nishikawa T. Oral clonidine does not alter vecuronium neuromuscular blockade in anaesthetized patients. *Can J Anaesth* 1995;42(6):511-5.
53. Handa F, Tanaka M, Nishikawa T, Toyooka H. Effects of oral clonidine premedication on side effects of intravenous ketamine anesthesia: a randomized, double-blind, placebo-controlled study. *J Clin Anesth* 2000;12(1):19-24.
54. Pawlik MT, Hansen E, Waldhauser D, Selig C, Kuehnel TS. Clonidine premedication in patients with sleep apnea syndrome: a randomized, double-blind, placebo-controlled study. *Anesth Analg* 2005;101(5):1374-80.
55. Stuhmeier KD, Mainzer B, Cierpka J, Sandmann W, Tarnow J. Small, oral dose of clonidine reduces the incidence of intraoperative myocardial ischemia in patients having vascular surgery. *Anesthesiology* 1996;85(4):706-12.
56. De Deyne C, Struys M, Heylen R, De Jongh R, Van der Laenen M, Buyse L, et al. Influence of intravenous clonidine pretreatment on anesthetic requirements during bispectral EEG-guided sevoflurane anesthesia. *J Clin Anesth* 2000;12(1):52-7.

57. Schneemilch CE, Bachmann H, Ulrich A, Elwert R, Halloul Z, Hachenberg T. Clonidine decreases stress response in patients undergoing carotid endarterectomy under regional anesthesia: a prospective, randomized, double-blinded, placebo-controlled study. *Anesth Analg* 2006;103(2):297-302, table of contents.
58. Lipszyc M, Engelman E. Clonidine does not prevent myocardial ischemia during noncardiac surgery. *Anesthesiology* 1991;75(3A):A93.
59. Matot I, Sichel JY, Yofe V, Gozal Y. The effect of clonidine premedication on hemodynamic responses to microlaryngoscopy and rigid bronchoscopy. *Anesth Analg* 2000;91(4):828-33.
60. Fehr SB, Zalunardo MP, Seifert B, Rentsch KM, Rohling RG, Pasch T, et al. Clonidine decreases propofol requirements during anaesthesia: effect on bispectral index. *Br J Anaesth* 2001;86(5):627-32.
61. Rhee K, Kang K, Kim J, Jeon Y. Intravenous clonidine prolongs bupivacaine spinal anesthesia. *Acta Anaesthesiol Scand* 2003;47(8):1001-5.
62. Vanderstappen I, Vandermeersch E, Vanacker B, Mattheussen M, Herijgers P, Van Aken H. The effect of prophylactic clonidine on postoperative shivering. A large prospective double-blind study. *Anaesthesia* 1996;51(4):351-5.
63. Watanabe T, Inagaki Y, Ishibe Y. Clonidine premedication effects on inhaled induction with sevoflurane in adults: a prospective, double-blind, randomized study. *Acta Anaesthesiol Scand* 2006;50(2):180-7.
64. Bernard JM, Bourreli B, Hommeril JL, Pinaud M. Effects of oral clonidine premedication and postoperative i.v. infusion on haemodynamic and adrenergic responses during recovery from anaesthesia. *Acta Anaesthesiol Scand* 1991;35(1):54-9.
65. Bernard JM, Hommeril JL, Passuti N, Pinaud M. Postoperative analgesia by intravenous clonidine. *Anesthesiology* 1991;75(4):577-82.
66. Sarkar S, Acharya A, Pahari S. Effect of oral clonidine premedication on haemodynamic response to tourniquet deflation following epidural anaesthesia for lower extremity surgeries. *Indian J Anaesth* 2006;50(4):266-270.
67. Wright PM, Carabine UA, McClune S, Orr DA, Moore J. Preanaesthetic medication with clonidine. *Br J Anaesth* 1990;65(5):628-32.
68. Pouttu J, Scheinin B, Rosenberg PH, Viinamaki O, Scheinin M. Oral premedication with clonidine: effects on stress responses during general anaesthesia. *Acta Anaesthesiol Scand* 1987;31(8):730-4.
69. Eagle KA, Froehlich JB. Reducing cardiovascular risk in patients undergoing noncardiac surgery. *N Engl J Med* 1996;335(23):1761-3.
70. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324(7329):71-86.
71. Reilly IA, FitzGerald GA. Inhibition of thromboxane formation in vivo and ex vivo: implications for therapy with platelet inhibitory drugs. *Blood* 1987;69(1):180-6.
72. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;2(8607):349-60.
73. Biondi-Zoccai GG, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006;27(22):2667-74.
74. Naesh O, Friis JT, Hindberg I, Winther K. Platelet function in surgical stress. *Thromb Haemost* 1985;54(4):849-52.
75. Beving H, Zhao C, Albage A, Ivert T. Abnormally high platelet activity after discontinuation of acetylsalicylic acid treatment. *Blood Coagul Fibrinolysis* 1996;7(1):80-4.
76. Fatah K, Beving H, Albage A, Ivert T, Blomback M. Acetylsalicylic acid may protect the patient by increasing fibrin gel porosity. Is withdrawing of treatment harmful to the patient? *Eur Heart J*

1996;17(9):1362-6.
77. McDaniel MD, Pearce WH, Yao JS, Rossi EC, Fahey VA, Green D, et al. Sequential changes in coagulation and platelet function following femorotibial bypass. *J Vasc Surg* 1984;1(2):261-8.
78. Wood EH, Prentice CR, McGrouther DA, Sinclair J, McNicol GP. Trial of aspirin and RA 233 in prevention of post-operative deep vein thrombosis. *Thromb Diath Haemorrh* 1973;30(1):18-24.
79. Goldman M, McCollum C. A prospective randomized study to examine the effect of aspirin plus dipyridamole on the patency of prosthetic femoro-popliteal grafts. *Vascular Surgery* 1984;July/August:217-221.
80. Donaldson DR, Salter MCP, Kester RC, Rajah SM, Hall TJ, N. S, et al. The influence of platelet inhibition on the patency of femoro-popliteal Dacron bypass grafts. *Vascular Surgery* 1984;July/August:217-221.
81. Kretschmer G, Pratschner T, Prager M, Wenzl E, Polterauer P, Schemper M, et al. Antiplatelet treatment prolongs survival after carotid bifurcation endarterectomy. Analysis of the clinical series followed by a controlled trial. *Ann Surg* 1990;211(3):317-22.
82. McCollum C, Alexander C, Kenchington G, Franks PJ, Greenhalgh R. Antiplatelet drugs in femoropopliteal vein bypasses: a multicenter trial. *J Vasc Surg* 1991;13(1):150-61; discussion 161-2.
83. Lindblad B, Persson NH, Takolander R, Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. *Stroke* 1993;24(8):1125-8.
84. Nielsen JD, Holm-Nielsen A, Jespersen J, Vinther CC, Settgast IW, Gram J. The effect of low-dose acetylsalicylic acid on bleeding after transurethral prostatectomy--a prospective, randomized, double-blind, placebo-controlled study. *Scand J Urol Nephrol* 2000;34(3):194-8.
85. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355(9212):1295-302.
86. Findlay JM, Lougheed WM, Gentili F, Walker PM, Glynn MF, Houle S. Effect of perioperative platelet inhibition on postcarotid endarterectomy mural thrombus formation. Results of a prospective randomized controlled trial using aspirin and dipyridamole in humans. *J Neurosurg* 1985;63(5):693-8.
87. Tytgat SH, Laman DM, Rijken AM, Klicks R, Voorwinde A, Ultee JM, et al. Emboli rate during and early after carotid endarterectomy after a single preoperative dose of 120 mg acetylsalicylic acid--a prospective double-blind placebo controlled randomised trial. *Eur J Vasc Endovasc Surg* 2005;29(2):156-61.
88. Renney JT, O'Sullivan EF, Burke PF. Prevention of postoperative deep vein thrombosis with dipyridamole and aspirin. *Br Med J* 1976;1(6016):992-4.
89. Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. *N Engl J Med* 1977;297(23):1246-9.
90. McKenna R, Galante J, Bachmann F, Wallace DL, Kaushal PS, Meredith P. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. *Br Med J* 1980;280(6213):514-7.
91. Alfaro MJ, Paramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thromb Haemost* 1986;56(1):53-6.
92. Green RM, Roedersheimer LR, DeWeese JA. Effects of aspirin and dipyridamole on expanded polytetrafluoroethylene graft patency. *Surgery* 1982;92(6):1016-26.
93. Taylor DW, Barnett HJ, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. *Lancet* 1999;353(9171):2179-84.
94. Hiralal R, Guyatt G, Bhandari M, Cook D, Berwanger O, de Beer J, et al. A survey of evaluating surgeons' perioperative usage of acetyl-salicylic acid (ASA) and their willingness to enrol their patients

in a perioperative ASA randomized controlled trial. *Submitted* 2009.
95. Devereaux PJ, Yusuf S, Yang H, Choi PT, Guyatt GH. Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? *CMAJ* 2004;171(3):245-7.
96. Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):299S-339S.
97. Lowenthal DT, Saris S, Paran E, Cristal N, Sharif K, Bies C, et al. Efficacy of clonidine as transdermal therapeutic system: the international clinical trial experience. *Am Heart J* 1986;112(4):893-900.
98. Pettinger WA. Pharmacology of clonidine. *J Cardiovasc Pharmacol* 1980;2 Suppl 1:S21-8.
99. Lowenthal DT. Pharmacokinetics of clonidine. *J Cardiovasc Pharmacol* 1980;2 Suppl 1:S29-37.
100. Langley MS, Heel RC. Transdermal clonidine: A preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs* 1988;35:123-142.
101. Cerskus AL, Ali M, Davies BJ, McDonald JW. Possible significance of small numbers of functional platelets in a population of aspirin-treated platelets in vitro and in vivo. *Thromb Res* 1980;18(3-4):389-97.
102. O'Brien JR. Effects of salicylates on human platelets. *Lancet* 1968;1(7546):779-83.
103. Bradlow BA, Chetty N. Dosage frequency for suppression of platelet function by low dose aspirin therapy. *Thromb Res* 1982;27(1):99-110.
104. Patrono C, Ciabattoni G, Patrignani P, Pugliese F, Filabozzi P, Catella F, et al. Clinical pharmacology of platelet cyclooxygenase inhibition. *Circulation* 1985;72(6):1177-84.
105. Schirmer U, Schurmann W. [Preoperative administration of angiotensin-converting enzyme inhibitors]. *Anaesthesist* 2007;56(6):557-61.
106. Bertrand M, Godet G, Meersschaert K, Brun L, Salcedo E, Coriat P. Should the angiotensin II antagonists be discontinued before surgery? *Anesth Analg* 2001;92(1):26-30.
107. Coriat P, Richer C, Douraki T, Gomez C, Hendricks K, Giudicelli JF, et al. Influence of chronic angiotensin-converting enzyme inhibition on anesthetic induction. *Anesthesiology* 1994;81(2):299-307.
108. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971;44(526):793-7.
109. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976;34(6):585-612.

TABLE 1: POISE-2 Pilot results*

Outcome	Clonidine (N=30)	Clonidine Placebo (N=30)	ASA (N=30)	ASA Placebo (N=30)
Death	0	0	0	0
MI	0	2	1	1
Stroke	1	0	1	0
Cardiac arrest	0	1	1	0
Clinically significant hypotension	6	10	9	7
Clinically significant bradycardia	4	2	6	2
Bleeding	8	10	9	9
CHF	0	1	1	0

* Data from the first 60 patients included in the pilot; CHF = congestive heart failure

TABLE 2: Meta-analysis of trials evaluating perioperative clonidine

Outcome	Trial	Clonidine group n/N	Control group n/N	Relative risk	95% CI	I^2
Mortality						
	Ellis[30]	0/30	1/31	0.34	0.01 to 8.13	
	Wallace[31]	1/125	4/65	0.13	0.01 to 1.14	
	Quintin[33]	0/11	1/10	0.31	0.01 to 6.74	
	Stuhmeier[55]	1/145	2/152	0.52	0.05 to 5.72	
	Total	**2/311**	**8/258**	**0.27**	**0.07 to 0.99**	**0%**
Myocardial infarction						
	Ellis[30]	0/30	2/31	0.21	0.01 to 4.13	
	Wallace[31]	5/125	3/65	0.87	0.21 to 3.51	
	Stuhmeier[55]	0/145	4/152	0.12	0.01 to 2.14	
	POISE-2 Pilot*	0/30	2/30	0.20	0.01 to 4.00	
	Total	**5/330**	**11/278**	**0.45**	**0.15 to 1.33**	**0%**
Nonfatal cardiac arrest						
	Ellis[30]	0/30	1/31	0.34	0.01 to 8.13	
	POISE-2 Pilot*	0/30	1/30	0.33	0.01 to 7.87	

	Total	**0/60**	**2/61**	**0.34**	**0.04 to 3.17**	**0%**
Stroke					
	Wallace[31]	1/125	0/65	1.57	0.06 to 38.04	
	Schneemilch[57]	0/40	5/40	0.09	0.01 to 1.59	
	POISE-2 Pilot*	1/30	0/30	3.00	0.13 to 70.83	
	Total	**2/195**	**5/135**	**0.69**	**0.07 to 6.37**	**37%**
Congestive heart failure					
	Ellis[30]	4/30	5/31	0.83	0.25 to 2.79	
	Wallace[31]	0/125	2/65	0.10	0.01 to 2.15	
	POISE-2 Pilot*	0/30	1/30	0.33	0.01 to 7.87	
	Total	**4/185**	**8/126**	**0.58**	**0.20 to 1.67**	**0%**
Myocardial ischemia					
	Ellis[30]	7/30	8/31	0.90	0.37 to 2.18	
	Wallace[31]	18/125	20/65	0.47	0.27 to 0.82	
	Morris[46]	4/21	4/18	0.86	0.25 to 2.95	
	Pawlik[54]	0/15	1/15	0.33	0.01 to 7.58	
	Stuhmeier[55]	35/145	59/152	0.62	0.44 to 0.88	
	Lipszyc[58]	8/20	5/20	1.60	0.63 to 4.05	

Matot[59]	0/18	2/18	0.20	0.01 to 3.89	
Total	**72/374**	**99/319**	**0.66**	**0.49 to 0.89**	**8%**

* = POISE-2 Pilot results after recruitment of 60 patients

TABLE 3: Meta-analysis of perioperative clonidine trials, clinically important hypotension results

Outcome and Subgroup	Trial	Outcome definition	Clonidine group n/N	Control group n/N	Relative risk	95% CI	I^2
Clinically important hypotension							
Low-dose clonidine (< 0.3mg/day)							
	Nader[37]	MAP 20% lower than baseline BP	2/7	2/8	1.14	0.21 to 6.11	
	Lemes[44]	MAP < 60 mmHg or 30% lower than baseline BP	1/33	0/35	3.18	0.13 to 75.33	
	Mayson[45]	SBP 25% lower than baseline BP	18/24	13/19	1.10	0.75 to 1.61	
	Morris[46]	MAP 20% lower than baseline BP	5/21	3/18	1.43	0.40 to 5.17	
	Sia[47]	SBP 20% lower than baseline BP	4/50	3/50	1.33	0.31 to 5.65	
	Stapelfeldt[48]	SBP < 90 mmHg	15/17	12/17	1.25	0.88 to 1.78	
	Stuhmeier[55]	MAP < 70 mmHg	20/145	26/152	0.81	0.47-1.38	
	Schneemilch[57]	MAP 20% lower than basline BP and treated with cafedrine/theoadrenaline	19/40	5/40	3.80	1.57 to 9.18	
	Fehr[60]	MAP < 50mmHg or >20% drop from pre-induction value	10/25	10/25	1.00	0.51 to 1.97	
	Rhee[61]	MAP 30% lower than baseline BP	5/52	1/26	2.50	0.31 to 20.31	

	Vanderstappen[62]	MAP 20% lower than preinduction value treated with ephedrine	4/140	2/140	2.00	0.37-10.74
	Watanabe[63]	SBP < 90mmHg	8/22	4/20	1.82	0.65-5.12
	POISE-2 Pilot*	SBP < 90 mm Hg that required an intra-aortic balloon pump, inotropic agent, fluid resuscitation, or study drug discontinuation	6/30	10/30	0.60	0.25 to 1.44
	Subtotal		**117/606**	**91/580**	**1.19**	**0.95 to 1.49** **12%**
High-dose clonidine (≥ 0.3mg/day)						
	Ellis[30]	SBP < 90 mmHg, unresponsive to fluid challenge	2/30	3/31	0.69	0.12 to 3.84
	Wallace[31]	SBP < 80mmHg lasting ≥ 5 minutes	24/125	11/65	1.13	0.59-2.17
	Quintin[33]	DBP < 90mmHg lasting more than 3 minutes intraoperatively or more than 5 minutes postoperatively	5/11	2/10	2.27	0.56 to 9.20
	Pluskwa[40]	SBP < 100 mmHg lasting more than 3 minutes	12/14	8/15	1.61	0.96 to 2.70
	Owen[49]	MAP 20% lower than baseline BP	14/15	4/14	3.27	1.41 to 7.56
	Park[50]	SBP < 90 mmHg	8/22	2/22	4.00	0.95 to 16.75
	Parlow[51]	SBP < 90 mmHg	2/10	0/10	5.00	0.27 to 92.62
	Takahasi[52]	SBP < 80mmHg	17/21	5/17	2.75	1.28 to 5.92

	Matot[59]	Intraprocedural drop in SBP more than 30% from preinduction value or absolute SBP < 90mmHg	2/18	0/18	5.00	0.26 to 97.37	
	Bernard[64]	MAP < 60mmHg	2/16	0/16	5.00	0.26 to 96.59	
	Bernard[65]	MAP $\leq$ 60mmHg	3/25	0/25	7.00	0.38 to 128.87	
	Sarkar[66]	SBP < 80mmHg and treated with ephedrine	2/22	1/21	1.91	0.19 to 19.52	
	Wright[67]	SBP < 80mmHg	14/30	0/30	29.00	1.81-465.07	
	Subtotal		**107/359**	**36/294**	**2.13**	**1.47 to 3.09**	**18%**
All trials (i.e., both low and high-dose)							
	Total		**231/1031**	**132/941**	**1.51**	**1.20 to 1.91**	**31%**

OR = odds ratio; SBP = systolic blood pressure; MAP = mean arterial blood pressure; BP = blood pressure; DBP = diastolic blood pressure; * = POISE-2 Pilot results after recruitment of 60 patients

TABLE 4: Meta-analysis of perioperative ASA trials

Outcome	Trial	ASA group n/N	Control group n/N	Relative risk	95% CI	I^2
Mortality						
	Wood[78]	2/9	2/9	1.00	0.18 to 5.63	
	Goldman[79]	0/22	2/31	0.28	0.01 to 5.53	
	Donaldson[80]	4/33	0/32	8.74	0.49 to 155.96	
	Kretschmer[81]	4/32	11/34	0.39	0.14 to 1.09	
	McCollum[82]	40/286	46/263	0.80	0.54 to 1.18	
	Lindblad[83]	1/117	5/115	0.20	0.02 to 1.66	
	Nielsen[84]	1/26	0/27	3.11	0.13 to 73.09	
	PEP Trial[85]	456/8726	472/8718	0.97	0.85 to 1.09	
	Total	**508/9251**	**538/9229**	**0.85**	**0.63 to 1.14**	**24%**
Vascular mortality						
	Wood[78]	0/9	1/9	0.33	0.02 to 7.24	
	Donaldson[80]	4/33	0/32	8.74	0.49 to 155.96	
	Kretschmer[81]	1/32	10/34	0.11	0.01 to 0.78	
	McCollum[82]	15/286	31/263	0.44	0.25 to 0.81	
	Lindblad[83]	0/117	5/115	0.09	0.00 to 1.60	

	Nielsen[84]	1/26	0/27	3.11	0.13 to 73.09	
	PEP Trial[85]	243/8726	263/8718	0.92	0.78 to 1.10	
	Total	**264/9229**	**310/9198**	**0.59**	**0.28 to 1.25**	**61%**
Nonfatal myocardial infarction						
	McCollum[82]	14/286	14/263	0.92	0.45 to 1.89	
	Nielsen[84]	0/26	1/27	0.35	0.01 to 8.12	
	PEP Trial[85]	43/8726	27/8718	1.59	0.98 to 2.57	
	POISE-2 Pilot	1/31	1/29	0.94	0.06 to 14.27	
	Total	**58/9069**	**43/9037**	**1.31**	**0.88 to 1.94**	**0%**
Nonfatal stroke						
	Findlay[86]	0/10	2/12	0.24	0.01 to 4.42	
	Kretschmer[81]	1/32	2/34	0.53	0.05 to 5.58	
	McCollum[82]	13/286	17/263	0.70	0.35 to 1.42	
	Lindblad[83]	5/117	7/115	0.70	0.23 to 2.15	
	PEP Trial[85]	37/8726	34/8718	1.09	0.68 to 1.73	
	Tytgat[87]	3/50	3/50	1.00	0.21 to 4.72	
	POISE-2 Pilot	1/31	0/29	2.81	0.12 to 66.40	
	Total	**60/9252**	**65/9221**	**0.91**	**0.64 to 1.29**	**0%**

Nonfatal pulmonary embolism					
	Wood[78]	0/9	1/9	0.33	0.02 to 7.24
	Renney[88]	1/85	1/75	0.88	0.06 to 13.86
	Harris[89]	0/44	1/51	0.39	0.02 to 9.22
	McKenna[90]	1/9	3/12	0.44	0.05 to 3.60
	Alfaro[91]	0/30	1/30	0.33	0.01 to 7.87
	PEP Trial[85]	36/8726	46/8718	0.78	0.51 to 1.21
	Total	**38/8903**	**53/8895**	**0.74**	**0.49 to 1.11** **0%**
Major bleeding					
	McKenna[90]	1/9	0/12	3.90	0.18 to 85.93
	Green[92]	1/75	0/88	3.51	0.15 to 84.98
	McCollum[82]	18/286	9/263	1.84	0.84 to 4.02
	Lindblad[83]	2/117	1/115	1.97	0.18 to 21.38
	Nielsen[84]	1/26	2/27	0.52	0.05 to 5.39
	PEP Trial[85]	182/8726	122/8718	1.49	1.19 to 1.87
	POISE-2 pilot	9/31	9/29	0.94	0.43 to 2.03
	Total	**214/9270**	**143/9252**	**1.47**	**1.19 to 1.80** **0%**

TABLE 5: Sample size calculations

Primary Outcome (all-cause mortality or nonfatal MI at 30 days)			**Power (2-sided α = 0.05)**		
Control event rate	**% of patients not receiving or prematurely discontinuing study drug ***	**Hazard Ratio**	**N = 9000**	**N=10,000**	**N=11,000**
5.6%	10%	0.75	76.9%	81.1%	84.6%
6.1%	10%	0.75	80.3%	84.3%	87.5%

* Based on POISE-2 Pilot among patients discontinuing clonidine prematurely the discontinuation rate was 80% on the first day and 20% on the second day.

TABLE 6: Meta-analysis of trials evaluating preoperative management of ACE-I and ARB medications

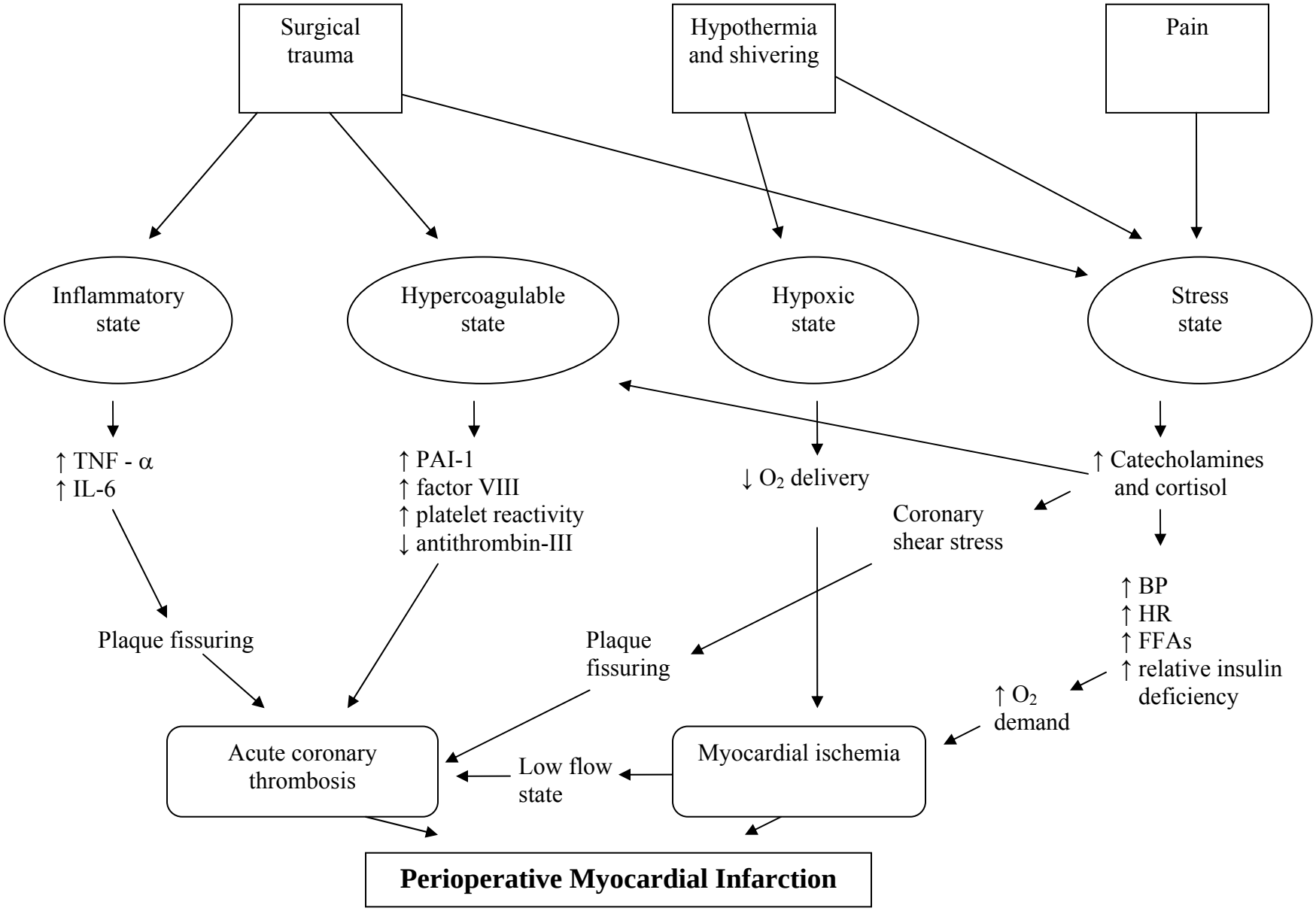
Hypotension						
Trial	**Trial Definition of Intraoperative Hypotension**	**ACE-I/ARB in Immediate Preoperative Period n/N**	**Control group n/N**	**Relative risk**	**95% CI**	**I^2**
Schirmer[105]	Mean arterial blood pressure <60 mmHg	17/50	5/50	4.6	1.6 to 13.8	
Bertrand[106]	Systolic blood pressure <80 mmHg longer then 1 minute	19/19	12/18	20.3	1.05 to 392.5	
Coriat[107]	Systolic blood pressure <90 mmHg	16/21	6/30	12.8	3.34 to 49.1	
Total		**52/90**	**23/98**	**7.7**	**3.4 to 17.2**	**0%**

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

TABLE 7: POISE-2 trial timeline

Phase	Time (months)	Tasks
1 (planning)	6	1. Meeting of investigators for discussion of protocol and finalization of procedures 2. Translation of the protocol into non-English languages 3. Development of all study aids 4. Study approval by local ethics committee 5. Health Canada Approval and regulatory approval in other countries 6. Drug packaging and kit preparation, 7. Development of randomization sequence 8. Shipping trial materials 9. Ensure local teams are ready to start recruitment to avoid delays during recruitment phase
2 (recruitment)	36	Recruitment of 10,000 patients
3 (short-term follow-up)	1	All patients are actively followed for 1 month including all patients enrolled at the end of the recruitment phase
4 (completion of short-term study)	6	1. Data clean-up 2. Confirmation and classification of events 3. Data analysis 4. Publication of primary and secondary results
5 (long-term follow-up)	5	All patients are actively followed for 1 year.
6 (completion of long-term study)	6	1. Data analysis 2. Publication of primary and secondary results

FIGURE 1: Physiological changes that occur with surgery and how they may result in a myocardial infarction

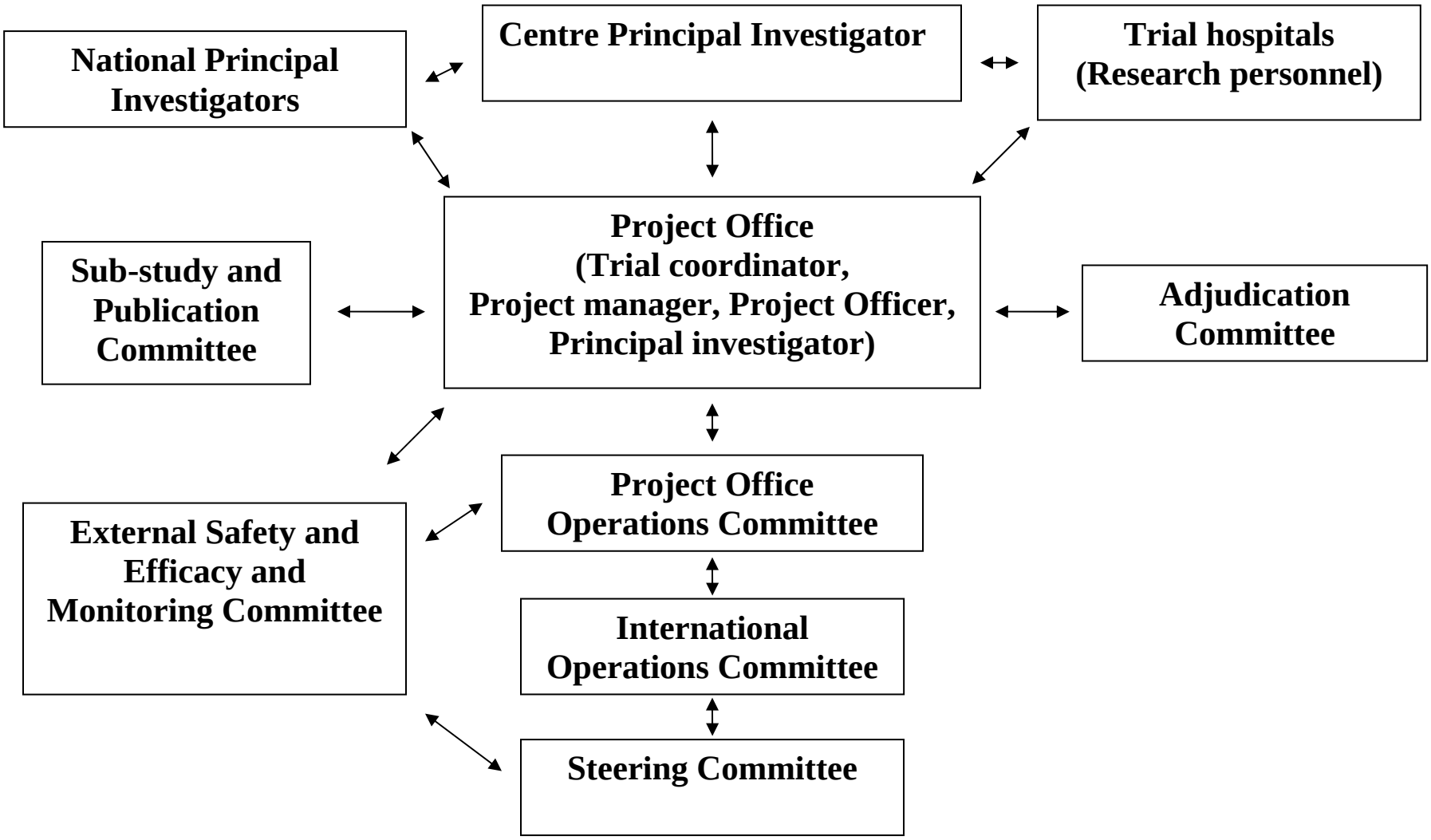


LEGEND

Figure 1: Physiological changes that occur with surgery and how they may result in a myocardial infarction

TNF-α = tumor necrosis factor α, IL-1 = interleukin-1, IL-6 = interleukin-6, CRP = C-reactive protein, PAI-1 = plasminogen activator inhibitor -1, O_2 = oxygen, BP = blood pressure, HR = heart rate, FFAs = free fatty acids

FIGURE 2: POISE-2 Organizational Structure



APPENDIX: POISE-2 outcome definitions

1. 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).

2.0 Myocardial infarction

The diagnosis of MI 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 (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 $\geq$ 30 milliseconds

    C. ECG changes indicative of ischemia (i.e., ST segment elevation [$\geq$ 2 mm in leads V_1, V_2, or V_3 OR $\geq$ 1 mm in the other leads], ST segment depression [$\geq$ 1 mm], or symmetric inversion of T waves $\geq$ 1 mm) in at least two contiguous leads

    D. coronary artery intervention (i.e., PCI or CABG surgery)

    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
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

3. 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.

4. Cardiac Revascularization Procedures

Cardiac revascularization procedures include PCI and CABG surgery.

5. 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.

6. Pulmonary embolus (PE)

The diagnosis of PE 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
4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following:

    A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan

    B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan

7. Deep venous thrombosis (DVT) of leg or arm

The diagnosis of DVT 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

3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography

8. 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.

9. Re-hospitalization for Vascular Reasons

Re-hospitalization for vascular reasons is defined as re-hospitalization for MI, 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.

10. Life-threatening bleeding

Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

11. Major bleeding

Major bleeding is defined as bleeding that is not specified under "life- threatening bleeding" above, and results in a postoperative hemoglobin ≤ 70 g/L and the patient receiving a transfusion of ≥ 2 units of red blood cells; results in a hemoglobin drop of ≥ 50 g/L and the patient receiving a transfusion of ≥ 2 units of red blood cells; results in the patient receiving a transfusion of ≥ 4 units of red blood cells within a 24 hour period; leads to one of the following interventions (i.e., embolization, superficial vascular repair, nasal packing); OR is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

12. Clinically important hypotension

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.

13. Clinically important bradycardia

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

15. 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).

16. New acute renal failure requiring dialysis

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