The Poise Study

PeriOperative ISchemic Evaluation study

A large, simple trial of metoprolol versus placebo in patients undergoing noncardiac surgery at moderate and high risk of a perioperative cardiac event

An International Collaborative Initiative

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Study Flow Chart

Study Overview

Patients undergoing noncardiac surgery and:
1. age ≥ 45
2. expected length of hospital stay ≥ 24 hours
3. Atherosclerotic cardiovascular disease or high risk for coronary artery disease

Informed Consent

RANDOMIZATION

Blinded

Metoprolol
PO or IV x 30 days

Placebo
PO or IV x 30 days

Short term follow-up
30 days

Short term follow-up
30 days

Long term follow-up*

Long term follow-up*

*Mechanisms and duration of long term follow-up will vary by country. For countries with central tracking of deaths and hospitalizations, 1 to 2 years (mean 1.5 years) of patient follow-up is envisaged. In other locations a minimum of 1 year of follow-up is required.
| **Title**               | The POISE Study  
A large, simple trial of metoprolol versus placebo in patients undergoing noncardiac surgery at moderate and high risk of a perioperative cardiac event |
|------------------------|------------------------------------------------|
| **Project Office**     | Canadian Cardiovascular Collaboration  
McMaster University, HGH McMaster Clinic, 237 Barton Street East, Hamilton, Ontario L8L 2X2, CANADA |
| **Study Size**         | 10,000 patients |
| **Study Design**       | Multicentre randomized controlled trial of:  
Metoprolol vs placebo: blinded |
| **Primary Objective**  | To determine the impact of perioperative administration of metoprolol on cardiovascular events (defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal cardiac arrest) at 30 days in moderate and high risk patients (defined as patients with atherosclerotic cardiovascular disease or high risk of coronary artery disease) undergoing noncardiac surgery. |
| **Secondary Objective**| To determine the impact on cardiovascular events at 1 year |
| **Inclusion Criteria** | Patients undergoing noncardiac surgery are eligible if they:  
1. are \( \geq 45 \) years of age  
2. have an expected postoperative length of stay \( \geq 24 \) hours for surgical reasons; AND  
3. fulfill any one of the following 6 criteria  
   A. coronary artery disease  
   B. peripheral vascular disease  
   C. history of stroke due to atherothrombotic disease  
   D. hospitalization for congestive heart failure within 3 years of randomization  
   E. undergoing major vascular surgery; OR  
   F. any 3 of the following 7 criteria: scheduled for high risk surgery (i.e. intraperitoneal or intrathoracic), emergency/urgent surgery, any history of congestive heart failure, history of a transient ischemic attack (TIA), diabetes and currently on an oral hypoglycemic agent or insulin therapy, preoperative serum creatinine > 175 \( \mu \text{mol/L} \) (> 2.0 mg/dl), or age > 70 years |
| **Treatment Regimen**  | Metoprolol or matching placebo starting preoperatively and continuing for 30 days |
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1. INTRODUCTION AND RATIONALE

Noncardiac surgery is associated with significant cardiac morbidity and mortality. There exists strong biologic rationale, promising observational data on physiological outcomes, and preliminary clinical trial data suggesting that beta-blockers may prevent perioperative cardiac events in the short term (i.e. first 30 postoperative days) and perhaps long term (i.e. 6-12 months postoperatively). We are undertaking a large simple multicentre randomized controlled trial (RCT) to definitively evaluate the short and long term efficacy of perioperative metoprolol (a selective β1-adrenergic receptor antagonist) versus placebo on major cardiac events in moderate and high risk patients undergoing noncardiac surgery.

1.1 Magnitude of the problem and current practice patterns

Perioperative cardiac events frequently complicate noncardiac surgery resulting in significant morbidity, mortality, and cost.\(^1\) In 1990, approximately 25 million Americans underwent noncardiac surgery, of whom 7 to 8 million had or were at risk of coronary artery disease.\(^2\) Up to 1 million of these patients had a perioperative cardiac complication, resulting in $20 billion in costs.

Despite the magnitude of this problem, few studies have evaluated interventions to lower perioperative cardiac risk.\(^3\) A recent Canadian study assessing consultants’ perioperative cardiac drug recommendations demonstrated important variations in practice that may affect patient outcomes.\(^4\) This study also demonstrated that preoperative consultants infrequently recommended starting perioperative beta-blockers (i.e. 2.5%) and the overall incidence of perioperative beta-blocker usage was low at 11%.\(^4\) Until clear evidence from well designed adequately powered RCTs is available,
these variations in practice patterns are likely to persist because clinicians remain uncertain as to which approaches are beneficial.

1.2 Physiological changes with noncardiac surgery

Patients undergoing major noncardiac surgery enter a state of high physiological stress marked by a rise in epinephrine, norepinephrine, and cortisol. These factors increase perioperative heart rates and hence myocardial oxygen demands. Several studies have demonstrated an association between tachycardia and perioperative ischemia.

Free fatty acids also rise during major noncardiac surgery. Myocardial oxygen demand increases with rising concentrations of free fatty acids, as they require aerobic metabolism. Free fatty acids in the setting of myocardial ischemia damage myocardial cell membranes and cause calcium overload and arrhythmias. Thus the net effect of increasing free fatty acid levels in the perioperative period is one of increased oxygen demands and direct toxicity to ischemic myocardial cells.

1.3 Beta-blockers cause potentially beneficial changes in surgical patients

Beta-blockers reduce adrenergic activity resulting in reduced free fatty acid levels, and this results in a shift in myocardial metabolism away from free fatty acids towards glucose, and hence decreased oxygen demand. Beta-blockers decrease enzyme leakage, free fatty acid uptake, and lactate production in isolated hearts subjected to experimental ischemia. Beta-blockers also improve glucose utilization, and mitochondria and microvasculature preservation.
Two cohort studies suggest perioperative beta-blockers reduce perioperative heart rates in patients undergoing vascular surgery, and six small RCTs have demonstrated decreased perioperative heart rates with beta-blocker administration.

Eight RCTs have assessed the effectiveness of perioperative beta-blockers to prevent perioperative ischemia. Most studies had blinded evaluators assess holter monitor recordings and defined perioperative ischemia as 1mm of ST depression for > 1 minute. Figure 1 demonstrates the meta-analysis plot for these studies. In total 712 patients were randomized and a moderate number of patients had ischemic events (72 control patients versus 37 beta-blocker patients, OR 0.33, 95% CI 0.17-0.63). Despite the limitation of only a moderate number of events, this statistically significant result provides encouraging evidence that perioperative beta-blockers prevent perioperative ischemia.

1.4 Beta-blockers may reduce the short term risk of perioperative cardiac events

Ten small RCTs have evaluated the effects of perioperative beta-blockers in patients undergoing noncardiac surgery. In total 855 patients (467 beta-blocker, 388 placebo) were randomized. There were very few clinically important events in these studies (i.e. only 20 deaths of which 15 were cardiac, and 18 nonfatal myocardial infarctions). The follow-up for the short term events ranged from immediately post surgery until 30 days post surgery. Figure 2 demonstrates there were very few deaths (8 in the beta-blocker arm and 12 in the placebo arm) and a non-significant P value. Figures 3 and 4 demonstrate that there were 15 cardiac deaths (3 in the beta-blocker arm and 12 in the placebo arm) and a non-significant P value. Figures 5 and 6 demonstrate 18 nonfatal myocardial infarctions (2 in the beta-blocker arm and 16 in
the placebo arm) a difference on the border of conventional levels of statistical significance. Although promising, these apparent beneficial trends are untrustworthy because of the potential for publication biases, wide confidence intervals, and the fact that the majority of the data are derived from a single study (i.e. Poldermans’ study) of highly selected individuals.25

Poldermans et al evaluated the efficacy of bisoprolol (a selective β₁-adrenergic receptor antagonist) in preventing perioperative cardiac death and nonfatal myocardial infarction in a highly select group of patients with a positive dobutamine echocardiography study undergoing elective vascular surgery.25 The rate of death or myocardial infarction in the control group was unusually high, at 34%. This small unblinded study of 112 patients reported a 91% relative risk reduction (RRR) for the combined outcome of cardiac death and nonfatal myocardial infarction, 80% for cardiac death and 100% for nonfatal myocardial infarction. As a result of these findings the safety committee stopped the study early after the planned interim analysis. However, the number of events in this trial was small, the control event rate unusually high, and the impact unexpectedly large. These considerations raise concerns as to the reliability of the findings of the study. Furthermore, early termination may inflate estimates of benefit.

There are a number of reasons why the results of the meta-analysis of available trials warrant cautious interpretation. The total number of events is very small, and the majority of these events are derived from Poldermans’ RCT. Several large trials of beta-blockers after myocardial infarction,14,32 have shown a moderate benefit (25% RRR) suggesting that the very large RRRs seen in Polderman’s study are implausible. Furthermore, when initial small studies show remarkably large benefits, subsequent trials
tend to demonstrate a much more modest – or even an absent – treatment effect.\textsuperscript{33,34} For example, a meta-analysis of RCTs of magnesium in acute myocardial infarction demonstrated a statistically significant 50% reduction in death with approximately 1000 patients randomized and a moderate number of deaths (i.e. 128) (p<0.001), figure 7.\textsuperscript{33} However, when the larger study was completed there was no benefit; in fact there was a trend toward excess mortality with magnesium (p=0.07).\textsuperscript{34}

1.5 **Perioperative beta-blockers may reduce the long term risk of cardiac events**

If short term perioperative beta-blocker use prevents subsequent postoperative mortality during long term follow-up, the mechanism may be related to decreasing perioperative ischemia. Eagle has hypothesized that perioperative ischemia results in unstable coronary plaques that are prone to fissuring weeks to months later, resulting in cardiac events (e.g. myocardial infarction and cardiac death).\textsuperscript{35} As shown above beta-blockers decrease perioperative ischemia. Eagle’s hypothesis, if correct, would explain how beta-blockers might, even after their discontinuation, affect postoperative cardiac events.

**Table 1** summarizes the three studies that have assessed the association between perioperative ischemia and long term cardiac outcomes.\textsuperscript{24,36,37}
Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Study description</th>
<th>F/U(^a) duration</th>
<th>Definition of myocardial ischemia</th>
<th>Association between perioperative ischemia and long term cardiac outcomes</th>
</tr>
</thead>
</table>
| Wallace\(^24\) | A substudy of Mangano’s RCT\(^27\) which evaluated the holter results of 200 patients | 2 years             | \(\geq 1\) mm of ST depression Or \(\geq 2\) mm of ST elevation lasting \(\geq 1\) minute            | Predictor of death during 2yrs post-discharge<br>Predictor<br>RR (95%CI)<br>Ischemia day 0-2 post-op<br>Incidence of myocardial ischemia<br>Days post-op | atenolol control Pvalue
| Pasternack\(^36\) | 385 vascular surgery patients with continual perioperative ECG monitoring        | 1.7 years           | \(\geq 1\) mm of downsloping ST depression. Group 1 – patients who had \(\geq 1\)% of perioperative monitoring demonstrating silent ischemia Group 2 – patients who had <1% | Actuarial freedom at 2 yrs<br>Outcome<br>Late MI\(^\|^\) 90.7% 98.4%<br>Late 89.5% 99.2% <0.001 Cardiac Death<br>In multivariate regression only total perioperative time ischemic \(\geq 1\)% and age were significant predictors for these outcomes |
| Mangano\(^37\) | 444 consecutive patients with or at high risk of CAD*, D/C\(^^\) home post-op stable. Patients had perioperative holter | 2 years             | \(\geq 1\) mm of ST depression Or \(\geq 2\) mm of ST elevation lasting \(\geq 1\) minute            | Predictor of cardiac events during 2 years post discharge<br>Perioperative predictors<br>MII\(^\|^\) or U/A\(^^\) 20 (7.5-53) .0001 Cardiac ischemia 2.2 (1.1-4) .03 |

\(^a\)F/U – follow-up<br>\(^\|^\)MI – myocardial infarction<br>\(^\|^\)U/A – unstable angina

These studies demonstrate an association between perioperative ischemia and long term cardiac outcomes. In two of the studies the association persisted after taking...
into account the known predictors of long term cardiac outcomes in multivariate analyses.\textsuperscript{36,37} The survival curves from these studies for the patients with perioperative ischemia and the patients without perioperative ischemia showed continued divergence even up to 2 years after surgery. These findings suggest the possibility that prevention of perioperative ischemia through use of a beta-blocker may result in a decrease in long term cardiac events.

One RCT of 200 patients has evaluated the long term effects of perioperative beta-blocker administration.\textsuperscript{27} In this study, Mangano and colleagues administered atenolol or placebo for a maximum duration of 7 postoperative days. Although Mangano’s data demonstrated little difference in mortality during the first 7 postoperative days (i.e. 4 deaths in the atenolol group and 2 deaths in the placebo group) there was an apparent difference in mortality rates between groups in the first six months post hospital discharge (i.e. and 8% absolute risk difference), followed by an additional absolute risk difference of 3% between the groups during the second six months post hospital discharge. If the events that occurred during the initial 7 postoperative days, when patients were receiving the study drug, are included in the analyses the findings are no longer statistically significant (i.e. 2 year mortality rate 13% in the atenolol group and 23% in the placebo group, P value = 0.07).\textsuperscript{38} These data highlight the need for further data to definitively establish if perioperative beta-blockers can prevent cardiac events both during the early phase and long term follow-up.

1.6 Summary of background and rationale

The real short and long term benefits of perioperative beta-blocker use are likely to be more modest than that suggested by the small perioperative studies discussed. A
more realistic and plausible estimate of any potential benefit is a relative risk reduction of 20-25%. However, the currently available trials provide the impetus for a large, adequately powered definitive trial.

1.7 Need for information on a broader population and the risk-benefit ratio

The available RCTs are too small to provide strong inferences regarding the intervention’s impact on perioperative cardiovascular death, nonfatal myocardial infarction, or nonfatal cardiac arrest in moderate and high risk patients undergoing noncardiac surgery. A large trial would also allow evaluation of the potential risks associated with perioperative beta-blockers (congestive heart failure, clinically significant bradycardia, and hypotension). A trial with broad simple entry criteria, that includes moderate and high risk patients undergoing all types of noncardiac surgeries, would ensure feasibility, rapid recruitment, and results that are widely generalizable. A trial primarily targeted at evaluating the impact on major clinical outcomes can be very simple, which in turn makes a large study practical. Therefore, a simple large RCT to address the short and long term efficacy of perioperative beta-blockers in moderate and high risk patients undergoing noncardiac surgery would best address unanswered and crucial questions about beta-blockers effectiveness in preventing major ischemic events in patients undergoing noncardiac surgery.

1.8 Investigational drug

In this study we will use IV metoprolol and oral metoprolol controlled release (CR). The dissolution and absorption properties of metoprolol CR result in stable plasma concentrations with minimum fluctuations over a 24-hour period. Two large RCTs have evaluated metoprolol CR. The metoprolol CR randomised intervention trial in
congestive heart failure (MERIT-HF) study evaluated metoprolol CR in 3991 patients with chronic heart failure and demonstrated a decrease in total mortality with no major safety concerns.\textsuperscript{40} Over 10,000 patients with acute myocardial infarction have been randomized in the Second Chinese Cardiac Study (CCS-2), a study evaluating metoprolol CR or placebo in the setting of acute myocardial infarction.\textsuperscript{41} Early experience from the first 10,000 participants have confirmed the safety of metoprolol CR (personnel communication with Dr. Zheng-Ming Chen)

2. PLAN OF INVESTIGATION

2.1 Study objectives

Primary Efficacy Objectives:

1. To determine the impact of perioperative administration of metoprolol (a selective $\beta_1$-adrenergic receptor antagonist) on 30 day risk of cardiovascular events (defined as cardiovascular death, nonfatal myocardial infarction or nonfatal cardiac arrest) in moderate and high risk patients (i.e. patients with atherosclerotic cardiovascular disease or patients at high risk for coronary artery disease) undergoing noncardiac surgery.

Secondary Efficacy Objectives:

1. To determine the impact of perioperative administration of metoprolol on the long term (minimum of 1 year of follow-up) risk of total mortality, cardiovascular death and nonfatal myocardial infarction.

2. To determine the effect of perioperative metoprolol on the length of hospital stay and length of ICU/CCU stay.
3. To determine the effect of perioperative metoprolol on the 30 day risk of clinically significant atrial fibrillation, rehospitalization for cardiac reasons, nonfatal myocardial infarction, nonfatal cardiac arrest, cardiovascular death, and total mortality, and the need for revascularization procedures (i.e. coronary artery bypass surgery and percutaneous transluminal coronary angioplasty).

Safety Objectives:

1. To determine the impact of metoprolol on the 30 day risk of congestive heart failure.
2. To determine the impact of metoprolol on the 30 day risk of clinically significant bradycardia (i.e. bradycardia requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation).
3. To determine the impact of metoprolol on the 30 day risk of clinically significant hypotension (i.e. systolic blood pressure < 90 mm Hg requiring fluid resuscitation, intraaortic balloon pump, an inotropic agent, or study drug discontinuation).

2.2 Study design

This is a randomized controlled trial of metoprolol versus placebo in 10,000 moderate and high risk patients undergoing non-cardiac surgery. Participants, health care providers, data collectors, and judicial assessors of outcomes (i.e. the individuals who ultimately decide whether or not a patient meets criteria for the outcome being evaluated) will be blind to whether patients receive metoprolol or placebo.

2.3 Sample size and study power for the 30 day follow-up

Several large studies using multivariate analysis have demonstrated that patients with coronary artery disease have a high risk of perioperative cardiac events. Most recently, Gilbert et al. prospectively evaluated 2035 patients undergoing non-cardiac
surgery in Canada\textsuperscript{43} and found that patients with angina and an expected length of hospital stay greater than 24 hours had a 6.6\% event rate of perioperative cardiac death and nonfatal myocardial infarction (data courtesy of Dr. Gilbert).

Patients undergoing major vascular surgery are at high risk of perioperative cardiac events.\textsuperscript{3} The metoprolol after vascular surgery (MaVS) study is an RCT designed to evaluate the effect of metoprolol to decrease a broad composite outcome (cardiac death, nonfatal myocardial infarction, unstable angina, new congestive heart failure, and dysrhythmias requiring treatment like atrial fibrillation) in patients undergoing major vascular surgery. This study has randomized 400 patients and there has been a 7\% event rate of perioperative cardiac death and nonfatal myocardial infarction (data courtesy of Dr. Yang). Likewise, due to the strong correlation between peripheral vascular disease and coronary artery disease,\textsuperscript{3} patients with a history of peripheral vascular disease undergoing other noncardiac surgeries have a high risk of perioperative cardiac events.\textsuperscript{3} Frequently, the extent of coronary artery disease is not appreciated in patients with peripheral vascular disease as their claudication masks their coronary artery disease by limiting their exercise capacity.\textsuperscript{3}

Several large studies have identified congestive heart failure as an independent predictor of perioperative cardiac outcomes.\textsuperscript{42} The majority of patients with a history of congestive heart failure have underlying coronary artery disease.\textsuperscript{44} Likewise patients with a history of stroke have a high likelihood of coronary artery disease.

Several risk indices exist for predicting perioperative cardiac events.\textsuperscript{45,46,47,48} Using published data from these indices and unpublished data (courtesy of Dr. Goldman), from the revised cardiac risk index,\textsuperscript{48} we would anticipate patients at high risk for
coronary artery disease as indicated by any three of seven risk factors (high-risk type of surgery [i.e. intrathoracic or intraperitoneal], emergency/urgent surgery, any history of congestive heart failure, history of a transient ischemic attack (TIA), diabetes and currently on an oral hypoglycemic agent or insulin therapy, preoperative serum creatinine >175 µmol/L (> 2.0 mg/dl), or age > 70 years) will have an expected rate of cardiac death, nonfatal MI, or nonfatal cardiac arrest of at least 5.3% during their hospitalization.

Data from our screening study suggests that 25% of the POISE patients will be eligible as a result of 3 of the 7 risk factors and that 75% of the patients will be eligible based on one of the other criteria. Therefore, we anticipate a 6% event rate in the control arm at 30 days.

We propose to target a sample size of 10,000 patients, which will have 90% power to detect a 25 relative risk reduction (RRR) for the primary outcome with an $\alpha = 0.05$ (two-sided), anticipating a 6% event rate in the control arm Table 2.

**Table 2:** Sample size calculations for 30-day follow-up

<table>
<thead>
<tr>
<th>Primary Study Outcome: cardiac death, nonfatal MI, nonfatal cardiac arrest</th>
<th>Total number of patients (2-sided $\alpha = 0.05$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo event rate = 6% at 30 days follow-up postoperatively</td>
<td></td>
</tr>
<tr>
<td><strong>Control event rate</strong></td>
<td><strong>Treatment event rate</strong></td>
</tr>
<tr>
<td>6%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

These considerations suggest that a trial of 8000 – 10,000 patients will have high power to detect a 25% RRR in the primary outcome.
3. ELIGIBILITY CRITERIA

3.1 Inclusion criteria

All patients undergoing non-cardiac surgery are eligible if they:

1. are $\geq 45$ years of age

2. have an expected postoperative length of stay $\geq 24$ hours for surgical reasons (i.e. NOT for social reasons as with a patient living out of town); AND

3. fulfill any one of the following 6 criteria:

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

      i. history of angina

      ii. prior myocardial infarction

      iii. prior positive exercise stress test

      iv. prior documentation of cardiac ischemia on nuclear stress testing

      v. prior coronary artery angiographic evidence of atherosclerotic stenosis $>50\%$ of vessel diameter

      vi. ECG with pathological Q waves in two contiguous leads

   B. peripheral vascular disease as defined by any one of the following 3 criteria

      i. Intermittent claudication (i.e. leg pain on walking that disappears in $< 10$ minutes on standing) that is known or likely to be due to atherosclerotic disease

      ii. An ankle/arm systolic blood pressure ratio $\leq 0.90$ in either leg at rest

      iii. Angiographic or doppler study demonstrating $> 70\%$ stenosis
C. history of stroke (i.e. focal neurological deficit that persisted for at least 1 week after onset) thought due to atherothrombotic disease (i.e. NOT a lacunar stroke, hemorrhagic stroke, nor embolic stroke secondary to atrial fibrillation)

D. hospitalization for congestive heart failure within 3 years of randomization

E. undergoing major vascular surgery (i.e. vascular surgery excluding arteriovenous shunts for dialysis, vein stripping procedures, and carotid endarterectomies); OR

F. any 3 of the following 7 risk factors
   i. high-risk type of surgery (i.e. intrathoracic or intraperitoneal)
   ii. any history of congestive heart failure
   iii. diabetes and currently on an oral hypoglycemic agent or insulin therapy
   iv. preoperative serum creatinine >175 µmol/L (> 2.0 mg/dl)
   v. age > 70 years
   vi. history of a transient ischemic attack (TIA) (i.e. a transient focal neurological deficit that lasted less than 24 hours and thought to be vascular in origin)
   vii. emergency/urgent surgery (i.e. surgery which must be undertaken within 24 hours of acute presentation to hospital)

3.2 Exclusion criteria

1. contraindication to metoprolol including any of the following: significant bradycardia (heart rate < 50 beats per minute); second or third degree heart block without a pacemaker; asthma that has been active within the last decade (i.e. a
clinical diagnosis of asthma and use of regular inhaled steroids, or beta agonists at least once per week over the period of a month, any time in the last ten years); and a history of COPD with bronchospasm on pulmonary function tests (i.e. an increase in FEV1 ≥ 12% and of at least 200 ml, 15 minutes after inhalation of a beta 2 – agonist).

2. clinical plan to use a beta-blocker preoperatively or during the first 30 postoperative days

3. prior adverse reaction to a beta-blocker

4. CABG surgery with complete revascularization in the preceding 5 years and no evidence of cardiac ischemia since the CABG surgery

5. patients undergoing low risk surgical procedures (e.g. transurethral procedures [transurethral prostatectomies (TURPs), stone baskets, etc], ophthalmologic procedures under topical or regional anesthesia [cornea transplants, cataract surgery, etc], and surgeries with limited physiological stresses [digital re-implantation, nerve repairs, etc] )

6. concurrent use of verapamil; OR

7. prior enrollment in this trial

4. PATIENT RECRUITMENT AND INFORMED CONSENT

We will recruit patients through multiple mechanisms. These will include but not be restricted to preoperative assessment clinics, physicians’ clinics, emergency rooms, and hospital wards. Once a patient has been identified and their eligibility confirmed written informed consent will be obtained.
5. RANDOMIZATION

5.1 Procedures for randomization

Patients will be randomized by phoning the study coordinating center. A computer generated random number list will be used at the study coordinating center to randomize patients. Randomization will be stratified by center. All patient randomized are irrevocably in the study and will be followed and analyzed in the group to which they are allocated regardless of whether or not they receive the assigned treatment or fulfill the eligibility criteria. We will therefore randomize patients as close to the time of surgery as possible to avoid randomizing patients who subsequently have surgery postponed/cancelled or develop an event prior to surgery.

5.2 Baseline variables

Prior to surgery the following information will be obtained from each study participant and recorded on the Randomization Case Report Form: age, type of surgery, history of coronary artery disease, risk factors for coronary artery disease, history of CABG surgery, history of congestive heart failure, history of TIA or stroke, history of peripheral vascular disease, history of asthma, history of COPD with documented reactive airway disease, history of renal failure, cardiac medications, any history of adverse reactions to beta-blockers, heart rate, and blood pressure.
6. ADMINISTRATION OF STUDY MEDICATION

Medical orders will include all drug administration protocols.

6.1 Metoprolol or placebo

Four to two hours prior to surgery patients will take their first dose of oral metoprolol or placebo. This first dose will be metoprolol CR 100 mg (i.e. one half of a 200 mg tablet) or half a placebo tablet.

At anytime during the first 6 postoperative hours if the patient’s heart rate is $\geq 80$ beats per minute (bpm) and their systolic blood pressure (SBP) $\geq 100$ mm Hg they will immediately receive the second dose of the study drug. Patients able to take medications orally will take metoprolol CR 100 mg (i.e. one half of a 200 mg tablet) or half a placebo tablet. Patients who are not able to take medications orally will receive IV metoprolol or IV placebo by slow infusion or IV push. The slow infusion will be run in over a 1 hour period and will consist of 15 mg of metoprolol or placebo in a minibag of Normal Saline. Alternatively, the first dose can be 5 mg of metoprolol or placebo administered by IV push (i.e. injected over a 2 minute period). This IV push dose will be administered every five minutes for a maximum of three doses if the patient’s systolic blood pressure (SBP) is $\geq 100$ mm Hg and their heart rate is $\geq 50$ beats per minute (bpm) at the end of each five minute interval.

Patients who did not receive a dose of the study drug during the first 6 postoperative hours will receive their second dose of the study medication at 6 hours post surgery if they fulfill the standard SBP and heart rate requirements listed below. Patients able to take medications orally will take metoprolol CR 100 mg (i.e. one half of a 200 mg tablet) or half a placebo tablet. Patients who are not able to take medications orally will
receive IV metoprolol or IV placebo by slow infusion or IV push, as described above. The IV metoprolol will be administered every 6 hours until a patient is able to switch back to oral medications. Starting on the morning of the first day after surgery, and each day thereafter for 30 days, patients who are able to take the study medication orally will take metoprolol CR 200 mg (i.e. one tablet) or one placebo tablet.

7. MONITORING AND DOSE ADJUSTMENTS TO STUDY MEDICATION

7.1 Metoprolol/placebo

The patient’s heart rate and systolic blood pressure will be documented prior to giving metoprolol or placebo. For both the oral and IV formulation if the patient’s SBP is ≥ 100 mm Hg and their heart rate is ≥ 50 bpm the study medication will be administered.

For the oral formulation if the heart rate is consistently below 45 bpm or SBP < 100 the metoprolol dose will be held and the subsequent dosages will be halved (i.e. metoprolol CR 100 mg or matching placebo). If a heart rate is 45-49 and the SBP ≥ 100 the patient will have their dose held for 12 hours.

For patients receiving the slow IV formulation the patient’s SBP and heart rate will be documented 10 minutes after commencing the infusion and when half the IV formulation has been administered (i.e. 30 minutes into the infusion) and at the end of the infusion (i.e. 60 minutes after starting the infusion). If the patient’s SBP < 100 mm Hg OR their heart rate is < 50 bpm the infusion will be immediately stopped. If the patient should have their IV dose stopped during an infusion for a SBP is < 100 mm Hg OR their heart rate is < 50 bpm their subsequent IV doses will be 10 mg of metoprolol or placebo.
If at any time a patient is suspected to be in congestive heart failure or bronchospasm they will have their study medication held until the attending physician decides if it is safe to continue. Physicians are encouraged to restart the study medication after congestive heart failure has resolved and the dose for oral metoprolol will be half the prior dose (i.e. metoprolol CR 100 mg or matching placebo) and the IV dose will be decreased to 10 mg of metoprolol or placebo.

If a patient develops first degree AV block with a PR interval > 0.30 seconds or second or third degree AV block the study drug should be held. Once the attending physician feels it is safe to restart the study medication the dose for oral metoprolol should be half the prior dose (i.e. metoprolol CR 100 mg or matching placebo) and the IV dose will be decreased to 10 mg of metoprolol or placebo.

Physicians are encouraged to restart the study medication after a dose has been held for hypotension or bradycardia at the doses indicated above once these signs have resolved. The clinical and study staffs are encouraged to discuss any adverse events prior to discontinuation of the study medication.

8. OTHER MANAGEMENT AT THE DISCRETION OF THE TREATING PHYSICIAN

Outside of the study medication all decisions surrounding drug utilization will be at the discretion of the attending physician, including decisions on antiplatelet therapy, anticoagulation therapy, and other antiischemic therapies. We will encourage physicians not to prescribe beta-blocker therapy during the initial 30 postoperative days when the study medication is being administered. If however, specific indications for beta-blocker
therapy arise, the study medications can be stopped and open label beta-blockers can be instituted. Any open label usage of beta-blocker therapy during the first 30 postoperative days will be documented.

8.1 Approach to potential complications

Medical management of any complications that arise is at the discretion of the treating physician. The following recommendations for management of potential perioperative complications are for their consideration.

If a patient develops first degree AV block with a PR interval > 0.30 seconds the study medication should be withheld until the PR interval corrects. Likewise if second or third degree AV block occurs the study medication should be withheld until the block resolves or a permanent pacemaker is inserted. We encourage the physicians, in both of these situations, to restart the study drug, at the lower dosage recommended above, once the PR interval has corrected or the second or third degree block has resolved, especially if there was concomitant usage of another AV blocking drug that can be discontinued or the patient gets a permanent pacemaker.

If a patient develops rapid atrial fibrillation and the physician wants to use a beta-blocker as the rate controlling drug the study medication can be held and an open label beta-blocker can be administered. We encourage physicians to stop the open label beta-blocker and restart the study drug once the atrial fibrillation has resolved or the rate has been controlled with digoxin or cardizem.

If a patient develops bronchospasm we recommend holding the study medication and immediate use of a beta 2-agonist. If the bronchospasm resolves quickly with a beta 2-agonist or the diagnosis of bronchospasm is uncertain we encourage physicians to
restart the study medication and to monitor the first administration of the study drug very closely and to have a beta 2–agonist ready for use if necessary.

If a patient develops acute heart failure we recommend holding the study medication until the symptoms have resolved and then restarting the study medication at the lower dosage recommended above.

If a patient develops unstable angina and the treating physician feels a beta-blocker is needed in the acute setting then the study medication can be held and the patient can go onto an open label beta-blocker. We recommend physicians stop the open label beta-blocker and restart the study medication within a day or two of the patient’s symptoms resolving.

If a patient has a nonfatal cardiac arrest we recommend continuing the study medication immediately after the arrest unless it was due to asystole in which case the study drug should be discontinued.

If a patient experiences a myocardial infarction the study drug should be discontinued and an open label beta-blocker should be administered.

9. FOLLOW-UP

9.1 Short term follow-up

An ECG will be recorded 6 to 12 hours postoperatively and on the 1st, 2nd and 30th day after surgery. A troponin or CK-MB if troponin is not available will be drawn 6 to 12 hours postoperatively and on the 1st, 2nd, and 3rd day after surgery. Standard orders will dictate these tests are drawn. If a myocardial infarction is suspected, centers are encouraged to obtain more frequent ECGs and cardiac enzyme tests as is clinically
necessary. Patients’ charts will be assessed prior to hospital discharge for any primary or secondary outcomes. Patients will be contacted by phone at 30 days. If patients indicate they have experienced an outcome their physician will be contacted to acquire the appropriate documentation.

9.2 Long term follow-up

Long term follow up (minimum of 1 year) for death and nonfatal myocardial infarction will be undertaken in all patients. The approach may vary by country. In Canada we will obtain the long term follow-up data on nonfatal myocardial infarctions through the Canadian Institute for Health Information (CIHI). In Canada we will also obtain the long term follow-up mortality data through Statistics Canada. Both institutions have a lag time of approximately two years before they are able to provide data. For example, the most recent data that they can currently provide is for 1999. Because of this delay in data availability we will work with both institutions to determine patient outcomes at a single point in time (i.e. 2½ years after the last patient is randomized). With the 2 year lag in data availability at both institutions, we will get 6 months follow-up on the last patient randomized and 2½ years follow-up on the first patient randomized (mean follow-up of 1 –1.5 years). Study personnel will contact patients by phone at 1 year post surgery if they are enrolled in a country other than Canada with no national health administrative database.
10. STUDY OUTCOMES

There will be adjudication of the primary outcomes (i.e. cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) by a blinded adjudication committee. Clinical centers will therefore forward supporting documents for these outcomes.

10.1 Sub classification of death

All deaths will be classified as either cardiovascular or non-cardiovascular. Cardiovascular death is defined as any death with a cardiovascular cause and includes those deaths following a cardiovascular procedure (e.g. percutaneous transluminal coronary angioplasty), cardiac arrest, myocardial infarction, pulmonary embolus, stroke, hemorrhage, or deaths due to an unknown cause. Non-cardiovascular death is defined as deaths due to a clearly documented non-cardiovascular cause (e.g. trauma, infection, malignancy). Clinical centers will forward relevant clinical notes, laboratory tests, diagnostic imaging tests, and autopsy information from any patient who dies, to assist in confirming the cause of death, to the central coordinating office.

10.2 Myocardial infarction

The diagnosis MI requires either one of the following:

1. a typical rise of troponin OR a typical fall of an elevated troponin OR a rapid rise and fall of CK-MB. An increased troponin value (i.e. above the decision limit for MI) is a measurement exceeding the 99th percentile of a reference control group with a coefficient of variation ≤ 10%. An increased CK MB value (i.e. above the decision limit for MI) is one that exceeds the 99th percentile for CK MB values in a
reference control group. One of the following must also exist for the diagnosis of myocardial infarction:

A. ischemic symptoms (e.g. chest, epigastric, arm, wrist, or jaw discomfort OR shortness of breath lasting at least 20 minutes)

B. development of pathologic Q waves on the ECG (Q wave changes must be present in any two contiguous leads, and be $\geq 1$ mm in depth, further Q waves in leads I, II, aVL, aVF, V4, V5, or V6 must be $\geq$ to 30 ms

C. ECG changes indicative of ischemia (new or presumed new ST segment elevation or depression in at least two contiguous leads OR new or presumed new symmetric inversion of T waves $\geq 1$ mm in at least two contiguous leads)

D. coronary artery intervention (e.g. coronary angioplasty)

E. new or presumed new cardiac wall motion abnormality on echocardiographic or radionuclide imaging

2. Pathologic findings of an acute MI

Any patient suffering a myocardial infarction must have relevant clinical notes documenting ischemic symptoms, ECGs, diagnostic imaging tests, and all cardiac enzyme tests forwarded to the central coordinating office.

10.3 Nonfatal cardiac arrest

Nonfatal cardiac arrest is defined as a successful resuscitation from either documented or presumed ventricular fibrillation or sustained ventricular tachycardia or asystole. Any patient suffering a nonfatal cardiac arrest must have relevant clinical notes documenting the event, ECGs and/or ECG rhythm strips forwarded to the central coordinating office.
10.4 Congestive heart failure

The definition of congestive heart failure requires both clinical (i.e. any of the following signs: elevated jugular venous pressure, respiratory rales, crepitations, or presence of S3) and radiographic evidence (e.g. vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

10.5 Clinically significant bradycardia

Clinically significant bradycardia is defined as bradycardia requiring a temporary pacemaker, sympathomimetic agent, atropine, or study drug discontinuation.

10.6 Clinically significant hypotension

Clinically significant hypotension is defined as a systolic blood pressure < 90 mm Hg requiring fluid resuscitation, intraaortic balloon pump, an inotropic agent, or study drug discontinuation.

10.7 Clinically significant atrial fibrillation

Clinically significant atrial fibrillation is defined as 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.

10.8 Rehospitalization for cardiac reasons

Rehospitalization for cardiac reasons is defined as rehospitalization for congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, arrhythmia, or heart block.
11. CENTRAL ADJUDICATION OF CLINICAL EVENTS

A committee of clinicians who are blinded to the treatment allocation will adjudicate the primary endpoints. The decisions from the adjudication committee will be used for all statistical analyses of the primary outcomes.

12. DATA ANALYSIS

The intention to treat principle will guide all analyses, whereby all events in all randomized patients will be included in the group to which the patients were randomized up to the pre-specified time points.

12.1 Main analysis (metoprolol versus placebo)

We will tabulate the number of primary outcomes by treatment group. Time-to-the first occurrence of one of the components of the primary outcome (i.e. cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) will be presented using the Kaplan-Meier estimator. The rate of occurrence of this primary outcome between the two groups will be compared using the log-rank statistic. Treatment effect, as measured by the hazard ratio and its associated 95% confidence interval, will be derived by employing Cox proportional hazards model. Statistical significance will be claimed if the computed p-value is $< 0.05$. We will also calculate the relative and absolute risk reductions and the associated 95% confidence intervals.

12.2 Secondary analyses (metoprolol versus placebo)

We will tabulate the number of secondary outcomes by treatment group. The rate of occurrence of each secondary outcome (i.e. the incidence of revascularization procedures [i.e. coronary artery bypass surgery and percutaneous transluminal coronary
angioplasty], atrial fibrillation, rehospitalization for cardiac reasons, myocardial
infarction, nonfatal cardiac arrest, cardiovascular death, and total mortality) will be
compared using the log-rank statistic. We will compare the length of hospital stay and
length of ICU/CCU stay using an unpaired t-test or a non-parametric test if the data are
not normally distributed. The subgroup analyses (i.e. patients with diabetes, renal failure,
coronary artery disease, hypertension, congestive heart failure, cerebrovascular disease,
peripheral vascular disease, patients who receive an epidural or spinal anesthesia, men
and women, types of surgeries, and effects among patients at different ages) will be
compared using a Cox proportional hazards model, and a subgroup effect will be claimed
if the interaction term of treatment and subgroup is statistically significant.

12.3 Safety analysis (metoprolol versus placebo)

We will tabulate the number of safety outcomes by treatment group. The rate of
occurrence of each safety outcome (i.e. congestive heart failure, clinically significant
bradycardia, and clinically significant hypotension) will be compared using the log-rank
statistic.

12.4 Interim analysis and data monitoring

The independent External Safety and Efficacy and Monitoring Committee
(ESEMC) will ensure patient safety, prepare interim analyses of efficacy data, provide
feedback to the Steering Committee and ensure the study follows the highest standards of
ethics. The exact approach for the guidelines for the monitoring of the trial will be
developed in direct discussions with the ESEMC at their first meeting. Below we outline
an approach that we have frequently used in large trials. Additionally, the ESEMC
chairperson will receive reports on the 30 day data of serious adverse events and
discontinuation of treatments after the first 1000 patients have been obtained and when
2500, 5000, and 7500 patients have been included. Subsequently, reports will be
coordinated with regular interim reports unless the ESEMC requests a different schedule.
At any time during the study if safety concerns arise the ESEMC chairperson will
assemble a formal meeting of the full committee. The ESEMC will make their
recommendations to the steering 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 project officer, co- principal investigators, study
chair, and deputy project officer to explore all possibilities before a decision is made.
Statistical guidelines for the monitoring of efficacy and safety are outlined below.

12.5 Monitoring for efficacy and harm

Three interim efficacy analyses will occur when 25%, 50% and 75% of the 30-
day (Metoprolol vs placebo) data are available. These analyses will be based on the
combined outcome of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest. The
ESEMC will employ the modified Haybittle-Peto rule of four standard deviations for
analyses in the first half of the study and three standard deviations for all analyses in the
second half.\textsuperscript{49,50} For a finding in favor of treatment to be considered significant these
predefined boundaries will have to be exceeded in at least two consecutive analyses, three
or more months apart. The corresponding critical $P^2$ values are 16.0 (i.e. $\alpha = 0.0001$) for
the first two planned analyses and 12.25 ($\alpha = 0.00047$) for the third analysis. The $\alpha$-level
for the final analysis will remain the conventional $\alpha = 0.05$ given the infrequent interim
analyses, their extremely low $\alpha$ levels, and the requirement for confirmation with a
subsequent analysis.
The ESEMC will also monitor the study to assess if there is an adverse impact of beta-blockers on mortality. For these analyses, a three standard deviations excess in mortality in the first half and a 2.6 standard deviations excess in the second half would trigger discussions about stopping for harm.

If the intervention should surpass the modified Haybittle-Peto rule then the ESEMC will advice the Steering Committee of such a finding and recommend stopping the study. The ESEMC in making such a recommendation will also consider the consistency of the secondary endpoints and subgroups and any relevant external data.

13. REPORTING SERIOUS ADVERSE EVENTS

We define serious adverse events as those which are fatal, life threatening or fulfill a definition of being clinically significant. Serious adverse events can be “expected” (i.e. the safety outcomes we have predefined) or “unexpected” if they would not be expected among perioperative patients given standard therapies and not previously described with metoprolol. Previously described serious adverse effects and events that are part of the clinical course of patients should be recorded on the 30-day Assessment Case Report Form and forwarded to the Central Coordinating Office. Only unexpected and not previously described serious adverse events that are believed with a reasonable level of certainty to be associated with the study medication need to be reported immediately (i.e. within 24 hours of knowledge of the event) to the Central Coordinating Office. For such events a Serious Adverse Event Case Report Form should be completed and immediately mailed to the Central Coordinating Office, who will then inform the sponsor and the regulatory bodies.
14. TRIAL ORGANIZATION

The Canadian Cardiovascular Collaboration Project Office, McMaster University, Hamilton, Canada is the coordinating center for this study and is primarily responsible for the development of the trial protocol, organization of the study, development of the randomization scheme, the study database, data internal consistency checks, data analysis and coordination of the study centers. This study is funded by the Canadian Institutes for Health Research (CIHR). Astra-Zeneca has kindly agreed to supply the study drug. The study’s co-principal investigators are Drs P.J. Devereaux and Homer Yang, chair of the Steering Committee is Dr. Salim Yusuf, chair of the Event Adjudication Committee is Dr. Gordon Guyatt, deputy project officer is Dr. Peter Choi, project coordinator is Joanne Pasquale, and project manager is Susan Chrolavicius.

The study will also have an operations committee, a Canadian steering committee, international steering committee (with two representatives from all countries that join this study), an adjudication committee, and an External Safety and Efficacy and Monitoring Committee.

The main POISE manuscript will be submitted under group authorship, with the roles of all investigators acknowledged in an appendix. All investigators who have enrolled at least 12 patients will be acknowledged (an additional name is granted to those centres enrolling 30 or more patients). Subsequent publications will be authored by specific individuals on behalf of the POISE Investigators. Individuals selected to lead the writing of these subsequent publications will depend on their role in the study and contribution, scientific interest, and scientific expertise.
14.1 Study centers

The Principal Investigator at each participating center is responsible for:

1. obtaining ethics approval from the institutional review board or the ethics board
   (the project office will provide whatever support is necessary);

2. ensuring the protocol is followed;

3. ensuring all physicians and nurses involved in the perioperative care of patients
   undergoing non-cardiac surgery are aware and informed about this study. This
   will involve organizing and presenting educational in-services about the study and
   distributing posters and pocket protocols;

4. routinely confirming that all surgical patients going through the preoperative
   clinics, are being screened for the trial, and that all eligible consenting patients are
   being randomized;

5. develop a mechanism to recruit all patients that do not go through the
   preoperative clinic such as direct admits through the emergency room or patients
   who do not attend a preoperative clinic because they see a preoperative consultant
   in their office;

6. ensuring that randomized patients are followed appropriately;

7. ensuring that all Case Report Forms are promptly completed and forwarded to the
   Coordinating Office, and that all inquires from the Coordinating Office regarding
   patient forms or other matters are addressed promptly;

8. ensuring that a simple screening log is kept of all non-cardiac surgery patients
   who meet the eligibility criteria to record the primary reasons for exclusion. This
   will be sent to the central coordinating office every month.
15. OTHER CONSIDERATIONS

15.1 Approval of study protocol

Each center’s principal investigator is responsible obtaining approval of the study protocol and Consent Form from the appropriate local Ethics Committee, Institutional Review Board (IRB) and/or the appropriate regulatory authorities in accordance with local legal requirements. Study approval must be obtained before recruitment can start at any given site. The Coordinating Center will require documentation of the Ethics Committee/IRB approval before patients can be randomized at a given center.

15.2 Confidentiality and blinding

All patient names and 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 study is completed or a recommendation is made to terminate the trial.

15.3 Record maintenance

The investigator agrees to obtain and maintain a:

1. correctly completed Informed Consent Form for each patient included in the study;

2. personal list of patient Identification Numbers and patient names to enable hospital records to be found at a later date; all these records must be kept for at least two years after the last approval of the study drug.
15.4 Unblinding

Legitimate situations such as a large overdose of the study drug may require unblinding. We will avoid unblinding of metoprolol/placebo whenever possible by using 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. Usually 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 National Coordinating Office. If after these steps the local study investigator believes emergency unblinding is essential for the patient’s management then it can be undertaken.

15.5 Withdrawals

Patients can choose to stop their study medication at any time during the course of the study. We will follow patients who make this decision in the same way as all other patients. If patients stop study medications, the clinical investigators will explore whether the drug could be restarted safely.

16. POTENTIAL SIGNIFICANCE OF THE STUDY

If this study demonstrates metoprolol prevents perioperative cardiac events it will have profound implications for perioperative medicine internationally.
17. REFERENCES


13 Oliver MF, Opie LH. Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. Lancet 1994; 343: 155-158.


