Northern Health

STUDY TITLE

A single centre, open label, randomised controlled study of ivabradine in the prevention of peri-operative myocardial injury, in patients undergoing emergent orthopaedic surgery.

STUDY INVESTIGATOR(S)

Principal Investigator

Title and Name	Professor William van Gaal	
Appointment/s	Director of Cardiology	
Department / Affiliation with Northern Health	Department of Cardiology, Northern Hospital. Department of Medicine, University of Melbourne.	
Qualifications	MBBS, FRACP	
Phone	(03) 8405 8000	Fax:
Mobile/ Pager		Email: william.vangaal@nh.org.au
Is this person the contact person for the project?	Yes / No (please circle / highlight)	

Associate Investigator

Title and Name	Dr Chee Loong (Dominic) Chow	
Appointment/s	Cardiology Registrar	
Department / Affiliation with Northern Health	Department of Cardiology, Northern Hospital. Department of Medicine, University of Melbourne.	
Qualifications	MBBS	
Phone	(03) 8405 8000	Fax:
Mobile/ Pager	0433 005 688	Email: dominic.chow2@nh.org.au
Is this person the contact person for the project?	Yes / No (please circle / highlight)	

Title and Name	Professor Raphael Hau	
Appointment/s	Director of Orthopaedics	
Department / Affiliation with Northern Health	Department of Orthopaedics, Northern Hospital.	
Qualifications	MBBS, FRACS	
Phone	(03) 8405 2531	Fax:
Mobile/ Pager	0408 380 505	Email: raphael.hau@nh.org.au
Is this person the contact person for the project?	Yes / No (please circle / highlight)	

Title and Name	Dr Carol Chong
Appointment/s	Geriatric Consultant

Department / Affiliation with Northern Health	Department of Medicine, Northern Hospital.	
Qualifications	MBBS, FRACP	
Phone	(03) 8405 8000	Fax:
Mobile/ Pager		Email: carol.chong@nh.org.au
Is this person the contact person for the project?	Yes / No (please circle / highlight)	

1. INTRODUCTION

More than 230 million major surgical operations are performed every year worldwide[1]. Among patients undergoing major non-cardiac surgery, the overall incidence of perioperative myocardial infarction (MI) is 3%, and in higher risk populations as high as 34%[2]. Perioperative MI is associated with morbidity and mortality rates as high as 40%[3]. The universal definition classifies perioperative MI as a rise and fall of cardiac biomarkers (preferably troponin) with at least one measurement above the 99th percentile of the upper reference limit, in the setting of either symptoms or electrocardiogram (ECG) evidence of ischaemia, or imaging evidence of necrosis[4]. However, the majority of post-operative troponin elevations is asymptomatic without ECG or imaging evidence of MI, but still confers a substantially increased risk of death[5, 6].

Specifically in the setting of emergent orthopaedic surgery, peri-operative myocardial injury (PMI) defined by any troponin I elevation occurred in 52.9% of patients. Most of these patients were asymptomatic, with only 9.8% meeting the universal definition for MI. PMI was independently associated with a dramatic increase in mortality (37% vs 2.1%, $p<0.001$)[7]. One theory has been postulated to contribute to PMI. Surgery imposes a significant physiological stress on the body, and is associated with a rise in catecholamines. This in turn increases heart rate and myocardial oxygen demand[8, 9], which predisposes the patient to myocardial ischaemia[10-12]. In addition, high catecholamine levels result in an increase in free fatty acid levels, which can damage myocardial cell membranes[13].

2. BACKGROUND

Given the significant impact of post-operative tachycardia, and the association between asymptomatic heart rate-related ST-segment depression and death[14], the role of peri-operative β-blockers as a negative chronotropic agent has gained much attention in the last two decades. Most initial studies were plagued by either small sample sizes failing to demonstrate consistent benefit[15, 16], or limitations in the integrity of methodology (such as lack of blinding and failure to use intention-to-treat analysis)[17]. The POISE-trial is the largest trial to date demonstrating a reduction in myocardial infarction in patients receiving metoprolol succinate peri-operatively[18]. Unfortunately, it was also associated with an increased risk of stroke and mortality. In the post-hoc population attributable risk (PAR) analysis, clinically significant hypotension (defined as systolic blood pressure <90mmHg

requiring specific intervention) had the largest PAR for death (37.3%) and stroke (14.7%)[19].

Ivabradine is an orally bioavailable, specific inhibitor of the I_f current in the sinoatrial node[20]. Being a pure heart rate lowering agent in patients with sinus rhythm, it does not affect blood pressure or myocardial contractility[21]. As a result, it should provide the benefit of a negative chronotropic agent without the detrimental effects of hypotension.

3. AIM(S) OF STUDY/ OBJECTIVES

This study aims to establish the effect of heart rate reduction with Ivabradine on reducing the incidence of peri-operative myocardial injury (primary outcome), and mortality at 1 year (secondary outcome).

4. HYPOTHESIS

4a. Primary Hypothesis

H_A: Heart rate reduction targetting 60 beats per minute or lower with Ivabradine reduces the incidence of peri-operative myocardial injury.

4b. Secondary Hypotheses

H_A: Heart rate reduction below 60 beats per minute with Ivabradine reduces 1-year mortality.

H_A: Ivabradine reduces the incidence of peri-operative myocardial infarction.
H_A: Ivabradine does not increase the incidence of clinically significant hypotension, defined by systolic blood pressure <90 mmHg requiring active intervention.
H_A: Ivabradine does not increase the incidence of peri-operative stroke

5. STUDY DESIGN

This study will be a prospective, single-centre, open-label, randomised controlled trial, examining the outcomes of patients planned for emergent orthopaedic surgery to receive standard medical therapy (placebo group) versus the addition of ivabradine (intervention group) to a target heart rate of <60 beats per minute. An open-label design is employed to allow treating physicians to actively titrate heart rates to target. The potential response bias is minimal, as both the independent and dependent variables (peri-operative heart rate, and PMI respectively) are hard, objective outcomes.

6. STUDY SETTING/LOCATION

Activities related to this study will be conducted at the Northern Hospital, Epping (Victoria).

7. STUDY POPULATION

Patients above the age of 60 who require emergent orthopaedic long bone surgery (such as internal fixation of fractured neck of femur or humerus) will be elligible. This population is specifically selected for the high incidence of PMI, and its significant association with 1-year mortality in previous literature. The role of ivabradine in reducing PMI in this population therefore has potential significant impact on patient outcomes.

8. ELIGIBILITY CRITERIA

8a. Inclusion criteria

Patients above the age of 60 who present to the emergency department requiring emergent orthopaedic long bone surgery would be elligible. Emergent surgery will be defined as non-elective surgery mainly for trauma (e.g. long bone fractures). Types of surgeries therefore would include (but not limited to) open reduction and internal fixation, hemiarthroplasties, and general anaesthetic and manipulation of plaster.

8b. Exclusion criteria

The following exclusion criteria apply:

- Current ivabradine use
- Permanent atrial fibrillation prior to randomisation
- Heart rate <60 beats per minute
- Pacemakers, sick sinus syndrome, any atro-ventricular, bundle branch, or fascicular blocks
- Concomitant CYP3A4 inhibitor use (such as ketoconazole, macrolides or cyclosporin)
- Severe hepatic impairment, defined as serum AST/ ALT above 3 times upper limit of normal
- Acute decompensated heart failure
- Known active malignancy

9. STUDY OUTCOMES

9a. Primary Outcome

The primary outcome of this study is the incidence of peri-operative myocardial injury (PMI).

9b. Secondary Outcome(s)

Secondary outcomes of this study are:

- Clinically significant bradycardia (defined as heart rate below 40 beats per minute requiring active intervention above withdrawal of negative chronotropes)
- Mortality at 30-day, 6-month, and 12-month time points
- Myocardial infarction (a rise of troponin >99th percentile of the upper reference limit, in the setting of either symptoms or electrocardiogram evidence of ischaemia)
- Ischaemic-driven coronary revascularisation
- Ischaemic stroke (presence of both clinical neurological deficit and imaging [CT or MRI] evidence of an acute ischaemic stroke)

10. STUDY PROCEDURES

10a. Recruitment of participants

This study aims to recruit a total of 200 patients, over a recruitment period of 18 months (About 4 patients per week). In collaboration with the orthopaedic team, patients presenting to the Emergency Department requiring emergent orthopaedic surgery will be screened for elligibility.

10b. Randomisation

After informed consent, patients will be randomised with a wed-based software (Sealed Envelope™), in a 1:1 permuted block-randomisation method. Group allocation is concealed until actual assignment, which will happen immediately following the registration of a patient into the web-based software for randomisation. This will be an open-label study, to allow the treating physician to titrate the dose of ivabradine peri-operatively, in the treatment arm.

10c. Study procedure

All randomised patients will have the following baseline data collected:

- Demographics: age, race and sex
- Cardiovascular risk profile: hypertesion, diabetes mellitus, dyslipidaemia, family history of ischaemic heart disease, smoking status, BMI, eGFR, known coronary artery disease, known peripheral vascular disease
- Heart rate and blood pressure
- Concomitant use of aspirin and statins
- Baseline troponin and electrocardiogram

Treatment [Ivabradine, Brand Name: Coralan, Manufacturer: Servier Laboratories (Aust.) Pty Ltd (Manufacturer code: SE)] protocol for patients allocated to treatment arm only

Open-label Ivabradine will be administered to the following parameters:

- HR 60-90bpm at randominsation: Start at 5.0mg orally twice daily between 2 and 48 hours prior to surgery, and continued for 7 days
- HR >90bpm at randomisation: Start at 7.5mg orally twice daily between 2 and 48 hours prior to surgery, and continued for 7 days
- HR will be reviewed on a daily basis, and ivabradine adjusted accordingly. If HR remains above 60bpm, its dose can be increased by 2.5mg orally twice daily (to a maximum of 15mg maximum per day)
- If HR drops below 50bpm during treatment, its dose can be reduced by 2.5mg twice daily on each review. If HR remains below 50bpm despite only on 2.5mg twice-daily dose, ivabradine can be ceased

Vital signs (heart rate and blood pressure) monitoring for all patients

- Pre-operative (baseline) vital signs will be recorded as an average of three (automated machine) readings prior to randomisation
- Intra-operative vital signs will be derived from the anaesthetic sheet, as an average of the readings during surgery and in the immediate, recovery period

- 72 hours of Holter monitoring will commence within 24 hours post-operatively, and mean daily vital signs recorded
- Any arrhythmia such as atrial fibrillation, its frequency and duration, will be recorded

Troponin I measurements and ECG for all patients

- All safety bloods (such as haematology, biochemistry and coagulation profiles) will be done locally, prior to randomisation to screen for elligibility (such as renal function)
- Troponin I samples and ECG will be collected pre-operatively (baseline, 2 to 48 hours pre-operatively), and on post-operative day 1 (12 to 24 hours post-operatively), day 2 (36 to 48 hours post-operatively) and day 3 (60 to 72 hours post-operatively).
- All samples will be processed and frozen on-site to -80 °Celsius, and batch delivered to Covance® Singapore at the end of the recruitment period for troponin assay.

Follow-up procedures

Patients will be followed up at 30 days, 6 months, and 12 months by telephone interviews. Participants will be assessed qualitatively about all study outcomes (cardiac events/ myocardial infarction, revascularisation, stroke), as well as any other serious adverse events (SAE)/ adverse events (AE). Additional information to also be obtained from their primary and secondary care records. Mortality end points will be confirmed with either hospital care records, or the Birth, Marriages and Deaths registry.

For patients who were randomised, but had their surgeries cancelled for any reason, intervention with ivabradine will be terminated and troponin I measurement will not be collected. Holter monitoring, as well as telephone follow-up at 30 days, 6 months and 12 months will continue to take place, however. This is to allow the study outcomes (with the exception of PMI) to be performed on both intention-to-treat and per-protocol/ on-treatment basis.

10d. Measurement tools used

All baseline data elements will be collected from the patient directly (in a medical interview between the investigator and the participant). All vital sign parameters will be collected from medical records, Holter monitors for heart rate measurements, and automated blood pressure machines for blood pressure measurements.

10e. Safety considerations/Patient safety

All adverse events will be reported within 5 working days, and all serious adverse events reported within 24 hours of the study team being notified. All patients who are randomised (regardless of treatment arm, or withdrawal of study intervention) will be followed up by mandatory telephone interview, as per protocol, at 30 days, 6 months, and 1 year.

In the event of a potential complication with Ivabradine, every attempt will be made to actively monitor and reverse them. Patients who have hypersensitivity reactions to

Ivabradine will have study intervention withdrawn, and standard medical procedures followed.

10f. Data monitoring

Any reported adverse events and serious adverse events will be adjudicated by two independent physicians from the study team, to determine if they were attributable to study intervention. Study team will meet up quarterly to discuss all reported AE and SAE. Cumulatively collected data will be analysed yearly as an ongoing surveillance. Early termination of the trial will be considered If >50% absolute reduction in PMI is observed in the treatment group, such that it would be unethical to continue the trial at the disadvantage of the placebo cohort; or if Ivabradine shows a >20% incidence of clinically significant bradycardia or stroke.

11. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

11a. Sample size and statistical power

Sample size estimation was made based on outcome measures in previous literature[7], that PMI (primary outcome of this study) was observed in 52% of patients undergoing emergent othopaedic surgery. Assuming a significance level (α) of 0.05, in order to detect an absolute reduction of 20% with ivabradine with a study power of 80%, a sample size of 92 patients is required in each arm. Allowing for 5% attrition rate in each arm (which is a conservative estimation, as we expect the attrition rate to be much lower, given the primary outcome is collected within 2 days post-operatively, and therefore unlikely to be missed), a total of 200 patients will need to be randomised.

11b. Statistical methods

The primary outcome of PMI will be calculated and reported by cumulative incidence, and compared between the treatment arms for significant differences. Study end point analysis will be conducted on an intention-to-treat principle, as well as the per-protocol basis.

All time-to-event outcomes (such as mortality, myocardial infarction and stroke) will be calculated from the date of randomisation to the date of first documented event, and examined by time-to-event survival analysis (log rank test), and presented in a Kaplan-Meier curve. Cox Proportional Hazard models will be used to examine a range of covariates and their possible interactions.

Descriptive statistics will be presented as counts and percentage frequencies, mean ± standard deviation (SD) or median with inter-quartile range (IQR) to summarise patient characteristics and outcomes. Categorical variables will be evaluated using the Chi-square test or Fishers Exact test on occasions of frequencies of less than 5. Continuous variables will be analysed with logistic regression. Multivariate logistic regression will be used to identify significant correlations, with only variables having a p-value of <0.1 on univariate analysis being included in the multivariate analysis. A two-tailed p-value of 0.05 was considered indicative of statistical significance.

12. ETHICAL CONSIDERATIONS

The study will be conducted in full conformance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of Australia.

Participation in this study is voluntary, after informed consent is obtained. The informed consent process ensures that participants can read and understand both verbal and written information given, to make an informed decision about their voluntary participation.

All collected data elements will be sufficiently de-identified, and stored in a study-specific electronic file, for further analysis purposes. Re-identification of patient is possible, and will only be performed if medically indicated, for example to adjudicate on a reported adverse event.

13. OUTCOMES AND SIGNIFICANCE

The incidence of PMI in this study population is high (as demonstrated on previous literature), and is strongly associated with 1-year mortality. Examining the effects of Ivabradine in reducing PMI therefore has significant importance in improving patient oucomes.

14. BUDGET (Mandatory Field)

STUDY TITLE: A single centre, open label, randomised controlled study of ivabradine in the prevention of peri-operative myocardial injury, in patients undergoing emergent orthopaedic surgery.

Has this protocol received research funding or grant/s? (List all grants and funding including pending applications for funds)

Source of Grant / Funding	Amount	Date
Department of Cardiology	$ 26500	20/10/2016

ITEM	COST $	Department Responsible
Troponin I measurements 200 patients x 4 each = 800 measurements	$ 24000	Pathology
Study drug (Ivabradine) 100 patients x $15/patient	$ 1500	Cardiology/ Pharmacy
Online randomisation (Sealed Envelope)	$ 1000	Cardiology

Total funds requested	$ 26500	

IN-KIND SUPPORT (include estimation of staff time, administration costs etc.)	**COST $**	**Department Responsible**
Investigators staff time	$ 0	Cardiology
Total in-kind support	$ 0	

Declaration by delegated department head/s at the site where the Principal Investigator / Coordinating Principal Investigator will conduct the research for the purpose of resourcing the research project.

I certify that:

- I have read the project details in this Protocol for the research project application named above;
- I have discussed this research project and the resource implications for this Department, with the Principal Investigator / Site Coordinator; and
- I accept the costs as indicated above for my department and that there are suitable and adequate facilities and resources for the research project to be conducted at this site. This is for 'Actual costs' and 'In Kind' contribution.

My signature indicates that I support this research project being carried out using such resources.

Name of Department:	Department of Cardiology, Northern Health
Name of Head of Department:	Professor William van Gaal
Signature:	
Date:	24/10/2016

Northern Health

15. TIMELINE

The timeline is intended for you to clearly outline the proposed time for all the different elements and activities of your research. The template below is a guide and it is acknowledged not all activities will apply to every project.

Activities	Period of time from October 2016 to October 2017													Location
	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct -17	
Development of research/project proposal														TNH
Submit Ethics Application														TNH
Recruitment and Data collection														TNH
Data cleaning and Ongoing Surveillance														TNH
TNH Research Week Presentation/Abstract														TNH
External Conference Presentation														External venue

16. APPENDIX

Include in this section relevant supplementary documents such as data collection forms, questionnaires, brochures/flyers etc.

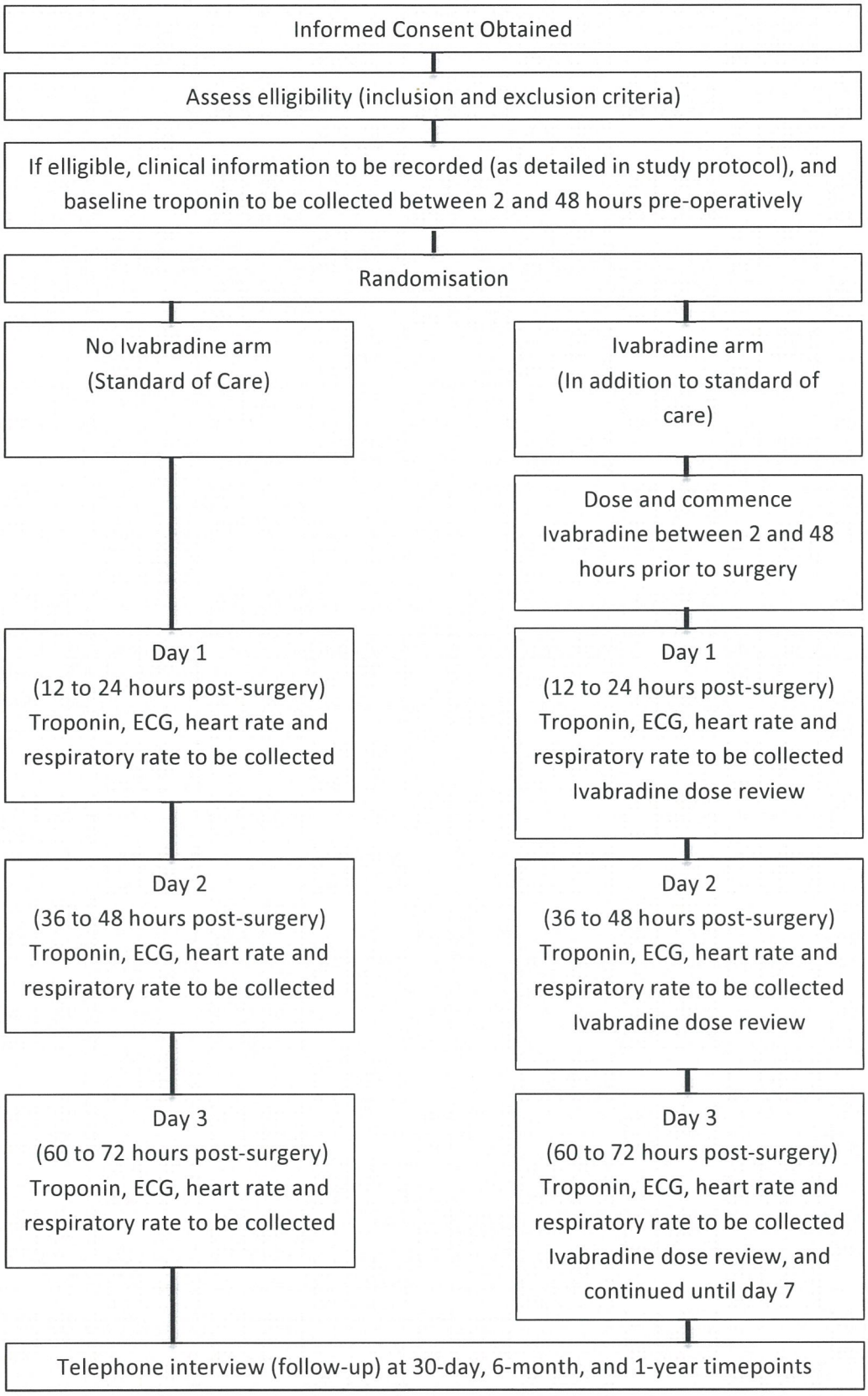
17. REFERENCES

World Medical Association Declaration of Helsinki (1964)
Note for guidance on good clinical practice (CPMP/ICH/135/95 - Annotated with TGA comments)
National Statement on Ethical Conduct in Human Research (2007)

1. Weiser, T.G., et al., *An estimation of the global volume of surgery: a modelling strategy based on available data.* Lancet, 2008. **372**(9633): p. 139-44.
2. Poldermans, D., et al., *The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group.* N Engl J Med, 1999. **341**(24): p. 1789-94.
3. Lindenauer, P.K., et al., *The potential preventability of postoperative myocardial infarction: underuse of perioperative beta-adrenergic blockade.* Arch Intern Med, 2004. **164**(7): p. 762-6.
4. Thygesen, K., et al., *Universal definition of myocardial infarction.* Circulation, 2007. **116**(22): p. 2634-53.
5. Chong, C.P., et al., *Cardiac injury and troponin testing after orthopaedic surgery.* Injury, 2011. **42**(9): p. 855-63.
6. Landesberg, G., et al., *Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery.* J Am Coll Cardiol, 2003. **42**(9): p. 1547-54.
7. Chong, C.P., et al., *Incidence of post-operative troponin I rises and 1-year mortality after emergency orthopaedic surgery in older patients.* Age Ageing, 2009. **38**(2): p. 168-74.
8. Sametz, W., et al., *Perioperative catecholamine changes in cardiac risk patients.* Eur J Clin Invest, 1999. **29**(7): p. 582-7.
9. Parker, S.D., et al., *Catecholamine and cortisol responses to lower extremity revascularization: correlation with outcome variables. Perioperative Ischemia Randomized Anesthesia Trial Study Group.* Crit Care Med, 1995. **23**(12): p. 1954-61.
10. Mangano, D.T., et al., *Perioperative myocardial ischemia in patients undergoing noncardiac surgery--II: Incidence and severity during the 1st week after surgery. The Study of Perioperative Ischemia (SPI) Research Group.* J Am Coll Cardiol, 1991. **17**(4): p. 851-7.
11. Stone, J.G., et al., *Risk of myocardial ischaemia during anaesthesia in treated and untreated hypertensive patients.* Br J Anaesth, 1988. **61**(6): p. 675-9.
12. Stone, J.G., et al., *Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent.* Anesthesiology, 1988. **68**(4): p. 495-500.
13. Oliver, M.F. and L.H. Opie, *Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias.* Lancet, 1994. **343**(8890): p. 155-8.
14. Landesberg, G., et al., *Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia.* J Am Coll Cardiol, 2001. **37**(7): p. 1839-45.
15. Yang, H., et al., *The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial.* Am Heart J, 2006. **152**(5): p. 983-90.
16. Juul, A.B., et al., *Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial.* BMJ, 2006. **332**(7556): p. 1482.
17. Devereaux, P.J., et al., *Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence?* CMAJ, 2004. **171**(3): p. 245-7.

18. Group, P.S., et al., *Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial.* Lancet, 2008. **371**(9627): p. 1839-47.
19. Alonso-Coello, P., et al., *Should physicians initiate beta-blocker therapy in patients undergoing non-cardiac surgery? Insights from the POISE trial.* Pol Arch Med Wewn, 2008. **118**(11): p. 616-8.
20. DiFrancesco, D. and J.A. Camm, *Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease.* Drugs, 2004. **64**(16): p. 1757-65.
21. Joannides, R., et al., *Comparative effects of ivabradine, a selective heart rate-lowering agent, and propranolol on systemic and cardiac haemodynamics at rest and during exercise.* Br J Clin Pharmacol, 2006. **61**(2): p. 127-37.

Appendix 1: Study activities (Flow chart)



Appendix 2: Structured telephone interview at 30-day, 6-month, and 1-year timepoints.

1. Have you presented to the emergency department or been admitted to hospital since you were last contacted by the study team?
    a. What was the medical diagnosis?
    b. What investigations were performed to confirm the diagnosis?
2. Have you been diagnosed with a heart attack since last contact with study team?
3. Have you been diagnosed with a stroke since last contact with study team?
4. Are there any recent changes to your medications? What are they?
5. Are you taking blood thinners such as ticagrelor (Brilinta), clopidogrel (Plavix), or prasugrel (Effient)?
6. Are you taking any cholesterol-lowering medication(s)?
7. What is your current smoking status?