RRESEARCH PROTOCOL - IRB19-1797

"The ORION Trial"

Metoprolol to Reduce Perioperative Myocardial Injury

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SYNOPSIS

Study Title	**The ORION Trial -** Metoprolol to Reduce Perioperative Myocardial Injury
Objectives	a) Determine the efficacy and safety of titrated postoperative beta-blocker therapy to reduce myocardial injury. b) Determine the clinical utility of pre-operative high-sensitivity cardiac troponin levels for identifying patients who may benefit from postoperative beta-blocker therapy.
Hypotheses	1) In patients with high cardiovascular risk undergoing major, non-cardiac surgery, postoperative therapy with the beta-blocker metoprolol will significantly reduce postoperative myocardial injury without causing clinically significant hypotension. 2) Postoperative β-blocker therapy is more effective in patients with elevated preoperative hs-cTn ("high-risk"- patients).
Study Period	Planned enrollment duration: 5 years Planned study treatment duration: Day of surgery to 3 days (72 hrs) postop Long term outcomes follow-up: 30-day and 1-year postop
Number of Patients	600 randomized subjects
Study Treatment	Consented subjects will be randomized at approximately 15 minutes prior to extubation who meet **ALL** the following criteria: 1) heart rate >65/min 2) systolic blood pressure (SBP) >110 mmHg (SBP >120 mmHg if >79 yrs) 3) minimal active bleeding, and 4) no active wheezing; To one of 2 treatment groups using a 1:1 randomization for: A. metoprolol tartrate or B. placebo. Administration of study drug: a) OR prior to extubation: IV metoprolol tartrate 5mg (or placebo 5mL) to achieve target heart rate of 65/min; may be repeated x2 if HR > 65/min and SBP >110 mmHg (SBP > 120 mmHg if > 79 yrs). Total maximum dose = 15 mg metoprolol or 15mL placebo IV); b) Post-operative unit: 25mg oral metoprolol tartrate or placebo prior to discharge from post-op; c) Hospital floor: 25mg oral metoprolol tartrate or placebo every 8 hours thereafter until end of post-operative day three (POD3).Oral metoprolol will not be administered if HR <65 bpm and SBP <110 mmHg (or <120 mmHg if age >79 yrs)
Study Design	Multi-center, double-blind, randomized, placebo-controlled trial
Inclusion and Exclusion Criteria	**Inclusion:** 1) Age ≥ 50 years 2) Beta-blocker naïve [30 days prior to surgery] 3) Previously diagnosed coronary artery disease (CAD), OR

	a) History of peripheral vascular disease (PVD), OR b) Chronic kidney disease (CKD) [eGFR ≤60ml/min], OR c) History of a positive stress test, OR d) At high risk for CAD (must meet at least 2 criteria) i. Age ≥ 70 years ii. Hypertension iii. Diabetes requiring oral medication or insulin iv. Current smoker or some days smoker within the past 2 years 4) Major non-cardiac, elective surgery under general anesthesia **Exclusion:** 1. History of stroke or transient ischemia attack (TIA) 2. Previously diagnosed carotid disease, i.e., either 70% unilateral or 50% bilateral carotid stenosis. 3. Heart rate ≤55bpm 4. Congestive heart failure with New York Heart Association (NYHA) Functional Classification of III-IV or known left ventricular heart failure with ejection fraction ≤50% 5. Severe valvular regurgitation 6. Second or third degree AV block without pacemaker 7. Active asthma or COPD with symptoms or resolving symptoms on day of surgery 8. Anemia [Hb≤9g/dL] 9. Allergy to beta-blockers 10. Unwilling or unable to give consent for participation 11. Undergoing any carotid endarterectomy, endovascular, endoscopic, superficial, or ambulatory procedures 12. Pregnancy or lactating women 13. Prisoners
Measurements	1. 12-lead continuous Holter-ECG monitoring through 72 hours postoperative 2. Continuous vital sign monitoring with VISI mobile through 72 hours postop (heart rate, blood pressure, respiratory rate, pulse oximetry) 3. 12-lead ECGs: preoperative; postop.; daily on post op days 1 - 3 4. Serial cardiac biomarkers including high-sensitivity cardiac troponin plasma levels [hs-cTn] at 7 time points: preoperative clinic visit, preoperative holding area, prior to first IV metoprolol dose in OR, post-operative unit arrival, and approx. 24 hrs, 48 hrs, and 72 hrs postop 5. Daily adverse event monitoring until discharge from hospital 6. Long-term follow-up at 30 days and 1 year
Study Endpoints	**Primary efficacy endpoint**: Myocardial injury (new hs-cTn elevation) **Primary safety endpoint**: Clinically relevant hypotension **Secondary study endpoints** are: a) MACE (Major Adverse Cardiac Events), including myocardial infarction; cardiac arrest; death b) Myocardial ischemia duration (based on 12-lead Holter ECG) c) Stroke d) Cumulative vasopressor requirements post-operatively e) Incidence rate and cumulative bradycardia duration (HR <50/min) f) Unplanned ICU admission g) Length of hospital stay, and h) Length of ICU stay

1. BACKGROUND AND RATIONALE

Perioperative adverse cardiac events are a significant public health concern. Often referred to as a "hidden epidemic", perioperative adverse cardiac events kill twice as many Americans per year as all motor vehicle deaths combined (2011: 32,367 motor vehicle deaths compared to an estimated 63,000 postoperative cardiac deaths after non-cardiac surgery).[6] Despite the substantial incidence and associated mortality of perioperative adverse cardiac events, few recommended preventive therapies exist. In fact, there is currently no medical treatment that can be recommended for the prevention of perioperative adverse cardiac events based on robust scientific evidence. Preoperative β-blocker therapy has become highly controversial (the new 2014 AHA guidelines no longer recommend preoperative β-blockers for the majority of patients).[8,9] Perioperative statin therapy has nearly exclusively been explored in retrospective studies,[42-44] and the only randomized controlled trial in patients undergoing non-cardiac surgery was performed by the same group whose research has been questioned for potential misconduct.[45] Two recent large clinical trials showed that neither clonidine (an α2 adrenergic agonist; hazard ratio [HR] 1.08, 95% CI 0.93 – 1.26) nor aspirin (HR 0.99, 95% CI 0.86-1.15), prevent perioperative adverse cardiac events. Thus, there is currently no evidence-based treatment for prevention of perioperative adverse cardiac events and therefore the critical unmet need to identify such treatment that is both safe and effective.

This research is significant because it studies an important public health problem and provides a potential treatment option to the vexing problem of perioperative β-blocker therapy. If successful, our novel approach would translate into approximately 1 in 4 postoperative MIs prevented and approximately 15,000 lives saved each year without increasing the risk of stroke and death in the general U.S. surgical population (assuming a similar effectiveness as seen in the POISE trial: absolute risk reduction from 5.1% to 3.6%, relative risk reduction ~30%, number needed to treat = 66 to prevent one MI).

2. STUDY METHODS

2.1 Study Design Summary

This is a multi-center (University of Chicago Medicine [USA]; The Alfred Health [Australia]), double-blind clinical trial that will randomize 600 patients with CAD (or at high risk for CAD), and undergoing major non-cardiac surgery, to postoperative metoprolol tartrate or placebo. All patients will be beta-blocker naïve for at least 30 days prior to surgery and be randomized 1:1 to receive metoprolol tartrate or placebo. Patients will receive up to 3 IV doses of study drug (placebo or IV metoprolol tartrate 5mg) prior to extubation, and subsequently an oral dose (placebo or 25mg metoprolol tartrate) in the post-operative unit, and then oral dosing at approx. every 8 hours thereafter through postop day 3 (72 hrs). From arrival in the preop holding area through up to 72 hours postop or end of study treatment (whichever occurs first), patients will be continuously monitored with Holter ECG, a mobile hemodynamic monitor (VisiMobile), daily follow-up visits to include 12-lead ECG, and blood collections for serial cardiac biomarkers for high-sensitivity troponin. Primary efficacy endpoints are *myocardial ischemia and myocardial injury* as determined by ST-depression/elevation on 12-lead ECG, and hs-cTn elevation. Primary safety endpoint is clinically relevant hypotension. Secondary outcomes include major adverse cardiac events, stroke, and 30-day and 1-year mortality.

Due to feasibility and accessibility restrictions, The Alfred Health (TAH), will not be using the continuous monitoring device (VisiMobile), nor will it use any form of continuous telemetry for ECG recording. However,

all other methods of data collection and monitoring will be done, including a daily stat 12-lead ECG recording, blood draws, and other information determining the patients' recovery progress during hospital admission.

The aim of the ORION trial is to compare the use of post-operative metoprolol to placebo for efficacy (myocardial ischemia and myocardial injury) and safety (clinically relevant hypotension) outcomes in Beta-blocker naïve patients with high cardiac risk undergoing elective, major, non-cardiac surgery with general anesthesia.

Additional sites may be added to the study at a later date to also assist in recruitment, Ethics committee approval will be obtained then from each, but no data/samples will be shared until that approval and/or agreements have been confirmed.

Additional Australian sites include:

Fiona Stanley

Dandenong

Geelong Hospital

Waikato

2.2 Study Population

Participants will be recruited from patients with planned, elective, non-cardiac surgery, to be performed at the University of Chicago Medicine, Chicago IL [USA]; and The Alfred Health, Melbourne, [AU].

2.2.1 Inclusion Criteria

1. Age ≥ 50 years
2. Beta-blocker naïve [30 days prior to surgery]
3. Previously diagnosed CAD, or
    a) History of PVD, or
    b) CKD [eGFR ≤60ml/min], or
    c) History of positive stress test or
    d) At high risk for CAD (must meet at least 2 criteria):
        i. Age ≥ 70 years
        ii. Hypertension
        iii. Diabetes requiring oral medication or insulin
        iv. Current smoker or some days smoker within the past 2 years
4. Major non-cardiac, elective surgery under general anesthesia

2.2.2 Exclusion Criteria

Subjects will **not** be enrolled if any of the following criteria exist:

1. History of stroke, or TIA
2. Previously diagnosed carotid disease, i.e., either 70% unilateral or 50% bilateral carotid occlusion.
3. Heart rate ≤55bpm
4. Congestive heart failure with New York Heart Association (NYHA) Functional Classification of III-IV or left ventricular heart failure with ejection fraction ≤50%
5. Severe valvular regurgitation

6. Second or third degree AV block without pacemaker
7. Active asthma or COPD with symptoms or resolving symptoms on day of surgery
8. Anemia [Hb≤9g/dL]
9. Allergy to beta-blockade drugs
10. Unwilling or unable to give consent for participation
11. Undergoing any carotid endarterectomy, endovascular, endoscopic, superficial, or ambulatory procedures
12. Pregnancy or lactating women
13. Prisoners

2.2.3 Screening and Enrollment

Screening and recruitment at UCM Anesthesia Perioperative Medicine Clinic (APMC), which conducts preoperative visits for approx. 19-35 patients/day; or during a preoperative stay in the hospital for eligible inpatients. The purpose of the APMC is to perform standardized assessments prior to surgery..Pre-screening will be conducted by coordinator review of the APMC schedule to identify patients who meet the criteria for age, eligible surgical procedure, and planned general anesthesia. If a patient is deemed eligible, the patient's medical history will be further evaluated by review of the electronic medical record (EMR) to apply inclusion and exclusion criteria. Eligible patients will be approached in APMC by a study team member who will discuss study aims, procedures, risks, and benefits of participation.

The screening and recruitment plan at TAH will be approved and in accordance with their local Ethics Committee; while following institutional guidelines regarding research patient enrollment in a pre-operative clinical setting,

Occasionally, patients undergoing elective surgery will be recruited from inpatient hospital units. These patients will be identified by routine screening of the OR schedule then following the same process as described above, utilizing the EMR to further assess inclusion/exclusion criteria prior to approaching for informed consent and study participation.

2.2.4 Informed Consent Process

After determining clinical eligibility, the study will be discussed with patients, including all research related procedures, subject involvement, risks and benefits. Patients will be provided the opportunity to ask questions and if agreeable and demonstrate verbal understanding, we will obtain written informed consent prior to any study related procedures. Subjects will be provided with a signed and dated copy of the consent form document.

After obtaining informed consent, patients will be enrolled in the trial. Final decision for randomization will be made in the operating room when patient meets criteria for study drug administration.

2.2.5 Randomization and Blinding

Randomization will be performed respectively by UCM Investigational Drug Services (IDS), and TAH drug services), using a 1:1 computer-generated randomization sequence, which will be concealed from investigators and the research team through study completion. Consented patients will be randomly assigned to receive metoprolol tartrate or an identical appearing placebo in a 1:1 ratio using permutation blocks (n=4 per block). Study subjects, clinicians and research team will be blinded to the randomization assignment. Similarly, the adjudicators, whom will determine severity and relatedness of potential adverse events (AEs) and serious adverse events, will be blinded and only receive the information necessary to make a decision regarding relatedness to study treatment.

Perioperative intravenous doses of study drug will be prepared respectively by each institutions drug services department, using identical syringes for administration of 5mg metoprolol tartrate in 5mL (1mg/mL) or 5mL placebo (normal saline). Post-operative oral doses will be dispensed in identical capsules; active capsules will contain an over-encapsulated metoprolol tartrate 25 mg tablet with lactose monohydrate backfill and placebo capsules will contain lactose monohydrate for equal weight and feel.

It's the responsibility of the respective research pharmacies to maintain documentation of medication procurement and preparation, as well as randomization, dispensing, and accountability logs. All medications and blinding supplies will be stored in a secure location within the research pharmacy and maintained under controlled environmental conditions.

2.2.6 Screening log of patients excluded from trial

The study team will maintain a log of all patients screened for this trial to include:

- Eligible and consented
- Eligible and non-consented (reason for refusal)
- Ineligible due to exclusion criteria, indicating the unmet exclusion criteria

2.3 Risks and Benefits

2.3.1 Risks

Risks associated with metoprolol: Metoprolol is one of the most commonly used β-blockers.

Likely:	Reduction in heart rate and blood pressure,
Less likely:	Bronchospasm, clinically significant hypotension and bradycardia, dizziness nausea, diarrhea
Rare:	Stroke, death, heart failure, cardiac arrhythmias, blurred vision, hepatitis, psoriasis flare up, itching, rash

Risks associated with blood collection: The blood draw may cause bleeding, bruising, or pain. There is also a rare risk of infection from venipuncture. Risk from blood collection from a catheter is primarily infection. Maximum blood collection is up to approx 37mL collected for up to 72 hours postop.

Risks involving ECG: and hemodynamic monitoring includes mild skin irritation from the electrodes.

Risk of confidentiality breach is also possible.

The patient will not be penalized or accrue any additional risks if they are randomized to the "placebo" group. No standard of care will be affected by this study. If deemed necessary, an un-blinding of the primary care team by investigational pharmacy may be activated to ensure the appropriate care can be given to the patient.

2.3.2 Benefits

Participation in this clinical trial may provide additional benefit from continuous hemodynamic monitoring and daily post-operative ECGs which help detect silent cardiac events that otherwise may go unnoticed. Subjects will also receive daily post-operative follow-up visits from a member of the study team for assessment of any AEs and SAEs.

This clinical trial has the potential to significantly reduce risk of adverse perioperative cardiac events for patients in the metoprolol group. The anticipated additional benefit of this research is to provide validation of an evidence-based approach utilizing hs-cTn assays in clinical practice to improve preoperative cardiac risk stratification.

2.4 Withdrawal

2.4.1 Early Withdrawal of Subjects

Early withdrawal may occur per PI discretion if deemed in the best interest of the subject. Subjects may also withdraw from study participation at any time. At the time of withdrawal, the metoprolol (or placebo) will be stopped. Patients who desire withdrawal from the protocol will be asked if they may be contacted at 30-days and 12-months to complete follow up.

2.4.2 How and When to Withdraw Subjects Before Randomization

Patients who do not meet criteria to receive study drug in the OR prior to extubation will be withdrawn per protocol and will not undergo any further interventional study related procedures or treatments.

3.4.3 Follow-up for Withdrawn Subjects

The research team may continue to monitor withdrawn subjects for adverse events and serious adverse events during hospitalization.

2.5 Study Drug

2.5.1 Description of Study Drug

Metoprolol is a β1-selective β-blocker. The estimated oral bioavailability of immediate-release metoprolol tartrate tartrate is about 50%.[56] Median elimination half-life of oral immediate-release metoprolol tartrate is between 3-5 hours in normal metabolizers. Peak plasma concentrations are reached after 2-3 min. for IV and 1-2 hours for oral metoprolol tartrate.

2.5.2 Treatment Regimen

At approx. 15 minutes before planned extubation in the OR, the patient's hemodynamic status will be assessed to determine if randomization criteria are met to allow study drug administration. These criteria are:

1) heart rate >65/min
2) systolic blood pressure > 110 mmHg (if subject > 79 yrs, SBP target is > 120)
3) minimal active bleeding
4) no active wheezing;

Subjects who meet randomization criteria will receive the study drug. Subjects that do not meet the randomization criteria will be withdrawn.

Participants will be administered study drug using a double-blind, randomization as described above. Subjects will be randomized to one of the following two groups:

- In the ***Beta-Blocker arm***, patients will receive up to 3 doses of **5mg IV Metoprolol tartrate** prior to extubation to achieve target heart rate of 65/min, for a total of up to **15mg IV Metoprolol tartrate,** followed by 25mg immediate-release **oral 25mg Metoprolol tartrate** in the post-operative unit and every 8 hours thereafter for up to POD 3 (72 hours)
- In the ***Placebo arm***, patients will receive up to 3 doses of **5mL IV normal saline (placebo)** prior to extubation, for a total of up to **15mL IV placebo** followed by an oral matching placebo capsule (lactulose) in the PACU and every 8 hours thereafter for up to POD 3 (72 hours)

At least 2 hours after the first intraoperative dose and while in the Post-operative unit, the patient may receive an oral dose of study drug (placebo vs oral metoprolol tartrate 25mg) if HR >65 bpm and SBP >110 mmHg (if subject > 79 yrs, SBP target is > 120) and no active or minimal bleeding or no active wheezing. This regimen will

be repeated on the floor every 8 hours with oral study drug (placebo vs 25mg metoprolol tartrate) through postoperative day 3. Patients who cannot receive oral medications per clinical orders, may receive IV study drug (metoprolol tartrate 5mg or placebo 5mL) to be administered over 2 minutes. If IV study drug is administered on the floor, additional monitoring via hospital telemetry should be active. Of note, the first oral dose administered on the floor should be given at least 4 hours following the Post-operative unit dose.

Rescue Medication

If patients develop clinically significant hypotension (defined as systolic blood pressure < 90 mmHg), clinicians are encouraged to raise and maintain a systolic blood pressure > 110 mmHg. We will provide clinicians with an optional rescue protocol that includes administration of IV drugs (e.g. phenylephrine, ephedrine, etc.) and/or IV fluid bolus. Likewise, if patients develop clinically significant bradycardia (defined as HR < 50/min), clinicians are encouraged to raise the heart rate >60/min. Options may include IV glycopyrrolate, ephedrine, and atropine.

2.5.3 Justification for Metoprolol Intervention

The rationale for the metoprolol regimen is the following:

1. IV metoprolol is the only AHA-recommended standard of care parenteral β-blocker for acute MI in non-surgical settings
2. The IV dosing regimen is identical to the MIAMI trial and COMMIT trial
3. Data for bisoprolol are sparse and an IV formulation is not FDA-approved
4. Atenolol has lower effectiveness compared to metoprolol and is no longer considered a first-line β-blocker; furthermore, atenolol depends on renal excretion which may be affected by perioperative acute kidney injury
5. Esmolol (ultra-short acting IV β-blocker) must be administered via IV infusion which excludes discharge of postoperative patients to a regular floor; thus, using esmolol would severely limit the eligible patient population to patients being admitted to an ICU or other monitored environment
6. All perioperative MI studies have shown that >90% of perioperative adverse cardiac events occur between the day of surgery and postoperative day 3; therefore, we decided on a short-term β-blocker intervention (3 days) that will cover this high-risk period compared to a 30-day course
7. The daily oral metoprolol dose in this trial is 25% lower than in the POISE trial (150 mg vs. 200 mg) which we expect to retain the effectiveness of β-blockade while lowering the risk of hypotension and stroke.

2.5.4 Provision, Storage, and Packaging, Dispensing of Study Drug

Drug procurement and dispersing will be in accordance with respective institutional guidelines. Formulations of metoprolol tartrate and placebo will be prepared and provided by respective institutional drug services department. Active study drug (metoprolol tartrate) will be provided in IV formulation in 3 separate syringes each containing 5mg at a concentration of 1mg/mL.

2.5.5 Potential Adverse Reactions Related to Study Drug Administration

Likely: Reduction in heart rate and blood pressure,
Less likely: Bronchospasm, clinically significant hypotension, dizziness, bradycardia, nausea, and diarrhea
Rare: Stroke, death, cardiac arrhythmias, depression, heart failure, blurred vision, hepatitis, psoriasis flare up, itching, rash

2.6 Study Outcomes

2.6.1 Primary Outcome Measures

Primary efficacy endpoint: Myocardial injury (hs-cTn elevation)

Primary safety endpoints: Clinically relevant hypotension

2.6.2 Secondary Outcome Measures

1) MACE (Major Adverse Cardiac Events), including myocardial infarction, cardiac arrest, death
2) Myocardial ischemia (ST-depression/elevation duration)
3) Stroke
4) Cumulative vasopressor requirements in post-operative unit
5) Incidence rate and cumulative bradycardia duration (HR <50/min)
6) Unplanned ICU admission
7) Length of hospital stay
8) Length of ICU stay

2.6.3 Endpoint Definitions

Myocardial Injury: for statistical purposes, we will use the Δhs-cTn = difference between baseline and peak postoperative hs-cTn as continuous variable. To define an "event", myocardial injury will be defined as a new hscTn elevation >99th percentile, or a 50% increase if the baseline hscTn is already elevated >99th percentile.

Clinically relevant hypotension is defined as cumulative hypotensive time (duration of syst. BP <90 mmHg); Symptomatic hypotension as event is defined when there was a clinical intervention due to hypotension and/or the patient developed clinical symptoms due to hypotension.

MACE are defined as MI, cardiac death or coronary revascularization

Myocardial Ischemia is defined as ST depression or elevation of ≥0.2 mV in one lead or ≥0.1 mV in two contiguous leads lasting ≥10 min

Myocardial infarction will be assessed according to the Third Universal Definition of myocardial infarction (rising pattern of cTn with at least one elevation > 99th percentile plus new ECG changes indicative of myocardial ischemia and/or clinical symptoms). New Q-waves, ST-segment depression or T-wave inversion ≥ 0.1mV, or ST-elevation ≥ 0.2 mV in at least two contiguous leads are considered indicative of myocardial ischemia. The diagnosis of MI will be made and adjudicated by an attending cardiologist.

Deaths will be reviewed by two independent physicians and classified as either cardiac or non-cardiac

Sudden unexplained deaths will be classified as cardiac unless evidence to the contrary (e.g. autopsy)

Stroke will be defined as focal or global cerebral, spinal, or retinal dysfunction of sudden onset that either: 1) persists for > 24 hours and has no known corresponding hemorrhage on brain imaging, or 2) persists for < 24 hrs and is associated with infarction of central nervous system tissue documented on brain imaging.

3. STUDY PROCEDURES

3.1 Trial Activities Prior to the Day of Surgery

- Subject will have provided written informed consent
- Research team will document medical/surgical history, relevant laboratory and radiological results, planned surgery and concomitant medications
- Preop vital signs and 12 lead ECG will be obtained
- Blood sample #1 (5mL) will be conducted for hs-cTn

4.2 Day of surgery study procedures

- The research team will confirm subject continues to meet all inclusion/exclusion criteria per protocol and wishes to continue with study participation
- Research team will inform clinical team of study participation and procedures
- Medical history and concomitant medications will be reviewed for any changes in health status since date of consent
- Study subject will undergo preop collection of blood for hs-cTn and 12 lead ECG if not already obtained prior to day of surgery.
- Holter monitoring will be initiated
- A member of the study team will be present in the OR for hemodynamic data collection at induction and to evaluate for randomization criteria prior to administration of study drug (Sect 3.5.2)
- Prior to extubation and before administration of study drug, blood sample #2 (5mL) may be collected for hs-cTn
- At approx **15 minutes prior to extubation** and if the patient meets hemodynamic criteria, the anesthesia team will follow guidelines to administer the study drug per protocol:
  - ❖ A slow injection over 1 minute of IV study drug (5mL IV metoprolol tartrate (5mg) or normal saline (placebo)
  - ❖ If after 5 min, HR >65 bpm and SBP >110 mmHg, administer a second dose of IV study drug (5mL)
  - ❖ If after an additional 5 min, HR >65 bpm and SBP >110 mmHg, admin a third dose of IV study drug
- Total dose of intra-operative study drug is up to 15mg IV metoprolol tartrate or 15mL normal saline placebo, for a targeted HR of 65 bpm
- NOTE: If the patient is greater than 79 years old, the systolic BP target will be >120 mmHg.

4.3 Post-operative Unit

- Upon arrival to post-op unit blood sample #3 (5mL) will be collected to measure hs-cTn. An additional 5mL sample of blood will be collect for DNA isolation, if not drawn previously.
- A 12 lead ECG will be obtained by a member of the study team
- ViSi Mobile continuous hemodynamic monitoring will be initiated (at UCM)
- Following a minimum of 2 hours after the first intraoperative dose of study drug, and if still in the post-operative unit, the patient may receive one dose of oral study drug (placebo vs 25mg oral over-encapsulated metoprolol tartrate) if HR >65 bpm and SBP >110 mmHg and no active or minimal bleeding. If the patient is greater than 79 years old, the SBP parameter will be >120 mmHg. The target HR is 65 bpm.
- If the subject cannot tolerate oral medication, study drug may be administered intravenously as 5mg IV metoprolol tartrate.

4.4 Trial Activities for post-operative treatment period (POD1 – POD3)

- At least 4 hours after receiving study drug in the post-operative unit, and 6-8 hours after the first intraoperative dose, the patient will be assessed for oral study drug treatment. If the HR >65 bpm and SBP >110 mmHg and there is no active or minimal bleeding, the patient will be given 25mg over-encapsulated, oral metoprolol tartrate or matching placebo (or by IV route as stated above with telemetry monitoring requirements). If the patient is greater than 79 years old, the systolic BP target will be >120 mmHg. The target HR is 65 bpm.

- This dosing regimen will be repeated every 8 hours with 25mg oral metoprolol tartrate or placebo through post-operative day 3
- On the morning of POD 1-3, subjects will undergo blood collection for hs-cTn, blood samples #4, #5, and #6 (or through hospital discharge, whichever occurs first)
- 12-lead ECG will be obtained on POD 1-3 and will be evaluated by a member of the study team for outcomes measures and AEs/SAEs

Total blood collection during the study treatment will be up to 6 blood samples (approx. 30 mL) and 1 blood collection for DNA (7mL) for a total of approx. 37mL or about 3 tablespoons. Continuous hemodynamic monitoring using the Visi-Mobile will be performed through end of treatment on POD3 (approx. 72 hours postop) or hospital discharge, whichever occurs first. Patients will be followed through hospital discharge for any AEs/SAEs.

30-day Follow-Up

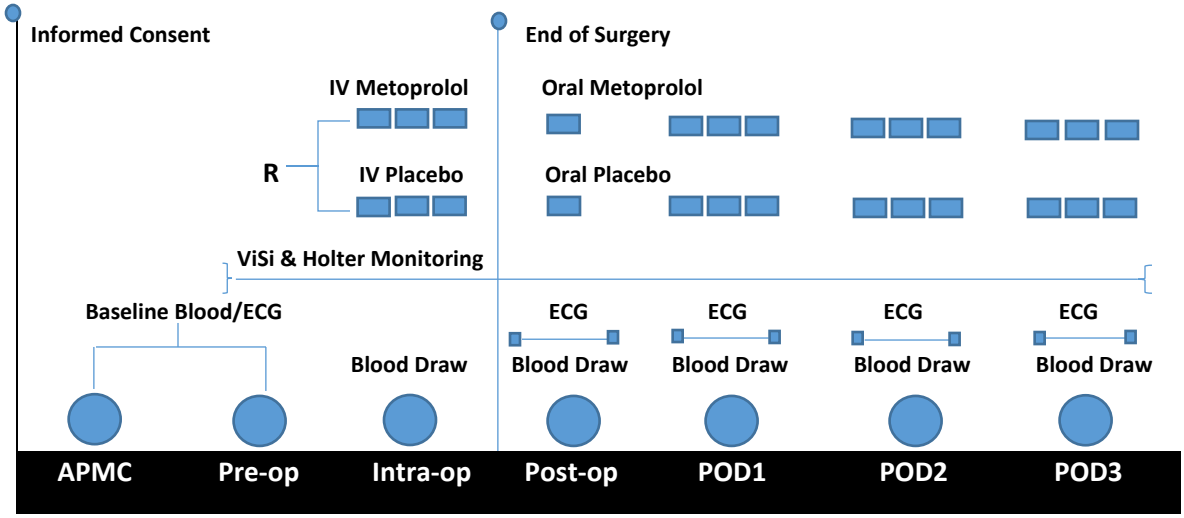
- Approximately 30 days following day of surgery, patients will be contacted by telephone to assess for outcome measures, adverse events, and changes in medications. If a patient cannot be contacted after multiple attempts at up to 5 varying time points, a chart review will be conducted to complete the 30-day follow-up.

1-year Follow-Up

- Approximately 1 year following the day of surgery, patients will be contacted by telephone for an assessment of 1-year morbidity and mortality, using the same survey tool for outcomes measured at Day 30, inclusive of major vascular events.
- This will be the final contact with study participants

4.5 Summary of Trial Intervention and Procedures

An overview of trial flow is summarized in the diagram below



5 SAFETY AND ETHICAL CONSIDERATIONS

5.1 Protection of Human Subjects

5.1.1 Human Subjects Involvement and Characteristics

The principal investigators will submit this protocol to the UC Human Research Protection Office for Internal Review Board approval. Research personnel will approach all potentially eligible patients who fulfil inclusion and exclusion criteria for consent. As defined in the eligibility criteria, patients with conditions that predispose them to risk of adverse events associated with decreased heart rate or blood pressure secondary to the administration of a Beta-blocker will be excluded. These conditions include but are not limited to history of stroke, TIA, carotid disease, and hemodynamic instability. Patient participation will be at the discretion of the PI and clinical care team and all other aspects of routine clinical care will not be affected by their participation in the study.

This trial will not include vulnerable populations and will not enroll children (<18 yrs of age). All participants must be able to provide verbal understanding and informed consent. Prisoners will not be enrolled in this study.

5.1.2 Potential Risks

- Protocol-specific risks associated with participation may include minor bruising and/or discomfort from blood draws
- Study-drug specific risks include:
  - Likely: hypotension, bradycardia,
  - Less likely: Bronchospasm, allergic reaction, dizziness nausea, diarrhea, severe hypotension or bradycardia
  - Rare: stroke, death, cardiac arrhythmias, blurred vision, heart failure, psoriasis flare up, severe allergic reaction

Participants risk the possibility of confidential information accidentally being disclosed

5.1.3 Adequacy of protection against risks

- All subjects that participate will provide verbal understanding of risks and sign informed consent prior to enrollment in the study. Subjects will be informed that participation is voluntary, and they may refuse to participate and withdraw from the study at any time without penalty. Subjects will be told that in the event of a physical injury as the direct result of study procedures, the team will do everything to limit the injury at no cost to the patient, within the limits of the respective study sites.
- All patients will receive general anesthesia by a team led by Board-certified/eligible anesthesiology faculty that operates at the highest standards of current medical practice and has an extensive experience in perioperative care for major vascular and other non-cardiac surgery. Patients will be fully monitored according to and exceeding of the American Society of Anesthesiology standards to quickly assess any adverse event or complication from the time in the preoperative holding area through operating room and post-anesthesia care unit.
- Blood draws will be completed by clinical staff with extensive experience in phlebotomy and blood collections.
- Patient's participation will be continuously assessed with ongoing study treatment at the discretion of the PI and the clinical care team.
- Hemodynamic parameters designed to ensure subjects receive study drug as appropriate and when indicated (HR >65bpm and SBP >110 mmHg. If a patient is over 79 year of age, the SBP target will be 120 mmHg.)
- The clinical care team will be provided with the guidelines for providing rescue medications if a patient develops clinically significant hypotension (defined as SBP <90 mmHg) or bradycardia (HR <50 bpm).
- Serious adverse events will be reported to the respective institutional IRB/Ethics committee according to current IRB/Ethics committee guidelines. Adequate clinical care readily available at the University of Chicago Medicine, and The Alfred Health, major tertiary care hospitals with around-the-clock anesthesia attending staffing and ICU availability.
- The attending surgeon and the surgery staff caring for the subject will be informed of the subject's participation and provided detailed information related to study drug administration
- The research team will be in open and continuous discussion with clinical team to ensure that there is no disruption in routine medical supervision, comfort, and recovery
- Extensive measures will be taken to prevent any confidentiality breach of participants' information as described below

5.1.4 Inclusion of Women

There is no exclusion of any sex/gender or racial/ethnic group for these studies. This study actively encourages the participation of women. The study goal is equivalent numbers of women and men.

5.1.5 Inclusion of Minorities

This study actively encourages the participation of minorities. Minority recruiting will typically match the demographic composition of the University of Chicago community from which subjects will be recruited.

5.1.6 Inclusion of Children

Subjects <18 yrs will not be studied in these investigations.

5.1.7 Clincaltrials.gov requirements

The proposed research will be registered in ClinicalTrials.gov once the protocol has been reviewed and approved by UC IRB.

5.2 Data Management Practices

All research data will be recorded and saved to a secure password protected research designated server at the resptive study sites. Data will be de-identified and stored under lock and key (secured building, locked office, locked cabinet) and only the research team will access.

5.3 Ethical Measures Pertaining to Clinical Care

The research team will inform the clinical team of any relevant information that is ascertained as a result of the research monitoring (Holter, 12 lead ECG, VisiMobile hemodynamic monitoring, patient self-reported symptoms, etc).

5.4 Linkages to Subjects and Access to Identifiers

Any information that is obtained in connection with research that can be identified with a subject will remain confidential. Medical information, case report forms, pharmacokinetic and genetic data will be given a code and only the research personnel will have access to this information. The original informed consent forms will be kept by the PI for 7 years and a copy will be given to all subjects.

6 ADVERSE EVENT REPORTING

6.1 Definitions of Adverse Events

An **Adverse Event** is an unfavorable change in health that occurs in a patient during their enrollment in the clinical trial, even if it is not associated with the investigational study drug.

An **Unanticipated Problem** is an incident, experience, or outcome that meets all of the following criteria:

1. Is unexpected in nature, severity, or frequency
2. Is related or possibly related to participation in the research
3. Suggests that the research places subjects or other

A **Serious Adverse Event** is an unfavorable change in health that:

- Results in death
- Is life-threatening
    - In the definition of serious adverse-events, the term “life-threatening” refers to an event during which the subject was at risk of death at the time of the event. It does not include an event which hypothetically may have caused death, had it been more severe.
- Requires hospitalization or prolongation of the existing hospitalization, unless
    - The hospitalization was pre-planned before the study
    - Emergency room visits without hospital admission
    - Hospitalization for elective surgery for a condition that was pre-existing at the time of initial enrollment.
- Results in a persistent or significant disability or incapacity
    - This refers to an event which causes a substantial disruption of a person’s ability to conduct normal life functions. This does not include events of relatively minor significance such as uncomplicated nausea and vomiting, diarrhea, or accidental trauma (e.g. sprained ankle) which may interfere or prevent daily life functions but is temporary or does not constitute a substantial disruption.

- Resulting in a congenital anomaly or birth defect

6.2 Classification of Adverse Events

Adverse events assessment will be performed by the PI to assign a rating for severity and causality, per institutional and federal guidelines. The PI will consider alternative causes for the event, including underlying medical conditions, concurrent medical therapy, risk factors, prior reactions of similar nature within this class of drugs, and the temporal relationship of the event in context of the study drug pharmacokinetics.
Relationship to study drug will be classified as:

- None – An event for which there is no causal relationship between the study drug and the event and an alternative explanation is more likely.
- Unlikely – An event for which the relationship between the event and the study drug is not clearly established or uncertain.
- Probable – An event for which there is most likely a causal relationship between the study drug and the event and an alternative explanation is less likely.

Severity for adverse events will be based on the PIs clinical judgment. Severity will be classified as:

- Mild – An event that causes minimal discomfort to the subject and does not interfere with the functions of daily living.
- Moderate – An event that interferes with, but does not prevent the subject from performing the functions of daily living.
- Severe – An event that is incapacitating and prevents the subject from performing functions of daily living.

6.3 Adverse Events Data Collection Procedures

The investigators will closely monitor subjects for evidence of adverse events. All adverse events will be reported and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, severity, etiology, relationship to the study drug (none, unlikely, probable) and any treatment required. The clinicians will manage any postoperative event related to the patient's surgical procedure as standard of care.

6.4 Procedures for Serious Adverse Events

All Serious Adverse Events or Unanticipated Problems will be reported to the IRB/Ethics committee and respective study site DSMB in accordance with institutional and federal guidelines. Unblinding will be at the discretion of the PI with the collaborative efforts of the primary care team to determine the necessity. Study drug storage, logging, and distribution is the responsibility of the respective institutional drug service departments, and they will be responsible for notifying the care team of the patient's randomized study arm.

6.5 Summary of Adverse Event Classification and Reporting

- All **serious adverse events** will be reported to the IRB within **7 calendar days** of initial receipt of the information
- All **unanticipated problems** will be reported to the IRB within **10 calendar days** of initial receipt of the information

SAEs will also be assessed for causality and severity per the Division of Clinical & Translational Research Standard Operating Procedures.

7 STATISTICAL PLAN

7.1 Sample Size Determination and Power

This trial will randomize 600 study subjects to achieve a minimum of 500 evaluable subjects, which would provide a power (1-β) of 0.99. For the primary efficacy analysis, we have based our estimate of the needed sample size based on our experience in the VINO trial conducted by Nagele et al. at WU School of Medicine. We observed a standard deviation of 4.0 ng/L for the peak change in cTn from baseline. Using a two-sided α=.025, a difference between the two groups of 1.5 ng/L, and a conservative estimate of 250 usable peak values in each group we calculated a power (1-β) of 0.99.

7.2 Interim Analysis

A blinded interim analysis for safety after 50% of patients have been enrolled, will be conducted. The interim analysis will not assess futility or early stopping other than for safety concerns. The DSMB will review the safety record and formally assess a statistically significant trend in increased rates of strokes and deaths at an alpha-level of 0.025. It is at the discretion of the DSMB to stop the trial for other safety concerns, such as in-creased hypotension.

7.3 Statistical Methods and Analysis Plan

a) **Hypothesis 1** (*In patients with high cardiovascular risk undergoing major, non-cardiac surgery, postoperative therapy with the beta-blocker metoprolol will significantly reduce postoperative myocardial injury without causing clinically significant hypotension*): The primary analysis will be intention-to-treat. The main comparison between metoprolol and placebo arm for the primary efficacy endpoints will be comparing the Δhs-cTn between both arms (Δhs-cTn = difference between baseline and peak postoperative hs-cTn). These will be tested with a simple t-test (α= 0.05). For the analysis of the primary safety endpoint (hypotension) the difference in cumulative hypotensive time will be tested with a t-test. Transformations will be used if there are substantial departures from the distributional assumptions for these t-tests. For secondary analyses of the hs-cTn values, we will fit a repeated measures analysis of variance model showing the time course of the average elevation and allow a test of the area under the curve with the use of an appropriate contrast statement. Secondary endpoints will be analyzed like the safety endpoint. We will also augment all analyses by repeating all analyses with an appropriate vector of covariates to an ANOVA model for continuous outcomes and for logistic regression for dichotomous variables.

b) **Hypothesis 2** (*Postoperative β-blocker therapy is more effective in patients with elevated preoperative hs-cTn ("high-risk"- patients*). To determine if postoperative β-blocker therapy is more effective in patients with elevated preoperative hs-cTn, we plan the following analyses: The first goal will be to identify a cutoff preoperative hs-cTn concentration that defines high-risk patients using ROC analyses. Using this hs-cTn cutoff, we will compute the interaction of being in the high risk group and randomization group on the Δhs-cTn (difference between baseline and peak postoperative hs-cTn) We will consider a two-sided p-value < 0.05 for the interaction term (high-risk group * metoprolol) as statistically significant. Exploratory analyses will extend this model adjusting for known covariates of perioperative cardiac risk such as age, sex, eGFR, heart failure, etc.

8 DATA AND SAFETY MONITORING

8.1 Data Sources and Quality Assurance

8.1.1 Sources of Material

The following "materials" will be obtained from all study patients for research purposes only:

- Blood tests for hs-cTn: approximately 5mL at up to 6 time points over a 3-day period and an additional 7mL for DNA, for a total of up to approximately 37 ml blood
- 12-lead ECG and digital recording of continuous Holter ECG (up to 72 hours postop)
- Monitoring of vital signs: VisiMobile provides continuous hemodynamic monitoring (for 72 hours postop)
- Daily post-op assessments for AEs/SAEs
- Information from the patient's medical record including progress notes, lab results and diagnostic testing

Results from some of these tests will not available until several weeks after the patient has completed the study and will not enter the patient's clinical record. Blood samples will be stored in a -80º F freezer in a secure location, allowing only research team access. All samples will be de-identified with a study ID. All data will be for research purposes only. In the event of an incidental finding, the PI will discuss such findings with the clinical team and/or primary care physician.

8.1.2 Data Quality Assurance

In order to optimize the accuracy and quality of data, we will:

- Educate all members of the study team to study protocol, manual of procedures and work in accordance with good clinical practice
- Provide manual of procedures and guidelines for data acquisition and the completion of the CRF to ensure consistency
- Utilize a system of validation measures for the CRF to help protect against user error

8.2 Confidentiality and Security

All electronic data (except for an electronic key linking study ID to PHI) will be de-identified of protected health information that could link the data or blood samples to an individual subject. We will only use pre-assigned patient study ID numbers to label blood samples, Holter ECG, and hemodynamic information. The numbers are linked to subject data and identifiers using an electronic key. Only the research team will have access to the electronic key, which will be kept password-protected on a secured network. All research files will be stored in a locked and secure location only accessible to the study team. Electronically stored info will be encrypted and stored in a password protected database.

8.3 Minimization of Bias

Potential biases will be minimized by the study design of this double-blinded randomized controlled trial. Randomization will be performed by respective study site drug services department, utilizing a 1:1 randomization sequence, which will be concealed from investigators until the completion of the study. Health care providers, study personnel and patients will be blinded to the assigned intervention group (placebo vs. metoprolol). Similarly, the adjudicators will also be blinded and only receive information necessary to make a decision. Patient recruitment from preoperative clinics reduce selection bias since this is a clearly defined and easily accessible population that is well-representative of patient undergoing non-cardiac surgery with high cardiac risk. All patients attending the preoperative clinics will be screened according to routine operating procedures, with IRB/Ethics committee approval for a partial waiver of consent, irrespective of race, sex and religion. A

standardized method of assessing reasons for dropouts and withdrawals will be utilized at multiple time-points throughout the study. This will be an intention to treat analysis to avoid bias during data analysis.

8.4 Data and Safety Monitoring Board

A **data and safety monitoring board (DSMB)** will be established for this study at each site consisting of two senior anesthesiologists who are not directly involved in the study, one biostatistician, and one cardiologist. The DSMB is responsible for overseeing the overall safety of the study and will meet before the start of the trial to discuss the study protocol and DSMB charter. The board will meet annually to review all adverse and serious adverse events. Should there be a serious adverse event that potentially increases the risks to the participants, the study will be stopped, an investigation will be conducted, and a findings report will be generated before the study is resumed. These individuals will review; make decisions on adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct. The DSMB will review the consent periodically and/or as needed consider whether the consent form requires revision. At intervals, as noted above, the DSMB will also review formal interim analyses. In addition to regular meetings, it may be necessary to convene the DSMB urgently on an ad hoc basis to discuss new data or other information that raises questions about equipoise, safety, or conduct of the trial.

It is expected that all DSMB members will attend every meeting and conference call. However, it is recognized that this may not always be possible. A quorum for voting is half of the standing members plus one. The board may wish to decide if particular expertise is needed with the quorum for a particular meeting. All standing monitoring board members are voting members. The board may decide in advance whether ad hoc members can vote and whether absent members can vote electronically on proposed issues in advance.