RESEARCH PROTOCOL

NOVEL STRATEGY FOR PERIOPERATIVE BETA-BLOCKER THERAPY
PILOT STUDY

Peter Nagele, MD
Associate Professor
Division of Clinical and Translational Research
Department of Anesthesiology
Washington University School of Medicine
660 S. Euclid Ave
Campus Box 8054
Saint Louis, MO, 63110
Tel: 314-286-1715
Fax: 314 286-2948
E-mail: nagelep@anest.wustl.edu

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1. SYNOPSIS

<table>
<thead>
<tr>
<th>Study Title</th>
<th>NOVEL STRATEGY FOR PERIOPERATIVE BETA-BLOCKER THERAPY – PILOT</th>
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<tbody>
<tr>
<td>Objective</td>
<td>Determine the efficacy and safety of postoperative beta-blocker therapy to reduce myocardial injury in patients with high cardiovascular risk. Determine the clinical utility of pre-operative high-sensitivity cardiac troponin levels for identifying patients who will benefit from postoperative beta-blocker therapy.</td>
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<tr>
<td>Hypothesis</td>
<td>In patients with high cardiovascular risk undergoing major, non-cardiac surgery, postoperative therapy with the beta-blocker, metoprolol, will significantly reduce postoperative cardiac injury without causing clinically significant hypotension. Postoperative β-blocker therapy is more effective in patients with elevated preoperative hs-cTn (“high-risk”- patients).</td>
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<tr>
<td>Study Period</td>
<td>Planned enrollment duration: 6 months Planned study duration: up to 3 days per subject</td>
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<tr>
<td>Number of Patients</td>
<td>30 consented patients, 20 evaluable subjects</td>
</tr>
<tr>
<td>Study Treatment</td>
<td>Postsurgical: 5mg metoprolol, IV, prior to extubation, every 5 minutes to achieve target heart rate of 65/min, up to 15mg; then 25mg metoprolol, oral, every 8 hours for 72 hours.</td>
</tr>
<tr>
<td>Study Design</td>
<td>Open-label</td>
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</tbody>
</table>
| Inclusion and Exclusion Criteria | Inclusion:  
1. Age ≥ 50 years  
2. American Society of Anesthesiologists [ASA] physical status classification III-IV  
3. Beta-blocker naïve [30 days prior to surgery]  
4. Previously diagnosed coronary artery disease (CAD), OR  
   - History of peripheral vascular disease(PVD), OR  
   - Chronic kidney disease(CKD) [eGFR ≤60ml/min] OR  
   - At high risk for CAD (must meet at least 2 criteria)  
      a. Age ≥ 70 years  
      b. Hypertension  
      c. Diabetes requiring oral medication or insulin  
      d. Current smoker or some days smoker within the past 2 years  
5. Major non-cardiac, elective surgery under general anesthesia  
Exclusion:  
1. History of stroke, or TIA  
2. Previously diagnosed carotid disease, OR either 70% unilateral or 50% bilateral carotid occlusion.  
3. Heart rate ≤55bpm  
4. Systolic blood pressure ≤110 mmHg, or ≤120 mmHg for patients >79 yrs-old  
5. Congestive heart failure with New York Heart Association(NYHA) Functional Classification of III-IV or left ventricular heart failure with ejection fraction ≤50%  
6. Moderate or severe valvular regurgitation  
7. Second or third degree AV block without pacemaker  
8. Active asthma or COPD with symptoms or resolving symptoms on day of surgery  
9. Anemia [Hb≤9g/dL]  
10. Allergy to beta-blockade drugs  
11. Hemodynamic instability  
12. Uncontrolled hemorrhage  
13. Unwilling or unable to give consent for participation  
14. Planned spinal or epidural anesthesia  
15. Undergoing any carotid endarterectomy, endovascular, endoscopic, superficial, or ambulatory procedures |
| Measurements | 1. 12-lead ECG monitoring for up to 72 hours with possible spot 12-lead ECGs  
2. Mobile hemodynamic monitoring for up to 72 hours  
3. High-sensitivity cardiac troponin plasma levels [hs-cTn] at up to 7 time points: baseline, pre-operative, peri-operative, post-operative, 24 hrs, 48 hrs, and 72 hrs. |
4. Daily adverse event monitoring until discharge.
5. Phone visit at 30 days
2. STUDY PROTOCOL

Background and Significance

Perioperative adverse cardiac events are a significant public health concern. Often referred to as "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). 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). Perioperative statin therapy has nearly exclusively been explored in retrospective studies, 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. 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 offers a potential 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).

Preliminary Data

Clinical Trial Experience Since 2007, the PI’s research team has screened more than 7,800 patients and enrolled more than 1,150 patients into 5 randomized controlled trials or prospective cohort studies at Barnes- Jewish-Hospital (see Table 1). The VINO trial was an NIH-funded (K23 GM087534) single-center randomized controlled trial with a very similar population, clinical trial structure and outcomes assessment including collaboration with BJH Investigational Pharmacy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients Screened</th>
<th>Patients enrolled</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-VINO</td>
<td>RCT</td>
<td>~100</td>
<td>N=63</td>
<td>Healthy, ASA I-II</td>
<td>Biomarker (tHcy)</td>
</tr>
<tr>
<td>VISION</td>
<td>Prospective cohort</td>
<td>~350</td>
<td>N=97</td>
<td>CAD, elevated cardiac risk, ASA III-IV</td>
<td>cTn</td>
</tr>
<tr>
<td>VINO</td>
<td>RCT</td>
<td>6,831</td>
<td>N=625</td>
<td>CAD, elevated cardiac risk, ASA III-IV</td>
<td>cTn, hs-cTn, MACE</td>
</tr>
<tr>
<td>QTc (unpublished)</td>
<td>Prospective cohort</td>
<td>~420</td>
<td>N=300</td>
<td>General adult OR population</td>
<td>QTc, myocardial ischemia</td>
</tr>
<tr>
<td>Stress Test (unpublished)</td>
<td>Prospective cohort</td>
<td>~100</td>
<td>N=67</td>
<td>Patients undergoing cardiac stress testing</td>
<td>hs-cTn</td>
</tr>
</tbody>
</table>

Table 1: RCT: randomized controlled trial; ASA – American Society of Anesthesiologists; tHcy – plasma total homocysteine; CAD – coronary artery disease; cTn – cardiac troponin; MACE – major adverse cardiac events; hs-cTn – high sensitivity cardiac troponin; QTc – corrected QT-

Detection of myocardial ischemia with Holter ECG
In 2013 we enrolled 300 patients in a study to detect QTc-prolongation and myocardial ischemia using the identical 12-lead Holter ECG system and software presented in this application (DR181 12Lead Holter Digital Heart Monitor Recorder (NorthEast Monitoring, Maynard, MA). To the right is a strip from a patient in this study who developed a significant ST-depression in leads II, III, avF, V4-6. (Figure 2).

c) Detection of perioperative myocardial injury using high-sensitivity cardiac troponin

In an ancillary study to our VINO trial, we were among the first to demonstrate the use of hs-cTn in the perioperative setting by measuring the difference between baseline and postoperative peak hs-cTn (Δhs-cTn), which quantifies the extent of perioperative myocardial injury. 99% of patients had a detectable hs-cTn at baseline and hs-cTn increased postoperatively in >80% of patients.41 [Figure 3]

Cumulatively, we have shown that we have the necessary expertise in conducting clinical trials, the ability to meet recruitment goals, and the ability to use 12-lead Holter ECG as well as hs-cTn to detect and quantify perioperative myocardial ischemia and injury.

Objective

- Determine the efficacy and safety of postoperative beta-blocker therapy to reduce myocardial injury in patients with high cardiovascular risk.
- Determine if pre-operative hs-cTn level can predict which patients will benefit from post-operative beta-blocker therapy.

Aim 1: Determine if postoperative β-blocker therapy reduces myocardial ischemia and injury

- Sub-Aim 1: Efficacy: To determine whether titrated, postoperative β-blocker therapy reduces postoperative hs-cTn elevation and/or ST-segment depression/elevation.
- Sub-Aim 2: Safety: To determine whether titrated, postoperative β-blocker can be safely administered without causing prolonged hypotension.
Aim 2. To determine if preoperative hs-cTn can identify patients who benefit from postoperative β-blocker therapy.

**Patient Selection**

**Inclusion:**
1. Age ≥ 50 years
2. American Society of Anesthesiologists [ASA] physical status classification III-IV
3. Beta-blocker naïve [30 days prior to surgery]
4. Previously diagnosed CAD, OR
   a. History of PVD, OR
   b. CKD [eGFR ≤60ml/min] OR
   c. 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
5. Major non-cardiac, elective surgery under general anesthesia

**Exclusion:**
1. History of stroke or TIA
2. Heart rate ≤55bpm
3. Congestive heart failure with NYHA Functional Classification of III-IV, OR
   a. left ventricular heart failure with ejection fraction ≤50%
4. Baseline systolic blood pressure (SBP) ≤110 mmHg, or SBP ≤120 mmHg for patients greater than 79 years-old
5. Moderate or 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. Hemodynamic instability
11. Uncontrolled hemorrhage
12. Unwilling or unable to give consent for participation
13. Planned spinal or epidural anesthesia
14. Undergoing any carotid endarterectomy, endovascular, endoscopic, superficial, or ambulatory procedures

**Design and Procedures**

**Study Design**
The goal of this open-label pilot trial is to fine-tune the practicality of the trial intervention before commencing a large clinical trial and improve the efficiency.

**Study Procedures, Follow-Up and Assessment**

*a) Protocol:* Within an hour before surgery, patients will be connected to the 12-lead Holter ECG and a mobile hemodynamic monitor in the holding area of the operating room. We may also have spot ECGs if needed for calibration of Holter leads, if necessary. This monitor is a small cuff that fits on the patients’
finger with a securing strap at the wrist, and a chest strap that can capture continuous blood pressure measurements, heart rate, SpO2, respiratory rate, skin temperature, and potentially cardiac output. The patient will also have blood drawn for a baseline hs-cTn in holding before surgery. Perioperative care is at the discretion of the attending surgeon and anesthesiologist and will not be influenced by the protocol. These interventions and data collected are for research only, and will not enter the clinical record of the patients. The hemodynamic and troponin data collected will be analyzed for correlation with primary and secondary outcomes.

b) Intervention:

i) Drug: Metoprolol is a β1-selective β-blocker. The estimated oral bioavailability of immediate-release metoprolol tartrate is about 50%.56 Median elimination half-life of oral immediate-release metoprolol 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. In this trial, metoprolol tartrate will be administered first as intravenous injection (IV) followed by an immediate-release oral tablet. Metoprolol formulations for this trial will be prepared by BJH Investigational Pharmacy.

ii) Dosing regimen:

1. IV metoprolol
15 minutes before planned extubation patients will receive metoprolol. A rapid injection of 5 mg IV metoprolol will be administered. After 5 minutes, if HR > 65/min and BP > 110 mmHg, a second 5 mg IV dose will be administered (otherwise the treatment will stop). After 5 additional minutes, if HR > 65/min and BP > 110/mmHg, a third dose of 5 mg IV metoprolol will be given. The total IV metoprolol dose is 15 mg. Target HR is 65/min. If the patient is greater than 79 years-old, the systolic BP parameter will be >120mmHg.

2. Oral metoprolol
Before leaving the PACU (post-anesthesia care unit), patients will receive 25 mg oral metoprolol if HR > 65/min and BP > 110/min and no active or minimal bleeding (floor dosing should not be within 4 hours of PACU dosing). This regimen will be repeated every 8 hours with 25 mg metoprolol until postoperative day 3. If patients cannot tolerate oral medication, IV metoprolol as described above will be administered. Target HR is 65/min. If the patient is greater than 79 years-old, the systolic BP parameter will be >120mmHg.

3. Rescue
If patients develop clinically significant hypotension (defined as systolic blood pressure < 90 mmHg) clinicians will be instructed to administer IV phenylephrine as first line therapy, and a crystalloid fluid bolus, if hypovolemia is suspected, to maintain a systolic blood pressure > 110 mmHg. If patients develop clinically significant bradycardia (defined as HR < 50/min), 0.1 mg IV glycopyrrolate will be administered and repeated until HR > 60/min. Alternatively, if both bradycardia and hypotension are present, IV ephedrine may be administered.

Justification of 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 settings4; (2) the IV dosing regimen is identical to the MIAMI trial34 and COMMIT trial57; (3) although potentially superior, 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) although a potentially attractive option, 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.

Pre-Study Period
Patients will be recruited from patients with planned, elective surgery to be performed at Barnes-Jewish Hospital, St. Louis, MO. Screening and recruitment will occur in our preoperative anesthesia assessment clinic which sees between 90-115 patients/day or during the preoperative stay in the hospital. For elective surgery, patients undergo a standardized assessment including a physical exam, a thorough history which includes all current medications, laboratory tests and, if indicated per standard of care, additional cardiac workup such as dobutamine stress echocardiography, nuclear stress test or cardiac catheterization. For urgent or emergent surgery, an abbreviated assessment that includes pertinent medical facts is typically obtained. Eligible patients will be approached by a study team member and written, informed consent will be obtained.

Study Period
From the morning of surgery until 72 hours after surgery, all patients will be continuously monitored by the Holter ECG, the continuous hemodynamic monitor, and the serial cardiac biomarkers obtained to detect myocardial ischemia. Every aspect of perioperative care (surgical procedure, drug use, monitoring, etc.) will not be regulated by standard of care, except the administration of metoprolol.

Observations and Measurements
Study Endpoints
Primary efficacy endpoints:
a) Myocardial ischemia (ST-depression/elevation) b) Myocardial injury (hs-cTn elevation)

Primary safety endpoints:
a) Clinically relevant hypotension, b) daily follow up visits for duration of hospitalization.

Endpoint Definitions: 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 Injury as Δhs-cTn = difference between baseline and peak postoperative hs-cTn; Clinically relevant hypotension is defined as cumulative hypotensive time (duration of syst. BP <90 mmHg); MACE are defined as MI, cardiac death or coronary revascularization. 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).1 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 investigators 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.
There will be a daily post-surgery follow-up visits by until the subject is discharged from the hospital. The study team will monitor the subject for adverse events until discharge.

Thirty days after subject discharge, a member of the research team will conduct a phone visit to assess subject status and collect additional adverse event information, if any.

**Statistical Methods**
For the pilot study, we will only use descriptive statistics as the study is vastly underpowered to detect any meaningful effects.

**Sample Size**
50 potential participants will be consented in order to achieve at minimum of 20 evaluable subjects

**Management of Intercurrent Events**

**Adverse Experiences**
The investigator will closely monitor subjects for evidence of adverse events. All adverse events will be reported and followed until satisfactory clinical resolution. Adverse events are defined as an untoward medical event potentially related to the use of our study drug requiring clinical or rescue interventions. The description of the adverse experience will include the time of onset, duration, severity, etiology, relationship to the study drug (none, unlikely, possible, probable, highly probable), and any treatment required.

**Premature Discontinuation and Subject Stopping Rules**
If a subject is withdrawn from the study, the subject will be replaced in order to provide the required number of evaluable subjects. Subjects will be withdrawn if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study. The PI will oversee implementation of the rescue protocol and make the final determination about the subject’s participation in the trial.

**Potential Risks**
*Risks associated with metoprolol:* Metoprolol is one of the most commonly used β-blockers.
- Likely: Reduction in heart rate and blood pressure, dizziness
- Less likely: Bronchospasm, depression, heart failure, clinically significant hypotension and bradycardia, nausea, diarrhea
- Rare: Stroke, death, 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 80ml [slightly more than 5 tablespoons] across 72 hours.

*Risks involving obtaining an ECG* and hemodynamic monitoring include mild skin irritation from the electrodes.

Risk of confidentiality breach is also a possible risk.

**Procedures to Minimize Potential Risks**
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.

Subjects will be informed that participation in the study is voluntary and that they might refuse to participate and may 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, they will be cared for by a member of the investigating team at no cost, within the limits of the Washington University compensation plan.

Adverse events will be reported to the IRB without delay according to current FDA and IRB guidelines. Adequate clinical care in case of an adverse event is assured as surgery will be performed at Barnes-Jewish-Hospital, a major tertiary care hospital with around-the-clock anesthesia attending staffing and ICU availability.

The attending surgeon and the surgery staff caring for the subject will be informed about the subject’s participation and the details of study drug administration.

The research team will be in open and continuous discussion with patients and surgical staff to ensure that there is no disruption in the patient’s clinical care, comfort, and recovery.

Data and Safety Monitoring Plan

Adverse Event Monitoring
The Division of the candidate has developed standard operating procedures (SOPs) for data and safety monitoring. In light of the small population and attendant risk, the PI will provide data and safety monitoring for the pilot study.

An expert colleague from anesthesiology, not involved in the study, will be designated to serve in a monitoring capacity [DSM]. This individual will make decisions regarding adverse events and reporting, as well as the overall safety of study for continuation purposes. The DSM will review all adverse events after enrollment is met or every six months, whichever comes first. The DSM will be notified immediately of any serious adverse events in order to adjudicate the study’s status in light of the SAE. SAEs will be reported per the criteria established by WUSTL IRB and Department of Anesthesiology SOPs.

Protection of Human Subjects
The study will be conducted under appropriate Washington University Institutional Review Board protocols and consent forms approvals. The study will be conducted under the supervision of the PI, a board-certified Anesthesiologist with extensive clinical and human research experience and a GCP-certified pharmacist with several years of experience in the conduct of human studies.

Sources of Materials
The following “materials” will be obtained from all study patients for research purposes only:

- Blood for lab tests (hs-cTn): approximately 7 ml at up to 7 time points over a 3 day period = total of approximately 84 ml blood.
- ECG: digital recording of continuous Holter ECG
- Monitoring of vital signs: records of continuous vital sign monitoring (for 72 hours after surgery)
- Daily post op follow-up assessments
- Information from the patient’s medical record including progress notes, lab results and diagnostic testing
Results from these tests will not be available until several weeks after the patient has completed the study (due to batched analysis of lab samples) and will not enter the patient’s clinical record. All data will be for research purposes only. In the case that we detect a pathological finding that could influence patient outcome, for example ECG changes consistent with an acute myocardial infarction or hemodynamics consistent with hypotension, we will inform the patient’s primary care team.

We will collect all pertinent perioperative data that might influence the outcome of the patient, e.g. current medication, past medical history, physical characteristics, intraoperative variables (complications, blood loss, etc.) and postoperative variables.

All data will be de-identified of protected health information that could link the data or blood samples to an individual patient. We will only use pre-assigned patient study ids to mark blood samples, holter ECG, and hemodynamic information. The numbers correspond to de-identified patient data from the study. Only the PI has access to the master list that links individual patients to the de-identified numbers. This list is stored in a locked space in the PI’s office.

**Information Security Policy**

We will collect hemodynamic information during the patients’ hospitalization using mobile monitors. These devices may receive, store and/or transmit potentially Protected Health Information, and will be located in Approved Secure Data Center with Washington University Psychiatry & Anesthesiology Information Services approved encryption methods to secure the information stored on or transmitted outside the secure clinical network. Servers that are not located in an Approved Secure Data Center are required to have all information stores of protected information encrypted. The holter ECG and continuous hemodynamic monitors are programmable so that we can use patient study ids to identify participants and avoid using PHI. The mobile monitors allow the transfer of patient hemodynamic data via the secured wireless network to a centralized encrypted server for data storage.

Laptops and workstations that contain Protected Information are required to have Full Disk Encryption, meaning that the entire drive is encrypted, not just a few files and folders. Any and all mobile devices e.g. smart phones and tablets that connect to the secure clinical network that may contain or transmit Protected Information (e.g. emails) are required to accept Information Security Standards to encrypt and protect the devices. External storage media (i.e. backup tapes, removable drives, etc.) will need to have the Protected Information encrypted. Files that contain protected information that are transmitted across the Internet (e.g. e-mail attachments sent to non-WUSM or BJC addresses, or file transfers to other entities) will need to have the attachments encrypted or use a School of Medicine approved secure encrypted method to deliver the files.

**Recruitment and Informed Consent**

We will identify patients through our Center for Preoperative Assessment and Planning (CPAP) based on the CPAP patient schedule. We will identify potential study subjects according to their cardiovascular risk profile (CAD). If patients meet inclusion criteria, they will be approached in the CPAP clinic to voluntarily participate in the study. If they agree, we will obtain written informed consent. During the discussion with the potential subject in CPAP, it will be emphasized that their participation is voluntary, that they are under no pressure or obligation to participate and that there will be no change in their care should they decide not to participate.
Potential Benefits of the Proposed Research to the Subjects and Others
The clinical trial has the potential to significantly reduce the risk for perioperative cardiac events for patients in the metoprolol group.

The results from postoperative β-blocker therapy will provide strong evidence for using and ultimately implementing this approach into clinical practice as well as serving as a foundation for a large multi-center clinical trial. The anticipated benefit of this research for society is that its findings will serve as an evidence-based foundation to consider the implementation of hs-cTn into clinical practice to improve preoperative cardiac risk stratification.

Inclusion of Women
Studies actively encourage the participation of women in the research. As a matter of operational policy, our studies routinely and deliberately attempt to include equivalent numbers of women and men.

Inclusion of Minorities
All of our studies actively encourage the participation of minorities in the research. Our minority recruiting typically matches the demographic composition of the Washington University community from which subjects will be recruited (78% white, 21% Black, <1% Hispanic).