Risk Factor Control before Orthopedic Surgery

OPTIMIZE – OS Trial

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With the increasing longevity of the US population, orthopedic surgery is commonly being performed. Although orthopedic surgery has a tremendous benefit improving patient morbidity and quality of life, adverse cardiovascular events in the perioperative period are a major concern. With this in mind, the objective of **OPTIMIZE - OS** (**O**ptimization of **P**re-surgical **T**esting with an **I**ntensive **M**ultifactorial **I**ntervention to Minimi**Z**e Cardiovascular **E**vents **– O**rthopedic **S**urgery) trial is to determine the best management strategy for patients undergoing orthopedic surgery. OPTIMIZE will be a prospective randomized trial that will enroll patients during pre-surgical testing before orthopedic surgery. This trial will investigate different strategies aimed at lowering cardiovascular events following orthopedic surgery. The study will compare an intensive multifactorial intervention comprising behavioral modification and polypharmacologic therapy aimed at several modifiable risk factors versus usual care. The trial hypothesis is that a personalized optimization approach is superior to usual care in reducing a composite of death, myocardial infarction, stroke, transient ischemic attack, myocardial necrosis, venous thromboembolism or thrombosis requiring reoperation at 30-days. Secondary endpoints include length of stay, major bleeding, each individual endpoint from the primary endpoint, and quality of life.

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ABBREVIATIONS

AE-adverse event
CRF-Case Report Form
CAD-coronary artery disease
DM-diabetes mellitus
HbA1c -glycosolated hemoglobin A1c
HDL-C- High Density Lipoprotein Cholesterol
hs-CRP-high sensitivity C-reactive protein
IRB-Institutional Review Board
LDL-low density lipoprotein cholesterol
SAE-Serious Adverse Event
SD-standard deviation

1. SPECIFIC AIMS

Orthopedic surgery is increasingly being performed in the US population and as the population ages; surgery will be performed on older patients with more cardiovascular comorbidities. The risk of cardiovascular complications is a major concern during the perioperative period. Perioperative cardiovascular events are a major cause of short- and long-term morbidity and mortality in subjects undergoing non-cardiac surgery. Intensive lifestyle and pharmacological therapies targeting modifiable risk factors are effective at decreasing cardiovascular events in high-risk individuals; however, they remain underused in the perioperative period. Furthermore, the effectiveness of an intensive multifactorial approach aimed at minimizing cardiovascular events during the perioperative period has not been tested.

We propose the following aims:

- To demonstrate that a short-term intensive multifactorial intervention comprising behavioral modification and polypharmacologic therapy aimed at several modifiable risk factors in high-risk subjects undergoing orthopedic surgery treatment will decrease cardiovascular events in the postoperative period

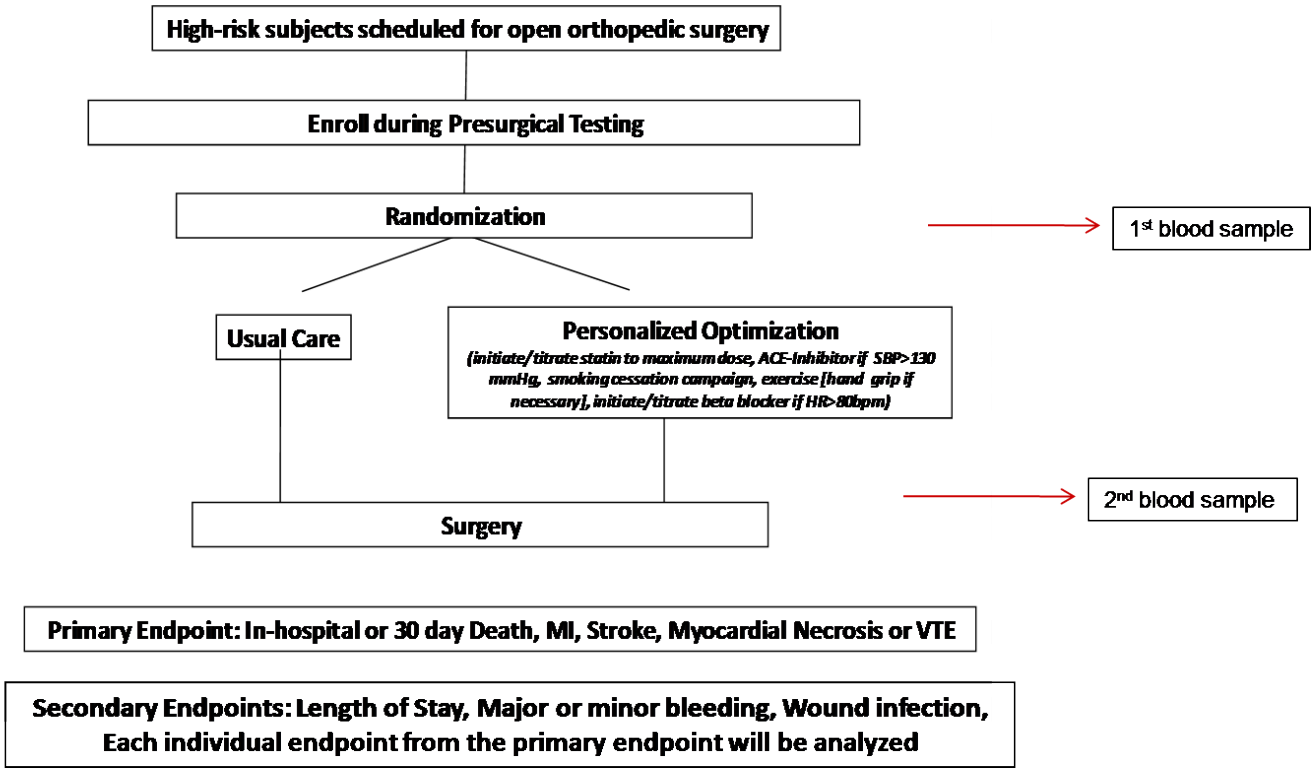
- To demonstrate that a short-term intensive multifactorial intervention comprising behavioral modification and polypharmacologic therapy aimed at several modifiable risk factors in high-risk subjects undergoing orthopedic surgery treatment will improve the subjects risk factor profile prior to surgery

- To investigate the relationship between modifiable risk factors (e.g. smoking, blood pressure, lipid profile, platelet activity, and inflammatory markers) and cardiovascular events in the postoperative period

The primary hypothesis is that a short-term intensive multifactorial intervention comprising behavioral modification and polypharmacologic therapy aimed at several modifiable risk factors in high-risk subjects undergoing orthopedic surgery will decrease cardiovascular events in the postoperative period

The secondary hypothesis is that a short-term intensive multifactorial intervention comprising behavioral modification and polypharmacologic therapy aimed at several modifiable risk factors in high-risk subjects undergoing orthopedic surgery will improve the subjects risk factor profile prior to surgery

The overall study design can be illustrated in the following figure:



2. BACKGROUND AND SIGNIFICANCE

With the ageing population, more subjects are requiring orthopedic surgery for improvement in quality of life. Since the presence of clinical comorbidities predisposing to cardiac

complications rises with increasing age, an increasing number of surgical procedures in patients with cardiac risk factors are to be expected. The risk of cardiovascular complications are a major concern for the surgeon and the anesthesiologist during the perioperative period. Perioperative cardiovascular events (e.g. myocardial infarction, stroke, venous thromboembolism) are a major cause of morbidity and mortality and increased length of stay in subjects undergoing orthopedic surgery. Non-fatal cardiovascular events during the perioperative period predict long-term cardiovascular morbidity and mortality following surgery.

The catecholamine surge, tachycardia, hypertension, hypercoagulability and increased platelet activity associated with surgery may lead to a perioperative cardiovascular event. Another potential mechanism of a perioperative cardiovascular event is the rupture of an unstable coronary plaque, perhaps because of the systemic inflammatory response to surgery.

Currently, there is a well known cardiac risk work-up prior to surgery. Nonetheless, many subjects are still experiencing adverse perioperative cardiovascular complications. With this in mind, the purpose of this study is to investigate whether a short-term intensive multifactorial intervention comprising behavioral modification and polypharmacologic therapy aimed at several modifiable risk factors is beneficial in high-risk subjects undergoing non-emergent orthopedic surgery.

2.1. RELEVANT STUDIES:

Statins are effective in the setting of primary and secondary prevention of cardiovascular events in the nonsurgical setting. They represent a class of medicines that are potent lipid lowering, anti-inflammatory and plaque stabilizing agents. These beneficial mechanistic pleiotropic effects of statins, including inhibition of the inflammatory response, reduced thrombosis, enhanced fibrinolysis, decreased platelet reactivity, and improvement of microcirculation vasoreactivity, all together culminate in a protective effect that could be readily evident in the setting of ischemia–reperfusion injury. in a retrospective cohort study of more than 750,000 subjects who underwent noncardiac surgery, Lindenauer and colleagues observed that statin therapy is associated with a reduced risk of postoperative death. In a randomized trial in subjects undergoing vascular surgery, use of statins were able to lower myocardial ischemia and mortality in following vascular surgery independent of baseline cholesterol levels.

Several trials have demonstrated that high-dose statin started the day before a cardiovascular intervention was effective in decreasing the periprocedural myocardial necrosis in subjects undergoing percutaneous coronary intervention. In addition to the lipid lowering effect, other pleiotropic effects of short-term duration statins are to modify the inflammatory response, improve endothelial function, plaque stability and thrombus formation. With this in mind, we believe that high dose statin for at least 3 days prior to orthopedic surgery would be effective at decreasing perioperative cardiovascular events.

Beta blockers are widely used in the perioperative period. Multiple randomized trials noted a reduction of cardiovascular events in patients undergoing noncardiac surgery. Concerns about beta blockers arose following the POISE trial. IN this trial, the reduction in myocardial infarction

with the use of beta-blockers was offset by an increased risk of bradycardia, hypotension, stroke and death. In this trial, subjects received a high-dose of beta-blocker independent of baseline heart rate. Multiple other studies showed a decrease in the incidence of MI, stroke and death with perioperative beta blocker use. The discrepancy between trials is likely due to the different beta blocking dosing regimens used. The POISE trial initiated beta blocker therapy 2-4 hours prior to surgery, prescribing patients up to 400 mg of metoprolol succinate on the day of surgery, whereas other trials (such as the DECREASE trial) initiated low-dose beta-blockers (bisoprolol 2.5 or 5 mg oncedaily) on average a month prior to surgery. Given the increased catecholamine surge postoperatively, use of a low-dose beta-blocker in individuals with an elevated heart rate (similar to the design in the current trial) might further reduce the risk of cardiac complications.

ACE-inhibitors are effective blood pressure lowering drugs in a variety of settings including those with cardiovascular disease and risk factors. Two land-mark trials (HOPE and EUROPA) demonstrated that ACE inhibitors could affect the atherosclerotic process and reduce ischemic events and complications independent of their effects on heart function and blood pressure. Guidelines have incorporated the use of ACE-inhibitors in patients with known cardiovascular disease or diabetes and some other risk factors. In an observational study of 481 subjects, ACE inhibitors before surgery confer myocardial protection (reducing cardiac troponin release) in patients undergoing CABG. Additionally, renin-angiotensin system suppression with an ACE-inhibitor may also have a renal protective effect, preserving glomerular filtration rate in patients undergoing aortic abdominal aneurysm repair or coronary artery bypass graft surgery.

3. RESEARCH DESIGN AND METHODS

3.1. STUDY OBJECTIVES

The objectives of this study are to determine the efficacy, tolerability and safety of a 3-21 day intensive multifactorial intervention comprising behavioral modification and polypharmacologic therapy aimed at several modifiable risk factors in high-risk subjects undergoing orthopedic surgery will decrease cardiovascular events in the postoperative period (in-hospital or 30-days whichever is sooner). We will compare this intervention with a standard of care approach.

The primary efficacy objective is the composite of cardiovascular events – including death, myocardial infarction (MI), stroke, transient ischemic attack (TIA), myocardial necrosis (MN), or venous thromboembolism (VTE)

Other markers of Efficacy

1. the reduction in the composite of death, MI, stroke, TIA, or MN
2. the reduction in the composite of death, MI, stroke, or TIA
3. the reduction in composite of death, MI, stroke, TIA, MN, VTE or reoperation
4. the reduction in length of stay
5. the reduction in each individual endpoint
6. the reduction in reoperation

Tolerability

1. Assessed by reviewing compliance with study medication
2. Assessed by reviewing compliance with lifestyle intervention

Safety

1. The number of adverse events reported and their severity
2. Reoperation
3. Major bleeding
4. Any transfusion within 48 hours of the surgery
    i. PRBC
    ii. Platelets
    iii. Cryo
    iv. FFP
5. Clinically relevant minor bleeding
6. Wound complication
7. Wound drainage

The secondary objective is to demonstrate that a short-term intensive multifactorial intervention comprising behavioral modification (smoking cessation, physical activity, and nutrition counseling) and polypharmacologic therapy (high-dose statins, ACE-inhibitors, beta blockers, and aspirin) aimed at several modifiable risk factors in high-risk subjects undergoing orthopedic surgery will improve the subjects risk factor profile (smoking, blood pressure, lipid profile, platelet activity, and sedentary lifestyle) measured immediately prior to surgery.

1. The percent change from baseline in LDL-C, HDL-C, TC, and TG
2. The percent change from baseline in active smokers
3. The percent change from baseline in SBP and DBP
4. The percent change from baseline in hs-CRP,
5. The percent change from baseline in platelet activity
6. The percent change from baseline in nutrition survey
7. The percent change from baseline in exercise survey

Characteristics of Research Population

Number of Subjects

We plan to enroll 550 subjects with approximately 500 completing the study – 250 subjects in each group. This number will allow for an estimated 40% reduction in risk. We anticipate a drop out rate of 10% as predicted by OR cancellation rates. Subjects will be identified for study inclusion by the Pre-Admission (PAT) schedule. Members of the critical care staff who are also co-investigators in this study routinely review the PAT schedule.

Gender, Age, Racial and Ethnic Origin of Subjects

We will recruit both males and females and recruitment will be open to all racial and ethnic origins. We will recruit subjects aged 21 and older.

Vulnerable Subjects

We will be recruiting subjects over the age of 65, but will not recruit any subject with a documented or self reported history of cognitive dysfunction.

3.2. INCLUSION CRITERIA

- ≥ 21 years of age
- Subjects undergoing open orthopedic surgery of the hip, knee or spine
- Surgery is scheduled at least 3 days after PAT visit and no more than 21 days.
- High risk subject cohort
    - Coronary artery disease, or
    - Cerebrovascular disease (prior stroke, TIA or carotid artery disease (>70% stenosis), or
    - Peripheral artery disease, or
    - Prior Venous thromboembolism or arterial thromboembolism, or
    - Age ≥ 60 years and 2 of the following
        - Renal insufficiency (creatinine clearance < 60ml/min)
        - Diabetes
        - COPD
        - Hypertension
        - Active smoker or stopped less than 30 days prior to consent
        - Cancer (excluding BCC)
        - Heart Failure

3.3. EXCLUSION CRITERIA

- Known intolerance to statins
- Subject is already on maximum dose statin (atorvastatin/Lipitor 80mg daily or rosuvastatin/crestor 40mg daily)
- Bilateral renal artery stenosis
- End stage renal disease (receiving dialysis or CrCl <30ml/min)
- Known allergy or intolerance to ACE-inhibitor (other than cough) or Angiotensin receptor blocker (e.g. angioedema, hyperkalemia)
- Known allergy or intolerance to beta blockers
- Known sick sinus syndrome not treated with permanent pacemaker
- Known greater than first degree AV block not treated with a pacemaker
- Excessive alcohol intake
- Acute Coronary Syndrome requiring hospitalization within 1 month
- Stroke within 1 month
- Known pregnancy
- Severe co-morbid condition with life expectancy < 6 months
- Inability to give informed consent or adhere to follow-up as per protocol
- Current participation in another investigational drug or device trial

3.4. SCREENING AND RECRUITMENT

An informational flier will be given to each patient during their pre surgical visit at their orthopedic surgeon's office. If the patient has co-morbidities that determine enrollment in the study, their surgeon will briefly introduce the study to the patient. He or She will tell the patient that more information will be given to them in PreSurgical (PreAdmission) testing. If the patient agrees to learn more about the study, a member of the study team will call the patient prior to their PAT visit using the script, attached. If a patient does not want to be spoken to in PAT, or changes their mind at any time, they can let the surgeon's office staff, study staff or PAT staff know and the staff will communicate this to a member of the study team via email, phone, text or personal communication. Any patient not refusing communication regarding research may be approached in vis phone prior to PAT and/or prior to any PAT procedures being performed, if a pre phone call was unsuccessful.

Subjects will be pre-screened by the surgeon at the time of their clinically indicated appointment for potential inclusion/exclusion. The research team will obtain a list of scheduled appointments for the day and assess the list for patients who have potential eligibility for the study. All potentials subjects will be pre-screened again daily by the study staff. Based on preliminary data, approximately 20% of the pre-screened patients are expected to be eligible for the study. A member of the research staff will call the subjects prior to their appointment. All study related discussion will occur in a private setting. The study personnel will discuss the study in its entirety during the patients PAT visit in accordance with HIPAA and PPHS standards.

3.5. TIME FRAME

Enrollment will begin in the beginning of 2013, once Institutional Review Board approval is obtained. The study will take approximately up to 24 months to enroll 550 subjects.

3.6. INFORMED CONSENT

Only current, Institutional Review Board (IRB) stamped consent forms will be used to obtain informed consent. The subject's signed and dated informed consent form will be obtained before conducting any procedure specific to the study. A copy of the completed written informed consent form will be provided to the subject and placed in their patients records and the original ICF will be maintained in the study binder. A note will be placed in the subjects' medical chart indicate their participation in this research protocol.

Consent will be presented to each subject in a private setting. The study staff will limit distractions and interruption to the best of their ability. Prior to signing the informed consent form, subjects will be given full oral and written information about the nature, purpose, potential risks and benefits of the study. Subjects will be notified of the voluntary nature of the study and that subjects may discontinue at any time without affecting their health care. Subjects will be given the opportunities to ask questions and allowed sufficient time to consider the study information.

Cost to subjects:

All study related costs will be provided by Departmental funds. Participants will not incur any study related costs. The cost of routine care will be charged to the patient and/or the patients insurance.

3.7. RANDOMIZATION

A blocked randomization scheme with random block size will be performed. The study statistician will arrange the randomization code before the study begins based on the expected number of participants estimated using power and sample size analysis. The randomization will be performed using routines for random number generation available in SAS. Envelops with study arm assignments will be given to the project manager. Randomization concealment will be ensured, as the randomization code will not be released until the patients are recruited in the trial (informed consent is signed) and all baseline measures are taken. Specifically, upon certifying an eligibility checklist for a potential participant deemed eligible, the study physician will notify the research assistant who will open the next envelope. Study staff who perform assessments will be blinded to participants' intervention assignment.

Subjects will be approached for enrollment by the research coordinator or a member of the clinical research team. If informed consent is obtained, subjects will be randomized (see figure above) in a 1:1 manner to either:

- Usual Care (in accordance with national guidelines)
- Personalized optimization (multifactorial intervention comprising behavioral modification and polypharmacologic therapy aimed at several modifiable risk factors)

3.8. METHODS

Study Overview

Following randomization, study participants will be assigned into one of two groups: usual care or personalized optimization.

Subjects in the usual care group will receive standard of care counseling and treatment in accordance with national guidelines. This will include medical clearance, if appropriate, for surgery.

Subjects in the personalized optimization group will receive an intensive multifactorial intervention comprising behavioral modification (smoking cessation, physical activity, and nutrition counseling) and polypharmacologic therapy (high-dose statins, ACE-inhibitors, beta blockers, and aspirin) aimed at several modifiable risk factors.

A. Statins –

Initiate/titrate statin to maximum dose. All subjects whether they are on a statin at baseline or not, should be placed on maximum dose statin (atorvastatin 80mg daily). (if a subject is on a statin other than the ones being used, we will switch therapies to the ones being used in the trial till the day of surgery). Medicine will be taken daily, including the day of the operation. Following surgery, all subjects will receive their usual care. See appendix #2 for how we will deal with different circumstances.

B. Beta blockers
If the subject's heart rate is elevated (HR >75bpm) – will treat with a low-dose beta blocker (metoprolol 25mg). Medicine will be taken daily, including the day of the operation. The appendix #2 details different circumstances for beta blocker use. If the subject is on a beta-blocker at baseline that is not maximally dosed and the HR remains >75bpm, we will give metoprolol 25mg to be taken twice daily. Following surgery, all subjects will be treated as usual care.

C. ACE-inhibitors / Angiotensin Receptor Blocker (ARB)
If blood pressure is elevated SBP > 130 mmHg or if DBP >90 mmHg – will treat with a low-dose ACE-inhibitor (lisinopril 5mg). Medicine will be taken daily, including the day of the operation. The appendix #2 details different circumstances for ACE-inhibitor/ARB use. If the subject is on an ACE-inhibitor or ARB at baseline that is not maximally dosed and the SBP > 130 mmHg or if DBP >90 mmHg, we will give lisinopril 5mg daily). Following surgery, all subjects will be treated as usual care.

D. Smoking cessation
If the subject is a smoker, will counsel the subject on quitting, start a behavioral intervention program, and will offer nicotine replacement therapy till the day of surgery. Subjects will be given the number for the quit hotline. The goal will be to reduce the number of cigarettes smoked during the period of time before surgery if they cannot (or do not) intend to quit altogether.

E. Physical activity
Will discuss the importance of increasing physical activity prior to surgery. Many subjects will be unable to exercise using traditional methods (thus requiring orthopedic surgery). We will encourage different forms of physical activity depending on what is tolerated (e.g. hand grip exercise, arm rowing, or walking).

A target heart rate will not be used for monitoring. We will encourage some exercise – based on simple stretches, yoga, walking, bicycling, swimming – for up to 30 minutes a day. A hand out with simple exercises will be handed out. Physical activity will be monitored based on the subject's survey response to how much activity they have done.

F. Nutrition counseling
Will discuss the importance of improving nutrition prior to surgery. Will encourage an ideal healthy heart diet which includes: consumption of fruits and vegetables (>4.5 cups/day), fish (>two 3.5-oz servings/week), fiber rich whole grains (> three 1-oz-equivalent servings/day), limit sodium intake (AHA goal is <1500 mg/d), and limit sugar sweetened beverages (AHA goal is <36-oz/week). We will also counsel the subject to

refrain from fried foods and fast foods during the period prior to surgery. (see Appendix 1)

3.9. TABLE 1: STUDY SCHEDULE

	Treatment Period			
	Baseline Pre- Surgical Testing	Pre-operative	POD2^	Discharge or 30 calendar days*
Informed Consent	X			
Demographics	X			
Medical History	X			
Physical exam and vitals	X	X		
Lipid profile	X	X		
Platelet Activity Profile	X	X	X	
Basic Metabolic Panel	X (SOC)			
Inflammatory Markers	X	X	X	
Smoking assessment	X	X		
Lifestyle Assessment	X	X		
ECG	X (SOC)		X	
Troponin			X	
Adverse Event Assessment		X	X	X
Review of concomitant medications	X	X	X	X
Study drug dispensing	X			
Review medication compliance	X	X		
Cardiovascular endpoint assessment			X	X
Biospecimen collection	X	X	X	

ECG and blood work are routine clinical care

^ +/- 1 day; *whichever is sooner

SOC, standard of care

Baseline Visit/Pre-Admission testing:

A. Inclusion/exclusion criteria
B. Informed consent
C. Randomization
D. Blood collection
    a. Lipid panel
    b. Inflammatory markers
    c. Platelet activity
E. ECG
F. Collection of data from medical chart
    a. Demographics
    b. Medical history
    c. Surgical history
    d. Medication history
    e. Smoking history
    f. Physical exam
    g. Lifestyle survey
G. Treatment group: dispense treatment medications, instruction for smoking cessation, instruction for exercise and nutrition

Pre-operative:

A. Patient in the treatment group may receive phone calls by a member of the research staff to encourage protocol compliance and answer any questions.
B. Adverse event assessment

Day of Surgery:

A. Blood collection
    a. Lipid profile
    b. Inflammatory markers
    c. Platelet activity
B. Treatment group interview regarding protocol compliance
C. Lifestyle survey
D. Collection of data from medical chart
    a. Laboratory results

PACU:

A. Blood collection
    a. Troponin (usual care, if clinically indicated)

B. Collection of data from medical chart
    a. Surgical record
        i. Planned surgery
        ii. Actual surgery
        iii. Incision time
        iv. Surgery end time
        v. Surgical events
    b. Anesthesia record
        i. Anesthesia start time
        ii. Anesthesia end time
        iii. Anesthesia medication administration
        iv. Anesthesia type
        v. Anesthesia events
    c. Laboratory results
    d. Physical exam
    e. Vital signs

POD 2 +/- 1 day:

A. ECG
B. Blood collection
    a. Troponin
    b. Platelet activity and inflammatory biomarkers
C. Collection of data from medical chart
    a. Adverse events
    b. Review of concomitant medication
    c. Review of cardiovascular end-points
    d. Laboratory results
    e. Physical exam
    f. Vital signs

POD 3, Discharge or 30 days (whichever is sooner):

A. Collection of data from medical chart
    a. Adverse events
    b. Review of concomitant medication
    c. Review of cardiovascular end-points
    d. Laboratory results
    e. Physical exam
    f. Vital signs

Long-term follow-up (phone calls every 6 months for 3 years)

During the prior 6-months did the subject experience any of the following events:

Death	O yes	Ono
Reoperation	O yes	Ono
MI	O yes	Ono
Coronary Stent	O yes	Ono
CABG	O yes	Ono

Stroke/TIA	❍ yes ❍no
DVT	❍ yes ❍no
PE	❍ yes ❍no

3.10. TREATMENT COMPLIANCE

Patients will be expected to comply with all study related procedures. Compliance will be measured by pill counting and by the validated Moriskey survey which assesses compliance. Patients may be withdrawn from the study for any of the following reasons:

a. Cancelation of surgery
b. At patient's request

3.11. PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Atorvastatin will be supplied in 80mg tablets. Subjects randomized to the multiple intervention arm will be given 80mg of atorvastatin to take daily from randomization till the day of surgery. Based on the inclusion criteria, subjects will take this regimen for anywhere between 3-21 days. We estimate the average to be approximately 7-days. Atorvastatin will be provided free of charge to the participant. Atorvastatin is an approved drug for subjects with cardiovascular disease or those without CHD, but with multiple risk factors.

Lisinopril will be supplied in 5mg tablets. Any subject randomized to the multiple intervention arm with a SBP above 130mmHg or DBP above 90mmHg will receive lisinopril 5mg to be taken daily till the day of surgery. A dose of 5mg was chosen because its effect on systolic blood pressure is minimal and we know that lisinopril has a cardioprotective effect. If the subject has a K>5mEq/L, the subject will not receive an ACE-inhibitor or ARB.

Metoprolol will be supplied in 25mg tablets. Any subject randomized to the multiple intervention arm with a HR above 75 bpm will receive metoprolol 25mg to be taken twice daily till the day of surgery.

Lisinopril, atorvastatin and metoprolol will be provided free of charge to the participants in the treatment arm. All medicines will be provided in a pill box with clear instructions on their use. Subjects will be asked to bring back their pill box for pill counting on day of surgery.

All study medications will be stored in locked cabinets accessible only to study staff. Once the patient has been consented and randomized to the treatment arm, a licensed practitioner will dispense the necessary medications into a 'days of the week' pill box labeled with the patients name. Individualized, specific instructions for self-administration will be included with the pill box along with a 24 hour contact number for questions or concerns. A licensed practitioner will then personally present the pill box, instructions and contact numbers to each treatment participant. If there are extra pills, we will destroy any returned medication as per hospital protocol.

3.12. CONCOMITANT MEDICATIONS

All concomitant medications will be maintained at the same dosage during the course of the study unless the changes to the medications or the dose are clinically mandated.

- If a subject randomized to the multiple intervention arm is taking a different statin, they will stop that drug and be given atorvatstain 80mg. See appendix #2 for examples.
- If a subject randomized to the multiple intervention arm is taking a different ACE-inhibitor that is not maximally dosed and their systolic blood pressure is greater than 130mmHg, we will provide 5mg lisinopril daily. See appendix #2 for examples.
- If a subject randomized to the multiple intervention arm is taking a different beta-blocker that is not maximally dosed and their heart rate is greater than 75 bpm, we will provide metoprolol 25mg daily. See appendix #2 for examples.

3.13. BLOOD TESTS

Following enrollment, subjects will have their blood drawn and another blood draw immediately before surgery. Blood collection will be done using standard aseptic phlebotomy techniques. In short, after cleansing of the venipuncture site with an alcohol wipe and removal of excess alcohol with sterile gauze, a tourniquet will applied to the patient's bicep region. A 19g or 21g butterfly needle will be inserted into the antecubital vein and free-flowing blood will be collected with minimal trauma and stasis. The needle will be removed when blood collection is complete and sufficient pressure will be applied using sterile gauze at the puncture site until cessation of bleeding. A sterile band-aid will be applied to cover the venipuncture site. For each patient, no more than 30 cc (≈ 2 tablespoons) of blood will be collected in red (no anticoagulant) top, lavender (EDTA anticoagulant) top, green (heparin) and blue (sodium citrate anticoagulant) top tubes. Approximately 15 cc of blood will be used for the different measurements of platelet function and inflammation, and approximately 15 cc of blood will be used to for plasma and sera separation (for cardiovascular biomarkers). The samples will be stored in HJD 15th floor Musculoskeletal lab before being transferred to Dr. Berger's lab in Smilow 8th floor for analysis without any identifying information other than a code number. The code number will not be based on any information that could be used to identify the subject (for example, social security number, initials, birth date, etc). The master list linking names to code numbers will be kept in a locked file cabinet, separate from all research information.

The specimen will be analyzed upon completion of the study for cardiovascular biomarkers as described above. We can only measure this at the end of the study because we will need to analyze this in bulk for quality control. These serum and plasma samples will not be used or stored for any research other than what is describe in this protocol.

3.14. DATA ANALYSIS and POWER ANALYSIS

The primary objective of these analyses is to compare the effects of a personalized optimization approach on a composite of cardiovascular events. The secondary objective is to compare the effects of a personalized optimization approach on a panel of cardiovascular biomarkers, including lipid values, metabolic and inflammatory risk and platelet activity, as well as healthy lifestyle. This study will allow us to determine if measures of cardiovascular

biomarkers or lifestyle change are mediators of cardiovascular risk reduction observed in response to randomization.

Data Management. All subjects will be assigned a unique identification number at random upon study entry. All subsequent data will be stored on a secure electronic database. Identifying information will be kept in a locked secure location by a member of the research study. All entries will be double-checked against source documents for accuracy.

Descriptive analyses Descriptive statistics (means, medians, frequencies) will be used to characterize demographic, dietary, clinical, and laboratory variables of the study participants in each study group. Distribution of the primary outcome variables and other demographic, dietary, and clinical variables will be examined among study participants.

Overview of Univariate Analyses for Aims 1,2, and 3 All comparison between the treatment and control group will be based on intention-to-treat analysis. The intention-to-treat population is defined as all subjects randomized in the trial, and classified based on randomized treatment assignment. All statistical tests will be 2-sided. Appropriate multiple testing procedures will be applied. Continuous variables will be compared using t-test and/or Wilcoxon sum rank test as appropriate. Categorical variables will be compared using chi-square test and/or Fisher's exact test. Many lipid parameters are continuous variables, and many of them are apparently not normally distributed, and therefore nor-parametric statistical methods are appropriate in many analyses.

In addition to analyses outlined in the overview, the following analyses specific to each aim are planned.

Aim 1: Effect of intervention on frequency of cardiovascular events in postoperative period Logistic regression models will be fit to quantify an effect of intervention on occurrence of a specific cardiovascular event or on a binary indicator of at least one of the cardiovascular events . Multinomial regression model will be used to quantify an effect of intervention on a number of cardiovascular events. Odds Ratios and Relative Risk will be inferred accompanied by 95% Confidence Intervals. Assumptions will be checked and transformations, such as log- and Box-Cox, will be considered.

Aim 2: Effect of intervention on risk profile prior surgery Analysis of variance (ANOVA) will be used to examine an effect of intervention on risk profile factors prior to surgery. Multivariate Analyses of Variance (MANOVA) will be employed to examine an effect of intervention on a multivariate vector of risk factors.

Aim 3: Relationship between modifiable risk factors and cardiovascular events Logistic and multinomial regression models will be used to examine the relationship between cardiovascular events and modifiable risk factors. Main effects of modifiable risk factors will be examined based on univariate regression models. Additive and synergistic effects will be examined based on multivariate regression models. Treatment – by- modifiable risk factors interactions will be estimated to examine whether the intervention can mediate the effect of modifiable risk factors. Odds Ratios and Relative Risk will be inferred accompanied by 95% Confidence Intervals. Multivariate models will be constructed based on a combination of our *a*

priori biomedical knowledge and statistical model choice techniques. Dimensionality reduction techniques will be considered to aggregate effects of multiple risk factors, e.g. to infer a principal combination of platelet activity measures.

Analysis of Missing Data Missing data will be investigated by inferring a relationship between baseline characteristics/risk factors and a 0-1 indicator that defines whether or not a measurement is observed. This analysis will help to identify factors that are likely to cause measurements to be missing. These analyses will employ regression techniques (e.g., multiple linear, non-linear, and log-linear), possibly with model averaging and model selection. The goal for addressing missing data carefully is not because we intend to impute missing values, but rather to better understand its causes.

Sample Size and Power Analysis. Power is estimated for the primary endpoint of a composite of cardiovascular events in the table below assuming a sample size of 550 per treatment group with 10% loss to follow-up, estimated proportion of events based on prior data from this group, the presence of a clinically meaningful 40% difference in events between groups. These calculations demonstrate that with a sample of 500 subjects (250 per treatment group) the two-sided z-test of proportion has 80% power to detect clinically important differences in a composite of cardiovascular events at the 0.05 significance level.

Estimated Reduction in Risk	Estimated Event Rate		
	25%	30%	35%
30%	932	734	594
35%	670	528	428
40%	500	396	322
45%	386	306	248
50%	304	242	198

3.15. INTERIM ANALYSIS FOR SAFETY AND EFFICACY

Interim analysis will be performed when 50% of participants are enrolled.

The trial will be stopped for *efficacy* based on the following power analyses. With 125 participants per treatment arm, two-sided Fisher's exact test of proportions will have 80% power to detect the following differences in event rates between the two study arms.

Expected event rate in the usual care arm	25%	30%	35%	Significance level
Estimated event rate in the intervention arm	11%	15%	19%	0.05
	12%	16%	20%	0.10
	14%	18%	22%	0.20

The trial will be stopped for *safety* based on the following power analyses. With 125 participants per treatment arm, two-sided Fisher's exact test of proportions will have 80% power to detect the following differences in event rates between the two study arms.

Expected event rate in the usual care arm	25%	30%	35%	Significance level
Estimated event rate in the intervention arm	42%	48%	53%	0.05
	40%	46%	51%	0.10
	38%	44%	49%	0.20

Overall power and analysis lan was performed using the following program:
Hintze, J. (2008) PASS 2008 NCSS LCC Kaysville, Utah

5. SAFETY MONITORING PLAN

Our assessment of moderate risk does not preclude the potential for anticipated and/or unanticipated adverse events, serious or otherwise. It is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

5.1. ATTRIBUTION OF ADVERSE EVENTS

Adverse events will be monitored for every subject participating in the study and attributed to the study procedures/design by the Principal Investigator (Jeffrey S Berger) according to the following categories:

a. Definite: Adverse event(s) will clearly be related to the intervention.
b. Probable: Adverse event(s) will likely be related to the intervention.
c. Possible: Adverse event(s) may be related to the intervention.
d. Unlikely: Adverse event(s) will doubtfully be related to the intervention.
e. Unrelated: Adverse event(s) will clearly not be related to the intervention.

5.2. PLAN FOR GRADING ADVERSE EVENTS

The following scale will be used in defining/grading the severity of adverse events noted during the study:

- **0** No adverse event
- **1** Mild adverse event
- **2** Moderate adverse event
- **3** Severe adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or congenital anomaly/birth defect
- **4** Life-threatening or disabling adverse event

- **5** Fatal adverse event

5.3. PLAN FOR REPORTING SERIOUS UNANTICIPATED ADVERSE EVENTS

a. Serious unanticipated adverse events will be reported within 48 hours to the IRB
b. Serious anticipated adverse events will be reported within 48 hours to IRB whenever their magnitude or frequency exceeds expectations
c. Adverse events will be deemed serious in nature if graded as 3 or higher according to the scale in item #2 above.

5.4. PLANS FOR REVISING AND REPORTING NON-SERIOUS ANTICIPATED AND UNANTICIPATED ADVERSE EVENTS

The principal investigator, Jeffrey S Berger will continually be monitoring the frequency and severity of the adverse events in conjunction with the NYUMC IRB to determine if modifications to the protocol or consent form are required.

6. REPORTING OF SERIOUS ADVERSE EVENTS

A summary of unanticipated and anticipated (UNATP and ATP respectively) adverse events will be reported to IRB at a minimum of every 12 months (including when re-approval for the protocol is sought). The summary will include the number of subjects enrolled and a summary of graded adverse events to date per the following table:

Attribution	Grade 1	Grade 2	**Grade 3**	**Grade 4**	Grade 5
Unrelated	UNATP/ATP	UNATP/ATP	UNATP/ATP	UNATP/ATP	UNATP/ATP
Unlikely					
Possible					
Probable					
Definite					
Totals					
Total subjects enrolled to date					

6.1. PERSONNEL RESPONSIBLE FOR THE SAFETY REVIEW AND ITS FREQUENCY

An independent Data and Safety Monitoring Board (DSMB) will be established. The DSMB will be responsible for monitoring the data and conducting performance of safety reviews at a

minimum of every 6 months. Reports for anticipated/unanticipated serious adverse events and the form outlined above under item #4 for routine adverse events. During the review process, the DSMB will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment and will relay this information to the PI.

The DSMB will be composed of 3 individuals who have expertise in the field, experience in the conduct of clinical trials, and statistical knowledge.

7. POTENTIAL RISKS/PROTECTION AGAINST RISK

The risks associated with this study are deemed to be moderate for the following reasons:

1) The risks associated with phlebotomy are more than minimal.
2) The risk associated with statins are more than minimal. Statins in the doses used in this research plan have been well tolerated in previous clinical use and clinical research studies of normal subjects, subjects at risk for cardiovascular disease and patients with cardiovascular disease without major adverse effects.
3) The risks associated with beta blockers are considered more than minimal, although in our experience and in the literature low-dose (dose used in the research plan) beta blockers and ACE-inhibitors have been very well tolerated in both subjects at risk for cardiovascular disease and patients with established cardiovascular disease.
4) The risks associated with other multifactorial approach are minimal.
5) Proper subject selection according to inclusion/exclusion criteria as described in the protocol minimizes the risks to study subjects.

7.1. ALLERGIC REACTIONS

Patients with a hypersensitivity reaction to the study medication will discontinue the study medications and treated in the standard manner using histamine receptor blockers and or corticosteroids in accordance with the severity of the hypersensitivity of the reaction. To minimize this risk, we are excluding subjects with a known intolerance to statins.

7.2. HYPOTENSION/BRADYCARDIA

Patients receiving an ACE-inhibitor and/or beta blocker may be at risk for hypotension or bradycardia, and a reduction in the dose of the concomitant agent may be necessary. This study will only provide ACE-inhibitors and beta-blockers to subjects with an elevated blood pressure and heart rate, respectively (thus, the risk for hypotension/bradycardia is low).

7.3. MUSCLE DAMAGE

Atorvastatin which can rarely lead to a very serious, possibly fatal condition called rhabdomyolysis. Rhabdomyolysis is the breakdown of muscle fibers that leads to the release of muscle fiber contents into the bloodstream which is harmful to the kidney and may cause kidney damage. Patients develop muscle pain, weakness and/or tenderness must seek medical attention immediately. Since this study uses statin therapy for a very short period of time, these risks are very rare.

For beta blockers, we will only be giving low-dose beta blocklers to subjects with a heart rate > 75bpm – thus, the side effects from the heart rate lowering should be minimal. Nonetheless – we will tell the subject that if they feel light headed, pre-syncopal or any syncope – they should stop the therapy.

For ace-inhibitors, we will only be giving low-dose ace-inhibitors to subjects with an elevated blood pressure – thus, the side effects from the blood pressure lowering should be minimal. Nonetheless – we will tell the subject that if they feel light headed, pre-syncopal or any syncope or if they develop angioedema – they should stop the therapy.

For statins, everyone randomized to the intervention arm will be getting high dose atorvastatin – since the subject will be receiving the drug for a short period of time (3 – 21 days) – we do not expect any serious side effects. We will counsel the subject that if they develop severe cramping symptoms – they should stop their therapy and let the research coordinator know.

Otherwise, since the side effects are trivial for such a short period of time – there will be no tests or monitoring.

7.4. BLOOD COLLECTION

The participant will be asked to give a small sample of blood at each collection. The discomfort associated with giving blood include pain, bruising, and rarely, fainting or infection.

8. POTENTIAL BENEFIT TO THE SUBJECTS

The study participant may benefit from closer than usual follow-up care. The participant may not be helped by taking part in this study, but their participation may lead to knowledge that will help others.

9. DATA MANAGEMENT

Patient data will be recorded directly on to CRF with unique patient number assigned at study entry. The study coordinator will transfer information from the CRF to an electronic access database created specifically for this study using only the unique patient number. Laboratory results will be transposed directly to the database. All entered data will be double checked.

10. ETHICAL ASPECTS OF THE PROPOSED RESEARCH

10.1. ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. In this study we are using an FDA approved drug outside its current indication and subjects will be informed of this before obtaining informed consent. Similar studies have been conducted in the past (as described in Relevant Studies Section) without excess of adverse events reported.

10.2. CONFIDENTIALITY

Personal and medical information about the study participant will be kept confidential. This information will include any information about the study participant that the study doctor needs to do the study, including information from the tests. The study participant records also will include other identifying information about them, such as their name and address.

The study participant information will be kept in secured file. The study participants have the right to see and copy their information. At any time, the study participant may ask to see their personal information (such as name and address) and correct it if necessary. However, if the study participants sign this form, they might not be able to see or copy some of their information until after all participants finish the study.

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http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020702Orig1s060lbl.pdf
(Labeling for atorvastatin)

12. Appendices

Appendix #1

Tips for Reducing Sodium in the Diet

- Read the Nutrition Facts label to compare and find foods lower in sodium. You'll be surprised to find that even foods in the same category have different amounts of sodium!
- Choose fresh fruits and vegetables, when possible.
- Limit the amount of processed foods you eat and your portion size.
- Avoid adding salt when cooking and/or eating.
- Learn to use spices and herbs to enhance the taste of your food. Most spices naturally contain very small amounts of sodium, but read the label to be sure.
- Add fresh lemon juice instead of salt to fish and vegetables.
- Specify how you want your food prepared when dining out. Ask for your dish to be prepared without salt.
- Take control of what's in your food by cooking more at home.
- Choose foods with potassium. They counter the effects of sodium and may help lower your blood pressure.

Tips for Reducing Sugar in Your Diet:

Take sugar (white and brown), syrup, honey and molasses off the table — out of sight, out of mind!

- Cut back on the amount of sugar added to things you eat or drink regularly like cereal, pancakes, coffee or tea. Try cutting the usual amount of sugar you add by half and wean down from there, or consider using an artificial sweetener.
- Buy sugar-free or low-calorie beverages.
- Buy fresh fruits or fruits canned in water or natural juice. Avoid fruit canned in syrup, especially heavy syrup.
- Instead of adding sugar to cereal or oatmeal, add fresh fruit (try bananas, cherries or strawberries) or dried fruit (raisins, cranberries or apricots).
- When baking cookies, brownies or cakes, cut the sugar called for in your recipe by one-third to one-half. Often you won't notice the difference.
- Instead of adding sugar in recipes, use extracts such as almond, vanilla, orange or lemon.
- Enhance foods with spices instead of sugar; try ginger, allspice, cinnamon or nutmeg.
- Substitute unsweetened applesauce for sugar in recipes (use equal amounts).
- Try non-nutritive sweeteners such as aspartame, sucralose or saccharin in moderation. Non-nutritive sweeteners may be a way to satisfy your sweet tooth without adding more

calories to your diet. The FDA has determined that non-nutritive sweeteners are safe.

Fruits and Vegetables

An average adult consuming 2,000 calories daily should aim for 4.5 cups of fruits and vegetables a day. Also, variety matters, so try a wide range of fruits and veggies

Go fish

The American Heart Association recommends eating fish (particularly fatty fish) at least two times (two servings) a week. Each serving is 3.5 ounce cooked, or about ¾ cup of flaked fish. Fatty fish like salmon, mackerel, herring, lake trout, sardines and albacore tuna are high in omega-3 fatty acids.

Tips for eating fish:

- Enjoy fish baked or grilled, not fried.
- Choose low-sodium, low-fat seasonings such as spices, herbs, lemon juice and other flavorings in cooking and at the table.

Fiber

Try to get about 25 grams of fiber each day.

Whole-grain choices

- whole-grain bread (such as 100% whole-wheat bread)
- whole-grain cereal (about 1 cup wheat flakes)
- whole-grain cereal, brown rice, or whole-wheat pasta

whole-grain crackers

Appendix #2:

Statins Therapy:
In the personal optimization arm, all subjects will receive 80mg atorvastatin starting at PAT.

- If the subject is on no statin – they will be counseled to take atorvavstatin 80mg daily through the day of surgery.
- If the subject is on another statin, we will provide oral and written instructions to hold their baseline statin and take the atorvastatin 80mg daily till the day of surgery.

Following surgery, subjects will go back on their baseline regimen and will be treated as per usual postoperative care.

Beta-blockers:
In the personal optimization arm, all subjects with a heart rate above 75 beats per minute (bpm) will receive 25mg metoprolol twice daily starting at PAT.

- If the subject is not on a beta blocker – they will be counseled to take metoprolol 25mg twice daily till the day of surgery.
- If the subject is on a beta blocker that is not maximally dosed (see table below), we will provide metoprolol 25mg twice daily to be given throughthe day of surgery.
- If the subject is on a beta blocker that is maximally dosed, they will not be given an additional beta blocker

Following surgery, both groups will be treated as per usual postoperative care.

Beta Blocker	Maximum Dose
Atenolol (tenormin)	100mg daily
Betaxolol (Kerlone)	20 mg daily
Bisoprolol (Zebeta)	20 mg daily
Carvedilol (Coreg , Coreg CR)	50 mg daily
Labetalol (Normodyne)	2400 mg daily
Metoprolol tartrate (Lopressor)	400 mg daily (300mg in the elderly >65 years of age)
Metoprolol-succinate (Toprol-XL)	200mg daily
Nadolol (Corgard)	320mg daily
Pindolol (Visken)	60mg daily
Propranolol (Inderal)	640 mg/day
Sotalol (Betapace)	320 mg daily
Timolol (Blocadren)	60 mg daily

ACE-Inhibitors/Angiotensin Receptor Blocker (ARB):^
In the personal optimization arm, all subjects with a systolic blood pressure (SBP) >130mmHg or diastolic blood pressure (DBP) >90mmHg will receive 5mg lisinopril daily starting at PAT.

- If the subject is not on an ACE-inhibitor or ARB – they will be counseled to take lisinopril 5mg daily through the day of surgery.*
- If the subject is on an ACE-inhibitor or ARB that is not maximally dosed (see table below), we will provide lisinopril 5mg daily to be given till the day of surgery.*
- If the subject is on an ACE-inhibitor or ARB that is maximally dosed, they will not be given an additional ACE-inhibitor or ARB

Following surgery, both groups will be treated as per usual postoperative care.
^if the subject has a K>5mEq/L, the subject will not receive an ACE-inhibitor or ARB

*if the subject has known cough intolerance to ACE-inhibitor, they are excluded from the study

Angiotensin Converting Enzyme (ACE) Inhibitors	Maximum Dose
Benazepril (Lotensin)	80 mg daily
Captopril (Capoten)	150 mg daily
Enalapril (Vasotec)	40 mg daily
Fosinopril (Monopril)	80 mg daily
Lisinopril (Prinivil, Zestril)	80 mg daily
Moexipril (Univasc)	30 mg daily
Perindopril (Aceon)	16 mg daily
Quinapril (Accupril)	80 mg daily
Ramipril (Altace)	20 mg daily
Trandolapril (Mavik)	8 mg daily

Angiotensin II Receptor Blockers	Maximum Dose
Candesartan (Atacand)	32 mg daily
Eprosartan Mesylate (Teveten)	400 mg daily
Irbesartan (Avapro)	300 mg daily
losartan (Cozaar)	100 mg daily
Olmesartan (Benicar)	40 mg daily
Telmisartan (Micardis)	80 mg daily
Valsartan (Diovan)	320 mg daily