

**A double-blind, placebo-controlled, randomized study examining the effects of nebivolol compared to atenolol on endothelial function and cardiovascular risk in patients with early vascular disease.**

**EVIDENCE: Early Vascular Impairment-Determine Efficacy of Nebivolol, Comparator Examination**

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## STUDY SCHEMA

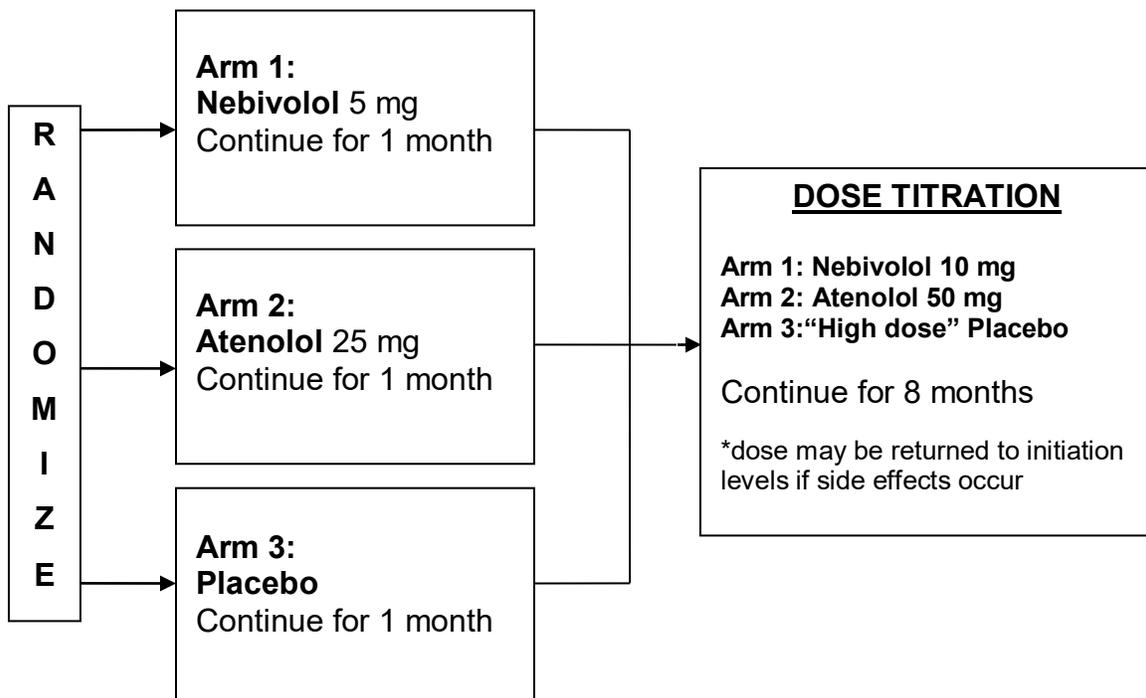
### Study Population:

- Males and females between 18 and 80 years of age with early vascular disease
- Borderline blood pressure (120-145/80-90 mm Hg)
- Borderline or abnormal small artery elasticity ( $C_2$ ) as measured by pulse contour analysis
- Treatment-naïve for all blood pressure medications including diuretics for at least 30 days prior to baseline visit
- No known history of cardiovascular disease

### Accrual Goals:

75 patients enrolled.

### Treatment Plan:



### Schedule of Assessments:

- **Blood pressure at rest at 0, 1, 3, 6 and 9 months**
- **Small artery elasticity ( $C_2$ ) and flow-mediated dilation at 0, 1, 3 and 9 months**
- **Rasmussen Disease Score assessments** (large artery elasticity, carotid intima-medial thickness, electrocardiogram (ECG), treadmill exercise test and left ventricle ultrasound) **at 0, 3 and 9 months**
- **Cardiac Health Biomarkers** (Total cholesterol, LDL, HDL, triglycerides, glucose, hsCRP, microalbuminuria and NT-proBNP) **at 0, 3 and 9 months**

## 1. INTRODUCTION AND SCIENTIFIC RATIONALE

$\beta$ -blockers have been widely used for the treatment and prevention of cardiovascular disease for more than three decades. In recent years,  $\beta$ -blocker usage has declined as studies have shown that traditional  $\beta$ -blockers have little effect on peripheral resistance, which is increased in individuals with endothelial (vascular) dysfunction [1-3]. Recently, nebivolol, a third generation  $\beta$ -blocker, was approved for use in the United States.

Nebivolol is a highly selective  $\beta_1$ -blocker with vasodilating effects that reduce peripheral resistance. Vasodilation is mediated by nebivolol's action at multiple points in the nitric oxide (NO) pathway [4]. The NO-mediated vasodilation of nebivolol is novel among  $\beta$ -blockers and is particularly promising as impaired vascular function in patients with cardiovascular disease may be due in part to decreased endothelial NO bioavailability [5]. Studies in patients with hypertension and/or coronary artery disease have shown that nebivolol improves endothelial function while non-vasodilating  $\beta$ -blockers do not [6, 7]. The efficacy of nebivolol on endothelial function in low to moderate risk populations has not been well documented.

We propose to study nebivolol in subjects with early vascular disease, using atenolol as an active comparator, as both drugs are selective  $\beta_1$ -blockers with no  $\alpha$ -blocking capabilities. These drugs differ in the fact that atenolol does not have vasodilating properties [6]. We hypothesize that both drugs will likely lower blood pressure through  $\beta_1$ -receptor blocking but only nebivolol will improve impaired endothelial function, presumably through NO-mediated vasodilation. A placebo arm will also be employed to further differentiate these two treatment strategies.

## 2. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled study comparing the efficacy of nebivolol and atenolol at improving small artery elasticity and reducing cardiovascular disease risk in subjects with early vascular disease. Approximately 75 subjects with borderline/elevated blood pressures and impaired endothelial function, as measured by arterial elasticity scores, will be recruited and assigned to treatment groups using a block randomization scheme. Patients will be randomly allocated to nebivolol, atenolol or placebo, and then followed for 9 months.

## 3. METHODOLOGY

The Rasmussen Disease Score (RDS) test panel is the chosen methodology for this study. The 10 parameters of the RDS were selected because of their ability

to quantify early structural and functional abnormalities in the vasculature and left ventricle which appear long before cardiovascular disease is present [8].

The RDS tests include: large and small artery elasticity (measured by pulse contour analysis), resting blood pressure, mild treadmill exercise test, carotid IMT, left ventricle mass, ECG, retinal vasculature evaluation, as well as quantification of serum NT-proBNP, and microalbuminuria. Please see Section 8 for a more detailed description of these parameters. Quantitative results from these tests are converted into categorical classifications based on values stratified by age and gender when appropriate. The categorical data is scored as follows: normal = 0 points, borderline = 1 point, abnormal = 2 points. Point values from all parameters are summed to create the RDS, with values ranging from 0-20. Scores of 0-2 are classified as normal, 3-5 as early disease, and 6+ as advanced disease. Previous research has shown that the RDS is a powerful predictor of future cardiovascular events [9].

The small artery elasticity ( $C_2$ ) parameter is of particular interest as it is responsive to changes in NO levels [10] and is an effective and reliable predictor of future hypertension [11] and other cardiovascular events [12]. Changes in  $C_2$  will serve as the primary outcome of this study. Similar studies using anti-hypertensive or lipid-lowering interventions have found significant improvements in  $C_2$  values [13, 14].

Brachial artery flow-mediated dilation (FMD) measurements will also be measured as an index of endothelial function [15], although this method appears to be less sensitive to functional changes related to NO bioavailability than  $C_2$  [10]. Utilizing both FMD and  $C_2$  will allow comparison with previous studies and take advantage of a large sample size to further examine the relative sensitivity of each method for reliably measuring endothelial dysfunction.

The duration of intervention for this study is 9 months which is the minimum time to adequately detect improvement in left ventricle (LV) mass values. LV mass measurements are a critical component of a comprehensive assessment of cardiovascular health and have improved within this temporal window as a result of anti-hypertensive intervention [14, 16].

## **4. OBJECTIVES**

### **4.1. Primary Objective**

This study will compare the effects of nebivolol against atenolol and placebo on endothelial function. Endothelial function will be measured by pulse contour analysis of the small arteries and scored in terms of arterial elasticity over a 9 month study period.

## 4.2. Secondary Objectives

- 4.2.1 Evaluate the effects of nebivolol as compared to atenolol and placebo on cardiovascular health in subjects with early vascular disease as measured by change in Rasmussen Disease Score (RDS) over a 9 month study period.
- 4.2.2 Evaluate changes in each RDS component over the 9 month study period in all treatment groups.
- 4.2.3 Evaluate the changes in risk factor and biomarker measurements from baseline to 3 and 9 month time points in all treatment groups.
- 4.2.4 Compare the sensitivity of pulse contour analysis and flow-mediated dilation methodologies for measuring functional changes in the endothelium and quantifying endothelial dysfunction.

## 5. SELECTION OF PATIENTS

Study entry is open to patients regardless of gender or ethnic background. Patients will be recruited from the Rasmussen Center for Cardiovascular Disease Prevention at the University of Minnesota, Fairview Clinics, and through advertisements or flyers posted at the University of Minnesota and surrounding communities.

### 5.1 Inclusion criteria

- Males and females 18-80 years of age
- Borderline blood pressure (120-145/80-90 mm Hg)
- Borderline or abnormal small artery elasticity (C<sub>2</sub>) as measured by pulse contour analysis
- Treatment-naïve for all blood pressure medications including diuretics for at least 30 days prior to baseline visit
- Able to walk on a treadmill for 3 minutes
- Female patients with reproductive potential must use an approved contraceptive method if appropriate (for example, intrauterine device [IUD], birth control pills, or barrier device) during and for 1 month after the last dose of study drug.
- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

## 5.2 Exclusion criteria

- History of intolerance to  $\beta$ -blockers or clear contraindications to their use
- Current pharmaceutical treatment of blood pressure
- Known history of cardiovascular disease (myocardial infarction, coronary artery bypass graft, unstable angina, uncontrolled arrhythmias, stroke, etc.)
- Known history of diabetes
- Known history of hepatic, renal, or gastrointestinal disorder
- Known history of any illness that may cause additional risk (as determined by study investigator)
- Pregnant or lactating women. When used during pregnancy,  $\beta$ -blockers may cause fetal harm.
- Participation in a concomitant clinical trial

## 5.3 Concomitant Therapy

Concomitant medications may include aspirin, birth control pills, lipid lowering agents, anti-platelet medications, psychotropic agents, vitamins or warfarin. The following medications may not be taken during the trial:

- Anti-hypertensive medications
- Vasoactive medications
- Cardiac medications (including  $\beta$ -blockers)

Since statins are known to positively influence arterial elasticity, it is necessary to control their use. Any study subject taking statins must be on a stable dose for 8 weeks prior to the baseline visit. This time window was chosen based on a previous study examining the effects of statin combined with an anti-hypertensive medication on  $C_2$  [13]. There was not a significant improvement in  $C_2$  between the 8 week and 28 week time points in the groups receiving a statin.

Subjects will be instructed to maintain their established statin regimen throughout the duration of the study.

## 6. RANDOMIZATION PROCEDURES

Randomization will occur after informed consent has been obtained and after eligibility is confirmed by measuring blood pressure and small artery elasticity. Two 1:1:1 randomization lists (one for subjects taking a statin and one for subjects without statin therapy) generated by variable block randomization will be used to assign each subject to a study arm at the time of enrollment. This method will allow stratification of statin therapy.

## 7. TREATMENT PLAN

### 7.1 Administration Schedule

Depending on assigned treatment group, subjects will take nebivolol, atenolol, or placebo. Matching medications necessary for maintaining the double-blind nature of the study will be provided by Forest, Inc.

**Nebivolol** 5 mg will be taken once daily with or without food by mouth for the first month. At the 1 month visit, nebivolol will be increased to 10 mg per day and will be taken for up to 8 months.

**Atenolol** 25 mg will be taken once daily with or without food by mouth for the first month. At the 1 month visit, atenolol will be increased to 50 mg per day and will be taken for up to 8 months.

**Placebo** will be taken in the same manner as nebivolol and atenolol treatment groups.

Patients will return to clinic at 1, 3, 6 and 9 months (+/- 1 week) for evaluation and a compliance check.

Patients will be instructed to return all study drug bottles and any remaining tablets to each appointment where subject compliance will be assessed by performing tablet counts.

Patients who demonstrate non-compliance during the study will be counseled regarding proper administration of study medication. In cases of continued and/or extreme non-compliance, study participation may be discontinued.

### 7.2 Dose Modification

If subjects develop intolerable side effects during the study, the investigator may down-titrate to the starting dose with patient permission.

### 7.3 Study Drug Dispensing

Study medications and placebos will be dispensed by the University of Minnesota Medical Center, Fairview Investigational Drug Service (IDS) according to the specified blinded randomization protocol at the baseline, 1 month, 3 month and 6 month visits. Study patients

who drop out prior to the 3 month time point will be replaced by alternate patients who meet study criteria and will not toward overall enrollment goal. Each patient will receive one bottle of study medication or placebo, labeled according to applicable regulatory requirements.

#### **7.4 Emergency Treatment Unblinding**

The IDS pharmacist will have the ability to unblind for individual patients only in case of an emergency where the further treatment of the patient is dependent upon knowing the study medication that the patient has been receiving. In the event of pregnancy, the patient's treatment assignment will be unblinded due to the potential effect of active medication on the developing fetus.

#### **7.5 Supportive Care Guidelines**

All supportive measures consistent with optimal patient care will be given throughout the study.

#### **7.6 Duration of Therapy**

Patients will receive protocol therapy for 9 months unless any of the following occurs:

- Patient withdraws consent,
- Continued and/or extreme non-compliance,
- Intercurrent illness that prevents further administration of study drugs,
- Study physician feels study treatment is not in the best interest of the patient,
- Unacceptable adverse events(s).

#### **7.7 Follow-up**

Subjects not experiencing adverse events will be considered completed at the 9 month study visit. For patients experiencing adverse events or if treatment related toxicity is present at the final visit, an additional follow-up visit will occur in 30 days ( $\pm$  one week).

Patients may continue on treatment beyond study using commercially available drug(s) at the discretion of the treating physician; however drug assignment will not be unblinded until the last patient completes study drug treatment.

## 8. STUDY PARAMETERS

### 8.1 Schedule of Events

Procedure/measurement	Screen	Baseline	1 Month	3 Months	6 Months	9 Months
Resting blood pressure	x		x	x	x	x
Arterial elasticity (small and large)	x		x	x		x
Treadmill exercise test		x		x		x
Carotid intima-medial thickness		x		x		x
Electrocardiogram		x		x		x
Left ventricle ultrasound		x		x		x
Retinal photo		x		x		x
Flow-mediated dilation		x	x	x		x
Blood draw		x		x		x
Urine sample collection		x		x		x
Physical examination		x		x		x
Medical history		x				

Blood and urine analysis	Code	Baseline	1 Month	3 Months	6 Months	9 Months
Pro-brain natriuretic peptide	ProBNP	x		x		x
Microalbumin, urine	UMA	x		x		x
high sensitivity C-reactive protein	hsCRP	x		x		x
Lipid panel	BLIP	x		x		x
Fasting glucose	Glu	x		x		x
Urine pregnancy test (if appropriate)	HCGU	x				

### 8.2 Description of Study Parameters

**Resting Blood Pressure:** Sitting blood pressure (BP) is measured by standard sphygmomanometry at rest. Blood pressure will be measured 4 times on each arm and averaged. The arm with the highest average will be used to obtain future resting blood pressure values.

**Small and Large Artery Elasticity:** Radial artery pulse waves are registered with the CV Profiler (Hypertension Diagnostics, Eagan, Minnesota). Small artery ( $C_2$ ) and large artery ( $C_1$ ) elasticity are derived from the pulse contour analysis.

**Treadmill Exercise Test:**

Standing blood pressure is measured before exercise, at the end of a 3-minute workload at 5 METS on the basis of a treadmill speed of 2.3 mph at a slope of 7%, and after a 1-minute recovery period.

**Carotid Intimal-Media Thickness:** Ultrasound with a Sonosite MicroMaxx unit is employed to measure intimal-media thickness 1 cm distal to the carotid bulb and to identify localized carotid plaques.

**Electrocardiogram:** A standard 12-lead electrocardiogram is evaluated for evidence of hypertrophy, repolarization abnormalities, or conduction abnormalities.

**Left Ventricular Mass Index:** Left ventricular (LV) ultrasound is performed with Sonosite ultrasound equipment, and left ventricular mass index (LVMI) is calculated according the formula of Devereux.

**Optic Fundus Photo:** A retinal photo of each eye will be acquired using a digital camera. Each photo will be used to measure and record vascular structure in the retina.

**Flow-Mediated Dilatation:** Endothelium-dependent flow-mediated dilation (FMD) of the right brachial artery will be measured using a SonoSite MicroMaxx ultrasound unit. Reactive hyperemia will be induced by inflation of a blood pressure cuff on the forearm for 5 minutes. The brachial artery will be scanned continuously in M-mode 30s before and 90s after cuff deflation. These recorded images will be used to obtain artery diameter measurements and compared to a scan taken during resting conditions. This procedure will be repeated after a 10 minute recovery period and the measurements will be averaged.

**Blood and Urine Analysis:** Blood and urine samples will be tested by Fairview Diagnostic Laboratory at the University of Minnesota. Fairview Labs normal and abnormal test ranges will be used to evaluate test results.

**Physical Examination:** A study physician will perform a standard physical examination to assess the general health of the subject.

**Medical History:** Each subject will be asked questions pertaining to their own and familial medical history. Special care will be used to collect any information related to cardiovascular events and risk factors.

## 9. STUDY ENDPOINTS

### 9.1 Primary Endpoint

Change in small artery elasticity (a marker for endothelial function) from baseline to 9 months after intervention initiation.

### 9.2 Secondary Endpoints

9.2.1 Change in Rasmussen Disease Score (RDS) from baseline to 9 months after intervention initiation. Each test is scored as 0 for normal, 1 for borderline, and 2 for abnormal. The criteria for normal, borderline, and abnormal has been established on the basis of large public databases. The ten cardiovascular tests provide total scores ranging from 0 (low risk) to 20 (high risk).

9.2.2 Change in each of the CDS components as measured from baseline to 3 and 9 months.

- Blood pressure at rest
- Large artery elasticity
- Treadmill exercise test
- Carotid intima-medial thickness
- Electrocardiogram (ECG)
- Left ventricle ultrasound
- Retinal vasculature
- Microalbuminuria
- NT-proBNP

9.2.3 Change in risk factor and biomarker measurements as measured from baseline to 3 and 9 months.

- Total cholesterol, LDL, HDL, and triglycerides
- hsCRP
- blood glucose

9.2.4 Difference in endothelial function quantification and sensitivity to change between pulse contour analysis and flow-mediated dilation from baseline to 9 months after intervention initiation.

## 10. ADVERSE EVENT REPORTING

For serious adverse event reporting purposes, toxicity information will be collected beginning with the 1<sup>st</sup> dose of study drug and continuing to approximately 30 days after the last dose of study drug or at the time the patient switches to commercially available drug (if patient decides to continue treatment beyond 1 year off study).

### 10.1 Definitions

Federal regulations [45CFR46.103(b)(5) and 21CFR56.108(b)(1)] require the IRB to ensure that researchers promptly report “any unanticipated problems involving risk to subjects or others” (UPIRTSOs). The IRB defines a UPIRTSO as any problem or event which in the opinion of the local researcher was unanticipated, reflects new and increased risk to the subjects, and was possibly related to the research procedures.

Problems/events that are unanticipated and involve new or increased risk to subjects should be reported *only* if in the opinion of the local researcher they are **possibly, probably or definitely related** to the research procedures.

### 10.2 Reporting Requirements

Agency	Criteria for reporting	Timeframe	Form to Use	Submit to:	Copy AE to:
U of MN IRB	Pose new or increased risk, unexpected, at least possibly related	10 Working Days	UPIRTSO form found on the IRB's Web site at <a href="http://www.research.umn.edu/irb/download/">http://www.research.umn.edu/irb/download/</a> .	MMC 820	Study file

### 10.3 Additional Events Requiring Reporting To the IRB

In addition the following events/problems meet the IRB’s definition of UPIRTSO and should be reported to the IRB (but not the DSMC) within the 10 working day time frame:

- Any event (including on-site and off-site adverse events, injuries, side effects, deaths or other problems) which in the opinion of the local investigator was unanticipated, involved new or increased risk to subjects or others, and was possibly related to the research procedures;

- Any accidental or unintentional change to the IRB-approved protocol that increases risk or has the potential to recur;
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject;
- Any publication in the literature, safety monitoring report (including Data and Safety Monitoring Reports), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
- Any breach in confidentiality that may involve risk to the subject or others;
- Any complaint of a subject that cannot be resolved by the research staff; or
- Any other possibly related event which in the opinion of the investigator constitutes an unanticipated risk.

#### **10.4 Events Not Requiring Reporting Until Time Of Annual Review**

Those unanticipated problems/events that reflect new or increased risk to the subjects that the local investigator deems unlikely or not related to the research procedure DO NOT meet the IRB's definition of UPIRTSO and should be reported in summary form (using a table or spreadsheet) only at the time of IRB continuing review. Accompanying documentation (sponsor report forms, etc.) should NOT be included with this summary. If received, such accompanying documentation will be returned to the investigator.

#### **10.5 Reporting of SAEs to Forest Research Institute (FRI)**

##### **Serious Adverse Event (SAE)**

A serious adverse event is one that:

- Results in death
- Is an immediate threat to life
- Requires inpatient hospitalization, or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect.

##### **Causality Assessment**

For all AEs, the Investigator must provide an assessment of causal relationship to the IP. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the IP caused the event?

**Yes:** There is a possible or probable relationship (ie, there is a reasonable or strong temporal relationship, and the events are unlikely to be attributable to other drugs, underlying diseases, or other factors). Dechallenge and/or rechallenge (if available) is positive.

**No:** The relationship is unlikely or nonexistent (ie, there is no strong temporal relationship and/or the use of other drugs, underlying diseases, or other factors provide plausible explanations for the event), or the patient did not take the IP.

The Sponsor (Principal Investigator) is required to inform Forest Global Drug Safety of all SAEs. Forest Global Drug Safety must be notified immediately regarding any SAE that occurs after informed consent is obtained.

The Principal Investigator must report the event within 24 hours of first knowledge of any AE that meets one of the criteria for an SAE, to Forest Global Drug Safety on an SAE report form. If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center must transmit the SAE report form to the SAE fax number **(631) 858-7906** within 24 hours of first awareness of the event at the study center.

Supplemental information shall be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

### **Reporting of Pregnancy to Forest Research Institute**

Study center personnel must report every pregnancy on a pregnancy report form as soon as possible (within 24 hours of first awareness of the pregnancy to the pregnancy fax number, **(631) 858-7906**), even if no AE has occurred, and follow it to term. If, however, the pregnancy is associated with an SAE (eg, if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form must be filed.

Fax all relevant SAE or pregnancy information to Forest Global Drug Safety. Contact information for Forest Global Drug Safety, personnel is as follows:

FOREST GLOBAL DRUG SAFETY DEPARTMENT  
Fax: (631) 858-7906

## 11. DATA AND SAFETY MONITORING PLAN

Weekly meetings of the study's principal investigator and staff will be held to discuss matters related to the safety of protocol participants, validity and integrity of the data, enrollment rate, retention of participants, adherence to protocol, and data completeness.

## 12. STATISTICAL CONSIDERATIONS

This is a randomized, double-blinded, placebo-controlled Phase II study to obtain a preliminary estimate of the effects of nebivolol compared to atenolol and placebo on endothelial function (measured by arterial elasticity) and cardiovascular disease risk (measured by RDS).

### 12.1 Statistical Methodology

The primary analysis of the study is descriptive, to obtain a point estimate and 95% confidence interval of the difference in small artery elasticity ( $C_2$ ) between nebivolol and atenolol treatment arms and nebivolol and placebo at the end of the observation period (9 months). Point estimates and 95% confidence intervals for the improvement in  $C_2$  within each treatment will also be presented.

Secondary analysis estimating difference in Rasmussen Disease Score (RDS) improvement between the nebivolol and atenolol treatment groups along with nebivolol and placebo groups at the end of the observation period (9 months) will also be completed.

Other secondary analyses include estimates of the associations among changes in RDS as well as risk factor and biomarker measurements from baseline to the 3, and 9 month time points in the two positive comparator groups.

Unpaired t-tests will be used to compare the means of  $C_2$  (small artery elasticity) as well as all RDS test component and biomarker values for each subject group at each time point. Paired t-tests will be used to compare baseline values and values from subsequent time points within one group. A P-value of  $< 0.05$  will be considered statistically significant.

Comparison of sensitivity and variability for C<sub>2</sub> and flow-mediated dilation (FMD) methodologies used in quantifying endothelial function of each group over the 9 month study period will also be included in the secondary analyses. Data will be analyzed within and between test groups with a significance level of  $P \leq 0.05$ .

## **12.2 Design and Sample Size Justifications**

A sample size of 25 subjects per arm will be adequate to detect a difference in small artery elasticity of 3.3 units (ml/mm Hg x 100) between positive comparators when power = 0.9 and  $\alpha = 0.05$ . This is assuming a standard deviation of  $\pm 3.57$  units. This assumption is made based on a previous clinical trial measuring small artery elasticity in patients undergoing anti-hypertensive therapy [14].

Subjects in the previous study were not selected on the basis of C<sub>2</sub> as they are in EVIDENCE. Therefore, it is reasonable to assume that our actual standard deviation will be much smaller than our estimate giving us a conservative population sample of 75. Assuming a smaller deviation of 3.0 (instead of 3.57) we would still have an adequate sample with a dropout rate of 7.6%. If rates of attrition exceed 7.6%, subjects will be replaced

## **13. ADMINISTRATIVE REQUIREMENTS**

### **13.1 Good Clinical Practice**

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

### **13.2 Ethical Considerations**

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The protocol, informed consent, written information given to the patients, other recruitment

materials and any revisions to these documents will be provided to the IRB by the investigator.

### 13.3 Monitoring and Auditing

This study will be monitored according to FDA/GCP guidelines.

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

### 13.4 Record Retention

The investigator will retain study records, including source data, copies of case report form, and all study correspondence in a secured facility for at least 2 years after the last study related publication.

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