

Short Title: Imaging Guided Lipid Therapy

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PROTOCOL TITLE

The RIGHT study: Risk stratification with Image Guidance of HMG coa reductase inhibitor Therapy

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Précis

The overall aim of this proposal is to compare the effectiveness of an image guided approach to lipid lowering to standard therapy guided by clinical risk factors and blood lipid levels. Men and women over age 55 who are candidates for statin therapy will be randomized to usual cholesterol lowering care, or to care guided by MRI images of the carotid arteries. Participants randomized to the second, imaging guided, group will be assigned to LDL cholesterol targets according to the degree of atherosclerosis seen by MRI. The study endpoints will be the total degree of plaque regression seen, the dosage of statin drugs required to achieve that reduction, and the rate of cardiovascular events.

FDG-PET is hypothesized to enable visualization of anti-inflammatory effects of statins that most likely occur before anatomic regression of the plaques can be demonstrated on MRI.¹ A pilot substudy is to be conducted to explore this relationship. A subgroup of patients participating in the main study will be asked to participate in FDG PET imaging. The purpose of this pilot study is to determine if FDG avid lesions undergo a greater degree of morphologic regression with therapy controlling for the reduction in LDL cholesterol and the dosage of statins required to achieve that target.

Although contrast-enhanced coronary CT angiography (CTA) with multidetector computed tomography (MDCT) has been used extensively to characterize coronary artery plaque composition, there is little data regarding its reproducibility. A recent study demonstrated excellent reproducibility for this technique but this study was performed using the older 64 detector row CT scanners². A pilot substudy will be conducted to study the reproducibility of coronary CT angiography using the newer generation of 320 detector row CT scanners.

1.0 Introduction

1.1 Study Objectives:

The purpose of this study is to evaluate the hypothesis that use of atherosclerosis imaging to set targets for cholesterol lowering therapy will result in greater regression of atherosclerosis than standard therapy.

The primary efficacy endpoint of this study is the wall volume of the internal carotid arteries as measured by magnetic resonance imaging.

Secondary endpoints are

- A. Arterial stenosis and plaque volume measured by coronary MDCTA
- B. Dosage of statin medications required to achieve LDL targets.
- C. Combined incidence of stroke, nonfatal MI, myocardial revascularization, hospitalization for unstable angina or heart failure and death.
- D. FDG plaque uptake within the carotid and coronary arteries.

E. Reproducibility of arterial stenosis and plaque volume measured by MDCTA.

1.2 Background and Rationale

The overall aim of this proposal is to compare the efficacy of an image guided lipid lowering strategy, with that of the standard lipid lowering approach i.e., guided by clinical risk factors and blood lipid levels.

The clinical efficacy of lipid modifying therapy to reduce cardiovascular (CV) endpoints has been demonstrated in multiple trials. Current recommendations for the initiation and titration of lipid therapy rely on evaluation of clinical and laboratory markers to estimate risk. Approximately half of patients with cardiovascular disease present with sudden death as their first indication of underlying atherosclerosis. Most patients who suffer a first heart attack fall into a “low risk” categorization by commonly used risk scores. Although cardiovascular disease is the most common cause of death in women, it is virtually impossible for women to reach the level of intermediate or high risk by current risk scores unless they are diabetic or over 70 years of age.³ Therefore, the effectiveness of current guidelines for estimation of cardiac risk remain in question. Better approaches to focus aggressive lipid modification strategies are needed in order to reduce the incidence of adverse events in lower risk individuals, and to ensure that patients at the greatest risk receive the most intensive available therapies. Use of noninvasive imaging to determine atherosclerotic burden is a promising strategy to achieve the end of tailoring risk modifying therapy to those most at risk.

Previous studies including our own have demonstrated the ability of lipid-modifying drugs, specifically HMG-CoA reductase inhibitors, to induce measurable regression of atherosclerosis. We propose to compare two different approaches to achieve atherosclerotic plaque regression and stabilization using the primary endpoints of carotid atherosclerotic plaque volume and composition defined by MRI. We also propose to measure coronary plaque regression defined by 320 detector row CT angiography, in order to evaluate whether carotid and coronary plaque regression occur in parallel. Finally, we propose to compare the benefit of these two lipid lowering strategies on clinical CV events. In order to achieve all of these objectives, state-of-the-art MRI techniques refined from our previous trial in similar population will be employed to quantify atherosclerotic plaque volume and composition in the carotid arteries, and to measure carotid arterial distensibility and pulse wave velocity. The newest generation of 320 detector CT scanners will be used to measure atheroma volume in the coronary arteries and differentiate between calcified and non-calcified lipid-rich and/or fibrous lesions. We hypothesize that guidance of lipid modifying therapy using imaging assessment of atherosclerosis to intensify or reduce lipid lowering therapy in patients with respectively greater or lesser plaque volume at the baseline examination will result in greater plaque regression and stabilization than standard NCEP guided therapy with the same or superior safety and/or treatment adherence profiles.

In a subset of individuals we plan to look at plaque inflammation using FDG PET. Molecular imaging compliments traditional anatomical imaging

approaches that identify plaque structure and composition.

It is widely postulated in the literature that ¹⁸F-fluorodeoxyglucose (FDG) imaging can improve risk assessment and prognostication through the identification of high-risk “vulnerable” plaques, plaques that demonstrate heightened inflammation, neovascularization or apoptosis. The primary target is the carotid and coronary arteries, imaging will also include the ascending and descending aorta, and the iliac arteries. Successful FDG PET imaging has been performed in large vascular beds, including the carotid arteries, and recent preliminary reports suggest the potential for noninvasive coronary plaque imaging. The advantage of nuclear imaging is that multiple vascular beds can be imaged with a single radionuclear isotope administration.

In a subset of 60 individuals we plan to study the reproducibility of arterial stenosis and plaque volume as measured by MDCTA.

At present, there is no available data on the reproducibility of 320 detector row MDCT for measuring arterial stenosis and plaque volume. This data will allow investigators to determine whether measured changes in stenoses and plaque morphology exceed that expected from the limits of measurement error in CTA and thus make the results of ongoing trials more reliable.

Consistent with such objectives, our specific aims are:

1st Aim

To examine whether image guided lipid lowering therapy is superior to NCEP guided therapy in promoting carotid atherosclerotic plaque regression and stabilization.

2rd Aim

To investigate whether the observed change in carotid atherosclerosis volume measured by MR, parallels observed change in coronary atherosclerosis volume measured by MDCT angiography.

3rd Aim

To examine whether MRI guided plaque regression and stabilization produces greater reduction in clinical CV events than standard NCEP guided therapy.

4th Aim

To examine the statin dosages required to promote plaque regression and stabilization differ between conventional and image guided strategies.

5th Aim

To investigate whether FDG PET activity predicts carotid morphological plaque regression and stabilization in both the carotid and coronary arteries and compare the efficacy of PET based prediction with MRI.

6th Aim

To correlate FDG uptake in the carotid, coronary, aortic, and iliac arteries with absolute values and changes in hematological biomarkers of vascular inflammation, thrombosis and atheroprotection at and between each time point.

7th Aim

To explore the variability of FDG uptake within willing individuals who are participating in the main study.

8th Aim

Reproducibility of arterial stenosis and plaque volume measured by MDCTA.

Thus, for the purpose of accomplishing these aims, we propose to compare an imaging-guided lipid modification strategy with standard therapy in a randomized, controlled clinical trial. The results of this trial will be directly applicable to improvement of strategies for plaque stabilization and prevention of atherosclerotic events.

1.3 Design

Study design: This is a randomized, controlled clinical trial in which 200 men and women aged 55 and older will be randomized to one of two treatment arms. The study duration will be 24 months. The control group will receive standard care with NCEP ATP III R guided statin therapy as determined by clinical risk factors. The imaging intervention group will have lipid targets assigned according to the severity of atherosclerotic plaque measured as wall volume in the common and internal carotid arteries by MRI. Patients in the lowest tertile of carotid wall volume (using the MESA study as a reference population⁽⁴⁾) will have statin therapy adjusted to a target LDL between 100-130 mg/dL. Patients in the middle tertile will receive statin therapy to an LDL target of 70-100 mg/dL. Patients in the highest tertile will receive statin therapy to achieve LDL-c levels below 70 mg/dL. Participants will be randomized in a equal ratio into imaging guided and control groups, respectively. This recruitment goal is designed to account for an estimated 20% attrition rate and maintain adequate power at the 24 month endpoint.

Measure	Method	Location	Frequency in the study
Plaque thickness	MRI – with and without contrast	2 carotid sites	Baseline, 12 and 24 months
Plaque area	MRI – with and without contrast	2 carotid sites	Baseline, 12 and 24 months
Plaque volume	MRI – with and without contrast	2 carotid sites	Baseline, 12 and 24 months
Fibrous/Lipid intra-plaque ratio	MRI – with and without contrast	2 carotid sites	Baseline, 12 and 24 months

Treatment and Assessments

At the initial study visit, all participants will undergo measurements of carotid arterial wall volume using contrast enhanced MR. For participants randomized to the imaging intervention arm, measured wall volume will be compared against the MESA population, and treatment targets will be assigned according to the magnitude of plaque volume. Participants with mild or no atherosclerosis, defined as the lowest tertile of wall volume, will have statin therapy adjusted to a target range of 100-130 mg/dL. Participants in the middle tertile will receive statin therapy adjusted to achieve a target LDL 70-100 mg/dL. Participants with the most severe atherosclerosis will receive statin therapy to an LDL target between 40 and 70 mg/dL. Participants in the control arm will have lipid sub-fraction targets determined according to estimated 10 year cardiovascular risk, as per standard NCEP guidelines.

Allowable statin compounds and maximum dosages are:

compound	maximum allowable dose	comments
atorvastatin	80 mg /day	
fluvastatin	80 mg/ day	
lovastatin (immed. release)	80mg/day	

extended release	60 mg/day	
pravastatin	80 mg/ day	either 40 mg immediate release twice daily OR 80 mg extended release once daily
rosuvastatin	40 mg/ day	
simvastatin	80 mg/day	

Subjects assigned to both arms of the study will undergo carotid MR for plaque evaluation at baseline, 12 and 24 months of followup. 320 detector row MDCT angiography will be performed at baseline and 24 months. Only unscheduled visits for evaluation of drug toxicity or potential clinical events will not coincide with intervention visits.

Carotid MRI

Participants will undergo 2D and 3D carotid MRI using a 3 Tesla scanner and surface carotid coils. Baseline non-contrast carotid images will be acquired with dual 3 inch surface coils (phased array) positioned immediately below the angle of the mandible on each side of the neck. The protocol will be same as previously used in studies performed at the N.I.H. by Wasserman et al ⁽⁵⁾, adapted by Drs. Bluemke and Lima as part of the MESA carotid MR imaging protocol and used by Drs Sibley, Lima and Bluemke in the NIA Plaque study. (AHA Scientific Sessions 2009, manuscript under review) Initial images will be acquired as a three-dimensional volume using a 3D variable flip angle TSE sequence (SPACE) at 0.8 mm³ isotropic resolution, in 64 partitions using GRAPPA with 2-fold acceleration. This sequence will be T2 weighted with a TR=1300 ms and TE 123 ms. The 3D volume data will be used to determine the course and orientation of the common and internal carotid arteries bilaterally, and to determine the location of the carotid flow divider (bifurcation). This sequence will be used to guide placement of baseline non-contrast images covering two 2.4 cm arterial volumes on each side of the neck, selected to include the areas of maximal atherosclerotic involvement assessed as perpendicular plaque thickness. Targets will then be imaged cross-sectionally with a DIR fast spin echo pulse sequence, ECG gated, with black blood and fat suppression. Slice thickness will be 2.0 mm with in plane resolution of 500-600 microns. Images will be obtained with both short TE=5msec (PDW weighted images) and long TE=60msec (T2 weighted images) with inversion times adjusted to minimize blood pool signal (approximately 600 ms) and repetition times of one and two cardiac cycles (RR intervals). After contrast administration the same carotid targets will be re-imaged as described above. Inversion time will be reduced from 600 to 200 msec to account for the effect of circulating gadolinium contrast.

Data Analyses of Carotid MR imaging

Co-investigators blinded to the results of treatment group assignment and patient characteristics will be responsible for the measurement of all MR outcome variables, specifically lumen area, wall volume fibrous content and lipid core. Measurements will be performed using commercially available semiautomatic contouring software (QPlaque, Medis Inc) workstation. Vessel contours will be reviewed by an experienced MR physician. Measurements for the primary study endpoints will be obtained from the post-contrast enhanced sequences as these provide the best definition of the vessel wall and lipid core.⁽⁴⁾ T2 images will be used for confirmation of these measurements on the post-contrast series when necessary. As previously reported, the lipid component of plaque is hypointense on T2 images, while fibrous components are isodense⁽⁶⁻⁸⁾. The primary study outcome variables will be measured from the 2-D carotid images and derived from these measurements of wall thickness in the radial direction. The calculated area in each slice will be summed for the slices acquired of the relevant vessel, allowing volume calculation of wall and plaque components. Identical measurements will be performed on the 3D sequences for purposes of calculating accuracy and agreement with the current standard 2D approach for use in future investigations.

Coronary angiography by 320 detector row MDCT

1) Coronary calcium scan

Will be performed using the following protocol:

-No contrast.

-CT Imaging: tube voltage = 120kV, tube current = 140 mA, gantry rotation speed = 0.35 seconds, slice thickness = 0.5 mm, rows = 256-320, range = 128-160 mm. X-ray tube will be on for a total of 0.35 seconds. Estimated radiation dose = 1.5 mSv.

2) Rest Coronary arterial imaging

Coronary arterial imaging will be performed during a 4-5 ml/sec intravenous iodinated contrast (ISOVUE[®]-370) infusion using the following parameters: If heart rate is < 66 bpm prospective ECG gating at 70-80% of one R-R interval, X-ray exposure time ranges from 0.423 – 0.350 sec (depending on heart rate). If heart rate is ≥ 66 bpm prospective ECG gating at 40-80% of two R-R intervals, X-ray exposure time ranges from 1.174 sec – 0.714 sec (depending on heart rate) tube voltage = 120kV, tube current = 300 -580 mA depending on BMI and gender, gantry rotation speed = 0.35 or 0.375 seconds, slice thickness = 0.5 mm, rows = 256-320, range = 128-160 mm. The automated bolus tracking feature will be used to judge contrast bolus arrival and optimize image quality.

The estimated radiation dose for the entire cardiac computed protocol (Calcium scoring (1.5 mSv) + Coronary arterial imaging (3-9 mSv) is 4.5 mSv to 10.5 mSv depending on patient heart rate, BMI, and gender. Beta-blockers will be used to control the heart rate and thus maintain the radiation dose as low as reasonably achievable. Depending on patient size, a maximum of 2 ml/kg iodinated contrast will be used up to a maximum of 130 ml.

Beta Blockade

In order to optimize image quality by reducing cardiac motion, participants will receive beta blockade on the day of the scan. Participants will have heart rate and blood pressure measured, and will be assessed for contraindications to beta blockade (bradycardia, heart block, active wheezing, history of adverse reaction).

Since the approach to pre-scan beta-blockade is unique to the individual participant, the supervising physician customizes the dose on an individual subject to achieve a goal heart rate of less than 60 beats per minute. A net dose of metoprolol 25-200 mg or atenolol 50-100 mg or diltiazem 90-360 mg will be administered orally potentially in divided doses over a period of approximately 1-2 hours titrated to achieve a heart rate less than 60 beats per minute. In addition, metoprolol or diltiazem 5-30 mg intravenously may be administered in divided doses at the judgment of the supervising physician if heart rate is not adequately controlled and the subject appears capable of tolerating the additional medication. Vital signs will be obtained and documented following metoprolol administration. If at any time the heart rate is <50 bpm and/or the systolic BP is <100, the supervising physician will be notified. All participants will be assessed for symptoms of bradycardia, hypotension and orthostasis after scan completion.

Nitrate therapy

The use of short acting nitrates (i.e. sublingual nitroglycerine) just prior to MDCT is required for patients with systolic blood pressure >110mmHg to allow for accurate assessment of the degree of coronary artery stenosis, reduce vasospasm and to standardize vasomotor tone. Potential contraindications to nitroglycerine use should be reviewed prior to administration (known allergy or severe intolerance, critical aortic stenosis, pre-existing hypotension). If the patient cannot receive nitroglycerine (due to intolerance, borderline blood pressure, investigator judgment), the patient may still proceed with the study. Known risks of nitroglycerine use include headache, reduction in blood pressure, hypotension.

CT image analysis

CT angiogram images will be reconstructed and post-processed on a separate workstation using Vitrea (Vital Images, Inc) software. The coronary tree will be segmented for analysis using a 16 segment AHA model according to the CORE-64 protocol⁽⁹⁾. Vessels larger than 1.5 mm in luminal diameter will be analyzed. The worst lesion per segment will be assessed. Luminal stenosis will be measured using semi-automated software. The spatial volume contained within the visible external wall of the vessel and the volume of the vessel lumen will be measured. A standardized under-patient phantom will be included in each scan to permit between-scan correction of density measurements.

Informed written consent will be obtained for each participant. Exclusion criteria will include contraindications for CT imaging or contrast administration and arrhythmia.

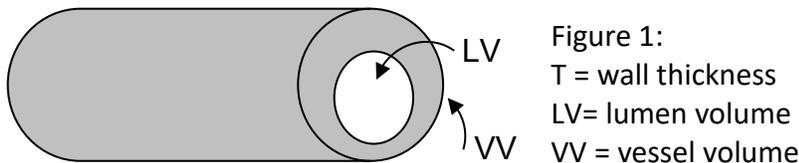
Coronary calcification

Coronary calcification will be measured by the Agatston⁽¹⁰⁾ method, correcting lesion area by the density of calcification in the lesion. A density independent volume score will also be calculated. Total coronary artery calcium scores will be generated by summing the values from the left main, left anterior descending, left circumflex and right coronary arteries. Readers will be blinded to subject identity.

Plaque quantification

Raw data will be reconstructed at 0.5 mm slice-thickness by a multi-segment reconstruction algorithm. The baseline axial MDCT images with adequate reconstruction phase will be post processed and analyzed by commercial software (Sure Plaque, Toshiba Medical Systems). Lumen and wall boundaries of target vessels will be semi-automatically detected on cross sectional images. Under the guide of stretched multiplanar reconstructed image (SPR), two experienced readers will review and edit lumen and outer wall contours of coronary segments of the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX) and right coronary artery (RCA) from ostium to vessel diameter > 2.0mm from cross sectional image by each 1.0 mm in length. Segments with artifact, blur, or stent will be excluded. Volume estimates are obtained by multiplying cross sectional area by slice thickness. Coronary wall volume is computed by subtracting lumen volume from vessel volume.

To quantify coronary lumen volume, vessel wall volume, and total vessel volume by MDCTA we will obtain three indices from MDCTA analysis of the lumen and vessel borders: 1) coronary lumen volume/ vessel volume (LV/VV), 2) coronary wall volume/ vessel volume (WV/VV) and 3) coronary wall volume/ lumen volume (WV/LV) (Fig. 1). The greatest value for all indices obtained for each vessel and patient will be recorded.



Outer contour – volume circumscribed by the outer border of the vessel wall (mm^3)

Lumen – volume circumscribed by the inner border of the vessel wall (mm^3)

Wall volume = Outer contour volume – lumen volume (mm³)

PET Substudy

A subgroup of 60 patients will be recruited to participate in PET scanning which will be performed twice, once at study initiation and after 6 months of trial-directed statin therapy.

Information including cardiovascular risk factors and other medication, including anti-inflammatory drugs, use will be collected. The total cholesterol and LDL levels and the dosage of statins required to achieve that target will be recorded.

Inclusion Criteria:

Participants who are not participating in the CT Reproducibility study are eligible.

Exclusion Criteria:

Patients who are unable or unwilling to comply with the physical activity restrictions or fast for 12 hours prior to FDG PET scanning will be excluded. Due to the need for dietary manipulation and the maintenance of strict glycemic control we will exclude diabetic patients from our initial study sample. Blood glucose measurements before injection must be within normal limits, less than 200 mg/dL (11 mmol/L).

Hematological Biomarkers Markers:

Blood tests for inflammatory markers will be incorporated into the baseline and 6 month blood draws. Standard investigations will include C-reactive protein, matrix metalloproteinase -3 and -9, interleukin-18, cathepsin K, fibrinogen, adiponectin, and plasminogen activator.¹²⁻¹³ A tube of blood will be stored at -70°C for testing of further markers defined at a later date.

FDG PET Preparation:

Study subjects will be asked to fast for 12 hours prior to PET scan. On the morning of the PET study, a low carbohydrate meal will be provided to study participants. Patients will be asked to avoid exercise 24 hours prior to scanning.

Carotid and Cardiac FDG PET Imaging Technique:

On the morning of the scan, Metoprolol 50 – 100 mg PO will be administered to slow the heart rate and optimize the acquisition of diastole.¹

The dose of FDG administered, duration between FDG injection and PET image acquisition, and the method of quantification of FDG uptake will be standardized.¹⁵ The injected dose of 18F-fluorodeoxyglucose will be 5.2 MBq/kg (140 mCi/kg) of lean body mass to a maximum of 12.5 mCi.

Patients will be kept resting comfortably in a semi-dark room. Scanning will be initiated after 90 minutes.¹⁶⁻²⁰ Typically, extended time imaging will be performed of the coronary and carotid beds first, followed by a 5 – 15 minute break and imaging of the remainder of the body.

The initial acquisition will be centered over the heart in 3-dimensional mode for at least 20 minutes. When feasible, both cardiac and respiratory gating will be performed. Images will be acquired in list-mode allowing for both single phase and segmented reconstructions.

Subjects will be placed in a head holder and mobility-restricted with padding and tape-reminders. Using ultrasound, performed prior to the FDG injection, the carotid bifurcation will be located and a single-bed position high-resolution carotid PET scan will be performed using 3D mode with a minimum acquisition time of 9 minutes.²¹

After a short break, lasting 5 – 15 minutes, body PET scanning will be performed. Body imaging will use standard 3D mode techniques and will consist of sequential emission images obtained with 16 cm fields of view each acquired over at least a 2 minute interval. Scanning will extend from the skull base to mid-thigh obtained in the cranial-caudal direction.

CT imaging or MRI is necessary for attenuation correction and signal localization.

CT / MR Acquisition:

All studies will be performed according to routine protocol using a dedicated PET/CT system, or when available, a dedicated MR/PET. These devices are comprised of a PET scanner coupled to either a multislice CT or MRI scanner. With PET/CT, the PET and CT components are mounted back-to-back and mechanically calibrated to ensure alignment of the CT and PET planes; the imaging protocol consists of an initial CT acquisition followed by the PET study. During 2011, the NIH is slated to receive the Siemens Biograph mMR (molecular MR) which is the first integrated MR/PET scanner; this state-of-the-art machine incorporates a ring of lutetium oxy-orthosilicate crystal PET detectors inside the bore of a 3T MRI magnet and allows for simultaneous MRI and PET acquisitions.

CT or MRI scanning will be performed from skull base to mid-thighs using appropriate respiratory and cardiac gating. CT parameters (Biograph, Siemens PET/CT) include a spiral acquisition using 120 kVp and 115 mA with a section thickness of 2.5 mm; no oral or intravenous contrast material will be administered for the CT. The MR acquisition (Verio, Siemens) will employ the Total imaging matrix (Tim) coil technology using

standard parameters with field of view and matrix size adjusted to the imaged body part.

High Resolution Carotid MRA:

In order to facilitate the comparison between MRI and PET imaging prior to the availability of the integrated MR/PET unit, an additional high resolution carotid MRA examination will be performed at the 6 month time point. This gadolinium enhanced study will use the standard carotid MRA study protocol and be scheduled on the same day or within a 2 week interval from the PET scan. Carotid positioning will be reproduced through positioning technique using careful measurement, such as the distance between the chin and sternal notch, and employing mobility-restricting equipment, like the head holder and tape reminders.

Image Reconstruction and Registration of Carotid and Cardiac FDG PET Imaging:

PET image reconstruction will use standard filters for a fully iterative process using optimized spectral content measure with at least 2 iterations and 28 subsets. High resolution reconstruction of the neck will be performed using at least 256 x 256 matrices; other vascular beds will be reconstructed using at minimum the standard 128 x 128 matrices.

Matching PET/CT and MR/PET images will be fused.¹¹ Both vendor specific software and open source programs will be used for region of interest delineation for partial volume correction and for vessel wall and lumen for calculation of vessel wall FDG uptake.²²

Imaging of the thorax will be viewed as both summed and gated reconstructions. For the gated reconstruction, 8-frames per cardiac cycle will be binned and the usable frames from middle to late diastole that have minimal blurring will be extracted and summed to enhance count density of the coronary arteries and warped for co-registration with the diastolic and respiratory gated CT / MR data.

Data Analyses of FDG PET Imaging:

For each patient scan, quantitative analysis will be performed of carotid and coronary arteries, aortic arch, ascending and descending aorta, abdominal aorta and iliac vascular territories. Arterial wall lesions with radioactivity concentrations above the mean blood-pool activity, and/or with calcification detected by CT and with morphology consistent with that of a plaque will be considered plaque and included in the assessment. CT / MR evaluation will be performed to identify atherosclerotic plaque as abnormal wall thickening with or without the presence of other features, like a lipid core or focal calcification, on a segment by segment basis.

Maximum standardized uptake value (SUV_{max}) corrects for patient weight and injected dose-decay:

$$\text{SUV}_{\text{max}} (\text{g} / \text{ml}) = \frac{\text{maximum activity (Bq / ml)} \times \text{weight (kg)}}{(\text{dose (Bq)} \times 1000 (\text{g/kg}))}$$

Target (plaque) -to-background (blood) ratio (TBR) normalizes vessel wall FDG uptake to the circulating FDG concentration. Once an region of interest (ROI) is defined, either an FDG avid plaque or an FDG negative area with plaque features identified on CT or MR, the TBR is derived from an mean signal within the ROI divided by the mean signal from a large adjacent vein, typically the jugular vein for the carotids and the inferior vena cava for the aorta and iliac vessels.

The target-to-background ratio is calculated:

$$\text{TBR} = \frac{\text{mean voxel value within ROI (MBq/ml)}}{\text{mean voxel value within jugular vein ROI (MBq/ml)}}$$

MDCT Reproducibility Substudy

A subgroup of 60 participants with CT angiography performed in a single R-R interval (scanning heart rate ≤ 64 bpm) and estimated radiation dosage under 10.5 mSv will return 4 weeks after a protocol scheduled CT for a second reproducibility CT scan. The reproducibility CT angiography will be performed according to the same methods as the baseline imaging (pg 10). Coronary calcium scanning will be omitted to reduce radiation dosage, as the reproducibility of calcium scoring has been well studied. Participants in the reproducibility subset will undergo a total of three CT angiography studies over the 24 month study period. The 10.5 mSv estimated dosage inclusion criterion will ensure that reproducibility patients do not cumulatively receive more than the currently consented radiation dosage limit. In fact, for the reproducibility CT angiogram, scan parameters will be set to limit imaging to a single heartbeat regardless of patient heart rate or arrhythmias. This will ensure that radiation exposure cannot exceed the 21 mSv consented limit for the combination of main protocol and reproducibility substudy angiograms in each study year.

Sixteen to twenty-four patients (total, n=60) will be selected from three groups: (a) patients with a calcium score of 0-99, (b) patients with a calcium score 100-399 and (c) patients with a calcium score of > 400. These 60 scans will be interpreted by two readers, allowing assessment of both intra and interobserver variability as well as repeatability limits.

Inclusion Criteria:

Patients will be selected who had a one RR interval initial CT scan with less than 10.5 mSv estimated radiation dosage.

Exclusion Criteria:

Patients who will participate in the PET substudy.

The repeat CT scans will be performed using the same protocol as the initial CT scan. The data obtained from the repeat CT scan will be analyzed in the same manner as that obtained during the initial scan.

2.0 Eligibility Assessment and Enrollment

2.1 Inclusion Criteria

- A. Men and Women \geq 55 years of age
- B. candidates for lipid lowering therapy under NCEP ATP III guidelines without contraindication to statin therapy
- C. Willing to modify therapy to enroll in the study
- D. Willing to travel to the NIH for follow-up visits.
- E. Able to understand and sign informed consent
- F. Lab Eligibility parameters:
 - eGFR > 45 mL/min/m²
 - For age > 60 test GFR within 1 week prior to contrast; For age \leq 60 test within 4 weeks

Inclusion Criteria for the PET Substudy:

Participants who are not participating in the CT Reproducibility study are eligible.

Inclusion Criteria for the Reproducibility Substudy:

Patients will be selected who had a one RR interval initial CT scan with less than 10.5 mSv estimated radiation dosage and who will not be participating in the PET Substudy.

2.2 Exclusion Criteria

- A. Ineligibility for MR imaging due to:
 - Previous pacemaker implantation
 - Automatic implantable cardioverter-defibrillator (AICD)
 - Metal implants or other ferromagnetic devices, or
 - Foreign material
- B. Claustrophobia
- C. Contra-indication or allergy to statin medications.

- D. Current statin therapy at or above the maximum dosage permitted per study protocol (section 1.3,above).
- E. Use of fibrates, ezetimibe, niacin, or bile acid binding agents within 6 months of screening visit.
- F. Pregnancy and nursing.
- G. Liver failure defined clinically and by laboratory data.
- H. Mental, neurologic or social condition preventing understanding of the rationale, procedures, risks and potential benefits associated with the trial.
- I. Any other conditions that precludes safety for MRI and/or CT imaging per the researcher's evaluation.

Exclusion for participation for Gadolinium contrast: Participants may still undergo all other study evaluations.

(Inclusive of the above exclusion criteria):

1. Allergy to gadolinium for scans using contrast; will be eligible for non-contrast scans.
2. Acute renal failure, renal transplant, dialysis and renal failure (eGFR <45 mL/min/m² and/or clinically diagnosed).
3. Individuals with a history of liver transplant or severe liver disease.
4. Individuals with hemoglobinopathies or severe asthma.

Exclusion for participation for iodinated contrast: Participants may still undergo all other study evaluations

Prior hypersensitivity reaction to iodinated contrast injection, renal dysfunction (defined as eGFR < 45 mL/min/ m²) or a current clinical diagnosis of renal failure.

Exclusion Criteria for the PET Substudy:

Patients who are unable or unwilling to comply with the physical activity restrictions or fast for 12 hours prior to FDG PET scanning will be excluded. Due to the need for dietary manipulation and the maintenance of strict glycemic control we will exclude diabetic patients from our initial study sample. Blood glucose measurements before injection must be within normal limits, less than 200 mg/dL (11 mmol/L).

Exclusion Criteria for the Reproducibility Substudy:

Patients who did not have a one RR interval initial CT scan.

Patients who will participate in the PET Substudy.

2.3 Screening Evaluation

On- Study Assessments:

Study activities below (see Appendix B for Flow Chart) specify the required study tests and procedures for participants.

Baseline visit tests and procedures will be completed 2 weeks before the first dose of study medication, unless otherwise noted.

At the baseline visit, the Investigator and/or study staff will:

- A. Review the study procedures and determine that the eligible patient is willing to comply with all protocol requirements;
- B. Review the inclusion and exclusion criteria with the patient and determine if the patient can be a participant in the study;
- C. Record previous and concomitant medications, including vitamin and herbal supplements for the 4 weeks before the first dose of study medication;
- D. Complete patient medical history and physical examination including vital signs, height, and weight;
- E. Collect blood and complete laboratory safety evaluations:
 - Complete blood count (CBC) with platelet and differential,
 - Chemistry Labs: Electrolyte Panel, Creatine, Billirubin (total), Aspartate Amino-Transferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (Alk Phos), Uric acid, Protein (total), Albumin, Calcium, Phosphorous, and Magnesium),
 - 12 hour Fasting Cholesterol (Chol) tests: Chol Total, High density lipoprotein (HDL), Triglycerides, and calculated Low density lipoprotein (LDL)
 - Creatine kinase (CK)
 - High sensitivity C-Reactive Protein (CRP)
 - Urine pregnancy test (for women of childbearing age)
 - Additional 2 tubes of blood will be stored for possible additional testing (not to include genetic or DNA analysis)
- F. Review baseline carotid MRI study regarding feasibility of enrollment;

- G. NIH Pharmacy will randomize patients to protocol.
- H. CT angiography scan will be performed at baseline and at 24 month endpoint. Reproducibility sub-study patients will have an additional CT angiography 4 weeks after either baseline or 24 month scan.
- I. Carotid MRI 0, 12, 24 months both non-contrast and post gadolinium administration. Total scan time will be approximately 1 hour.
- J. Scheduled study visits which are part of the trial expected procedures will be made by one of the Investigators including the Nurse Coordinator. Clinical follow up will be made at the time of one of 7 scheduled clinic visits or in response to notification of any perceived clinical alteration.

Study Calendar – Appendix B

2.4 Registration Procedures

Upon completion of the screening process, eligible subjects will be enrolled on the study and will begin treatment after being randomized by the NIH Pharmaceutical Development Services.

2.5 Randomization Procedures

Eligible participants will be open-label randomized by the NIH Pharmaceutical Development Service in to either the image guided therapy arm or the standardized treatment arm using a random number table used by the NIH Pharmaceutical Development Service Department. Double blinding is not feasible in light of the need for study physicians to titrate drugs to LDL targets.

The treatment group assignments will be blinded to the MRI and CT readers. If a participant should need to come off study for any reason, they will be informed which arm they were randomized to.

3.0 Subjects Implementation

3.1 Study Design

This is a randomized, controlled clinical trial in which 200 men and women aged 55 and older will be randomized to one of two treatment arms. The study followup will be 24 months. The control group will receive standard care with NCEP ATP IIIIR guided statin therapy as determined by clinical risk factors.

The imaging intervention group will have lipid targets assigned according to the severity of atherosclerotic plaque measured as wall volume in the common and internal carotid arteries by MRI. Patients in the lowest tertile of carotid wall volume (using the MESA study as a reference population⁽⁴⁾) will have statin therapy adjusted to a target LDL between 100-130 mg/dL. Patients in the middle tertile will receive statin therapy to an LDL target of 70-100 mg/dL. Patients in the highest tertile will receive statin therapy to achieve LDL-c levels between 40 and less than 70 mg/dL. Participants will be randomized in equal numbers to the two study arms.

We estimate we will accrue approximately 3-4 subjects a month, leading to full accrual within 50 months.

3.2 Protocol Evaluation/Study Calendar

Treatment Arms: Randomized 1 (Arm A):1 (Arm B)

A. Statin therapy with lipid targets determined by plaque imaging.

1. Lowest tertile of plaque volume:
LDL 100-130 mg/dL achieved with statin therapy
2. Middle tertile:
LDL 70-100 mg/dL achieved with statin therapy
3. Highest tertile:
LDL below 70 achieved with statin therapy

B. Standard lipid therapy as determined by NCEP guidelines

Protocol Evaluation

A. Main Study Subjects will have a total of 7 visits (Screen plus follow up visits). PET sub-study subjects will have an additional 1-3 visits. Reproducibility sub-study subjects will have a single additional visit. Visits 2 will follow the Protocol Evaluation schema in Appendix B. Visits will occur within +/- 30 days due for unforeseen events.

B. Safety Measures (each visit, starting with week 0):

- Safety labs: Hepatic panel (Alk Phos, ALT, AST, Bilirubin (total & direct) and creatine kinase measured during the course of the study. Urine HCG test for women of childbearing age. Blood glucose measurements prior to PET imaging.
- Review of interim medical history and evaluation for interim adverse events, off treatment or off study criteria.

Complete review and recording of participant medications including over the counter and herbal compounds.

- Prior to CT and MRI scanning: Obtain MRI Screening Questionnaire (MRI scan days only) and estimated glomerular filtration rate (eGFR) the day of receiving iodinated contrast or gadolinium based contrast. Urine HCG test for women of childbearing age.

C. Research Blood Samples (collected at imaging visits)

- Additional 2 tubes of blood will be stored for possible additional testing (not to include genetic or DNA analysis).

3.2.1 Statin titration

Statin medications will be titrated over the initial 6 months of the study to reach protocol defined LDL cholesterol targets. Should a participant's LDL fluctuate after the 6 month visit, bringing them outside of their target range, statin dosage may be increased or decreased as necessary to return them to their protocol assigned target. Participants who have not reached their LDL target after the 6 month dose adjustment will be removed from study treatment as per off-treatment criterion 3, below. (3.4.1)

3.2.2 Response to abnormal results

All clinically abnormal test results will be relayed to participants' primary care physician(s) or other designated third party. Participants will be instructed to consult with their physician for follow up and referral to specialists as appropriate.

In addition, abnormal laboratory values potentially due to statin treatment (ALT, AST, alkaline phosphatase, CK > 1000 U/L) that are asymptomatic and less than 3 times the upper limit of normal as specified by the NIH Clinical Center clinical laboratory will be repeated within 2 weeks of the initial result. If results are stable or improved, further testing will occur at normally scheduled study intervals. Should results worsen, increases in statin dosage that immediately preceded the abnormal result will be reversed and laboratory results repeated in 2 weeks. ALT, AST, alkaline phosphatase reaching more than 3 times the upper limit of normal or CK >1000 U/L will be considered a serious adverse event as per section 8.1

3.3 Concurrent Therapies

N/A

3.4 Criteria for removal from Treatment/Protocol

3.4.1 Off Treatment Criteria:

Subjects who come off treatment will be returned to usual care for cardiac risk factors as directed by their primary physician. If they consent to continue imaging follow up, they will complete imaging as per protocol and be analyzed according to their original treatment group assignment.

1. Occurrence of a clinical cardiovascular event including myocardial infarction, acute coronary syndrome, angina, heart failure, stroke or revascularization.
2. Inability to continue on study medications (adverse reaction, not wanting to adhere to the study medications)
3. Inability to reach our study LDL target after 6 months of titration (study visit 4)
4. Elevations of liver enzymes three times the upper limits of normal or any elevation accompanied by symptoms compatible with hepatitis, i.e.: fatigue, sluggishness, anorexia and weight loss.
5. Myopathy defined as muscle pain with serum creatinine kinase concentrations > 1000 U/L.

3.4.2 Off Study Criteria

Request of the patient or the attending physician.

Any other clinical or laboratory abnormality which cannot be confidently excluded as a side effect from study medications will lead to discontinuation of an individual patient from the trial.

Subjects who come off study for any reason will be referred back to their primary physician.

4.0 Supportive Care

Study investigators and support staff will provide further consultation to participants by in-person visits, phone or electronic communication as needed to address participant concerns regarding study therapy or imaging evaluation.

5.0 Data Collection and Evaluation

5.1 Data Collection

Standard forms for patient history, labs, imaging results.

Vital status will be recorded on a case report form. Complete records must be maintained on each patient, which will consist of the hospital chart with any supplementary information obtained from patient, outside laboratories, progress notes, reports, consults, or tests.

The relational database storing the entire information set will be based on coded identification. The confidentiality and security of the data files in the computer will be maintained by ensuring password protection on all computer accounts. Protection against loss of data is essential to our data management. Quality control procedures will also include:

- 1) Assurance or the prevention of possible errors;
- 2) Assessment, or the detection of errors after they have occurred and;
- 3) Feedback, or the correction of system failures which originated the error and is necessary to avoid errors in the future. Detailed checklists are used for data collection and trial procedures.

Any protected patient information will be stored on a password protected secure database at NIH. Any information will be de-identified by study ID # and cleaned of PHI.

5.2 Response Criteria

A. Lipid targets will be used as response criteria study.

5.3 Toxicity Criteria

Table: Safety Parameters to be monitored during the study

Safety issues	Measure	Method	Concern	Discontinuation	Discont. Freq.
Liver Function	ALT, AST	Standard	2 x normal	3 x normal	2%

Liver Function	Alk. Phosphatase	Standard	2 x normal	3 x normal	<1%
Muscle Injury	CK	Standard	3 x normal	>1000 U/L	<1%
Hepatitis	Symptoms/LFTs	History	LFT elev.	Clin. Diagn.	<1%

6.0 Statistical Section

Data from the recently concluded NIA Plaque Study, a randomized double-blind trial of the effect of niacin vs. placebo on MRI plaque volumes were collected on 145 subjects at baseline, and at 18-month follow-up. For the primary endpoint in the proposed study, carotid wall volume, the standard deviation of the differences between 18 months and baseline was 125 mm³, combining data from both the left and right arteries. The baseline mean for the entire group was 300.0. Since the proposed study has a longer duration (24 months) than the NIA Plaque Study, and since we have the benefit of improvements in MRI technology, we anticipate a larger effect size than was seen in the NIA Plaque Study. The sample size calculations were based on finding a 40% decrease in plaque volume in the image-guided arm compared to a 20% decrease in the conventional treatment arm at 24 months using a two-sample t-test. The table below shows the power to detect this difference at the 5% level of significance, assuming 80 subjects in each group. These power calculations were based on comparing the change from baseline at a single time point. However, the primary analysis will employ a mixed model, which will include multiple observations per patient. Therefore, 80 patients in each group will certainly provide adequate power. As discussed below we assume that the attrition rate will be 0.20 at the 24-month follow-up. Thus, recruiting 200 study participants will be sufficient for this study. These calculations were based on the optimal allocation of equal numbers to the two arms. However a 3/1 ratio of image-guided to conventional therapy did not meaningfully reduce the power.

Decrease in plaque volume (Image guided arm)		Decrease in Plaque Volume (Control Arm)		
		35%	20%	25%
	15%	0.85	0.62	0.33
	40%	0.96	0.85	0.62
	45%	0.99	0.96	0.85

Power of a two-sample t test to detect the indicated difference in change from baseline at 24 months

For the secondary end-point of this study, the task is to test the null hypothesis that the hazard rate, which is assumed to be constant across all study months, is identical in the two groups (image guided vs.

traditional risk-factor based care). This hypothesis will be tested in a study in which subjects are entered and then followed until either (a) the terminal event occurs, or (b) they drop out of the study, or (c) the study ends and the patient is censored while still being actively followed. The study design calls for an accrual period of 50 months and a follow-up period of 24 months. Computation of power for this analysis is based on a hazard ratio of 0.50. Specifically, it assumes hazard rates of 1.00 for the standard care group, versus 0.50 for the image guided group. Since the hazard rate is constant across months, this is equivalent to median survival times of 0.69 years for the standard treatment versus 1.39 years for the image guided intervention group.

The power analysis for the secondary outcome (clinical events) was based on the paper by Brown et al.²⁴ This paper reported mortality rates at 30 months in two treatment groups ($2/48 = 0.042$ and $3/46 = 0.065$) and a control ($10/52 = 0.192$). We used these rates, as well as the combination for the two treatment groups ($5/94 = 0.053$). The calculation of power was based on the log-rank test⁽²⁵⁾ assuming a 24 month study. Using a two-sided test at the 5% level of significance, we obtained the following results.

Power of the log-rank to detect the indicated difference from control

Treatment Mortality Rate Sample Size/group	0.042	0.053	0.065
50	0.57	0.47	0.38
80	0.82	0.71	0.59
100	0.91	0.82	0.70

We assume that the attrition rate will be 0.20 in the 24-month follow-up. Thus, recruiting 200 study participants with 160 anticipated to complete 24 months of follow-up will be sufficient for this study.

Data Analysis:

1. The intent-to-treat and missing data:

The intent-to-treat (ITT) approach will be used for the primary analysis. According to this generally recommended approach, comparisons are made according to randomized treatment assignment, regardless of any changes in dose, schedule or treatment arm. In an ITT analysis, all randomized study participants are included in their assigned treatment groups, regardless of compliance with the assigned treatment regimen. On the other hand, the weakness of ITT is that it assesses the effect of treatment for subjects known not to have used the treatment enough to have any effect. While conventional ITT will be the method used to analyze and report the primary results, in order to derive valid estimates of

treatment effect accounting for compliance with therapy, model-based analytical methods will also be employed, and non-ITT analysis will be performed.

In fact, in the present study, we do not foresee noncompliance as a problem since treatment administration is under the control of the study physician rather than the patient. Dropout, however, is always a potential problem. In this study we have assumed a dropout rate of 20%, since we anticipate a lower dropout rate than the 25% in the previous trial. This is because we are using three scans over two years rather than four over 18 months as in the previous study, and many of the previous dropouts were related to MRI anxiety. Thus we do not anticipate problems with differential dropout. In addition, approximately one-third of the dropouts in the previous study were due to problems with niacin flushing, which again will not be a problem in the present study.

2. Multiple outcome measures:

In this clinical trial, we will evaluate multiple outcome measures: changes in plaque architecture and composition measured by MRI, and time to events, including the incidence of cardiovascular and cerebrovascular outcomes and disease-specific death. The following approaches to evaluate multiple outcome measures will be implemented: (i) defining a primary outcome measure; (ii) correcting for multiple testing, such as Bonferroni adjustment; (iii) with data on major clinical events, adopting a combined endpoint, such as time to first cardiovascular event or death, whichever occurs first.

3. Data Analysis:

Standard statistical methods⁽²⁴⁾ will be used to describe the demographic characteristics, clinical manifestations and basic summary statistics as rates or means (medians). Confidence intervals will also be computed. If necessary, permutation methods⁽²⁶⁾ will be employed.

For Hypotheses 1, 2, and 4:

Linear mixed (random-effects) models⁽²⁷⁾ will be used to study differential changes over time in plaque size and composition and drug dosage between the two treatments. Each model will include main effects of time from baseline and treatment, with interactions tested separately. To decide on the correlation structure for these models, variation due to random effects, serial correlation and measurement error will be examined using the variogram. These models will also be used to isolate specific comparisons of outcome variables at specific time points between the two arms. The required assumptions of normally distributed errors and random effects can be checked by an analysis of standardized residuals, which are now available for the mixed model. In the event that the assumptions are not satisfied, usually because of skewed error distributions, data transformations from the Box-Cox power family will be considered. The most commonly used member of this family is the logarithmic transformation, which usually corrects a problem with right skewness.

For Hypothesis 3:

For the time-to-event data, both the Kaplan-Meier estimate and the Cox proportional hazards model will be employed. The primary analysis will compare the two treatments using a log-rank test. Secondary analyses will use the Cox model to include adjustment for covariates. A non-parametric proportional hazards model will also be used to explore possible transformations of independent variables in the models⁽²⁸⁾.

For Hypothesis 5, 6, and 7:

Using appropriate parametric and non-parametric tests at and between both the baseline and 6 month time points, a comparison of the presence or absence of atherosclerotic plaque by PET and CT / MRI will be performed. FDG accumulation (with both TBR and SUV_{max}) will be compared across different plaque morphology and compositions defined by MR / CT (for example, presence of a lipid core or calcification). Correlation between imaging findings and changes will be made with age, gender, traditional risk factors (height, weight, hypertension, etc.), absolute values and changes in statin dose, total cholesterol, LDL, HDL, triglycerides and hematological biomarkers markers of inflammation, thrombosis and atheroprotection.

For Hypothesis 8:

Agreement between the two blinded readers of semiquantitative measures of CT angiographic stenosis will be measured using weighted kappa. Quantitative analyses of coronary arterial wall volume, lumen volume and plaque composition will be assessed using the intraclass correlation coefficient (ICC) and Bland-Altman plots.

7.0 Human Subject Protection

7.1 Rationale for Subject Selection

Individuals over age 55 from all racial/ethnic groups are eligible to participate. NIH employees over age 55 who meet the eligibility requirements are eligible to be screened and considered for protocol participation.

Recruitment and enrollment of NIH employee subjects will be consistent with NIH HRPP SOP 14 F Section 3.1. We intend to allow enrollment of staff who are affiliated or subordinate to the Principal Investigator, including technologists, nurses, scientists, students and family members. We believe we can offer them the opportunity to participate without coercion. Consent for such subjects will not be obtained from individuals in their supervisory chain of command. Refer

to the NIH Policy Manual, 2300-630-3 - Leave policy for NIH Employees Participating in NIH Medical Research Studies.

This age group is the most likely group to suffer the clinical events consequent to atherosclerosis. Atherosclerosis and concomitant cardiovascular events are the leading cause of death in all major racial/ethnic subgroups in industrialized nations. Efforts to reduce the burden of cardiovascular disease is powerfully relevant to persons of all ethnicities. Our planned enrollment has been selected to be representative of the general gender and ethnic demographic subgroups of the greater Washington DC area (appendix F). The advent of MRI techniques powerful enough to allow for precise quantification of plaque growth and regression, as well as alterations of plaque architecture and composition, has made available a number of novel indices of atherosclerotic burden and plaque vulnerability. This study is designed to investigate the comparative effectiveness of image guided lipid therapy with standard NCEP guided therapy with HMG-CoA reductase agents on the progression of carotid and coronary atherosclerosis as sub-clinical markers of cardiovascular atherosclerotic disease.

PET Substudy

A subgroup of 60 patients will be recruited to participate in PET scanning

Reproducibility Substudy

A subgroup of 60 participants who had one RR interval CT scan will be asked to return 4 weeks after their initial scan for a second scan using the same protocol. The inclusion criteria for this substudy -- single heartbeat (one RR interval) scan with <10.5 mSv estimated dosage -- are selected to keep radiation exposure as low as can be achieved while assessing the reproducibility limits of this method. Additionally, the protocol indicated and reproducibility scans will cumulatively administer less than the 21 mSv radiation dosage specified in the consent document. Patients will not undergo calcium scanning during the reproducibility scan and they will not be eligible for the PET substudy. Sixteen to twenty-four patients will be selected from three groups: (a) patients with a calcium score of 0-99, (b) patients with a calcium score -100-399 and (c) patients with a calcium score of > 400. These 60 scans will be interpreted by two readers, allowing assessment of both intra and interobserver variability as well as repeatability limits.

A comprehensive strategy of advertising and recruitment through the NIH clinical center patient recruitment and referral center will be

utilized including radio and internet PSAs as well as print flyers. (Appendix G) The Johns Hopkins Clinical Trial Unit database will also be used to identify qualifying participants, pending IRB approval at that institution. This database contains a rich population of patients in preventive cardiology clinics who have identified themselves as interested in participation in clinical trials.

Searches of the electronic medical record, radiology records and patient registries at Suburban hospital will be performed to identify and recruit patients meeting inclusion criteria for this study under a HIPAA waiver granted by the Suburban Privacy Board.

7.2 Participation of Children:

Atherosclerotic disease is not a disease of childhood and will not be eligible for participation in this study, based on the fact they are unlikely to have this disease.

7.3 Evaluation of Benefits and Risks/Discomforts:

Phlebotomy

Associated risks include anemia and hematoma and minor pain at the puncture site.

Beta-Blockers (Atenolol and Metoprolol)

Atenolol and metoprolol are FDA approved selective β_1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension, angina or myocardial infarction. The side-effects include tiredness and dizziness (10%), depression (5%), rash (5%), diarrhea (5%) shortness of breath (3%), chest pain (1%), wheezing (1%). Palpitations, congestive heart failure, peripheral edema, syncope, chest pain, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, heartburn, hypotension, mental confusion, short-term memory loss, headache, somnolence, nightmares, and insomnia reported in very rare instances (<1%).

Calcium-channel Blockers (Diltiazem)

Diltiazem is a FDA approved cardiovascular medication for the treatment of hypertension, angina or rate control of atrial fibrillation/flutter or conversion of supraventricular tachycardia. The side-effects of chronic use include lower extremity edema (2-15%), headache (5-12%), first degree AV block (2-8%), bradycardia (2-6%),

hypotension (<2%-4%), vasodilation (2-3%), extrasystoles (2%), flushing (1-2%), dizziness (3-10%), nervousness (2%), rash (1-4%), dyspepsia (1-6%), constipation (<2-4%), vomiting (2%), diarrhea (1-2%), weakness (1-4%), myalgia (2%), rhinitis (<2-10%), pharyngitis (2-6%), dyspnea (1-6%), bronchitis (1-4%), cough (<3%) and sinus congestion (1-2%).

StatinTherapy

HMG CoA-Reductase inhibitors (statins) are generally well tolerated. Clinically important adverse effects of the drugs include increases in serum transaminase concentrations and myositis, with and without complicating rhabdomyolysis. ⁽²⁹⁾ Statin monotherapy can result in elevation of liver enzymes, most often ≤ 3 times the upper limit of normal. These elevations typically normalize without lasting injury upon discontinuation of the drug. Their clinical significance is uncertain given the extremely rare occurrence of statin related toxic hepatitis⁽¹⁶⁾.

In 7 studies to date reporting rates of clinical myositis, elevation of creatinine kinase (CK) > 10 times the upper limit of normal and rhabdomyolysis, the combined incidence of these events has been less than 0.7%^(10, 31-35). The highest reported rate of rhabdomyolysis was 0.53%, observed with simvastatin 80 mg daily. ⁽³⁶⁾

The use of high dose, intensive statin therapies to achieve very low LDL levels is a recent development. Available data, including three large randomized controlled trials (the A to Z, TNT and IDEAL studies), indicate that high-dose statins (atorvastatin 80 mg daily, simvastatin 80 mg daily) are associated with low rates of serious musculoskeletal (<0.6%) and hepatic (<1.3%) injury. ^(33, 34, 36, 37)

Ionizing Radiation

Low dose CTA angiography and FDG PET/CT (as used in this protocol) carries a conservatively estimated lifetime additional risk of malignancy less than 0.2% in women and less than 0.1% in men, on a background lifetime risk of approximately 30%.³⁸⁻⁴⁰ The primary prevention population targeted for this study is unlikely to receive significant degrees of medical radiation during the 24 months of study follow up.

This study uses statin drugs for the FDA approved indications of treatment of hypercholesterolemia. The study is not designed or intended to test new indications, dosages, routes or study populations for statin drugs. The research question underlying this protocol is strictly limited to the issue of risk stratification approaches, not to how that risk is treated. The use of statins in this study meets the six conditions for IND exemption.

1. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
2. it is not intended to support a significant change in the advertising for the product;
3. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
5. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21CFR 312.7]; and
6. it does not intend to invoke provisions regarding emergency research under 21 CFR 50.24.

Gadolinium enhanced MR

The use of MR contrast containing gadolinium chelates is generally considered to be safe, with an extremely rare incidence of idiopathic allergic reactions. Use in a population with severe (stage 4 to 5) renal dysfunction is the exception to this rule. Patients with severe or end-stage renal impairment and concomitant gadolinium chelate exposure are at risk for development of the fibrosing disorder nephrogenic fibrosing dermopathy (NSF), with 2.5-5% of patients with end-stage renal disease on dialysis developing NSF subsequent to gadodiamide exposure. The FDA currently defines the at-risk population as patients with estimated GFR <30 mL/min/m² or those with any degree of renal dysfunction due to the hepatorenal syndrome or peri-hepatic transplant period.^{41, 42} The FDA has no reports of NSF in patients with mild-to-moderate renal insufficiency (ie, eGFR>29 ml/min/m²) or normal renal function

(<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108919.htm>). To ensure participant safety and provide a wide safety margin, participants with estimated GFR < 45 mL/min/m² will be ineligible for gadolinium chelate contrast administration during this study.⁴³

Iodinated contrast

The primary known risks of nonionic iodinated contrast as utilized in MDCT angiography are hypersensitivity reactions and contrast induced nephropathy. Mild to moderate adverse events such as nausea, injection site pain or urticaria occur in less than 3 percent of patients. Serious adverse events, such as hypotensive collapse, shock and death are reported in less than 1 in 10,000 patients. These reactions are generally considered idiosyncratic. Contrast induced nephropathy (CIN) is defined by an increase in creatinine more than 1 mg/dL or 50% above baseline. The risk of CIN in patients with normal renal function is considered to be negligible. The inclusion criteria for this

study require baseline GFR >45 mL/min/m² as calculated by the MDRD equation to minimize risk of nephropathy. Furthermore, injection of less than 100 ccs of iodinated contrast medium is considered to present minimal risk of CIN. The proposed MDCT angiographic protocol utilizes ~60cc of contrast.⁴⁴

F-18 Fluorodeoxyglucose

F-18 fluorodeoxyglucose (FDG) is an analog of glucose with an excellent safety record. In a four year multicenter study of 81,801 FDG administrations, involving one-third of the United States PET facilities, not a single adverse reaction was detected with 95% confidence limits from 0-3.7/100,000.⁴⁴ This finding is consistent with observations made across all radiopharmaceuticals. In a prospective study of over 750,000 administrations in 18 major United States medical centers the prevalence of reactions was 2.3/100,000 with 95% confidence limits of 1.2-3.4/100,000.⁴⁶

7.4 Risks/Benefits Analysis

The principal risks to participants are intensive statin therapy, exposure to ionizing radiation as part of the coronary CT angiogram, receipt of iodinated contrast and receipt of gadolinium based contrast. As noted in 7.3, above, large clinical trials have demonstrated low rates of significant adverse events due to statins, few if any of which persist after drug discontinuation. The study population has been specifically selected to be at the lowest risk for ionizing radiation, and the CT protocol carefully tailored to ensure delivery of the lowest possible dosage necessary to generate diagnostic images. The limitation of enrollment to patients with GFR > renders the risk of iodinated and gadolinium based contrast negligible.

The level of risk to the research participants was initially determined to be greater than minimal risk (45 CFR 46 102). As of January 2017, the study status of this protocol changed to “data analysis only” and the level of risk of this study is now minimal.

This research involves the prospect of direct benefit to individual subjects through potential identification of clinically silent atherosclerotic disease and according intensification of statin therapy that would not otherwise be indicated in usual clinical care. This carries the likelihood of significant reduction (16-21% relative risk reduction) of the risk of clinical cardiovascular events.⁴⁷

7.5 Consent Process and Documentation

Patients asked to participate in PET imaging will be consented separately for their participation in the main protocol and the substudy. Patients asked to participate in the Reproducibility Substudy will be consented separately for their participation in the main protocol and the substudy. The investigational nature

and objective of this trial, the procedures involved and their possible risk and discomforts, potential benefits, and possible alternative therapies will be explained to participants. The subject will be provided with a copy of the consent with enough time to review it and ask questions prior to the consent process. Participants will be enrolled after eligibility criteria have been determined and a signed informed consent document has been obtained. Consent for NIH employee will not be obtained from individuals in their supervisory chain of command.

The following investigators are authorized to obtain informed consent from the study subjects and are marked with an asterisk (*) on page 1 of the protocol:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- Mark Ahlman, M.D.
- [REDACTED]

7.6 Data Safety and Monitoring

The entire study data set will be managed by the principal investigator. The entire data set will be contained in a secure database located on the NIH server. The forms to record data for this study will be generated and carefully reviewed for completeness, discrepant, inappropriate, and illogical responses. The data will be checked for duplicate entries, with range checks on each field and consistency checks between fields with linked information. In cases of incoherent or missing data, the study coordinator will be immediately contacted and, if necessary, the form returned for CRF correction by the data manager. If multiple problems are found, a larger percentage of patient records will be audited. Non-image study data will be managed through the NICHD Clinical Trials Database system and stored on secure, redundant servers. Study image data will reside on the PACS.

A data safety and monitoring board will review all laboratory and safety data. At regular 6-month intervals the DSMB will monitor the safety and efficacy of image guided therapy compared with the standard therapy control arm. This will include evaluation of enrollment, compliance, follow-up, laboratory results, data management, and quality control. The DSMB will decide at each of these reviews whether the study will continue as originally designed. Efficacy analyses will be conducted for two interim analyses (at the end of year one and year two) and one final evaluation. The members of the DSMB, pending acceptance, will be Kiang Liu, PhD (Northwestern University, Chicago) – biostatistics and epidemiology; Victor Ferrari, MD (University of Pennsylvania) – cardiology and cardiovascular imaging, and Gary Plotnick, MD (University of Maryland)—general cardiology.

Data confidentiality:

Patient image data will be maintained on PACS database systems within the Department of Radiology with security and redundancy at the level of the clinical PACS system used by the NIH clinical center. The confidentiality and security of the data files containing PHI will be maintained by ensuring password protection on all computer accounts. Protection against loss of data is essential to our data management. Copies of the study database files will reside in an independent back-up hard drive.

Data reporting will be done through presenting in national meetings and publishing in journals.

7.7 Compensation

Patients will not receive direct financial compensation for participation in the main study. They will receive statin medication without charge for statins available on formulary at the NIH clinical center (simvastatin, atorvastatin). Patients who are already taking non formulary statins (lovastatin, fluvastatin, pravastatin and do not wish to switch to a formulary agent will not be compensated for their drug therapy. Participants will be compensated for travel to and from the NIH Clinical Center. For NIH Employees enrolled on this study, refer to NIH Policy Manual, 2300-630-3 – Leave policy for NIH Employees Participating in NIH Medical Research Studies.

Reimbursement for the PET and CT reproducibility substudies will be consistent with NIH guidelines.

For the PET substudy, participants will receive up to \$450 total for the 3 additional visits based on the following:

- Phlebotomy: 1 inconvenience unit
- IV placement: 1 inconvenience unit
- PET with IV contrast: 8 inconvenience units
- MRI with IV contrast: 8 inconvenience units
- Maximum \$50 for visit (\$20 for the first hour and \$10 for each following hour with a maximum of 4 hours per visit)

For the CT Reproducibility substudy, participants will receive up to \$150 for the visit based on the following:

- Phlebotomy: 1 inconvenience unit

- IV placement: 1 inconvenience unit
- CT with IV contrast: 10 inconvenience units
- Maximum \$30 for visit (\$20 for the first hour and \$10 for each following hour with a maximum of 2 hours per visit)

7.8 Conflicts of Interest

This study has no external sponsors or funding sources. No investigator has a relevant conflict of interest.

8.0 Safety Reporting Requirements:

8.1 Adverse Event Definition

Expected Events not reportable

Bruising or extravasation from the intravenous injection, mild contrast allergies that do not require treatment (e.g. headache, pain at site, warmth, flushing, nausea, less than 5 hives) and additional findings on the MRI that require additional workup outside of the study.

Asymptomatic bradycardia (HR <60 bpm) or hypotension (systolic blood pressure <90 mmHg) following beta blockade or nitrates.

Orthostatic symptoms (excluding syncope) following beta blockade or nitrates that resolve without medical intervention.

Muscle discomfort or myalgias without significant (>3 x ULN) elevations of CK.

Expected Events reportable at time of Continuing Review

ALT, AST or alkaline phosphatase elevations between 2-3 times the upper limit of normal *or* requiring discontinuation of statin therapy. (Elevations >3 times the upper limit of normal will be considered a serious adverse event as per below).

Serious Adverse Event reporting

A Serious adverse event is defined as one of the following (in accordance with FDA 21 CFR312.32 and the NIH intramural guidance for principal investigators on reporting adverse events)

- death from any cause,

- life threatening event, i.e., an event that places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred.
- any event that requires or prolongs in-patient hospitalization
- any event that results in persistent or significant disability/incapacity
- any congenital anomaly/birth defect diagnosed in a child of a subject who participated in this study.
- other medically important events that in the opinion of the investigator may jeopardize the subject or may require intervention to prevent ongoing injury.

Unexpected Adverse Events

Unexpected adverse events are those that are not described in the published medical literature, in this protocol, or in the informed consent, as being associated with statin therapy and routine CT or MR scanning. Such events might include concurrent unrelated medical illnesses such as ischemic heart disease, stroke, cancer, pneumonia, and other common illnesses seen in the general population but we will attempt to screen for these illnesses with the history and physical exam.

These unexpected adverse events will be recorded by the PI, but if they are clearly unrelated to the protocol they will not be reported to the IRB. If they are coincident with research procedures and are possibly related to the protocol they will be reported to the IRB according to NIH guidelines.

8.2 IRB Adverse Event Reporting Guidelines

All serious events will be recorded in the patient chart and in the research folder maintained by the research nurse. In accordance with NHLBI policy, serious adverse events that do not meet criteria for unanticipated problem will be reported to clinical director and IRB chair within 14 days of learning of event using the SAE form in PTMS. Deaths must be reported within 7 days.

All non serious adverse events will be tracked and reported to the IRB with the annual continuing review report.

8.3 IND/IDE:

An investigational device exemption is not applicable for this study.

The magnetic resonance magnets and coils used to perform carotid imaging are 510k approved devices being used in accordance with their labeling (21 CFR 812 § 812.2.(c)). Imaging sequences that are not commercially available (research sequences or works-in-progress) may be used during image acquisition. These sequences conform to marketed device standards with respect to FDA established safety criteria for static field strength, acoustic noise, dB/dt, RF heating, biocompatibility and performance. Consistent with an IDE exempt investigation, any non-commercial imaging sequences will be used solely to address the research questions of this protocol, and not to address the safety or effectiveness of the sequences themselves.

The CT scanners used to perform CT angiography are 510k approved devices being used in accordance with their labeling (21 CFR 812 § 812.2.(c)). No investigational CT applications are proposed.

9.0 Multi-Institutional Guidelines: N/A

10.0 Pharmaceutical Information

Beta Blocker (Package insert) Clinical Pharmacology information:

Lopressor is a beta-adrenergic receptor blocking agent. In vitro and in vivo animal studies have shown that it has a preferential effect on beta1 adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, Lopressor also inhibits beta2 adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Relative beta1 selectivity has been confirmed by the following: (1) In normal subjects, Lopressor is unable to reverse the beta2 -mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective (beta1 plus beta2) beta blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, Lopressor reduces FEV1 and FVC significantly less than a nonselective beta blocker, propranolol, at equivalent beta1-receptor blocking doses.

Lopressor has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta blockade. Lopressor crosses the blood-brain barrier

and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Animal and human experiments indicate that Lopressor slows the sinus rate and decreases AV nodal conduction.

In controlled clinical studies, Lopressor has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics, at dosages of 100-450 mg daily. In controlled, comparative, clinical studies, Lopressor has been shown to be as effective an antihypertensive agent as propranolol, methyldopa, and thiazide-type diuretics, and to be equally effective in supine and standing positions.

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, Lopressor reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta2-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In controlled clinical trials, Lopressor, administered two or four times daily, has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100-400 mg daily. A controlled, comparative, clinical trial showed that Lopressor was indistinguishable from propranolol in the treatment of angina pectoris.

In a large (1,395 patients randomized), double-blind, placebo-controlled clinical study, Lopressor was shown to reduce 3-month mortality by 36% in patients with suspected or definite myocardial infarction.

Patients were randomized and treated as soon as possible after their arrival in the hospital, once their clinical condition had stabilized and their hemodynamic status had been carefully evaluated. Subjects were ineligible if they had hypotension, bradycardia, peripheral signs of shock, and/or more than minimal basal rales as signs of congestive heart failure. Initial treatment consisted of intravenous followed by oral administration of Lopressor or placebo, given in a coronary care or comparable unit. Oral maintenance therapy with Lopressor or placebo was then continued for 3 months. After this double-blind period, all patients were given Lopressor and followed up to 1 year.

The median delay from the onset of symptoms to the initiation of therapy was 8 hours in both the Lopressor- and placebo-treatment groups. Among patients treated with Lopressor, there were comparable reductions in 3-month mortality for those treated early (≤ 8 hours) and those in whom treatment was started later. Significant reductions in the incidence of ventricular fibrillation and in chest pain following initial intravenous therapy were also observed with Lopressor and were independent of the interval between onset of symptoms and initiation of therapy.

The precise mechanism of action of Lopressor in patients with suspected or definite myocardial infarction is not known.

In this study, patients treated with metoprolol received the drug both very early (intra-venously) and during a subsequent 3-month period, while placebo patients received no beta-blocker treatment for this period. The study thus was able to show a benefit from the overall metoprolol regimen but cannot separate the benefit of very early intravenous treatment from the benefit of later beta-blocker therapy. Nonetheless, because the overall regimen showed a clear beneficial effect on survival without evidence of an early adverse effect on survival, one acceptable dosage regimen is the precise regimen used in the trial. Because the specific benefit of very early treatment remains to be defined however, it is also reasonable to administer the drug orally to patients at a later time as is recommended for certain other beta blockers.

Iodine contrast (Package Insert) **isovue (iopamidol) injection, solution**

Intravascular injection of a radiopaque diagnostic agent opacifies those vessels in the path of flow of the contrast medium, permitting radiographic visualization of the internal structures of the human body until significant hemodilution occurs.

Following intravascular injection, radiopaque diagnostic agents are immediately diluted in the circulating plasma. Calculations of apparent volume of distribution at steady-state indicate that iopamidol is distributed between the circulating blood volume and other extracellular fluid; there appears to be no significant deposition of iopamidol in tissues. Uniform distribution of iopamidol in extracellular fluid is reflected by its demonstrated utility in contrast enhancement of computed tomographic imaging of the head and body following intravenous administration.

The pharmacokinetics of intravenously administered iopamidol in normal subjects conform to an open two-compartment model with first order elimination (a rapid alpha phase for drug distribution and a slow beta phase for drug elimination). The elimination serum or plasma half-life is approximately two hours; the half-life is not dose dependent. No significant metabolism, deiodination, or biotransformation occurs.

Iopamidol is excreted mainly through the kidneys following intravascular administration. In patients with impaired renal function, the elimination half-life is prolonged dependent upon the degree of impairment. In the absence of renal dysfunction, the cumulative urinary excretion for iopamidol, expressed as a percentage of administered intravenous dose is approximately 35 to 40 percent at 60 minutes, 80 to 90 percent at 8 hours, and 90 percent or more in the 72-to 96-hour period after administration. In normal subjects, approximately one percent or less of the administered dose appears in cumulative 72- to 96-hour fecal specimens.

ISOVUE may be visualized in the renal parenchyma within 30-60 seconds following rapid intravenous administration. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1 to 3 minutes, with optimum contrast occurring between 5 and 15 minutes. In patients with renal impairment, contrast visualization may be delayed.

Iopamidol displays little tendency to bind to serum or plasma proteins.

No evidence of in vivo complement activation has been found in normal subjects.

*Animal studies indicate that iopamidol does not cross the blood-brain barrier to any significant extent following intravascular administration.

*ISOVUE (Iopamidol Injection) enhances computed tomographic brain imaging through augmentation of radiographic efficiency. The degree of enhancement of visualization of tissue density is directly related to the iodine content in an administered dose; peak iodine blood levels occur immediately following rapid injection of the dose. These levels fall rapidly within five to ten minutes. This can be accounted for by the dilution in the vascular and extracellular fluid compartments which causes an initial sharp fall in plasma concentration. Equilibration with the extracellular compartments is reached in about ten minutes, thereafter the fall becomes exponential. Maximum contrast enhancement frequently occurs after peak blood iodine levels are reached. The delay in maximum contrast enhancement can range from five to forty minutes depending on the peak iodine levels achieved and the cell type of the lesion. This lag suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine within the lesion and outside the blood pool, although the mechanism by which this occurs is not clear. The radiographic enhancement of nontumoral lesions, such as arteriovenous malformations and aneurysms, is probably dependent on the iodine content of the circulating blood pool.

In CECT head imaging, ISOVUE (Iopamidol Injection) does not accumulate in normal brain tissue due to the presence of the blood-brain barrier. The increase in x-ray absorption in normal brain is due to the presence of contrast agent within the blood pool. A break in the blood-brain barrier such as occurs in malignant tumors of the brain allows the accumulation of the contrast medium within the interstitial tissue of the tumor. Adjacent normal brain tissue does not contain the contrast medium.

In nonneural tissues (during computed tomography of the body), Iopamidol diffuses rapidly from the vascular into the extravascular space. Increase in x-ray absorption is related to blood flow, concentration of the contrast medium, and extraction of the contrast medium by interstitial tissue of tumors since no barrier exists. Contrast enhancement is thus due to the relative differences in extravascular diffusion between normal and abnormal tissue, quite different from that in the brain.

The pharmacokinetics of Iopamidol in both normal and abnormal tissue have been shown to be variable. Contrast enhancement appears to be greatest soon after administration of the contrast medium, and following intraarterial rather than intravenous administration. Thus, greatest enhancement can be detected by a series of consecutive two- to three-second scans performed just after injection (within 30 to 90 seconds), i.e., dynamic computed tomographic imaging.

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Appendices:

Appendix A:

Meal Suggestions the Evening Before and Morning of ^{18}F -FDG PET Scanning¹³

Permitted Foods

- Chicken, turkey, fish, steak, ham, bacon
- Meat-only sausages, hotdogs (plain, without the bun), hamburgers (plain, without the bun or vegetables)
- Fried eggs (prepared without milk or vegetables)
- Water

Not-Permitted Foods

- Foods containing carbohydrates, sugars, and Splenda (McNeil Nutritionals)
- Milk, cheese
- Bread, bagels, cereal, muffins, cookies, crackers, pasta
- Rice, beans
- Peanut butter, nuts
- Fruit, fruit juice, vegetables
- Candy, chewing gum, mints, cough drops
- Alcohol
- Caffeinated foods or beverages (coffee, tea)

Appendix B: Protocol Evaluation

Visit number ¹	1 Screen ³	2 M 0	3 M 3	4 M 6	5 M 12	6 M 18	7 ⁸ M 24
<i>Procedure</i>							
Obtain consent	X						
Enrollment criteria	X						
History & Physical	X				X		X
Screen Labs ⁴	X						
Randomization		X					
Adverse event review		X	X	X	X	X	X
Concomitant Med. Review ⁵		X	X	X	X	X	X
Carotid MRI		X			X		X
MRI Questionnaire ⁶		X			X		X
eGFR		X			X		X
CT angiography		X					X
PET Imaging		X		X			
Carotid MRI (PET Participants Only)				X			
Drug Dispensing & Dose Adjustment		X	X	X	X	X	X
Safety Labs ⁷		X	X	X	X	X	X
Research Blood	X	X		X	X		X

¹Visits with in +/- 30 days due for unforeseen events. M (month). Delays in visit will need to be discussed and pre-approved with the research team.

²Baseline: H&P and laboratory studies (see section 2.3) should be completed with in 2 weeks of initiating treatment.

³Within 2 weeks of starting drug the screening process can be completed.

⁴ See section Screening Evaluation, E for a list of the screening labs.

⁵Concomitant medication review will be performed to update subject medication list.

⁶MRI Questionnaire will be completed prior to MRI scan (See Appendix C).

⁷See section Safety Measures, 3.2 for list of safety labs.

⁸Subjects will be taken off treatment/study after the final visit and referred back to their primary physician or have the option to enroll on another protocol if one is available and they meet the eligibility criteria.

Appendix C: NCEP standard care guidelines.

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

Scott M. Grundy, James I. Cleeman, C. Noel Bairey Merz, H. Bryan Brewer, Jr, Luther T. Clark, Donald B. Hunninghake, Richard C. Pasternak, Sidney C. Smith, Jr, Neil J. Stone, for the Coordinating Committee of the National Cholesterol Education Program and Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association
Circulation 2004;110:227-239

TABLE 3. Recommendations for Modifications to Footnote the ATP III Treatment Algorithm for LDL-C

-
- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
 - In high-risk persons, the recommended LDL-C goal is <100 mg/dL.
 - An LDL-C goal of <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.
 - If LDL-C is \geq 100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
 - If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
 - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are \geq 200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
 - For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; an LDL-C goal <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence. When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
 - Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
 - When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
 - For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.
-

Appendix D: Instructions for pre-study and follow-up Blood tests

Blood Studies:	Blood Tube/Comments:	Destination:
CBC w/PLT & Diff	1 Lavender (3 mL)	Clinical Lab Bldg. 10
Chemistry	1 Red/Yellow Rim SST (4mL)	Clinical Lab Bldg. 10
12-HR Fasting Chol	1 Red/Yellow Rim SST(4mL)	Clinical Lab Bldg. 10
CK	1 Red/Yellow Rim SST (4 mL)	Clinical Lab Bldg. 10
hs-CRP	1 Red/Yellow Rim SST (4 mL)	Clinical Lab Bldg. 10
Hepatic Panel	1 Red/Yellow Rim SST (4 mL)	Clinical Lab Bldg. 10
Research Blood	2 Red/Yellow Rim SST (8 mL)	Clinical Lab Bldg. 10

Appendix E: MRI Safety Questionnaire

NIH - MRI Safety Questionnaire

How much do you weigh? _____

Please provide a Yes or No for every item.

- Yes ___ No ___ Have you had a previous MRI?
- Yes ___ No ___ Are you claustrophobic?
- Yes ___ No ___ Have you ever had an injury to the eye involving a metallic object?
(metallic slivers, shavings, foreign body, etc.)
If yes, explain: _____
- Yes ___ No ___ Cardiac pacemaker
- Yes ___ No ___ Internal electrodes or pacemaker wires
- Yes ___ No ___ Implantable programmable device
(neural stimulator, medication pump, defibrillator, programmable shunt)
- Yes ___ No ___ Any type of electronic, mechanical, or magnetic implant
- Yes ___ No ___ Aneurysm clip
- Yes ___ No ___ Stent, filter, intravascular coil
- Yes ___ No ___ Metal fragments in skin or body
- Yes ___ No ___ Surgical clips, staples, or metallic sutures
- Yes ___ No ___ Ear surgery or implants
- Yes ___ No ___ Eye surgery or implants
- Yes ___ No ___ Metal plates, pins, screws, nails, wires, rods, surgical mesh
- Yes ___ No ___ Any type of metal object (shrapnel, BB, bullet)
- Yes ___ No ___ Artificial limb or joint
- Yes ___ No ___ Prosthesis (penile, breast, eye, other)
- Yes ___ No ___ Tissue expander
- Yes ___ No ___ Prosthetic heart valve
- Yes ___ No ___ Any I.V. access port or catheter (Broviac, Port-a-cath, Hickman, PICC line)
- Yes ___ No ___ Swan-Ganz catheter
- Yes ___ No ___ Radiation seeds or implants
- Yes ___ No ___ Dental braces, spacers, retainer, bridges, dentures
Permanent Removable
- Yes ___ No ___ Hearing aid (*remove before entering MR scanner room*)
- Yes ___ No ___ Transdermal drug patch
- Yes ___ No ___ Have you recently used a silver-containing dressing or cream on your skin?
(Silvadene, silver sulfadiazine, silver nitrate)
- Yes ___ No ___ Tattoos or tattooed eyeliner
- Yes ___ No ___ Body piercing location: _____
- Yes ___ No ___ IUD, diaphragm, or pessary
- Yes ___ No ___ Are you pregnant or possibly pregnant?
- Yes ___ No ___ Are you breast-feeding?

-
- Yes ___ No ___ Have you ever had an allergic reaction to CT or x-ray contrast agent?
If yes, please describe: _____
 - Yes ___ No ___ Have you ever had an allergic reaction to MRI contrast agent?
If yes, please describe: _____
 - Yes ___ No ___ Have you had an MRI with contrast today?
 - Yes ___ No ___ Do you have any drug allergies?
If yes, please list: _____
 - Yes ___ No ___ Do you have normal kidney function?
 - Yes ___ No ___ Are you on DIALYSIS?

All patients receiving intravenous MR contrast material must have their kidney function tested within 1 week prior to the scan.

Date of your creatinine (kidney function) blood test: _____

Loose metallic objects are dangerous in the MR environment. The MR scanner magnet is ALWAYS on. Before entering the MR scanner room, you must remove all metallic objects including hearing aids, dentures, partial plates, keys, beeper, cell phone, glasses, hair pins, jewelry, body piercing, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, tools, clothing with metal fasteners or underwires, clothing with metallic threads, steel-toed boots or shoes.

I attest that the above information is correct to the best of my knowledge.

Signature of the Patient or Legal representative

BD 5/09

Appendix F: Targeted enrollment table

Principal Investigator/Program Director (Last, First, Middle): Bluemke, David A MD PhD

Targeted/Planned Enrollment Table**This report format should NOT be used for data collection from study participants.**

Study Title: Randomized Trial of Imaging Versus Risk Factor Based Therapy for Plaque Regression

Total Planned Enrollment: 200

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	15	15	30
Not Hispanic or Latino	85	85	170
Ethnic Category: Total of All Subjects *	100	100	200
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	4	4	8
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	13	13	26
White	82	82	164
Racial Categories: Total of All Subjects *	100	100	200

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

Appendix G

- 1) Radio and internet PSA text:
*Public Service Announcement IRB App 01-2010
Plaque 10-CC-XXXX*
-

Clinical Research Trials/Studies Patient Recruitment

“The National Institutes of Health invites you to participate in a study to investigate if using Magnetic Resonance Imaging (MRI) is an effective method of measuring plaque that builds up inside of arteries in comparison to other measurement methods, to estimate your risk of heart disease and stroke. Call 1-866-999-1116, or TTY 1-866-411-1010, for information. Or visit <http://clinicaltrials.gov> . All study-related tests and treatments are provided at no cost. The NIH is a non-profit government agency and part of the Department of Health and Human Services.”

*This information is time sensitive. Please air before _____.
Please contact me (craggka@mail.cc.nih.gov or 301-402-8568) prior to airing after this date.*

DRAFT: 03/23/2010