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Précis

In high risk patients undergoing invasive angiography, intravascular ultrasound (IVUS) has shown reduction of plaque for patients treated with HMG-CoA reductase inhibitors (statins). However, there is no accepted *noninvasive* method to determine if treatment for atherosclerosis results in reduction of coronary artery plaque.

Coronary artery CT angiography (CCTA) is noninvasive and can accurately determine the degree of coronary artery stenosis. In addition, the extent of calcified and noncalcified plaque may be directly measured using this technology at low radiation dose using state-of-the-art CT scanners. Several retrospective studies have previously suggested that CCTA may be able to show plaque regression in the coronary arteries due to statin therapy.

The primary aim of this proposal is to determine the change in coronary artery plaque volume in individuals treated with high intensity statin therapy as defined by 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

Men and women who meet the inclusion and exclusion criteria will undergo CCTA examination for the presence or absence of coronary artery plaque. Individuals with evidence of noncalcified coronary plaque by CCTA and who meet criteria for HMG-CoA reductase (statin) therapy will be evaluated for a total of 36 months. The change of coronary artery plaque (progression or no change, or regression) in individuals with noncalcified plaque at baseline will be measured by CCTA at yearly intervals.

1 INTRODUCTION

STUDY AIMS:

At present, approximately 50% of the U.S. population age 40-75 years are eligible for HMG-CoA reductase (statin) therapy (Vogel 2014). Statin therapy is the primary medical therapy that has shown definitive evidence for reduction of cardiovascular events in the population due to coronary artery disease (Stone, Robinson et al. 2014). The benefit of statin therapy is presumed to be the reduction and/or stabilization of coronary artery plaque. However, an accepted method that can reproducibly and *noninvasively* detect reduction of coronary artery plaque is not currently available.

Data in the literature and our own preliminary data indicate that, on average, atherosclerotic plaque decreases due to statin therapy. However, the atherosclerotic response to statin therapy is variable; although the *average* extent of plaque decreases in a study population, some individuals show plaque progression despite "appropriate" statin therapy.

Coronary computed tomography angiography (CCTA) is accurate for documenting the presence or absence of coronary artery stenosis. However little information is available about the use of CCTA to document change in coronary plaque over time during statin therapy. Thus, *the primary aim of this study is to determine the mean change of non-calcified plaque over the study period (24 months) in adults treated with high intensity statin therapy* (as defined by the 2013 ACC/AHA Guidelines to Reduce Cardiovascular Risk (GRCR). We will also examine cardiovascular risk factors associated with coronary plaque increase or decrease over the study period.

Study subjects will have target plaque lesions quantitatively analyzed for volume change over time. Using anatomical landmarks, a target plaque volume will be defined at baseline and follow up examinations. Semiautomatic software will be used to trace lumen and outer vessel boundaries to determine non-calcified plaque volume.

In addition to CCTA coronary artery analysis, novel preliminary studies suggest that some coronary artery plaques have abnormal cardiac magnetic resonance (CMR) T1 signal and increased uptake of sodium fluoride hypothesized to indicate intraplaque hemorrhage and active microscopic calcification, respectively. We will correlate CMR T1 and sodium fluoride signal with CCTA determined change in plaque during statin therapy.

Primary Aim: Determine the mean change in noncalcified plaque volume in study subjects treated with high intensity statin therapy over a 24 month interval.

In addition to the 24 months follow-up period specified for the primary endpoint, we plan to follow the patients for an extended period of 12 months to study the long-term effects of the statin therapy. As a result, the patients will be followed for a total of 36 months with the first 24 months for the primary endpoint and the additional 12 months for the secondary endpoints. The secondary endpoints include:

1) Change in noncalcified plaque volume assessed by CCTA at the end of 36 months;
2) Effects of covariates including age, sex, race, body mass index and baseline plaque volume on the change of plaque volume measured by CCTA at 24 and 36 months.

3) (Pilot study): The relationship of CMR T1 high signal intensity plaque and change in T1 signal by CMR over time to CCTA plaque characteristics.
4) (Pilot study): the relationship of coronary artery plaque by CCTA to sodium fluoride (F18-NaF) uptake using positron emission tomography (PET) scanning:
    a. Determine if F18-NaF signal correlates with CCTA defined plaque volume and CAC score.
    b. Determine the change in F18-NaF signal in relationship to statin therapy

a. Determine the change in F18-NaF signal in relationship to statin therapy.

BACKGROUND AND RATIONALE

CCTA is currently used to document the presence and degree of coronary artery stenosis. However, very little information is available to determine if CCTA can document *change* in the extent coronary plaque over time. Individuals who have elevated cholesterol levels are prescribed HMG-CoA reductase inhibitor ("statin") therapy; such therapy may be for the duration of an individual's life. Although the cardiovascular benefits of statin therapy have been documented in population-based studies, the benefit for an *individual* in terms of reduction of coronary artery plaque is much less well known. The use of CCTA has not been previously evaluated in this regard.

In this study, we will determine the change in CCTA defined noncalcified plaque over a 36-month interval during the course of statin therapy. We will identify a group of subjects with moderate or greater cardiovascular risk (as defined by the 2013 ACC/ AHA GRCR guidelines and 2018 ACC/AHA guidelines). Study subjects will undergo so-called "high-intensity" statin therapy according to the GRCR guidelines. A high intensity therapy will be chosen because changes in soft plaque are expected to be small; high intensity therapies are more likely to result in CCTA detected change in plaque volume. Eligible subjects will not previously have received high intensity statin therapy for more than 90 days prior to enrollment. Our underlying hypothesis is that CCTA will detect a decrease in soft plaque volume; we will also correlate decrease in plaque volume with other cardiovascular risk factors.

Study subjects will be treated with high-intensity statin therapy as defined by the 2013 ACC/AHA GRCR guidelines and 2018 ACC/AHA guidelines: rosuvastatin 20-40 mg or atorvastatin 40-80 mg. The maximum statin dose will be administered that is tolerated by the patient and that maintains LDL-C ≥ 25 mg/dl. High-intensity statin therapy is defined in the GRCR guidelines as lowering LDL-C on average by approximately ≥ 50%.

Study subjects will undergo state of the art cardiac imaging for 36 months at 12 month intervals using coronary computed tomography angiography for determination of plaque volume.

CORONARY PLAQUE EVALUATION IN ASYMPTOMATIC SUBJECTS

Background for Primary Aim.

Coronary artery disease is the most common cause of morbidity and mortality not only in the United States but also world-wide (Lozano, Naghavi et al. 2012). Assuming attainment of 40 years of age, symptomatic coronary heart disease occurs in 49% of men and 32% of women over their lifetime (Stone, Robinson et al. 2014). Accounting for both stroke plus heart disease, Vogel has estimated that ideally 61% of men and 48% of women age 40-75 years should be considered for statin therapy (Vogel 2014).

Statin therapy is the primary medical therapy that has shown definitive evidence for reduction of cardiovascular events due to coronary artery disease (Stone, Robinson et al. 2014). Coronary artery disease (CAD) results in formation of atherosclerotic plaques that may result in stable angina or acute coronary syndrome due plaque rupture or ulceration. Atherosclerotic plaques that are prone to rupture have a large lipid core, thin fibrous cap and inflammation (Kern and Meier 2001). Therefore medications that promote plaque regression, stability and/ or reduce inflammation may reduce occurrence of coronary syndrome and/ or stroke may also reduce the rate of major cardiovascular events (MACE). Studies that use MACE as an endpoint are very costly, involve thousands of patients and require lengthy time course. Therefore, plaque regression using imaging as a surrogate endpoint for MACE has been investigated.

IVUS and plaque regression. Intravascular ultrasound (IVUS) of the coronary arteries has been the primary modality by which plaque regression has been investigated, although the modality is only relevant to high risk patients since it involves an invasive angiogram. A recent meta-analysis evaluated 11 studies and 7864 patients that used IVUS to quantify plaque atheroma change due to targeted statin therapy at baseline and a median follow up of 18 months (D'Ascenzo, Agostoni et al. 2013). Nine statin treatment studies evaluated patients with stable angina, while 2 evaluated patients with acute coronary syndrome. The mean change in plaque volume was 0.5% (-0.25-1.0, 95% CI). The rate of plaque regression was significantly related to incidence of MI or revascularization.

MRI and plaque regression. MRI scanning and computed tomography coronary angiography (CCTA) are minimally invasive technology (using intravenous peripheral injections) and are capable of imaging plaque as well as plaque components. Studies that have evaluated MRI of plaque and plaque components have focused mostly on the carotid artery due its larger size. Recently, our group demonstrated that plaque composition in the carotid artery by MRI is associated with cardiovascular events in the MESA study (Zavodni, Wasserman et al. 2014). Two prospective MRI studies have shown reduction of carotid artery plaque secondary to statin therapy (Lima, Desai et al. 2004, Corti, Fuster et al. 2005, Sibley, Vavere et al. 2013). However, two years of rosuvastatin did not decrease carotid artery plaque volume by MRI in a different study (Underhill, Yuan et al. 2008). No studies have shown regression of *coronary* plaque with MRI; low spatial resolution (~1 mm or more) of the technique makes this very challenging for coronary artery disease. Subjects may be co-enrolled in Protocol 18-H-0118 MRI results may be shared across both Protocols. This collaboration may improve the understanding of cardiovascular disease and its relationship to other disease states, translating the newer technology to improve diagnosis and management of cardiovascular disease and to carefully characterize cardiovascular disease using updated, novel imaging methods.

CT calcium score and plaque regression. Non-contrast CT scanning is used to detect calcified coronary artery plaque. A comprehensive review of the natural history of CAC score in patients at low, intermediate and high cardiovascular risk shows the *CAC score increases at an annualized rate CAC from 21% to 51% (mean, about 20% increase/ year) (Priester and Litwin 2009).* Further, nearly all intervention trials (predominately statin therapy) show *increased CAC score despite therapy*, most commonly with no significant change between statin and control groups (Priester and Litwin 2009). Maturation of unstable or noncalcified plaque as a *result* of statin therapy has been suggested on various IVUS studies (Nicholls, Tuzcu et al. 2007). Thus, CAC score is not appropriate for assessing plaque regression.

CT angiography of noncalcified plaque. CCTA has matured to a routine clinical tool with excellent sensitivity (>= 80%) and specificity (99%) for coronary artery *stenosis* (Budoff, Dowe et al. 2008, Mowatt, Cummins et al. 2008). Although CCTA is clinically used to determine coronary stenosis, our group (Kwan, May et al. 2014) and others have developed approaches to quantify nonstenotic plaque and/ or total plaque burden. One such measure is the plaque volume index (PVI), which is the total coronary plaque volume (Figure 1) normalized by the coronary artery length. In our study of 224 patients with type 2 diabetes, greater PVI was associated with age, gender, duration of diabetes and obesity. In addition, the segmental plaque score, segmental stenosis score and segmental involvement score are methods that can quantify the regional presence of soft plaque (Johnson, Dowe et al. 2009, Johnson and Dowe 2014).

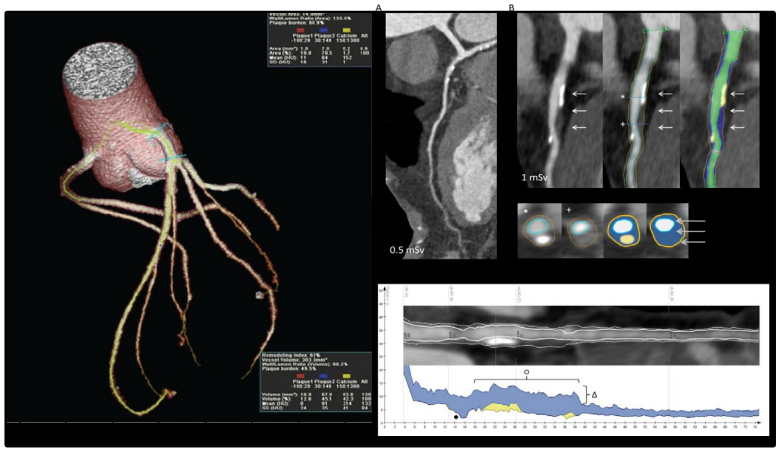


Figure 1. Derivation of plaque volume index (PVI) from CCTA. After identifying the coronary tree (left), the coronary artery wall boundaries are contoured for the entire coronary tree (right) in a manner analogous to IVUS. The amount of plaque (in mm3) divided by the total coronary length is the PVI. From (Kwan, May et al. 2014)

Several studies to date have evaluated the *natural history of increase in plaque volume* detected by CCTA (Table 2) and the potential of CCTA to track plaque progression. Schmid et al. all found a 25% change in noncalcified plaque volume in 50 patients in the left main and left anterior descending artery in 12 months (Schmid, Achenbach et al. 2008). Lehman et al. evaluated 69 patients with acute coronary syndrome and optimal medical therapy. Limitations include retrospective studies, small sample size and older CT scan technology.

Table 2. Natural history of atheroma growth by CCTA. ACS acute coronary syndrome; CAD coronary artery disease

Authors	N (patients)	Indication for CTA	Study type	Time	Results	Annualized plaque growth
Schmid et al. (Schmid, Achenbach et al. 2008)	50 (86% men, mean age 58)	Suspected CAD	Prospective	17 months	25% increase in noncalcified plaque volume	18%/ year

Lehman et al. (Lehman, Schlett et al. 2009)	69 (59% male, mean age 55)	Ruled out ACS	Prospective	24 months	25% increase in plaque volume	12%/ year
Zeb et al. (Zeb, Li et al. 2013)	40 (83% male, mean age 64	Asymptomatic CAD	Retrospective	13.3 months	10% increase in noncalcified plaque volume	9%/ year
Lo et al. (Lo, Lu et al. 2015)	37 (HIV+, 80% male)	Asymptomatic CAD	Prospective Randomized	12 month	Non-calcified Placebo: +20% Atorva.: -19 %	20%/ year

CCTA of coronary plaque during statin therapy. Several studies have shown the potential of CCTA to detect coronary plaque regression. A case report by Johnson et al. showed an example of a patient receiving atorvastatin 40 mg qd with a plaque area that decreased over 26 months from 20 mm^2 to 11mm^2 (Figure 2). In our ongoing NIH RIGHT study, we have observed reduction of coronary plaque in certain patients (Figure 3). Papadopoulou et al. evaluated 32 patients with acute coronary syndrome over 39 months with moderate statin therapy. They found a slight increase in total atheroma volume increase over this period of 6.7%. Unfortunately they used different types of CT scanners over this study period (as did the study by Hoffman et al. (Hoffmann, Frieler et al. 2010)). Thus technical scan factors could have played a role in changes in plaque measurements.

A summary of clinical trials showing the results of CCTA measurement of plaque during the course of anti-hyperlipidemic therapy is shown in the table below (Sandfort, Lima et al. 2015). Overall, 3/5 studies show a very low rate of plaque growth or actual regression of plaque in 3 of 5 studies. Two of these studies

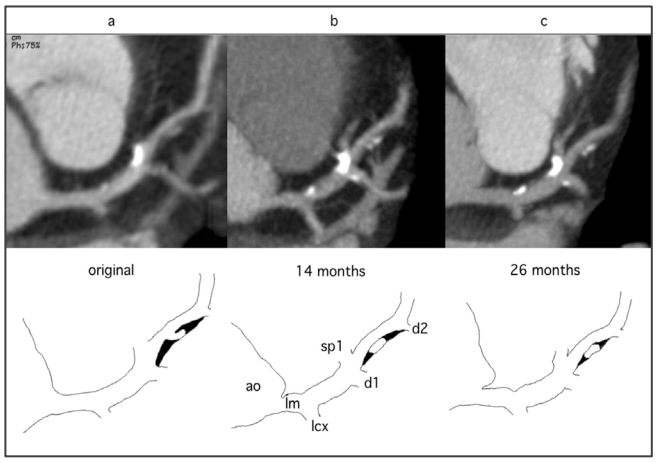


Figure 2. Regression of plaque after statin therapy, case report study from **(Johnson, Dowe et al. 2006)**

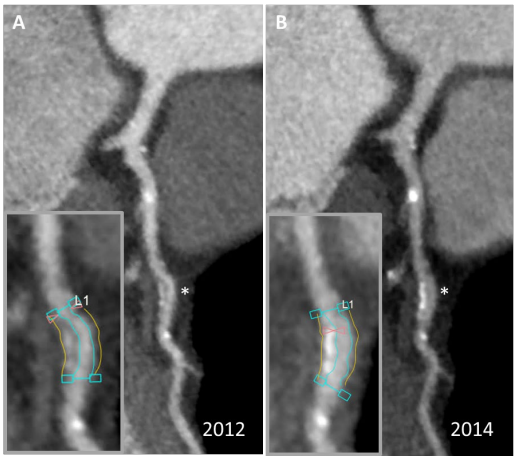


Figure 3. Regression of total plaque by 22% and concomitant increase of calcification during statin therapy for two years (atorvastatin 20 mg, NIH data).

were retrospective, and only 1 was an intervention trial in patients without acute coronary syndrome (n= 12 subjects). Limitations of these studies include small sample size and outdated CT scan technology. *Thus, no prospective study has been conducted of plaque regression in statin treated subjects without acute coronary syndrome with adequate sample size that would allow for adjustment of cardiovascular risk factors likely to affect the success of statin therapy.*

Table 3. CCTA assessment of atheroma in response to therapy

Authors	N (patients)	Indication for CTA	Study type	Time	Results	Annualized plaque growth
Hoffman et al. (Hoffmann, Frieler et al. 2010)	63 (71% male, mean age 63)	Suspected CAD	Retrospective observational, statin treatment, varied dose not reported	25 months 16 slice CT @baseline, 64 slice CT @follow-up	NCP increased from 21 mm^3 to 29 mm^3 (38%)	18%/ year
Tardif et al. (Tardif, L'allier et al. 2010)	28 (90% male, mean age 57)	ACS	Prospective, interventional, VIA-2291 treatment	6 months	Placebo, 6% increase VIA-2291, -4.9% decrease	-10%/ year for treatment arm
Burgstahler et al. (Burgstahler, Reimann et al. 2007)	12 (100% male, mean age 61)	Elevated CV risk, PROCAM score>3rd quintile (Agatston mean 257)	Prospective, atorvastatin 20 mg	16 months	NCP decreased by 24%	-18%/ year
Papadopoulou et al. (Papadopoulou, Neefjes et al. 2012)	32 (81%, mean age 53)	ACS	Prospective, observational, atorvastatin 40 mg (n=29), simvastatin 40 mg, 1 patient rosuvastatin 10 mg, 2 patients	39 months	Normalized atheroma volume increased by 47mm^3 (6.7%)	+1.7%/ year
Zeb et al. (Zeb, Li et al. 2013)	60 (83% male, mean age 64	Asymptomatic CAD	Retrospective	13.3 months	28% decrease in noncalcified plaque volume	-25%/ year

Preliminary Data related to the Primary Aim

a) Plaque reduction intervention, preliminary data. In an ongoing study (10-CC-0214, The RIGHT Study: Risk Stratification With Image Guidance of HMG Coa Reductase Inhibitor Therapy" (NCT01212900), Bluemke PI), we are evaluating the effect of statin therapy on carotid artery atherosclerosis using cardiac magnetic resonance imaging in adult, asymptomatic study subjects. High resolution 3 tesla carotid magnetic resonance imaging (MRI) was performed on 106 asymptomatic subjects at baseline and 12 months after therapy. The median age was 65 years and 64% of subjects were male. Carotid wall area of the internal carotid artery was measured and the mean volume change of the arterial wall was calculated. Univariate and multivariable models incorporating cardiovascular risk factors were used for analysis (Sandfort, Sibley et al. 2014).

Statin treatment was monitored and serum LDL was measured at 6 months and one year. The on-treatment LDL was 76 mg/dL; there was significant reduction of LDL during the study (50% of the untreated LDL level). The average decrease in carotid atherosclerosis over 12 months was -0.3 ± 2.4 mm^2. There was progression of carotid plaque in 46 subjects (43 %) and regression of plaque in 60 subjects (57 %)

In univariate analysis, obesity and hypertension were associated with progression of carotid plaque while statin dose was associated with regression (obesity: odds ratio for progression 4.6, CI 1.8-12.4, p < 0.01; hypertension: odds ratio 2.4, CI 1.1-5.3, p < 0.05; statin dose: odds ratio for progression 0.4, CI 0.18-0.87, p < 0.05). In a multivariable logistic regression model, obesity remained significantly associated with progression (odds ratio 4.2, CI 1.6-12.1, p <0.01) while statin use remained associated with regression (odds ratio for progression 0.38, CI 0.16-0.88, p <0.05). The median percent change in atheroma volume

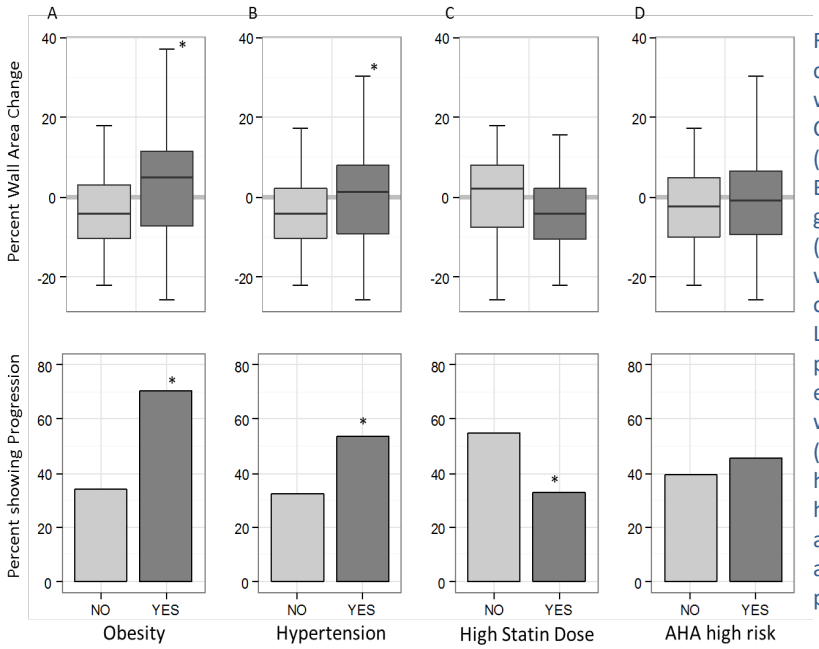


Figure 4: Upper part: Univariate comparison of continuous carotid wall change measurements. A: Change for subjects with low BMI (light grey) vs. high BMI (dark grey). B: Change in subjects with (dark grey) and without hypertension (light grey). C: Change in subjects with a AHA risk ≤ 7.5 % (light grey) or AHA risk > 7.5 % (dark grey). Lower part: Corresponding percentage of subjects experiencing progression of carotid wall area measurements (change>0). Obese subjects and hypertensive subjects have a higher median wall area change and more frequently show carotid artery disease progression (* p<0.05).

in obese subjects was +3.4 % vs. -3.0 % in nonobese subjects (p<0.05).
Progression was not associated with change in LDL levels (p>0.05).

a) Experience of the investigators in measuring coronary plaque, preliminary data. In a collaboration with investigators at the University of Utah, Intermountain Healthcare and Johns Hopkins, we analyzed CT scans of diabetic patients undergoing CCTA as an adjunct to their diabetes care in the FACTOR-64 study published in JAMA (Muhlestein, Lappe et al. 2014). In that study, CCTA screening for coronary stenosis was investigated to determine if the cardiovascular events were reduced in diabetic patients. Over 1.7 years, cardiovascular event rates in 448 diabetic patients were similar in the group with CCTA compared to the group without imaging intervention. Although the follow-up period was relatively short, the study demonstrated that an outcome of detection of coronary stenosis is not sufficient to define at diabetic patients who are at higher risk for cardiovascular disease. However, we also analyzed total plaque volume by CCTA in 128 diabetic patients in the FACTOR-64 study. Risk factors that were associated with a greater degree of total coronary artery plaque volume were age, gender and body mass index (Kwan, May et al. 2014). Greater calcium score was associated with lower amounts of noncalcified plaque.

We applied similar methodology in our NIH cohort (10-CC-0214, The RIGHT Study: Risk Stratification With Image Guidance of HMG Coa Reductase Inhibitor Therapy" (NCT01212900)). We evaluated 202 study subjects with low to moderate cardiovascular risk (Kwan, May et al. 2014).The average age of study subjects was 65.5±6.9 years (36% women) with median coronary artery calcium score was 73 (IQR 1-434). Total coronary plaque index was greater in men than women (42.1±9.2 vs. 34.3±8.3 mm2, p<0.001). In

multivariable analysis controlling for all risk factors, total plaque index was remained greater in men than women (by 5.01 mm2; p=0.03), and in those with higher simvastatin dose (by 0.44 mm2/10 mg eq.; p=0.02). Noncalcified plaque index was positively correlated with systolic blood pressure (beta = 0.80 mm2/10 mmHg, p=0.03), diabetes (beta = 4.47 mm2, p=0.03), and LDL –C level (beta = 0.04 mm2/mg/dl, p =0.02); the association with LDL-C remained significant (p=0.02) after additional adjustment for CAC score.

In summary, the above studies demonstrate a) ability to recruit patient cohorts relevant to the present study; b) technical expertise in assessing total coronary artery plaque as well as plaque volume components and c) certain risk factors such as obesity are associated with noncalcified plaque. The proposed study is a logical extension to our prior published work in this area. *Importantly, in an NIH study population with favorable LDL response to statin therapy, slightly less than half of study subjects showed atheroma progression in the carotid arteries. We have identified cardiovascular risk factors, especially obesity and hypertension, related to atheroma progression despite optimal guideline oriented statin therapy. A gap in our knowledge is the effect of statin therapy for plaque reduction in asymptomatic subjects in the coronary arteries.*

Background for Secondary Aims of Comparison of Cardiac CT to Cardiac MRI.

Magnetic resonance imaging of intraplaque hemorrhage. In the carotid arteries, there is now strong evidence that high T1 signal within an atheromatous plaque is due to intraplaque hemorrhage (McNally, Kim et al. 2012). In the Rotterdam study, intraplaque hemorrhage was considered an indicator of unstable plaque and was more prevalent in men compared with women. Hypertension and current smoking were risk factors for the presence of intraplaque hemorrhage (van den Bouwhuijsen, Vernooij et al. 2012). Intraplaque hemorrhage was more frequently found on the ipsilateral side of subcortical brain infarction and was associated with disruption of the surface of plaque (Truijman, de Rotte et al. 2014, de Rotte, Truijman et al. 2015, van den Bouwhuijsen, Bos et al. 2015, van Dijk, Truijman et al. 2015). These observations strongly support the role of intraplaque hemorrhage as a contributor to unstable atheromatous plaque.

For the coronary arteries, the challenges of demonstrating intraplaque hemorrhage are greater due to small plaque size. However, recent studies have demonstrated abnormal T1 signal related to coronary artery plaques on non contrast CMR imaging (Kawasaki, Koga et al. 2009). Increased T1 signal is present on MRI in the presence of hemorrhage or protein and is postulated to represent regions of unstable plaque. T1 signal has been shown to change over time following myocardial infarction (Ibrahim, Makowski et al. 2009) and has proven to be a strong predictor of subsequent coronary artery events in individuals with high cardiovascular risk (Noguchi, Yamada et al. 2011, Noguchi, Kawasaki et al. 2014). In the current study, we propose that T1 high signal intensity plaques may be characterized in relationship to CCTA features of low density plaque and irregular plaque signal. We propose to assess change in T1 plaque signal in comparison to NaF activity in the coronary arteries (see next section).

18F-Sodium Fluoride (NaF) for evaluation of coronary artery plaque: PET sub study. 18F-Sodium Fluoride (NaF) is a 510k FDA approved agent for positron emission tomography (PET). The agent has recently been investigated to identify high-risk coronary plaque as well as carotid plaque. In 37/40 patients, the highest coronary NaF signal was seen in the culprit plaque in patients with myocardial infarction (Joshi, Vesey et al. 2014). In the carotid artery, NaF signal was present in all carotid plaque ruptures in symptomatic

patients. NaF is thought to target active microcalcification in atherosclerotic plaques (Chen and Dilsizian 2013). Currently, little is known about the initiation and progression of plaque, partly because of lack of a noninvasive imaging modality targeting molecular calcification. Inter-observer repeatability of coronary NaF uptake measurements (maximum tissue/background ratio) was excellent (intra-class coefficient 0.99) (Dweck, Chow et al. 2012). Activity was higher in patients with coronary atherosclerosis (n = 106) versus control subjects (1.64 ± 0.49 vs. 1.23 ± 0.24; p = 0.003) and correlated with the calcium score (r = 0.652, p < 0.001), although 40% of those with scores >1,000 displayed normal uptake. Patients with increased coronary 18F-NaF activity (n = 40) had higher rates of prior cardiovascular events (p = 0.016) and angina (p = 0.023) and higher Framingham risk scores (p = 0.011).

Thus NaF has been proposed as a promising new approach for the assessment of coronary artery plaque biology. Prospective studies are needed to assess whether coronary NaF uptake represents a novel marker of plaque vulnerability and future cardiovascular risk. By comparison, CAC score by CT is a risk marker which cannot be modified. *Thus, an unresolved issue is if NaF uptake can be modified by statin therapy,* which would be expected if NaF relates to cardiovascular risk.

Summary. Cardiac CT angiography (CCTA) provides a non-invasive method of evaluating both calcified and noncalcified plaque volume. Plaque regression has been demonstrated by coronary artery IVUS and carotid artery MRI. The potential for tracking plaque progression/ regression is suggested in high risk patients using CCTA. Several retrospective and small prospective studies suggest that CCTA may be useful to track plaque reduction. Comparison to CMR is useful to fully phenotype plaque characteristics due to novel studies of T1-weighted high signal plaque. NaF PET appears as a novel agent that may also be useful to explore the relationship between treatment and PET signal with regards to CCTA plaque characteristics and CMR T1 signal. No prior studies have evaluated the change in plaque volume in patients evaluated under 2013 AHA/ACC GRCR guidelines for high intensity statin therapy.

DESIGN

Primary Endpoint: The primary endpoint of this study is the change in noncalcified plaque volume after 24 months.

Secondary Endpoints: In addition to the 24 months follow-up period specified for the primary endpoint, we plan to follow the patients for an extended period of 12 months to study the long-term effects of the statin therapy. As a result, the patients will be followed for a total of 36 months with the first 24 months for the primary endpoint and the additional 12 months for the secondary endpoints. The secondary endpoints include:

1) Change in noncalcified plaque volume assessed by CCTA at the end of 36 months;
2) Effects of covariates including age, sex, race, body mass index and baseline plaque volume on the change of plaque volume measured by CCTA at 24 and 36 months.
3) The relationship of CMR T1 high signal intensity plaque and change in T1 signal by CMR over time to CCTA plaque characteristics.
4) (Pilot study): the relationship of coronary artery plaque by CCTA to sodium fluoride (F18-NaF) uptake using positron emission tomography (PET) scanning:
    a. Determine if F18-NaF signal correlates with CCTA defined plaque volume and CAC score.
    b. Determine the change in F18-NaF signal in relationship to statin therapy.

In order to achieve the primary aim, we will evaluate men (age 40-75) and women (age 40-75) with a screening/ baseline CT scan of the coronary arteries. Study subjects will be followed over time if they a) have noncalcified coronary artery plaque, b) have not been treated with GRCR defined high intensity statin treatment for more than 90 days prior to enrollment and c) agree to receive high intensity statin treatment. The study duration will be 36 months. Subjects eligible based off their screening/baseline CT scan of the coronary arteries will receive Rosuvastatin or another high intensity statin treatment. Study subjects will also undergo CMR scan to detect T1 high signal intensity plaque and for comprehensive cardiovascular phenotyping. Correlation of NaF signal on PET scanning will also be performed.

For the primary aim, subjects fulfilling basic inclusion/exclusion criteria and giving informed consent to the study will be examined using CT angiography (3rd generation CT scanner, advanced dose reduction techniques). If noncalcified plaque is present, the subject will have follow-up CCTA at 12, 24 and 36 months. Additional correlative testing is detailed in the study calendar. The primary outcome parameter is change in noncalcified plaque volume. Noncalcified plaque volume will be assessed based on the largest noncalcified atheroma at baseline CCTA.

OVERVIEW OF ENROLLMENT

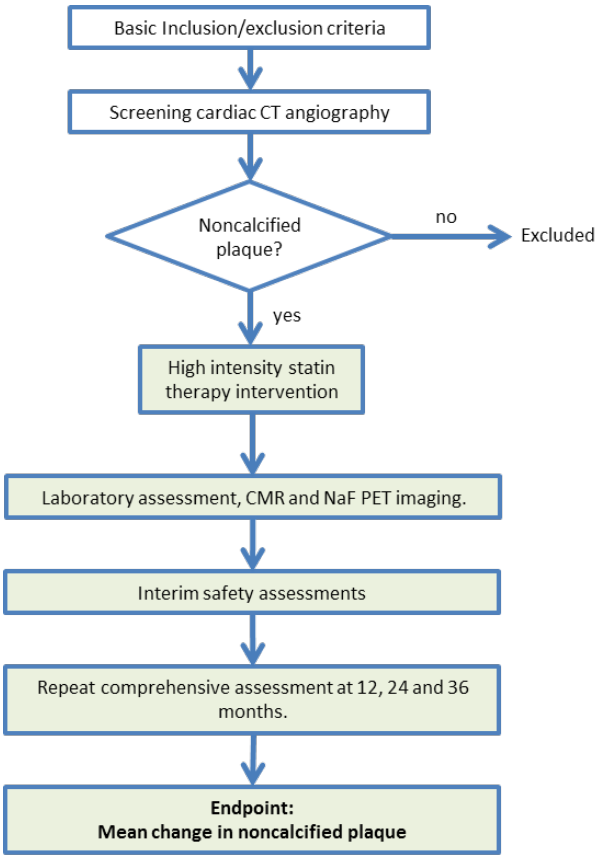
All participants will be screened for their willingness/ability to participate in the various study procedures (see Appendix for MRI screening questionnaire) and those unwilling/unable to participate in a specific procedure will be excluded from that study. Prior to enrollment onto the study, potential research subjects will be sent a Study Questionnaire form to assist the research team in confirming diagnosis and determining which tests will be appropriate for the subject (see appendix E). The questionnaire will also guide medical record gathering prior to the visit to aid consultants. The initial screening visit will consist of laboratory evaluation initial laboratory assays in addition to a focused clinical exam and history. The objectives of the screening visit are a) exclude any contraindication for CCTA, nitrates or beta blockers (e.g. history of hyperthyroidism, aortic stenosis or prior use of sildenafil); b) determine lipid levels and c) determine if noncalcified plaque is present. Study subjects already receiving high intensity therapy for more than 90 days prior to enrollment will not be considered. Study subjects will be eligible for at least moderate statin therapy according to ACC/AHA 2013GRCR criterion and 2018 ACC/AHA guidelines. Note that study subjects at low GCRC cardiovascular risk (using traditional risk factors) but with CAC score > 75th percentile for age, gender and ethnicity will be classified to be moderate risk. Specific inclusion/ exclusion criteria are indicated in Sections 2.1 and 2.2 below.

If a) noncalcified coronary plaque is identified on CCTA, and b) the study subject qualifies for at least moderate statin therapy, the study subject will be enrolled for statin therapy and follow-up. Only study subjects with a noncalcified plaque component extending over 4 mm will be considered for further follow-up in the study.

IMAGING - OVERVIEW

Imaging consists of CCTA for plaque evaluation at baseline, 12 months 24 months, and 36 months. Cardiac MRI may be performed at baseline, and 24 months (optional). A clinical report of imaging and lab results will be offered to all subjects and – if requested by the subject – can be sent to a physician.

A study of F18 NaF PET imaging will be conducted; participation in the PET study will be considered to be optional for participants. Lack of participation will not exclude subjects from the study cohort.



CT IMAGING

CT Imaging protocol

1. Coronary calcium scan
2. Coronary computed tomography angiography (CCTA)
3. Cardiac cine CT

If a subject has had eGFR measured within the prior 6 weeks and is not on diuretics, ACE inhibitors (angiotensin converting enzyme inhibitors), ARBs (angiotensin receptor blockers), and has had no major change in clinical status, then the eGFR does not need to be rechecked. Otherwise, the eGFR will be measured.

CCTA will be performed during an intravenous iodinated contrast infusion. A test bolus of iodinated contrast (approximately 20 ml) will be used to judge contrast bolus arrival time and optimize image quality. CCTA examination is performed with 60-80 ml iodinated contrast according to Clinical Center guidelines.

4. Radiation and iodine contrast dose

The estimated average radiation dose for the entire cardiac computed protocol will be less than or equal to 2.1 rem per year. Iodinated contrast dose will be in accordance with current CT Clinical Center guidelines.

Medication to facilitate imaging

Beta Blockade

In order to optimize image quality by reducing cardiac motion, participants may receive beta blockade on the day of the scan if the expected heart rate is > 60/min. Participants will have heart rate and blood pressure measured, and will be assessed for contraindications to beta blockade (bradycardia, active wheezing and history of adverse reaction).

Beta blockade will proceed according to NHLBI and CC clinical standards: 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 5-20 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 (blood pressure, Heart rate) 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, and the subject becomes symptomatic the supervising physician will be notified. All participants who receive beta blockers will be assessed for symptoms of bradycardia, hypotension and orthostasis after scan completion.

Nitrates

The use of short acting nitrates (i.e. sublingual nitroglycerine) will be used according to NHLBI and CC standards for CCTA for study subjects with systolic blood pressure >100mmHg 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, prior PDE5 (e.g. sildenafil) use. If the patient cannot receive nitroglycerine (due to intolerance, borderline blood pressure, investigator judgment, contraindication), 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 dedicated CCTA software. Readers will be blinded as to subject and date of the CT angiogram examination.

Coronary calcification

Coronary calcification will be measured by the Agatston (Agatston, Janowitz et al. 1990) method. The volume, calcium mass and a voxel based calcium density analysis will also be performed. 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.

Total plaque quantification

Raw data will be reconstructed at approximately 0.5 mm slice-thickness. The baseline axial MDCT images with adequate reconstruction phase will be post processed and analyzed by commercial software (e.g. Medis QAngioCT). Lumen and wall boundaries of target vessels will be semi-automatically detected on cross sectional images. Under the guide of multiplanar reconstructed images, 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. Segments with artifact or blur will be excluded. Volume estimates of plaque extent are obtained by multiplying cross sectional area of plaque by slice thickness. Plaque wall volume is computed by subtracting lumen volume from vessel volume.

In order to assess target plaque lesions, the inner and outer contours of the vessel will be determined independently and blinded for the time of the exam (i.e., dates of scans will be masked for analysis and order of performance mixed). For comparison an index lesion will be selected (based on largest non-calcified plaque component and sufficient image quality on both exams). Using proprietary software developed in conjunction with the software manufacturer, both vessels will be visually aligned based on anatomical landmarks and the lesion will be selected on both exams (baseline and follow up). The software provides the volume measurements for each lesion.

An improved tool for the co-registration step (fully automatic co-registration) is under development and may also be used.

CARDIAC MRI (CMR) (OPTIONAL)

CMR will be performed using a high field (1.5 or 3T) scanner. The aim of the cardiac study is to a) identify high signal intensity T1 coronary artery plaque. The CMR protocol will include localization images with coronary CMR to localize plaque volume. Myocardial structure, function and tissue composition will be performed per NIH Clinical Center standard protocol for comprehensive phenotyping to characterize subclinical disease that may be present. In a population of middle and older adults in the U.S.,

approximately 9% of study subjects have evidence of myocardial damage defined by myocardial scar or abnormalities in cardiac wall motion (Turkbey et al, JAMA 2015, 314(18)); of myocardial scars, approximately 80% are undetected by clinical correlation/ ECG (Barbier, Bjerner et al. 2006, Schelbert, Cao et al. 2012).

18F NAF PET IMAGING

For 18F-NaF uptake, the coronary arteries are visually identified, and regions of interest will be drawn around areas of maximal uptake in the left main stem, left anterior descending artery, circumflex artery, and the right coronary artery. The maximum standard uptake value (SUV) is recorded from these regions. The SUV is the decay-corrected tissue concentration of 18F-NaF divided by the injected dose/body weight. However, SUV measurements in vascular structures are influenced by variability in 18F-FDG and 18F-NaF activity in the blood. Therefore, SUV measurements are divided by an averaged mean SUV value in the blood pool, derived from 5 circular regions of interest drawn in the center of the superior vena cava. This provides maximum tissue/background ratios (TBRs) as a measure of arterial tracer uptake.

2. ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1. INCLUSION CRITERIA

A. Men ≥ 40 and ≤ 75 years of age; women ≥ 40 and ≤ 75 years of age
B. Willing to travel to the NIH for follow-up visits.
C. Willing to start or modify statin therapy.
D. Able to understand and sign informed consent.
E. Serum Creatinine ≤ 1.5 mg/dL within 30 days in accordance with the NIH Clinical Center Radiology and Imaging Sciences SOP. (http://intranet.cc.nih.gov/radiology/policies/ct_iv_contrast_sop.html)
F. Eligible for primary prevention statin therapy
   1) Eligible for at least moderate intensity statin according to 2013 ACC/AHA GRCR (i.e., ≥5% 10 year cardiovascular risk, https://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp) OR
   2) low (<5%) 10 year cardiovascular risk per 2013 ACC/ AHA and with coronary artery calcium score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity determined per MESA study (http://www.mesa-nhlbi.org/calcium/input.aspx).

2.2. EXCLUSION CRITERIA

A. Allergy or prior clinically relevant adverse reaction to Rosuvastatin (does not include minor muscle pain).
B. High intensity statin treatment for more than 90 days prior to enrollment
C. LDL ≥ 190 mg/ml
D. Physician-diagnosed heart attack
E. Physician-diagnosed stroke or TIA
F. Physician-diagnosed heart failure
G. Having undergone procedures related to cardiovascular disease (CABG, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries)

H. Active treatment for cancer
I. Prior hypersensitivity reaction to iodinated contrast injection
J. Known hyperthyroidism.
K. Acute renal failure, renal transplant, dialysis and renal failure clinically diagnosed.
L. History of liver transplant or severe liver disease or unexplained elevation of baseline ALT>3x upper limit of normal
M. Pregnancy and nursing
N. Mental, neurologic or social condition preventing understanding of the rationale, procedures, risks and potential benefits associated with the trial.
O. Any other conditions that precludes safety for MRI and/or CT imaging per the researcher's evaluation.
P. Individuals with hemoglobinopathies or severe asthma.
Q. Severe renal excretory dysfunction, estimated glomerular filtration (eGFR) rate < 30 mL/min/1.73m2 body surface area according to the Modification of Diet in Renal Disease criteria
Glomerular filtration rate will be estimated using the MDRD 2005 revised study formula:
eGFR (mL/min/1.73m2) = 175 x (standardized serum creatinine)-1.154 x (age)-0.203 x 0.742 (if the subject is female) or x 1.212 (if the subject is black)

2.3. SCREENING EVALUATION

On-Study Assessments:

Study activities below (see Appendix A for overview) specify the required study tests and procedures for participants. A Telehealth platform visit may be utilized to review subject eligibility at baseline visit in accordance with the NIH-approved telehealth policy.

Baseline visit tests and procedures will be completed within 4 weeks before the first dose of study medication, unless otherwise noted. Results from procedures and laboratory tests from other NIH IRB approved protocols that subjects may have participated in within 4 weeks of enrollment in this study may be used as part of the screening evaluation for this study. 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 study start.

Special consideration of drug interaction is necessary in the following context: In regard to interaction with CT associated medications (beta blocker, calcium antagonists, Nitroglycerin): **Phosphodiesterase inhibitors (e.g. Viagra), antiarrhythmic drugs**.

Special consideration of drug interaction with Rosuvastatin: **Coumadin, Niacin, Fenofibrate, Colchicine.**

D. Record known diagnoses. Relevant in the context of study associated medications: **Asthma (contraindication for beta blocker use)**

E. Record vital signs, height and weight (at Baseline visit)

F. Collect blood and complete laboratory screening and or clinical evaluations that may include the following:

- Fasting lipid panel
- Whole blood serum creatinine
- Complete blood count (CBC),
- Chemistry Labs: Electrolyte Panel, Creatinine, eGFR, Aspartate Amino-Transferase (AST), Alanine Aminotransferase (ALT), Creatine kinase (CK), hsCRP
- HbA1c, fasting glucose
- C-reactive protein (CRP)
- Lipoprotein profile
- Urine pregnancy test (for women of childbearing age)
- Other laboratory measures available in CRIS that may be required to ensure participant safety
- Research blood (10 mL)

G. Baseline CT is performed.

H. Review baseline CT study for regarding continuation of study (presence of CAD):

- Noncalcified plaque component extending over 4 mm
- Study subject must be either 1) at least moderate 10 year cardiovascular risk according to ACC/AHA 2013 criteria OR 2) low risk ACC/AHA risk and CAC score ≥300 or ≥ 75th percentile for age, gender and ethnicity.

I. If accepted into study for follow up:

- Cardiac MRI (optional)
- PET study (optional)

J. Perform follow-up lipid panel, creatine kinase and liver function testing at 3 months.

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 the scheduled clinic visits or in response to notification of any perceived clinical alteration.

We expect a some subjects will have ongoing statin treatment when screened for eligibility. We will allow an estimation for the native LDL based on the following statin efficacy chart by multiplying the measured LDL with the correction factor that corresponds to the current statin drug and dosage (source: FDA website).

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin†	Simva	%↓ LDL-C	Correction Factor
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	30%	**1.43**
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%	**1.61**

20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%	**1.69**
40 mg	-----		-----	-----	10 mg	10/20 mg		47%	**1.89**
80 mg	-----		-----	-----	20 mg	10/40 mg	-----	55%	**2.22**
	-----		-----	-----	40 mg		-----	63%	**2.70**

2.4. REGISTRATION PROCEDURES

Upon completion of the screening process, eligible subjects will be enrolled on the study and will begin treatment.

3. SUBJECT IMPLEMENTATION

3.1 STUDY DESIGN

This is an interventional trial in which 190 adult men and women will receive high intensity statin treatment. The study duration will be when subjects complete their 36 month visit.

3.2 PROTOCOL EVALUATION/STUDY CALENDAR

Treatment:

High intensity statin therapy:

- High intensity lipid lowering therapy: rosuvastatin, target dose 40 mg (Nicholls et al., 2011).
- If the drug is not tolerated by a patient during the study, alternatives are rosuvastatin 20 mg or atorvastatin 80 mg. Statin dose will be reduced if the serum LDL is below 25 mg/dL (Everett, Mora et al. 2014)

Failure to meet target therapies will not result in removal from the study but will instead be assessed on an intention-to-treat basis.

Protocol Evaluation:

A. Study Subjects will have a study visits for imaging at baseline, 12, 24 and 36 months, 18 and 30 month assessments will be done via telephone, Telehealth platform and or e-mail (**Appendix A, Study Calendar**). **Note: After Amendment O Protocol dated 7/02/2020- no longer enrolling in sub-studies:** The PET study subjects will have additional visits. Up to 60 subjects will be accrued to the PET sub study. 30 subjects will be asked to return within 30 days for repeat visit to insure CCTA data reproducibility. Visits will follow the Protocol Evaluation schema in Appendix A. Visits will occur within +/- 12 weeks due for unforeseen events.

B. Clinical Laboratory Measures will be done before starting study drug at baseline enrollment then as clinically indicated per Safety Announcement by the FDA 2.28.2012:

- Serum creatinine kinase, lipid panel and liver function tests will be measured at baseline enrollment and at 3 months after start of drug treatment and annually thereafter when clinically indicated.

- If symptoms indicating possible muscle or liver alterations appear (muscle pain, fatigue, jaundice, abdominal pain, anorexia) the study drug will be paused and a timely evaluation including lab testing for liver and muscle enzymes will be recommended and offered. Depending on the results of the evaluation the drug can be resumed (if association with statin is unlikely), reduced or stopped (based on clinical judgment).
- HbA1c will be measured during the course of the study.
- Urine HCG test for women of childbearing age. Blood glucose measurements also 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) Urine HCG test for women of childbearing age.

Response to abnormal results

All clinically abnormal test results will be relayed to participants and/or their referring providers. Participants will be instructed to consult with their physician for follow up and referral to specialists as appropriate. Abnormal lab results may be repeated or reassessed at PI discretion as part of the subject's clinical care.

If ALT, AST, alkaline phosphatase reaches more than 3 times the upper limit of normal without symptoms indicating liver disease or CK is greater than 1000 U/L without muscle symptoms the study drug will be paused and results will be repeated within 2 weeks. Other causes of the abnormalities should also be considered. Restarting the study drug depends on clinical judgment.

ALT, AST, alkaline phosphatase reaching more than 3 times the upper limit of normal or CK >1000 U/L with muscle symptoms will be reported at the time of Continuing Review (see 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.

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. Elevations of liver enzymes more than three times the upper limits of normal that persists in repeat testing and cannot be explained by other factors than statin use.
4. Myopathy defined as muscle pain with serum creatinine kinase concentrations > 1000 U/L. Any other relevant 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.

3.4.2 OFF STUDY CRITERIA

1. Request of the patient or their personal physician.
2. Pregnancy or nursing
3. Subjects who come off study for any reason will be referred back to their personal physician.
4. Per PI discretion

4. SUPPORTIVE CARE

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

5. DATA COLLECTION AND EVALUATION

5.1. HUMAN SPECIMEN USE, DISPOSITION, TRACKING AND STORAGE OF SAMPLES AND DATA

During the course of participating on this study, blood, tissue and data may be collected for correlative laboratory research studies. Specimens collected strictly for research purposes will not be read by a pathologist.

Biospecimen management: Specimens and their derivatives (e.g., genomic material, cell lines) will be coded and stored in conformity with DIR Policy (e.g., BSI). Coded biospecimens may be sent to collaborators outside of the NIH with IRB approval in accordance with applicable NIH and DIR Policy for sharing research resources, including an executed material transfer agreement. Biospecimens with subject personal identifiers may be sent to associate investigators and collaborators outside of the NIH only after approvals of both NHLBI and local IRBs, an executed reliance agreement with NHLBI's IRB, or an extension of the NIH's FWA through an Individual Investigator Agreement.

Data Management: The principal investigator, associate investigators, research nurses and/or a data manager will assist with the data management efforts. Data will be abstracted from Clinical Center progress notes as well as intake forms and the case report forms. Laboratory data from NIH will be reviewed using CRIS. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts to ensure that data are verifiable

and evaluable. Data will be abstracted from Clinical Center progress notes as well as from progress notes forwarded from the subjects' home physician.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. Laboratory values from referring home physicians will be entered into the system. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts to ensure that data are verifiable and evaluable.

Research data will be prospectively collected by authorized Investigator personnel and entered into an NHLBI, 21 CFR 11 compliant, database which will consist of the study specific set of electronic CRFs (e-CRFs) used for capturing, managing and reporting clinical research data.

The database will maintain complete data records on each research subject. Subjective and objective patient experiences during the duration of the study will be documented in the patient medical record notes. These protocol notes will serve as the primary source material from which data will be collected in the database. Any pertinent supplementary information obtained from outside laboratories, outside hospitals, radiology reports, laboratory reports, or other patient records will be used as additional sources for data collection.

We will maintain the confidentiality of identifiable private information collected in this Clinical Trial and protect the privacy of the individual human subjects. Primary data containing individually identifiable information obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH information security standards. Neither individual personal identifiers nor the key linking coded data to individuals will be released without prior IRB approval and an executed confidential disclosure agreement (CDA) or material transfer agreement (MTA). Identifiable data will not be sent outside NIH without prior IRB approval or appropriate conditions for disclosure outlined in the executed CDA or MTA.

Standard forms for patient history, labs, imaging results. Digital source documentation from CTDB (Clinical Trials Database) will be used. CTDB is a password protected secure database at the NIH Clinical Center. 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 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.

Storage: All samples will be stored in the laboratory of Dr. Mehta. Collected samples will be de-identified prior to storage in the laboratory of the principal investigator following current NHLBI DIR BSI Policy. Efforts to ensure protection of patient information include;

- Each sample is assigned a unique number.
- Vials holding patient samples are labeled with the sequential laboratory accession ID number that does not contain any personal identifier information.
- An electronic database is used to store patient information related to the coded samples
- The laboratory is located in a controlled access building and laboratory doors are kept locked. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.

Data sharing and future use of data

Research data may be shared with qualified non-collaborator recipients following publication of the primary research results after removal of PII and IRB or OHSRP approval. Future research use of data not defined in the research protocol may occur only after IRB review and approval or an exemption from the NIH Office of Human Subjects Research Protections (OHSRP). Refusal of a research subject participant to permit future use of data--other than required in the protocol or by the FDA--will be honored. Limitations in data sharing and future use of data due to contractual obligations (e.g., CRADAs) or intellectual property proceedings (such as patent filings) will be honored.

Future use of biospecimens

Following analyses of biospecimens for primary research purposes as described in the protocol, remaining samples suitable for future research must be stored in manner that conforms with DIR policy (such as BSI) or in a publicly accessible research biospecimen repository following IRB approval. Biospecimens may be destroyed only when permitted by the clinical director and approved by the IRB.

Any future research use of biospecimens not defined in the research protocol in which NHLBI investigators are engaged in research (e.g., they are undertaking research activities and hold the key that identifies research subjects) requires IRB review and approval. Coded biospecimens (NHLBI investigators hold the key that identifies research subjects) to be shared outside of NIH for future research use requires IRB review and approval (for research collaborations) or submission of a determination to OHSRP (for non-collaborative research), and an executed transfer agreement. Unlinked biospecimens (no key to identify research subjects exists) to be shared outside of NIH for future research use requires submission of a determination to OHSRP and an executed transfer agreement. There are a few types of biospecimens that do not require IRB or OHSRP approval for future research use outside of NIH, such as specimens from deceased individuals (refer to OHSRP SOP5, Appendix 1 for complete list); an executed transfer agreement is required in these special cases. Refusal of a research subject participant to allow for future use of biospecimens-other than required in the protocol or the FDA-will be honored.

Tracking: Samples will be ordered and tracked through CRIS Research Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the

medical record. Samples will not be sent outside NIH without IRB notification and an executed MTA or CTA.

***End of study procedures**:* Samples from consenting subjects will be stored until they are no longer of scientific value. At the completion of the protocol (termination), samples and data will be maintained in a repository for future research.

Loss or destruction of samples: Should we become aware that a major breech in our plan for tracking and storage of samples has occurred, the IRB will be notified.

Loss or destruction of data: Should we become aware that a major breech in the plan to protect patient confidentiality and trail data has occurred, the clinical director and IRB will be notified.

Publication Policy: Given the research mandate of the NIH, patient data including the results of testing and responses to treatment will be entered into an NIH-authorized and controlled research database. Any future research use will occur only after appropriate human subject protection institutional approval such as prospective NIH IRB review and approval or an exemption from the NIH Office of Human Subjects Research Protection (OHSRP).

Privacy and Confidentiality: All efforts, within reason, will be made to keep subjects' protected health information (PHI) and private identifiable information (PII) private. Using or sharing ("disclosure") such data must follow federal privacy rules. Under certain circumstances, the United States Office of Human Research Protections (OHRP), The US Food and Drug Administration (FDA), and the NIH Intramural Institutional Review Board (IRB), will be able to inspect and copy confidential study-related records which identify participants by name. Therefore, absolute confidentiality cannot be guaranteed.

5.2. RESPONSE CRITERIA

Response to high-intensity therapy will be assessed according to GRCR 2013 guidelines and are expected to result in LDL levels by 50%. To be consistent with new clinical practice guidelines for lipid lowering therapy, specific lipid targets will not be used as response criteria to guide therapy.

6. STATISTICAL CONSIDERATIONS

Primary Endpoint: The primary endpoint of this study is the change in noncalcified plaque volume after 24 months.

Secondary Endpoints: In addition to the 24 months follow-up period specified for the primary endpoint, we plan to follow the patients for an extended period of 12 months to study the long term effects of the statin therapy. As a result, the patients will be followed for a total of 36 months with the first 24 months for the primary endpoint and the additional 12 months for the secondary endpoints. The secondary endpoints include:

1) Change in noncalcified plaque volume assessed by CCTA at the end of 36 months;
2) Effects of covariates including age, sex, race, body mass index and baseline plaque volume on the change of plaque volume measured by CCTA at 24 and 36 months.

3) The relationship of CMR T1 high signal intensity plaque and change in T1 signal by CMR over time to CCTA plaque characteristics.
4) (Pilot study): the relationship of coronary artery plaque by CCTA to sodium fluoride (F18-NaF) uptake using positron emission tomography (PET) scanning:
   a. Determine if F18-NaF signal correlates with CCTA defined plaque volume and CAC score.
   b. Determine the change in F18-NaF signal in relationship to statin therapy

Preliminary Information: One study in the literature was conducted as a pilot study with similar goals (Burgstahler et al. 2007). This pilot study investigated 22 noncalcified plaques in 12 patients before and after lipid lower therapy for 18 months. The mean patient age (61) and cardiovascular risk profile was similar to that expected in our cohort. The medication used was atorvastatin 20 mg. The mean (±sd) volume of all plaques was reduced by statin therapy form 0.042±0.029 mL to 0.030±0.014 mL ($P<0.05$). The mean reduction of plaque volume was 0.012 mL with the standard deviation 0.017 mL.

Statistical Hypotheses: Because the study of Burgstahler et al. (2007) is based on a small sample size, we would like to consider a somewhat conservative assumption on the mean and sd for the plaque volume reduction than the preliminary information provided by this study. Specifically, we hypothesize that the patients with high intensity statin treatment will have at least 0.008 mL mean reduction of plaque volume at the end of the 24 months treatment period. Let

Δ = mean reduction of plaque volume at 24 months.

The statistical setting is to test the null hypothesis "H_0: $\Delta=0$" versus the two-sided alternative of "H_1: $\Delta\neq0$" at 0.05 significance level with 90% power. The null hypothesis suggests that the mean plaque volume reduction is the same at the beginning of the study and the end of 24 months, while the alternative suggesting changes of the mean plaque volume at the two time points. Based on the information provided in Burgstahler et al. (2007), we believe that it is reasonable to conduct a statistical test to detect an effective Δ of at least 0.008 mL under the somewhat conservative assumption that the sd of Δ is 0.03 mL.

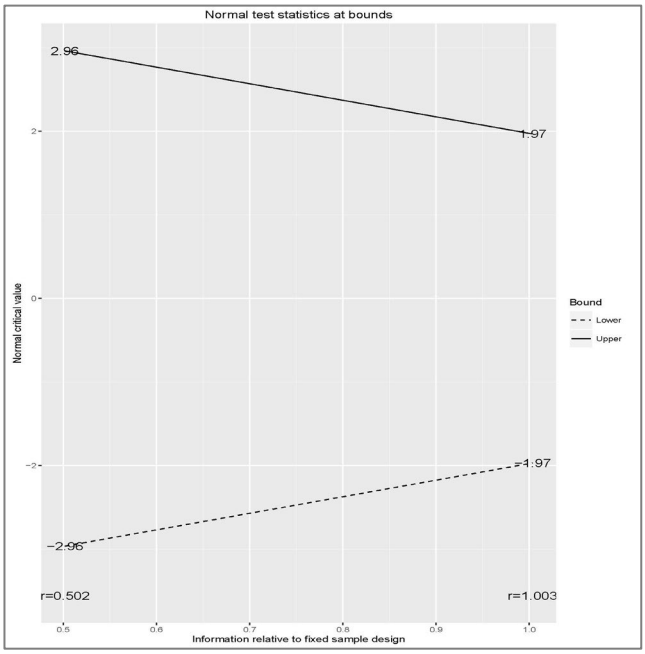
Sample Size Justification: We plan to conduct a group sequential trial with one interim analysis when approximately half of the patients completed the 24 months follow-up. Using the Lan-DeMets O'Brien-Fleming approximate spending function, our test requires n=151 patients to be followed at the end of the 24 months to reach the required 0.05 significance level and 90% power. Assuming approximately 20% dropout at the 24 month time point, the number of enrolled subjects will be 190.

Interim Analysis: The interim analysis will be conducted when n_1=76 patients completed the 24 months follow-up period. The lower and upper stopping boundaries for the interim analysis are Z_1=-2.96 and 2.96, respectively, where Z_1 is the test statistic for the statistical hypotheses H_0 and H_1 at the interim look (see Figure 1 below). The corresponding nominal p-value at this interim look is 0.0015. The study will be considered for stopping due to efficacy if the test statistic Z_1 crosses the upper bound, i.e., $Z_1 > 2.96$, while, the study will be considered for stopping due to futility if the test statistic Z_1 crosses the lower bound, i.e. $Z_1 < -2.96$. However, the DSMB will make the decision on whether the study should be stopped at the interim look.

Final Analysis: In the most like event the study is proceeded to the final stage, the final analysis for the primary endpoint will be determined by the test statistic Z_2 with all N=151 patients completed the 24 months follow-up. The null hypothesis H_0 of no difference of the mean plaque volume between the baseline and the 24 months will be rejected if $|Z_2| > 1.97$ (see Figure 1 below).

Software: Sample sizes and stopping boundaries of the group sequential design are computed using the R "gsDesign" package, version 3.1.3 (2015-03-09). Details of the statistical methods and theory of the design are described in C. Jennison and B. W. Turnbull (2000, "Group Sequential Methods with Applications to Clinical Trials", Chapman and Hall/CRC, Boca Raton, FL).

Figure. Stopping boundaries with one interim look based on the Lan-DeMets O'Brien-Fleming approximate spending function.



Noncompliance and Missing Data: Given our past experience in similar clinical trials, we do not anticipate noncompliance as a major problem. However, despite the best possible effort, there are inevitably noncompliant patients and/or patients with missing data. We categorize the noncompliance and missing data into the following three situations:

1) ***Noncompliant patients with complete follow-up examinations at baseline and 24 months***: The primary analysis of these patients, including both the interim analysis and the final analysis of the primary endpoint, will be carried out using the intent-to-treat (ITT) principle. Under the ITT principle, the observed plaque volumes at baseline and 24 months from these patients will be included in the primary analysis.
2) ***Noncompliant patients with missing examinations at 24 months***: Since plaque volume normally does not decrease without significant intervention, we will apply the ITT principle to these patients using the approach of setting their plaque volumes at 24 months to be the same as their baseline values.
3) ***Compliant patients with missing examination at 24 months***: We expect that only a small portion of the patents will fall into this category, since our study coordinators will give their best efforts to contact and keep track these patients. For the primary analysis, we will include these patients using the same approach as 2) by setting their plaque volumes at 24 months to be the same as their baseline values.

4) ***Secondary analysis of the above patients***: In addition to the ITT and missing data approaches mentioned in 1)-3), our secondary analysis of the primary endpoint (change of plaque volume between baseline and 36 months) will also include: a) non-ITT approach of including only treatment compliant patients in the analysis, b) complete data approach of using only patients with observed plaque volumes in both baseline and 36 months. As a sensitivity analysis, we will compare the results obtained from a) and b) above with the primary analysis of 1)-3). This sensitivity analysis will provide useful insights into the characteristics of the patients with noncompliance and/or missing plaque volume data at 24 and 36 months.

Secondary Analysis with Subgroups and Covariates: Regression models will be considered for the analysis of secondary endpoints.

1) ***Cross-Sectional Data:*** Regression models with cross-sectional outcome and covariates, i.e. data without repeated measurements over time, will include multivariable linear and nonlinear models. Nonparametric smoothing methods, such as splines and local polynomials, will be used to explore the relationships between the outcome and covariates. The flexible ANOVA F Goodness-of-Fit tests will be used to test the adequacy of the parametric linear and nonlinear regression models.
2) ***Longitudinal Outcome and Covariate Data:*** For data including repeatedly measured outcome and/or covariates over time, we will consider the commonly used linear and nonlinear mixed effects models to explore the time trends of the outcome variables and corresponding covariate effects. Similar to the exploratory analysis with cross-sectional data, we will also consider the flexible nonparametric longitudinal regression methods, such as the time-varying coefficient models and models of functional data analysis, to evaluate the appropriateness of the parametric mixed effects models.
3) **For Secondary endpoint 3** (relationship of CCTA plaque to T1 CMR signal): CMR high signal intensity plaque is postulated to represent "unstable" plaque or plaque containing hemorrhage and/ or protein. CCTA plaque characteristics that are thought to be associated with unstable plaque include spotty calcification and low density plaque. Since this aim represents an exploratory aim with the use of technologically advanced CMR imaging, the incidence of CMR T1 high signal intensity plaque is unknown. We will therefore use descriptive statistics to relate the presence or absence of T1 high signal intensity to the presence or absence of various CCTA plaque characteristics. In addition, we will determine if T1 signal changes in various plaques over the study period; if T1 signal changes (e.g. due to plaque healing), we would expect that this would be more common in the presence of unstable plaque features by CCTA. For this aim, the number of T1 high signal intensity plaques at baseline that do not show high signal at 24 months will be determined. The percentage of these plaques that demonstrated unstable CCTA plaque characteristics at baseline will be determined. Data for both the 12 and 24 month time points will be considered because at present the time course of change of high T1 signal intensity plaques is not known
4) **For Secondary endpoint 4** (pilot study, relationship of CCTA plaque to F18-NaF signal). A comparison of the presence or absence of NaF signal by PET will be performed. NaF signal (with both TBR and SUVmax) will be compared across different plaque morphology and compositions defined by CCTA (for example, presence of a lipid core or calcification) in order to gain an understanding of the relationships between these two imaging modalities. 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.

Safety Monitoring of Adverse Events: Because the statin treatment is known to be safe and involve minimal risk, we do not plan a statistical stopping rule. Any adverse events will be reported to the DSMB. Continuation or stopping of the study because of the safety reasons will be made following the recommendations of the DSMB.

7. HUMAN SUBJECT PROTECTION

7.1. RATIONALE FOR SUBJECT SELECTION

Individuals age 40-75 (men) and 40-75 (women) from all racial/ethnical groups are eligible to participate. NIH employees who meet the eligibility requirements are eligible to be screened and considered for protocol participation. Subjects may be referred from other NIH protocols.

A comprehensive strategy of advertising and recruitment through the NIH clinical center patient recruitment and referral center will be utilized including social media and internet PSAs as well as NIH Newsletters. Walter Reed National Military Medical Center may also be a recruitment site for referring patients for participation on this protocol.

Recruitment and enrollment of NIH employee subjects will be consistent with NIH HRPP SOP 14 F.. NIH employees may voluntarily participate in this protocol. Neither participation nor refusal to participate as a subject in this protocol will have an effect, either beneficial or adverse, on the participant's employment or position at NIH. Employee subjects' privacy and confidentiality will be respected by protocol and consenting staff the same as for all subjects' participation in research protocols. However, all subjects will be made aware that there are limits to these protections. The PI, through the consenting staff members, will make the "NIH Information Sheet on Employee Research Participation" available to employees who are considering enrolling in research (SOP 14F, Appendix B). 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. Instead, an associate investigator authorized in the protocol to obtain consent in this protocol and who is also a co-worker may obtain consent from a NIH employee without independent monitoring, as the IRB has waived this requirement for this protocol. Refer to the NIH Policy Manual, 2300-630-3 - Leave policy for NIH Employees Participating in NIH Medical Research Studies. See Appendix B

This age group is the most likely to benefit from an early medical intervention strategy to reduce cardiovascular events in the future.

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 are 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.

Reproducibility Sub study (No longer recruiting after Amendment O Protocol dated 7/02/2020)

A subgroup of 30 participants who had CCTA defined coronary plaque will be asked to return 4 weeks after their initial CCTA scan for a second CT study using the same CCTA protocol. Additionally, the initial CCTA and reproducibility CCTA will be in accordance for total annual radiation dose exposure at the NIH as determined by the radiation safety committee. Eight to twelve 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 30 scans will be interpreted by two readers, allowing assessment of both intra and interobserver variability as well as repeatability limits.

Subjects who participate in the Reproducibility sub study will not have the cardiac MRI performed.

7.2. PARTICIPATION OF CHILDREN:

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

7.3. EXCLUSION OF PREGNANT WOMEN:

The risk from radiation exposure is increased in children and especially in the fetus. This can be explained by a higher rate of mitosis earlier in life (Hall 2009, Goodman and Amurao 2012). It is generally conceived that X-ray imaging should be only used in vital indications in pregnant women. In the context of this study this is not the case and therefore pregnancy is an exclusion criteria (§46.204 Code of Federal Regulations. Condition "Any risk is the least possible for achieving the objectives of the research" is not met)

7.4. EXCLUSION OF PERSONS UNABLE TO GIVE CONSENT

The research question on progression of atherosclerosis can be answered without enrolling subjects who are unable to give consent. According to NIH HRPP SOP 14E v1: 14E.6.1 A: "Ensure there is a compelling justification for including adults who cannot consent (e.g., the research question cannot be answered by enrolling only adults who can consent; participation offers the potential for important clinical benefit)." we do not plan to enroll subjects who are unable to give consent.

7.5. 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 β1 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%).

Nitroglycerine

Nitroglycerine is a FDA approved medication for the treatment of angina pectoris due to coronary artery disease. Nitroglycerine pumpspray given to 51 chronic stable angina patients in single doses of 0.4, 0.8 and 1.6 mg as part of a study exhibited an adverse event profile that was generally mild to moderate. Adverse events occurring at a frequency greater than 2% included: headache, dizziness, and paresthesia. Less frequently reported events in this trial included (≤2%): dyspnea, pharyngitis, rhinitis, vasodilation, peripheral edema, asthenia, and abdominal pain. A notable drug interaction with phosphodiesterase inhibitors is known which can amplify the vasodilatory effects of Nitroglycerine, resulting in severe hypotension.

Statin Therapy

This study uses statin drugs for the FDA approved indications of treatment of hypercholesterolemia and atherosclerosis. The study is not designed or intended to test new indications, dosages, routes or study populations for statin drugs.

In this study a subgroup of subjects who - based on current AHA guidelines – would receive moderate intensity statin therapy (e.g. Atorvastatin 20 mg) would receive Rosuvastatin. In this context the issue of drug safety of Rosuvastatin will be addressed.

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 (Knopp 1999).

Statin induced myopathy

In 7 studies 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% (Sacks, Pfeffer et al. 1996, Downs, Clearfield et al. 1998, Colhoun, Betteridge et al. 2004, LaRosa, Grundy et al. 2005, Pedersen, Faergeman et al. 2005). The highest reported rate of rhabdomyolysis was 0.53%, observed with simvastatin 80 mg daily (de Lemos, Blazing et al. 2004).

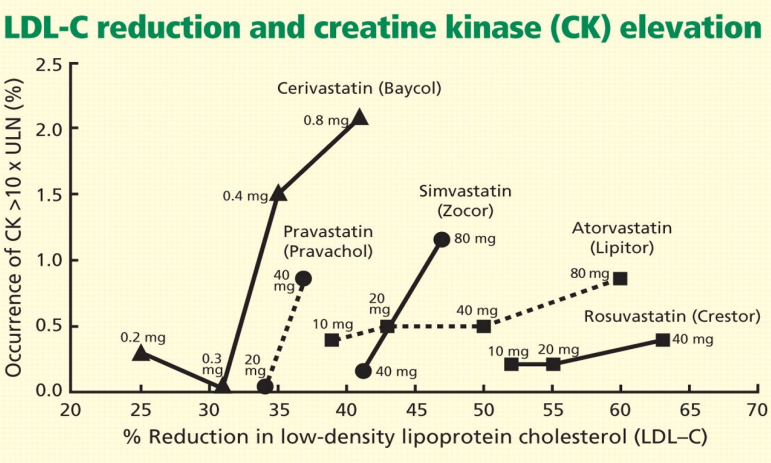
The use of high dose, intensive statin therapies to achieve very low LDL levels is a recent development. Available data, including three large randomized controlled trials (the A to Z, TNT and IDEAL studies),

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 (de Lemos, Blazing et al. 2004, LaRosa, Grundy et al. 2005, Pedersen, Faergeman et al. 2005) (Davidson and Robinson 2007).

We expect the population in this planned study to be similar to the JUPITER trial population in which Rosuvastatin was tested (primary prevention, age>50, no prior CVD). In the JUPITER trial (Ridker, Pradhan et al. 2012) the rate of myopathy was extremely low and not significantly different between experimental and placebo group (10 vs. 9 cases, 17802 trial participants). There was only one case of Rhabdomyolysis that occurred after closure of the trial in a 90 year old patient with pneumonia and trauma induced muscle damage. Other analyses show that Rosuvastatin compares favorably to other less potent statins when comparing the occurrence of CK elevations (see graph) (Brewer 2003).

Liver toxicity

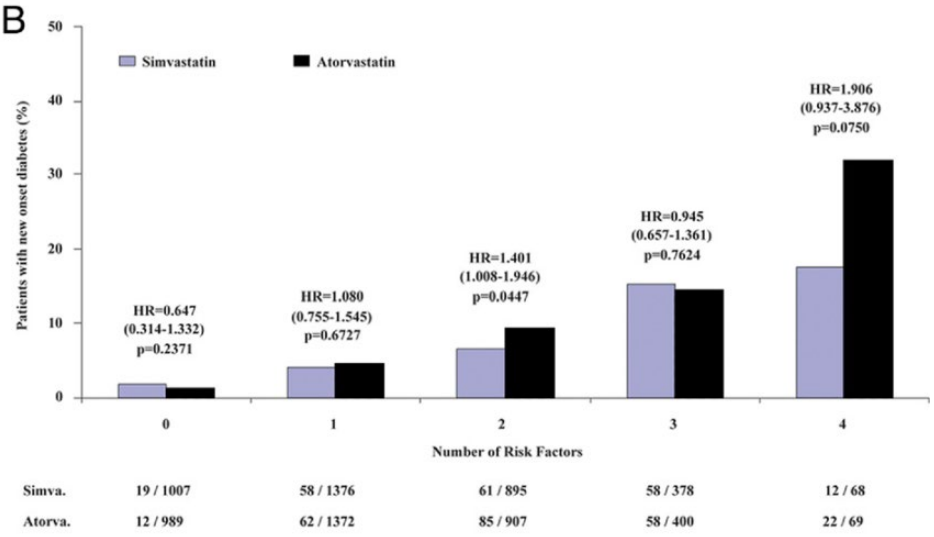
Statin monotherapy can result in elevation of liver enzymes, most often ≤3 times the upper limit of normal. These elevations typically normalize without lasting injury upon discontinuation of the drug. Their clinical significance is uncertain given the extremely rare occurrence of statin related toxic hepatitis (Bays 2006, Bays, Cohen et al. 2014).



New onset diabetes

Meta-analyses of 91,140 subjects in statin trials showed a small but unexpected increase of new onset diabetes type 2 in patients treated with statins (Sattar, Preiss et al. 2010); greater age was a risk factor for new onset diabetes, but not BMI or LDL reduction. A smaller meta-analysis 3 clinical trials identified other possible risk factors for new onset diabetes in atorvastatin treated patients (Waters, Ho et al. 2011). We reflect this information on the consent form, as age and greater risk for onset of diabetes during statin

therapy.



Conclusion

Overall Rosuvastatin is a drug that has been tested in multiple large trials and has vast post marketing experience indicating a very low risk for adverse events.

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% (Cronin, Marsden, & O'Doherty, 1999; Einstein, Henzlova, & Rajagopalan, 2007; Mejia et al., 1991). The primary prevention population targeted for this study is unlikely to receive significant degrees of medical radiation during the 36 months of study follow up.

Note that study participants cannot participate in all three studies (the main study, PET sub study, and reproducibility sub study) when total radiation exposure exceeds RSC limits (5.0 rem/12 months)

The following table provides radiation exposure at all required time points for participants, including optional sub-study participation:

Radiation dose estimates: Average maximum radiation exposure

Examination component	Baseline – < 12 months (rem)	12 month visit (rem)	24 month visit (rem)	36 month visit (rem)
CT: Main Study	2.134	2.134	2.134	2.134
PET sub-study	0.285*2 = 0.57 (total)	N/A	0.285	N/A

CT Reproducibility sub-study	2.134	N/A	N/A	N/A
Yearly Totals	**Baseline – < 12 months (rem)**	**12 month visit (rem)**	**24 month visit (rem)**	**36 month visit (rem)**
Total for Subjects undergoing Main CT plus PET*	2.704	2.134	2.419	2.134
Total for Subjects undergoing Main CT plus Reproducibility CT*	4.268	2.134	2.134	2.134
Total for Subjects undergoing Main CT only	2.134	2.134	2.134	2.134

*No subjects undergo both PET substudy and reproducibility substudy (No longer recruiting after Amendment O Protocol dated 7/02/2020)

Statin Use

Statins will be used for approved indications.

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/m^2 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.

7.6. RISKS/BENEFITS ANALYSIS

The principal risks to participants are high intensity statin therapy , exposure to ionizing radiation as part of the coronary CT angiogram and receipt of iodinated 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.

7.7. CONSENT PROCESS AND DOCUMENTATION

Note: Effective January 21, 2019, a witness to the signature of the written long form research consent at an NIH site (whether initially approved by an IRB before or after January 21, 2019) is no longer a requirement.

Patients asked to participate in PET imaging will be consented separately for their participation in the main protocol and the sub study. Patients asked to participate in the Reproducibility sub study will be consented separately for their participation in the main protocol and the sub study. 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 investigators roles are listed on the Study Personnel page, which identify who is authorized to obtain informed consent from the study subjects.

Telephone Consent and or Telehealth platform

Participants may be contacted by telephone, and or Telehealth NIH-approved platform to obtain informed consent for new subjects. For subjects actively participating in the study who may need to be re-consented due to changes to the informed consent or procedures. For instance, when new risk information relevant to a subject's ongoing participation is discovered, notification to the subject may be required (applies to all consent documents). Many subjects may have travelled to the NIH CC previously and a return trip would be inconvenient. The telephone consents will be obtained by those investigators designated as authorized to obtain inform consent on the Study Personnel page. Telehealth procedure will follow the NIH- approved policy.Procedures for obtaining telephone consent are as follows:

• The informed consent document will be sent to the patient either by mail (U.S. Postal Service or Fed-Ex), fax, or e-mail prior to the phone conversation. If mailed, a pre-addressed return envelope may be included.

• A telephone call will be scheduled between the participate and designated investigator to allow time for the participate to thoroughly read over the consent. The protocol will be discussed and explained during the scheduled telephone call and any questions will be answered.

• If the patient agrees to participate, the patient will print, sign and date the informed consent document with the date of the telephone conversation.

• The patient is to return the signed document by mail or fax to the investigator. Upon receiving consent, the investigator will print, sign and date the consent with date the telephone conversation occurred and date of receipt of the consent document. this document will be designated as both the original and telephone consent.

• A copy of the fully executed document will be returned to the patient by mail or secure email for the patient's record. The original consent will be sent to medical records to be placed in the patients electronic chart.

• The informed consent process will be documented on a CRIS progress note (Progress Note – Documentation of Consent) by the investigator.

7.8. 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 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.

NIH Intramural IRB: Prior to implementation of this study, the protocol and the proposed patient consent forms will be reviewed and approved by the properly constituted IRB operating according to the 45 CFR 46. This committee will also approve all amendments to the protocol or informed consent, and conduct continuing annual review so long as the protocol is open to accrual or follow up of subjects.

A data safety and monitoring board lead by Victor Ferrari, M.D., at the University of Pennsylvania will review all laboratory and safety data. At regular 12-month intervals the DSMB will monitor the safety of the lipid lowering therapy with Rosuvastatin. 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. Analyses will be conducted for two interim analyses (at the end of year one and year two) and one final evaluation.

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.

7.9. COMPENSATION

Patients will not receive direct financial compensation for participation in the main study. They will receive the medications Rosuvastatin or Atorvastatin without charge. 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. (See Appendix B)

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

For the CT Reproducibility sub study, 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)

For the PET sub study, participants will receive up to $390 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
- Maximum $30 for visit ($20 for the first hours and $10 for each following hours with a maximum of 2 hours per visit)

7.10. CONFLICTS OF INTEREST

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

8. SAFETY REPORTING REQUIREMENTS:

8.1. DEFINITIONS

Please refer to Policy 801 for current definitions.

AE assessment:

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized to describe the severity of AEs.

8.2. IRB REPORTING GUIDELINES

Reports to the IRB and CD:
Expedited Reporting:
Events requiring expedited reporting will be submitted to the IRB per Policy 801 “Reporting Research Events”.

Reports to the IRB at the time of Continuing Review:
The PI or designee will refer to HRPP Policy 801 “Reporting Research Events”, to determine IRB reporting requirements.

Reports to the CD:

The PI or designee will refer to NHLBI DIR guidelines to determine CD reporting requirements.

8.3. IND/IDE:

The magnetic resonance magnets and coils used to perform cardiac 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. However, custom tools (software) sequences may be different than what is normally done in a routine clinical scan, 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, all scans done will be performed within FDA safety guidelines. There is no potential for serious risk to the health, safety, or welfare of the subjects using the MRI scanner in these ways. The use of these custom components of the device constitutes a non-significant risk device study. This protocol is therefore eligible for abbreviated IDE requirements of 21 CFR 812.2(b). 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 (Somatom Force, Siemens; Toshiba Aquilion ONE) used to perform CT angiography are 510k approved devices and are used in accordance with the labeling (21 CFR 812 § 812.2.(c)).

Computed tomography (CT) x-ray imaging has been utilized in the field of medicine for over 3 decades. During this period, introductions of advances in both hardware and software technology have expanded the diagnostic capability of the modality. As CT continues to evolve with even greater capabilities, the potential for providing clinicians with information not currently available today continues to increase.

The Toshiba Aquilion ONE CT system is currently being used for studies in both general CT radiology and CT cardiac imaging. One of the unique aspects of the Aquilion ONE CT system is its ability to acquire whole organ volume images in a single rotation by utilizing an x-ray detector that is configured as 320 detector rows with a 0.5 mm width, providing a z-axis coverage of 16 cm of anatomy. In line with the evolutionary changes to CT systems, the Aquilion ONE will be upgraded with new technology that will expand its capabilities. The changes being made to the Aquilion ONE will provide enhancements to image acquisition capabilities, reduce ionizing radiation dose, and improve subject access to the system. All of these features assist in enhancing the safety of the currently installed Aquilion ONE CT system.

The SOMATOM Force is a whole body X-ray Computed Tomography System which features two continuously rotating tube-detector systems and functions according to the fan beam principle. The SOMATOM Force produces CT images in DICOM format, which can be used by postprocessing applications commercially distributed by Siemens and other vendors. The system software is a command-based program used for patient management, data management, X-ray scan control, image reconstruction, and image archive/evaluation.

9 PHARMACEUTICAL INFORMATION

Rosuvastatin (Package insert)

1 INDICATIONS AND USAGE

1.1 Hyperlipidemia and Mixed Dyslipidemia CRESTOR is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipid altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and nonpharmacological interventions alone has been inadequate. Pediatric Patients 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH) Adjunct to diet to reduce Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year postmenarche, 10-17 years of age with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: LDL-C > 190 mg/dL or > 160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.

1.2 Hypertriglyceridemia CRESTOR is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.

1.3 Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia) CRESTOR is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).

1.4 Homozygous Familial Hypercholesterolemia CRESTOR is indicated as adjunctive therapy to other lipidlowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia.

1.5 Slowing of the Progression of Atherosclerosis CRESTOR is indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

1.6 Primary Prevention of Cardiovascular Disease In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to: • reduce the risk of stroke • reduce the risk of myocardial infarction • reduce the risk of arterial revascularization procedures

1.7 Limitations of Use CRESTOR has not been studied in Fredrickson Type I and V dyslipidemias. 2 DOSAGE AND ADMINISTRATION 2.1 General Dosing Information The dose range for CRESTOR is 5 to 40 mg orally once daily. The usual starting dose is 10-20 mg. CRESTOR can be administered as a single dose at any time of day, with or without food. 4 When initiating CRESTOR therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy. After initiation or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly. The 40 mg dose of CRESTOR should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle Effects Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including CRESTOR. These risks can occur at any dose level, but are increased at the highest dose (40 mg). CRESTOR should be prescribed

with caution in patients with predisposing factors for myopathy (e.g., age ≥ 65 years, inadequately treated hypothyroidism, renal impairment). 7 The risk of myopathy during treatment with CRESTOR may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir [see Dosage and Administration and Drug Interactions]. CRESTOR therapy should be discontinued if markedly elevated creatinine kinase levels occur or myopathy is diagnosed or suspected. CRESTOR therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

5.2 Liver Enzyme Abnormalities and Monitoring It is recommended that liver enzyme tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including CRESTOR. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to CRESTOR therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials. In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking CRESTOR versus 0.5% of patients treated with placebo. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, 8 reduction of dose or withdrawal of CRESTOR is recommended. CRESTOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease [see Clinical Pharmacology (12.3)]. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of CRESTOR [see Contraindications (4)].

5.3 Concomitant Coumarin Anticoagulants Caution should be exercised when anticoagulants are given in conjunction with CRESTOR because of its potentiation of the effect of coumarin-type anticoagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs [see Drug Interactions (7.4)].

5.4 Proteinuria and Hematuria In the CRESTOR clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among CRESTOR treated patients. These findings were more frequent in patients taking CRESTOR 40 mg, when compared to lower doses of CRESTOR or comparator HMG-CoA reductase inhibitors, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on CRESTOR therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

5.5 Endocrine Effects Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR [see Adverse Reactions (6.1)]. Although clinical studies have shown that CRESTOR alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if 9 CRESTOR is administered concomitantly with drugs that may

decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Nitroglycerine (Package insert):

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the latter. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load).

The mechanism by which nitroglycerin relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin and presumably, a more favorable supply-demand ratio is achieved.

While the large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of exertional angina is unclear.

Nitroglycerin is rapidly metabolized in vivo, with a liver reductase enzyme having primary importance in the formation of glycerol nitrate metabolites and inorganic nitrate. Two active major metabolites, 1,2-and 1,3-dinitroglycerols, the products of hydrolysis, although less potent as vasodilators, have longer plasma half-lives than the parent compound. The dinitrates are further metabolized to mononitrates (considered biologically inactive with respect to cardiovascular effects) and ultimately glycerol and carbon dioxide.

Therapeutic doses of nitroglycerin may reduce systolic, diastolic and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased, or unchanged. Patients with elevated left ventricular filling pressure and systemic vascular resistance values in conjunction with a depressed cardiac index are likely to experience an improvement in cardiac index. On the other hand, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced.

In a pharmacokinetic study when a single 0.8 mg dose of Nitrolingual®Pumpspray was administered to healthy volunteers (n = 24), the mean Cmax and tmax were 1,041pg/mL • min and 7.5 minutes, respectively. Additionally, in these subjects the mean area-under-the-curve (AUC) was 12,769 pg/mL • min.

In a randomized, double-blind single-dose, 5-period cross-over study in 51 patients with exertional angina pectoris significant dose-related increases in exercise tolerance, time to onset of angina and ST-segment depression were seen following doses of 0.2, 0.4, 0.8 and 1.6 mg of nitroglycerin delivered by metered pumpspray as compared to placebo.

Additionally the drug was well tolerated as evidenced by a profile of generally mild to moderate adverse events.

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.

<u>Iodine contrast</u> (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 non-neural 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.

12 CLINICAL PHARMACOLOGY

Gadolinium: The use of gadolinium for this protocol is not off-label. For the subjects receiving gadolinium contrast agents, the placement of a peripheral intravenous line may result in mild discomfort, vasovagal reactions or bruising. The gadolinium contrast agents that will be used are commercially available and routinely used in hospitals and radiology practices. Experience with a large number of subjects has shown that these commercially available gadolinium chelates are safe and without side effects in the majority (>98%) of subjects. When side effects do occur, they are usually mild and transient. These include coldness in the arm during the injection, headache and nausea. More severe reactions (shortness of breath, wheezing, or hypotension) are extremely rare. Gadolinium has been used in over 5000 studies at NIH within the dosage limits described without any major side effects. This protocol will follow the NIH Clinical Center Policy and Screening Procedures for Administration of Gadolinium Based Contrast Agents for MRI and the NHLBI DIR Policy for the Administration of Gadolinium-Based Contrast Agents for Clinical Research Protocols.

The US Food and Drug Administration issued a warning that administration of gadolinium (updated September 9, 2010), the contrast imaging agent used in this protocol, has been associated with development of a disease called nephrogenic systemic fibrosis (NSF). The syndrome is rare (approximately 600 cases reported worldwide as of September 2010 out of several million administrations of gadolinium), but disabling and in some cases, fatal. All cases to date have occurred in subjects with severe renal disease, including subjects on dialysis. Most of the reported cases have been attributed to the gadolinium contrast agent gadodiamide (Omniscan). Most recent information indicates the condition is associated with severe renal insufficiency. Subjects with severe renal excretory dysfunction, estimated glomerular filtration rate < 30 mL/min/1.73m2 body surface area according to the Modification of Diet in Renal Disease criteria, will not receive gadolinium contrast agent during the PET/MRI.

On December 19, 2017, the FDA is requiring a new class warning and other safety measures for all gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these drugs. Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and FDA has concluded that the benefit of all approved GBCAs continues to outweigh any potential risks. However, after additional review and consultation with the Medical Imaging Drugs Advisory Committee, FDA is requiring several actions to alert health care professionals and patients about gadolinium retention after an MRI using a GBCA, and actions that can help minimize problems. These include requiring a new patient Medication Guide, providing educational information that every patient will be asked to read before receiving a GBCA. FDA is also requiring manufacturers of GBCAs to conduct human and animal studies to further assess the safety of these contrast agents.

To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. FDA received reports of adverse events involving multiple organ systems in patients with normal kidney function. A causal association between these adverse events and gadolinium retention could not be established.

In response to the December 2017 MedWatch warning on gadolinium accumulation from the FDA, the healthy subjects may undergo no more than two gadolinium exposures during a 12-month period, per NHLBI policy.

In accordance with the FDA Drug Safety Communication of 05/16/2018, the Medication Guide for gadobutrol (or other macrocyclic gadolinium contrast agent if applicable) will be made available to all subjects with scans that will involve gadolinium-based contrast agent administration.

12.2 Pharmacodynamics

Gadobutrol leads to distinct shortening of the relaxation times even in low concentrations. At pH 7, 37°C and 1.5 T, the relaxivity (r1) - determined from the influence on the relaxation times (T1) of protons in plasma - is 5.2 L/(mmol·sec) and the relaxivity (r2) - determined from the influence on the relaxation times (T2) - is 6.1 L/(mmol·sec). Gadobutrol is a highly water-soluble, extremely hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7.6 of about 0.006.

12.3 Pharmacokinetics

Distribution

After intravenous administration, gadobutrol is rapidly distributed in the extracellular space. After a gadobutrol dose of 0.1 mmol/kg body weight, an average level of 0.59 mmol gadobutrol/L was measured in plasma 2 minutes after the injection and 0.3 mmol gadobutrol/L 60 minutes after the injection. Gadobutrol does not display any particular protein binding. In rats, gadobutrol does not penetrate the intact blood-brain barrier.

Metabolism

Gadobutrol is not metabolized. Gadobutrol is excreted in an unchanged form via the kidneys. In healthy subjects, renal clearance of gadobutrol is 1.1 to 1.7 mL/(min·kg) and thus comparable to the renal clearance of inulin, confirming that gadobutrol is eliminated by glomerular filtration.

Within two hours after intravenous administration more than 50% and within 12 hours more than 90% of the given dose is eliminated via the urine. Extra-renal elimination is negligible.

Specific Populations

Gender

Gender has no clinically relevant effect on the pharmacokinetics of gadobutrol.

After intravenous injection of 0.1 mmol gadobutrol/kg body weight, the elimination half-life was 5.8 ± 2.4 hours in mild to moderately impaired patients (80 > CLCR > 30 mL/min) and 17.6 ± 6.2 hours in severely impaired patients not on dialysis (CLCR 30 mL/min). The mean AUC of gadobutrol in patients with normal renal function was 1.1 ± 0.1 mmol·h/L, compared to 4.0 ± 1.8 mmol·h/L in patients with mild to moderate renal impairment and 11.5 ± 4.3 mmol·h/L in patients with severe renal impairment.

Complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function about 80% of the administered dose was recovered in the urine within 5 days.

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APPENDICES

Appendix A: Study Calendar*

Visit number[1]	1 Screen	2 M0[3]	3 M 3	(4)[9] M6	5 M12	*6 M18	7 M24	*8 M30	9[8] M36
Procedure									
Obtain consent	X								
Enrollment criteria	X								
History & Physical[2]	X				X		X		X
Screen Labs[4]	X								
Adverse event review	X		X	X	X	X	X	X	X
Concomitant Med. Review[5]	X		X	X	X	X	X	X	X
Cardiac MRI		X					X		
MRI Questionnaire[6]		X					X		
Creatinine	X		X	X	X		X		X
CT angiography	X				X		X		X
PET imaging subgroup	X		X				X		
Drug dosing/ adjustment		X	X	X	X	X	X	X	X
Clinical Labs[7]	X		X	X	X		X		X

[1]Visits within +/- 12 weeks due for unforeseen events. M (month). Delays in visits will need to be discussed and pre-approved with the research team.

[2]Baseline: H&P and laboratory studies (see section 2.3) should be completed within 4 weeks of initiating treatment.

[3]Baseline MRI can be completed within 4 weeks of screening procedures.

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

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

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

[7]See section Clinical Laboratory Measures, 3.2 for list of Clinical labs.

[8]Subjects 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.

[9] Visit pertains only to those participants whose statin dose is increased on 3M visit in order to meet LDL target. All other participants will be asked to return at M12

*** contacted via telephone, e-mail or Telehealth**

Appendix B. SOP 14F: NIH INFORMATION SHEET ON STAFF RESEARCH PARTICIPATION (APRIL 2016)

As an NIH employee, contractor, Special Volunteer, Guest Researcher, or trainee, you may participate in intramural research studies unless it is prohibited by your Institute or Center (IC), or if you are excluded by the criteria of the protocol in which you want to enroll. The inclusion of NIH staff in a particular protocol must also be approved by the IRB. You may be motivated by altruism, a commitment to research in your own or related fields, or want access to clinical trials of potential direct therapeutic benefit. When deciding, you should make an informed decision about participation. This information sheet offers some points to consider for NIH staff who are considering research participation at NIH. First, similar to any individual who is considering research participation, you should seek adequate information about the study purpose, what is required of you in terms of procedures, interventions and time, and the potential risks and benefits of participation. For more information, see the NIH Clinical Center's public website "Are Clinical Studies for You?" at http://www.cc.nih.gov/participate/studies.shtml.

When you are thinking about participation in a research study that is being conducted by your supervisor, or others with whom you work closely in your laboratory, branch, or unit, you should consider some additional factors:

A. Possible bias: Are you confident that you can be unbiased about reporting answers, side effects, or other information that could influence the study outcome or risk to you?

B. Confidentiality: Has the principal investigator (PI) spoken about what information will be collected from you as part of the study? Has the PI discussed what information will be available to those within, and outside, the study team? If applicable, are you comfortable sharing your medical history (including, for example, mental health history or STDs) and your social history (e.g. substance use) with study investigators who may be your coworkers, or with the possibility of them discovering something about your health during the study (e.g. pregnancy status or a new diagnosis)? Although every effort will be made to protect your information and keep it private and confidential, your information may, depending on the nature of the protocol, become available in medical records or to authorized users outside of the study team. Discuss any concerns with the PI.

C. Pressure: Do you perceive any pressure or expectations from your supervisor or colleagues regarding participation? Could that pressure influence your decision or make it difficult for you to choose whether or not to participate? Remember that it is your choice whether or not to participate and that your decision to participate or not should not have an effect, either beneficial or adverse, on your position at NIH.

Appendix B: LEAVE POLICY FOR NIH EMPLOYEES PARTICIPATING IN NIH MEDICAL RESEARCH STUDIES (NIH POLICY MANUAL 2300-630-3)

A. Policy

An NIH employee may take part in an NIH funded biomedical research protocol approved by the NIH Institutional Review Board (IRB), if that protocol specifies that employees may participate. Commissioned Corps Officers should contact the Commissioned Corps Office (301) 402-9239 for authorization requirements and limitations in participating in a biomedical research protocol study. The protocol statement should include the time period and duration that participants will be expected to spend in the study and whether or not compensation will be offered. A copy of this statement shall be provided to the employee upon request.

The employee's supervisor should request a copy of the protocol statement from the employee to determine the appropriate leave that may be granted. Supervisors should contact the Principal Investigator to ascertain whether or not the employee will receive financial compensation and/or will accrue medical benefits.

The employee's supervisor shall determine if the employee may be absent from duty for the necessary period(s) of time. With the approval of the supervisor, an employee may be granted appropriate leave to participate in an NIH biomedical research study as a volunteer subject during his/her normal tour of duty.

Annual Leave or Leave Without Pay shall be requested by an employee participating in an NIH biomedical research study from which compensation is offered and accepted by the employee.

Annual Leave, Sick Leave or Leave Without Pay shall be requested by an employee participating in an NIH biomedical research study from which medical benefits are gained by the employee.

Excused Absence may be granted to an employee if:

The employee earns no money, and

The employee gains no medical benefits from participating in the study.

An employee may participate in an NIH biomedical research study after the employee's tour of duty without being charged annual leave, sick leave or leave without pay. An employee participating in a biomedical research study outside of his/her tour of duty must notify their supervisor of this activity when participation may impact the employee's ability to perform work during his/her tour of duty.

An employee may be granted excused absence to donate blood or blood products through the facilities of the Clinical Center, Department of Transfusion Medicine provided there is no compensation received. The donation of blood or blood products is not considered to constitute participation in a biomedical research study and is not covered by this manual. Further information on the leave policy for blood donors is contained in the NIH Civilian Leave Guide.

B. References:

HHS Personnel Instruction 630-1 (Absence and Leave)

NIH Leave Guide for Civilian Employees

Commissioned Corps Officer's Handbook, 1998

C. Internal Controls:

The purpose of this manual issuance is to assure that all work and related activities are conducted in full accord with statutory, regulatory and policy requirements.

Office Responsible for Reviewing Internal Controls Relative to this Chapter is OD/OHR/WRD/Benefits and Payroll Liaison Branch (Issuing Office).

Through this issuance, the Office of Human Resources, Office of the Director, NIH is accountable for the method used to ensure that internal controls are implemented and working.

Frequency of Review: Every 3 years

Method of Review: Conduct surveys among Ics

Review Report is sent to the Director, Office of Human Resource, NIH

D. Records Retention and Disposal:

All records (e-mail and non-e-mail) pertaining to this chapter must be retained and disposed of under the authority of NIH Manual 1743, "Keeping and Destroying Records," Appendix 1, NIH Records Control Schedule, Item 1900-D-3, Time and Attendance Report Files.

NIH e-mail messages. NIH e-mail messages (messages, including attachments, that are created on NIH computer systems or transmitted over NIH networks) that are evidence of the activities of the agency or have informational value are considered Federal records. These records must be maintained in

accordance with current NIH Records Management guidelines. Contact your IC Records Officer for additional information.

All e-mail messages are considered Government property, and, if requested for a legitimate Government purpose, must be provided to the requester. Employees' supervisors, NIH staff conducting official reviews or investigations, and the Office of Inspector General may request access to or copies of the e-mail messages. E-mail messages must also be provided to members of Congress or Congressional committees if requested and are subject to Freedom of Information Act requests. Since most e-mail systems have back-up files that are sometimes retained for significant periods of time, e-mail messages and attachments may be retrievable from a back-up file after they have been deleted from an individual's computer. The back-up files are subject to the same request as the original messages.

Appendix C: MRI Safety Questionnaire

NIH - MRI Safety Questionaire

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, jewelrey, 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 D: Targeted enrollment table

Targeted/Planned Enrollment Table

This report should NOT be used for data collection from study participants

Study Title: CT COMPARE: CT Coronary Angiography to Measure Plaque Reduction

Total Planned Enrollment: 175

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	7	8	15
Not Hispanic or Latino	80	80	160
Ethnic Category: Total of All Subjects*	**87**	**88**	**175**
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	4	4	8
Native Hawaiian or Other pacific Islander	1	1	2
Black or African American	12	12	24
White	69	70	139
Racial Categories: Total of All Subjects*	**87**	**88**	**175**

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

Appendix E: Pre-Screening Questionnaire

NIH Protocol #16-H-0089 Screening Questionnaire

Thank you for your interest in our study! To help us evaluate whether or not you are eligible for participation, please provide as much of the following information as you are able to.

Have you ever been a patient at the National Institutes of Health before?

First/Middle/Last Name:

Date of Birth:

Street Address:

City/State/Zip Code:

Telephone Numbers:

Please note we are asking for the following information in order to calculate your cardiovascular risk to determine if you are a good candidate for our study. The information will not be used for any other purposes.

Please provide your Gender: _____
Please provide your Race (optional): _____
Please provide your Age: ____

From your last cholesterol test:
Total Cholesterol:_ _____
HDL: _____
LDL: _____
Date test was performed: _____

Have you been diagnosed with high blood pressure? ☐ Yes
☐ No

What was your last blood pressure reading (home measurement is acceptable):

_____

List any medications you take for high blood pressure:

_____

Do you have diabetes? ☐ Yes ☐ No

If yes, do you take insulin? ☐ Yes ☐ No

Do you take any other medications for diabetes? ☐ Yes ☐ No

Have you ever smoked before? ☐ Yes ☐ No

If yes, did you smoke within the last 30 days? ☐ Yes ☐ No

Do you have any allergies to foods or medications? Please list the allergen and reaction:

_____

Did you ever have a CT scan of your heart or Calcium Score performed before? *If yes, please provide details*:

_____

Are you claustrophobic? ☐ Yes ☐ No

Do you have kidney disease or have you ever been told that your kidneys are not working well? *If yes*, please provide your most recent creatinine result (a measure of kidney function): _____

Do you any history of the following:

Chest pain/angina ☐ Yes ☐ No

Heart attack ☐ Yes ☐ No

Stroke ☐ Yes ☐ No

Heart surgery /Stent ☐ Yes ☐ No

Heart failure ☐ Yes ☐ No

Atrial fibrillation ☐ Yes ☐ No

Kidney disease ☐ Yes ☐ No

Hyperthyroidism ☐ Yes ☐ No

If you answered yes to any of the above, please provide details:

_____

_____

_____

Do you have any other ongoing medical problems? (*if yes, please provide a brief description*):

_____

___

_____
___

What cholesterol “statin” medication and dose do you currently take?

_____
When did you start taking this medication? _____
Please list any other cholesterol medications you have taken in the last 5 years:

_____
_____
_____

Please list any prescription medications and doses you currently take:

_____
_____
_____
_____
_____
_____

Your approximate height and weight: _____

Once you have completed this form, please email or fax to:
Andrew Keel, RN
Email: Andrew.Keel@nih.gov
Fax: (301) 648-5674
We will be in touch with more information once we receive this form. Thank you!