Official Title: Carotid Plaque Composition by Magnetic Resonance Imaging During Lipid Lowering Therapy

NCT00715273

Study Protocol and Statistical Analysis Plan - 06APR2016

This final protocol version reflects the extension of clinical events monitoring and open-label study as supported by American Heart Association and Alpha Phi grants.

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Study Protocol and Procedures
(April 2016)

Study Title: CAROTID PLAQUE COMPOSITION BY MRI DURING LIPID-LOWERING, supported by NHLBI (R01 HL063895)

Short tile: CPC

A. Study Protocol

A.1. Study Objectives/Aims:

(1) To test the primary hypothesis that intensive lipid therapy decreases carotid plaque lipid content assessed by CE-MRI. To achieve this goal, we will (a) perform carotid CE-MRI scans for all 180 study subjects at baseline, 1, 2, and 3 years; (b) perform quantitative assessments of plaque lipid content; (c) compare the plaque lipid content between pre- and post-treatment for all 3 therapy groups; (d) demonstrate the time-course of plaque lipid content change during intensive lipid modification over 3 years by assessing serial carotid CE-MRI examinations.

(2) To test the secondary and exploratory hypotheses that intensive lipid therapy is associated with plaque regression and decreased plaque enhancement assessed by CE-MRI. To achieve this goal, we will (a) perform quantitative assessments of plaque volume and enhancement; (b) compare the plaque volume and enhancement between pre- and post-treatment for all 3 therapy groups; (c) examine the relationship between plaque lipid and volume and enhancement characteristics; (d) demonstrate the time-course of plaque volume and enhancement change during intensive lipid modification over 3 years.

(3) To examine the association of factors including clinical risk factors, lipids, lipoprotein heterogeneity, inflammatory markers, oxidative stress markers and carotid plaque characteristics (lipid, volume, and enhancement). To achieve this goal, we will (a) perform laboratory testing on lipids, lipoprotein heterogeneity, inflammatory markers, oxidative stress markers at baseline and on therapy; (b) describe the change in each of these measurements between baseline and on treatment; (c) determine the statistical significance of each measured risk variable and its change in relation to the change in plaque characteristics.

(4) To investigate the effects of HDL-raising and very intensive LDL-lowering on carotid plaque characteristics over 3 years. To achieve this goal, we will (a) perform quantitative assessment of plaque lipid, volume, and enhancement at all 4 time points blinded to the MRI time sequence and treatment; (b) compare the change in plaque characteristics over 3 years between single and double therapy for HDL-raising effect, between double and triple therapy for more intensive LDL-lowering effect, and single and triple therapy for more LDL-lowering plus HDL-raising effect.

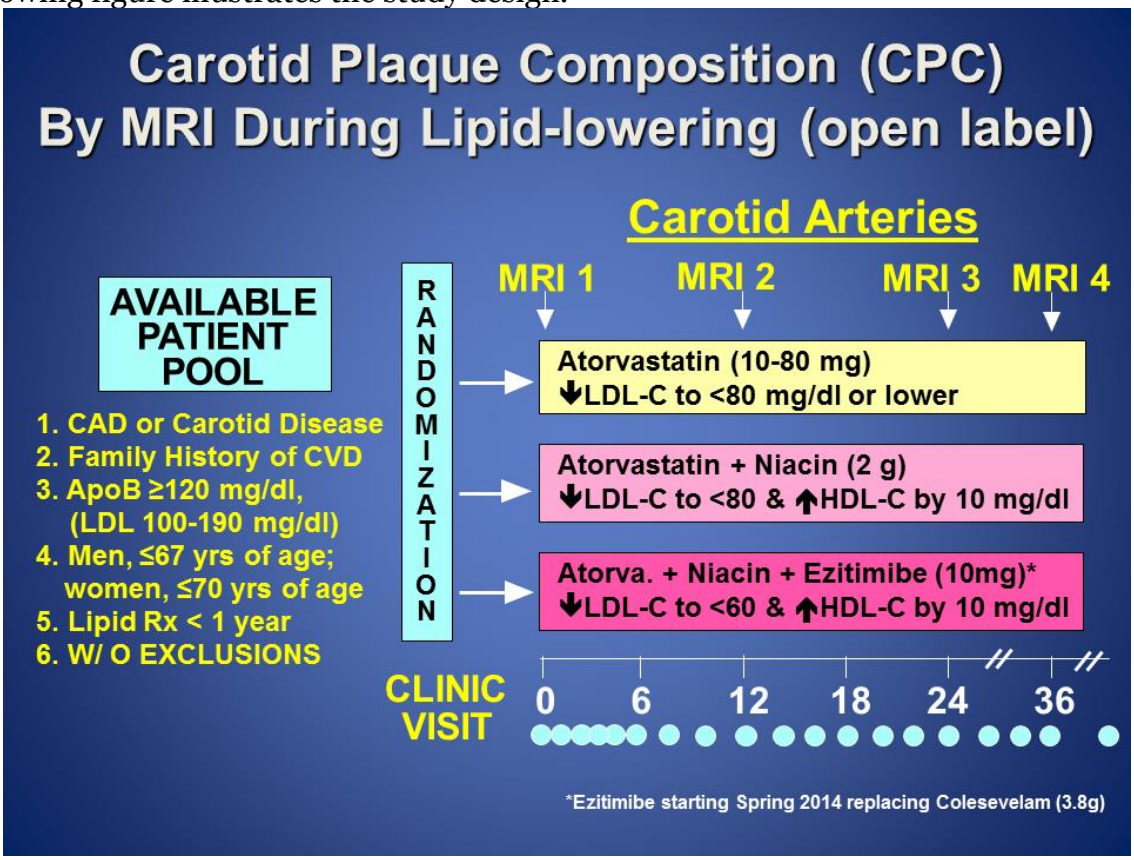
(5) To determine if carotid plaque characteristics predict future major cardiovascular events. To achieve this goal, we will (a) continue to conduct clinical follow-up for a median of 5 years to collect cardiovascular events including fatal/non-fatal MI or stroke, hospitalization/revascularization for worsening ischemia, and mortality; (b) determine whether plaque characteristics (lipid content, volume and enhancement) at baseline and its change during therapy are statistically associated with cardiovascular events.

This study employs the state-of-the-art technique to assess both the magnitude and mechanisms of benefit of lipid therapy. It will be one of the first studies to examine the effects of lipid-lowering therapy on human atherosclerotic plaques in vivo and will provide novel insights into our understanding of atherosclerotic plaque pathology and the mechanisms of lipid-lowering therapy preventing ischemic events.

A.2. Study Design:
This project is a randomized open-label study.

In this research project we will perform carotid MRI studies in 180 CAD patients with a family history of cardiovascular disease and ApoB ≥120 mg/dl (LDL-C levels 100-190 mg/dl). Fifty percent of these subjects will be women. The qualified subjects will be randomized to one of three treatment groups: (1) single therapy - atorvastatin alone; (2) double therapy – atorvastatin plus Niacin (2 g/day); (3) triple therapy – atorvastatin, Niacin plus ezetimibe (10 mg/day). . The treatment target for LDL-C will be ≤80 mg/dl for the single and double therapy groups and ≤60 mg/dl for the triple therapy group. The HDL-C target for two niacin-treated groups will be 10-12 mg/dl increase. All patients will undergo MRI examination of both carotid arteries annually for three years, a total of 4 examinations. If subjects are enrolled in the trial extension a "late time" scan may be performed at a median time of six years.

Following figure illustrates the study design.



*If subjects are enrolled in the trial extension a "late time" scan may be performed at a median time of six years.

In order to determine if carotid plaque characteristics predict future major cardiovascular events, we will ask the study participants who have completed the original 3-year protocol and carotid MRI examinations to continue on their randomized therapy for up to 11 more years. We will (a) continue to conduct clinical follow-up during the extension to collect cardiovascular events including fatal/non-fatal MI or stroke, hospitalization/revascularization for worsening ischemia, and mortality; (b) determine whether plaque characteristics (lipid content, volume and enhancement) at baseline and its change during therapy are statistically associated with cardiovascular events.

Duration: a mean of 5 years and maximum of 11 years

A.3. Primary Efficacy Parameters:

Primary endpoint: The primary endpoint of this study is carotid plaque lipid composition identified by MRI. The determination of plaque lipid content for each carotid artery will be performed using the automated interactive system. These measurements will be performed from the MRI scans at four time points blinded to time sequence of MRI examinations, patient treatment, lipid levels and clinical course.

Secondary endpoints: 1) carotid plaque fibrous tissue and calcium compositions, 2) carotid lumen area and wall area by MRI. Again, the measurements of minimum lumen area, maximum outer vessel wall circumference, and plaque fibrous tissue and calcium contents will be performed from the MRI scans at four time points blinded to time sequence of MRI examinations, patient treatment, lipid levels and clinical course.

Cardiovascular events: Any cardiovascular events such as death from any cause, non-fatal myocardial infarction, stroke, and revascularization procedures (PCI or CABG) due to unstable ischemia will be recorded and verified.

A.4. Planned Sample Size: In order to have **180** patients with coronary artery disease or carotid stenosis $\geq$ 15% by ultrasound to complete the study, up to **240** subjects will be enrolled.

A.5. Operating Sites and Investigators:

(1) UWMC/HMC Cardiology.
(2) Yakima Heart Center.
(3) University of Southern California.

The 2 non-UW sites have their local IRB approvals.

B. Study Procedures

B.1. Subject Recruitment:

Potential subjects with coronary artery disease and/or carotid artery disease will be selected from UWMC Cath lab with Dr. Doug Stewart as the primary subject contact cardiologist. Dr. Xue-Qiao Zhao is the principal investigator and contact cardiologist for HMC and NW hospital recruitment. Dr. Duane Monick will act as the primary subject contact cardiologist from the Yakima Heart Center. Dr. Patrick Colletti will act as the primary contact cardiologist from University of Southern California.

Subjects will be selected based the following inclusion and exclusion criteria. An initial contact letter will be sent out to the potential subjects by the above-mentioned physicians, co-investigators for this study, at each site. In this initial contact letter, the research program is introduced and further study contact information is provided for subjects to consider. Individuals who are interested in the research program will contact the study coordinators or the investigators for more information and possibly for a screening visit.

B.2. Inclusion and Exclusion Criteria:

Inclusion Criteria

1. Men 67 years of age or younger; women 70 years of age or younger.
2. Family history of cardiovascular disease.
3. At least one 50% stenosis or three 30% coronary lesions post MI, PCI or CABG. Or carotid stenosis >15%.
4. A confirmed fasting ApoB ≥ 120 mg/dL.
5. Willing to participate in the study and sign an informed consent form.
6. Medically stable with no contraindications to MRI.
7. Have not been treated with lipid-lowering therapy for more than one year.

Exclusion Criteria

1. Younger than 21 years of age.
2. Have pacemakers or metal implants.
3. Have immediate plans for carotid endarterectomy.
4. History of drug or alcohol abuse in last five years.
5. Active liver disease or hepatic dysfunction as defined by elevations of more than 1.5 times the ULN for AST or ALT.
6. Serum CK ≥ three times ULN
7. GFR ≤ 59 mL/min/1.73 m^2 prior to randomization.
8. Bowel obstruction.
9. Hypertriglyceridemia (serum triglycerides ≥ 500 mg/dL).
10. Peptic ulcer disease.
11. A fasting glucose level ≥ 150 mg/dL or HbA1c ≥ 8%.
12. Uncontrolled hypertension as defined as either a systolic reading of ≥ 200 mmHg and/or a diastolic reading of ≥ 95 mmHg.
13. Women who are or have plans of being pregnant in the future.

B.3. Screening and Eligibility Assessment:

All subjects who are interested in participation will receive a telephone screening using an IRB-approved script to get a general idea of subject's demographics and any major inclusion/exclusion criteria. Potential subjects will be invited to one of the 5 study locations as described above for their screening visit. Subjects will be given a screening consent by the study coordinators; the investigators will follow up with additional questions. If subjects do not have further questions and are willing to be screened for the study, screening procedures will be carried out per protocol. Please note that subjects do not need to stop their statin therapy for study screening. Adjusted ApoB levels will be calculated based on the type and dose of statin that subjects are receiving. Carotid MRI and/or ultrasound exams will be performed using the pre-designed

imaging protocol that will be provided later under MRI scan protocol and ultrasound sub-study protocol.

After receiving all the screening information, subject's eligibility will be assessed by a team of investigators and study coordinators. A checklist on inclusion and exclusion criteria will be completed and signed by one of the investigators including Drs. Zhao, Stewart, Hatsukami, Monick, or Colletti.

All screened subjects will be given the screening results and will be informed regarding their eligibility for the study.

B.4. Subject Enrollment:

The qualified subjects will be invited to take the next step - baseline evaluation and study randomization.

Subjects who are willing to consider participating in the study will be given a main study informed consent by the study coordinators; the investigators will follow up with additional questions. The informed consent process will take as long as needed. The following items will be discussed in detail: study purpose, procedures, what randomization means, medication(s), any possible side effects, anticipated risk and discomfort, subject's right to withdraw from the program at any time, and additional questions.

After obtaining the study consent, vital signs including blood pressure, heart rate, weight, height, and waist circumference will be taken. Blood sample will be collected for laboratory measurements required by the study design. Canadian Angina Function Class will be used to assess subjects' ischemia status. Subjects will be also asked to confirm if they have on-going conditions such heartburn, nausea, intestinal gas, muscle aching, flushing, glucose increase and fatigue. The baseline evaluation will be by a team of investigators including Drs. Zhao, Hatsukami, Monick, or Colletti and coordinators and/or nurses at each site.

B.5. Randomization:

As mentioned in the study design, subject's lipid therapy will be randomly assigned to one of three treatment groups: (1) single therapy - atorvastatin alone,; (2) double therapy – atorvastatin plus Niacin (2 g/day); (3) triple therapy – atorvastatin, Niacin plus ezetimibe (10 mg/day). .

This randomization will also be stratified based on (a) gender, (b) diabetes (yes or no), (c) smoking (yes in past 2 months or no), and (d) triglycerides ≥200 mg/dl (yes or no) to ensure the clinical and lipid characteristics will evenly distributed among the 3 treatment groups.

Randomization will be conducted using a computer program with information entered by the study coordinators.

B.6. Atorvastatin Dosage Determination and Adjustment:

The first dose of Atorvastatin is determined based on the following conditions:

(1) Subjects post Acute Coronary Syndrome (ACS) will continue their high dose atorvastatin, 40-80 mg daily, prescribed by their physicians. If a subject is taking a different statin, such as simvastatin, the subject will discontinue simvastatin and begin atorvastatin, 40-80 mg, if tolerated.
(2) In subjects without ACS, first dose of atorvastatin is determined based on subjects' LDL-C levels at screening visit. The adjusted LDL-C level can be calculated based on the type of statin and dosage that subject is currently taking. If LDL-C ≥110 mg/dl, atorvastatin 40 mg daily will be initiated. If LDL-C < 110 mg/dl, atorvastatin 20 mg daily will be initiated.

The treatment target for LDL-C will be ≤80 mg/dl for the single and double therapy groups and ≤60 mg/dl for the triple therapy group. In order to reach the LDL-C target, atorvastatin titration during the study will be conducted as followings:
(1) Titration up: At 3 month follow-up visit, a blood sample is taken and LDL-C assessed. If subject's LDL-C did not reach the predefined target of ≤ 80 mg/dl for single and double therapy groups or ≤ 60 mg/dl for the triple therapy group, the atrovastatin dose will double. This process will be repeated at 5, 8 and 12 months and every 4 months after through out the study. 80mg atorvastatin is the highest possible dose that will be administered.
(2) Titration down: At 3 month follow-up visit, a blood sample will be taken and LDL-C assessed. If subject's LDL-C < 40 mg/dl and > 25 mg/dl with normal AST/ALT lab values and does not report nausea or fatigue, careful monitoring will be conducted. No change will be made in the atorvastatin dosage. If subject has symptoms of fatigue and/or nausea and/or AST/ALT elevation per safety protocol, atorvastatin will be halved or stopped depending on the decision of the investigator. If subject's LDL-C < 25 mg/dl and no symptoms or liver enzyme elevation, atorvastatin will be halved. If subject has symptoms or AST/ALT elevation per safety protocol, atorvastatin will be stopped. This process will be repeated at 5, 8 and 12 months and every 4 months after throughout the study.

B.7. Niacin Dosing Up Schedule

Based on our 20 years of experience of using niacin in our previous studies, we designed a dosing-up schedule to help subjects to build the niacin tolerance and to better handle the side effects. This will also help to define a tolerable dose for each subject.

Medication initiation: take 500 mg, 1 tablet, with dinner daily.
1-month F/U visit: take 1000 mg, 2 tablets, with breakfast and dinner daily.
2-month F/U visit: take 1500 mg, 3 tablets, 1 at breakfast and 2 with dinner daily.
3-moth F/U visit: take 2000 mg, 4 tablets, 2 with breakfast and 2 with dinner daily.

This dosing-up can last as long as 6 months based on how well the subjects can tolerate each dosage level.

Aspirin (81-325mg) is recommended 30 minutes before taking niacin.

B.8. Study Medication Information and Instruction

In addition to the medication information listed in the study informed consent form, we will also provide subjects a separate document as shown below with the drug

information for the 3 medications used in CPC. **Pertinent Medication Information for the Carotid Plaque Composition by MRI During Lipid-lowering Study**

There are three study medications used in this study.

1. **Lipitor (atorvastatin)**

   A member of the drug class known as statins, used for lowering cholesterol. Lipitor helps decrease the amount of LDL or 'bad' cholesterol in the blood by blocking an enzyme called HMG-CoA reductase, an enzyme that makes cholesterol. Statins reduce total cholesterol, as well as LDL-cholesterol, in the blood, which slows the progression of heart disease. Lipitor is generally well tolerated. In less than 1% of people, it may cause muscle aches or certain abnormalities of muscle-related blood tests. These problems are rare and are reversible by stopping the medication. In the study, blood sugar, liver function and muscle tests are taken often.

2. **Slo-Niacin (slow-release niacin)**

   Slo-niacin is a medication used to raise levels of HDL or 'good' cholesterol and lower triglycerides. The risks from Slo-Niacin include a warm flushing sensation that occurs shortly after taking the medication, which may be difficult to tolerate. Slo-niacin may uncommonly (2-4% of users) cause a skin rash, increased blood sugar or cause mildly abnormal liver tests. Fatigue, nausea, loss of appetite and muscle aches may be drug-associated side effects, although generally rare.

3. **Zetia (ezetimibe)**

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   Ezetimibe works by preventing cholesterol absorption in the intestine. It is generally well tolerated. Side effects may include headache, dizziness, diarrhea, sore throat, runny nose, sneezing and joint pain. Rare side effects include hives, rash, itching or swelling, hoarseness, upset stomach, tiredness, unusual bleeding, pain, flu-like symptoms, muscle pain or weakness or chest pain.

The medication instruction sheet as shown below is also provided to all subjects at the study medication initiation visit.

Directions for CPC Study Medication Schedule

Morning Dosing Directions (AM):

Take One ezetimibe pill and 1-2 pills of Slo-niacin (or half of the daily dose indicated on the bottle) as instructed, with breakfast.

Evening/Night Dosing Directions (PM):

Take 1-2 Atorvastatin pills with dinner, as indicated on the bottle. Take 1-2 pills of Slo-niacin (or half of the daily dose indicated on the bottle) with dinner or before bed.

Valuable Information:

Niacin can sometimes cause a flushing feeling when you first start taking it. If this occurs, there are a few suggestions to help stop or reduce this feeling. The flushing feeling usually goes away over time if you continue to take niacin.

Some helpful ideas for reducing niacin-related flushing:

1. Take your medication in the morning and right before bed.
2. If you use a daily aspirin, take it 30 minutes before your niacin (either morning or evening). Do not take more than 325 mg Aspirin daily without first talking to your doctor.
3. 'Flushing' is reduced by food in your stomach. Enjoy a low-fat snack before you take niacin. An ounce of cheese with a few crackers, a cup of milk or yogurt with fresh fruit are a few examples.
4. Avoid hot drinks, alcohol and spicy foods with dinner as this can sometimes encourage flushing from niacin.

The study medication dispensing process is described under B.11.

B.9. Clinical and Laboratory Follow-up Procedures:
After randomization, the study subjects will be seen monthly for six months and bi-monthly for the remaining 30 months of the 36-month protocol. A total of 22 visits will be conducted for this study as shown in the procedure table below. This clinic visit protocol is developed based on the successful FATS and HATS (RO1 HL49546) clinic visit models. The clinical visits will be done by a team of investigators, coordinators and nurses as well at each of 3 study sites.

Participants who complete the first 3 years of the study and are willing to continue on the randomized therapy and will be followed every 4 months for up to 11 more years.
Table. Clinical Follow-up Protocol

Visit	Entry Criteria	Con-sent	Med. Hx	Family Hx	Vital Signs	Diet Coun-seling	AE/ Side Effects	Drug Disp.	Com-pliance	Safety Moni-toring	Meds Adj.
Screening	X	X			X						
Baseline		X	X	X	X	X		X			
Non-blood draw visits*					X	X	X	X	X	X	X
Blood draw visits**					X	X	X		X	X	

*: C1, 2, 4, 6, 10, 14, then every 4 months up to C130. **: C3, 5, 8, 12, then every 4 months up to C132.

At these visits, subjects will undergo questioning about side effects and symptomatic state, and vital signs will be taken. At approximately 60% of the visits, blood will be drawn (<50 ml). The Table below provides the laboratory parameters collected/measured in this study.

Table. Laboratory Measurement Schedule for the Carotid Plaque Composition Study

Visit	SCR.	C0	C3/5/8	C12	C16/20	C24	C28/32	C36	Non-annual Visits C40/44/52/56/64/68/76/80/88/92/100/104/112/116/124/128	Annual Visits C48/60/72/84/96/108/120/132	TX
TC/TG/LDL/ HDL/VLDL	X	X	X	X	X	X	X	X	X	X	X
HDL2&3/IDL/ LDLT/HDLT		X		X		X		X		X	
ApoB, A1, A2, ApoE, Lp(a)	X	X		X		X		X		X	
AST/ALT, CPK		X	X	X	X	X	X	X	X	X	X
BILI/ ALK PHOS/T4/TSH		X									
Creatinine/ Uric Acid		X		X		X		X		X	

Fasting glucose/ HgA1C**	X	X	X	X	X	X	X	X	X	X	X
Insulin/ Fibrino./ HsCRP		X		X		X		X		X	
Plasma storage		X		X				X		X	

*: SCR=screening; C0 = baseline; C3, 10, 24, 36,..... = 3, 10, 24, 36,..... months in the study. TX = test for possible side effects of the study treatment. **: This schedule is for diabetic subjects. For non-diabetic patients fasting glucose is measured at S, C0, C12, C24, C36, C48, C60, and every 12 months up to C132.

Dietary counseling will be targeted at weight reduction with goals based on the level of obesity, with additional emphasis on the use of mono-unsaturated fats in a fat-limited (25-30%) diet. Dietary counseling will be provided to subjects by a certified research dietitian.

One week in advance of the next scheduled visits, subjects will receive a form letter from the study coordinators reminding them of the date and time, whether to fast, and to return unused drug supplies. One or two days before the visit they will again be reminded by telephone call from research assistance or the study coordinators, and the visit confirmed or changed. All scheduling is initiated by a computer program with capability to shift dates, making the associated adjustments in compliance calculations and drug distribution. Each clinical visit will take about 30 minutes.

B.10. Study Medication Dispensing

All three medications are FDA approved drugs. Pfizer, Upsher-Smith, and Merck, Sharp and Dohme Corp are the three companies providing the medications (atorvastatin, Niacin, and ezetimibe). A drug supply record on each medication keeps tracking the quantity requested and received. All medication is stored at Harborview Investigational Drug Services (HMCIDS), as well as all documentation of drug dispensing.

With instruction from the UWMC Investigational Drug Services and Harborview Investigational drug Services, a study medication dispensing procedure has been developed as following.

(1) A medication card as shown below with the study name, drug information, and emergency contact information will be provided to each enrolled subject at the study medication initiation visit and repeat on their annual visits.

Study Name: Carotid Plaque Composition
Study Investigator: Xue-Qiao Zhao, MD (206-744-8305)
Study Coordinator: 1-866-866-0175
1. Lipitor (atorvastatin): 10-80mg/day

2. Slo-niacin (niacin): 1.5-2g/day
3. Zetia (erxetimibe) 10 mg/day

(2) The medication bottles/kits will be labeled with (a) study name, (b) subject name, (c) subject Harborview ID number, (d) medication name, (e) dispensing date, (f) expiration date, (g) total quantity, (h) instruction, and (i) a federal statement limiting use to the given study.

(3) For each enrolled subject at each scheduled study visit, a study medication prescription which is signed by the study doctor will be generated from our computer system based on the randomization, atorvastatin dosage determination and niacin dosing-up schedule, and duration between visits.

(4) Prescription requests are delivered to HMCIDS prior to the study visit and are then dispensed by HMCIDS.

(5) Each medication dispensing record will be saved in the subject medication folder.

(6) Medications will be dispensed to subjects in person at the end of each scheduled visit. All medication information and instruction will be reviewed with the subject at time of dispensing by an investigator.

(7) Subjects will receive two pill organizers, one for ezetimibe and niacin taken in the morning and one for atorvastatin and niacin at bed time, to help them to remember to take the study medications. We will also recommend placing the morning pill organizer in the kitchen and the night pill organizer maybe in the bathroom, this will help subjects to link the medication taking with their routine activities for optimal compliance.

(8) Subjects will be required to bring back all unused medications for compliance calculation. Unused medication will be returned to HMCIDS for destruction

C. Safety Monitoring and Procedures

C.1. Subject Safety and Monitoring Plan:

Objectives:

(1) Monitor study progress and subject safety
(2) Assure adverse event recording and reporting
(3) Assure investigator communication with IRB and NHLBI
(4) Assure protocol compliance
(5) Assure data accuracy
(6) Verification of initial study design and further modifications

Level of risk assessment: low level of risk

(1) It is therapeutic study using all FDA approved drugs (Atorvastatin, Niacin, Ezetimibe).
(2) Not an IND study
(3) The study doesn't include vulnerable populations.
(4) Study subjects are not at high risk, they are either with stable CAD or with sub-clinical atherosclerosis.

(5) Primary endpoint of the study is carotid plaque lipid composition as assessed by MRI.

Safety monitoring will be provided by: study team

(1) Investigators and study coordinators
(2) Real time monitoring plan on management of risk to subjects
(3) Annual review and report to IRB due to the lower level of risk

C.2. Safety Parameters:

(1) Vital signs
(2) Liver function: ALT/AST
(3) Muscle enzyme: CPK
(4) Fasting glucose levels

C.3. Safety Monitoring Procedures:

Clinical monitoring:

As discussed previously, at each of the clinical follow-up visits, subjects will undergo questioning about side effects and symptomatic state and vital signs will be taken. If any expected conditions or symptoms possibly related to the medications are reported as severe at C1 visit or persistently being moderate at ≥ 3 visits, the study safety monitor, Dr. Xue-Qiao Zhao, will be informed. Then, Dr. Zhao will provide specific instructions on study medication change based on both his professional opinion and predefined monitoring protocol. For example, flushing and itching are most common side effects from niacin. In addition to a recommendation of taking aspirin 30 minutes prior taking niacin, taking niacin after dinner will further reduce these side effects, etc.

Laboratory monitoring:

There are three safety aspects we stress in this study: ALT/AST for liver function; CPK for muscle side effect; and glucose levels for diabetes control. If any of these is outside of the normal range, appropriate procedures will be taken:

(1) Compare current results to baseline or previous values. This helps the investigators determine whether or not study medications could be the possible cause of the abnormal lab value.

(2) Be thorough in evaluation of patient's side effects and confirm no other changes in life style or other medications could be the cause of such lab value change.

(3) Determine if the result is only slightly elevated (less than 1.5 x Upper Limit of Normal (ULN) or glucose <160 mg/dl), monitor patient closely and repeat the test at the next visit usually within 2-4 months per protocol.

(4) If the result is 1.5-2.5 x ULN ALT/AST or CPK (or glucose ≥ 160 mg/dl), a repeat blood draw will be ordered within 1 month and subject will be closely monitored by telephone follow-up. Subject's primary care physician will be notified and patient will continue the study medications.

(5) If the result is ≥ 3 x ULN ALT/AST or CPK, a repeat blood draw will be ordered within 2 weeks and subject's primary care physician will be notified, the study medications will be reduced or stopped, patient will be monitored closely by telephone follow-up and repeat lab test(s) will be ordered until the values normalize. If glucose >200 mg/dl, home glucose monitoring will be ordered and niacin will be reduced to half dose. If >240 mg/dl, home glucose monitoring will be ordered and niacin will be stopped until glucose levels return to <160 mg/dl.

Steps 3-5 are also outlined in the Table below for Lab Safety Monitoring.

Lab Safety Monitoring Protocol in CPC

	Sample at 3 months		**Sample at 5 months**		**Sample at 8 months and all blood draw visits thereafter**	
	Condition	**Strategy**	**Condition**	**Strategy**	**Condition**	**Strategy**
AST ALT CPK Safety:	If <1.5X ULN	Careful Monitoring & repeat test @ C5	If <1.5X ULN	Careful Monitoring & repeat test @ C8	If <1.5X ULN	Careful Monitoring & repeat test @ C12
	If 1.5-2.5X ULN	Monitoring. Letter to PCP & repeat test within 1 M	If 1.5-2.5X ULN	Monitoring. Letter to PCP & repeat test within 1 M	If 1.5-2.5X ULN	Monitoring. Letter to PCP & repeat test within 1 M
	If >3.0X ULN	Monitoring. Letter to PCP & repeat test within 2 Wk. Lower or stop meds	If >3.0X ULN	Monitoring. Letter to PCP & repeat test within 2 Wk. Lower or stop meds	If >3.0X ULN	Monitoring. Letter to PCP & repeat test within 2 Wk. Lower or stop meds
Glucose Safety:	If 126-159 mg/dl	Careful monitoring	If 126-159 mg/dl	Careful monitoring	If 126-159 mg/dl	Careful monitoring
	If ≥160 mg/dl	Letter to PCP & repeat test within 1 M	If ≥160 mg/dl	Letter to PCP & repeat test within 1 M	If ≥160 mg/dl	Letter to PCP & repeat test within 1 M
	If >200 mg/dl	Repeat test within 2 Wk. Half niacin dose	If >200 mg/dl	Repeat test within 2 Wk. Half niacin dose	If >200 mg/dl	Repeat test within 2 Wk. Half niacin dose
	If >240 mg/dl	Glucose monitoring & stop niacin	If >240 mg/dl	Glucose monitoring & stop niacin	If >240 mg/dl	Glucose monitoring & stop niacin

ULN=Upper Limit of Normal

In addition, the following Table **(Dosage Adjustment Protocol for CPC)** provides basic guidance for dosage adjustment related to both reaching LDL-C and HDL-C targets and dealing with potential drug side effects.

Dosage Adjustment Protocol for CPC (Updated 01Aug2010)

	Sample at 3 months		**Sample at 5 months**		**Sample at 8 months**		**Sample at 12 months and all visits thereafter**	
	Target	**Strategy**	**Target**	**Strategy**	**Target**	**Strategy**	**Target**	**Strategy**
Single				If >80,		If >80,		If >80,

Rx Group:	LDL-C≤ 80 mg/dl	--	LDL-C ≤80 mg/dl	double statin dose, or (max dose 80mg)	LDL-C ≤80 mg/dl	double statin dose, or (max dose of 80mg)	LDL-C≤ 80 mg/dl	double statin dose, or (max dose 80mg)
Double Rx Group:	LDL-C ≤ 80 mg/dl	--	HDL-C+5 from base.	Improve compliance	HDL-C+8 from base.	Improve compliance	HDL-C+10 from base.	Improve compliance
	--	--	LDL-C≤80 mg/dl	If >80 mg/dl, double statin dose, or (max. dose 80 mg)	LDL-C≤80 mg/dl	If >80 mg/dl, double statin dose, or (max. dose 80 mg)	LDL-C≤80 mg/dl	If >80 mg/dl, double statin dose, or (max. dose 80 mg)
Triple Rx Group:	--	--	HDL-C+5 from base.	Improve compliance	HDL-C+8 from base.	Improve compliance	HDL-C+10 from base.	Improve compliance
	LDL-C≤ 60 mg/dl	--	LDL-C≤ 60 mg/dl	If >60, double statin dose, or (max. dose 80)	LDL-C≤ 60 mg/dl	If >60, double statin dose, or (max. dose 80)	LDL-C≤ 60 mg/dl	If >60, double statin dose, or (max. dose 80)
LDL Safety:	If SX/LCF or LDLC< 25	Half statin dose or stop meds	If SX/LCF or LDLC< 25	Half statin dose or stop meds	If SX/LCF or LDLC< 25	Half statin dose or stop meds	If SX/LCF or LDLC< 25	Half statin dose or stop meds
	If ASX and LDLC< 40	Careful monitoring	If ASX and LDLC< 40	Careful monitoring	If ASX and LDLC< 40	Careful monitoring	If ASX and LDLC< 40	Careful monitoring
	If SX LDLC< 40	Half statin dose or stop meds	If SX LDLC< 40	Half statin dose or stop meds	If SX LDLC< 40	Half statin dose or stop meds	If SX LDLC< 40	Half statin dose or stop meds

SX=symptomatic, ASX=asymptomatic,
LCF=low cholesterol flu-like symptoms including muscle aching, nausea and fatigue.

Please note that renal function monitoring is described under Carotid Imaging Protocols below.

D. Carotid Imaging Protocols

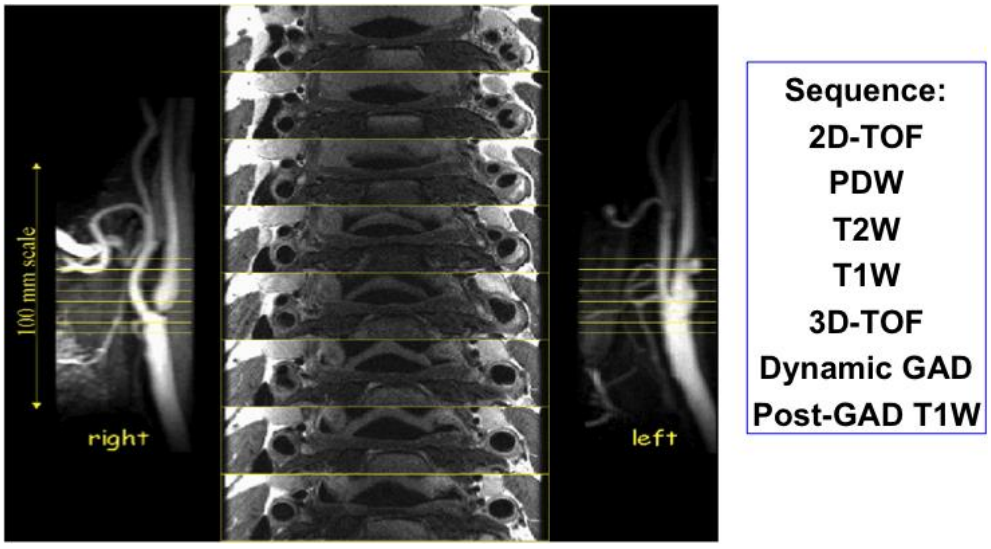
D.1. MRI Scan Protocol:

Prior to the carotid MRI scans, subjects will be required to fill-out the *Magnetic Resonance (MR) Procedure Screening Form provided by the MRI center (Attachment 1)*. This form will be reviewed by both the study coordinator and by the MRI center staff

to ensure subject's eligibility for MRI scans. For subjects with coronary stents, we will check MRI safety compatibility of a particular stent or surgical implant by visit www.mrisafety.com or contacting the manufacturer directly.

Subjects from the UW and Yakima sites will receive their carotid MRI scans at the Bio-Molecular Imaging Center (BMIC) (Chun Yuan, Director) for high-resolution animal and human imaging. A 3T Philips Achieva Quasar Dual 3.0T (Software Release 1.2.2) whole body scanner is available for use at this center as a full time research scanner. This scanner also includes the Philips ViewForum Workstaton (Software Release 4.1). Subjects enrolled at the USC site will receive their MRI scans at the USC Imaging Center of Department of Radiology using a standard scan protocol designed by the Vascular Imaging Lab at the University of Washington.

Subjects will be placed in the supine position in the MR scanner with the neck extended to bring the carotid arteries into a more superficial location relative to the skin. A custom designed head holder will be used to minimize patient movement. Two separate phased-array carotid coils will be used for simultaneous bilateral carotid imaging. A standard 3-plane localizer will be used to identify the carotid arteries. Then, 6 more sequences will be applied to generate carotid images. Ten cc of gadolinium contrast material will be administrated intravenously though a power injector. Images of 4 locations, centered either on the carotid bifurcation or on the plaque, will be simultaneously acquired using axial 2D spoiled gradient-recalled echo imaging without cardiac gating. These images will be obtained at 10 time points separated by a repetition interval of 15 seconds. Post-contrast T1-weighted images will be acquired 5-7 minutes after gadolinium contrast administration. The total scan time for each patient will be about 50 minutes. Following figure is an example of carotid arteries oblique and cross-sectional views by MRI.



D.2. Renal Function Monitoring:

A gadolinium agent used in this study is FDA-approved. However, in a very small percentage of patients with impaired kidney function, gadolinium has been suspected to cause a side effect called nephrogenic systemic fibrosis, or nephrogenic fibrosing

dermopathy (NSF/NFD). To monitor the renal function, calculated creatinine clearance will be drawn and glomerular filtration rate (GFR) will be measured within 4 weeks of use of gadolinium agent during the carotid MRI scans. If GFR< 30ml/min/1.73m^2 is found at any measurement, or a ≥ 50% drop in GFR from the previous testing point, the subject will be excluded from the study and renal function measurement will be repeated and recorded. If necessary, the subject will be referred to nephrology for further evaluation and treatment.

D.3. MRI Analysis Protocol

1. Image Blinding and Matching Process

The MR image analysis will be carried out at the Vascular Image Lab, directed by Drs. Yuan and Hatsukami, in Department of Radiology at the University of Washington. The original MRI examination identification (ID) number, image date/time, and series information will be replaced with a new and randomly generated MRI analysis ID number. A master log file containing both original and new image information, and study subject ID, will be generated at the time of renaming. This blinding process will ensure that MRI reviewers are fully blinded to patient information and time sequence during the image analysis. It will also protect patient confidentiality in accordance to HIPAA guidelines.

Prior to image review, all across-sectional images from TOF, T1, PD, T2, and post-CE T1 weightings will be co-registered using the carotid bifurcation as a physical landmark.

2. Visual Assessment of Atherosclerotic Lesion Type

A previously published MRI-based AHA lesion classification scheme will be used for this evaluation: type I-II = near-normal wall thickness; type III = diffuse wall thickening or small eccentric plaque; type IV-V = plaque with a necrotic core; type VI = complex plaque with a possible surface defect, hemorrhage, or thrombus; type VII = calcified plaque; and type VIII = fibrotic plaque without a necrotic core.

3. Quantitative Measurements of Plaque Volume and Tissue Composition

(a) Plaque Volume Measurement: Contours will be placed around the lumen and outer-wall boundaries of carotid artery. These contours may be created manually or automatically. The arterial wall area = outer-wall area – lumen area. The wall volume will be calculated as: wall area x 2 mm (slice thickness). Wall/outer wall ratio will be used as a normalized wall index that is adjusted for differences in carotid artery size in the common carotid, bifurcation, and internal carotid arteries.

(b) Plaque Tissue Content Measurement Using Automated Plaque Tissue Segmentation: As introduced in the preliminary studies, the Vascular Imaging Laboratory at the University of Washington has developed an semi-automated system (MEPPS) and has shown that MEPPS is capable of achieving accuracy similar to results achieved by manual review by expert reviewers for quantifying plaque composition. The automated segmentation is based on the fact that various tissue contents such as lipid, calcium, loose matrix and fibrous tissue have different signal characteristics from each weighting as shown in the Table below. The system first determines the probability that each MRI pixel belongs to each of the 4 tissue types (lipid, calcification, loose matrix, and fibrous tissue). Then, it uses the competing active contours to identify the boundaries of high-probability regions for each tissue type.

Table. Tissue Classification Criteria

	TOF	T1W	PDW	T2W	>80% SI↑Post contrast T1W
LRNC with (A) No or little Hemorrhage	o	o/+	-/o	-/o	-
(B) Fresh Hemorrhage	+	+	-/o	-/o	-
(C) Recent Hemorrhage	+	+	+	+	+
Calcification	-	-	-	-	-
Loose Matrix	o	-/ o	+	+	+
Dense (Fibrous) Tissue	-	o	o	o	+

The classification into the subgroups is based on the following signal intensities (SI) relative to adjacent muscle. LRNC = Lipid-Rich/Necrotic Core. + = hyper-intense, o = iso-intense, - = hypo-intense.

The steps for measuring plaque volume and automated segmentation include the following:

Step 1. Image matching: After loading the 5 MRI sequences (pre-contrast T1, post-contrast T1, T2, PD, TOF) onto the CASCADE computer interface, the images will be manually matched to each other by using the carotid bifurcation as a landmark. An example is shown in Figure 1 below.

Step 2. Lumen and wall boundary detection: Using information available from the multi-contrast weighted images, the lumen and wall boundary of the carotid artery will be identified and outlined by expert reviewers. An example is shown in Figure 2 with lumen boundary in red and outer wall boundary in blue.

Step 3. Registration: After manual boundary detection, the CASCADE Program will automatically identify and outline the lumen and wall boundary of the carotid artery in the remaining 4 sequences. An example is shown in Figure 3 below. Expert readers will review the outlines generated by CASCADE, and have the opportunity to manually override errors in the automated outlines that may occur as a result of marginal image quality or flow artifact.

Step 4. Auto-segmentation: The CASCADE Program will automatically identify and quantify the tissue component within the arterial wall. Expert readers will then review the output of CASCADE to insure correct classification of the plaque components. An example is shown in Figure 4 below with loose matrix in purple and lipid content in yellow.

The image analysis for this study will be performed at the time of completing both MRI examinations. By doing so, a region of each carotid artery, covered by both baseline and 2-year scans, will be identified and image analysis will be performed within the region. This will allow the same reviewers to analyze all images and therefore to reduce the inter-reader variability. The analysis will be performed at Vascular Imaging Lab using CASCADE with automated tissue segmentation capability using MEPPS.

(c) Plaque Tissue Composition: This will be calculated based on each identified tissue volume and wall volume at each given location: tissue volume/wall volume x (100%), and presented as percentage.

(d) Summary of Plaque Variables: CASCADE can produce a list of comprehensive plaque assessments. Plaque burden measurements will include the carotid lumen, wall, and outer-wall area in mm^2, wall thickness in mm, and wall/outer-wall ratio (a normalized wall index that is adjusted for carotid artery size difference) that is equivalent to the % of atheroma area used in the coronary intravascular studies. The plaque tissue characteristics will be presented as absolute measurement in mm^2 and as a proportion of the corresponding vessel wall area, expressed as in % lipid, % loose matrix, % calcium, % fibrous tissue and % hemorrhage. Additionally, the plaque integrity will also be evaluated and described as ruptured, thin or thick fibrous cap, with and without ulceration, with and without thrombus.

Figure 1.

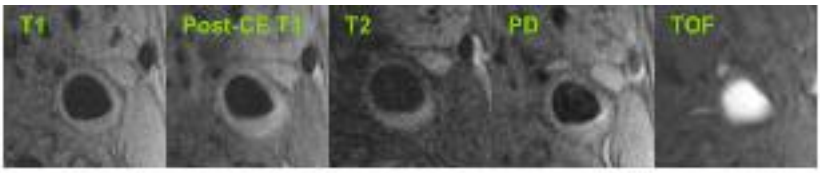


Figure 2.

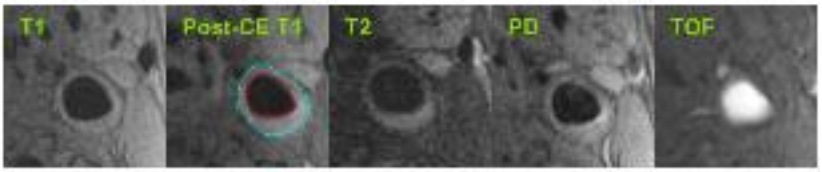


Figure 3.

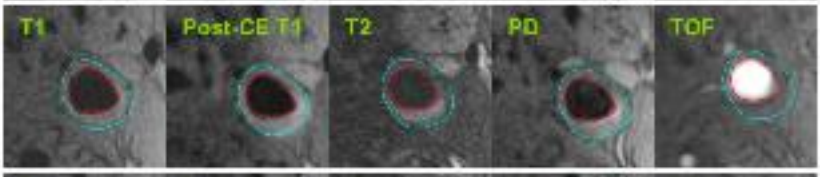
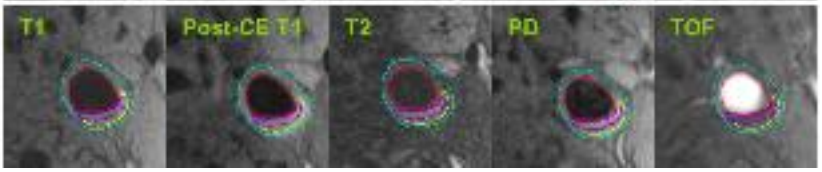


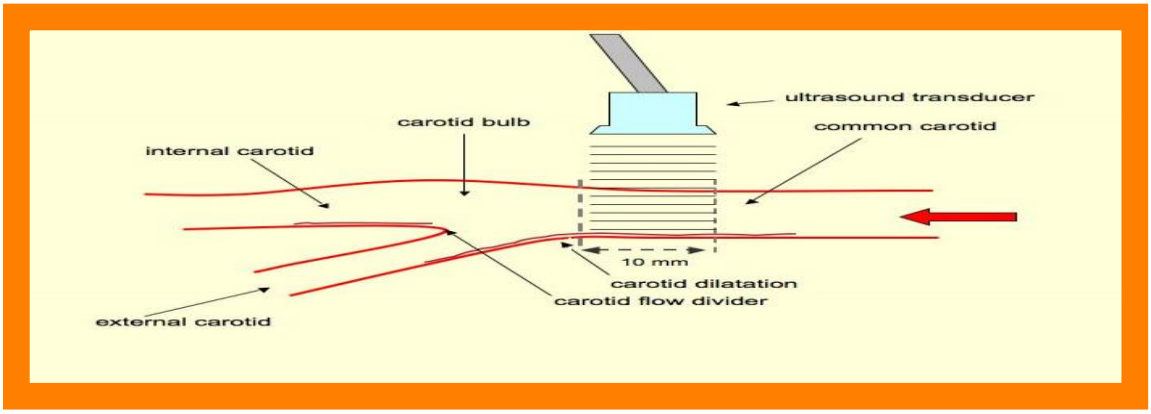
Figure 4.



Ultrasound Examination:
A carotid ultrasound sub-study for assessment of carotid intima media thickness (CIMT) has been added to this study protocol as a sub-study. If the patient agrees after reviewing the informed consent, the carotid ultrasound exams will take place on the same date as the carotid MR scans: baseline, C12, C24 and C36 post randomization.

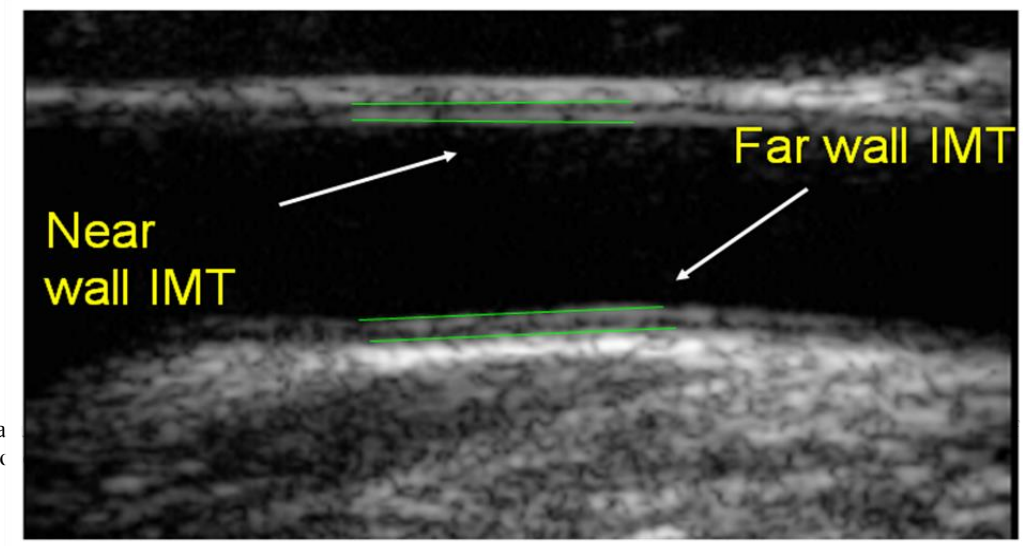
All ultrasound scans will be done using the SonoSite Micromaxx System (Bothell, WA) and equipped with a 10.0 Mhz transducer. This system was used in the ARBITER-2/3 and 6 studies. B-mode scans of the right and left common carotid arteries, carotid bulbs and internal carotid arteries will be performed as illustrated in the follow-up figure. Any plaque or wall thickness > 1.5 mm will be identified using both oblique and cross-sectional views and recorded using a carotid artery map for location. Then, common

carotid arteries and carotid bulbs will be focused on IMT scans using both anterior and lateral angles to cover about 60% of the carotid wall. A digital cine-loop of each vessel will be recorded digitally. The images will be transferred and stored onto CDs at the



Coronary Atherosclerosis Research Lab.

CIMT measurements will occur on desktop computers (Dell 2.4 GHz, Pentium 4, 1 GB RAM) using an automated IMT detection program by SonoSite. The CIMT of the 10mm adjacent segment distal to the carotid bulb of the far wall of the common carotid artery at both anterior and lateral angles of both the right and left side will be measured from 4-6 reprehensive images with automated IMT detection and the mean CIMT will be reported. A carotid IMT example is shown below. Both the sonographer and person performing the IMT measurement will be blinded to the treatment group. Inter-observer and intra-observer variability will be determined on a subset of cases and reported for the automated CIMT analysis.



Cardiology fellows, for example, Dr. Binh An Phan, performed the carotid ultrasound exams and IMT measurements as their research projects.

E. Study Documentations

E.1. Regulatory Documents

(1) Grant Application and Sponsor Communications – including the original grant, award notifications, study communications with NHLBI and industry supporters, and study progress reports.

(2) IRB Binder – including the IRB applications and modifications, both submitted materials and approved documents. Each of the study sites has a site-specific IRB binder.

(3) Approved Consent Binder – starting with a consent/HIPAA log showing all approved consent forms for this study and HIPAA Authorization as well as hard copies of consent forms and HIPAA forms.

(4) Investigators Binder – including a study responsibility and delegation log, CVs for each investigator and copies of their licenses. Human subject protection training certificates are also included in this binder.

(5) Protocol Binder – including protocols for the main study, sub-studies and extensions and procedure manual as well.

(6) Laboratory Binder – including lab certifications, laboratory reference ranges and blood sample handling forms.

Please note that this study does not require FDA 1572 since there is no IND.

E.2. Subject Files

Each enrolled subject will have documentation folder. The left hand side of the folder contains:
(a) Singed consent forms and HIPAA Authorization forms, and a consent process document that describes how the consent been conducted has been added since December 2010;
(b) Screening material including medical records for vascular disease or carotid image evaluations;
(c) Screening and baseline lab results;
(d) Eligibility assessment checklist;
(e) Medical history and concurrent medication list;
(f) Family history;

(g) Subject contact information including primary care physician or vascular care specialty contacts if available;
(h) Clinical and imaging schedules;
(i) Procedure checklist;
(j) Progress notes for non-scheduled visits, telephone calls, and other subject-related communications.

The right hand side includes all scheduled clinical follow-up notes, data collection and AE reports. The CRF pages and AE record sheet used in this study are included as Attachment 2.

E.3. Lab Results

Each enrolled subject will have a lab results folder. As described earlier, designated study coordinators will review all lab results upon receiving the report in hard copies or phone report for any urgent critical results. If an abnormal result been identified, study safety monitor (Dr. Xue-Qiao Zhao) will be notified. Actions will be taken per the safety monitoring protocol.

E.4. Study Medication Records

Each enrolled subject will have study medication folder containing study medications dispensing information at each visit. HMCIDS also keeps study drug receipt, dispensing, and destruction logs in its pharmacy starting July 2012.

F. Data Collection and Statistical Analysis

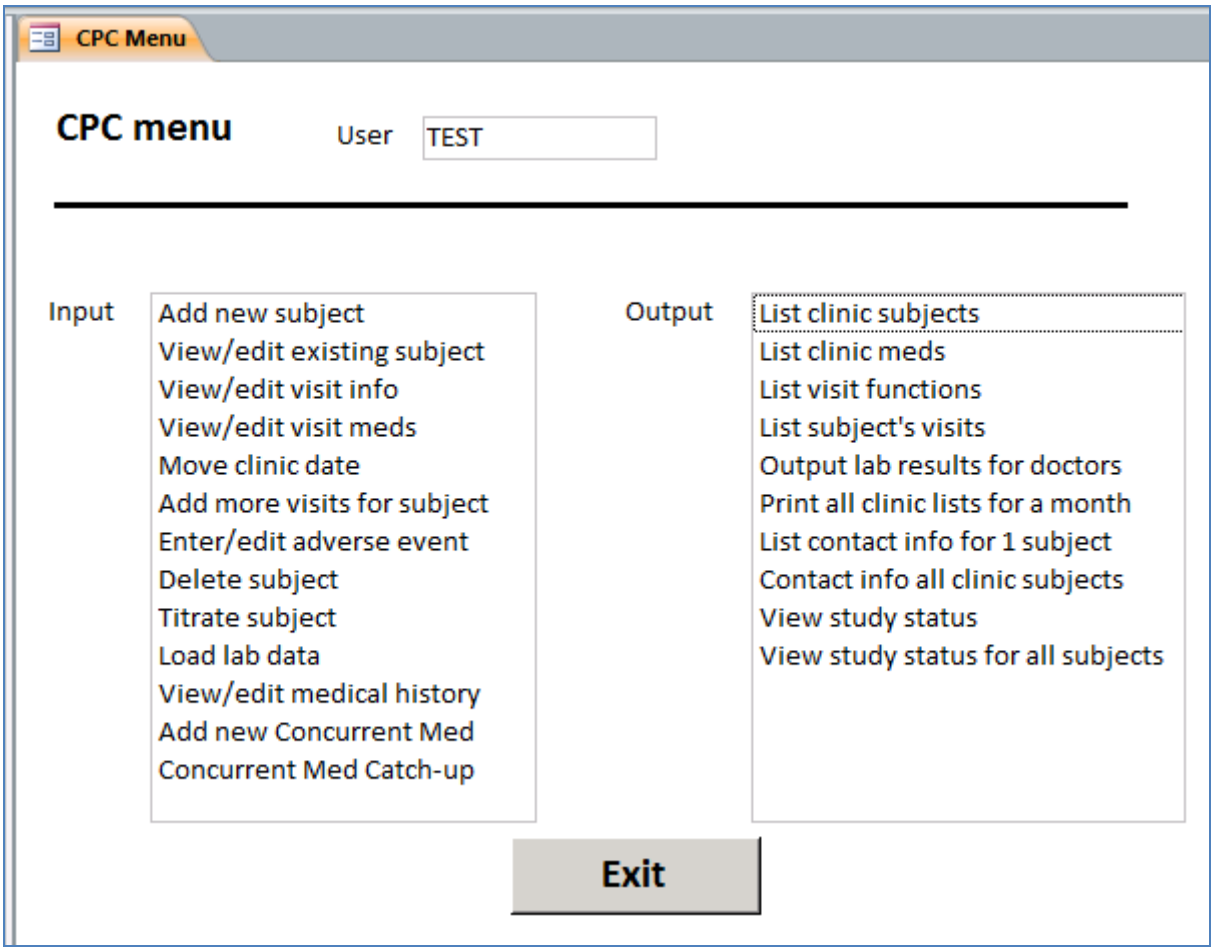
F.1. Data Collection:

Data is collected from subjects on their health history and familial health history. Data will be collected throughout the study from subjects regarding their health status and concomitant medications usage. Lab values resulting from analysis of blood samples will be collected at about one-half of study visits. All lab samples are identified by a study number only. Subjects will have four MR scans recorded on CDs during the study. Individually identifiable data is recorded in individual study charts for each subjects, and in a password-protected study database. Individually identifiable data will be accessible only to the study investigators.

F.2. Database Management:

A multi-dimensional ACCESS database will be designed by a database manager based on the specific study design, protocols and procedures. It will be co-managed by the database manager and a study coordinator. The following is an overview of the database with all necessary functions for the data input and output required by the study design. Attachment 3 is a multi-relational data table in CPC Study Database.

Available CPC Database modules for Data Entry and Study Management



Data entry will be completed by study coordinators after each scheduled or non-scheduled visit, for each adverse event, and for all lab results. Study coordinators will initial and date at each of the data entry. The accuracy of data entry will be checked periodically by database manager or by other study coordinators.

F.3. Statistical Analysis:

1. Descriptive Statistics: Prior to more formal analysis we will explore the data to detect outliers or other distribution problems and display the data in graphical and tabular format using histograms, boxplots, scatterplots, frequency listings for dichotomous and categorical variables and descriptive statistics for all patients and subcategories of patients. We will also calculate the various outcome measures, such as percent lipid in the carotid arterial wall, as a mean per MRI slice, in order to control for the varying number of MRI slices per subject. Throughout the analyses we will take account of potential differences in MRI measurements due to the effect of scan platform or study site. The site effect is a difference among measurements that cannot be explained away by subject characteristics, such as age and gender or study site. We can formally test for a site effect, describe its magnitude and adjust for it using random effects models. Similarly, the platform (fixed) effect can be addressed by using a dummy variable for the platform. The site and platform effects are confounded (because groups of sites use one of the two platforms). Even so, the site effect can be addressed by a model that nests the sites within platform.

2. Difference between baseline and 3 years: Differences of primary and secondary endpoints between baseline and 3 years after intensive lipid-lowering therapy will be compared using paired 2-tailed t tests to determine the significance. A multivariate analysis will be performed based on a logistic regression model with plaque lipid composition as the dependent variable to detect the independent patient or therapy variables that are predictive of plaque lipid composition change over a 3-year interval.

3. Treatment effect with different lipid therapies: This set of analyses addresses the primary and secondary endpoints of determining the treatment effect on lipid composition, plaque wall volume and wall thickness. The simplest form of this analysis will be a t-test or nonparametric Mann-Whitney test comparing the two treatment groups on the change in an outcome variable between baseline and the 3-year MRI assessment. In order to control for important covariates, we will carry out multivariate linear regression, with the 3-year change in the outcome, such as percent of wall volume that is lipid-rich necrotic core, being the dependent variable and independent variables of treatment group (dichotomous). We will also evaluate baseline value of the outcome variable, and any other variables that need to be controlled, such as age and gender. We can also test for an interaction between variables in affecting the outcome by using an interaction term in the model. We will not automatically test all possible interactions. If main effects are included in a final regression model, it would be natural to test to see if there is an interaction between some of the main effects. Choice of which interactions to try will be driven by biological plausibility. For example, if treatment and baseline lipid composition are important and statistically significant main effects in a model, it would be natural to test to see if their interaction is also important. In general, quite large sample sizes are needed to detect interactions, unless they are very strong. However, the sign and magnitude and even marginal statistical significance of an interaction are informative, even if the interaction term is not ultimately included in the model. This comment on use of statistical interaction terms applies to the regression analyses for all of our aims. We routinely carry out statistical diagnostics on these analyses, such as examining residuals.

4. Risk of cardiovascular events: This set of analyses will focus on the risk of CV events in relation to plaque characteristics and the changes over time in the plaque. We will use methods of survival analysis (failure-time analysis) for this part of the study. We will use Kaplan-Meier plots, the log rank test and the Cox proportional hazards model for these analyses. The outcome variable is time to a first CV event during the study period, and those who do not have an event by the end of follow-up surveillance will be considered as censored. The two branches of this endeavor are (i) the relation of plaque volume and characteristics at one cross-sectional moment in time (such as baseline) to the risk of a subsequent event; and, (ii) the relationship between plaque "velocity"—the rate of change of plaque characteristics over time—to subsequent risk of an event. The velocity and cross-sectional status of plaque are two quite different biological concepts, and it may happen that one or the other alone, and not both, are important. For the first analysis, (i), each patient will have up to two time intervals: baseline to an event or to the 3-year MRI assessment, and then from the 3-year MRI assessment forward to the end of follow-up. By using two intervals per person, one initiated at baseline and the other initiated at 3 years, we will always be using the most recent MRI data on plaque status to compare to subsequent follow-up. This analysis is

carried out by using time-varying covariates. For the analysis of CV risk in relation to plaque "velocity", (ii), the methodology is the same, except that each person will have only one interval, from the 3-year MRI scan onward. Independent variables will be the rate of change of plaque characteristics during the first 3 years (e.g., annual % change in lipid composition), as well as the value of plaque variables at the 3-year point, a new "baseline". For both the baseline and velocity part of these analyses we will attempt to build a multivariate model(s) that will allow us to characterize the CV risk for a given patient. These models will use not only the MRI variables but currently identified risk factors as well, such as age and gender. Our modeling will also address an important issue: Do the plaque variables, even if statistically significant, really add to the prediction of cardiovascular risk? In other words, are the plaque variables really adding something independent of what is already known about risk? We can address this issue by comparing a Cox proportional hazards model with traditional risk factors only, such as age, gender, and smoking status, to a model that includes these traditional factors and also includes any important plaque variables that have detected. We can use either the change in a pseudo-R^2 statistic (based on likelihood) or use logistic regression and note the increase in the area under the ROC curve when the plaque variables are added into the model with the traditional risk factors. This comment applies to any analyses where there are traditional (known) risk factors available. While statistical significance of a plaque variable may help us to understand the biology better, it is also helpful to know if the use of plaque variables notably increases the prediction of CV events for individuals.

5. Correlation among baseline plaque, plaque changes and laboratory variables: This set of analyses deal with correlation between baseline plaque characteristics and plaque progression or between laboratory measurements, such as lipids and inflammatory markers, and plaque composition and progression. The simplest form of these analyses will be the Pearson or Spearman correlation (and scatterplots) between pairs of variables, such as the change over two years in plaque lipid composition vs. the corresponding change in HDL-C concentration. The correlations will be based on a pair of variables, one each selected from these separate sets of variables: (a) baseline plaque variables, (b) baseline laboratory measurements, (c) rate of change of plaque variables over time, (d) rate of change of laboratory measurements over time. Each different pair of variables and their correlation test a hypothesis of interest. For example, selection of the change in plaque over time and change in a laboratory variable over time tests the hypothesis that these items progress or regress in parallel. These analyses are readily expanded to include covariates in multivariate models. For example, if baseline HDL-Cand baseline plaque lipid composition are both related to progression, we would want to try including them as independent variables in a model for progression in order to tease out the independent effect of each of the two variables.

The study will be able to detect even rather weak correlations. With our sample size of at least 180 patients who have compete data for up to 3 years we will be very likely to detect a true correlation of $r = \pm 0.18$ or larger between variables of interest. We are assuming 80% power, 2-sided test, $p<0.05$.

Drs. Zhao, Yuan, Hatsukami at the University of Washington, and Polissar (biostatistician at Mountain-Whisper-Light Statistics) developed the statistical analysis

plan. Analyses will be carried out in SAS, STATA, R and SPSS and performed by the Mountain-Whisper-Light Statistics.