ARIC Manuscript Proposal # 1339

1.a. Full Title: Does Carotid intima-media thickness (CIMT)/ plaque characteristics on carotid ultrasound predict the presence of high-risk plaques on carotid MRI in ARIC cohort.

b. Abbreviated Title (Length 26 characters): CIMT and high-risk plaques on carotid MRI.

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___SV__ [please confirm with your initials electronically or in writing]

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3. Timeline: We plan to analyze the data as soon as approval is obtained. Manuscript will be prepared as soon as analysis is done. We plan to do the analysis, as well as prepare the manuscript for submission within 1 year.

4. Rationale: Carotid intima-media thickness (CIMT) has been associated with increased risk of future cardiovascular events [Chambless LE. Am J Epidemiol 1997;146(6):48394]. At the plaque level, presence of lipid rich necrotic core and thin fibrous cap identifies plaques more likely to rupture and subsequently cause events.
(vulnerable plaques) [Davies MJ, British Heart Journal. 1993;69:377-381]. Though both of these imaging modalities (ultrasound and MR) can predict subsequent increased risk of cardiovascular events, the relationship between CIMT and the presence of lipid core on carotid MRI (CMRI) remains unknown. It is logical to think that patients with more atherosclerotic burden (as measured by CIMT) would have more high-risk unstable plaques. Overall, a higher total atherosclerotic burden would be associated with more vulnerable plaques. A thicker IMT predicts a higher risk of cardiac events likely because patients with thicker IMT have higher number of high risk (vulnerable) plaques. In one of the abstracts presented at 48th meeting of Cardiovascular Disease Epidemiology and Prevention Colorado Springs, CO [Long Term Prediction of MRI Measures of Carotid Wall Thickness, Wall Volume, and Plaque: The Atherosclerosis Risk in Communities (ARIC) Study, Wagenknecht LE et al], an analysis of lipid core restricted to the 1180 participants (67% of 1769) with maximum wall thickness >=1.5mm showed that lipid core was observed in 48% (569/1180) of patients. One would assume that a thicker carotid on MRI would correlate with a thicker IMT.

One would also assume that the process of atherosclerosis in carotids would not be very different than that in coronary arteries. More plaque at least in the initial stages would lead to more outward (positive) remodeling. An artery with more outward remodeling would likely have higher volumes and a thicker wall.

Similarly, though it is known that CIMT differs between males and females as well as different ethnic groups (greatest in Caucasian males, and lowest in African American females in ARIC cohort, Howard et al Stroke. 1993;24:1297-1304), it is currently un-known if these racial/ gender differences in CIMT measurements also translate into different degrees of racial/gender predilection for the presence of lipid rich cores on CMRI.

Identification of CIMT measurement parameter that can predict the presence of lipid rich core/ thin fibrous cap on CMRI has important clinical, as well as research implications. Though measurement of CIMT using B mode is operated dependant, and is subject to more measurement error than the automated MRI protocols, Carotid ultrasonography is relatively less expensive, and more accessible than CMRI.

Identification of high risk features of a plaque using CIMT measurements will lead to better identification of subjects for future studies, as well as identification of high risk patients on CIMT who need aggressive risk factor modification. When designing future trials, screening will likely be done by ultrasound for inclusion to reduce excessive number of MRIs. This analysis has the potential to identify various cut-offs for CIMT that could predict the likelihood of having a lipid rich core.

ARIC population is ideal for this analysis as CIMT measurements are available on all patients who underwent carotid MRI measurements. Similarly, presence of a bi-racial ARIC cohort also serves as strength of this analysis.

MRI of the carotid arteries were done in nearly 2000 patients in the ARIC cohort. The ARIC MRI cohort included 1200 participants whose carotid artery wall thickness as measured by carotid B mode ultrasound on visit 3,4 was at least >68 percentile (The IMT cut-offs were 1.35, 1.00, 1.28, and 1.22 mm at Forsyth County, Jackson, Minneapolis suburbs, and Washington County, respectively, representing the 73rd, 69th, 73rd, and 68th percentiles of maximal IMT from Exam 4), and a cohort random sample of nearly 800 participants whose carotid intima-media thickness was <68
percentile. The carotid MRI procedure included measurements of maximal wall thickness, carotid wall volume, luminal area, lipid core volume and maximum area, and fibrous cap thickness using gadolinium enhanced MRI on the thicker internal carotid artery using a 1.5 T magnet.

5. Main Hypothesis/Study Questions:
Carotid intima-media thickness/ presence of plaques as measured by B mode carotid ultrasonography is an independent predictor for the presence of lipid rich core/ thin fibrous cap on CMRI.

Study questions:
1. To determine if there is an association between carotid intima media thickness measured by B mode ultrasonography and presence of lipid rich core on CMRI
2. To determine if there is an association between carotid intima media thickness measured by B mode ultrasonography and presence of thin fibrous cap.
3. To determine which measurement on B mode ultrasonography predicts lipid rich core or thin fibrous cap (mean of the mean IMT thickness, mean of the maximum IMT thickness).
4. To determine if CIMT thickness of a particular segment predicts lipid rich core/ thin fibrous cap better than others (Common carotid, Carotid bulb, internal carotid).
5. To determine if the presence of any plaque on B mode ultrasonography can predict the presence of lipid rich core or thickness of fibrous cap on CMRI.
6. To determine if particular plaque characteristics (with or without acoustic shadowing) are associated with presence of lipid rich core or thin fibrous cap on CMRI.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

The study population comprises of all ARIC patients who underwent carotid MRI in year 18 of the study. All these patients already had CIMT measurements done on visits 1, 3 and 4. Of the 1901 CMRI performed, a total of 1769 have been reported to be of good quality. These patients will form the study population. Stepwise description of analysis to be done is described below:

1. The initial analysis will identify the mean of the mean CIMT (baseline (visit 1) as well as visits3 and 4), mean of the maximum CIMT as well as mean/ maximum CIMT for each segment on the carotid US in patients with and without lipid rich cores on CMRI. We will also try to ascertain how many patients have available data for each of the parameters described below. This is explained below in a dummy table form:

<table>
<thead>
<tr>
<th>Carotid US measurement</th>
<th>Lipid rich core present on CMRI n =</th>
<th>Lipid rich core absent on CMRI n =</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of the mean CIMT (baseline)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>visit 1) n =</td>
<td>Mean of the maximum CIMT (baseline visit 1) n =</td>
<td></td>
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<tr>
<td>Mean of the mean CIMT (visit 3,4) n =</td>
<td>Mean CIMT Left Common carotid (baseline visit 1) n =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of the maximum CIMT (visit 3,4) n =</td>
<td>Mean CIMT Left Carotid Bulb (baseline visit 1) n =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CIMT Left Internal Carotid (baseline visit 1) n =</td>
<td>Mean CIMT Left Common carotid (visit 3,4) n =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CIMT Left Carotid Bulb (visit 3,4) n =</td>
<td>Mean CIMT Left Internal Carotid (visit 3,4) n =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum CIMT Left common carotid (baseline visit 1) n =</td>
<td>Maximum CIMT Left carotid bulb (baseline visit) n =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum CIMT Left Internal carotid (baseline visit 1) n =</td>
<td>Maximum CIMT Left common carotid (visit 3,4) n =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum CIMT</td>
<td></td>
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<td></td>
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<tr>
<td>Left carotid bulb (visit 3,4)</td>
<td>n =</td>
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</tr>
<tr>
<td>Maximum CIMT</td>
<td>Left Internal carotid (visit 3,4)</td>
<td>n =</td>
<td></td>
</tr>
</tbody>
</table>

The measurement mean of the mean CIMT/ mean of the maximum CIMT denotes the mean/ maximum of all 6 segments (Left/right common carotid, left/right carotid bifurcation (bulb), and Left/right internal carotid artery) using imputed values that are known to be on average 2.3 sites per person in the ARIC cohort.

As it is known that the CIMT in the ARIC cohort were not any different between the right and the left side (Howard et al. Stroke. 1993;24:1297-1304), we will use the 3 segments on the left side to do the segment specific analysis.

“n” for CIMT variables in table 1 denotes number of patients with available values for that particular IMT parameter.

Please note that though IMT was measured on visit 2, we will not use visit 2 IMT for analysis, since there would only be very little difference between visit 1 and visit 2 and therefore, visit 2 IMT has not been mentioned as part of the analysis. Visit 3, and 4 have been included as they are far apart in time from visit 1 and may have more predictive power than using visit 1 alone.

This descriptive table will give us an idea as to which CIMT parameter best predicts lipid rich core on CMRI. This table will also tell us about the number of missing values for each parameter. The CIMT parameter that best predicts presence of lipid rich core with least amount of missing values will be selected for further analysis.

2. The CIMT parameter selected above will then be adjusted for covariates like age, gender, race, hypertension, total cholesterol, presence of diabetes, use of statins, as well as thickness of the carotid wall on CMRI, and hazard ratios will then be determined to see if they remain significant after adjustment of covariates. Thickness of the carotid wall on MRI has been added as a covariate for adjustment as presence of a lipid core detected by CMRI is strongly associated with carotid wall thickness. We are much more likely to detect a core for a thicker wall probably because of the resolution constraints of CMRI.

3. The same parameter used in step 2 will then be used as a continuous variable on x axis and percentage of patients with lipid rich core on Y axis for that CIMT parameter. This would provide an estimate of percentage of patients with lipid rich core for each IMT cutoff.

4. The next set of analyses would try to see if there is an association between CIMT association and the thickness (or thinness) of the fibrous cap (repeat steps 1-3 including table).

5. Next question to be answered is if presence of plaque on baseline CIMT measurement predicts the presence of lipid rich core on CMRI. This would also be adjusted for covariates described above. This analysis is only going to be descriptive, and will not try to correlate the location of plaque on CIMT with location of plaques seen on CMRI.
6. Similarly, it has been shown that plaques with acoustic shadowing (AS) are associated more with ischemic strokes compared to those without acoustic shadowing in the ARIC cohort (Hunt KJ, et al, Stroke, 2001,32(5):1120-6). We will try to answer the question if plaques with or without acoustic shadowing are associated with lipid rich core on CMRI.

7. The next question pertains to the relationship between plaques/plaque characteristics (with or without AS) and thickness or thinness of fibrous cap on CMRI.

LIMITATIONS ANTICIPATED:
1. It is anticipated that the numbers may be low for segmental analysis especially for the internal carotid segment and may be for common carotid. This might limit segment specific analysis as proposed. (On average IMT in ARIC has been imputed for 2.3 sites per person on the basis of sex- and race-specific multivariate linear models of mean IMT as a function of age, BMI, and arterial depth [Hunt KJ, et al, Stroke, 2001,32(5):1120-6]).
2. Presence of a lipid core detected by CMRI is strongly associated with wall thickness. We are much more likely to detect a core for a thicker wall probably because of the resolution constraints of CMRI. It might be difficult to show that thicker walls detected by ultrasound are associated with cores by MRI for this reason.
3. There may be very few patients in the <68 percentile group with lipid rich cores. If that is the case, separate analyses may need to be done for <68 percentile and ≥68 percentile groups.
4. We will not able to correlate location of plaque seen on CIMT with the location of plaque seen on CMRI with current analysis.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes  ___×__ No

   b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ____ Yes  ____ No

5. This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes  ___×__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___×___ Yes ________ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ______ Yes ___×_ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* __________)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________  __________  __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.