

ARIC Manuscript Proposal #2046

PC Reviewed: 12/11/12
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Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Associations between measures of plaque burden, plaque characteristics and cardiovascular outcomes: The ARIC Carotid MRI Study

b. Abbreviated Title (Length 26 characters): Plaque burden, characteristics and outcomes.

2. Writing Group:

Writing group members: Salim S. Virani MD, Wensheng Sun PhD, Rhiannon Dodge MS, Vijay Nambi MD PhD, Josef Coresh MD PhD, Thomas H. Mosley MD, A. Richey Sharrett MD DrPH, Eric Boerwinkle PhD, Christie M. Ballantyne MD, Bruce A. Wasserman MD. Others are welcome.

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:

Magnetic Resonance Imaging (MRI) of the carotid arteries is an imaging modality that can measure both plaque burden as well as plaque composition. Traditionally, presence of lipid rich necrotic core and thin fibrous cap identifies plaques more likely to rupture (vulnerable plaques) [Davies MJ, British Heart Journal. 1993;69:377-381], but as shown in the ARIC MRI cohort, presence of lipid rich core is dependent on wall thickness [Wagenknecht L, Circulation Cardiovascular Imaging 2009; 2:314-322]. At the population

level, it is not well known whether plaque composition measures (presence of lipid rich core as well as thin fibrous caps) can predict future cardiovascular events independent of the measures of plaque burden (arterial wall thickness or arterial wall volumes).

In addition, none of the studies have thus far evaluated the association between carotid plaque burden/ morphology on MRI and adverse cardiovascular outcomes in a prospective manner. The only study that evaluated cardiovascular disease association with carotid plaque morphology on MRI only focused on measures of plaque burden (wall thickness, wall area and wall volumes) rather than composition and showed that these measures of plaque burden were associated with a prior history of major cardiovascular events [Mani V, Journal of Cardiovascular MRI, 2009;11:10). It is important to note that in this manuscript, the authors evaluated prior history of cardiovascular events as the outcome measure rather than future occurrence of cardiovascular events and that associations between measures of plaque composition (for example presence or absence of lipid rich core or fibrous cap thickness) and future adverse cardiovascular outcomes were not evaluated.

Given the systemic nature of atherosclerosis, prior studies have shown that burden of atherosclerosis in carotid arteries predicts adverse cardiovascular outcomes in other vascular beds including the coronary vascular bed. Therefore, it is possible that the carotid plaque burden or components could also predict events in other vascular beds for e.g. the coronary arterial tree. This is important as it is much easier to image carotid arteries to determine both plaque burden and plaque composition compared with coronary arteries.

Knowledge of whether plaque burden or plaque morphology characteristics predict outcomes is also important from a clinical trial stand point as multiple novel agents are currently being evaluated in clinical trials using carotid MRI plaque composition and plaque morphology measures as imaging surrogates. It would also be invaluable to know what plaque characteristics should be focused on as imaging surrogates for incident cardiovascular events.

5. Main Hypothesis/Study Questions:

Aim:

To identify if measures of plaque burden (carotid wall thickness, wall volumes and normalized wall index) or measures of plaque composition (presence of lipid rich core, fibrous cap thickness) are associated with future cardiovascular events.

Hypothesis:

We hypothesize that measures of plaque burden will be independent predictors of future cardiovascular events. We also hypothesize that that presence or size of lipid rich core and mean fibrous cap thickness will be associated with future cardiovascular events but this relationship will be attenuated once measures of plaque burden are included in the adjustment model.

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).

Carotid MRIs were performed on nearly 2000 participants in the ARIC-MRI study. The ARIC MRI cohort included 1200 participants whose carotid artery intima media thickness (CIMT) as measured by B mode ultrasound on visit 3 or 4 was approximately \geq 68th percentile (though the cut-offs varied depending on the field center). 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. A random sample of nearly 800 participants whose CIMT was approximately <68th percentile (though this again varied by field center) was also studied. The carotid MRI procedure included measurements of multiple variables (please see below) using gadolinium-enhanced MRI on the thicker internal carotid artery with a 1.5 T magnet.

Similarly, prospective follow-up of these patients has also been performed for development of major adverse cardiovascular events. The outcome of interest will be incident cardiovascular disease (CVD) events defined as the composite of incident coronary heart disease (CHD) events or incident ischemic strokes. Incident CHD events will include CHD death, myocardial infarction, or the occurrence of coronary artery bypass surgery or angioplasty. Standard ARIC study criteria will be used to define ischemic stroke. In the ARIC MRI cohort, there have been 112 CVD events since the ARIC MRI visit.

Inclusion: ARIC participants who are part of the ARIC Carotid MRI Study with good quality MRI (n = 1,769 per prior publications from the ARIC MRI study)

Carotid MRI variables used for the analysis will include:

Measures of plaque burden:

Carotid wall thickness

Total wall volume (GDISCA-TOTAL WALL VOLUME)

Maximal wall thickness (GDSICA-MAXWALLTHICK-MAXCORE)

Lumen area (LUMENAREA_MAXMEANWALL1)

Vessel wall area (VESSELWALL AREA_MAXMEANWALL1)

Normalized wall index (NWI) = wall area/ total vessel wall area

Measures of plaque composition:

Lipid core:

Total lipid core volume (GDSICA-TOTALLIPIDCOREVOLUME)

Max lipid core area (GDSICA-MAXLIPIDCOREAREA-NEW2)

Lipid core (present/absent) (LIPID_core)

Lipid core present in two adjacent slices (CORE_in_two)

(note: restricted to those with maximum wall thickness \geq 1.5 mm)

Fibrous cap thickness

Mean cap thickness (MEAN-CAP-THICKNESS-2ADJACENT)

Mean minimum cap thickness (MEAN-MIN-CAP-THICKNESS-2ADJACENT)
(note: restricted to participants with lipid core present)

STATISTICAL ANALYSIS [PLAN]:

For continuous MRI variables, analyses will be performed in two ways. First, we will perform multivariate proportional hazards analyses describing the association between per standard deviation increase in continuous MRI variable (for e.g. total wall volume, carotid wall thickness) and CVD outcomes. Next, we will perform multivariate proportional hazards analyses across quartiles of each continuous MRI variable with the adjustment model described below. Quartile 1 will be used as the referent quartile for these analyses except for fibrous cap thickness measures where quartile 4 will be used as the referent category.

Similar analyses will be performed for the categorical variable (presence or absence of lipid rich core) with absence of detectable lipid rich core as the referent category.

Adjustment models used for the above analyses will include:

Model 1: age, sex, race, and ARIC study field center

Model 2: Model 1 + smoking, body mass index, prior history of CHD or ischemic stroke, blood glucose, blood pressure, total cholesterol, use of blood pressure-lowering medication, cholesterol lowering medication use, aspirin use, diabetes medication use, and hs CRP.

Model 3(for analyses involving lipid rich core measures only): Model 2 + carotid wall thickness.

For adjustment for standard risk factors, outside of age, sex, and race, the analysis will consider both concurrent (cross-sectional) measures of risk factors as well as cumulative exposure or rate of change of exposure. The cumulative exposures will be determined for continuous variables as the area under the curve of exam-specific values plotted versus exam time, divided by time between first and last exam. This can be interpreted as the estimated mean daily value over the period. For dichotomous risk factors the cumulative indicator is the proportion of time exposed.

We will also perform exploratory analyses to determine if maximum calcification area or presence of intra-plaque hemorrhage are predictors of adverse cardiovascular outcomes.

LIMITATIONS ANTICIPATED:

The use of cholesterol lowering medications in the ARIC cohort increased from less than 3% at baseline to nearly 36% at the time of the carotid MRI study. Measures of carotid plaque burden as well as plaque characteristics are affected by these medications. To circumvent this, we will include cholesterol lowering medication use as a covariate in the adjustment model. Similarly, stratified analyses (by cholesterol lowering medication use) will be performed. We anticipate that our analyses pertaining to the association between plaque characteristics and ischemic strokes will be underpowered secondary to small number of ischemic strokes since the ARIC MRI visit. Therefore, these analyses will be

performed as a meta-analysis by combining data with the MESA cohort as a separate manuscript proposal.

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

(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.csc.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)?

1. Wagenknecht L, Wasserman B, Chambless L, Coresh J, Folsom A, T M, Ballantyne C, Sharrett R, Boerwinkle E. Correlates of carotid plaque presence and composition as measured by magnetic resonance imaging: the Atherosclerosis Risk in Communities Study. *Circulation Cardiovascular Imaging* 2009; 2:314-322.

2. Virani SS, Nambi V, Hoogeveen R, Wasserman BA, Coresh J, Gonzalez F 2nd, Chambless LE, Mosley TH, Boerwinkle E, Ballantyne CM. Relationship between circulating levels of RANTES (regulated on activation, normal T-cell expressed and secreted) and carotid plaque characteristics: the Atherosclerosis Risk in Communities (ARIC) Carotid MRI study. *Eur Heart J*. 2011 Feb;32(4):459-68.

3. Virani SS, Catellier DJ, Pompeii LA, Nambi V, Hoogeveen RC, Wasserman BA, Coresh J, Mosley TH, Otvos JD, Sharrett AR, Boerwinkle E, Ballantyne CM. Relation of Cholesterol and Lipoprotein Parameters with Carotid Artery Plaque Characteristics: the

