ARIC Manuscript Proposal #2816

PC Reviewed: 8/12/16	**Status: CA**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations of carotid intima media thickness with prevalent and future number of silent brain infarctions

b. Abbreviated Title (Length 26 characters): **Carotid IMT and SBI**

2. Writing Group:

Writing group members: Melissa Caughey, Ye Qiao, Bruce Wasserman, Thomas Mosley, Rebecca Gottesman, Gwen Windham

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

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3. Timeline: 1-year after acceptance of manuscript proposal

4. Rationale:

The arterial wall is composed of 3 layers: the intima (endothelial cells), the media (smooth muscle cells), and the adventitia (collagen and external elastic lamina). Early in the atherogenesis process, monocytes migrate into the sub-endothelial space, and differentiate into macrophages which oxidize low density lipoproteins. Concurrently, vascular smooth muscle cells migrate from the media to the intima, and proliferate. This cellular influx and proliferation results in expansion of the intima, a precursor to atherosclerosis. Accordingly, carotid artery intima media thickness (IMT), which is visible and quantifiable by high-resolution ultrasonography, is considered an indicator of subclinical atherosclerosis. However, IMT measurements, which are the distance between the lumen-intima and media-adventia interfaces, include both intima thickness and media thickness. Thus, the IMT not only reflects pre-atherosclerotic intimal thickening, but also smooth muscle hypertrophy and hyperplasia, which may be the result of poor blood pressure control or aging.

The carotid artery is considered to have 4 segments: the common carotid artery (CCA), the bifurcation, the internal carotid artery (ICA), and the external carotid artery. Plaque develops in regions of low shear stress, and in the carotid artery is most commonly observed at the bifurcation or ICA. Consequently, IMT of the ICA and bifurcation are considered more influenced by atherosclerosis, while IMT of the CCA is more reflective of blood pressure[1].

The European Society of Cardiology (ESC) has defined abnormal IMT by a thickness exceeding 0.9 mm[2]. This threshold, though considered conservative, was derived from maximal IMT values and their associated risk with myocardial infarction and stroke in the Cardiovascular Health Study[3]. Following this landmark publication from the CHS, numerous studies have reported associations of IMT with both prevalent and future cardiovascular disease. Associations from previous reports appear to be systemic, extending well beyond the anterior cerebral circulation of the carotid artery distribution. However, the extent to which carotid IMT associates with cerebral small vessel disease is debatable.

Silent brain infarctions (SBI) of the small deep penetrating arteries are thought to result from microthrombi (atherosclerotic or thrombotic), or from constriction and eventual occlusion of the small vessels by lipohyalinosis. As a crude measure, the SBI etiology is often considered lipohyalinosis when the infarct diameter < 7 mm, and atheromatous or embolic when the diameter exceeds 7 mm[4]. Overall, the most predictive risk factors of SBI are age and hypertension, but diabetes and smoking have also been implicated. The Rotterdam Scan Study reported a significant association between CCA-IMT and incident silent brain infarction (SBI) on MRI; however, these models were only adjusted for age and sex[5]. In contrast, an analysis from the Framingham Study, which adjusted for demographics and stroke risk factors, reported no association between prevalent SBI and CCA-IMT, but a significant association between SBI and the ICA-IMT[6]. This suggests the association between IMT and SBI may be driven more by atherosclerosis than blood pressure. In support of this, a hospital-based study of asymptomatic Japanese patients reported no association between SBI and CCA-IMT in patients without plaque in the carotid bifurcation[7].

Whether the CCA-IMT associates with prevalent and incident SBI after adjustment for comorbid risk factors remains inconclusive. The ARIC Study is well suited to investigate this topic.

5. Main Hypothesis/Study Questions:

1. Cross-sectional: Is abnormal (>0.9) IMT of the common carotid artery in stroke-free individuals associated with greater number of prevalent SBI at the visit 3 MRI examination, and greater prevalence rate of SBI (using participant age at visit 3 as the time variable)?
2. Descriptive: Is abnormal CCA-IMT more related to SBIs of the anterior, rather than posterior cerebral circulation? What is the distribution of SBI sizes (< 3mm, 3-7mm, ≥ 7 mm, or combination) in relation to normal and abnormal CCA-IMT measurements?
3. Longitudinal: Is abnormal CCA-IMT at cohort visit 3 associated with new SBI at the subsequent Brain MRI and visit 5 MRI examinations? Do participants with abnormal CCA-IMT have a greater growth rate of number of new SBI from visit 3 to follow up exams (at Brain MRI and v5 MRI)?

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 cross-sectional analysis will include ARIC Study participants who were imaged by carotid ultrasound and brain MRI at the 3rd cohort examination (1993-1995). In the cohort study, mean CCA-IMT was averaged from 11 measurements of the posterior wall in both left CCA and right CCA. For the purposes of this analysis, abnormal CCA-IMT will be considered an IMT >0.9 mm, when the left and right mean CCA-IMT are averaged. Abnormal IMT will be modeled as a predictor of SBI count using Poisson regression, with ln(age) of the participant used as the offset. Models will be adjusted for CVD risk factors, and will also be examined after consideration of carotid plaque/shadowing presence. The 20-year growth rates in SBI count associated with v3 CCA-IMT will be analyzed using Poisson regression with a generalized estimator equation and a first-order autoregressive correlation. For this analysis, all available brain MRI examinations (1993-1995, 2004-2006, and 2011-2013) of participants imaged by carotid ultrasound in 1993-1995 will be included.

Anticipated Limitations

Many advancements in ultrasound imaging quality have been realized over the past 2 decades. The 1993-1995 carotid ultrasound data is admittedly dated. Nonetheless, images were acquired with an 8 MHz probe, achieving an axial resolution of 0.1 mm, which is sufficient for this analysis. MRI image resolution has also improved substantially, and scanners were upgraded from 1.5 T to 3.0 T magnets at the 2011-2013 examination. However, we will use consistent definitions to classify SBI at all 3 examinations.

Additionally, this longitudinal analysis of elderly participants will be heavily influenced by survival bias. To overcome this limitation, we will conduct a sensitivity analysis using inverse probability weighting for the probability of non-missingness.

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

b. If Yes, is the author aware that the file ICTDER03 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 ICTDER 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 __x__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 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

___x___ 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)?

MS# 1723: Associations between lacune subtypes and retinal microvascular disease, renal markers and intima-media thickness in ARIC

MS# 1188: Carotid wall thickness and risk of ischemic stroke subtypes: The Atherosclerosis Risk in Communities Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

_x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* `1999.01` Brain MRI (PI = Mosley)

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

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted

in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.
13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _x___ No.

References

1. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment, *JACC Cardiovasc Imaging* 2014;7:1025-1038.

2. Taylor J. 2013 ESH/ESC guidelines for the management of arterial hypertension, *Eur Heart J* 2013;34:2108-2109.

3. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK,Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group, *N Engl J Med* 1999;340:14-22.

4. Fisher CM. Lacunar strokes and infarcts: a review, *Neurology* 1982;32:871-876.

5. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM, Rotterdam Scan Study. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study, *Stroke* 2003;34:392-396.

6. Romero JR, Beiser A, Seshadri S, Benjamin EJ, Polak JF, Vasan RS, Au R, DeCarli C, Wolf PA. Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cognitive impairment: the Framingham study, *Stroke* 2009;40:1590-1596.

7. Inoue K, Matsumoto M, Shono T, Toyokawa S, Moriki A. Increased intima media thickness and atherosclerotic plaques in the carotid artery as risk factors for silent brain infarcts, *J Stroke Cerebrovasc Dis* 2007;16:14-20.