ARIC Manuscript Proposal #2488

PC Reviewed: 1/13/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Prevalence and Risk Factors of Intracranial Atherosclerosis in the ARIC Cohort

b. Abbreviated Title (Length 26 characters):

Prevalence and Risk Factors of ICAD

2. Writing Group:
Writing group members:

Ye Qiao, Eliseo Guallar, Li Liu, Yiyi Zhang, Fareed Suri, Alvaro Alonso, Rebecca Gottesman, Bruce A. Wasserman. Others welcome.

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

F**irst author**:

Name: Ye Qiao
Address: Johns Hopkins Hospital, 367 East Park Building, 600 North Wolfe Street, Baltimore, MD 21287.
Phone: 410-955-2353
E-mail: yqiao4@jhu.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Bruce A. Wasserman
Address: Johns Hopkins Hospital, 367 East Park Building, 600 North Wolfe Street, Baltimore, MD 21287.
Phone: 410-614-9200
Fax: 410-502-5955
E-mail: bwasser@jhmi.edu

3. Timeline:
The manuscript will be complete within 2-3 months upon the approval of this proposal.

4. Rationale:

Intracranial atherosclerotic disease (ICAD) is a major cause of ischemic stroke worldwide [1-3]. However, its prevalence may be underestimated due to the lack of an appropriate diagnostic tool to depict the intracranial vessel wall [3, 4]. The diagnosis of ICAD traditionally has depended on stenosis measurements by angiographic techniques [4, 5], but ICAD may not necessarily cause proportional luminal narrowing as vessels are capable of compensatory dilatation (remodeling) to accommodate these changes, particularly early on [6, 7]. Therefore, the degree of luminal narrowing may underestimate the severity of ICAD and vessel wall thickening. Mazighi et al, in an autopsy study of patients with fatal stroke, noted a stenosis of ≥ 30% in only 50% of ICAD lesions [8]. MRI vessel wall imaging has emerged as a powerful tool for extracranial (e.g. carotid) plaque characterization, enabling the determination of stroke risk from carotid plaque rupture [9-11]. Historically, the application of this technique to ICAD has been limited by technical constraints, in particular scanner resolution. Recent advances in MRI at 3T have made it possible to detect ICAD and measure ICAD burden[12, 13].

In ARIC-NCS study, we have implemented vascular sequences (i.e., 3D vessel wall imaging (VWI) and MRA) in the brain MRI exam to determine ICAD prevalence, and examine ICAD stenosis and burden in relation to risk factors and vascular markers (contemporaneous and change from earlier baseline measures).

Age, hypertension, and diabetes mellitus are independent risk factors for ICAD [14]. The Northern Manhattan Stroke Study determined that diabetes mellitus conferred a higher risk for ICAD-related stroke than stroke related to extracranial atherosclerotic disease [15]. Most studies of ICAD risk factors were conducted in symptomatic patients [16-19] or patients referred for a family history of stroke [20]. Most involve older adults, in whom traditional risk factors (e.g. blood pressure, cholesterol level) may have been altered by comorbidities and medical treatment [15]. Mid-life measures of vascular risk factors may be better predictors of atherosclerosis later in life than current measures since earlier measures may be more representative of its long-term cumulative effects with less influence by treatment [21].

5. Main Hypothesis/Study Questions:

- To estimate the prevalence of ICAD (defined as eccentric wall thickening based on VWI, with or without luminal stenosis) by race, sex and age in ARIC participants aged 70-89 years.

  Hypothesis: We expect prevalence of ICAD to increase with age, to be higher in African Americans compared with Whites, and to be higher in males compared with females.

- To relate known risk factors and vascular markers for cardiovascular disease, measured repeatedly from middle-age beginning over 20 years ago, with ICAD presence and burden.

  Hypothesis: We expect cardiovascular risk factors (e.g., total and HDL cholesterol, blood pressure, diabetes mellitus, smoking) measured in midlife (ages 45-64) and cumulatively since midlife to better predict ICAD presence and burden than current measurements at visit 5 after adjusting for age, sex and race.

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).

Study Design:
The study will use data from 2,000 ARIC participants who underwent brain MRI to measure intracranial atherosclerosis in visit 5. The vascular MRI protocol consisted of a 3-dimensional time-of-flight MR angiogram (TOF MRA) and a 3-dimensional high-isotropic resolution VWI sequence centered at the Circle of Willis. Qualitative analysis of the MRI images included plaque presence by vessel territory (RMCA, LMCA, RPCA, LPCA, ACA, BA, VA, RICA, and LICA), number of plaques, and the ordinal degree of narrowing (i.e., no detectable stenosis, <50%, 51%-70%, 71-99%, and occlusion) for the most stenotic plaque per territory. An atherosclerotic plaque was defined as eccentric wall thickening, with or without luminal stenosis seen on VWI.

Quantitative measurements were obtained at designated vessel segments (supraclinoid ICA, M1 of MCA, A1 of ACA, proximal and distal BA, and V4 of VA) over a fixed length for all participants and for the largest plaque identified for each vascular territory in the qualitative assessment. For each vessel segment and plaque, we recorded lumen size and stenosis, wall/plaque thickness, area, volume, and normalized wall index (wall area/outer wall area)

In this manuscript, we will use the data from participants who have a complete set of qualitative and quantitative MRI measurements.

Inclusion:
Image quality and protocol adherence scores of adequate or excellent on both MRA and VWI.

Exclusion:
Poor or failed exams

Primary endpoints:

- Presence of plaque per participant (in any designated vessel territory, including those plaques with no detectable stenosis)

Secondary endpoints (included not limited):

- Presence of plaque by vessel segment (e.g., n_rmca_plaq, n_lmca_plaq, n_raca_plaq, etc)
- Total number of plaques (n_plaq)
- MRA Diameter Degree of stenosis (%)
- VWI VesselWall Segment Average (mm^2)
- VWI VesselWall Segment Maximum (mm^2)
- VWI Vessel Segment Wall Volume (mm^3)
- VWI Normalized Wall Index (%)
- VWI Walltichkness Segment Average (mm)
- VWI Walltichkness Segment Maximum (mm)

For prevalence of ICAD, we will use Stata *svy* commands with sampling weights and strata to account for oversampling of participants with cognitive impairment in ARIC-NCS and provide estimates referable to the overall ARIC population.

Exposure of interest will be traditional cardiovascular risk factors measured over 20 years including age, sex, race, BMI, smoking, alcohol consumption, physical activity, total cholesterol, LDL and HDL cholesterol, triglycerides, metabolic syndrome, fasting glucose/diabetes, blood pressure/hypertension, history of cardiovascular event, use of antiplatelet drugs, use of statin and use of antihypertensive medications.

To evaluate the association between risk factors and endpoints, logistic and multinomial logistic regression will be used for categorical outcome (presence of plaque, degree of stenosis), zero-inflated negative binomial regression will be used for count data (number of plaques), and linear regression will be used for continuous outcomes (wall thickness). We will first evaluate individual risk factor in the model adjusting for age, sex, race, and enrollment center. Risk factors associated with the outcome will then be included simultaneously in the same model (with age, sex, race forced into the model regardless of their significance). Potential interactions by time since risk factor measurements, by sex and by race will also be examined by including interaction terms the models.

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)?

The current proposal is most related to manuscript proposal MS2448- Prevalence of Intracranial Atherosclerotic Stenosis (ICAS) and its Association with Vascular Risk Factors (Suri).

Based on a conference call in September with Drs. Ye Qiao, Eliseo Guallar, Bruce Wasserman, Fareed Suri, Alvaro Alosnsn, and Aaron Folsom, a consensus was reached to address the prevalence and risk factors of ICAD using two distinct approaches:

I. Prevalence of intracranial atherosclerotic stenosis, measured as luminal narrowing on MRA, and its association with cross-sectional vascular risk factors at visit 5 (see MS2448).
II. Prevalence of ICAD, defined as eccentric wall thickening based on VWI, with or without luminal stenosis, and its association with risk factors and vascular markers (contemporaneous and change from earlier baseline).

We expect prevalence estimates to differ based on the two approaches. Our preliminary data shows that 11.3% of ARIC participants with ICAD had lesions that were not detectable based on stenosis (i.e., on MRA).

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

_X_ A. primarily the result of an ancillary study (list number* 2009.27, 2009.28**)**

___ 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/

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.

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