ARIC Manuscript Proposal #3440

PC Reviewed: 8/13/19  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title

Prevalence and Risk Factors for Intracranial Aneurysms in the ARIC Cohort

b. Abbreviated Title (Length 26 characters)

Risk factors for aneurysms

2. Writing Group

Writing group members:

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

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3. Timeline

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

Intracranial aneurysms are associated with an increased risk of subarachnoid hemorrhage and are an important incidental finding in brain magnetic resonance imaging (MRI). Clinical management of asymptomatic intracranial aneurysms is controversial, partly due to uncertainties in the epidemiology and natural history of intracranial aneurysms. Indeed, the prevalence of intracranial aneurysms in the general population is unknown due to the lack of systematic community-based population angiographic studies of intracranial aneurysms. A meta-analysis of 68 studies estimated a prevalence of intracranial aneurysms of 2.8% (95% CI 2.0–3.9%), but these studies were largely autopsy-based or clinical series conducted in highly selected samples. In the Rotterdam study, the prevalence of intracranial aneurysms was 1.8%, but the diagnosis was based solely on brain MRI imaging (no MR angiogram), with low sensitivity for identifying intracranial aneurysms, particularly small intracranial aneurysms (< 4 mm). A cross-sectional study in China using magnetic resonance angiography (MRA) found a prevalence of 7.0%.

MRA is a non-invasive method that provides reliable imaging of intracranial artery atherosclerosis and other arterial abnormalities, including intracranial aneurysms. A recent comparison of 3T time-of-flight (TOF) MRA with digital subtraction angiography for identifying small aneurysms (<5 mm) showed very high accuracy for MRA (97%), indicating that MRA can be reliably used to establish the prevalence of intracranial aneurysms in population studies. In the ARIC-NCS study (Visit 5) and ARIC Visits 6 and 7, we have been implementing intracranial vascular sequences (i.e., 3D vessel wall imaging and MRA) to determine the prevalence of intracranial atherosclerosis and its relation to mild cognitive impairment and dementia. In these images, we have identified and characterized the presence of intracranial aneurysms.

Risk factors for intracranial aneurysms are also not well defined. Most studies are cross-sectional studies that evaluate risk factors for prevalent ruptured aneurysms. Age, female gender, hypertension, diabetes, cigarette smoking, intracranial atherosclerosis, and morphology of the aneurysm (e.g., aneurysm size, irregular shape, and aspect ratio) are risk factors for prevalent ruptured intracranial aneurysms. There are very limited data on risk factors for the presence of unruptured intracranial aneurysms in the general population. In a case-control study, current smoking, hypertension, and family history of stroke were risk factors for unruptured intracranial aneurysms, but risk factors were based on self-reported questionnaires (not measured).

Hence, the main objective of this study was to evaluate the prevalence and risk factors for intracranial aneurysms in the Atherosclerosis Risk in Communities (ARIC) cohort.

5. Main Hypothesis/Study Questions

- To estimate the prevalence of intracranial aneurysms by race, sex and age in ARIC participants.

Hypothesis: We expect prevalence of intracranial aneurysms to increase with age, to be higher in African Americans compared with Whites, and to be higher in women compared with men.
• To relate known risk factors and vascular markers for cardiovascular disease, measured repeatedly from middle-age in study participants, with the presence of intracranial aneurysms.

**Hypothesis:** We expect cardiovascular risk factors (e.g., total and HDL cholesterol, blood pressure, diabetes mellitus, smoking) to be associated with higher frequency of intracranial aneurysms after adjusting for age, sex, race.12

• To relate the presence of intracranial atherosclerosis, measured in the same MRI exam, with the presence of intracranial aneurysms.

**Hypothesis:** We expect intracranial atherosclerosis to be associated with higher frequency of intracranial aneurysms after adjusting for age, sex, race.12 We will also evaluate if intracranial atherosclerosis is associated with the presence of intracranial aneurysms after further adjusting for known risk factors and vascular markers.

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. Among them, 1,000 will have repeated MRI exams in visits 6 and 7 (scans are currently underway). The vascular MRI protocol consisted of a 3-dimensional TOF MRA and a 3-dimensional high-isotropic resolution vessel wall imaging sequence centered at the Circle of Willis. At least 2 different analysts will review images from both visit 5 and visit 6/7 to capture intracranial aneurysms with maximized sensitivity. Images from both visits will also be reviewed by neurointerventionalists at the Johns Hopkins Hospital to check false negatives and positives. The images from visits 6/7 will be used primarily for QA/QC (e.g., to detect aneurysms missed at visit 5), although they will also allow us to identify the appearance of new aneurysms or the progression of existing ones.

An intracranial aneurysm was defined as an outpouching (bulge or ballooning) of an intracranial artery. Infundibula, defined as a pyramidal dilatation measuring less than 3 mm at the origin of a vessel with an artery arising from the apex, were not included in the definition of aneurysms.

Intracranial aneurysm measurements in V5 and in V6/V7 include:

- Presence of intracranial aneurysms by vessel territory (RMCA, LMCA, RPCA, LPCA, ACA [anterior communicating artery aneurysms will be categorized separately and a side will be assigned if possible], BA, VA, RI CA, and LICA).
- Number of intracranial aneurysms.
- Size of intracranial aneurysms (i.e., maximum width and depth). Intracranial aneurysms were categorized based on the size (largest dimension) as <3 mm, 3–7 mm, or >7 mm.

**Inclusion**

Image quality and protocol adherence scores of adequate or excellent.
Primary endpoints
- Prevalence of intracranial aneurysms.

Secondary endpoints (included not limited)
- Prevalence of intracranial aneurysms by vessel segment
- Number of intracranial aneurysms per participant
- Distribution by size and maximum width / depth of intracranial aneurysms

Descriptive endpoint
- Incidence and progression of intracranial aneurysms between V5 and V6/V7 (we anticipate that there will be not enough cases of incidence / progression for a formal statistical analysis of the determinants of progression, but we will report incidence and progression rates and the features common to these cases).

Statistical analysis

For prevalence of intracranial aneurysms, 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. Prevalence of intracranial aneurysms will be estimated and compared across subgroups of sex, race and age. In addition, we will report the prevalence of infundibula overall and by subgroups of sex, race, and age.

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) as well as the presence of intracranial atherosclerosis.

To evaluate the cross-sectional associations between risk factors and endpoints, logistic and multinomial logistic regression will be used for the primary outcome (presence of intracranial aneurysms), zero-inflated negative binomial regression will be used for count data (number of intracranial aneurysms), and linear regression will be used for continuous outcomes (maximum length/depth). We will first evaluate individual risk factors in a model adjusting for age, sex, and race/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). In addition, we will evaluate models including age, sex, race/enrollment center and intracranial atherosclerosis. These models will also be further adjusted by cardiovascular risk factors. Potential interactions by time since risk factor measurements, by sex and by race will also be examined by including interaction terms in the models.

For progression of intracranial aneurysms from V5 to V6/V7, we anticipate that there will be not enough cases of incidence / increased size for a formal statistical analysis of the determinants of progression, but we will report incidence and progression rates and the features common to these cases.
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)?

No prior manuscript proposals have used information on intracranial aneurysms.

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* 2015.32, 2009.27)
    ____  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.csc.c.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.
References


