ARIC Manuscript Proposal #2448

PC Reviewed: 10/14/14  Status: A  Priority: 2
SC Reviewed: _________ Status: _____ Priority: ____

1.a. Full Title: Prevalence of Intracranial Atherosclerotic Stenosis (ICAS) and its Association with Vascular Risk Factors.

b. Abbreviated Title (Length 26 characters): Prevalence ICAS

2. Writing Group:
   Writing group members: Bruce Wasserman, Haitao Chu, Ye Qiao, Eliseo Guallar, Yiyi Zhang, Li Liu, Xiaoye Ma, Adnan I Qureshi, Alvaro Alonso, Aaron Folsom.

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

First author: M. Fareed K. Suri
Address: 420 Delaware Ave, MMC 295
          Minneapolis, MN 55455
          Phone: 612-626-9517       Fax: 612-625-7950
          E-mail: suri0027@umn.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 Wasserman
   Address:

   Phone:            Fax:
   E-mail:

3. Timeline: This study is based on qualitative image analysis of magnetic resonance angiography (MRA) performed for ICAD and Cognitive Impairment (ICAD cognitive impairment (ICAD-CI)) Study. Qualitative image analysis is expected to be complete by January 2014. The statistical analysis and manuscript preparation will be completed in October 2014.

4. Rationale: Although every year about 70,000 to 90,000 strokes are estimated to be secondary to ICAD\(^2\)\(^3\) in U.S. and approximately 75% of them are secondary to previously asymptomatic ICAD, the actual prevalence of ICAD in the general population is unknown.\(^1\) Previous studies that estimated the prevalence of ICAD in US were either
autopsy studies \(^4\) or were limited to high risk groups (e.g. patients referred for carotid stenosis)\(^7\) and do not provide general population estimates because of selection bias. Two recent population based studies reported prevalence of ICAD in China.\(^8,9\) The prevalence of ICAD in Chinese population is known to be higher\(^10,11\) and so these estimates cannot be used for US population.

Estimation of prevalence of intracranial atherosclerotic disease (ICAD) is one of the primary objectives of the ICAD-CI study. High resolution vascular MRI in about 2000 ARIC subjects provides a unique opportunity to estimate the prevalence of intracranial atherosclerosis in US elderly population.

Prevalence of cerebral atherosclerosis among different races has been reported in a few studies. McGarry studied carotid and intracranial atherosclerosis in a sample of 1093 randomly selected autopsied cases.\(^1\) Prevalence of carotid atherosclerotic lesion was similar, but the prevalence of intracranial atherosclerosis was considerably higher in African-American. Sacco et al reviewed the etiology of ischemic stroke among 438 patients in Northern Manhattan Stroke Study.\(^2\) Adjusted odds were 4 times more for intracranial compared with extracranial atherosclerosis for stroke when African-Americans or Hispanics were compared to Whites. Wityk et al studied the prevalence of carotid and intracranial atherosclerosis in patients admitted to a hospital with either ischemic stroke or TIA and did not note a difference in prevalence of intracranial atherosclerosis between white and African American patients.\(^3\)

The association of race with stroke secondary to ICAD is not completely explained by disparities in classic vascular risk factors.\(^2\) If disparities in classical risk factors such as hypertension and diabetes mellitus do not explain the differential prevalence of ICAD between races, it is unlikely that current strategies will result in reduction of ICAD related strokes in certain population as targeted by the national health promotion initiative, “Healthy People 2010”.

A recent AHA/ASA scientific statement highlights the importance of better understanding racial disparities in stroke.\(^4\) “Racial and ethnic disparities in stroke exist …. Acknowledging the presence of disparities and understanding the factors that contribute to them are necessary first steps. More research is required to understand these differences and find solutions.”

Proposed analysis will determine a. if, after age and gender adjustment, there is racial disparity in prevalence of intracranial atherosclerosis, and b. if these differences can be explained by classical vascular risk factors.

5. **Main Hypothesis/Study Questions:**

1. Estimate prevalence of moderate to severe ICAD, measured as luminal narrowing, in ARIC-NCS study subjects who have undergone MRI examination.
2. To determine if moderate to severe ICAD will be more prevalent in African Americans compared with whites, and if this disproportionately higher prevalence of ICAD in African Americans can be fully explained by the higher rates of hypertension, hyperlipidemia, diabetes mellitus, and a cigarette smoking history.

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:** Cross-sectional

**Inclusion:** All subjects who have received vascular MRA for ICAD-CI Study

**Exclusion:**
1. Failure of protocol adherence (see Appendix ‘A’ for definition [not yet available])
2. Poor image quality (see Appendix ‘A’ for definition)

**Outcome:**
- Prevalence of stenosis per vessel
- Prevalence of stenosis per person
- Prevalence of stenosis according to demographic and vascular risk factors
- Prevalence of intracranial atherosclerosis in White and African-American, stratified by age groups and gender
- To determine if ICAD is more prevalent in African-Americans compared to whites, we will fit logistic regression models with race as the primary independent variable, adjusting for age and gender; we will run additional models adjusting for vascular risk factors, including (but not limited to) hypertension, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, history of hyperlipidemia, LDL levels, HDL levels, use of statins, cigarette smoking, and body mass index.

**Methodology:**
We will use qualitative vessel wall analysis data for luminal stenosis for this manuscript. Our primary analysis will be based on the following intracranial vessels.
- Intracranial internal carotid artery
- Bilateral middle cerebral artery (MCA) M1-M3 segments
- Dominant vertebral artery intracranial segment (VA)
- Basilar artery (BA)
- Distal smaller vessels are unlikely to have atherosclerosis without the involvement of larger proximal anterior cerebral artery (ACA) A1 segment
- Posterior cerebral artery (PCA) P1-3 segments

Following information will be reported (sample tables attached as Appendix -A
1. Prevalence of intracranial stenosis per vessel in total, African-American and White population.
2. Per-person prevalence of intracranial stenosis in study sample (using maximum stenosis recorded in any vessel per person).
3. Per-person prevalence of stenosis according to demographic information and vascular risk factors (MCA-M1,ICA,VA,BA)
4. Estimated US prevalence in population aged 70-89 years.
5. Logistic regression models with race as the primary independent variable, adjusting for age and gender; we will run additional models adjusting for vascular risk factors, including but not limited to hypertension, diabetes mellitus, hyperlipidemia, use of statins, cigarette smoking, and body mass index

**Limitations:**
1. We are using all subjects who have received ARIC-NCS MRI. Although the subject selection for MRI was based on stratified sampling, this is not a random sample and does not provide the prevalence estimate of the general population.
2. Motion artifact has affected the quality of MRI for some subjects. The confidence level of the image analysis is recorded by the analyst and is graded as ‘not confident’, ‘somewhat confident’ and ‘confident’. Additional analysis will be done after excluding vessel segments and subjects with ‘not confident’ image analysis and will be reported if results are significantly different.

3. There is no standard method to determine the intracranial vasculature atherosclerosis burden. Stenosis severity is the best known prognostic indicator for risk of stroke. We are using the standard clinical stenosis severity cut-offs to report the prevalence of atherosclerosis burden. This may not be a true representation of atherosclerosis burden, as a participant may have multiple areas of intracranial atherosclerosis without any significant stenosis.

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 ICTDER03 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.cscu.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)?

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: 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/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

**References**

# Appendix A: Sample analyses

1. Prevalence of intracranial stenosis per vessel

<table>
<thead>
<tr>
<th>Total vessels</th>
<th>None</th>
<th>&lt;50%</th>
<th>50-69%</th>
<th>70-99%</th>
<th>Total occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Per-person prevalence of stenosis according to demographic information and vascular risk factors (some suggested variables)

<table>
<thead>
<tr>
<th>N=</th>
<th>&lt;50%</th>
<th>50-69%</th>
<th>70-99%</th>
<th>Total occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 70-79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 80-89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Prevalence of intracranial stenosis per vessel for African-American and White population

<table>
<thead>
<tr>
<th>Total vessels</th>
<th>&lt;50%</th>
<th>50-69%</th>
<th>70-99%</th>
<th>Total occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA W</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Logistic regression models with race as the primary independent variable, adjusting for age and gender; we will run additional models adjusting for vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, use of statin medications, cigarette smoking, and body mass index.