ARIC Manuscript Proposal #2578

PC Reviewed: 7/13/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Markers of Hyperglycemia and Intracranial Atherosclerotic Stenosis Using High Resolution Magnetic Resonance Angiography in a General Population: The ARIC-NCS Study

b. Abbreviated Title (Length 26 characters):
Glycemic markers and ICAS

2. Writing Group:

Writing group members:
Akira Fujiyoshi, Fareed Suri, Alvaro Alonso, Elizabeth Selvin, Haitao Chu, Eliseo Guallar, Ye Qiao, Yiyi Zhang, Bruce Wasserman, Aaron R. Folsom

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

First author: Akira Fujiyoshi
Address: Division of Epidemiology and Community Health
University of Minnesota

Phone: 612-624-1818 Fax: 612-624-0315
E-mail: fujiy001@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: Aaron R. Folsom
Address: Division of Epidemiology and Community Health
University of Minnesota
Phone: 612-626-8862
Fax: 612-624-0315
E-mail: folso001@umn.edu

3. Timeline:
Start as soon as data becomes available

4. Rationale:
Intracranial atherosclerotic stenosis (ICAS) is a common cause of stroke. Approximately 8% of ischemic strokes[1] and 34% of dementia[2] are attributed to ICAS in the U.S.

There are few epidemiological studies of ICAS in general populations. While the determinants of ICAS seem to include conventional cardiovascular risk factors including advanced age and hypertension, the association of diabetes mellitus (DM) with ICAS is less well documented.[3] In addition, while the effect of long-term hyperglycemia on microvascular diseases (ex. nephropathy, neuropathy) is established,[4] less well established is the effect on *macro*-vascular disease such as ICAS.

A recent ARIC study by Selvin and colleagues has shown that higher levels of glycated hemoglobin (HbA1c), a marker of long-term glucose level, at baseline independently predicted increased risk of incident ischemic stroke among initially non-diabetic persons.[5] The study also suggested that HbA1c in high normal range (6.0 to <6.5%) can identify persons at increased risk for stroke before the diagnosis of diabetes.

In the ARIC study, other glycemic markers such as fructosamine and glycated albumin have been shown to be predictive of diabetes and chronic kidney disease,[6] and more recently with coronary heart disease, ischemic stroke, heart failure and mortality,[7] but their association with intracranial atherosclerosis remains unclear.

These two markers have advantages over HbA1c, such as being unaffected by presence of anemia nor altered red cell turnover, and can be measured in serum or plasma. There is a growing interest in these markers as a complement/alternative to HbA1c given their potential advantages. However, paucity of data showing associations with clinical and subclinical diseases has been a barrier to their use.[8] Therefore, the association between glycemic markers and ICAS warrants further investigation.

5. Main Hypothesis/Study Questions:
(1) Primary question: Are glycemic markers measured at visit 5 independently associated with prevalent ICAS? (i.e. cross-sectional association)

(2) Secondary question: Are glycemic markers, specifically HbA1c, fructosamine, and glycated albumin assessed at baseline (visit 2) associated with prevalent ICAS at visit 5 independent of conventional risk factors? (i.e. longitudinal association)

Of note, acknowledging that the possibility of informative censoring may yield biased estimates at some degree, we will carefully evaluate and interpret the results of this secondary analysis including consistency with the published results on the association between the glycemic markers and clinical events.[5, 7]

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 Question
Design: Cross-sectional (primary) and longitudinal (secondary)

Inclusion/exclusion

Inclusion: the participants who had MRA exams with adequate or excellent image quality and protocol adherence scores to measure ICAS in Visit 5 (approximately n=1800, 67-90 years at Visit 5)

Exclusion: Those participants who have missing outcomes and relevant covariates.

For the cross-sectional analysis: those with treated diabetes or history of stroke at visit 5.

For the longitudinal analysis: those with treated diabetes or history of stroke at baseline (visit 2).

Measures of exposure

Glycated hemoglobin (HA1c), glycated albumin, and fructosamine (all measured at visits 2 and 5)

Outcome measures (visit 5)

Primary endpoint

Presence of any ICAS in any segment assessed

Degree of stenosis based on categorical assessment of ICAS (i.e. categorized as no detectable stenosis, <50%, 51%-70%, 71-99%, and occlusion)

Secondary endpoints

- Total number of ICAS in all analyzed segments per participant
- Presence of significant stenotic lesions (such as ≥51%)

Other covariates

The conventional risk factors we will use for adjustment are primarily those assessed at the visit 5 examination (cross-sectional analysis) and visit 2 examination (for the longitudinal analysis). These include age, sex, race, study center, body mass index (kg/m^2), smoking, alcohol consumption, physical activity, total cholesterol, LDL and HDL cholesterol, triglycerides, blood pressure/hypertension, history of cardiovascular disease (coronary heart disease, heart failure), use of antiplatelet drugs, use of statin and use of antihypertensive medications.

Analytic plan

We will calculate odds ratios (and 95% confidence intervals) of prevalence of any ICAS (and that of ICAS ≥51%) by levels of glycemic markers at visit 5 (cross-sectional analysis) or visit 2 (longitudinal analysis) using multivariable logistic regression. Separate models will be run for the cross-sectional and the longitudinal analyses. The exposure variables (glycemic markers) will be treated as categorical variables first to investigate possible non-linear relationship (Given the limited sample size we will consider categorizing either in tertiles/quartiles or using other approaches described below). Then, we will consider modeling as continuous variables or using splines to address potential non-linear relationship as needed.

We will estimate the strength of the association between ICAS and each explanatory variable, HbA1c, fructosamine, and glycated albumin, separately. In a recent ARIC

study, Selvin and colleagues divided fructosamine and glycated albumin into categories defined by the 70th, 71-96th, and >96th percentiles among those with no DM diagnosis, and these percentiles corresponded to HbA1c categories of <5.7, 5.7 to<6.4, and 6.4+ (%). [7] We plan to use similar strategy or similar absolute cutoff values in categorizing the three markers (recognizing that sample size may be limited for the upper category). In sensitivity analyses, we will further adjust for fasting glucose to investigate if the association of the studied marker is independent of conventional risk factors.

Consideration will be given to run ordinal logistic regressions since the outcome variable can be categorized as ordinal (0= no stenosis, 1=<50%, 2=51%-70%, 3=71-99%, 4=occlusion). To account for the probability sampling of being selected to the brain MRI, we will apply the weights provided by the ARIC Coordinating Center. In addition, we will use inverse probability weighting or multiple imputation to control for potential selection bias due to survival and non-response to visit 5, as recommended by the ARIC-NCS analysis committee.

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

_____ Yes **__X__** No overlap found

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 following two proposals are most related.
1) Proposal #2488 "Prevalence and Risk Factors of Intracranial Atherosclerosis in the ARIC Cohort" (First and last authors: Ye Qiao, and Bruce A. Wasserman)

We have communicated Dr. Wasserman's group at Johns Hopkins, and they consider that our proposal does not overlap with the previous proposal.

2) Proposal #2448 "Prevalence of Intracranial Atherosclerotic Stenosis (ICAS) and its Association with Vascular Risk Factors" (First and last authors: Fareed Suri, and Aaron Folsom)

The proposal (#2448) describes basic characteristics of ICAS including a cross-sectional association with conventional risk factors. The main focus on the present proposal is on a longitudinal association of long-term glycemic markers.

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, 2009.16, 2006.15)

___ 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.

REFERNCES

1. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. *Stroke* 1995;**26**:14-20.

2. Dolan H, Crain B, Troncoso J, Resnick SM, Zonderman AB, Obrien RJ. Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of Aging cohort. *Ann Neurol* 2010;**68**:231-240.

3. Suri MF, Johnston SC. Epidemiology of intracranial stenosis. *J Neuroimaging* 2009;**19 Suppl 1**:11S-16S.

4. Selvin E, Francis LM, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL, Steffes MW. Nontraditional markers of glycemia: associations with microvascular conditions. *Diabetes Care* 2011;**34**:960-967.

5. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010;**362**:800-811.

6. Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M, Coresh J. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *Lancet Diabetes Endocrinol* 2014;**2**:279-288.

7. Selvin E, Rawlings AM, Lutsey P, Maruthur N, Pankow JS, Steffes M, Coresh J. Fructosamine and Glycated Albumin and the Risk of Cardiovascular Outcomes and Death. *Circulation* 2015.

8. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lernmark A, Metzger BE, Nathan DM. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2011;**57**:e1-e47.