ARIC Manuscript Proposal #2977

PC Reviewed: 5/9/17 **Status:** _____ **Priority:** _2_
SC Reviewed: _____ **Status:** _____ **Priority:** ____

1.a. Full Title:

Relationship of migraine with visual aura and incident atrial fibrillation in the Atherosclerosis Risk In Communities study

b. Abbreviated Title (Length 26 characters):
Migraine with aura and atrial fibrillation

2. Writing Group:
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3. Timeline: 05/30/2017 (proposal submission)
             06/30/2017 (data acquisition)
             07/30/2017 (abstract submission to ISC 2018)
             12/31/2017 (manuscript submission)

4. Rationale:

Epidemiological studies have shown that migraine with visual aura is associated with increased risk of stroke based on meta-analysis of diverse cohorts of patients (IR 2.51, CI 95%, 1.52-4.14). Migraine with aura was associated with an increased risk of stroke/TIA symptoms and ischemic stroke events in the ARIC study population a decade ago (Strang et al., 2005). Since then, additional new/recurrent strokes have accumulated. Our recently investigation found that migraine with visual aura is independently associated with increased risk of cardioembolic stroke in ARIC. (Androulakis 2016) In this paper and the associated editorial (Sposato and Peterlin, 2016), questions have been raised if the association between migraine with visual aura and cardioembolic stroke may be explained by a higher rate of atrial fibrillation (AF) in this cohort. Among ARIC participants, headaches were classified at earlier visits as migraine with visual aura, migraine without aura, or non-migraine headaches.

A recent study assessed incident AF and its association with outcome in the ARIC cohort. After exclusions, 15 080 participants (mean [SD] age, 54.2 [5.8] years; 8290 women [55.5%]; 3831 black individuals [25.4%]) were included in this analysis. During a mean (SD) follow-up of 20.6 (6.2) years, there were 2348 cases of incident AF. The incident rates of AF per 1000 person-years were 8.1 (95%CI, 7.7-8.5) in white individuals and 5.8 (95% CI, 5.2-6.3) in black individuals. The rates of stroke, heart failure, CHD, and mortality were higher in black individuals with AF than white individuals with AF. (Magnani 2016)

Therefore, we propose to study the association between migraine with aura and AF as a potential mechanism explaining the previously reported association between migraine with aura and cardioembolic stroke.

5.   Main Hypothesis/Study Questions:

Is migraine with visual aura/migraine without aura independently associated with increased incidence of atrial fibrillation?

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 methodological limitations or challenges if present).

1. Study design:

Inclusion/Exclusion: Participants in the ARIC study completed a third clinic examination (1993 to 1995), when a lifetime history of headaches was ascertained. All participants at visit 3 will be included. Participants with missing headache information and those who do not meet the criteria as above will be excluded. Subjects with prior history of atrial fibrillation will be excluded. Those with race other than whites or black will be excluded due to limited sample size.

Main exposure: Headaches will be classified at earlier visits as migraine with visual aura, migraine without aura, or non-migraine headaches. (Androulakis 2016)

Main Outcome: Incident AF will be assessed by 3 methods: study ECGs, Hospital discharge codes, and death certificates. Standard, 10-second, 12-lead ECGs were obtained at baseline and at each of the subsequent follow-up examinations. Tracings were performed in the supine position using MAC PC Personal Cardiographs (Marquette Electronics Inc) and transmitted electronically to the ARIC ECG Reading Center (Epidemiological Cardiology Research Center, Wake Forest School of

Medicine, Winston Salem, North Carolina), where they underwent automated reading and coding. Tracings with AF were reviewed by a cardiologist. Incident AF was identified from hospitalizations or death certificates using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 427.31 or 427.32. (Alonso et al, 2009)

Co-variates: Age, gender, race (categorized as white, black, or other), smoking status, alcohol use, highest level of education, coronary artery disease (CAD), congestive heart failure (CHF) assessed by self-report. Body mass index was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic blood pressures of 140mmHg or higher, a diastolic blood pressure higher than 90mmHg, or use of medications to treat hypertension. Blood samples were obtained after individuals had fasted for 8 hours. Diabetes was determined by self-report of a physician diagnosis of diabetes, non-fasting blood glucose level of 200 mg/dL or higher, fasting blood glucose level of 126mg/dL or higher (to convert glucose to millimoles per liter, multiply by 0.0555), or use of insulin or other oral hypoglycemic medications. Physical activity is considered significant if performed for 4hrs/week for at least a month. Prevalent CAD was defined by electrocardiographic evidence of previous myocardial infarction (MI), history of physician diagnosed MI, or previous coronary revascularization procedure (bypass, angioplasty). Prevalent CHF was defined by the reported current intake of heart failure medication at visit 3 or evidence of manifest HF with presence of specific cardiac and pulmonary symptoms. PAD will be defined as Ankle Brachial Index (ABI) less than 0.90 (highly sensitive and specific for angiographically-diagnosed PAD). (Weatherly et al 2007) Abnormal ABI a marker of cardiovascular disease has been associated with Migraine. (Jurno et al 2010) We will also consider other markers of PAD captured in the ARIC study: 1) Rose Intermittent Claudication Questionnaire 2) Positive self-report of PAD determined during annual follow-up.

Gender interaction: Since female gender is associated with migraine, as well as atrial fibrillation related stroke outcome, we propose to test the specific gender interaction with and migraine→AF association.

Statistical analysis: All participants, with or without migraine, will be assessed for follow-up data on atrial fibrillation. Initially, the cumulative event-free rates for the time to incident atrial fibrillation will be estimated by the Kaplan-Meier product limit method, and the two groups, migraine with visual aura and migraine without aura will be compared by the log-rank test. Subsequently, the Cox proportional hazards ratio will be used to identify if migraine with visual aura is a risk factor for incident AF after adjusting for significant cofounders. The expected covariates assessed for cofounding and effect measure modification include risk factors for AF and medication.

The Cox proportional hazards ratio will be used to identify association between migraine with visual aura and incident AF after adjusting for significant, identifiable confounders. Several models may be run including covariates --demographic (i.e. age, race, sex), vascular risk factors (i.e. BMI, physical activity, hypertension, smoking, alcohol, socioeconomic status, CAD, CHF and PAD) and medications (example antimigraine drugs and oral contraceptives). These covariates will initially be assessed for evidence of significant confounding of migraine with visual aura→AF, before being included in a final model.

In order to test the link between Migraine with visual aura→AF→Cardioembolic Stroke, we will also look at the relationship between incident AF→stroke subtype. In essence we would be testing if AF is a mediator of the migraine with visual aura→cardioembolic stroke association. Since migraine with aura is a disease that manifests earlier in life than AF, it is unlikely that AF is a confounder.

Exposure Variable	Migraine with visual aura
Outcome Variable	Incidence of AF
Covariates	Sex Age Race BMI Physical activity Hypertension Diabetes Smoking Status Alcohol use Socioeconomic Status CAD CHF PAD Medications
Analysis	Cox proportional hazards ratio

2. Limitation:
1. Ascertainment of atrial fibrillation: conducted using 3 methods: study ECGs, Hospital discharge codes, and death certificates. It is possible that due to lack of long-term monitoring paroxysmal atrial fibrillation may be missed.
2. Headache classification: Headache classification criteria used in previous ARIC publications is different from the ICHD III beta criteria published in 2013. The migraine criteria used in ARIC is much stricter and more likely to have missed migraine diagnoses in patients who presented with bilateral headache, or lasted less than one year, or had history of migraine at younger ages, but likely have included migraineurs with high frequency migraine episodes in mid to later life.

Despite the limitations, this will be the first study to evaluate association between migraine and AF in both men and women. This proposal has important clinical implications and may help us better understand migraine-stroke link. For instance: if migraine with visual aura is associated with atrial fibrillation, clinicians should initiate full work up for AF in migraine with visual aura patients, and consider anticoagulation if warranted. Hence the results may help clinicians regarding stroke prevention strategy for migraineurs.

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)?**

1. Stange PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, Szklo M. Headache, cerebrovascular syndromes, and stroke: the Atherosclerosis Risk in Communities study. Neurology. 2005, May 10:64 (9):1573-7

2. Androulakis XM, Kodumuri N, Dennis L, Rosamond WD, Gottesman RF, Yim E, Sen S. Ischemic Stroke Subtypes and Relationship with Migraine with Aura in the Atherosclerosis Risk in Communities (ARIC) Study. Neurology 2016;87(24):2527-2532.

3. Sposato LA, Peterlin BL. Cardioembolism as the unsuspected missing link between migraine and ischemic stroke. Neurology. 2016;87(24):2504-2505.

4. Magnani JW, Norby FL, Agarwal SK, Soliman EZ, Chen LY, Loehr LR, Alonso A. Racial Differences in Atrial Fibrillation-Related Cardiovascular Disease and Mortality: The Atherosclerosis Risk in Communities (ARIC) Study. JAMA Cardiol. 2016;1(4):433-41.

5. Alonso A1, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009;158(1):111-7.

6. Weatherley BD1, Nelson JJ, Heiss G, Chambless LE, Sharrett AR, Nieto FJ, Folsom AR, Rosamond WD. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord. 2007;7:3.

7. Jurno ME1, Chevtchouk L, Nunes AA, de Rezende DF, Jevoux Cda C, de Souza JA, Moreira Filho PF. Ankle-brachial index, a screening for peripheral obstructive arterial disease, and migraine - a controlled study. Headache. 2010;50(4):626-30.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____Yes ___x_ No

11.b. If yes, is the proposal

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

            ____   **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.