

ARIC Manuscript Proposal #2534

PC Reviewed: 4/14/15
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Vascular events and relationship with stroke subtypes among migraine patients in the atherosclerosis risk in communities study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: **X. Michelle Androulakis MD, MS Souvik Sen MD, MS, MPH, Lauren Dennis MHA, Wayne D Rosamond, PhD, MS Rebecca Gottesman, MD, PhD Eyal Shahr, MD, MPH**

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

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3. Timeline: 03/30/2015

4. Rationale:

Epidemiological studies have shown that migraine with 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). Additional increased risk of ischemic stroke was found in women using oral contraceptives (OR 7.02; 95% CI, 1.51-32.68) and in smokers (OR 9.03; CI 95%, 4.22-19.34). Migraine with aura is associated with increased risk of TIA and non-disabling stroke compared with women with no history of migraine in WHS (women health study). Migraine with aura was associated with an increased risk of stroke/TIA symptoms and ischemic stroke events in the ARIC study population almost 10 years ago (Strang et al., 2005). Since then, a total of 987 first ever stroke events were identified during a median 19 year follow up in a recent study (Jones et al 2013). A total of 183 recurrent stroke events were identified during the same period (as of end of follow up, 12/31/2008). We expect more stroke events for this proposed study. Based on ARIC classification, all participants have completed a headache questionnaire at visit three. Among those who reported a lifetime history of severe headaches, headaches were separated as: migraine with aura, migraine without aura, or non-migraine headache. Total headache cases were 2706 (Hamedani et al., 2013). There is paucity of data regarding the ischemic stroke subtypes in these patients (ARIC participants) with history of migraine and/or headache. Data from WHS study suggest that most of the ischemic stroke among migraine with aura patients is due to “infarct of unknown mechanism” (Rist et al., 2010); however, no statistical analysis was performed among different stroke subtypes. We propose to investigate the relationship between ischemic stroke subtypes, vascular event subtypes and migraine with/without aura among ARIC cohort participants.

5. Main Hypothesis/Study Questions:

1. Is migraine with aura/migraine without aura associated with increased risk of ischemic stroke? If so, is it highly associated with stroke of undetermined etiology (cryptogenic stroke) compared to other stroke subtypes (large artery atherosclerosis, cardioembolism, and small vessel occlusion)?
2. Is migraine with aura/migraine without aura associated with increased risk of vascular event subtypes?

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).

7. Study design:

The ARIC study is an ongoing prospective cohort study designed to investigate the etiology of atherosclerosis and the variation in cardiovascular disease and risk factors by race and socioeconomic status. Participants were recruited from 4 locations: Forsyth County, NC; Jackson, MS; Northwestern suburbs of Minneapolis, MN; Washington County, MD. A total of 15,792 participants were enrolled at the first visit, which occurred between 1987 and 1989. This is an analysis of ischemic stroke subtype and vascular events among the ARIC cohort members through 2012/2013. The analyses will include both cross-sectional and longitudinal elements.

All participants, with or without migraine, will be assessed for stroke subtype and follow-up data on stroke recurrence will be included in the analysis. For purposes of question 1, a table will be constructed with stroke subtypes (R) and with or without migraine with/without aura (C) and an R x C χ^2 test will be used to detect any association between the two. Similarly for question 2, a table will be constructed with primary vascular event subtypes (stroke, MI, vascular death) and those with/without migraine with/without aura (C) and an R x C χ^2 test will be used to detect any association between the two. In both cases, odds ratio will be computed overall and stratified by risk factors and medication (estrogen, antiplatelet, lipid lowering and antihypertensive meds) to assess for effect measure modification.

Limitation:

1. Misclassification of ischemic stroke subtype: In the ARIC study, "cardioembolic stroke" is not based on a scientifically rigorous definition. According to the algorithm, it requires the presence of a possible cardio-embolic source. Presence of a possible cardioembolic source may not necessarily mean cardioembolism as the etiology of the ischemic stroke. Also, artery-to-artery embolic stroke (e.g., dislodged carotid plaque) is classified in ARIC as "atherothrombotic". Lacunar stroke in ARIC is based on some imaging features, regardless of the presence or absence of a "lacunar stroke syndrome". The definition may miss lacunar strokes with negative scans. Also, some lacunar strokes may be cardioembolic in etiology. Current methodology does not allow for clear distinction between these subtypes within a stroke etiological type.
2. Headache classification: Headache classification criteria used in previous ARIC publications is different from the ICHD II criteria. The criteria is much stricter and more likely to have missed migraine diagnoses in patients who presented with bilateral headache, or lasted less than one year, but likely have included migraineurs with high frequency migraine episodes.

Despite the limitations, this will be the first study to evaluate association between stroke etiological subtypes, vascular events, and migraine in **both men and women**; only number of cases, not statistical analysis, was performed to evaluate the association between migraine status and ischemic stroke subtype among women due to low case count (Rist et al., 2010). This proposal has important clinical implications and may help us better understand migraine pathophysiology. For instance: do recurrent migraine events promote formation of microemboli and cerebral hypoperfusion in small vessels? Therefore, increasing the risk of cryptogenic stroke? Additionally, results may help clinicians regarding stroke prevention strategy for migraineurs.

Inclusion

Participants in the ARIC study completed a third clinic examination (1993 to 1995), when a lifetime history of headaches was ascertained. Participants with headaches characteristic fulfill ARIC definition of migraine with/without aura or headache will be included.

All stroke diagnoses (first and recurrent) are based on computer derived diagnosis and physician medical record review, with differences adjudicated by a second physician reviewer. Classification required evidence of sudden or rapid onset of neurological symptoms lasting >24 hours or leading to death, in the absence of evidence of a non-stroke cause. Strokes are further classified according to etiologic subtype as thrombotic

brain infarction, lacunar infarction, cardioembolic stroke, ICH, or SAH according to criteria adopted from NSA.

Exclusion

Participants with missing headache information and those who do not meet the criteria as above will be excluded.

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.csc.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)?

Hamedani AG, Rose KM, B Peterlin L, Mosley TH, Coker LH, Jack CR, Knopman DS, Alonso A, Gottesman RF. Migraine and white matter hyperintensities: the ARIC MRI study. *Neurology*. 2013;81(15):1308-13.

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

Carson AP, Carson APL, Rose KM, Sanford CP, Ephross SA, Stang PE, Hunt KJ, Brown AC, Szklo M. Lifetime prevalence of migraine and other headaches lasting 4 or more hours: the Atherosclerosis Risk in Communities (ARIC) study. *Headache*. 2004; 44(1):20-8.

Rose KM, Carson AP, Sanford CP, Stang PE, Brown CA, Folsom AR, Szklo M. Migraine and other headaches: associations with Rose angina and coronary heart disease. Neurology. 2004 ;63(12):2233-9.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

Yes 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.csc.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.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.