

ARIC Manuscript Proposal # 2534a

PC Reviewed: 7/11/2017
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Stroke subtypes, Transient ischemic attacks and relationship with migraine in the Atherosclerosis Risk In Communities study

b. Abbreviated Title (Length 26 characters):

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. _____ **[please confirm with your initials electronically or in writing]**

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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).

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3. Timeline: 04/30/2015

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 with migraine using oral contraceptives (OR 7.02; 95% CI, 1.51-32.68) and in smokers (OR 9.03; CI 95%, 4.22-19.34) (MacClellan LR et al 2007). 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). It remains unclear whether the association between migraine with aura and stroke varies by stroke subtypes. Data from the 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. Among ARIC participants, headaches were classified at earlier visits as migraine with aura, migraine without aura, or non-migraine headaches. Since the initial work from Strang and colleagues, additional new/recurrent strokes and headaches cases have accumulated. We propose to evaluate prospectively on the relationship between migraine with/without aura (in late midlife) and subsequent stroke subtypes and TIAs in ARIC.

5. Main Hypothesis/Study Questions:

- A. 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)?
- B. Subgroup analysis: to determine if onset of headaches in migraine is associated with increased risk of ischemic stroke.
- C. Is migraine with aura/migraine without aura associated with increased risk of TIAs?

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:

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. Initially, the cumulative event-free rates for the time to vascular event (stroke, TIA, MI, and vascular death) will be estimated by the Kaplan-Meier product limit method, and the two groups, those with migraine with aura and those with migraine without aura, will be compared by the log-rank test. Subsequently, the Cox proportional hazards ratio will be used to identify risk factors for vascular events after adjusting for significant cofounders. The expected covariates assessed for confounding and effect measure modification include stroke risk factors and medication.

Limitation:

1. Misclassification of ischemic stroke subtype: 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. Even though current classification does not allow for clear distinction between these subtypes within a stroke etiological type, we don't necessarily expect misclassification to differ on the basis of migraine history.

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 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. All participants at visit 3 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 Nation Stroke Association.

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
 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 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>

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.

Leah R. MacClellan, PhD; Wayne Giles, MD; John Cole, MD; Marcella Wozniak, MD; Barney Stern, MD; Braxton D. Mitchell, PhD; Steven J. Kittner, MD. Probable Migraine with Visual Aura and Risk of Ischemic Stroke: The Stroke Prevention in Young Women Study. 2007;

Pamela M. Rist et al, Migraine and functional outcomes from ischemic cerebral events in women, *Circulation* 2010

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.