

ARIC Manuscript Proposal #3471

PC Reviewed: 9/10/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1. a. Full Title: Introducing a risk score for predicting ischemic stroke in migraine with aura

b. Abbreviated Title (Length 26 characters): Migraine with aura and risk for stroke (MARS)

2. Writing Group:

Tushar Trivedi MD, MPH, Alexandra Vezzetti PA-C, Petr Melikov MD PhD, Alvaro Alonso MD PhD, Lin Yee Chen MD, Elsayed Z. Soliman MD, Jared Magnani MD, MSc, Rebecca F. Gottesman MD PhD, Wayne D Rosamond, PhD, MS, Souvik Sen MD, MS, MPH

Corresponding author: Souvik Sen

Address: 1 Medical Park, Suite 230

Phone: 803.545.6073

E-mail: souvik.sen@uscmed.sc.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: **Wayne Rosamond PhD, MS**

E-mail: wayne_rosamond@unc.edu

3. **Timeline:** September 2019 (proposal submission)
November 2019 (data acquisition and analysis)
December 2020 (manuscript submission)

4. Rationale:

Migraine with visual aura has been associated with an increased risk of ischemic stroke (1,2). In recent ARIC studies we have shown an increased risk of atrial fibrillation and autonomic dysfunction among migraineurs (with aura) play an important role to link this association (3,4). Clinical course of migraine is variable, and identification of migraineurs at risk of ischemic stroke remains a challenge. To address this challenge, we propose to conduct a prospective analysis in a large cohort of well-characterized patients with migraine (with and without aura). Our main objective is to develop a risk score derived from a combination of independent predictors of ischemic stroke among those suffering with migraine with aura. The internal validity of this score will then be tested in the cohort of migraineurs with aura, migraineurs without aura and those without history of migraines. The proposed clinical scale can be used by clinicians for predicting ischemic stroke risk among those suffering with migraine with aura and considering preventive prophylaxis. Also it can be utilized by researchers for designing and interpreting clinical trials, and by policymakers for allocating limited health care resources.

5. Main Study Question/Objective:

To develop a clinical risk score for predicting ischemic stroke risk among those suffering with migraine with aura. This score will be derived from a combination of independent predictors of ischemic stroke among a cohort of participants with migraine with aura.

We also would evaluate the performance of stroke prediction scores to ARIC participants with migraine with aura and see if they work similarly to those without headache or with migraine without aura.

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:

Inclusion/Exclusion: Participants in the ARIC study completed a third clinic examination (1993 to 1995), when a lifetime history of headaches was ascertained. Any participant with missing information for headache history will be excluded. Subjects with prior history of ischemic stroke at visit 3 will also be excluded. Those with race other than whites or black will be excluded due to limited sample size.

Outcome of interest: Incident ischemic stroke.

Co-variates: We have shown in previous studies Atrial Fibrillation and Autonomic Dysfunction (as measured through Heart Rate variability) are potential mediators of the relationship between Migraine with aura and ischemic stroke. These variables will be included in the analysis. Heart Rate Variability (time and frequency domain) will be used as a marker for autonomic dysfunction, which has been measured at Visit 4 using 6 minutes EKG data. Further, we will consider following traditional cardiovascular risk factors as potential risk factor for ischemic stroke among migraineurs with aura: age, gender, education, race (categorized as white, black, or other), smoking status, alcohol use, coronary artery disease (CAD), congestive heart failure (CHF) assessed by self-report. Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared. Hypertension defined as a systolic blood pressures of 140 mmHg or higher, a diastolic blood pressure higher than 90mmHg, or use of medications to treat hypertension. Diabetes as determined by self-report of a physician diagnosis of diabetes. Autonomic dysfunction as measured using Heart Rate Variability (time and frequency domain) which has been calculated using 6 minutes EKG data. Prevalent CAD as defined by electrocardiographic evidence of previous myocardial infarction (MI), history of physician diagnosed MI, or previous coronary revascularization procedure (bypass, angioplasty). Medications including use of beta blockers, antimigraine drugs and oral contraceptives, and antiplatelet drugs.

Statistical analysis:

Primary analysis: We will prospectively evaluate participants in ARIC cohort with history of migraine with aura. Among this group the association of potential risk factors for ischemic stroke will be tested. Multivariate Cox proportional-hazards model will be used to determine the contribution of these variables. Finally, to develop a practical prognostic score, we will assign the risk factors identified by multi- variate analysis weighted points proportional to the β regression coefficient values (rounded to the nearest integer). A risk score will be calculated for each participant and the sub cohort will be divided into three categories: low risk, intermediate risk, and high risk. Survival will be estimated by the Kaplan–Meier method, and differences in survival between groups will be assessed using the log-rank test.

Secondary analyses: We also would evaluate the performance of stroke prediction scores to ARIC participants with migraine with aura and see if they work similarly to those without headache or with migraine without aura. We will test discrimination of the model using C-statistic and calibration (e.g. modified Hosmer-Lemeshow test for survival analysis).

Hypothetical table shells (some data shown is from previous manuscript/analysis):

Table 1: Baseline characteristics of participants with migraine with aura and hazard ratios for ischemic stroke

Risk Factors	Prevalence (N= 31/363)	Hazards Ratio	B Regression Coefficient
Age (>65)		1.9 (p=0.05)	0.65
Gender (F)		1.5 (p=0.10)	0.18
HTN		1.8 (p = 0.08)	0.56
DM		3.7 (p=<0.01)	1.31
SDNN (<100 msec)*		1.7 (0.04)	0.56
BMI		1.2 (0.32)	
CAD		0.8 (0.60)	
Smoking History		0.6 (0.21)	
Race (White)		1.3 (0.54)	

*SDNN = Standard Deviation for RR interval, low SDNN (<100 msec) suggest low heart rate variability, that is marker for autonomic dysfunction

Table 2: Weighted score for risk factors corresponding β regression coefficients

Risk Factor	Weighted score
Diabetes Mellitus	
Age (>65)	
Autonomic dysfunction - SDNN <100 msec	
Hypertension	
Gender (F)	

* Assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by the lowest β value, and rounded to the nearest integer.

Table 3. Prognostic Index (Hypothetical numbers):

High Risk Group	10-15
Moderate Risk Group	5-9
Low Risk Group	0-4

Figure 1 (Hypothetical data) Kaplan–Meier Survival Curves for the Development Cohort According to the Prognostic Classification.

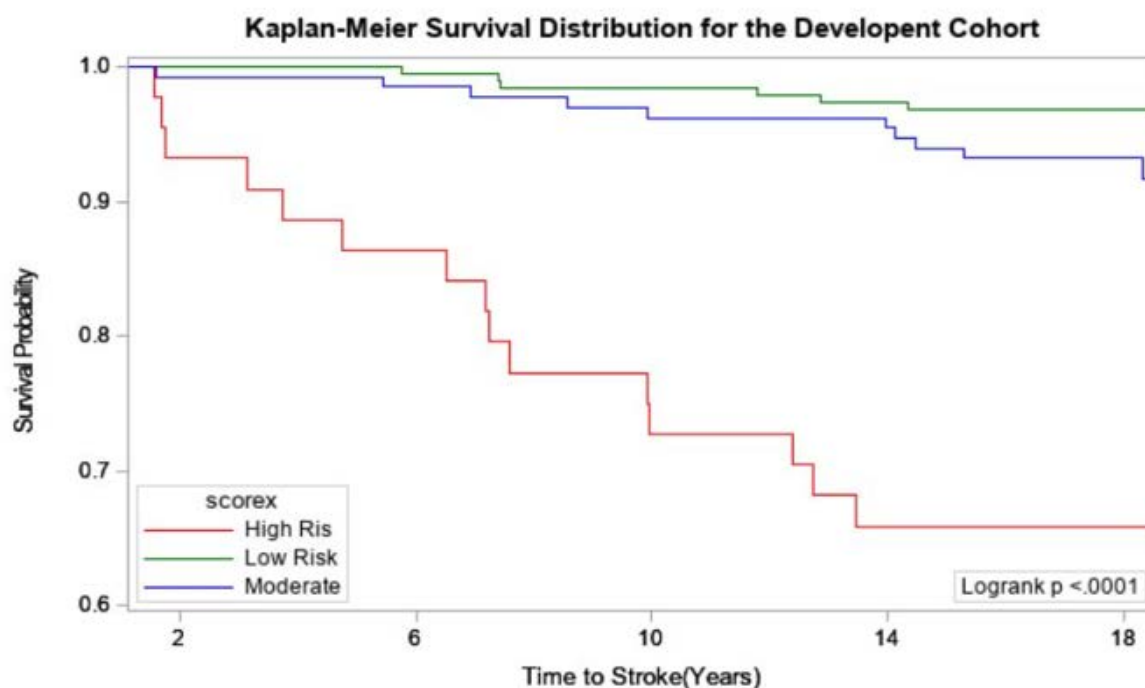


Figure 4: For internal validity we will run the prognostic index Kaplan-Meier survival curves on a cohort of migraineurs without aura and those with no history (Hypothetical figure not shown – but we would expect log rank p values would not be significant here between different risk score groups).

Limitation:

1. An important limitation of this risk score at this point would be lack of information on external validity. However, we plan to address this in the future by running the risk score scale on external datasets, which have information on both migraine with aura and incidental ischemic stroke. The availability of such dataset with heart rate variability data may be limited.
2. Another potential limitation of the study is limited size of the sub cohort of migraine with aura, and those who subsequently had ischemic stroke in this population. This may lead to model instability and wide confidence interval ranges. Hence we will assess the performance of

stroke prediction scores to ARIC participants with migraine with aura and see if they work similarly to those without headache or with migraine without aura.

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

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)?

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**

____ **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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.

Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ☒ No.

References:

1. Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, et al. Headache, cerebrovascular syndromes, and stroke: the Atherosclerosis Risk in Communities study. *Neurology*. 2005, 64:1573-7
2. Androulakis, X. M., Kodumuri, N., Giamberardino, L. D., Rosamond, W. D., Gottesman, R. F., Yim, E., & Sen, S. (2016). Ischemic stroke subtypes and migraine with visual aura in the ARIC study. *Neurology*, 87(24), 2527-2532.
3. Sen, S., Androulakis, X.M., Duda, V., Alonso, A., Chen, L.Y., Soliman, E.Z., Magnani, J., Trivedi, T., Merchant, A.T., Gottesman, R.F. and Rosamond, W.D., 2018. Migraine with visual aura is a risk factor for incident atrial fibrillation: A cohort study. *Neurology*, 91(24), pp.e2202-e2210.
4. Trivedi, T., Androulakis, M., Redd, K.T., Alonso, A., Soliman, E., Magnani, J., Gottesman, R., Rosamond, W. and Sen, S., 2019. Is Low Heart Rate Variability, a Marker of Autonomic Dysfunction, the Missing Link Between Migraine With Visual Aura and Cardioembolic Stroke?. *Stroke*, 50(Suppl_1), pp.A14-A14.