PC Reviewed: 3/10/15   **Status: A**   **Priority: 2**

SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title:

The CHA2DS2-VASc Score and the Risk of Ischemic Stroke by Atrial Fibrillation Status: The Atherosclerosis Risk in Communities (ARIC) Study.

   b. Abbreviated Title (Length 26 characters): CHA2DS2-VASc Score and Stroke

2.   Writing Group:
Writing group members: M. Chadi Alraies, Faye L. Lopez, Elsayed Z. Soliman, Alvaro Alonso, Lin Y. Chen, and others welcome

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

First author: M. Chadi Alraies, MD

Address: Department of Medicine
                University of Minnesota Medical School
                Division of Cardiovascular Medicine
                420 Delaware street SE, MMC 508
                Minneapolis, MN 55455, USA
            Phone: (216) 255-0008   Fax: (612) 624-4937
            E-mail: alrai005@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).

            Lin Y. Chen, MD, MS
            Cardiac Arrhythmia Center, Cardiovascular Division,
            Department of Medicine,
            University of Minnesota Medical School,
            420 Delaware Street SE, MMC 508,
            Minneapolis, MN 55455.
            Phone: 612-625-4401   Fax: 612-624-4937
            E-mail: chenx484@umn.edu

3.   Timeline:
            Statistical Analysis: 1 month

            Manuscript preparation: 3 months

4. Rationale:

Atrial fibrillation (AF) is the most common clinically significant heart rhythm disorder[1]. AF is a major independent predictor of ischemic stroke, resulting in a 5-fold increase in risk [1-3]. Several mechanisms may underlie this association: (1) blood stasis in the left atrium, particularly in the left atrial appendage (LAA) leading to clot formation and embolization, [4,5] (2) embolization from other sources, e.g., atherosclerotic plaques in the aorta,[6] and (3) shared risk factors such as hypertension, diabetes, or coronary heart disease. Recent evidence indicates a lack of temporal association between AF episodes and stroke events, which argues against stroke in patients with AF being entirely cardio-embolic.[7] This may suggest that AF is a marker of a patient population at increased risk for stroke due to atherothrombosis, hypertension, etc.[8,9]

The CHA2DS2-VASc score is a validated clinical prediction tool that is commonly used to estimate the risk of ischemic stroke and determine the need for anticoagulation in patients with AF.[8,10]. Recent studies have shown that the CHA2DS2-VASc score can also be used to predict the risk of ischemic stroke in patients without AF. A study of acute coronary syndrome patients without a history of AF reported that the incidence of stroke or TIA increased with increasing CHA2DS2-VASc score ($p < 0.001$, C-statistic=0.68), with an absolute annual incidence $\geq 1\%$ with CHA2DS2-VASc ≥ 4. The mortality rate was also greater in patients with higher CHA2DS2-VASc scores ($p<0.0001$)[11]. Another recent study demonstrated the ability of CHA2DS2-VASc scores in predicting postoperative strokes in patients undergoing various cardiac surgeries (odds ratio, 1.25 per 1-point increase in the CHA2DS2-VASc scores; 95% confidence interval, 1.05 to 1.5; p=0.014).[12] However, it remains unknown whether the CHA2DS2-VASc can predict ischemic stroke in individuals without AF in the general population. In addition, it is unclear for each stratum of CHA2DS2-VASc score, the extent to which the presence of AF adds to the risk of stroke. In other words, what is the incremental stroke risk that AF confers, over and above the CHA2DS2-VASc score?

We hypothesize that (1) the CHA2DS2-VASc has good discrimination for ischemic stroke in individuals without AF in the general population, and (2) depending on the CHA2DS2-VASc score, AF may play a greater or lesser role relative to vascular risk factors in determining the risk of stroke. For example, in patients with high CHA2DS2-VASc score (5-9), vascular risk factors play a more important role in determining the risk of stroke than AF. The increase in risk for stroke is mainly due to atherothrombosis, hypertension, and other atherosclerotic risk factors. Conversely, in patients with moderately high CHA2DS2-VASc score (2-4), AF may play a more important role in determining the risk of stroke.

The findings from our study may have important clinical and public health implications. First, if individuals with high CHA2DS2-VASc scores are found to have a high risk of stroke regardless of AF, it will raise the question of whether we should anticoagulate patients with a high CHA2DS2-VASc score in the absence of AF. Second, our findings may inform the selection of patients for procedures to ligate or occlude the left atrial appendage to prevent stroke: patients with a high CHA2DS2-VASc score may be deemed to be unsuitable because vascular risk factors (which will not be addressed by the procedure) may play a more important role in determining stroke risk.

5.   Main Hypothesis/Study Questions:

Aim #1: Evaluate the model discrimination of CHA2DS2-VASc score for ischemic stroke in ARIC participants without AF

Hypothesis #1: The CHA2DS2-VASc score will have good discrimination for ischemic stroke in ARIC participants without AF.

Aim #2: Compare the incidence of ischemic stroke for each stratum of CHA2DS2-VASc score between participants with and without AF

Hypothesis #2: For each stratum of CHA2DS2-VASc score, the incidence of ischemic stroke will be higher in participants with AF than those without AF. However, the incidence rate difference or ratio will be less in higher CHA2DS2-VASc stratum (6-9) than in moderate CHA2DS2-VASc stratum (2-5).

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 population

Aim #1
All ARIC participants without prevalent AF at visit 1.
Exclusion criteria: Missing covariates, race other than white/black, and prevalent stroke at baseline.

Aim #2
We will study the entire ARIC cohort.
Exclusion criteria: Prevalent AF at visit 1, use of anticoagulants within 1 year of AF ascertainment, missing covariates, race other than white/black, prevalent stroke.

Ascertainment of Atrial Fibrillation

The date of incident AF was defined as the date of the first evidence of its occurrence, and only 1 event will be considered per participant. AF cases will be identified from:

1. Hospital discharge record using *International Classification of Diseases, 9th edition* (ICD-9) code 427.31 or 427.32, not in the context of open chest cardiac surgery.
2. ECGs performed during study visits 1 – 4

Ascertainment of Ischemic Stroke

Stroke: Incident stroke events were identified in ARIC from annual telephone interviews, study visits, and surveillance of the ARIC community hospitals for all participants' hospitalizations. Hospital reports were abstracted and reviewed if the discharge diagnosis included a

cerebrovascular disease code (ICD-9 codes 430 to 438), if a cerebrovascular procedure was mentioned in the discharge summary, or if a CT or MR report showed evidence of cerebrovascular disease. ARIC adapted the National Survey of Stroke criteria for its stroke definition.[11] A computerized algorithm and physician reviewer independently classified the diagnosis of definite or probable stroke and the stroke subtype, with differences adjudicated by another physician.

Covariates

CHA2DS2-VASc score variables: Age, sex, heart failure, hypertension, diabetes, ischemic stroke (during follow-up), peripheral artery disease, and coronary heart disease

Statistical analysis

Aim #1

We will compute the CHA2DS2-VASc score for each participant at baseline. Participants will be categorized into 3 groups: CHA2DS2-VASc = 0-1 (referent group), CHA2DS2-VASc = 2-5, and CHA2DS2-VASc = 6-9. Person-years at risk will be calculated from the date of baseline until the date of ischemic stroke, death, loss to follow-up, or end of follow-up, whichever occurs first. To estimate the association of CHA2DS2-VASc score categories with risk of ischemic stroke, we will calculate hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards models. Participants will be censored at incidence of AF or when anticoagulants are initiated during follow-up.

We will compute the area under the receiver operator characteristic curve (AUC) for 10-year risk using methods which will account for censoring[13] to determine model discrimination.

Aim #2

Participants with incident AF will be identified. Each participant with incident AF will be matched with 3 other participants without AF by calendar year, age, race, and by CHA2DS2-VASc score. Follow-up time will be calculated from the date of AF ascertainment (similar date for matched subjects) until the date of ischemic stroke, death, loss to follow-up, or end of follow-up, whichever occurs first. Participants will be censored when anticoagulants are initiated during follow-up.

We will compute stroke incidence rates separately for participants with and without AF, stratified by CHA2DS2-VASc = 0-1, CHA2DS2-VASc = 2-5, and CHA2DS2-VASc = 6-9. Stroke incidence rate differences and ratios between AF and non-AF groups will be computed for each CHA2DS2-VASc category and will be compared across CHA2DS2-VASc categories using the Cochran–Mantel–Haenszel (CMH) test.

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)?

#2291 - Arterial structure and Function and Stroke in Atrial Fibrillation (Chen and Bekwelem)

#2290 - Obesity, Smoking and Alcohol Consumption with Ischemic Stroke in Atrial Fibrillation (Chen and Kwon)

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

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

__X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.12 AF ancillary study

*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.

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