ARIC Manuscript Proposal # 3014

PC Reviewed: 7/11/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Metabolic Syndrome with Ischemic Stroke Risk in Atrial Fibrillation.

b. Abbreviated Title (Length 30 characters): Metabolic Syndrome and Stroke in AF

2. Writing Group:
Writing group members: Writing group members: Joseph J. Decker, Faye L. Norby, Mary R. Rooney, Elsayed Soliman, Pamela L. Lutsey, Jim Pankow, Alvaro Alonso, Lin Y. Chen, others welcome.

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

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3. Timeline:
Statistical analysis: 3 months
Manuscript preparation: 4 months

4. Rationale:

The $CHADS_2$ and CHA_2DS_2-VASc scores are two validated risk stratification schemes for predicting stroke among patients with atrial fibrillation (AF). [1],[2] The $CHADS_2$ score includes congestive heart failure, hypertension, age >75, diabetes mellitus and prior stroke or transient ischemic attack (TIA). Although the $CHADS_2$ score allows for simple risk stratification, it has notable limitations with regards to the classification of patients as low or intermediate risk. Specifically, one study found that patients with a $CHADS_2$ score of 0 may have up to a 3.2% annual risk of ischemic stroke. [3] Additionally, the $CHADS_2$ scoring system classifies a large proportion of AF patients (61.9%) in the intermediate risk category.

The CHA_2DS_2-VASc score was promulgated to address the limitations of the $CHADS_2$ score and includes additional risk factors of vascular disease, age between 65 and 74 years, and female sex. In comparison to the $CHADS_2$ score, CHA_2DS_2-VASc has been shown to have better performance at identifying 'truly low risk' patients and categorizes a lower proportion of patients into the intermediate category (15.1%). [4] Despite these improvements, the CHA_2DS_2-VASc remains limited by a modest discriminatory power (C statistic, 0.61). [5]

The metabolic syndrome is a proinflammatory and prothrombotic state, which has been independently associated with an increased risk of new-onset AF and an increased risk of ischemic stroke. [6],[7] Current ATP III criteria define the metabolic syndrome as the presence of any three of the following five traits:

- Abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in)
- Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
- Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL cholesterol
- Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure
- Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose

Previously, in a small cohort of Taiwanese patients (n=721), the risk of stroke in patients with AF who had metabolic syndrome was assessed. This study demonstrated a graded association between the increasing number of components of metabolic syndrome and the risk of thromboembolic events and found that their proposed $CHADS_2$-MS score was superior to the $CHADS_2$ score in predicting thromboembolic risk. [8] Additionally, this study showed that patients with AF who had a $CHADS_2$ score of 0 or 1 and metabolic syndrome had a significantly increased risk of thromboembolic events than those who had a $CHADS_2$ score of 0 or 1 without metabolic syndrome. [8] This finding suggests that the metabolic syndrome may refine stroke risk stratification, particularly in patients who would otherwise be classified as low or intermediate risk based on a $CHADS_2$ score. However, it is unknown whether components of the metabolic syndrome would improve risk prediction of stroke, over and above the CHA_2DS_2-VASc score in the US population.

Therefore, we aim to assess the association between the metabolic syndrome and the risk of ischemic stroke in participants with AF in the ARIC study. We also aim to determine whether the metabolic syndrome would improve risk prediction of stroke, benchmarked against the CHA_2DS_2-VASc score.

5. Main Hypothesis/Study Questions:
Aim 1: Identify components of the metabolic syndrome (abdominal obesity, elevated triglycerides, low HDL) which are associated with increased risk of ischemic stroke, independent of CHA_2DS_2-VASc variables, in participants with AF.

Aim 2: Evaluate improvement in model discrimination (as measured by C-statistic) and risk classification (NRI and IDI) of the CHA_2DS_2-VASc score for ischemic stroke, from adding components of the metabolic syndrome.

6. Design and analysis (study design, inclusion/exclusion, outcome andother 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
We will include all individuals with incident AF in the ARIC cohort through the end of 2014. Incident AF was determined by resting ECGs obtained during 5 study examinations and hospital discharge records. We will exclude participants on anticoagulants within one year of AF diagnosis, missing metabolic syndrome data points, missing covariates, and race/ethnicity other than white or black.

Exposure measurement
Components of the metabolic syndrome not included in the CHA_2DS_2-VASc score including abdominal obesity, elevated triglycerides and low HDL. Abdominal obesity is defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in). Elevated triglycerides is defined as ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides. Low high-density lipoprotein (HDL) cholesterol is defined as <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL cholesterol. We will measure components of the metabolic syndrome based on the visit prior to the development of AF.

Outcome measurement
Ischemic stroke: Potential cases of stroke were identified from review of hospital records and death certificates. Further classification of stroke was then adjudicated by a panel of physicians with assistance of a computerized algorithm utilizing validated criteria from the National Survey of Stroke by the National Institute of Neurological Disorders. [9] Strokes were classified as definite or probable thrombotic stroke, definite or probable cardioembolic stroke, definite or probable subarachnoid hemorrhage, definite or probable brain hemorrhage, and possible stroke of undetermined type. All definite thrombotic strokes were further sub-typed as definite thrombotic lacunar and definite thrombotic non-lacunar strokes.

The primary endpoint in our study will be definite ischemic stroke. Ischemic stroke will include all definite thrombotic strokes and all definite cardioembolic strokes. Further

details on stroke identification and specific classification criteria in the ARIC study have been previously described. [10],[11]

Covariates

Age at time of AF ascertainment, sex, race, heart failure (HF), systolic blood pressure, diastolic blood pressure, use of anti-hypertensive medications, previous stroke or TIA, coronary heart disease (CAD), previous MI, peripheral arterial disease (PAD), diabetes mellitus, fasting blood glucose, aspirin use and warfarin use. Covariate data will be obtained from visit or annual phone follow-up prior to the development of AF.

Statistical analyses

We will estimate the association of abdominal obesity, elevated triglycerides and low HDL (all modeled as dichotomous variables based on definitions above) with incident ischemic stroke using Cox proportional hazard models adjusted for age, sex, race, study center (Model 1), and additionally CHA_2DS_2-VASc variables (HF, hypertension, diabetes, CAD, previous MI and PAD, history of stroke or TIA)(Model2).

We will test whether adding abdominal obesity, elevated triglycerides and low HDL to the CHA_2DS_2-VASc score will improve risk prediction of 1-year ischemic stroke risk and 5-year ischemic stroke risk. The components of metabolic syndrome will be modeled as dichotomous variables, using the definitions previously described. To assess model discrimination, we will compute the C-statistic using methods that account for censoring. To test model calibration, "goodness-of-fit" of the observed and expected number of events within estimated risk decile groups will be compared using the Grønnesby-Borgan statistic. Finally, to assess improvement in risk classification, categorical and continuous net reclassification improvement (NRI) and relative integrated discrimination improvement (IDI) for 1-year and 5-year risk prediction will be calculated. For categorical NRI, we will use the following categories for 1-year stroke risk: <1%, 1-<2%, and ≥2%.

Additionally, we will test whether the risk of AF-related ischemic stroke is stronger in individuals with components of metabolic syndrome than those without by testing for interaction. We will also evaluate whether the risk of ischemic stroke increases with increasing number of components of metabolic syndrome.

A preliminary analysis indicates that we have approximately 2,734 incident AF cases after baseline through 2014. Of these, 159 had incident stroke following AF.

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)?
S.M. Rodriguez-Colon, J. Mo, Y. Duan, et al. Metabolic syndrome clusters and the risk of incident stroke: the Atherosclerosis Risk in Communities (ARIC) Study. Stroke, 40 (2009), pp. 200–205.

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* _____)

___ 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.htmshows 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 __X No.

References:

1. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial fibrillation. *JAMA* 2001;285(22):2864-2870. PMID:11401607.

2. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns H. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach The Euro Heart Survey on Atrial Fibrillation. *Chest* 2010;137(2):263-272. PMID:19762550.

3. Olesen J.B., Torp-Pedersen C., Hansen M.L., and Lip G.Y.: The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. Thromb Haemost 2012; 107: pp. 1172-1179

4. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. European Heart Journal. 2012;33(12):1500–1510.

5. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns H. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach The Euro Heart Survey on Atrial Fibrillation. Chest

2010;137(2):263-272. PMID:19762550.

6. Watanabe H., Tanabe N., Watanabe T., Darbar D., Roden D.M., Sasaki S., and Aizawa Y. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. Circulation 2008; 117: pp. 1255-1260.

7. S.M. Rodriguez-Colon, J. Mo, Y. Duan, *et al.* Metabolic syndrome clusters and the risk of incident stroke: the Atherosclerosis Risk in Communities (ARIC) Study. Stroke, 40 (2009), pp. 200–205.

8. Tsai CT, Chang SH, Chang SN, Hwang JJ, Wu CK, Wang YC, et al. Additive effect of the metabolic syndrome score to the conventional CHADS2 score for the thromboembolic risk stratification of patients with atrial fibrillation. Heart Rhythm. 2014;11:352–7. doi: 10.1016/j.hrthm.2013.11.014.

9. Robins M WF. The National Survey of Stroke. Study design and methodology. *Stroke* . 1981;12:I7-11.

10. Rosamond WD, Folsom AR, Chambless LE, Wang C, Mcgovern PG, Howard G, et al. Stroke Incidence and Survival Among Middle-Aged Adults. *Stroke* . 1999;30:736–743.

11. Atherosclerosis Risk in Communities Study. Copies F, Contact P, Hill C. ARIC Manual 3: Surveillance component procedures,: Manual of OperationsVersion 6.2.