PC Reviewed: 1/14/14   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Arterial Structure and Function and Stroke in Atrial Fibrillation: The ARIC, Cardiovascular Health Study (CHS), and Rotterdam Study (RS)

  b. Abbreviated Title (Length 28 characters): Arterial Indices and Stroke in AF

2.   Writing Group:
      Writing group members: Wobo Bekwelem, Faye L. Lopez, Elsayed Soliman, Sunil Agarwal, Gregory Lip, Wei Pan, Aaron R. Folsom, Alvaro Alonso, Lin Y. Chen, others welcome.

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

      F**irst author**: Wobo Bekwelem, MD
      Address: Lillehei Heart Institute, Cardiovascular Division
                  Department of Medicine
                  University of Minnesota Medical School
                  420 Delaware Street SE, MMC 508
                  Minneapolis, MN 55455

                  Phone: (612) 625-7924   Fax: (612) 626-4411
                  E-mail: bekwe001@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).
      Name: Lin Y. Chen, MD, MS
      Address: 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

                  OR

Alvaro Alonso, MD, PhD
Division of Epidemiology and Community Health
School of Public Health, University Of Minnesota
1300 S. 2nd Street, Suite 300,
Minneapolis, MN 55416

Phone: (612) 626-859   Fax: (612) 624-0315
E-mail: alonso@umn.edu

3. Timeline:

Statistical Analysis: 3 months
Manuscript preparation: 3 months

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, causing considerable morbidity, mortality, and socioeconomic burden. AF afflicts more than 2 million Americans, and this figure is projected to increase to 5 to 12 million by 2050.[1, 2] Much of the morbidity associated with AF is attributable to a 5- to 6-fold increased risk of ischemic stroke.[3] Whereas the attributable risks for most stroke risk factors decline with advancing age, the attributable risks for stroke associated with AF dramatically increase with age, from 1.5% for those 50 to 59 years of age to 23.5% for those 80 to 89 years of age.[4]

Multiple risk factors of atherosclerosis have been associated with increased risk of stroke in AF. Indices of arterial structure and function, such as carotid intima-media thickness (cIMT) and pulse pressure (a surrogate of arterial stiffness) have been shown to be associated with AF. There is also compelling evidence from cohort studies that increased cIMT[5,6] and arterial stiffness[7-9] are associated with incident ischemic stroke in the general population. However, to our knowledge, no study has examined the effect of these indices of arterial structure and function on the risk of stroke in a large cohort of community dwelling individuals with AF.

Furthermore, numerous risk stratification schemes have been developed to define the risk of stroke and to guide warfarin therapy in AF patients. The major limitation of existing risk stratification schemes are poor discrimination and calibration[10]. A recent study from the Birmingham Atrial Fibrillation Treatment of the Aged showed that the predictive power of eight stroke risk stratification schemes was especially poor in patients >75 years (C statistic range, 0.55–0.62)[11]. Perhaps the most widely used of the published clinical risk scores is the $CHADS_2$ score (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus and prior Stroke or transient ischemic attack).[12] Despite its popularity, this score has limitations. First, a large proportion of AF patients (61.9%) are classified in the intermediate risk category. Second, even patients classified as low risk may experience event rates of 1.4% per year. Third, other risk factors such as peripheral

arterial disease were not included.[13] In response to these shortcomings, a revised score was developed, CHA_2DS_2-VASc, that also incorporates sex, vascular disease, and age 65–74 years.[14] CHA_2DS_2-VASc does classify a smaller proportion of patients into the intermediate category (15.1%), but suffers from modest discriminatory power (C statistic, 0.61).[14]

Therefore, we propose to assess the association of cIMT and carotid distensibility indices with incident ischemic stroke in AF participants in ARIC, and externally validate our findings in the Cardiovascular Health Study CHS) and the Rotterdam Study (RS). We will evaluate the role of pulse wave velocity in the RS. We also propose to evaluate the ability of these factors to improve risk prediction of stroke in participants with AF.

5.   Main Hypothesis/Study Questions:

Aim: Identify arterial indices that improve risk prediction of ischemic stroke in AF.
Hypotheses: Higher cIMT, lower carotid distensibility, and the presence of carotid plaque (a) are associated with ischemic stroke in AF, and (b) improve risk prediction of ischemic stroke in AF, over $CHADS_2$ and CHA_2DS_2-VASc scores.

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
All individuals with incident AF in the ARIC study through the end of 2010. The baseline for this analysis is visit 2 when cIMT and carotid distensibility data were available. Exclusion criteria: Participants with prevalent AF or atrial flutter at visit 2, participants with prevalent stroke at visit 2, , missing cIMT or carotid distensibility information, missing covariates, and race/ethnicity other than white or black.

Exposure measurement
cIMT (Exam 2)
cIMT was assessed in three segments: the distal common carotid (1 cm proximal to dilation of the carotid bulb), the carotid artery bifurcation (1 cm proximal to the flow divider), and the proximal internal carotid arteries (1 cm section of the internal carotid artery immediately distal to the flow divider). At each segment, 11 measurements of the far wall (in 1-mm increments) were attempted. The mean of the mean IMT measurements across these segments of both the right and the left sides was estimated.

Plaque: Trained readers adjudicated plaque presence or absence if two of the following three criteria were met: abnormal wall thickness (defined as cIMT >1.5mm), abnormal shape (protrusion into the lumen, loss of alignment with adjacent arterial wall boundary), and abnormal wall texture (brighter echoes than adjacent boundaries).[15, 16]

Carotid distensibility (Exam 2)

We will use arterial diameter data collected on the left common carotid artery (1 cm below the origin of the carotid bulb) during B-mode ultrasound examination of the carotid arteries. The diastolic arterial diameter (DAD) and the arterial diameter change (ADC) between systole and diastole from the left carotid artery during cardiac cycles will be used for this analysis.

The following indices will be analyzed:
1. Adjusted arterial diameter change (AADC) = ADC simultaneously adjusted for DBP, PP, PP^2, DAD, and height (in micrometers)
2. Peterson's elastic modulus (Ep) = (PPxDAD)/ADC (in kilopascals)
3. Young's elastic modulus (YEM) = [EpxDAD/2xIMT)] (in kilopascals)
4. stiffness index (β index) = Ln(SBP/DBP)/(ADC/DAD)
5. Distensibility coefficient (DC) = 2/Ep (10^{-3}/kPa).

DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure

Outcome measurement

Incident AF

AF cases will be identified from:
1) Hospital discharge records (ICD-9 code 427.31 and 427.32 – Atrial fibrillation/flutter)
2) ECGs performed during study visits

Incident ischemic Stroke

Incident stroke events were identified in ARIC from annual telephone interviews, study visits, surveillance of the ARIC community hospitals for all participants' hospitalizations, review of death certificates, physician questionnaires, coroner/medical examiner reports, and informant interviews. Hospital reports were reviewed if the discharge diagnosis included a cerebrovascular disease code (ICD-9 codes 430 to 438), if a cerebrovascular procedure was mentioned in the summary, or if the CT or MR report showed evidence of cerebrovascular disease. ARIC adapted the National Survey of Stroke criteria for its stroke definition. A computerized algorithm and physician reviewer independently confirmed the diagnosis of stroke. **Only incident stroke events that occurred after ascertainment of AF will be included in our analyses**.

Covariates

Covariates will be measured at the visit before AF ascertainment. These include age at time of AF ascertainment, sex, race, BMI, smoking status, alcohol consumption, systolic blood pressure, hypertension, eGFR, heart failure, diabetes, coronary heart disease, previous MI, peripheral arterial disease, aspirin use, and warfarin use.

Statistical analyses

cIMT, AADC, Ep, YEM, β index, and DC will be categorized into quintiles or used as continuous variables. In order not to assume linearity, the association of exposure variables with stroke will also be assessed using restricted cubic spline (RCS) plot with 5 knots, adjusted for age and sex. Cox proportional-hazards regression will be used to

assess cIMT, carotid plaque, and carotid distensibility indices in relation to incident stroke. Participants who developed stroke before incident AF will be censored.

> Model 1 will adjust for age, sex, race, and study center.
> Model 2: Model 1 + BMI, smoking status, alcohol consumption, systolic blood pressure, hypertension, heart failure, diabetes, eGFR, coronary heart disease, previous MI, peripheral arterial disease, aspirin use, and warfarin use

We will use the $CHADS_2$ and CHA_2DS_2–VASc scores as benchmarks to assess the role of arterial indices in enhancing risk prediction for stroke in AF. Several models will be considered: 1) benchmark + cIMT, 2) benchmark + plaque, 3) benchmark + cIMT + plaque, 4) benchmark + DC, 5) benchmark + AADC, 6) benchmark + Ep, 7) benchmark + YEM, and 8) benchmark + β index. We will describe the area under the receiver operator characteristic curve (AUC) for 5-year risk using methods which will account for censoring[18] for each of the models to determine model discrimination. Bootstrapping will be performed to conduct an internal validation[19] of the expanded models and to obtain confidence intervals for the differences in adjusted AUC between the models. To adjust for the over-optimism that can occur when the fit of the model is tested using the same data in which it was described, we will employ the method proposed by Harrell et al.[20]

We will calculate the net reclassification improvement (NRI) which examines the net effect of adding a marker to the risk prediction scheme using a statistic described by Pencina and colleagues,[23] and also "categoryless" NRI which assesses any upward or downward improvement reclassification; values greater than zero indicate improved reclassification.[24] Using Cox-proportional hazards, the 5-year ischemic stroke risk for each of the models will be calculated, and individuals will be classified into <5%, 5–10%, and >10%. The number of individuals who change risk groups (i.e., reclassified after adding arterial indices) will be described. To test the model calibration, we will compare the "goodness-of-fit" of the observed and expected number of events within estimated risk decile groups using the Grønnesby-Borgan statistic.[22] Large values of the test statistic (i.e., significant 'p' values) suggest poor model fit. Finally, we will estimate the integrated discrimination improvement (IDI)[23] which is the difference in an R^2-like statistic between the $CHADS_2$/CHA_2DS_2–VASc and $CHADS_2$/CHA_2DS_2–VASc plus models.

Limitations
1) It is possible that nonhospitalized stroke events that were not validated in the studies could influence the results. However, the magnitude of any potential underestimation of the rate of stroke is likely to be small (<5%).[25]
2) There may be misclassification of AF. However, prior analysis within the ARIC cohort to determine the validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity in the ascertainment of AF events.[26] In addition, the incidence of AF in ARIC is comparable to those obtained in other population-based studies.[2, 26,27]
3) Through the end of 2010, approximately 1,996 participants developed AF of who approximately 169 developed ischemic stroke after ascertainment of AF. We will meta-

analyze the results from ARIC with results from CHS and the RS to optimize statistical power.

4) Carotid measurements were obtained before AF ascertainment. However, carotid arterial indices increase with time suggesting that pre-AF measurements are likely to correlate with post-AF measurements. We found that cIMT from Visit 1 and 2 were strongly correlated (Pearson's correlation coefficient, r=0.6, p<0.0001).

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 ICTDER03 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**

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group? **____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)?
MS **#1897**: Chen - Improving Prediction of Atrial Fibrillation Using Carotid Intima-Media Thickness and Carotid Distensibility: The ARIC Study

The authors of the above manuscript proposal are included in the current proposal.

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
        _x_   A. primarily the result of an ancillary study   (Chen – Arterial Structure and Function and Atrial Fibrillation [2011.14])
        __   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.cscc.unc.edu/aric/forms/

12. 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.

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