**ARIC Manuscript Proposal # 1897**

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| **PC Reviewed: 2/14/12** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Improving Prediction of Atrial Fibrillation Using Carotid Intima-Media Thickness and Carotid Distensibility: The ARIC Study

**b. Abbreviated Title (Length 26 characters)**: Arterial Indices and Atrial Fibrillation

**2. Writing Group**:

Writing group members: Lin Y. Chen, Faye Lopez, Wei Pan, Aaron R. Folsom, Alvaro Alonso, others welcome.

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


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**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] Despite extensive literature on risk factors of AF, it is still difficult to determine an individual's risk of developing AF in a given time frame.[3] Only two risk scores have been developed to predict incident AF in the community. The Framingham AF risk score[4] has a moderately good discrimination (C statistic, 0.78) and incorporates age, sex, body mass index, systolic blood pressure (SBP), hypertension medication, PR interval, cardiac murmur, and heart failure. More recently, a risk score for AF was developed from Atherosclerosis Risk in Communities (ARIC) study.[5] This has moderately good discrimination (C statistic, 0.78) and incorporates age, race, height, SBP, hypertension medication, smoking status, cardiac murmur, left ventricular hypertrophy (LVH) and left atrial enlargement (LAE) from ECG, diabetes, heart failure, and coronary heart disease (CHD). The Framingham AF risk score, however, performed only modestly when tested in other cohorts such as CHS whites (C statistic, 0.68), and CHS African-Americans (C statistic, 0.66).[6]

Recently, evidence has emerged that structural and functional changes in the arteries may increase AF risk.[7, 8] **Increased arterial stiffness has been proposed to increase AF risk by causing left ventricular hypertrophy,[9] impaired ventricular relaxation,[10, 11] and left atrial enlargement.[12]** Supporting this hypothesis, the Framingham Heart Study reported that higher pulse pressure (a surrogate measure for increased proximal aortic stiffness)[13] independently predicts incident AF.[7] The Rotterdam Study[8] reported that the risk of AF was almost 2-fold higher in the highest quartile of cIMT than in the lowest quartile. Thus, arterial indices are potential factors that can be used to improve risk prediction of AF, over and above the two existing clinical risk scores. Measurement of cIMT and carotid distensibility indices potentially represents a non-invasive and patient-acceptable method that can be employed at the bedside. The potential utility of cIMT in risk prediction is underscored by the recommendation of a Class IIa indication for cardiovascular risk assessment in asymptomatic adults at intermediate risk by the 2010 American Heart Association Task Force on Practice Guidelines.[14]

**5. Main Hypothesis/Study Questions**:

**Aim: Identify arterial indices that improve risk prediction of AF.**

Hypotheses: Higher cIMT and lower carotid distensibility (a) are associated with higher incidence of AF, and (b) improve risk prediction of AF, over and above Framingham AF and ARIC AF risk 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**

We will study the entire ARIC cohort.
Exclusion criteria: Participants with AF or atrial flutter on a baseline ECG, missing cIMT, missing carotid distensibility, missing covariates, and race/ethnicity other than white or black

**Exposure measurement**

cIMT (Exam 1)

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. 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)

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 – Atrial fibrillation)
2) ECGs performed during study visits 1 – 4
3) Death certificates

**Covariates**

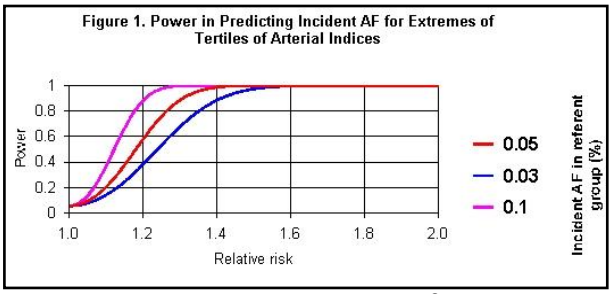
Age, sex, race, height, SBP, hypertension medication, smoking status, cardiac murmur, ECG-based LVH, ECG-based LAE, diabetes, heart failure, and CHD.

**Statistical analysis**

cIMT, AADC, Ep, YEM, and β index will be categorized into tertiles or used as continuous variables. Cox proportional-hazards regression will be used to assess cIMT and carotid distensibility indices in relation to incident AF. Model 1 will adjust for age, sex, race, and ARIC field center. Model 2 will additionally adjust for height, SBP, hypertension medication, smoking status, cardiac murmur, ECG-based LVH, ECG-based LAE, diabetes, heart failure, and CHD.

We will use the **Framingham risk score for AF**[4] (FRS-AF) and the **ARIC risk score for AF**[5](ARIC-AF) as benchmarks to assess the role of arterial indices in enhancing risk prediction of AF. Several models will be considered: 1) benchmark + cIMT, 2) benchmark + plaque, 3) benchmark + cIMT + plaque, 4) benchmark + AADC, 5) benchmark + Ep, 6) benchmark + YEM, and 7) benchmark + β index. We will describe the area under the receiver operator characteristic curve (AUC) for 10-year risk using methods which will account for censoring[17] for each of the models to determine **model discrimination**. Bootstrapping will be performed to conduct an internal validation[18] 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.[19]

Using Cox-proportional hazards, the 10-year AF risk for each of the models will be calculated, and individuals will be classified into <5%, 5–15%, and >15%.[4] 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.[20] Large values of the test statistic (i.e., significant 'p' values) suggest poor model fit. 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,[21] and also **"categoryless" NRI** which assesses any upward or downward improvement reclassification; values greater than zero indicate improved reclassification.[22] Finally, we will estimate the **integrated discrimination improvement (IDI)**[21] which is the difference in an $R^2$-like statistic between the FRS-AF/ARIC-AF and FRS-AF/ARIC-AF plus models. AUC, NRI, and IDI will be calculated for 10-year follow-up and confidence intervals will be furnished by bootstrapping.




Power Calculation

Figure 1 shows the statistical power for predicting incident AF. Assuming an AF risk of 5% in the referent category, we will achieve a power of 99% in detecting a relative risk of 1.5 comparing the extremes of tertiles of arterial indices. Considering that the risk of AF in the highest quartile of cIMT was almost 2-fold higher than the lowest quartile in the Rotterdam Study,[8] we are more than adequately powered for the study aim.

**Limitations**

1) There may be misclassification of AF outcome events. 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.[23] In addition, the incidence of AF in ARIC is comparable to those obtained in other population-based studies.[2, 23, 24]
2) Most AF cases were ascertained more than 10 years after baseline carotid ultrasound examination. We will conduct a sensitivity analysis by examining cIMT at Visit 2 for the entire cohort, and cIMT obtained at Visits 3 and 4 in a sample of the ARIC cohort in relation to incident 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 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)?**

Manuscript proposal #1578: Prediction of atrial fibrillation in the community: the CHARGE Consortium
The lead author of this proposal (Alvaro Alonso) is 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 (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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