1.a. Full Title: Development of a Risk Score for Predicting Atrial Fibrillation in a Bi-racial Cohort: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): AF Risk Prediction

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3. Timeline:
- Manuscript Preparation: March 2009
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4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, and is associated with increased stroke and cardiovascular morbidity and mortality\(^1\). AF currently affects more than 2.2 million Americans, and the lifetime risk for development of AF in men and women over 40 years of age is 1 in 4\(^2\). AF is an important risk factor for incident stroke\(^3\)-\(^5\) and heart failure\(^4\),\(^6\), and also carries poor prognosis in heart failure patients\(^7\).

Risk factors for AF include increasing age\(^8\),\(^9\), male gender\(^8\),\(^10\), obesity\(^11\), hypertension\(^12\),\(^13\), diabetes\(^14\),\(^15\), metabolic syndrome\(^16\), obstructive sleep apnea\(^17\),\(^18\), chronic obstructive pulmonary disease\(^19\),\(^20\), and heavy alcohol intake\(^21\)-\(^23\). Additionally, recent cardiac surgery\(^19\),\(^20\) and structural abnormalities, such as left ventricular hypertrophy, left atrial enlargement\(^24\), and restrictive left ventricular diastolic filling\(^25\), increase the risk of incident AF.

Although some of the previously mentioned risk factors have been well studied in relation to incident AF on a population level, information on a person’s individual risk of developing AF is lacking. This information may aid in risk stratification and in the selection of appropriate candidates for preventive therapies. Risk scores have been successfully developed for coronary heart disease\(^26\), stroke\(^27\), and heart failure\(^28\). Additionally, a risk score has been developed for predicting stroke or death with new-onset AF\(^29\); however, a risk score for the prediction of AF has not been developed. Therefore, we propose to develop a risk score for predicting AF incidence using the Atherosclerosis Risk in Communities study for both black and white men and women.

5. Main Hypothesis/Study Questions:

We aim to determine a risk score for atrial fibrillation based on a combination of known risk factors that maximizes discrimination, i.e., the ability to predict who will have an incident event and who will not using Cox regression and receiver operating characteristic (ROC) curves.

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).

Individuals without ECG or who had diagnosed AF or atrial flutter at baseline will be excluded from analyses. We will additionally exclude those who did not fast for at least 8 hours before the baseline exam. We will censor individuals who develop atrial
flutter without AF at their atrial flutter diagnosis date. The independent variables in this analysis include, but are not limited to, age, sex, race, education, income, BMI/obesity, waist circumference, height, systolic and diastolic blood pressure, pulse pressure, hypertension treatment, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, lipid lowering medication, diabetes, smoking, alcohol intake, physical activity, myocardial infarction, heart failure, and ECG-based left ventricular hypertrophy. The dependent variable is incident AF. Incident cases of atrial fibrillation will be identified through hospital discharge codes (ICD-9 code 427.31), death certificates (underlying cause of death ICD-9 code I48 or 427.3), and ECG’s performed during follow-up visits. Individuals who develop both atrial flutter and AF during follow-up will be considered as having an event and will be censored at the earliest date of either AF or atrial flutter.

We will follow the methods described by Sullivan, et al\textsuperscript{30} to determine a risk score for AF. The 10-year risk of developing AF will be estimated, and we may also consider estimating the 5- and 15-year risks. First, we will stratify each independent variable into categories and run Cox regression analyses to obtain the regression coefficients for the categories of each variable. Second, we will determine the reference values for each category. We will use the midpoint value of each category as the reference, except for categories that may have extreme outliers. For example, if \( \geq 160 \) is the highest category for systolic blood pressure (SBP), we will use the midpoint between 160 and the 99\textsuperscript{th} percentile of the observed SBP as the reference. Third, we will pick one category for each risk factor as the referent or “base” category. This category will be assigned 0 points and the other categories for that variable will be assigned positive numbers if they reflect a less healthy state and negative numbers if they reflect a more healthy state than the base category. Fourth, we will calculate how far each category is from the base category in regression units by the following equation:

\[
\beta_i(W_{ij} - W_{i\text{REF}}),
\]

where \( \beta_i \) is the regression coefficient, \( W_{ij} \) is the reference value of each category, and \( W_{i\text{REF}} \) is the base category for a particular variable. Fifth, a constant will be set corresponding to the number of regression units that equate to 1 point. For example, we would multiply the regression coefficient for a continuous age variable by 5 if the age categories were set up in 5-year increments. Sixth, we will divide the \( \beta_i(W_{ij} - W_{i\text{REF}}) \) for each category by the constant to determine the points associated with each category. Finally, we will determine the risk of developing AF associated with each possible point total by multiplying the constant by each point total (if we use the continuous age regression coefficient to determine the constant, we will also need to add this back in our calculations).

Once the risk score for AF is completed, we will use ROC curves and estimate the area under the curve (AUC) to assess the performance of our risk score. To conduct the ROC curve analysis, we will use the methodology developed by Chambless and Diao, which takes into account the presence of censoring in survival data\textsuperscript{31}. For our risk score determination, we will consider each of the above mentioned independent variables. However, we may find that some of these variables do not contribute to the risk score (by not increasing the AUC compared to a risk score without that variable), and these will be excluded when appropriate. By comparing ROC curves, we will determine whether the risk scores should be computed separately by sex and/or race, or if a pooled risk score is as predictable as these separate risk scores. We will use bootstrapping to determine a
confidence interval around our ROC curve, taking at least 1000 samples with replacement, for internal validation of our risk score. We will additionally compare our risk score to the Cox regression equation to see if our risk score predicts AF as well as plugging in specific values for each variable into a regression equation. Finally, we will use the ARIC and calibrated Framingham CHD risk scores to predict AF, in order to determine whether or not a separate risk score for AF better predicts incident events than a validated CHD risk score.

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.cscce.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 # 1351: Alonso, et al. Incidence of atrial fibrillation in a bi-racial cohort: the ARIC study
**MS # 1156: Soliman, et al.** Ethnic distribution of electrocardiographic predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the ARIC Study

**MS # 1389: Chamberlain, et al.** Metabolic Syndrome and Risk of Incident Atrial Fibrillation among Whites and Blacks in the Atherosclerosis Risk in Communities (ARIC) Study

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 (list number* __2008.09_)
   ____  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/](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.

References:


