ARIC Manuscript Proposal # 1628

PC Reviewed: 4/13/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Absolute and attributable risk of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Low risk factor profile and AF

2. Writing Group:
Rachel Huxley, Alvaro Alonso, Aaron R. Folsom, Sunil K. Agarwal, Laura Loehr, Elsayed Z. Soliman, Rich Maclehose, others welcome

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

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3. Timeline:
Data analysis – 3 months
First draft of the manuscript – 3 months

4. Rationale:
Atrial fibrillation (AF) is the most common form of cardiac arrhythmia seen in clinical practice, affecting an estimated 2.2 million Americans [1]. Individuals with AF have between two to seven times the risk of stroke compared with unaffected individuals, and

moreover, AF doubles the mortality rate from cardiovascular disease and overall mortality [2,3]. AF primarily affects older individuals and it is more prevalent in Whites than in African Americans [4,5], although the reasons for this are unknown.

Several prospective cohort studies have reported on a range of possible risk factors for AF with equivocal results. Still, evidence exists for an association of several risk factors with the risk of AF. These factors include cardiac disorders such as heart failure, valvular heart disease, myocardial infarction, and cardiovascular risk factors such as hypertension, obesity, diabetes, metabolic syndrome, and smoking [6]. However, results are conflicting about the association of other lifestyle factors such as alcohol consumption [7] or physical activity [8], with the incidence of AF. The discrepancies in study findings may be due in part to one or more of the following methodological limitations: smaller effect size, limited power, exposure misclassification, under-ascertainment of AF, and competing risk of death. More importantly, previous studies have not considered the burden of AF among individuals with an optimal risk -profile for AF.

The ARIC study provides an ideal opportunity to study the association between an optimal risk factor profile and the incidence of AF. Moreover, large number of events in both Whites and African-Americans may help to elucidate whether differences exist between these groups, which previously has not been possible. We understand that the power to detect such differences will be limited for many risk factors.

5. Main Hypothesis/Study Questions:

i. To determine the risk of AF among individuals with an optimal risk factor profile based on the absence of major established risk factors for AF.

ii. To determine the population attributable fraction of AF due to these risk factors

iii. To evaluate whether differences exist between whites and African-Americans regarding their risk of AF and the attributable risk from established risk factors for AF.

We hypothesize that the incidence of AF among individuals with an optimal risk factor profile will be lower from those with borderline risk factors. Also, given the higher prevalence of established cardiovascular risk factors in African-Americans, we hypothesize that population attributable risks from these risk factors will be higher in African-Americans than whites.

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).

We will assess the association between optimal risk factor profile and AF risk using a longitudinal data analysis approach. For all analyses, we will exclude individuals with

ECG-based AF or unreadable ECGs at visit 1, those with missing variables for any of the covariates and those who did not fast before blood samples were collected.

Exposure

Based on previous epidemiologic evidence [6, 8] we will categorize individuals as having an optimal risk factor profile if they meet all the following criteria:

- No history of cardiac disease (heart failure or coronary artery disease)
- Systolic blood pressure (BP) <120 mmHg and diastolic BP <80 mmHg and no use of antihypertensive medication
- Body mass index < 25 kg/m^2
- Fasting blood glucose <100 mg/dL and no use of antidiabetic medication and no history of physician-diagnosed diabetes
- Never smoker

Borderline risk factor profile will be defined as having any of the following criteria and no elevated risk factor profile characteristics (see below):

- Systolic BP 120-139 mmHg and/or diastolic BP 80-89 mmHg, and no use of antihypertensive medication
- Body mass index 25-<30 kg/m^2
- Fasting blood glucose 100-125 mg/dL and no use of antidiabetic medication and no history of physician-diagnosed diabetes
- Former smoker

Elevated risk factor profile will be defined as having any of the following criteria:

- History of cardiac disease (heart failure or coronary artery disease)
- Systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or use of antihypertensive medication
- Body mass index ≥30 kg/m^2
- Fasting blood glucose ≥126 mg/dL or non-fasting blood glucose ≥200 mg/dL or use of antidiabetic medication or history of physician-diagnosed diabetes
- Current smoker

Outcome

Incident cases of AF identified in the follow-up through the end of 2007 from three sources: ECGs done at study visits, presence of AF ICD9 (427.31 or 427.32) code in a hospital discharge, or AF listed as any cause of death. Hospitalizations with AF associated with cardiac surgery (ICD-9 codes 35.X, 36.X) will not be considered events. Date of AF incidence will be the earliest of any AF diagnosis.

Statistical analysis

Means and standard deviations (SD) for the continuous variables and percentages for the categorical variables will be obtained separately for men and women and for White and African American participants. We will determine the age- and gender-standardized prevalence of optimal and borderline risk factors, and the age- and gender-standardized incidence of AF by levels of optimal risk factors, separately in whites and African-Americans. Associations between an optimal risk factor profile at baseline and the

incidence of AF will be estimated using Cox proportional hazards models. Separate analyses will be conducted in men and women, and in whites and African-Americans and models will adjust for age, study site, education, income and height. We will explore the assumption of proportional hazards adding to the model an interaction term between follow-up time and exposure of interest, computing Schoenfeld residuals, and by inspection of the log(-log[survival function]) curves.

Population attributable fractions will be computed according to the following formula [9]:

$$PAF = \sum_{i=0}^{k} pd_i \left(\frac{RR_i - 1}{RR_i} \right)$$

where pd_i is the proportion of cases falling into *i*th exposure level and RR_i is the relative risk comparing *i*th exposure level with unexposed group (*i*=0). Relative risks will be obtained from log-binomial models fitted with SAS PROC GENMOD. Alternatively, we will estimate PAFs and their 95% confidence intervals using the SAS macro developed by Spiegelman et al [Spiegelman D, et al. Canc Causes Contr 2007;18:571-9]. Differences between PAFs will be tested by bootstrapping.

Limitations

In our primary analysis, the main concern is that misclassification may exist in outcome ascertainment although preliminary analyses suggest a positive predictive value of ~90% for AF diagnosis done through hospital discharge codes, implying a limited amount of misclassification [4]. Additional limitations include residual confounding and misclassification of the exposure at baseline and due to their time-varying nature.

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)?

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* 2008.12)

___ 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.

6. References

1. A.S. Go, E.M. Hylek and K.A. Phillips *et al.*, Prevalence of diagnosed atrial fibrillation in adults. National implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, *JAMA* **285** (2001), pp. 2370–2375.
2. W. Rosamond, K. Flegal and K. Furie *et al.*, Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, *Circulation* **117** (2008), pp. e25–e146.
3. E.J. Benjamin, P.A. Wolf and R.B. D'Agostino *et al.*, Impact of atrial fibrillation on the risk of death: the Framingham Heart Study, *Circulation* **98** (1998), pp. 946–952. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study.
4. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ and Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: The

Atherosclerosis Risk in Communities (ARIC) study American Heart Journal 2009; 158:111-117.
5. Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. Diabetes Care 2009; 32:1851-56.
6.Benjamin E, et al. Prevention of atrial fibrillation: report from a National Heart, Lung, and Blood Institute Workshop. Circulation 2009;119:606-18.
7. Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in women. JAMA. 2008;300(21):2489-96.
8. Mozaffarian D, et al. Physical activity and incidence of atrial fibrillation in older adults: the Cardiovascular Health Study. Circulation 2008;118:800-7.
9. Rockhill B, et al. Use and misuse of population attributable fractions. Am J Publ Health 1998;88:15-19.

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