ARIC Manuscript Proposal # 1840

PC Reviewed: 9/13/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
New-onset atrial fibrillation and risk of all-cause mortality and cardiovascular disease in whites and African Americans: the ARIC study

b. Abbreviated Title (Length 26 characters): AF and CV outcomes

2. Writing Group:
Alvaro Alonso, Sunil K Agarwal, Elsayed Z. Soliman, Lin Y Chen, Faye L Lopez, Laura R. Loehr, others welcome

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

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3. Timeline:
We plan to submit preliminary results to the AHA EPI/NPAM meeting (deadline October 1). A final manuscript will be submitted for publication before the conference in March 2012.

4. Rationale:

Atrial fibrillation (AF), the most common arrhythmia in clinical practice, affects more than 2 million individuals in the US.[1] This number is expected to increase with population aging and an increased prevalence of some cardiovascular risk factors.[2] AF has been associated with a higher risk of overall mortality, ischemic stroke, and heart failure.[3-7] However, a majority of these studies have been conducted in mostly white populations. The impact of AF on mortality and cardiovascular disease (CVD) in African Americans is not well defined. This is particularly relevant given the higher incidence of CVD in African Americans compared to whites.[8]

We propose to use data from the ARIC cohort to estimate the impact of new-onset of AF on subsequent risk of CV outcomes, particularly stroke, and overall mortality in whites and African Americans separately.

5. Main Hypothesis/Study Questions:

Aim 1: To calculate all-cause mortality rates in whites and African American with and without AF.

Aim 2: To estimate the association between AF and all-cause mortality in whites and African Americans after accounting for differences in CV risk factors.

Aim 3: To calculate rates of stroke, heart failure, and CHD in whites and African Americans with and without AF

Aim 4: To estimate the association between AF and stroke, heart failure, and CHD in whites and African Americans after accounting for differences in CV risk factors.

- ➔ We hypothesize that all-cause mortality, stroke, CHD, and heart failure rates will be higher in individuals with AF compared to those without AF in both racial groups.
- ➔ We hypothesize that the difference in all-cause mortality, stroke, CHD, and heart failure rates associated with AF will be larger in African Americans than whites, given the higher CV risk in the former.
- ➔ We hypothesize that AF will be associated with a higher risk of all-cause mortality, stroke, CHD, and heart failure even after adjustment for CV risk factors, and that this association will be of similar magnitude in both whites and African Americans.

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).

<u>Study design</u>

Prospective analysis of the ARIC cohort

Exclusion/inclusion criteria

For all analysis, we will exclude individuals with prevalent AF, those with low quality or missing ECG, and will apply the usual exclusion criteria by race/center (nonwhites in the Minnesota and Washington Co centers, nonwhite or non-African-American in Forsyth Co).

For each outcome, we will apply additional exclusion criteria:

- All-cause mortality: no additional exclusion criteria
- CHD: prevalent CHD at baseline
- Heart failure: prevalent heart failure at baseline
- Stroke/ischemic stroke: prevalent stroke at baseline

Main exposure variable

New onset of AF, identified from study ECGs, hospitalizations, or death certificates.[9] AF associated with cardiac surgery will not be included.

Main outcome variables

- All-cause mortality
- Total stroke
- Ischemic stroke [numbers by race might be too small to study this outcome]
- Heart failure
- CHD (defined as definite or probable MI, or fatal CHD)

Other variables

Variables to be consider as covariates in the models include: race, age, sex, center, education, body mass index, smoking (current, past, never; pack-years), hypertension (systolic blood pressure, use of antihypertensive medications), diabetes, alcohol intake, hypercholesterolemia (total cholesterol, LDL-cholesterol, use of lipid lowering medications). We will use information from baseline and follow-up visits.

Statistical analysis

Aims 1 and 3

For each different outcome (all-cause mortality, stroke, heart failure, CHD), person-time will be computed from baseline to event occurrence or censoring, and assigned to the AF group starting on the date of the first diagnosis of AF for individuals who developed AF during follow-up. Otherwise, person-time will be assigned to the non-AF group (from baseline to AF diagnosis in those who developed AF; from baseline to end of follow-up in those who did not develop the arrhythmia). Incidence rates will be calculated dividing the number of events by the AF-exposed person-time and non-AF-exposed person-time. Calculations will be performed separately for whites and African Americans, standardizing by age and sex using the overall ARIC age/sex distribution as standard population. If

the number of events is sufficient, we will calculate age, sex and race-specific rates by AF status.

Aims 2 and 4
We will use Cox proportional hazards models with AF as a time-dependent exposure to determine the association of AF incidence with death and other CVD outcomes. We will run race-specific models adjusting initially for age and sex, and then additionally adjusting for other variables, using them as time-dependent covariates if appropriate. In individuals developing AF, time-dependent covariates will be updated up to the AF diagnosis but not afterwards (to avoid adjusting for potential mediators).

Limitations
Two major limitations can be highlighted:

1. AF ascertainment is mostly based on hospital discharge codes. Therefore, it is probable that some AF events will be missed (if only identified and managed in outpatient setting) and that the date of AF onset is not accurate for a proportion of cases.
2. The number of some events by race (e.g. stroke) could by limited, leading to imprecise estimates of rates and hazard ratios.

These limitations will be properly acknowledged in the manuscript.

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

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

No overlapping manuscript proposals.

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.

1. Go AS, Hylek EM, Phillips KA, Chang YC, Henault LE, Selby JV, Singer DE. 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.* 2001;285:2370-2375.
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TSM. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation.* 2006;114:119-125.
3. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98:946-952.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22:983-988.
5. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol.* 2000;35:1628-1637.
6. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial

fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation.* 2003;107:2920-2925.

7. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, Albert CM. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. *JAMA.* 2011;305:2080-2087.

8. Hozawa A, Folsom AR, Sharrett AR, Chambless LE. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors. *Arch Intern Med.* 2007;167:573-579.

9. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J.* 2009;158:111-117.