ARIC Manuscript Proposal #2210

PC Reviewed: 9/10/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Trajectories of cardiovascular risk factors and atrial fibrillation in a 25 year follow-up; the ARIC study

b. Abbreviated Title (Length 26 characters): **CV risk factors in AF**

2. Writing Group:

Faye Lopez, Alvaro Alonso, Sunil Agarwal, Elsayed Soliman, Lin Chen, Lindsay Smith, Laura Loehr, others welcome

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

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3. Timeline:

Data analysis: 2 months
First draft of the manuscript: 4 months
We expect to submit an abstract with preliminary results to the AHA Epi conference (submission deadline Oct 2013)

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a lifetime risk of 1 in 4 in the general population, with an increasing prevalence as the population ages.[1] Major risk factors for AF include age, white race, obesity, smoking, hypertension, diabetes, and a history of myocardial infarction (MI) and heart failure.[2-6] These risk factors are similar to the risk factors for cardiovascular disease (CVD) in general, which often precedes an AF event.[7]

The development of AF is associated with subsequent increased risk of cardiovascular death,[8, 9] heart failure,[10] and stroke.[11] Despite the extensive literature on risk factors for AF, little attention has been devoted to the timing of risk factor development in relation to AF diagnosis, with the exceptions of stroke as an outcome of AF, and heart failure as both a risk factor for and outcome of AF. While it is known that AF is a risk factor for stroke and, therefore, most often precedes it, [12] AF and heart failure show a bidirectional relation, and the existing severity of specific cardiovascular risk factors, along with age and gender, may determine whether AF or heart failure occurs first in the individual.[13, 14] However, no information exists on the timing, relative to AF diagnosis, of the development of other AF risk factors such as hypertension or obesity. This information can be useful to better understand the pathogenesis of AF and, therefore, develop preventive strategies.

In addition, we have shown that healthcare utilization, particularly CVD-related utilization, is higher among patients with AF than among non-AF individuals even after adjusting for CVD risk factors. [15] Exploring how trajectories in CVD risk factor prevalence differ between individuals with and without AF could help to elucidate observed differences in healthcare utilization. Thus, describing the long term trajectories in the prevalence of risk factors preceding AF diagnosis and the subsequent development of disease after diagnosis, and comparing trajectories with those in individuals without AF, in a long-term, population-based study is highly relevant. The biracial ARIC study with a 25 year follow-up and a large number of incident AF cases offers a unique opportunity to describe these trajectories.

5. Main Hypothesis/Study Questions:

Aims:

1. To describe longitudinal patterns of CVD risk factors before and after incident atrial fibrillation.
2. To compare patterns of longitudinal trends in CVD risk factors among those with and without AF

For Aim 1, we hypothesize that risk factors more distant in the potential causal pathway, such as obesity, hypertension and diabetes, have high prevalence many years before the diagnosis of AF, while more proximal risk factors such as heart failure or coronary heart disease, develop concurrently with, or close to the time of AF diagnosis.

For Aim 2, we hypothesize the patterns in those without AF will follow the normal age trends of US prevalence rates, while those with AF will have rates above the normal parameters even many years prior to AF.

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 population:</u>

- Inclusion criteria: Individuals at visit 1.
- Exclusion criteria: race/ethnicity other than white or black, those with prevalent AF at visit 1, those missing information on covariates of interest.
- For Aim 1, we will only include individuals with incident AF during follow-up
- For Aim 2, in addition to AF cases included in Aim 1, we will match up to 3 individuals without AF to each AF case by sex, year of birth, race and field center.

Variables and Covariates:

- Main outcome variables: prevalence of major AF risk factors at study visits: smoking, obesity/BMI, hypertension/blood pressure, diabetes, stroke, heart failure, MI.[2]
- Main independent variable: incident AF, time before or after incident AF
- Covariates measured at baseline (visit 1): gender, race, center, education, and height
- Covariates measured at every visit (including visit 5): age, smoking status, BMI, systolic blood pressure, diastolic blood pressure, antihypertensive medication, HDLc, total cholesterol, diabetes
- Other covariates /outcomes measured during follow-up: incident stroke, heart failure and MI

Statistical Analysis

Aim 1: In those with AF, we will assess the prevalence of the different cardiovascular (CV) risk factors as a function of time before or after diagnosis of AF. To do so, we will create a long dataset with one observation per person-visit and fit generalized estimating equations (GEE) models with a logistic link with time in years before/after AF diagnosis as the main independent variable. Time of AF diagnosis (index date) will be defined as t=0, and the time at visit *i* (t_i) will be calculated as: t_i = visit *i* date – index date. This model will be used to calculate predicted probabilities of the different CV risk factors as a function of time to/since AF diagnosis. We will also estimate temporal changes in prevalence of CV risk factors with respect to the AF diagnosis.

Initial models will adjust for age at AF diagnosis, sex, race and center. In additional models we will adjust for other covariates including education, height and CV risk factors.

Aim 2: We will conduct a similar analysis to Aim 1, but include individuals without AF, to determine if longitudinal trends in CV risk factors differ depending on whether the person develops atrial fibrillation. To do so, time*AF status terms will be included in the models. For AF cases, time at each visit will be calculated as described in Aim 1; for non-cases, time will be calculated similarly using the index date of the corresponding AF case.

We will test whether any of the observed trends differ with regards to race/sex.

To limit the potential selection bias derived from missing data (participants failing to participate in any particular visit), we will use inverse probability weighting as described before. [16, 17] Briefly, observations will be weighted by the inverse of their probability of attending a particular visit given their past history of covariates.

Limitations:
Misclassification of the outcomes are possible, as is misclassification of the main independent variable, with AF diagnosis having a positive predictive value of ~90%.[3] Also, the study data does not capture outpatient AF cases.

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 ICTDER 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

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 2097 (Smith): Healthcare utilization among atrial fibrillation patients

MS 2098 (Smith): Temporal trends in mortality associated with atrial fibrillation complicating acute myocardial infarction

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

References

1. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study, *Circulation* 2004;110:1042-1046.

2. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kaab S, Couper D, Harris TB, Soliman EZ, Stricker BH, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium, *J Am Heart Assoc* 2013;2:e000102.

3. 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.

4. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults, *Circulation* 1997;96:2455-2461.

5. Sanoski CA. Prevalence, pathogenesis, and impact of atrial fibrillation, *Am J Health Syst Pharm* 2010;67:S11-6.

6. Wang TJ, Parise H, Levy D, D'Agostino RB S, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation, *JAMA* 2004;292:2471-2477.

7. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study, *JAMA* 1994;271:840-844.

8. 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.

9. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, Tsang TS. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study, *J Am Coll Cardiol* 2007;49:986-992.

10. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study, *Am J Med* 2002;113:359-364.

11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study, *Stroke* 1991;22:983-988.

12. Cardiogenic brain embolism. Cerebral Embolism Task Force, *Arch Neurol* 1986;43:71-84.

13. Schnabel RB, Rienstra M, Sullivan LM, Sun JX, Moser CB, Levy D, Pencina MJ, Fontes JD, Magnani JW, McManus DD, Lubitz SA, Tadros TM, Wang TJ, Ellinor PT, Vasan RS, Benjamin EJ. Risk assessment for incident heart failure in individuals with atrial fibrillation, *Eur J Heart Fail* 2013;15:843-849.

14. 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.

15. Smith LG, Lutsey PL, Loehr LR, Kuchaska-Newton A, Chen LY Chamberlain AM Wruck LM, Duval S, Stearns SC, Alonso A. Impact of atrial fibrillation on healthcare utilization in the community: the Atherosclerosis Risk in Communities (ARIC) Study, Submitted ARIC manuscript, #2097, 2013.

16. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models, *Am J Epidemiol* 2008;168:656-664.

17. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, Evans DA, Mendes de Leon CF. Accounting for bias due to selective attrition: the example of smoking and cognitive decline, *Epidemiology* 2012;23:119-128.