

## ARIC Manuscript Proposal #2274

PC Reviewed: 12/10/13  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

### 1.a. Full Title:

Atrial Fibrillation and Risk of Myocardial Infarction: The Atherosclerosis Risk in Communities (ARIC) Study

### b. Abbreviated Title (Length 26 characters):

AF and MI risk

### 2. Writing Group:

Writing group members:

Elsayed Z Soliman MD, MSc, MS  
Faye Lopez MS, MPH  
Lin Y. Chen MD, MS  
Zhu-Ming Zhang MD  
Lindsay Bengtson PhD, MPH  
Laura Loehr MD  
Mary Cushman MD, MSc  
Alvaro Alonso MD, PhD

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

**First author:** Elsayed Z Soliman, MD, MSc, MS

**Address:** Epidemiological Cardiology Research Center (EPICARE)  
Wake Forest Health Sciences, Medical Center Blvd., Winston-Salem,  
North Carolina 27157

**Phone:** 336-716-8632; Fax: 336-716-0834; E-mail: [esoliman@wakehealth.edu](mailto:esoliman@wakehealth.edu)

**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Alvaro Alonso MD, PhD

Address: University of Minnesota  
1300 S 2nd St, Suite 300  
Minneapolis, MN 55454

Phone: 612 626 8597; E-mail: [alonso@umn.edu](mailto:alonso@umn.edu)

### **3. Timeline:**

The projected timeline for this manuscript is 10-12 months from the time of submitting the proposal to journal submission.

### **4. Rationale:**

In addition to being a known risk factor for stroke, we recently showed that atrial fibrillation (AF) could be also a risk factor for myocardial infarction (MI) (1). In the Reasons for Geographic and Racial Differences in Stroke (REGARDS), AF was associated with about 2-fold increased risk of MI (hazard ratio [HR], 1.96 [95% CI, 1.52-2.52]). This association remained significant (HR, 1.70 [95% CI, 1.26-2.30]) after further adjustment for several cardiovascular risk factors and potential confounders, and was significantly higher in women (HR, 2.16 [95% CI, 1.41-3.31]) than in men (HR, 1.39 [95% CI, 0.91-2.10]) and in blacks (HR, 2.53 [95% CI, 1.67-3.86]) than in whites (HR, 1.26 [95% CI, 0.83-1.93]); interaction  $P = .03$  and  $P = .02$ , respectively (1). These results, however, are yet to be validated in an independent cohort. Also, whether AF would improve prediction of hard coronary heart disease (MI or coronary death) is currently unknown.

The mechanism by which AF could lead to MI is not understood at this stage. Possible explanations include direct thromboembolism from the left atrium, AF-induced increase in peripheral prothrombotic risk through systemic platelet activation, thrombin generation and inflammation, and poorly controlled ventricular response resulting in demand infarction (Type 2 MI) (1). Examining whether the association between AF and MI differs by the type of MI (ST elevation MI (STEMI) vs. non-STEMI (NSTEMI)) may give indication on the potential mechanisms by which AF could lead to MI. That is to say, a stronger association between AF and non-STEMI would suggest that the mechanism is more likely to be through increased oxygen demand due to episodes of uncontrolled ventricular rate. On the other hand, a stronger association between AF and STEMI would be more suggestive of thromboembolism leading to total occlusion of one of the coronary arteries. *Agree!*

We sought to validate the association between AF and MI observed in REGARDS, to examine whether the AF association with MI differs by the type of MI, and whether AF would improve prediction of hard coronary heart disease (MI or coronary death). The ARIC study, with its biracial population and well ascertained AF and CHD events, provides a unique opportunity to address these aims.

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

This study aims to:

- 1) Examine the association between AF and incident MI in the ARIC study; all population and stratified by sex and race.
- 2) Examine whether the association between AF and MI differs by the type of MI (STEMI vs. NSTEMI)
- 3) Examine whether adding AF to the Framingham 10-year hard CHD (MI and coronary death) risk score would improve prediction and reclassification. In additional analyses, we will also examine the additive predictive value of AF to the new AHA risk score.

**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:**

All ARIC participants free of CHD at baseline and with follow up data will be included in this study. Non-white and non-black individuals will be excluded.

**Summary of variables of interest:**

Demographic and clinical variables at baseline: Age, race, sex, education level, study site, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, total cholesterol, HDL cholesterol, current smoker, eGFR, diabetes, prior CHD, prior stroke, prior heart failure.

Exposure: Atrial fibrillation: In ARIC, AF cases have been ascertained from study ECGs (2), and hospital discharge ICD codes (3). AF will be used as time-dependent variable

Outcome: Incident MI and fatal CHD

**Brief Analysis:**

**Aim # 1 analysis plan:**

Baseline characteristics of the analysis population will be tabulated by AF status.

Age-adjusted incidence rates of MI per 1000 person-years in participants with and those without AF will be calculated in the entire population and in pre-specified age (using 65 years as a cut point), sex, and race subgroups. Kaplan-Meier survival curves will be plotted to compare event-free survival in participants with AF vs. those without.

Cox proportional hazards analysis will be used to examine the association between AF as time dependent variable and incident MI in a series of models with incremental adjustments as follows: model 1 adjusted for age, sex, race, study site, education level, and income; model 2 adjusted for model 1 covariates plus total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, BMI, diabetes, use of antihypertensive medications, warfarin, aspirin, statin, history of other cardiovascular disease (stroke, peripheral vascular disease, heart failure) and estimated glomerular rate (eGFR). In an additional model, we will examine whether using death as a competing risk affect the results.

Models with identical incremental adjustment for the main analysis will be examined in subgroups of participants stratified by age (using 65 years as a cut point), sex, and race. Interaction between AF and each of these variables will be examined in the full model. If significant interaction by sex and race is observed (similar to REGARDS), we also will examine the age-adjusted risk of MI associated with AF in black men, black women, white men and white women, separately.

**Aim # 2 analysis plan:** This would be similar to the main analysis for aim # 2 but with the outcome as STEMI and NSTEMI, separately.

**Aim #3 analysis:** For this aim, ARIC visit 4 will be considered as the baseline from which the components of Framingham CHD risk score and the new AHA risk score will be identified. Prevalent AF will be defined as ECG evidence of AF in visits 1 to 4 and/or hospital discharge ICD codes indicating AF until visit 4. The main outcome will be hard

CHD (MI or fatal coronary death) occurring after visit 4. Participants with CHD at or before visit 4 will be excluded. Risk estimates and reclassification for incident hard CHD (MI and coronary death) during a 10-year follow-up will be assessed using the 10-year Framingham CHD Risk Score (4). For risk estimates, Model 1 will be the Framingham base model (age, total cholesterol, HDL-Cholesterol, systolic blood pressure, treatment for hypertension, smoking status), while model 2 will include the base model plus AF. We will calculate the area under the curve (C-statistic) based on adding AF to the Framingham base model. Continuous Net Reclassification Index (NRI) and categorical NRI, with cut-offs of <10%, 10-20% and >20% along with the Integrated Discrimination Improvement (IDI) will be calculated, and the distribution of risk will be compared using model 2 vs. model 1 (5, 6).

In an additional analysis, we will replace the Framingham base model with the 10-year AHA CHD risk score model in which ARIC was used as validation cohort (age, race, gender, smoking (yes/no), diabetes (yes/no), hypertension medication use, systolic blood pressure, HDL cholesterol, and total cholesterol) (6).

#### Limitations

Most AF cases in ARIC are from hospital discharge ICD codes. This could lead to under-ascertainment of AF cases not requiring hospitalization. However, utilization of AF cases from study scheduled ECG, despite being a small number, should minimize this concern. Also, some cases of paroxysmal AF may be missed resulting in misclassification bias; a limitation shared by most of the studies examining AF.

Statistical power may be an issue for aim #3. This is because we are not using all AF cases occurring during all follow up period, rather AF cases detected in the period between the baseline and visit 4 (about 400 AF cases).

**7.a. Will the data be used for non-CVD analysis in this manuscript?**

Yes  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  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.csc.unc.edu/ARIC/search.php>

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)?**

None.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**

Yes  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.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

## References

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