

ARIC Manuscript Proposal # 1508

PC Reviewed: 05/12/09
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Hemostatic markers and risk of atrial fibrillation: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Hemostasis and atrial fibrillation

2. Writing Group:

Alvaro Alonso, Alanna Chamberlain, Weihong Tang, Sunil K. Agarwal, Elsayed Z. Soliman, Marietta Ambrose, Aaron R. Folsom, 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]

First author: **Alvaro Alonso**
Address: Div of Epidemiology & Community Health
University of Minnesota
1300 S 2nd St, suite 300. Minneapolis, MN 55454
Phone: 612-626-8597 Fax: 612-624-0315
E-mail: alonso@umn.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: **Aaron R. Folsom**
Address: Div of Epidemiology & Community Health
University of Minnesota
1300 S 2nd St, suite 300. Minneapolis, MN 55454
Phone: 612-626-8862 Fax: 612-624-0315
E-mail: folsom@epi.umn.edu

3. Timeline:

Data analysis – 3 months

First draft of the manuscript – 3 months

4. Rationale:

Prospective epidemiologic studies have found that elevated levels of certain markers of hemostatic function are associated with higher risk of developing coronary heart disease (CHD),¹ stroke,² and chronic kidney disease.³ In fact, certain hemostatic markers could play a direct role in the pathogenesis of these disorders, for example enhancing thrombus formation in ischemic stroke or CHD. Also, they could be markers of other underlying processes involved in the pathogenesis of cardiovascular (CV) disease, such

as fibrinogen and inflammation, or von Willebrand factor (vWf) and endothelial dysfunction.

Atrial fibrillation (AF) is the most frequent clinically relevant cardiac arrhythmia. AF is characterized by a prothrombotic state, and AF patients have altered levels of hemostatic markers.⁴ However, no previous studies have assessed whether hemostatic markers measured before the clinical diagnosis of AF could predict AF risk. Since AF shares some pathological mechanisms with other CV disorders, and development of heart failure or CHD are well-known risk factors for the developing of AF, hemostatic markers could also predict the occurrence of AF. Moreover, finding associations between hemostatic markers and the risk of AF could provide insights into the pathogenesis of the arrhythmia.

Stroke is a major complication in AF patients.⁵ Existing risk scores for prediction of stroke in AF patients include clinical variables but no biomarkers.⁶ Little information exists on the predictive value of biomarkers for stroke in AF patients. A previous study, including 994 AF patients treated with aspirin, enrolled in the SPAF III trial, found that vWf predicted the risk of stroke in AF patients but the association became imprecise and non-significant after adjustment for potential confounders.⁷ The analysis included only 39 incident strokes. In the Rotterdam study, among 162 participants with AF at baseline, hemostatic markers were not associated with stroke or other cardiovascular outcomes. Again, the number of events was relatively small (24 strokes, 26 cardiovascular deaths).⁸

The ARIC study is an excellent setting to study prospectively the association between hemostatic markers and incidence of AF. Although one previous prospective study has assessed the association between fibrinogen (as a marker of inflammation) and AF incidence,⁹ the present proposal would be the first attempt to comprehensively address the role of hemostatic markers as predictors of AF. Also, ARIC data could be used to assess the role of hemostatic markers in the prediction of stroke and other cardiovascular outcomes in patients with AF. Though this secondary analysis has limitations, discussed below, its results could offer relevant information, useful for future clinical studies.

5. Main Hypothesis/Study Questions:

The main aim is to assess the association between hemostatic markers measured at baseline and the risk of AF during follow-up in the ARIC cohort. We hypothesize that higher levels of some hemostatic markers measured in ARIC Visit 1 will be associated with the incidence of AF independently of other risk factors. Associations will be stronger for vWf, fibrinogen, and factor VIII activity (FVIIIc), markers previously associated with other cardiovascular outcomes, than for other markers (protein C, VII activity, activated PTT, and antithrombin III).

As a secondary aim, we will explore whether hemostatic markers measured at baseline predict the risk of stroke and CV disease in AF patients, after adjustment for potential confounders.

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 hemostatic markers and AF risk, and between hemostatic markers and stroke risk in AF patients using a cohort approach. For all analyses, we will exclude individuals with ECG-based AF or unreadable ECGs at visit 1. For the secondary analysis, we will include only those individuals who developed AF during follow-up and did not have history of stroke before the AF diagnosis. These participants will constitute the cohort to study stroke incidence (entry in the cohort is the date of AF incidence).

Exposure

At baseline, the following hemostatic markers were measured: fibrinogen, factor VII activity, factor VIII activity, von Willebrand factor antigen, protein C, antithrombin III activity and activated partial thromboplastin time.¹⁰ These will be the main independent variables in all analyses.

Outcome

Incident cases of AF will be identified in the follow-up through the end of 2005 from three sources: ECGs done at study visits, presence of AF ICD9 (427.31) 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. Atrial flutter without AF was not considered an event. We expect approximately 1200 incident cases of AF during the follow-up through 2005.

For the secondary analysis, the main outcome variables will be ischemic stroke, cardiovascular events (definite or probable myocardial infarction + definite CHD death + stroke), and total mortality. Because stroke surveillance is currently available only through 2004, follow-up for this analysis will end on December 31, 2004. We will include additional follow-up data if it becomes available before manuscript preparation.

Statistical analysis

Association between hemostatic markers at baseline and the incidence of AF will be estimated using Cox proportional hazards models. Models will include individual hemostatic markers first as continuous variables and will estimate hazard ratios (HR) and 95% confidence intervals (CI) associated with 1 standard deviation increment of individual hemostatic markers. Additional analyses will include quartiles of hemostatic markers, with the lowest quartile as the reference category. Analyses will be adjusted by the following potential confounders: age, race, gender, study site, education, income, smoking, alcohol intake, body mass index, height, left ventricular hypertrophy (defined by ECG), systolic blood pressure, use of anti-hypertensive medication, diabetes, HDL-cholesterol, LDL-cholesterol, history of heart failure, and history of coronary heart disease. We will explore the assumption of proportional hazards adding to the model an interaction term between follow-up time and exposure of interest, and computing Schoenfeld residuals. We will also conduct stratified analysis by gender, race, and age, and prevalent CHD to explore potential interactions.

To study the predictive value of hemostatic markers for stroke and CV disease, we will use a Cox proportional hazards model. Beginning of follow-up will occur on the date a participant is diagnosed with AF. In addition to previously defined confounders, models will include the time between hemostatic markers measurement and AF diagnosis as a continuous variable. Preliminary analysis show that approximately 60 cases of stroke

occurred in AF patients without stroke history. The number of other outcomes will be larger.

We will additionally use c statistic and reclassification measures to determine the additive predictive ability of hemostatic markers over previously characterized risk factors for AF.

Limitations

In our primary analysis, two main limitations are of concern. First, factors both associated with hemostatic markers and the incidence of AF could account for any observed association (or lack thereof). Still, our analysis will include the main known risk factors for AF limiting the extent of unmeasured confounding. Second, misclassification exists in outcome ascertainment. Preliminary analyses suggest a positive predictive value of ~90% for AF diagnosis done through hospital discharge codes, implying a limited amount of misclassification (Alonso et al, submitted).

The secondary analysis will include a limited number of strokes (~60 cases), but this compares favorably with other published studies. A more significant problem, though, is that measurements of hemostatic factors were taken before the diagnosis of AF. Therefore, hemostatic markers measured at baseline will not reflect accurately the existing levels at AF diagnosis. Using data from ancillary studies in ARIC, we have estimated the correlation of vWf and fibrinogen between visits: 0.75, 0.77 and 0.72 for the correlation of vWf at visit 1 with vWf measured at visits 2, 3 and 4, respectively; and 0.48, 0.45 and 0.61 for the correlation between fibrinogen at visit 1 with fibrinogen at visits 2, 3, and 4 respectively. These results suggest moderate correlation over time. We will try to address this problem adjusting for the time between blood draw and AF diagnosis, and using regression/calibration,¹¹ though we acknowledge that there are relatively poor solutions.

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.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)?

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* 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.csc.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

1. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease : the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 1997;96:1102-8.
2. Folsom AR, Rosamond WD, Shahar E, et al. Prospective study of markers of hemostatic function with risk of ischemic stroke. *Circulation* 1999;100:736-42.
3. Bash LD, Erlinger TP, Coresh J, Marsh-Manzi J, Folsom AR, Astor BC. Inflammation, hemostasis, and the risk of kidney function decline in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Kidney Dis* 2009;(in press.).
4. Watson T, Shantsila E, Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 2009;373:155-66.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-8.
6. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;290:1049-56.
7. Conway DSG, Pearce LA, Chin BSP, Hart RG, Lip GYH. Prognostic value of plasma von Willebrand factor and soluble P-selectin as indices of endothelial damage

and platelet activation in 994 patients with nonvalvular atrial fibrillation. *Circulation* 2003;107:3141-5.

8. Heeringa J, Conway DSG, Van der Kuip DAM, et al. A longitudinal population-based study of prothrombotic factors in elderly subjects with atrial fibrillation: the Rotterdam Study 1990-1999. *J Thromb Haemost* 2006;4:1944-9.
9. Mukamal KJ, Tolstrup JS, Friberg J, Gronbaek M, Jensen G. Fibrinogen and albumin levels and risk of atrial fibrillation in men and women (the Copenhagen City Heart Study). *Am J Cardiol* 2006;98:75-81.
10. Papp AC, Hatzakis H, Bracey A, Wu KK. ARIC hemostasis study, I: development of blood collection and processing system suitable for multicenter hemostatic studies. *Thromb Haemost* 1989;61:15-9.
11. Spiegelman D, McDermott A, Rosner B. Regression calibration method for correcting measurement-error bias in nutritional epidemiology. *Am J Clin Nutr* 1997;65:1179S-86S.