

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]

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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).

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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

___ 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

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