**ARIC Manuscript Proposal #1812**

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| **PC Reviewed: 7/12/11** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Biomarkers of atrial fibrosis and risk of incident atrial fibrillation: the Atherosclerosis Risk in Communities Study (ARIC)

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

**2. Writing Group**:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _RH__ **[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**:

Atrial fibrillation (AF) is a tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. It is one of the most frequently sustained cardiac arrhythmias seen in clinical practice, affecting an estimated 2.2 million Americans [1]. Individuals with AF have between two to seven times the risk of stroke compared with unaffected individuals; moreover, AF doubles the rate of cardiovascular disease mortality and all-cause mortality [2,3]. AF is usually initiated by ectopic electrical activity, frequently originating in the pulmonary veins. In addition to this, AF requires the presence of an appropriate substrate, both structural and electrical, to persist. Structural abnormalities and factors such as atrial stretch and autonomic dysfunction are potentially involved in the development of ectopic cardiac activity that can trigger the onset of AF. If the substrate is adequate, the initial electrophysiological alterations will lead to the development and perpetuation of AF [4,5].

Although clinical studies have indicated a potential link between fibrosis and AF, they are limited by their cross-sectional design [4,5].There are currently no prospective data on the relationship between atrial fibrosis and risk of subsequent AF. Fibrosis markers, such as the matrix metalloproteinases (MMP), are of particular interest since atrial fibrosis has been identified as a fundamental substrate for the development of AF. In addition, heart failure, a major cause of AF, leads to atrial fibrosis, which, in turn, increases the risk of AF.

The ARIC study provides an excellent setting for a prospective study of the association between markers of atrial fibrosis and incident AF in both whites and African-Americans. Further, information on a large number of socio-demographic, physiological, and biochemical risk factors will enable adjustment for known and unknown confounders allowing a more accurate estimate of the association to be determined.

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

We hypothesize that markers of atrial fibrosis, namely MMP-1, MMP-2, MMP-9, tissue inhibitor of metalloproteinase (TIMP)-1, TIMP-2 and C-terminal propeptide of collagen type 1 (CICP), will be independently associated with risk of incident 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).**

We will assess the association between markers of fibrosis and AF risk using a case-cohort design. The aforementioned biomarkers have been measured in 630 incident AF cases and a random sample of 630 cohort participants in serum samples from visit 2. Cases will be defined as individuals who developed incident AF during the follow-up through the end of 2005. The subcohort was randomly selected from eligible individuals at visit 2, and frequency matched by age (<55, >=55), sex, and race.

*Exclusions*
The following individuals will be excluded from all analyses:

- Those with missing or unreadable ECGs at visit 1 or 2
- Those with prevalent AF at visit 2 (defined as AF by ECG in visit 1 or 2, or AF hospitalization between visits 1 and 2)
- Those with missing variables for any of the covariates

*Sensitivity analyses*
- Given that HF is a major cause of fibrosis, and that in turn, fibrosis is postulated to increase the risk of AF [5], we will repeat the analyses in those with and without prevalent HF.

*Statistical analysis*
We will follow appropriate methodology for the analysis of case-cohort studies [6]. In brief, we will define risk sets (study participants at risk of the outcome) at each time point, such that the cases outside the sub-cohort are excluded from the risk set before failure; cases outside the sub-cohort are included in the risk set at failure; cases inside the sub-cohort are included in the risk set at failure; cases in the sub-cohort before failure as well as non-cases in the sub-cohort are included in the risk set with a weight equal to the inverse of the sampling frequency. The sampling frequency is the proportion of people in the sub-cohort relative to the full cohort. All sub-cohort individuals are assumed to enter the study at visit 2 (baseline for this analysis). Cases not in the sub-cohort begin contributing event time just prior to their failure time. All individuals (in the sub-cohort or non-sub-cohort cases) complete their follow up time at the event time or when censored.

For each biomarker, we will estimate Cox models adjusting for age, sex, race and study center to study the nature of the association between the biomarker and AF risk. Then, we will add other covariates potentially associated with the risk of AF and with markers of fibrosis (education, physical activity, smoking, BMI, systolic/diastolic BP, BP medications, diabetes, prevalence of coronary heart disease, prevalence of heart failure, left ventricular hypertrophy) and other biomarkers (C-reactive protein and NT-proBNP), also measured in these participants in visit 2 samples.

We will initially explore the dose-response relationship between each exposure-outcome pair using restricted cubic splines. The spline terms will allow us to examine the functional shape of the dose response curve and, potentially determine appropriate categorizations of the biomarkers. Depending on the shape of the biomarker outcome association, we will include the biomarker in the regression models as a continuous variable (after a log transformation if appropriate) if a linear association is found, or we will create quintiles according to the distribution of the biomarker. Finally, we will

study the risk associated to biomarker level higher than pre-specified cut- points (90th, 95th, and 99$^{th}$ percentiles). Analyses will be conducted for each biomarker separately.

*Limitations*
The main concern is that misclassification may exist in outcome ascertainment although preliminary analyses suggest a positive predictive value of ~90% for AF diagnosis done through hospital discharge codes, implying a limited amount of misclassification [7]. Additional limitations include residual confounding and misclassification of the exposure at baseline and due to their time-varying nature.

**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.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)?**

Filion et al. High-Sensitivity Cardiac Troponin T and the Risk of Incident Atrial Fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study

**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* 2006.15 and 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.**

## 6. References


1. A.S. Go, E.M. Hylek and K.A. Phillips *et al.*, 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* **285** (2001), pp. 2370–2375.
2. W. Rosamond, K. Flegal and K. Furie *et al.*, Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, *Circulation* **117** (2008), pp. e25–e146.
3. E.J. Benjamin, P.A. Wolf and R.B. D'Agostino *et al.*, Impact of atrial fibrillation on the risk of death: the Framingham Heart Study, *Circulation* **98** (1998), pp. 946–952. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study.
4. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation. A systematic review of the published data. J Am Coll Cardiol 2007;50:2021-8.
5. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol. 2008;51:802-9.
6.Barlow WE, Ichikawa L, Rosner D, Izumi S. Analysis of case-cohort designs. J Clin Epidemiol 1999;52:1165-72.
7. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ and Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: The Atherosclerosis Risk in Communities (ARIC) study American Heart Journal 2009; 158:111-117.


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