

ARIC Manuscript Proposal # 1389

PC Reviewed: 08/12/08
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Metabolic Syndrome and Risk of Incident Atrial Fibrillation among Whites and Blacks in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): MetSyn and AFib in ARIC

2. Writing Group:

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

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3. Timeline:

Statistical Analysis:	August 2008 – October 2008
Manuscript Preparation:	October 2008
Manuscript Revision:	November 2008
Manuscript Submission:	December 2008

4. Rationale:

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, and is associated with increased stroke and cardiovascular morbidity and mortality.¹ AF currently affects more than 2.2 million Americans, and the lifetime risk for development of AF in men and women over 40 years of age is 1 in 4.²

The metabolic syndrome is clinically defined as a clustering of three or more of the following five atherosclerotic risk factors: abdominal obesity, elevated triglycerides, low HDL-c, elevated blood pressure, and impaired glucose tolerance.³ Some of the metabolic syndrome risk factors, such as obesity and type II diabetes, have been implicated in the development of AF. For example, a meta-analysis pooling data from 123,249 participants in 16 cohort studies reported a 49% increased risk of developing AF among obese individuals (BMI \geq 30) compared to nonobese individuals (BMI $<$ 30).⁴ Further, patients with new-onset diabetes had a 1.49-fold increased risk of incident AF compared to those without diabetes in a prospective study of 15,245 participants.⁵ Additionally, recent studies have suggested that the metabolic syndrome is associated with paroxysmal AF.^{6,7} Finally, the metabolic syndrome, as well as the individual components of obesity, elevated blood pressure, low HDL-c, and impaired insulin tolerance showed an increase risk of AF in a Japanese prospective cohort study.⁸

Knowledge on the association between the metabolic syndrome and AF among African-Americans is limited. A couple studies have suggested that atrial fibrillation is less common in blacks than whites.^{9,10} However, it is well known that blacks have higher prevalence of metabolic syndrome and most of its components than whites.¹¹ Therefore, we propose to determine the risk of incident AF due to the metabolic syndrome and individual components of the metabolic syndrome among blacks and whites in ARIC.

References:

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5. Main Hypothesis/Study Questions:

We hypothesize that, in both whites and blacks, the incidence of AF will be higher among those with the metabolic syndrome at baseline compared to those without the metabolic syndrome, and that the risk of AF will increase with increasing number of metabolic syndrome components.

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).

Individuals without ECG or who had diagnosed AF or atrial flutter at baseline will be excluded from analyses. We will conduct a sensitivity analysis excluding non-fasters. If the associations are different in fasters and non-fasters, those who did not fast at least 8 hours before blood draw will be excluded from analyses. Independent variables in our analysis include waist circumference, triglycerides, HDL, blood pressure, and fasting blood glucose. The metabolic syndrome will be defined as having 3 or more of the following conditions: 1) a waist circumference of >88 cm in women or >102 cm in men, 2) triglycerides ≥ 150 mg/dL (or on lipid medication), 3) HDL <50 mg/dL in women or <40 mg/dL in men (or on lipid medication), 4) blood pressure $\geq 130/\geq 85$ mmHg and/or a history of treated hypertension, and 5) impaired glucose tolerance, which is defined as ≥ 110 mg/dL according to the NCEP-ATP III and ≥ 100 or a history of diabetes according to the AHA/NHLBI (or on diabetes medication). We will define the metabolic syndrome according to both NCEP-ATP III and AHA/NHLBI and conduct analyses for both definitions. The dependent variable is incident AF. Incident cases of atrial fibrillation will be identified through hospital discharge codes (ICD-9 code 427.31) and ECG's performed during follow-up visits. Individuals who develop both atrial flutter and AF during follow-up will be considered as having an event, and follow-up will be censored at

the first occurrence of either AF or atrial flutter. Those that develop lone atrial flutter will not be considered as having an event, and will be censored at the date of diagnosed atrial flutter. However, we may conduct a sensitivity analysis including those with lone atrial flutter as events to determine if the results differ compared to when these individuals are excluded.

First, we will assess pooled and race-specific rates of AF incidence by presence or absence of metabolic syndrome at baseline using Poisson regression. Then, Cox proportional hazards regression will be used to determine the hazard ratios of AF by prevalence of metabolic syndrome at baseline. The associations will be adjusted for age, sex, race, field center, education, smoking status and amount, drinking status and amount of alcohol consumed, ECG-defined left ventricular hypertrophy, and presence of CHD and heart failure at baseline. We will conduct analyses pooling all AF cases, but will additionally run separate analyses for ECG-based and hospital-based AF to determine potential differences in the associations, although power may be limited in these subgroup analyses. Interaction tests by race and sex will be conducted, and analyses will be reported separately by race and/or sex if evidence of heterogeneity by these variables is present. We will also report the association of AF with the individual components of the metabolic syndrome, adjusting for the above-mentioned confounders, as well as the additional components of the metabolic syndrome. We will additionally test whether the risk of AF increases monotonically with greater number of metabolic syndrome components. Also, we will create an indicator for metabolic syndrome (yes, no) and adjust for individual components to determine whether there is an association with AF beyond the components that the metabolic syndrome contributes. Additionally, time-dependent Cox regression analyses will be run using the metabolic syndrome, as well as individual metabolic syndrome components, as the time-dependent variables. We will also use inverse probability weighting to adjust for censoring in our data. Finally, we will use Cox regression to depict race-specific cumulative incidence of AF by presence of metabolic syndrome at baseline, after controlling for confounding variables.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

MS # 1351: Incidence of atrial fibrillation in a bi-racial cohort: the ARIC study

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/atic/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.