ARIC Manuscript Proposal #2354

PC Reviewed: 5/13/14   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Metabolomics and incident atrial fibrillation in African Americans: the ARIC study

 b. Abbreviated Title (Length 26 characters): **Metabolomics and AF**

2.   Writing Group:
      Alvaro Alonso, Bing Yu, Lin Chen, Elsayed Soliman, Laura Loehr, Morgan Grams, Waqas Qureshi, Danny Alexander, Eric Boerwinkle

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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3.   Timeline:
Analysis will be started as soon as the proposal is approved. We expect to have a first draft 6 months after approval.

4.   Rationale:
Atrial fibrillation is a common cardiac arrhythmia associated with an increased risk of stroke, other cardiovascular disease, and mortality.[1] Over the last two decades, numerous

risk factors and biomarkers for atrial fibrillation have been identified. However, the pathophysiological mechanisms underlying these associations are far from clear. Metabolomics provides a novel approach to understand the pathways involved in the development of disease. Two previous publications have used metabolomics techniques to examine the impact of AF on cardiac tissues.[2, 3] To date, however, no published studies have explored prospectively the association of molecules identified using metabolomics profiling with the incidence of AF. Therefore, we propose to assess the associations of a panel of molecules identified in the context of metabolomics profiling with the incidence of AF in the ARIC cohort.

5. Main Hypothesis/Study Questions:
The main aim of this analysis is to determine whether molecules identified as part of an untargeted metabolomics profile are associated with the incidence of AF. We hypothesize that our analysis will identify novel molecules associated with the risk of AF among African Americans.

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 conduct a prospective analysis with visit 1 as the baseline and incident AF through the end of 2011 as the outcome.

Inclusion criteria
African-American individuals free of AF at baseline with available metabolomics profiles. We will exclude participants with prevalent AF or missing ECG at the baseline visit.

Assessment of metabolites
Metabolite profiling of baseline fasting serum samples was done in 1,977 ARIC participants from the Jackson field center using an untargeted, gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry-based metabolomics quantification protocol.

For the present analysis we will only include named compounds, and exclude compounds with missing values or values below the limit of detection in >80% of the samples or with low medium-term reliability (defined as reliability coefficient<0.60 measured in 2 samples collected 4-6 weeks apart in 60 individuals).

Following the same approach as in a previous ARIC analysis,[4] metabolites with missing/below detection limit in <50% of the samples will be analyzed as continuous variables, assigning the lowest detected value for that metabolite to those with missing/below detection limit. Metabolites with missing/below detection limit between 50-80% will be analyzed as ordinal variables with the following levels: (1)

Missing/below the detection limit, (2) Detected levels below the median, and (3) Detected levels at or higher than the median.

Outcome ascertainment
Incident atrial fibrillation will be identified as previously described.[5, 6] Specifically, we will identify new cases of AF from study ECGs, hospital discharge codes, and death certificates. Follow-up through the end of 2011 will be considered. We expect to include approximately 170 incident AF events in this analysis.

Statistical analysis
We will assess the association of each metabolite with incident AF using Cox proportional hazards models. In a first model, we will adjust for age and sex. In a second model we will additionally adjust for risk factors for AF: smoking, body mass index, systolic blood pressure, antihypertensive medications, prevalent diabetes, prevalent heart failure, and prevalent CHD. In a final model, we will additionally adjust for eGFR. In the manuscript, we will present models with and without adjustment for eGFR, and our interpretation of the findings will carefully consider results from the different models. Given the limited number of events, we will try to keep our multivariable models as parsimonious as possible.

We will apply a modified stepwise Bonferroni procedure to correct for multiple comparisons, as described previously.[4]

In sensitivity analyses, depending on the results, we might consider excluding users of some medications (diabetes meds, ACE inhibitors, ARBs) and adjusting for biomarkers of inflammation.

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 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 _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

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)?
MS 1837 – Metabolomics of heart failure
MS 1918 – Metabolomics, blood pressure, and hypertension

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* 2008.12, 2008.16)**
___ **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/

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.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

Bibliografia

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2. Mayr M, Yusuf S, Weir G, Chung Y-L, Mayr U, Yin X, Ladroue C, Madhu B, Roberts N, De Souza A, Fredericks S, Stubbs M, Griffiths JR, Jahangiri M, Xu Q, Camm AJ. Combined

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