ARIC Manuscript Proposal #3189

PC Reviewed: 6/12/18                          Status: _____                          Priority: 2
SC Reviewed: _________                          Status: _____                          Priority: _____

1.a. Full Title: Metabolomics, cardiac electrophysiology, and sudden cardiac death: the ARIC study

b. Abbreviated Title (Length 26 characters): Metabolomics, ECG and SCD

2. Writing Group

Writing group members: Rebecca Mitchell, Dan Arking, Eliseo Guallar, Nona Sotoodehnia, Alvaro Alonso, Eric Boerwinkle, additional authors welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _RM_ [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:
Manuscript to be completed in <1 year after approval

4. Rationale:
Application of metabolomics to the study of sudden cardiac death (SCD), and related electrocardiographic endophenotypes (e.g. QT interval, PR interval, QRS interval), has been limited. Metabolomic approaches could potentially identify novel biomarkers of SCD and
provide new clues regarding the etiopathogenesis of this lethal arrhythmia. We propose to take advantage of the ARIC metabolomics data obtained in ~4000 additional study participants at visit 1 and explore their association with electrocardiographic measures as well as incident SCD.

5. Main Hypothesis/Study Questions:
The primary aim of this analysis is to study the association of molecules measured through untargeted metabolomic profiling with incident SCD and related electrocardiographic traits.

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 examine visit 1 ECG metrics (QT, QRS, and PR intervals) for their association with metabolites and conduct a prospective study of participants with metabolomic data for SCD. Eligible participants will be followed up through the end of 2016.

Assessment of metabolites
Metabolite profiling in baseline serum samples was performed in 1,977 ARIC participants from the Jackson field center in 2010 and in an additional ~2,000 ARIC participants in 2014 using an untargeted, gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry-based metabolomics quantification protocol. The second sample set includes primarily European-Americans.

Based on both practical and theoretical considerations, we will limit the analysis to those metabolites with acceptable reliability (r>0.6), no obvious batch effect, low missing rate (< 25% in both batches) and shared between African Americans and European Americans. It is estimated that there are to be 245 named metabolites that satisfy these criteria.

Metabolites with missing/below detection limit in <25% of the samples will be analyzed as continuous variables, assigning the lowest detected value for that metabolite to those with missing/below detection limit.

Main outcome variable
SCD has been adjudicated in the ARIC cohort through 2012 by expert review of all fatal cases of CVD, resulting in 158 SCD cases with metabolomics data.

Statistical analysis
We will conduct two separate analyses. The first one will focus on ECG traits, using linear regression to assess the association of metabolites with visit 1 measures of QT, QRS, and PR intervals. Covariates will include age, sex, heart rate, height, race, batch, and collection center. If there are significant differences in metabolite profiles between whites and blacks, we will consider running separate analyses and then combining results in a meta-analysis. In the second analysis, we will assess the association of each metabolite with incident SCD using Cox regression. Hazard ratios will be calculated per 1-standard deviation difference in the concentrations of each metabolite. In addition to the above covariates, we will also conduct analyses including prevalent CVD, prevalent T2D, BMI, smoking status, lipids, and SBP/DBP.
We will also take into account kidney function as well as medications that modify ECG traits (e.g. CCBs), as these factors may also influence metabolite levels.

We will apply a modified stepwise Bonferroni procedure to correct for multiple comparisons.

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 #2354 Metabolomics and AF (Alonso)—previous publication including data from 1919 participants. The new proposal will extend the findings from MS#2354 with a larger sample size and into the European-American population.

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

__X__ A. primarily the result of an ancillary study (list number* 2008.16 and 2014.20)

____ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes  __X__ No.