ARIC Manuscript Proposal #2929

PC Reviewed: 02/13/2017	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Circulating electrolytes and the prevalence of atrial fibrillation and supraventricular ectopy

b. Abbreviated Title (Length 26 characters): **Circulating electrolytes and arrhythmias**

2. Writing Group:
Writing group members: Alvaro Alonso, Lin Yee Chen, Mary R. Rooney, Faye L. Norby, Amy K. Saenger, Elsayed Z. Soliman, Wesley T. O'Neal, Katie Hootman, Elizabeth Selvin, Sunil K. Agarwal, Pamela L. Lutsey

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 to be completed upon approval of manuscript and availability of new analytes being measured in visit 5 stored samples.

4. Rationale:

Prior research in ARIC has found associations of lower circulating concentrations of magnesium (Mg) and higher concentrations of phosphorus (P) with an increased risk of atrial fibrillation (AF).[1, 2] Similar findings for Mg have been reported in the Framingham Heart Study,[3] and for P in the Multi-Ethnic Study of Atherosclerosis (MESA).[4] However, limited information exists on the association of other circulating electrolytes (such as calcium [Ca], chloride [Cl], sodium [Na] and potassium [K]) with the risk of AF, though some limited evidence suggests that low serum K and high Cl may be associated with increased AF risk.[5, 6] Moreover, no prior research has explored the association of these circulating electrolytes with the burden of other supraventricular arrhythmias, including supraventricular tachycardia (SVT) or paroxysmal atrial contractions (PACs), in the community.

Given the role that electrolytes play in cardiac electrophysiology and prior evidence linking their circulating concentrations with AF risk, exploring the association of these molecules with diverse supraventricular arrhythmias can provide informative pathophysiological insights. Specifically, characterizing the association of electrolytes with these arrhythmias may refine our understanding of their contribution to atrial electrophysiology which could, in turn, inform the development of preventive or treatment strategies for AF. Therefore, we will take advantage of analytes newly measured in visit 5 samples as well as the information collected during the visit 5 ZioPatch pilot study (PIs: Lin Chen, Sunil Agarwal) to determine the cross-sectional association of selected electrolytes (Mg, P, Cl, K, Ca, Na) with the prevalence of AF and the burden of supraventricular arrhythmias (SVT, PACs, sinus pauses) in the ARIC cohort.

5. Main Hypothesis/Study Questions:
Low concentrations of Mg and K, and high concentrations of P, Na, Cl and Ca will be associated with higher prevalence of AF and higher burden of SVT and PACs.

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).

Study population
We will include all visit 5 participants with available electrolytes measurements for the analysis of prevalent AF (n>6,000), while we will only include those with ZioPatch data (n ~330) for the analysis of arrhythmia burden.

Main independent variables
Visit 5 serum Mg, P, Na, Cl, K, Ca. All of these biomarkers were measured on the Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Measurement methods are as follows:

Mg: Colorimetric (xylidyl blue) method
P: Photometric (molybdate) method
Na, Cl, K: Ion Selective Electrode, Indirect
Ca: Colorimetric (NM-BAPTA) method

Outcome variables

Prevalent AF will be defined as presence of AF in the visit 5 ECG or AF previously diagnosed via study ECGs in prior visits or hospitalization discharge codes, as described elsewhere.[7] We will also categorize the subset of participants with ZioPatch assessments according to their AF burden as no AF, paroxysmal AF (>0, <100%), and persistent AF (100% burden).

Supraventricular arrhythmias: presence of PACs (yes/no), number of PACs per day, presence of SVT (yes/no), burden of SVT (n. of episodes per day), presence of sinus pause >3 seconds (yes/no).

Covariates

Previously identified risk factors for AF,[8] measured at visit 5: Age, sex, race, study site, smoking, systolic and diastolic blood pressure, use of antihypertensive medication (diuretics, ACEI/ARBs, others), diabetes, prevalent HF, prevalent CHD, body mass index, height. We will also consider left atrial volume index, left ventricular ejection fraction, alcohol intake, and a measure of physical activity as potential confounders.

Statistical analysis

The shape of the associations of individual electrolytes with the different outcomes will be explored using restricted cubic splines. Based on this analysis, electrolytes will be categorized or analyzed as continuous variables.

Analyses of binary endpoints (AF, presence of PACs, SVT, sinus pauses) will be done with unconditional logistic regression, while multinomial logistic regression will be used for the analysis using AF burden (non AF, paroxysmal AF, persistent AF) as endpoint. Analyses of continuous variables (PAC and SVT burden) will be done with linear regression. We will consider log transforming PAC and SVT burden.

We will conduct initial analyses adjusting for age, sex and race. In subsequent analyses, we will adjust for the potential confounders listed above and we will evaluate the need to adjust for other electrolytes. In addition to adjusting for type of antihypertensive medication, we will also conduct sensitivity analyses excluding participants using diuretics and ACEI/ARBs.

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 #1819 Mg and AF in ARIC (Misialek)
MS #1893 Serum Mg, P, Ca and heart failure (Lutsey)
MS #1845 Phosphorus and AF (Norby)
MS #2280 AF and subclinical arrhythmia burden (Agarwal).

The present manuscript goes beyond the results reported in previous analyses, using newly measured electrolytes at visit 5 and data recorded with the ZioPatch at visit 5. The first and/or senior authors of the previous manuscripts are also coauthors in this proposal.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
_X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _2008.06 (ARIC-NCS) _____ _____)

*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.

1. Misialek JR, Lopez FL, Lutsey PL, et al. Serum and dietary magnesium and incidence of atrial fibrillation in whites and in African Americans--Atherosclerosis Risk in Communities (ARIC) Study. *Circ J.* 2013;77:323-329.
2. Lopez FL, Agarwal SK, Grams ME, et al. Relation of serum phosphorus levels to the incidence of atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol.* 2013;111:857-862.
3. Khan AM, Lubitz SA, Sullivan LM, et al. Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. *Circulation.* 2013;127:33-38.
4. Mathew JS, Sachs MC, Patton KK, et al. Fibroblast growth factor-23 and incident atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS). *Circulation.* 2014;130:298-307.
5. Krijthe BP, Heeringa J, Kors JA, et al. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol.* 2013;168:5411-5415.
6. Svagzdiene M, Sirvinskas E. Changes in serum electrolyte levels and their influence on the incidence of atrial fibrillation after coronary artery bypass grafting surgery. *Medicina (Kaunas).* 2006;42:208-214.
7. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J.* 2009;158:111-117.
8. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF Consortium. *J Am Heart Assoc.* 2013;2:e000102.