ARIC Manuscript Proposal # 3185

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

1.a. Full Title: Serum magnesium and burden of atrial and ventricular arrhythmias: the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): **Serum Mg & arrhythmias**

2. Writing Group:

Writing group members: Mary R Rooney, Pamela L Lutsey, Alvaro Alonso, Elizabeth Selvin, Jim Pankow, Lin Yee Chen

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

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3. Timeline: Data analysis can begin immediately. We anticipate a manuscript draft will be prepared in approximately one year.

4. Rationale:

Magnesium (Mg) plays many essential physiologic functions, including its role in cardiac electrophysiology.[1,2] In nutrition sciences, severe Mg deficiency is widely thought to result in dysrhythmias, including AF.[3,4] Intravenous Mg has a well-established role in managing torsade de pointes, a type of ventricular arrhythmia, in the setting of long QT-interval syndrome.[5] Based on current evidence, Mg supplementation is often administered as a prophylaxis to prevent post-operative atrial fibrillation (AF) events.[6] However, its use for preventing AF post-operatively can

be controversial.[7] Whether improved Mg status is related to a reduction in AF risk in the general population remains an ongoing area of research.

Three prospective observational studies, including ARIC, have documented associations between low serum Mg and an increased risk of developing AF.[8-10] In ARIC, serum Mg was examined in relation to incident AF (hospital discharge, study visit ECGs and death certificates). Those in the lowest serum Mg quintile had an HR=1.34 (95% CI: 1.16-1.54) compared to those in the middle quintile after multivariable adjustment.[8] Similarly, in the Framingham Offspring study, those in the lowest serum Mg quartile had a higher AF risk compared to the highest quartile [HR=1.52 (95% CI: 1.00-2.31)].[9] In an Israeli HMO, both mild and moderate hypomagnesemia were associated with higher AF risk over longer follow-up (25 months) but not with short-term AF risk (3 months).[10] Additionally, an experimental study lends support to these epidemiologic findings. Of 14 healthy women who were fed an extremely low diet in Mg, 3 of the women developed AF. Their AF resolved quickly after Mg repletion.[11].

Much of the research on Mg and ventricular arrhythmias has been conducted in populations with existing medical conditions (e.g. congestive heart failure, myocardial infarction, diabetes). Intravenous Mg has had conflicting results in reducing the frequency of ventricular arrhythmias after an acute myocardial infarction. Additionally, among obese Canadian participants (n=750) with type 2 diabetes, participants with serum Mg ≤0.70 mmol/L had a 2.5-fold higher prevalence of premature ventricular contraction (PVC)—as measured using a Holter monitor—than those with serum Mg >0.70 mmol/L (50% vs 21%).[12] Otherwise, little is known about the relationship of serum Mg concentrations and ventricular arrhythmias among community-dwelling adults.

Previous studies examining the Mg-AF relationship have not had sufficient length of ECG-monitoring to characterize associations between serum Mg concentrations across AF sub-types (e.g. permanent, paroxysmal). We will leverage the 2-weeks of continuous ECG recording to characterize associations of serum Mg concentrations across the spectrum of AF burden and other arrhythmias in over 2,000 ARIC visit 6 participants.

5. Main Hypothesis/Study Questions:

Objectives

To evaluate associations between:

1) Serum Mg and AF burden
2) Serum Mg and PAC burden and SVT burden
3) Serum Mg and PVC burden and NSVT burden
4) Serum Mg and sinus pauses

Hypothesis

Low serum Mg concentrations will be associated with a higher prevalence and burden of atrial and ventricular arrhythmias at visit 6.

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 Design

This will be a cross-sectional analysis at visit 6. Individuals who wore the Zio® XT Patch and have serum Mg measurement at visit 6 are eligible for this analysis.

- *Exposure*: Serum Mg

- *Outcomes*: AF (binary; 0%, >0-<100%, 100%), PAC burden (average PAC count [a] per day), SVT burden (average SVT per day), NSVT burden (average NSVT per day), PVC burden (average PVC count [b] per day), sinus pauses (binary)

  [a] PAC count refers to the number of isolated, couplet and triplet PACs [e.g. # isolated PACs + 2*(# couplet PACs) + 3*(# triplet PACs)]
  [b] PVC count refers to the number of isolated, couplet and triplet PVCs [e.g. # isolated PVCs + 2*(# couplet PVCs) + 3*(# triplet PVCs)]

- *Covariates:* age, sex, race, study center, educational attainment, smoking status, drinking status, body mass index, physical activity, diabetes, systolic and diastolic blood pressure, antihypertensive medication use (diuretics, ACEI/ARBs, others), antiarrhythmic medication use, coronary heart disease, heart failure, proton pump inhibitors

- *Potential mediator:* serum potassium (K)

Data analysis

We will present unadjusted mean±SD and proportions for the covariates stratified by serum Mg. Linear regression will be used for analyses involving continuous outcomes. Where appropriate, we will log-transform continuous arrhythmia burdens. Restricted cubic splines will be used to visualize the association between Mg and arrhythmias, and to categorize Mg as appropriate. Unconditional logistic regression will be used to assess the association between serum Mg and binary measures of arrhythmias. Multinomial logistic regression will be used for categorical outcomes (e.g. AF burden).

Additionally, circulating K plays an important role in cardiac electrophysiology and hypokalemia can frequently co-occur with hypomagnesemia. We will include serum K (measured at visit 6) in the fully-adjusted model to test whether the serum Mg-arrhythmia associations are independent of serum K concentrations.

- Model 1 = age, sex, race, study center
- Model 2 = Model 1 + educational attainment, smoking status, drinking status, ethanol intake, body mass index, diabetes, systolic and diastolic blood pressure, antihypertensive medication use (diuretics, ACEI/ARBs, others), antiarrhythmic medication use
- Model 3 = Model 2 + serum K

In sensitivity analyses, we will exclude users of proton pump inhibitors as well as users of ACEI/ARBs and diuretics, all of which can contribute to low circulating Mg concentrations. We will also exclude those with a history of CVD (MI, HF, CHD) and those taking antiarrhythmic medications. Last, to increase precision, we will consider using the average of visit 5 and visit 6 serum Mg concentrations.

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)?
#1819 (Misialek) Mg and AF in ARIC
#2929 (Alonso) Circulating electrolytes and arrhythmias
- This analyses is based on based on circulating electrolytes (including Mg) and arrhythmias based on ECG at visit 5, and the small subset (n~325) with ZioPatch data at visit 5. Analyses are complete for this analysis.

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* 2014.18 2009.18)
___ 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.

References

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