

ARIC Manuscript Proposal #3760

PC Reviewed: 1/12/21
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Circulating magnesium and risk of major adverse cardiac events among patients with atrial fibrillation in the ARIC cohort

b. Abbreviated Title (Length 26 characters): Mg and CVD events in AF

2. Writing Group:

Writing group members: Linzi Li, Pamela L. Lutsey, Lin Y. Chen, Elsayed Z. Soliman, Mary Rooney, Alvaro Alonso

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. LL [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:

A draft manuscript will be ready to submit for Publications Committee Review in Summer 2021.

4. Rationale:

Magnesium (Mg), as one of the most abundant cations in the human body, plays a critical role in several physiological, biochemical and cellular processes that regulates cardiovascular function. Mg is related to the pathogenesis and mechanism of some cardiovascular diseases, such as heart failure (HF), hypertension and cardiac arrhythmias [1]. Mg exerts antiarrhythmic properties into cells through modulation of myocardial excitability, influencing the risk of cardiac arrhythmias

[2]. About two decades ago, researchers found that serum Mg < 0.7 mmol/L, combined with signal average P wave duration, could identify the majority of patients with atrial fibrillation (AF) after coronary artery bypass surgery on the first postoperative day [3]. Later studies also suggest that Mg supplementation reduced AF incidence after cardiac surgery (e.g. RR=0.69, 95% CI 0.56-0.86 in a meta-analysis), showing its preventive effect on AF [4-6]. In the community-based Framingham Offspring Heart Study and the Atherosclerosis Risk in Communities (ARIC) Study, an inverse association between serum Mg and the risk of AF has been described [7, 8]. Serum Mg is also related to coronary artery disease (CAD) prognosis. Researchers have reported serum Mg was associated with coronary heart and vascular disease deaths and hospitalizations and all-cause mortality inversely in the National Health and Nutrition Examination Survey (NHANES) [9] [10]. In a northern German population-based sample, low serum Mg (< 0.73 mmol/L) independently predicted all-cause mortality and cardiovascular mortality, adjusting for established cardiovascular risk factors [11]. Among patients with myocardial infarction (MI), low serum Mg (< 0.87 mmol/L) was associated with major adverse cardiac events (MACE), including death, MI, stroke and any revascularization [12].

AF—a very common cardiac arrhythmia—shares risk factors and usually co-exists with coronary artery disease [13]. However, there is little information regarding the association between serum Mg and MACE among patients with AF, or the prognosis of AF patients. Moreover, the role of supplemental Mg in secondary prevention of AF is unknown. Therefore, we propose to investigate how serum Mg is related to MACE (cardiovascular death, stroke, MI), CAD and heart failure (HF) among patients with AF.

The ARIC study has rigorously assessed AF and cardiac events endpoints, and measurements of cardiovascular risk factors. We anticipate that this study could fill in a gap in the literature and suggest a role for intervening upon low serum Mg for secondary prevention of AF complications.

5. Main Hypothesis/Study Questions:

We hypothesize that lower concentrations of serum Mg are associated with increased risk of MACE (cardiovascular death, stroke, MI), CAD and heart failure (HF) among patients with AF.

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

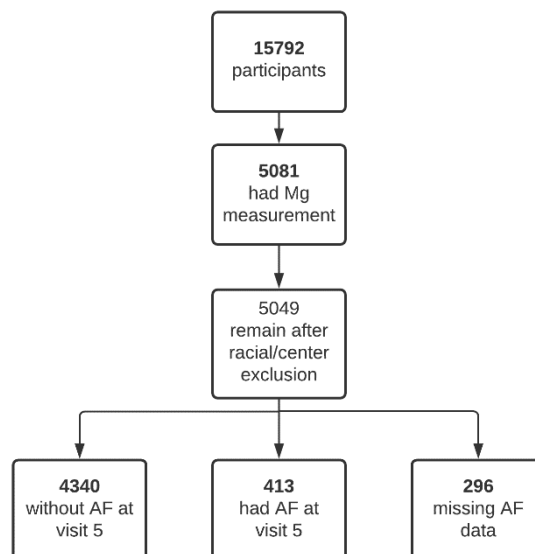
Prospective cohort study

Baseline: visit 5. At visit 5, Mg measurements are available and numbers of incident AF events are sufficient.

Follow-up: through 2018

Inclusion and exclusion criteria

- Inclusion: ARIC participants who had Mg measurements and had AF at visit 5 (including those who had prevalent AF at ARIC enrollment).
- Exclusion: Participants who had missing Mg measurements; those who did not have AF or had missing AF data at visit 5; non-whites from the Minneapolis and Washington County field centers, and individuals other than white or African American.
- The figure below provides sample size estimates:



Exposure

Serum Mg measured at visit 5 (2011-2013), using a colorimetric (xylydyl blue) method.[14]

Outcomes

Endpoints occurred from the end of visit 5 through 2018.

Combined endpoint: major adverse cardiac events (MI, stroke, cardiovascular death)

Separate endpoints: HF, MI, stroke and cardiovascular death

The following table shows approximate numbers of events among eligible participants based on current available data.

Table. Outcome frequencies among AF patients at visit 5 (N=413)

Outcome	N(%)
HF	51 (12.4)
Stroke	24 (5.8)
MI	95 (23.0)
Cardiovascular death	71 (17.2)
Any events except cardiovascular death	156 (37.8)
Any events above	186 (45.0)

Covariates

Age, sex, race/study center, BMI, smoking status, drinking status, SBP, LDL, HDL, diabetes, use of anti-hypertension medication, use of blood cholesterol medications, serum potassium, eGFR, MI history, stroke history, HF history.

Statistical analysis plan

First, we will explore the distribution of serum Mg in the sample and calculate its quintiles. Serum Mg will be categorized based on quintiles and, separately, using the normal range of thresholds of 1.7 and 2.2 mg/dL [15]. We will describe the baseline characteristics of our study population according to these categories, in frequencies (percentages) and means (standard deviations) for categorical variables and continuous variables respectively. For each outcome-specific analysis (HF, stroke, MI) we will exclude those who had prior history before visit 5, but not for the combined endpoint. The incidence rates of outcomes will be calculated. Serum Mg will be modeled in both quintile categories and normal/abnormal categories (1.7-2.2mg/dL) and as a continuous variable. Next, we will use Cox proportional hazard regression to generate HR's and 95% CI's for the association between serum Mg and the risk of MACE, HF, MI, stroke and cardiovascular death. We propose the following models:

- 1) crude model
- 2) model 1+ age, sex, race/study center
- 3) model 2+ BMI, smoking status, drinking status, SBP, LDL, HDL, diabetes, use of anti-hypertension medication, use of blood cholesterol medications, serum potassium, serum creatinine, use of anticoagulants, use of aspirin

4) model 3+MI history, stroke history, HF history

Sensitivity Analyses

In order to reduce the impact of missing covariates, we will consider use of multiple imputation by chained equations to impute missing values. After imputation, we will examine the robustness of the previous results.

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.csc.c.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

_____ 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)?

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* _____)**

___ **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 <https://www2.csc.c.unc.edu/aric/approved-ancillary-studies>

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.csc.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.

1. Kolte, D., et al., *Role of magnesium in cardiovascular diseases*. *Cardiol Rev*, 2014. **22**(4): p. 182-92.
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3. Zaman, A.G., et al., *The role of signal averaged P wave duration and serum magnesium as a combined predictor of atrial fibrillation after elective coronary artery bypass surgery*. *Heart*, 1997. **77**(6): p. 527.
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8. Khan, A.M., et al., *Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study*. *Circulation*, 2013. **127**(1): p. 33-38.
9. Gartside, P. and C. Glueck, *The important role of modifiable dietary and behavioral characteristics in the causation and prevention of coronary heart disease hospitalization and mortality: the prospective NHANES I follow-up study*. *Journal of the American College of Nutrition*, 1995. **14**(1): p. 71-79.
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12. An, G., et al., *Association between low serum magnesium level and major adverse cardiac events in patients treated with drug-eluting stents for acute myocardial infarction*. *PLoS One*, 2014. **9**(6): p. e98971.
13. Akao, M., *Atrial fibrillation and coronary artery disease: Resembling twins?* *J Cardiol*, 2014. **63**(2): p. 169-70.
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15. Francisco, U.o.C.S. *Magnesium blood test*. 2020; Available from: <https://www.ucsfhealth.org/medical-tests/003487>.