

**ARIC Manuscript Proposal # 1819**

**PC Reviewed:** 7/12/11  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

1. **a. Full Title:** Serum and dietary magnesium and the incidence of atrial fibrillation in whites and African Americans: the ARIC study

**b. Abbreviated Title (Length 26 characters):** Mg and AF in ARIC

2. **Writing Group:**

Writing group members: Jeffrey R. Misialek, Faye L. Lopez, Rachel R. Huxley, James M. Peacock, Lin Y. Chen, Elsayed Z. Soliman, Sunil K. Agarwal, Alvaro Alonso

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

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3. **Timeline:**

Data analysis: 1-2 months from manuscript approval date.

First draft of the manuscript: 3-4 months from the manuscript approval date.

#### 4. Rationale:

Atrial fibrillation (AF) is becoming a growing concern in the United States. With a current estimate of over two million affected individuals, AF is anticipated to double its current prevalence by 2050.<sup>1</sup> Besides being the most frequent cardiac arrhythmia observed in clinical practice, AF has been associated with increased risk of cardiovascular disease (CVD), heart failure, stroke, and overall mortality.<sup>2</sup> Various studies have investigated potential risk factors of AF to gain a better insight of its causation and prediction. Some of the known AF risk factors are age, gender, race, cigarette smoking, hypertension, obesity, diabetes, heart failure, coronary heart disease (CHD), left ventricular hypertrophy, metabolic syndrome, and inflammatory biomarkers.<sup>2-7</sup>

After cardiac surgery, magnesium deficiency is a common issue that may result in postoperative AF episodes.<sup>8</sup> As a result, magnesium has been suggested as a possible prophylactic treatment to prevent postoperative AF events, but the body of evidence has resulted in mixed conclusions for this specific population.<sup>9-13</sup> To our knowledge, the association between serum magnesium (Mg) level and incident AF cases has not been investigated. Previous epidemiologic studies have investigated whether serum Mg and dietary Mg are associated with CVDs. Serum Mg has been shown to be usually predictive of the total Mg levels in the body<sup>14</sup> while dietary Mg is a factor that can modify serum Mg levels in addition to exercise and the intake of calcium, potassium, or alcohol.<sup>15,16</sup> From previous ARIC studies, high levels of serum Mg have been associated with a lower risk of hypertension,<sup>17</sup> coronary heart disease (CHD),<sup>18,19</sup> diabetes,<sup>20</sup> and sudden cardiac death (SCD),<sup>21</sup> but dietary Mg intake based on a food frequency questionnaire has not shown any association in four of these studies.<sup>17,18,20,21</sup> Accordingly, this analysis of the ARIC study would be the first to prospectively explore the association between serum Mg or dietary Mg intake and AF incidence in order to determine if the same inverse association exists between Mg and AF risk.

In addition, the race-specific associations between Mg and AF risk can be analyzed within the biracial ARIC population. Because many studies researching risk factors for AF were based on predominately white populations,<sup>5</sup> it is important to determine if the Mg-AF association is the same or different between African-Americans and whites. Overall, the incidence of AF is lower in African-Americans<sup>1,22</sup> even though they have higher stroke rates and a higher prevalence of risk factors for AF and stroke.<sup>23</sup> With the ARIC study population, race, along with age and gender, can be examined to determine if there is any interaction between the serum Mg or dietary Mg intake and these variables.

## 5. Main Hypothesis/Study Questions:

Aim #1: To determine if serum Mg level is associated with the incidence of AF in the ARIC study.

Aim #2: To determine if dietary Mg intake is associated with the incidence of AF in the ARIC study.

Aim #3: To determine if race (white vs. African-American) modifies the association between serum Mg level and AF.

Aim #4: To determine if race (white vs. African-American) modifies the association between dietary Mg intake and AF.

We hypothesize that individuals with lower serum Mg levels will have an increased risk for AF, and those with a low dietary Mg intake will have an increased risk for AF. In addition, we hypothesize that the Mg-AF association in both instances will be present and of a similar magnitude in white and African-American individuals.

## 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:

A follow-up data analysis will be performed utilizing longitudinal data from the ARIC cohort, using visit 1 as baseline.

### Inclusion/exclusion criteria:

We will exclude individuals (1) with prevalent AF or atrial flutter at baseline based on electrocardiogram (ECG), (2) missing baseline ECG data, (3) missing baseline serum Mg or dietary Mg data, (4) not fasting at least eight hours before the baseline examination, (5) missing other covariates, (6) with a race other than white or African-American, (7) non-whites from the Minnesota and Washington County sites, and (8) for the dietary analysis only, those with extreme caloric intakes or low-quality dietary data.

### Variables of interest:

#### *Main outcome of interest: Atrial fibrillation incidence*

The time to incident AF cases from baseline through December 31, 2008, will be the main outcome variable. Incident AF cases were ascertained from three sources: ECGs completed during the study exams, ICD-9 codes of 427.31 or 427.32 from hospital discharges, and death certificates that include AF as a cause of death (ICD-9 code 427.3 or ICD-10 code I48). AF incidence date will be defined as the date of the first ECG showing AF, the first hospital discharge date for an AF or atrial flutter diagnosis, or date when death occurred due to AF, whichever occurred first.<sup>3,6</sup>

*Main independent variables of interest: Serum Mg and Dietary Mg Intake*

In the ARIC study, serum Mg was assessed through laboratory tests at visits 1 and 2. Initially, we will explore the shape of the association between Mg and AF risk using restricted cubic splines. If appropriate, serum Mg will be divided into ranked quartiles based on the two visit measurements. For those individuals who attended both visits and were censored after that visit, the mean value of their two serum Mg measurements will be used for ranking. For individuals who did not attend visit 2 or were censored before the visit, their visit 1 serum Mg measurement will be used for ranking. We will also assess linear associations based on the spline model. For dietary Mg intake, a food frequency questionnaire was used to determine the content of Mg ingested by the individual. Mg content was multiplied by each food item's daily consumption frequency, and a total was generated by summing all the items together. Mg intake will also be divided into ranked quartiles for analysis if appropriate.

*Covariates*

From visit 1, other measured covariates to be included in the analysis of serum Mg are age, gender, race, study site, body mass index (BMI), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), serum potassium, serum creatinine, smoking status, drinking status, educational level, systolic blood pressure, diabetes mellitus, use of diuretics, use of other antihypertensive meds, and a history of stroke, heart failure, or CHD. For dietary Mg, total energy intake will be included in all models along with a model with these correlated dietary covariates with Mg: potassium, calcium, dietary fiber, protein, caffeine, and polyunsaturated to saturated fat ratio.

Statistical analysis:

Cox proportional hazards models will be used to determine the association between serum Mg and incident AF. The following models will be used to analyze the serum Mg-AF association:

- Model 1: adjustment for age, gender, race, and ARIC study site
- Model 2: Model 1 + adjustment for BMI, HDL-c, LDL-c, serum potassium, serum creatinine, smoking status, drinking status, education level, systolic blood pressure, diabetes, use of diuretics, and use of other antihypertensive meds
- Model 3: Model 2 + history of heart failure, CHD, and stroke
- Model 4: Model 3 + incidence of heart failure, CHD, and stroke as time-dependent covariates

Dietary Mg and incident AF will be evaluated with the same Cox proportional hazard models except all models will be adjusted for total energy intake and Model 2 will include dietary covariates that are correlated with Mg intake: potassium, calcium, dietary fiber, protein, caffeine, and polyunsaturated to saturated fat ratio.

Effect modification will also be evaluated by age, gender, and race conducting stratified analysis and including multiplicative terms between the effect modifier and Mg measures in the models.

We expect to include more than 1500 incident events of AF, which will provide sufficient power to study the association of serum Mg or dietary Mg intake with AF risk in the entire sample. However, limited power might exist to study race-specific associations, particularly in African-Americans, and the Mg-AF association by the three different AF ascertainment sources.

Strengths and limitations:

Strengths of the study include the large sample size and power to measure associations between magnesium and AF and the sizable sample of African-Americans to evaluate risk factors of interest in relation to AF. However, there are a couple of limitations. Although hospital discharge codes being used for identifying incident AF cases have shown to be valid,<sup>3</sup> there is some likelihood of AF cases being missed in outpatient settings. In addition, there may be some misclassification of the Mg exposure since there is no follow-up information on serum Mg or dietary Mg after visit 2. As a result, if Mg levels happened to change over time, there is no additional information to examine such changes from follow-up data.

**7. a. Will the data be used for non-CVD analysis in this manuscript?**

Yes  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 ICTDER03 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  No

**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.unc.edu/ARIC/search.php>

Yes, no overlap found.  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)?**

No previous manuscript proposals in ARIC have specifically examined the association between serum Mg/dietary Mg and atrial fibrillation. Other ARIC manuscripts have explored the association between individual serum Mg/dietary Mg and CVD.

**#438 Mg and CHD**

**#1196 Mg and sudden death**

**#1268 Mg and stroke**

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

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)\* 2008.12)

\*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

12. **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.**

#### References:

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults. National implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA*. 2001; 285:2370-2375.
2. Benjamin EJ, Levy D, Vaziri SM. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994; 271(11):840-4.
3. 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.
4. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004; 292(20):2471-7.
5. Benjamin EJ, Chen P-S, Bild DE, et al. Prevention of atrial fibrillation: report from an NHLBI workshop. *Circulation*. 2009; 119:606-618.
6. Chamberlain AM, Agarwal SK, Ambrose M, et al. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the atherosclerosis risk in communities (ARIC) study. *Am Heart J*. 2010; 159:850-856.

7. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a Risk Factor for Atrial Fibrillation. *Circulation*. 2003; 108:3006-3010.
8. Kiziltepe U, Eyiletten ZB, Sirlak M, et al. Antiarrhythmic effect of magnesium sulfate after open heart surgery: Effect on blood levels. *Int J Cardiol*. 2003; 89:153-158.
9. Miller S, Crystal E, Garfinkle, et al. Effects of magnesium on atrial fibrillation after cardiac surgery: a meta analysis. *Heart*. 2005; 91:618-623.
10. Reinhart, K, Baker WL, Siv ML. Review: Beyond the Guidelines: New and Novel Agents for the Prevention of Atrial Fibrillation After Cardiothoracic Surgery. *J Cardiovasc Pharmacol Ther*. 2011; 16:5-13.
11. Koniari et al. Pharmacologic prophylaxis for atrial fibrillation following cardiac surgery: a systematic review. *Journal of Cardiothoracic Surgery*. 2010; 5:121.
12. Ho KM and Lewis JP. Prevention of Atrial Fibrillation in Cardiac Surgery: Time to Consider a Multimodality Pharmacological Approach. *Cardiovascular Therapeutics*. 2010; 28:59-65.
13. Kaplan M, Kut MS, Icer UA, et al. Intravenous magnesium sulfate prophylaxis for atrial fibrillation after coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2003; 125:344-352.
14. Assessment and oral management of micronutrient deficiency. In: Alpers DH, Clouse RE, Stenson WF, editors. *Manual of nutritional therapeutics*. 2nd ed. Boston: Little, Brown and Company, 1988; 90-94.
15. Fletcher GF, Sweeney ME, Fletcher BJ. Blood magnesium and potassium alterations with maximal treadmill exercise testing: effects of beta-adrenergic blockade. *Am Heart J*. 1991; 121:105-110.
16. Rylander R, Megevand Y, Lasserre B, et al. Moderate alcohol consumption and urinary excretion of magnesium and calcium. *Scand J Clin Lab Invest*. 2001; 61:401-405.
17. Peacock JM, Folsom AR, Arnett DK, et al. Relationship of serum and dietary magnesium to incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol*. 1999; 9:159-165.
18. Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 1998; 136:480-490.
19. Ma J, Folsom AR, Melnick SL, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. *J Clin Epidemiol*. 1995; 48:927-940.
20. Kao WH, Folsom AR, Nieto FJ, et al. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Arch Intern Med*. 1999; 159:2151-2159.

21. Peacock JM, Ohira T, Post W, et al. Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk of Communities (ARIC) Study. *Am Heart J.* 2010; 160:464-470.
22. Ruo B, Capra AM, Jensvold NG, et al. Racial Variation in the Prevalence of Atrial Fibrillation Among Patients With Heart Failure. *J AM Coll Cardiol.* 2004; 43:429-435.
23. Soliman EZ, Alonso A, Goff DC, Atrial fibrillation and ethnicity: the known, the unknown, and the paradox. *Future Cardiology.* 2009; 5.6:547-557.