

## ARIC Manuscript Proposal # 1845

PC Reviewed: 9/13/11  
SC Reviewed: \_\_\_\_\_

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

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

**1.a. Full Title:** Serum phosphorus levels and the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities study

**b. Abbreviated Title (Length 26 characters):** Phosphorus and AF

### 2. Writing Group:

Faye L. Lopez, Sunil K. Agarwal, Elsayed Z. Soliman, Laura R. Loehr, Lin Y. Chen, Rachel R. Huxley, Pam L. Lutsey, Alvaro Alonso, others welcome

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

Data analysis: 2 months

First draft of the manuscript: 3 months

We expect to submit an abstract with preliminary results to the AHA Epi conference (submission deadline Oct 2011)

#### **4. Rationale:**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, currently affecting over 2.3 million US adults and is expected to more than double in the next five decades.<sup>1</sup> AF is associated with increased risks of heart failure, stroke and cardiovascular death,<sup>2</sup> including a 9-fold higher risk of mortality within the first four months after AF, compared to those without AF.<sup>3</sup> Some major predictors for AF include age, white race, obesity, heart failure, coronary heart disease, left ventricular hypertrophy, and hypertension, along with certain lifestyle factors.<sup>4-6</sup> These predictors are similar to the risk factors for cardiovascular disease (CVD) in general, which often precedes an AF event.<sup>2</sup> Literature on non-traditional risk predictors for AF is scarce, and phosphorus may be one such marker.

Phosphorus is the second most abundant mineral in the body and is essential for numerous biological functions including cellular signal transduction, mineral metabolism and energy exchange.<sup>7</sup> Serum phosphorus mainly occurs in an inorganic form, and remains in a fairly narrow range with abnormal concentrations likely to be the result of disease.<sup>8</sup> Excess phosphorus levels have been independently linked with calcification of the aorta and coronary arteries,<sup>9,10</sup> along with substantially increased cardiovascular morbidity and mortality in patients receiving chronic dialysis,<sup>11</sup> and in those with chronic kidney disease (CKD).<sup>12</sup> Higher levels of serum phosphate have also been associated with increases in mortality and the risk of cardiovascular events in those with prior myocardial infarctions,<sup>7</sup> along with an increased risk of CVD and heart failure in those free of CKD.<sup>13-15</sup> Hyperphosphatemia is more common in blacks than whites, but it appears that adjusting for income modifies this relationship.<sup>16</sup>

Recently, we have shown an increased risk of AF associated with CKD.<sup>17</sup> In CKD, phosphorus excretion is impaired resulting in increased phosphatemia. Given the calcification properties of excess serum phosphorus levels, coupled with the increase in risk of CVD events, the relationship between serum phosphorus levels and the risk of AF as a mediator of the association between CKD and AF is worth exploring. To date, no study has looked at this relationship, and previous studies on serum phosphorus and cardiovascular outcomes have primarily focused only on whites. This study would be the first to estimate the association of serum phosphorus with the incidence of AF, taking advantage of the large number of incident AF cases, the biracial sample and ample follow-up time in the ARIC cohort.

## **5. Main Hypothesis/Study Questions:**

- i. To determine whether serum phosphorus levels are associated with the incidence of atrial fibrillation in ARIC participants
- ii. To determine if race (white vs. black) modifies the association between serum phosphorus levels and AF

We hypothesize an independent relationship between high serum phosphorus levels and an increased risk of incident AF. We hypothesize this relationship will be of similar magnitude in whites and blacks.

As an exploratory aim, we will examine whether eGFR modifies the association between serum phosphorus levels and AF risk.

## **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).**

This study will assess the association between serum phosphorus levels and the incidence of AF using a longitudinal data analysis approach. Data will first be obtained from the baseline exam on those participants who have measures of phosphorus and other covariates. For this analysis, we will exclude individuals with prevalent AF at baseline, those not fasting for 8 hours, and those with missing variables in any of the covariates. We will also exclude the small number of participants who reported a race other than white or black.

### *Covariates:*

Main outcome variable: time to AF from baseline through 2008.

Main independent variable: serum phosphorus

Covariates measured at baseline (visit 1): age, gender, race, center, education, height, income, smoking status, drinking status, serum calcium levels, body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, estimated glomerular filtration rate (eGFR), prevalent stroke, prevalent heart failure, prevalent coronary heart disease, and electrocardiograph based left-ventricular hypertrophy.

### *Statistical Analysis*

We will assess the association between baseline serum phosphorus levels and AF incidence using Cox proportional hazards models. First, we will explore the shape of the association of phosphorus levels with AF incidence using restricted cubic splines. Due to low phosphorus levels possibly causing cardiac arrhythmias, a J-shaped association between phosphorus levels and AF may be present. Based on this analysis, we will decide whether to model phosphorus as a continuous or categorical variable (e.g. quartiles or clinically significant categories).

The following four models will be used to assess the association between phosphorus levels and incident AF cases:

Models:

- 1: adjust for age, gender and race
- 2: adjust for age, gender, race, center, education, income, height, smoking status, drinking status, BMI, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes mellitus, eGFR, and calcium levels.
- 3: model 2, and additionally adjust for prevalent stroke, heart failure, and CHD
- 4: model 3, and additionally adjust for incident stroke, heart failure and CHD as potential mediators

A sensitivity analysis will be conducted using the same models and excluding those with an eGFR < 90 mL/min per 1.73 m<sup>2</sup> at baseline.

Interactions between serum phosphorus levels and the variables of race, sex and eGFR will be examined.

### *Limitations:*

Misclassification of the outcome is possible, with AF diagnosis having a positive predictive value of ~90%.<sup>4</sup> Misclassification of the exposure is also possible due to variations in serum levels. The ARIC study does not contain information on thyroid profiles, which would potentially be a strong confounder in this study.

**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

**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.cscce.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)?**

**10. 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\* 2008.12)

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.cscce.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:*

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