ARIC Manuscript Proposal #2088

PC Reviewed: 3/12/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of fibroblast growth factor 23 (FGF-23) with incidence of atrial fibrillation: the ARIC study

b. Abbreviated Title (Length 26 characters): FGF-23 and AF

2. Writing Group:
Alvaro Alonso, Jeffrey Misialek, John Eckfeldt, Liz Selvin, Josef Coresh, Lin Y. Chen, Elsayed Soliman, Sunil Agarwal, Pamela L. Lutsey, others welcome

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]**

First author: **Alvaro Alonso**
Address: 1200 S 2nd St
University of Minnesota
Minneapolis, MN 55454
Phone: 612-626-8597
E-mail: alonso@umn.edu

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).
Name: **Pamela L. Lutsey**
Address: 1200 S 2nd St
University of Minnesota
Minneapolis, MN 55454
Phone: 612-624-5812
E-mail: lutsey@umn.edu

3. Timeline:
Data analysis will start immediately using available FGF-23 measures and will be finalized once FGF-23 assays for the entire cohort are completed.

4. Rationale:
Fibroblast growth factor 23 (FGF-23) is a hormone involved in the regulation of phosphorus homeostasis, vitamin D metabolism and bone mineralization. Secreted

primarily by osteocytes in response to increased serum phosphorus levels, FGF-23 reduces the expression and activity of Na/Pi cotransporters in the proximal tubules, lowers serum calcitriol levels, and suppresses PTH synthesis.[1] In individuals with chronic kidney disease (CKD), FGF-23 levels are elevated, possibly in response to the reduced renal ability to eliminate phosphorus. Different studies have shown that, in individuals with CKD, FGF-23 levels are predictive of disease progression and overall adverse outcomes, including higher mortality and risk of cardiovascular disease.[2,3]

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with an increased risk of stroke, heart failure and mortality.[4] CKD has been described as a potential risk factor for AF.[5] However, the mechanisms linking CKD and AF risk are not well understood. Increase of FGF-23 level occurring in CKD could partly mediate this association. Experiments in animal models have found that FGF-23 has a direct effect in the myocardium, leading to left ventricular hypertrophy (LVH).[6] Also, an association between FGF-23 and left ventricular hypertrophy has been found in cross-sectional studies.[6,7] LVH, in turn, has been associated with higher risk of heart failure (HF) and AF.[8,9] Therefore, exploring the association between FGF-23 and AF risk could help to understand better the interplay between kidney dysfunction and AF risk.

5. Main Hypothesis/Study Questions:

We hypothesize that higher levels of FGF-23 will be associated with increased risk of AF independently of kidney function and other known risk factors for 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

Cohort analysis of ARIC participants with data on FGF-23 measured at visit 2 free of AF, followed up through the end of 2009.

Exclusion criteria

Individuals will be excluded if they meet any of the following criteria:

- Prevalent AF at visit 2
- Missing or low quality baseline ECG
- Missing FGF-23 measurements
- Non-whites in Minneapolis and Washington County, non-whites non-blacks in Forsyth county

Main outcome measure

Incident AF, occurring between visit 2 and end of 2009 (end of 2010, if data are available). AF incidence will be identified from ECGs done at the study visits, presence of

AF diagnosis in hospitalization discharge summaries, or AF listed as a cause of death, as described in previous publications.[10]

Main independent variable

FGF-23 measures as part of ancillary study 2009.17 in visit 2 serum. FGF-23 has been measured using ELISA. Preliminary QC data suggest adequate validity of FGF-23 measurements (CV:14.5%; Pearson r = 0.88, with >3 SD outliers removed).

Other covariates

Age, sex, race, study center, education, BMI, height, smoking, systolic and diastolic blood pressure, use of antihypertensive meds, diabetes, prevalent coronary heart disease, prevalent heart failure, ECG-derived left ventricular hypertrophy, eGFR, serum phosphorus, serum calcium, hsCRP, NTproBNP, PTH.

Statistical analysis

We will use Cox regression models to estimate the association between FGF-23 and AF incidence. Appropriate transformations of FGF-23 will be done if the variable is non-normally distributed. We will explore the shape of the FGF-23 / AF association using restricted cubic splines, and will model FGF-23 based on this analysis (e.g. quartiles, continuous, etc.)

We will obtain hazard ratios and 95% confidence intervals running the following models:

- Model 1: age, sex, race-adjusted
- Model 2: Model 1 + study center, education, BMI, height, smoking
- Model 3: Model 2 + systolic and diastolic blood pressure, use of antihypertensive meds, diabetes, prevalent CHD, prevalent HF [variables included in the CHARGE AF risk score], hsCRP, ECG-based left ventricular hypertrophy
- Model 4: Model 3 + eGFR, serum phosphorus, serum calcium, PTH

We will conduct stratified analysis by sex, race, age, and eGFR categories.

To explore whether a potential association between FGF-23 and AF risk is mediated by HF risk, we will conduct an additional analysis in which we will exclude individuals with prevalent HF and censor those who developed HF at the time of HF.

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)?

No previous proposals use FGF-23 data

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* 2009.17)

___ 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.

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