

ARIC Manuscript Proposal #2143

PC Reviewed: 5/14/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Association of fibroblast growth factor-23 levels with risk and progression of chronic kidney disease: the Atherosclerosis Risk in Communities (ARIC) study

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

2. Writing Group:

Writing group members: Casey M. Rebholz, Morgan Grams, Josef Coresh, Elizabeth Selvin, Pamela L. Lutsey, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. CMR [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: Fibroblast growth factor-23 (FGF-23) biomarker has already been measured from ARIC visit 2 stored serum samples from 1990-1992 (through Dr. Pam Lutsey's ancillary study: 5R01HL103706-02, "Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort"), and end points and covariates have been collected through the overall ARIC study. The analysis and manuscript preparation is expected to begin immediately, and we anticipate submitting a draft for ARIC review within 3-6 months of receipt of the final dataset.

4. Rationale:

Chronic kidney disease (CKD) is increasingly recognized as a global public health issue due to its high prevalence and the concomitant increase in risk of cardiovascular disease, end-stage renal disease, and mortality (Hemmelgarn *et al.*, 2010; KDIGO, 2013; Levey *et al.*, 2011). Existing prediction models for CKD incidence and progression utilizing established risk factors demonstrate modest-to-acceptable discriminatory performance (Echouffo-Tcheugui & Kengne, 2012). Exploring novel biomarkers for CKD may improve the identification of high-risk individuals and contribute to understanding of CKD pathogenesis. Recently, FGF-23 has been proposed as a marker of kidney injury and may be useful in risk stratification for clinical events (Wolf, 2012; Wolf, 2010).

FGF-23 is a bone-derived hormone with several endocrine functions in the renal proximal tubule, including the induction of urinary phosphorus excretion and inhibition of vitamin D activation (Shimada *et al.*, 2004). Several epidemiologic studies have recently investigated the relationship between FGF-23 and cardiovascular endpoints as well as overall mortality among individuals with and without CKD, with mixed results (Dominguez *et al.*, 2013; Faul *et al.*, 2011; Gutiérrez *et al.*, 2008; Isakova *et al.*, 2011; Ix *et al.*, 2012; Parker *et al.*, 2010; Scialla *et al.*, 2013; Taylor *et al.*, 2011). The association between FGF-23 and cardiovascular disease appears to be stronger among those with CKD than those without CKD (Dominguez *et al.*, 2013; Ix *et al.*, 2012). In the Mild to Moderate Kidney Disease Study, a cohort study of 177 CKD patients followed for a median of 53 months, FGF-23 independently predicted progression of kidney disease (defined by doubling of serum creatinine or end-stage renal disease) after adjustment for age, gender, glomerular filtration rate (GFR), proteinuria, and serum levels of calcium, phosphate, and parathyroid hormone (Fliser *et al.*, 2007). In the Chronic Renal Insufficiency Cohort study of 3,879 participants, FGF23 was independently associated with risk of end-stage renal disease (ESRD) among those with GFR 30-44 mL/min/1.73m² and ≥ 45 mL/min/1.73m², but not among those with GFR < 30 mL/min/1.73m² (Isakova *et al.*, 2011). Further research is warranted to better understand the relationship between FGF-23 and disease outcomes including ESRD, incident CKD, and kidney disease progression.

5. Main Hypothesis/Study Questions:

The primary hypothesis is that FGF-23 will be positively and independently associated with risk of incident ESRD. The secondary hypothesis is that FGF-23 will be positively and independently associated with incident CKD. The tertiary hypothesis is that FGF-23 will be positively and independently associated with kidney disease progression.

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 analysis of ARIC participants with measurements of FGF-23 from stored serum samples taken during ARIC visit 2 (1990-1992, “baseline” for

this manuscript). These study participants will be followed through visit 5 and/or the most recent surveillance year (currently 2010).

Exclusions: Participants missing FGF-23 or other covariables of interest, or those participants with ESRD at ARIC visit 2, will be excluded from all analyses.

Exposure: The primary exposure variable is FGF-23 levels at ARIC visit 2.

Outcome:

Incident ESRD will be assessed from ARIC visit 2 through follow-up. ESRD will be defined by ICD-9 discharge billing codes for hospitalizations (39.95, 54.98, V45.1, V56, V42, 403.01, 403.91), United States Renal Data System (USRDS) registry of cases reported to the Centers for Medicare & Medicaid Services, dialysis, transplantation, or estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73m² (stage 5) based on measurements performed at ARIC follow-up visit 4 or subsequent visits. Secondary outcome variables include incident CKD and renal disease progression. Renal disease progression will be defined as a change to a more severe kidney disease stage or ≥25% decrease in GFR following the 2013 CKD clinical practice guidelines (Bash *et al.*, 2009; KDIGO, 2013; Levey *et al.*, 2011). For the analysis of incident CKD, those participants with CKD at ARIC visit 2 will be excluded, and incident CKD will be assessed from ARIC visit 2 through follow-up (uniform ascertainment at visits 3, 4 and 5). We recognize the limitations of selective losses between visits, particularly during the long interval between visits 4 and 5 (~15 years). To overcome this limitation, we will explore definitions of incident CKD cases, which include ICD-9 discharge billing codes during hospitalization surveillance (581-589, 403-404, 593.9, 250.4), eGFR less than 60 mL/min/1.73m² (stage 3-5) based on measurements performed at ARIC follow-up visit 4 or subsequent visits, or, in the subset of carotid MRI ancillary ARIC study participants (n=2,066), eGFR less than 60 mL/min/1.73m² at either visit 4 or the MRI visit.

Throughout the manuscript, GFR will be estimated by CKD-EPI equations using standardized creatinine. Secondary analyses will examine cystatin C and the combination of creatinine and cystatin C when available (visits 2, 4 and 5) (Inker *et al.*, 2012). eGFR will be expressed continuously and in clinically-relevant categories (stage 5: <15, stage 4: 15-29, stage 3b: 30-44, stage 3a: 45-59, stage 2: 60-89, stage 1: ≥90 mL/min/1.73m²).

Statistical Analyses:

For descriptive purposes, we will examine the associations of FGF-23 at ARIC visit 2 with characteristics of study participants assessed at ARIC visit 2, including age, gender, and race. We will examine the cross-sectional associations of FGF-23 at ARIC visit 2 with measures of kidney function assessed at ARIC visit 2 (GFR, serum creatinine). We will use means and proportions to describe the participant characteristics and kidney function measures according to quartile or quintile of FGF-23, and test for differences using χ^2 and analysis of variance. The distribution of FGF-23 levels in this study population will be examined using a scatterplot and tests of normality. If a skewed distribution is apparent, we will consider transformations, e.g. logarithmic transformation and categorization by quantiles.

Survival analysis using Cox proportional regression models will be used to assess the association between FGF-23 and incidence of kidney disease outcomes during follow-up with random effects models used to model decline of eGFR over time. We will use cubic splines to visually depict and examine the shape of the associations. We will explore the influence of interaction by race, sex, and age in multivariable models. We will stratify the results by race, sex, and age category, if indicated. Clustering and adjustment for race-center will be examined. Potential covariates for multivariable analyses include: age, sex, race-center, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, diabetes status, history of cardiovascular disease, cigarette smoking status, alcohol drinking status, education level (visit 1), physical activity (visit 1), antihypertensive medication use, lipid-lowering medication use, C-reactive protein, eGFR (using both creatinine and cystatin C), parathyroid hormone, phosphorus, calcium, 25-hydroxy-vitamin D, and 3-epi-25-hydroxy-vitamin D₃. The literature suggests that confounding by eGFR will be important and should be examined carefully.

Limitations: We recognize a number of limitations including: availability of kidney function measures only at visits (2, 3, 4, and 5 for creatinine; 4 only for albuminuria); selective drop outs; correlation of FGF23 with eGFR which may reflect bidirectional causation. The analysis will address each of these and the discussion will acknowledge and place them in the context of the strengths of the paper.

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 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 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.unc.edu/ARIC/search.php>

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)?

#2108 - FGF-23 and incident coronary heart disease, heart failure, and total mortality

#2088 - FGF-23 and atrial fibrillation

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

The primary exposure for this proposed manuscript was measured for ancillary study #2009.17 (PI: P. Lutsey, "Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort). In addition, some of the measurements (cystatin C, C-reactive protein) from ancillary study #2009.16 (PI: E. Selvin, "Short-term markers of glycemia and long-term outcomes") will be utilized in defining outcomes and as covariates.

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.csc.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.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.

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