ARIC Manuscript Proposal #3707

PC Reviewed: 9/8/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of fibroblast growth factor-23 (FGF-23) at late-life with echocardiographic parameters: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): FGF23 and cardiac echo

2. Writing Group:

Writing group members: Yasuyuki Honda, Junichi Ishigami, Manabu Hishida, Amy Karger, Dalane Kitzman, Josef Coresh, Elizabeth Selvin, Pamela Lutsey, Amil Shah, Kunihiro Matsushita, others welcome

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

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3. Timeline: Data for this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Fibroblast growth factor 23 (FGF-23), a hormone mainly secreted by bone osteocytes, reduces phosphate reabsorption and suppresses activation of 1,25-dihydroxyvitamin D in renal proximal tubule.[1] FGF-23 levels increase with progression of chronic kidney disease (CKD)[2] and may contribute to increased risk of cardiovascular disease (CVD) in CKD. Indeed, FGF-23 level has been associated with CVD risk in patients with CKD[3, 4] and end-stage renal disease (ESRD).[5]

There are several plausible mechanisms linking FGF-23 to CVD in CKD patients. For example, FGF-23 was found to stimulate renin-angiotensin system, and induce cardiomyocyte hypertrophy and fibrosis in animal models.[6-9] FGF-23 also increased sodium reabsorption in kidney.[10] Indeed, FGF-23 has been related to cardiac structural abnormalities (e.g., left ventricular hypertrophy [LVH]) as well as functional abnormalities (e.g., left ventricular [LV] dysfunction) among patients with CKD[8, 11, 12] and ESRD,[13, 14] while most of these studies were limited to small number of patients (n<300).[11-14]

In the general population, although conflicting results were seen for coronary heart disease[15-18] and stroke,[15, 16] FGF-23 has been consistently associated with heart failure.[15-17] In addition, a few cross-sectional studies have reported the positive association of FGF-23 with LVH,[19, 20] further supporting the pathophysiological contribution of FGF-23 to the development of heart failure.

However, to the best of our knowledge, no community-based studies have explored the comprehensive associations of FGF-23 with cardiac structure and function. Therefore, we propose to examine the association of FGF-23 with cardiac echo parameters in participants of the Atherosclerosis Risk in Communities (ARIC) study who attended visit 5 (2011-2013). ARIC will also allow us to explore whether cumulative exposure of FGF-23 from mid-life (visits 2 [1990-1992] and 3 [1993-1995]) to late-life (visit 5) shows a similar or stronger association with cardiac structure and function compared to when we only analyze FGF-23 at a single time point during older ages.

5. Main Hypothesis/Study Questions:

Hypothesis 1: FGF-23 levels visit 5 will be associated with cardiac abnormalities as assessed by echocardiographic parameters.

Hypothesis 2: The association of FGF-23 with cardiac abnormalities will be strengthened when we take into account cumulative exposure of FGF-23 from mid-life (i.e., visits 2 and 3) to late-life (i.e., visit 5).

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: Observational cohort study

FGF-23 levels at visit 5 will be used for our primary analysis (Hypothesis 1). In the secondary analysis (Hypothesis 2), we will explore cumulative FGF-23 from mid-life (visits 2 and 3) to late-life (visit 5).

Inclusions:

-All Black and White ARIC participants who attended visit 5 (2011-2013)

Exclusions:

Primary analysis:

-Missing serum FGF-23 levels at visit 5

-Missing echocardiographic parameters

-Missing covariates on variables of interest at visit 5

Secondary analysis:

- Missing serum FGF-23 levels at visits 2, 3 or 5
- Missing echocardiographic parameters
- Missing covariates on variables of interest at visit 5

Exposures (Independent variables) :

Primary exposures: FGF-23 levels at visit 5

Secondary exposures: Weighted average of FGF-23 levels at visits 2, 3, and 5

Outcomes (Dependent variables) :

According to clinical guidelines[21, 22] and previous literature in the context of FGF-23 and cardiac abnormalities,[12-14, 19, 20, 23] we will use the variables below as primary parameters.

Primary parameters:

a) LV structure
   LV mass index
b) LV systolic function
   Ejection fraction
c) LV diastolic function
   Left atrial volume

Other parameters:

a) LV structure
   Relative wall thickness, LV end-diastolic/systolic volume/diameter
b) LV systolic function
   LV outflow tract velocity time integral, mid-wall fractional, longitudinal, circumferential strain, tissue doppler mitral annular peak systolic velocity, and arterial elastance / LV end-systolic elastance
c) LV diastolic function
   E wave, E /A ratio, tissue doppler E', E /E' ratio, E wave deceleration time, and isovolumetric relaxation time
d) Right ventricle (RV) and pulmonary artery
    a. RV structure
       RV end systolic/diastolic area and RV volume
    b. RV systolic function
       RV fractional area change and tricuspid annular peak systolic myocardial velocity
    c. Hemodynamics
       Peak tricuspid regurgitation velocity, peak RV-right atrium gradient, and pulmonary vascular resistance

Covariates at visit 5:

Demographics: Age, sex, race, study center, and education level (at visit 1)
Physical information: Body mass index and systolic and diastolic blood pressure.
Behavioral factors: Smoking status, alcohol use, and physical activity

Comorbidities: Diabetes, dyslipidemia, hypertension, and history of coronary heart disease, heart failure, or stroke.
Medications: Use of antihypertensive medication and cholesterol lowering medication.
Laboratory examinations: Total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR) and natriuretic peptide (NT-proBNP).

Statistical Analysis:

1) We will compare baseline characteristics according to the quartiles of FGF-23 levels at visit 5 and summarize as mean (SD) or median (IQI), and number (proportion) for categorical variables.
2) We will use both linear and logistic regression models to quantify the association of FGF-23 levels with echocardiographic parameters (continuously for the former and categorically for the latter). We will implement several models to account for the impact of potential confounders. Model 1 will be crude. Model 2 will be adjusted for sociodemographic variables (age, sex, race, study center, and education levels). Model 3 will further adjust for other cardiovascular risk factors (smoking, alcohol use, physical activity, diabetes, lipids, blood pressure, antihypertensive medications, and history of coronary heart disease, heart failure, or stroke). Model 4 will additionally include eGFR.
3) We will conduct subgroup analyses by stratifying the study sample into key demographic and clinical subgroups (e.g., age, sex, race, smoking status, or other clinical comorbidities [diabetes, hypertension, kidney function, or history of coronary heart disease, heart failure, and stroke]). The interactions will be tested by using log-likelihood ratio tests comparing models with and without interaction terms.
4) We will repeat the analyses taking into account FGF-23 at visits 2 and 3 in our secondary analysis. Specifically, we will model weighted average of FGF-23 across visits 2, 3 and 5. For covariates, our primary approach will be to keep visit 5 covariates but explore also models with weighted average covariates when possible (e.g., blood pressure and lipids).

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/mantrack/maintain/search/dtSearch.html

__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)?

#1972: The association of kidney disease measures with left ventricular and atrial structure and function: The Atherosclerosis Risk in Communities (ARIC) Study
#2226: Fibroblast growth factor 23, serum phosphorus, and echocardiographic measures of cardiac structure and function: The Atherosclerosis Risk in Communities Study (ARIC)

The most relevant proposal is MP #2226. This study proposed non-concurrent cross-sectional design and prospective design. For the cross-sectional analysis, the authors used FGF-23 at visits 2 and echocardiographic parameters at visit 3, which was restricted to only African American in Jackson heart center with approximately 2600 participants. They also used FGF-23 at visit 2 in the prospective analysis, while we will use newly measured FGF-23 at visit 5.

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

___ A. primarily the result of an ancillary study (list number* _2017.20_____)

___ 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.cscc.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.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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