ARIC Manuscript Proposal #2108

PC Reviewed: 4/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Fibroblast growth factor-23 and incident coronary heart disease, heart failure, and total mortality: The Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): FGF23 & incident CHD & HF

2. Writing Group: Pamela L Lutsey, Jim Pankow, Alvaro Alonso, Joe Coresh, Elizabeth Selvin, Erin Michos, Sunil Agarwal, Laura Loehr, John Eckfeldt, Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __X__

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3. Timeline: Data analyses will begin immediately. Goal completion is June 2013.

4. Rationale:
Fibroblast growth factor 23 (FGF23) is a bone-derived endocrine hormone involved in the regulation of phosphorus homeostasis, vitamin D metabolism and bone mineralization. Its primary physiologic actions are to induce urinary phosphorous excretion, inhibit activation of calcitriol [1,25$(OH)_2$D], and suppress PTH synthesis[1-3].

FGF23 levels are correlated inversely with renal function[4, 5], and in patients with chronic kidney disease (CKD), elevated serum FGF23 levels predict the progression of renal failure[6], as well as total mortality[7, 8].

Given interrelations between FGF23 and CKD[2, 3] and the established role of CKD in elevating CVD risk[9], together with accruing evidence suggesting that low levels of vitamin D may increase CVD risk[10], evaluation of whether FGF23 is associated with CVD incidence is warranted. This is especially true for cardiac conditions, given recent experimental work in rodent models suggesting that FGF23 may have a direct pathophysiological role in inducing left ventricular hypertrophy[11].

Recently, the Cardiovascular Health Study reported that FGF23 is positively associated with risk of incident heart failure, cardiovascular events, and total mortality[12]. An interaction was present, whereby relations were stronger among individuals with mild/moderate CKD. Elevated FGF23 was also associated with mortality and recurrent CVD events among participants of the Heart and Soul Study, all of whom had prevalent coronary heart disease (CHD)[13]. Conversely, FGF23 was not related to CHD in a small case-control study nested within the Health Professionals Follow-Up Study[14].

Clearly, additional research is warranted. One of the most intriguing questions is whether FGF23 is simply a marker of CKD, or whether it is associated with CHD and HF independent of kidney function.

5. Main Hypothesis/Study Questions:

We hypothesize that FGF23 will be positively associated with risk of incident coronary heart disease, heart failure and total mortality, independent of traditional CVD risk factors.

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 from visit 2 through the 2010 events follow-up.

Inclusion/Exclusion

Participants with prevalent CHD and/or HF at visit 2 will be excluded, as will those who are neither African American nor white, and African Americans from the MN and MD centers.

Variables

Exposures: Serum FGF23 (measured in visit 2 serum)

Outcomes:

- Incident CHD based on validated myocardial infarction and fatal CHD
- Incident HF based on hospital ICD codes
- Combined outcome of incident CHD or HF

- Mortality as death from any cause, based on active surveillance of all ARIC participants.

Potential effect modifiers: Age, race, sex, and eGFR (modeled as ≥90, 60-89, and 15-59 ml/min/1.73 m^2). eGFR will be estimated using both creatinine and cystatin-C.

Other confounders: Age, race, sex, education, physical activity, smoking status, BMI, diabetes, LDL-C, HDL-C, triglycerides, and antihyperlipidemic medication use, systolic blood pressure, antihypertensive medication.

Additional variables of interest: Serum phosphorous, parathyroid hormone, eGFR and FGF23 are physiologically interrelated. We intend to carefully describe these interrelations, and are cognizant of the difficulty of differentiating between confounding and mediation in situations such as this.

Data analysis

Visit 2 will serve as baseline for the current analysis. Visit 2 participant characteristics will be described using means and proportions stratified by levels of the exposures. Additionally we will use cubic splines and general linear regression to examine relations between serum phosphorous, parathyroid hormone, eGFR and FGF23.

Cox proportional hazards regression will be used to explore relations between FGF23 and risk of incident CHD, HF, and total mortality. We will use cubic splines to visually depict the associations, and aid in selecting the most appropriate exposure representation.

Our first model will adjust for age, sex, and race. Model 2 will additionally adjust for education, physical activity, smoking status and BMI. Model 3 will further adjust for prevalent diabetes, systolic BP, hypertension medication use, lipid medication use, LDL-C and HDL-C . Additional mediation models will also adjust for eGFR, serum phosphorous and PTH. Mediation will be considered present if beta coefficients are altered by 10% or more upon inclusion of potential mediators in the statistical models. Cross-product terms will be used to evaluate whether age, race, sex, and/or eGFR modify relations of FGF23 to incident CHD, HF and total mortality. Stratified results will be presented, as appropriate.

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 __ X __ 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 related proposals exist.

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

2009.17 (Lutsey PI)
- "Serum vitamin D and cardiovascular disease risk in the biethnic ARIC cohort"

2009.16 (Selvin PI)
- "Short-term markers of glycemia and long-term outcomes"
- Numerous biomarkers which may be confounders and/or effect modifiers in the present analysis are being measured as part of this grant (e.g. CysC, CRP, BNP and TNT).

___ 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.

References

1. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T. Fgf-23 is a potent regulator of vitamin d metabolism and phosphate homeostasis. *J Bone Miner Res*. 2004;19:429-435
2. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. *Kidney Int*. 2012;82:737-747
3. Heine GH, Seiler S, Fliser D. Fgf-23: The rise of a novel cardiovascular risk marker in ckd. *Nephrology Dialysis Transplantation*. 2012;27:3072-3081
4. Shigematsu T, Kazama JJ, Yamashita T, Fukumoto S, Hosoya T, Gejyo F, Fukagawa M. Possible involvement of circulating fibroblast growth factor 23 in the development of secondary hyperparathyroidism associated with renal insufficiency. *Am J Kidney Dis*. 2004;44:250-256
5. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, Juppner H, Wolf M. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol*. 2005;16:2205-2215
6. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, Ritz E, Kronenberg F, for the MSG. Fibroblast growth factor 23 (fgf23) predicts progression of chronic kidney disease: The mild to moderate kidney disease (mmkd) study. *J Am Soc Nephrol*. 2007;18:2600-2608
7. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Juppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med*. 2008;359:584-592
8. Isakova T XHYW, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA*. 2011;305:2432-2439
9. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296-1305
10. Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin d and risk of cardiovascular disease: A meta-analysis of prospective studies. *Circulation: Cardiovascular Quality and Outcomes*. 2012;5:819-829
11. Faul C, Amaral AP, Oskouei B, Hu M-C, Sloan A, Isakova T, Guti, xE, rrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St. John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-o M, Kusek JW, Keane MG, Wolf M. Fgf23 induces left ventricular hypertrophy. *The Journal of Clinical Investigation*. 2011;121:4393-4408
12. Ix JH, Katz R, Kestenbaum BR, de Boer IH, Chonchol M, Mukamal KJ, Rifkin D, Siscovick DS, Sarnak MJ, Shlipak MG. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: Chs (cardiovascular health study). *Journal of the American College of Cardiology*. 2012;60:200-207
13. Parker BD, Schurgers LJ, Brandenburg VM, Christenson RH, Vermeer C, Ketteler M, Shlipak MG, Whooley MA, Ix JH. The associations of fibroblast growth factor 23 and uncarboxylated matrix gla protein with mortality in coronary artery disease: The heart and soul study. *Ann Intern Med*. 2010;152:640-648

14. Taylor EN, Rimm EB, Stampfer MJ, Curhan GC. Plasma fibroblast growth factor 23, parathyroid hormone, phosphorus, and risk of coronary heart disease. *American Heart Journal*. 2011;161:956-962