Fibroblast Growth Factor-23 and Incident Coronary Heart Disease, Heart Failure, and Cardiovascular Mortality: The Atherosclerosis Risk In Communities Study

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Background—Fibroblast growth factor-23 (FGF-23) is a hormone involved in phosphorous regulation and vitamin D metabolism that may be associated with cardiovascular risk, and it is a potential target for intervention. We tested whether elevated FGF-23 is associated with incident coronary heart disease, heart failure, and cardiovascular mortality, even at normal kidney function.

Methods and Results—A total of 11 638 Atherosclerosis Risk In Communities study participants, median age 57 at baseline (1990–1992), were followed through 2010. Cox regression was used to evaluate the independent association of baseline serum active FGF-23 with incident outcomes. Models were adjusted for traditional cardiovascular risk factors and estimated glomerular filtration rate. During a median follow-up of 18.6 years, 1125 participants developed coronary heart disease, 1515 developed heart failure, and 802 died of cardiovascular causes. For all 3 outcomes, there was a threshold, whereby FGF-23 was not associated with risk at <40 pg/mL but was positively associated with risk at >40 pg/mL. Compared with those with FGF-23 <40 pg/mL, those in the highest FGF-23 category (≥58.8 pg/mL) had a higher risk of incident coronary heart disease (adjusted hazard ratio, 95% CIs: 1.65, 1.40 to 1.94), heart failure (1.75, 1.52 to 2.01), and cardiovascular mortality (1.65, 1.36 to 2.01). Associations were modestly attenuated but remained statistically significant after further adjustment for estimated glomerular filtration rate. In stratified analyses, similar results were observed in African Americans and among persons with normal kidney function.

Conclusions—High levels of serum FGF-23 were associated with increased risk of coronary heart disease, heart failure, and cardiovascular mortality in this large, biracial, population-based cohort. This association was independent of traditional cardiovascular risk factors and kidney function. (J Am Heart Assoc. 2014;3:e000936 doi: 10.1161/JAHA.114.000936)

Key Words: Atherosclerosis Risk In Communities • cardiovascular mortality • coronary heart disease • epidemiology • fibroblast growth factor 23 • heart failure

Fibroblast growth factor 23 (FGF-23) is a hormone that is secreted primarily by osteocytes and to a lesser extent by osteoblasts. It is involved in the regulation of phosphorus homeostasis, vitamin D metabolism, and bone mineralization. Specifically, it induces urinary phosphorous excretion, inhibits activation of calcitriol [1,25(OH)2D], and suppresses parathyroid hormone (PTH) synthesis.1–3 Levels of FGF-23 are correlated inversely with renal function,4,5 and in patients with chronic kidney disease (CKD), elevated serum FGF-23 levels predict the progression of renal failure,6 and death.7,8

The potential role of FGF-23 in the development of cardiovascular disease, particularly independent of kidney function, is unclear. FGF-23 may influence cardiovascular risk through the CKD or vitamin D pathways; CKD is an established risk factor for cardiovascular disease,9 and accruing evidence suggests that low levels of vitamin D may increase cardiovascular risk.10 Furthermore, recent experimental work in rodent models suggests FGF-23 may have a direct pathophysiologic role in inducing left ventricular hypertrophy (LVH),11 a marker of cardiac remodeling associated with increased risk of sudden cardiac death and progression to heart failure (HF).12 Several studies have shown FGF-23 to be associated with cardiovascular events among patients with CKD13–16 and in those with prevalent coronary heart disease (CHD).17 In the general population,
information is more limited,18,19 although it is suggestive of an association, particularly among individuals with impaired kidney function.18,19 Information is lacking for those with normal renal function, and prior studies have not had adequate power to examine these associations among African Americans.

Using data from the prospective, community-based Atherosclerosis Risk in Communities (ARIC) Study, we tested the hypothesis that active, intact FGF-23 is positively associated with risk of incident CHD, HF, and cardiovascular mortality, independent of traditional cardiovascular risk factors and markers of kidney function.

### Methods

#### Study Population

The ARIC study is a population-based prospective cohort of 15,792 men and women (aged 45 to 64 years at baseline) who, between 1987 and 1989, were recruited from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland.20 A total of 4 cohort reexaminations have taken place: 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), and 2011–2013 (visit 5). Local institutional review boards approved the ARIC protocol, and all participants gave informed consent.

Serum FGF-23 was measured in samples collected at ARIC visit 2 (1990–1992); we are therefore using visit 2, which was attended by 14,348 participants, as “baseline” for the present analysis. Excluded from the analysis are participants who had prevalent CHD or HF at visit 2 (n=1368), self-identified as neither African American nor white and African Americans from the Minnesota and Maryland centers (n=85), had missing FGF-23 data (n=751), and had missing data on any covariate (n=506). Our final analytic sample included 11,638 participants.

#### FGF-23 and Other Variables

At visit 2, ARIC participants underwent interviews, fasting venipuncture, and measurement of blood pressure and anthropometrics. Trained interviewers ascertained basic demographic data, medical history, smoking status, and medication use. Participants were asked to bring to the visit all medications, vitamins, and supplements taken in the 2 weeks before the examination; all medication names were transcribed and coded. Physical activity (Baecke21 questionnaire) was not assessed at visit 2, so values from visit 1 were carried forward. Height and weight were measured, and body mass index (BMI) calculated as weight/height² (kg/m²). Sitting blood pressure was measured in triplicate with a random-zero sphygmomanometer; the mean of the latter 2 measurements were used in this analysis. Diabetes was defined by fasting blood glucose >126 mg/dL, nonfasting glucose >200 mg/dL, a self-report of physician diagnosis, or current medication use for diabetes. Left ventricular hypertrophy was determined by the Cornell definition, based on 12-lead electrocardiograms.22

Fasting (12-hour) blood samples were drawn, and plasma and serum were frozen at −70°C until analyzed. Intact FGF-23 was measured, in singlicate, in serum using a 2-site ELISA (FGF-23 ELISA Kit, Kainos Laboratories, Inc) at the Advanced Research and Diagnostic Laboratory, University of Minnesota, Minneapolis, Minnesota, in 2012–2013. The coefficient of variation (CV) for FGF-23 based on ARIC blind duplicate samples was 16.6%, while the CV from internal laboratory QC samples was 8.8% at 41.4 pg/mL. Serum phosphorus was measured in 2012–2013 on a Roche Modular P Chemistry Analyzer using a colorimetric method (CV=3%), and serum B-type natriuretic peptide (NT-proBNP) and serum high-sensitivity troponin T (hs-TnT) were measured using sandwich immunoassay methods on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation). Lipids were measured at the time of ARIC visit 2 (1990–1992). Total plasma cholesterol23 and triglycerides24 were determined via enzymatic methods. High-density lipoprotein cholesterol (HDL-C) was measured after dextran-magnesium precipitation,25 and the Friedewald equation26 was used to calculate low-density lipoprotein cholesterol (LDL-C) in those with triglyceride levels <400 mg/dL. Cystatin C was measured in 2012–2013 using the Gentian cystatin C reagent on the Roche Modular P Chemistry analyzer, and serum creatinine was measured in 1990–1992 using a modified kinetic Jaffe reaction. Estimated glomerular filtration rate (eGFR) was calculated using the 2012 CKD EPI equation, which incorporates both cystatin C and creatinine.27 eGFR was categorized according to established clinical cut-points: ≥90, 60 to 89, and 15 to 59 mL/min per 1.73 m². No participants in our sample had an eGFR <15. Urine was not collected at ARIC visit 2 but was available at visit 4. Urinary creatinine was measured by the Jaffe method and albumin by a nephelometric method either on the Dade Behring BN100 (Dade Behring, Inc, Deerfield, IL) or Beckman Image Nephelometer. The albumin–creatinine ratio (ACR) was calculated.

Prevalent CHD was defined by self-reported prior physician diagnosis of MI or coronary revascularization, prevalent MI by 12-lead ECG at visit 1, or an incident-adjudicated CHD event between ARIC visits 1 and 2. Preexisting HF was defined by any of the following: (1) an affirmative response to, “Were any of the medications you took during the last 2 weeks for heart failure?” (2) stage 3 or “manifest heart failure” according to Gothenburg criteria,28,29 or (3) incident HF hospitalization between ARIC visits 1 and 2.

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Outcome Ascertainment

Incident cardiovascular events and deaths through December 31, 2010, were identified through (1) annual telephone calls to ARIC cohort participants (or proxy), (2) active surveillance of local hospital discharge indexes, (3) search of state death records, and (4) linkage to the National Death Index. ARIC criterion and procedures for validating potential CHD events have been described previously. In brief, incident CHD was defined as the first occurrence of a validated definite or probable hospitalized MI or a definite CHD death. HF incidence was defined as the first occurrence of either a hospitalization that included an International Classification of Diseases, 9th Revision (ICD-9) discharge code of 428 (428.0 to 428.9) among the primary or secondary diagnoses or a death certificate with an ICD-9 code of 428 or an ICD-10 code of 150 among any of the listed diagnoses or underlying causes of death. Cardiovascular mortality was defined as death with ICD-9 code 401-459 or ICD-10 code I10-I99.

Statistical Analysis

Characteristics of participants at visit 2 are described using statistical analysis. The primary analysis, Cox proportional hazards regression was used to determine associations between FGF-23 and risk of incident CHD, HF, and cardiovascular mortality. Restricted cubic splines were used to explore the dose–response association between FGF-23 and outcomes and to aid in selecting the most appropriate exposure modeling. For all outcomes, there appeared to be a threshold whereby FGF-23 was unrelated to risk at levels <40 pg/mL but was associated with greater risk beyond that point. To convey this association, we used levels ≥40 pg/mL as the reference category (contains 45.3% of the analytic sample). Levels ≥40 pg/mL were divided into quartiles (each quartile contains 13.7% of the full study population). Given inherent interest, we also report the linear association (per 1 SD) between FGF-23 and outcomes. FGF-23 is a novel biomarker; as such, there are presently no cutpoints used clinically for elevated FGF-23. Our first model adjusted for basic demographics (age, sex, and race). Model 2 additionally adjusted for education, physical activity, smoking status, and BMI. Model 3 further adjusted for prevalent diabetes, systolic BP, hypertension medication use, lipid medication use, LDL-C, and HDL-C. In additional models, we also adjusted, separately, for eGFR, serum phosphorus, PTH, NT-proBNP, hs-TnT, and LVH. Cross-product terms were used to evaluate whether age, race, sex, or eGFR modified associations between FGF-23 categories and outcomes. The proportional hazards assumption was evaluated by inspection of ln(−ln) survival curves for FGF-23 categories. SAS version 9.3 was used.

Results

Our analytic sample included a total of 11,638 participants (female participants 57%, African American 25%, and mean age 57 years). Mean (±SD) FGF-23 was 43.9 (±16.4) pg/mL. Levels of FGF-23 were correlated positively with serum phosphorous (r=0.11) and PTH (r=0.11) and inversely with eGFR (r=−0.25). Relative to participants with FGF-23 concentrations below 40 pg/mL, those in the highest category (≥58.8 pg/mL) were slightly older, more likely to be African American, and overall had a worse cardiovascular risk factor profile, particularly in regard to hypertension and CKD (Table 1). For example, 9.3% of participants in the top category of FGF-23 had an eGFR <60 mL/min per 1.73 m², while among participants in the lowest category of FGF-23 only 1.0% had an eGFR <60 mL/min per 1.73 m².

Incident CHD

During a median of 18.6 (maximum 20.9) years of follow-up, 1125 incident CHD events accrued (median [SD] time to event 10.2 [5.4] years). FGF-23 was positively and significantly associated with risk of incident CHD when modeled linearly (per 1 SD), regardless of level of adjustment (Table 2). However, as illustrated in the restricted cubic spline models (Figure – Panel A), there was a threshold effect whereby there was no association between FGF-23 and risk at levels <40 pg/mL, but at ≥40 pg/mL there was a positive association. Hence, the reference group, which contains 45.3% of the full analytic sample, includes participants with FGF-23 concentrations <40 pg/mL. Levels ≥40 pg/mL were split into quartiles. After demographic adjustments, people in the highest category of FGF-23 (≥58.8 pg/mL) were at 1.65 (95% CI 1.40 to 1.94) times greater risk of incident CHD, relative to those at <40 pg/mL (Table 2). The association was similar with additional adjustment for behaviors (model 2: 1.63 [1.38 to 1.92]) and only modestly attenuated with further adjustment for cardiovascular risk factors (model 3: 1.44 [1.22 to 1.70]) and eGFR (model 4: 1.32 [1.11 to 1.56]). Results were essentially unchanged when model 4 was additionally adjusted for serum phosphorous (hazard ratio [HR] 1.30 [1.09 to 1.54]) and PTH (HR 1.31 [1.10 to 1.55]). In sensitivity analyses when follow-up time was restricted to the first 5 years, a total of 229 events accrued (53 in the upper category), and results were somewhat stronger: model 1: 1.89 (1.34 to 2.66) and model 4: 1.40 (0.97 to 2.02).
There was no evidence of interaction by age, sex, race, or eGFR on the association between FGF-23 and incident CHD.

Given inherent interest, race- and eGFR-stratified results are presented in Tables 3 and 4, respectively. Associations were qualitatively stronger in African Americans, relative to whites. It is important to note that in the analytic sample, only 309 ARIC participants had an eGFR < 60 mL/min per 1.73 m² at visit 2. Thus, power is more limited when restricted to this group.
Incident HF

A total of 1515 incident HF events occurred through a median of 18.6 years of follow-up (maximum 20.9 years). Among those who experienced events, median (SD) time to event was 11.4 (5.3) years. When modeled continuously (per 1 SD), FGF-23 was positively associated with HF risk, regardless of degree of adjustment (Table 2). A threshold effect was also observed between FGF-23 and risk of incident HF (Figure – Panel B).

Compared with those in the referent category (<40 pg/mL), the HR (95% CI) among those in the top category of FGF-23 (≥58.8 pg/mL) was 1.75 (1.52 to 2.01) after demographic adjustments (Table 2). Further adjustment for behaviors (1.63 [1.42 to 1.88]), cardiovascular risk factors (1.46 [1.27 to 1.68]), and eGFR (1.30 [1.13 to 1.51]) modestly attenuated the association. Also adjusting for serum phosphorous and PTH had little impact on the HRs: 1.27 (1.09 to 1.47) for phosphorous and 1.30 (1.12 to 1.51) for PTH. Results were stronger in sensitivity analyses when follow-up time was restricted to the first 5 years of follow-up: N events total/top category (230/62); model 1: 2.28 (1.63 to 3.18) and model 4: 1.48 (1.03 to 2.11).

The relation between FGF-23 and incident HF was not modified by age, sex, or race, although qualitatively associations were somewhat stronger in blacks than in whites (Table 3). There was no statistically significant interaction of the HF and FGF-23 association by eGFR category; however, stratified results are presented in Table 4.

Incident Cardiovascular Mortality

A total of 802 participants died of cardiovascular causes during follow-up. The median time to event was 11.2 (SD 4.1) years. A positive association was observed between FGF-23 when modeled per 1 SD and cardiovascular mortality. Similar to other outcomes, there was evidence of a threshold association (Figure – Panel C). Relative to those with FGF-23 concentrations <40 pg/mL, those in the highest category (≥58.8 pg/mL) had a HR for cardiovascular mortality of 1.65 (1.36 and 2.01) after demographic adjustments (model 1) (Table 2). In the fully adjusted model (model 4), the HR (top versus bottom category) for cardiovascular mortality was 1.28 (1.04 to 1.57). Results were similar when serum phosphorous

| Table 2. Serum FGF-23 and Risk of Incident CHD, HF, and Cardiovascular Mortality: The ARIC Study 1990–2010 |
|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Serum FGF-23 (pg/mL) | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Per 1 SD (16.40 pg/mL) |
|----------------------|---------|---------|---------|---------|---------|------------------------|
| Median               | 32.8    | 42.2    | 47.2    | 53.5    | 67.2    |                        |
| Range                | 2.9 to 40.0 | 40.1 to 44.6 | 44.7 to 50.1 | 50.2 to 58.7 | 58.8 to 481.0 |                        |
| N total (%)          | 5272 (45.3) | 1591 (13.7) | 1592 (13.7) | 1591 (13.7) | 1592 (13.7) |                        |
| Incident CHD         |         |         |         |         |         |                        |
| N events             | 438     | 141     | 145     | 183     | 218     |                        |
| Model 1              | 1.00 (Ref) | 1.05 (0.87, 1.27) | 1.05 (0.87, 1.27) | 1.34 (1.13, 1.60) | 1.65 (1.40, 1.94) | 1.14 (1.09, 1.18) |
| Model 2              | 1.00 (Ref) | 1.06 (0.88, 1.28) | 1.06 (0.88, 1.29) | 1.35 (1.13, 1.60) | 1.63 (1.38, 1.92) | 1.12 (1.08, 1.17) |
| Model 3              | 1.00 (Ref) | 1.02 (0.84, 1.23) | 1.00 (0.83, 1.21) | 1.24 (1.04, 1.48) | 1.44 (1.22, 1.70) | 1.11 (1.06, 1.16) |
| Model 4              | 1.00 (Ref) | 1.01 (0.83, 1.22) | 0.98 (0.81, 1.19) | 1.19 (1.00, 1.42) | 1.32 (1.11, 1.56) | 1.08 (1.03, 1.13) |
| Incident HF          |         |         |         |         |         |                        |
| N events             | 583     | 183     | 221     | 220     | 308     | 1515                   |
| Model 1              | 1.00 (Ref) | 1.04 (0.88, 1.22) | 1.21 (1.03, 1.41) | 1.22 (1.05, 1.43) | 1.75 (1.52, 2.01) | 1.15 (1.11, 1.18) |
| Model 2              | 1.00 (Ref) | 1.04 (0.88, 1.23) | 1.19 (1.02, 1.39) | 1.21 (1.03, 1.41) | 1.63 (1.42, 1.88) | 1.12 (1.09, 1.15) |
| Model 3              | 1.00 (Ref) | 1.04 (0.88, 1.23) | 1.14 (0.97, 1.33) | 1.14 (0.97, 1.33) | 1.46 (1.27, 1.68) | 1.11 (1.07, 1.15) |
| Model 4              | 1.00 (Ref) | 1.03 (0.87, 1.21) | 1.12 (0.96, 1.31) | 1.08 (0.92, 1.26) | 1.30 (1.13, 1.51) | 1.08 (1.04, 1.13) |
| Incident cardiovascular mortality |         |         |         |         |         |                        |
| N events             | 295     | 114     | 110     | 126     | 157     | 802                    |
| Model 1              | 1.00 (Ref) | 1.26 (1.01, 1.56) | 1.15 (0.92, 1.43) | 1.32 (1.07, 1.62) | 1.65 (1.36, 2.01) | 1.15 (1.10, 1.20) |
| Model 2              | 1.00 (Ref) | 1.27 (1.03, 1.58) | 1.17 (0.94, 1.46) | 1.33 (1.08, 1.64) | 1.65 (1.36, 2.01) | 1.14 (1.10, 1.19) |
| Model 3              | 1.00 (Ref) | 1.26 (1.02, 1.55) | 1.10 (0.89, 1.38) | 1.25 (1.02, 1.55) | 1.51 (1.24, 1.84) | 1.13 (1.08, 1.19) |
| Model 4              | 1.00 (Ref) | 1.24 (0.99, 1.54) | 1.07 (0.86, 1.34) | 1.14 (0.92, 1.41) | 1.28 (1.04, 1.57) | 1.08 (1.02, 1.15) |

Model 1: Adjusted for age, sex, and race. Model 2: Adjusted for model 1 plus education, physical activity, smoking, and BMI. Model 3: Adjusted for model 2 plus prevalent diabetes, systolic BP, HTN medication use, lipid medication use, LDL cholesterol, and HDL cholesterol. Model 4: Adjusted for model 3 plus eGFR category (Inker 2012 cystatin C and creatinine; 3-level category). FGF-23 indicates fibroblast growth factor-23; CHD, coronary heart disease; HF, heart failure; ARIC, Atherosclerosis Risk In Communities; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein.
was included with model 4 covariates (1.23 [1.01 to 1.52]) and when PTH was included with model 4 covariates (1.28 [1.04 to 1.58]). Restricting follow-up time to the first 5 years did yield stronger magnitudes of association: N events total/top category (96/30); model 1: 2.45 (1.50 to 3.99) and model 4: 1.61 (0.96 to 2.70).

There were no statistically significant interactions by age, or sex. The association between FGF-23 and cardiovascular mortality was stronger among blacks relative to whites ($P$-interaction model 1=0.02; $P$-interaction model 4=0.02) (Table 3). eGFR category modified the association between FGF-23 and cardiovascular mortality in demographic-adjusted models ($P$-interaction=0.05) but not after accounting for behaviors and cardiovascular risk factors. eGFR-stratified results are presented in Table 4.

**Discussion**

In this large, biracial, population-based cohort, we observed a threshold effect in the association of FGF-23 and risk of incident CHD, HF, and cardiovascular mortality. A positive association was present between FGF-23 and risk of outcomes at FGF-23 levels above 40 pg/mL, whereas at levels <40 pg/mL there was no association. Relative to participants at <40 pg/mL, those in the highest category of FGF-23 (≥58.8 pg/mL) were at 44% greater risk of incident CHD, 46% greater risk of HF, and 51% greater risk of cardiovascular mortality, after adjustment for demographics, behaviors, and traditional cardiovascular risk factors. These associations were independent of serum phosphorus, and additional adjustment for markers of kidney function only modestly attenuated the associations. Furthermore, even

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**Sensitivity Analyses**

In sensitivity analyses, we explored the impact of adjusting for eGFR as a continuous variable and estimating GFR by using alternate equations. Results were similar regardless of how eGFR was modeled or calculated (data not shown). We also adjusted (separately) for ln(NT-proBNP) and ln(hs-TnT) and LVH presence by using the Cornell criteria. The results were attenuated only slightly (data not shown). Notably, the ARIC population was relatively young at visit 2, when the serum used for FGF-23 measurement was collected, and only 2% of the sample had LVH according to the Cornell criteria.

In order to further isolate our sample to people free of renal impairment, we restricted our analysis to participants who attended visit 4 (when urine was collected), were at visit 4 free of prevalent CHD or HF, had an albumin-to-creatinine ratio of >30 at visit 4, and an eGFR ≥60 at visit 2 (analytic sample=8397). After adjustment for cardiovascular risk factors, the HR’s comparing those in the top FGF-23 category to those with FGF-23 <40 pg/mL were as follows: MI: 1.36 (1.06, 1.76); HF: 1.29 (1.04, 1.60), cardiovascular mortality: 1.57 (1.15, 2.14).

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**Figure.** Association of serum FGF-23 with risk of incident CHD, HF, and cardiovascular mortality: the ARIC Study 1987–2010. Biomarkers modeled as restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles and are adjusted for age, sex, and race. Black line represents hazard ratio; gray shaded area, 95% confidence interval. A, FGF-23 and incident CHD. B, FGF-23 and incident HF. C, FGF-23 and incident cardiovascular mortality. ARIC indicates Atherosclerosis Risk In Communities; CHD, coronary heart disease; FGF-23, fibroblast growth factor-23; HF, heart failure.
when our analysis was restricted to individuals estimated to have normal kidney function (eGFR ≥ 90 mL/min per 1.73 m²), elevated FGF-23 was associated with greater risk of incident CHD and HF independent of traditional cardiovascular risk factors. Finally, the associations were at least as strong, and in some cases qualitatively stronger, among African Americans, a relatively understudied group. These findings extend the results of prior studies by showing that FGF-23 may be a risk factor for cardiovascular disease and mortality among those with normal kidney function, that elevated FGF-23 is associated with greater risk of CHD, and by having adequate power to examine the association between FGF-23 and outcomes in African Americans.

There are several mechanisms through which elevated FGF-23 may increase the risk of CHD and HF. First, FGF-23 may directly contribute to remodeling of the left ventricle by

### Table 3. Serum FGF-23 and Risk of Incident CHD, HF, and Cardiovascular Mortality Stratified by Race: The ARIC Study 1990−2010

| Serum FGF-23 (pg/mL) Group | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Per 1 SD (16.40 pg/mL) |
|---------------------------|--------|--------|--------|--------|--------|----------------------|
| Median                    | 32.8   | 42.2   | 47.2   | 53.5   | 67.2   |                      |
| Range                     | 2.9 to 40.0 | 40.1 to 44.6 | 44.7 to 50.1 | 50.2 to 58.7 | 58.8 to 481.0 |                      |
| N total                   |        |        |        |        |        |                      |
| Blacks                    | 1237   | 361    | 399    | 412    | 426    | 2835                 |
| Whites                    | 4035   | 1230   | 1193   | 1179   | 1166   | 8803                 |

**Incident CHD**

**African Americans**

| N events | Model 1 | Model 2 |
|----------|---------|---------|
|          | 1.00 (Ref) | 1.00 (Ref) |
|          | 1.39 (0.98 to 1.96) | 1.41 (0.99 to 1.99) |
|          | 0.90 (0.61 to 1.33) | 0.90 (0.61 to 1.33) |
|          | 1.48 (1.07 to 2.04) | 1.27 (0.91 to 1.76) |
|          | 1.88 (1.39 to 2.53) | 1.41 (1.03 to 1.94) |
|          | 1.26 (1.16 to 1.38) | 1.13 (1.03 to 1.24) |

**Whites**

| N events | Model 1 | Model 2 |
|----------|---------|---------|
|          | 1.00 (Ref) | 1.00 (Ref) |
|          | 0.94 (0.75 to 1.18) | 0.89 (0.71 to 1.12) |
|          | 1.11 (0.89 to 1.37) | 1.01 (0.81 to 1.25) |
|          | 1.29 (1.05 to 1.59) | 1.17 (0.95 to 1.44) |
|          | 1.56 (1.28 to 1.89) | 1.28 (1.04 to 1.57) |
|          | 1.11 (1.05 to 1.17) | 1.06 (0.99 to 1.13) |

**Incident HF**

**African Americans**

| N events | Model 1 | Model 2 |
|----------|---------|---------|
|          | 1.00 (Ref) | 1.00 (Ref) |
|          | 0.91 (0.67 to 1.25) | 0.97 (0.71 to 1.33) |
|          | 1.26 (0.96 to 1.64) | 1.23 (0.94 to 1.61) |
|          | 1.19 (0.91 to 1.56) | 0.97 (0.74 to 1.29) |
|          | 1.88 (1.49 to 2.38) | 1.32 (1.02 to 1.69) |
|          | 1.28 (1.19 to 1.37) | 1.12 (1.04 to 1.21) |

**Whites**

| N events | Model 1 | Model 2 |
|----------|---------|---------|
|          | 1.00 (Ref) | 1.00 (Ref) |
|          | 1.09 (0.90 to 1.33) | 1.07 (0.88 to 1.30) |
|          | 1.18 (0.98 to 1.43) | 1.08 (0.89 to 1.30) |
|          | 1.24 (1.03 to 1.50) | 1.12 (0.93 to 1.36) |
|          | 1.67 (1.41 to 1.99) | 1.30 (1.09 to 1.56) |
|          | 1.12 (1.08 to 1.17) | 1.07 (1.02 to 1.12) |

**Incident cardiovascular mortality**

**African Americans**

| N events | Model 1 | Model 2 |
|----------|---------|---------|
|          | 1.00 (Ref) | 1.00 (Ref) |
|          | 1.47 (1.03 to 2.11) | 1.48 (1.03 to 2.13) |
|          | 1.71 (1.23 to 2.39) | 1.65 (1.18 to 2.31) |
|          | 1.51 (1.07 to 2.12) | 1.21 (0.86 to 1.72) |
|          | 2.18 (1.61 to 2.96) | 1.58 (1.14 to 2.18) |
|          | 1.30 (1.22 to 1.40) | 1.15 (1.07 to 1.24) |

**Whites**

| N events | Model 1 | Model 2 |
|----------|---------|---------|
|          | 1.00 (Ref) | 1.00 (Ref) |
|          | 1.16 (0.88 to 1.52) | 1.13 (0.86 to 1.49) |
|          | 0.87 (0.65 to 1.17) | 0.78 (0.58 to 1.06) |
|          | 1.23 (0.94 to 1.60) | 1.10 (0.84 to 1.44) |
|          | 1.38 (1.06 to 1.78) | 1.11 (0.85 to 1.45) |
|          | 1.07 (0.99 to 1.16) | 1.00 (0.91 to 1.10) |

Model 1: Adjusted for age, sex, and race. Model 2: Adjusted for model 1 plus education, physical activity, smoking, BMI, prevalent diabetes, systolic BP, HTN medication use, lipid medication use, LDL cholesterol, HDL cholesterol, and eGFR category (Inker 2012 cystatin C and creatinine; 3-level category). ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor-23; HDL, high-density lipoprotein; HF, heart failure; HTN, hypertension; LDL, low-density lipoprotein.

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### Table 4. Serum FGF-23 and Risk of Incident CHD, HF, and Cardiovascular Mortality Stratified by Baseline Kidney Function: The ARIC Study 1990–2010

| Serum FGF-23 (pg/mL) | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Per 1 SD (16.40 pg/mL) |
|----------------------|---------|---------|---------|---------|---------|------------------------|
| Median               | 32.8    | 42.2    | 47.2    | 53.5    | 67.2    |                        |
| Range                | 2.9 to 40.0 | 40.1 to 44.6 | 44.7 to 50.1 | 50.2 to 58.7 | 58.8 to 481.0 |                        |

| eGFR ≥90 | 3491 | 938 | 882 | 808 | 617 | 6736 |
| eGFR 60 to <90 | 1730 | 630 | 682 | 724 | 827 | 4593 |
| eGFR <60 | 51 | 23 | 28 | 59 | 148 | 309 |

#### Incident CHD

| eGFR ≥90 | N events | 273 | 57 | 50 | 68 | 75 | 523 |
| Model 1  | 1.00 (Ref) | 0.75 (0.56 to 0.99) | 0.70 (0.52 to 0.95) | 1.05 (0.80 to 1.36) | 1.56 (1.21 to 2.01) | 1.07 (0.97 to 1.17) |
| Model 2  | 1.00 (Ref) | 0.76 (0.57 to 1.02) | 0.68 (0.50 to 0.92) | 1.04 (0.79 to 1.35) | 1.50 (1.16 to 1.94) | 1.06 (0.96 to 1.17) |

| eGFR 60 to <90 | N events | 157 | 81 | 91 | 99 | 107 | 535 |
| Model 1  | 1.00 (Ref) | 1.46 (1.12 to 1.91) | 1.44 (1.11 to 1.86) | 1.49 (1.16 to 1.92) | 1.45 (1.13 to 1.85) | 1.10 (1.03 to 1.16) |
| Model 2  | 1.00 (Ref) | 1.38 (1.06 to 1.81) | 1.38 (1.06 to 1.79) | 1.36 (1.05 to 1.75) | 1.28 (1.00 to 1.64) | 1.07 (1.00 to 1.14) |

| eGFR <60 | N events | 8 | 3 | 4 | 16 | 36 | 67 |
| Model 1  | 1.00 (Ref) | 0.97 (0.26 to 3.70) | 0.92 (0.28 to 3.07) | 1.87 (0.80 to 4.39) | 1.60 (0.74 to 3.45) | 1.16 (1.02 to 1.32) |
| Model 2  | 1.00 (Ref) | 1.04 (0.26 to 4.14) | 0.89 (0.26 to 3.01) | 1.74 (0.72 to 4.20) | 1.46 (0.66 to 3.25) | 1.12 (0.97 to 1.30) |

#### Incident HF

| eGFR ≥90 | N events | 322 | 72 | 93 | 85 | 87 | 659 |
| Model 1  | 1.00 (Ref) | 0.81 (0.63 to 1.05) | 1.10 (0.87 to 1.38) | 1.13 (0.89 to 1.44) | 1.49 (1.17 to 1.89) | 1.09 (1.00 to 1.18) |
| Model 2  | 1.00 (Ref) | 0.84 (0.65 to 1.09) | 1.04 (0.83 to 1.31) | 1.10 (0.86 to 1.40) | 1.34 (1.06 to 1.71) | 1.06 (0.98 to 1.16) |

| eGFR 60 to <90 | N events | 241 | 105 | 118 | 114 | 159 | 737 |
| Model 1  | 1.00 (Ref) | 1.26 (1.00 to 1.58) | 1.24 (0.99 to 1.54) | 1.14 (0.91 to 1.43) | 1.47 (1.20 to 1.80) | 1.08 (1.03 to 1.14) |
| Model 2  | 1.00 (Ref) | 1.23 (0.98 to 1.55) | 1.19 (0.96 to 1.49) | 1.10 (0.88 to 1.37) | 1.29 (1.05 to 1.58) | 1.05 (0.99 to 1.12) |

| eGFR <60 | N events | 20 | 6 | 10 | 21 | 62 | 119 |
| Model 1  | 1.00 (Ref) | 0.72 (0.29 to 1.80) | 1.00 (0.47 to 2.15) | 1.01 (0.54 to 1.86) | 1.10 (0.66 to 1.82) | 1.19 (1.09 to 1.30) |
| Model 2  | 1.00 (Ref) | 0.74 (0.28 to 1.92) | 1.02 (0.46 to 2.23) | 0.84 (0.43 to 1.61) | 1.21 (0.70 to 2.08) | 1.22 (1.11 to 1.34) |

#### Incident cardiovascular mortality

| eGFR ≥90 | N events | 158 | 55 | 43 | 39 | 38 | 333 |
| Model 1  | 1.00 (Ref) | 1.24 (0.91 to 1.69) | 1.01 (0.72 to 1.41) | 1.02 (0.72 to 1.44) | 1.28 (0.90 to 1.83) | 1.06 (0.94 to 1.20) |
| Model 2  | 1.00 (Ref) | 1.31 (0.96 to 1.79) | 0.97 (0.69 to 1.36) | 1.03 (0.72 to 1.46) | 1.31 (0.92 to 1.88) | 1.08 (0.96 to 1.21) |

| eGFR 60 to <90 | N events | 130 | 54 | 60 | 74 | 82 | 400 |
| Model 1  | 1.00 (Ref) | 1.19 (0.86 to 1.63) | 1.14 (0.84 to 1.55) | 1.31 (0.98 to 1.74) | 1.33 (1.01 to 1.75) | 1.06 (0.98 to 1.16) |
| Model 2  | 1.00 (Ref) | 1.16 (0.84 to 1.59) | 1.13 (0.83 to 1.54) | 1.25 (0.94 to 1.67) | 1.23 (0.93 to 1.64) | 1.04 (0.95 to 1.14) |

Continued
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Table 4. Continued

| Serum FGF-23 (pg/mL) | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Per 1 SD (16.40 pg/mL) |
|---------------------|---------|---------|---------|---------|---------|------------------------|
| eGFR <60            |         |         |         |         |         |                        |
| N events            | 7       | 5       | 7       | 13      | 37      | 69                     |
| Model 1             | 1.00 (Ref) | 2.31 (0.72 to 7.39) | 1.98 (0.69 to 5.69) | 1.63 (0.65 to 4.12) | 1.77 (0.79 to 3.99) | 1.14 (1.03 to 1.25) |
| Model 2             | 1.00 (Ref) | 3.23 (0.93 to 11.19) | 1.85 (0.62 to 5.50) | 1.41 (0.53 to 3.76) | 1.51 (0.64 to 3.52) | 1.05 (0.94 to 1.17) |

Model 1: Adjusted for age, sex, and race. Model 2: Adjusted for model 1 plus education, physical activity, smoking, BMI, prevalent diabetes, systolic BP, HTN medication use, LDL cholesterol, and HDL cholesterol. FGF-23 indicates fibroblast growth factor-23; CHD, coronary heart disease; HF, heart failure; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; BP, blood pressure; HTN, hypertension; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

eccentric or concentric hypertrophy. This is supported by experimental rodent models and observational human studies that have shown high circulating FGF-23 to be associated with LVH in the elderly and both LVH prevalence and incidence in populations with kidney impairment. Additionally, high circulating FGF-23 has been associated with endothelial dysfunction and inflammation. Whether FGF-23 is associated with atherosclerosis is controversial. It is possible that phosphate excess, which is upstream to high FGF-23, induces vascular calcification and atherosclerosis, independent of FGF-23. Prior work has shown elevated serum phosphorous to be associated with vascular calcification, the development of LVH, and greater risk of incident cardiovascular disease (P. L. Lutsey, PhD, MPH, unpublished data, 2014).

Enhanced understanding of the relation between FGF-23 and cardiac pathophysiology may also provide insight into the mechanisms through which CKD increases the risk of CHD and HF. Levels of FGF-23 are correlated inversely with renal function and are known to increase dramatically in advanced CKD. It is difficult to disentangle the relations between FGF-23 and kidney function as estimated by using GFR. However, in the present analysis, associations between FGF-23 and incident CHD and HF were independent of eGFR and remained present when analyses were restricted to those with normal kidney function (eGFR ≥ 90 mL/min per 1.73 m²), suggesting that FGF-23 may have actions independent of kidney disease quantified by reduced eGFR. We used both serum creatinine and cystatin to provide a better estimate of eGFR.

The Heart and Soul Study previously reported a positive association between FGF-23 and recurrent cardiovascular disease. FGF-23 was also positively associated with risk of incident HF and total cardiovascular events in the Cardiovascular Health Study18 and with cardiovascular mortality in the Uppsala Longitudinal Study of Adult Men. Both of these cohorts are population-based studies of elderly individuals, and in both interactions were present, whereby associations were stronger among individuals with impaired kidney function but substantially weaker or absent among those with normal kidney function. We observed no such interaction in the younger ARIC study population; associations between FGF-23 and incident HF and CHD were equally strong among individuals with normal kidney function. In ARIC, elevated FGF-23 was associated with an ≈50% greater risk of incident CHD. This is in contrast to 3 smaller population-based studies which have shown no relation between FGF-23 and risk of CHD. FGF-23 has, however, been associated with greater risk of atherosclerotic events among patients with CKD.

Identifying novel biomarkers for cardiovascular disease may enhance our etiologic understanding and improve our ability to identify high-risk individuals and possibly lead to new therapeutic targets. Importantly, given the relatively modest magnitudes of association between FGF-23 and the outcomes presented here, it is unlikely that the use of FGF-23 would improve risk prediction. However, because FGF-23 is physiologically active (unlike cystatin C and serum creatinine, which are markers for CKD, as opposed to causal risk factors), it may be a potential target for intervention. Three pharmacologic strategies have been proposed: oral phosphate binders, FGF-23 blocking agents, and FGF receptor antagonists. Oral phosphate binders, the only of these options presently available, are commonly given to patients on dialysis and those with severe renal failure and have been shown to be effective in lowering FGF-23 levels. Clinical trials will need to demonstrate that lowering FGF-23 is efficacious in reducing cardiovascular disease (or possibly surrogates) and/or mortality before there would be justification for the widespread use of these agents.

Strengths of this study are the prospective design, biracial population-based sample, detailed ascertainment of established cardiovascular risk factors, active outcome surveillance, large number of events, and corresponding power for subgroup analyses. Also, importantly, the assay used in the present study detects biologically active intact FGF-23, while many prior studies have used an assay that measures inactive C-terminal FGF-23 concentrations. Perhaps the major limitation of the present study is that FGF-23 was measured in singlicate at a single point in time and was associated with moderate analytic error (CV 16%). As a result, regression dilution bias may have attenuated relative hazard estimates.
This concept is supported by associations between FGF-23 and incident CHD, HF, and cardiovascular mortality. These associations were independent of traditional cardiovascular disease risk factors and were present both in the absence of reduced kidney function and among African Americans. These data are of interest from a pathophysiologic perspective and suggest the potential of FGF-23 as a target for therapeutic intervention to reduce risk of CHD, HF, and cardiovascular mortality.

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Disclosures

None.

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