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Fibroblast Growth Factor-23 and Death, Heart Failure, and Cardiovascular Events in Community-Living Individuals

CHS (Cardiovascular Health Study)

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Objectives This study sought to determine the association of fibroblast growth factor (FGF)-23 with death, heart failure (HF), and cardiovascular disease (CVD) in the general population, as well as the influence of chronic kidney disease (CKD) in this setting.

Background FGF-23 increases renal phosphorus excretion and inhibits vitamin D activation. In end-stage renal disease, high FGF-23 levels are associated with mortality. The association of FGF-23 with death, HF, and CVD in the general population, and the influence of CKD in this setting, are unknown.

Methods Plasma FGF-23 was measured in 3,107 community-living persons ≥65 years of age in 1996 and 1997, and participants were followed through 2008. HF and CVD events were adjudicated by a panel of experts. Associations of FGF-23 with each outcome were evaluated using Cox proportional hazards models, and we tested whether associations differed by CKD status.

Results Both lower estimated glomerular filtration rate and higher urine albumin to creatinine ratios were associated with high FGF-23 at baseline. During 10.5 years (median) follow-up, there were 1,730 deaths, 697 incident HF events, and 797 incident CVD events. Although high FGF-23 concentrations were associated with each outcome in combined analyses, the associations were consistently stronger for those with CKD (p interactions all <0.006). In the CKD group (n = 1,128), the highest FGF-23 quartile had adjusted hazards ratios (HR) of 1.87 (95% confidence interval [CI]: 1.47 to 2.38) for all-cause death, 1.94 (95% CI: 1.32 to 2.83) for incident HF, and 1.49 (95% CI: 1.02 to 2.18) for incident CVD events compared with the lowest quartile. Corresponding HRs in those without CKD (n = 1,979) were 1.29 (95% CI: 1.05 to 1.59), 1.37 (95% CI: 0.99 to 1.89), and 1.07 (95% CI: 0.79 to 1.45).

Conclusions FGF-23, a hormone involved in phosphorous and vitamin D homeostasis, is independently associated with all-cause death and incident HF in community-living older persons. These associations appear stronger in persons with CKD. (J Am Coll Cardiol 2012;60:200–7) © 2012 by the American College of Cardiology Foundation

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Fibroblast growth factor (FGF)-23 is a 32KDa hormone secreted into blood from bone osteocytes. Its 2 functions are to induce urinary phosphorus excretion and to inhibit activation of vitamin D; both actions occur in the renal proximal tubule. Rare human disorders of FGF-23 excess are characterized by high renal phosphorus excretion, low serum phosphorus levels, calcitriol deficiency, osteomalacia, and spontaneous fractures (1). Recent in vitro and rodent studies also suggest that FGF-23 may directly influence cardiac myocytes to hypertrophy (2).

Circulating FGF-23 concentrations are often several orders of magnitude higher in patients with end-stage renal disease and are strongly associated with mortality risk in that setting (3). The association of FGF-23 with mortality was recently extended to individuals with moderate to severe chronic kidney disease (CKD), and to populations with known prevalent cardiovascular disease (CVD) (4–7). Little is known about FGF-23 levels in community-living individuals without CKD or CVD (8).

The purpose of this study was to examine the relationship of FGF-23 with all-cause death, incident heart failure (HF), and incident CVD events in a free-living population of older persons with long-term follow-up, and considerable numbers of events. We aimed to determine the strength of the association of FGF-23 with kidney function at the baseline visit and to examine the extent to which associations of FGF-23 with longitudinal outcomes were dependent on presence of concomitant CKD. Because FGF-23 exerts its main biological effects at the renal proximal tubule (9–11), and is tightly linked with kidney dysfunction (12), we hypothesized that FGF-23 might provide novel insights into mechanisms linking CKD with adverse outcomes in community-living older persons.

Methods

Participants. The CHS (Cardiovascular Health Study) is a community-based study of older adults that was designed to evaluate risk factors for CVD. The study design and protocols have been described previously (13,14). In brief, eligibility required age ≥65 years, expectation to remain in the area for 3 years after recruitment, no active cancer treatment, and the ability to provide consent. Between 1989 and 1990, 5,201 participants were recruited from 4 U.S. communities using Medicare eligibility lists. An additional 687 African Americans were recruited in 1992 and 1993. In-person examinations were performed annually through 1998 and 1999 and again in 2005 and 2006. Telephone interviews were conducted semiannually from 1989 to 1999 and biannually thereafter. We conducted FGF-23 measurements at the 1996-97 study visit, selected as it was the first visit at which urine albumin to creatinine ratio (ACR) was measured. Among 3,406 individuals who participated, we excluded individuals with insufficient blood specimens for FGF-23 measurement (n = 69), missing creatinine (n = 1), cystatin C (n = 0), urine ACR (n = 92), or covariate data (n = 137) resulting in a final analytic sample of 3,107 participants for this analysis.

Measurements. FGF-23. Fasting (8-h) ethylenediamine tetraacetic acid specimens collected at the 1996-97 study visit were stored at −70°C until 2010, when they were thawed and measured for FGF-23 using a C-terminal ELISA kit (Immutopics, San Clemente, California) (15). Our estimates of the intra-assay and interassay coefficients of variation ranged from 7.4% and 10.6%.

OUTCOMES. Methods of ascertainment for, and adjudication of, death, HF, and CVD events have been described previously (16–19). In brief, deaths were identified by review of obituaries, medical records, death certificates, the Centers for Medicare and Medicaid Services healthcare-utilization database for hospitalizations, and from household contacts. The study achieved 100% complete follow-up for ascertainment of mortality status.

All HF and CVD events were adjudicated by the CHS Events Committee. Participants with history of HF were excluded in analyses evaluating incident HF, and likewise, those with prevalent CVD (history of myocardial infarction [MI], percutaneous coronary intervention, coronary artery bypass graft surgery, transient ischemic attack, stroke, or claudication) were excluded in incident CVD events analyses. Incident HF required a physician's diagnosis of HF, and adjudication by the Events Committee required symptoms, signs, chest radiographic findings, and treatment of HF (16,17). We evaluated a composite CVD outcome defined as incident fatal or nonfatal MI, incident fatal or nonfatal stroke, and CVD death, whichever came first. MI was ascertained from hospital records and was indicated by a clinical history of cardiac symptoms, elevated cardiac enzyme concentrations, and serial electrocardiographic changes (17). Cases of possible stroke were adjudicated by a committee of neurologists, neuroradiologists, and internists on the basis of interviews with patients, medical records, and brain imaging studies (18). CVD death was defined as death caused by coronary heart disease, HF, peripheral arterial disease, or cerebrovascular disease (19).

OTHER MEASUREMENTS. Information on baseline confounders were obtained at the 1996-97 study visit concurrent with FGF-23 and included age, sex, race, self-reported health status and CVD risk factors including hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications), impaired fasting glucose (fasting glucose 100 to 125 mg/dl), diabetes (fasting glucose ≥126 mg/dl or use of antiglycemic medica-

Abbreviations and Acronyms

ACR = albumin to creatinine ratio(s)
CI = confidence interval
CKD = chronic kidney disease
CVD = cardiovascular disease
eGFR = estimated glomerular filtration rate
FGF = fibroblast growth factor
HF = heart failure
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction

tions or insulin), smoking (current, former, or never), body mass index, total cholesterol, use of lipid lowering medications, and C-reactive protein concentrations (20).

Cystatin C concentrations were measured using a BN II nephelometer (Siemens, Munich, Germany) (10). Estimated glomerular filtration rate (eGFR) was calculated using the equation: eGFR = 76.7 × cystatin C (mg/l)$^{-1.19}$ (21). In companion analyses, we calculated eGFR using serum creatinine and the CKD-epidemiology equation (22). A random morning urine sample was obtained and measured for urine albumin by rate nephelometry and creatinine using a Kodak Ektachem 700 Analyzer (Kodak, Rochester, New York), and urine ACR was calculated in microgram/gram.

Statistical analysis. We categorized participants into quartiles based on the distribution of FGF-23 in the study sample and evaluated the distribution of confounders across FGF-23 categories. Next, we evaluated the unadjusted correlation of eGFR and ACR with FGF-23 using Spearman correlation coefficients. Next, we constructed natural piecewise cubic spline functions with FGF-23 as the dependent variable and with prespecified knots placed at the quartiles of the distributions of eGFR and ACR. The spline function evaluating eGFR as the predictor of FGF-23 was adjusted for age, sex, race, and ACR; conversely, the spline of ACR predicting FGF-23 was adjusted for age, sex, race, and eGFR.

Cox regression was used to evaluate the association of FGF-23 with each outcome. In models evaluating incident HF and CVD, persons with prevalent disease at baseline were excluded. The primary analyses evaluated FGF-23 quartiles using the lowest quartile as the reference category. We also evaluated FGF-23 as a continuous variable after log base 2 transformation, interpreted as "per doubling." For each outcome, an initial model was adjusted for age, sex, and race. A second model added self-reported health status, estrogen use among women (23), prevalent CVD and HF (where applicable), traditional CVD risk factors, and C-reactive protein levels. A final model added eGFR and natural log ACR. Next, we stratified patients by eGFR <60 ml/min/1.73 m^2 versus greater and tested interactions of FGF-23 by eGFR for each outcome. Similarly, we tested interactions by urine ACR dichotomized at 30 mg/g. In both cases, associations were stronger in persons with CKD, so we defined a single variable of CKD (eGFR <60 ml/min/1.73 m^2 or ACR ≥30 mg/g) and evaluated an FGF-23 × CKD interaction term in the final adjusted model for each outcome. All analyses were also repeated in a sensitivity analysis using eGFR by the CKD-epidemiology collaboration equation (22) in place of eGFR by cystatin C.

Table 1 Baseline Characteristics by Quartiles of FGF-23: The Cardiovascular Health Study

	FGF-23 Quartiles			
	1	2	3	4
FGF-23 range, RU/ml	<51	51–70	71–100	>100
Number of participants	792	785	774	756
Demographics				
Age, yrs	77 ± 5	77 ± 5	78 ± 5	79 ± 5
Female	421 (53)	444 (57)	491 (63)	503 (67)
Black race	180 (23)	115 (15)	96 (12)	106 (14)
Self-reported health fair or poor	137 (17)	152 (19)	139 (18)	266 (35)
Prevalent HF and CVD				
History of HF	25 (3)	41 (5)	55 (7)	150 (20)
History of MI	60 (8)	59 (8)	93 (12)	127 (17)
History of stroke	42 (5)	52 (7)	38 (5)	58 (8)
History of claudication	16 (2)	16 (2)	27 (4)	39 (5)
CVD risk factors				
Hypertension	457 (58)	482 (61)	492 (64)	523 (69)
Glycemia status				
Impaired fasting glucose	38 (5)	51 (7)	66 (9)	60 (8)
Diabetes	81 (10)	103 (13)	114 (15)	155 (21)
Current smoker	42 (5)	46 (6)	77 (10)	75 (10)
Body mass index, kg/m^2	26.3 ± 4.3	26.7 ± 4.2	27.3 ± 4.6	27.5 ± 5.3
Total cholesterol, mg/dl	200 ± 37	202 ± 38	204 ± 41	203 ± 42
Lipid lowering medication	72 (9)	80 (10)	106 (14)	106 (14)
C-reactive protein, mg/l	1.83 (0.91–3.89)	2.19 (0.99–4.64)	2.85 (1.28–5.64)	3.12 (1.50–6.79)
Kidney function				
eGFR, ml/min/1.73 m^2	81 ± 18	74 ± 17	69 ± 16	58 ± 19
Urine ACR, mg/g	6.86 (4.28–14.33)	8.37 (4.50–17.51)	8.34 (4.71–18.97)	13.36 (6.01–54.41)

Values are n, mean ± SD, n (%), or median (interquartile range).
ACR = albumin to creatinine ratio; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; FGF = fibroblast growth factor; HF = heart failure; MI = myocardial infarction; RU = relative units.

Results

Among the 3,107 participants, mean age was 78 ± 5 years and 60% were women. Nine percent had a history of HF and 29% had a history of CVD at baseline. The mean eGFR was 71 ± 19 ml/min/1.73 m^2, and median urine ACR was 8.8 (interquartile range [IQR]: 4.7 to 20.4) mg/g. The distribution of FGF-23 was right skewed, with a median 70 (IQR: 53 to 99) relative units (RU)/ml.

Compared with participants in the lowest FGF-23 quartile, those with higher levels were older, more frequently women and Caucasian, reported poorer health status, and had more than 2-fold greater prevalence of HF, MI, and claudication at baseline, whereas the prevalence of prior stroke was similar across quartiles (Table 1). Individuals with higher FGF-23 concentrations also had a higher prevalence of most traditional CVD risk factors, lower eGFR, and higher ACR.

The unadjusted Spearman correlation of FGF-23 with eGFR and ACR were −0.42 and 0.20, respectively ($p < 0.001$ for each). Spline functions demonstrated that the relationships of eGFR and ACR with FGF-23 were independent of one another. The relationship of eGFR with FGF-23 appeared to increase consistently at eGFR levels <80 ml/min/1.73m^2, independent of age, sex, race, or urine ACR (Fig. 1A). Similarly, urine ACR levels greater than 30 mg/g were associated with progressively higher FGF-23 levels, independent of age, sex, race, and eGFR (Fig. 1B).

During a median 10.5 (IQR: 5.9 to 11.5) years of follow-up, 1,730 participants died, 697 had incident HF, and 797 had incident CVD events. There was a graded relationship of higher FGF-23 levels with higher event rates for each outcome (Table 2). Associations were particularly strong for all-cause mortality and HF. These associations were modestly attenuated with adjustment for traditional CVD risk factors. Further adjustment for eGFR and urine ACR attenuated each association by about one-half. Nonetheless, compared with the lowest FGF-23 quartile, the highest quartile remained associated with 40% greater death risk and 50% greater HF risk compared with the lowest quartile. The association with incident CVD was weaker by the point estimate and not statistically significant after adjustment for eGFR and ACR. Results were similar when eGFR was estimated using creatinine instead of cystatin C (data not shown).

We observed that the associations of FGF-23 with each outcome were significantly stronger among individuals with CKD (all p interactions <0.006) (Fig. 2). Among persons without CKD, statistically significant associations were observed for FGF-23 with all-cause mortality and incident HF, but no association was observed for incident CVD events (Table 3). In contrast, among those with CKD, associations were particularly strong for death and incident HF and were weaker for incident CVD events. When evaluating the components of the composite incident CVD outcome, high FGF-23 had the strongest association with CVD death, followed by incident stroke. No association was observed between FGF-23 and incident MI irrespective of CKD status (Online Table 1).

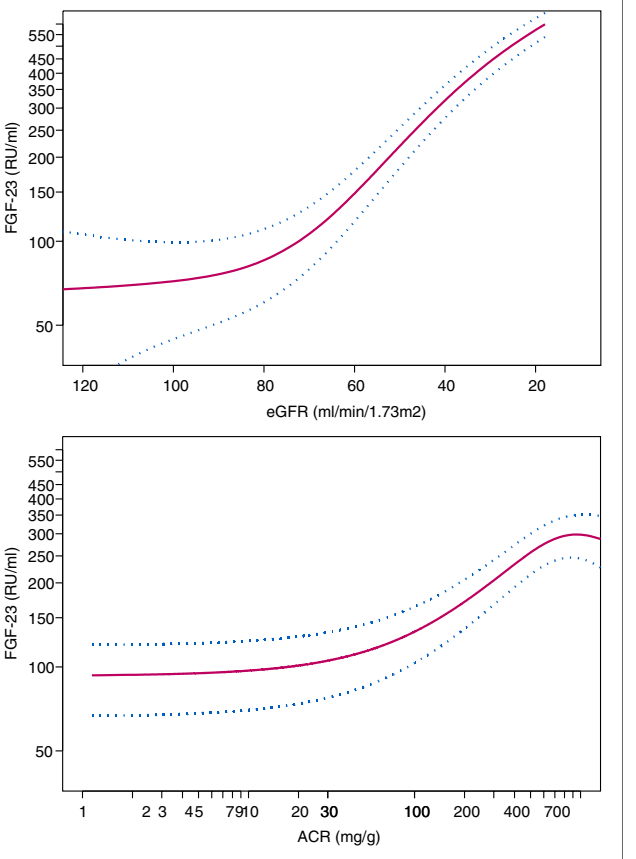

Figure 1 **Relationship of eGFR and Urine ACR With FGF-23 in Community-Living Individuals**

Cubic spline function demonstrating the adjusted cross-sectional association of **(A)** estimated glomerular filtration rate (eGFR) estimated by cystatin C and **(B)** albumin to creatinine ratio (ACR) with plasma fibroblast growth factor (FGF)-23 levels. **Red lines** represent the adjusted point estimates, and **blue lines** represent the 95% confidence intervals. The y axis demonstrates the change in log FGF-23. The spline function for eGFR **(A)** was adjusted for age, sex, race, and urine ACR. Spline function for ACR **(B)** was adjusted for age, sex, race, and eGFR. The extreme 2.5% of the distribution of eGFR and ACR were excluded to avoid improbable extrapolations based on extremes of the data.

We conducted sensitivity analyses where we used the CKD-epidemiology equation rather than cystatin C to estimate GFR. In all cases, results were similar when results were adjusted for and stratified by CKD-epidemiology–defined eGFR (data not shown). Lastly, because FGF-23 was correlated with CKD severity, we tested whether the stronger associations within the CKD stratum might reflect differing severity of CKD. To investigate this possibility, we evaluated the final model with additional adjustment for eGFR and urine ACR within the CKD strata. Results were similar to the stratified analyses presented previously (hazard ratio [HR] per doubling of FGF-23: 1.29 [95% confidence interval (CI): 1.19 to 1.41] for all-cause death, 1.36 [95% confidence interval: 1.18 to 1.57] for incident HF, and

Table 2 Association of FGF-23 With Incident HF, CVD, and All-Cause Death: The Cardiovascular Health Study

	FGF-23 Quartiles				Linear Model	
	1	2	3	4	Per Doubling of FGF-23	p Value*
FGF-23 range, RU/ml	<51	51–70	71–100	>100		
All-cause mortality						
Annual event rate	4.8% (350/792)	5.6% (397/785)	6.2% (419/774)	10.3% (554/756)		
Age- sex- race-adjusted	1.00 (ref)	1.18 (1.02–1.36)	1.29 (1.12–1.48)	2.29 (2.00–2.62)	1.65 (1.53–1.77)	<0.001
+ CVD risk factors†	1.00 (ref)	0.98 (0.77–1.25)	1.16 (0.92–1.47)	1.87 (1.49–2.36)	1.49 (1.31–1.69)	<0.001
+ Kidney function‡	1.00 (ref)	1.03 (0.89–1.19)	1.05 (0.90–1.21)	1.42 (1.22–1.65)	1.25 (1.14–1.36)	<0.001
Incident HF§						
Annual event rate	2.2% (147/767)	2.7% (169/744)	3.0% (172/719)	5.3% (209/606)		
Age- sex- race-adjusted	1.00 (ref)	1.28 (1.02–1.60)	1.37 (1.10–1.71)	2.47 (1.99–3.07)	1.76 (1.57–1.97)	<0.001
+ CVD risk factors†	1.00 (ref)	1.21 (0.97–1.51)	1.27 (1.01–1.59)	2.07 (1.66–2.58)	1.62 (1.44–1.83)	<0.001
+ Kidney function‡	1.00 (ref)	1.10 (0.88–1.38)	1.10 (0.88–1.39)	1.55 (1.22–1.97)	1.41 (1.23–1.61)	<0.001
Incident CVD‖						
Annual event rate	3.7% (188/600)	4.5% (213/587)	4.8% (205/558)	6.5% (191/461)		
Age- sex- race-adjusted	1.00 (ref)	1.23 (1.01–1.50)	1.31 (1.07–1.60)	1.74 (1.42–2.14)	1.36 (1.20–1.53)	<0.001
+ CVD risk factors†	1.00 (ref)	1.17 (0.96–1.43)	1.21 (0.99–1.48)	1.50 (1.22–1.86)	1.24 (1.10–1.41)	0.001
+ Kidney function‡	1.00 (ref)	1.14 (0.93–1.39)	1.13 (0.92–1.40)	1.30 (1.04–1.63)	1.12 (0.98–1.29)	0.100

Values are n, % (n events/n at risk), or HR (95% CI). *The p value for the linear Cox model. †Adjusted for age, sex, race, health status (fair or poor vs. better), current smoking, prior stroke, prior MI, prior HF, prior claudication, hypertension, diabetes (NL, IFG, DM), BMI, estrogen use (women), total cholesterol, lipid medication use, natural log (CRP). ‡Adjusted for CVD risk factor model ("+") and eGFR and natural log (ACR). §Excludes 271 participants with prevalent HF at baseline. ‖Excludes 901 participants with prevalent CVD at baseline.

BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; DM = diabetes mellitus; HR = hazard ratio; IFG = impaired fasting glucose; NL = normal level; ref = reference; other abbreviations as in Table 1.

1.15 [95% confidence interval: 0.99 to 1.35] for incident CVD events).

Discussion

We demonstrate that high FGF-23 levels are associated with all-cause mortality and incident HF; associations that were particularly strong among persons with CKD. Comparatively, the association of FGF-23 with incident CVD events was more modest, and driven principally through its association with CVD death. No independent association was observed between FGF-23 and incident MI irrespective of CKD status.

We believe the findings of stronger associations in CKD are robust, in part because of the highly significant p values for interaction. In parallel, a recent study found that high FGF-23 was associated with greater left ventricular mass in a European cohort, and this association was also stronger in persons with CKD (24). Yet the mechanisms responsible for stronger associations in CKD are uncertain. It is possible that the processes manifested or caused by higher FGF-23 levels will be particularly harmful in persons with CKD. For example, recent studies suggest that FGF-23 may cause increases in left ventricular mass in vitro and in rodent models (2). Higher FGF-23 may also indicate an elevated dietary phosphorus load, and thus a greater need to excrete phosphorus into the urine (25). Alternatively, high FGF-23 may limit conversion of 25-hydroxy vitamin D to the active hormone calcitriol (26). Higher phosphorus load and calcitriol deficiency may be particularly harmful in patients with CKD. Recent studies have identified both higher serum phosphorus and calcitriol deficiency as independent risk factors for CVD events (27–29), and in some of our prior studies, we have observed that hyperphosphatemia and vitamin D deficiency are more strongly associated with subclinical CVD in individuals with CKD than in those without (30,31).

Another possibility is that high FGF-23 may reflect a component of kidney dysfunction that is not captured by the standard clinical markers of eGFR and urine ACR: renal endocrine resistance to FGF-23 action. Whereas eGFR and ACR reflect different aspects of kidney function, neither is a marker of renal endocrine responsiveness. ACR and eGFR are both strongly and independently associated with CVD events (11,32) and measuring both in combination has improved the ability to identify risk of death and CKD progression (33,34). Here, we demonstrated that despite the correlation of FGF-23 with both markers, it provided unique risk information about death, HF, and CVD events. Moreover, the relative strengths of association of FGF-23 with each outcome have striking similarities to our prior work evaluating eGFR by cystatin C and creatinine in community-living cohorts. Elevated concentrations of these markers are consistently more strongly associated with death and incident HF than with MI. For example, in CHS, we previously showed that the highest quintile of cystatin C was associated with a more than doubling in risk for all-cause mortality and incident HF, compared with only a 30% higher relative risk for MI (9,10,35). These findings have proven consistent in many other studies and settings (36–40). Much less is known about the comparative strength of associations of FGF-23 with these outcomes. However, in a prior study evaluating FGF-23 in a cohort with prevalent CVD and with a spectrum of kidney function similar to individuals evaluated here, we also observed that high FGF-23 was more strongly associated with all-cause mortality and HF than with recurrent MI (adjusted HR were

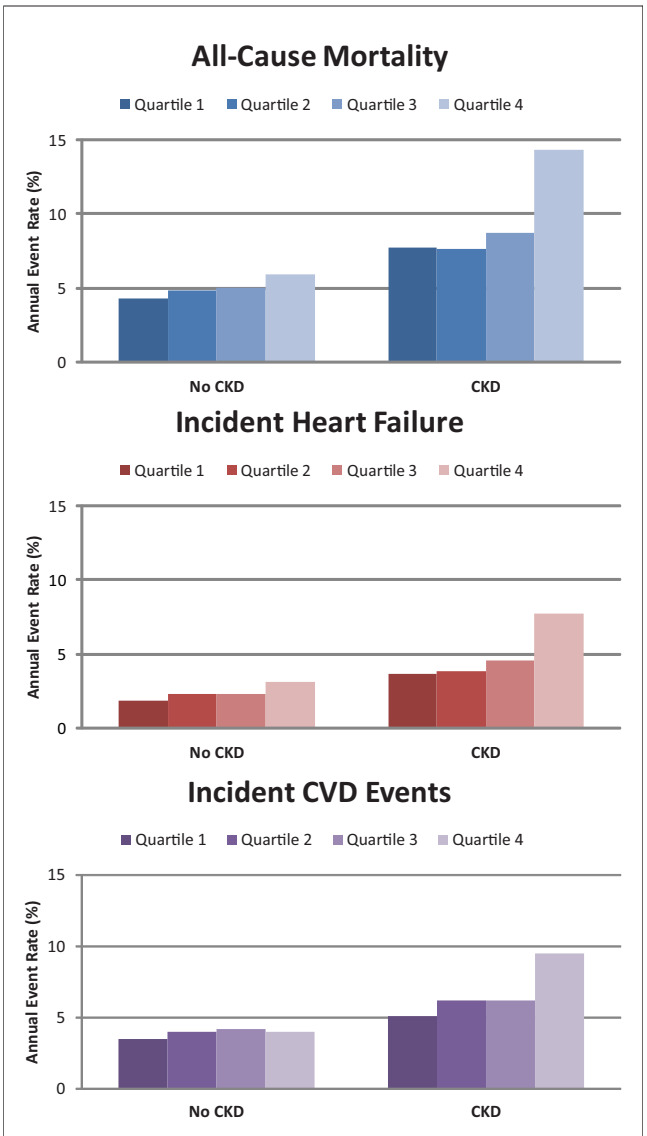

Figure 2 **Associations of FGF-23 Quartiles and Risk of All-Cause Mortality, Incident HF, and Incident CVD Events: The Cardiovascular Health Study**

Annual event rates of **(A)** all-cause mortality, **(B)** incident heart failure (HF), and **(C)** incident cardiovascular disease (CVD) events by quartiles of fibroblast growth factor (FGF)-23, stratified by chronic kidney disease (CKD) status. Patients with prevalent HF and CVD at the baseline examination were excluded from **B and C**, respectively.

1.54, 1.31, and 1.05, respectively) (6). The consistency of these findings and the similar pattern to that observed for eGFR lead us to propose the novel hypothesis that high FGF-23 may be marking a novel axis of kidney dysfunction, and that its measurement may provide information about other dimensions of kidney function beyond that obtained by measurement of eGFR and ACR.

The 2 pathways hypothesized herein linking FGF-23 with adverse outcomes are not mutually exclusive. At any level of eGFR and ACR, a higher FGF-23 may indicate impaired renal endocrine resistance. At the same time, higher FGF-23 may directly lead to adverse cardiovascular consequences by mechanisms of calcitriol deficiency, altered phosphorus homeostasis, or direct effects on cardiac myocytes (2,41,42). The mechanisms linking CKD to HF, CVD, and death have remained elusive despite intensive research (43) and widespread recognition of the importance of this relationship to public health (44). The strength of association of FGF-23 with these outcomes in individuals with CKD reported here and elsewhere (3,6) suggests that further research focused on FGF-23 mechanisms may provide important insights into CVD risk among persons with CKD.

To our knowledge, only 1 prior study has examined the association of FGF-23 with CVD in community-living individuals not selected based on pre-existing CKD or CVD. In the HPFS (Health Professionals Follow-up Study), Taylor et al. (8) reported no statistically significant association of FGF-23 with the composite outcome of nonfatal MI and fatal coronary heart disease. These findings are consistent with our own. In combined analysis among persons with and without CKD, we observed strong associations of FGF-23 with death and HF, but we observed null findings with CVD events. Moreover, in the HPFS, among the 422 coronary heart disease cases, 333 (79%) were nonfatal MI events, and in our study the association of FGF-23 with MI was particularly modest. Participants in HPFS had significantly higher eGFR at baseline compared with those in the CHS. The HPFS investigators reported that results were similar when restricting to persons with eGFR $\geq$60 ml/min/1.73 m^2. However, they did not report interactions by CKD, nor did they show associations separately in those with eGFR $<$60 ml/min/1.73 m^2, perhaps because power was too low to do so within the CKD strata. The HPFS did not evaluate associations with HF or all-cause death. Thus, the present study considerably extends the findings of FGF-23 in the general population by evaluating long-term follow-up and considerably greater number of events; provides the first comparison of strengths of association between death, HF, and CVD in the general population; and examines associations separately in those with and without CKD.

Study strengths. Strengths of our study include the external validity of a large community-based population, long duration and complete follow-up, large number of events, adjudication of HF and CVD events by a panel of experts, and availability of cystatin C and urine ACR measurements concurrent with FGF-23.

Study limitations. Sophisticated measures of subclinical CVD and other measures of mineral metabolism complementary to FGF-23 (serum phosphorus, calcitriol, and klotho) were not available to provide additional insights to underlying mechanisms. All participants were recruited in U.S. cities and were older and of black or white race. Results may differ in other settings. Results are observational in nature, so residual confounding may persist and causal effects of FGF-23 cannot be determined.

Table 3 Association of FGF-23 With Incident HF, CVD, and All-Cause Death Stratified by CKD: The Cardiovascular Health Study

	FGF-23 Quartiles				Linear Model	
	1	2	3	4	Per Doubling of FGF-23	p Value*
FGF-23 range, RU/ml	<51	51–70	71–100	>100		
CKD (n = 1,128)						
All-cause mortality						
Annual event rate	7.7 (90/141)	7.6 (150/235)	8.7 (191/285)	14.3 (404/467)		
Adjusted hazard ratio†	1.00 (ref)	0.97 (0.75–1.26)	1.09 (0.84–1.41)	1.87 (1.47–2.38)	1.41 (1.30–1.52)	<0.001
Incident HF‡						
Annual event rate	3.7 (38/136)	3.8 (63/213)	4.6 (81/256)	7.7 (145/350)		
Adjusted hazard ratio†	1.00 (ref)	0.97 (0.64–1.46)	1.16 (0.78–1.73)	1.94 (1.32–2.83)	1.52 (1.33–1.72)	<0.001
Incident CVD§						
Annual event rate	5.1 (39/104)	6.2 (71/156)	6.2 (76/184)	9.5 (126/257)		
Adjusted hazard ratio†	1.00 (ref)	1.09 (0.74–1.63)	1.09 (0.73–1.62)	1.49 (1.02–2.18)	1.24 (1.09–1.43)	0.002
No CKD (n = 1,979)						
All-cause mortality						
Annual event rate	4.3 (270/651)	4.8 (247/550)	5.0 (228/489)	5.9 (150/289)		
Adjusted hazard ratio†	1.00 (ref)	1.10 (0.93–1.32)	1.15 (0.96–1.38)	1.29 (1.05–1.59)	1.07 (0.98–1.17)	0.15
Incident HF‡						
Annual event rate	1.9 (109/631)	2.3 (106/531)	2.3 (91/463)	3.1 (64/256)		
Adjusted hazard ratio†	1.00 (ref)	1.19 (0.90–1.56)	1.11 (0.84–1.48)	1.37 (0.99–1.89)	1.17 (1.02–1.33)	0.023
Incident CVD§						
Annual event rate	3.5 (149/496)	4.0 (142/431)	4.2 (129/374)	4.0 (65/204)		
Adjusted hazard ratio†	1.00 (ref)	1.12 (0.89–1.42)	1.16 (0.91–1.42)	1.07 (0.79–1.45)	0.99 (0.87–1.13)	0.899

Values are n, % (n events/n at risk), or HR (95% CI). CKD defined as either eGFR <60 ml/min/1.73 m^2 or urine ACR >30 mg/g. *The p value for the linear Cox model. †Adjusted for age, sex, race, health status (fair or poor vs. better), current smoking, prior stroke, prior MI, prior HF, prior claudication, hypertension, diabetes (NL, IFG, DM), BMI, estrogen use (women), total cholesterol, lipid medication use, natural log (CRP). The p values for interaction in the adjusted model were <0.001 for all-cause mortality, 0.008 for incident HF, and 0.006 for incident CVD. ‡Excludes 271 participants with prevalent heart failure at baseline. §Excludes 901 participants with prevalent CVD at baseline.

CKD = chronic kidney disease; other abbreviations as in Tables 1 and 2.

Conclusions

In community-living older persons, very modest decrements in eGFR and elevations in urine ACR are each independently associated with higher FGF-23. High FGF-23, in turn, is associated with all-cause mortality and incident HF; associations that are particularly strong in persons with CKD. The association of FGF-23 with incident CVD events was modest in comparison. Measurement of FGF-23 may provide new insights to kidney function beyond eGFR and ACR and to the elusive mechanisms linking CKD to CVD events.

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Key Words: cardiovascular disease ■ elderly ■ fibroblast growth factor-23 ■ heart failure ■ kidney disease ■ mineral metabolism.

APPENDIX

For a table showing the associations of FGF-23 with components of incident CVD event outcome stratified by CKD as found in the CHS, please see the online version of this article.