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FGF23 and Cause-specific Mortality in Community-living Individuals – the Health, Aging, and Body Composition Study

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Abstract

Objectives: Fibroblast growth factor (FGF)-23 is a key regulator of mineral metabolism and has been linked with left ventricular hypertrophy in animal models. Most existing epidemiologic studies evaluated a C-terminal FGF23 assay which measures both the intact (active) hormone and inactive fragments. The relationship of intact FGF23 with cause-specific mortality is unknown.

Design: Prospective analyses of data from Health, Aging, & Body Composition (HABC) study

Setting: Community-living adults aged 70–79 years with longitudinal follow up.

Participants: 2763 older adults who participated in the HABC study

Measurements: Plasma intact FGF23 levels were measured from samples drawn in 2000 and 2001, and participants were followed through 2012. Mortality and its causes were determined by an adjudication committee. Associations of FGF23 with all-cause and cause-specific mortality were evaluated using Cox proportional hazards models adjusted for demographics, prevalent cardiovascular disease (CVD) and its risk factors, and kidney function.

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Results: Median baseline intact FGF23 was 47 (IQR 37, 60) pg/ml and mean estimated glomerular filtration rate (eGFR) was 72 ± 18 ml/min/1.73m^2. During 8.3 years (median) follow-up, there were 821 deaths. In adjusted analysis, each two-fold higher FGF23 was associated with risk for all-cause mortality (HR 1.24 [95% CI 1.12, 1.37]). When evaluating cause-specific mortality, higher FGF23 was associated with cardiovascular mortality (HR 1.31 [95% CI 1.11, 1.54]), but not significantly with cancer (HR 1.01 [95% CI 0.83, 1.23]), gastrointestinal bleed (HR 2.49 [95% CI 0.86, 7.21]), and kidney failure (HR 1.25 [95% CI 0.77, 2.03]), dementia (HR 0.84 [95% CI 0.56, 1.26]), sepsis (HR 0.73 [95% CI 0.31, 1.73]) or pulmonary disease related mortality (HR 1.40 [95% CI 0.87, 2.27]).

Conclusion: Although higher intact FGF23 concentrations are associated with all-cause mortality in community-living individuals, the association appears limited to certain death sub-types, particularly CVD. Future studies are needed to evaluate potential mechanisms linking FGF23 concentrations with specific causes of death.

Keywords

FGF23; assays; mortality; cause-specific

Introduction

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphorus and vitamin D metabolism. It is secreted by osteocytes and released into the circulation where it interacts with the kidney to induce phosphaturia and inhibits production of calcitriol by binding to a fibroblast growth factor receptor-klotho complex. Elevated levels of circulating FGF23 have been associated with poor clinical outcomes in different patient populations including in persons with prevalent cardiovascular disease, acute and chronic kidney disease,[1–4] and in the general population.[5,6] Data are scarce regarding relationships of FGF23 with cause-specific mortality apart from cardiovascular and heart failure related mortality.

Most existing studies evaluating FGF23 and clinical endpoints have utilized an assay that measures the C-terminal aspect of the hormone, thus measuring both intact, biologically active FGF23 and its C-terminal degradation fragments. Recent studies have demonstrated that both iron deficiency[7–10] and inflammation[11] induce FGF23 cleavage, which increases C-terminal fragments without significantly influencing the concentrations of the intact, biologically active hormone.[12] Iron deficiency[13] and inflammation[14] are also independently associated with mortality. Systematic reviews evaluating associations of FGF23 with clinical endpoints have demonstrated heterogeneity of strengths of association by the type of assay used, and have consistently found that associations are stronger using the C-terminal vs. intact FGF23 assay.[15,16] Because factors such as kidney function, iron deficiency and inflammation may have confounded the strong associations of C-terminal FGF23 with clinical outcomes reported in prior studies, the true strength of the associations of intact, biologically active, FGF23 hormone with clinical endpoints remains uncertain.

We measured intact FGF23 as it would uniquely allow for closer evaluation of the active form of FGF23 and therefore assess the biological actions of the hormone while minimizing

the confounding effects of low iron states and inflammation. In the present study, we evaluate a large population of community-living older adults. Their age and long-term follow-up allowed detailed assessment of cause-specific mortality. Our purpose was to investigate the relationship of intact FGF23 with different causes of death, and to examine if associations differed across subtypes of death in a prospective cohort of community-dwelling well-functioning older adults.

Methods

The Health Aging and Body Composition (Health ABC) study is a prospective population-based cohort of well-functioning older adults that was designed to evaluate the impact of changes in weight and body composition on age-related physiologic and functional changes. Details of the study design have been described elsewhere.[27] Briefly, adults aged 70 to 79 (N=3,075) were recruited from Medicare eligibility lists from March 1997 through July 1998 at two field centers in Pittsburgh, PA, and Memphis, TN. White participants were recruited from a random sample of the Medicare eligibility lists; black participants were recruited from all age-eligible individuals residing in the respective communities. Subjects were eligible if they reported no difficulty walking one-fourth of a mile, climbing 10 steps, or performing basic activities of daily living; were free of life-threatening illness; planned to remain in the geographic area for ≥3 years; and not enrolled in lifestyle intervention trials. All participants gave informed consent and the study was approved by the institutional review boards at the University of Tennessee Health Science Center and the University of Pittsburgh. Of the 3,075 participants enrolled at baseline, 2,921 participants were alive and returned for a follow up visit 3 years later, which was the visit at which we measured FGF23. We excluded 312 of these participants with missing FGF23 and cystatin C measurements, for a final analytic study sample of 2,763 individuals.

Exposure

The primary exposure was the plasma intact FGF23 concentration, measured using specimens thawed for the first time (Kainos Laboratories Tokyo, Japan). The FGF23 assay has a limit of detection of 3 pg/mL and the coefficient of variation (between-batch) was 6.1–10.7% across the analyses.

Urine albumin and creatinine, serum albumin, low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol and cystatin C were measured at year 1. Cystatin C was measured using a particle–enhanced immunonephelometric assay.[17] Urine albumin was measured using a particle–enhanced turbidimetric inhibition immunoassay. A modified Jaffe method measured urine creatinine. Serum albumin was measured using the bromocresol green method. Measures of mineral metabolism including calcium, phosphorus, and parathyroid hormone (PTH) were measured concurrent with FGF-23 measurement, from frozen stored samples. Intact PTH was measured in ethylenediamine tetraacetic acid (EDTA) plasma using a 2-site immune-radiometric assay kit (N-tact PTHSP; DiaSorin). Serum calcium and phosphate levels were measured using direct quantitative colorimetric determination (Stanbio Laboratory, Boerne, TX, USA).

Outcomes

Outcomes in this study included all-cause mortality as well as cause-specific mortality, which was classified as cardiovascular, cancer, or death from other causes. As we found associations with “other causes”, we subsequently wished to explore this outcome in more depth. Thus, as a secondary analysis, we examined relationships of FGF23 with death from other causes, sub classified as gastrointestinal (GI) bleed-, kidney failure-, dementia-, sepsis-, pulmonary-, and “other” causes of deaths; the latter for those not categorized into the afore-mentioned categories. Kidney failure was recognized as an underlying cause of death when there was an inability to tolerate dialysis due to poor or infected access or refusal of dialysis and when kidney was the predominant failing organ. Pulmonary related mortality was defined as mortality from chronic obstructive pulmonary disease (COPD), pulmonary fibrosis (or another chronic lung condition), pneumonia and respiratory failure (even when it is the consequence of a non-pulmonary underlying cause resulting in the subject developing acute respiratory distress syndrome (ARDS) and/or becoming ventilator dependent). The Health ABC Study Diagnosis and Disease Ascertainment Committee reviewed all hospital records, death certificates, informant interviews, and autopsy data to adjudicate immediate and underlying causes of death.[18]

Statistical Methods

We compared baseline characteristics and demographics of our study population according to ascending quartiles of FGF23. We used Cox regression models to evaluate the association of FGF23 with each outcome. We evaluated FGF23 quartiles using the lowest quartile as the reference category. We also evaluated FGF23 as a continuous variable after log base 2 transformation, interpreted as “per two-fold higher.” We based model selection and addition of covariates on prior clinical knowledge. For each outcome, models were adjusted for age, sex, recruitment site, education, race, body mass index (BMI), diabetes, history of cardiovascular disease (CVD), systolic blood pressure (SBP), hypertension (HTN) medication use, smoking history, serum albumin, C-reactive protein (CRP) concentrations, statin use, total cholesterol, calcium, phosphate, and parathyroid hormone (PTH). An additional model added estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (ACR) to isolate the influence of kidney function on parameter estimates. The eGFR was estimated using an equation that included serum cystatin C concentration, age, sex, and race derived in the CKD-EPI study.[19] Finally, we also assessed for effect modification by baseline chronic kidney disease (CKD) status (eGFR < 60 ml/min/1.73m^2 versus greater), baseline CRP concentrations (≤2.50 versus >2.51), race (black versus non-black) for the outcome all-cause mortality. The proportional hazards assumption was satisfied for all models by visual inspection of the log negative and log survival curves and by Schoenfeld residuals. All analyses were performed using SPSS statistical software (release 26.0, SPSS Inc, Chicago, IL). A two-sided p-value <0.05 was considered statistically significant for all analyses including interaction terms.

Results

Among the 2,763 community-living older adults in this study, the mean age was 75±3 years, 55% were women, 40% black, and 25% had a baseline eGFR of < 60ml/min/1.73m^2. The

median intact FGF23 concentrations was 47 (IQR 37, 60) pg/ml. Additional baseline characteristics are shown in Table 1. Across quartiles of FGF23, those in the highest quartile (> 60 pg/ml) had a greater burden of comorbid conditions including diabetes, hypertension, heart failure, cerebrovascular disease and coronary artery disease. Additionally, those in the highest quartile were more likely to have eGFR < 60ml/min/1.73m^2, spot urine ACR >30mg/g, and higher concentrations of C-reactive protein and PTH. We found a significant but weak correlation between intact FGF23 and C-reactive protein (R=0.06; P<0.05).

Associations between intact FGF 23 and all-cause mortality

The median follow-up time was 8.3 years. During this period, 821 subjects died, of whom 307 (37%) died from cardiovascular causes, 245 (30%) from cancer, and 267 (33%) from other causes (Table 2; Supplementary Table 1). In fully-adjusted models, each two-fold higher intact FGF23 level was associated with 24% (HR 1.24 [95% CI 1.12, 1.37]) higher risk of all-cause mortality. The adjusted association was nominally stronger for cardiovascular mortality, where risk was 31% (HR 1.31 [95% CI 1.11, 1.54]) higher. In contrast, we found no association of intact FGF23 with cancer-related mortality where the association was near unity (Figure 1). Across quartiles of FGF23, those in the highest quartile demonstrated 31% (HR 1.31 [95% CI 1.05, 1.62]) risk of all-cause mortality and 54% risk of cardiovascular mortality (HR 1.54 [95% CI 1.08, 2.18]) compared to lowest quartile (Supplementary Table 1). These findings appeared similar irrespective of baseline CKD status, baseline C-reactive protein concentrations and race (p interactions all > 0.29).

Associations between FGF23 and additional causes of mortality

In secondary analysis, we evaluated associations of intact FGF23 with different sub-types if within the “other causes” category of deaths. In these analyses, FGF23 was not significantly associated with any sub-category of death, although for several outcomes, the number of events was small, and the point estimates were strong. For example, each two-fold higher intact FGF23 was associated with 2.49 fold risk of mortality from gastro-intestinal bleeding (95% CI 0.86, 7.21), however only 8 events were observed. Associations with other causes of death were more modest in magnitude (Table 2).

Discussion

In this study among well-functioning, community-living older adults, we demonstrate that higher concentrations of intact FGF23 are independently associated with risk of all-cause mortality. However, we found that this association varied across different causes of death. We observed particularly strong associations of higher intact FGF23 with mortality related to cardiovascular diseases, and did not find independent associations of FGF23 with mortality related to cancer. The findings with “other” causes of death is more complicated, as higher FGF23 was significantly associated with this composite cause of death, but not with any subgroup of causes of death within it (gastrointestinal bleeding, kidney failure, pulmonary diseases, dementia, or sepsis), likely owing to small number of deaths in many of these subcategories.

As we found considerable variation in the associations of FGF23 with different causes of death, these analyses give insights to pathways through which FGF23 may be influencing risk of adverse outcomes in community-living older individuals. Because FGF23 causes cardiac hypertrophy in animal models, there is clear biological plausibility linking higher levels of FGF23 with cardiovascular mortality. This was consistent with the strong association with CVD mortality relative to the lack of appreciative association with cancer mortality.

The association with “other” causes of death requires a nuanced approach to interpretation. As a group of death causes, a two-fold higher FGF23 was significantly associated with a 1.33 fold higher risk of “other” causes of death; an association that was similar in strength to that with CVD mortality. We therefore investigated subgroups within “other” causes of death, where no individual cause was found to be associated with higher FGF23 concentrations. In many of these subcategories, the number of events is small, so it is possible that true associations with some of these causes of death exist, but were missed due to limited power. For example, we observed a large point estimate (2.5 fold) with gastrointestinal bleed-related death, although there were only 8 deaths in this category, and the association did not reach statistical significance in the final models. Relationships of FGF23 with these causes of death necessitate adequately powered follow-up studies in the future to further explore the relationship between FGF23. Our findings for these endpoints should be viewed as hypothesis generating.

We have previously shown in the Cardiovascular Health Study, a separate cohort of community-living older adults, that higher concentrations of FGF23 were associated with all-cause mortality. Others have demonstrated associations specifically with cardiovascular mortality in community-living cohorts.[6,22,23] However, our prior study, and those of other investigators have predominantly used the C-terminal FGF23 assay, which captures not only the biologically active hormone, but also its c-terminal fragments with unclear physiologic activity. Given recent findings that inflammation and iron deficiency can influence FGF23 cleavage, and systematic reviews suggesting stronger associations of the C-terminal FGF23 assay with clinical outcomes, it remains unclear if these previous studies were confounded by iron deficiency, inflammation, or other factors. The present study benefits from use of an assay that is specific to the intact, biologically active hormone. Therefore, we confirm that intact FGF23 is independently associated with all-cause and cardiovascular mortality in community-living older individuals. This finding opens the possibility for consideration of trials targeting FGF23 lowering in community-living individuals, as are being evaluated in other study populations.[24]

Our findings require evaluation in context of several prior studies evaluating FGF23 and cause-specific mortality in a variety of settings. Marthi et al. identified prospective studies reporting associations between FGF-23 and risk of cardiovascular events.[25] They found no difference between FGF-23 concentrations and cardiovascular and non-cardiovascular outcomes (calculated indirectly) and suggested that cardiovascular mortality was non-causal. However, the analyses were limited by lack of data on the nature of the non-cardiovascular causes of death impeding complete assessment of different death types. In addition, the majority of studies utilized C-terminal assay (26/34). The Health ABC study allowed us to

obtain detailed covariates and more information on specific causes of death. We measured intact FGF-23 in all individuals and were able to compare effect estimates across death types. The Northern Manhattan study is among the few studies that have reported associations FGF23 with cause-specific mortality in persons with normal kidney function. They reported higher C-terminal FGF23 was associated with both vascular and nonvascular mortality in a general population cohort selected for high risk of cancer death.[26] The selection of persons at high risk of cancer death, the implications of this study to the general population remained unclear. We provide evidence that indeed higher FGF23 is associated with non-cardiovascular death in the general population, but that these relationships appear quite variable depending upon the cause of death. Interestingly, we found no relationship with cancer mortality. The cancer mortality outcome had substantial statistical power (N=245 outcomes), thus this result is likely robust.

This study has several unique strengths. We evaluated a relatively large cohort of older community dwelling adults, a population with high event rates, and had more than 8 years of follow-up data. Thus, we had the opportunity to test our hypothesis and evaluate relationships with subtypes of mortality. Additionally, we used an assay measuring biologically active (intact) FGF23, which is less likely to be affected by low iron states and inflammation. Finally, the Health ABC cohort has detailed ascertainment of risk factors, covariates, and outcomes and the ability to adjust for measures of baseline kidney function and inflammation.

This study also has important limitations. As with other observational studies, there remains the possibility of residual confounding, and we cannot determine cause-effect of the reported associations. Our study population only included older blacks and whites and most had normal or near-normal kidney function; therefore, it remains unknown whether the results are generalizable to younger populations, persons of other race/ethnicities, or persons with advanced CKD. We observed lower number of events for some of the secondary outcomes such as GI bleed. Since FGF23 measurements were made only at one time-point, it remains possible that longitudinal changes may differently influence associations with outcomes.

In conclusion, intact FGF23 is independently associated with all-cause and cardiovascular mortality in community-living older individuals. Although higher FGF23 concentrations are associated with all-cause mortality, the association appears restricted to certain death types, and did not extend to deaths caused by cancer, GI bleed, renal failure, pulmonary diseases, dementia, or sepsis. These findings suggest specificity in the associations of FGF23 with clinical outcomes, and provides an opportunity to garner information into biological mechanisms linking FGF23 with clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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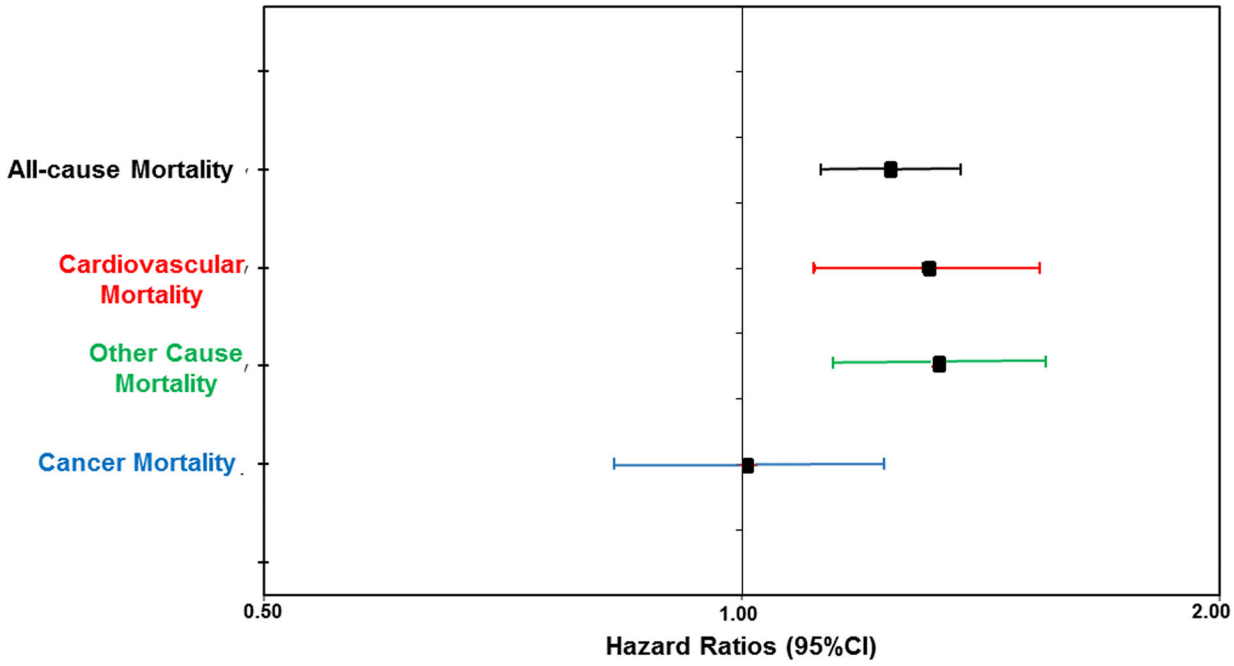

Figure 1: Association of intact FGF23 concentrations (per-two fold higher) with all-cause mortality, CVD mortality, and other causes of death

Hazard ratios (HRs) represented per two-fold higher concentrations of FGF23. FGF23 concentrations presented after log transformation. Model is adjusted for age, gender, site, education, race, body mass index (BMI), history of myocardial infarction (MI), systolic blood pressure (SBP), prevalent diabetes and cardiovascular disease (CVD), hypertension (HTN) medications, smoking, albumin, C-reactive protein concentrations, statin use, total cholesterol, calcium, phosphate, PTH, estimated glomerular filtration pressure (eGFR) and urine albumin to creatinine ratio (UACR).

Table 1
Baseline Characteristics by Quartiles of FGF23 in Community-Living Older Adults

Variable	Full cohort	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Range		<37	37–46	46.6 -- 60	>60
N	2763	688	695	691	689
Age (years)	75 (3)	75 (3)	75 (3)	75 (3)	75 (3)
Female	1413 (55%)	381 (55%)	360 (52%)	324 (47%)	348 (51%)
Black	1094 (40%)	300 (44%)	260 (37%)	257 (37%)	277 (40%)
Education					
< High School	660 (24%)	181 (26%)	156 (23%)	158 (23%)	165 (24%)
Current Smoker	266 (10%)	83 (12%)	62 (9%)	60 (9%)	61 (9%)
Body Mass Index (kg/m^2)	27.2 (4.8)	26.7 (4.6)	26.8 (4.7)	27.4 (4.7)	28.0 (5.1)
Diabetes	1020 (37%)	227 (33%)	250 (36%)	258 (37%)	285 (41%)
Hypertension	2130 (77%)	495 (72%)	511 (74%)	547 (79%)	577 (84%)
Systolic Blood Pressure (mmHg)	134 (21)	133 (20)	133 (20)	133 (21)	135 (23)
Diastolic Blood Pressure (mmHg)	70 (12)	70 (12)	70 (12)	70 (12)	70 (12)
HTN med use	1582 (57%)	330 (48%)	363 (52%)	411 (60%)	478 (70%)
Total Cholesterol (mg/dL)	206 (39)	206 (38)	208 (40)	203 (38)	205 (40)
Statin use	440 (16%)	96 (14%)	87 (13%)	131 (19%)	126 (18%)
Prevalent CHD	624 (23%)	128 (19%)	139 (20%)	161 (23%)	196 (28%)
Prevalent CHF	111 (4%)	14 (2%)	18 (3%)	20 (3%)	59 (9%)
Prevalent stroke	267 (10%)	74 (11%)	57 (8%)	68 (10%)	68 (10%)
Prevalent CVD	778 (28%)	175 (25%)	174 (25%)	193 (28%)	236 (34%)
Serum albumin (g/dL)	3.98 (0.31)	3.99 (0.30)	3.99 (0.31)	3.97 (0.31)	3.98 (0.33)
C-reactive protein (mg/L)	2.9 [1.2, 6.5]	2.9 [1.2, 6.1]	2.7 [1.1, 6.1]	2.7 [1.2, 6.1]	3.5 [1.4, 8]
eGFR (ml/min/1.73m^2)	72 (18)	77 (17)	77 (17)	72 (17)	64 (20)
eGFR < 60	683 (25%)	108 (16%)	121 (17%)	171 (25%)	283 (41%)
Urine Albumin/Creatinine ratio (mg/g)	7.6 [3.9, 19]	7.2 [3.6, 15.8]	7.0 [3.8, 16.3]	7.3 [3.4, 17.5]	6.6 [4.7, 31.3]
UACR ≥ 30	481 (18%)	91 (13%)	100 (15%)	117 (17%)	173 (26%)
Calcium (mg/dL)	8.87 (0.43)	8.80 (0.39)	8.83 (0.41)	8.89 (0.44)	8.95 (0.47)
Phosphorus (mg/dL)	3.55 (0.48)	3.51 (0.44)	3.52 (0.47)	3.53 (0.48)	3.65 (0.51)
Parathyroid hormone (pg/ml)	34 [25, 45]	32 [23, 42]	31 [24, 41]	34 [26, 45]	38 [28, 56]

Values are n, mean (SD), n (%), or median (interquartile range). CHF chronic heart failure, CVD cardiovascular disease, eGFR, estimated glomerular filtration rate; FGF23, Fibroblast growth factor 23; HDL, high density lipoprotein, LDL low density lipoprotein, UACR, urine albumin creatinine ratio.

Table 2
Associations of Intact FGF23 with Mortality and its Subtypes

All-cause Mortality				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23 (per 2-fold higher)	821/2763	4.1	1.45 (1.33, 1.58)	1.24 (1.12, 1.37)
Cardiovascular Mortality				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23 (per 2-fold higher)	309/2763	1.5	1.56 (1.38, 1.76)	1.31 (1.11, 1.54)
Cancer Mortality				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23 (per 2-fold higher)	245/2763	1.2	1.06 (0.87, 1.29)	1.01 (0.83, 1.23)
Other Causes of Death				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23 (per 2-fold higher)	267/2763	1.3	1.61 (1.42, 1.84)	1.33 (1.14, 1.56)
Sub-categories of "Other causes of Death"				
Pulmonary Related Deaths (includes COPD, Pneumonia and respiratory failure)				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23 (per 2-fold higher)	40/2763	0.15	1.38 (0.92, 2.07)	1.40 (0.87, 2.27)
Dementia				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23 (per 2-fold higher)	56/2763	0.28	0.96 (0.62, 1.50)	0.84 (0.56, 1.26)
GI bleed				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23 (per 2-fold higher)	8/2763	0.04	2.09 (1.38, 3.16)	2.49 (0.86, 7.21)
Renal Failure				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23 (per 2-fold higher)	24/2763	0.12	2.48 (2.07, 2.96)	1.25 (0.77, 2.03)
Sepsis				
			Model 1	**Model 2**
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23(per 2-fold higher)	15/2763	0.07	0.70 (0.34, 1.42)	0.73 (0.31, 1.73)
Others				

			Model 1	Model 2
	Events/N	**Incident Rate (%/year)**	**HR (95% CI)**	**HR (95% CI)**
FGF23(per 2-fold higher)	124/2763	0.61	1.54 (1.26, 1.89)	1.43 (1.12, 1.82)

Model 1 = unadjusted analysis.

Model 2 = adjusted for M1 + diabetes, SBP, HTN meds, BMI, smoking, prevalent CVD, albumin, CRP, statin use, total cholesterol, calcium, phosphate, PTH, eGFR and UACR

BMI, Body mass index; CVD, cardiovascular disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FGF23, Fibroblast growth factor 23; HTN, Hypertension; N, PTH, Parathyroid hormone, Number; UACR, urine albumin creatinine ratio.