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FGF23, Frailty, and Falls in SPRINT:

FGF23, Frailty, and Falls

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Abstract

Background/Objectives: Chronic kidney disease (CKD) is associated with frailty. Fibroblast growth factor 23 (FGF23) is elevated in CKD and associated with frailty among non-CKD older adults and individuals with human immunodeficiency virus. Whether FGF23 is associated with frailty and falls in CKD is unknown.

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Author Contributions

1. Study concept and design: AJ, ZY, MS, JHI, MC
2. Acquisition of subjects and/or data: JHI, MS, MC
3. Analysis and interpretation of data: AJ, ZY, MS, JHI, MC
4. Preparation of manuscript: all authors

Design: Cross-sectional and longitudinal observational study

Setting: Systolic Blood Pressure Intervention Trial (SPRINT), a randomized trial evaluating standard (SBP<140 mmHg) vs. intensive (SBP<120 mmHg) blood pressure lowering on cardiovascular and cognitive outcomes among older adults without diabetes.

Participants: 2376 participants with CKD (estimated glomerular filtration rate (eGFR)<60 mL/min/1.73m^2).

Measurements: The exposure variable was intact FGF23. We used multinomial logistic regression to determine the cross-sectional association of intact FGF23 with frailty and Cox proportional hazards analysis to determine the longitudinal association with incident falls. Models were adjusted for demographics, comorbidities, randomization group, antihypertensives, eGFR, mineral metabolism markers, and frailty.

Results: After adjustment, the odds ratio for prevalent frailty vs. non-frailty per two-fold higher FGF23 was 1.34 (95% CI, 1.01–1.77). FGF23 levels in the highest quartile vs. the lowest quartile demonstrated >2-fold increased fall risk (hazard ratio 2.32 (95% CI, 1.26–4.26)), and the hazard ratio per two-fold higher FGF23 was 1.99 (95% CI, 1.48–2.68).

Conclusions: Among SPRINT participants with CKD, FGF23 was associated with prevalent frailty and falls.

Keywords

fibroblast growth factor 23; falls; frailty; chronic kidney disease; biomarkers

INTRODUCTION

Fibroblast growth factor (FGF23) is a bone-derived hormone that promotes phosphate excretion into urine and inhibits 1-α-hydroxylase reducing serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels to suppress phosphate absorption from the intestine.[1] FGF23 also inhibits parathyroid (PTH) synthesis[2] limiting bone resorption of calcium and phosphate. Thus, FGF23 induces negative phosphate balance.[3]

Extracellular phosphate is necessary to allow mineralization of bone matrix, while intracellular phosphate plays an important role in energy production in the form of phosphocreatine and adenosine triphosphate (ATP),[4] which are needed for muscles to properly function. Hypophosphatemic rickets is characterized by excess FGF23 along with frequent fractures and muscle weakness that severely affect activities of daily living.[5] Experimental studies have shown that inhibition of FGF23 through injections of FGF23 neutralizing antibodies increased serum phosphate and $1,25(OH)_2D$ levels as well as grip strength and spontaneous movements in hypophosphatemic mice.[6] Consequently, FGF23 may play an important role not only in bone mineralization but also in the maintenance of muscle mass and function given its interplay with vitamin D and the critical role of phosphate in energy (ATP).

Chronic kidney disease (CKD) is associated with an increased risk of frailty.[7] Circulating FGF23 levels are elevated in CKD, increase as kidney disease progresses,[8] and are

associated with adverse clinical outcomes.[9–13] Among community-dwelling older adults without kidney disease and individuals with human immunodeficiency virus (HIV), FGF23 is associated with frailty.[14,15] Frailty increases risk of falls,[16,17] and risk of falling is higher among those with CKD compared to those without kidney disease.[18] An important consequence of falling is fracture. Not only do individuals with CKD have an increased risk of fracture compared to the general population,[19] but fracture in those with CKD is costly[20] and associated with a high mortality risk.[21] A biomarker to identify individuals with CKD at risk for frailty and falls, who would benefit from monitoring and early intervention, may improve these outcomes. Whether serum FGF23 levels are associated with an increased risk of falls in CKD is unknown. We hypothesized that higher serum intact FGF23 concentrations would be associated with prevalent frailty and greater risk of falls in CKD. To test this hypothesis, we conducted an analysis of participants with CKD (baseline eGFR <60 mL/min.1.73m^2) from the Systolic Blood Pressure Intervention Trial (SPRINT).

METHODS

Study Population

SPRINT[22] was a randomized, controlled, open-label trial conducted at 102 clinical sites in the United States and Puerto Rico. SPRINT tested the hypothesis that a systolic blood pressure goal <120 mm Hg would reduce cardiovascular disease events more than a standard goal (<140 mm Hg) among 9361 hypertensive participants. Study-group assigned blood pressure targets were achieved by adjusting baseline antihypertensive regimens.[22] At enrollment, participants were ≥50 years, had a systolic blood pressure of 130 to 180 mm Hg and an increased risk of cardiovascular events defined by ≥1 of the following: clinical or subclinical cardiovascular disease other than stroke; CKD with a Modification of Diet in Renal Disease eGFR of 20–60 mL/min/1.73m^2; a 10-year Framingham cardiovascular risk score ≥15%; or an age ≥75 years. Major exclusion criteria were diabetes, prior stroke, polycystic kidney disease, proteinuria >1 g/day, or any solid organ transplant. For this FGF23 ancillary study, serum cystatin C (Gentian, Moss, Norway) was measured in participants to identify the subpopulation with CKD defined as eGFR <60 mL/min/1.73m^2, using the CKD Epidemiology Collaboration combined creatinine and cystatin C equation;[23] 2486 participants met these criteria and baseline serum FGF23 levels were measured in this subset. SPRINT was approved by the institutional review board at each participating study site and this FGF23 ancillary study was approved at the Veterans Affairs San Diego Healthcare System.

Serum FGF23

Serum samples from the baseline study visit were stored at −70°C; a first-thaw aliquot was used to measure intact FGF23 in 2015 with a two-site ELISA (Kainos Laboratories, Tokyo, Japan), with an interassay coefficient of variation of 8.6% at 22.5 pg/mL and 3.2% at 85.1 pg/mL, with an analytic range of 2.2–800 pg/mL.[24,25] All measurements were made in duplicate in each sample and averaged to provide a single value for each participant. Measurements were at the SPRINT Central Laboratory (University of Minnesota, Minneapolis, MN).

Frailty

A deficit accumulation approach was used to construct a measure of frailty, the frailty index, in SPRINT using 36 total items and is described elsewhere[26] and in Supplemental Table 1 and Supplemental Material. We excluded the renal component of the frailty for this analysis. Among participants ≥75 years, gait speed was measured based on a 4-meter walk test and was included in the frailty index, yielding 37 items in this subset. The frailty index was calculated as the sum of the score for each deficit, divided by the total number of non-missing items. Each item was weighed equally and participants who had 30 or more non-missing items were included. Participants were classified as non-frail (frailty index ≤ 0.10), pre-frail (0.10 < frailty index ≤ 0.21), or frail (0.21 < frailty index).[26–29]

Falls

Injurious falls were pre-specified as a safety event of interest in SPRINT.[30] Site staff asked participants about falls at quarterly study visits using a standardized data collection form. Site staff may have also learned about serious adverse events (SAE) at as-needed visits or in other ways, such as participant-initiated contact, investigator involvement in participant care, or electronic medical record notifications. A fall was defined as a sudden, unintentional change in position in which the participant came to rest on the ground, floor, or a lower level not as the result of syncope or overwhelming external force. A fall due to syncope was not counted as a fall, because syncope was captured separately. An injurious fall was defined as a SAE if it was fatal or life threatening, resulted in significant or persistent disability, required hospitalization, or investigators judged it to represent a significant hazard or harm to the participant that might require intervention to prevent a subsequent event. Falls defined as SAEs were included in this analysis.

Other measurements

Participant age, sex, race, past medical history, and smoking status were obtained by questionnaire at the baseline visit. Blood pressure was measured three times after a 5-minute seated rest using an automated BP device (Model 907; Omron Healthcare), and the mean value was used. Body mass index was calculated as weight in kilograms divided by height in meters squared. Serum PTH was measured using an intact PTH immunoassay (e411 analyzer; Roche, Indianapolis, IN), with an interassay coefficient of variation of 4.9% at 35.1 pg/mL and 2.5% at 210.4 pg/mL, with an analytic measurement range of 1.2–5000 pg/mL.[31] Fasting serum cholesterol, high density lipoprotein (HDL) cholesterol, creatinine, urine albumin, and urine creatinine were measured at the Central Laboratory on a Roche c501 instrument.[32] The CKD Epidemiology Collaboration combined creatinine and cystatin C equation[23] was used to estimate GFR.

Statistical Analysis

Baseline characteristics were compared across FGF23 quartiles. To examine whether FGF23 was independently associated with prevalent frailty, we used multinomial logistic regression with non-frailty as the reference and pre-frailty and frailty as the alternative outcomes. FGF23 was treated as a continuous variable, using $\log_2$ transformation, such that coefficients could be interpreted as “per two-fold higher.” Cox proportional hazards models examined

the association between baseline FGF23 and falls. We assessed the proportional hazards assumption for each covariate by including the interaction of the covariate and time in the model. If the interaction covariate did not have a significant coefficient, then we considered the proportional hazards assumption met for the covariate and removed the interaction from the final model. We did not find evidence of violation of the assumption of our analysis. Quartiles of FGF23 were evaluated, using the lowest FGF23 quartile as the reference group. Because no clinically meaningful cut-point for FGF23 levels has been established in CKD, we evaluated FGF23 in quartiles similar to previous publications examining FGF23 in SPRINT and to allow for better understanding of the relationship between FGF23 and outcomes across a range of FGF23 levels.[33] Similar to the multinomial regression models, the Cox model was also fit with FGF23 as a continuous variable ($\log_2$) to allow for interpretation as "per two-fold higher." A sequence of multivariable models were evaluated for each analysis. Model 1 adjusted for age, sex, race (white vs. other), and randomized treatment arm. Model 2 added smoking (never, former, current), cardiovascular disease, congestive heart failure, body mass index (BMI), systolic and diastolic blood pressures, eGFR, urine albumin-to-creatinine ratio (UACR), number of antihypertensive medications at baseline, and baseline serum calcium, phosphorus, and PTH. The frailty index was added to the Cox proportional hazards model 3 as a continuous variable to examine whether FGF23 was associated with falls independent of frailty. Analyses were repeated using data from a subset of participants ≥75 years because gait speed was included in the frailty index only for this group and they experienced over 80% of falls. Finally, we tested the interaction between $\log_2$ FGF23 and randomization to intensive blood pressure lowering in order to determine if treatment randomization modified the association of FGF23 and falls. All statistical analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC). P-values <0.05 were considered statistically significant for all analyses including the interaction terms.

RESULTS

Among the 2486 SPRINT participants with an eGFR <60 mL/min/1.73m^2 at the baseline study visit, 110 participants had missing baseline data and were not included in this analysis. Of the 110 participants who were excluded, 19 were missing BMI, 3 were missing serum calcium levels, 3 were missing serum phosphorus levels, 1 was missing PTH level, 77 were missing urine albumin-to-creatinine ratio, and 11 were missing frailty index calculations. The baseline characteristics of the 110 excluded participants did not differ from the final analytic cohort. Baseline characteristics of the final analytic cohort (N = 2376) are presented in Table 1. The mean age was 73 ± 9 years, 40% were female, and 67% were white. Median baseline FGF23 [IQR] was 66 [52–88] pg/mL. Thirty-six percent of the participants were frail, 53% were pre-frail, and 11% were non-frail. Participants with FGF23 in the highest quartile were more likely to be female, had greater history of heart failure, lower eGFR, higher UACR and PTH, and were more likely to be frail. The proportion of participants randomized to the standard vs. intensive arms of the trial were similar across FGF23 quartiles.

Higher baseline serum FGF23 was associated with prevalent frailty. In the unadjusted model, for every two-fold higher baseline serum FGF23 the odds of frailty compared to non-frailty was 1.75 (95% CI, 1.38–2.22). The association was somewhat attenuated after

adjustment for demographics, cardiovascular disease and kidney function parameters, and markers of mineral metabolism an odds ratio of 1.34 (95% CI,1.01–1.77). In the unadjusted model, for every two-fold higher FGF23, the odds of pre-frailty compared to non-frailty was 1.41 (95% CI, 1.12–1.77). However, after full adjustment the association was attenuated (Figure 1). Neither sex nor race had an effect on the association of FGF23 and frailty (p-value for interaction terms >0.05).

During a median follow-up of 39 [31–46] months, there were 102 falls (Table 2) and 5 deaths. Median [IQR] baseline FGF23 level was higher (80 [59–102] pg/mL) in the fall group compared to the group without falls (66 [52–87] pg/mL), while there was no difference between groups in baseline calcium, phosphate, and PTH levels (Supplemental Table 2). In the unadjusted analysis, the hazard ratio (HR) for falls among participants with baseline FGF23 levels in the highest quartile vs. the lowest quartile was 2.22 (95% CI, 1.29–3.84). This association was not attenuated after adjusting the model for demographics, cardiovascular disease and kidney function parameters, markers of mineral metabolism, and frailty index with a 2.32 (95% CI, 1.26–4.26) hazard. In the fully adjusted model, for every two-fold higher FGF23, the risk of falls increased by nearly 2-fold (HR 1.99 (95% CI, 1.48–2.68)) (Table 2). There was no interaction between FGF23 and randomization to intensive blood pressure lowering (p = 0.8).

Gait speed was measured among SPRINT participants ≥75 years and included in the frailty index. We repeated the analysis in this sub-cohort of participants ≥75 years with CKD (N = 1192) (baseline characteristics in Supplemental Tables 3 and 4) and results were similar. The HR for falls among participants ≥75 years with baseline FGF23 levels in the highest quartile vs. the lowest quartile was 1.95 (95% CI, 1.00–3.80) and for every 2-fold increase in FGF23 levels the HR for falls was 1.82 (95% CI, 1.28–2.60) in the fully adjusted models. Notably the addition of the frailty index including gait speed did not change the magnitude of the HR (Table 2).

Similar to the total cohort and the subgroup ≥75 years, SPRINT participants <75 years (N = 1184) with FGF23 levels in the highest quartile had a greater risk of fall compared to those with FGF23 levels in the lowest quartile and a 4-fold greater risk of fall for every doubling of FGF23 in the fully adjusted models (Supplemental Table 5).

DISCUSSION

In this analysis of SPRINT participants with baseline CKD (eGFR <60 mL/min/1.73m^2), higher serum intact FGF23 levels were independently associated with greater prevalence of frailty. There was also a strong association of higher FGF23 with risk of falls that remained even after accounting for baseline frailty status. These findings are consistent with the reports in community-living older adults and individuals with HIV predominantly without CKD,[14,15] and extend similar findings to persons with moderate to severe CKD.

Sarcopenia, the loss of muscle mass with aging or chronic disease, and frailty, reduced homeostatic reserves, which increases risk for negative health-related events, both contribute to each other, are often studied in parallel, and share a unique core condition, which is

physical function impairment.[33] Sarcopenia is prevalent in CKD and thus contributes to frailty. Indeed, only 11% of the current CKD cohort was non-frail compared to 19% non-frail in the total SPRINT cohort.[26] Numerous mechanisms, including inflammation, increased oxidative stress, and mitochondrial dysfunction, are linked to the development and progression of sarcopenia.[35,36] FGF23 is also associated with energy molecule signaling[37] and mitochondrial function,[38] and along with phosphorus is associated with sarcopenia.[39,40] Similar to non-CKD older community-dwelling adults and individuals with HIV,[14,15] we found a significant and independent relationship between FGF23 levels and prevalent frailty among SPRINT participants with CKD. The relationship was somewhat attenuated by addition of comorbidities and markers of mineral metabolism to our statistical models. While FGF23 may simply be a marker of disease severity, it may also contribute to frailty via effects on muscle strength as suggested by the strong and independent relationship with falls demonstrated in our analysis and the association with slow walking speed in non-CKD older community-dwelling adults.[14]

The association between elevated FGF23 and falls was not attenuated, and in fact increased slightly in strength, after adjustment for demographics, clinical factors including eGFR and comorbidities, markers of mineral metabolism, and the frailty index. While the pathophysiology of falls is complex, impaired balance related to the ability to efficiently contract lower extremity muscles and muscle weakness, certainly plays a role in fall risk.[41] In preclinical studies, FGF23 has been described in energy molecule signaling[37] and it reduces reactive oxygen species in skeletal muscle.[38] These preclinical studies and our findings support a potential role for FGF23 in muscle function independent of phosphorus, other markers of mineral metabolism, and frailty. Further, FGF23 may play an important role in sensory neurons, specifically nociceptive signaling; FGF23 enhances hyperalgesia in rodent models and inhibition of FGF receptor 1 attenuates allodynia in rats.[42,43]

The timed 4-meter walk test (gait speed) is a widely used measure of physical performance, which is inversely associated with inflammation,[44] atherosclerosis,[45] and mortality.[46] Low 25(OH)D levels are associated with both proximal and distal muscle weakness, but 25(OH)D supplementation only improves proximal and not distal muscle strength. Therefore, it was hypothesized that inhibition of active vitamin D by FGF23 may more strongly affect proximal muscle strength and walking speed compared to distal muscle and grip strength.[47] Indeed, among non-CKD older community-dwelling adults, higher levels of FGF23 were associated with slow gait speed but not grip strength.[14] Contrary to this observation, we found that addition of gait speed (i.e., timed 4-meter walk test) to the final model did not attenuate the relationship between FGF23 and falls among SPRINT participants ≥75 years with CKD. In our analysis, gait speed was added to frailty index while among non-CKD older community-dwelling adults gait speed was assessed as an individual component of frailty.

Our study has many strengths including a large cohort of individuals with CKD, standardized data collection, and a precise definition of falls. Despite these and other strengths, our study was limited by the lack of 25(OH)D and $1,25(OH)_2D$ measurements; however, among non-CKD older community-dwelling adults, 25(OH)D did not attenuate the association between FGF23 and frailty.[14] We also did not have the ability to adjust for

inflammatory markers, which may also contribute to frailty and falls. Inflammation has been found to increase concentrations of inactive fragments of FGF23 in prior analyses, which are captured by “c-terminal” FGF23 assays but not the intact FGF23 assay used here. Thus, the use of the intact FGF23 assay provides an additional strength to our analysis, as it makes residual confounding by inflammatory stress a less likely explanation for our results. In SPRINT, only data on injurious falls were collected as SAEs; as such, participants may have experienced less severe falls that were not recorded. Because frailty was measured at baseline, we were only able to analyze the cross-sectional relationship between FGF23 and frailty, which makes reverse causality a possibility. Finally, individuals with diabetes and proteinuria >1 g/day were excluded from SPRINT and all participants were volunteers in a clinical trial, which limits the generalizability of our findings.

In conclusion, among SPRINT participants with CKD, higher intact FGF23 was significantly associated with prevalent frailty and increased risk of falls. Whether FGF23 is simply a marker of disease severity or contributes to frailty and falls through muscle energy use or through altered vitamin D metabolism requires further investigation. Because FGF23 is independently associated with frailty among both CKD and non-CKD older community-dwelling adults and among individuals with HIV,[14,15] it could potentially be used as a marker for frailty in the clinical setting. However, these findings must be confirmed in other CKD and non-CKD cohorts, including individuals with diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Statement

Anna Jovanovich reports receiving study drug from Shire. Joachim H. Ix is supported by an investigator-initiated research grant from Baxter International.

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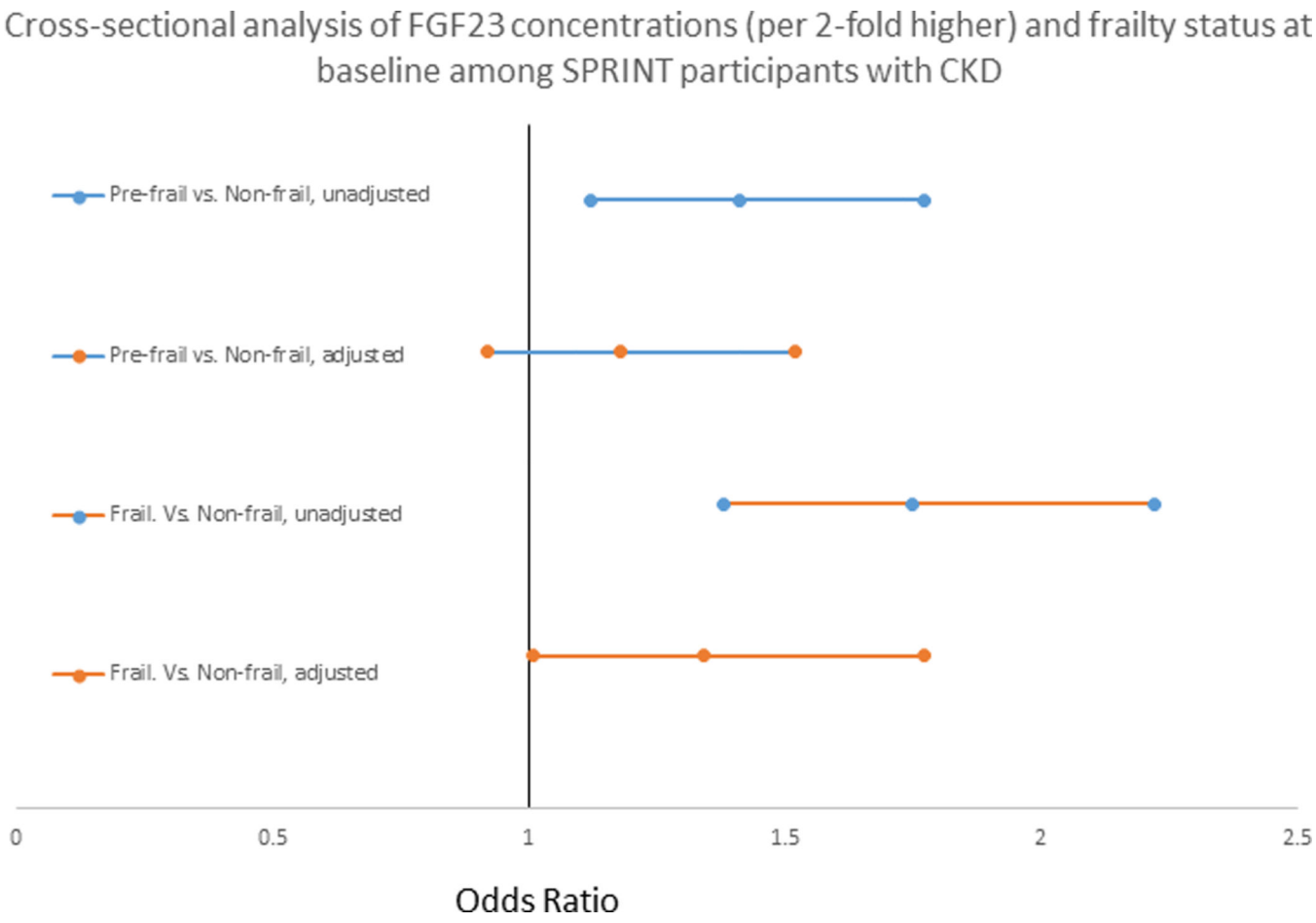

Figure 1.

The cross-sectional analysis of FGF23 concentrations (per 2-fold higher) and frailty status at baseline among SPRINT participants with CKD. The adjusted model included age, sex, race, randomized treatment arm, smoking, cardiovascular disease, congestive heart failure, body mass index, systolic and diastolic blood pressures, estimated glomerular filtration rate, urine albumin to creatinine ratio, number of antihypertensive medications at baseline, and serum concentrations of calcium, phosphorus, and parathyroid hormone.

Table 1.

Baseline characteristics of SPRINT participants with CKD

	Total Cohort N = 2376	FGF23 Q1 N = 591	FGF23 Q2 N = 594	FGF23 Q3 N = 595	FGF23 Q4 N = 596
FGF23, pg/mL	**66.2 [51.7–87.6]**	**<52.8**	**52.8–67.2**	**67.3–89.0**	**≥89.1**
Age, years	73 ± 9	73 ± 9	74 ± 8	73 ± 9	73 ± 10
Female	948 (40)	216 (37)	220 (37)	245 (41)	267 (45)
Race, White	1559 (67)	357 (60)	415 (70)	403 (68)	384 (64)
Treatment randomization					
Standard	1168 (49)	278 (47)	281 (47)	306 (51)	303 (51)
Intensive	1208 (51)	313 (53)	313 (53)	289 (49)	293 (49)
Prevalent CVD	605 (26)	136 (23)	157 (26)	158 (27)	154 (26)
Prevalent heart failure	153 (6)	35 (6)	35 (6)	32 (5)	51 (9)
eGFR-CrCys, mL/min/1.73m^2	49 ± 11	53 ± 10	51 ± 9	49 ± 11	42 ± 12
UACR, mg/g	87 ± 253	71 ± 247	58 ± 172	80 ± 224	139± 334
SBP, mmHg	140 ± 16	141 ± 17	140 ± 16	139 ± 17	139 ± 17
DBP, mmHg	74 ± 12	76 ± 13	74 ± 12	74 ± 13	73 ± 13
Antihypertensive medication, number	2.2 ± 1.0	2.0 ± 1.0	2.1 ± 1.0	2.2 ± 1.0	2.3 ± 1.0
Smoking					
Never	1075 (45)	251 (43)	283 (48)	269 (45)	272 (47)
Former	1087 (46)	260 (44)	274 (46)	282 (47)	271 (46)
Current	214 (9)	80 (14)	37 (6)	44 (7)	53 (9)
Body mass index, kg/m^2	30 ± 6	29 ± 6	29 ± 5	30 ± 6	30 ± 6
Serum Calcium, mg/mL	9.6 ± 0.5	9.5 ± 0.4	9.6 ± 0.5	9.6 ± 0.6	9.6 ± 0.6
Serum Phosphate, mg/mL	3.6 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	3.6 ± 0.5	3.7 ± 0.6
Serum PTH, pg/mL	56 ± 33	50 ± 24	50 ± 25	55 ± 32	68 ± 45
Frailty (w/o GFR)					
Non-frail	265 (11)	69 (12)	90 (15)	58 (10)	48 (8)
Pre-frail	1247 (53)	320 (54)	321 (54)	316 (53)	290 (48)
Frail	864 (36)	202 (34)	183 (31)	221 (37)	258 (43)

Data presented as N (%), mean ± SD, or median [IQR]

Abbreviations: FGF23, fibroblast growth factor 23; CVD, cardiovascular disease; eGFR-CrCys, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PTH, parathyroid hormone

Table 2.

Association of FGF23 concentrations and risk of falls among SPRINT participants with CKD

	Events/Total	Unadjusted	Model 1	Model 2
SPRINT participants with CKD (n = 2376)				
Log_2 FGF23	102/2376	1.80 (1.39 – 2.31)	1.99 (1.48 – 2.67)	1.99 (1.48 – 2.68)
Quartile 1	20/591	REFERENCE	REFERENCE	REFERENCE
Quartile 2	18/594	0.98 (0.52 – 1.86)	1.03 (0.54 – 1.95)	1.05 (0.55 – 1.99)
Quartile 3	25/595	1.25 (0.68 – 2.28)	1.32 (0.71 – 2.46)	1.34 (0.72 – 2.49)
Quartile 4	39/596	2.22 (1.29 – 3.84)	2.31 (1.26 – 4.25)	2.32 (1.26 – 4.26)
SPRINT participants ≥ 75 years and CKD (n = 1192)				
Log_2 FGF23	81/1192	1.57 (1.16 – 2.11)	1.80 (1.27 – 2.56)	1.82 (1.28 – 2.60)
Quartile 1	18/298	REFERENCE	REFERENCE	REFERENCE
Quartile 2	15/298	0.84 (0.43 – 1.68)	0.96 (0.48 – 1.93)	0.99 (0.49 – 1.99)
Quartile 3	20/297	1.14 (0.60 – 2.16)	1.18 (0.61 – 2.30)	1.19 (0.61 – 2.34)
Quartile 4	28/299	1.67 (0.92 – 3.02)	1.90 (0.98 – 3.71)	1.95 (1.00 – 3.80)

Model 1: adjusted for age, gender, race, randomized treatment arm, smoking, CVD, CHF, body mass index, systolic and diastolic blood pressures, eGFR, UACR, # antihypertensive medications at baseline, and serum calcium, phosphorus, and PTH concentrations

Model 2: adjusted for covariables in model 1 plus frailty index (and gait speed among SPRINT participants ≥75 years)