Cinacalcet, Fibroblast Growth Factor-23, and Cardiovascular Disease in Hemodialysis

The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial

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Background—Patients with kidney disease have disordered bone and mineral metabolism, including elevated serum concentrations of fibroblast growth factor-23 (FGF23). These elevated concentrations are associated with cardiovascular and all-cause mortality. The objective was to determine the effects of the calcimimetic cinacalcet (versus placebo) on reducing serum FGF23 and whether changes in FGF23 are associated with death and cardiovascular events.

Methods and Results—This was a secondary analysis of a randomized clinical trial comparing cinacalcet to placebo in addition to conventional therapy (phosphate binders/vitamin D) in patients receiving hemodialysis with secondary hyperparathyroidism (intact parathyroid hormone ≥300 pg/mL). The primary study end point was time to death or a first nonfatal cardiovascular event (myocardial infarction, hospitalization for angina, heart failure, or a peripheral vascular event). This analysis included 2985 patients (77% of randomized) with serum samples at baseline and 2602 patients (67%) with samples at both baseline and week 20. The results demonstrated that a significantly larger proportion of patients randomized to cinacalcet had ≥30% (68% versus 28%) reductions in FGF23. Among patients randomized to cinacalcet, a ≥30% reduction in FGF23 between baseline and week 20 was associated with a nominally significant reduction in the primary composite end point (relative hazard, 0.82; 95% confidence interval, 0.69–0.98), cardiovascular mortality (relative hazard, 0.66; 95% confidence interval, 0.50–0.87), sudden cardiac death (relative hazard, 0.57; 95% confidence interval, 0.37–0.86), and heart failure (relative hazard, 0.69; 95% confidence interval, 0.48–0.99).

Conclusions—Treatment with cinacalcet significantly lowers serum FGF23. Treatment-induced reductions in serum FGF23 are associated with lower rates of cardiovascular death and major cardiovascular events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00345839.

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Mineral metabolism is altered early in the course of chronic kidney disease (CKD)[1] as documented by elevations in the serum concentrations of fibroblast growth factor-23 (FGF23) and parathyroid hormone (PTH) in 70% and 30%, respectively, of patients with estimated glomerular filtration rate of 50 mL·min^{-1}·1.73 m^{-2}. The levels of both hormones continue to rise over time as CKD progresses, presumably to maintain normal concentrations of phosphate and calcium

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in serum. In patients with CKD, elevated serum concentrations of FGF23 are associated with mortality,[2] progression of CKD,[2,3] left ventricular hypertrophy,[4,5] and cardiovascular events[6,7] independently of phosphate, PTH, and a variety of demographic and other clinical factors.

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Among patients with end-stage renal disease receiving dialysis, levels of FGF23 can be increased by 2 to 3 orders of magnitude. Among patients with exceptionally high serum FGF23 concentrations, higher levels remain associated with poorer survival[8–10] and ventricular hypertrophy.[11] In animal models, FGF23 induces cardiomyocyte hypertrophy[4] and acutely increases intracellular free calcium with possible induction of arrhythmias,[12] suggesting a direct role in cardiovascular disease. High serum concentrations of phosphate, PTH, calcium, and 1,25 dihydroxy vitamin D (calcitriol) stimulate FGF23. Preliminary studies show that the calcimimetic cinacalcet lowers FGF23 in patients receiving dialysis.[13,14] However, it is unknown whether therapies that may lower serum FGF23 concentrations improve outcomes. We examined this question in the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) trial. We hypothesized that treatment with cinacalcet (Sensipar/Mimpara) would reduce serum FGF23 concentrations compared with baseline and that patients treated with cinacalcet who experienced a significant reduction in FGF23 would experience fewer deaths and cardiovascular events than those whose serum FGF23 remained unchanged or increased.

Methods

Study Population and Design

A total of 3883 patients with secondary hyperparathyroidism (intact PTH ≥300 pg/mL) receiving hemodialysis were enrolled in the EVOLVE trial. The trial was designed to assess the benefits and risks of treatment with cinacalcet compared with placebo in addition to standard of care (calcitriol or vitamin D analogs and phosphate binders) on the primary composite end point of mortality and major cardiovascular events (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event). Study design,[15] baseline characteristics,[16] and primary results, including a CONSORT (Consolidated Standards of Reporting Trials) diagram,[17] have previously been published. The trial was sponsored by Amgen Inc and was led by an academic Executive Committee with direct oversight of all final analyses and publications. The Executive Committee had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the writing of this report. Approval from ethics committees at all participating sites and informed consent from all patients were obtained.

During the trial, additional serum samples were obtained at prespecified visits in 394 of 467 sites. Serum FGF23 concentrations were measured from these stored samples by a Luminex-based microbead assay (HBNMAG-51K, Millipore, Billerica, MA) that uses polyclonal capture and detection antibodies. The levels with the Millipore assay were tightly correlated with levels by the Kainos intact assay (Figure I in the online-only Data Supplement) in internal validation studies performed at Amgen. The comparison revealed normal serum values for healthy adults (median) for serum FGF23 was 30 pg/mL (25th–75th percentile, 24–40 pg/mL) with the Kainos ELISA and 12 pg/mL (25th–75th percentile, 8–42 pg/mL) with the Millipore assay. The Millipore assay demonstrated better overall percent recovery of human FGF23 spiked into human sera (80% versus 56% for 1 ng/mL). The intra-assay coefficient of variation (the ratio of the standard deviation to mean) was 12% for both assays; the interassay coefficient of variation was 13% for Millipore and 7% for Kainos.

All other demographic and laboratory data analyzed were collected with the primary EVOLVE trial.[16–18] All end points were adjudicated by an independent Clinical Events Committee.

Statistical Analysis

As previously reported,[17] the primary analysis of the main study (an unadjusted log-rank test using the intention-to-treat approach) did not reach significance. Among the goals of this post hoc analysis was the assessment of whether baseline serum FGF23 concentrations and changes in FGF23 concentrations in patients treated with cinacalcet were associated with death and major cardiovascular events as defined in the primary trial.

To test the associations among baseline serum FGF23 concentrations and the effect of reductions in FGF23 observed in patients treated with cinacalcet on outcomes, relative hazards and 95% confidence intervals were calculated with Cox proportional hazards regression, stratified by country and diabetes status. The association of baseline FGF23 (week 0; log transformed) with outcomes was evaluated with multivariable Cox regression using a backward selection procedure. Other baseline variables evaluated in this model were those used in the multivariable regression analysis from the primary analyses.[17] The analysis was performed on all patients with baseline serum FGF23 values, representing 77% of the original cohort.

To examine changes in FGF23, we identified a subset of patients who had serum from both weeks 0 and week 20 that allowed measurement of FGF23 values. The 20-week time point was selected because 91% of patients randomized to cinacalcet were still maintained on their original treatment assignment and the majority of patients had samples drawn at this time point. FGF23 values at weeks 0, 20 and 100 were summarized descriptively using the FGF23 cohort. We compared values between randomized treatment groups at week 20 using the Wilcoxon rank-sum test. We also generated Pearson correlation coefficients to assess the relation among changes in serum FGF23 and changes in plasma PTH, corrected serum calcium, and serum phosphate.

We examined the effect of changes in FGF23 from baseline to week 20 on subsequent outcomes within the groups randomized to cinacalcet or placebo using multivariable Cox regression analysis. Variables identified in a univariate analysis as possible confounders[19] (ie, if the variable changed the point estimate for FGF23 by >10% or was associated with the outcome) were included in the final model. We adjusted for baseline FGF23, sex, race, vascular access, smoking, and week 20 covariates (age, blood pressure, dialysis vintage, previous medical history, the cumulative paricalcitol equivalent dose of vitamin D sterols, the Quételet index [body mass index], and percent reduction from baseline in FGF23). We a priori considered a ≥30% reduction in FGF23 to represent a meaningful decline because a ≥30% reduction in PTH has been used clinically to assess the efficacy of pharmacological therapies used to treat secondary hyperparathyroidism.[20,21] We also examined associations with a ≥50% decline in FGF23 in patients randomized to the cinacalcet group. The proportion of patients achieving these reductions were compared between the 2 treatment groups by use of a χ^2 test.

Finally, aiming to understand the relations among change in FGF23 and changes in other biochemical measures of CKD–mineral bone disorder (MBD), we categorized patients into below target, within target, and above target categories for PTH, calcium, and phosphate on the basis of the Kidney Disease Outcomes Quality Initiative (K/DOQI) CKD-MBD guidelines[22] at 20 weeks and determined the percent change in FGF23 for patients in each of these categories.

The analyses presented here are not adjusted for multiplicity, and we considered 2-tailed values of $P<0.05$ statistically significant in this post hoc analysis. We conducted all statistical analyses using SAS 9.3 (SAS Institute Inc, Cary, NC).

Results

Baseline Serum FGF23 Levels Predict Mortality

Of the 3883 randomized patients, 2985 (77%) had baseline serum FGF23 concentrations and 2602 (67%) had both baseline and week 20 values; the latter represents the week 20 FGF23 cohort. Differences in baseline characteristics of patients in the original cohort,[17] FGF23 baseline cohort, and week 20 FGF23 cohort were minor (Table 1). After adjustment for baseline characteristics in a multivariable Cox regression analysis, higher baseline serum FGF23 concentrations were associated with an increased risk of the primary composite end point of the EVOLVE trial (death or first myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event; Table 2). Although higher baseline FGF23 concentrations were associated with death or major cardiovascular events, baseline FGF23 concentrations did not modify the effect of cinacalcet on death or major cardiovascular events [log(FGF23)×treatment interaction; P=0.75].

Cinacalcet Decreases Serum FGF23 Concentrations

Median baseline serum FGF23 concentrations were 5555 pg/mL (10th–90th percentiles, 600–19 380 pg/mL) and 5600 pg/mL (10th–90th percentiles, 570–19 380 pg/mL) in patients randomized to cinacalcet and placebo, respectively (P=0.86). At week 20, FGF23 values were 2255 pg/mL (10th–90th percentiles, 170–14 470 pg/mL) in cinacalcet-treated patients compared with 5580 pg/mL (10th–90th percentiles, 550–19 710 pg/mL) in placebo-treated patients (P<0.001). Figure 1 shows the serum FGF23 concentrations in patients randomized to cinacalcet or placebo at baseline, week 20, and week 100, showing sustained suppression in patients randomized to cinacalcet. A significantly larger proportion of patients randomized to cinacalcet compared with placebo had a reduction in serum FGF23 ≥30% (64% versus 28%) or ≥50% (50% versus 15%; P<0.001 for both comparisons). The reduction in serum FGF23 in patients randomized to cinacalcet was observed regardless of whether patients also received calcitriol or other vitamin D sterols. The percent change in FGF23 correlated directly with the percent change in PTH (r=0.214, P<0.001), albumin-corrected serum calcium (r=0.378, P<0.001), and serum phosphate (r=0.519, P<0.001).

Reduction in FGF23 Is Associated With Reduced Cardiovascular Mortality and Morbidity

Characteristics of patients who did or did not achieve a ≥30% reduction in FGF23 by randomized treatment group are shown in Table 3. Characteristics of patients who did or did not achieve a ≥50% reduction in FGF23 by randomized treatment group are shown in Table I in the online-only Data Supplement. As shown in Figure 2, among patients randomized to cinacalcet, a ≥30% reduction in serum FGF23 between baseline and week 20 was associated with a reduction in the relative hazard (after week 20) of the primary composite end point, cardiovascular mortality, sudden cardiac death, heart failure, and the tertiary cardiovascular composite end point (CV death, myocardial infarction, heart failure, and hospitalization for unstable angina). Follow-up time from baseline was 4.2 years (1.0–5.0 years) and from week 20 was 3.9 years (1.0–4.6 years). The associations among FGF23 reduction and all-cause mortality, classic atherosclerotic end points (myocardial infarction, unstable angina, peripheral vascular event, and stroke), fracture, and parathyroidectomy were not statistically significant. A ≥50% reduction in FGF23 in the patients randomized to cinacalcet showed similar results with a more pronounced association with the heart failure end point (Figure 3). Among patients randomized to placebo, a ≥30% reduction in FGF23 in patients was not associated with a reduction in cardiovascular events compared with patients with a <30% reduction in FGF23 (Figure II in the online-only Data Supplement).

Association of PTH, Calcium, and Phosphate With FGF23 Reduction

To understand the interrelations among many of the biochemical parameters of CKD-MBD in patients with secondary hyperparathyroidism, we performed the following exploratory analysis. We categorized patients as below target, within target, or above target for PTH, calcium, and phosphate per the K/DOQI guidelines and determined the percent change in FGF23 within each group (Figure 4A and 4B). For the 3 measured parameters of mineral metabolism, values below the K/DOQI target range were associated with more pronounced reductions in FGF23 levels in patients randomized to cinacalcet.

Discussion

Cinacalcet is known to lower serum PTH while also lowering serum calcium. In the present study, we showed that cinacalcet also reduced serum FGF23, and this decrease was associated with lower risks of cardiovascular mortality and selected cardiovascular events, including heart failure and sudden death. Whether the observed associations in the present study were a direct effect of FGF23 or an indirect effect cannot be discerned. However, the observation was independent of demographic factors and comorbid conditions; reductions in serum PTH, calcium, or phosphate; and the cumulative dose of vitamin D sterols.

FGF23 is involved in the regulation of mineral metabolism, stimulating phosphaturia, decreasing the synthesis of 1,25 dihydroxy vitamin D, and inhibiting PTH secretion. FGF23 is upregulated in response to 1,25 dihydroxy vitamin D, PTH, calcium, and possibly phosphate. Therefore, the management of CKD-MBD is difficult in that the intended improvement of one parameter often leads to unwanted alterations in other parameters. Another randomized trial showed that cinacalcet, but not calcitriol, significantly lowered FGF23 even after accounting for changes in serum calcium and phosphate.[23] We conducted exploratory analyses to attempt to determine whether the FGF23 lowering in the present study was dependent on other known modifiers of FGF23 secretion. Figure 4 shows more pronounced reductions in FGF23 in patients with larger reductions of PTH, calcium, and phosphate, even to levels considered below target by K/DOQI.[22] In patients with serum calcium concentrations above K/DOQI targets, because of either unremitting tertiary hyperparathyroidism or poor adherence, randomization to cinacalcet resulted in very little FGF23 lowering. In rodents with CKD, calcium treatment increases FGF23 but also lowers PTH.[24] Thus, it is unclear whether the FGF23 lowering is directly mediated by calcium or indirectly

Table 1. Baseline Characteristics of Patients Overall and in the FGF23 Cohorts

Demographics	All Patients in Study (n=3883)	Baseline		Baseline and Week 20	
		Baseline FGF23 Cohort (n=2985)	Not in Baseline FGF23 Cohort (n=898)	Week 20 FGF23 Cohort (n=2602)	Not in Week 20 FGF23 Cohort (n=1281)
Age, y					
Median	55.0	54.0	56.0	54.0	56.0
10th, 90th percentile	35.0, 73.0	34.0, 73.0	36.0, 74.0	35.0, 73.0	35.0, 74.0
Female sex, %	40.6	40.7	40.5	40.5	41.0
Race or ethnic group, %					
White	57.7	58.0	56.6	57.6	57.8
Black	21.6	20.1	26.5	20.2	24.4
Other	20.8	21.9	16.9	22.2	17.9
Body mass index, kg/m^2					
Median	26.3	26.2	26.6	26.3	26.5
10th, 90th percentile	20.5, 36.6	20.4, 36.5	20.8, 36.8	20.4, 36.6	20.7, 36.5
Dialysis, mo					
Median	45.3	46.7	39.2	47.2	41.1
10th, 90th percentile	9.1, 145.9	9.4, 147.4	8.4, 135.1	9.5, 148.0	8.5, 134.2
Blood pressure, mm Hg					
Systolic					
Median	140	140	143	140	142
10th, 90th percentile	110, 177	110, 176	116, 178	110, 176	114, 177
Diastolic					
Median	80	80	80	80	80
10th, 90th percentile	60, 100	60, 100	60, 99	60, 100	60, 100
Medical history					
History of diabetes mellitus, %	33.5	31.6	40.0	31.2	38.2
Type 1	4.0	3.9	4.3	3.7	4.4
Type 2	29.6	27.8	35.6	27.6	33.7
History of cardiovascular disease, %	95.0	94.6	96.2	94.6	95.8
Hypertension	92.1	91.5	94.1	91.6	93.2
Heart failure	23.3	22.7	25.3	21.8	26.4
Peripheral vascular disease	16.4	15.8	18.0	15.6	17.9
CABG	7.4	7.3	8.0	7.0	8.3
PCI	6.7	6.8	6.7	6.6	7.1
Myocardial infarction	12.4	12.4	12.7	11.9	13.5
Stroke	9.1	8.8	10.1	8.9	9.6
Transient ischemic attack	4.5	4.3	5.1	4.3	4.8
Amputation	6.4	5.9	8.1	5.9	7.6
Atrial fibrillation	11.0	11.2	10.4	11.0	11.0
History of parathyroidectomy, %	4.6	4.7	4.1	5.0	3.7
History of fracture, %	19.8	19.5	20.7	19.6	20.3
Laboratory parameters					
iPTH, pg/mL					
Median	693	703	668	701	682
10th, 90th percentile	363, 1694	370, 1734	341, 1538	367, 1751	354, 1588
Corrected calcium, mg/dL					
Median	9.8	9.8	9.8	9.8	9.8
10th, 90th percentile	9.0, 10.7	9.0, 10.7	9.0, 10.7	9.0, 10.7	9.0, 10.7

(*Continued*)

Table 1. Continued

Demographics	All Patients in Study (n=3883)	Baseline		Baseline and Week 20	
		Baseline FGF23 Cohort (n=2985)	Not in Baseline FGF23 Cohort (n=898)	Week 20 FGF23 Cohort (n=2602)	Not in Week 20 FGF23 Cohort (n=1281)
Phosphate, mg/dL					
Median	6.2	6.2	6.2	6.3	6.2
10th, 90th percentile	4.9, 8.4	4.9, 8.4	4.9, 8.3	4.9, 8.4	4.9, 8.4
Calcium×phosphate, mg^2/dL^2					
Median	60.7	60.8	60.4	60.8	60.5
10th, 90th percentile	47.8, 81.9	47.8, 81.9	47.7, 81.8	47.9, 81.8	47.6, 82.2
FGF23, pg/mL					
Median	5590	5590	NA	5590	NA
10th, 90th percentile	580, 19540	580, 19540	NA, NA	590, 19380	NA, NA
25(OH) D, ng/mL					
Median	17	17	17	18	17
10th, 90th percentile	8, 37	8, 37	8, 38	8, 37	8, 37
1,25 $(OH)_2$ D, pg/mL					
Median	8.8	8.6	9.2	8.6	8.9
10th, 90th percentile	4.9, 23.5	4.9, 23.3	4.9, 23.7	4.9, 23.4	4.9, 23.5
Bone-specific alkaline phosphatase, μg/L					
Median	23.03	22.94	23.25	22.92	23.24
10th, 90th percentile	11.51, 68.00	11.39, 70.21	11.87, 62.79	11.37, 69.16	11.75, 66.06
Albumin, g/dL					
Median	3.7	3.7	3.6	3.7	3.7
10th, 90th percentile	3.2, 4.1	3.2, 4.1	3.2, 4.1	3.2, 4.1	3.2, 4.1
Cholesterol (mg/dL)					
Total					
Median	162	163	159	163	159
10th, 90th percentile	115, 223	116, 224	114, 221	117, 223	114, 224
LDL					
Median	86	87	84	87	84
10th, 90th percentile	48, 138	48, 138	47, 138	49, 138	47, 140
HDL					
Median	41	41	40	41	40
10th, 90th percentile	27, 62	27, 62	28, 62	27, 62	28, 61
Medications, %					
Vitamin D use	59.5	59.7	58.9	60.1	58.3
Vitamin D sterol	58.2	58.2	58.2	58.6	57.5
Nutritional vitamin D	2.9	3.4	1.3	3.6	1.6
Phosphate binder use	88.4	88.8	87.1	89.3	86.6
Calcium-containing	53.1	53.8	50.9	54.8	49.7
Non–calcium-containing	35.3	35.0	36.2	34.6	36.8
β-Adrenergic antagonists	46.9	45.8	50.8	46.3	48.3
ACE inhibitors/angiotensin II receptor blockers	43.8	43.1	46.1	43.3	44.7
Antiplatelet agents	37.9	36.8	41.4	36.3	41.0
Statins	32.5	30.6	38.6	30.5	36.5
Erythropoietin	85.0	85.5	83.1	85.2	84.5
Iron supplements	56.9	58.4	52.0	58.7	53.3

n is the number of randomized patients. Percentages are based on n. ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass graft; FGF23, fibroblast growth factor-23; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; NA, not applicable; and PCI, percutaneous coronary intervention.

Table 2. Multivariable Cox Regression Model on Time to Primary Composite End Point

Parameters	Hazard Ratio (95% CI)	*P* Value
Treatment (cinacalcet/placebo)	0.88 (0.79–0.98)	0.02
Baseline FGF23 per 1-SD increase (log-scale)	1.16 (1.10–1.23)	<0.001
Age, y	1.03 (1.03–1.04)	<0.001
Baseline serum albumin per 1-SD difference	0.84 (0.80–0.89)	<0.001
History of peripheral vascular disease	1.37 (1.20–1.57)	<0.001
Systolic blood pressure per 10 mm Hg	1.02 (1.00–1.05)	0.06
Dialysis vintage	1.01 (1.00–1.03)	0.01
History of heart failure	1.23 (1.08–1.39)	<0.01
History of coronary artery disease	1.49 (1.30–1.70)	<0.001
History of cardiac arrhythmia	1.30 (1.13–1.49)	<0.001
History of valvular heart disease or angina	1.26 (1.11–1.43)	<0.001
History of transient ischemic attack	1.28 (1.02–1.61)	0.03
History of dyslipidemia	0.87 (0.77–0.98)	0.02
Tobacco use (reference=never)		
Former	1.12 (0.99–1.26)	0.07
Current	1.62 (1.40–1.88)	<0.001

Baseline variables were included using backward elimination regression analysis. CI indicates confidence interval; and FGF23, fibroblast growth factor-23.

through PTH. Other studies demonstrated that lower serum calcium resulted in lower serum FGF23 concentrations, thereby preventing FGF23 suppression of PTH secretion.[25] The analyses shown here are consistent with observations in rodents that calcium may be involved in the regulation of FGF23.

The FGF23 lowering by cinacalcet appeared to be related to reductions in predominantly nonatherosclerotic cardiovascular events, with the most pronounced reduction in heart failure and sudden cardiac death events. The mechanisms by which a reduction in FGF23 or cinacalcet reduces the risks of heart failure and sudden cardiac death are likely multifactorial. First, FGF23 is a direct cardiotropic hormone, inducing cardiomyocyte hypertrophy and cell signaling, consistent with activation of fetal (growth) pathways.[4] Faul et al[4] demonstrated that progression of left ventricular hypertrophy was more pronounced in patients with CKD with higher serum FGF23 concentrations and that the change in serum FGF23 predicted the magnitude of change in left ventricular mass. In the 5/6-nephrectomy rat model, treatment with the calcimimetic R-568 or enalapril improved cardiac fibrosis, and the effects were additive.[26] In a small study of patients receiving hemodialysis, treatment with cinacalcet improved diastolic dysfunction and reduced left ventricular mass index.[27] Second, cinacalcet may reduce cardiac and arterial calcification. In rodent models, treatment with a calcimimetic lowered heart calcium content compared with control animals, whereas calcimimetic plus calcium did not.[28] Other studies showed that calcimimetics reduced arterial calcification compared with calcitriol and paricalcitol.[29,30] In a randomized trial of patients receiving hemodialysis, treatment with cinacalcet and low-dose vitamin D compared with flexible doses of vitamin D alone slowed the progression of coronary artery calcification on electron-beam computed tomography, with nominally significant changes as assessed with the volumetric method of

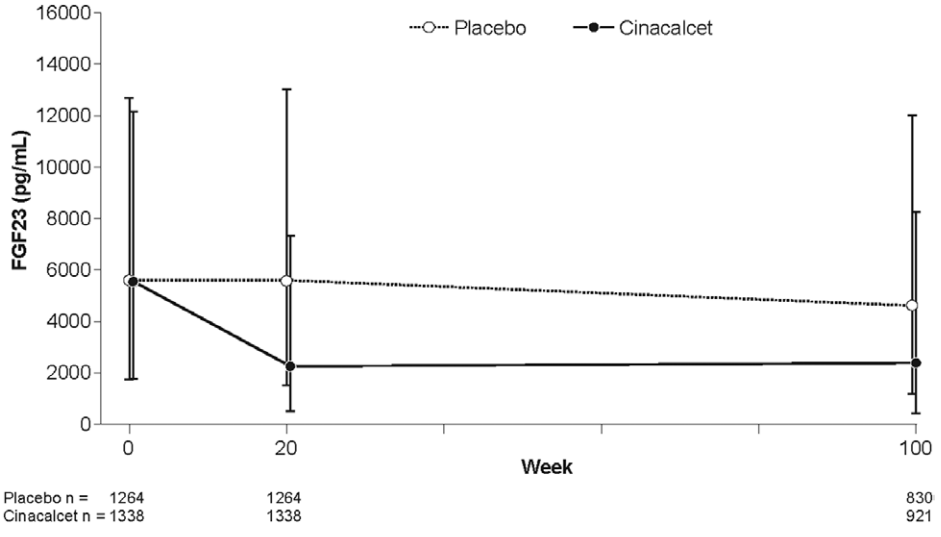

Figure 1. Median (quartiles 1 and 3) fibroblast growth factor-23 (FGF23) values from baseline and weeks 20 and 100 (FGF23 cohort). The reduction of FGF23 with cinacalcet occurred within the first 20 weeks and was maintained throughout the study. In the patients randomized to cinacalcet, 91% were receiving study drug at 20 weeks and 79% at 100 weeks. In the patients randomized to placebo, 3% of patients had been placed on commercial cinacalcet at 20 weeks and 13% at 100 weeks.

Table 3. Baseline Characteristics in Randomized Patients by Achievement of ≥30% Reduction in FGF23 From Baseline to Week 20

	Placebo (n=1264)			Cinacalcet (n=1338)		
Demographics	<30% Reduction (n=910)	≥30%Reduction (n=354)	*P* Value	<30% Reduction (n=477)	≥30% Reduction (n=861)	*P* Value
Age, y			0.72			0.08
Median	54.0	54.0		53.0	55.0	
10th, 90th percentile	35.0, 72.0	34.0, 74.0		32.0, 74.0	35.0, 74.0	
Female sex, %	38.4	43.5	0.09	38.6	42.5	0.16
Race or ethnic group, %			0.45			0.53
White	58.0	54.2		56.6	59.2	
Black	19.8	20.9		20.3	20.2	
Other	22.2	24.9		23.1	20.6	
Body mass index, kg/m^2			0.37			0.03
Median	26.4	26.1		26.8	26.0	
10th, 90th percentile	20.7, 37.0	20.2, 36.0		20.5, 37.6	20.1, 35.9	
Dialysis vintage, mo			0.06			<0.001
Median	46.0	52.0		39.9	50.6	
10th, 90th percentile	9.7, 153.9	12.7, 139.4		7.3, 145.0	10.7, 147.9	
Blood pressure, mm Hg						
Systolic			0.11			0.02
Median	140	145		140	140	
10th, 90th percentile	110, 177	111, 180		111, 178	110, 174	
Diastolic			0.11			0.06
Median	80	80		80	80	
10th, 90th percentile	60, 100	61, 100		60, 100	59, 98	
Medical history						
History of diabetes mellitus, %	31.6	30.8	0.77	31.9	30.7	0.65
Type 1	4.2	3.7		3.4	3.5	
Type 2	27.5	27.4		28.5	27.2	
History of cardiovascular disease, %	94.9	92.4	0.08	95.6	94.5	0.40
Hypertension	92.2	89.5	0.13	90.6	92.3	0.26
Heart failure	21.8	22.3	0.83	22.6	21.3	0.56
Peripheral vascular disease	16.3	15.3	0.66	13.4	16.3	0.17
CABG	7.6	6.2	0.40	6.5	7.1	0.69
PCI	6.6	5.9	0.67	7.8	6.2	0.26
Myocardial infarction	11.4	12.4	0.62	10.9	12.8	0.31
Stroke	10.2	10.5	0.90	7.5	7.7	0.94
Transient ischemic attack	4.1	3.4	0.59	6.1	3.9	0.08
Amputation	6.4	5.9	0.77	5.0	5.8	0.55
Atrial fibrillation	11.6	11.6	0.97	11.9	9.5	0.16
History of parathyroidectomy, %	5.4	4.5	0.53	3.8	5.5	0.17
History of fracture, %	21.6	18.6	0.24	18.9	18.1	0.74
Laboratory parameters						
PTH, pg/mL			0.35			<0.001
Median	685	731		658	740	
10th, 90th percentile	364, 1678	373, 1835		360, 1523	376, 1951	
Corrected calcium (mg/dL)			0.34			0.18
Median	9.8	9.7		9.7	9.8	
10th, 90th percentile	9.0, 10.8	9.0, 10.6		9.0, 10.8	9.0, 10.7	

(*Continued*)

Table 3. Continued

Demographics	Placebo (n=1264) <30% Reduction (n=910)	Placebo (n=1264) ≥30%Reduction (n=354)	*P* Value	Cinacalcet (n=1338) <30% Reduction (n=477)	Cinacalcet (n=1338) ≥30% Reduction (n=861)	*P* Value
Phosphate (mg/dL)			0.20			0.66
Median	6.2	6.3		6.2	6.3	
10th, 90th percentile	4.9, 8.4	5.0, 8.5		4.8, 8.5	5.0, 8.2	
Calcium×phosphate, mg^2/dL^2			0.12			0.54
Median	60.3	61.8		60.9	60.8	
10th, 90th percentile	47.3, 82.1	49.4, 81.7		47.0, 82.3	48.9, 81.2	
FGF23, pg/mL			0.03			0.22
Median	5305	6465		5710	5500	
10th, 90th percentile	530, 18510	870, 21680		340, 20290	750, 18910	
25 (OH) D, ng/mL			0.61			0.87
Median	18	18		17	18	
10th, 90th percentile	8, 38	8, 37		8, 37	8, 38	
1,25 $(OH)_2$ D, pg/mL			0.64			0.04
Median	9.1	8.3		9.5	8.2	
10th, 90th percentile	4.9, 22.3	4.9, 21.8		4.9, 25.0	4.9, 23.7	
Bone-specific alkaline phosphatase, μg/L			<0.001			<0.001
Median	21.52	26.02		19.00	25.67	
10th, 90th percentile	10.99, 61.76	12.08, 79.20		10.79, 57.07	12.05, 88.98	
Albumin, g/dL			0.78			0.25
Median	3.7	3.7		3.6	3.7	
10th, 90th percentile	3.2, 4.1	3.2, 4.1		3.2, 4.1	3.2, 4.1	
Cholesterol, mg/dL						
Total			0.55			0.58
Median	165	164		161	162	
10th, 90th percentile	117, 225	118, 223		115, 225	117, 221	
LDL			0.07			0.74
Median	89	84		87	86	
10th, 90th percentile	52, 137	50, 138		48, 136	47, 139	
HDL			0.58			0.22
Median	41	41		39	41	
10th, 90th percentile	28, 63	27, 65		27, 59	27, 62	
Medications, %						
Vitamin D use	62.5	55.1	0.02	59.5	59.8	0.92
Vitamin D sterol	61.0	52.3	<0.01	58.7	58.5	0.95
Nutritional vitamin D	3.6	4.5	0.46	3.4	3.3	0.92
Phosphate binder use	89.7	90.4	0.70	86.4	90.1	0.04
Calcium-containing	54.8	55.4		55.1	54.2	
Non–calcium containing	34.8	35.0		31.2	35.9	
β-Adrenergic antagonists	46.3	39.8	0.04	48.6	47.6	0.72
ACE inhibitors/angiotensin II receptor blockers	42.1	41.0	0.72	46.1	44.0	0.46
Antiplatelet agents	34.8	37.9	0.32	36.7	37.0	0.90
Statins	29.0	32.2	0.27	30.4	31.4	0.72
Erythropoietin	83.8	84.2	0.88	86.0	86.6	0.73
Iron supplements	57.6	56.2	0.66	60.2	60.0	0.97

n is the number of randomized patients. Percentages are based on n. The Wilcoxon rank-sum test was used for continuous variables, and the χ^2 test was used for categorical variables. ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass graft; FGF23, fibroblast growth factor-23; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; and PTH, parathyroid hormone.

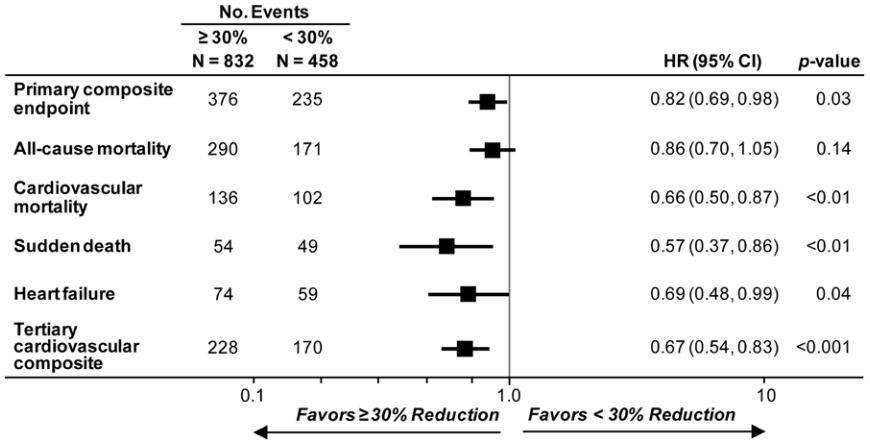

Figure 2. Relative hazard (HR) of achieving a ≥30% reduction in fibroblast growth factor-23 (FGF23) from baseline to week 20 vs not achieving such a reduction on clinical outcomes (patients randomized to cinacalcet from FGF23 cohort). Stratified by history of diabetes mellitus and country and adjusted for baseline FGF23, sex, race, vascular access, smoking, and week 20 covariates (age, blood pressure, dialysis vintage, medical history, cumulative paricalcitol equivalent dose of vitamin D sterols, body mass index, and percent reduction from baseline in FGF23). Patients with missing covariates are excluded. Annualized event rates for patients with ≥30% versus <30% reduction: primary composite end point, 13.7 (95% confidence interval [CI], 12.4–15.0) vs 16.2 (95% CI, 14.4–18.2); all-cause mortality, 9.6 (95% CI, 8.6–10.7) vs 10.2 (95% CI, 8.8–11.8); cardiovascular mortality, 4.6 (95% CI, 3.9–5.5) vs 6.2 (95% CI, 5.1–7.5); sudden death, 1.9 (95% CI, 1.4–2.4) vs 3.0 (95% CI, 2.3–4.0); heart failure, 2.7 (95% CI, 2.1–3.3) vs 4.0 (95% CI, 3.1–5.1); and tertiary cardiovascular composite, 8.2 (95% CI, 7.3–9.3) vs 11.7 (95% CI, 10.1–13.4).

evaluation.[31] Large-artery calcification will lead to arterial stiffness and increased afterload pressure, contributing to left ventricular hypertrophy. Third, elevated levels of FGF23 are associated with endothelial dysfunction.[32] Finally, it remains possible that activation of the calcium-sensing receptor with cinacalcet has direct effects on left ventricular hypertrophy and arterial smooth muscle calcification.[33,34] In isolated cardiomyocytes, activation of the calcium-sensing receptor with increased extracellular calcium or a calcimimetic induced an increase in intracellular calcium and calcineurin/nuclear factor of activated T cells signaling, pathways known to be involved in arrhythmias and left ventricular hypertrophy.[35] However, we cannot discern true mechanisms from this study; thus, the results must be considered hypothesis generating.

There are several strengths to these analyses, including the relatively large sample size (the randomized trial largest in size and longest in duration ever conducted in the hemodialysis population); diverse patient population; broad range of severity of hyperparathyroidism; detailed clinical assessment; allowing for adjustment by baseline demographic, clinical, and laboratory variables; stringent control of the FGF23 assay; and most important, independent adjudication of all major end points. There are also several important limitations. First, baseline and week 20 FGF23 values were not available

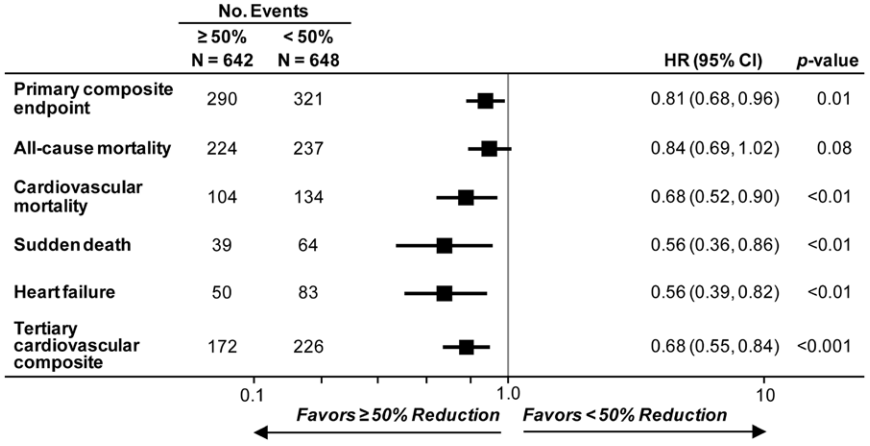

Figure 3. Relative hazard of achieving a ≥50% reduction in fibroblast growth factor-23 (FGF23) from baseline to week 20 vs not achieving such a reduction on clinical outcomes (patients randomized to cinacalcet from FGF23 cohort). Stratified by history of diabetes mellitus and country and adjusted for baseline FGF23, sex, race, vascular access, smoking, and week 20 covariates (age, blood pressure, dialysis vintage, medical history, cumulative paricalcitol equivalent dose of vitamin D sterols, body mass index, and percent reduction from baseline in FGF23). Patients with missing covariates are excluded. Annualized event rates for patients with ≥50% vs <50% reduction: primary composite end point, 13.6 (95% confidence interval [CI], 12.2–15.1) vs 15.5 (95% CI, 14.0–17.1); all-cause mortality, 9.6 (95% CI, 8.4–10.8) vs 10.1 (95% CI, 8.9–11.4); cardiovascular mortality, 4.6 (95% CI, 3.8–5.5) vs 5.8 (95% CI, 4.9–6.9); sudden death, 1.7 (95% CI, 1.2–2.4) vs 2.8 (95% CI, 2.2–3.6); heart failure, 2.3 (95% CI, 1.7–3.1) vs 3.9 (95% CI, 3.2–4.9); and tertiary cardiovascular composite, 8.0 (95% CI, 6.9–9.3) vs 10.9 (95% CI, 9.6–12.3).

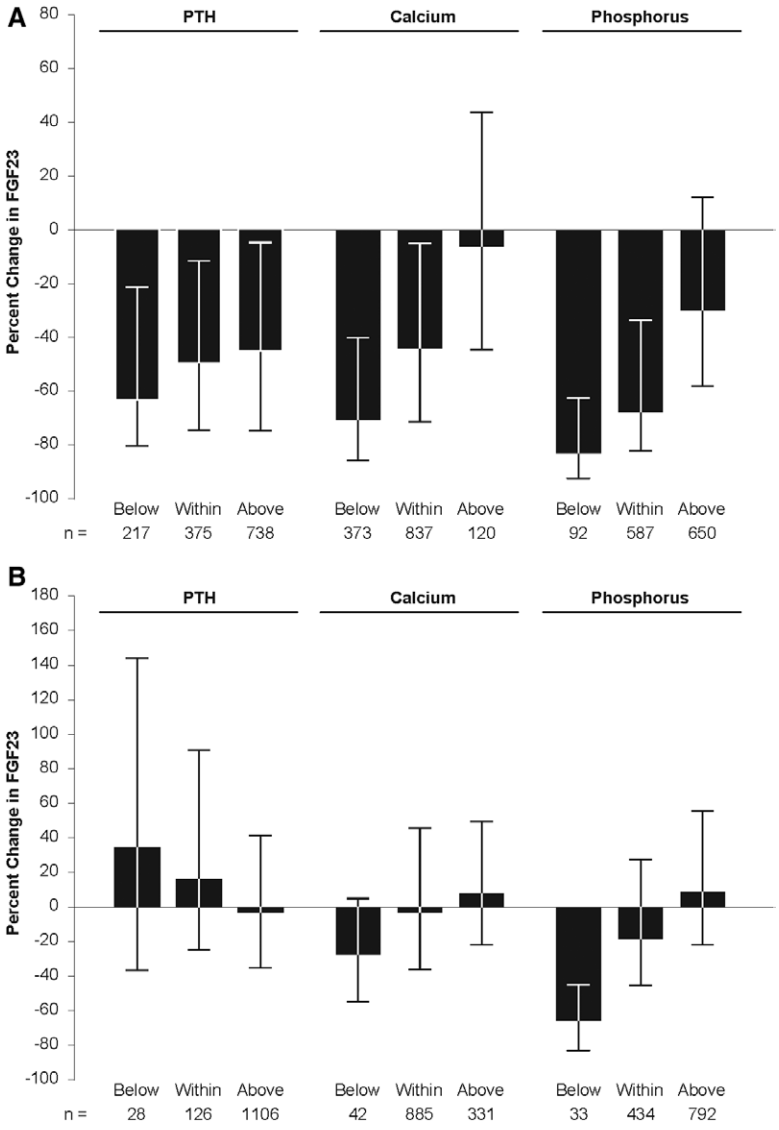

Figure 4. Patients randomized to cinacalcet in the fibroblast growth factor-23 (FGF23) cohort. Exploratory analyses to examine the relationship of changes in parathyroid hormone (PTH), calcium, and phosphate levels from baseline to week 20 with change in FGF23. The bar graphs represent the median (quartiles 1 and 3) for percent change in FGF23 in patients who achieved PTH, calcium, and phosphate levels below, within, or above 2003 National Kidney Foundation Kidney Disease Outcomes Quality Initiative targets at 20 weeks of treatment with cinacalcet (**A**) or placebo (**B**).

in all trial participants, although clinical characteristics of patients with and without baseline and week 20 FGF23 data were similar. Second, we analyzed the change in FGF23 at 20 weeks, whereas events occurred up to 5 years. Because more than two-thirds of patients discontinued study drug (with >1 in 5 patients randomized to placebo placed on commercial cinacalcet),[17] we elected not to examine outcomes based on changes in FGF23 beyond 20 weeks. Had fewer patients discontinued study drug or had a larger proportion of patients provided serum samples as the trial progressed, we might have been able to derive more precise estimates of the associations among FGF23 concentrations and outcomes, as well as the persistence of the FGF23-lowering effect of cinacalcet. The relatively small number of patients randomized to placebo who experienced ≥30% reduction in FGF23 and differences in cointerventions (eg, parathyroidectomy, changes in phosphate binder type or dose, changes in the provision or dose of calcitriol or vitamin D sterols) could explain why a significant reduction in events in these patients was not observed. Third, we cannot rule out a "healthy responder" effect. In other words, a sizable cinacalcet-induced decline in FGF23 could reflect factors associated with favorable outcomes for which we were unable to adjust. Finally, we arbitrarily chose a 30% reduction in FGF23 as representing a change that was clinically meaningful on the basis of other studies of therapeutics to lower PTH. Additional studies are required to define the optimal FGF23 target reduction or target end value.

Conclusions

In this post hoc analysis of the EVOLVE trial, we confirmed the association between serum FGF23 and cardiovascular events and mortality in a large and diverse population of patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism.[17] We demonstrated an FGF23-lowering effect of cinacalcet that far exceeded that observed in patients treated with placebo, along with conventional agents used to manage CKD-MBD (ie, phosphate binders and vitamin D sterols). In roughly two thirds of patients randomized to cinacalcet, FGF23 declined by at least 30% (in roughly half, the decline was at least 50%). Finally, these sizable reductions in FGF23 were associated with lower risks of the primary composite end point, heart failure events, and sudden death.

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CLINICAL PERSPECTIVE

The results of this study suggest an important kidney-bone-cardiovascular link. Fibroblast growth factor-23 (FGF23) is made in the bone in response to elevated parathyroid hormone and $1,25(OH)_2$-vitamin D and increased dietary intake of phosphorus. FGF23 binds to its receptor and klotho coreceptor in the kidney to increase urinary phosphate and to decrease $1,25(OH)_2$-vitamin D synthesis and in the parathyroid gland to reduce parathyroid hormone secretion as part of a negative feedback loop. In animals, FGF23 directly induces cardiac hypertrophy in a klotho-independent manner. Levels of FGF23 increase with progressive kidney disease and, by the time a patient reaches dialysis, can be 100-fold greater than in individuals without kidney disease. The present study, a secondary analyses of the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial, which randomized patients receiving hemodialysis to cinacalcet versus placebo for the treatment of secondary hyperparathyroidism, demonstrates that cinacalcet reduces serum FGF23 levels. Furthermore, in patients randomized to cinacalcet, a ≥30% decrease in FGF23 was associated with a reduction in mortality, heart failure, and nonatherosclerotic cardiovascular events, including sudden cardiac death. The latter is the leading cause of cardiovascular death in patients undergoing hemodialysis. The present study is the first to demonstrate that a reduction in FGF23 in patients receiving cinacalcet is associated with a reduction in hard clinical end points. It is important to emphasize that this is a secondary analyses and that the mechanisms by which a reduction in FGF23 or cinacalcet reduces the risks of heart failure and sudden cardiac death are likely multifactorial and cannot be discerned by this study.