Effects of Cinacalcet on Fracture Events in Patients Receiving Hemodialysis: The EVOLVE Trial

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ABSTRACT

Fractures are frequent in patients receiving hemodialysis. We tested the hypothesis that cinacalcet would reduce the rate of clinical fractures in patients receiving hemodialysis using data from the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events trial, a placebo-controlled trial that randomized 3883 hemodialysis patients with secondary hyperparathyroidism to receive cinacalcet or placebo for ≤64 months. This study was a prespecified secondary analysis of the trial whose primary end point was all-cause mortality and non-fatal cardiovascular events, and one of the secondary end points was first clinical fracture event. Clinical fractures were observed in 255 of 1935 (13.2%) patients randomized to placebo and 238 of 1948 (12.2%) patients randomized to cinacalcet. In an unadjusted intention-to-treat analysis, the relative hazard for fracture (cinacalcet versus placebo) was 0.89 (95% confidence interval [95% CI], 0.75 to 1.07). After adjustment for baseline characteristics and multiple fractures, the relative hazard was 0.83 (95% CI, 0.72 to 0.98). Using a prespecified lag-censoring analysis (a measure of actual drug exposure), the relative hazard for fracture was 0.72 (95% CI, 0.58 to 0.90). When participants were censored at the time of cointerventions (parathyroidectomy, transplant, or provision of commercial cinacalcet), the relative hazard was 0.71 (95% CI, 0.58 to 0.87). Fracture rates were higher in older compared with younger patients and the effect of cinacalcet appeared more pronounced in older patients. In conclusion, using an unadjusted intention-to-treat analysis, cinacalcet did not reduce the rate of clinical fracture. However, when accounting for differences in baseline characteristics, multiple fractures, and/or events prompting discontinuation of study drug, cinacalcet reduced the rate of clinical fracture by 16%–29%.

Patients with end stage renal disease (ESRD) on dialysis have increased risk of fractures compared with the general population.[1] Fracture incidence rates vary by geographic region, although rates are consistently higher in patients with CKD than matched controls from the same country.[2–6] Depending on the study, 10%–52% of patients receiving dialysis

have experienced one or more fractures (reviewed in Kaji et al.[2] and Kidney Disease Improving Global Outcomes[7]). In nondialysis populations, secondary analyses of fracture studies show increased rates in patients with eGFRs<60 ml/min per 1.73 m[2].[8,9] Risk factors associated with fractures in patients with CKD include older age, female sex, lower serum albumin, prior kidney transplantation, peripheral vascular disease, muscle weakness, falls, and the administration of psychoactive medications.[2,3,10–14] Thus, abnormalities of bone in terms of both quality and quantity, variable biochemical abnormalities, and multiple comorbid conditions are likely to contribute to the pathogenesis of fractures in ESRD. The complexity and nature of CKD-mineral and bone disorder (MBD) may also render conventional therapy for osteoporosis and osteopenia ineffective or possibly harmful in CKD or ESRD.

Secondary hyperparathyroidism is known to be associated with renal osteodystrophy. However, it is unclear whether the incidence of fractures in patients receiving dialysis has decreased in recent years despite active treatment of secondary hyperparathyroidism.[15–18] Most previous studies of fracture in CKD and ESRD were cross-sectional or had limited follow-up, and/or fracture assessment was made from claims data rather than prospectively collected or adjudicated. Importantly, despite the availability and widespread use of phosphate binders and vitamin D sterols, no randomized controlled trials evaluated whether any drug or other therapeutic strategies (*e.g.*, parathyroidectomy) lowered the risk of fracture in CKD and/or ESRD.

The objectives of this analysis were to determine fracture sites, frequency of and risk factors for clinical fracture events, and the effect of cinacalcet on clinical fracture rates in patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism using data from the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial.[19] We hypothesized that secondary hyperparathyroidism is a major cause of bone loss and increased bone fragility, and therefore treatment with cinacalcet would reduce clinical fractures.

RESULTS

Baseline Characteristics
The baseline characteristics of the population,[20] trial design,[21] disposition of trial participants (Consolidated Standards of Reporting Trials diagram), primary results,[22]

and effect on the risk of severe unremitting hyperparathyroidism[23] were previously published. The trial population was diverse in terms of age, sex, race/ethnicity, and comorbidity; the median dialysis vintage was 45.3 months.[22] Baseline demographic, medication, and laboratory values pertinent to fracture risk are listed in Table 1. Using an unadjusted intention-to-treat analysis, the effect of cinacalcet on the primary composite end point, composed of all-cause mortality or first nonfatal cardiovascular event (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event), was not statistically significant (relative hazard, 0.93; 95% confidence interval [95% CI], 0.85 to 1.02).[24]

Fracture Events during the Study
Radiographic imaging was not routinely performed; thus, all fracture events were reported by study sites and thus should be considered clinical fractures. During the trial, 667 fractures

Table 1. Baseline demographics, medical history, medication use, and laboratory values for the EVOLVE study participants

Demographic	Cinacalcet Group (n=1948)	Placebo Group (n=1935)
Age (yr)	55.0 (35.0, 74.0)	54.0 (35.0, 73.0)
Women	41.5	39.7
Body mass index (kg^2/m^2)	26.3 (20.4, 36.4)	26.4 (20.6, 36.7)
Region		
Australia	3.8	3.9
Canada	3.7	3.8
Europe	30.7	30.5
Latin America	17.7	17.7
Russia	7.3	7.2
United States	36.7	37.0
Race		
Black	21.0	22.1
White	57.7	57.7
Other	21.3	20.2
Medical history		
Dialysis vintage (mo)	45.4 (8.5, 142.0)	45.1 (9.8, 149.6)
Tobacco use		
Never	55.7	56.7
Former	28.1	26.7
Current	16.0	16.5
Proton pump inhibitor use	30.2	28.6
Vitamin D use	59.3	59.6
Hormone replacement therapy	7.7	7.3
Calcium-containing phosphate binder use	53.2	53.0
Alcohol use	16.9	18.6
Laboratory parameters		
Serum albumin (g/dl)	3.7 (3.2, 4.1)	3.7 (3.2, 4.1)
Serum BALP (ng/ml)	23.1 (11.5, 71.0)	22.9 (11.5, 66.6)
Serum calcium (mg/dl)	9.8 (9.0, 10.7)	9.8 (9.0, 10.7)
Plasma intact PTH (pg/ml)	694.5 (362.0, 1707.0)	690.0 (363.0, 1683.0)
Serum phosphorus (mg/dl)	6.3 (4.9, 8.3)	6.2 (4.9, 8.4)
Serum 25-hydroxy cholecalciferol (μg/L)	17.0 (8.0, 37.0)	18.0 (8.0, 38.0)

Data are presented as a percentage or median (10th percentile, 90th percentile). Adapted from Chertow et al.[20]

were reported; 622 (93.7%) were adjudicated as true fracture events by the Clinical Events Committee. There were 493 patients that experienced at least one confirmed fracture (255 of 1935 [13.2%] randomized to placebo and 238 of 1948 [12.2%] randomized to cinacalcet). Fifty-nine participants experienced two fractures (29 and 30 in the placebo and cinacalcet groups, respectively) and 29 experienced three or more fractures (14 and 15 in the placebo and cinacalcet groups, respectively).

Fracture Sites

More than one-half of fractures in both groups involved predominantly cortical bone at nonhip sites. Supplemental Table 1 shows the total number of fracture events by site and incidence rates stratified by age, sex, and race. Figure 1 shows the unadjusted incidence of fractures by site, age, and randomized treatment assignment. Vertebral fractures were recorded in only 1.2% of the total patient population, in a total of 51 fracture events, almost certainly an underestimate because screening radiographs were not performed.

Clinical Fracture Rates

Cumulative clinical fracture rates were 4.7 (95% CI, 4.2 to 5.3) and 4.3 (95% CI, 3.8 to 4.8) per 100 patient-years in the placebo and cinacalcet groups, respectively. As shown in Figure 1, clinical fracture rates in patients aged <65 years were virtually identical (3.8; 95% CI, 3.3 to 4.4) in both groups. However, among patients aged ≥65 years, clinical fracture rates were 8.6 (95% CI, 7.1 to 10.4) in the placebo group and 6.0 (95% CI, 4.8 to 7.3) in the cinacalcet group (P<0.01). Figure 2 shows the cumulative incidence plot of time to first fracture for patients aged <65 years and patients aged ≥65 years using an intention-to-treat analysis.
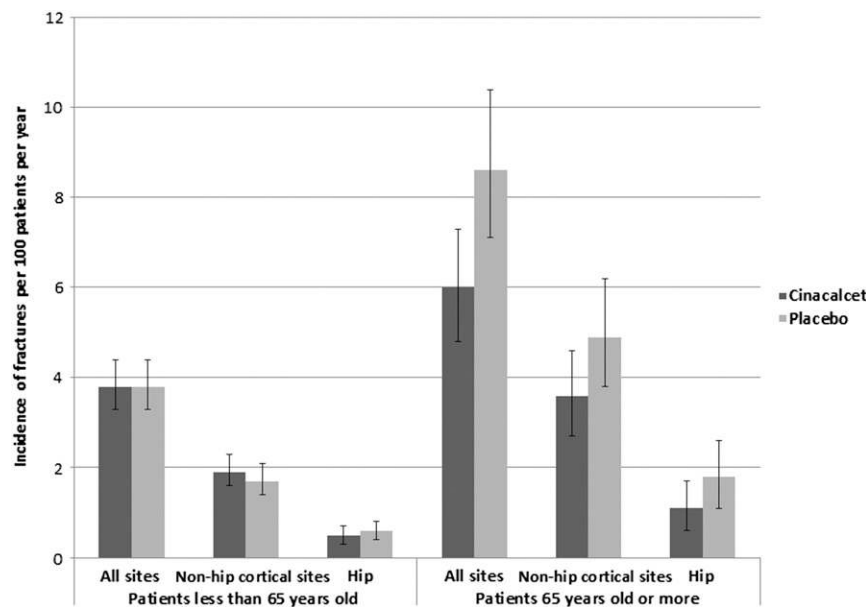
Effect of Cinacalcet on First Clinical Fracture

Intention-to-Treat Analyses

As previously reported using an unadjusted intention-to-treat analysis,[22] the effect of cinacalcet on clinical fracture was not statistically significant (relative hazard, 0.89; 95% CI, 0.75 to 1.07). Despite randomization, median age was higher in patients randomized to cinacalcet, as was the proportion of elderly patients.[22] After adjustment for age and other baseline characteristics, including fracture-related risk factors (previous fracture, history of tobacco use, provision of hormone replacement therapy and proton pump inhibitors, along with bone-related laboratory values), the relative hazard was 0.84 (95% CI, 0.69 to 1.01; P=0.07) (Table 2). Older age, female sex, diabetes, history of stroke and previous fracture, and tobacco use were associated with an increased rate of fracture, as were higher baseline bone-specific alkaline phosphatase (BALP), higher baseline serum calcium, and higher and lower baseline plasma parathyroid hormone (PTH) (Table 2). Supplemental Figure 1 shows a Forest plot for first clinical fracture by prespecified baseline clinical characteristics, and Supplemental Figure 2 shows the same by cointerventions for CKD-MBD using the multivariable-adjusted intention-to-treat analyses.

Lag-Censoring Analysis

As previously reported, more than two-thirds of patients in both groups discontinued the study drug for a variety of protocol-specified and nonprotocol-specified reasons.[22] Moreover, kidney transplantation and provision of PTH-lowering therapies (parathyroidectomy and off-protocol use of cinacalcet) were more common in patients randomized to placebo. Using a prespecified lag-censoring analysis (censoring time >6 months after stopping the study drug), the relative hazard for fracture was 0.72 (95% CI, 0.58 to 0.90; P=0.003) (Supplemental Table 2). Figure 3 shows effect modification by prespecified baseline clinical characteristics, and Figure 4 shows effect modification by cointerventions for CKD-MBD. Using the lag-censoring approach, the relative benefit of cinacalcet (or the relative harm of placebo plus conventional therapy) was more pronounced in patients treated with calcium-based phosphate binders (relative hazard, 0.55; 95% CI, 0.40 to 0.74; P=0.01) than in patients not treated, or treated with other, noncalcium-based phosphate binders (relative hazard, 0.98; 95% CI, 0.72 to 1.35). The relative benefit of cinacalcet appeared to be more pronounced among patients with baseline dialysate calcium ≥3.0 mEq/L, although the interaction (treatment group×dialysate calcium) was not significant (P=0.15).

Figure 1. Unadjusted fracture rates by site, age, and treatment group. Fractures are more common at nonhip cortical sites compared with the hip, and are more common in patients aged ≥65 years. Bar graphs represent the mean±SD.
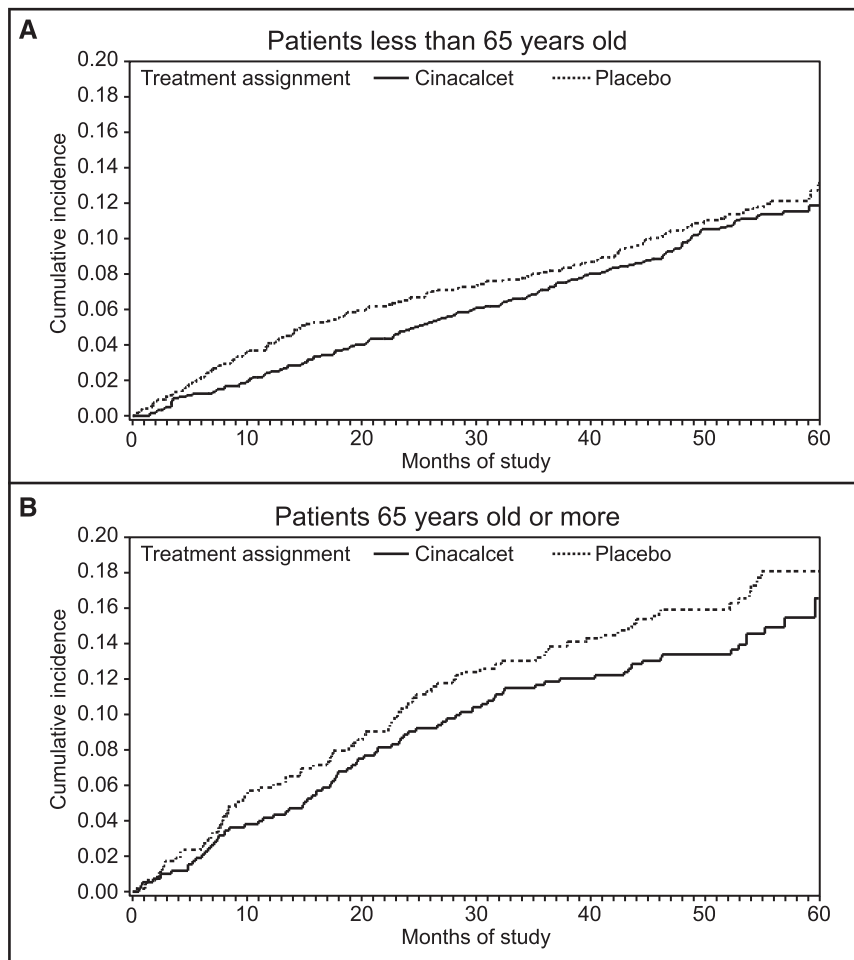
Figure 2. Cumulative incidence of fractures. Cumulative incidence of clinical fractures in patients aged <65 years (top) and aged ≥65 years (bottom). Patients randomized to cinacalcet are shown with the solid line, and patients randomized to placebo are shown with the dashed line.

Censoring at Cointerventions
When we censored at time of the cointerventions of para-thyroidectomy, kidney transplant, or provision of commercial cinacalcet, the relative hazard of fracture was 0.71 (95% CI, 0.58 to 0.87, P=0.001) (Supplemental Table 3).

Effect of Cinacalcet on Cumulative Clinical Fractures
When considering the risk of all clinical fractures (first plus subsequent) during the study, the unadjusted and multivariable-adjusted relative hazards (cinacalcet versus placebo) were 0.89 (95% CI, 0.76 to 1.05; P=0.16) and 0.83 (95% CI, 0.72 to 0.98; P=0.02). Using the lag-censoring approach, the relative hazard was 0.77 (95% CI, 0.63 to 0.94; P=0.01) (Supplemental Table 4).

Effect of Cinacalcet on Clinical Fractures in Older Versus Younger Patients
The adjusted relative hazards for clinical fractures by intention to treat were 0.92 (95% CI, 0.73 to 1.16) in patients aged <65 years

and 0.69 (95% CI, 0.49 to 0.95) in patients aged ≥65 years (P value for treatment by age [continuous] interaction, P=0.06). Figure 3 shows unadjusted relative hazards using the lag-censoring approach; corresponding adjusted relative hazards were 0.79 (95% CI, 0.58 to 0.90) and 0.60 (95% CI, 0.41 to 0.88), with a corresponding interaction P=0.28.

DISCUSSION

In the EVOLVE trial, we compared the relative safety and efficacy of cinacalcet and placebo along with conventional therapy for secondary hyperparathyroidism (typically phosphate binders and vitamin D sterols). The primary composite end point of the trial was all-cause mortality and nonfatal cardiovascular events; however, clinical fracture was a key secondary outcome, and reported fracture events were adjudicated along with major cardiovascular end points. Because we did not screen for fractures at baseline or at any fixed intervals or routinely perform imaging analysis to assess for vertebral fractures that are often asymptomatic,[25] we almost certainly ascertained just a small fraction of all fractures that occurred during the trial. Moreover, the trial was powered for its adjudicated cardiovascular composite end point. Had our assumptions held, we would have had relatively low power to detect a clinically meaningful difference in all clinical fractures. Power was further reduced by very high rates of discontinuation of the study drug in both groups (actually higher in the placebo group), high rates of kidney transplantation in younger patients, and differential application of parathyroidectomy and commercial (off-protocol) cinacalcet in patients randomized to placebo compared with cinacalcet, as previously detailed.[22] Despite factors reducing the power to detect a difference, the results in this secondary analysis were consistent across unadjusted, multivariable-adjusted, lag-censoring, and PTH-lowering event–censoring analyses, with point estimates of the rate reduction ranging from 16% to 29% in patients randomized to cinacalcet when differences in baseline characteristics (principally in age) were accounted for. These findings were nominally significant for the adjusted intention-to-treat analysis of cumulative fractures, and for both lag-censoring analyses (time to first fracture, and cumulative fractures).

The incidence of clinical fractures in this study was >4% per year. Two cross-sectional studies in dialysis patients found that

Table 2. Multivariable Cox regression of the effect of cinacalcet on the occurrence of first clinical fracture, by intention-to-treat analysis

Variable[a]	Relative Hazard (95% CI)	P Value
Treatment (cinacalcet/placebo)	0.84 (0.69 to 1.01)	0.07
Age (yr)[b]	1.38 (1.22 to 1.55)	<0.001
Sex (ref=women)	0.78 (0.64 to 0.96)	0.02
Race (ref=white)		
Black	0.48 (0.35 to 0.66)	<0.001
Other	0.75 (0.57 to 1.00)	0.05
Geographical region (ref=United States)		
Russia	0.49 (0.30 to 0.82)	0.01
Latin America	1.03 (0.72 to 1.47)	0.87
Europe	0.76 (0.57 to 1.02)	0.06
Canada	0.97 (0.62 to 1.50)	0.89
Australia	0.59 (0.34 to 1.04)	0.07
Tobacco use (ref=never)		
Current	1.54 (1.18 to 1.99)	0.001
Former	0.91 (0.72 to 1.15)	0.43
Dialysis vintage (yr)	1.05 (0.95 to 1.15)	0.35
Type of vascular access (ref=natural fistula)		
Permanent catheter	1.46 (1.09 to 1.94)	0.01
Graft	1.51 (1.15 to 1.96)	0.003
Other	1.35 (0.74 to 2.49)	0.33
Alcohol use	1.39 (1.10 to 1.76)	0.01
Calcium-containing phosphate binder use	1.16 (0.95 to 1.42)	0.14
Hormone replacement therapy	1.26 (0.94 to 1.70)	0.13
Proton pump inhibitor use	1.19 (0.97 to 1.47)	0.09
History of cardiovascular disease[c]	0.95 (0.61 to 1.48)	0.83
History of peripheral vascular disease	0.84 (0.64 to 1.11)	0.23
Other cardiac disease history (valvular heart disease and angina)	1.27 (1.02 to 1.58)	0.03
Amputation history	0.87 (0.56 to 1.36)	0.54
History of diabetes	1.46 (1.15 to 1.83)	0.002
History of bone fracture	1.67 (1.36 to 2.06)	<0.001
History of stroke	1.67 (1.29 to 2.17)	<0.001
Hemoglobin	0.99 (0.89 to 1.09)	0.78
Serum phosphorus (mg/dl)	1.07 (0.96 to 1.18)	0.23
Serum calcium (corrected) (mg/dl)	1.11 (1.01 to 1.23)	0.03
Serum BALP (ng/ml)	1.09 (1.00 to 1.20)	0.05
Serum 25-hydroxy cholecalciferol (μg/L)	1.00 (0.90 to 1.12)	0.99
Plasma intact PTH (pg/ml)[d]		
Log transformed	0.04 (0.00 to 0.76)	0.03
Squared log transformed	1.28 (1.02 to 1.60)	0.04

ref, reference value.

[a]Both treatment and BALP have time-dependent effect; the effects shown in the table are time-averaged effects. Unless otherwise specified, all continuous variables were standardized; one unit is equivalent to 1 SD.

[b]Age by treatment interaction was not statistically significant ($P=0.06$).

[c]History of cardiovascular disease includes history of coronary artery disease, cardiac arrhythmia, coronary artery bypass graft, hypertension, heart failure, and myocardial infarction.

[d]The hazard ratios of the linear and squared PTH terms should be interpreted together and indicate that PTH had a nonlinear association with fractures; fracture rate is increased at the lower and higher ends of baseline PTH in this group of patients with secondary hyperparathyroidism.

21% of patients in each patient population had prevalent vertebral fractures.[26,27] The clinical fracture rates observed in the EVOLVE trial were slightly higher than in analyses from the prospective observational Dialysis Outcomes and Practice Patterns Study (DOPPS), in which the reported incidence was 2.6% per year when reported in 2006,[3] and was 3% in a more recent DOPPS III report with a median follow-up of only 1.6 years.[4] Readers should be reminded that patients enrolled in the EVOLVE trial were of longer dialysis vintage, and had more severe secondary hyperparathyroidism than the general hemodialysis population, perhaps explaining these differences. In this study, and in both of these DOPPS observational studies,[3,28] fractures increased in older age groups. Fracture rates were much higher in older compared with younger patients, as virtually all other studies in the general population and CKD and ESRD populations have shown. The
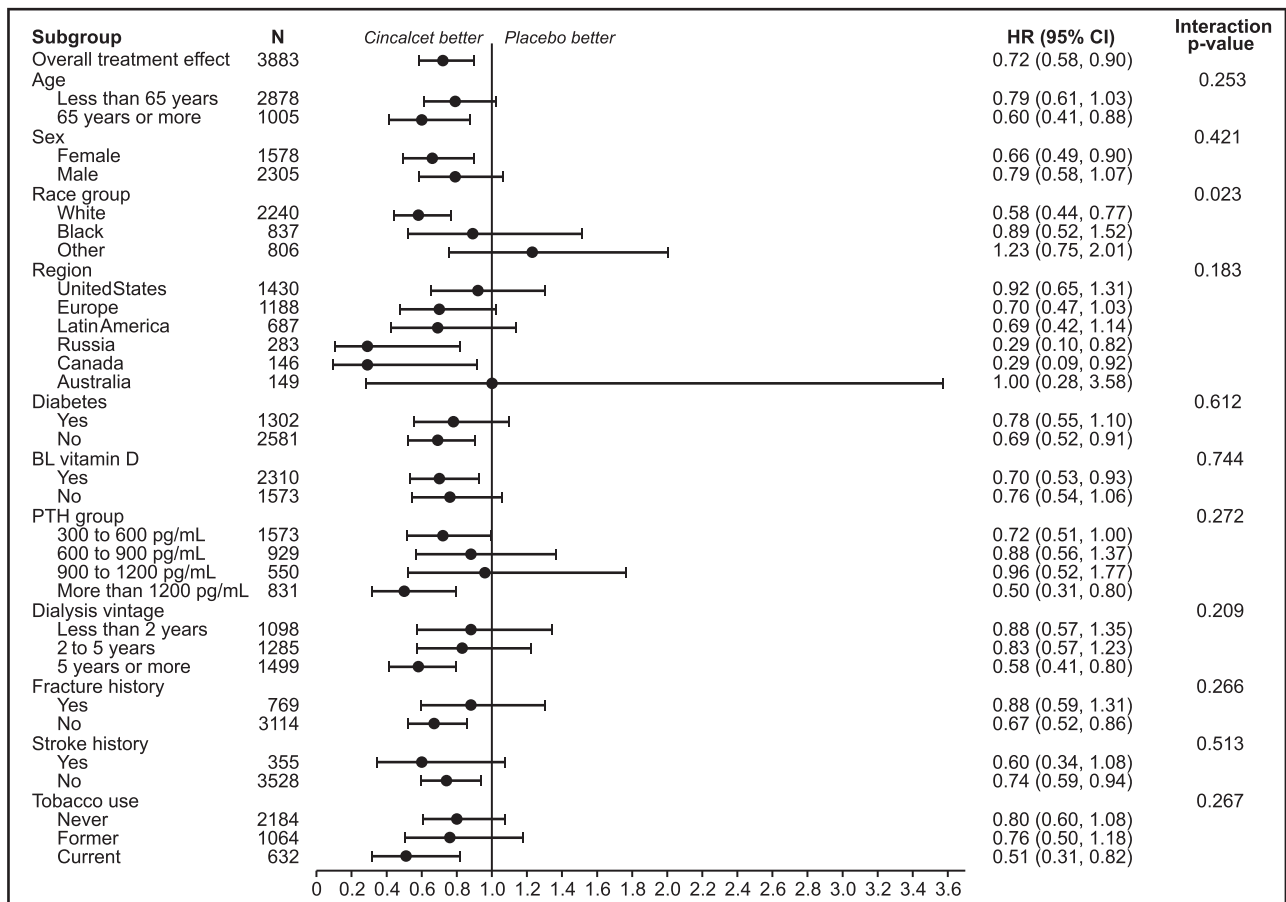
Subgroup	N	Cincalcet better	Placebo better	HR (95% CI)	Interaction p-value
Overall treatment effect	3883			0.72 (0.58, 0.90)	
Age					0.253
Less than 65 years	2878			0.79 (0.61, 1.03)	
65 years or more	1005			0.60 (0.41, 0.88)	
Sex					0.421
Female	1578			0.66 (0.49, 0.90)	
Male	2305			0.79 (0.58, 1.07)	
Race group					0.023
White	2240			0.58 (0.44, 0.77)	
Black	837			0.89 (0.52, 1.52)	
Other	806			1.23 (0.75, 2.01)	
Region					0.183
UnitedStates	1430			0.92 (0.65, 1.31)	
Europe	1188			0.70 (0.47, 1.03)	
LatinAmerica	687			0.69 (0.42, 1.14)	
Russia	283			0.29 (0.10, 0.82)	
Canada	146			0.29 (0.09, 0.92)	
Australia	149			1.00 (0.28, 3.58)	
Diabetes					0.612
Yes	1302			0.78 (0.55, 1.10)	
No	2581			0.69 (0.52, 0.91)	
BL vitamin D					0.744
Yes	2310			0.70 (0.53, 0.93)	
No	1573			0.76 (0.54, 1.06)	
PTH group					0.272
300 to 600 pg/mL	1573			0.72 (0.51, 1.00)	
600 to 900 pg/mL	929			0.88 (0.56, 1.37)	
900 to 1200 pg/mL	550			0.96 (0.52, 1.77)	
More than 1200 pg/mL	831			0.50 (0.31, 0.80)	
Dialysis vintage					0.209
Less than 2 years	1098			0.88 (0.57, 1.35)	
2 to 5 years	1285			0.83 (0.57, 1.23)	
5 years or more	1499			0.58 (0.41, 0.80)	
Fracture history					0.266
Yes	769			0.88 (0.59, 1.31)	
No	3114			0.67 (0.52, 0.86)	
Stroke history					0.513
Yes	355			0.60 (0.34, 1.08)	
No	3528			0.74 (0.59, 0.94)	
Tobacco use					0.267
Never	2184			0.80 (0.60, 1.08)	
Former	1064			0.76 (0.50, 1.18)	
Current	632			0.51 (0.31, 0.82)	

0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6

Figure 3. Forest plot of treatment effect of cinacalcet on clinical fracture rate by prespecified baseline characteristics using lag-censoring analysis. HR, hazard ratio.

effect of cinacalcet appeared to be more pronounced in older patients. Although effect modification by age (the treatment × age interaction) was not statistically significant, the power to detect interventions with a relatively small number of events and a modest overall treatment effect is quite low. This observation could be explained by one of several factors: a true difference in the treatment effect, bias introduced by differential application of cointerventions (including kidney transplantation, parathyroidectomy, and provision of commercial cinacalcet), differential susceptibility to the effects of secondary hyperparathyroidism for which cinacalcet is prescribed, or lower event rates in younger patients, reducing statistical power. Given the high mortality, increased hospitalization rates, and costs associated with fractures,[3,28–30] our study suggests that a reduction in fractures could have important personal health and societal financial benefits.

Given the mechanism of action of cinacalcet to reduce PTH release, it is probable that improvements in secondary hyperparathyroidism led to the observed effects on clinical fracture rates. This is further supported by the association between baseline increased BALP (indicating higher bone turnover) and fracture. The reduction in clinical fractures observed with

cinacalcet treatment in this study was similar to that observed in a case control study of surgical parathyroidectomy in the United States that demonstrated a 32% reduction in subsequent hip fractures.[31] The importance of PTH as a biomarker of abnormal bone is controversial.[32,33] Cohort studies have shown an increased risk of fracture associated with low PTH[12,29,30] or very high PTH.[3,12,30,34] Some studies have found no significant relation to PTH.[35,36] A meta-analysis suggested a direct effect of PTH.[37] These apparently conflicting results may be attributable to the relative short $t_{1/2}$ and normal oscillatory release of PTH such that a single value may not predict future outcomes. The results of this study evaluating the effect of cinacalcet, which reduces PTH,[38] on reducing fracture rates supports an important role of PTH in the pathogenesis of fractures in patients with CKD.

This study demonstrated that nonhip cortical fractures were more common than hip fractures, although we did not search for radiographic evidence of asymptomatic spine fractures. We therefore cannot assume that cinacalcet exerts a similar effect on predominately cancellous bone sites such as the spine. Hyperparathyroidism predominately reduces cortical bone area[39,40] and measures of cortical bone by dual x-ray absorptiometry or computed tomography are more predictive of
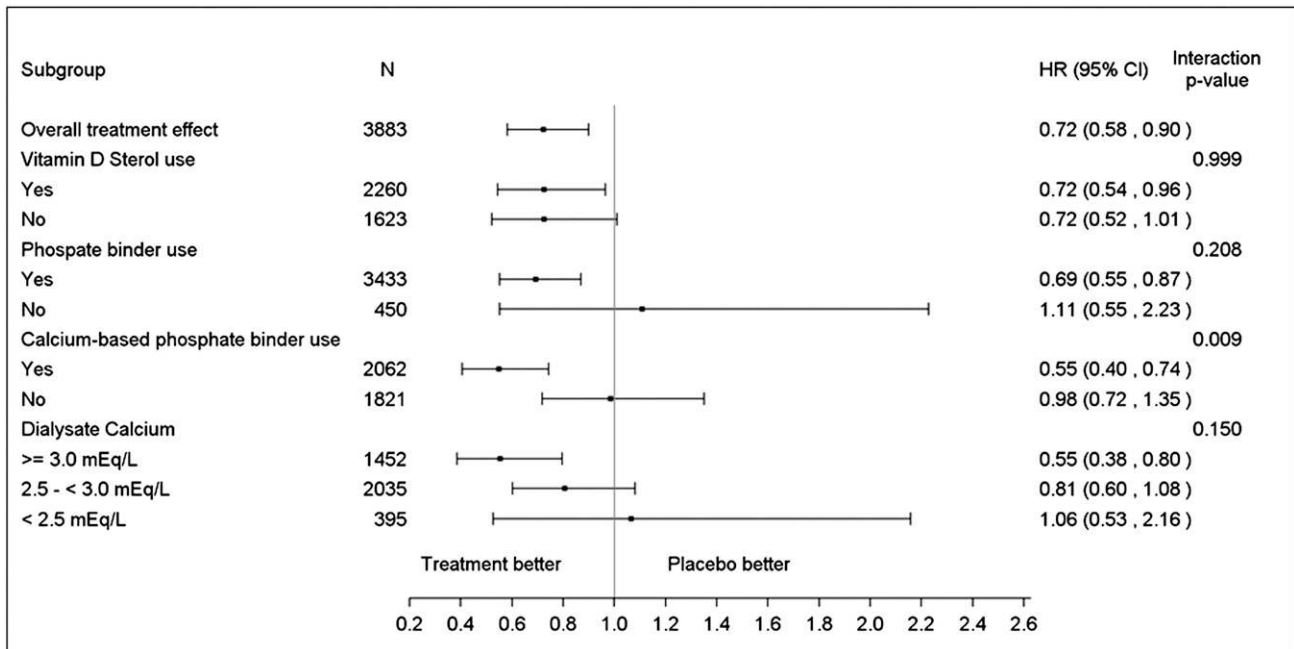
Figure 4. Forest plot of treatment effect of cinacalcet on clinical fracture rates by concomitant medications using lag-censoring analyses. HR, hazard ratio.

fractures than other sites.[41,42] In humans with secondary hyperparathyroidism, parathyroidectomy improves bone mineralization, reduces osteoclast bone resorption, enhances osteoblast bone formation, and leads to osteocytic death (thereby improving osteocytic osteolysis).[43,44] In a uremic rat model with secondary hyperparathyroidism, treatment with a calcimimetic agent reduced osteitis fibrosa cystica, increased cortical bone mineral density, and corrected the CKD-induced loss of diaphyseal stiffness.[45] In a different rat model of CKD, elevated PTH led to increased cortical porosity and increased fragility assessed by three-point bending studies.[46] However, even in the absence of PTH, there were cortical bone abnormalities and fragility due to altered collagen crosslinking in CKD rats.[47] Our trial did not utilize bone imaging or bone biopsy; thus, abnormalities of bone quality and the mechanism(s) of the observed effects of cinacalcet cannot be definitely determined. However, the results of this study, previous imaging studies, and experimental studies in animals are compatible with the construct that cortical bone may be preferentially altered in CKD/ESRD.

The strengths of these analyses include a randomized design, relatively large sample size, continued follow-up throughout the trial in 95% of participants, diversity (in age, sex, race/ethnicity, and clinical features of ESRD), breadth of comorbidity, laboratory data available at study entry, and most importantly, adjudication of clinical fracture end points by a trained Clinical Events Committee blinded to treatment assignment and other clinical features such as laboratory data. There are also several important limitations. By design, only patient-reported clinical fractures were identified; by not screening for asymptomatic fractures, we probably ascertained a small fraction of the fractures

sustained by patients during the trial. We did not distinguish traumatic from atraumatic fractures and falls are a major determinant of fractures.[13] Unfortunately, we did not collect data on muscle strength, falls, or physical activity in the EVOLVE trial. Although we accounted for the use of selected concomitant medications (phosphate binders, vitamin D sterols, and several other drugs prescribed at baseline), it is possible that participants took other medications at baseline or throughout the trial that might have made clinical fractures more or less likely. A large number of participants stopped taking cinacalcet for both protocol-specified and nonspecified reasons. In addition, it is highly likely that the observed treatment effect was attenuated by reduced adherence to, and "crossover" of, treatment and was further confounded by the effects of kidney transplantation and parathyroidectomy. Finally, the relatively small sample size may have precluded our ability to detect significant interactions between cinacalcet use and age or other covariates.

In summary, an unadjusted intention-to-treat analysis did not show a significantly reduced risk of clinical fracture in the group randomized to cinacalcet. However, when accounting for differences in baseline characteristics, multiple fractures, and/or events prompting discontinuation of the study drug, cinacalcet reduced the rate of clinical fracture by 16%–29%.

CONCISE METHODS

Study Population and Design
In the EVOLVE trial, 3883 patients with secondary hyperparathyroidism receiving hemodialysis were randomized 1:1 to receive either

cinacalcet (Sensipar; Amgen Inc) or placebo in addition to conventional therapies for CKD-MBD (*i.e.,* instructions for dietary phosphorus restriction, phosphate binders, and vitamin D sterols).[48] Eligible participants were on hemodialysis three times per week with plasma PTH concentrations $\geq$300 pg/ml (31.8 pmol/L), serum calcium phosphate product $\geq$45 mg^2/dl^2 (3.63 mmol^2/L^2), and serum calcium $\geq$8.4 mg/dl (2.1 mmol/L). The dose of the study drug was titrated once every 4 weeks during the first 20 weeks and every 8 weeks during the subsequent follow-up period (from a starting dose of 30 mg to a maximum dose of 180 mg daily), depending on blood levels of PTH and calcium. The dialysis prescription, other medical procedures, and doses of phosphate binders, vitamin D sterols, calcium supplements, and other medications were administered at the discretion of the treating physicians. Rates of withdrawal from cinacalcet, often related to gastrointestinal symptoms, were high; crossover from placebo to commercially available cinacalcet also reduced the trial's power to detect a statistically significant result.[22] The trial was led by an academic executive committee and was sponsored by Amgen Inc. Ethics committee approval was obtained at all participating sites; all patients gave informed consent. The EVOLVE trial is registered with ClinicalTrials.gov (NCT00345839).

Clinical Fracture Events

An independent Clinical Events Committee adjudicated all primary and secondary end points.[22] Clinical fracture was a prespecified key secondary end point. Clinical fractures were ascertained at each visit by study personnel. Furthermore, all adverse events were screened for all components of the primary and secondary end points, such that clinical fractures that might have occurred in conjunction with other events were submitted for adjudication. Routine radiographic imaging was not performed to detect asymptomatic fractures. For the purpose of our analyses, fracture events were categorized as clinical vertebral and nonvertebral fractures, the latter being further subdivided into hip fractures (femur and intertrochanteric/subtrochanteric), nonhip predominantly cortical fractures (upper or lower extremities, ribs, or pelvis), and other nonvertebral fractures.

Biochemical Determinations

Biochemical markers of CKD-MBD including plasma intact PTH (normal range, 11–72 pg/ml) and serum concentrations of total calcium (8.3–10.6 mg/dl), phosphorus (2.2–5.1 mg/dl), 25-hydroxy vitamin D (11–72 ng/ml), and BALP (2.9–22.6 ng/ml) were analyzed at a central laboratory.

Sample Size Determination

Although the trial's sample size was determined based on assumptions surrounding the primary composite end point (time to death, nonfatal myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event), we prospectively calculated the power to detect differences in fracture rates based on the following assumptions: fracture rate of 4% per year in the placebo group, 1.5-year enrollment period, 4-year total study duration, lost to follow-up rate of 1% per year, a "drop-out" (withdrawal from treatment) rate of 10% per year in the cinacalcet group, and a "drop-in" (use of commercial cinacalcet) rate of 10% in the placebo group. Based on 3800 patients enrolled, we calculated the power to be approximately 60% to detect a 30% effect size using a two-sided α=0.044.

Statistical Analyses

The primary analysis for the effect of cinacalcet was conducted using the intention-to-treat principle. Prespecified secondary analyses included a multivariable proportional hazards (Cox) regression analysis adjusting for baseline characteristics, including age, sex, race (white, black, or other), geographic region, history of diabetes mellitus, history of cardiovascular diseases, and other variables known to be related to fracture in the general population (previous fracture, smoking, or use of hormone replacement therapy). Further covariates were selected by a process of backward elimination. Additional prespecified secondary analyses included a lag-censoring analysis, in which follow-up time >6 months after discontinuation of the study drug was censored, and a prespecified analysis censoring at cointerventions of parathyroidectomy, transplantation, and administration of commercial cinacalcet in the placebo arm.[22] We used fractional polynomial regression to examine the association of baseline PTH with fractures.[49] To examine the effect of cinacalcet on serial clinical fracture events, we utilized the Prentice–Williams–Petersen extension of Cox regression. We tested for effect modification by age, sex, race, geographic region, dialysis vintage (time since initiation of dialysis), diabetes, and baseline PTH using multiplicative interaction terms. We also explored whether the effect of cinacalcet on clinical fractures was more or less pronounced with differences in the prescription (at baseline) of phosphate binders, vitamin D sterols, and dialysate calcium.

All inference tests were performed without adjusting for multiple comparisons. Because the effects of randomization to cinacalcet versus placebo on the primary composite end point did not reach statistical significance on an unadjusted log-rank test,[22] comparisons yielding two-tailed *P* values<0.05 were deemed nominally significant. All statistical analyses were conducted at Stanford University using SAS 9.3 software (SAS Institute Inc., Cary, NC).

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