Kidney International, Vol. 67 (2005), pp. 760–771

TECHNICAL NOTE

Achieving NKF-K/DOQI™ bone metabolism and disease treatment goals with cinacalcet HCl

SHARON M. MOE, GLENN M. CHERTOW, JACK W. COBURN, L. DARRYL QUARLES, WILLIAM G. GOODMAN, GEOFFREY A. BLOCK, TILMAN B. DRÜEKE, JOHN CUNNINGHAM, DONALD J. SHERRARD, LAURA C. MCCARY, KURT A. OLSON, STEWART A. TURNER, and KEVIN J. MARTIN

Indiana University School of Medicine, Indianapolis, Indiana; UCSF School of Medicine, San Francisco, California; VA Greater Los Angeles Healthcare System and David Geffen School of Medicine at UCLA, Los Angeles, California; Duke University Medical Center, Durham, North Carolina; UCLA School of Medicine, Los Angeles, California; Denver Nephrologists, Denver, Colorado; Hôpital Necker, Paris, France; University London College Hospitals, London, UK; University of Washington and VA Puget Sound Health Care Systems, Seattle, Washington; Amgen, Inc., Thousand Oaks, California; and St. Louis University, St. Louis, Missouri

Achieving NKF-K/DOQI™ bone metabolism and disease treatment goals with cinacalcet HCl.

Background. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI™) has established guidelines for treatment of secondary hyperparathyroidism (HPT). The ability of cinacalcet HCl (Sensipar™) treatment to improve achievement of target levels of parathyroid hormone (PTH), calcium, phosphorus, and calcium-phosphorus product (Ca × P) was investigated in subjects on dialysis with secondary HPT.

Methods. Data were combined from three placebo-controlled, double-blind, 26-week studies with similar design that randomized 1136 subjects on dialysis to receive traditional therapy plus cinacalcet or placebo. Oral cinacalcet was titrated from 30 to 180 mg/day. Achievement of K/DOQI goals was determined for each treatment group overall and for subgroups defined by baseline intact PTH (iPTH) and Ca × P levels.

Results. Cinacalcet-treated subjects were more likely to achieve a mean iPTH ≤300 pg/mL (31.8 pmol/L) than were control subjects on traditional therapy (56% vs. 10%, $P < 0.001$). Cinacalcet-treated subjects were more likely to achieve concentrations of serum calcium within 8.4 to 9.5 mg/dL (2.10–2.37 mmol/L) and serum phosphorus within 3.5 to 5.5 mg/dL (1.13–1.78 mmol/L) than were control subjects (49% vs. 24% and 46% vs. 33%, $P < 0.001$ for each). Cinacalcet also improved achievement of Ca × P < 55 mg^2/dL^2 (4.44 $mmol^2/L^2$) and concurrent achievement of Ca × P < 55 mg^2/dL^2 (4.44 $mmol^2/L^2$) and iPTH ≤300 pg/mL (31.8 pmol/L) (65% vs. 36% and 41% vs. 6%, $P <$ 0.001 for each).

Conclusion. In subjects on dialysis with secondary HPT, cinacalcet facilitates achievement of the K/DOQI-recommended targets for PTH, calcium, phosphorus, and Ca × P.

Key words: calcimimetic, cinacalcet HCl, NKF-K/DOQI guidelines, secondary hyperparathyroidism (HPT), chronic kidney disease (CKD), dialysis.

Secondary hyperparathyroidism (HPT) is a common complication of chronic kidney disease (CKD). Complex interactions among serum calcium, phosphorus, and 1,25-dihydroxyvitamin D_3 (calcitriol) are associated with progressive increases in parathyroid hormone (PTH) when the glomerular filtration rate (GFR) falls below approximately 60 mL/min/1.73 m^2 [1–3]. In patients with CKD on dialysis, elevated PTH is associated with increased mortality, considerable musculoskeletal morbidity, and bone pain [4–8]. Secondary HPT is also complicated by increased calcium-phosphorus product (Ca × P) levels, which may be exacerbated by the use of vitamin D sterols and calcium-based phosphate binders. Ca × P levels are elevated [>55 mg^2/dL^2 (4.44 $mmol^2/L^2$)] in approximately 50% of patients on dialysis [4], and are associated with an increased risk of cardiac, visceral, and vascular calcification [9–11] and cardiovascular mortality [4, 5].

Recognizing the clinical significance of secondary HPT among patients with CKD, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI™) has recently published Clinical Practice Guidelines for Bone Metabolism and Disease [12]. The K/DOQI guidelines for stage 5 CKD (estimated GFR <15 mL/min/1.73m^2 or on dialysis) recommend treatment goals for intact PTH [iPTH, 150 to 300 pg/mL (15.9 to 31.8 pmol/L)], total corrected serum calcium [8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L)], serum phosphorus [3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L)], and Ca × P [<55 mg^2/dL^2 (4.44 $mmol^2/L^2$)] [12].

Traditional therapies for treating secondary HPT and associated disorders of mineral metabolism, including dietary phosphate restriction, oral phosphate binders, calcium supplementation, and vitamin D sterols, are inadequate for many patients [13–16]. Dietary phosphate

Table 1. Key study design characteristics for studies A, B, and C

	Study A	Study B	Study C
Eligibility criteria	iPTH ≥300 pg/mL; serum calcium ≥8.4 mg/dL; hemodialysis duration >3 months	iPTH ≥300 pg/mL; serum calcium ≥8.4 mg/dL; hemodialysis duration >3 months	iPTH ≥300 pg/mL; serum calcium ≥8.4 mg/dL; hemodialysis or peritoneal dialysis >1 month
Study duration	26 weeks; 12 weeks dose titration, 14 weeks efficacy assessment	26 weeks; 12 weeks dose titration, 14 weeks efficacy assessment	26 weeks; 16 weeks dose titration, 10 weeks efficacy assessment
Regions of study conduct	United States, Canada	European community, Australia	United States, Canada, Australia
Study dates	Dec 2001-Dec 2002	Feb 2002-Jan 2003	May 2002-March 2003
Randomization ratio	1:1Cinacalcet:control	1:1Cinacalcet:control	3:1Cinacalcet:control
Number of patients enrolled	Cinacalcet205 Control205	Cinacalcet165 Control166	Cinacalcet294 Control101
Randomization stratification	Baseline iPTH level and baseline Ca × P level	Baseline iPTH level and baseline Ca × P level	Dialysis modality; hemodialysis patients were further stratified according to baseline iPTH level
Cinacalcet dose range	30 to 180 mg once daily	30 to 180 mg once daily	30 to 180 mg once daily
Target iPTH	100 to 250 pg/mL	100 to 250 pg/mL	100 to 250 pg/mL

restriction is associated with low adherence, and may compromise dietary protein intake [3, 13]; calcium-based phosphate binders may lead to gastrointestinal discomfort [12] and contribute to hypercalcemia [17, 18]; some non–calcium-containing phosphate binders may be associated with gastrointestinal discomfort and metabolic acidosis [12, 19], and vitamin D sterols may lead to hypercalcemia and hyperphosphatemia as a result of increased intestinal absorption of both calcium and phosphorus [10, 11, 20]. It is recognized, therefore, that achievement of the K/DOQI targets with these therapeutic options is challenging [10].

The calcimimetic cinacalcet HCl (Sensipar™), hereafter called cinacalcet, is a new treatment option for secondary HPT that has been shown to reduce PTH while simultaneously lowering serum calcium, phosphorus, and Ca × P levels in study subjects undergoing hemodialysis [21–23]. In light of the recently published K/DOQI guidelines, we analyzed the efficacy of cinacalcet in facilitating achievement of the K/DOQI targets in subjects on dialysis with secondary HPT. The data were collected in three geographically diverse, but similarly designed double-blind, placebo-controlled, randomized clinical trials.

METHODS

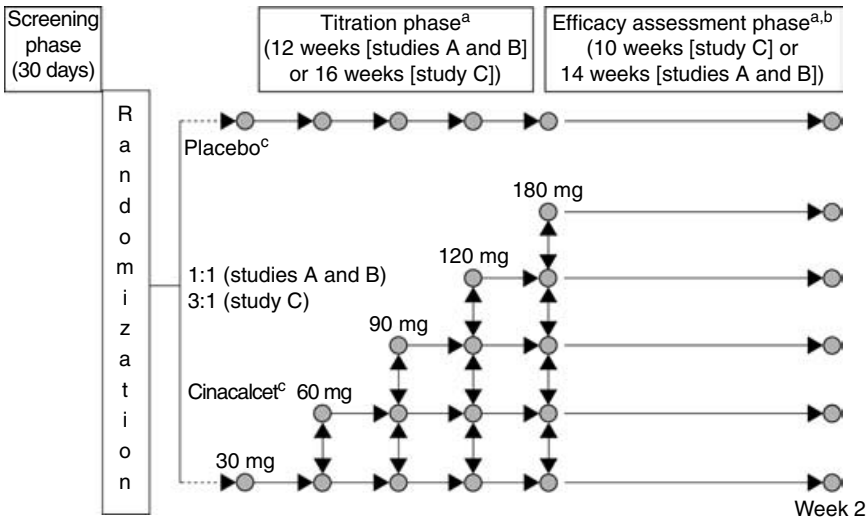
Subjects

A total of 1136 subjects were enrolled in the three studies (designated studies A, B, and C) included in this analysis. The studies were conducted at 182 centers in North America, Europe, and Australia. The Institutional Review Board for each study center approved the study protocol and amendments, and written informed consent was obtained from study subjects before the initiation of any study-specific procedures. Key aspects of each study are defined in Table 1.

The studies had similar enrollment criteria (Table 1). Patients were excluded if they had a history of an unstable medical condition, or had required a change in dose or brand of vitamin D in the preceding 30 days. Additionally, in studies A and B, patients were excluded if they had changed their dose or brand of phosphate binder, oral calcium supplement, or dialysate calcium concentration in the preceding 30 days.

Study design

The three studies included in this analysis were of similar design and duration (Table 1, Fig. 1). Study subjects were randomized in a 1:1 (studies A and B) or 3:1 (study C) ratio to receive cinacalcet (665 subjects) or placebo (471 subjects). In studies A and B, randomization was stratified by mean baseline iPTH level [300 to 500, 501 to 800, or >800 pg/mL (31.8 to 53.0, 53.1 to 84.8, or >84.8 pmol/L)] and by baseline Ca × P level [≤70 or >70 mg^2/dL^2 (≤5.65 or >5.65 $mmol^2/L^2$)]. In study C, randomization was stratified by dialysis modality, and randomization of hemodialysis patients was further stratified by baseline iPTH level. Each 26-week, randomized, double-blind, placebo-controlled study consisted of a 12-week (studies A and B) or 16-week (study C) dose-titration phase and a 14-week (studies A and B) or 10-week (study C) evaluation phase. Blood samples for the measurement of iPTH, serum calcium, serum phosphorus, and Ca × P were obtained at least every 2 weeks during the dose-titration and evaluation phases. Subjects initially received 30 mg cinacalcet (or placebo) orally, once daily. Doses were increased every 3 or 4 weeks, provided the subject's previous iPTH concentration was ≥200 pg/mL (21.2 pmol/L), and serum calcium was ≥7.8 mg/dL (≥1.95 mmol/L). Dose titration continued until the iPTH was reduced to <200 pg/mL (21.2 pmol/L) or until the highest dose of study drug (180 mg/day cinacalcet or placebo) was reached. If subjects experienced symptoms attributed to hypocalcemia or an adverse event considered to be related to the study medication, or if iPTH concentrations were <100 pg/mL (10.6 pmol/L) on two or more consecutive



[a]Study drug dose could also have been reduced according to protocol-specified rules.

[b]Dose titration was also allowed every 3 or 4 weeks.

[c]The placebo and cinacalcet treatment groups followed the same titration rules.

Fig. 1. Integrated efficacy study design schema.

visits, study drug (cinacalcet or placebo) was stopped, or the dose reduced.

Concomitant medication

Throughout the studies, subjects continued to receive their secondary HPT therapies, including vitamin D sterols and phosphate binders, if prescribed. Except during the screening phase, phosphate binders or oral calcium supplements could be adjusted at any time at the discretion of the treating physician. Vitamin D sterols were held constant, with the following exceptions specified by the protocol. If iPTH concentrations increased by ≥50% from baseline for three consecutive visits, or if a subject experienced symptoms attributed to hypocalcemia and/or a serum calcium concentration <8.4 mg/dL (<2.10 mmol/L), despite an increase in oral calcium, the vitamin D dose could be increased. If iPTH concentrations were <100 pg/mL (10.6 pmol/L) for three consecutive study visits and the subject was receiving the lowest dose of study medication, vitamin D doses could be reduced or withheld. Reductions in doses of vitamin D were also permitted if serum calcium was ≥11 mg/dL (≥2.74 mmol/L), serum phosphorus was ≥6.5 mg/dL (≥2.10 mmol/L), or Ca × P was ≥70 mg^2/dL^2 (5.65 $mmol^2/L^2$).

Outcomes measures

For this secondary analysis, the efficacy of cinacalcet during the evaluation phase was determined by assessing the proportion of subjects with a mean iPTH value ≤300 pg/mL (31.8 pmol/L), mean serum calcium 8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L), mean serum phosphorus 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L), mean Ca × P <55 mg^2/dL^2 (4.44 $mmol^2/L^2$), and both a mean iPTH value ≤300 pg/mL (31.8 pmol/L) and mean Ca × P <55 mg^2/dL^2 (4.44 $mmol^2/L^2$) during the evaluation phase. Results are presented for the total population and by subgroups assigned according to baseline iPTH and Ca × P levels. The iPTH ≤300 pg/mL (31.8 pmol/L) target (the upper limit of the K/DOQI-recommended range) was used for these analyses rather than the K/DOQI range of 150 to 300 pg/mL (15.9 to 31.8 pmol/L) because the phase 3 studies were initiated before the release of the K/DOQI guidelines [12], and were designed to evaluate achievement of iPTH ≤250 pg/mL (26.5 pmol/L) by titrating to iPTH levels of 100 to 250 pg/mL (10.6 to 26.5 pmol/L). The achievement of this primary end point [mean iPTH ≤250 pg/mL (26.5 pmol/L)] has been previously reported for studies A and B [23]. Baseline and evaluation phase values for iPTH, serum calcium, serum phosphorus, and Ca × P are reported as medians because the values were not normally distributed, and were skewed toward the upper end of the range, reflecting the high percentage of patients with severe secondary HPT in these studies. Values for the doses of cinacalcet used by subjects achieving the iPTH ≤300 pg/mL (31.8 pmol/L) target were not normally distributed and are expressed as medians. The safety of cinacalcet was assessed by evaluating the frequency, severity, and relationship to treatment of all reported adverse events, as well as changes in laboratory parameters and vital signs compared with placebo.

Statistical analysis

Subject-level data were combined from the three studies. A logistic regression model that included treatment group and study design as independent variables and the primary end point of the studies (achievement of iPTH ≤250 pg/mL) as the dependent variable indicated that the study itself was not significantly associated with iPTH reduction ($P = 0.32$), and there was no significant interaction between study and treatment group ($P = 0.50$). Therefore, treatment effect did not differ between studies, and it was considered appropriate to combine data from the three studies.

Baseline demographic and laboratory values, expressed as *N* (%) or median [interquartile range (Q1, Q3)] were obtained during the screening period for all randomized subjects. Efficacy analyses included all subjects with at least one value recorded during the evaluation phase (547 cinacalcet, 409 placebo). For categorical variables, the Cochran-Mantel-Haenszel (CMH) test [24], stratified by study, was used to examine differences between treatment groups. Results are expressed as the percentage of subjects achieving iPTH ≤300 pg/mL (31.8 pmol/L), Ca × P < 55 mg^2/dL^2 (4.44 $mmol^2/L^2$), both iPTH ≤300 pg/mL (31.8 pmol/L) and Ca × P < 55 mg^2/dL^2 (4.44 $mmol^2/L^2$), or the K/DOQI target ranges for serum calcium and phosphorus, or as median [interquartile range (Q1, Q3)] for biochemical measures. The safety analysis included all subjects who received at least one dose of study drug (656 cinacalcet, 470 placebo). All statistical calculations were performed by using SAS software (version 8.2, SAS Institute, Cary, NC, USA), and two-tailed *P* values < 0.05 were considered statistically significant.

RESULTS

Of the 1136 subjects enrolled in the studies, 1126 (99%) received at least one dose of study medication (656 cinacalcet, 470 placebo), 956 subjects (84%) entered the evaluation phase, and 840 subjects (74%) completed the studies. At study entry, no clinically meaningful differences in demographics, biochemical laboratory parameters, or use of concomitant medications existed between the cinacalcet and control groups (Table 2). More than 20% of subjects overall had severe secondary HPT (iPTH >800 pg/mL) at baseline, with study C having the highest fractional enrollment of these patients (35%).

Table 2. Baseline demographics and biochemistries[a]

	Cinacalcet ($N = 665$)	Control ($N = 471$)	Total ($N = 1136$)
Sex			
Female	258 (39)	176 (37)	434 (38)
Male	407 (61)	295 (63)	702 (62)
Race			
White	324 (49)	265 (56)	589 (52)
Black	245 (37)	155 (33)	400 (35)
Other	96 (14)	51 (11)	147 (13)
Age			
<65	510 (77)	335 (71)	845 (74)
=65	155 (23)	136 (29)	291 (26)
Dialysis modality[b]			
Hemodialysis	631 (95)	459 (97)	1090 (96)
Peritoneal dialysis	34 (5)	12 (3)	46 (4)
iPTH *pg/mL*	596 (429, 863)	564 (411, 785)	
Serum calcium *mg/dL*	9.9 (9.3, 10.4)	9.8 (9.4, 10.5)	
Serum phosphorus *mg/dL*	6.0 (5.1, 7.1)	6.2 (5.1, 7.1)	
Ca × P mg^2/dL^2	60.2 (49.0, 70.5)	61.3 (50.7, 70.8)	
Vitamin D sterol use	437 (66)	318 (68)	755 (66)
Phosphate binder use	617 (93)	438 (93)	1055 (93)

Abbreviations are: PTH, parathyroid hormone; Ca, corrected total serum calcium; P, serum phosphorus; Ca × P, calcium-phosphorus product. Note: To convert PTH in pg/mL to ng/L, multiply by 1.0; calcium in mg/dL to mmol/L, multiply by 0.2495; phosphorus in mg/dL to mmol/L, multiply by 0.3229; Ca × P in mg^2/dL^2 to $mmol^2/L^2$, multiply by 0.0807.

[a]Values are *N* (%) or median (Q1, Q3).

[b]Difference between cinacalcet and control groups is the result of the 3 to 1 cinacalcet to control stratification in study C, which was the only study in which both peritoneal dialysis and hemodialysis patients were enrolled.

Efficacy of cinacalcet in achieving K/DOQI treatment goals

iPTH. In accordance with the study enrollment criteria, almost all subjects had iPTH values at baseline that exceeded the recommended K/DOQI target. After treatment, 56% of subjects treated with cinacalcet achieved mean iPTH concentrations at or below the upper limit of the K/DOQI target range [≤300 pg/mL (31.8 pmol/L)], compared with 10% of control subjects ($P < 0.001$; Table 3). The median (Q1, Q3) iPTH concentrations during the evaluation phase were 258 (160, 524) pg/mL [27.3 (17.0, 55.5) pmol/L] and 605 (410, 854) pg/mL [64.1 (43.5, 90.5) pmol/L] for cinacalcet and control subjects, respectively (Fig. 2A), compared with baseline values of 596 (429, 863) pg/mL [63.2 (45.5, 91.5) pmol/L] and 564 (411, 785) pg/mL [59.8 (43.6, 83.2)] pmol/L, respectively. Thirty-three percent of cinacalcet-treated subjects and 9% of control subjects had a mean iPTH value of 150 to 300 pg/mL (15.9 to 31.8 pmol/L), corresponding to the full K/DOQI range. Thirty-seven percent of cinacalcet-treated subjects had mean iPTH levels of 100 to 250 pg/mL (10.6 to 26.5 pmol/L), the target range specified by the titration guidelines in the original studies.

Ca × P. At baseline, 37% and 34% of cinacalcet-treated and control subjects, respectively, had mean Ca × P values below the K/DOQI target of 55 mg^2/dL^2 (4.44 $mmol^2/L^2$). After treatment, 65% of subjects receiving cinacalcet achieved the Ca × P target, compared with 36% in the control group ($P < 0.001$; Table 3). During the evaluation phase, the median (Q1, Q3) Ca × P concentration was 48.1 (39.3, 60.4) mg^2/dL^2 [3.88 (3.17, 4.87) $mmol^2/L^2$] in the cinacalcet-treated group, but remained above the K/DOQI target at 58.7 (51.3, 67.0) mg^2/dL^2 [4.74 (4.14, 5.41) $mmol^2/L^2$] in the control group (Fig. 2B).

Table 3. Overall achievement of the K/DOQI targets at baseline and during the evaluation phase in cinacalcet and control subjects

K/DOQI target	Cinacalcet ($N = 547$)	Control ($N = 409$)	
iPTH ≤300 pg/mL[b]	*N* (%)	*N* (%)	
Baseline	2 (<1)	2 (<1)	*P* value[a]
Post treatment	307 (56)	42 (10)	<0.001
Serum calcium 8.4–9.5 *mg/dL*			
Baseline	176 (32)	133 (33)	
Post treatment	270 (49)	100 (24)	<0.001
Serum phosphorus 3.5–5.5 *mg/dL*			
Baseline	179 (33)	126 (31)	
Post treatment	250 (46)	136 (33)	<0.001
Ca × P <55 mg^2/dL^2			
Baseline	203 (37)	139 (34)	
Post treatment	357 (65)	148 (36)	<0.001
iPTH ≤300 *pg/mL*[b] and Ca × P <55 mg^2/dL^2			
Baseline	0 (0)	0 (0)	
Post treatment	224 (41)	25 (6)	<0.001

Abbreviations are: iPTH, intact parathyroid hormone; Ca × P, calcium-phosphorus product. Note: To convert PTH in pg/mL to pmol/L, multiply by 0.105; calcium in mg/dL to mmol/L, multiply by 0.2495; phosphorus in mg/dL to mmol/L, multiply by 0.3229; Ca × P in mg^2/dL^2 to $mmol^2/L^2$, multiply by 0.0807.

[a]Comparing achievement of the K/DOQI target between cinacalcet HCl and control during the evaluation phase.

[b]K/DOQI target for PTH is 150 to 300 pg/mL.

Serum phosphorus. Approximately one third of subjects in each treatment group had mean serum phosphorus values within the K/DOQI range [3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L)] at baseline (Table 3). After treatment, 46% of subjects given cinacalcet achieved a mean serum phosphorus level within this range, compared with 33% of control subjects ($P < 0.001$, Table 3). The median (Q1, Q3) serum phosphorus level during the evaluation phase was 5.3 (4.4, 6.4) mg/dL [1.71 (1.42, 2.07) mmol/L] in the cinacalcet group, compared with 5.9 (5.1, 6.7) mg/dL [1.91 (1.65, 2.16) mmol/L] in the control group (Fig. 2C).

Serum calcium. At baseline, 32% and 33% of subjects in the cinacalcet and control groups, respectively, had mean serum calcium concentrations within the K/DOQI target range [8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L), adjusted for serum albumin; Table 2]. Following treatment with cinacalcet, a significantly greater proportion of subjects achieved the K/DOQI target range for serum calcium, compared with control subjects (49% vs. 24%, $P < 0.001$; Table 3). The median (Q1, Q3) serum calcium concentration during the evaluation phase decreased to 9.1 (8.5, 9.7) mg/dL [2.27 (2.12, 2.42) mmol/L] in the cinacalcet group, compared with a slight increase to 9.9 (9.5, 10.4) mg/dL [2.47 (2.37, 2.59) mmol/L] in the control group (Fig. 2D).

iPTH and Ca × P. The combined end point of iPTH ≤300 pg/mL (31.8 pmol/L) and Ca × P < 55 mg^2/dL^2 (4.44 $mmol^2/L^2$) was achieved by 41% of cinacalcet-treated subjects compared with only 6% of control subjects ($P < 0.001$; Fig. 3, Table 3). In addition, the proportion of cinacalcet-treated subjects achieving this combined end point continued to increase throughout the study (Fig. 3).

Achievement of K/DOQI goals in individual studies

Achievement of the four key K/DOQI treatment goals for secondary HPT was also examined in the individual studies. Achievement was comparable among studies and similar to the combined analysis (Figs. 4A to C).

Subgroup analysis

Achievement of K/DOQI targets was analyzed for subgroups defined by baseline iPTH and Ca × P. After treatment, 81 and 60% of cinacalcet-treated subjects in the iPTH 300 to 500 and 501 to 800 pg/mL (31.8 to 53.0 and 53.1 to 84.8 pmol/L) subgroups achieved an iPTH ≤300 pg/mL (31.8 pmol/L) compared with 21 and 4%, respectively, of control subjects (Fig. 5A). Among those with baseline iPTH >800 pg/mL (84.8 pmol/L), a level at which parathyroidectomy is often recommended, 22% of subjects receiving cinacalcet achieved the iPTH ≤300 pg/mL (31.8 pmol/L) target after only 26 weeks of therapy, compared with 1% of control subjects. Similar proportions of cinacalcet-treated subjects (46% to 60%) achieved an iPTH ≤300 pg/mL (31.8 pmol/L) regardless of Ca × P subgroup (Fig. 5B). There was no effect of gender or duration of dialysis (vintage) on the PTH suppressive effects of cinacalcet.

In all subgroups, the proportion of subjects achieving the Ca × P <55 mg^2/dL^2 (4.44 $mmol^2/L^2$) target was greater in the cinacalcet group compared with the control group. Among subjects with a Ca × P ≤70 mg^2/dL^2 (5.65 $mmol^2/L^2$) at baseline, 71% to 80% achieved the K/DOQI target for Ca × P in the cinacalcet subgroups during the evaluation phase, and the magnitude of response was similar for all iPTH subgroups [300 to 500, 501 to 800, and >800 pg/mL (31.8 to 53.0, 53.1 to 84.8, and >84.8 pmol/L)]. By comparison, in control subjects who had Ca × P >70 mg^2/dL^2 (5.65 $mmol^2/L^2$) at baseline, the percentage of subjects who achieved the Ca × P target declined as iPTH increased (61%, 38%, and 25% for the respective baseline iPTH subgroups). In subjects with Ca × P levels >70 mg^2/dL^2 (5.65 $mmol^2/L^2$), cinacalcet treatment enabled 37% of subjects to reduce their Ca × P value to <55 mg^2/dL^2 (4.44 $mmol^2/L^2$), compared with 10% of control subjects (Fig. 5B). Trends across subgroups for achievement of K/DOQI targets for serum calcium and phosphorus were similar to those observed for achievement of Ca × P (Fig. 5A and B).

Concomitant therapy

The proportions of cinacalcet-treated subjects with a decrease, no change, or increase in vitamin D sterol dose from baseline compared with the evaluation phase were

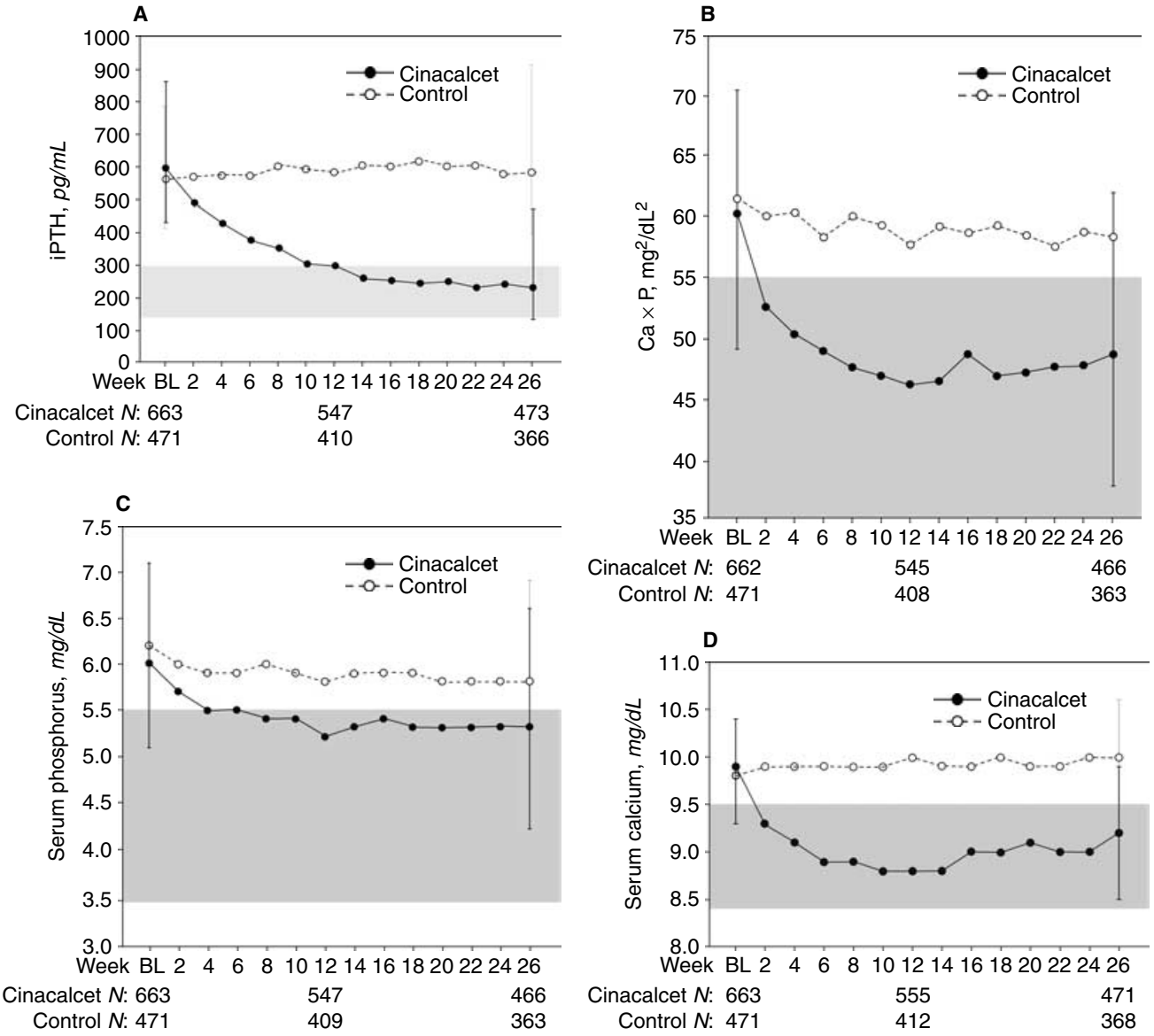


Fig. 2. Median (*A*) iPTH, (*B*) Ca × P, (*C*) serum phosphorus, and (*D*) serum calcium levels of subjects in the cinacalcet or control groups at each study visit. Error bars indicate interquartile ranges, Q1 and Q3. The shaded region for each graph indicates the K/DOQI target range. BL, baseline.

generally similar to the proportions of control subjects with these changes (Table 4). Changes in calcium-based phosphate binders and sevelamer were also similar, with the exception that more control subjects required an increase in sevelamer (Table 4). For studies A and C, there was uniformity of calcium-based phosphate binder brand type, allowing for data on elemental calcium intake to be calculated. The median (10%, 90% range) change in elemental calcium intake from binder per day was 0 (–500, 500) mg and 0 (–501, 334) mg in the cinacalcet and control arms, respectively. More subjects in the cinacalcet group initiated calcium-based binders during the study compared with control (13% vs. 8%, $P = 0.02$); elemental calcium intake for these subjects was similar in both groups. Overall, the estimated exogenous calcium intake from phosphate binders was essentially unchanged in cinacalcet-treated and control subjects. Median doses of vitamin D and sevelamer were also similar between treatment groups at baseline and end of study.

Safety data

Cinacalcet, at doses ranging from 30 to 180 mg once per day, was generally well tolerated by study subjects. For the 307 subjects who achieved a mean iPTH ≤300 pg/mL (31.8 pmol/L), 79% were receiving doses of 30 or 60 mg of cinacalcet at the time of their first iPTH measurement ≤300 pg/mL, and the median dose of cinacalcet was 30 mg.

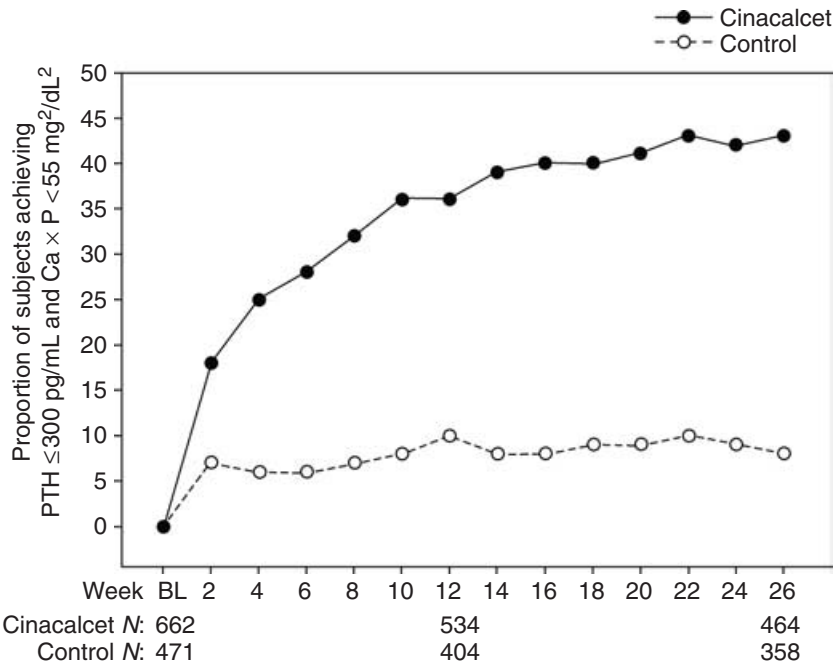


Fig. 3. Proportion of subjects with both mean iPTH ≤300 pg/mL and mean Ca × P level <55 mg²/dL² by study week. BL, baseline.

Adverse events that occurred ≥5% more frequently in cinacalcet-treated subjects compared with control subjects were nausea (31% vs. 19%, respectively) and vomiting (27% vs. 15%, respectively). These events were generally mild to moderate in severity and brief in duration. In the cinacalcet group, only 8% and 9% of subjects had two or more episodes of nausea or vomiting, respectively. A similar number of serious adverse events occurred in each group (29% vs. 31% in the cinacalcet and control groups, respectively). Fifteen percent of cinacalcet-treated subjects withdrew from the study because of adverse events, compared with 8% of control subjects. Withdrawals due to adverse events in the cinacalcet group were primarily due to nausea or vomiting. A total of 29 subjects died during the studies (2% of the cinacalcet group and 3% of the control group); none of the deaths were considered to be related to treatment.

In the combined studies, serum calcium concentrations below 7.5 mg/dL (1.88 mmol/L) occurred on at least two consecutive measurements in 5% of cinacalcet-treated subjects and <1% of control subjects. These values were rarely associated with symptoms, and returned to a value above 8.0 mg/dL (2.00 mmol/L) after modifying the doses of calcium supplements, phosphate binders, vitamin D, or cinacalcet. One subject in each treatment group withdrew because of hypocalcemia.

DISCUSSION

Secondary HPT is associated with significant morbidity and mortality [4–8]. Evidence suggests that maintaining metabolic parameters within the K/DOQI target ranges is of significant clinical relevance [12], and recent observational data demonstrate that the K/DOQI treatment goals are not easily achieved, or maintained, with traditional therapeutic options for secondary HPT [10]. This secondary analysis of three large randomized, placebo-controlled studies of nearly identical design demonstrates that treatment with cinacalcet effectively reduces iPTH, calcium, phosphorus, and Ca × P to below the upper limits of the recommended K/DOQI target ranges in subjects on dialysis with secondary HPT. Nearly all subjects had iPTH values >300 pg/mL (31.8 pmol/L) at baseline, consistent with eligibility criteria, and approximately two thirds of subjects had baseline values for serum calcium, phosphorus, and Ca × P above the K/DOQI targets. Significantly, more than half of subjects treated with cinacalcet achieved a mean iPTH ≤300 pg/mL (31.8 pmol/L), and 41% simultaneously achieved both a mean iPTH level ≤300 pg/mL (31.8 pmol/L) and a mean Ca × P value <55 mg^2/dL^2 (4.44 $mmol^2/L^2$), reflecting the ability of cinacalcet to reduce both iPTH and Ca × P. Cinacalcet also increased achievement of K/DOQI targets in subjects with iPTH >800 pg/mL (84.8 pmol/L) and in those with elevated Ca × P, despite a relatively short treatment time, thereby demonstrating its utility in subjects who have laboratory values that preclude the use of vitamin D. Furthermore, cinacalcet was highly effective in bringing subjects with less severe abnormalities in PTH and Ca × P into target, confirming its efficacy in mild, as well as in moderate to severe, secondary HPT.

Elevated serum calcium and phosphorus concentrations may predispose patients to soft-tissue and vascular calcification [9, 25] and an increased risk of cardiovascular

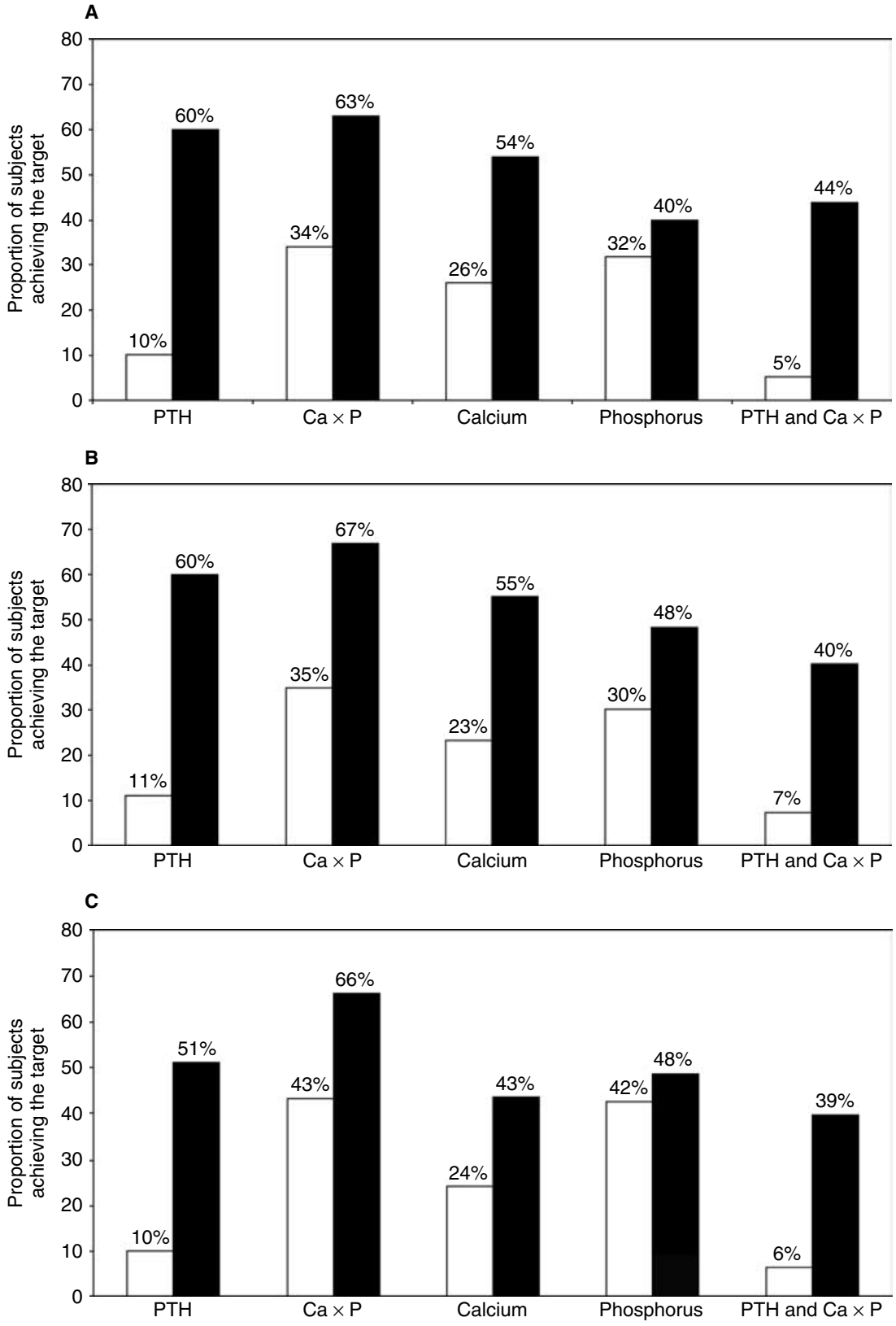


Fig. 4. Achievement of K/DOQI targets during the evaluation phase of each individual study. (*A*) Study A, (*B*) Study B, and (*C*) Study C. The targets were iPTH ≤300 pg/mL, serum calcium 8.4 to 9.5 mg/dL, serum phosphorus 3.5 to 5.5 mg/dL, and Ca × P <55 mg^2/dL^2.

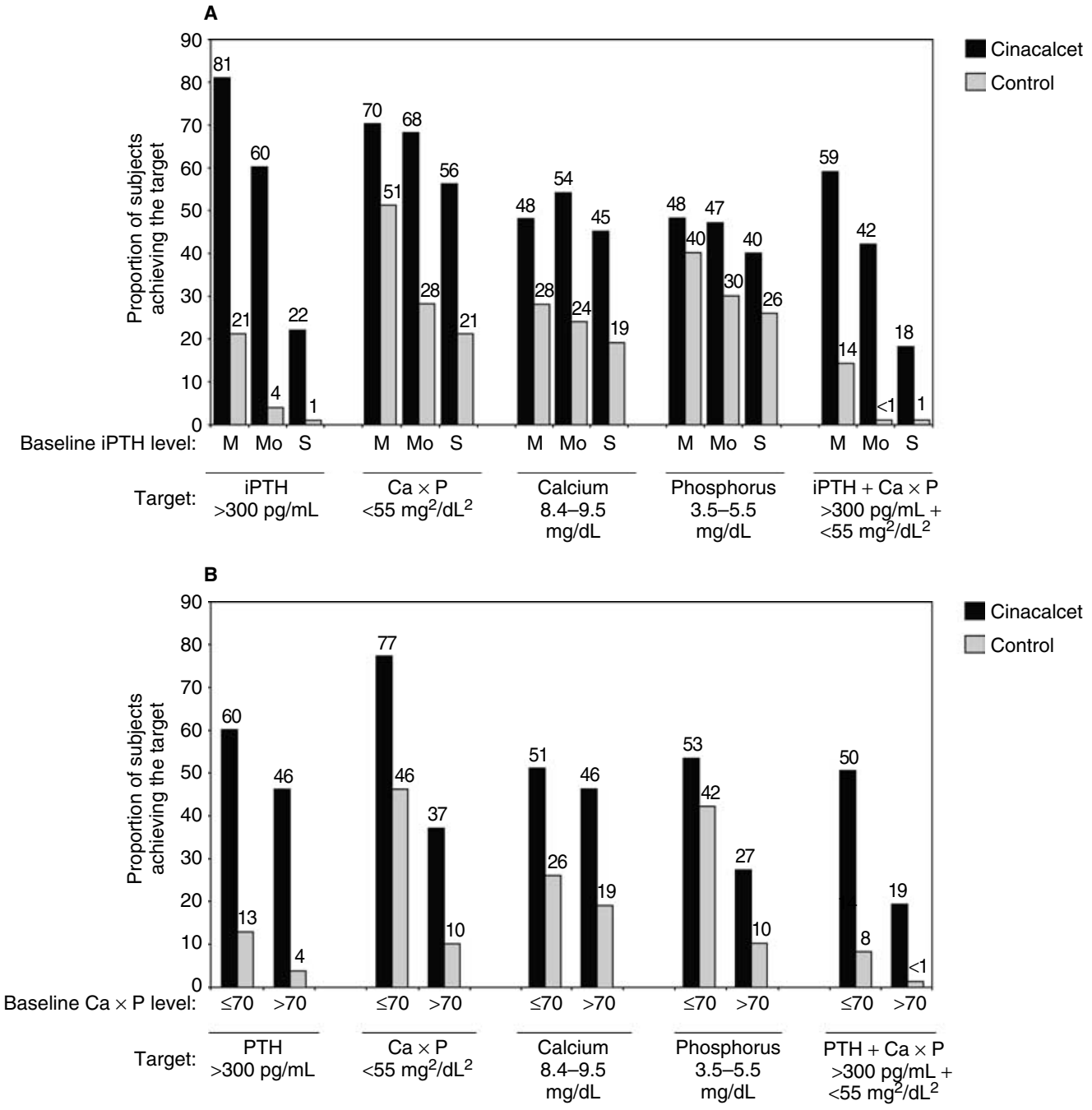


Fig. 5. Achievement of K/DOQI targets during the evaluation phase according to subgroups defined by (*A*) PTH level at baseline [M, mild, iPTH 300–500 pg/mL (*N* = 191 cinacalcet, *N* = 169 control); Mo, moderate, iPTH 501–800 pg/mL (*N* = 190 cinacalcet, *N* = 148 control); S, severe, iPTH >800 pg/mL (*N* = 164 cinacalcet, *N* = 91 control)] and (*B*) Ca × P level at baseline [≤70 mg²/dL² (*N* = 391 cinacalcet, *N* = 299 control); >70 mg²/dL² (*N* = 155 cinacalcet, *N* = 110 control)].

and all-cause mortality [4, 5]. In this study, cinacalcet controlled PTH while simultaneously reducing calcium and phosphorus, the most challenging hurdle in achieving the K/DOQI guidelines [5]. In contrast, most studies evaluating treatment of secondary HPT with vitamin D demonstrate an increase in serum calcium and/or phosphorus [26–29]. Vitamin D is effective in suppressing PTH and, therefore, likely decreases the efflux of calcium and phosphorus from bone [14]. However, these potential positive effects may be outweighed by enhanced intestinal absorption of calcium and phosphate, which may lead to a net increase in calcium and phosphorus in the serum [10, 11, 18]. In contrast, both calcium and phosphorus concentrations decrease in response to cinacalcet treatment,

Table 4. Changes in concomitant medication use

Dose changes[a]	Cinacalcet	Control
Proportion of patients with change in vitamin D sterol dose[b]		
Decrease	14%	15%
No change	27%	30%
Increase	11%	12%
Proportion of patients with change in calcium-based phosphate binder dose[c]		
Decrease	3%	6%
No change	26%	24%
Increase	16%	17%
Proportion of patients with change in sevelamer dose		
Decrease	5%	1%
No change	31%	25%
Increase	24%	36%

[a]Changes represent mean over efficacy-assessment phase compared to baseline for patients using vitamin D at both baseline and the efficacy-assessment phase.
[b]Excludes patients using more than 1 type of vitamin D sterol.
[c]Excludes patients using more than 1 type of calcium-based phosphate binder.

most likely as a result of decreased mineral efflux from bone in response to reductions in PTH, without an additional intestinal source of mineral [21, 22]. Based on the data demonstrating similar changes in vitamin D and phosphate binder use in the two arms, reductions in calcium and phosphorus were likely attributable to cinacalcet therapy.

These analyses provide information on the achievement of K/DOQI targets after intervention with cinacalcet treatment in a large number of geographically diverse subjects. Nonetheless, some important limitations should be noted. These studies were 6 months in duration, and longer-term maintenance of subjects within K/DOQI target ranges must be demonstrated, including effects on bone. Preliminary results indicate that cinacalcet is effective in reducing iPTH and Ca × P levels in subjects for up to 3 years [abstract; Moe et al, *J Am Soc Nephrol* 14:463A, 2003], suggesting the effects of cinacalcet are sustained over time. In addition, because the maximal reduction of iPTH in response to cinacalcet occurs approximately 4 hours after dosing [26], the measurement of iPTH at approximately 24 hours after dosing may underestimate the total iPTH suppression that occurs.

The impact of several aspects of the study design on the achievement of the K/DOQI targets is also notable. Because the K/DOQI guidelines were only recently developed, the dosing algorithm for iPTH was not prospectively designed to achieve the K/DOQI target range. Instead, the phase 3 study target for iPTH was selected as 100 to 250 pg/mL (10.6 to 26.5 pmol/L), consistent with clinical practice at the time of protocol development [30–32]. Thus, some subjects may have been titrated to iPTH levels below the lower end of the K/DOQI target [150 pg/mL (15.9 pmol/L)], while remaining within the range accepted by the protocol. Many factors can influence the optimal PTH level; K/DOQI recommends iPTH 150 to 300 (15.9 to 31.8 pmol/L) as a value supported by available evidence to represent adequate control of PTH in patients on dialysis [12]. Finally, because the study protocols limited changes in vitamin D sterols during the study, the achievement of K/DOQI targets for Ca × P, calcium, and phosphorus reported here may underestimate actual achievement of these targets when cinacalcet is used in clinical practice without restrictions on vitamin D use.

CONCLUSION

Significantly more cinacalcet-treated subjects achieved K/DOQI targets for PTH, calcium, phosphorus, and Ca × P compared with control subjects on traditional therapy, across a broad population and regardless of severity of disease. More effective control of secondary HPT facilitated by cinacalcet may ultimately improve outcomes among patients with CKD.

ACKNOWLEDGMENTS

This manuscript is dedicated to the late Jack Coburn, who has been an inspiration to the field of renal osteodystrophy, and to all of us as scientists. The authors wish to thank the investigators, staff, and patients who participated in the cinacalcet 20000172 (Study A), 20000183 (Study B), and 20000188 (Study C) studies. Holly Brenza Zoog assisted in the preparation of the manuscript. This work was supported by Amgen, Thousand Oaks, California.

APPENDIX

In addition to the authors, the following investigators participated in the three phase 3 studies:

20000172: A. Abu-Alfa (New Haven, CT); S. Acchiardo (Memphis, TN); M. Anger (Thornton, CO); J. Anzalone (Wenatchee, WA); J. Arruda (Chicago, IL); M. Avram (Brooklyn, NY); M. Belledonne (Rockville, MD); J. Brennan (Fort Worth, TX); D. Bushinski (Rochester, NY); E. Brown (Stamford, CT); P. Campbell (Edmonton, Canada); R. Clark (Lafayette, LA); L. Cohen (Cincinnati, OH); R. Cohen (Philadelphia, PA); C. Corpier (Dallas, TX); D. Coyne (St. Louis, MO); R.M. Culpepper (Mobile, AL); M. Curzi (Walnut Creek, CA); J. Diego (Miami, FL); M. Faber (Detroit, MI); G. Fadda (San Diego, CA); A. Fine (Winnipeg, Canada); D. Fischer (Cincinnati, OH); L. Garret, Jr. (Raleigh, NC); M. Germain (W. Springfield, MA); G. Hercz (Toronto, Canada); Y. Jean-Claude (New York, NY); M. Kaplan (Nashville, TN); M. Koren (Jacksonville, FL); K.S. Kant (Cincinnati, OH); A. Kshirsagar (Chapel Hill, NC); M. Joy (Chapel Hill, NC); J. Lewis (Birmingham, AL); J. Lindberg (New Orleans, LA); B. Ling (Ashville, NC); N.D. Makoff (Los Angeles, CA); N. Mansour (Memphis, TN); B. Michael (Philadelphia, PA); S. Mischel (Hammond, IN); G. Nassar (Houston, TX); N. Pokroy (Las Vegas, NV); R. Provenzano (Detroit, MI); S.N. Rahman (Houston, TX); R. Raja (Philadelphia, PA); S. Rosansky (Columbia, SC); C. Shadur (Des Moines, IA); D. Sherrard (Seattle, WA); M. Silver (Cleveland, OH); S. Soroka (Halifax, Nova Scotia); D. Spiegel (Denver, CO); S. Sprague (Evanston, IL); R. Sreedhara (New Port Richey, FL); C. Stehman-Breen (Seattle, WA); J.R. Sterrett (Patterson, NJ); J. Strom (Boston, MA); K. Tucker (Simi Valley, CA); I. Wahba (Portland, OR); D. Wombolt (Norfolk, VA); S. Zeig (Pembroke Pines, FL).

20000183: A. Albertazzi (Modena, Italy); A. Alvestrand (Huddinge, Sweden); U. Bahner (Würzburg, Germany); J. Barata (Amadora, Portugal); J. Berglund (Danderyd, Sweden); Y. Berland (Marseille, France); J. Braun (Nürnberg, Germany); H.S. Brink (Enschede, Netherlands);

G. Cancarini (Brescia, Italy); G. Cannella (Genova, Italy); F. Caravaca (Badajoz, Spain); J. Chanard (Reims, France); G. Civati (Milano, Italy); P. Conlon (Dublin, Ireland); A.L.M. De Francisco (Santander, Spain); H. Deuber (Erlangen, Germany); A. Disney (Woodville, Australia); P. Evenepoel (Leuven, Belgium); A. Ferreira (Vila Franca de Xira, Portugal); R. Fiedler (Halle/Salle, Germany); A. Fournier (Amiens, France); J. Frazão (Porto, Portugal); H. Geiger (Frankfurt, Germany); P. Gerlag (Veldhoven, The Netherlands); R. Gokal (Manchester, United Kingdom); A. Gomes da Costa (Lisbon, Portugal); M. González (Barcelona, Spain); E. Hagen (Amersfoort, The Netherlands); W. Höerl (Wien, Austria); H. Holzer (Graz, Austria); B. Hutchison (Nedlands, Australia); E. Imbasciati (Lodi, Italy); M. Jadoul (Brussels, Belgium); P. Jaeger (Nice, France); D. Johnson (Woolloongabba, Australia); P. Kerr (Clayton, Victoria, Australia); R. Kramar (Wels, Austria); M. Laville (Lyon, France); F. Locatelli (Lecco, Italy); A. Martín-Malo (Córdoba, Spain); G. Mayer (Innsbruck, Austria); G. Mellotte (Dublin, Ireland); P. Messa (La Spezia, Italy); U. Neyer (Feldkirch, Austria); K. Ølgaard (Copenhagen, Denmark); P. Ponce (Corroios, Portugal); H. Reichel (Villingen-Schwenningen, Germany); E. Ritz (Heidelberg, Germany); J. Rodicio (Madrid, Spain); H. Saha, (Tampere, Finland); G. Stein (Jena, Germany); H.K. Stummvoll (Linz, Austria); M. Suranyi (Liverpool, Australia); C. Tielemans (Brussels, Belgium); V. Torregrosa (Barcelona, Spain); P. Ureña-Torres (Aubervilliers, France); M. Van den Dorpel (Rotterdam, The Netherlands); Y. Vanrenterghem (Leuven, Belgium); R. Walker (Parkville, Australia); B. Wikström (Uppsala, Sweden); M. Wilkie (Sheffield, United Kingdom).

20000188: H. Abboud (San Antonio, TX); S. Adler (Hawthorne, NY); A. Agarwal (Columbus, OH); H. Al-Bander (San Leandro, CA); J. Alexiewicz (San Diego, CA); J. Arruda (Chicago, IL); H. Azad (Orange, CA); L. Balsam (East Meadow, NY); V. Bansal (Maywood, IL); P. Barre (Montréal, Canada); S. Blumenthal (West Allis, WI); M. Borah (San Francisco, CA); C. Charytan (Flushing, NY); R. Clark (Lafayette, LA); S. Cooksey (Pittsburgh, PA); S. Cournoyer (Greenfield Park, Canada); B. Culleton (Calgary, Canada); C. Deziel (Montréal, Canada); D. Domoto (St. Louis, MO); M. Esquenazi (Miami, FL); G. Fadda (San Diego, CA); F. Finkelstein (New Haven, CT); M. Fraenkel (Heidelburg, Germany); A. Gillies (Newcastle, Australia); J. Goodwin (Raleigh, NC); V. Gura (Beverly Hills, CA); J. Kappel (Saskatoon, Canada); G. Kightley (Richmond, VA); N. Kopyt (Allentown, PA); SS. Lam (New Westminster, Canada); S. Langlois (Québec, Canada); M. LeBlanc (Montréal, Canada); D. LeGault (Grand Rapids, MI); M. Leiserowitz (Las Vegas, NV); Y.H. Lien (Tucson, AZ); J. Lindberg (New Orleans, LA); N.M. Lunde (Arden Hills, MN); R. Lynn (Bronx, NY); J. MacLaurin (Columbus, OH); R. Mehta (San Diego, CA); N. Mittman (Brooklyn, NY); W. Mullican (Evansville, IN); S. Murphy (St. John's, Canada); J. Navarro (Tampa, FL); S. Noble (Shreveport, LA); R. Ouseph (Louisville, KY); S. Roger (Gosford, Australia); L. Roy (Montréal, Canada); M. Salifu (Brooklyn, NY); W. Shapiro (Brooklyn, NY); C. Spalding (Albuquerque, NM); M. Spira (Los Angeles, CA); S. Sprague (Evanston, IL); M. Stegman (Memphis, TN); V. Thakur (New Orleans, LA); T. Vokes (Chicago, IL); M. Weinberg (Providence, RI); G. Wong (Mississauga, Canada); S. Zeig (Pembroke Pines, FL).

Reprint requests to Sharon M. Moe, M.D., Associate Professor of Medicine, Associate Dean for Research Support, Indiana University School of Medicine, 1001 W. 10th Street, OPW 526, Indianapolis, IN 46202.
E-mail: smoe@iupui.edu

REFERENCES

1. Feinfeld DA, Sherwood LM: Parathyroid hormone and $1,25(OH)_2D_3$ in chronic renal failure. *Kidney Int* 33:1049–1058, 1988
2. Slatopolsky E, Bricker NS: The role of phosphorus restriction in the prevention of secondary hyperparathyroidism in chronic renal disease. *Kidney Int* 4:141–145, 1973
3. Martinez I, Saracho R, Montenegro J, Llach F: The importance of dietary calcium and phosphorous in the secondary hyperparathyroidism of patients with early renal failure. *Am J Kidney Dis* 29:496–502, 1997
4. Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: A national study. *Am J Kidney Dis* 31:607–617, 1998
5. Ganesh SK, Stack AG, Levin NW, *et al*: Association of elevated serum PO_4, Ca × PO_4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 12:2131–2138, 2001
6. Pasieka JL, Parsons LL: A prospective surgical outcome study assessing the impact of parathyroidectomy on symptoms in patients with secondary and tertiary hyperparathyroidism. *Surgery* 128:531–539, 2000
7. Sherrard DJ, Hercz G, Pei Y, *et al*: The spectrum of bone disease in end-stage renal failure—An evolving disorder. *Kidney Int* 43:436–442, 1993
8. Malluche H, Faugere M: Renal bone disease 1990: An unmet challenge for the nephrologist. *Kidney Int* 38:193–211, 1990
9. Goodman WG, Goldin J, Kuizon BD, *et al*: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342:1478–1483, 2000
10. Block G, Port FK: Calcium phosphate metabolism and cardiovascular disease in patients with chronic kidney disease. *Semin Dial* 16:140–147, 2003
11. Moe SM, Drueke TB: Management of secondary hyperparathyroidism: The importance and the challenge of controlling parathyroid hormone levels without elevating calcium, phosphorus, and calcium-phosphorus product. *Am J Nephrol* 23:369–379, 2003
12. National Kidney Foundation: K/DOQI clinical practice guidelines: Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 42(Suppl 4):S1–S201, 2003
13. Aparicio M, Combe C, Lafage MH, *et al*: In advanced renal failure, dietary phosphorus restriction reverses hyperparathyroidism independent of changes in the levels of calcitriol. *Nephron* 63:122–123, 1993
14. Andress DL, Norris KC, Coburn JW, *et al*: Intravenous calcitriol in the treatment of refractory osteitis fibrosa of chronic renal failure. *N Engl J Med* 321:274–279, 1989
15. Martin KJ, Gonzalez EA, Gellens ME, *et al*: 19–Nor-1-alpha-25-dihydroxyvitamin D_2 (paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 9:1427–1432, 1998
16. Salusky IB, Kuizon BD, Belin TR, *et al*: Intermittent calcitriol therapy in secondary hyperparathyroidism: A comparison between oral and intraperitoneal administration. *Kidney Int* 54:907–914, 1998
17. Ginsburg DS, Kaplan EL, Katz AI: Hypercalcaemia after oral calcium- carbonate therapy in patients on chronic haemodialysis. *Lancet* 1:1271–1274, 1973
18. Gonella M, Calabrese G, Vagelli G, *et al*: Effects of high $CaCO_3$ supplements on serum calcium and phosphorus in patients on regular hemodialysis treatment. *Clin Nephrol* 24:147–150, 1985
19. Henderson J, Altmann P: Sevelamer. *Nephron Clin Pract* 94:c53–58, 2003
20. Gallieni M, Brancaccio D, Antonucci F, *et al*: Twice versus thrice weekly administration of intravenous calcitriol in dialysis patients: A randomized prospective trial. *Clin Nephrol* 53:188–193, 2000
21. Lindberg JS, Moe SM, Goodman WG, *et al*: The calcimimetic AMG 073 reduces parathyroid hormone and calcium × phosphorus in secondary hyperparathyroidism. *Kidney Int* 63:248–254, 2003
22. Quarles LD, Sherrard DJ, Adler S, *et al*: The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. *J Am Soc Nephrol* 14:575–583, 2003
23. Block GA, Martin KJ, de Francisco ALM, *et al*: Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *New Engl J Med* 350:1516–1525, 2004
24. Kuritz SJ, Landis JR, Koch GG: A general overview of Mantel-Haenszel methods: Applications and recent developments. *Annu Rev Public Health* 9:123–160, 1988
25. Block GA, Port FK: Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: Recommendations for a change in management. *Am J Kidney* Dis 35:1226–1237, 2000
26. Goodman WG, Hladik GA, Turner SA, *et al*: The calcimimetic

agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. *J Am Soc Nephrol* 13:1017–1024, 2002
27. Teng M, Wolf M, Lowrie E, *et al*: Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 349:446–456, 2003
28. Sprague SM, Llach F, Amdahl M, *et al*: Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int* 63:1483–1490, 2003
29. Quarles LD, Yohay DA, Carroll BA, *et al*: Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD. *Kidney Int* 45:1710–1721, 1994
30. Gallieni M, Brancaccio D, Padovese P, *et al*: Low-dose intravenous calcitriol treatment of secondary hyperparathyroidism in hemodialysis patients. *Kidney Int* 42:1191–1198, 1992
31. Quarles LD, Lobaugh B, Murphy G: Intact parathyroid hormone overestimates the presence and severity of parathyroid-mediated osseous abnormalities in uremia. *J Clin Endocrinol Metab* 75:145–150, 1992
32. Hutchison AJ, Whitehouse RW, Boulton HF, *et al*: Correlation of bone histology with parathyroid hormone, vitamin D3, and radiology in end-stage renal disease. *Kidney Int* 44:1071–1077, 1993