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The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis

Paolo Raggi[1], Glenn M. Chertow[2], Pablo Urena Torres[3], Botond Csiky[4], Agostino Naso[5], Kaldun Nossuli[6], Moustafa Moustafa[7], William G. Goodman[8], Nicole Lopez[8], Gerry Downey[9], Bastian Dehmel[10], Jürgen Floege[11] and on behalf of the ADVANCE Study Group

[1]Division of Cardiology, Emory University, Atlanta, GA, USA, [2]Division of Nephrology, Stanford University School of Medicine, Palo Alto, CA, USA, [3]Service de Nephrologie Dialyse, Clinique du Landy, Saint Ouen, France, [4]Fresenius Dialysis Center, University of Pecs, Pecs, Hungary, [5]Department of Nephrology, University of Padova, Padova, Italy, [6]Washington Nephrology Associates, Bethesda, MD, USA, [7]South Carolina Nephrology and Hypertension Center, Inc., Orangeburg, SC, USA, [8]Amgen Inc., Thousand Oaks, CA, USA, [9]Amgen Ltd., Uxbridge, UK, [10]Amgen GmbH, Zug, Switzerland and [11]Division of Nephrology, RWTH University of Aachen, Aachen, Germany

Correspondence and offprint requests to: Paolo Raggi; E-mail: praggi@emory.edu

Abstract

Background. This prospective, randomized, controlled trial compared the progression of vascular and cardiac valve calcification in 360 prevalent adult hemodialysis patients with secondary hyperparathyroidism treated with either cinacalcet plus low-dose vitamin D sterols or flexible doses of vitamin D sterols alone.

Methods. Eligible subjects were on hemodialysis for ≥3 months with parathyroid hormone (PTH) >300 pg/mL or PTH 150–300 pg/mL with calcium–phosphorus product >50 mg^2/dL^2 while receiving vitamin D. All subjects received calcium-based phosphate binders. Coronary artery calcification (CAC) and aorta and cardiac valve calcium scores were determined both by Agatston and volume scoring using multi-detector computed tomography. Subjects with Agatston CAC scores ≥30 were randomized to cinacalcet (30–180 mg/day) plus low-dose calcitriol or vitamin D analog (≤2 μg paricalcitol equivalent/dialysis), or flexible vitamin D therapy. The primary end point was percentage change in Agatston CAC score from baseline to Week 52.

Results. Median (P10, P90) Agatston CAC scores increased 24% (−22%, 119%) in the cinacalcet group and 31% (−9%, 179%) in the flexible vitamin D group (P = 0.073). Corresponding changes in volume CAC scores were 22% (−12%, 105%) and 30% (−6%, 133%; P = 0.009). Increases in calcification scores were consistently less in the aorta, aortic valve and mitral valve among subjects treated with cinacalcet plus low-dose vitamin D sterols, and the differences between groups were significant at the aortic valve.

Conclusions. In hemodialysis patients with moderate to severe secondary hyperparathyroidism, cinacalcet plus low-dose vitamin D sterols may attenuate vascular and cardiac valve calcification.

Keywords: calcification; cinacalcet; hemodialysis; secondary hyperparathyroidism; vitamin D

Introduction

Vascular and cardiac valve calcification are common among patients with chronic kidney disease (CKD) [1,2]. Risk factors associated with the presence and extent of cardiovascular calcification include advanced age, diabetes, tobacco use and, among patients requiring dialysis, longer dialysis vintage [3–6]. Some reports suggest that alterations in calcium and phosphorus metabolism and persistent elevations in plasma parathyroid hormone (PTH) are additional contributors [3–6]. As in the general population, cardiovascular calcification is associated with cardiovascular disease and mortality among patients receiving dialysis, and the disorder progresses rapidly once established [6–9].

A few studies have examined longitudinal changes in vascular and cardiac valve calcification among patients on dialysis [10]. Some indicate that interventions known to affect mineral metabolism systemically, like reducing oral calcium intake from phosphate binders, can decrease rates of progression [11–13]. Clinical reports and experimental evidence also suggest that reductions in plasma PTH after parathyroidectomy diminish the progression of vascular calcification in CKD [14–18], although changes in calcium and phosphorus metabolism after the procedure may contribute to these effects. Whether non-surgical strategies for controlling secondary hyperparathyroidism (sHPT) alter the progression of cardiovascular calcification in humans is unknown.

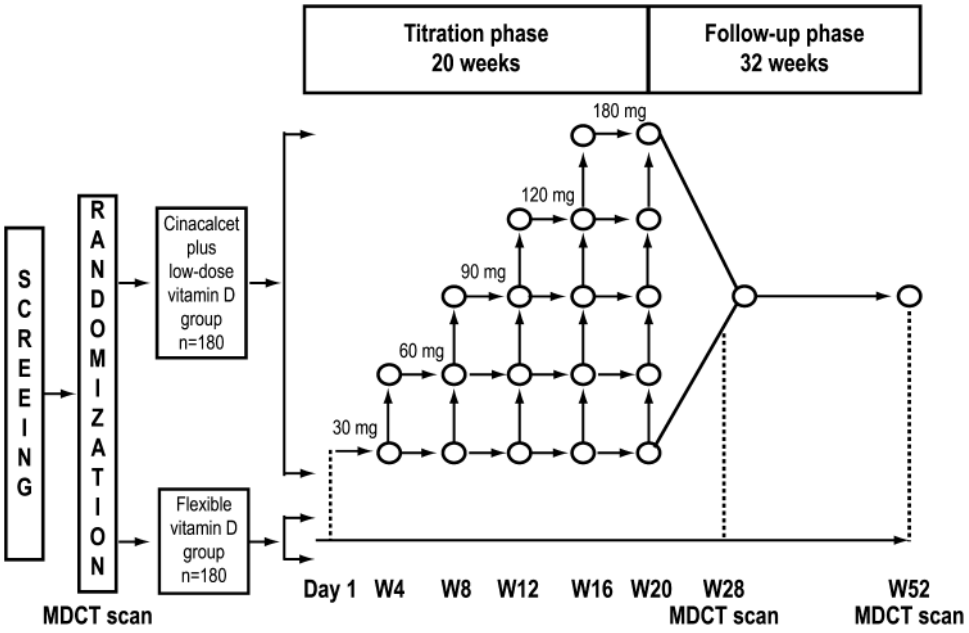

Fig. 1. Study design. MDCT = multi-detector computed tomography.

Cinacalcet and vitamin D sterols both lower plasma PTH concentrations among patients with sHPT, but they have opposite effects on serum calcium and phosphorus concentrations in those with little or no residual kidney function [19–21]. The ADVANCE study (a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in subjects with chronic kidney disease receiving hemodialysis) was undertaken to test the hypothesis that better control of PTH together with lower serum calcium and phosphorus concentrations during treatment with cinacalcet reduces the progression of cardiovascular calcification compared with conventional vitamin D therapy among hemodialysis patients with sHPT. We thus measured vascular and cardiac valve calcification using multi-detector computed tomography (MDCT) before and after 52 weeks of treatment with either cinacalcet plus low doses of calcitriol or vitamin D analogs, or flexible doses of vitamin D sterols alone.

Materials and methods

Patient selection

Details about the ADVANCE study design, characteristics of study participants at baseline, and procedures for measuring vascular and cardiac valve calcification have been published previously [22]. Subjects were 18 years or older, had undergone hemodialysis for ≥3 months, and had biochemical evidence of sHPT with PTH concentrations >300 pg/mL or levels 150–300 pg/mL with Ca × P values >50 mg^2/dL^2 during treatment with vitamin D sterols. Albumin-corrected serum calcium concentrations were ≥8.4 mg/dL, and coronary artery calcification (CAC) scores at screening were ≥30 in all subjects as measured by MDCT. Subjects were randomized to the two treatment arms according to baseline Agatston CAC scores that in the general population define meaningful thresholds: scores = 30–399 (they provide sufficient reproducibility and identify patients at low to intermediate risk), score >400 (representing moderate to high cardiovascular risk) and score >1000 (previous published work demonstrated that this threshold identifies patients at extremely high risk). Additional inclusion and exclusion criteria are summarized elsewhere [22]. Overall, 360 subjects from 90 sites in North America, Europe and Australia participated in the study. The protocol and all study procedures were reviewed and approved by the appropriate ethics committee or independent review board at each site. All participants gave written informed consent. The trial was conducted according to principles of the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT00379899).

Study protocol

Subjects assigned to treatment with cinacalcet using doses of 30–180 mg/day also received low doses of vitamin D sterols equivalent to ≤2 μg paricalcitol with each dialysis (Figure 1) [22]. The control group received flexible doses of vitamin D sterols either orally or intravenously. The therapeutic objective in both groups was to maintain PTH concentrations <300 pg/mL. Calcium-based phosphate-binding agents were used exclusively.

Imaging evaluation

Randomized patients underwent imaging of the chest at baseline and at 28 and 52 weeks using an MDCT scanner with a minimum of 16 slices. Only subjects with baseline Agatston total CAC scores ≥30 were studied to enhance detection of interval changes during follow-up. Previous reports indicate that patients on dialysis without detectable CAC are unlikely to develop new lesions within this interval [23]. Moreover, reproducibility of CAC measurements is greater with higher scores [24], and baseline values above zero are needed to calculate percent change in CAC during follow-up. For each subject, all imaging procedures were done on the same equipment using the same parameters at each session to permit valid image comparisons. Image acquisition was done with either prospective or retrospective electrocardiogram gating with most performed with prospective gating.

Scans started in the upper thorax above the origin of the left main coronary artery, advancing caudally to the level of the diaphragm to include the coronary arteries, the aortic and mitral valve, and portions of the ascending and descending thoracic aorta. All foci within these structures with an attenuation >130 Hounsfield units and a minimum area of 1 mm^2 were considered to be calcified lesions. Images were reconstructed with a 2.5–3.0-mm thickness. Total calcium scores represent the aggregate score for all calcified lesions within the area of interest. Calcium scores were calculated both by the Agatston method [25] and by the volume method [24] as described previously. The variability of the Agatston score is slightly greater than that of the volume score [24]. The Agatston score, however, incorporates the concept of plaque density therefore reflecting the amount of calcium deposited within a calcified lesion. The

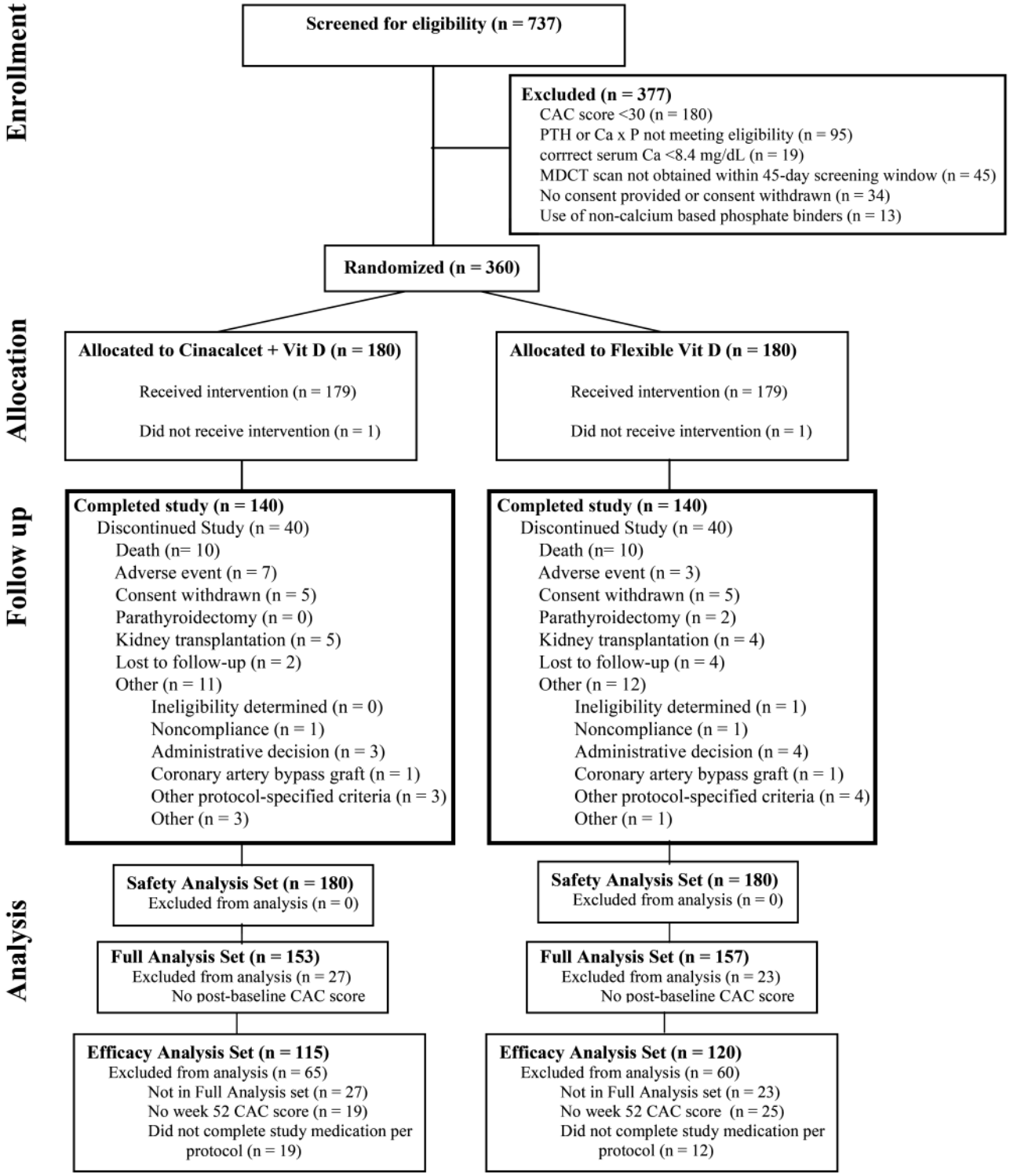

Fig. 2. Subject disposition.

Agatston score was therefore chosen a priori as the primary end point for the current study.

One experienced investigator (PR) reviewed all scans for consistency of interpretation. To assess intra-reader variability, scans from all time points were re-evaluated by the same investigator, blinded to the original result, in a stratified random sample of 10% of enrolled subjects ($n = 36$ subjects and 92 scans). The intra-class correlation coefficient, (between-subject variance)/(between-subject variance + within-subject variance), was 0.958 calculated using a mixed effects model analyzing CAC scores adjusting for visit as a fixed effect and subject as a random effect. The inter-reader correlation coefficient was 0.99 as determined by independent assessments of 35 scans.

Statistical analysis

The primary end point was the percent change in Agatston CAC score from baseline to Week 52. It was estimated that 330 subjects were required to achieve 85% power to detect an absolute difference of 15% between treat-

Table 1. Baseline demographic, disease and medication characteristics

	Cinacalcet group $n = 180$	Control group $n = 180$	All subjects $n = 360$
Sex, *n* (%)			
Women	68 (38)	85 (47)	153 (43)
Men	112 (62)	95 (53)	207 (58)
Age, years	61.2 (12.6)	61.8 (12.8)	61.5 (12.7)
Race, *n* (%)			
White	116 (64)	120 (67)	236 (66)
Black	45 (25)	40 (22)	85 (24)
Hispanic or Latino	11 (6)	14 (8)	25 (7)
Other	8 (4)	6 (3)	14 (4)
Body mass index and blood pressure			
Body mass index, kg/m^2	26.8 (5.2)	27.7 (6.5)	27.2 (5.9)
Systolic blood pressure, mmHg	141.9 (22.8)	140.3 (23.8)	141.1 (23.3)
Diastolic blood pressure, mmHg	76.5 (12.0)	74.9 (13.0)	75.7 (12.5)
Dialysis characteristics			
Median time on hemodialysis (P10, P90), months	37.5 (9.3, 105.0)	36.7 (10.0, 107.5)	36.7 (9.5, 107.0)
Time on dialysis, *n* (%)			
<12 months	26 (14)	26 (14)	52 (14)
12–36 months	62 (34)	62 (34)	124 (34)
>36 months	92 (51)	92 (51)	184 (51)
Medication use history, *n* (%)			
History of calcium-based phosphate binder use	150 (83)	151 (84)	301 (84)
History of sevelamer use	47 (26)	47 (26)	94 (26)
History of lanthanum use	8 (4)	12 (7)	20 (6)
History of other non-calcium-based phosphate binder use	20 (11)	14 (8)	34 (9)
History of calcimimetic use	17 (9)	16 (9)	33 (9)
Baseline vitamin D use	135 (75)	143 (79)	278 (77)
Medical history, *n* (%)			
Diabetes mellitus	75 (42)	81 (45)	156 (43)
Hypertension	168 (93)	170 (94)	338 (94)
Peripheral vascular disease	44 (24)	48 (27)	92 (26)
Cerebrovascular accident	23 (13)	19 (11)	42 (12)
Myocardial infarction	17 (9)	16 (9)	33 (9)
Coronary artery disease	51 (28)	48 (27)	99 (28)
Congestive heart failure	24 (13)	49 (27)	73 (20)
Laboratory parameters			
PTH, pg/mL, median (P10, P90)	432 (243, 1056)	424 (257, 1176)	426 (246, 1106)
Corrected serum calcium, mg/dL	9.4 (0.6)	9.4 (0.6)	9.4 (0.6)
Serum phosphorus, mg/dL	6.0 (1.8)	5.6 (1.8)	5.8 (1.8)
Corrected Ca × P, mg^2/dL^2	55.8 (16.8)	52.5 (17.2)	54.2 (17.1)
Albumin, g/dL	3.8 (0.4)	3.9 (0.5)	3.9 (0.5)
Total cholesterol, mmol/L	4.3 (1.2)	4.2 (1.1)	4.2 (1.2)
LDL cholesterol, mmol/L	2.2 (0.9)	2.3 (0.9)	2.3 (0.9)
HDL cholesterol, mmol/L	1.2 (1.2)	1.1 (0.4)	1.2 (0.9)
Triglycerides, mmol/L	2.0 (1.5)	1.8 (1.2)	1.9 (1.4)
CRP, mg/L, median (P10, P90)	7.5 (1.0, 36.8)	7.4 (1.3, 40.4)	7.4 (1.1, 38.8)

Data are based on the safety analysis set. Values are means (SD) unless otherwise indicated.
Ca × P, calcium–phosphorus product; CRP, C-reactive protein; HDL, high-density lipoprotein; P10, 10th percentile; P90, 90th percentile; LDL, low-density lipoprotein; PTH, parathyroid hormone; cinacalcet group, cinacalcet plus low-dose vitamin D sterols group; control group, flexible doses of vitamin D sterols group.

ment groups based on a two-sided $\alpha = 0.05$ and SD of 35% [22]. The primary efficacy analysis utilized data from all subjects who completed treatment per protocol and who had baseline and Week 52 CAC scores (efficacy analysis set) (Figure 2). Secondary end points included the percent and absolute change from baseline in calcification scores for the coronary artery, thoracic aorta, aortic valve and mitral valve at 52 weeks and the proportion of subjects with >15% progression of CAC from baseline to Week 52.

The Agatston scoring method was used for the primary analysis as specified by protocol, and additional analyses were performed using volume scores. To include subjects without evidence of calcification in the thoracic aorta (score = 0) when describing relative changes after 52 weeks, all zero scores were transformed to the actual score +1. Because more subjects had no evidence of calcification in the aortic or mitral valve at baseline, the percent change in cardiac valve calcification was calculated only for those with detectable valve calcification at baseline.

Multivariable linear regression was used to assess the magnitude of change and the strength of association between the change in CAC score from baseline to Week 52 and treatment group, adjusted for baseline covariates and baseline CAC strata. All pre-specified clinically important baseline covariates were considered for inclusion in both models, and a backwards elimination method was used to generate the models. Two-tailed P-values <0.05 were considered statistically significant.

Secondary biochemical end points included absolute and percent changes in mean PTH, calcium, phosphorus and Ca × P values from baseline to end of study as assessed at Week 44–52 in the efficacy analysis set. All biochemical determinations were done in laboratories affiliated with study sites. Immunometric PTH assays differed among facilities, but each site used the same assay throughout the study. Mean daily doses of cinacalcet and Ca-based phosphate binders and mean weekly doses of vitamin D sterols were determined for subjects in the efficacy analysis set. Results include doses of zero for each interval. Doses of vitamin D considered to be equivalent were 2 μg paricalcitol = 1 μg doxercalciferol = 1 μg alfacalcidol = 0.5 μg calcitriol, all given intravenously thrice weekly, and 0.5 μg alfacalcidol or 0.25 μg calcitriol given orally everyday.

Table 2. Baseline calcium scores at four anatomical sites using the Agatston and volume methods

Anatomic location[a]		Agatston calcification score		Calcium volume score, mm^3	
		Cinacalcet group (n = 115)	Control group (n = 120)	Cinacalcet group (n = 115)	Control group (n = 120)
Total coronary artery		695 (98, 1959)	590 (71, 2583)	464 (94, 1565)	466 (77, 1968)
Thoracic aorta		2114 (8, 14 836)	1552 (9, 8097)	1706 (9, 11 691)	1329 (16, 6014)
Aortic valve		2 (0, 907)	0 (0, 281)	4 (0, 710)	0 (0, 218)
Mitral valve		0 (0, 1125)	6 (0, 978)	0 (0, 973)	12 (0, 887)
Aortic valve, calcium detectable at baseline[b]	n	57 137 (42, 1517)	51 88 (6, 522)	57 132 (36, 1280)	51 87 (11, 451)
Mitral valve, calcium detectable at baseline[b]	n	53 229 (24, 2930)	65 147 (9, 2689)	53 211 (39, 2420)	65 118 (16, 2112)

Cinacalcet group, cinacalcet plus low-dose vitamin D sterols group; control group, flexible doses of vitamin D sterols group.
[a]Data are based on the efficacy analysis set, and all values are median (P10, P90).
[b]Data are based on subjects with detectable valvular calcification at baseline, and all values are median (P10, P90).

Differences between treatment groups were compared using a generalized Cochran–Mantel–Haenszel (CMH) test on ranks, stratified by CAC score at baseline. The stratum-adjusted median differences and corresponding 95% confidence intervals were determined by inverting the CMH test and conducting a numerical search. Analyses were conducted using SAS (version 9.13, SAS Institute, Cary, NC, USA).

Summaries of safety included all randomized subjects. Incidence rates for all adverse events were tabulated by system organ class and treatment group, and assessed by type, frequency and severity, and reported relationship to treatment.

Results

Study population

As reported previously [22], 737 patients consented to participate in the study and underwent biochemical and radiographic screening procedures (Figure 1); 360 were randomized to one of two treatment groups (Figure 2). Of these, baseline Agatston CAC scores were 30–399 in 134 subjects (37%), 400–999 in 94 subjects (26%) and ≥1000 in 132 subjects (37%). The mean (SD) age of randomized subjects was 61.5 (12.7) years; 58% were men, and 24% were black [22]. Median (P10, P90) dialysis vintage was 36.7 (9.5, 107.0) months. Baseline characteristics were balanced between groups except for mean serum phosphorus concentrations and history of congestive heart failure, which appeared to be nominally higher and lower, respectively, in the cinacalcet plus low-dose vitamin D group than in the flexible dose vitamin D group (Table 1).

A total of 280 subjects (n = 140 in each group) completed the study. The most common reasons for early withdrawal included death (6% for all randomized subjects), adverse event (3%), consent withdrawn (3%) and kidney transplantation (3%). A total of 235 subjects were available for efficacy analysis (Figure 2), 115 in the cinacalcet plus low-dose vitamin D group and 120 in the flexible vitamin D group. Demographic and biochemical features did not differ among randomized subjects, those who completed the study, and those in the efficacy analysis set (data not shown).

Cardiovascular calcification

Median values for CAC at baseline were similar in each treatment group whether expressed as Agatston or volume scores (Table 2). All randomized subjects had evidence of

Table 3. Percent change in Agatston and volume calcium scores from baseline to Week 52

Anatomic location		Cinacalcet group (n = 115)	Control group (n = 120)	Treatment difference (95% CI)[a]	P-value (CMH statistic)
Total coronary artery	n	115	119		
	Agatston	24 (−22, 119)	31 (−9, 179)	−10.3 (−22.6, 0.8)	0.073
	Volume	22 (−12, 105)	30 (−6, 133)	−13.3 (−23.8, −3.3)	0.009
Thoracic aorta	n	89	102		
	Agatston	19 (−11, 103)	33 (−8, 187)	−10.4 (−23.7, 0.0)	0.055
	Volume	16 (−3, 103)	29 (−3, 158)	−7.5 (−19.6, 1.3)	0.095
Aortic valve	n	56	51		
	Agatston	6 (−100, 105)	52 (−86, 200)	−44.7 (−85.8, −6.1)	0.014
	Volume	9 (−100, 88)	35 (−84, 184)	−31.6 (−56.8, −0.8)	0.035
Mitral valve	n	52	64		
	Agatston	12 (−39, 443)	54 (−55, 823)	−34.8 (−71.6, 0.6)	0.053
	Volume	14 (−34, 250)	42 (−31, 439)	−21.1 (−54.6, 6.3)	0.125

Data are based on the efficacy analysis set, and all values are median (P10, P90). Percent change summaries for aortic and mitral valves include only patients with detectable baseline calcification.
Generalized CMH, Cochran–Mantel–Haenszel; cinacalcet group, cinacalcet plus low-dose vitamin D sterols group; control group, flexible doses of vitamin D sterols group.
[a]Stratum-adjusted median difference from control group and corresponding confidence interval are determined by inverting the van Elteren test and performing a numerical search.

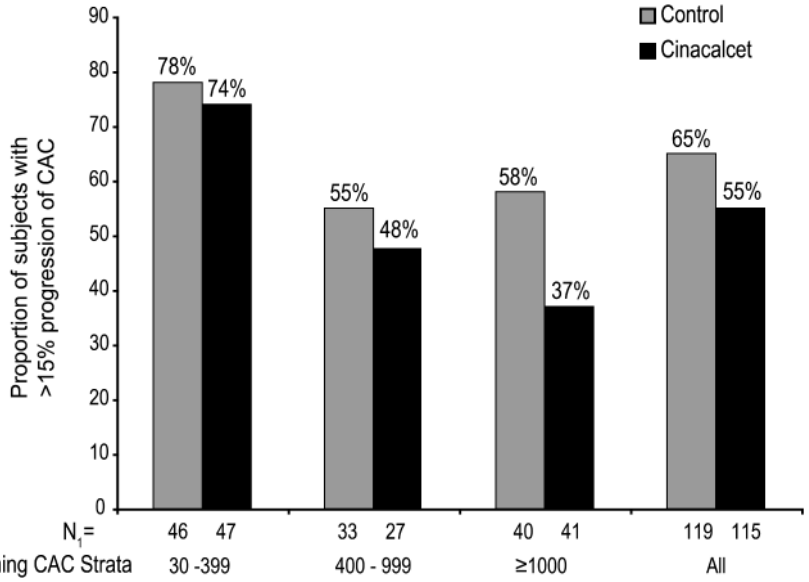

Fig. 3. Proportion of subjects with an increase in Agatston total coronary artery calcium (CAC) score >15% from baseline to Week 52 in each treatment group and in each randomization stratum.

CAC based upon eligibility criteria, but not all of them had detectable calcification at other sites. Accordingly, 91% had calcification of the thoracic aorta, 50% had mitral valve calcification, and 46% had aortic valve calcification at baseline. Median baseline calcification scores at all sites were similar in each group by both scoring methods (Table 2).

For the primary end point, the median (P10, P90) percent change in Agatston total CAC score from baseline to Week 52 was 24% (−22%, 119%) in the cinacalcet plus low-dose vitamin D group and 31% (−9%, 179%) in the flexible vitamin D group (stratified median treatment difference = −10.3%, 95% CI = −22.6–0.8%, generalized CMH P-value = 0.073) (Table 3). The corresponding median (P10, P90) absolute change in Agatston total CAC score from baseline to Week 52 in each group was 93.90 (−179.40 and 677.30) and 148.90 (−46.25 and 937.65) (stratified median treatment difference = −34.4, 95% CI = −92.6–13.0, generalized CMH P-value = 0.152).

The proportion of subjects demonstrating a >15% progression in Agatston total CAC score over 52 weeks was 55% (63/115) in the cinacalcet plus low-dose vitamin D

Table 4. Multivariate analysis

Variable	Percent change[a] (Primary end point)		Absolute change (Secondary end point)		
	Estimate[b,c] (Standard error)	% change[b,c]	P-value[b]	Estimate[b,c] (Standard error)	P-value[b]
Intercept	−1.73 (0.64)		0.008	−741.4 (464.9)	0.112
Treatment[d]	−0.22 (0.08)	−14.3	0.006	−144.8 (57.48)	0.012
Screening total CAC score stratification					
30–399 vs >1000	0.53 (0.09)	43.9	<0.001	−190.53 (65.42)	0.004
400–1000 vs >1000	0.11 (0.10)	8.2	0.265	−147.01 (74.23)	0.049
Baseline serum biochemistries					
Ca (mg/dL)	0.18 (0.07)	13.7	0.006	104.92 (48.04)	0.030
P (mg/dL)	0.10 (0.02)	7.2	<0.001	41.95 (15.89)	0.009
PTH (100 pg/mL)	−0.03 (0.01)	−1.8	0.011		NS
Baseline medical history					
Time on hemodialysis (year)	−0.03 (0.01)	−2.0	0.003	−15.08 (7.20)	0.037

[a]Due to the distribution of the residuals being non-normal, the response variable was the within-subject difference of the $\log_2$-transformed total CAC score. A positive value of the estimate indicates that a unit increase or change in category in the covariate results in an increase in the progression of calcification when all other covariates in the model are held constant. The percent increase or decrease in the progression of calcification when all other covariates in the model are held constant was determined by using the following formula: 100 × [1–2** (estimate)].
[b]Based on GLM adjusting for treatment, baseline CAC score stratification factor, baseline PTH (only for the primary end point), baseline corrected serum calcium, baseline serum phosphorus and time on hemodialysis.
[c]A positive value of the estimate indicates that a unit increase or change in category in the covariate results in an increase in the progression of calcification when all other covariates in the model are held constant.
[d]Cinacalcet plus low-dose vitamin D group vs flexible dose vitamin D group.

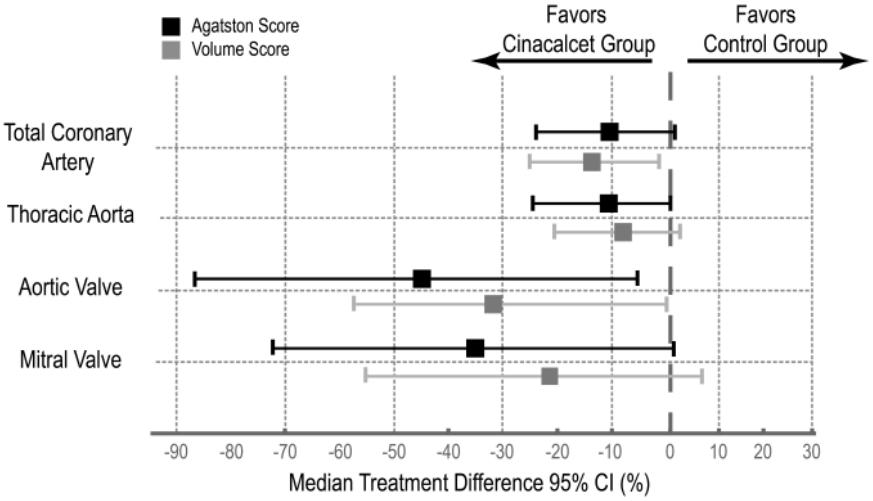

Fig. 4. The median difference (95% CI) between treatment groups in percent change in coronary artery calcium (CAC) scores from baseline to Week 52 at four anatomical sites as measured by the Agatston (solid squares) and volume (shaded squares) methods. Cinacalcet group indicates subjects given cinacalcet plus low-dose vitamin D sterols; control group indicates subjects given flexible doses of vitamin D sterols.

group and 65% (77/119) in the flexible vitamin D group (CMH P-value = 0.094) (Figure 3). Among subjects with baseline scores >1000, 15/41 or 37%, of subjects in the cinacalcet plus low-dose vitamin D group compared with 23/40, or 58%, in the flexible vitamin D group had increases in total CAC >15% after 52 weeks (Figure 3).

A multivariable analysis of the primary end point indicated a stronger treatment effect of cinacalcet than in the

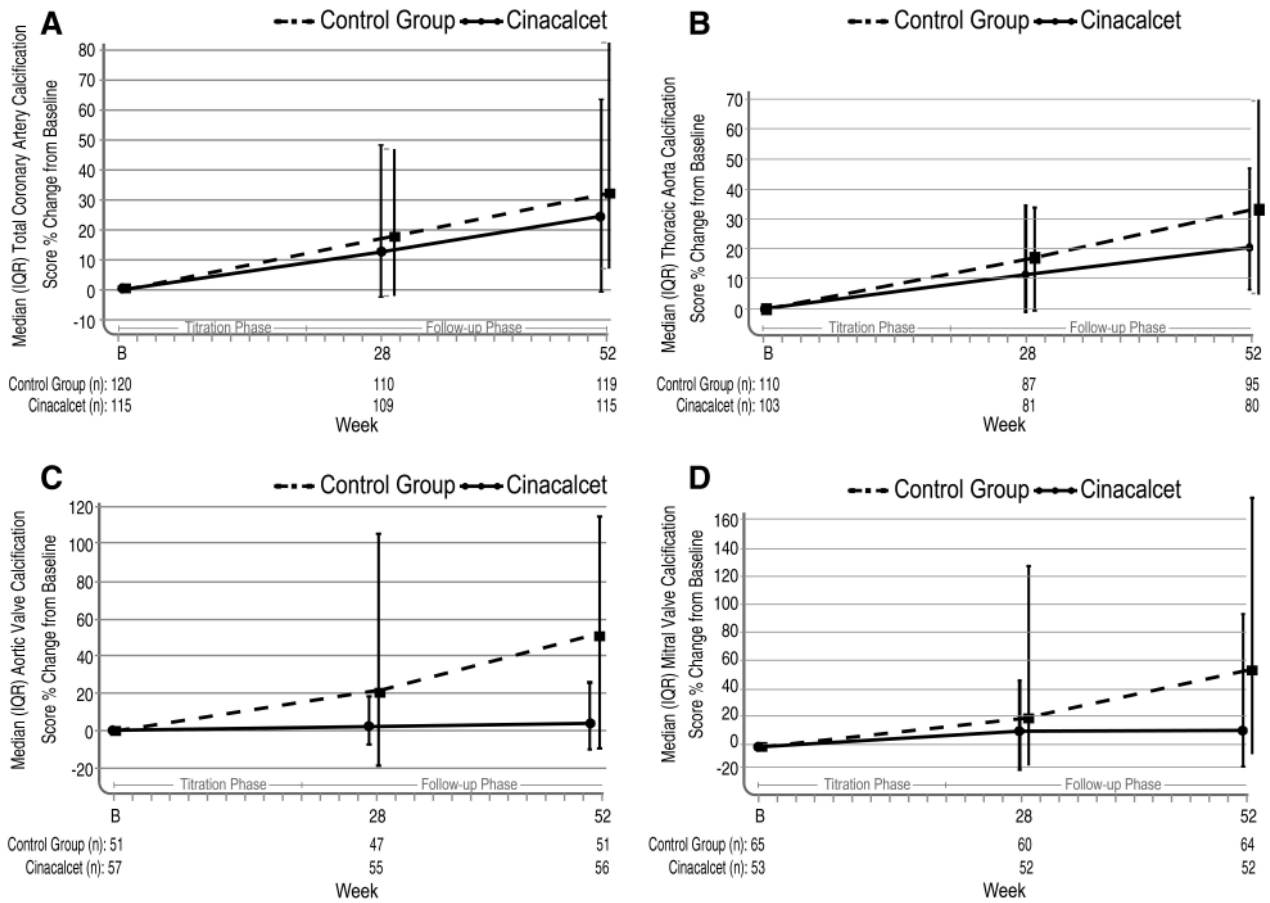

Fig. 5. The median percent change (IQR) from baseline values in Agatston calcification scores over 52 weeks in each treatment group: (**A**) total coronary artery, (**B**) thoracic aorta, (**C**) aortic valve and (**D**) mitral valve. Cinacalcet (solid symbols) denotes subjects given cinacalcet plus low-dose vitamin D sterols; control group (shaded symbols) denotes subjects given flexible doses of vitamin D sterols.

Table 5. Baseline biochemistries of efficacy analysis set

		Cinacalcet group $n = 115$	Control group $n = 120$	All subjects $n = 235$
Median PTH (P10, P90)	pg/mL	417 (239, 1045)	412 (265, 1091)	413 (247, 1046)
	pmol/L	44 (25, 111)	44 (28, 116)	44 (26, 111)
Corrected serum calcium	mg/dL	9.4 (0.7)	9.3 (0.5)	9.3 (0.6)
	mmol/L	2.4 (0.2)	2.3 (0.1)	2.3 (0.2)
Serum phosphorus	mg/dL	6.1 (1.9)	5.4 (1.7)	5.8 (1.8)
	mmol/L	2.0 (0.6)	1.8 (0.6)	1.9 (0.6)
Corrected	mg^2/dL^2	56.8 (17.4)	50.4 (16.0)	53.5 (17.0)
Ca × P	$mmol^2/L^2$	4.6 (1.4)	4.1 (1.3)	4.3 (1.4)

Data are based on the efficacy analysis set, and values are mean (SD) unless otherwise indicated.
Ca × P, calcium–phosphorus product; P10, P90, 10th and 90th percentile; PTH, parathyroid hormone; cinacalcet group, cinacalcet plus low-dose vitamin D sterols group; control group, flexible doses of vitamin D sterols group.

non-parametric primary analysis using baseline serum calcium, serum phosphorus, plasma PTH levels, years on dialysis, and baseline CAC score stratification factor as covariates. The estimated rate of progression was 14.3% lower in the cinacalcet plus low-dose vitamin D group (95% CI: −23.1%, −4.5%) (P-value = 0.006; Table 4). A multivariable model for absolute change in CAC score from baseline to Week 52 estimated a difference between groups of −144.8 units (95% CI: −257.5, −32.1) (P-value = 0.013), with smaller increases among subjects receiving cinacalcet plus low-dose vitamin D. Baseline PTH was not included in the model for absolute change because values were not significantly associated with absolute changes in CAC over 52 weeks (Table 4).

As secondary end points, both the percent and absolute change in Agatston scores for the thoracic aorta and the percent change in Agatston score for the aortic and mitral valve were nominally less in the cinacalcet plus low-dose vitamin D group than in the flexible vitamin D group (Table 3). Median treatment differences (95% CI) were −10.4% (−23.7, 0.0%) and −39.4 (−203.3, 36.9), respectively, for percent and absolute change in the thoracic aorta. The median treatment difference was −44.7% (−85.8%, −6.1%) for the aortic valve and −34.8% (−71.6%, 0.6%) for the mitral valve. The difference between groups in volume scores at 52 weeks for each site evaluated was qualitatively similar (Table 3, Figure 4). Moreover, the difference between groups in median va-

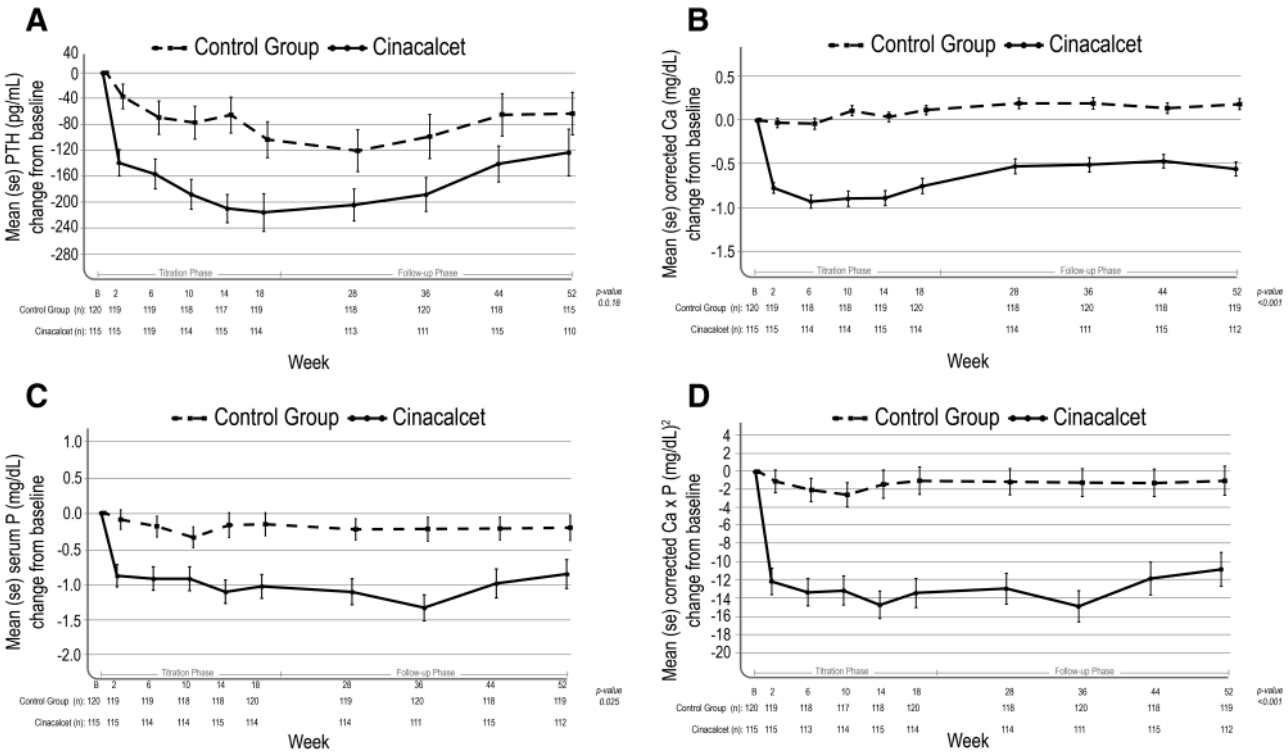

Fig. 6. The mean (SE) absolute change from baseline values at each study visit for (**A**) parathyroid hormone (PTH), (**B**) serum calcium, (**C**) serum phosphorus and (**D**) calcium–phosphorus product (Ca × P) according to treatment group. Cinacalcet (solid symbols) denotes subjects given cinacalcet plus low-dose vitamin D sterols; control group (shaded symbols) denotes subjects given flexible doses of vitamin D sterols.

lues at each site was greater at 52 weeks than at 28 weeks (Figure 5).

Biochemical results

At baseline, plasma PTH, serum calcium and calcium–phosphorus product (Ca × P) values did not differ between groups (Table 5). Despite randomization, mean (SD) serum phosphorus concentrations at baseline were higher among subjects given cinacalcet plus low-dose vitamin D sterols than in those treated with flexible doses of vitamin D sterols, 6.1 (1.9) mg/dL versus 5.4 (1.7) mg/dL, respectively.

Plasma PTH, serum calcium and phosphorus concentrations, and Ca × P values differed substantially between groups during treatment (Figure 6). The median (P10, P90) decrease in plasma PTH from baseline to end of study (mean of Week 44–52) was greater in subjects treated with cinacalcet plus low-dose vitamin D sterols compared with those given flexible doses of vitamin D sterols. Values were −132 (−509, 182) pg/mL among subjects receiving cinacalcet and −65 (−392, 282) pg/mL among those given flexible dose of vitamin D sterols (P = 0.018) (Figure 6).

Medication doses

Among subjects treated with cinacalcet plus low-dose vitamin D sterols, the median (IQR) dose of cinacalcet was 30 (24, 60) mg/day at Week 44 and 29 (18, 58) mg/day at Week 52. Corresponding mean doses were 42 and 37 mg/day, respectively. The mean weekly dose of vitamin D sterols, expressed as microgram equivalents of paricalcitol, decreased from 9.4 μg at baseline to a nadir of 5.0 μg at Week 36 (Figure 7A). Thereafter, the mean weekly dose of vitamin D sterols increased. In contrast, the average weekly

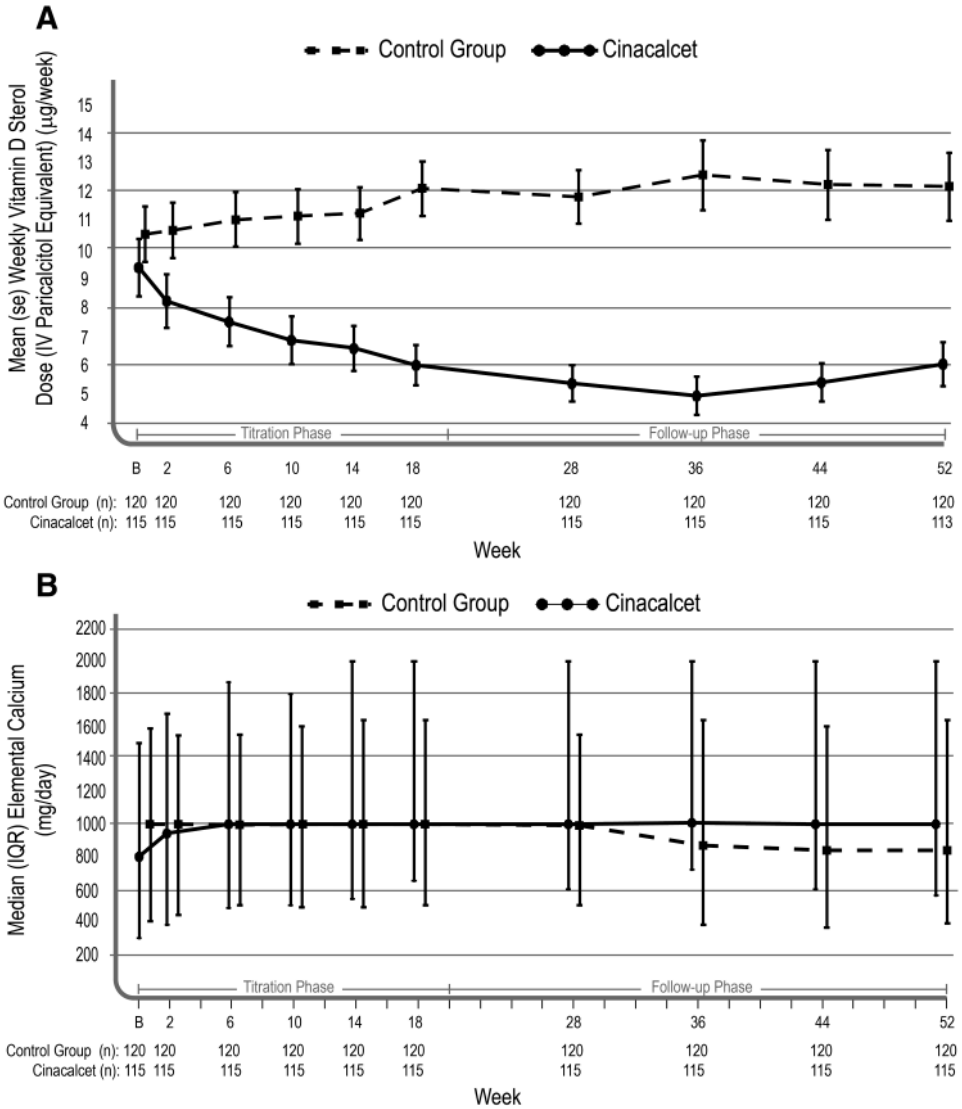

Fig. 7. The mean (SE) weekly dose of vitamin D sterol, expressed in microgram equivalents of paricalcitol (**A**), and the median (IQR) dose of elemental calcium provided from calcium-containing phosphate binders (**B**) at each study visit in each treatment group. Cinacalcet (solid symbols) denotes subjects given cinacalcet plus low-dose vitamin D sterols; control group (shaded symbols) denotes subjects given flexible doses of vitamin D sterols.

dose of vitamin D sterols among subjects randomized to flexible doses of vitamin D sterols rose progressively during the study, reaching a maximum of 12.6 μg at Week 36 (Figure 7A). The median daily amount of elemental calcium ingested from calcium-based phosphate binders was unchanged during the study in both treatment groups, and the median daily oral dose of calcium was similar at each interval of follow-up (Figure 7B).

Adverse events

Adverse events occurred in 156 of 180 (87%) subjects randomized to treatment with cinacalcet plus low-dose vitamin D sterols and in 156 of 180 (87%) subjects assigned to treatment with flexible doses of vitamin D sterols. Serious adverse events were reported in 88 (49%) and 82 (46%) subjects, respectively, in each treatment group. There were 24 deaths during the study, 12 in each group. Adverse events attributed to treatment with cinacalcet occurred in 53 (29%) subjects and included gastrointestinal disorders (n = 37; 21%) and hypocalcemia (n = 12; 7%). Adverse events ascribed to treatment with vitamin D sterols developed in three subjects (2%) in the cinacalcet group and in seven subjects (4%) managed with flexible doses of vitamin D sterols with hypercalcemia occurring in one (1%) and five (3%) subjects, respectively.

Discussion

Available strategies for managing sHPT have divergent effects on calcium and phosphorus metabolism systemically. Treatment with vitamin D sterols may lower plasma PTH but often raises serum calcium and/or phosphorus concentrations, changes that have been implicated in the development of soft tissue and cardiovascular calcification in patients undergoing hemodialysis. In contrast, calcimimetic agents such as cinacalcet reduce plasma PTH while modestly lowering serum calcium and phosphorus concentrations. The current study examined the potential impact of these disparate biochemical responses on the progression of established cardiovascular calcification during the treatment of sHPT.

We report modestly smaller increases in calcification scores over 52 weeks at four discrete anatomical sites as measured by MDCT among subjects treated with cinacalcet plus low doses of vitamin D sterols compared with those treated with flexible doses of vitamin D analogs. Although a statistically significant difference between groups was not observed for the primary study end point, i.e. the percent change in Agatston CAC score from baseline to 52 weeks, differences between treatment groups were seen for interval changes CAC volume scores and for changes in Agatston and volume scores at the aortic valve. Moreover, smaller increases in calcification scores during follow-up were found consistently by both scoring methods at all anatomical sites evaluated. The findings thus suggest, but do not show conclusively, that treatment with cinacalcet and low doses of vitamin D sterols may attenuate the progression of established cardiovascular calcification among patients receiving hemodialysis.

In the general population, Raggi *et al.* have demonstrated that an increase of 15%/year in CAC scores is closely associated with an unfavorable outcome [26]. The slower rates of progression reported in the current study are encouraging, and it is hoped that such changes ultimately will prove beneficial for clinical outcomes. However, a definitive answer to this question must await the results of the EVOLVE clinical trial [27].

All randomized subjects in the current study had evidence of CAC at baseline. Progression of calcification scores as reported here thus was not unexpected based upon previous work showing that vascular and cardiac valve calcification, when present, generally increases over time and advances more rapidly among patients on dialysis than in the general population [2]. For those with extensive CAC at baseline as judged by Agatston scores >1000, a smaller proportion of subjects receiving cinacalcet plus low-dose vitamin D sterols compared with those given flexible doses of vitamin D sterols experienced a ≥15% increase in CAC, a change associated with adverse outcomes in the general population [26,28,29].

Despite the high prevalence of sHPT among patients on dialysis, a few of the very limited number of prospective randomized controlled trials (RCTs) in this field of clinical research have directly compared the efficacy of alternative therapeutic regimens. Most have compared the effect of selected pharmacological interventions to that of placebo on PTH concentrations or on other biochemical markers [10,30]. ADVANCE is unique in its use of MDCT to assess the impact of two different clinical strategies for managing sHPT on the progression of cardiovascular calcification. Nevertheless, CAC scores and measures of aortic and cardiac valve calcification represent intermediate, or surrogate, outcomes. Little is known about the progression of CAC on clinical outcomes including cardiovascular events among patients with CKD, and measures that attenuate the progression of CAC have not yet been shown to reduce mortality or the risk of cardiovascular events. Ample data from the general population and among patients with CKD indicate, however, that the presence and extent of vascular calcification are associated with overt cardiovascular disease and premature death [6–9]. As such, ADVANCE provides new information about an important pathologic process that extends beyond simple biochemical outcomes, but the sample size and short duration of follow-up preclude any definitive assessment of clinical outcomes.

The precise mechanisms responsible for the development and progression of soft tissue and vascular calcification in CKD remain uncertain. Results from clinical studies and data from experiments in animal models suggest that abnormalities in calcium and phosphorus metabolism, specifically high concentrations in serum, contribute to this pathological process [31,32]. Persistent elevations in serum calcium and phosphorus levels can be aggravated by the large doses of vitamin D sterols used often to treat sHPT because these compounds promote intestinal calcium and phosphorus absorption [21,33–35]. In the current study, plasma PTH, serum calcium and phosphorus concentrations, and Ca x P values, and the interval change from baseline for each parameter, differed substantially between

treatment groups over 52 weeks (Figure 6), results consistent with previous reports [19,20,36]. Although plasma PTH increased towards the end of the study in both groups, mean values were consistently lower among subjects treated with cinacalcet plus low-dose vitamin D sterols than among those treated with flexible doses of vitamin D sterols.

Further insight into the role of these biochemical factors on progression of vascular calcification among dialysis patients can be gained by considering the current results in the context of other studies such as Treat-to-Goal [11,37] and Calcium Acetate Renagel Evaluation-2 (CARE-2) [38]. In Treat-to-Goal, an RCT that compared the use of sevelamer with calcium-based phosphate binders for managing hyperphosphatemia in patients on hemodialysis, sevelamer attenuated the progression of CAC over 12 months compared with that observed in calcium-treated subjects, while serum calcium and phosphorus concentrations did not differ significantly. Such findings suggest that substantive differences in oral calcium intake can affect the progression of vascular calcification in this population. In ADVANCE, the median daily dose of oral calcium did not differ between treatment groups (Figure 7B), and calcium-free phosphate binders were not used. Any disparity between groups in the progression of calcification scores in the current study thus is likely attributable to differences in the serum biochemical profile and the correspondingly lower calcium, phosphorus and PTH concentrations among subjects receiving cinacalcet, not to differences in oral calcium load.

Additionally, median PTH concentrations were substantially lower in Treat-to-Goal than in either ADVANCE or CARE-2. Relatively low PTH concentrations have been associated with a higher prevalence of soft tissue and vascular calcification among patients receiving dialysis [39]. As such, the higher PTH concentrations among subjects in ADVANCE may have attenuated any disparity between treatment groups in the progression of cardiovascular calcification. Other differences in patient demographics among these studies could also account for variations in treatment effects. Further work is needed to clarify the role of alterations in serum biochemical parameters and changes in other factors known to modulate extra-osseous calcification, such as matrix Gla protein, osteocalcin, pyrophosphates, and alpha 2-Heremans-Schmid glycoprotein (fetuin A) on vascular calcification among patients with CKD [40].

Strengths of the study include the relatively large sample size and the inclusion of a diverse study sample by age, sex, race/ethnicity, vintage, primary cause of ESRD, and geography. The participation of subjects given calcium-based phosphate binders exclusively helped mitigate potential confounding from the use of calcium-free compounds. Variability in the results for calcification scores was reduced by relying upon a single reader, blinded to subject identification and treatment, to assess all MDCT scans. Although MDCT cannot distinguish between medial and intimal calcification [41], measurements of total CAC by MDCT are well validated, reproducible, and reasonably precise [24,25,42,43]. Finally, whereas changes in calcification scores did not differ significantly between groups at all sites evaluated, the consistency of the difference at each anatomic site renders the results credible.

There are also important limitations to the study, including its open-label design. A follow-up interval of 12 months may have been insufficient to detect differences in the progression of vascular calcification, which occurs over many years [11–13,44]. The widening disparity in calcification scores between groups at Week 28 and 52 supports this contention. The use of calcium-based phosphate binders exclusively among study participants helped to reduce effects related to other therapeutic interventions, but it limits the ability to generalize the results because calcium-free phosphate binders are prescribed commonly, either alone or together with calcium salts. Consequently, the independent effect of cinacalcet on the progression of vascular and cardiac valve calcification among patients receiving sevelamer, lanthanum carbonate or other calcium-free phosphate-binding agents remains to be determined.

Because the doses of vitamin D sterols differed substantially between treatment groups, the slower progression of calcification scores among subjects treated with cinacalcet plus low-dose vitamin D sterols cannot be attributed solely to the use of cinacalcet. The smaller doses of vitamin D analogs could also contribute to these findings. The effect of vitamin D sterols on vascular calcification has been suggested to be dose-dependent, but it may also be modified by vitamin D-mediated increases in serum calcium and phosphorus concentrations or by other recognized mediators of vascular calcification [40,45]. Finally, although subjects randomized to cinacalcet and low-dose vitamin D sterols were to receive the equivalent of ≤2 μg paricalcitol per dialysis session as specified in the study protocol, the doses of vitamin D actually given were substantially higher, reducing inter-group separation. Whether the observed differences in the progression of calcification would have been more pronounced with stricter adherence to the study protocol is unknown.

In summary, results from ADVANCE suggest, but do not demonstrate conclusively, that cinacalcet may attenuate vascular and cardiac valve calcification in patients on hemodialysis with moderate to severe sHPT. Findings from the ongoing Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) study [27] will help determine whether cinacalcet can reduce the exceptionally high rates of mortality and cardiovascular events among patients on hemodialysis.

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(See related article by Olgaard et al. Calcimimetics, vitamin D and ADVANCE in the management of CKD-MBD. *Nephrol Dial Transplant* 2011; 26: 1117–1119)

Clinical investigators. The following investigators (listed alphabetically) enrolled patients for this study:

Joseph Abdallah, Kansas Nephrology Physicians, P.A., Wichita, KS USA; Teresa Adragao, Nefroclinica - Centro De Hemodialise Do Estoril, Estoril, Portugal; Marcello Amato, ASL 4 - Ospedale Misericordia e Dolce, Prato, Italy; Patrice Amguhl, Stadtspital Waid, Zurich, Switzerland; John Anderson, Johns Hopkins Bayview Medical Center, Baltimore, MD USA; Jozsef Balla, Debreceni Egyetem, Orvos es Egeszsegtudomanyi Centrum, Debrecen, Hungary; Kym Bannister, Royal Adelaide Hospital, Adelaide, SA Australia; Vinod Bansal, Loyola University Medical Center, Maywood, IL USA; Geoffrey Block, Denver Nephrology, PC, Denver, CO USA; Andreas Bock, Kantonsspital Aarau AG, Aarau, Switzerland; Johann Braun, KfH Nierenzentrum Nürnberg - Rothenburger Straße, Nürnberg, Germany; Jorge Busse, Nephrology Associates of South Miami, Inc, Miami, FL USA; Jorge Cerda, Capital District Renal Physicians, Albany, NY USA; Paul Chidester, Paul D. Chidester MD, FACP, PC, Chesapeake, VA USA; Michel Chonchol, University of Colorado at Denver, Health Sciences Center, Denver, CO USA; Stephen Chow, Entralogix - Don Mills, Toronto, ON Canada; Dalila Corry, Holy Cross Renal Center, Mission Hills, CA USA; Serge Cournoyer, Hôpital Charles-Lemoyne, Greenfield Park, QC Canada; Botond Csiky, FMC Dialysis Centre Kozpont Pecs, Pecs, Hungary; Timothy Curley, Nephrology Associates of Tidewater, Chesapeake, VA USA; Alex Disney, The Queen Elizabeth Hospital, Woodville, SA Australia; Sandra Donnelly, St. Michael's Hospital, Toronto, ON Canada; Dominique Durand, Hôpital Larrey, Toulouse Cedex 09, France; Georg Eisenbach, Medizinische Hochschule Hannover, Hannover, Germany; Robert Fassett, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; Sandor Ferenczi, B. Braun Avitum Hungary Zrt. 11. sz. Dializis Kozpont, Gyor, Hungary; Jürgen Floege, Medizinische Einrichtung der RWTH Aachen, Aachen, Germany; Robert Geronemus, South Florida Nephrology Associates, Lauderdale Lakes, FL USA; Walid Ghantous, Fresenius Medical Care (FMC), Evanston, IL USA; Andrey Gurevich, St. Petersburg medical academy of postgraduate education, Saint Petersburg, Russia; Konstalin Gurevich, St. Petersburg State Institution of Public Health, City hospital 12, Saint Petersburg, Russia; Carmel Hawley, Princess Alexandra Hospital, Woolloongabba, QLD Australia; Antero Helantera, Paijat-Hameen Keskussairaala, Lahti, Finland; Robert Heyka, The Cleveland Clinic Foundation, Cleveland, OH USA; Edward Himot, Georgia Kidney Associates, Inc., Marietta, GA USA; Anthony Hodsman, St. Joseph's Health Care, London, ON Canada; Eero Honkanen, Helsinki University Hospital, Helsinki, Finland; Ashley Irish, Royal Perth Hospital, Perth, WA Australia; Rafael Javier, Mid-Michigan Physicans LLC, Lansing, MI USA; Rosa Jofre, Hospital Gregorio Marañón, Madrid, Madrid Spain; Dominique Joly, Hopital Necker Enfants Malades, Paris, France; Kotagal Shashi Kant, University of Cincinnati, College of Medicine, Cincinnati, OH USA; Mark Kaplan, Nephrology Associates, Nashville, TN USA; István Kiss, B. Braun Avitum Hungary Zrt. 1. sz. Dializis Kozpont, Budapest, Hungary; Nagy Lajos, B. Braun Avitum 8th Dialysis Center, Tatabanya, Hungary; Martine Leblanc, Hopital Maisonneuve-Rosemont, Montreal, QC Canada; Francesco Locatelli, Azienda Ospedaliera Alessandro Manzoni, Lecco, Italy; Charmaine Lok, Toronto General Hospital, Toronto, ON Canada; Robert Malecki, Miedzyleski Szpital Specjalistyczny, Warszawa, Poland; David Mendelssohn, Humber River Regional Hospital, Toronto, ON Canada; Piergiorgio Messa, Policlinico Di Milano, Milano, Italy; Kaj Metsarinne, Turku University Central Hospital, Turku, Finland; Todd Minga, Nephrology Associates Research Center, Coastal Kidney Center, Panama City, FL USA; Louise Moist, London Health Sciences Centre, London, ON Canada; Moustafa Moustafa, South Carolina Nephrology & Hypertension Center, Inc, Orangeburg, SC USA; Agostino Naso, Azienda USSL 16 di Padova, Padova, Italy; Mohammad Nassri, Davita of Orangeburg and St. Matthews, Orangeburg, SC USA; G Edward Newman, G Edward Newman MD PLLC, Knoxville, TN USA; Kaldun Nossuli, Washington Nephrology Associates, Bethesda, MD, USA; Adam Pearlman, Metropolitan Nephrology, Alexandria, VA USA; Eugenia Pedagogos, The Royal Melbourne Hospital, Parkville, VIC Australia; Odete Pereira, Nefronorte - Centro Renal do Norte, Lda, Paredes, Portugal; José Portolés, Fundación Hospital Alcorcón, Alcorcón, Spain; Wajeh Qunibi, University of Texas, Health Science Center-San Antonio, San Antonio, TX USA; Junaid Qureshi, AKDHC Medical Research Services, Phoenix, AZ USA; Thomas Rakowski, Clinical Research & Consulting Center, LLC, Fairfax, VA USA; Kenneth Rappaport, Clinical Research Associates, LLC, Palm Beach Gardens, FL USA; Simon Roger, Gosford Hospital, Gosford, NSW Australia; Michael Roppolo, Renal Associates of Baton Rouge, Baton Rouge, LA USA; Louise Roy, CHUM Hospital St. Luc, Montreal, QC Canada; Andrzej Rydzewski, Centralny Szpital Kliniczny MSWiA, Warszawa, Poland; Jozsef Samik, B. Braun Avitum Hungary zRt. 4. sz. Dializis Kozpont, Kaposvar, Hungary; Rosa Sanchez-Hernandez, Hospital General de Segovia, Segovia, Spain; Dámaso Sanz Guajardo, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; Ehsan Shahmir, Vacavilla and Creekside Davita Units, Vacaville, CA USA; Amit Sharma, Boise Kidney and Hypertension Institute, Meridian, ID USA; Douglas Shemin, Rhode Island Hospital, Providence, RI USA; Jeffrey Silberzweig, The Rogosin Institute, Woodside, NY USA; Paul Sohi, Saint John Regional Hospital, Saint John, NB Canada; Amy Sprague, Davita, Evans, GA USA; Stuart Sprague, Evanston Hospital, Kellogs Cancer Center, Evanston, IL USA; Pusadee Suchinda, Carolina Diabetes and Kidney Center, Sumter, SC USA; Wladyslaw Sulowicz, Niepubliczny Zaklad Opieki Zdrowotnej, Stacja Dializ Oswiecim, Krakow, Poland; Michael Suranyi, Liverpool Hospital, Liverpool, NSW Australia; David Tharpe, Clinical Research Center, Inc., Birmingham, AL USA; Pablo Urena Torres, Clinique du Landy, Saint-Ouen, France; Giuseppe Villa, Fondazione S. Maugeri Irccs, Pavia, Italy; Nand Wadhwa, State University of New York, Stony Brook, Brooklyn, NY USA; Zofia Wankowicz, Wojskowy Instytut Medyczny, Klinika Nefrologii ze Stacja Dializ, Warszawa, Poland; Rudolf Wuethrich, Universitaetsspital Zuerich, Zurich, Switzerland; Alexander Zemtchenkov, St. Petersburg institution of public health, City Mariinsky Hospital, Saint Petersburg, Russia

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