Vitamin D Analogues and Coronary Calcification in CKD Stages 3 and 4: A Randomized Controlled Trial of Calcitriol Versus Paricalcitol

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Rationale & Objective: Mineral and bone disorder in chronic kidney disease (CKD) is associated with progression of coronary artery calcification (CAC). Mineral and bone disorder often is treated with calcitriol and other vitamin D receptor activators, including paricalcitol, agents that may have differential effects on calcium, phosphate, and parathyroid hormone levels. Accordingly, we investigated whether these agents have differential effects on CAC progression in patients with CKD.

Study Design: Randomized, double-concealed, 48-week clinical trial.

Setting & Participants: CKD stage 3 or 4 with secondary hyperparathyroidism with CAC score > 0 and no prior treatment with activated vitamin D.

Intervention: Calcitriol versus paricalcitol.

Outcomes: The primary outcome was log-transformed CAC change. Secondary outcomes included percent change in CAC volume, valvular calcifications, and bone mineral metabolism markers.

Results: Among 44 individuals randomly assigned, mean age was 65 years and mean estimated glomerular filtration rate was 27 mL/min/1.73 m^2.

Median CAC score was 140 (IQR, 55-277) Agatston units at baseline. There was no significant difference in CAC progression between treatment arms ($P = 0.06$). After adjustment for baseline CAC score (log), treatment group remains nonsignificant ($P = 0.08$). Further adjustment for creatinine level and/or CKD stage did not change the association. In secondary analyses adjusting for dose level of activated vitamin D, treatment group was significant ($P = 0.01$), and when dose level was also included in the model, the coefficient for individuals in the paricalcitol group was significantly associated with CAC progression ($P = 0.02$). An interaction term between dosing level and CKD stage was significant at the highest dosing level ($P = 0.04$).

Limitations: Pilot single-center study.

Conclusions: In patients with CKD with secondary hyperparathyroidism naive to activated vitamin D therapy, there was no difference in CAC or valvular progression in participants receiving calcitriol compared with paricalcitol during a 48-week period.

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Coronary artery calcification (CAC) is a strong predictor of coronary artery disease and congestive heart failure events, regardless of kidney function.[1] Patients with

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chronic kidney disease (CKD) have a very high mortality rate, with cardiovascular disease (CVD) accounting for ∼50% of deaths.[2,3] CAC, which is common among individuals with CKD, may be responsible for some of this increased risk.[4]

CKD–mineral and bone disorder (CKD-MBD) is a multifactorial systemic disorder defined as abnormal mineral metabolism, altered bone structure and composition, and/or vascular calcification occurring in individuals with CKD.[5] Secondary hyperparathyroidism (SHPT) is a common complication of CKD. Therapy with oral calcitriol, the active form of vitamin D$_3$, is often used for the treatment of this complication but is often hindered by the occurrence of hypercalcemia that requires discontinuation of the drug with consequent recurrence of parathyroid hormone (PTH) oversecretion.

Paricalcitol is a synthetic biologically active vitamin D analogue of calcitriol with modifications to the side chain (D$_2$) and the A (19-nor) ring. Paricalcitol's biological actions are mediated through binding of the vitamin D receptor, which results in the selective activation of vitamin D–responsive pathways. Calcitriol and paricalcitol have been shown to reduce PTH levels by inhibiting PTH synthesis and secretion.[6,7] In hemodialysis patients, individuals treated with paricalcitol absorbed 14% less calcium compared with calcitriol-treated individuals despite similar PTH level changes.[6,7] The paricalcitol dose needed to produce the same level of hypercalcemia is approximately 10 times that of calcitriol.[8,9]

Paricalcitol is at least as potent as calcitriol in decreasing serum PTH levels while reportedly causing less vascular calcification in animal studies. Several studies that examined aortic calcification found paricalcitol to have fewer hypercalcemic properties than calcitriol[6,8-10] while also improving echocardiographic indexes of diastolic function and left ventricle septal and posterior wall thickness.[11]

In an observational study in hemodialysis patients, the use of paricalcitol as compared to calcitriol was associated

PLAIN-LANGUAGE SUMMARY

Coronary calcification leads to poor outcomes, including increased risk for death. Activated vitamin D is used for the treatment of mineral and bone disorders in individuals with moderate to severe chronic kidney disease. We performed a randomized, double-concealed, 48-week clinical trial to determine the differential effects of paricalcitol and calcitriol on mineral metabolism and coronary calcifications. We report that in individuals with no prior treatment with activated vitamin D, there was no major difference in the progression of coronary or valvular calcification.

with better survival,[12] whereas a small clinical trial suggested that paricalcitol is associated with potentially reaching target reduction levels of intact PTH (iPTH) in a shorter time and with a lower dose compared with the use of calcitriol in CKD stages 3 and 4.[13] However, in a randomized clinical trial of 227 individuals with advanced non–dialysis-dependent CKD, paricalcitol did not change left ventricular mass index or improve diastolic dysfunction measures compared with placebo.[14]

Individuals with CKD have a high prevalence of CAC and more rapid progression of CAC than the non-CKD population.[15-19] However, the pathogenesis of CAC and its prevention are not completely understood. To date, there are no randomized controlled trials evaluating the effects of vitamin D analogues on vascular calcification in patients with CKD with SHPT despite this being a recommended area of research in the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD guideline.[5] Accordingly, the objective of this randomized double-blinded study was to determine the differential effects of oral calcitriol and paricalcitol on CAC in patients with moderate to severe CKD. Our hypothesis was that participants with SPHT who were treated with paricalcitol would have slower progression of CAC compared with those treated with calcitriol, based on previous in vivo animal data.[6]

METHODS

This was a randomized, double-blinded, single-center, clinical trial of activated vitamin D on CAC progression. Participants were followed up during a 48-week period using noncontrast electrocardiogram-gated computed tomography (CT) of the coronary artery bed. Mineral metabolism markers such as levels of iPTH, vitamin D, phosphate, calcium, and a basic metabolic panel were performed at baseline and 48 weeks. The randomization was performed by the Investigational Drug Service after it was determined that a patient was eligible for the study. Participants were randomly assigned by stratum: diabetes mellitus (DM; yes/no) and CKD (stage 3/stage 4). Participants were then assigned using 1:1 randomization to each of the treatment groups.

The study team used a double-blind methodology for administration of the study treatment. This was achieved by using an electronic 21CFR11-compliant inventory tracking system, which includes electronic signatures and time-date stamps for each transaction, based on the randomization table generated by the Investigational Drug Service electronically using www.randomization.com, which is hosted by the Department of Food Science at Tufts University. Quadruple masking was achieved by blinding participants, care providers, investigators, and outcomes assessors to treatment group allocation. Both medications were placed in capsules that appeared identical to preserve blinding.

Study Population

Inclusion criteria included adults older than 25 years with CKD stage 3 or 4 (estimated glomerular filtration rate [eGFR] $\geq$ 15 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) and SHPT with any CAC score > 0 that had not been treated previously with activated vitamin D. SHPT was diagnosed per the KDIGO CKD-MBD guideline as any level higher than the upper limit of normal for the laboratory assay.[5]

Exclusion criteria included participants with no CAC, prior coronary revascularization or cardiac devices, patients weighing >300 lb due to technical issues, iPTH level > 1,500 pg/mL (>165 pmol/L), history of parathyroidectomy, human immunodeficiency virus positivity, history of a solid-organ transplant, rapid atrial fibrillation, or receiving bone-altering therapies including cinacalcet or bisphosphonates. Other exclusion criteria included institutionalized patients, pregnant patients, those with language barriers, and mental incapacity.

A total of 89 participants had a screening visit. Forty-five were not eligible because they did not meet inclusion/exclusion criteria. Therefore, we randomly assigned 44 participants to either calcitriol or paricalcitol treatment. Forty participants completed the study. Figure 1 presents the recruitment schematic.

Study Design

Participants were treated for SHPT over a period of 48 weeks with either oral calcitriol or oral paricalcitol per the manufacturer's recommendation. Doses were titrated based on calcium, phosphate, and PTH levels at weeks 4, 12, 24, and 36 based on the CKD-MBD guidelines available.[5,20] There was a differential PTH target depending on CKD stage (CKD stage 3, 35-70 pg/mL [3.85-7.7 pmol/L] and CKD stage 4, 70-110 pg/mL [7.7-12.1 pmol/L]). Participants randomly assigned to calcitriol treatment started at 0.25 µg 3 times a week. If PTH was still not at goal at the 12-week visit, calcitriol dosage was increased to 0.5 µg 3 times a week. Participants taking paricalcitol started at 2 µg 3 times a week and titrated up during the next visit according to PTH levels. If PTH was still not at goal at the 12-week visit, paricalcitol dosage was increased to 4 µg 3 times a week. If clinically indicated by a very
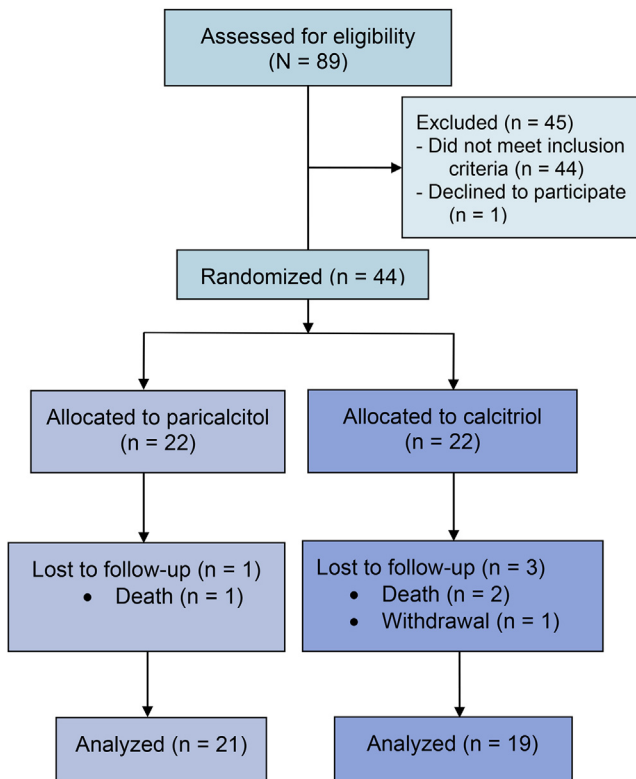
Figure 1. Flow chart shows the participant recruitment process.

high PTH and a low calcium level, therapy was initiated with calcitriol, 0.5 μg, 3 times a week, or paricalcitol, 4 μg, 3 times a week.

In all participants at baseline, 25-hydroxyvitamin D (25 [OH]D) was measured and those with levels < 30 ng/mL and CKD stage 3 were initiated on ergocalciferol treatment, as per recommendation of the Kidney Disease Outcomes Quality Initiative (KDOQI).[20] Ergocalciferol supplementation was not found to be as effective in CKD stage 4 compared with its use in CKD stage 3.[21]

Phosphate and calcium levels were maintained in the normal range, using phosphate binders when necessary. Phosphate binders were prescribed as per their health care provider. The calcium-phosphorus product goal was <55 mg/dL. Calcium target level was <9.5 mg/dL and phosphate target level was <4.6 mg/dL. Visits with safety laboratory tests (calcium, phosphate, iPTH, and 25[OH]D) were performed at baseline; 4, 8, and 12 weeks; and every 3 months thereafter. Urinary albumin-creatinine ratio was measured in participants who underwent urine dipstick testing that was positive for albuminuria with albumin excretion > 30 mg/dL.

Measuring CAC

CT is a noninvasive technique for measuring CAC and is considered the gold standard.[22] Electrocardiogram-gated multislice CT was used to measure both CAC and valvular calcification. We performed all studies on a dual-source 64-slice scanner (Somatom Definition; Siemens

Medical Solutions). Reconstruction of the contiguous 3-mm thick transverse images, starting at the root of the aorta cephalad through the coronary sinuses and continuing caudally through the coronary tree, was performed. All scans were evaluated by a single radiologist concealed to the other study data. CAC was measured based on the number of plaques, density, and area of calcification. Total score was calculated based on the methods first described by Agatston et al.[23] We included only foci that showed >130 Hounsfield units (HU) and contained 6 or more adjacent pixels. The Agatston CAC score includes the area of a calcified coronary plaque in a CT slice and a density factor (based on the maximal CT number [HU] of the plaque). Calcium volume score is determined by the total summation of all areas of calcification multiplied by the slice thickness.[24]

Efficacy End Points

The primary outcome of the study was difference in log-transformed CAC scores. CAC scores were increased by 1 Agatston unit (AU) to be able to log transform because we included a participant who was initially read as having calcification, which was later found to be an artifact in the second scan. The second scan was read as having no calcification and the initial scan was corrected.

A priori selected secondary outcomes included: (1) percent change from baseline in CAC score at week 48 between the treatment arms, calculated as (CAC score at week 48 + 1 − CAC score at baseline + 1)/(CAC score at baseline + 1)] × 100; (2) absolute change from baseline in CAC score, calculated as (CAC score at week 48 − CAC score at baseline); (3) proportion of participants with a >15% increase in CAC score at week 48; (4) progression of CAC using the calcium volume score [the square root difference in CAC volume at week 48 [sqrt(post) − sqrt (pre) > 2.5][24]; and (5) absolute and percent change in aortic and valvular calcification at week 48 and changes in calcium phosphate, iPTH, and 25(OH)D levels.

Patient Safety

The study was approved by the Institutional Review Board of the University of Pennsylvania (IRB # 807564) and written informed consent was signed by all participants. Adverse effects were collected up to 30 days after trial completion.

Statistical Analysis

All statistical analysis was performed using Stata, version 15, software (StataCorp; 2015) LP. For the primary end point, we compared between treatment groups using analysis of variance test. We adjusted our models for baseline CAC score. For continuous variables, comparisons of treatment groups were performed using t test or Wilcoxon test, depending on the data distribution. Comparisons of proportions were made using χ^2 test or Fisher exact test. We used linear regression to evaluate whether the log CAC score difference was different by treatment group for

Table 1. VCOR Participant Characteristics, Total and Stratified by Treatment Group

Variable	Total	Calcitriol	Paricalcitol
No.	44	22	22
Age, y (n = 44)	65.6 (9.3)	65.8 (7.4)	65.5 (11.0)
Sex			
Men	26 (59.1%)	17 (77.3%)	9 (40.9%)
Race			
White	15 (34.1%)	8 (36.4%)	7 (31.8%)
African American	29 (65.9%)	14 (63.6%)	15 (68.2%)
Diabetes	25 (56.8%)	13 (59.1%)	12 (54.6%)
Chronic kidney disease			
Stage 3	22 (50.0%)	11 (50.0%)	11 (50.0%)
Stage 4	22 (50.0%)	11 (50.0%)	11 (50.0%)
Serum creatinine, mg/dL	2.7 (1.0)	2.6 (0.9)	2.7 (1.0)
Estimated glomerular filtration rate, mL/min/1.73 m^2	27.4 (11.2)	29.9 (13.0)	25.0 (8.3)
Albumin, g/dL	3.8 (0.5)	3.8 (0.4)	3.7 (0.5)
Calcium, mg/dL	9.3 (0.5)	9.3 (0.4)	9.3 (0.5)
Albumin-corrected calcium, mg/dL	9.5 (0.4)	9.4 (0.3)	9.5 (0.4)
Phosphate, mg/dL	4.0 (0.8)	3.9 (0.8)	4.0 (0.8)
Parathyroid hormone, pmol/L	16.8 (10.6)	16.0 (8.9)	17.5 (12.3)
25-Hydroxyvitamin D, ng/mL	27.1 (12.5)	24.2 (8.1)	30.0 (15.4)
Urinary albumin-creatinine ratio, μg/mg (n = 20), median (IQR)	838.5 (396.5-1,110)	884 (615-1,103)	696 (387-1,117)
Proteinuria (n = 37)	25 (67.6)	11 (61.1)	14 (73.7)
Systolic blood pressure, mm Hg	137.3 (22.2)	137.0 (18.6)	137.5 (25.7)
Diastolic blood pressure, mm Hg	77.3 (14.7)	77.8 (14.8)	76.8 (15.1)
Mean arterial pressure, mm Hg	97.3 (16.1)	97.5 (15.4)	97.1 (17.2)
Pulse pressure, mm Hg	60.0 (14.8)	59.3 (10.3)	60.7 (18.5)

Note: Values for categorical variables are given as number (percent); values for continuous variables are given as mean (standard deviation). Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; calcium in mg/dL to mmol/L, ×0.2495; parathyroid hormone in pmol/L to pg/mL, ×9.43.
Abbreviation: VCOR, Vitamin D and Coronary Calcification Study.

our main outcome. We performed multivariable regression models with baseline CAC score (log), kidney function (eGFR and CKD stage), and dosing level of activated vitamin D. We also evaluated an interaction between CKD stage and dosing level of activated vitamin D in a fully adjusted model.

RESULTS

Study Population

Table 1 describes demographic and physiologic characteristics of the complete cohort and by treatment group. Mean age was 65.6 (SD, 9.3) years. The cohort had a high percentage of men (59%), individuals with DM (57%), and individuals who identified as African American (66%). Half the participants had CKD stage 3. There were no differences in levels of calcium, phosphate, 25(OH)D, and iPTH between the 2 study arms. Although there were differences in sex distribution between treatment groups, there were no other significant differences between treatment groups. Table 2 describes the dosing level at the end of the study.

Effect on CAC

Table 3 presents median values for CAC scores, volumes, and changes in total and stratified by treatment. Median CAC score was 140 (interquartile range [IQR], 55-277)

AU at baseline and 240 (IQR, 92-465) AU at the end of the study.

There was no difference between groups in the primary outcome, the difference in log-transformed CAC score (0.52 [0.77] for the paricalcitol group compared to 0.16 (0.30) for the calcitriol group, P = 0.06; Fig 2). Using the Hokanson square-root follow-up criterion, 7 of 21 (33%) paricalcitol-treated participants experienced progression of CAC compared with 2 of 19 (10.5%) calcitriol-treated patients (P = 0.09). On further subgroup analysis according to initial CKD stage presentation, differences between treatment groups were more pronounced in the CKD stage 4 group compared with the CKD stage 3 group (Fig 3). Median annual change in CAC score in participants with CKD stage 3 was 29.1 (IQR, 1.7-76.1), while those with CKD stage 4 had a median annual CAC score change of 92.6 (IQR, 31-184.7; P = 0.04). In participants with CKD stage 3, the median annual CAC change was 22.1 (IQR, 0-90.7) in the group receiving calcitriol compared to 37 (IQR, 1.7-73.9) in the group receiving paricalcitol. In participants with CKD stage 4, median annual CAC change was 65.4 (IQR, 27.9-93.6) in the group receiving calcitriol compared to 113.2 (IQR, 57.3-227.7) in the group receiving paricalcitol.

After adjustment for log-transformed baseline CAC score, treatment group remained nonsignificant

Table 2. Coronary Artery Calcification Outcomes

Variable	All (n = 44)	Calcitriol (n = 19)	Paricalcitol (n = 21)	*P* for Calcitriol vs Paricalcitol
Baseline CAC, AU	140 [55-277]	151 [67-428]	107 [54-213]	0.37
Follow-up CAC, AU	240 [92-465]	273 [73-531]	175 [104-444]	0.76
Baseline CAC volume, mm^3	99 [44-99]	127 [47-323]	75 [41-174]	0.31
Follow-up CAC volume, mm^3	150 [76-367]	190 [72-402]	144 [79-329]	0.77
Change in score, AU	59 [10-107]	31 [0-94]	60 [14-120]	0.39
Annualized CAC score change, AU/y	60 [11-111]	34 [0.2-100]	64 [14-128]	0.36
Percentage change, AU	32 [7.3-69.0]	21 [0.3-40.0]	48.3 [13.6-86.0]	0.03
Percentage change/time between scans, AU/y	33.8 [7.8-69.5]	22.6 [0.3-40.2]	51.4 [14.2-90.0]	0.03

Note: Variables expressed as median [interquartile range].
Abbreviations: AU, Agatston units; CAC, coronary artery calcification.

(P = 0.08). Further adjustment for GFR and/or CKD stage did not change the association. However, when dose level was also included in the model, the coefficient for individuals in the paricalcitol group was significantly associated with CAC progression (log) (coefficient, 0.49 [SE, 0.21]; P = 0.02). When dose level was included as an ordinal variable along with baseline CAC score (log) and eGFR, the coefficient for individuals on the paricalcitol group remained significant (coefficient, 0.48 [SE, 0.21]; P = 0.03) and the highest dose level was also associated with CAC progression (coefficient, 0.73 [SE, 0.34]; P = 0.04). The addition of an interaction term between dose level (ordinal value) and CKD stage yielded similar results with the paricalcitol treatment group (coefficient, 0.66 [SE, 0.22]; P = 0.005) associated with CAC progression but CKD stage 3 (coefficient, −1.04 [SE, 0.48]; P = 0.05) was protective. The interaction term had a graded response and was significant at level 3 dosing (coefficient, 1.57 [SE, 0.74]; P = 0.04)

Median CAC change in non-DM was similar between the 2 arms (57 vs 38; P = 0.53). However, the median CAC change in those with DM appeared higher in the paricalcitol group but did not achieve statistical significance (32 vs 111; P = 0.2). Using the Hokanson square-root follow-up criterion in participants with DM, 5 of 11 (46%) of those treated with paricalcitol experienced progression of CAC compared with 0 of 11 (0%) of those treated with calcitriol (P = 0.01).

We evaluated CAC change based on calcium and phosphate levels at baseline. In the highest tertile of calcium levels, 44% were progressors versus 22% in the lowest tertile (P = 0.76). The highest tertile for phosphate level showed 30% progressors versus 0% in the lowest tertile (P = 0.04). We then divided the cohort into tertiles based on combined calcium and phosphate levels (calcium-phosphate product). Those in the highest tertile had 36.3% progressors compared with 11.76% for those in the lowest tertile (P = 0.30). When divided into tertiles according to iPTH level, the highest tertile had 36% progressors compared with 13% in the lowest tertile (P = 0.38).

Effect on Cardiac Valve Calcification

Table 4 describes median values for aortic and mitral valve calcification scores, volumes, and changes in total and stratified by treatment. Median aortic valve Agatston score for all participants at baseline and week 48 was 12 (IQR, 0-72) AU and 26 (IQR, 1-103) AU, respectively. In the calcitriol group, median aortic score was 3.3 (IQR, 0-34) AU at baseline and 18 (IQR, 0-45) AU after 48 weeks of treatment, whereas in the paricalcitol group, median aortic score was 28 (IQR, 0-109) AU at baseline and 37 (IQR, 8-147) AU after 48 weeks of treatment. There was no difference in percentage change between the calcitriol and paricalcitol groups (32% vs 36%; P = 0.85). Similarly, there were no changes in median mitral valve calcification change between treatment groups. At baseline, 15 participants had no valvular calcification and by follow-up, this group was reduced to 10. Although 24 participants had 1 calcified valve at baseline, this had increased to 35 by the follow-up visit. Five participants had calcifications on both aortic and mitral valves at baseline, and this increased to 9 by week 48.

Effects on Markers of Mineral Metabolism

PTH was suppressed on average 11.5% during the study period, and only 22% of participants had PTH suppression > 30%. Throughout the course of the study, there was

Table 3. Valve Calcification Outcomes, Total and Stratified by Treatment Group

	Variable	All	Calcitriol	Paricalcitol	*P*
Aortic valve calcification	Baseline score, AU	12.5 [0-72.3]	3.3 [0-34.3]	28 [0-109]	0.2
	Follow-up score, AU	26 [1-102.5]	18 [0-45.1]	37 [8.3-147]	0.2
	% change	34 [0-104.3]	36 [0-89]	32 [0-120]	0.9

Note: Variables expressed as median [interquartile range].
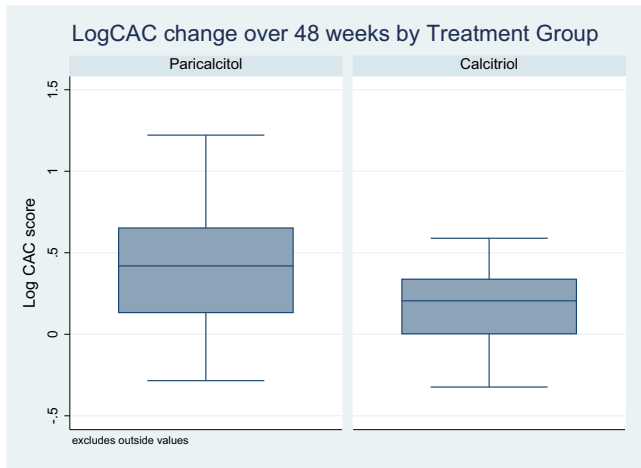Abbreviation: AU, Agatston units.

Figure 2. Boxplot shows the difference in percent change between both treatment arms. *P* = 0.06. Abbreviation: CAC, coronary artery calcification.

an increase in calcium and phosphate levels with a decrease in iPTH levels in both groups. There were no statistically significant differences between the 2 treatment groups. However, there was a significant decrease in 25(OH)D levels between the start and conclusion of the study (mean, 27.7 [SD, 12.5] vs 22.3 [SD, 10.1]; *P* = 0.007; Fig 4).

Adverse Events

During the study period, 3 participants started dialysis, 2 from the paricalcitol group. One episode of hypercalcemia was recorded in the paricalcitol group, and 1 episode of severe hyperphosphatemia was recorded in the calcitriol group. Three participants died, 2 of whom were in the calcitriol group.
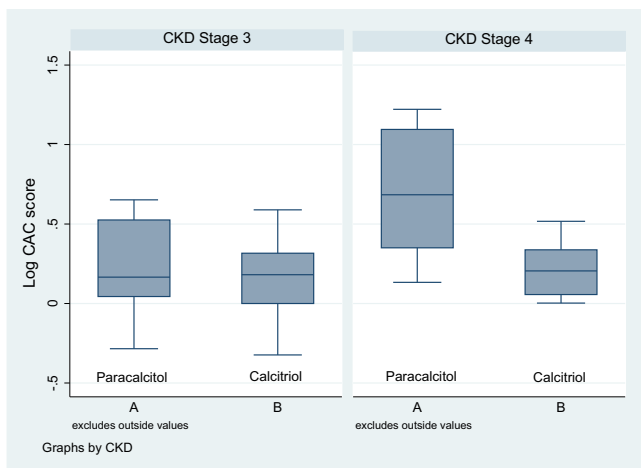
Figure 3. Boxplot shows the difference in percent change between both treatment arms stratified by chronic kidney disease (CKD) stage. *P* = 0.91 for CKD3; *P* = 0.02 for CKD4. Abbreviation: CAC, coronary artery calcification.

Table 4. Dosing Level for Activated Vitamin D at the End of the Study

Group	No Activated Vitamin D	Level 1	Level 2	Level 3
All participants	15.4%	33.3%	30.8%	20.5%
Calcitriol arm	5.3%	21.1%	42.1%	31.6%
Paricalcitol arm	25%	45%	20%	10%

Note: Level 1 is 0.25 μg 3 times a week of calcitriol or 2 μg 3 times a week of paricalcitol. Level 2 is 0.50 μg 3 times a week of calcitriol or 4 μg 3 times a week of paricalcitol. Level 3 is 0.50 μg daily of calcitriol or 4 μg daily of paricalcitol.

DISCUSSION

In this randomized controlled trial, there was no difference in progression of coronary and valvular calcification in individuals with CKD stages 3-4 between calcitriol and paricalcitol during a 48-week period. However, after adjustment for baseline CAC score (log), we found an interaction between higher dose of treatment and CAC progression. Likewise, we demonstrated no difference in valvular calcification change between treatment groups. Participants in the higher phosphate tertile were more likely to have CAC change compared with the lowest tertile.

The updated 2017 KDOQI CKD-MBD guidelines recommend management of CKD-MBD based on serial assessments of phosphate, calcium, and PTH levels, considered together. It no longer recommends routine treatment of high PTH levels with activated vitamin D or analogues in non–dialysis-dependent patients with CKD. Prior guidelines recommended treatment in patients with CKD 3 for PTH levels higher than the reference limit for the assay. Despite these changes, our study is relevant because our patients achieved on average a PTH suppression that remained 2 times higher than the reference limit, and dosing of the study medication was based on the combined assessment of calcium, phosphate, iPTH, and vitamin D.

Mizobuchi et al[6] found that different types of activated vitamin D have different effects on vascular calcification in uremic rats. After a 30-day follow-up, calcitriol significantly increased serum calcium-phosphate product levels and aortic calcium content, whereas paricalcitol had no effect. Paricalcitol treatment did not increase the messenger RNA and protein expression of the bone-related markers Runx2 and osteocalcin in the aorta.[6] Another study by Slatopolsky et al[10] on uremic rats found paricalcitol to be as effective at decreasing serum PTH levels with significantly less effect on ionized calcium and phosphate levels. Brown et al[8] investigated possible causes for the lower calcium and phosphate levels in paricalcitol-treated rats and found the most likely mechanism to be paricalcitol's lower potency in stimulating calcium and phosphate intestinal absorption.

Animal studies have demonstrated that extremely high calcitriol doses induce vascular calcification.[25,26] A study in
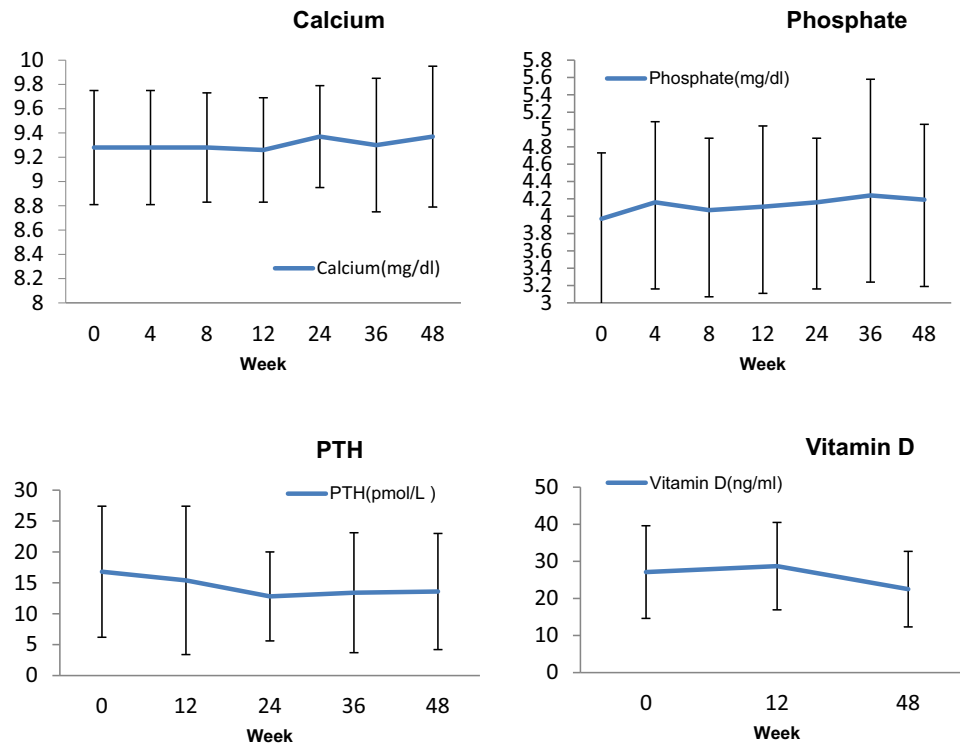
Figure 4. Mineral metabolism markers stratified by treatment group. Abbreviation: PTH, parathyroid hormone.

long-standing dialysis patients found the length of treatment with vitamin D analogues to be associated with CAC among other cardiovascular markers.[27] In the Vitamin D and Coronary Calcification (VCOR) Study reported here, all participants were naive to vitamin D analogues.

CAC has been demonstrated to have a strong association with CVD. A study following up 1,541 participants for an average of 5.9 years found CAC to be significantly associated with CVD, myocardial infarction, and heart failure incidence in patients with CKD not receiving dialysis, in addition to improving CVD risk prediction.[4] Different studies in patients with CKD have demonstrated markedly increased CAC prevalence and progression rates. Multiple studies have found an association between lower GFRs and mineral metabolism with CAC progression.[15,19,28] In contrast, Russo et al[16] found that calcium, phosphate, and iPTH levels did not predict CAC progression in individuals with CKD. Male sex and diabetes have also been associated with CAC progression.[17]

The annualized percent change in CAC in our cohort was 32.2%, a higher value than previously reported (14%) by Mehrotra et al.[29] However, our inclusion criteria included the presence of CAC to participate in the study and therefore had higher risk for CAC progression. The mean annualized square root of CAC progression was also higher than previously reported in an observational study (2.2 vs 0.96). However, the mean eGFR in our cohort was much lower compared with participants with CAC in this observational study (27.3 [SD, 11.2] vs 44.4 [SD, 15.9]).[28]

Our study did not find differences in rates of progression of cardiac valve calcification between the 2 treatment groups. Our prevalence of valvular calcification is higher than in previous studies, likely because we selected for participants with CAC. A study by Leskinen et al[30] reported a combined aortic and mitral calcification prevalence of 31% for the CKD group compared with 12% in the control group. Risk factors for developing cardiac valve calcification in the CKD group included age, diabetic status, and CKD duration.[30]

A study by Kim et al[31] investigated the prevalence of cardiac valvular calcification and its relationship with coronary artery disease in a cohort of 1,166 patients who were divided into a CKD and a non-CKD group. Cardiac valve calcification was found to statistically correlate with coronary artery disease in the CKD group while not achieving statistical significance in the non-CKD group.[31]

Although our study has multiple strengths, including treatment of coexisting vitamin D deficiency, randomization, double-masked status, and inclusion only of individuals with baseline measurable CAC, we have to acknowledge several limitations. The study included a relatively small number of participants and had a limited follow-up period. There is no placebo group because most patients had already been assigned to start activated vitamin D therapy by their providers. In addition, it was a single-center study with several post hoc analyses. Last, this study is not generalizable to the dialysis population.

In conclusion, in this randomized controlled trial, there was no difference in CAC or valvular progression in participants receiving calcitriol compared to paricalcitol during a 48-week period in individuals with CKD stages 3 and 4. Our pilot study provides support for an appropriately powered placebo control trial of activated vitamin D therapy in individuals with CKD.

ARTICLE INFORMATION

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REFERENCES

1. Matsushita K, Sang Y, Ballew SH, et al. Subclinical atherosclerosis measures for cardiovascular prediction in CKD. *J Am Soc Nephrol*. 2015;26:439-447.
2. Kasiske BL. Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis*. 1998;2(5 suppl 3):S142-S156.
3. US Renal Data System. *USRDS 2005 Annual Data Report*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2005.
4. Chen J, Budoff MJ, Reilly MP, et al. Coronary artery calcification and risk of cardiovascular disease and death among patients with chronic kidney disease. *JAMA Cardiol*. 2017;2:635-643.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2009;1:S1-S130.
6. Mizobuchi M, Finch JL, Martin DR, Slatopolsky E. Differential effects of vitamin D receptor activators on vascular calcification in uremic rats. *Kidney Int*. 2007;72:709-715.
7. Lund RJ, Andress DL, Amdahl M, Williams LA, Heaney RP. Differential effects of paricalcitol and calcitriol on intestinal calcium absorption in hemodialysis patients. *Am J Nephrol*. 2010;31:165-170.
8. Brown AJ, Finch J, Slatopolsky E. Differential effects of 19-nor-1,25-dihydroxyvitamin D2 and 1,25-dihydroxyvitamin D3 on intestinal calcium and phosphate transport. *J Lab Clin Med*. 2002;139:279-284.
9. Finch JL, Brown AJ, Slatopolsky E. Differential effects of 1,25-dihydroxy-vitamin D3 and 19-nor-1, 25-dihydroxy-vitamin D2 on calcium and phosphorus resorption in bone. *J Am Soc Nephrol*. 1999;10:980-985.
10. Slatopolsky E, Finch J, Ritter C, et al. A new analog of calcitriol, 19-nor-1, 25-(OH) 2 D 2, suppresses parathyroid hormone secretion in uremic rats in the absence of hypercalcemia. *Am J Kidney Dis*. 1995;26:852-860.
11. Bodyak N, Ayus JC, Achinger S, et al. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. *Proc Natl Acad Sci U S A*. 2007;104:16810-16815.
12. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med*. 2003;349:446-456.
13. Coyne DW, Goldberg S, Faber M, Ghossein C, Sprague SM. A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3-4 CKD. *Clin J Am Soc Nephrol*. 2014;9:1620-1626.
14. Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA*. 2012;307:674-684.
15. Kramer H, Toto R, Peshock R, Cooper R, Victor R. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. *J Am Soc Nephrol*. 2005;16:507-513.
16. Russo D, Palmiero G, De Blasio AP, Balletta MM, Andreucci VE. Coronary artery calcification in patients with CRF not undergoing dialysis. *Am J Kidney Dis*. 2004;44:1024-1030.
17. Kestenbaum BR, Adeney KL, de Boer IH, Ix JH, Shlipak MG, Siscovick DS. Incidence and progression of coronary calcification in chronic kidney disease: the Multi-Ethnic Study of Atherosclerosis. *Kidney Int*. 2009;76:991-998.
18. He J, Reilly M, Yang W, et al. Risk factors for coronary artery calcium among patients with chronic kidney disease (from the Chronic Renal Insufficiency Cohort Study). *Am J Cardiol*. 2012;110:1735-1741.
19. Budoff MJ, Rader DJ, Reilly MP, et al. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis*. 2011;58:519-526.
20. Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42 (suppl 3):1-201.
21. Zisman AL, Hristova M, Ho LT, Sprague SM. Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. *Am J Nephrol*. 2007;27:36-43.

22. Disthabanchong S, Boongird S. Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease. *World J Nephrol*. 2017;6:100-110.

23. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827-832.

24. Hokanson JE, MacKenzie T, Kinney G, et al. Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability. *AJR Am J Roentgenol*. 2004;182:1327-1332.

25. Henley C, Colloton M, Cattley RC, et al. 1,25-Dihydroxyvitamin D3 but not cinacalcet HCl (Sensipar®/Mimpara®) treatment mediates aortic calcification in a rat model of secondary hyperparathyroidism. *Nephrol Dial Transplant*. 2005;20:1370-1377.

26. Bas A, Lopez I, Perez J, Rodriguez M, Aguilera-Tejero E. Reversibility of calcitriol-induced medial artery calcification in rats with intact renal function. *J Bone Miner Res*. 2006;21:484-490.

27. Briese S, Wiesner S, Will JC, et al. Arterial and cardiac disease in young adults with childhood-onset end-stage renal disease—impact of calcium and vitamin D therapy. *Nephrol Dial Transplant*. 2006;21:1906-1914.

28. Bundy JD, Chen J, Yang W, et al. Risk factors for progression of coronary artery calcification in patients with chronic kidney disease: the CRIC study. *Atherosclerosis*. 2018;271:53-60.

29. Mehrotra R, Budoff M, Hokanson JE, Ipp E, Takasu J, Adler S. Progression of coronary artery calcification in diabetics with and without chronic kidney disease. *Kidney Int*. 2005;68:1258-1266.

30. Leskinen Y, Paana T, Saha H, et al. Valvular calcification and its relationship to atherosclerosis in chronic kidney disease. *J Heart Valve Dis*. 2009;18:429-438.

31. Kim IY, Kim MJ, Lee DW, et al. Cardiac valve calcification is associated with presence and severity of coronary artery disease in patients with pre-dialysis chronic kidney disease. *Clin Exp Nephrol*. 2015;19:1090-1097.