Vitamin D Therapy and Cardiac Structure and Function in Patients With Chronic Kidney Disease

The PRIMO Randomized Controlled Trial

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Context Vitamin D is associated with decreased cardiovascular-related morbidity and mortality, possibly by modifying cardiac structure and function, yet firm evidence for either remains lacking.

Objective To determine the effects of an active vitamin D compound, paricalcitol, on left ventricular mass over 48 weeks in patients with an estimated glomerular filtration rate of 15 to 60 mL/min/1.73 m^2.

Design, Setting, and Participants Multinational, double-blind, randomized placebo-controlled trial among 227 patients with chronic kidney disease, mild to moderate left ventricular hypertrophy, and preserved left ventricular ejection fraction, conducted in 11 countries from July 2008 through September 2010.

Intervention Participants were randomly assigned to receive oral paricalcitol, 2 µg/d (n=115), or matching placebo (n=112).

Main Outcome Measures Change in left ventricular mass index over 48 weeks by cardiovascular magnetic resonance imaging. Secondary end points included echocardiographic changes in left ventricular diastolic function.

Results Treatment with paricalcitol reduced parathyroid hormone levels within 4 weeks and maintained levels within the normal range throughout the study duration. At 48 weeks, the change in left ventricular mass index did not differ between treatment groups (paricalcitol group, 0.34 g/$m^{2.7}$ [95% CI, –0.14 to 0.83 g/$m^{2.7}$] vs placebo group, –0.07 g/$m^{2.7}$ [95% CI, –0.55 to 0.42 g/$m^{2.7}$]). Doppler measures of diastolic function including peak early diastolic lateral mitral annular tissue velocity (paricalcitol group, –0.01 cm/s [95% CI, –0.63 to 0.60 cm/s] vs placebo group, –0.30 cm/s [95% CI, –0.93 to 0.34 cm/s]) also did not differ. Episodes of hypercalcemia were more frequent in the paricalcitol group compared with the placebo group.

Conclusion Forty-eight week therapy with paricalcitol did not alter left ventricular mass index or improve certain measures of diastolic dysfunction in patients with chronic kidney disease.

Trial Registration clinicaltrials.gov Identifier: NCT00497146

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ALTHOUGH PRIMARILY RECOMmended for improving bone health, treatment with vitamin D recently has been suggested for other conditions, including cardiovascular disease (CVD).[1-3] Multiple lines of evidence suggest a link between vitamin D and CVD, including experimental studies identifying vitamin D receptors in vascular smooth muscle, endothelial cells, and possibly cardiac tissue[1,4] and observational studies, small clinical trials, and meta-analyses suggesting that vitamin D therapy reduces cardiovascular events.[2,3] Convincing data demonstrating that vitamin D therapy improves cardiovascular health, however, are lacking.

For editorial comment see p 722.

Patients with chronic kidney disease (CKD) frequently develop deficiency of 1,25-dihydroxyvitamin D_3 (calcitriol) because of a lack of its precursor, 25-

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hydroxyvitamin D_3, and impaired activity of the kidney enzyme 1α-hydroxylase, which converts this precursor to the active hormone.[5] Altered vitamin D metabolism leads to secondary hyperparathyroidism, the primary indication for calcitriol therapy.[6] Observational studies in patients with CKD report associations between vitamin D deficiency and increased risk of cardiovascular events and between therapy with calcitriol or related analogs and reduced events.[7-10] Experimental models suggest that intermediate end points for these observations include a reduction of left ventricular hypertrophy (LVH), improved left ventricular diastolic function, and reduced episodes of heart failure.[11-15] Given both the altered vitamin D metabolism and elevated rates of cardiovascular events found among patients with CKD, vitamin D therapy may reduce their risk of CVD-related morbidity and mortality.

The efficacy of vitamin D therapy to modify intermediate cardiac end points has not been prospectively tested, although large-scale outcome trials have recently been initiated.[16] We therefore conducted PRIMO (Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity), an investigator-initiated, industry-sponsored, multinational, double-blind, randomized placebo-controlled trial, to test the hypothesis that 48-week treatment with paricalcitol (19-nor-1,25-$[OH]_2$ vitamin D_2) reduces left ventricular mass, improves diastolic function, reduces CVD events, and improves cardiac biomarkers in patients with LVH and CKD.

METHODS

Study Population

Details of the PRIMO study design have been previously published.[17] In brief, eligibility criteria included 2-dimensional transthoracic echocardiographic evidence of mild to moderate LVH (septal wall thickness of 1.1-1.7 cm in women and 1.2-1.8 cm in men)[18] without asymmetric septal hypertrophy or valvular disease; left ventricular ejection fraction greater than 50%; and estimated glomerular filtration rate (eGFR) of 15 to 60 mL/min/1.73 m^2. Individuals taking renin-angiotensin-aldosterone system (RAAS) inhibitors followed the same regimen for at least 1 month prior to screening and throughout the study. Eligibility also included a serum intact parathyroid hormone (iPTH) level between 50 and 300 pg/mL; serum calcium level between 8.0 and 10.0 mg/dL; serum phosphorus level of 5.2 mg/dL or lower; and serum albumin level of 3.0 g/L or higher. Major exclusion criteria included receiving any active vitamin D therapy, anticipated dialysis initiation or death within 1 year, clinically significant coronary artery disease, cerebrovascular accident or acute renal failure within 3 months, and systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg at screening. Nutritional vitamin D (cholecalciferol or ergocalciferol) was limited to 400 IU/d. Demographic and clinical characteristics were collected prospectively by site investigators. Self-reported participants' race/ethnicity was obtained given its potential influence on susceptibility to change in left ventricular mass.[19]

The study was approved by local and central institutional review and ethics committees, and all participants signed written informed consent statements prior to study initiation.

Study Design

During a 6-week screening period, left ventricular mass, renal function, and laboratory measures were evaluated. On treatment day 1, participants were randomized 1:1 to receive paricalcitol capsules or placebo. Randomization was stratified with respect to country, sex, and baseline RAAS inhibitor use. Baseline physical examination was performed and medical history was recorded. Blood samples were collected for measurement of cardiac biomarkers.

Participants assigned to receive paricalcitol started at 2 µg/d with a protocol-specified dose reduction to 1 µg/d if serum calcium exceeded 11 mg/dL, with identical protocol-specified capsule reduction in placebo. Participants returned for study visits at weeks 4, 8, 12, 18, 24, 30, 36, 42, and 48, during which vital signs and serum iPTH were measured and adverse events and concomitant medications were recorded. Limited nonfasting blood was collected at all visits except at weeks 24 and 48, when a full chemistry panel was performed.

Efficacy End Points

The primary end point was change from baseline left ventricular mass index (LVMI) over 48 weeks by cardiovascular magnetic resonance (CMR) imaging. Prespecified secondary end points included transthoracic echocardiographic measures of left ventricular diastolic function (peak early diastolic lateral mitral annular tissue velocity (E′), isovolumetric relaxation time, ratio of early mitral inflow wave velocity E-wave (E) velocity to E′, and E-wave deceleration time); CMR measures of left ventricular end systolic and diastolic volume indexes and ejection fraction; CVD events leading to hospitalization or death; and change in cardiac biomarkers.

Cardiac Imaging

CMR Data. Eligible candidates underwent CMR to establish baseline, week 24, and week 48 LVMI. Cardiac magnetic resonance examinations were performed using an electrocardiograph-gated, breath-hold, 2-dimensional, steady-state free precession cine with contiguous, left ventricular, short-axis stack of images acquired from just above the base to below the apex of the left ventricle with a section thickness of 10 mm (no gap), spatial resolution of 2.0 × 2.0 mm, field of view of 32 cm, and temporal resolution of 50 ms.[20] All left ventricular mass measurements were made at a central CMR core laboratory (Perfuse) with investigators blinded to treatment group and temporal sequence. The reproducibility and overall excellent quality of the core CMR laboratory have been previously published,[21] and any intercenter deviations in CMR image section thickness were subsequently reread after imple-

menting additional quality control measures. Measurements were made by manual planimetry of the endocardial and epicardial left ventricular borders (to define the left ventricular myocardial area). The area of each section at end diastole was multiplied by section thickness and myocardial density. All section values were summated (QMASS MR, version 6.2.3, Medis Inc).[22] Left ventricular papillary muscles and trabeculations were excluded from mass measurements. Left ventricular mass index was obtained by normalizing left ventricular mass to height to the 2.7th power.[23]

Echocardiographic Data. From 2-dimensional, M-mode, and Doppler (spectral, color, tissue) images, the following continuous variables were obtained: E′ (cm/s), E/E′, isovolumic relaxation time (seconds), and deceleration time (seconds).[24] Left ventricular volumes were derived as previously described[13] and left ventricle mass estimated from linear dimensions according to published formulas.[18] To determine the full extent of structural and functional changes, exploratory echocardiographic measures included left ventricular mass, left ventricular volume in end diastole and end systole, left ventricular posterior wall and septal thickness, left ventricular internal dimension, left atrial volume, and mitral regurgitation jet area.

Cardiovascular Events

Prespecified end points included cardiovascular hospitalizations and deaths. An independent adjudication committee blinded to treatment assignment reviewed all hospitalizations (no deaths occurred during the study period) and adjudicated those related to cardiovascular events. Admission and discharge records, interventions during hospitalizations, and hospital course were reviewed in detail. Criteria used to define cardiovascular events were similar to those used previously.[25] Committee members independently assigned all the same cases to cardiovascular-related hospitalizations (100% agreement).

Laboratory Measurements

Details of all laboratory measurements have been previously published.[17,26] In brief, we measured iPTH (Immulite 2000, Siemens; normal range, 12-65 pg/mL) at each visit. Levels of cardiac troponin T (Roche Diagnostics; normal range, <0.01 ng/mL) and B-natriuretic peptide (BNP; Abbott Diagnostics; normal range, <100 pg/mL) were measured at 0 and 48 weeks. Because cardiac troponin T and BNP are altered by changes in renal function,[27,28] results were adjusted post hoc for changes in eGFR. Vitamin D compounds alter serum creatinine levels independent of GFR[17,26,29-32]; therefore, prespecified analyses included GFR estimated by both a serum creatinine–based equation (eGFR [mL/min/1.73 m^2] = 186 × [Cr] − 1.154 × [age] − 0.203 × [0.742 if female] × [1.210 if African American])[33] and a cystatin C–based equation (eGFR [mL/min/1.73 m^2] = 99.43 × $cystatin^{-1.58}$).[34]

Sample Size Determination

Because little was known about the variability of LVMI changes in CKD during the planning stage, we prospectively implemented an information-based adaptive design that allowed sample size reestimation when 50% of the data were collected.[17,26] No changes to our initial sample size estimate of 220 participants (110 per group) were necessary to achieve more than 85% power to detect a clinically meaningful difference in LVMI of 2.7 g/$m^{2.7}$ (absolute left ventricular mass difference of approximately 10 g) between groups with a 2-sided $\alpha = .05$.

Patient Safety

Safety was evaluated as serious adverse events during the 48 weeks of treatment and 30 days following discontinuation of study drug. The number of participants with hypercalcemia (2 consecutive measurements of serum Ca^{2+} greater than 10.5 mg/dL [corrected to serum albumin of 4.0 g/dL]) and the number requiring dose reductions (from 2 to 1 µg/d) were compared between treatment groups. An external data monitoring committee (independent of the steering committee and study sponsor) operated under a formalized charter to monitor safety and efficacy and to assess LVMI variability so as to recommend sample size adjustment.

Statistical Analysis

All analyses were performed using SAS software, version 9.2 (SAS Institute Inc). Means and standard deviations were used to summarize distributions and means with 95% confidence intervals were used to summarize group differences unless otherwise specified. Efficacy analyses were conducted in the intention-to-treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug and with at least 2 primary end point measurements. All analyses were also prospectively performed on a subpopulation with more severe LVH (LVH population), defined as the sex-stratified upper 3 quartiles of baseline LVMI.

The primary efficacy analysis used a maximum-likelihood, mixed-effects repeated-measures model (MMRM) with all longitudinal observations in the ITT population. The model included terms of treatment, visit, and treatment × visit interaction with baseline LVMI, sex, RAAS use, and country as covariates. As a penalty of the interim analysis, the final statistical significance level for the primary outcome was to be adjusted using the $\gamma(-8)$ function.[17,26] However, the information at interim analysis was small and the penalty was negligible. A 2-sided $P<.05$ was retained for LVMI in the final analysis. A sensitivity analysis was conducted using multiple imputation techniques to account for missing data or loss to follow-up.

Changes from baseline to all postbaseline visits for other continuous variables measured on CMR or echocardiographic imaging were analyzed by the same MMRM. Biomarkers and other laboratory variables were analyzed using an MMRM with terms of treatment, country, visit, and treatment × visit in-

teraction as fixed categorical effects and with baseline as a continuous covariate. Means and 95% confidence intervals from the MMRM are presented throughout. These analyses were performed using PROC MIXED with denominator degrees of freedom estimated by the Satterthwaite approximation. Within-participant errors were estimated using unstructured covariance unless otherwise specified. *P* values for postbaseline visits represent the significance level between treatment groups at a specific postbaseline visit from the mixed-effects model. Overall *P* values represent the significance level for the overall treatment group effect with both follow-up times (24 and 48 weeks) combined. Post hoc analyses controlling for change in estimated eGFR by cystatin C were performed for both log-transformed BNP and percentage of participants with cardiac troponin T levels of 0.01 or higher.[27,28] Estimated GFR adjustment was also conducted to examine the partial correlation between change in left atrial volume index and change in log-transformed BNP levels.

Safety measures were assessed in participants receiving at least 1 dose of study drug. The frequency of at least 1 adverse event was compared between groups using the Fisher exact test. Hospitalizations were examined using the Fisher exact test for frequency (multiple events per participant are counted only once) and Poisson regression for event rates (the total number of separate events is considered even if recurring within the same participant).

RESULTS

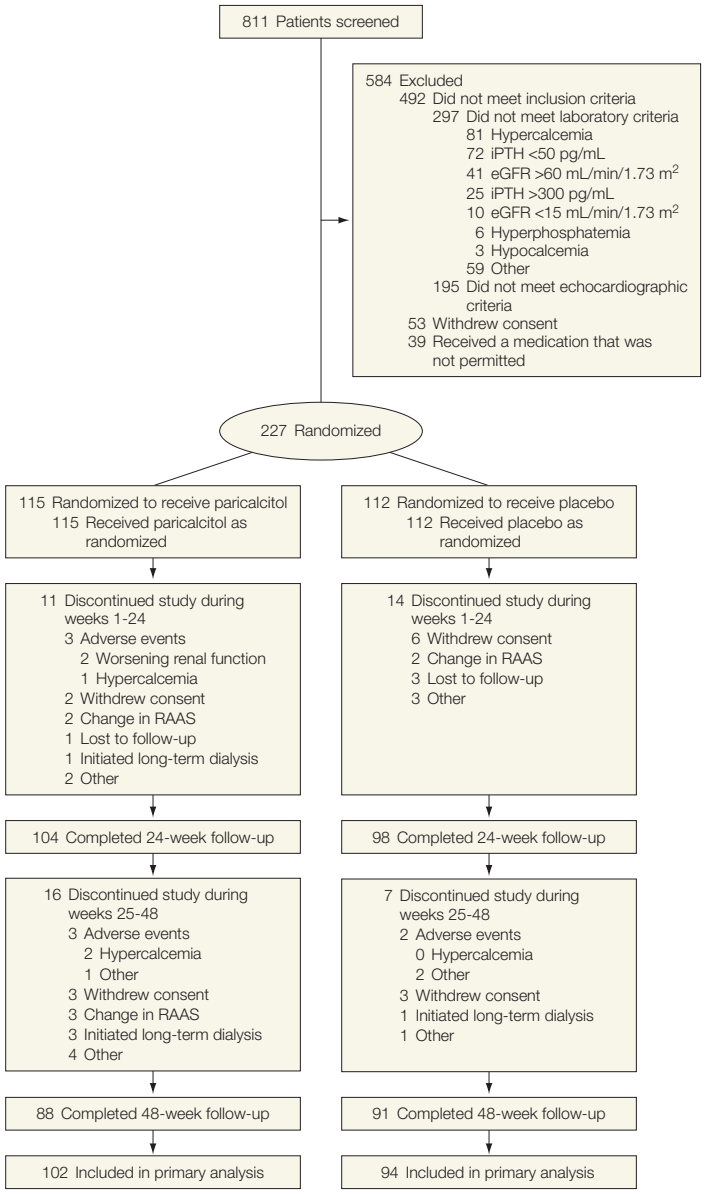
Enrollment and Study Population

A total of 811 participants from 60 centers in 11 countries were screened from July 2008 through September 2010, leading to enrollment of 227 participants; 115 were randomly assigned to receive paricalcitol and 112 to receive placebo (FIGURE 1). Demographics were balanced between groups (TABLE 1). Participants were predominantly male and had hypertension. Other CVD risk factors were frequent in both groups. Blood pressure was well controlled in both groups. Most participants were receiving RAAS inhibitors, and the use of diuretics and erythropoiesis-stimulating agents (9.6% in paricalcitol group vs 9.3% in placebo group) also were balanced. Baseline eGFR was lower and urine albumin-creatinine ratio higher in the group randomized to paricalcitol.

Baseline cardiac imaging (TABLE 2) showed that left ventricular ejection fraction was well preserved in both groups. Peak early diastolic lateral mitral annular tissue velocity (E′), a measure of diastolic function, was below normal, consistent with impaired diastolic function.[35]

Serum iPTH levels were approximately 1.5 times the upper limit of nor-

Figure 1. Randomization and Treatment



Twenty-four– and 48-week data (postbaseline visits) represent the number of participants included in the primary analysis using a mixed-effects repeated-measures model. iPTH indicates intact parathyroid hormone; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.

mal at baseline. Treatment with paricalcitol reduced iPTH within the first 4 weeks, and levels remained in the normal range throughout the study duration (FIGURE 2). Overall, 85.7% of the paricalcitol group and 16.5% of the placebo group demonstrated a reduction of iPTH of greater than 30% by week 48 ($P<.001$). Levels of bone-specific alkaline phosphatase also had a larger decrease in the paricalcitol group (eTable 1; available at http://www.jama.com). Serum calcium levels increased a mean of 0.32 mg/dL (95% CI, 0.19-0.45 mg/dL) in the paricalcitol group and decreased 0.25 mg/dL (95% CI, –0.37 to –0.12 mg/dL) in the placebo group (between-group difference in baseline-to-48-week change, $P<.001$). Serum phosphorus levels increased 0.23 mg/dL (95% CI, 0.07-0.39 mg/dL) in the paricalcitol group and increased 0.04 mg/dL (95% CI, –0.12 to 0.20 mg/dL) in the placebo group (between-group difference in baseline-to-48-week change, $P=.05$). Systolic ($P=.82$) and diastolic ($P=.33$) blood pressure and heart rate ($P=.44$) did not markedly differ throughout the study period between groups (eTable 2).

Table 1. Baseline Characteristics by Treatment Group

Characteristics	Paricalcitol (n = 115)	Placebo (n = 112)
Age, mean (SD), y	64 (11)	66 (12)
Male, No. (%)	79 (68.7)	79 (70.5)
Race, No. (%)		
White	84 (73.0)	84 (75.0)
African American	13 (11.3)	12 (10.7)
Asian	14 (12.2)	15 (13.4)
Other	4 (3.5)	1 (0.9)
Cardiovascular history, No. (%)		
Hypertension	111 (96.5)	107 (95.5)
Smoking, past or current	62 (53.9)	61 (54.5)
Peripheral vascular disease, arterial	14 (12.2)	15 (13.4)
Diabetes	63 (54.8)	57 (50.9)
Diabetic nephropathy	33 (28.7)	40 (35.7)
Diabetic retinopathy	22 (19.1)	21 (18.8)
Renin-angiotensin-aldosterone system medications	90 (78.3)	87 (77.7)
Diuretics	45 (39.1)	39 (34.8)
Body mass index, mean (SD)[a]	30.5 (6.3)	29.9 (6.8)
Vital signs, mean (SD)		
Systolic blood pressure, mm Hg	135 (15)	135 (19)
Diastolic blood pressure, mm Hg	76 (12)	75 (10)
Heart rate, /min	70.2 (9.6)	68.2 (13.1)
Body weight, mean (SD), kg	86.5 (20.7)	84.8 (19.7)
Laboratory values, median (interquartile range)		
Albumin, g/dL	4.4 (4.2-4.6)	4.4 (4.2-4.6)
Potassium, mEq/L	4.6 (4.3-5.0)	4.5 (4.1-5.0)
Calcium, mg/dL	9.6 (9.2-9.8)	9.6 (9.3-9.9)
Phosphate, mg/dL	3.7 (3.3-4.2)	3.5 (3.1-4.0)
Intact parathyroid hormone, pg/mL	100.0 (66.0-174.0)	106.0 (71.0-153.5)
Hematocrit, %	37.4 (34.8-41.6)	38.4 (36.1-41.9)
Serum urea nitrogen, mg/dL	37.0 (30.0-47.9)	34.5 (26.1-42.0)
Creatinine, mg/dL	2.1 (1.6-2.7)	1.9 (1.6-2.4)
Estimated glomerular filtration rate by creatinine, mL/min/1.73 m^2	31.0 (24.0-43.0)	36.0 (26.0-42.0)
Cystatin C, mg/L	2.0 (1.6-2.4)	1.8 (1.5-2.2)
Estimated glomerular filtration rate by cystatin C, mL/min/1.73 m^2	32.5 (25.0-47.5)	38.1 (29.2-54.7)
Bone-specific alkaline phosphatase, U/L	24.1 (19.8-34.0)	23.0 (18.0-32.7)
Tri-iodothyronine, ng/dL	98.9 (85.3-114.0)	97.5 (80.9-114.8)
B-natriuretic peptide, pg/mL	70.0 (35.0-132.0)	82.0 (33.0-177.0)
Urine albumin, mg/dL	107.0 (9.8-530.1)	48.8 (10.5-288.9)
Urine albumin:creatinine ratio, mg/g	222.8 (42.7-855.1)	118.5 (27.6-750.2)
High-sensitivity C-reactive protein, mg/dL	0.15 (0.08-0.44)	0.16 (0.08-0.43)
Interleukin 6, ≥5 pg/mL, No. (%)	21 (19.3)	18 (16.4)
Cardiac troponin T, ≥0.01 µg/L, No. (%)	29 (26.9)	29 (26.4)

SI conversion factors: To convert albumin to g/L, multiply by 10; serum urea nitrogen to mmol/L, multiply by 0.365; bone-specific alkaline phosphatase to µkat/L, multiply by 0.0167; calcium to mmol/L, multiply by 0.25, creatinine to µmol/L, multiply by 88.4; cystatin to nmol/L, multiply by 74.9; high-sensitivity C-reactive protein to nmol/L, multiply by 9.524; intact parathyroid hormone to ng/L, multiply by 0.1053; phosphate to mmol/L, multiply by 0.323; tri-iodothyronine to nmol/L, multiply by 0.0154; and urine albumin:creatinine ratio to mg/mmol, multiply by 0.113.

[a]Body mass index is calculated as weight in kilograms divided by height in meters squared.

Efficacy End Points

The primary end point was change in LVMI at 48 weeks, which did not significantly differ between groups in the ITT analysis (TABLE 3). Results were similar when changes in left ventricular mass were not indexed to height (paracalcitol, 1.29 g [95% CI, –0.72 to 3.29 g] vs placebo, –0.20 g [95% CI, –2.19 to 1.80 g]; $P=.12$). We conducted a sensitivity analysis using multiple imputation techniques to account for participants with missing data or lost to follow-up and the conclusion remained the same for the primary end point ($P=.32$). In the LVH population, LVMI increased slightly at week 48 in the paricalcitol group (paricalcitol, 0.46 g/$m^{2.7}$ [95% CI, –0.15 to 1.08 g/$m^{2.7}$] vs placebo, –0.23 g/$m^{2.7}$ [95% CI, –0.87 to 0.41 g/$m^{2.7}$] ; $P=.05$) (eTable 3). In both the ITT and LVH analyses, CMR measures of left ventricular end-diastolic volume index and ejection fraction tended to increase in the paricalcitol group and decrease in the placebo group, but the comparisons did not reach statistical significance. The change in prespecified echocardiographic measures of diastolic function did not significantly differ between the paricalcitol and placebo groups (TABLE 4 [ITT population] and eTable 4 [LVH population]).

Cardiac Hospitalizations

The number of hospitalizations from any cause (paricalcitol, 15.7% vs placebo, 17.0%; $P=.86$) and from noncardiovascular causes (paricalcitol, 15.7% vs placebo, 11.6%; $P=.44$) did not differ between groups. In contrast, there were fewer hospitalizations for CVD events in the paricalcitol group (TABLE 5). Most CVD-related hospitalizations occurred near the study mid point (163 days; interquartile range, 104-241 days), and all events occurred in the LVH population. The most common cardiovascular event was congestive heart failure (paricalcitol, n=0; placebo, n=5).

Cardiac Biomarkers

Plasma levels of BNP increased in both groups; however, the increase was attenuated in the paricalcitol group compared with the placebo group in the ITT analysis (+21% vs +41%, respectively; $P=.14$) and in the LVH subgroup (+16% vs +50%, respectively; $P=.04$). After adjusting for changes in eGFR, changes in plasma levels of BNP remained similar (ITT, +23% vs +46%; $P=.11$; LVH subgroup, +19% vs +64%; $P=.02$). At baseline, 25.3% in the paricalcitol group and 26.1% in the placebo group had a serum cardiac troponin T level of at least 0.01 ng/mL. In the ITT analysis, participants with cardiac troponin T levels of at least 0.01 increased to 39.2% in the paricalcitol group and to 27.3% in the placebo group ($P=.01$). The difference between groups was reduced after controlling for changes in eGFR ($P=.05$). The results were similar in the LVH subgroup.

Exploratory End Points

As expected, LVMI as measured by echocardiography differed from that obtained by CMR,[36,37] but within each mode the baseline measures were similar (Table 2 and eTable 5). There was no evidence of change in LVMI by echocardiography (eTable 6 [ITT population] and eTable 7 [LVH population]). We then examined additional cardiac structural and functional changes potentially linked with reduced hospitalizations for congestive heart failure and noted a monotonic decline in left atrial volume index in the paricalcitol group but not in the placebo group (eTable 6 [ITT population], eTable 7 [LVH population], and the eFigure). Combining both treatment groups, changes in BNP levels significantly correlated with changes in left atrial volume index (ITT population, $r=0.24$; $P=.01$ and LVH population, $r=0.32$; $P=.005$).

Adverse Events

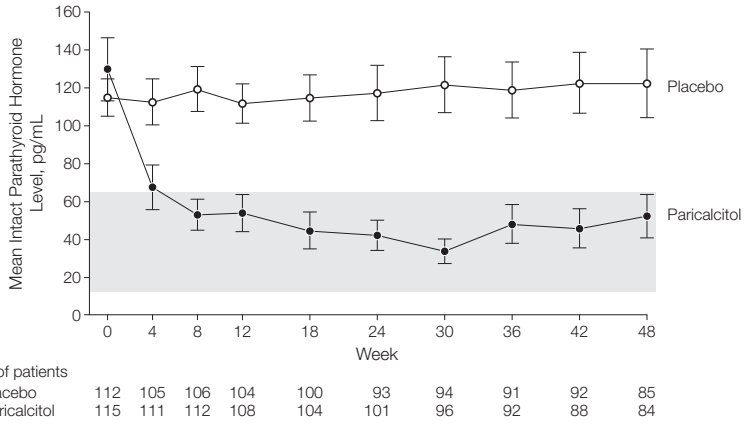
A similar number of participants in each group reached the final visit at 48 weeks (paricalcitol, 76.5% vs placebo, 81.3%; $P=.42$). There was no difference in the overall incidence of adverse events between groups (paricalcitol, 80.0% vs placebo, 77.7%; $P=.75$). More adverse events were judged to be probably or possibly drug related in the paricalcitol group (20.9% vs 5.4%; $P<.001$) (eTable 8). These events were primarily due to hypercalcemia (paricalcitol, 22.6% vs placebo, 0.9%; $P<.001$). There was a slightly higher number of participants withdrawing from the study because of adverse events in the paricalcitol group (9.6% vs 4.5%; $P=.19$), again primarily because of hypercalcemia. A similar number of participants reported serious adverse events in each group (paricalcitol, 17.4% vs placebo, 17.9%; $P=.93$) (eTable 8), and

Table 2. Baseline Imaging by Treatment Group

Imaging Procedures	Paricalcitol (n = 115)	Placebo (n = 112)
Cardiovascular magnetic resonance imaging, mean (SD)		
Left ventricular mass index, g/m$^{2.7}$	23.7 (7.3)	23.5 (8.3)
Left ventricular end-systolic volume index, mL/m$^{2.7}$	11.8 (4.5)	12.4 (6.5)
Left ventricular end-diastolic volume index, mL/m$^{2.7}$	31.1 (9.2)	31.4 (12.0)
Ejection fraction, %	64.6 (8.9)	64.2 (8.9)
Aortic compliance, 10^{-4} cm^2/mm Hg	84.6 (63.3)	93.5 (55.0)
Thoracoabdominal aortic plaque volume, mL[a]	0.02 (0.09)	0.03 (0.18)
Thoracoabdominal aortic wall volume, mL	0.52 (0.25)	0.49 (0.20)
Transthoracic echocardiography, mean (SD)		
Early diastolic mitral annular velocity (E′), cm/s	8.2 (2.5)	8.4 (2.4)
Early mitral inflow wave velocity/early diastolic mitral annular velocity ratio, E/E′	10.3 (3.9)	10.4 (4.1)
Transmitral E-wave deceleration time, s	0.224 (0.033)	0.224 (0.032)
Isovolumetric relaxation time, s × 1000	105.6 (16.3)	108.6 (17.9)

[a] Median (interquartile range) in both the paricalcitol and placebo groups is 0.0 (0.0-0.0).

Figure 2. Blood Levels of Intact Parathyroid Hormone During the Study by Treatment Group



Error bars indicate 95% CIs. The shaded area corresponds to the normal range of values.

none were judged to be related to the study drug.

Measures of renal damage (reduced eGFR and increased proteinuria) suggested worse renal disease at baseline in the paricalcitol group vs the placebo group (Table 1). Estimated GFR by creatinine-based methods showed a greater decline in the paricalcitol group (mean, –4.1 [SD, 0.9] mL/min/1.73 m^2 with paricalcitol vs –0.1 [SD, 0.7] mL/min/1.73 m^2 with placebo; $P<.001$). Estimated GFR by cystatin C–based methods also demonstrated a greater decline with paricalcitol (mean, –9.5 [SD, 2.7] mL/min/1.73 m^2 with paricalcitol vs –3.8 [SD, 2.7] mL/min/1.73 m^2 with placebo), but this difference was not statistically significant ($P=.06$). More participants in the paricalcitol group vs the placebo group initiated long-term dialysis (6 vs 1, respectively; $P=.12$), which tended to occur near the end of the study (median, 281 days; interquartile range, 151-301 days). The mean creatinine-based eGFR at study start among those initiating long-term dialysis was 23 (SD, 4) mL/min/1.73 m^2. Blinded field investigators did not attribute long-term dialysis initiation to study drug in any participant, similar to a blinded adjudication of medical rec-

Table 3. Repeated-Measures Analysis of Change in Cardiovascular Magnetic Resonance Imaging Measures From Baseline to 24 and 48 Weeks (Intention-to-Treat Population)[a]

	24 Weeks			48 Weeks			
Measures	Paricalcitol (n = 104)	Placebo (n = 98)	*P* Value[b]	Paricalcitol (n = 88)	Placebo (n = 91)	*P* Value[b]	Overall *P* Value[c]
Left ventricular mass index, g/$m^{2.7}$	0.27 (–0.15 to 0.68)	–0.15 (–0.57 to 0.27)	.05	0.34 (–0.14 to 0.83)	–0.07 (–0.55 to 0.42)	.15	.06
Left ventricular end-systolic volume index, mL/$m^{2.7}$	0.04 (–0.67 to 0.76)	0.002 (–0.72 to 0.72)	.91	0.58 (–0.25 to 1.41)	0.57 (–0.24 to 1.39)	.98	.94
Left ventricular end-diastolic volume index, mL/$m^{2.7}$	0.18 (–0.66 to 1.01)	–0.31 (–1.16 to 0.53)	.26	0.30 (–0.64 to 1.25)	–0.36 (–1.30 to 0.58)	.21	.19
Left ventricular ejection fraction, %	0.64 (–0.70 to 1.98)	0.28 (–1.07 to 1.64)	.61	0.62 (–0.90 to 2.14)	–0.54 (–2.06 to 0.98)	.18	.27
Aortic compliance, 10^{-4} cm^2/mm Hg	–6.35 (–16.88 to 4.19)	–1.64 (–12.61 to 9.33)	.44	–7.24 (–17.12 to 2.65)	–5.79 (–15.58 to 4.00)	.78	.51
Thoracoabdominal aortic plaque volume, mL	–0.006 (–0.03 to 0.02)	–0.03 (–0.05 to –0.002)	.22	–0.02 (–0.03 to –0.02)	–0.03 (–0.03 to –0.02)	.09	.15
Thoracoabdominal aortic wall volume, mL	0.006 (–0.04 to 0.05)	–0.03 (–0.08 to 0.01)	.09	–0.07 (–0.12 to –0.03)	–0.10 (–0.15 to –0.05)	.36	.13

[a] Values are adjusted least-squares means and 95% CIs estimated from the models. Models include treatment, visit, treatment × visit interaction, sex, baseline renin-angiotensin-aldersterone system inhibitor use, country, and baseline value.
[b] Test of significance of treatment group differences by visit from the mixed-effects model.
[c] Test of significance between treatment groups for the overall effect (24 weeks and 48 weeks combined) from the mixed-effects models.

Table 4. Repeated-Measures Analysis of Change in Transthoracic Echocardiographic Measures From Baseline to 24 and 48 Weeks (Intention-to-Treat Population)[a]

	24 Weeks			48 Weeks			
Measures	Paricalcitol (n = 104)	Placebo (n = 98)	*P* Value[b]	Paricalcitol (n = 88)	Placebo (n = 91)	*P* Value[b]	Overall *P* Value[c]
Early diastolic mitral annular velocity (E′), cm/s	–0.34 (–0.89 to 0.22)	–0.10 (–0.69 to 0.49)	.44	–0.01 (–0.63 to 0.60)	–0.30 (–0.93 to 0.34)	.43	.93
Early mitral inflow wave velocity/early diastolic mitral annular velocity ratio, E/E′	–0.30 (–1.21 to 0.60)	–0.38 (–1.35 to 0.58)	.87	0.16 (–0.98 to 1.31)	–0.33 (–1.52 to 0.85)	.47	.58
Transmitral E-wave deceleration time, s	0.006 (–0.003 to 0.01)	0.0001 (–0.009 to 0.009)	.22	0.008 (–0.0004 to 0.02)	–0.001 (–0.01 to 0.01)	.06	.06
Isovolumetric relaxation time, s × 1000	0.04 (–3.92 to 4.00)	–2.16 (–6.17 to 1.84)	.30	0.45 (–3.77 to 4.68)	–1.56 (–5.91 to 2.80)	.41	.29

[a] Values are adjusted least-squares means and 95% CIs estimated from the models. Models include treatment, visit, treatment × visit interaction, sex, baseline renin-angiotensin-aldersterone system inhibitor use, country, and baseline value.
[b] Test of significance for treatment group differences by visit from the mixed-effects model.
[c] Test of significance between treatment groups for the overall effect (24 weeks and 48 weeks combined) from the mixed-effects models.

ords at the study end. There were no deaths during the study period; however, 1 death occurred in each group more than 30 days after study completion.

COMMENT

The links among vitamin D deficiency, vitamin D therapy, and chronic disease are of considerable clinical and research interest. Although alterations in vitamin D metabolism have been associated with CVD and experimental data suggest that the vitamin D pathway is involved in modifying cardiac structure and function, corresponding clinical trial evidence is limited. Our goal was to rigorously examine whether an active vitamin D compound improves intermediate cardiac end points and thus inform larger outcome studies with vitamin D therapy. We found that paricalcitol at doses sufficient to suppress blood levels of iPTH did not reduce LVMI as measured by CMR over a 48-week period in participants with mild to moderate LVH. Additionally, paricalcitol did not modify certain echocardiographic measures of diastolic function. However, paricalcitol did reduce CVD hospitalizations and attenuate the increase in blood levels of BNP, particularly in those with prominent LVH at baseline.

We studied an active vitamin D compound rather than a nutritional vitamin D supplement because active vitamin D compounds (eg, calcitriol) have a greater than 100-fold affinity for the vitamin D receptor compared with the precursor 25-hydroxyvitamin D_3.[38] Furthermore, rats null for 1α-hydroxylase develop LVH in the setting of elevated levels of 25-hydroxyvitamin D_3 and almost absent levels of calcitriol.[39] In this rat model, LVH is attenuated following calcitriol administration, suggesting that the active hormone has the greatest effect on modification of this end point. Given our results with an active vitamin D analog, it is unlikely that nutritional vitamin D supplementation (ergocalciferol or cholecalciferol) of similar duration modifies LVH.

Table 5. Cardiovascular Hospitalizations by Treatment Group

Reason for Hospitalization	No. of Participants/ Cardiovascular Events	Follow-up, No. of Person-Years	Event Rate per 100 Person-Years	Study Day at Hospitalization
Placebo group	7/8	91.0	8.8	
Congestive heart failure[a]				16
Congestive heart failure				104
Chest pain				135
Chest pain				163
Aortic dissection				179
Congestive heart failure[a]				241
Congestive heart failure				289
Congestive heart failure				361
Paricalcitol group	1/1	94.3	1.1	
Chest pain				22
P value	.03		.04	

[a]These 2 hospitalizations were for the same participant.

Our results differ from reports of vitamin D therapy in animal models of LVH.[12,14,39,40] One possibility is that our sample size was too small. We used an adaptive design involving an interim analysis to ensure that our sample size provided more than 85% power to detect differences between groups.[26] Confidence intervals for the primary end point were narrow and exclude a clinically meaningful change, suggesting that a larger sample size would have yielded similar results. In fact, although not clinically meaningful, the results in the LVH population were contrary to our original hypothesis, suggesting a longer duration would also not have yielded a similar result. Notably, our primary end point was measured with CMR, a highly sensitive technique requiring a sample size markedly lower than that required in echocardiography studies.[41,42] We do not believe that either inadequate dose or poor adherence led to a neutral effect as the intervention resulted in a strong physiological response (marked reduction in blood levels of iPTH) in all treated participants. A significant determinant of LVH is blood pressure.[43] Stringent guidelines to manage blood pressure were not implemented; however, blood pressure was well controlled throughout the study period, which may have attenuated a treatment effect. Overall, 48 weeks of paricalcitol treatment does not influence LVH in humans.

Vitamin D deficiency is associated with congestive heart failure,[44] including in infants with vitamin D–deficient rickets.[45] In animal studies, calcitriol or related analogs such as paricalcitol augment diastolic relaxation and reduce end-diastolic pressures, reduce cardiac mRNA expression and blood levels of natriuretic peptides, and reduce episodes of congestive heart failure.[12,13,15,46] In prespecified analyses, paricalcitol attenuated the rise in BNP levels and was associated with fewer cardiovascular hospitalizations, primarily for congestive heart failure. This is consistent with previous observational studies suggesting that therapy with active vitamin D is associated with fewer CVD outcomes.[8-10,47,48] In post hoc analysis, paricalcitol also reduced left atrial volume, a measure linked to adverse cardiovascular events, particularly congestive heart failure.[49-52] Left atrial enlargement reflects chronically impaired diastolic relaxation and elevated end-diastolic pressures and is less prone to preload changes, which limit Doppler measures.[53] Left atrial stretch and ventricular stiffness result in release of natriuretic peptides, and we observed a correlation between reduced left atrial size and reduced BNP levels. Given the high risk of cardiovascular events and

heart failure in patients with CKD[51,52,54] and the paucity of available lusitropic agents, future outcome studies with paricalcitol should target patients with CKD and a history of congestive heart failure with preserved systolic function.

Treatment with paricalcitol was well tolerated. The most common adverse effect was hypercalcemia, which is known to occur with active vitamin D treatment.[6] More participants treated with paricalcitol initiated long-term hemodialysis; however, those randomized to the paricalcitol group had worse renal disease at baseline, an imbalance likely due to chance. Paricalcitol also increased serum creatinine and subsequently decreased creatinine-based measures of eGFR. Because paricalcitol and related agents inhibit renin expression,[12,55,56] elevated serum creatinine may have represented a true reduction in GFR, as reported with angiotensin-converting enzyme inhibitor use.[29] Alternatively, when GFR is examined by more direct measures including iothalamate and inulin clearance, active vitamin D compounds (including, most recently, paricalcitol) increase serum creatinine without altering renal function.[17,26,29-32] We therefore prospectively examined cystatin C–based measures of eGFR, which were more similar between groups. Although the precise mechanism is unclear, vitamin D receptor activation likely modifies protein (and thus creatinine) metabolism.[17,26,30] We could not exclude the possibility that paricalcitol may have adversely affected renal function, although this has not been previously observed.[57-59] Nevertheless, clinicians should be aware that active vitamin D compounds may alter serum creatinine without significantly changing renal function.

Our study has certain limitations. Although previous cross-sectional studies have reported that LVMI increases as GFR declines,[18,60,61] we did not find a significant increase in left ventricular mass in either group over 48 weeks despite a decline in kidney function. When patients with CKD and predominantly normal left ventricular mass were followed up for 2 years in randomized trials, little progression was observed.[4,62] We targeted patients with CKD and preexisting LVH, expecting more rapid progression, but this was not reported. In experimental models, vitamin D therapy consistently attenuates progression of LVH,[12,14,40] a finding we were unable to test. Importantly, despite the finding of no improvement in LVH (even with highly sensitive CMR), cardiovascular events and related biomarkers did differ.

In conclusion, in this 48-week study of patients with CKD and mild to moderate LVH, the active vitamin D compound paricalcitol did not regress left ventricular mass or improve certain Doppler measures of diastolic function. Paricalcitol appeared to be associated with fewer cardiovascular-related hospitalizations, an attenuated increase in blood levels of BNP, but a greater incidence of hypercalcemia; however, these results warrant further confirmation.

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