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ORIGINAL INVESTIGATION

Association of Activated Vitamin D Treatment and Mortality in Chronic Kidney Disease

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Background: Treatment of secondary hyperparathyroidism (SHPT) with activated vitamin D analogues is associated with better survival in patients receiving dialysis. It is unclear whether such a benefit is present in patients with predialysis chronic kidney disease (CKD).

Methods: We examined the association of oral calcitriol treatment with mortality and the incidence of dialysis in 520 male US veterans (mean [SD] age, 69.8 [10.3] years; 23.5% black) with CKD stages 3 to 5 and not yet receiving dialysis (mean [SD] estimated glomerular filtration rate, 30.8 [11.3]). Associations were examined by the Kaplan-Meier method and in Poisson regression models with adjustment for age, race, comorbidities, smoking, blood pressure, body mass index, use of phosphate binders, estimated glomerular filtration rate, proteinuria, white blood cell count, percentage of lymphocytes, and levels of parathyroid hormone, calcium, phosphorus, albumin, bicarbonate, and hemoglobin.

Results: Two hundred fifty-eight of 520 subjects received treatment with calcitriol, 0.25 to 0.5 μg/d, for a median duration of 2.1 years (range, 0.06-6.0 years). The incidence rate ratios for mortality and combined death and dialysis initiation were significantly lower in treated vs untreated patients ($P < .001$ for both in the fully adjusted models). Treatment with calcitriol was associated with a trend toward a lower incidence of dialysis. These results were consistent across different subgroups.

Conclusions: Treatment with the activated vitamin D analogue calcitriol appears to be associated with significantly greater survival in patients with CKD not yet receiving dialysis. Randomized clinical trials are required to verify the causality of these associations and to examine whether similar associations are seen with different activated vitamin D analogues.

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SECONDARY HYPERPARATHYROIDISM (SHPT) occurs frequently in patients with chronic kidney disease (CKD)[1] and is associated with various complications, including bone disease,[2,3] uremic pruritus,[4] cognitive and sexual dysfunction,[5,6] and higher cardiovascular morbidity[7,8] and mortality.[9,10] One of the mainstays of therapy for SHPT has been the use of activated vitamin D analogues,[11] including nonselective agents such as 1α,25-dihydroxyvitamin D_3 (calcitriol).[12] Administration of activated vitamin D analogues in patients receiving maintenance dialysis (hereinafter referred to as dialysis patients) has been associated with improved survival when these patients are compared with those not receiving such treatments.[10,13,14] Secondary HPT is not limited to dialysis patients. Patients with earlier stages of CKD also display SHPT, which tends to progress as kidney function deteriorates.[1] Suppression of SHPT with nonselective[15-17] and selective activated vitamin D analogues[18,19] in these earlier stages of CKD has been shown to be effective, but it is unknown whether the application of these therapeutic agents in the early stages of CKD is associated with survival benefits similar to those seen in patients who are already receiving dialysis. We examined outcomes (all-cause mortality and the initiation of maintenance dialysis) as a function of treatment status with oral activated vitamin D in 520 male US veterans with predialysis CKD stages 3 to 5.

METHODS

STUDY POPULATION AND DATA COLLECTION

We examined data from 1012 outpatients undergoing evaluation and treatment of CKD (excluding those requiring dialysis) at the Salem Veterans Affairs Medical Center (VAMC) from January 1, 1990, through June 30, 2005, and followed up until March 31, 2007. We excluded 11 female patients (1.1%) and 5 (0.5%) whose race was other than white or black to mitigate demographic heterogeneity. Of the remaining 996 patients, 543 (54.5%) had had at least 1 serum intact parathyroid hormone (PTH) level measurement before the initiation of maintenance dialysis. Twenty-two of these patients (4.1%), whose first serum PTH evaluation was performed after August 10, 2005 (when the assay for intact PTH measurement was changed at the Salem VAMC), were excluded given the significant intermethod variability between different PTH assays.[20] The medical records of the remaining 521 patients were reviewed for evidence of therapy with any vitamin D analogue, recording the date when the treatment was initiated and the doses of the administered medications. One patient whose activated vitamin D therapy was initiated at an outside institution was excluded. The final study population consisted of 520 patients.

Baseline characteristics of the population were recorded retrospectively because they were measured within 6 months of the time when PTH levels were first measured for patients who were never treated with activated vitamin D, or within 6 months of initiation of treatment with activated vitamin D. These included demographic and anthropometric characteristics, blood pressures, comorbid conditions (including the Charlson comorbidity index), use of calcium- and noncalcium-based phosphate binders, and laboratory results, as detailed elsewhere.[21,22] Estimated glomerular filtration rate (eGFR) was determined using the abbreviated equation developed for the Modification of Diet in Renal Disease Study[23] and categorized according to the staging system advocated by the Kidney/Dialysis Outcome Quality Initiative Clinical Practice Guidelines for CKD.[24] Serum calcium concentration was corrected for serum albumin concentration using the following formula[25]:

$$\text{Corrected Calcium Level} = \text{Measured Calcium Level} + 0.8 \times (4 - \text{Serum Albumin Level}).$$

Intact PTH level was measured in a single clinical laboratory at the Salem VAMC using a commercially available intact PTH assay (Allegro assay; Nichols Institute Diagnostics, San Clemente, California), with a normal range of 10 to 65 pg/mL (to convert PTH to nanograms per liter, multiply by 0.1053) and a coefficient of variation of less than 3.4%. To determine the effect of treatment with activated vitamin D on serum levels of calcium, phosphorus, and PTH, these variables were collected longitudinally with the averaging of the values collected within 6-month periods. A large proportion of the follow-up measurements of PTH levels was performed after August 10, 2005, and hence performed with a different assay (Immulite 2000 immunoassay; Diagnostic Products Corporation, Los Angeles, California). These values were corrected to be comparable with the baseline intact PTH values by using the following formula suggested by Souberbielle et al[20]:

$$\text{Immulite 2000 Intact PTH Level} = 1.32 \times \text{Allegro Intact PTH Level} + 13.9.$$

STATISTICAL ANALYSES

For descriptive statistics, variables with skewed distribution (proteinuria and PTH level) were transformed to their natural logarithm. Missing data points for the comorbidity index (1% missing); body mass index (4.8% missing); levels of serum phosphorus (0.2% missing), 24-hour urine protein (1% missing), blood cholesterol (1.7% missing), and serum albumin (0.8% missing); white blood cell count (3.7% missing); and percentage of lymphocytes (3.7% missing) were imputed using linear regression with all other patient characteristics serving as independent variables. Smoking status (3% missing) was analyzed as a categorical variable with 3 categories (nonsmoker, active smoker, and missing smoking status).

The starting time for survival analysis was either the date of the first PTH level measurement for patients who never received treatment with activated vitamin D, or was the date when treatment with activated vitamin D was started for those who did receive such treatment. The main outcome measure was predialysis all-cause mortality as a function of treatment status with activated vitamin D. Secondary outcome measures were the composite of predialysis all-cause mortality and end-stage renal disease (ESRD) and a separate analysis of ESRD. Patients were considered lost to follow-up if no contact with them was documented for more than 6 months, and they were censored in survival analyses at the date of the last documented contact with the medical center. Event rates were calculated using the person-years approach. The unadjusted associations of treatment with activated vitamin D and the outcome measures were examined using Kaplan-Meier plots and the log-rank test. Poisson regression models were used to adjust for the effect of multiple baseline confounding variables. The appropriateness of the models was tested with a goodness-of-fit test using the deviance statistic. Subgroup analyses were performed in groups divided by baseline age, race, presence of diabetes mellitus and atherosclerotic cardiovascular disease, and levels of PTH, serum calcium, phosphorus, albumin, and blood hemoglobin. To minimize secular trends, all analyses were repeated after excluding patients enrolled before January 1, 2001. We considered P values of less than .05 as statistically significant. Statistical analyses were performed using Stata statistical software, version 8 (StataCorp, College Station, Texas). The study protocol was approved by the Research and Development Committee at the Salem VAMC.

RESULTS

The mean (SD) age of the studied outpatients was 69.8 (10.3) years; 23.5% were black; and the mean eGFR was 30.8 (11.3) mL/min/1.73 m^2. Altogether, 90.8% of the participants were enrolled in the study after January 1, 2001. The activated vitamin D product used for the treatment of secondary hyperparathyroidism in this cohort was exclusively calcitriol. A total of 258 patients (49.6%) received treatment with calcitriol; 99.2% of them received the treatment after January 1, 2001; 91.0% of them received a dose of 0.25 μg/d without further adjustments; and 9.0% received a maximum dose of 0.5 μg/d after an initial starting dose of 0.25 μg/d. The baseline characteristics of the treated and nontreated patient groups are shown in **Table 1**. Patients treated with calcitriol were older, had lower diastolic blood pressure, were more likely to use phosphate binders, and had significantly higher PTH, lower eGFR, and lower serum calcium levels.

Postbaseline calcium, phosphorus, and PTH levels are shown in **Figure 1**, separately for calcitriol-treated and nontreated patients. Levels of PTH showed an approximately 33% drop during follow-up in the treated group ($P < .001$, repeated measures analysis of variance [ANOVA]) and no substantial change in the nontreated group ($P = .20$, repeated measures ANOVA). Serum calcium levels did not show significant changes during follow-up ($P = .07$ for the calcitriol-treated and $P = .08$ for the untreated groups, repeated measures ANOVA). Serum phosphorus levels showed a slight increase in the calcitriol-treated group ($P = .04$, repeated measures ANOVA) but not in the untreated group ($P = .17$, repeated measures ANOVA).

A total of 126 patients died before reaching the need for dialysis (mortality rate, 116 per 1000 patient-years;

Table 1. Baseline Characteristics of Individuals Stratified by Treatment Status With Calcitriol[a]

Characteristic	Calcitriol Treatment (n=258)	No Calcitriol Treatment (n=262)	P Value[b]
Age, y	70.8 (10.2)	68.6 (10.2)	.01
No. (%) black	65 (25)	57 (22)	.35
Diabetes mellitus, No. (%)	142 (55)	151 (58)	.35
ASCVD, No. (%)	153 (59)	151 (58)	.7
Smoking, No. (%)	64 (25)	58 (22)	.5
Comorbidity index	2.4 (1.6)	2.5 (1.7)	.58
Calcium use, No. (%)	93 (36)	76 (29)	.08
Sevelamer hydrochloride use, No. (%)	65 (25)	28 (11)	<.001
BMI	29.2 (6.0)	28.8 (5.6)	.4
SBP, mm Hg	144 (23)	145 (26)	.6
DBP, mm Hg	69 (14)	72 (16)	.02
PTH level, pg/mL, geometric mean (95% CI)	152 (143-163)	75 (66-83)	<.001
eGFR, mL/min/1.73 m²	29.1 (9.2)	32.4 (12.8)	<.001
Albumin level, g/dL	3.5 (0.4)	3.6 (0.5)	.64
Cholesterol level, mg/dL	179 (49)	186 (48)	.12
Bicarbonate level, mEq/L	25.7 (3.4)	25.5 (3.7)	.6
Calcium level, mg/dL	9.1 (0.5)	9.2 (0.6)	.03
Phosphorus level, mg/dL	4.0 (0.7)	4.0 (0.8)	.56
Alkaline phosphatase level, U/L	86.0 (1.5)	93.8 (55.3)	.09
Hemoglobin level, g/dL	12.5 (1.5)	12.5 (1.9)	.8
WBC count, ×1000 cells/μL	7.3 (1.9)	7.5 (2.6)	.29
Lymphocytes, % of WBC count	22.5 (8.2)	22.9 (8.5)	.6
Proteinuria, g/24 h, geometric mean (95% CI)	652 (551-781)	707 (591-846)	.56

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; SBP, systolic blood pressure; WBC, white blood cell.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; alkaline phosphatase to microkatals per liter, multiply by 0.0167; bicarbonate to millimoles per liter, multiply by 1.0; calcium to micromoles per liter, multiply by 0.25; cholesterol to millimoles per liter, multiply by 0.0259; hemoglobin to grams per liter, multiply by 10; lymphocytes to proportion of 1.0, multiply by 0.01; phosphorus to millimoles per liter, multiply by 0.323; PTH to nanograms per liter, multiply by 0.1053; and WBC to $\times 10^9$/L, multiply by 0.001.

[a] Unless otherwise indicated, data are expressed as mean (SD).

[b] Compared by means of an unpaired *t* test or χ^2 test.

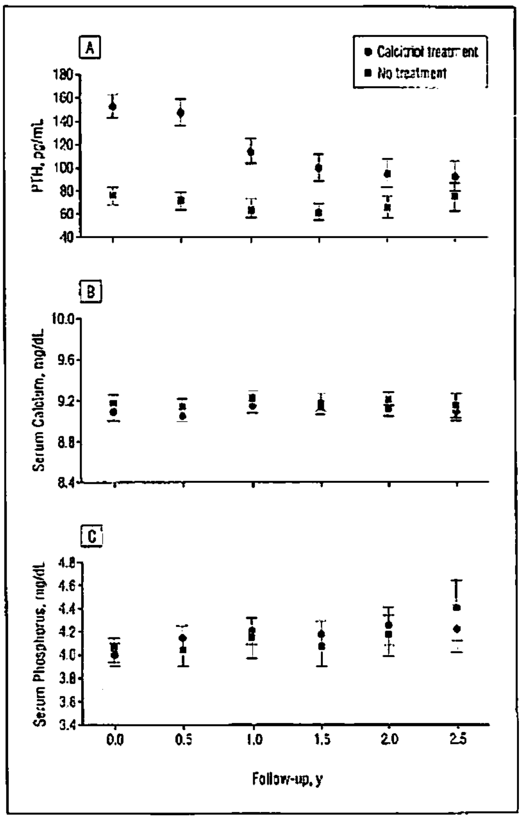

Figure 1. Serum parathyroid hormone (PTH) (A), calcium (B), and phosphorus (C) levels at baseline and at 6-month follow-up intervals in calcitriol-treated and untreated patients. Values represent geometric means (95% confidence intervals) for PTH concentrations and means (95% confidence intervals) for calcium and phosphorus concentrations. To convert calcium to micromoles per liter, multiply by 0.25; phosphorus to millimoles per liter, multiply by 0.323; and PTH to nanograms per liter, multiply by 0.1053.

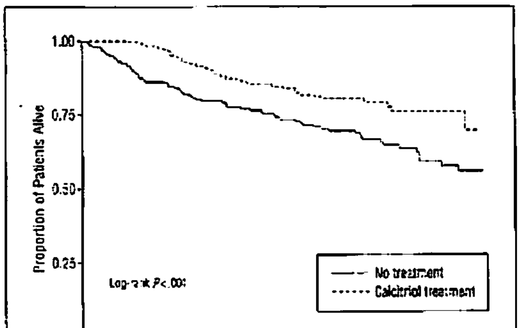

Figure 2. Kaplan-Meier curves for all-cause mortality, comparing calcitriol-treated vs untreated patients.

95% confidence interval [CI], 97-138) and in 131 patients was dialysis initiated (dialysis initiation rate, 121 per 1000 patient-years; 95% CI, 102-143) during a median follow-up of 2.1 years. Characteristics of the 5 patients lost to follow-up were not significantly different (data not shown). **Figure 2** shows the Kaplan-Meier survival curves for all-cause mortality in calcitriol-treated and nontreated patients, with patients who received calcitriol treatment displaying a significantly lower mortality rate ($P<.001$, log-rank test). The incidence rate ratios (calcitriol-treated vs nontreated patients) for predialysis mortality, the composite of predialysis mortality and ESRD, and ESRD alone in the unadjusted models, case mix–adjusted models (ie, for age, race, body mass index, systolic and diastolic blood pressure, smoking status, comorbidity index, presence of diabetes mellitus, and use of calcium-containing and non–calcium-containing phosphate binders), and case mix–adjusted plus laboratory variable–adjusted models (ie, for all the case mix variables plus levels of PTH, eGFR, calcium, phosphorus, albumin, cholesterol, hemoglobin, and 24-hour urine protein, white blood cell count, and percentage of lym-

Table 2. Incidence of Various Outcomes in Poisson Regression Models, Comparing Calcitriol-Treated vs Untreated Patients, Unadjusted and After Multivariable Adjustments for Various Confounders

Model No.	Covariates	Outcome, Rate Ratio (95% CI): Predialysis Mortality	Outcome, Rate Ratio (95% CI): Composite of Predialysis Mortality and ESRD	Outcome, Rate Ratio (95% CI): ESRD Alone
1	Unadjusted	0.53 (0.37-0.77)	0.72 (0.56-0.92)	0.95 (0.67-1.34)
2	Age, race, BMI, SBP, DBP, smoking status, comorbidity index, presence of diabetes mellitus, use of calcium-containing phosphate binders, and use of sevelamer hydrochloride	0.47 (0.32-0.69)	0.55 (0.42-0.72)	0.67 (0.46-0.97)
3	Model 2 plus eGFR, WBC count, percentage of lymphocytes in WBC, and levels of PTH, calcium, phosphorus, albumin, cholesterol, hemoglobin, and 24-h urine protein	0.35 (0.23-0.54)	0.46 (0.35-0.61)	0.75 (0.50-1.12)

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PTH, parathyroid hormone; SBP, systolic blood pressure; WBC, white blood cell.

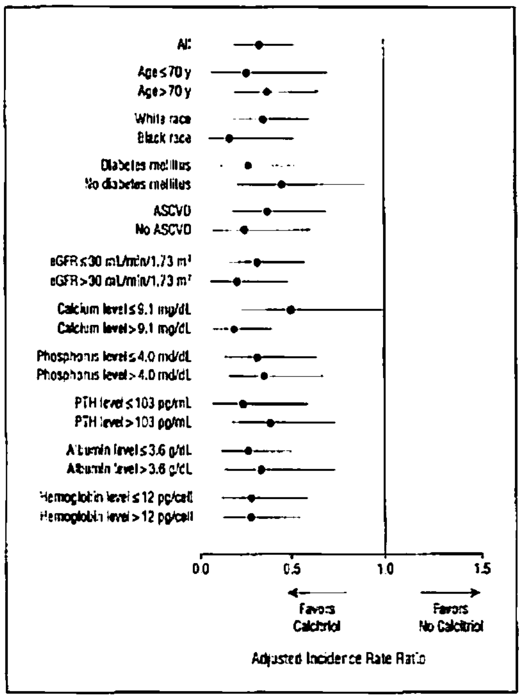

Figure 3. Incidence rate ratios (95% confidence intervals) for all-cause mortality before dialysis in the fully adjusted Poisson regression models comparing calcitriol-treated vs untreated patients for various subgroups. ASCVD indicates atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; and PTH, parathyroid hormone. To convert albumin to grams per liter, multiply by 10; calcium to micromoles per liter, multiply by 0.25; hemoglobin to grams per liter, multiply by 10; phosphorus to millimoles per liter, multiply by 0.323; and PTH to nanograms per liter, multiply by 0.1053.

phocytes in white blood cell count) are shown in **Table 2**. The incidence rate ratio for all cause-mortality indicated significantly favorable outcomes in the calcitriol-treated group in the unadjusted model, with magnification of the benefit after adjustments. The incidence rate ratio of mortality in treated vs untreated patients was 0.35 (95% CI, 0.23-0.54; $P<.001$) and for combined death and dialysis initiation was 0.46 (95% CI, 0.35-0.61) in the fully adjusted models. There was a nonsignificant trend between calcitriol treatment and the incidence of ESRD alone (without mortality) in unadjusted and fully adjusted models, whereas this association was statistically significant in the case mix–adjusted model, that is, an ESRD incidence rate ratio of 0.67 (95% CI, 0.46-0.97; $P=.03$). **Figure 3** shows the multivariable-adjusted incidence rate ratios of all-cause mortality from the fully adjusted model in various patient subgroups, indicating significantly lower all-cause mortality for patients treated with calcitriol in all of the examined subgroups. The results were not different when we restricted the analyses to the 472 patients enrolled after January 1, 2001 (data not shown).

COMMENT

We found that, in a male outpatient population with CKD stages 3 to 5, treatment of SHPT with low doses of an oral nonselective activated vitamin D was associated with significantly better survival. This benefit was present in all the examined subgroups, including patients with lower pretreatment PTH, higher calcium, and higher phosphorus levels, and also when we examined only a subset of contemporary patients. It is remarkable that the beneficial outcomes seen in patients treated with calcitriol in our study were present despite the following characteristics that should have worsened their prognosis compared with the patients who were not treated with this agent: older age, lower diastolic blood pressure (associated with higher mortality in CKD[22]), higher PTH level (associated with higher mortality in patients receiving dialysis[9,10]), lower eGFR (associated with higher mortality in CKD[23-26]), and a rise in serum phosphorus level (associated with higher mortality in dialysis patients[9,10] and possibly in patients with CKD[27]). These results complement earlier findings in patients receiving maintenance hemodialysis that indicated better survival in patients treated with any activated vitamin D analogue product (selective or nonselective) compared with those not receiving such therapy.[10,13,14]

The mechanism of action behind the higher survival associated with activated vitamin D therapy is unclear. Secondary HPT in itself is associated with higher cardiovascular morbidity[7,8] and mortality,[9,10] which could explain why suppression of PTH concentrations with activated vitamin D therapy would lead to lower mortality. The early separation of the unadjusted Kaplan-Meier survival curves in our study was followed by a relatively parallel course (Figure 2); this corresponded with the initial decline and subsequent equalization in PTH levels seen as a result of calcitriol treatment (Figure 1), hence it is possible that the early mortality benefit was a result of the lowering of PTH levels.

The effect of activated vitamin D treatment, however, may be much wider ranging. The vitamin D receptor is ubiquitous, and its stimulation with activated vitamin D has been shown to have a direct influence on the cardiovascular system by inhibiting the production of proteins implicated in arterial calcification,[28-30] by stimulating the production of proteins that are inhibitors of arterial calcification,[28,31] by inhibiting the production of cytokines that are involved in calcification and atheroma formation[32,33] and stimulating the production of cytokines that are inhibiting it,[34,35] and by preventing thrombosis.[36] Furthermore, activated vitamin D deficiency was associated with higher all-cause and cardiovascular mortality in a large cohort of hemodialysis patients,[37] and lower 1,25-dihydroxyvitamin D_3 levels have been associated with worsened coronary calcification,[38] also suggesting a PTH-independent link between vitamin D levels and survival. The fact that we found that treatment with calcitriol was beneficial, even in subgroups of patients with lower baseline PTH levels, and that the benefit was significant despite the low doses applied (which might have limited the PTH-lowering effect) suggest that these direct cardiovascular mechanisms, thus far described mostly in vitro and in laboratory animals, may indeed have important practical consequences. The broader question is whether activated vitamin D therapy should only be applied for the sole indication of suppressing SHPT, or whether it could become a therapy applied primarily as a means to prolong survival through its cardiovascular effects. Such an indication clearly cannot arise from results of observational studies such as ours but would require randomized controlled trials.

Currently, activated vitamin D therapy is only applied in CKD to treat SHPT.[11] This treatment can indeed be successful by using nonselective agents such as calcitriol.[15-17,39] The effect of such treatment on mortality is relevant for patients with any stage of CKD. A second important consideration is the effect on kidney function in patients with earlier stages of CKD who are not yet receiving dialysis. The application of higher doses of calcitriol has raised concerns over its potential to hasten the decline of kidney function,[40] which has been attributed to hypercalciuria and nephrocalcinosis, although hyperphosphatemia could also play a role.[41] Studies using lower doses (similar to those applied in our study) did not show worsened renal outcomes in patients receiving calcitriol when compared with placebo[42]; in fact, one study indicated a tendency toward slower progression of CKD in the group treated with 0.25 μg/d of calcitriol.[43] Our study is the first one, to our knowledge, to examine the association between calcitriol therapy and a hard renal end point such as the incidence of ESRD. We found a tendency toward a lower incidence of ESRD in the calcitriol-treated group, which makes it unlikely that such therapy is deleterious and raises the possibility of a renoprotective effect. Such an effect is indeed conceivable because therapy with paricalcitol, a selective vitamin D analogue, has been shown to lower proteinuria.[44]

One additional concern with calcitriol therapy is its potential to facilitate hypercalcemia and hyperphosphatemia. The serum calcium levels measured after the initiation of calcitriol therapy in our study did not show a significant rise. We did detect a small but significant rise in serum phosphorus level in calcitriol-treated patients. This could have been the result of the suppression of PTH levels and the subsequent lowering of phosphaturia, combined with increased intestinal phosphate absorption. The significance of this finding is unclear; higher serum phosphorus levels in patients with CKD who are not yet receiving dialysis have been associated with higher mortality in some[27] but not all studies.[45] Trials in patients with early CKD have shown that hypercalcemia and hyperphosphatemia were uncommon with dosages of calcitriol of no more than 0.25 to 0.5 μg/d,[17] such as the ones used in our study population. It is unclear whether the application of higher doses of calcitriol, with a concomitant increase in the incidence of potentially deleterious metabolic effects, would mitigate the beneficial associations detected in our study. Comparisons of survival in dialysis patients treated with calcitriol and selective vitamin D analogues (agents that have a wider safety margin[12]) indicated improved survival in patients treated with the selective analogue in one study[46] but no difference in another.[14] Similar comparisons have not been performed in patients with CKD who are not yet receiving dialysis.

Several limitations of our study need to be discussed. As in the case of any observational study, one cannot infer causality from the associations we describe. Because the decision to treat or not to treat patients with activated vitamin D in our study was not made randomly, the patient characteristics driving this decision might have influenced their outcomes. We studied exclusively men from a single institution; hence, our results may not be applicable to women or to patients living elsewhere, although previous studies examining the impact of activated vitamin D treatment on survival did not indicate interactions with race/ethnicity or sex.[10,13] We did not have causes of death available for our analyses; hence, we could not test the hypothesis that the association with lower all-cause mortality was a result of the cardiovascular effects of activated vitamin D. During our long-term cohort study, we noted a change in the intact PTH assay in the midst of the follow-up period. This and other possible secular trends may limit the homogeneity of our nonconcurrent cohort, such as reliability of our assessment of follow-up PTH levels. The main results of the study were not affected by this because all baseline PTH levels were measured by the same assay and because the multivariable models included only the baseline PTH values. We corrected for the differences in the 2 assays, as described in the "Methods" section, and the change in PTH levels that we described after this correction was not dissimilar from what has been reported in the literature dealing with the effect of similar doses of calcitriol in CKD.[39] Other secular trends such as changing therapeutic practices are also unlikely to have biased the results of our study because the cohort was made up largely of contemporary patients and the results were unaffected once the analyses were restricted to patients enrolled after January 1, 2001.

In conclusion, we found an association between treatment of SHPT with oral calcitriol and greater survival in outpatients with CKD stages 3 to 5 not yet receiving dialysis. This beneficial association remained significant even after extensive adjustments for confounders and was present in diverse subgroups of patients. We also noticed a trend toward slower progression of CKD. Although these associations are consistent with those seen in dialysis patients, randomized clinical trials are needed to examine causal associations. Future studies will have to clarify whether other treatment regimens (including selective vitamin D analogues) portend a similar or superior benefit.

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Author Contributions: Dr Kovesdy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kovesdy and Anderson. *Acquisition of data:* Kovesdy and Ahmadzadeh. *Analysis and interpretation of data:* Kovesdy, Anderson, and Kalantar-Zadeh. *Drafting of the manuscript:* Kovesdy and Anderson. *Critical revision of the manuscript for important intellectual content:* Kovesdy, Ahmadzadeh, Anderson, and Kalantar-Zadeh. *Statistical analysis:* Kovesdy and Anderson. *Obtained funding:* Kovesdy. *Administrative, technical, and material support:* Kovesdy and Ahmadzadeh. *Study supervision:* Kovesdy.
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