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Ratio of Paricalcitol Dosage to Serum Parathyroid Hormone Level and Survival in Maintenance Hemodialysis Patients

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Background and objectives: Several observational studies have indicated that vitamin D receptor activators (VDRA), including paricalcitol, are associated with greater survival in maintenance hemodialysis (MHD) patients; however, patients with higher serum parathyroid hormone (PTH), indicative of a more severe secondary hyperparathyroidism and higher death risk, are usually given higher VDRA dosages, which can lead to confounding by medical indication and attenuated survival advantage of high VDRA dosages. It was hypothesized that the ratio of the administered paricalcitol dosage to serum PTH level discloses better the underlying dosage–survival association.

Design, setting, participants, & measurements: The 3-yr mortality predictability of the administered paricalcitol during the first 3 mo of the cohort divided by averaged serum intact PTH during the same period was examined in 34,307 MHD patients from all DaVita dialysis clinics across the United States using Cox regression.

Results: MHD patients were 60.8 ± 15.4 yr of age and included 47% women, 34% black patients, and 47% patients with diabetes. Initially, the ratio of paricalcitol ($\mu\text{g}/\text{wk}$) to PTH (pg/ml) was divided into four groups: 0 (reference), 1 to <30 , 30 to <60 , and $>60 \times 10^{-3}$. Unadjusted, case mix–adjusted (demographics, comorbidity, and Kt/V), and malnutrition-inflammation complex syndrome–adjusted models, the death rate ratio for the paricalcitol/PTH index groups, were 0.99, 0.95, and 0.92. Restricted cubic splines analyses were consistent with a linear relation.

Conclusions: Higher weekly paricalcitol dosage per each unit of serum PTH seems to have an incremental association with greater survival in MHD patients. The observed dosage-response phenomenon needs to be confirmed in clinical trials.

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Disorders of minerals and bone metabolism are common in individuals with chronic kidney disease (CKD) (1–3) and may be related to exceptionally high mortality seen in this patient population (4–6). These disorders encompass a wide range of pathologic conditions, including the traditionally defined secondary hyperparathyroidism (SHPT), associated with increased circulating levels of parathyroid hormone (PTH) (7), calcium and phosphorus disarrays, disorders of vitamin D metabolism, renal osteodystrophy, and different types of vascular calcification (8). Because of this wide range of complications, the more inclusive term CKD mineral and bone disorder has been suggested (1,2).

Several of the abnormalities that characterizing CKD mineral and bone disorder seem amenable to therapeutic interventions

and hence have become a cornerstone of our day-to-day treatment of patients with CKD. One of these is SHPT, which is assumed to be, at least in part, the result of the progressive decline in activated vitamin D levels with advancing stages of CKD (3,9). Pharmacologic replacement therapy using vitamin D receptor activators (VDRA) has thus become a main strategy in the treatment of SHPT (10). The enthusiasm for VDRA was heightened by several observational studies in which VDRA administration was associated with greater survival in patients with CKD (11,12). Although a recent meta-analysis did not confirm these results (13), the association has been observed in patients with earlier stages of CKD (14) as well as those who had advanced stage 5 CKD and were undergoing maintenance hemodialysis (4,15–17).

Most of these studies observed a survival advantage for any dosage of VDRA *versus* no VDRA (14–16). One study that examined the association between the incremental categories of the VDRA dosage and survival in maintenance hemodialysis (MHD) patients found a paradoxically reduced survival with higher administered VDRA dosages (4). This seemingly counterintuitive observation, which defies the dosage-response phe-

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nomenon expected in causal associations (12,18), may be due to confounding by medical indication, in that patients with more severe hyperparathyroidism (which is associated with higher serum PTH levels), who usually have worse survival, may be given higher dosages of VDRA (17). We hypothesized that the amount of the prescribed VDRA dosage per unit of serum PTH is less amenable to confounding by indication and thus should better reveal the true effect of VDRA dosage on survival.

Materials and Methods

Patients

We extracted, refined, and examined data from all individuals who had stage 5 CKD and underwent MHD treatment from July 1 through December 31, 2001, in any one of the 560 outpatient dialysis facilities of a large dialysis organization in the United States (DaVita, Inc.) and followed them for 2.5 more years, until June 30, 2004. The study was approved by the institutional review committees of both Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research; because of the large sample size, the anonymity of the patients studied, and the noninvasive nature of the research, the requirement for informed consent was waived.

Clinical and Demographic Measures

The study cohort has been described previously (4,19–21). For minimization of measurement variability, all repeated measures for each patient during any of the two baseline calendar quarters (July 1 through December 31, 2001) were averaged, and the summary estimate was used in all models. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the first day that the patient entered the cohort. MHD patients who qualified for this study were ≥ 18 yr of age and required to have a dialysis vintage of ≥ 90 d during at least one half of the baseline calendar quarters.

The dosage of the injectable medications in the dialysis clinics, including the two administered VDRA paricalcitol (Zemlar; Abbott, Abbott Park, Chicago, IL) and calcitriol (Calcijex; Abbott), as well as recombinant human erythropoietin (EPOGEN; Amgen, Thousand Oaks, CA), were also calculated for each baseline calendar quarter. The dates of death or other censoring events such as kidney transplantation or leaving the country were obtained for all patients who did not survive or were lost up to June 30, 2004.

History of diabetes was available in the database, whereas histories of tobacco smoking and preexisting comorbid conditions were obtained by linking the DaVita database to Medical Evidence Form 2728 (22). The latter were categorized into 10 comorbid conditions: (1) Ischemic heart disease, (2) congestive heart failure, (3) status post cardiac arrest, (4) status post myocardial infarction, (5) pericarditis, (6) cardiac dysrhythmia, (7) cerebrovascular events, (8) peripheral vascular disease, (9) chronic obstructive pulmonary disease, and (10) cancer.

Laboratory Measures

Blood samples were drawn using uniform techniques in all of the DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, FL, typically within 24 h. All laboratory values were measured by automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of urea nitrogen, creatinine, albumin, calcium, phosphorus, bicarbonate, iron, and total iron-binding capacity, were measured monthly. Serum ferritin and intact PTH (iPTH; first-generation immunoradiometric PTH assay; Nichols, San Juan Capistrano, CA [23]) were usually measured quarterly. Kt/V was used to estimate dialysis dosage

and normalized protein equivalent of total nitrogen appearance, also known as normalized protein catabolic rate, an estimation of daily protein intake, was assessed monthly as a measure of protein intake. Most blood samples were collected before dialysis with the exception of the postdialysis serum urea nitrogen that was obtained to calculate urea kinetics.

Analytical Methods

At the time of the study, paricalcitol was administered to $>90\%$ of VDRA-receiving patients in DaVita clinics. The other VDRA, calcitriol, was administered to 4 to 7% of the remaining VDRA patients. To minimize the degree of heterogeneity in examining the medications, we studied only MHD patients who had received paricalcitol as the injectable VDRA or no VDRA at all. We defined the “paricalcitol index” as the average weekly dosage of administered paricalcitol (in $\mu\text{g}/\text{wk}$) over the 13-wk calendar quarter divided by the 13-wk averaged serum iPTH (in pg/ml) in the same calendar quarter, multiplied by the constant factor 1000.

We used Cox proportional hazards models with three levels of regression adjustment: (1) A minimally adjusted model that included mortality as the outcome measure, one of the three predictors under the study (paricalcitol dosage, serum iPTH, or the ratio of the two known as the paricalcitol index) and the entry calendar quarter; (2) case mix-adjusted models that included all of the above plus diabetes and 10 preexisting comorbid states, history of tobacco smoking, categories of dialysis vintage (<6 mo, 6 mo to 2 yr, 2 to 5 yr, and ≥ 5 yr), primary insurance (Medicare, Medicaid, private, and others), marital status (married, single, divorced, widowed, and other or unknown), the standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dosage as indicated by Kt/V (single pool), presence or absence of a dialysis access catheter, and residual renal function during the entry quarter (*i.e.*, urinary urea clearance); and (3) malnutrition-inflammation complex syndrome (MICS)-adjusted models, which included all of the covariates in the case-mix model as well as 13 surrogates of nutritional status and inflammation and the average dosage of recombinant human erythropoietin, and 11 laboratory variables as surrogates of the nutritional or inflammatory state, together also known as MICS, with known association with clinical outcomes in MHD patients: (a) protein equivalent of total nitrogen appearance as an indicator of daily protein intake, (b) serum albumin, (c) serum total iron-binding capacity, (d) serum ferritin; (e) serum creatinine, (f) serum phosphorus, (g) serum calcium, (h) serum bicarbonate, (i) peripheral white blood cell count, (j) lymphocyte percentage, and (k) blood hemoglobin.

Nonlinear associations for PTH, paricalcitol dosage, and paricalcitol-to-PTH ratio (paricalcitol index) as continuous mortality predictors were also examined by using restricted cubic splines (24). To limit the instability of such models at extreme predictor levels, we restricted model building to PTH values <1000 pg/ml (excluding 5.8% of patients with PTH >1000 pg/ml), paricalcitol dosages <60 $\mu\text{g}/\text{wk}$ (excluding 1.6% of patients) and paricalcitol indices <200 $\mu\text{g}/\text{wk}$ per pg/ml PTH $\times 1000$ (excluding 2.7% of patients with higher values).

In our view, results from the minimally adjusted models are likely to be underadjusted as a result of omission of potential confounders, whereas results from the fully (case mix and MICS) adjusted models may be overly conservative as a result of possible inclusion of biologic intermediates. Because we cannot be certain of the best model, we include all three levels of adjustment. Missing covariate data ($<2\%$ for most laboratory and demographic variables and $<3\%$ for the 10 comorbid conditions) were imputed by the mean of the existing values (except for ferritin, for which the median was used). All analyses were carried out with Stata 10.0 (Stata Corp., College Station, TX).

Results

The original 6-mo (July through December 2001) national database of all DaVita MHD patients included 47,156 patients. After exclusion of patients who did not continue hemodialysis treatment for >90 d by the middle of the base calendar quarters, 41,093 MHD patients remained for analysis, 306 of whom had missing core data such as age or gender. After exclusion of 4725 patients who did not have the electronic record of their baseline PTH measurements and 1755 patients who had received calcitriol as the injectable VDRA, the final cohort included 34,307 MHD patients, 30,705 of whom originated from the first calendar quarter data set and 3602 from the subsequent calendar quarter. The time of the follow-up analysis started from the first day of the calendar quarter that the patient met the aforementioned criteria.

The studied cohort included 23,727 MHD patients who received any dose of paricalcitol, as the only injectable VDRA, during the baseline calendar quarter and 10,580 patients who did not receive any injectable VDRA during the same period. Patients were 60.8 ± 15.4 yr of age (mean \pm SD) and included 47% women, 34% black patients, and 46% patients with diabetes. Among those who received paricalcitol, the average weekly dosage was 14.3 ± 10.9 μg (median 11.7 $\mu\text{g}/\text{wk}$; interquartile range [IQR] 7.0 to 18.2 $\mu\text{g}/\text{wk}$). The 13-wk averaged serum iPTH (normal range <65 pg/ml) in the same patients during the same period was 389 ± 375 pg/ml (median 274 pg/ml; IQR 168 to 472 pg/ml). The ratio of the two foregoing variables (*i.e.*, the paricalcitol index) was 68.9 ± 24.1 (median 35.2; IQR 22.4 to 59.6 $\mu\text{g}/\text{wk}$ per pg/ml \times 1000). The paricalcitol index was then divided into three *a priori* selected groups of 1 to <30, 30 to <60, and ≥ 60 $\mu\text{g}/\text{wk}$ per pg/ml \times 1000. Table 1 shows baseline demographic, clinical, and laboratory characteristics of the studied MHD patients, comparing those who did not receive any VDRA with those who received paricalcitol in any one of the three paricalcitol index groups. The VDRA-receiving groups had higher proportions of black patients and slightly lower prevalence of history of cardiovascular disease than the non-VDRA-receiving patients. The latter group had slightly lower serum albumin and ferritin concentrations.

For examination of the mortality predictability of serum PTH and paricalcitol dosage as well as the ratio of the two (paricalcitol index) after adjustment for the case-mix and MICS surrogates, restricted cubic splines were plotted as shown in Figures 1 through 3. The PTH–death association appeared J shaped with linear increase in death risk for PTH >200 pg/ml (Figure 1). The association between paricalcitol dosage and mortality resembled a distorted U shape or reverse J shape, with those who did not receive any VDRA having the highest death risk, whereas no dosage-response relation was observed for incrementally higher paricalcitol dosages (Figure 2); however, the association between the paricalcitol index (ratio of paricalcitol dosage to PTH) and survival was strictly decreasing, indicating greater survival with higher paricalcitol dosage per unit of PTH (Figure 3). The foregoing association was further studied *via* sensitivity analyses including across strata of PTH (<300 *versus* PTH ≥ 300 pg/ml); the greater survival with higher paricalcitol

index was more prominent among patients with PTH <300 pg/ml (data not shown).

As shown in Table 2 and Figure 4, using the no-VDRA group as the reference group, the case mix- and MICS-adjusted 3-yr death rates in MHD patients was 5 to 8% lower in MHD patients who received 30 to 60 and ≥ 60 ng/wk paricalcitol dose per each pg/ml of iPTH level ($P = 0.020$ and 0.002 , respectively).

Discussion

Examining the association between paricalcitol dosage and survival in 34,307 MHD patients in a large dialysis organization, we did not find any meaningful association between the absolute dosage of paricalcitol and survival among those who had received this VDRA. Nonetheless, increasing levels of the ratio of paricalcitol dosage to serum concentration of PTH were associated with better survival. This association was seen in analyses using both restricted cubic splines and categorical analyses based on four *a priori* selected groups of paricalcitol to PTH ratio.

Replacement of active vitamin D has been the cornerstone of therapy for SHPT in the CKD patient population (12). SHPT develops early in the course of CKD as a result of a combination of events that include deficiency of 1,25-dihydroxycholecalciferol (calcitriol), decreased expression of the vitamin D receptor and the calcium-sensing receptor, hyperphosphatemia, hypocalcemia, and PTH resistance (7,12). As kidney function declines in patients with CKD, their PTH levels become increasingly higher, mirrored by a progressive decline in activated vitamin D levels (3). Administration of synthetic activated vitamin D to replace physiologic levels of this hormone thus seems to be a plausible strategy to treat SHPT.

Nonetheless, the application of activated vitamin D in physiologic dosages often fails to correct SHPT, in part because of decreased expression of the vitamin D receptor in the parathyroid gland (25). This may be overcome by the administration of higher dosages of activated [1,25(OH)₂] vitamin D, but such pharmacologic dosages are more likely to induce adverse effects. Most relevant of these undesirable effects are hypercalcemia and hyperphosphatemia (26), which have themselves been associated with higher mortality in patients who are on dialysis (4,5). To circumvent such adverse effects, new agents that showed a more selective effect toward suppressing PTH production, with a lesser effect on intestinal and bone absorption of calcium and phosphorus, have been developed. These novel analogues of activated vitamin D (paricalcitol and doxercalciferol in the United States and alfacalcidol and maxacalcitol outside the United States) seem to have fewer effects on the vitamin D receptors in the gastrointestinal tract and bone, thus mitigating the calcium and phosphorus absorption and allowing for a wider therapeutic margin (12).

Despite these observations, the concept of VDRA selectivity and its utility in clinical practice has been a matter of ongoing debate (7). Recent findings from several large observational studies have suggested that the benefits of VDRA may extend beyond the traditional PTH-lowering effect and could result in direct cardiovascular and metabolic benefits (4,14–16). Hence, the greater survival of patients with CKD observed in association with the

Table 1. Baseline data of 34,307 MHD patients, including 30,075 patients from the first calendar quarter (July, August, and September 2001) and 3602 patients from the subsequent quarter (October, November, and December 2001)^a

Parameter	No VDRA (n = 10,580)	Paricalcitol-to-PTH Ratio ($\mu\text{g}/\text{wk}$ per pg/ml)		
		1 to <30 (n = 9575)	30 to <60 (n = 8277)	≥ 60 (n = 5875)
Age (yr; mean \pm SD)	61.80 \pm 15.60	59.40 \pm 15.70	60.90 \pm 15.00	60.80 \pm 14.80
Female gender (%)	45.0	49.0	46.0	46.0
Diabetes (%)	47.0	43.0	48.0	47.0
Race (%)				
black	22.0	38.0	41.0	47.0
Hispanic	14.0	17.0	16.0	14.0
Primary insurance Medicare (%)	67.0	69.0	72.0	72.0
Married (%)	44.0	39.0	42.0	40.0
Dialysis vintage 3 to 6 mo (%)	28.0	23.0	22.0	20.0
History of comorbid states (%)				
cancer	4.2	3.2	3.4	3.2
heart failure	27.0	25.0	27.0	26.0
PVD	12.0	10.0	11.0	10.0
ischemic heart dis.	20.0	16.0	17.0	17.0
acute myocardial infarction	6.5	4.2	4.9	4.7
chronic pulmonary disease	5.5	4.5	4.5	4.9
Tobacco smoking (mean \pm SD)	5.0	4.7	4.6	4.9
Kt/V single dose	1.54 \pm 0.32	1.54 \pm 0.31	1.55 \pm 0.30	1.54 \pm 0.29
nPCR (nPNA; g/kg per d; mean \pm SD)	1.00 \pm 0.26	1.02 \pm 0.24	1.00 \pm 0.23	0.97 \pm 0.24
Serum (mean \pm SD)				
creatinine (mg/dl)	8.90 \pm 3.30	9.90 \pm 3.30	9.60 \pm 3.20	9.60 \pm 3.10
albumin (g/dl)	3.72 \pm 0.42	3.83 \pm 0.35	3.83 \pm 0.34	3.81 \pm 0.37
TIBC (mg/dl)	200.00 \pm 45.00	200.00 \pm 41.00	199.00 \pm 40.00	197.00 \pm 41.00
ferritin (ng/ml)	652.00 \pm 527.00	669.00 \pm 498.00	692.00 \pm 503.00	693.00 \pm 490.00
bicarbonate (mg/dl)	22.10 \pm 2.90	21.60 \pm 2.60	22.00 \pm 2.60	22.20 \pm 2.60
calcium (mg/dl)	9.20 \pm 0.80	9.20 \pm 0.70	9.30 \pm 0.70	9.50 \pm 0.70
phosphorus (mg/dl)	5.50 \pm 1.70	6.10 \pm 1.50	5.80 \pm 1.40	5.60 \pm 1.30
iPTH (pg/ml)	242.00 \pm 336.00	552.00 \pm 480.00	342.00 \pm 239.00	188.00 \pm 151.00
Blood (mean \pm SD)				
hemoglobin (g/dl)	11.90 \pm 1.30	12.00 \pm 1.20	12.00 \pm 1.20	12.00 \pm 1.20
WBC count ($\times 1000$)	7.60 \pm 2.60	7.10 \pm 2.20	7.00 \pm 2.10	7.10 \pm 2.30
lymphocyte %	20.10 \pm 8.30	21.60 \pm 7.90	21.50 \pm 7.60	21.80 \pm 8.00
EPO dosage (U/wk ; mean \pm SD)	17.90 \pm 24.90	19.40 \pm 16.50	19.20 \pm 16.40	19.80 \pm 17.70
Paricalcitol dosage ($\mu\text{g}/\text{wk}$; mean \pm SD)	0.00 \pm 0.00	10.90 \pm 9.20	15.20 \pm 10.60	18.60 \pm 12.20
Paricalcitol index ($\mu\text{g}/\text{wk}$ per pg/ml ; mean \pm SD)	0.00 \pm 0.00	19.20 \pm 0.70	42.00 \pm 8.30	185.40 \pm 457.00

^aEPO, erythropoietin; iPTH, intact parathyroid hormone; MHD, maintenance hemodialysis; nPCR, normalized protein catabolic rate; nPNA, normalized protein nitrogen appearance; PVD, peripheral vascular disease; TIBC, total iron-binding capacity; VDRA, vitamin D receptor activator; WBC, white blood cell.

VDRA may be due to a combination of the salutary effects, including but not limited to the decline in PTH level.

We hypothesized that previous studies failed to observe a beneficial effect of increasing VDRA dosage because of confounding by indication (27–30). In an attempt to control this bias, we adjusted the administered paricalcitol dosage for the level of PTH and observed the expected dosage-response relation (Figures 3

and 4, Table 2). We also observed a J-shaped association between PTH and survival (Figure 1). This finding is consistent with two previous studies that reported U-shaped to J-shaped associations in MHD patients (4,5) and studies that found that lower levels of serum PTH, especially <150 pg/ml , were associated with decreased survival (4,31,32). These lower level associations, however, may be due to confounding by indication. The current guide-

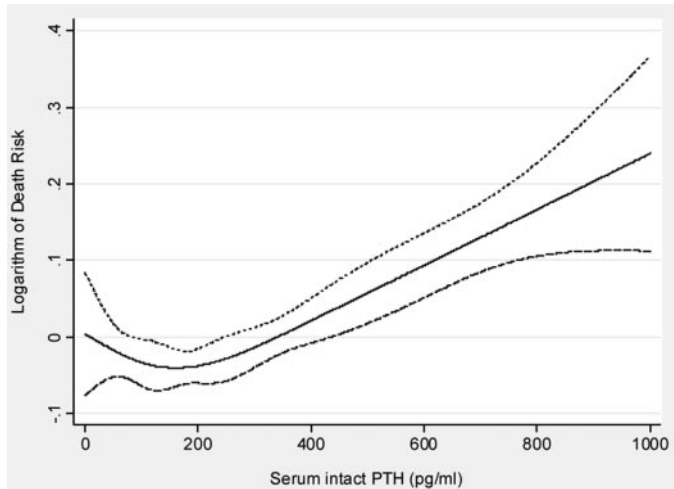


Figure 1. Association between the 13-wk averaged serum intact parathyroid hormone (iPTH) values <1000 pg/ml in 32,317 maintenance hemodialysis (MHD) patients (excluding 1990 patients with PTH >1000 pg/ml) in the base calendar quarter and the logarithm of the risk ratio of all-cause mortality over 3 yr on the basis of a multivariable regression spline model, adjusted for case mix and malnutrition-inflammation complex syndrome (MICS). Dashed lines are 95% pointwise confidence levels.

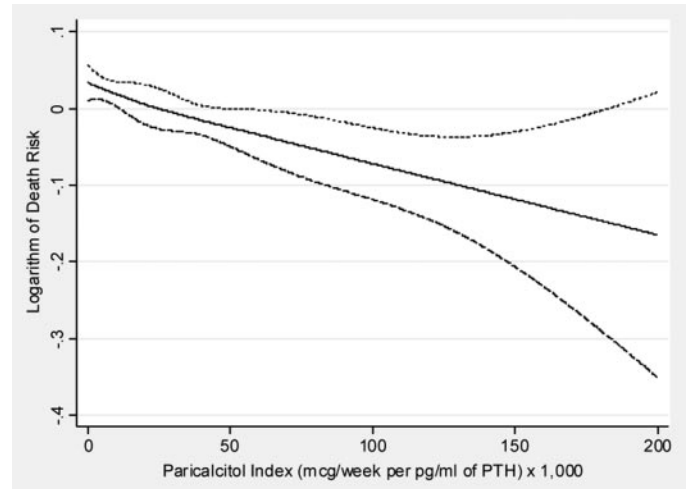


Figure 3. Association between the paricalcitol index (ratio of the administered paricalcitol dosage to serum PTH) in 33,381 MHD patients with a paricalcitol index <200 (excluding 926 patients with a paricalcitol index >200 $\mu\text{g}/\text{wk}$ per pg/ml) in the base calendar quarter and the logarithm of the risk ratio of all-cause mortality over 3 yr in a multivariable regression spline model, adjusted for case mix and MICS. Dashed lines are 95% pointwise confidence levels.

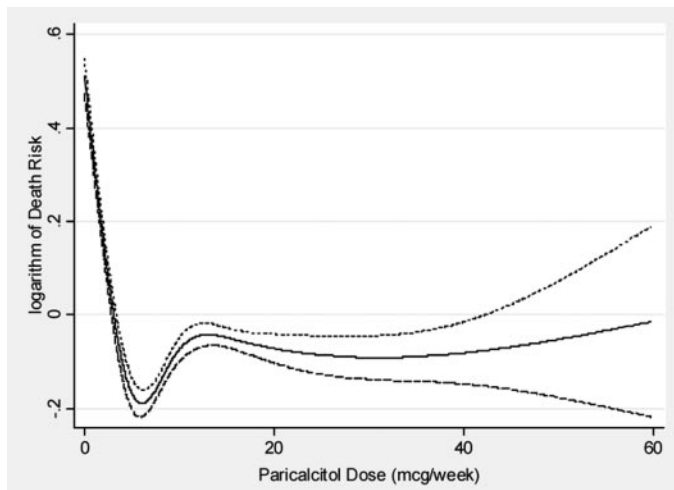


Figure 2. Association between the 13-wk averaged paricalcitol dosage <60 $\mu\text{g}/\text{wk}$ administered to 33,758 MHD patients (excluding 549 patients who received >60 $\mu\text{g}/\text{wk}$) in the base calendar quarter and the logarithm of the risk ratio of all-cause mortality over 3 yr on the basis of a multivariable regression spline model, adjusted for case mix and MICS. Dashed lines are 95% pointwise confidence levels.

lines recommend lowering the dosage or even discontinuation of VDRA in MHD patients with low PTH level, because of concerns about so-called “adynamic bone disease” (33).

A recent study of men who had early to moderate degrees of CKD and were not yet undergoing dialysis found a strictly increasing association between serum PTH and survival (34).

Elevated PTH levels have been shown to induce a wide range of cardiovascular, metabolic, hematologic, and immunologic abnormalities, including lower cardiac contractility, myocardial calcium deposition, vascular calcification, and abnormal immune function (34). If the PTH–survival association is causal, then it may explain why vitamin D analogs that lower the PTH level are associated with better survival. It is important to note that serum calcium was higher in the group with the highest paricalcitol-to-PTH ratio. Thus, it is possible that high calcium level led to relative PTH suppression and increased ratio (5); however, hypercalcemia is usually associated with increased mortality in MHD patients, whereas patients in the latter group of our study showed the greatest survival.

Our study is limited by its observational nature and by lack of data on home medication including oral VDRA or other types of vitamin D, multivitamins, phosphorus binders, and calcimimetics; however, most MHD patients who receive injectable VDRA do not take oral vitamin D medications, and this cohort preceded the use of the calcimimetics in the United States (mid-2004). Another limitation is the PTH assay reliability and fluctuation, especially because the iPTH may yield inaccurate values (35). Furthermore, our study covers only a 3-yr follow-up period; nonetheless, almost half of MHD patients are dead within 3 yr, and changes in practice pattern over longer periods of time may further confound the studied associations. Any insight into the short-term survival associations of dialysis patients is of major clinical relevance. We did not use more sophisticated statistical techniques such as marginal structural models (15). The strengths of our study include (1) contemporary nature, because all patient data were obtained from the 21st century (2001 through 2002); (2) uniform labora-

Table 2. Death RR and 95% CI across the four *a priori* selected paricalcitol index categories in 34,307 MHD patients^a

Paricalcitol Index Group ($\mu\text{g}/\text{wk}$ per pg/ml $\times 1000$)	Unadjusted		Case Mix Adjusted ^b		Case Mix and MICS Adjusted ^c	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
No VDRA (reference)	1.00	N/A	1.00	N/A	1.00	N/A
1 to <30	0.85 (0.81 to 0.98)	<0.001	0.93 (0.89 to 0.97)	<0.001	0.99 (0.95 to 1.04)	0.700
30 to <60	0.83 (0.80 to 0.87)	<0.001	0.88 (0.84 to 0.94)	<0.001	0.95 (0.90 to 0.99)	0.020
≥ 60	0.81 (0.77 to 0.85)	<0.001	0.88 (0.84 to 0.93)	<0.001	0.92 (0.87 to 0.96)	0.002

^aCI, confidence interval; MICS, malnutrition-inflammation complex syndrome; RR, rate ratio.

^bIncludes adjustment for age, gender, diabetes, standardized mortality ratio, race, vintage, primary insurance, marital status, dialysis dosage, dialysis catheter, and baseline comorbid states.

^cIncludes all case-mix covariates (see above) plus nPNA or nPCR; serum levels of albumin, creatinine, TIBC, calcium, phosphorous, bicarbonate, and ferritin; blood WBC and lymphocyte percentage; and EPO dosage.

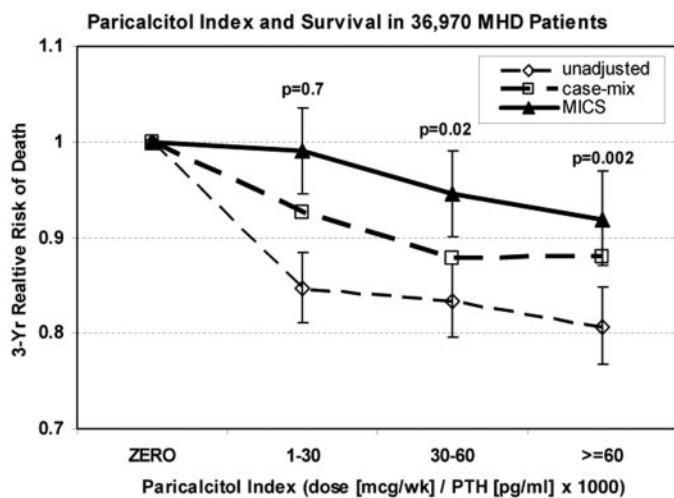


Figure 4. Association between the four *a priori* selected groups of paricalcitol index in the base calendar quarter and the risk ratio of all-cause mortality over 3 yr in a multivariable proportional hazard model at three levels of adjustment: (1) Minimally adjusted, (2) adjusted for case mix, and (3) adjusted for case mix and MICS. Error bars indicate 95% confidence levels.

tory measurements, with all laboratory data obtained from one facility, (3) large sample size; (4) 3-mo averaged laboratory data to minimize measurement variability; and (5) knowledge of the administered dosage of VDRA.

Conclusions

We found a dosage-response association between PTH-adjusted paricalcitol dosage and survival, using different adjustment level forms for the paricalcitol dosage. Because SHPT is common in CKD populations and can be effectively treated with active vitamin D analogs (12), our findings may have important clinical implications. Because of the association of renal osteodystrophy with cardiovascular calcification, cardiovascular disease, and death, VDRA treatment may be an effective measure to improve survival in CKD. The advent of several new analogs of the native activated vitamin D molecule has

widened therapeutic options but has also made therapeutic decisions more complicated. Treatment of SHPT has become even more complex with the arrival of the first calcimimetic (cinacalcet hydrochloride) (36) and with the discovery of novel mechanisms that are responsible for SHPT (37). Controlled trials are needed to verify the true relationships between the VDRA dosage and outcomes in MHD patients and to evaluate the effectiveness of current and future treatments, including vitamin D analogs, calcimimetics, and other medications, in improving survival of patients with CKD.

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