MORTALITY RATES DO NOT DIFFER AMONG PATIENTS PRESCRIBED VARIOUS VITAMIN D AGENTS

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♦ **Background:** Limited well-controlled research exists examining the impact of different formulations of oral vitamin D on clinical outcomes in dialysis patients, specifically those on peritoneal dialysis. For this retrospective mortality analysis, we compared mortality rates of patients on 3 of the most commonly prescribed vitamin D agents.

♦ **Methods:** We examined 2 years (7/1/2008 to 6/30/2010) of oral medication records of peritoneal dialysis patients from a large US dialysis organization. Patients were identified whose physicians prescribed a single form of vitamin D (calcitriol, paricalcitol, or doxercalciferol) for $\geq 90\%$ of all patient-months. We excluded incident patients (< 90 days on dialysis) and patients whose physicians treated < 5 peritoneal dialysis patients at a dialysis facility, and we assessed mortality.

♦ **Results:** The analysis inclusion criteria identified 1,707 patients. The subset in this analysis included 12.6% of all prevalent peritoneal dialysis patients and 11.8% of prevalent patient-months. Patients with physicians who predominately prescribed calcitriol had a lower mortality rate: 9.33 (confidence interval (CI) 7.06, 11.60) deaths per 100 patient-years than the doxercalciferol, 12.20 (CI 9.34, 15.06) or paricalcitol, 12.27 (CI 9.27, 15.28) groups. However, these differences were not statistically significant. A Cox proportional hazards model, adjusting for differences in age, vintage, gender, race, body mass index, and comorbidities also showed no significant differences.

♦ **Conclusions:** For this peritoneal dialysis population, instrumental variable analyses showed no significant difference in mortality in patients taking the most common oral vitamin D formulations (calcitriol, doxercalciferol, paricalcitol).

Active vitamin D and its analogs can be an effective therapy in the management of secondary hyperparathyroidism via suppression of parathyroid hormone levels (1). However, excessive administration of vitamin D compounds can cause oversuppression of parathyroid hormone, hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic bone disease. These elevated calcium and phosphorus levels can potentially lead to vascular calcification and increased risk of death (2–7).

The research on hypercalcemia, hospitalizations, and mortality with intravenous vitamin D formulations consists of primarily uncontrolled and placebo-controlled studies, which are not definitive (8–12). Two observational studies of approximately 3 years in duration found higher mortality rates in hemodialysis patients taking intravenous calcitriol compared to paricalcitol (13,14). Teng *et al.* (13) followed patients who began receiving treatment with paricalcitol or calcitriol (in a 4:1 dosing ratio) on or after 1 January 1999, and who were treated exclusively with that formulation. They reported an adjusted annual mortality rate that was 16% percent lower among paricalcitol-treated patients. They also reported a higher 2-year survival among patients who switched from calcitriol to paricalcitol compared to those who switched the other way (73% versus 64%, $p = 0.04$). In the second study, the authors (14) reported that mortality rates were identical in patients on doxercalciferol and paricalcitol but higher in patients on calcitriol. However, in adjusted models they found no statistically significant differences and concluded that the survival difference between vitamin D₂ analogs and calcitriol may be smaller than previously reported (14). To date, limited data are available regarding the effect, if any, of oral vitamin D preparations on mortality in peritoneal dialysis patients.

In the United States, calcitriol (Rocaltrol, Roche, Nutley, NJ, USA, and generic calcitriol), paricalcitol (Zemplar, Abbott, Abbott Park, IL, USA), and doxercalciferol (Hectorol, Sanofi, Cambridge, MA, USA) are among

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the most commonly prescribed oral active vitamin D compounds for patients on peritoneal dialysis. Prescribers differ in their preference for one oral vitamin D compound over another. However, little is known about the relative differences between achieved outcomes and mortality risk for those patients prescribed 1 of the 3 compounds. With regard to efficacy, a meta-analysis comparing oral versus intravenous vitamin D analogs concluded that there was no difference in efficacy with oral versus intravenous dosing (15). These conclusions were limited by the small sample size of most studies and therapeutically unequal dosing, with intravenous doses typically being twice as high as oral doses. A large prospective study in hemodialysis patients found paricalcitol and calcitriol were similarly effective in controlling hyperparathyroidism, although paricalcitol users had fewer episodes of sustained hypercalcemia (16). A recent randomized controlled study in hemodialysis patients found alfacalcidol and paricalcitol corrected parathyroid hormone levels equally when patients had calcium and phosphorus levels in the desired range but paricalcitol corrected low parathyroid hormone levels more efficiently (17). In peritoneal dialysis patients, oral paricalcitol controlled hyperparathyroidism in a rapid and sustained manner with little change to calcium and phosphorus levels, but this was in comparison to placebo (18). Doxercalciferol and calcitriol were similarly effective at controlling parathyroid hormone and suppressing the bone formation rate in a randomized controlled trial of pediatric patients on peritoneal dialysis (19). An analysis comparing the different oral vitamin D formulations' effects on laboratory values showed that in propensity-matched groups of patients on peritoneal dialysis, use of any of the 3 predominant oral vitamin D formulations (i.e., calcitriol, doxercalciferol, and paricalcitol) produced no clinically significant differences in key mineral and bone disease outcomes (i.e., calcium, phosphorus, parathyroid hormone, and albumin) over 3 months (20).

The objective of this retrospective analysis was to examine if differences exist in patient mortality based on the use of different formulations of oral vitamin D for patients on peritoneal dialysis, including continuous ambulatory peritoneal dialysis, continuous cycling peritoneal dialysis, and intermittent peritoneal dialysis. This question has particular relevance in the United States given the advent of the bundled prospective payment system. Despite the evidence of comparative effectiveness, the question of mortality differences between available oral vitamin D agents has not been addressed in this patient population.

SUBJECTS AND METHODS

STUDY DESIGN

We examined 2 years (7/1/2008 to 6/30/2010) of oral medication records of peritoneal dialysis patients from a large US dialysis organization (DaVita HealthCare Partners Inc., Denver, CO, USA). Physicians were identified who had 5 or more patients on peritoneal dialysis and prescribed 90% or more of oral vitamin D doses as 1 of the 3 most common formulations (i.e., calcitriol, paricalcitol, and doxercalciferol). The analysis was then restricted to include the prevalent patients of these physicians (i.e., those with more than 90 days on dialysis). The intent was to reduce channeling bias by selecting patients of physicians who prescribed a single formulation of oral vitamin D for nearly all of their patients. Channeling bias can occur in the context of drug assignment when patients of different health status (i.e., by age or comorbid conditions) are systematically prescribed different drugs or formulations of drugs based on that status. An assumption was made that the prescribing behavior of the physicians selected was not based on a patient-by-patient assessment but rather on an overall preference for 1 formulation due to perceived efficacy, safety, and costs.

STATISTICAL ANALYSIS

The analytical techniques included statistical testing for differences among the groups (calcitriol, paricalcitol, and doxercalciferol), an overall estimation of deaths by treated patient-months for each group, and an adjusted survival analysis. The 3 groups of patients were assessed via chi-square test and ANOVA, as appropriate, for differences in demographic factors (i.e., age, time on dialysis, gender, race, body mass index), cause of end-stage renal disease (ESRD), and comorbid conditions (by both Charlson comorbidity index and individual comorbidities).

The crude analysis of deaths by patient-months included data from the patients of all selected physicians. Patient exposure was defined as the formulation of vitamin D predominately prescribed by the physician. The time of exposure was the period from the first dialysis treatment by that physician in the observation period (7/1/2008 to 6/30/2010) to the last treatment by that physician in the period. A patient death was counted if it was reported within 90 days of the last recorded dialysis session. Regardless of the date of death, exposure time was not extended beyond the last date of dialysis.

A survival analysis (i.e., Cox proportional hazard analysis) of the 3 groups was performed via an unadjusted

model and with adjustment for patient demographics (i.e., age, time on dialysis, gender, race, and body mass index), cause of ESRD, and comorbid conditions (i.e., any cardiovascular disease, chronic obstructive pulmonary disease, diabetes, gastrointestinal bleed, and liver disease). Assessment was conducted by paired comparison of hazard ratios and visual inspection of survival curves.

RESULTS

SUMMARY OF VITAMIN D USAGE

A total of 13,581 prevalent peritoneal dialysis patients were treated from 7/1/2008 to 6/30/2010, providing 181,756 months of treatment data. During that time, patient-months on oral vitamin D were distributed fairly evenly across the calcitriol, doxercalciferol, and paricalcitol groups, as shown in Table 1. Only 16% of all peritoneal dialysis patients were not prescribed oral vitamin D.

The subset of data covered in this analysis includes 12.6% of patients (1,707) and 11.8% of patient-months.

These were the patients of the 187 physicians who had 5 or more peritoneal dialysis patients and 90% or more of their vitamin D prescription time in 1 of 3 formulations (Table 2). A total of 1,610 physicians were excluded from the study based on prescribing patterns. Because physicians were selected if they prescribed a single vitamin D formulation $\geq 90\%$ (but not necessarily 100%) of the time, some patients received treatment outside of their defined treatment group. In all, a different formulation of vitamin D was given in 3.13% of patient-months.

Mean doses of the different formulations of oral vitamin D could not be determined from the data; however, the protocols for oral vitamin D initiation and maximum dose administration at these centers is summarized in Table 3. All centers included in the analysis used this protocol. Dose adjustment rules (e.g., percent increases or decreases by laboratory cutoffs) were identical for each formulation.

TREATMENT GROUP CHARACTERISTICS

Patients in the 3 groups were similar across most comorbid measures, with the exception of the prevalence

TABLE 1
Vitamin D Usage: All Peritoneal Dialysis Patients Across the Large Dialysis Organization

Vitamin D usage	Patients ^a	Patient-months	All months (%)	Among patient-months with single vitamin D (%)
Calcitriol only	4,672	44,945	24.73%	30.35%
Doxercalciferol only	5,064	54,219	29.83%	36.61%
Paricalcitol only	5,089	48,949	26.93%	33.05%
Multiple formulations in month	2,975	4,386	2.41%	—
No oral vitamin D in month	5,438	29,257	16.10%	—
Totals	13,591	181,756	100.00%	

^a Patients may be included in more than 1 category of usage during the observation period.

TABLE 2
Vitamin D Usage: Peritoneal Dialysis Patients of Physicians Identified with 1 Formulation

Vitamin D usage	Physicians	Patients ^a	Patient-months	Patient-months on different formulation (%)
Calcitriol only	60	645	8,363	2.25%
Doxercalciferol only	53	519	6,880	3.30%
Paricalcitol only	74	552	6,256	4.12%
Total	187	1,707	21,499	3.13% ^b

^a Nine patients were treated by physicians in more than 1 group over the course of the observation period. Patient-time for these patients is allocated to groups based on their treatment history.

^b Composite percentage is shown.

TABLE 3
Dose Protocols

Initial parathyroid hormone (ng/L)	Calcitriol	Doxercalciferol	Paricalcitol
0–300	No initiation	No initiation	No initiation
301–600 and trending up	Initiate at 0.25 mcg capsule 3 days per week	Initiate at 1 mcg capsule 3 days per week	Initiate at 1 mcg capsule each day
601–800	Initiate at 0.25 mcg capsule each day	Initiate at 1 mcg capsule each day	Initiate at 1 mcg capsule 2 each day
>800	Initiate at 0.25 mcg capsule 2 each day	Initiate at 1 mcg capsule 2 each day	Initiate at 1 mcg capsule 3 each day
Maximum dose	7 mcg/week	60 mcg/week	none listed

of pre-existing cardiovascular disease (Table 4). Patients in the calcitriol group had a lower prevalence of ischemic heart disease (6.4%), while patients in the paricalcitol group had a higher percentage of congestive heart failure (6.6%). When all cardiovascular diseases were grouped, the differences across the formulations were statistically significant ($p = 0.0113$), with paricalcitol the highest (15.0%), followed by doxercalciferol (12.6%) and calcitriol (9.3%). The Charlson comorbidity index was not meaningfully different across the groups.

Some demographic- and dialysis-related factors were associated with physician selection of vitamin D formulation. Physicians whose prescribing patterns demonstrated a preference for paricalcitol had a higher proportion of female patients and Caucasian patients (versus African-American), and their patients had a lower mean dialysis vintage. Doxercalciferol-preferring physicians had a higher proportion of patients with hypertensive kidney disease. Patients in the group of physicians whose prescribing patterns demonstrated a preference for calcitriol were more likely to be Asian/Pacific Islander and had a mean age of approximately 2 years lower than patients in the other 2 groups. None of these findings were clinically significant.

Differences were also seen in the cause of ESRD. Patients whose ESRD was caused by diabetes were more likely to be taking paricalcitol (36.1%), those whose ESRD was caused by hypertension were more likely to be taking doxercalciferol (35.3%), and those whose cause was listed as Other were more likely to be taking calcitriol (42.6%). These findings are not clinically significant.

LABORATORY RESULTS

Mean phosphorus and calcium levels for patients, as well as mean ionic concentration of calcium in patient

dialysate solution are reported in Table 5. Laboratory values are the mean monthly values, and dialysate calcium concentrations are the mean quarterly values weighted by patient-time contributed.

Mean plasma calcium levels were significantly lower in the doxercalciferol group (ANOVA $p = 0.0007$), but mean phosphorus levels did not vary significantly among the formulations. The concentration of calcium in dialysate varied by formulation of vitamin D (lowest for paricalcitol and highest for doxercalciferol, ANOVA $p < 0.0001$). Of all the peritoneal dialysis treatments, 93.7% had a calcium concentration of 1.25 mmol/L (2.5 mEq/L) and 6.3% had a calcium concentration of 1.75 mmol/L (3.5 mEq/L).

The proportion of patients experiencing hypercalcemia over the course of the study differed between the calcitriol (23.3%) and paricalcitol (21.2%) groups. These differences were not significant ($p = 0.37$).

No significant difference was found in the number of transplants ($n = 161$) between those taking calcitriol (10.3%), doxercalciferol (8.7%), and paricalcitol (9.1%).

PHOSPHATE BINDER USE

There were substantial differences in the use of phosphate binders among patients on different formulations of vitamin D. Patients in the calcitriol group received 31.0% of their prescription phosphate binders in the form of calcium acetate (versus sevelamer or lanthanum carbonate). Patients in the paricalcitol and doxercalciferol groups received 20.9% and 18.3%, respectively, in the form of calcium acetate.

A non significant difference was also seen between those patients experiencing hyperphosphatemia: 66.4% of calcitriol patients, 63.6% of doxercalciferol patients, and 66.1% of paricalcitol patients).

TABLE 4
Patient Characteristics by Vitamin D Formulation

Patient Characteristics	Formulation			All (n=1,707)
	Calcitriol (n=643)	Doxercalciferol (n=516)	Paricalcitol (n=548)	
Gender				
Male	354 (55.1%)	294 (57.0%)	270 (49.3%)	918 (53.8%)
Female	289 (44.9%)	222 (43.0%)	278 (50.7%)	789 (46.2%)
Race/Ethnicity				
African-American	215 (33.4%)	180 (34.9%)	150 (27.4%)	545 (31.9%)
Caucasian	240 (37.3%)	207 (40.1%)	297 (54.2%)	744 (43.6%)
Hispanic	82 (12.8%)	82 (15.9%)	68 (12.4%)	232 (13.6%)
Asian/Pacific Islander	74 (11.5%)	33 (6.4%)	17 (3.1%)	124 (7.3%)
Native American	2 (0.3%)	1 (0.2%)	1 (0.2%)	4 (0.2%)
Other/Unknown	30 (4.7%)	13 (2.5%)	15 (2.7%)	58 (3.4%)
Mean age (yr)	53.03	54.96	55.14	54.30
Mean vintage (yr)	2.99	2.90	2.49	2.80
Mean BMI	27.14	27.87	28.72	27.88
Cause of ESRD				
Diabetes	200 (31.1%)	176 (34.1%)	198 (36.1%)	574 (33.6%)
Hypertension	148 (23.0%)	182 (35.3%)	137 (25.0%)	467 (27.4%)
Polycystic kidney disease	21 (3.3%)	25 (4.8%)	38 (6.9%)	84 (4.9%)
Other	274 (42.6%)	133 (25.8%)	175 (31.9%)	582 (34.1%)
Mean Charlson Index	4.15	4.29	4.32	4.25
Any cardiovascular disease ^a	60 (9.3%)	65 (12.6%)	82 (15.0%)	207 (12.1%)
Ischemic heart disease	41 (6.4%)	40 (7.8%)	45 (8.2%)	126 (7.4%)
Congestive heart failure	13 (2.0%)	15 (2.9%)	36 (6.6%)	64 (3.8%)
Cardiac arrest	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Myocardial infarction	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.1%)
Pericarditis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac dysrhythmia	2 (0.3%)	1 (0.2%)	5 (0.9%)	8 (0.5%)
Cerebrovascular event	5 (0.8%)	6 (1.2%)	3 (0.6%)	14 (0.8%)
Peripheral vascular disease	5 (0.8%)	7 (1.4%)	10 (1.8%)	22 (1.3%)
COPD	6 (0.9%)	8 (1.6%)	5 (0.9%)	19 (1.1%)
Diabetes	273 (42.5%)	229 (44.4%)	239 (43.6%)	741 (43.4%)
Gastrointestinal bleed	9 (1.4%)	5 (1.0%)	0 (0.0%)	14 (0.8%)
Liver disease	5 (0.8%)	4 (0.8%)	6 (1.1%)	15 (0.9%)

BMI = body mass index; ESRD = end-stage renal disease; COPD = chronic obstructive pulmonary disease.

^a Patients may have multiple comorbidities.

OVERALL MORTALITY

The first analysis of patient outcomes evaluated the total amount of time that patients on peritoneal dialysis were treated within each physician-based formulation group and the number of deaths that occurred among these patients during the observation period or within 90 days of their last recorded dialysis session during the period (Table 6). Overall mortality was 11.7% over the period or 11.1 deaths per 100 years of patient observation time. Patients with physicians in the calcitriol group had a lower crude mortality rate (9.33 deaths per

100 patient-years) than patients in the other 2 groups. However, confidence intervals overlapped substantially, and this analysis was not adjusted for differences among the patient groups.

SURVIVAL ANALYSIS

A Cox proportional hazards model showed that age and diabetic status were associated with higher mortality risk among all included patients. Both before and after adjustment for demographic factors, cause of ESRD, and comorbid conditions, the hazard ratios among

the groups were not statistically significant. A hazard ratio and 95% confidence interval for each contrast in the adjusted analysis is provided in Table 7. Survival curves, adjusted for the same factors, show no consistent differences based on the choice of oral vitamin D formulation (Figure 1). Adjustments for calcium levels were not attempted because such differences lie in the theoretical causal pathway between treatment type and mortality.

DISCUSSION

We conducted a retrospective, instrumental variables analysis of prevalent peritoneal dialysis patients and found no significant differences in mortality among the patients of physicians who preferentially chose 1 of the 3

available formulations of oral vitamin D for their patients. Specifically, over 2 years, no statistically significant differences were found with regard to overall mortality, adjusted mortality, or a contrast of adjusted proportional hazards among these formulations. Calcitriol had a lower mortality rate and hazard ratio in comparison with doxercalciferol and paricalcitol, but the differences were not statistically significant.

The calcitriol group had lower overall cardiovascular comorbidities at baseline and a lower mean age (approximately 2 years lower). Although these factors were included in adjusted models, residual confounding may remain. The calcitriol groups also received more calcium-based binders, perhaps indicating a consistent lack of concern about calcium-based treatments among high prescribers of calcitriol. Both calcitriol and paricalcitol

TABLE 5
Serum Phosphorus, Calcium Values and Calcium Dialysate Levels for Patients on Different Oral Vitamin D Compounds

	Phosphorus (mmol/L)	Calcium (mmol/L)	Calcium dialysate concentration (mEq/L)
	Mean (SD), <i>n</i>	Mean (SD), <i>n</i>	Mean (SD), <i>n</i>
Calcitriol	5.28 (1.16), <i>n</i> =638	9.17 (0.58), <i>n</i> =639	2.59 (0.27), <i>n</i> =640
Doxercalciferol	5.24 (1.22), <i>n</i> =511	9.07 (0.56), <i>n</i> =511	2.66 (0.35), <i>n</i> =507
Paricalcitol	5.34 (1.30), <i>n</i> =545	9.20 (0.49), <i>n</i> =545	2.55 (0.21), <i>n</i> =543
ANOVA <i>p</i> -value	0.4445	0.0007	<0.0001

SD = standard deviation.

TABLE 6
Mortality by Patient-Time

Physician formulation	Physicians	Patients	Use (%)	Deaths	Overall mortality	Deaths per 100 patient-years	95% confidence interval
Calcitriol	74	643	39.5%	65	10.1%	9.33	7.06, 11.60
Doxercalciferol	53	516	31.4%	70	13.6%	12.20	9.34, 15.06
Paricalcitol	60	548	29.1%	64	11.7%	12.27	9.27, 15.28
Overall	187	1,707		199	11.7%	11.11	

TABLE 7
Adjusted Hazard Ratios and 95% Confidence Intervals Between Active Vitamin D Formulations

Comparison	Adjusted hazard ratio	95% confidence interval
Doxercalciferol vs calcitriol	1.186	0.795, 1.768
Paricalcitol vs calcitriol	1.213	0.818, 1.797
Paricalcitol vs doxercalciferol	1.023	0.696, 1.502

Figure 1 — Survival curve among the 3 vitamin D formulations. The survival curve has been adjusted for demographic factors, cause of ESRD, and comorbid conditions. ESRD = end-stage renal disease.

groups had higher mean calcium lab values than the doxercalciferol group.

The findings from this study stand in contrast to retrospective observational studies of vitamin D analogs administered intravenously to hemodialysis patients. One such study reported higher mortality rates for patients on calcitriol compared to patients on paricalcitol (13). Another study reported lower unadjusted rates for patients on either paricalcitol or doxercalciferol versus calcitriol; however, these differences were not statistically significant in adjusted analyses (14). The reasons for potential differences in hemodialysis and peritoneal dialysis patients are unclear but may be related to different routes of administration, relative dosing differences, or uncontrolled or unmeasured confounding within the analyses. Previous studies with hemodialysis patients also took place when higher calcium baths and calcium-based binders were more often used.

These findings have clinical implications, particularly in light of recent legislative changes. Oral vitamin D formulations are currently included in the US Medicare prospective payment system bundled payment. Therefore, comparative effectiveness research on oral vitamin D is crucial in helping physicians provide the highest quality of care in the most cost-effective manner. Given the substantially lower price of calcitriol, these findings combined with the previously demonstrated equivalent efficacy would argue for its use in the treatment of bone and mineral disease in peritoneal dialysis patients. However, it is not possible to extrapolate these findings to hemodialysis patients.

Limitations of this study include its observational nature and the relatively low power of the study—54% or 78% power to detect a difference of 5% in the death

rate (i.e., higher or lower rate, respectively) between any 2 formulations. This is partly due to the relatively low death rate among this population of peritoneal dialysis patients and to the length of the study. Due to its design, the study also misclassified 3% of patients served by physicians who predominately prescribed a particular vitamin D formulation but prescribed a different 1 for those patients. These patients must be included in the analysis to properly implement the instrumental variables technique, but their inclusion could introduce bias, as the groups do not represent 100% utilization of only 1 form of vitamin D. Of course, no retrospective technique can guarantee that all residual confounding has been eliminated. There is a possibility of bias due to center effect (e.g., the centers that provide better overall treatment tend to prescribe more calcitriol). However, collinearity between center and formulation precludes adjusting for center in the models. Also, in contrast to studies of intravenous vitamin D, patient compliance with medication instructions cannot be easily assessed.

In conclusion, this retrospective analysis did not reveal any significant difference in mortality in ESRD patients on peritoneal dialysis taking any of the 3 oral active vitamin D preparations.

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DISCLOSURES

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