Mortality risk among hemodialysis patients receiving different vitamin D analogs

F Tentori[1], WC Hunt[2], CA Stidley[1,2], MR Rohrscheib[2], EJ Bedrick[2], KB Meyer[1,3], HK Johnson[1] and PG Zager[1,2], for the Medical Directors of Dialysis Clinic Inc.

[1]Dialysis Clinic Inc., Albuquerque, New Mexico, USA; [2]University of New Mexico, Albuquerque, New Mexico, USA and [3]Tufts-New England Medical Center, Boston, Massachusetts, USA

Intravenous vitamin D is standard therapy for secondary hyperparathyroidism in hemodialysis (HD) patients. In for-profit dialysis clinics, mortality was higher for patients on calcitriol compared to paricalcitol. Doxercalciferol, a second vitamin D2 analog, is currently available. We assessed mortality associated with each vitamin D analog and with lack of vitamin D therapy in patients who began HD at Dialysis Clinic Inc. (DCI), a not-for-profit dialysis provider. During the 1999–2004 study period we studied 7731 patients (calcitriol: $n = 3212$; paricalcitol: $n = 2087$; doxercalciferol: $n = 2432$). Median follow-up was 37 weeks. Mortality rates (deaths/100 patient-years) were identical in patients on doxercalciferol (15.4, 95% confidence interval (13.6–17.1)) and paricalcitol (15.3 (13.6–16.9)) and higher in patients on calcitriol (19.6 (18.2–21.1)) ($P < 0.0001$). In all models mortality was similar for paricalcitol versus doxercalciferol (hazard ratios = 1.0). In unadjusted models, mortality was lower in patients on doxercalciferol (0.80 (0.66, 0.96)) and paricalcitol (0.79 (0.68, 0.92)) versus calcitriol ($P < 0.05$). In adjusted models, this difference was not statistically significant. In all models mortality was higher for patients who did not receive vitamin D versus those who did (1.2 (1.1–1.3)). Mortality in doxercalciferol- and paricalcitol-treated patients was virtually identical. Differences in survival between vitamin D2 and D3 may be smaller than previously reported.

Kidney International (2006) **70,** 1858–1865. doi:10.1038/sj.ki.5001868; published online 4 October 2006

KEYWORDS: calcitriol; paricalcitol; doxercalciferol; vitamin D; mortality; hemodialysis

Correspondence: *PG Zager, Department of Internal Medicine, University of New Mexico, ACC 5, Albuquerque, New Mexico 87131, USA.*
E-mail: pzag@unm.edu

Received 4 April 2006; revised 18 July 2006; accepted 10 August 2006; published online 4 October 2006

Despite recent therapeutic advances, mortality remains high among patients with stage five chronic kidney disease maintained on hemodialysis (HD).[1] The excess mortality, largely attributable to atherosclerotic cardiovascular disease (ASCVD), remains significant even after controlling for age, diabetes, and hypertension.[1] These observations are consistent with the hypothesis that non-traditional ASCVD risk factors, including malnutrition, and inflammation, may contribute to the observed excess mortality.[2,3]

Another non-traditional risk factor, disordered mineral metabolism, has been postulated to play an important role in the pathogenesis of ASCVD among HD patients.[4–7] Abnormalities in serum calcium, phosphorus, and parathyroid hormone (PTH) have been associated with increased all-cause and ASCVD morbidity, and mortality.[8–14] The attributable risk for mortality associated with disorders of mineral metabolism (17.5%) has been described to be higher than that for inefficient dialysis (5.1%) and anemia (11.3%).[11] Accordingly, the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Improvement (KDOQI) work group has issued guidelines for serum calcium, phosphorus, calcium–phosphorus product, and PTH.[15]

Intravenous vitamin D is mainstream therapy for the treatment of secondary hyperparathyroidism among HD patients.[15,16] Calcitriol (1α,25-dihydroxyvitamin D3; Calcijex, Abbott Laboratories, North Chicago, IL, USA), the first available vitamin D analog,[17] effectively lowers serum PTH but also raises serum calcium by stimulating intestinal calcium absorption and bone resorption.[18] When used in conjunction with calcium-based phosphorus binders or dialysate with high calcium concentrations, calcitriol may increase the risk for hypercalcemia[19] and potentially for coronary artery calcification.[4,20] Two vitamin D2 analogs, paricalcitol (19-nor-1α,25-dihydroxyvitamin D2; Zemplar, Abbott Laboratories)[21–23] and doxercalciferol (1α-hydroxyvitamin D2; Hectorol, Genzyme)[24,25] are currently available for the treatment of secondary hyperparathyroidism. Although both these analogs have a vitamin D2 side chain, they differ in their binding kinetics and metabolism. Both paricalcitol and doxercalciferol resemble calcitriol in their ability to lower PTH but have more modest effects on serum calcium and phosphorus concentrations.[18,23,25,26]

Differences in clinical outcomes among HD patients receiving paricalcitol and calcitriol have been described.[27–29] In a retrospective analysis of patients on HD at for-profit facilities, Teng *et al.*[27] reported that mortality was lower among those treated with paricalcitol compared to calcitriol. Unfortunately, this report was restricted to patients dialyzed in facilities operated by a large for-profit provider and did not include patients who received doxercalciferol.

The present study was conducted to explore the relationship between each vitamin D analog currently available and mortality among patients starting HD at facilities operated by Dialysis Clinic Inc. (DCI), a not-for-profit organization. Mortality was also assessed for patients who did not receive vitamin D versus those who did.

RESULTS

Of the 14 967 patients who started HD at DCI during the study period, 8112 received vitamin D and 7731 survived $\geqslant$30 days after the first vitamin D administration. Twenty-eight percent of all patients received an initial dose of vitamin D within 30 days and 47% within 180 days of starting HD. Patients were censored at death ($n=1326$), kidney transplant ($n=352$), switch to peritoneal dialysis ($n=222$), prolonged absence from a DCI clinic ($n=967$), change in type of vitamin D ($n=2901$) or study end ($n=1963$).

Distributions of age, gender, and cause of ESRD in the study sample were similar to those of United States Renal Data Systems (USRDS) 2002 incident cohort[1] (data not shown). Reflecting DCI's total patient population, African Americans were over-represented in the study sample (44.5 versus 29.6%). Distributions of demographics and baseline laboratory values stratified by type of vitamin D are shown (Table 1). The proportions of female, White and Black subjects were similar in the three groups. As calcitriol was the first available vitamin D analog, follow-up time was longer for patients started on calcitriol versus paricalcitol and doxercalciferol ($P<0.0001$). Median time on HD before the first vitamin D administration was shorter for patients receiving calcitriol (18 days) compared to paricalcitol or doxercalciferol (37 days for both) ($P<0.0001$). The median number of vitamin D administrations per week was significantly, but only slightly, greater for calcitriol. Although the absolute dose of vitamin D (micrograms per week) differed between the three analogs, the effective dose, using

Table 1 | Study population demographic characteristics and baseline laboratory values by type of vitamin D

	Calcitriol (*n*=3212)	Paricalcitol (*n*=2087)	Doxercalciferol (*n*=2432)
Demographic characteristics			
Female[a]	48.7	49.0	47.9
Race[a]			
White	49.5	49.6	49.0
Black	44.5	42.8	46.0
Other/unknown	5.9	7.6	6.2
Cause of ESRD[a]			
Diabetes	44.6	45.4	44.4
Hypertension	26.0	25.7	27.1
Glomerulonephritis[b]	11.6	9.8	9.5
Other/unknown	17.7	19.1	19.0
Age (years)[c]	62 (32–83)	61 (32–83)	62 (33–83)
Follow-up (weeks)[c,d]	41 (2–171)	39 (2–153)	32 (2–124)
Time on HD before start of vitamin D (days)[c,d]	18 (0–328)	37 (0–615)	37 (0–749)
Vitamin D dose[e]			
No. of administrations/week[c,d]	2.7 (0.5–3.0)	2.6 (0.5–3.0)	2.6 (0.6–3.0)
Dose/week (μg)[c,d]	1.6 (0.3–4.7)	7.5 (1.3–18.7)	5.7 (1.1–12.3)
Baseline laboratory values[c]			
Calcium (mg/dl)[d]	8.5 (7.2–9.7)	8.8 (7.6–10.1)	8.8 (7.6–9.9)
Phosphorus (mg/dl)[d]	5.0 (3.1–7.4)	5.1 (3.4–7.6)	5.1 (3.3–7.5)
PTH (pg/ml)[d]	289 (52–862)	318 (98–903)	335 (103–881)
Hct (%)[d]	32.3 (25.6–39.1)	33.9 (27.1–40.0)	34.5 (27.3–40.6)
Kt/V[d]	1.3 (0.8–1.9)	1.4 (0.9–1.9)	1.4 (0.9–1.9)
Creatinine (mg/dl)[d]	6.5 (3.3–12.2)	6.9 (3.7–12.9)	6.9 (3.7–12.7)
Albumin (g/dl)[d]	3.55 (2.65–4.17)	3.60 (2.75–4.13)	3.60 (2.80–4.17)

ESRD, end-stage renal disease; Hct, hematocrit; HD, hemodialysis; PTH, parathyroid hormone.
[a]Percent.
[b]Significantly different by type of vitamin D, $P<0.05$ by Pearson χ^2 test.
[c]Median with fifth and 95th percentiles.
[d]Significantly different by type of vitamin D, $P<0.0001$ by Kruskal–Wallis test.
[e]Over the first 90 days after initiation of vitamin D.

the dose equivalencies accepted in current clinical practice (1:4 for paricalcitol to calcitriol; 0.6:1 for doxercalciferol to paricalcitol),[21,31] were similar in the three groups. Reflecting current clinical practice recommendations, the number of administrations and vitamin D dose were lower among patients receiving paricalcitol and doxercalciferol with baseline PTH <150 pg/ml compared to those with PTH $\geqslant 150$ pg/ml. However, this difference was not observed in calcitriol-treated patients (data not shown). Baseline serum calcium, phosphorus, PTH, hematocrit, *Kt/V*, creatinine, and albumin were lower among calcitriol- versus paricalcitol- or doxercalciferol-treated patients ($P<0.0001$). No differences in baseline laboratory values were observed between the paricalcitol and doxercalciferol group.

Mortality among patients receiving different vitamin D analogs

The overall mortality rate (deaths/100 patient-years) in the study population was lower (17.3. (95% confidence interval: 16.4–18.3)) than that of the 2002 USRDS HD prevalent cohort (20.9).[1] Mortality was significantly higher among patients receiving calcitriol (19.6 (18.2–21.1)) compared to those receiving paricalcitol (15.3 (13.6–16.9)) ($P<0.0001$) or doxercalciferol (15.4 (13.6–17.1)) ($P=0.0003$). Similar mortality rates were observed during the 2001–2004 period, when all three analogs were in use within DCI (overall: 16.3 (15.1–17.5); calcitriol: 19.9 (17.0–22.8); paricalcitol: 15.4 (13.4–17.3); doxercalciferol: 15.4 (13.7–17.2)). Kaplan–Meier survival curves for patients receiving calcitriol, paricalcitol, or doxercalciferol are shown (Figure 1). The survival curves for doxercalciferol- and paricalcitol-treated patients are similar. Calcitriol-treated patients had worse survival compared to those receiving either vitamin D2 analog ($P<0.0001$). In all models, all-cause mortality was similar among paricalcitol- versus doxercalciferol-treated patients. The estimates of the hazard ratios (HRs) for paricalcitol versus doxercalciferol ranged from 0.99 to 1.06 and were not significantly different from 1.0 (Table 2). In the unadjusted model, mortality was lower among patients receiving doxercalciferol (HR = 0.80 (0.69–0.91)) and paricalcitol (0.78 (0.69–0.89)) versus calcitriol ($P<0.05$). However, when models were adjusted for laboratory values and clinic standardized mortality (SMR), the HRs for doxercalciferol and paricalcitol versus calcitriol both increased and were not statistically significant.

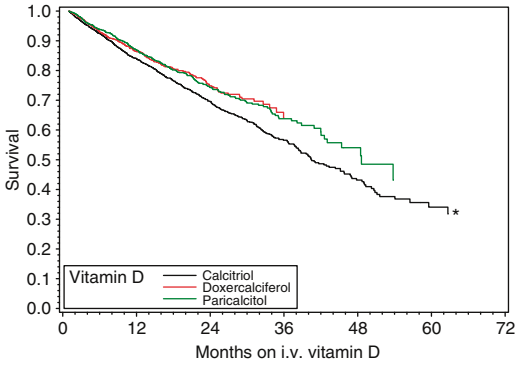

Figure 1 | Kaplan–Meier survival curves by type of vitamin D analog after the first vitamin D administration. *$P<0.001$ for patients receiving calcitriol compared to patients on paricalcitol or doxercalciferol.

Results of the intent-to-treat analyses also demonstrated virtually identical mortality among doxercalciferol- and paricalcitol-treated patients, with HRs ranging from 0.95 to 1.03. HRs tended to be lower among patients treated with either D2 analog versus calcitriol, but this difference was not statistically significant in models adjusted for laboratory values (HRs between 0.96 and 1.00). Similar results were obtained in analyses restricted to the 2001–2004 period.

ASCVD mortality was similar among doxercalciferol- and paricalcitol-treated patients and higher among patients receiving calcitriol in the unadjusted but not in the adjusted models (data not shown).

Mortality among patients who did not receive vitamin D therapy

Patients who did not receive vitamin D therapy ($n=6855$) were older, more likely to be male subjects and less likely to be Black subjects. At baseline they had higher serum calcium (8.8 (fifth–95th percentile: 7.5–10.0) versus 8.6 (7.2–9.9) mg/dl),

Table 2 | Hazard ratios (95% confidence intervals) for all-cause mortality for patients receiving doxercalciferol and paricalcitol compared to calcitriol-treated patients and for patients receiving paricalcitol versus calcitriol

Model	Covariates	Doxercalciferol vs calcitriol	Paricalcitol vs calcitriol	Paricalcitol vs doxercalciferol
1	Unadjusted[a]	0.80 (0.69, 0.91)[b]	0.78 (0.69, 0.89)[b]	0.99 (0.84, 1.15)
2	Age, gender, race, cause of ESRD, year started HD, and time on HD before first vitamin D administration[a]	0.80 (0.66, 0.96)[b]	0.79 (0.68, 0.92)[b]	0.99 (0.83, 1.17)
3	Model 2 plus baseline serum calcium, phosphorus, PTH, albumin, *Kt/V*, creatinine, and Hct labs[c]	0.88 (0.71, 1.09)	0.93 (0.78, 1.11)	1.06 (0.88, 1.27)
4	Model 3 plus clinic SMR[c]	0.93 (0.75, 1.15)	0.94 (0.79, 1.13)	1.02 (0.84, 1.23)
5	Model 4 with time-varying labs[c]	0.95 (0.77, 1.18)	0.95 (0.79, 1.13)	1.00 (0.82, 1.21)

ESRD, end-stage renal disease; Hct, hematocrit; HD, hemodialysis; PTH, parathyroid hormone; SMR, standardized mortality.
[a]Patients, n=7731; deaths, n=1326.
[b]$P<0.05$.
[c]Patients, n=6107; deaths, n=1029.

lower phosphorus (4.5 (2.6–7.4) versus 4.7 (2.8–7.5) mg/dl), and lower albumin (3.4 (2.5–4.1) versus 3.5 (2.6–4.1) g/dl) compared to patients who received any vitamin D analog. Serum calcium concentration did not change over the first 90 days on HD (9.0 mg/dl) Patients who did not receive vitamin D had a significantly increased mortality risk with a HR of 1.20 after adjustment for patient demographics, baseline laboratory values, and clinic SMR (Table 3).

Effects of vitamin D analogs on serum calcium, phosphorus, and PTH

Changes in serum calcium, phosphorus, and PTH concentrations over the first 3 months of vitamin D therapy were assessed in a subcohort of patients who received the same vitamin D analog and were followed for $\geqslant 90$ days (calcitriol: $n = 2667$; paricalcitol: $n = 1697$; doxercalciferol: $n = 2010$). In all vitamin D groups, serum calcium, and phosphorus concentrations increased rapidly over the first month of vitamin D therapy and slower thereafter (Figure 2). The mean increment in serum calcium was greater among calcitriol- (0.7 mg/dl; percent increase = 8.2%) compared to paricalcitol- or doxercalciferol-treated patients (0.5 mg/dl; 5.7% for both) ($P < 0.0001$). However, because of the lower mean serum calcium concentration at baseline, patients receiving calcitriol had lower mean serum calcium after 3 months on vitamin D. After 6 months of vitamin D therapy, serum calcium was similar in the three groups (data not shown). Serum PTH concentrations decreased similarly in the three vitamin D groups. However, the mean PTH concentrations at baseline and after 3 months of therapy were lower among calcitriol- versus doxercalciferol- and paricalcitol-treated patients (Figure 2).

Compliance with KDOQI guidelines for bone metabolism and disease

In an analysis restricted to patients who received a single type of vitamin D and who had a follow-up time $\geqslant 180$ days (calcitriol: $n = 1655$; paricalcitol: $n = 1129$; doxercalciferol: $n = 1354$), we assessed achievement of KDOQI guidelines for calcium, phosphorus, and PTH at baseline and after 6 months on vitamin D (Figure 3).[15] Compliance for the entire study group exceeded those previously reported for the US cohort in the Dialysis Outcomes and Practice Patterns Study.[32] At baseline, calcitriol-treated patients had worse compliance for calcium compared to either vitamin D2 analog $P < 0.001$) and better compliance for PTH compared to doxercalciferol ($P = 0.0037$). After 6 months, compliance with guidelines for calcium was similar in the three groups whereas compliance with PTH guidelines was lower among calcitriol-treated patients ($P < 0.05$).

Table 3 | Hazard ratios (95% confidence intervals) for all-cause mortality for patients who did not receive any vitamin D compared to those who received any type of vitamin D analogue

Model	Covariates	Hazard ratios (95% CI)
1	Unadjusted[a]	1.53 (1.43, 1.63)[b]
2	Age, gender, race, cause of ESRD, and year started HD[a]	1.28 (1.20, 1.37)[b]
3	Model 2 plus baseline calcium, phosphorus, PTH, albumin, *Kt/V*, creatinine, and Hct[c,d]	1.21 (1.10, 1.33)[b]
4	Model 3 plus clinic SMR[e]	1.20 (1.10, 1.32)[b]

CI, confidence interval; ESRD, end-stage renal disease; Hct, hematocrit; HD, hemodialysis; PTH, parathyroid hormone; SMR, standardized mortality.
[a]Patients, n=14 967; deaths, n=4238.
[b]$P < 0.05$.
[c]Patients, n=9355; deaths, n=2725.
[d]Baseline laboratory over the first 30 days on HD.
[e]Patients, n=9351; deaths, n=2723.

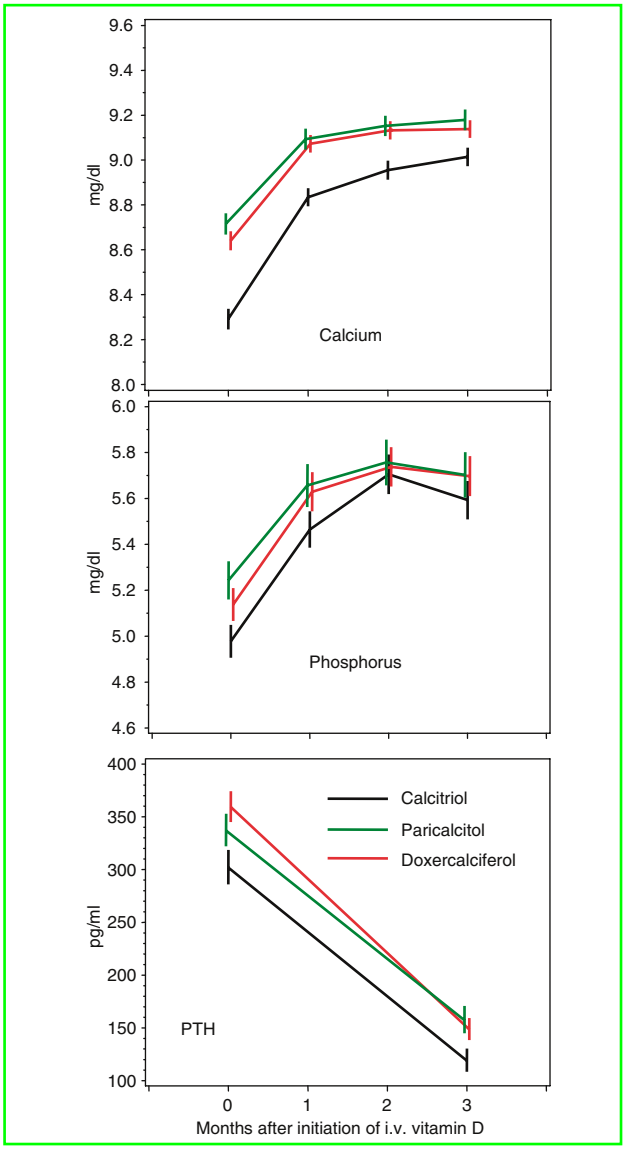

Figure 2 | Mean serum calcium, phosphorus, and PTH concentrations over the first 3 months of vitamin D therapy. Restricted to patients who received the same type of vitamin D and were followed for $\geqslant 90$ days (calcitriol: $n = 2667$; paricalcitol: $n = 1697$; doxercalciferol: $n = 2010$). Vertical bars indicate the 95% confidence interval for the mean. Geometric means are shown for PTH. Because PTH is measured quarterly, means are given only before initiation of vitamin D (month 0) and after 3 months.

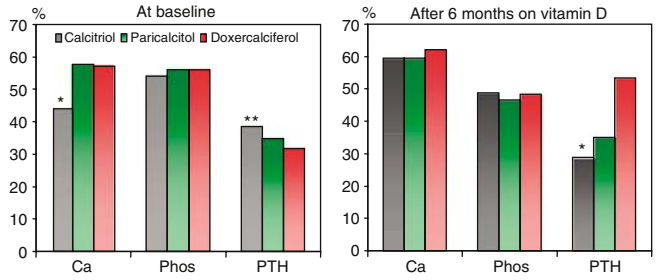

Figure 3 | Compliance rates with KDOQI guidelines for bone metabolism and disease at baseline and after 6 months of vitamin D therapy. Restricted to patients who received a single type of vitamin D and were followed for $\geqslant$180 days (calcitriol: $n=1655$; paricalcitol: $n=1129$; doxercalciferol: $n=1354$). Current KDOQI guidelines: calcium 8.4–9.5 mg/dl; phosphorus 3.5–5.5 mg/dl; PTH: 150–300 pg/ml. *$P<0.05$ for calcitriol versus paricalcitol and doxercalciferol; **$P<0.05$ for calcitriol versus doxercalciferol.

DISCUSSION

The major new finding of the present study is that paricalcitol-treated patients do not have a survival advantage compared to doxercalciferol-treated patients. In fact, the risks for all-cause and ASCVD mortality were identical in the paricalcitol and doxercalciferol groups. In all the models comparing these two vitamins D2 analogs, the estimates for the HRs were virtually 1.0. Therefore, at least within not-for-profit facilities, treatment with doxercalciferol compared to paricalcitol was not associated with increased mortality.

A second important finding of the present study is that the survival advantage of paricalcitol- versus calcitriol-treated patients may be significantly smaller than previously reported.[27] Although mortality risk was increased among patients receiving calcitriol versus paricalcitol and doxercalciferol in unadjusted models, these differences diminished and were not statistically significant in models adjusted for important covariates. These results suggest that within not-for-profit facilities, differences in mortality between patients receiving vitamin D2 versus vitamin D3 analogs may be smaller than previously reported.[27] Several factors, including differences in practice patterns and in racial composition may have contributed to the smaller differences observed in the current study compared to Teng *et al.*[27]

Finally, we confirmed the increased risk for mortality among patients who did not receive vitamin D therapy compared to those who did. Our results expand previous reports to patients on HD in a not-for-profit dialysis provider and receiving a third vitamin D analog.

Although the reasons for the higher mortality observed among calcitriol-treated patients have not clearly been identified, several factors related both to the vitamin D analogs mechanisms of actions and to the study population should be considered.

Vitamin D receptors are expressed in different tissues throughout the body, including vascular smooth muscle cells, lymphocytes, osteoblasts, and cardiac myocytes.[33,34] Human and animal studies have demonstrated that vitamin D affects a variety of biological processes, including renin expression,[35] inflammatory response,[36,37] oxidative stress,[38] apoptosis,[39] and atherosclerosis.[40,41] By activating Vitamin D receptors in different tissues, vitamin D analogs impact arterial calcification, atherosclerosis and inflammatory pathways in a manner independent of the effects on calcium, phosphorus, and PTH.[34] Because of the differences in structure, binding to Vitamin D receptors and metabolism[18] vitamin D2 and D3 analogs are likely to differ in the way they impact these processes, therefore contributing to differences in mortality observed.

Finally, differences in cellular toxicity reported for calcitriol and paricalcitol in animal studies[42,43] may also contribute to the observed difference in mortality. Compared to the vitamin D2 analogs, calcitriol may have a greater tendency to increase serum calcium concentration.[19,26] High serum calcium concentrations *per se* have been associated with increased mortality.[44] Furthermore, high calcium concentration contributes to arterial calcifications and subsequent increase in mortality.[34] However, in the present study although the mean increment in serum calcium was significantly higher among calcitriol-treated patients, mean serum calcium concentrations during the first 3 months of vitamin D therapy were lower in this group compared to paricalcitol and doxercalciferol. After 6 months of vitamin D therapy, serum calcium concentrations were similar among all three groups. Therefore it is unlikely that differences in serum calcium contributed to the difference in mortality observed in the three vitamin D groups.

Low serum PTH has also been associated with increased mortality risk.[13] After 3 months of therapy, mean PTH was below the current KDOQI recommendations[15] in all three vitamin D group. However, most of the follow-up of this study occurred before publication of the current guidelines (October 2003). The low PTH concentration observed among calcitriol-treated patients may have contributed to their increased mortality risk.

We recognize that selection bias may have contributed to the specific findings of the current study. The majority of calcitriol-treated patients began HD before the introduction of KDOQI guidelines. Although the analyses were adjusted for the year of initiation of HD, there may have been a significant residual vintage effect reflecting changing practice patterns. Patients who had lower serum calcium concentrations at baseline may have preferentially been placed on calcitriol. Confounding by clinic-level effects may also have contributed to the observed results. However, across DCI the choice of one vitamin D analog over the others is often made at a clinic- rather than a patient-level. Although DCI corporate guidelines for serum calcium, phosphorus, and PTH were in place during the study period, treatment of secondary hyperparathyroidism was not protocol driven. Because of the large number of clinics and the relatively small number of patients within most clinics, we did not construct separate models for each clinic. We did, however, take the clinic effect into account by creating models that included clinic SMRs as a covariate, as reported previously by other authors.[27,30] In these models, the estimates of the HRs for

doxercalciferol and paricalcitol versus calcitriol were closer to 1.0 than in models not including clinic SMR. These observations are consistent with the hypothesis that differences in practice patterns by clinic and possibly by physician within each clinic may have contributed to the observed differences in mortality.

In the present study, inclusion of clinically important covariates in the survival models resulted in HRs for doxercalciferol and paricalcitol versus calcitriol that were closer to 1.0. Similar changes in the HRs are also seen in the models reported by Teng *et al*. but, in contrast to the present study, the differences between calcitriol and paricalcitol remained statistically significant. This likely reflects the larger sample size and higher mortality rates of Teng's cohort. Increased mortality, attributed to difference in clinical practices, has been reported among patients receiving HD at for-profit compared to not-for-profit facilities.[45] These authors postulated that differences in staffing and shorter duration of HD sessions may have contributed to the increased mortality in for-profit facilities. Although data on these covariates were not included in the current study, similar differences in practice patterns may have occurred at DCI clinics during the study period contributed to the disparate results between the present study and that reported by Teng *et al.*[27] Furthermore, the higher proportion of Black subjects may also have contributed to the improved survival of the study sample.

Finally, it should be noticed that compliance rates with KDOQI guidelines for bone metabolism in the current study exceeded those previously reported for the US cohort in the Dialysis Outcomes and Practice Patterns Study.[32] This may have contributed to the overall lower mortality rates observed in the study population.

Overall these observations are consistent with the hypothesis that there may be confounding by important, yet unidentified, covariates that contribute to the differences in survival observed in the three vitamin D groups.

The present study has several limitations characteristic of most retrospective studies. Comorbidity was not assessed using a formal instrument, for example, Index of Coexistent Disease. However, analyses were adjusted for surrogate markers of comorbidity (age, gender, race, cause of ESRD, and serum albumin) that took into account the major comorbid factors among HD patients. Moreover, serum albumin concentration is an excellent surrogate for formal comorbidity assessment among ESRD patients. Analysis of the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Cohort Study demonstrated that lower serum albumin concentrations were associated with higher Index of Coexistent Disease severity scores.[46] Given the differences in vintage among patients receiving different vitamin D analogs, there may have been significant differences in baseline comorbidity. However, in the USRDS incident HD population, comorbidity has increased over time.[1] Therefore, as doxercalciferol- and paricalcitol-treated patients tended to start HD at a later date than calcitriol-treated patients it is unlikely that they had less baseline comorbidity. Another major limitation is that owing to lack of reliable data in the earlier years we were unable to include important covariates, including oral medications, type of vascular access, and parathyroidectomies.

Our study also has several unique strengths. The study sample included only incident patients starting HD at a DCI facility; therefore, we were able to rule out potential bias and confounders related to previous medical care that are typical of prevalent cohorts. All routine laboratory parameters were analyzed at the same laboratory. Finally, DCI's proprietary medical information system (DARWIN) ensured high quality of the data.

In summary, we demonstrated that doxercalciferol and paricalcitol are equivalent in their effects on serum calcium, phosphorus and PTH concentrations and in their relationships with mortality. In addition the differences in mortality risk between vitamin D2- and D3-treated patients may be smaller than reported previously. However, given the inherent limitations of retrospective analyses, a prospective randomized controlled clinical trial is needed to confirm these findings.

MATERIALS AND METHODS

Study sample

We studied 14 967 patients aged $\geqslant 20$ years who started chronic HD at a DCI facility during the period of 1 January 1999 to 30 September 2004 and who survived for $\geqslant 30$ days. Patients with prior renal transplant or peritoneal dialysis were excluded. Data were extracted from DCI's computerized medical information system (DARWIN). Dates and causes of death were obtained from the Centers for Medicare and Medicaid Services (CMS) Death Notification forms (2746), confirmed by direct contact with each facility and coded using the International Classification of Disease, ninth revision (ICD-9).

Laboratory methods

At DCI clinics all laboratory values included in the current study are measured monthly, except PTH, which is measured quarterly. Blood samples for routine laboratory determinations were drawn before initiation of HD and shipped to DCI central laboratory (Nashville, TN, USA) for analysis. Serum calcium was measured by Cresolphthalein Complexone (Roche, Nutley, NJ, USA), phosphorus by Phosphomolybdate-UV (Roche), PTH by N-tact IIPTH SP IRMA (DiaSorin, Stillwater, MN, USA), blood urea nitrogen by enzymatic urease (Roche), creatinine by enzymatic creatininase (Roche), hematocrit by Advia (Bayer, Tarrytown, NY, USA) and serum albumin by BCG (Roche). Dialysis dose, expressed as spKt/V (Kt/V), was computed using UREAKIN™. Results of laboratory studies are electronically imported into DARWIN.

Statistical methods

We compared survival by type of vitamin D among the 7731 patients who ever received vitamin D and who survived for $\geqslant 30$ days after the first administration. This 30-day period was chosen because it allowed time to obtain baseline data and only reduced the sample size by 381 patients. Follow-up was censored at death, kidney

transplant, switch to peritoneal dialysis, absence from DCI for $\geqslant$90 days, or study end. Follow-up was also censored if vitamin D type changed but not if vitamin D was interrupted or discontinued. Mortality risk was assessed using a series of Cox proportional hazard models. Model covariates included demographics (age at start of HD, gender, race, cause of ESRD, year started HD, and time on HD before first vitamin D administration) and laboratory values (serum calcium, phosphorus, PTH, albumin, creatinine, hematocrit, and Kt/V). Baseline values for each laboratory parameter were computed as the average of measurements taken in the 90-day period before start of follow-up. Patients with missing baseline measurements were excluded from adjusted models. Additional models were constructed in which laboratory values were treated as time-varying covariates, defined as the average value over the preceding 90 days. If a given value was missing we substituted the value for the previous 90-day period. To adjust for clinic-level effects models were adjusted for the SMR of the clinic where HD was initiated.[1,27,30] Clinics SMRs were calculated for the 1998–2003 period and categorized by quintiles.

Separate sets of models were constructed to conduct intent-to-treat analyses and for the 2001–2004 study period, when all three vitamin D analogs were used at DCI clinics.

We also compared mortality between patients who did not receive vitamin D therapy and those who received any vitamin D analog. For these analyses follow-up began 30 days after initiation of HD and patients were classified as not receiving vitamin D up to the day of first vitamin D administration. Follow-up was censored as described above. Baseline laboratory values were defined at the average of all measurements taken in the first 30 days of HD.

Changes in serum calcium, phosphorus, and PTH concentrations were evaluated among patients who received a single type of vitamin D therapy and had $\geqslant$90 days of follow-up. Mean serum calcium and phosphorus concentrations were computed for the 30 days before initiation of vitamin D and for 30-day intervals centered at each of the 3 succeeding months. As PTH was measured quarterly, mean values were computed only at initiation of vitamin D therapy and at 90 days.

Summary data for demographic and laboratory variables are presented as percents or medians with the fifth and 95th percentiles, as appropriate. Cox model results are summarized by HR and 95% confidence intervals. Comparisons between patients receiving different vitamin D analogs were performed by Pearson χ^2 and Kruskal–Wallis tests. Statistical significance was defined as $P<0.05$. Statistical analyses were conducted in SAS version 9.1 (Cary, NC, USA)

ACKNOWLEDGMENTS

We specially thank all DCI patients, without whom this study would not have been possible. We thank all DCI facilities and medical directors for their collaborative assistance; Richard Zager for his suggestions; Doug Lindsey, Meg Lamey, and Kelly Utterback for their technical support. This study was funded in part by an unrestricted grant from Genzyme and by Dialysis Clinic Inc. (DCI), a not-for-profit organization.

REFERENCES

1. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease. US Renal Data System, USRDS 2004 Annual Data Report: Atlas of End-stage Renal Disease in the United States. Bethesda, MD, 2004.
2. Kalantar-Zadeh K, Kopple JD. Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. *Am J Kidney Dis* 2001; **38**: 1343–1350.
3. Stenvinkel P, Heimburger O, Paultre F *et al.* Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 1999; **55**: 1899–1911.
4. Goodman WG, Goldin J, Kuizon BD *et al.* Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; **342**: 1478–1483.
5. Davies MR, Hruska KA. Pathophysiological mechanisms of vascular calcification in end-stage renal disease. *Kidney Int* 2001; **60**: 472–479.
6. Qunibi WY, Nolan CA, Ayus JC. Cardiovascular calcification in patients with end-stage renal disease: a century-old phenomenon. *Kidney Int* 2002; **82**(Suppl): 73–80.
7. Kestenbaum B, Sampson JN, Rudser KD *et al.* Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005; **16**: 520–528.
8. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium $\times$ phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; **31**: 607–617.
9. Ganesh SK, Stack AG, Levin NW *et al.* Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001; **12**: 2131–2138.
10. Marco MP, Craver L, Betriu A *et al.* Higher impact of mineral metabolism on cardiovascular mortality in a European hemodialysis population. *Kidney Int* 2003; **85**(Suppl): S111–S114.
11. Block GA, Klassen PS, Lazarus JM *et al.* Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004; **15**: 2208–2218.
12. Avram MM, Sreedhara R, Avram DK *et al.* Enrollment parathyroid hormone level is a new marker of survival in hemodialysis and peritoneal dialysis therapy for uremia. *Am J Kidney Dis* 1996; **28**: 924–930.
13. Avram MM, Mittman N, Myint MM, Fein P. Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. *Am J Kidney Dis* 2001; **38**: 1351–1357.
14. Melamed ML, Eustace JA, Plantinga L *et al.* Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: A longitudinal study. *Kidney Int* 2006; **70**(2): 351–357.
15. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 2003; **42**: S1–S202.
16. Ifudu O. Care of patients undergoing hemodialysis. *N Engl J Med* 1998; **339**: 1054–1062.
17. Slatopolsky E, Weerts C, Thielan J *et al.* Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihydroxy-cholecalciferol in uremic patients. *J Clin Invest* 1984; **74**: 2136–2143.
18. Brown AJ, Dusso AS, Slatopolsky E. Vitamin D analogues for secondary hyperparathyroidism. *Nephrol Dial Transplant* 2002; **17**(Suppl 10): 10–19.
19. Brown AJ, Dusso A, Slatopolsky E. Vitamin D. *Am J Physiol* 1999; **277**: F157–F175.
20. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002; **62**: 245–252.
21. Martin KJ, Gonzalez EA, Gellens ME *et al.* Therapy of secondary hyperparathyroidism with 19-nor-1alpha,25-dihydroxyvitamin D2. *Am J Kidney Dis* 1998; **32**: S61–S66.
22. Llach F, Yudd M. Paricalcitol in dialysis patients with calcitriol-resistant secondary hyperparathyroidism. *Am J Kidney Dis* 2001; **38**: S45–S50.
23. Martin KJ, Gonzalez EA, Gellens M *et al.* 19-Nor-1-alpha-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 1998; **9**: 1427–1432.
24. Frazao JM, Elangovan L, Maung HM *et al.* Intermittent doxercalciferol (1alpha-hydroxyvitamin D(2)) therapy for secondary hyperparathyroidism. *Am J Kidney Dis* 2000; **36**: 550–561.
25. Maung HM, Elangovan L, Frazao JM *et al.* Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1alpha-hydroxyvitamin D(2)) in dialysis patients with secondary hyperparathyroidism: a sequential comparison. *Am J Kidney Dis* 2001; **37**: 532–543.
26. Sprague SM, Llach F, Amdahl M *et al.* Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int* 2003; **63**: 1483–1490.
27. Teng M, Wolf M, Lowrie E *et al.* Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; **349**: 446–456.

28. Dobrez DG, Mathes A, Amdahl M *et al.* Paricalcitol-treated patients experience improved hospitalization outcomes compared with calcitriol-treated patients in real-world clinical settings. *Nephrol Dial Transplant* 2004; **19**: 1174–1181.
29. Shoji T, Shinohara K, Kimoto E *et al.* Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population. *Nephrol Dial Transplant* 2004; **19**: 179–184.
30. Lowrie EG, Teng M, Lacson E *et al.* Association between prevalent care process measures and facility-specific mortality rates. *Kidney Int* 2001; **60**: 1917–1929.
31. Zisman AL, Ghantous W, Schinleber P *et al.* Inhibition of parathyroid hormone: a dose equivalency study of paricalcitol and doxercalciferol. *Am J Nephrol* 2005; **25**: 591–595.
32. Young EW, Akiba T, Albert JM *et al.* Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2004; **44**: 34–38.
33. Stumpf WE, Sar M, Reid FA *et al.* Target cells for 1,25-dihydroxyvitamin D3 in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid. *Science* 1979; **206**: 1188–1190.
34. Andress DL. Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation. *Kidney Int* 2006; **69**: 33–43.
35. Li YC, Kong J, Wei M *et al.* 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002; **110**: 229–238.
36. Tabata T, Shoji T, Kikunami K *et al. In vivo* effect of 1 alpha-hydroxyvitamin D3 on interleukin-2 production in hemodialysis patients. *Nephron* 1988; **50**: 295–298.
37. Tokuda N, Kano M, Meiri H *et al.* Calcitriol therapy modulates the cellular immune responses in hemodialysis patients. *Am J Nephrol* 2000; **20**: 129–137.
38. Xiang G, Seki T, Schuster MD *et al.* Catalytic degradation of vitamin D up-regulated protein 1 mRNA enhances cardiomyocyte survival and prevents left ventricular remodeling after myocardial ischemia. *J Biol Chem* 2005; **280**: 39394–39402.
39. Elstner E, Linker-Israeli M, Said J *et al.* 20-epi-vitamin D3 analogues: a novel class of potent inhibitors of proliferation and inducers of differentiation of human breast cancer cell lines. *Cancer Res* 1995; **55**: 2822–2830.
40. Panichi V, De PS, Andreini B *et al.* Calcitriol modulates *in vivo* and *in vitro* cytokine production: a role for intracellular calcium. *Kidney Int* 1998; **54**: 1463–1469.
41. Aihara K, Azuma H, Akaike M *et al.* Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. *J Biol Chem* 2004; **279**: 35798–35802.
42. Zager RA. Calcitriol directly sensitizes renal tubular cells to ATP-depletion- and iron-mediated attack. *Am J Pathol* 1999; **154**: 1899–1909.
43. Sjoden G, Smith C, Lindgren U, DeLuca HF. 1 alpha-Hydroxyvitamin D2 is less toxic than 1 alpha-hydroxyvitamin D3 in the rat. *Proc Soc Exp Biol Med* 1985; **178**: 432–436.
44. Young EW, Albert JM, Satayathum S *et al.* Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2005; **67**: 1179–1187.
45. Devereaux PJ, Schunemann HJ, Ravindran N *et al.* Comparison of mortality between private for-profit and private not-for-profit hemodialysis centers: a systematic review and meta-analysis. *JAMA* 2002; **288**: 2449–2457.
46. Miskulin DC, Meyer KB, Athienites NV *et al.* Comorbidity and other factors associated with modality selection in incident dialysis patients: the CHOICE Study. Choices for Healthy Outcomes in Caring for End-Stage Renal Disease. *Am J Kidney Dis* 2002; **39**: 324–336.