http://www.kidney-international.org

see commentary on page 985

Oral active vitamin D is associated with improved survival in hemodialysis patients

Manuel Naves-Díaz[1], Daniel Álvarez-Hernández[1], Jutta Passlick-Deetjen[2], Adrian Guinsburg[3], Cristina Marelli[3], Diego Rodriguez-Puyol[4] and Jorge B. Cannata-Andía[1]

[1]Bone and Mineral Research Unit, Hospital Universitario Central de Asturias, Instituto Reina Sofía de Investigación, REDinREN del ISCIII, Universidad de Oviedo, Julián Claveria s/n, 33006 Oviedo, Spain; [2]Department of Nephrology, Heinrich Heine-University Duesseldorf and Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [3]Fresenius Medical Care Argentina SA, Buenos Aires, Argentina and [4]Nephrology Section and Research Unit, Hospital Príncipe de Asturias, Instituto Reina Sofía de Investigación, REDinREN del ISCIII, Alcalá de Henares, Madrid, Spain

Injection of active vitamin D is associated with better survival of patients receiving chronic hemodialysis. Since in many countries oral active vitamin D administration is the most common form of treatment for secondary hyperparathyroidism we determined the survival benefit of oral active vitamin D in hemodialysis patients from six Latin America countries (FME Register® as part of the CORES study) followed for a median of 16 months. Time-dependent Cox regression models, after adjustment for potential confounders, showed that the 7,203 patients who received oral active vitamin D had significant reductions in overall, cardiovascular, infectious and neoplastic mortality compared to the 8,801 patients that had not received vitamin D. Stratified analyses found a survival advantage in the group that had received oral active vitamin D in 36 of the 37 strata studied including that with the highest levels of serum calcium, phosphorus and parathyroid hormone. The survival benefit of oral active vitamin D was seen in those patients receiving mean daily doses of less than 1 μg with the highest reduction associated with the lowest dose. Our study shows that hemodialysis patients receiving oral active vitamin D had a survival advantage inversely related to the vitamin dose.

Kidney International (2008) **74,** 1070–1078; doi:10.1038/ki.2008.343; published online 16 July 2008

KEYWORDS: hemodialysis; mortality; oral calcitriol; Latin America

Correspondence: *Jorge B. Cannata-Andía, Head of the Bone and Mineral Research Unit, Instituto Reina Sofía de investigación, Hospital Universitario Central de Asturias, Julian Claveria s/n, Oviedo 33006, Spain.*
E-mail: cannata@hca.es

Received 20 December 2007; revised 30 April 2008; accepted 13 May 2008; published online 16 July 2008

Calcitriol deficiency is a common medical condition among patients with chronic kidney disease.[1,2] Calcitriol, the most active form of vitamin D, increases intestinal calcium absorption, effectively suppresses parathyroid hormone (PTH) secretion, prevents skeletal complications, and it has been the standard therapy for secondary hyperparathyroidism for more than two decades.[3] Calcitriol administration may also result in an elevation of serum calcium and phosphorus levels, which may facilitate vascular calcification and death.[4] Conversely, other studies have shown that the use of calcitriol and other forms of vitamin D derivatives is associated with improved survival in patients with cancer or infections.[5–7] More recently, a large historical cohort study has demonstrated a significant survival advantage of 20% in chronic hemodialysis patients receiving injectable active vitamin D.[8] In many countries, the most common form of administration of active vitamin D as treatment for secondary hyperparathyroidism is the oral route instead of the injectable form. Accordingly, this study examined the potential survival effect of oral active vitamin D in a large cohort of hemodialysis patients.

RESULTS

Baseline characteristics of the group that received oral active vitamin D ($n = 7203$) and the group that did not receive it ($n = 8801$) are shown in Table 1. Baseline serum levels of phosphorus and calcium-phosphorus product were significantly lower, whereas PTH was higher in the oral active vitamin D users. Patients who did not receive oral active vitamin D were older; and there were more diabetics. Throughout the whole follow-up there were 3110 deaths and 1792 lost to follow-up due to: renal transplantation (39.0%), switch to peritoneal dialysis (29.5%), voluntary withdrawal from therapy (16.1%), recovery of renal function (9.6%), unknown circumstances (3.7%), and transfer to a non-Fresenius dialysis unit (2.1%).

Survival analysis

The overall mortality rate was 19.4%; Venezuela (25.4%), Argentina (22.7%), Mexico (16.2%), Brazil (15.7%), Chile

Table 1 | Baseline data before the oral active vitamin D treatment[a]

Characteristics	Without Vitamin D (*N*=8801)	With Vitamin D (*N*=7203)	*P*-value
Age (year)	55.6 (16.0)	53.9 (15.9)	<0.001
Male patients (%)	58.4	58.3	0.81
Cause of renal failure (% of patients)			<0.001
Diabetes	28.7	24.5	
Nephroangioesclerosis	15.8	20.9	
Glomerulonephritis	9.9	12.6	
Other	45.6	42.0	
Vascular access (% of patients)			<0.001
Catheter	25.9	22.0	
Fistula	27.8	50.0	
Graft	3.3	5.8	
Unknown	43.0	22.2	
Weekly hours on dialysis (hour)	11.8 (0.9)	11.9 (0.7)	<0.001
Time on dialysis (year)	0.9 (2.4)	1.5 (3.3)	<0.001
Time on dialysis (year)[b]	0 (0–0.3)	0 (0–1.1)	<0.001
Dialysate calcium (mEq/l)	3.1 (0.4)	3.1 (0.6)	0.61
Weight (kg)	63.8 (14.3)	64.2 (14.2)	0.10
Calcium (mg per 100 ml)	9.1 (0.9)	9.1 (0.9)	<0.001
Body mass index (kg/m^2)	23.7 (4.7)	23.8 (4.6)	0.11
Phosphorus (mg per 100 ml)	5.0 (1.5)	4.9 (1.3)	<0.001
Calcium-Phosphorus product (mg^2 per (100 ml)^2)	45.6 (14.4)	44.6 (13.2)	<0.001
Parathyroid hormone (pg/ml)	213 (284)	421 (393)	<0.001
Parathyroid hormone (pg/ml)[b]	123 (57–247)	324 (169–534)	<0.001
Albumin (g per 100 ml)	3.7 (0.6)	3.7 (0.5)	<0.001
Total cholesterol (mg per 100 ml)	185 (53)	185 (50)	0.93
Hemoglobin (g per 100 ml)	9.1 (1.8)	9.6 (1.8)	<0.001
Ferritin (ng/ml)	433 (389)	449 (383)	0.044
Ferritin (ng/ml)[b]	320 (159–590)	340 (164–619)	0.019
Creatinine (mg per 100 ml)	7.8 (2.98)	8.2 (2.8)	<0.001
Kt/V[c]	1.37 (0.3)	1.3 (0.3)	<0.001
Calcium acetate (g)	66.3 (428.1)	81.7 (410.3)	0.48
Calcium acetate (g)[d]	25 (12–54)	32 (12–64)	<0.005
Calcium carbonate (g)	210 (1,454)	195 (1,324)	0.72
Calcium carbonate (g)[d]	30 (12–65)	49 (22–100)	<0.001
Aluminum hydroxide binders (g)	4.6 (9.6)	4.5 (7.0)	0.91
Aluminum hydroxide binders (g)[d]	1.0 (0.02–6)	1.0 (0.01–5)	0.73

[a]Baseline laboratory values represent the mean and standard deviation value over the 3 months before 90 days after initiating dialysis for the non-vitamin D group and the 3 months before initiating vitamin D therapy in the vitamin D group. The mean and standard deviation of baseline parathyroid hormone was obtained over 6 months.
[b]Baseline time on dialysis, parathyroid hormone and ferritin represent the median and interquartile range. In the case of the parathyroid hormone, the median and interquartile range were obtained over 6 months. A Mann–Whitney *U*-test has been made for comparison between groups.
[c]Delivered Kt/V=−ln ($R-0.008\times t$)+(4−3.5R) × UF/W, where R=post dialysis/pre dialysis blood urea nitrogen, t=dialysis hours, UF=pre dialysis-post dialysis weight change, and W=post dialysis weight.
[d]Calcium acetate, calcium bicarbonate, and aluminum hydroxide binders represent the median and interquartile range. A Mann–Whitney *U*-test has been made for comparison between groups. Calcium acetate and calcium bicarbonate as non-aluminic phosphate binders data were available in 4560 patients and aluminum hydroxide binders were available in 338 patients.

(14.6%); and Colombia (13.8%). The crude analysis using the Kaplan–Meier curve showed significant reduction of mortality risk in patients who received oral active vitamin D within 1 year compared to these who did not receive it ($P<0.001$, Figure 1). As the Figure 2 shows, the association of oral active vitamin D use with mortality reduction did not vary by country, including countries with both high and low overall death rates.

As primary exposure was time dependent and the Kaplan–Meier curve might have overestimated the survival benefit, additional analyses (models 2–5 in Table 2) were carried out after adjustment for potential confounders. There were no differences between the adjusted and unadjusted mortality risk among those patients who did and did not receive vitamin D therapy. Multivariable adjusted analyses revealed that patients who received oral active vitamin D had a significant 45% (hazard ratio, 0.55; 95% confidence interval (CI), 0.49–0.63) lower overall mortality risk compared to patients who did not receive oral active vitamin D (Table 2). Furthermore, cardiovascular, infectious, and neoplastic mortality risk were 45 (hazard ratio, 0.55; CI, 0.45–0.67), 48 (hazard ratio, 0.52; CI, 0.39–0.68), and 47% (hazard ratio, 0.53; CI, 0.34–0.82) lower, respectively, in patients on oral active vitamin D.

Similar results were observed when center instead of country was used as covariate in the multivariate analysis.

As once the patient was withdrawn from hemodialysis, no additional information about mortality was obtained, a

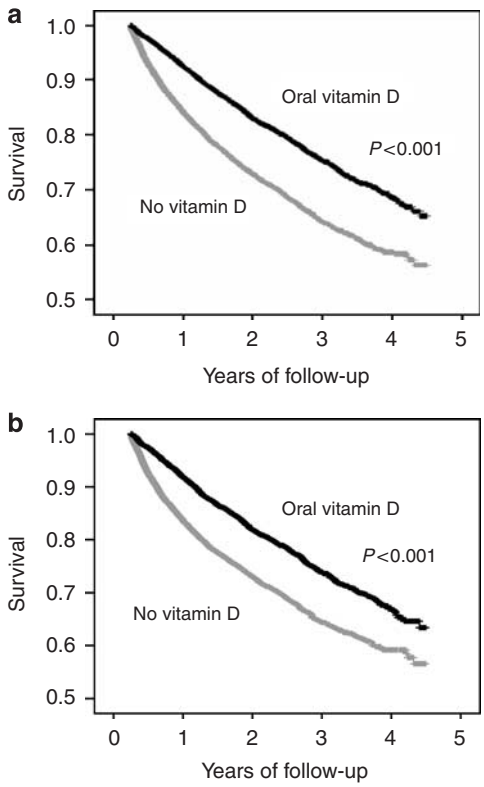

Figure 1 | Kaplan-Heier analysis of survival. (**a**) Survival curve of patients treated with oral active vitamin D (in dark; deaths, $n = 1280$; total number, $n = 7203$) compared with the untreated patients (in grey; deaths, $n = 1830$; total number, $n = 8801$). The crude analysis was carried out by the Kaplan–Meier curves. (**b**) Analysis restricted to those patients who started oral active vitamin D therapy within 90 days.

sensitivity analysis was carried out to examine the potential impact of the censored patients. The sensitive analysis revealed that censored patients (hazard ratio, 0.58; CI, 0.51–0.67) did not differ from those who were not censored (hazard ratio, 0.55; CI, 0.49–0.63) and the association of vitamin D with reduced mortality did not differ when participants were considered to have died at the time of censoring (hazard ratio, 0.58; CI, 0.53–0.65). The 244 patients censored, because they switched from oral active vitamin D to injectable active vitamin D, also showed a survival benefit (hazard ratio, 0.63; CI, 0.42–0.93).

The analysis of prevalent and incident hemodialysis patients showed also a significant reduction in the mortality risk rates in both groups. Overall mortality (hazard ratio, prevalent: 0.51; CI, 0.40–0.66 and hazard ratio, incident: 0.57; CI, 0.50–0.67), cardiovascular mortality (hazard ratio, prevalent: 0.59; CI, 0.40–0.88 and hazard ratio, incident: 0.53; CI, 0.42–0.67), infectious mortality (hazard ratio, prevalent: 0.61; CI, 0.37–1.02 and hazard ratio, incident: 0.50; CI, 0.38–0.75), and neoplastic mortality (hazard ratio, prevalent: 0.33, CI, 0.13–0.84 and hazard ratio, incident: 0.56; CI, 0.34–0.75). The association of vitamin D with reduced mortality was not altered when socioeconomic status was added to analyses in a subset of participants with available data ($n = 6961$ from Argentina).

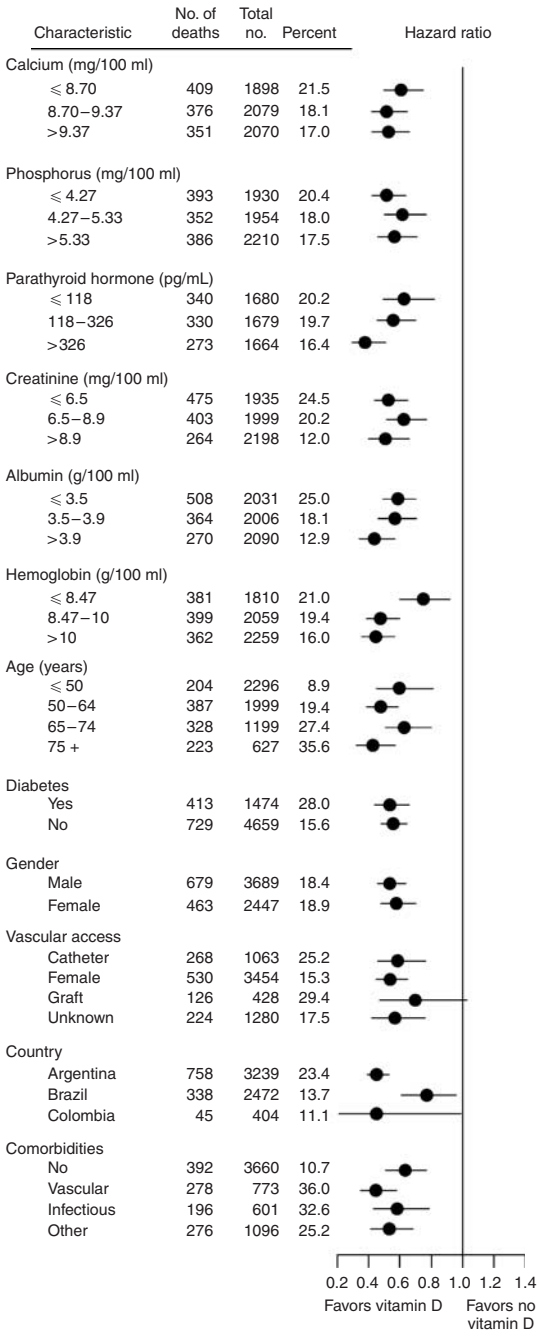

Figure 2 | Hazard ratios for mortality risk associated with oral active vitamin D treatment stratified by exposure characteristic. Each result reflects a multivariable adjusted model (age, gender, diabetes status, weekly hours on dialysis, Kt/V, center, baseline laboratory values, and comorbidity) according to Table 2. Percentage represents fraction of deaths within each stratum, circles represent the point estimates, and horizontal lines represent 95% confidence intervals. Reference category for each analysis is the corresponding group that did not receive oral active vitamin D.

Stratified analysis

As it has been mentioned, certain baseline characteristics differed between the two groups (Table 1). Patients who received oral active vitamin D treatment were 1.7 years

Table 2 | Cox proportional hazard analysis of mortality with oral vitamin D

Model	Covariates	No. of patients	Hazard ratio	95% confidence interval
1	Unadjusted	16,004	0.58	0.54–0.63
2	Age, gender, diabetes status, and time on dialysis	15,648	0.60	0.56–0.65
3	Model 2 plus Kt/V, and country	11,082	0.52	0.47–0.58
4	Model 3 plus vascular access, baseline values, and time-varying variables[a]	6136	0.58	0.51–0.65
5	Model 4 plus comorbidities	6136	0.55	0.49–0.63

Time-varying variables were serum calcium, phosphorus, and parathyroid hormone.
[a]The baseline values quoted were weight, albumin, creatinine, and hemoglobin.

younger with a 4.2% lower prevalence of diabetes. Other baseline characteristics such as body weight, serum creatinine, serum albumin, and serum hemoglobin levels were higher in patients who received oral active vitamin D treatment. In order to minimize the confounding effect of these baseline differences, we performed stratified analyses (Figure 2). Within each level of the stratified variables, the analysis was multivariable adjusted for all the potential confounders included in the final model shown in Table 2. In 36 of the 37 strata studied, we observed a significant survival advantage in the group that had received oral active vitamin D, including the stratum of patients with the highest serum calcium (tertile 3: >9.37 mg per 100 ml), phosphorus (tertile 3: >5.33 mg per 100 ml), and PTH levels (tertile 3: >326 pg/ml).

The stratification of the propensity score in tertiles confirmed a significant survival advantage in the group that had received oral active vitamin D (tertile 1—hazard ratio: 0.65, CI: 0.51–0.83; tertile 2—hazard ratio: 0.51, CI: 0.41–0.65; tertile 3—hazard ratio: 0.44, CI: 0.35–0.55).

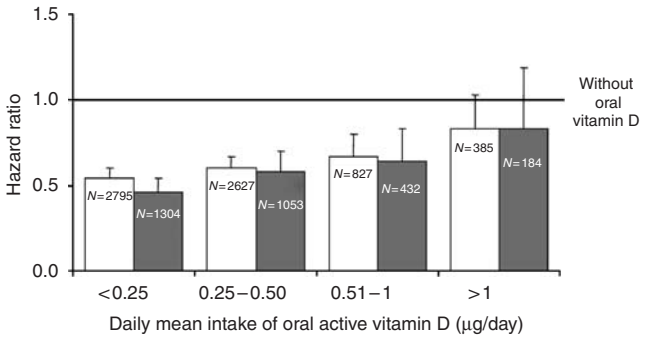

Figure 3 | Hazard ratio for mortality risk according to the different categories of daily mean intake of oral active vitamin D. This analysis was unadjusted (white bars) and adjusted by the covariates included in model 5 in Table 2 (grey bars). Reference category is the group that did not receive oral active vitamin D. The number of patients in each category of daily mean intake of oral active vitamin D was included in the columns. PTH median with interquartile range in the different categories of daily mean intake of oral active vitamin D (from lowest to highest dose) were 303 (182–462), 326 (149–539), 465 (255–724), and 491 (174–906) pg/ml, respectively.

Secondary analysis

To further examine the effect of different doses of oral active vitamin D, we analyzed the results of the four preestablished categories using unadjusted and adjusted analyses, using as covariates all those included in model 5 in Table 2. Patients who received oral active vitamin D in a mean daily dose lower than 0.25 μg, between 0.25–0.50 μg, and 0.51–1 μg showed a mortality reduction of 54% (hazard ratio, 0.46; CI, 0.39–0.54), 42% (hazard ratio, 0.58; CI, 0.49–0.70), and 36% (hazard ratio, 0.64; CI, 0.50–0.83), respectively. However, no significant reduction in mortality was observed with a mean daily dose higher than 1 μg (hazard ratio, 0.83; CI, 0.58–1.19; Figure 3). In the lower dose group (<0.25 μg) the cumulative dose was 78 μg and the duration of treatment was 540 days, meanwhile in the highest dose group (>1 μg) the cumulative dose was nine times higher (686 μg) and the duration of treatment shorter (314 days).

We also performed independent analyses in those patients whom the current clinical practice K/DOQI guidelines recommended the use of active vitamin D metabolites (baseline intact PTH >300 pg/ml and Calcium-Phosphorus product <55 mg^2 per (100 ml)^2).[9] A mean daily dose lower than 0.25 μg (mean 0.15 μg) and also a dose between 0.25 and 0.50 μg (mean 0.34 μg) significantly reduced the mortality risk rate by 55% (hazard ratio, 0.45; CI, 0.31–0.65) and by 60% (hazard ratio, 0.40; CI, 0.27–0.60), respectively, compared to oral active vitamin D nonusers. No significant reduction in mortality risk was found in patients receiving either a mean daily dose between 0.51 and 1 μg (mean 0.67; hazard ratio, 0.77; CI, 0.49–1.23) or a dose of more than 1 μg (mean 1.69; hazard ratio, 1.14; CI, 0.56–2.33). The analyses of prevalent and incident patients showed similar patterns; however, patients who started oral active vitamin D treatment within the first 90 days showed a slightly better results than patients who started the treatment later (hazard ratio, 0.57; CI, 0.48–0.68 vs hazard ratio, 0.74; CI, 0.62–0.87, respectively).

DISCUSSION

In the past few years, the detrimental or beneficial effect of active vitamin D treatment on the cardiovascular system and the risk of mortality has been a controversial issue. The concern about the harmful effect of vitamin D derivatives is mainly based on the fact that in experimental models high doses of vitamin D metabolites have shown to increase vascular calcifications[10,11] and some human data also support this notion.[12] On the other hand, experimental studies have shown that low and more physiological dose of active vitamin D may have a cardioprotective effect.[13,14] Observational

studies in patients on dialysis have also demonstrated morbidity[15] and a cardiovascular[16] or overall mortality advantage[8,17,18] for patients who are treated with active vitamin D derivatives vs those without treatment.

In addition, one epidemiological study reported a survival advantage when patients receiving new vitamin D analogs were compared to patients receiving an injectable calcitriol formulation.[19] However, this effect was less pronounced in a recent paper.[18] It was speculated that the potential survival advantage was mediated by the described less calcemic and phosphatemic effects of the new analogs, but the survival benefit was sustained for almost all levels of phosphorus and calcium.[18,19]

Although oral active vitamin D treatment is widely used, till date there is only one paper investigating survival using oral active vitamin D in a small cohort of patients.[16] The results of our study show for the first time a significant survival advantage of oral active vitamin D in a larger cohort of chronic hemodialysis patients. Similarly to others,[8] this advantage of oral active vitamin D appeared to be independent of other potential risk factors and confounders. In fact, the reduction in mortality risk was observed in 36 of the 37 multivariate strata analyzed, including baseline serum calcium, phosphorus, and PTH levels. The only stratum which did not achieve statistical significance was the one related to the use of grafts as vascular access, possibly due to the low number of patients.

Despite the potentially higher bioavailability of the injectable form of vitamin D compared to the oral form, our data show a higher reduction in the overall mortality risk compared to the results obtained with injectable active vitamin D.[8] The biological significance on survival benefit for oral active vitamin D users merits a detailed analysis.

The positive results in all causes of mortality suggest that the beneficial effect of active vitamin D is beyond its effect on calcium-phosphorus metabolism. In recent years, several experimental studies have demonstrated, among other actions, an important role of active vitamin D in the suppression of cell growth and regulation of immune response.[20,21] Moreover, nutritional and epidemiological evidence has linked abnormalities in the vitamin D system to susceptibility to infections, autoimmune diseases, and cancer.[22–24] Similarly in our study, neoplastic and infectious mortality were significantly reduced (47 and 48%, respectively) in patients receiving oral active vitamin D. Moreover, for neoplastic mortality risk this effect was more marked in patients who spent more time on dialysis (prevalent hemodialysis patients, 67%; incident hemodialysis patients, 44%), suggesting a long-term benefit of active oral vitamin D.

Besides these positive survival effects, the benefit of oral active vitamin D for the cardiovascular system is a controversial issue. It is well known that high doses of active vitamin D increase serum calcium and serum phosphorus, and also suppress serum PTH favoring through different mechanisms vascular calcification and mortality.[10–12,25,26] Conversely, physiological doses of active vitamin D have shown protective cardiovascular effects reducing the inflammatory response to cardiovascular injury, the myocardial cell hypertrophy and proliferation, and the renin-angiotensin system activation.[27] As it has been said, part of these paradoxical effects of vitamin D can be explained by the different dose of active vitamin D used. High pharmacological doses may favor and precipitate vascular calcifications whereas more physiological doses may have protective effects.

Our study shows that mean daily doses of oral active vitamin D lower than 1 μg showed a significant benefit in survival rate. Interestingly, the reduction in mortality risk was even seen at the lowest PTH tertile where a tendency to a higher mortality risk has been described,[28] and also, like others, with high serum and phosphorus levels.[19] In fact, a mean daily dose of oral active vitamin D lower than 0.25 μg was able to reduce the mortality risk by 53% in patients with PTH lower than 150 pg/ml (hazard ratio, 0.47; CI, 0.33–0.66) independently of serum calcium or phosphorus levels (data not shown). On the contrary, higher doses of oral active vitamin D did not have any effect in survival probably, in part, due to the increments in serum phosphorus levels observed in this group. In fact, during the whole follow-up period the mean phosphorus levels of the higher dose group was significantly higher (5.34 ± 1.24 mg per 100 ml) than the other groups. This fact may partially explain the greater survival benefit with intravenous paricalcitol compared to calcitriol found in previous studies.[19] Similarly, other authors have found a dose-dependent beneficial effect with paricalcitol with the lowest doses,[17] potency equivalent with the daily dose of our study. However, it is necessary also to consider that in our study the reduced number of patients in the higher dose group is a limitation in order to give a strong value to this finding.

There were some differences in the results obtained in incident and prevalent patients. Prevalent patients were younger (52 (16) vs 56 (16) years old) and obtained benefits in survival with doses of oral active vitamin D up to 1 μg per day, whereas in incident patients the beneficial effect was seen only up to 0.50 μg per day. In addition, prevalent patients also showed better outcomes regarding neoplastic mortality compared to incident patients. Regarding the doses, the whole set of results is consistent with the fact that lower doses which results in lower cumulative dose of oral active vitamin D are associated with more benefits in survival despite a more prolonged time of exposure.

The survival benefit of oral active vitamin D treatment were consistent in all centers and across countries despite the differences in mortality rates within each country described in the results.

Our study shows for the first time a survival beneficial effect of oral active vitamin D in a large cohort of hemodialysis patients followed up to 4 years, however, these interesting and encouraging results may have some limitations. It could have happened that patients with lower calcitriol and calcidiol serum levels were those who benefited most from oral active vitamin D treatment. Nevertheless,

even if this would have been the case, we still can claim a benefit of oral active vitamin D for all patients. Our study cannot rule out a possible influence of $25(OH)D_3$ (calcidiol) levels, a form of vitamin D that has—among others—also been related to improved outcomes.[29,30] The patients included in our study did not receive this form of vitamin D, and serum calcidiol and calcitriol levels were not measured. Calcidiol insufficiency has been reported worldwide but there are no studies evaluating mortality.

Although, at baseline the mean serum calcium and phosphorus was significantly higher and the PTH lower in the non-oral active vitamin D users, this fact is expected in studies of large populations even though the magnitude of the differences are small. Clinically relevant differences were only present when there were differences in PTH (Figure 2). In any case, these findings reflect that oral active vitamin D was adequately prescribed, as patients with moderately high levels of serum calcium and phosphorus and with no important serum PTH elevations did not receive oral active vitamin D treatment. In fact, the mean daily dose of oral active vitamin D used was related with the median serum PTH levels as stated in Figure 3.

We are also aware that some measured (Table 1) and unmeasured confounders (such as bone turnover markers, vascular calcification, inflammatory status, vitamin D receptor gene polymorphisms, or even socioeconomic status—only marginally addressed in this study), or other biases favoring the vitamin D-treated group cannot be completely excluded, despite the complete strata analysis carried out. Even considering the consistent results obtained using the propensity score, we cannot fully exclude some effect of confounding by indication, a common limitation in observational studies. In fact, the risk for confounding by indication may be increased by use of covariate data obtained at baseline rather than at the time of vitamin D initiation. Although a sensitivity analysis was carried out, it does not fully compensate the missing mortality data from part of the study population. Finally, even though it was not possible to standardize mortality, the adjustment by country and center should have balanced the results.

In summary, our study found that hemodialysis patients receiving oral active vitamin D showed a survival advantage. This biological benefit was seen after several stratified analyses, including different strata of calcium, phosphorus, and PTH levels and it seems to be inversely related to the vitamin D dose, observing a better survival with the lower doses.

MATERIALS AND METHODS

The study was performed in a historical cohort of chronic hemodialysis patients from six Latin American countries (Argentina, Brazil, Colombia, Chile, Mexico, and Venezuela) from the CORES study (Control of Renal Osteodystrophy in South America), who started hemodialysis, three times a week (98.8%) and two times a week (1.2%), in 183 different dialysis facilities associated or operated by Fresenius Medical Care. The entire study population ($n = 22,230$) consisted of patients older than 18 years who either initiated hemodialysis (incident patients—72.4% of the cohort) or were already on hemodialysis (prevalent patients—27.6% of the cohort) after 1 January 2000. Patients were followed for a period of time between 3 and 54 months (median 16 months) until 30 June 2004 or until they were lost to follow-up.

During the study period and once the patient was admitted to the hemodialysis center, demographic, clinical, laboratory, and other general data were collected prospectively and entered into a central database updated by medical personnel and stored by Fresenius Medical Care (FME register). From this database, the following data were analyzed: age, gender, weight, country, date of first dialysis, vascular access, primary cause of renal failure, dose of dialysis, medications administered during each hemodialysis session (name, date, dose, and route of administration), laboratory tests, and comorbidities occurring throughout the follow-up period. All missed hemodialysis treatments (for example, because of hospitalization or noncompliance) and all permanent discharges (for example, transplantation, voluntary withdrawal from therapy, transfer to a non-Fresenius dialysis unit, change to peritoneal dialysis, or lost to follow-up) were also analyzed. Deaths were defined using the International Classifications of Diseases (ICD-10) and they were grouped and classified according to the Table 3.

The non-aluminic phosphate binders used in this study were calcium acetate and calcium carbonate; neither sevelamer nor lanthanum carbonate were used. All the collected data were checked prospectively to ensure their accuracy and completeness. The study met the privacy standards implements by Fresenius with a waiver for informed consent.

Statistical analysis

Initial analysis. Between January 2000 and June 2004, 22,230 patients who initiated chronic hemodialysis in all the Fresenius dialysis facilities were included in the study. A total of 169 patients (0.8%) receiving only injectable active vitamin D or other formulations different to calcitriol ($1,25(OH)_2D_3$) or alphacalcidol ($1\text{-}\alpha(OH)D_3$) were excluded from the analysis. Therefore, this study includes only the analysis of patients receiving calcitriol or alphacalcidol referred in the paper as 'oral active vitamin D'. For the follow-up, data were censored if patients changed from oral active vitamin D to injectable active vitamin D type ($n = 244$), but not if vitamin D was interrupted or discontinued. Also 6057 (27.2%) patients who remained less than 90 days on chronic hemodialysis were excluded from the analysis. The reasons for these exclusions were: beginning of hemodialysis after April 2004 (41.8%); death (29.3%); switch to peritoneal dialysis (11.5%); recovery of renal function (7.1%); voluntary withdrawal from therapy (4.7%); unknown circumstances (3.3%); and renal transplantation (2.3%).

During the entire study period, 7203 (45.0%) of the 16,004 remaining patients received oral active vitamin D. Among them, 6962 patients (96.7%) received calcitriol (Rocaltrol, Roche Pharmaceuticals, Nutley, New Jersey, USA and Calcitriol Purissimus, Buenos Aires, Purissimus, Argentina), 212 patients (2.9%) were switched from calcitriol to alphacalcidol or vice versa and 29 patients (0.4%) received only alphacalcidol (Etalpha, Leo Pharma Inc., Plantation, Florida, US). Patients receiving oral active vitamin D for a period of less than 1 month ($n = 598$) were considered nonusers of oral active vitamin D for analysis purposes. Of patients who were treated with oral active vitamin D, 53% had started treatment within 90 days of initiating chronic hemodialysis, 69% within 180 days, and 85% within 365 days; the remaining 15% had started treatment after 1 year on hemodialysis. Oral active vitamin D exposure was studied as

Table 3 | International classification of diseases and related health problems (10th revision)

Vascular

Diseases of the circulatory system

- I05–I09 Chronic rheumatic fever
- I10–I15 Hypertensive diseases
- I20–I25 Ischemic heart diseases
- I26–I28 Pulmonary heart disease and disease of pulmonary circulation
- I30–I52 Other forms of heart disease
- I60–I69 Cerebrovascular diseases
- I70–I79 Diseases of arteries, arterioles, and capillaries

Infectious

Certain infectious and parasitic diseases

- A00–A09 Intestinal infectious diseases
- A15–A19 Tuberculosis
- A30–A49 Other bacterial diseases
- A50–A64 Infectious with a predominantly sexual mode of transmission
- A65–A69 Other spirochetal diseases
- A70–A74 Other diseases caused by chlamydiae
- A75–A79 Rickettsioses
- A80–A89 Viral infections of the central nervous system
- A90–A99 Arthropod-borne viral fevers and viral hemorrhagic lesions
- B00–B09 Viral infections characterized by skin and mucous membrane lesions
- B15–B19 Viral hepatitis
- B20–B24 Human immunodeficiency virus (HIV) disease
- B25–B34 Other viral diseases
- B35–B49 Mycoses
- B50–B64 Protozoal diseases
- B65–B83 Helminthiases
- B90–B94 Sequelae of infectious and parasitic diseases

Diseases of the respiratory system

- J00–J06 Acute upper respiratory infections
- J09–J18 Influenza and pneumonia
- J20–J22 Other acute lower respiratory infectious

Diseases of the skin and subcutaneous tissue

- L00–L08 Infectious of the skin and subcutaneous tissue

Diseases of the musculoskeletal system and connective tissue

- M00–M03 Infectious arthropathies

Diseases of the genitourinary system

- N70–N77 Inflammatory diseases of female pelvic organs

Neoplastic

Neoplams

- C00–C75 Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, hematopoietic, and related tissue
- C76–C80 Malignant neoplasms of ill-defined, secondary, and unspecified sites
- C81–C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic, and related tissue
- D00–D09 In sity neoplasms
- D10–D36 Benign neoplasms
- D37–D48 Neoplasms of uncertain or unknown behavior

Neurological

Diseases of the nervous system

- G00–G09; G20–G26; G30–G32; G35–G37; G40–G47; G60–G64; G80–G83; G90–G99

Respiratory

Diseases of the respiratory system

- J30–J39; J40–J47; J60–J70; J80–J84; J90–J94; J95–J99

Diabetes

Endocrine, nutritional and metabolic diseases

- E10–E14 Diabetes mellitus

a time-dependent variable in all analyses. In this manner, if a patient initiated oral active vitamin D treatment 1 year after initiating the study, then the 1-year survival before starting therapy was credited to the group with no treatment. Furthermore, once a patient received oral active vitamin D for more than 1 month, the patient remained in the active oral vitamin D group for all further analyses regardless of the number of doses of oral active vitamin D received and regardless of any changes in serum calcium and phosphorus that may have resulted from the oral active vitamin D administration. The mean time of oral active vitamin D exposure was 13 months.

In order to assure compliance, centers provided the oral active vitamin D to each individual patient and ensured that patients swallowed it at the end of the hemodialysis session.

Standard univariate analyses (χ^2, *t*-tests, and Mann–Whitney *U*-test) were performed, and values were reported as percentages, mean and standard deviation or median, and the interquartile range for descriptive purposes. The primary analysis used both, the Kaplan–Meier curves to examine crude survival and the Cox proportional hazard ratios to estimate mortality rate ratios for oral vitamin D users vs nonusers. Patients contributed as person-time until they underwent kidney transplantation, voluntarily withdrew from chronic hemodialysis, or reached the end of the follow-up period, whichever occurred first. Stratum-specific hazard ratios were examined to test whether there was a statistically significant effect in each stratum. The Cox model included the following baseline variables: age, gender, history of diabetes, time on dialysis, vascular access, weight, blood levels of albumin, hemoglobin, creatinine, and delivered dose of dialysis (Kt/V). To provide a better estimate of exposure, average of baseline laboratory values were obtained from all data recorded within the 3 months prior to the follow-up.

Serum levels of calcium, phosphorus, and PTH (the latter measured by the Nichols Advantage Chemiluminescence intact assay) were included in the Cox model as time-dependent variables. Serum calcium, phosphorus, and PTH reflected baseline levels for patients who did not receive oral active vitamin D, whereas for patients who received it, the calcium, phosphorus, and PTH levels included in the model were those collected before the initiation of therapy.

In order to account for a possible country effect on the mortality rate, all the analyses were carried out after adjusting them by country. Comorbidities were classified according to the ICD-10 and grouped into vascular, neoplastic, infectious, respiratory, neurological, or diabetes according to the Table 3.

Furthermore, in order to get an unbiased estimate of the treatment effects, we obtained propensity scores in logistic regression models using as covariates the differences in baseline characteristics. We divided the cohort in tertiles of propensity scores and examined the hazard ratio for mortality risk associated with oral active vitamin D treatment.

Secondary analysis. In addition to the study of oral active vitamin D intake as a dichotomous variable (yes vs no), the mean daily intake (total cumulative dose of vitamin D divided by the number of days on dialysis) of oral active vitamin D was analyzed and subdivided into four categories: less than a mean of 0.25 μg per day, between 0.25 and 0.50 μg per day, between 0.51 and 1 μg per day, and more than 1 μg per day. These categories were used to evaluate the relationship between the dose of oral active vitamin D and mortality.

All analyses of the data were carried out using SPSS version 12.0 for Windows.

DISCLOSURE

M Naves-Díaz (none), D Álvarez-Hernández (none), J Passlick-Deetjen (employee of Fresenius Medical Care), A Guinsburg (employee of Fresenius Medical Care), C Marelli (employee of Fresenius Medical Care), D Rodriguez-Puyol (none), JB Cannata-Andía (none).

ACKNOWLEDGMENTS

Language consultant was Marino Santirso Ruiz.
We thank the following CORES study participating centers—*FME Argentina*: Avellaneda, Bahia Blanca – Brown, Bahia Blanca - Hospital Español, Bahia Blanca – Pringles, Berazategui, Buenos Aires, Burzaco, Caballito, Cemic, Cemic – Saavedra, Chaco – Frangioli, Chaco – Resistencia, Chaco – Saenz Peña, Ciudad Evita, Ciudadela, Concepción de Tucumán, Concepción del Uruguay, Concordia, Cordoba 1, Córdoba 2, Corrientes, Corrientes – Bella Vista, Curuzú Cuatiá, Diagnóstico, Escobar, Florencio Varela, Florida, Formosa, General Roca, Gualeguaychú, Hospital Italiano, Hospital Alemán, Hospital San Bernardo, La Entrerriana, La Plata, Lomas, Mansilla, Martínez, Mendoza 1, Mendoza 2, Mendoza – Pelegrina, Mendoza – Rivadavia, Mendoza – Tunuyán, Merlo 1, Merlo 2, Monte Grande, Moreno, Morón, Necochea, Neuquén, Zapala, Patricios, Pilar, Posadas, Posadas IOT, Quilmes 1, Quilmes 2, Rosario, Rosario – Sanatorio Plaza, Salta, Rosario De La Frontera, San Fernando, San Justo, San Luis, San Martín de los Andes, Tres De Febrero, Tucumán 1, Tucumán 2, San Rafael, Santa Fe, Santa Fe – San Justo, Santa Fe – Reconquista, Santiago del Estero, Venado Tuerto, Villa Adelina, Villa Mercedes, Villa Regina. *FME Brasil*: CDR Anil – Rio de Janeiro – RJ, CDR Cascadura – Rio de Janeiro – RJ, CDR Botafogo – Rio de Janeiro – RJ, CDR IUN – Niterói – RJ, CDR São Lourenço – Niterói – RJ, CDR Rio Bonito – Rio Bonito – RJ, CDR São João de Meriti – São João de Meriti – RJ, CDR Nova Iguaçu – Nova Iguaçu – RJ, CDR Barra do Pirai – Barra do Pirai – RJ, CDR Barra Mansa – Barra Mansa – RJ, CDR Três Rios – Três Rios – RJ, CDR Paraíba do Sul – Paraíba do Sul – RJ, CDR Macaé – Macaé – RJ, Clinefron – Pádua – RJ, Nove de Julho – São Paulo – SP, Cetene – São Paulo – SP, Clínica Campinas – Campinas – SP, Neonefro – Atibaia – SP, Neonefro – Indaiatuba – SP, IMN – Belo Horizonte – MG, Nephron Brasília – Brasilia – DF, Nephron Mix Park – Brasilia – DF, Nephron Taguatinga – Brasilia – DF, Clínica São Marcos – Salvador – BA, Hemovida – Alagoinha – BA, Clinefro – Teresina – PI, Unirim – Parnaíba – PI, Nefroclínica – Recife – PE, Clínica do Rim – Petrolina – PE, Prorim – Aflitos – PE, Prontorim (Álvaro Weine) – Fortaleza – CE, Prorim (Santa Casa) – Fortaleza – CE, Pronefron – Fortaleza – CE. *FME Chile*: Nephrocare Barcelona, Nephrocare La Florida, Nephrocare La Serena. *FME Colombia*: Armenia, Blas de Lezo, Bocagrande, Cedial Cabecera Bucaramanga, Cedial Foscal Bucaramanga 1, Cedial Foscal Bucaramanga 2, Centro Bosque Medirenal, Clínica de los Andes, Clinica de Occidente 1, Clinica De Occidente 2, Cúcut, Dializar, Fray Bartolomé, Hospital San Vicente de Paul, Hospital Universitario, Imbanaco, Instituto del Riñón, Medirrenal Horizonte, Neiva, San José, Sincelejo, Unidad Renal Ibague, Unidad Renal Popayán, Unirenal. *FME México*: Medica Sur. *FME Venezuela*: Cabimas, Charavalle, Dpac – Cenesuca, Dpac – El Tigre, Dpac – Idu Valencia, Dpac – Los Cedros, Dpac – Maracaibo, Dpac – Maturin, Dpac – Puerto La Cruz, Dpac – Jnazart Maracay, El Tigre, Hemodialisis Cenesuca, Jnazart Caracas, Jnazart Maracay, Los Cedros, Madre Emilia, Majestic, Maracaibo Ctro Del Sol, Romulo Gallegos, Valencia. *Sources of support*: This work was supported in part by Fondo de Investigaciones Sanitarias (FIS 04/1567), Fundación para el Fomento en Asturias de la Investigación Científica Aplicada y la Tecnología (FICYT IB 05-060), and Instituto Reina Sofía de Investigación. Daniel Álvarez-Hernández was supported by a grant from Fondo de Investigaciones Sanitarias (FIS, BEFI 00099/03) and by ISCIII-Retic-RD06, REDinREN (16/06).

REFERENCES

1. Llach F, Yudd M. Pathogenic, clinical, and therapeutic aspects of secondary hyperparathyroidism in chronic renal failure. *Am J Kidney Dis* 1998; **32**(Suppl 2): S3–S12.

2. Slatopolsky E, Brown A, Dusso A. Pathogenesis of secondary hyperparathyroidism. *Kidney Int Suppl* 1999; **73**: S14–S19.
3. Ishimura E, Nishizawa Y, Inaba M *et al.* Serum levels of 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in nondialyzed patients with chronic renal failure. *Kidney Int* 1999; **55**: 1019–1027.
4. Salusky IB, Goodman WG. Cardiovascular calcification in end-stage renal disease. *Nephrol Dial Transplant* 2002; **17**: 336–339.
5. Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. *Recent Results Cancer Res* 2003; **164**: 371–377.
6. Tangpricha V, Flanagan JN, Whitlatch LW *et al.* 25-hydroxyvitamin D-1alpha-hydroxylase in normal and malignant colon tissue. *Lancet* 2001; **357**: 1673–1674.
7. Haug C, Muller F, Aukrust P *et al.* Subnormal serum concentration of 1,25-vitamin D in human immunodeficiency virus infection: correlation with degree of immune deficiency and survival. *J Infect Dis* 1994; **169**: 889–893.
8. Teng M, Wolf M, Ofsthun MN *et al.* Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol* 2005; **16**: 1115–1125.
9. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; **42**(Suppl 3): S1–S201.
10. Henley C, Colloton M, Cattley RC *et al.* 1,25-Dihydroxyvitamin D3 but not cinacalcet HCl (Sensipar/Mimpara) treatment mediates aortic calcification in a rat model of secondary hyperparathyroidism. *Nephrol Dial Transplant* 2005; **20**: 1370–1377.
11. Lopez I, Aguilera-Tejero E, Mendoza FJ *et al.* Calcimimetic R-568 decreases extraosseous calcifications in uremic rats treated with calcitriol. *J Am Soc Nephrol* 2006; **17**: 795–804.
12. Mallick NP, Berlyne GM. Arterial calcification after vitamin-D therapy in hyperphosphatemic renal failure. *Lancet* 1968; **2**: 1316–1320.
13. Wu J, Garami M, Cheng T *et al.* 1,25(OH)2 vitamin D3, and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes. *J Clin Invest* 1996; **97**: 1577–1588.
14. O'Connell TD, Berry JE, Jarvis AK *et al.* 1,25-Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation and hypertrophy. *Am J Physiol* 1997; **272**(Pt 2): H1751–H1758.
15. 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.
16. 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.
17. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006; **70**: 771–780.
18. Tentori F, Hunt WC, Stidley CA *et al.* Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 2006; **70**: 1858–1865.
19. 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.
20. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol* 2005; **289**: F8–F28.
21. Tangpricha V, Spina C, Yao M *et al.* Vitamin D deficiency enhances the growth of MC-26 colon cancer xenografts in Balb/c Mice. *J Nutr* 2005; **135**: 2350–2354.
22. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr* 2003; **89**: 552–572.
23. Garland C, Shekelle RB, Barrett-Connor E *et al.* Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* 1985; **1**: 307–309.
24. Kumagai T, O'Kelly J, Said JW *et al.* Vitamin D2 analog 19-nor-1,25-dihydroxyvitamin D2: antitumor activity against leukemia, myeloma, and colon cancer cells. *J Natl Cancer Inst* 2003; **95**: 896–905.
25. 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.
26. Qunibi WY, Nolan CA, Ayus JC. Cardiovascular calcification in patients with end-stage renal disease: a century-old phenomenon. *Kidney Int Suppl* 2002: **82**: 73–80.
27. Levin A, Li YC. Vitamin D and its analogues: do they protect against cardiovascular disease in patients with kidney disease? *Kidney Int* 2005; **68**: 1973–1981.
28. Guh JY, Chen HC, Chuang HY *et al.* Risk factors and risk for mortality of mild hypoparathyroidism in hemodialysis patients. *Am J Kidney Dis* 2002; **39**: 1245–1254.
29. Watson KE, Abrolat ML, Malone LL *et al.* Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation* 1997; **96**: 1755–1760.
30. Cannata-Andia JB, Rodriguez-Garcia M, Carrillo-Lopez N *et al.* Vascular calcifications: pathogenesis, management and impact on clinical outcomes. *J Am Soc Nephrol* 2006; **17**(Suppl 3): S267–S273.