

ORIGINAL ARTICLE

# Survival of Patients Undergoing Hemodialysis with Paricalcitol or Calcitriol Therapy

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## ABSTRACT

### BACKGROUND

Elevated calcium and phosphorus levels after therapy with injectable vitamin D for secondary hyperparathyroidism may accelerate vascular disease and hasten death in patients undergoing long-term hemodialysis. Paricalcitol, a new vitamin D analogue, appears to lessen the elevations in serum calcium and phosphorus levels, as compared with calcitriol, the standard form of injectable vitamin D.

### METHODS

We conducted a historical cohort study to compare the 36-month survival rate among patients undergoing long-term hemodialysis who started to receive treatment with paricalcitol (29,021 patients) or calcitriol (38,378 patients) between 1999 and 2001. Crude and adjusted survival rates were calculated and stratified analyses were performed. A subgroup of 16,483 patients who switched regimens was also evaluated.

### RESULTS

The mortality rate among patients receiving paricalcitol was 3417 per 19,031 person-years (0.180 per person-year), as compared with 6805 per 30,471 person-years (0.223 per person-year) among those receiving calcitriol ( $P<0.001$ ). The difference in survival was significant at 12 months and increased with time ( $P<0.001$ ). In the adjusted analysis, the mortality rate was 16 percent lower (95 percent confidence interval, 10 to 21 percent) among paricalcitol-treated patients than among calcitriol-treated patients. A significant survival benefit was evident in 28 of 42 strata examined, and in no stratum was calcitriol favored. At 12 months, calcium and phosphorus levels had increased by 6.7 and 11.9 percent, respectively, in the paricalcitol group, as compared with 8.2 and 13.9 percent, respectively, in the calcitriol group ( $P<0.001$ ). The two-year survival rate among patients who switched from calcitriol to paricalcitol was 73 percent, as compared with 64 percent among those who switched from paricalcitol to calcitriol ( $P=0.04$ ).

### CONCLUSIONS

Patients who receive paricalcitol while undergoing long-term hemodialysis appear to have a significant survival advantage over those who receive calcitriol. A prospective, randomized study is critical to confirm these findings.

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**T**HE ONE-YEAR MORTALITY RATE AMONG patients undergoing hemodialysis in the United States approaches 20 percent, and mortality rates among patients undergoing hemodialysis at every age exceed the rates among those not undergoing hemodialysis.<sup>1,2</sup> Methods to improve survival include increased doses of dialysis,<sup>3,4</sup> improved nutrition,<sup>5</sup> and management of anemia,<sup>6</sup> but the mortality rates remain high, despite considerable efforts targeting these factors.<sup>7</sup> Cardiovascular disease is the predominant cause of dialysis-related mortality.<sup>2</sup> Recently, the effect of secondary hyperparathyroidism and its management on vascular disease has garnered substantial attention.<sup>8-12</sup> Parenteral vitamin D effectively suppresses parathyroid hormone secretion and is therefore standard therapy for secondary hyperparathyroidism.<sup>13,14</sup> Yet such vitamin D administration often results in elevated calcium and phosphorus levels, which may accelerate vascular disease and hasten death.<sup>9,12,15,16</sup>

In 1998, paricalcitol (19-nor-1,25-dihydroxyvitamin D<sub>2</sub>) was approved for the treatment of hyperparathyroidism due to chronic renal failure. Paricalcitol suppresses parathyroid hormone faster than calcitriol.<sup>17</sup> When the appropriate dose is used, paricalcitol is associated with smaller changes in serum calcium and phosphorus than is calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>),<sup>18</sup> the standard form of injectable vitamin D used worldwide. Paricalcitol also suppresses parathyroid hormone levels in patients with substantially elevated phosphorus levels, a subgroup typically resistant to calcitriol.<sup>14,18</sup> Given the differences between these formulations and the associations of hyperparathyroidism, hyperphosphatemia, hypercalcemia, and an elevated calcium-phosphate product (the product of the calcium and phosphorus concentrations) with vascular disease and death,<sup>8,9,11,19,20</sup> we examined the survival rate at 36 months among 67,399 patients undergoing long-term hemodialysis who were treated with paricalcitol or calcitriol.

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## METHODS

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### STUDY POPULATION

We performed a historical cohort study of patients undergoing long-term hemodialysis at the U.S.-based dialysis facilities of Fresenius Medical Care North America. The primary study population consisted of all patients who started receiving treatment with paricalcitol (Zemplar, Abbott Laboratories) or calcitriol (Calcijex, Abbott Laboratories) on or after

January 1, 1999, and who were treated exclusively with that injectable vitamin D formulation until they died, their data were censored (when they switched to another vitamin D formulation, underwent renal transplantation, or transferred to another facility), or the end of the study period on December 31, 2001. Patients who had received any form of injectable vitamin D before January 1, 1999, were excluded. Among those who switched formulations during the study period, survival after switching was also examined. During the study period, Fresenius Medical Care distributed management guidelines that included a target value for intact parathyroid hormone of less than 300 pg per milliliter and a target value for the calcium-phosphate product of less than 70. Specific therapies to achieve these goals were not suggested, no policy was in place to use one vitamin D formulation preferentially, and clinical data had not suggested a survival benefit for any one formulation. Just before this study, a 4:1 dosing ratio of paricalcitol to calcitriol had been suggested in the literature.<sup>21</sup> This study met the privacy standards implemented by Fresenius. It was approved by the institutional review board of the Massachusetts General Hospital with a waiver for informed consent.

### ASCERTAINMENT OF EXPOSURES, OUTCOMES, AND COVARIATES

During the study period, demographic and laboratory information was collected prospectively and entered into a central data base updated and stored by Fresenius. No additional data were retrospectively abstracted from medical records. On a patient's admission to a dialysis facility, demographic information, including age, sex, race, date of first dialysis session, primary cause of renal failure, and diabetes status, was recorded. Data were collected on the hemodialysis prescription, laboratory tests, hospitalization, death, and medications administered during each hemodialysis session (name, date, dose, and route of administration). Test results from a central laboratory were automatically downloaded to the data base, minimizing data-entry errors. Records of all medications administered during each hemodialysis session undergo regular quality assessment and control measures because of their link with billing systems. All missed hemodialysis treatments, whether expected (e.g., because of hospitalization) or unexpected (e.g., because of non-compliance) and all permanent discharges (e.g., because of transplantation or death), together with

**Table 1. Base-Line Characteristics According to Vitamin D Therapy.\***

Characteristic	Paricalcitol (N=29,021)	Calcitriol (N=38,378)	P Value
Mean age (yr)	60.7	61.3	<0.01
Male sex (% of patients)	52	53	<0.01
Race (% of patients)			<0.01
White	53	55	
Black	39	36	
Other	8	9	
Diabetes (% of patients)	48	49	<0.01
Glycosylated hemoglobin (%)†	6.8	6.8	0.23
Primary cause of renal failure (% of patients)			<0.01
Diabetes	36	37	
Hypertension	38	36	
Glomerulonephritis	11	11	
Other	15	16	
Duration of dialysis (days)	620	530	<0.01
Vascular access (% of patients)			<0.01
Fistula	21	19	
Graft	27	26	
Catheter	23	21	
Unknown	29	34	
Body-mass index‡	28.6	28.4	<0.01
Body-surface area (m <sup>2</sup> )	1.87	1.85	<0.01
Blood pressure (mm Hg)			
Systolic	149	149	0.92
Diastolic	79	78	<0.01
Albumin (g/dl)	3.7±1.0	3.6±0.5	<0.01
Calcium (mg/dl)	8.7±0.8	8.5±0.9	<0.01

diagnoses coded according to the *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)*,<sup>22</sup> were recorded to complete the daily reconciliation of prescribed and administered treatments.

Base-line laboratory values were obtained by averaging all values obtained within three months before the date of evaluation. Quintiles of serum calcium and phosphorus levels were determined by aggregating the values for all patients. Fresenius used the same assay for intact parathyroid hormone measurements (Nichols Advantage Chemilumines-

cence) throughout the study period. Because of known lot-to-lot drifts in this assay, serum levels of parathyroid hormone were categorized according to yearly quintiles, and comparative quintiles across years were combined for the analysis.

The duration of dialysis was defined as the number of days from the initiation of long-term hemodialysis to the starting date of treatment with paricalcitol or calcitriol. To adjust for center-specific effects that may have contributed to survival differences, the models included the standardized mortality rates for each dialysis center.<sup>1,7</sup> The stand-

<b>Table 1. (Continued.)</b>			
<b>Characteristic</b>	<b>Paricalcitol (N=29,021)</b>	<b>Calcitriol (N=38,378)</b>	<b>P Value</b>
Phosphorus (mg/dl)	5.6±1.6	5.3±1.5	<0.01
Calcium–phosphate product	49±15	45±14	<0.01
Parathyroid hormone (pg/ml)	496±364	413±336	<0.01
Alkaline phosphatase (U/liter)	128±92	129±100	0.06
Cholesterol (mg/dl)			
Total	169±45	170±47	0.09
Low-density lipoprotein§	93±35	93±36	0.80
Hemoglobin (g/dl)	10.8±1.5	10.7±1.6	<0.01
Ferritin (ng/ml)	382±424	364±437	<0.01
White-cell count (mm <sup>-3</sup> )	8±3	8±3	0.57
Bicarbonate (mmol/liter)	21±4	20±4	<0.01
Creatinine (mg/dl)	7.8±3.2	7.6±3.1	<0.01
Dialysate calcium (mEq/liter)	2.66	2.67	<0.01
Urea reduction ratio (%)¶	67±9	67±10	0.08

\* Plus–minus values are means ±SD. Base-line laboratory values represent the mean value during the three months before initiation of treatment with injectable vitamin D. To convert the values for calcium to millimoles per liter, multiply by 0.250; to convert the values for phosphorus to millimoles per liter, multiply by 0.3229; to convert values for total and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586; to convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for dialysate calcium to millimoles per liter, multiply by 0.5.

† Data on glycosylated hemoglobin were available for 7513 patients.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Data on low-density lipoprotein cholesterol were available for 4134 patients.

¶ The urea reduction ratio, a measure of the adequacy of dialysis, is calculated as  $100 \times [1 - (\text{postdialysis blood urea nitrogen} \div \text{predialysis blood urea nitrogen})]$ .

ardized mortality rate was defined as a facility-specific, case-mix–adjusted mortality rate relative to all Fresenius dialysis centers throughout the United States. The standardized mortality rate was used to adjust for between-center variations in survival that were not accounted for by the typical explanatory variables, such as differences in nutritional status and adequacy of dialysis. In this study, more than 1000 dialysis centers were represented. The study entry period, defined as the calendar quarter during which a patient initiated vitamin D therapy, was examined as a measure of unknown confounding related to improvements in clinical practice over time.

#### STATISTICAL ANALYSIS

Standard univariate analyses (chi-square and t-tests) were performed, and values are reported as means ±SD for descriptive purposes. Mortality rates were calculated by dividing the number of patients who died during the follow-up period by the number

of person-years of observation. The Kaplan–Meier method was used to examine crude survival, and Cox proportional-hazards regression analysis was used to adjust for potential confounders. The primary analysis of survival included all patients; data were censored at the time of transfer to a non-Fresenius facility, kidney transplantation, or switch to another vitamin D formulation. Hazard ratios for death with 95 percent confidence intervals were calculated for patients treated with paricalcitol; patients treated with calcitriol served as the reference category in all analyses. Stratum-specific hazard ratios were examined to test for effect modification. Treatment-specific hazard ratios were calculated according to quintiles of base-line serum calcium, phosphorus, and parathyroid hormone levels. Follow-up analyses included laboratory values and data on subsequent survival for patients who switched from one vitamin D formulation to the other. All reported P values are based on two-sided tests.

## RESULTS

## BASE-LINE CHARACTERISTICS

Between January 1, 1999, and December 31, 2001, treatment with injectable vitamin D was initiated in 69,492 patients undergoing dialysis in Fresenius facilities. Of these, 67,399 (97 percent) were initially treated with paricalcitol or calcitriol and served as the primary study population (Table 1). Patients receiving paricalcitol were more likely than those receiving calcitriol to be black and to have arteriovenous fistulas for vascular access, and they were less

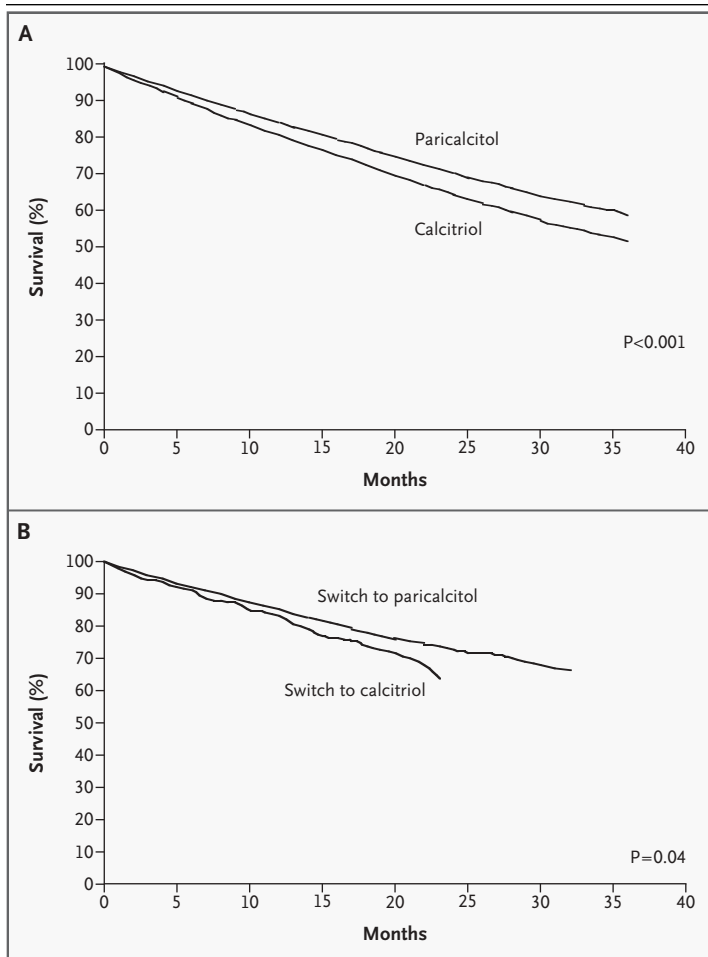
likely to have diabetes. Patients receiving paricalcitol also had higher base-line serum levels of calcium, phosphorus, and parathyroid hormone. Base-line measures of glucose control (for patients with diabetes), systolic blood pressure, lipids, and the adequacy of dialysis (as indicated by the urea reduction ratio) were similar in the two groups. The rate of hospitalization in the year before vitamin D therapy was started was similar in the two groups (28.1 percent in the paricalcitol group and 27.9 percent in the calcitriol group,  $P=0.38$ ), whereas the percentage of patients with unexpected absences from dialysis differed significantly (8.2 percent in the paricalcitol group vs. 7.3 percent in the calcitriol group,  $P<0.001$ ).

## CRUDE AND ADJUSTED SURVIVAL RATES

During the 36-month follow-up period, the mortality rates differed between the groups: among patients receiving paricalcitol, there were 3417 deaths during a total of 19,031 person-years of observation (0.180 per person-year), as compared with 6805 deaths during 30,471 person-years (0.223 per person-year) among those receiving calcitriol (rate ratio, 0.80; 95 percent confidence interval, 0.77 to 0.84;  $P<0.001$ ). The differences in survival were apparent within 12 months and continued to increase with time ( $P<0.001$ ) (Fig. 1A). Analysis of survival differences according to the year of study entry showed similar results (data not shown). The rates of death from specific causes (according to the ICD-9-CM classification) among patients receiving calcitriol and paricalcitol, respectively, were 0.128 and 0.106 per person-year from cardiovascular disease, 0.021 and 0.016 per person-year from infection, and 0.075 and 0.057 per person-year from other causes. Cox proportional-hazards regression analyses demonstrated that a notable change in the effect estimate occurred after adjustment for the period of study entry (Table 2). After further adjustments, the survival advantage associated with paricalcitol treatment was 16 percent (95 percent confidence interval, 10 to 21 percent). In the final model, in addition to therapy with paricalcitol, independent predictors of survival included serum albumin, calcium, and phosphorus levels ( $P<0.001$  for each variable).

## STRATIFIED MODELS

On formal testing for effect modification, the survival benefit of paricalcitol did not vary with any of the covariates tested. Nonetheless, we performed strat-



**Figure 1.** Kaplan–Meier Analysis of Survival According to the Type of Vitamin D Therapy.

Panel A shows the survival of patients treated with either paricalcitol or calcitriol who received the same therapy for the duration of the follow-up. Panel B shows the survival of patients who switched from calcitriol to paricalcitol or from paricalcitol to calcitriol during the follow-up period. The time of switching was approximately 900 days after the initiation of dialysis for both groups. P values were calculated with the use of the log-rank test.

ified analyses to determine whether the effect estimate was consistent across multiple strata (Fig. 2). In 28 of 42 strata, paricalcitol conferred a significant survival benefit, and in no stratum was calcitriol therapy favored.

The hazard ratios for death according to base-line quintiles of calcium, phosphorus, and parathyroid hormone differed between the groups (Fig. 3). The Cox models were adjusted for potential confounders (Table 2), and within each model, nine (n-1) covariates for the interaction between treatment and quintile were included. Within each quintile, the risk of death was lower in the paricalcitol group. Most notable was a significantly lower risk of death at all levels of serum calcium and parathyroid hormone.

**FOLLOW-UP ANALYSIS**

During 12 months of follow-up, the mean hemoglobin levels and urea reduction ratios were similar in the two groups (data not shown). The mean percent changes from base line in the levels of calcium, phosphorus, and parathyroid hormone are shown in Table 3. Three, 6, and 12 months after the initiation of vitamin D therapy, the mean (±SD) doses of paricalcitol per administration were 4.2±2.5, 4.3±2.7, and 4.3±2.8 µg, respectively, and the average doses of calcitriol per administration were 1.0±0.7, 1.1±1.0, and 1.3±1.2 µg, respectively. In a multivariate analysis stratified according to the vitamin D formulation, an increase in the dose of either formulation was not associated with a significant survival advantage or disadvantage (data not shown).

During the follow-up period, the frequency of unexpected absence from dialysis was similar in the two groups (16.1 percent in the paricalcitol group and 15.9 percent in the calcitriol group, P=0.35); however, the rates of transplantation differed (3.8 percent in the paricalcitol group and 3.3 percent in the calcitriol group, P<0.001). Ten percent of patients (6684 patients) terminated their initial vitamin D therapy more than one month before leaving the study (data censored or patient died) and did not initiate treatment with another injectable formulation. Removing these patients from the analysis did not appreciably change the effect estimates (data not shown). Finally, in a subgroup of patients who switched formulations, the 14,862 patients who switched from calcitriol to paricalcitol had a higher subsequent rate of two-year survival than the 1621 who switched from paricalcitol to

**Table 2. Multivariable Cox Proportional-Hazards Models Examining Hazard Ratios Associated with Paricalcitol Treatment as Compared with Calcitriol Treatment.\***

Model	No. of Patients	Hazard Ratio	95% Confidence Interval
Unadjusted	67,399	0.81	0.78–0.85
Adjusted			
Age, sex, race, diabetes status, and duration of dialysis	66,950	0.86	0.82–0.89
Age, sex, race, diabetes status, duration of dialysis, and study-entry period	66,950	0.90	0.86–0.95
Age, sex, race, diabetes status, duration of dialysis, study-entry period, and SMR†	66,950	0.89	0.85–0.94
Age, sex, race, diabetes status, duration of dialysis, study-entry period, SMR, and dialysis access	66,950	0.89	0.85–0.93
Age, sex, race, diabetes status, duration of dialysis, study-entry period, SMR, dialysis access, and base-line laboratory values‡	30,012	0.84	0.79–0.90

\* All categories for each covariate were included in the model. P<0.001 for each comparison.

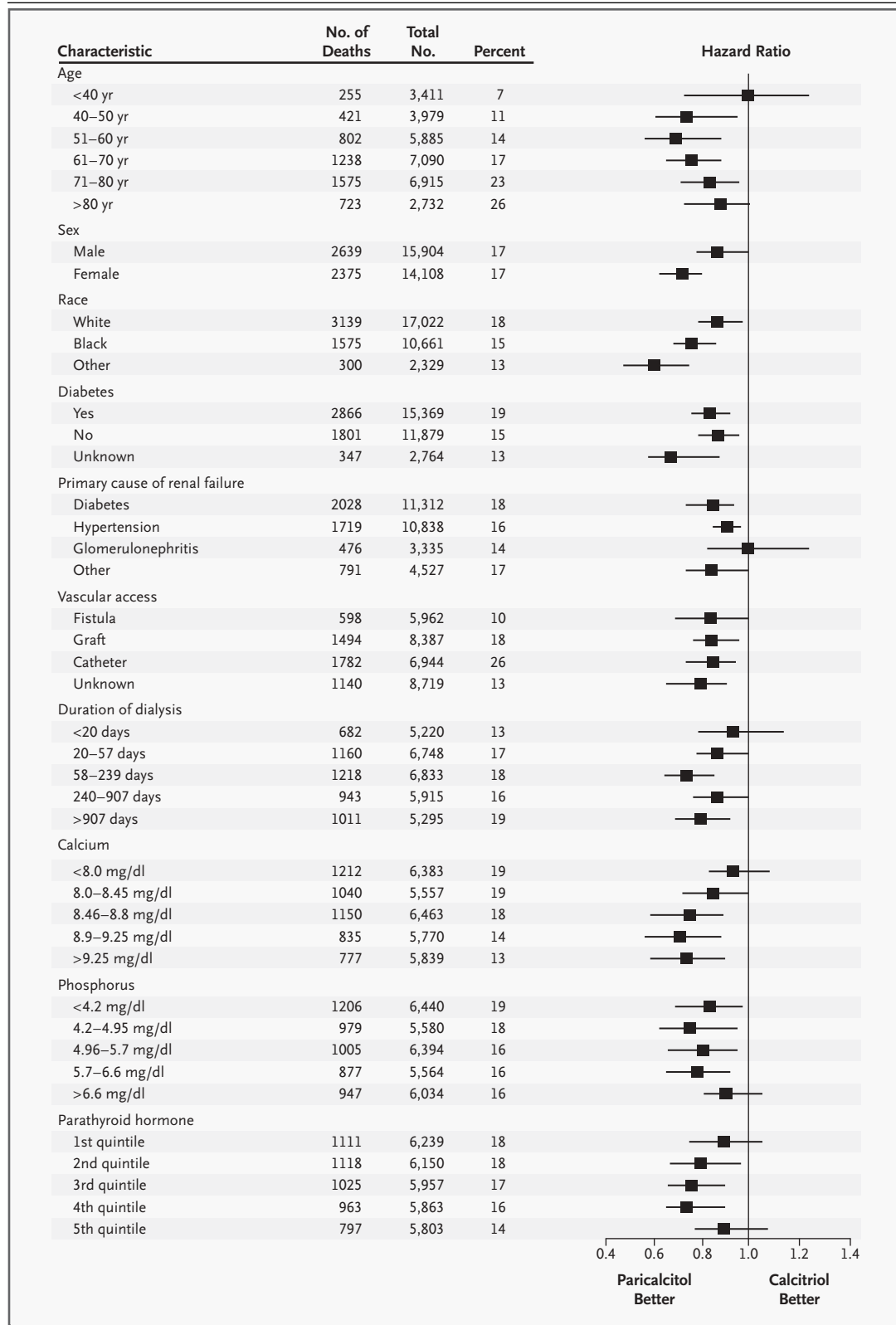
† SMR denotes the standardized mortality rate associated with each dialysis center.

‡ The laboratory values were those for albumin, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, ferritin, bicarbonate, dialysate calcium, and creatinine.

calcitriol (73 percent vs. 64 percent, P=0.04) (Fig. 1B). Multivariate analysis of this population was not performed because of incomplete data and the small number of patients who switched from paricalcitol to calcitriol.

**Figure 2 (next page). Hazard Ratios for Death Associated with Paricalcitol Treatment, as Compared with Calcitriol Treatment, with Stratification According to the Characteristics of the Patients.**

The percentages represent the fractions of patients within each stratum who died, the boxes represent point estimates, and the horizontal lines represent 95 percent confidence intervals. The reference category for each analysis is the corresponding group receiving calcitriol. Data on the duration of dialysis were missing for one patient. To convert values for calcium to millimoles per liter, multiply by 0.250, and to convert values for phosphorus to millimoles per liter, multiply by 0.3229.

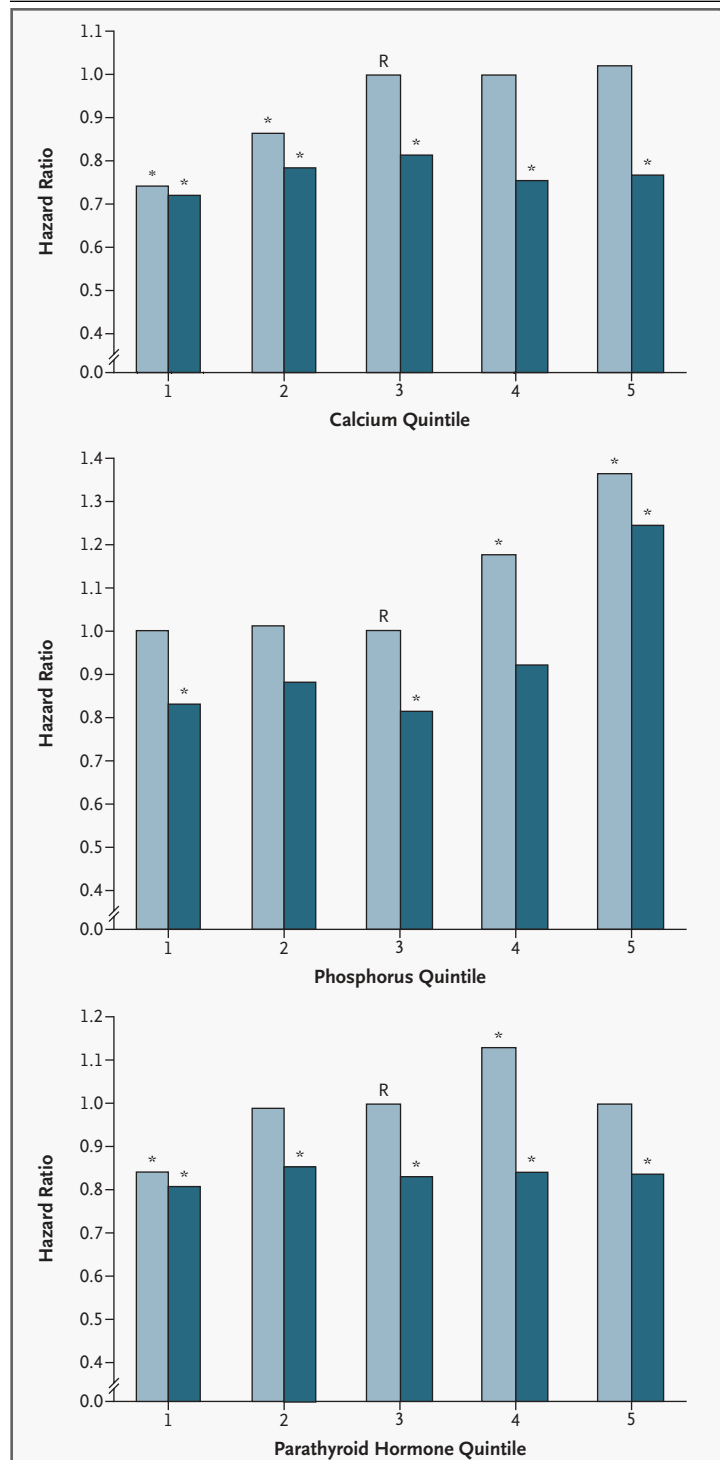


DISCUSSION

In this historical cohort study of 67,399 patients undergoing hemodialysis in whom injectable vitamin D therapy was initiated between 1999 and 2001, the patients treated with paricalcitol had a significant survival advantage as compared with those treated with calcitriol. This advantage appeared to be independent of base-line calcium, phosphorus, and parathyroid hormone levels and other potential confounders. The benefit of paricalcitol was suggested in several subgroups of patients, including blacks and patients with diabetes. In addition, those who switched from calcitriol to paricalcitol appeared to have a significant survival advantage over those who switched from paricalcitol to calcitriol.

Renal osteodystrophy encompasses a spectrum of disorders of bone and mineral metabolism, including secondary hyperparathyroidism, which is characterized by elevated parathyroid hormone levels with high bone turnover; adynamic bone disease, which is characterized by low bone turnover with parathyroid hormone levels of less than 150 pg per milliliter; and, in some patients, a combination of the two.<sup>23,24</sup> The development of renal osteodystrophy is related to the complex interaction among disordered mineral, bone, and parathyroid metabolism; calcium-based oral phosphate binders; dialysate calcium levels; and vitamin D therapy.<sup>24</sup> The goal of vitamin D therapy is to prevent skeletal complications by suppressing serum parathyroid hormone levels in patients with secondary hyperparathyroidism. However, vitamin D therapy can elevate calcium and phosphorus levels and oversuppress parathyroid hormone levels. Suppression of parathyroid hormone can lead to adynamic bone disease,<sup>25</sup> which itself is associated with skeletal complications.<sup>26-28</sup> Furthermore, emerging data suggest that the adverse consequences of the management of renal osteodystrophy have important roles in vascular calcification and the excess risk of death from cardiovascular causes among patients undergoing dialysis.<sup>8-11,15,20,29</sup> Few studies, however, have examined the independent effects of vitamin D therapy, and none, to our knowledge, have compared survival among patients receiving different types of vitamin D formulations.

Although our study is subject to the usual limitations of retrospective studies, including misclassification and bias, the prospective collection of data and contemporaneous comparison groups strengthen our findings.<sup>30</sup> In addition, the inclusion of pa-



**Figure 3. Hazard Ratios for Death According to Quintiles of Serum Calcium, Phosphorus, and Parathyroid Hormone at Base Line.**

Dark bars represent the effect of paricalcitol, and light bars represent the effect of calcitriol. R denotes the reference category for all analyses. The asterisks denote P<0.05.

**Table 3. Mean Percentage Changes in Calcium, Phosphorus, and Parathyroid Hormone Levels after Initiation of Vitamin D Therapy.\***

Laboratory Value	Paricalcitol		Calcitriol	
	mean change	interquartile range	mean change	interquartile range
	<i>percent</i>			
Calcium				
3 mo	4.7	-0.5 to 8.2	5.7	0.0 to 9.4
6 mo	6.2	0.0 to 10.6	7.6	1.0 to 12.3
12 mo	6.7	0.5 to 11.4	8.2	1.2 to 13.2
Phosphorus				
3 mo	9.2	-10.7 to 22.6	11.4	-10.2 to 25.9
6 mo	11.9	-11.2 to 27.9	14.6	-10.1 to 30.8
12 mo	11.9	-11.7 to 28.8	13.9	-10.7 to 31.0
Parathyroid hormone				
3 mo	-30	-63 to -14	-22	-65 to -9
6 mo	-26	-67 to -7	-20	-70 to -4
12 mo	-15	-63 to 2	-5	-65 to 8

\* The percent change from base line was calculated for each patient, and the means are shown. Generalized linear models were used to determine statistical significance. Values at 3 months represent the average values within 0 to 3.0 months after the start of vitamin D therapy, values at 6 months represent the average values within 3.1 to 6.0 months after the start of therapy, and values at 12 months represent the average values within 6.1 to 12.0 months after the start of therapy.  $P < 0.001$  for each comparison.

tients from such a large number of dialysis facilities (more than 1000) probably minimized bias.<sup>30</sup> Because all dialysis centers used a centralized standard data base that was linked to billing systems, the primary exposure, treatment with injectable vitamin D, and the primary outcome, survival, were well documented. Certain base-line characteristics, however, did differ between the groups.

Clinical data suggesting a survival benefit of paricalcitol over calcitriol have not been available. Nonetheless, in our study nonrandom assignment of therapy could have led to unequal susceptibility to the outcome.<sup>30</sup> Adjustment for base-line differences attenuated but did not eliminate the effect, the survival curves separated over time, and significant differences were noted when patients switched formulations; all of these observations provide support for a therapeutic effect. Although the exact duration of the effect of these medications and the specific reasons for switching are unknown, the survival

curves of the two groups switching medication separated over time. The latter finding suggests that an intention-to-treat analysis of the entire cohort would have misclassified patients. During the study period, most clinical nephrologists were aware that elevated calcium, phosphorus, and parathyroid hormone levels are associated with adverse consequences,<sup>29</sup> that blacks with renal disease in general have more severe secondary hyperparathyroidism,<sup>31</sup> and that diabetic patients undergoing dialysis tend to have lower parathyroid hormone levels than nondiabetic patients.<sup>32</sup> Therefore, given the data supporting the use of paricalcitol,<sup>17,18,33,34</sup> several base-line differences were expected. By comparison, base-line lipid profiles, glucose and blood-pressure control, and measures of the adequacy of dialysis were similar in the two groups, as were hemoglobin levels and the adequacy of dialysis at follow-up. However, with continued refinements in the analytic approach that addressed a number of confounders, the benefit of paricalcitol diminished, leaving open the possibility that unmeasured confounders (e.g., a specific “doctor effect”) account in part for the survival differences.

Although base-line measurements (e.g., values for serum lipids, glycosylated hemoglobin, and blood pressure) suggested that the use of oral medications was similar in the groups, incomplete information about oral medications is a limitation of this study. For example, accurate information about the use of calcium-based or non-calcium-based phosphate binders was unavailable. During the study period, most patients used calcium-based phosphate binders, and although aluminum-based binders were available, their use was limited because of known adverse events associated with aluminum accumulation. The use of sevelamer, a non-calcium-based binder introduced in October 1998, probably increased in this population. Although sevelamer use was recently associated with reduced vascular calcification as compared with the use of calcium-based binders,<sup>10</sup> it is unlikely that use of this medication explained our findings. The nationwide prescription of sevelamer among patients undergoing dialysis was approximately 10 percent in 1999, 20 percent in 2000, and 30 percent in 2001 (Burke S, Genzyme: personal communication), and our results remain significant even when each study year is analyzed separately. Furthermore, paricalcitol appeared to be beneficial among patients with low-to-normal mineral levels — the groups least likely to have received non-calcium-based binders.

The mechanism by which paricalcitol exerts its potential beneficial effect remains to be determined. Differential effects of paricalcitol and calcitriol on mineral metabolism suggest that the primary mechanism involves mineral and parathyroid hormone metabolism. The blunted effect of paricalcitol on gut absorption and bone resorption of minerals, as compared with that of calcitriol,<sup>17,18,35</sup> may lead to lower mineral loads, which could reduce the risk of vascular calcification and death from cardiovascular causes.<sup>8,10</sup> The relative survival advantage with paricalcitol, however, was largely consistent across strata of base-line mineral and parathyroid hormone levels (Fig. 3), suggesting a benefit that may extend beyond these base-line levels. Indeed, vitamin D receptors are ubiquitous throughout the body and, when activated, modify inflammation, immune function, cell growth, and cell differentiation.<sup>36</sup> Slight modifications of the parent compound (D-1,25-dihydroxyvitamin D<sub>3</sub>) dramatically affect cellular responses.<sup>33,34,37,38</sup> In vitro studies suggest that calcitriol, unlike paricalcitol, sensitizes cells to energy depletion and iron-mediated injury,<sup>39</sup> and data from animal models suggest that hydroxyvitamin D<sub>2</sub> compounds are much less toxic than hydroxyvitamin D<sub>3</sub> compounds.<sup>40</sup> In the present study, the use of paricalcitol was associated with a reduction in the rate of death from cardiovascular, infectious, and other causes. Elevated phosphorus and parathyroid hormone levels have been associated with increased mortality from vascular and nonvascular causes, including infection.<sup>20</sup> For data on causes

of death, we used ICD-9-CM codes, whose accuracy has been questioned,<sup>41</sup> and therefore further studies are needed to identify the exact mechanisms involved.

The patients in our study represented a broad spectrum of disease severity, and thus were representative of patients seen in routine clinical practice between 1999 and 2001, a period when clinical data did not suggest a difference in survival between patients using different vitamin D formulations. Before conclusions can be drawn about the role of paricalcitol in the management of secondary hyperparathyroidism, additional research is required. First, clinical conclusions should not be drawn until our findings have been confirmed by a prospective, randomized trial. Second, if these results are confirmed, the mechanisms that underlie them should be elucidated to determine whether they are explained by a protective effect of paricalcitol, a harmful effect of calcitriol, or both. For example, although we did not observe a dose-response effect on mortality associated with calcitriol, an increased dose of calcitriol relative to the dose of paricalcitol might explain our findings. Finally, further studies should address the question of whether therapy initiated before the onset of hemodialysis or after renal transplantation also affects survival.

Drs. Teng, Lazarus, and Ofsthun are employees of Fresenius Medical Care North America. Dr. Lowrie reports having served as a consultant to Fresenius Medical Care North America.

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