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Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients

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Elevated serum phosphorus and calcium are associated with arterial calcification and mortality in dialysis patients. Unlike calcium-based binders, sevelamer attenuates arterial calcification but it is unknown whether sevelamer affects mortality or morbidity. In a multicenter, randomized, open-label, parallel design trial we compared sevelamer and calcium-based binders on all-cause and cause-specific mortality (cardiovascular, infection, and other) in prevalent hemodialysis patients. A total of 2103 patients were initially randomized to treatment and 1068 patients completed the study. All-cause mortality rates and cause-specific mortality rates were not significantly different. There was a significant age interaction on the treatment effect. Only in patients over 65 years of age was there a significant effect of sevelamer in lowering the mortality rate. There was a suggestion that sevelamer was associated with lower overall, but not cardiovascular-linked, mortality in older patients. We suggest that further research is needed to confirm these findings.

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KEYWORDS: phosphorus; calcium; hemodialysis; phosphate-binders; sevelamer; mortality

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The annual mortality rate of patients undergoing hemodialysis in the United States is nearly 25%, approximately half of which is cardiovascular.[1] Hyperphosphatemia and hypercalcemia are important independent risk factors for both cardiovascular calcification[2–5] and cardiovascular morbidity and mortality in dialysis patients.[6–10]

Dietary restriction and conventional dialysis alone are ineffective in controlling hyperphosphatemia, thus the vast majority of dialysis patients require phosphate binders. Until recently, the predominant binders in use have been calcium acetate and calcium carbonate. However, these medications have been linked to arterial calcification.[2,11,12] Arterial calcification in hemodialysis patients is associated with arterial stiffening and with increased risk of mortality.[12–14] Sevelamer hydrochloride (Renagel®), a non-absorbed, phosphate-binding polymer, lowers serum phosphorus without promoting arterial calcification.[2,15–19]

Recently it has been shown that the presence and severity of coronary calcification is a predictor of all-cause mortality in patients new to dialysis. In addition, the use of calcium-based binders in an incident dialysis population was associated with a significantly higher mortality rate when compared to sevelamer.[20]

The DCOR (Dialysis Clinical Outcomes Revisited) trial compared all-cause mortality and cause-specific mortality (cardiovascular mortality, infection, and other causes) among hemodialysis patients treated with calcium-based phosphate binders and sevelamer. DCOR was an effectiveness trial that was designed to evaluate the treatment outcomes under usual care conditions in a prevalent population.

RESULTS

Patients

A total of 2103 subjects were randomized (1053 to sevelamer and 1050 to calcium-based binders) and 1068 patients completed (Figure 1). Overall the treatment groups were well balanced with respect to baseline demographics and renal history for the overall study population (Table 1) as well as by age subgroup (Table 2).

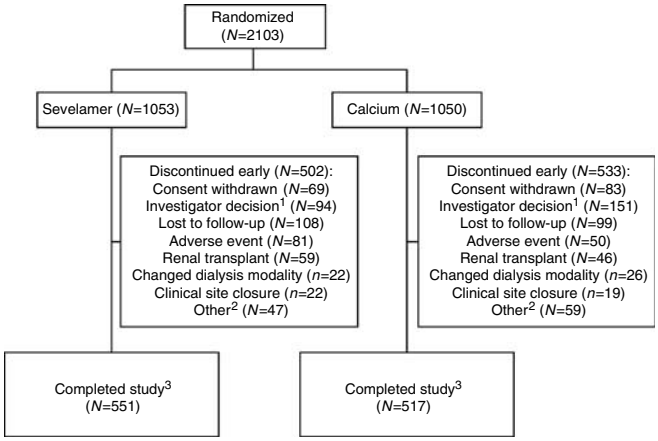

Figure 1 | Patient disposition. [1]Investigator decision included the following reasons: the subject did not continue on the assigned phosphate binder for one of the protocol-defined time periods, or the investigator felt that the patient was generally non-compliant; the investigator determined the patient no longer required phosphate binder therapy; the investigator decided that the patient needed a different primary binder; or the investigator felt that the patient could not be adequately followed for study purposes, such as if the patient frequently missed dialysis or had frequent or lengthy hospitalizations, and it became difficult for the site to follow the patient. [2]Other included the following reasons: the patient no longer required a phosphate binder, the patient did not take the assigned phosphate binder for more than 5 weeks, non-compliance, randomization errors, or patient did not meet inclusion/exclusion criteria. [3]Did not discontinue from the study before death or study cessation, whichever came first. In addition, there were 11 sevelamer patients and 18 calcium patients who discontinued early and died during the 90-day follow-up period. These patients were considered as completers for the mortality analyses resulting in a total of 562 completers in the sevelamer group and 535 completers in the calcium group.

A total of 502 and 533 subjects discontinued early in the sevelamer and calcium groups, respectively. There was no difference between the groups regarding time to early discontinuation (log-rank $P=0.15$). The follow-up time was similar for the sevelamer and calcium groups (mean 20.3 ± 13.9, median 19.6 vs mean 19.6 ± 13.6, median 18.5 months, respectively). Overall, 38% of subjects were treated for <12 months, 20% for 12–24 months, 25% for 24–36 months, and 17% for >36 months. More subjects randomized to calcium never took study medication, more dropped due to investigator decision (defined in Figure 1), and the discontinuations due to adverse events were mainly related to hypercalcemia. In contrast, more subjects randomized to sevelamer were discontinued due to adverse events that were mainly gastrointestinal. The baseline demographics and renal history among subjects who discontinued early were similar.

Of the subjects randomized to calcium, 70% took calcium acetate as PhosLo® tablets and 30% took calcium carbonate as TUMS®. Ninety-four percent remained on calcium acetate and 87% remained on calcium carbonate. The other subjects switched formulations but remained on calcium-based phosphate binders. The mean prescribed daily dose at study completion was 5.3 g for calcium acetate, 4.9 g for calcium carbonate, and 6.9 g for sevelamer.

Table 1 | Demographics and renal history

Variable	Total (*N*=2103)	Sevelamer (*N*=1053)	Calcium (*N*=1050)	*P*-value*
Race (N (%))				
Caucasian	1012 (48.1)	515 (48.9)	497 (47.3)	0.42
Black	988 (47.0)	494 (46.9)	494 (47.0)	
Asian	17 (0.8)	6 (0.6)	11 (1.0)	
Other	86 (4.1)	38 (3.6)	48 (4.6)	
Age (years)				
Mean ± s.d.	60.0 ± 14.7	59.9 ± 14.3	60.1 ± 15.2	0.60
Median	62.0	61.0	62.0	
Sex (N (%))				
Male	1143 (54.4)	574 (54.5)	569 (54.2)	0.90
Female	960 (45.6)	479 (45.5)	481 (45.8)	
Diabetes status (N (%))				
No	1047 (49.8)	521 (49.5)	526 (50.1)	0.79
Yes	1056 (50.2)	532 (50.5)	524 (49.9)	
Primary cause of ESRD[a] (N (%))				
Diabetes	890 (42.3)	447 (42.5)	443 (42.2)	0.63
Hypertension/large vessel disease	709 (33.7)	353 (33.5)	356 (33.9)	
Glomerulonephritis	213 (10.1)	110 (10.4)	103 (9.8)	
Secondary GN/vasculitis	40 (1.9)	16 (1.5)	24 (2.3)	
Interstitial nephritis/ pyelonephritis	54 (2.6)	24 (2.3)	30 (2.9)	
Neoplasms/tumors	19 (0.9)	10 (0.9)	9 (0.9)	
Cystic/hereditary/ congenital disease	61 (2.9)	27 (2.6)	34 (3.2)	
Miscellaneous conditions	117 (5.6)	66 (6.3)	51 (4.9)	
Dialysis duration (months)				
Mean ± s.d.	38.2 ± 39.6	38.8 ± 39.6	37.6 ± 39.6	0.53
Median	24.0	23.9	24.3	

ESRD, end-stage renal disease; GN, glomerulonephritis.
[a]Primary cause of ESRD: unknown is displayed under miscellaneous conditions.
*Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

All-cause and cause-specific mortality

There was no difference between treatment groups with respect to all-cause mortality, the primary end point (Figure 2a). There were 267 deaths in the sevelamer group and 275 deaths in the calcium group. The sevelamer group mortality rate was 15.0 per 100 patient-years and the calcium group mortality rate was 16.1 per 100 patient-years (hazard ratio = 0.93, 95% confidence interval (CI): 0.79–1.10; log-rank $P=0.40$). The Kaplan–Meier curve (Figure 2a) reveals no difference in mortality risk for those patients on study for less than 2 years. However, for those patients remaining on study for at least 2 years (43% of the population), a difference between groups, favoring sevelamer, appears to emerge (time–treatment interaction $P=0.02$).

Of the deaths, 53% were attributable to cardiovascular causes (289 (142 sevelamer and 147 calcium) of 542 total deaths; Figure 2d). Among sevelamer and calcium subjects, the cardiovascular mortality rate was 8.0 per 100 patient-years and 8.6 per 100 patient-years, respectively (hazard ratio = 0.93, 95% CI: 0.74–1.17; log-rank $P=0.53$).

Table 2 | Patient demographics and renal history by age subgroup

Variable	<65 years of age				≥65 years of age			
	Total (*N*=1176)	Sevelamer (*N*=598)	Calcium (*N*=578)	*P*-value*	Total (*N*=927)	Sevelamer (*N*=455)	Calcium (*N*=472)	*P*-value*
Race (N (%))								
Caucasian	448 (38.1)	236 (39.5)	212 (36.7)	0.61	564 (60.8)	279 (61.3)	285 (60.4)	0.53
Black	663 (56.4)	333 (55.7)	330 (57.1)		325 (35.1)	161 (35.4)	164 (34.7)	
Asian	6 (0.5)	3 (0.5)	3 (0.5)		11 (1.2)	3 (0.7)	8 (1.7)	
Other	59 (5.0)	26 (4.3)	33 (5.7)		27 (2.9)	12 (2.6)	15 (3.2)	
Age (years) (mean ± s.d.)	49.4 ± 10.3	49.8 ± 10.1	49.0 ± 10.5	0.21	73.4 ± 6.0	73.1 ± 5.7	73.7 ± 6.2	0.22
(Median)	51.0	51.0	51.0		73.0	73.0	73.0	
Sex (N (%))								
Male	684 (58.2)	354 (59.2)	330 (57.1)	0.48	459 (49.5)	220 (48.4)	239 (50.6)	0.51
Female	492 (41.8)	244 (40.8)	248 (42.9)		468 (50.5)	235 (51.6)	233 (49.4)	
Diabetes status (N (%))								
No	626 (53.2)	317 (53.0)	309 (53.5)	0.91	421 (45.4)	204 (44.8)	217 (46.0)	0.74
Yes	550 (46.8)	281 (47.0)	269 (46.5)		506 (54.6)	251 (55.2)	255 (54.0)	
Primary cause of ESRD[a] (*N* (%))								
Diabetes	465 (39.5)	235 (39.3)	230 (39.8)	0.49	425 (45.8)	212 (46.6)	213 (45.1)	0.66
Glomerulonephritis	151 (12.8)	82 (13.7)	69 (11.9)		62 (6.7)	28 (6.2)	34 (7.2)	
Secondary GN/vasculitis	32 (2.7)	13 (2.2)	19 (3.3)		8 (0.9)	3 (0.7)	5 (1.1)	
Interstitial Nephritis/pyelonephritis	32 (2.7)	17 (2.8)	15 (2.6)		22 (2.4)	7 (1.5)	15 (3.2)	
Neoplasms/tumors	8 (0.7)	5 (0.8)	3 (0.5)		11 (1.2)	5 (1.1)	6 (1.3)	
Hypertension/large vessel disease	385 (32.7)	195 (32.6)	190 (32.9)		324 (35.0)	158 (34.7)	166 (35.2)	
Miscellaneous conditions	65 (5.5)	37 (6.2)	28 (4.8)		52 (5.6)	29 (6.4)	23 (4.9)	
Cystic/hereditary/congenital disease	38 (3.2)	14 (2.3)	24 (4.3)		23 (2.5)	13 (2.9)	10 (2.1)	
Dialysis duration (mean ± s.d., median (months))	44.9 ± 44.7	45.0 ± 44.1	44.7 ± 45.3	0.93	29.9 ± 30.0	30.8 ± 31.0	28.9 ± 29.1	0.47
	31.3	30.8	31.5		20.0	19.8	20.0	

ESRD, end-stage renal disease; GN, glomerulonephritis.
[a]Primary cause of ESRD: unknown is displayed under miscellaneous conditions.
*Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

There were 47 deaths due to infection in the sevelamer group with a rate of 2.6 per 100 patient-years and 41 deaths due to infection in the calcium group with a rate of 2.4 per 100 patient-years (log-rank $P = 0.68$). There were 78 deaths due to other causes in the sevelamer group, with a rate of 4.4 per 100 patient-years, and 87 deaths due to other causes in the calcium group, with a rate of 5.1 per 100 patient-years (log-rank $P = 0.33$).

The adjusted hazard ratios and *P*-values were not notably different for any analyses presented above.

All-cause and cause-specific mortality by age

In a pre-specified analysis, a significant interaction between treatment and age (<65 years, ≥65 years) was observed for all-cause mortality ($P = 0.02$), but not with other baseline characteristics (race, sex, diabetes status, cause of kidney disease, and dialysis duration). In subjects ≥65 years of age (44% of the study population), the all-cause mortality rate was 18.2 per 100 patient-years for the sevelamer group and 23.4 per 100 patient-years for the calcium group (hazard ratio = 0.77, 95% CI: 0.61–0.96; Figure 2b). In subjects <65 years of age, the all-cause mortality rate was 12.5 per 100 patient-years for the sevelamer group and 10.6 per 100 patient-years for the calcium group; there was no difference between groups (hazard ratio = 1.18, 95% CI: 0.91–1.53).

No treatment-by age interaction was observed for cardiovascular mortality; however, subgroup results are presented to help better understand the all-cause mortality results. Among older sevelamer- and calcium-treated subjects, the cardiovascular mortality rate was 10.5 per 100 patient-years and 13.3 per 100 patient-years, respectively (hazard ratio = 0.78, 95% CI: 0.58–1.05). Among younger sevelamer and calcium subjects, the cardiovascular mortality rate was 6.1 per 100 patient-years and 5.1 per 100 patient-years, respectively (hazard ratio = 1.19, 95% CI: 0.82–1.73).

Hospitalizations

The mean number of hospitalizations/patient-year was 2.1 (median 1.0) for the sevelamer-treated patients and 2.3 (median 1.3) for the calcium-treated patients ($P = 0.0738$). In patients ≥65 years old, the mean number of hospitalizations/patient-year was 2.1 (median 1.3) for the sevelamer-treated patients and 2.9 (median 1.6) for the calcium-treated patients. In patients <65 years old, the mean number of hospitalizations/patient-year was 2.1 (median 0.9) for the sevelamer-treated patients and 1.8 (median 0.9) for the calcium-treated patients.

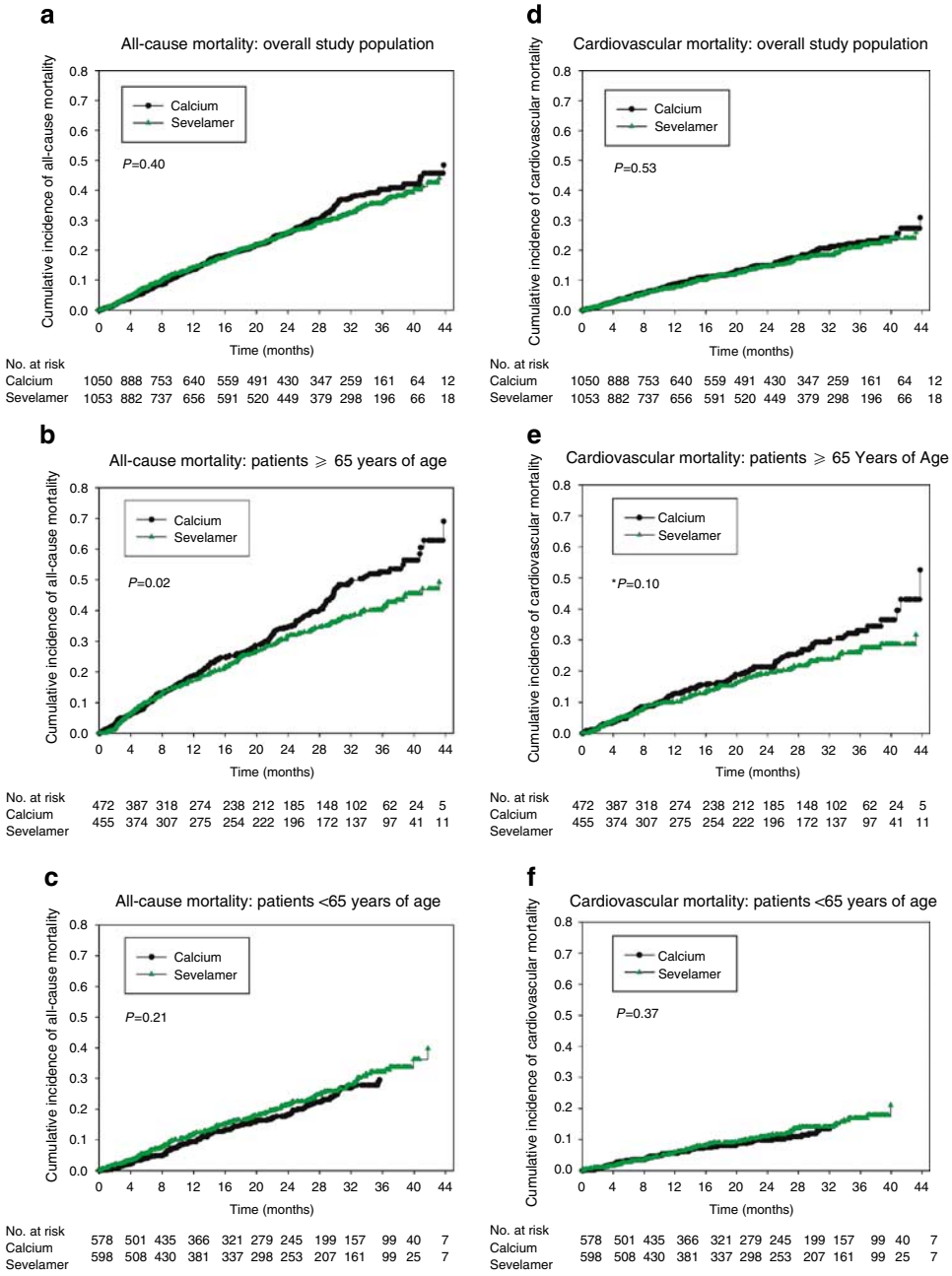

Figure 2 | Cumulative incidence of all-cause and cardiovascular mortality for the overall study population and in patients ⩾65 years of age and <65 years of age. (**a**) All-cause mortality in overall study population. (**b**) All-cause mortality in patients 65 years of age or order. (**c**) All-cause mortality in patients less than 65 years of age. (**d**) Cardiovascular mortality in overall study population. (**e**) Cardiovascular mortality in patients 65 years of age or order. (**f**) Cardiovascular mortality in patients less than 65 years of age. *This *P* value had incorrectly appeared online as *P*=0.02. This value is now corrected.

The mean hospital days/patient-year was 14.8 (median 5.0) for the sevelamer-treated patients and 17.4 (median 5.8) for the calcium-treated patients ($P = 0.0897$). In patients ⩾65 years old, the mean hospital days/patient-year was 16.6 (median 6.9) for the sevelamer-treated patients and 21.8 (median 7.9) for the calcium-treated patients. In patients ⩽65 years old, the mean hospital days/patient-year was 13.4 (median 3.4) for the sevelamer-treated patients and 13.8 (median 4.0) for the calcium-treated patients.

Laboratory data

Table 3 displays the time-weighted average levels of post-baseline serum phosphorus, calcium, calcium–phosphorus product, intact parathormone, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, and K_t/V obtained from each dialysis provider's central laboratory. Laboratory values were consistent with what is typically seen in US hemodialysis patients. The data demonstrate a higher serum calcium and lower intact parathormone level in the calcium subjects, and a lower total

Table 3 | Time-weighted average of post-baseline assessments for serum phosphorus, calcium, calcium–phosphorus product, intact parathormone, total cholesterol , LDL-, HDL-cholesterol, and K_t/V

	Sevelamer		Calcium		
	N	Time weighted mean ± s.d.	*N*	Time weighted mean ± s.d.	*P*-value*
Phosphorus (mmol/l)	843	1.87 ± 0.42	843	1.84 ± 0.42	<0.01
Calcium (mmol/l)	835	2.30 ± 0.18	837	2.38 ± 0.18	<0.0001
Calcium × phosphorus product ($mmol^2/l^2$)	835	4.33 ± 0.98	833	4.33 ± 1.04	0.60
Intact parathormone[a] (pg/ml)	774	278 (200, 476)	768	226 (142, 387)	<0.0001
Total cholesterol (mmol/l)	526	3.77 ± 0.87	529	4.16 ± 0.90	<0.0001
LDL cholesterol (mmol/l)	197	1.78 ± 0.67	202	2.20 ± 0.80	<0.0001
HDL cholesterol (mmol/l)	247	1.17 ± 0.39	248	1.15 ± 0.41	0.62
K_t/V	823	1.6 ± 0.3	827	1.6 ± 0.3	0.11

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
To convert values for phosphorus to mg/dl, divide by 0.3229. To convert values for calcium to mg/dl, divide by 0.25. To convert values for calcium × phosphorus product to mg^2/dl^2 divide by 0.0807. To convert values for cholesterol to mg/dl, divide by 0.02586.
[a]Presented as median (interquartile range).
*Wilcoxon rank sum test.

and LDL cholesterol in the sevelamer subjects. The laboratory values were also examined by age. Older subjects tended to have lower phosphorus values than the younger subjects (in subjects <65 years, sevelamer 1.97 ± 0.42 and calcium 1.94 ± 0.45 mmol/l (6.1 ± 1.3 and 6.0 ± 1.4 mg/dl); in subjects ⩾65 years, sevelamer 1.78 ± 0.39 and calcium 1.68 ± 0.36 mmol/l (5.5 ± 1.2 and 5.2 ± 1.1 mg/dl)).

Safety

There were eight subjects with a total of 11 possibly drug-related serious adverse events in the study. Eight related serious adverse events occurred in five subjects in the calcium group (calciphylaxis (three subjects); hypercalcemia, nausea, and vomiting (one subject); and cholecystitis and acute pancreatitis (one subject)), and three related serious adverse events occurred in three subjects in the sevelamer group (constipation (one subject), vomiting (one subject), and osteoporosis (one subject)). The sevelamer subject diagnosed with osteoporosis was a 72-year-old woman who had been treated intermittently for asthma with both oral and inhaled steroids and was diagnosed with osteoporosis during the trial.

DISCUSSION

Elevations of serum phosphorus and serum calcium in dialysis patients are independently associated with increased risk of arterial calcification[2–5] and death.[6–10] The dose of calcium-based phosphate binders has been linked with the severity of arterial calcification,[2,12] necessitating that limitations be placed on the use of these agents.[21,22] Sevelamer has been shown to lead to less calcification progression than calcium-based binders.[16–19] In subjects new to dialysis, calcium-based binders have recently been shown to be associated with higher all-cause mortality rate compared to sevelamer.[20] This study was conducted to determine whether these treatments differ with regards to clinical outcomes, and represents the largest prospective randomized clinical trial conducted among a prevalent dialysis population.

In this study, all-cause mortality was not significantly different in the overall population. However, the results suggest that sevelamer was associated with a lower mortality rate than calcium in older subjects (sevelamer: 18.2 per 100 patient-years; calcium: 23.4 per 100 patient-years; $P = 0.02$). Among younger subjects, sevelamer was associated with a higher mortality rate than calcium, though these rates were substantially lower than those for older subjects, and the difference was not statistically significant (sevelamer: 12.5 per 100 patient-years; calcium: 10.6 per 100 patient-years; $P = 0.21$). The findings in older subjects are consistent with earlier literature documenting that older hemodialysis patients tend to have greater calcification burden than younger patients. Therefore, it may be that a calcium effect on mortality could occur over a shorter follow-up time in older as compared with younger patients.[2,3,5,11–13] Furthermore, progression of calcification is greater among those patients with higher levels of arterial calcification at baseline.[16] Although not statistically significant, the potential benefit in younger subjects treated with calcium-based binders deserves further investigation.

Cardiovascular mortality was not found to be different between the treatment groups. The study, however, was not powered to detect differences in cardiovascular or other specific causes of death.

There was a trend for less hospitalization burden in the sevelamer-treated patients with regard to both number of hospitalizations/patient-year and number of days hospitalized; this was most prominent in the older patients. Hospitalizations in the study patients are analyzed further using the Centers for Medicare and Medicaid Services (CMS) database in a companion analysis.[23]

In addition to potential differential effects on arterial calcification between the treatments, other factors may be influencing the mortality rates. While a recent study showed no beneficial effect of cholesterol reduction on all-cause mortality in diabetic hemodialysis patients,[24] this could be a contributing factor. It is possible also that increase in vitamin D use during sevelamer therapy, as has been observed previously,[18] contributes to the results though benefits of vitamin D use on survival have not been observed

uniformly[10] and have only been reported in observational studies.[9,25,26]

A limitation of the present trial was that it was open label. Blinding was not possible because of the characteristic chemical odor of calcium acetate and the predictable lowering of serum cholesterol by sevelamer. Another limitation of the study was that 46% of subjects discontinued early. While there were no differences in the time to discontinuation among subjects who discontinued early, there remains the possibility that some unmeasured factors could have introduced additional bias. Finally, the decision to only follow subjects who discontinued early for 90 days may be criticized. This allowed the capture of mortality associated with medical events leading to early discontinuation. Extended follow-up beyond 90 days would have introduced bias due to cross-over to alternate therapy, as would be expected in patients who discontinued early. An intent to treat analysis was conducted using the CMS database; this analysis also failed to show a significant difference in overall all-cause mortality (W. St. Peter: Personal communication).[23]

The age subgroup findings are the product of a prospectively defined evaluation of six interactions with treatment. A significant interaction was required as a gating criterion to proceed with subgroup inferences to avoid inflation of the type I error rate based on the closed testing principle. A potential limitation of the findings is that the interaction assessments were not corrected for multiple comparisons using a conservative Bonferroni correction that would have yielded a non-significant treatment interaction inference. The Bonferroni correction, however, increases the risk for type II error, and there is no consensus that such correction is necessary in situations where the analysis was pre-specified based on sound biological or epidemiological reasons.[27]

Attempting to improve the high mortality rate in dialysis patients has been a daunting task. Three previous large, well-controlled outcomes studies targeting anemia correction to a normal hematocrit, increasing dialysis dose, and reducing LDL cholesterol have failed to improve survival in dialysis patients.[22,28,29] However, a recently published study by Block *et al.*[20] demonstrated a survival benefit in incident dialysis subjects receiving sevelamer. In contrast, the DCOR study, which evaluated a prevalent dialysis population, did not show a difference between treatments for the primary end point, all-cause mortality, although in older subjects, who would be most likely to have significant arterial calcification, there was an indication that sevelamer was associated with improved survival. The inconsistent findings of these two studies are potentially related to the differences in the study designs. Block *et al.* evaluated an incident dialysis population, adherence to the randomized treatment was excellent, and the subjects were followed for a longer duration, as compared to the DCOR study. In general, future studies in dialysis patients should be large, of long duration, and possibly enroll patients enriched for higher event rates.

MATERIALS AND METHODS

Study design

This was a multi-center, randomized, open-label, parallel design trial (Registration No. NCT00324571). Hemodialysis patients at 75 dialysis centers within the United States, belonging to Fresenius Medical Care, North America, Gambro Healthcare Inc., DaVita Inc., and Renal Care Group, were enrolled into this study from March 2001 through January 2002.

All subjects were 18 years of age or older, were on dialysis for more than 3 months, required phosphate binder therapy, and had Medicare as their primary insurance for the purpose of identifying study patients in the CMS database for additional analyses. Exclusion criteria included dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or bowel obstruction. The protocol was reviewed and approved by an Institutional Review Boards for all participating institutions. After providing written informed consent, subjects were randomized to receive sevelamer or a calcium-based phosphate binder with meals until the end of the study on 31 December 2004 (a treatment period of up to 45 months). Randomization was executed in blocks assuring a 1:1 ratio between treatment groups within strata defined by race (black and non-black), sex, diabetic status, and by age (<55 and $\geqslant 55$ years). Institutional balancing was used to assure comparable number of subjects between treatment groups within a site.[30] Calcium acetate (PhosLo®) use was encouraged, but subjects who do not tolerate calcium acetate could choose calcium carbonate (TUMS®) instead. Subjects who stopped using their assigned binder for more than 5 consecutive weeks or in aggregate for more than 20 weeks were discontinued from the study. The treating physician could prescribe all other medications according to current standards of clinical practice.

Follow-up occurred from the randomization date through the earliest of the following events: date of death, study cessation (31 December 2004 for most sites though a handful of sites only participated until 31 December 2003, the originally planned study end date), or, in the case of early termination, 90 days following discontinuation of the study drug. The protocol and statistical plan specified analysis of outcomes during this follow-up period rather than an intent to treat period. The 90-day follow-up period after early termination was included to avoid censoring outcomes associated with an event that led to early termination. However, a more extended follow-up period was deemed inappropriate because of the anticipated cross-over to the alternate therapy in those who terminated early, especially in those terminating due to adverse events or investigator decisions.

Cause of death was determined by the investigator and recorded on a case report form page using the death codes in the ESRD Death Notification Form (Form 2746). These data were the source for the primary end point analysis. Codes considered to be cardiovascular include acute myocardial infarction, pericarditis (including cardiac tamponade), atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest (cause unknown), valvular heart disease, pulmonary edema due to exogenous fluid, cerebrovascular accident (including intracranial hemorrhage), and ischemic brain damage/anoxic encephalopathy. The investigators also recorded hospitalization and discharge dates, demographics, and renal history data.

Post-baseline serum levels of phosphorus, calcium, intact parathyroid hormone, total cholesterol, LDL cholesterol, HDL cholesterol, and K_t/V were obtained from each dialysis provider's central laboratory.

Genzyme Corporation funded this study and wrote the protocol. Averion Inc (Southborough, MA, USA) monitored data collection and provided data management and statistical analysis. The primary author (Suki) reviewed all statistical analyses and authored this paper in collaboration with the other authors.

Interim analysis

There was a single pre-specified interim analysis at which a *P*-value of 0.006 was required to stop the study and a *P*-value of 0.048 was required to achieve statistical significance at the end of the study based on the O'Brien and Fleming sequential testing procedure.[31] A Data Monitoring Committee (DMC) conducted the interim analysis in two stages 1 year after the last patient enrolled. First, the DMC conducted a blinded analysis of aggregated mortality data. The aggregate death rate was 13.6 per 100 patient-years, substantially lower than the anticipated 17.8 per 100 patient-years. The DMC recommendation to extend the treatment by a year, to retain the original power of the study, was followed. Second, the DMC conducted an unblinded analysis on the primary end point data. The mortality difference was not significant (stopping rule: $P<0.006$). Results of this second analysis were not shared with the investigators, Genzyme, or anyone else involved with the study.

Statistical analysis

All randomized subjects were included in the analysis including those who were not dispensed medication ($n=63$) and those who were dispensed medication but did not complete the study (early discontinuations, $n=975$). The primary study end point was all-cause mortality. Secondary end points were cause-specific mortality (cardiovascular, infection, and other) and all-cause hospitalization.

The study was designed to have 80% power to detect a 22% decrease in all-cause mortality, assuming a mortality rate of 20 per 100 patient-years in the calcium group, and a two-sided-α of 0.05.

Survival curves were constructed using the Kaplan–Meier product limit method and compared with the log-rank test. Hazard ratios and 95% CI were calculated using Cox regression models with and without adjustment for race (black, non-black), age (<65 years of age, $\geqslant 65$ years of age), sex (male, female), diabetes (yes, no), primary cause of ESRD (diabetes, hypertension, other), and vintage (time since initiation of dialysis). Hazard ratios presented in the Results section are the unadjusted measures of effect. Homogeneity of the treatment effect with respect to each of these six prognostic factors was assessed by additional models that included a factor-by-treatment term. These factors were identified *a priori* and no other factors were assessed. While 55 years of age was used as a cut point for stratification of the randomization, as this reflected the median age observed in previous sevelamer trials,[16] 65 years of age was pre-specified for the data analysis since this is a traditional cut point used by CMS, FDA, and other regulatory agencies to define an elderly population. In order to control the potential inflation of type I error attributable to multiple testing of subgroups, a statistically significant interaction was required to make conclusions about strata-specific results. Such a gatekeeping strategy is commonly used in clinical trials and contains the type I error rate by the closed testing principle.

Hospitalizations and hospitalized days per patient-year of follow-up were compared using the Wilcoxon rank sum test.

The time-weighted averages of post-baseline assessments for serum phosphorus, calcium, calcium–phosphorus product, intact parathormone, total cholesterol, LDL cholesterol, HDL cholesterol, and K_t/V collected per normal clinical practice were summarized for subjects with available data, and differences between the treatment groups assessed using the Wilcoxon rank sum test.

All statistical analyses were performed using SAS Version 6.12 or higher (SAS Institute Inc., Cary, NC, USA) using a UNIX/Solaris server. All reported *P*-values are two-sided.

DISCLOSURE

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