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Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients

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Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients.

Background. Cardiovascular disease is frequent and severe in patients with end-stage renal disease. Disorders of mineral metabolism may contribute by promoting cardiovascular calcification.

Methods. We conducted a randomized clinical trial comparing sevelamer, a non-absorbed polymer, with calcium-based phosphate binders in 200 hemodialysis patients. Study outcomes included the targeted concentrations of serum phosphorus, calcium, and intact parathyroid hormone (PTH), and calcification of the coronary arteries and thoracic aorta using a calcification score derived from electron beam tomography.

Results. Sevelamer and calcium provided equivalent control of serum phosphorus (end-of-study values 5.1 ± 1.2 and 5.1 ± 1.4 mg/dL, respectively, $P = 0.33$). Serum calcium concentration was significantly higher in the calcium-treated group ($P = 0.002$), and hypercalcemia was more common (16% vs. 5% with sevelamer, $P = 0.04$). More subjects in the calcium group had end-of-study intact PTH below the target of 150 to 300 pg/mL (57% vs. 30%, $P = 0.001$). At study completion, the median absolute calcium score in the coronary arteries and aorta increased significantly in the calcium treated subjects but not in the sevelamer-treated subjects (coronary arteries 36.6 vs. 0, $P = 0.03$ and aorta 75.1 vs. 0, $P = 0.01$, respectively). The median percent change in coronary artery (25% vs. 6%, $P = 0.02$) and aortic (28% vs. 5%, $P = 0.02$) calcium score also was significantly greater with calcium than with sevelamer.

Conclusions. Compared with calcium-based phosphate binders, sevelamer is less likely to cause hypercalcemia, low levels of PTH, and progressive coronary and aortic calcification in hemodialysis patients.

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In the year 2000, there were approximately 280,000 patients undergoing dialysis for end-stage renal disease (ESRD) in the United States [1]. The annual mortality rate in dialysis patients is in excess of 20%, and cardiovascular mortality rates are on average 30-fold higher than in the general population with especially high rates among younger individuals [2]. Several factors have been proposed to contribute to the exceptionally high rate of cardiovascular disease in ESRD, including the adverse hemodynamic effects of dialysis, oxidative stress, inflammation, hypertension, hyperhomocysteinemia, and the relatively infrequent use of aspirin, lipid-lowering agents, and beta-adrenergic antagonists [3–7]. Disorders of mineral metabolism (principally hyperphosphatemia, hypercalcemia, and hyperparathyroidism) have also been proposed to play a role [8]. Epidemiological studies have shown a direct correlation between serum phosphorus and the calcium-phosphorus product and mortality in hemodialysis patients [9, 10]. Recently, Goodman et al showed a striking degree of coronary artery calcification in young adults with ESRD, using electron beam tomography (EBT) [11]. In that study, the calcium-phosphorus product and the dose of oral calcium ingested were significantly associated with the likelihood of coronary calcification.

Based on these findings, we hypothesized that sevelamer, a non-absorbed, non-calcium-containing polymer, would be less likely to lead to progressive cardiovascular calcification than calcium-based phosphate binders.

METHODS

Subjects

Subjects were adult (age ≥19 years) maintenance hemodialysis patients enrolled at 15 participating dialysis units: seven in the US, seven in Germany, and one in Austria. Patients with the following medical conditions were excluded from participation: serious gastrointestinal disease (including dysphagia, active untreated gas-

troparesis, severe motility disorder, major intestinal surgery, markedly irregular bowel function), ethanol or drug dependence or abuse, active malignancy, HIV infection, vasculitis, or whose diabetes mellitus or hypertension were so poorly controlled as to interfere with the conduct of the study as deemed by the investigator.

Written informed consent was obtained from all subjects. The study was conducted in compliance with the Declaration of Helsinki and Committees on Human Research at each of the participating Universities and dialysis units.

Study design and procedures

Power analysis. We hypothesized that a difference of 10 mg^2/dL^2 in the calcium-phosphorus product would be achievable and significant (assuming a change of 35 mg^2/dL^2 in the sevelamer group versus 25 mg^2/dL^2 in the calcium group). To calculate a target sample size, we considered a two-group *t* test with a two-sided alpha error rate of 5% and a common standard deviation of 20 mg^2/dL^2 based on previous trial experience. We estimated that 200 patients would provide 90% power of detecting a significant difference if one existed. The standard deviation of change in EBT score in ESRD patients was unknown and, therefore, we could not predict whether the chosen sample size would be sufficient to detect a difference in EBT scores.

Washout (run-in) phase. After screening, subjects underwent a two-week washout period in which all phosphate binders were withheld (weeks −2 to 0). Subjects who developed hyperphosphatemia (serum phosphorous >5.5 mg/dL) during the washout period were eligible for randomization.

Randomization. Patients were randomized in a 1:1 ratio to receive either sevelamer or calcium, stratified by site and the presence of diabetes at screening. The randomization schedule was computer generated using SAS 6.12 (Cary, NC, USA).

Treatment phase. Subjects were randomized to sevelamer (Renagel® 800 mg tablets; GelTex Pharmaceuticals, Waltham, MA, USA) or calcium-based binders. Subjects treated with calcium in the US received calcium acetate (PhosLo® 667 mg tablets; Braintree Pharmaceuticals, Inc., Braintree, MA, USA) and subjects in Europe were treated with calcium carbonate (Sertuerner® 500 mg tablets; Sertuerner Arzneimittel GmbH, Guetersloh, Germany). Due to the size, appearance, and taste of the tablets, neither the subjects nor the investigators were blinded to the treatment regimen. Adherence to treatment was estimated by pill counts.

The treatment phase lasted 52 weeks. During the first 12 weeks, the dose of phosphate binder was titrated every three weeks to achieve serum phosphorous and calcium concentrations in the target ranges of 3.0 to 5.0 mg/dL and 8.5 to 10.5 mg/dL, respectively. Serum calcium was adjusted for the serum albumin concentration using the formula: adjusted Ca = total measured calcium + $0.8 \times (-4.0$ g/dL albumin). Subjects could use aluminum as a rescue binder if the calcium-phosphorus product exceeded 72 mg^2/dL^2. After 12 weeks, the dose of phosphate binder, vitamin D (1,25-dihydroxy vitamin D_3, or synthetic analog, IV or PO, per the investigator), and the dialysate calcium concentration could be titrated every four weeks to achieve serum phosphorus and calcium levels in the aforementioned target ranges and a target range for intact parathyroid hormone (PTH) of 150 to 300 pg/mL. This range was chosen *a priori* based on expert opinion, with the rationale that intact PTH values in excess of 300 pg/mL were more likely to be associated with increased bone remodeling and osteitis fibrosa cystica, while intact PTH values <150 pg/mL were more likely to be associated with an abnormally low state of bone remodeling in ESRD patients [12].

Serum phosphorous and calcium were drawn weekly during the titration phase and monthly thereafter. Intact PTH was drawn at screening, baseline, 12 weeks and monthly thereafter. Total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides were drawn at baseline, 12 weeks, 24 weeks, and 52 weeks. LDL was calculated according to the Friedewald formula on nonfasting samples [13, 14]. All blood samples were analyzed at Quest Diagnostics (Van Nuys, CA, USA and Heston, Middlesex, UK). These laboratories used the same standardized assays.

Imaging procedures. Subjects underwent an EBT imaging procedure at days 0 and at 26 and 52 weeks. EBT imaging procedures were performed on C-150 scanners (GE-Imatron, South San Francisco, CA, USA) with a 100-msec scanning time and a single-slice thickness of three millimeters. Thirty-six to 40 tomographic slices were obtained for each subject during a single breath-holding period. Tomographic imaging was electrocardiographically triggered at 60 or 80% of the R-R interval (according to each individual imaging center's protocol) and proceeded from the level of the carina to the diaphragm. Thus, this imaging protocol prevented the visualization of a portion of the aortic arch. All areas of calcification with a minimal density of 130 Hounsefield units (HU) within the borders of the coronary arteries, aorta, mitral valve, and aortic valve were computed. A calcified plaque was considered present if at least three contiguous pixels with a density of ≥130 HU were detected (an area equivalent to 1.03 mm^2).

The acquired images were reviewed on a NetraMD workstation (ScImage, Los Altos, CA, USA). The total volume and density of calcification were derived for the coronary arteries and aorta, mitral valve, and aortic valve. The traditional calcium score originally described by Agatston et al [15] and an interpolated volume score

were calculated [16–18]. The Agatston score is obtained by multiplying the area of a calcified focus by a weighted density coefficient based on the peak density of the calcification [15]. The purpose of EBT imaging in our study was to investigate whether the treatments would contribute differently to calcium deposition in the arterial wall. Since the Agatston score is very sensitive to density, and density is directly related to the calcium content of the palque, this was considered the primary EBT end-point. The volumetric scoring method does not apply a scalar density factor but rather estimates the bulk of atherosclerosis [16], and was calculated for completeness. The median inter-scan variability is 8 to 10% for the Agatston score [17, 18] and 6 to 8% for the volume score [16].

Scans were considered of acceptable research quality only if the images were free from artifacts due to motion, respiration, or asynchronous electrocardiographic triggering. To ensure the continuity and consistency of the calcium score interpretation, a single expert investigator (PR) unaware of the patients' clinical status and treatment reviewed all EBT scans. However, a second reviewer analyzed a random sample of 10% of all the scans. The inter-rater agreement was 100% for the presence or absence of calcification, and >90% of total scores were within 15% of each other for the two reviewers.

For descriptive purposes, subjects were classified into four coronary calcification groups: none (calcium score = 0), mild to moderate (calcium score = 1 to 400), severe (calcium score = 401 to 1000), and very severe (calcium score >1000). This classification is a modification of the categorization proposed by Rumberger et al [19]. Calcium scores >400 indicate severe and extensive atherosclerotic disease. Non-uremic patients with calcification scores in this range are very likely to have obstructive coronary artery disease (CAD), with a high risk of developing symptomatic myocardial ischemia [19]. For this study, the classification was modified to accommodate the more extensive degree of calcification observed in the hemodialysis population. Therefore, the mild and moderate categories were combined into a single category. Additionally, a fourth group, "very severe," was introduced to categorize those subjects with markedly elevated calcium scores. There is no published classification scheme for aortic calcification scores. Therefore, we divided subjects into a group without aortic calcification and further divided the remaining subjects with calcification into tertiles.

Statistical analysis

Pretreatment characteristics were compared between the sevelamer and calcium groups using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. All laboratory analyses were performed using a last value carried forward approach. Changes from baseline to end-of-study within groups were compared with the Wilcoxon signed rank test. Between groups comparisons were performed using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

Evaluation of the change in calcification was performed in several ways owing to imperfections of each approach. The first method was calculation of the *absolute* change in calcification score (26- or 52-week value minus baseline value). While simple, this approach weighs more heavily those subjects with extensive baseline calcification who are more likely to experience larger nominal changes in calcification (in either direction) [18]. The *relative* (percent) change in calcification score was also calculated. While easy to interpret, this approach runs the risk of weighing more heavily those subjects with less extensive baseline calcification [18]. For example, a subject who experienced an increase in calcification score from 10 to 20 (100%) would be considered to have increased his or her calcification burden more than a subject whose score increased from 500 to 900 (80%). To avoid extreme percent increases among individuals with little or no baseline calcification, we excluded subjects with baseline calcification scores below 30 in the relative change analyses as done in a prior study [20]. We resolved to report absolute and relative effects of the study treatments on calcification, recognizing that qualitatively and quantitatively consistent results in both analyses would be required for our conclusions to be robust. To determine the effect of baseline calcification on subsequent calcification, we used mixed model regression on ranked changes of coronary artery and aortic calcifica-

Table 1. Baseline characteristics of study subjects

	Sevelamer ($N = 99$)	Calcium ($N = 101$)	P value
Age *years* (mean ± SD)	57 ± 14	56 ± 16	0.88
Sex *% female*	36%	34%	0.77
Race			
Black	17%	23%	0.34
White	71%	66%	
Other	12%	11%	
Diabetes *%*	32%	33%	1.0
Hypertension *%*	86%	83%	0.70
Smoker *%*	3%	8%	0.21
Primary Cause of ESRD *%*			
Hypertension	16%	17%	0.66
Glomerulonephritis	26%	16%	
Diabetes	23%	28%	
Polycystic kidney disease	9%	11%	
Other	26%	28%	
Dialysis vintage *years, median*	3.6	2.9	0.24
Phosphate binder use prior to study entry *%*			0.81
Calcium carbonate	38%	44%	
Calcium acetate	33%	36%	
Calcium + aluminum	14%	13%	
Sevelamer	3%	1%	
Other combinations	12%	6%	
Vitamin D usage at study entry *%*	56%	59%	0.67

Table 2. Main biochemical results at study completion

	Sevelamer ($N = 99$)		Calcium ($N = 101$)		
	Baseline	Final	Baseline	Final	*P* value
Phosphorus *mg/dL*	7.6 ± 1.8	5.1 ± 1.2	7.4 ± 1.9	5.1 ± 1.4	0.33
Calcium *mg/dL*	9.4 ± 0.7	9.5 ± 0.6	9.3 ± 0.7	9.7 ± 0.7	0.002
Hypercalcemia %	3%	5%	1%	16%	0.04
Calcium-phosphorus product mg^2/dL^2	71 ± 17	48 ± 12	69 ± 18	49 ± 14	0.12
Intact PTH *pg/mL*	232	224	200	138	0.11
Total-C *mg/dL*	181 ± 36	141 ± 28	184 ± 47	182 ± 49	<0.0001
LDL-C *mg/dL*	102 ± 30	65 ± 21	102 ± 37	103 ± 43	<0.0001
HDL-C *mg/dL*	44 ± 13	43 ± 10	46 ± 15	45 ± 12	0.16
Triglycerides *mg/dL*	148	137	139	150	0.22

Hypercalcemia was defined as calcium adjusted for albumin ≥10.5 mg/dL. Abbreviations are: PTH, parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Baseline values were established after two-week washout from previous phosphate binder. Values expressed as mean ± SD, except median for intact PTH and triglycerides. *P* value for Wilcoxon rank sum test comparing change from baseline across treatment groups. Final values are last values carried forward for subjects who dropped out.

Table 3. Baseline electron beam tomography (EBT) scores

	Sevelamer	Calcium	*P* value
Coronary			
N	92	94	0.51
Mean ± SD	1712 ± 2901	1125 ± 1583	
Median (interquartile range)	683 (78;2226)	600 (86;1413)	
Aorta			
N	92	94	0.39
Mean ± SD	3874 ± 6474	3233 ± 7644	
Median (interquartile range)	746 (35;4672)	367 (6;3527)	

P value refers to Wilcoxon rank sum test for comparison between groups. Seven subjects in each group did not undergo EBT testing at baseline.

Table 4. Absolute change from baseline calcification scores

	Sevelamer	Calcium	Between group *P* value
Coronary arteries at 26 weeks			
N	66	75	
Mean ± SD	−134 ± 697	110 ± 413	0.002
Median (interquartile range)	0 (−124; 53)	56 (0; 206)	
Within-group *P* value	0.51	0.0001	
Coronary arteries at 52 weeks			
N	62	70	
Mean ± SD	−46 ± 692	151 ± 471	0.04
Median (interquartile range)	0 (−33; 174)	37 (0; 330)	
Within-group *P* value	0.67	0.0002	
Aorta at 26 weeks			
N	66	75	
Mean ± SD	−595 ± 1723	230 ± 1697	0.03
Median (interquartile range)	0 (−201; 90)	11 (−3; 201)	
Within-group *P* value	0.27	0.02	
Aorta at 52 weeks			
N	62	70	
Mean ± SD	−532 ± 1706	185 ± 3100	0.01
Median (interquartile range)	0 (−258; 158)	75 (0; 441)	
Within-group *P* value	0.43	0.0007	

N denotes the number of individuals who remained active in the study after undergoing baseline EBT testing (Table 3). Within-group comparisons were made with Wilcoxon signed rank test, between group comparisons with Wilcoxon rank sum test. Corresponding *P* values for coronary artery volume scores were 0.08 at week 26 and 0.31 at week 52. Corresponding *P* values for aortic volume scores were 0.12 at week 26 and 0.45 at week 52.

tion, with baseline calcification and other predictors of calcification severity as covariates.

All probability values are two-tailed. *P* values <0.05 were considered statistically significant. All analyses were conducted using SAS 6.12 (Cary, NC, USA), with the exception of the regression analysis that was conducted using SAS 8.0.

RESULTS

Study subjects

Randomization began on May 26, 1999 and ended on January 19, 2000. The last subject completed the study on January 25, 2001. Baseline characteristics of study subjects are summarized in Table 1. Adherence to the prescribed dose was 86% in the sevelamer group and 80% in the calcium group ($P = 0.03$). Sevelamer subjects ingested an average of 6.5 ± 2.9 g of binder per day (equivalent to ~8 Renagel® 800 mg tablets) compared with calcium subjects who ingested an average dose of 4.3 ± 1.9 g per day. The average dose of calcium acetate in the United States was 4.6 g (equivalent to ~7 PhosLo® 667 mg tablets) and the average dose of calcium carbonate in Europe was 3.9 g (equivalent to ~8 Sertuerner® 500 mg tablets).

Biochemical end points

Table 2 summarizes the key biochemical end points. Baseline values represent laboratory test results obtained after a two-week phosphate binder-free washout period. Over the course of the study, 17% of sevelamer subjects and 43% of calcium subjects experienced at least

one hypercalcemic episode ($P = 0.0005$). Suppression of intact PTH below the 150 to 300 pg/mL target range was more common at the end of the study in the calcium group (57 vs. 30%, $P = 0.001$) despite the protocol-specified reduction or cessation of vitamin D for intact PTH below 150 pg/mL. Indeed, over the maintenance phase of treatment, vitamin D usage (expressed as an equivalent dose of 1,25-dihydroxy vitamin D_3) decreased by approximately 0.25 μg/week in the calcium-treated subjects and increased by approximately 0.25 μg/week in the sevelamer-treated subjects. Twelve percent of subjects in the calcium group required rescue aluminum for a calcium-phosphorus product >72 mg^2/dL^2 compared with 4% of subjects on sevelamer ($P = 0.07$). LDL cholesterol declined substantially for the sevelamer group (mean 37 ± 20%, $P < 0.0001$) but not the calcium treated group as expected per prior experience [21].

The effects of calcium and sevelamer on biochemical end points were consistent across study sites (US vs. Europe) and were not significantly influenced by age, gender, race, diabetes, or baseline vitamin D prescription (data not shown).

Cardiovascular calcification

At baseline, EBT detected coronary artery calcification in 83% and aortic calcification in 80% of study subjects. Mitral valve calcification was observed in 46% and aortic valve calcification in 35% of study subjects. Table 3 summarizes the baseline EBT scores for coronary arteries and aorta. Of the 200 randomized patients 14 did not undergo EBT imaging. Therefore, the data in Table 3 are based on an initial imaging cohort of 186 patients.

Absolute changes in calcification score

Absolute changes in calcification scores in the two treatment groups are summarized in Table 4.

There was significant progression of coronary artery and aortic calcification in the calcium group at both time points (mean and median scores positive), and no significant progression in the sevelamer group (mean scores negative, median scores zero). All comparisons between groups were statistically significant. Mitral valve and aortic valve scores did not change significantly in either group (data not shown).

Relative change in calcification score

Of the 25 subjects with no coronary calcification at baseline, 20 continued to have no calcification on repeat scans. Similarly, of the 32 subjects with no aortic calcification at baseline, 27 continued to have no calcification on repeat scans. These subjects were excluded from analyses of relative change (**Methods** section). Figure 1 shows the relative increase in coronary artery and aortic calcification at 26 and 52 weeks. The relative changes measured in calcium treated subjects were statistically significant

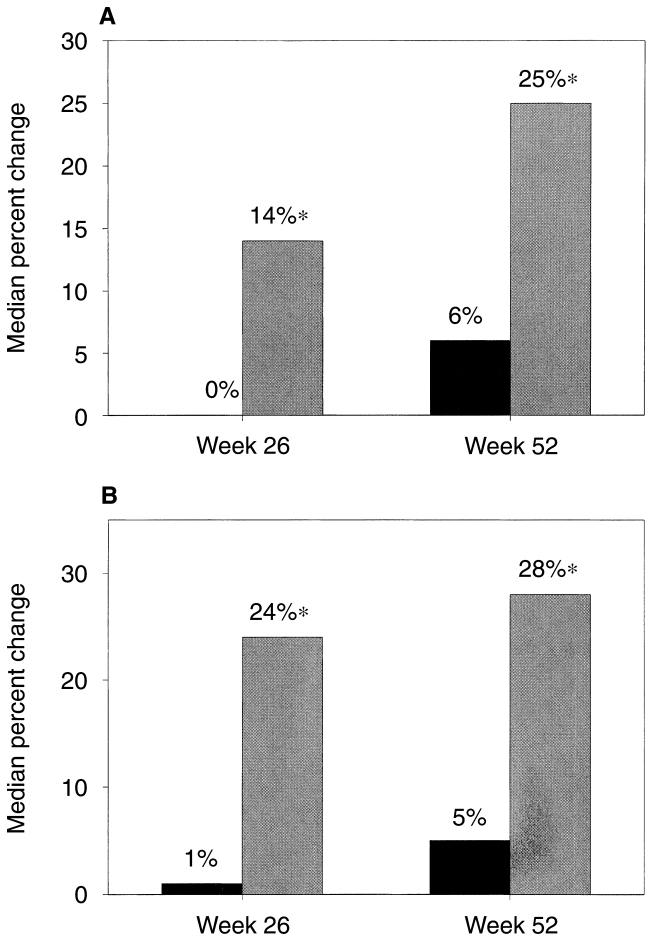

Fig. 1. (*A*) Median percentage change in coronary artery calcification scores from baseline to week 26 and week 52 in patients with calcification (scores ≥30) at baseline. *Indicates within-treatment, $P < 0.001$. Comparisons between calcium-treated (□) and sevelamer-treated (■) groups, $P = 0.01$ at week 26 and $P = 0.02$ at week 52. Corresponding values for volume score were 9% versus 18% ($P = 0.02$) for sevelamer and calcium at week 26, respectively, and 10% versus 28% ($P = 0.04$) for sevelamer and calcium at week 52, respectively. (*B*) Median percentage change in aortic calcification scores from baseline to week 26 and week 52 in patients with calcification (scores ≥30) at baseline. *Indicates within treatment, $P < 0.001$. Comparisons between calcium- and sevelamer-treated groups, $P = 0.01$ at week 26 and $P = 0.02$ at week 52. Corresponding values for volume score were 10% versus 23% ($P = 0.02$) for sevelamer and calcium at week 26, respectively, and 22% versus 37% ($P = 0.05$) for sevelamer and calcium at week 52, respectively.

while the relative score changes for sevelamer treated subjects were not. For the sevelamer treated subjects the median (interquartile range) percent changes at 52 weeks for the coronary arteries and aorta were 6% (−14 to 24%) and 5% (−21 to 39%), respectively. For the calcium treated patients the median (interquartile range) percent changes at 52 weeks were 25% (−5 to 63%) and 28% (3 to 79%) for the coronary arteries and aorta, respectively.

The between treatment comparisons were statistically significant (see Fig. 1 legend). Figure 2 shows an example

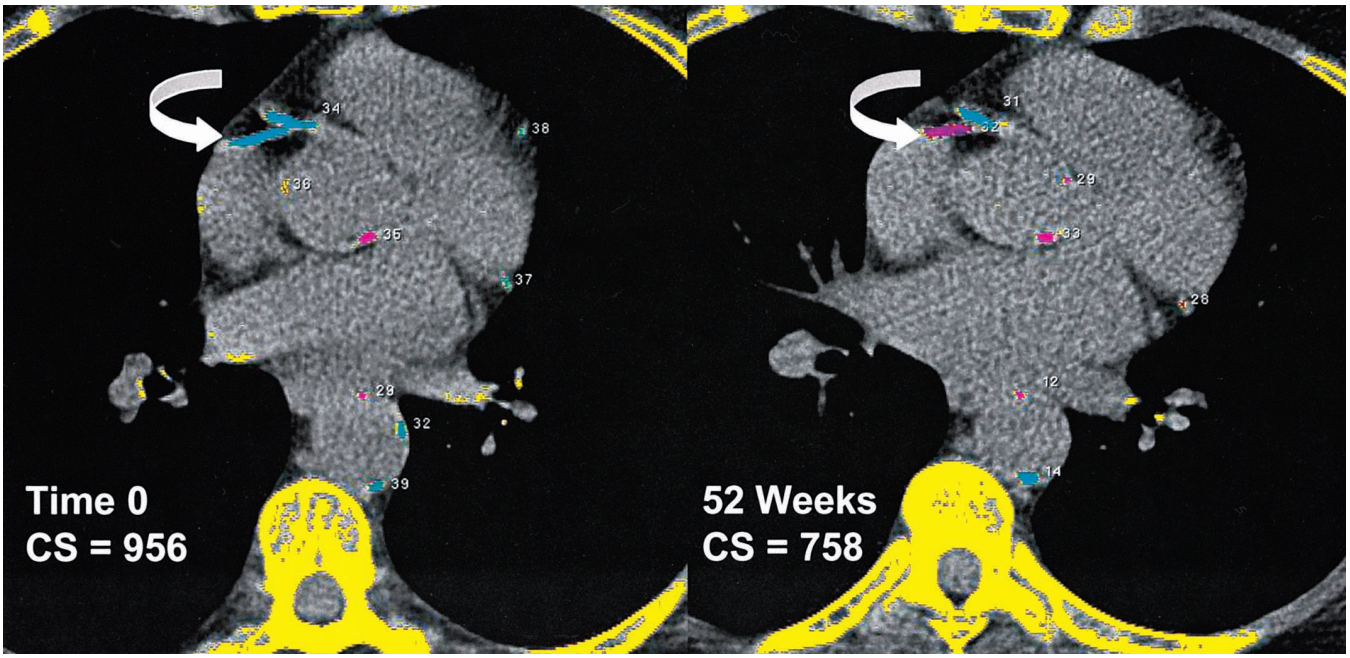

Fig. 2. Comparison of axial electron beam tomography (EBT) sections of the heart of a patient treated with sevelamer. The 52-week scan (right panel) shows a smaller total coronary artery calcium score than the initial scan (left panel). The computer software automatically assigns a color code to each plaque based on its density with a transition from various shades of red to blue as density increases. In this case the delayed scan demonstrates a less dense plaque in the middle of the right coronary artery (white arrows).

of comparative EBT scans in a patient treated with sevelamer.

Effect of baseline calcification and other factors

The degree of baseline calcification was directly correlated with the likelihood and degree of absolute progression over time. The between group differences in calcification were amplified in subjects with more severe baseline calcification of coronary arteries and aorta ($P = 0.03$ and $P = 0.04$ for the interaction, respectively). This was observed with both the Agatston score and the volume score ($P = 0.01$ and $P = 0.27$). Figure 3 illustrates the progression of coronary artery and aortic volume scores by baseline severity groupings.

Safety

In general all binders were well tolerated. Routine biochemical safety parameters were similar between the treatment groups except for serum bicarbonate, which was higher in the calcium treated subjects (22.1 ± 4.4 mEq/L vs. 19.2 ± 4.3 mEq/L, $P = 0.0003$) as the calcium salts provide base and sevelamer does not. There were six deaths in the sevelamer group and five deaths in the calcium group. A total of 37 subjects on sevelamer were hospitalized compared with 48 subjects on calcium ($P = 0.15$). Sevelamer-treated subjects were hospitalized for at total of 567 days compared with 980 days for the calcium-treated subjects ($P = 0.23$).

DISCUSSION

In this study, 200 hemodialysis subjects were randomized to receive either sevelamer or calcium salts for treatment of hyperphosphatemia. The control of serum phosphorus was equivalent with both agents, although subjects randomized to calcium experienced significantly more hypercalcemia and intact PTH levels below the targeted range. Furthermore, both coronary artery and aortic calcification progressed significantly with calcium but not with sevelamer. The difference was detectable as early as six months and continued to be significant at one year.

Calcium was initially thought to be especially effective in patients with ESRD, not only because of its efficacy as a phosphate binder, but also because of its direct effect (via normalizing or raising above normal the level of serum calcium) on secondary hyperparathyroidism and associated high turnover bone disease. However, recent evidence suggests that the use of high-dose calcium salts in ESRD might not be as benign as previously suspected [11]. Sevelamer is a nonabsorbed polymer (calcium and metal free) that has proved to be an effective phosphate binder [21, 22]. It also acts as a bile acid sequestrant and is therefore capable of reducing LDL cholesterol levels [21]. In an open label study sevelamer taken alone led to a gradual increase in intact PTH. Thus, a combination of sevelamer and vitamin D metabolites may be required to optimize control of hyperparathyroidism [23].

Vascular calcification is strongly associated with an in-

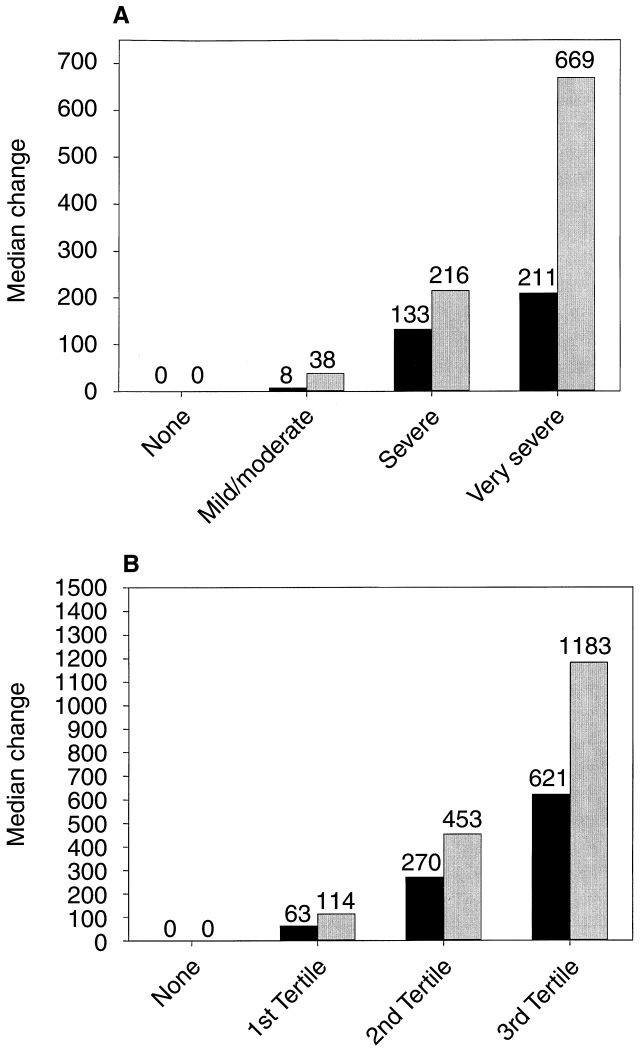

Fig. 3. (*A*) Nominal change in coronary artery coronary artery volume scores from baseline to week 52 by baseline calcification group. (*B*) Nominal change in aorta volume scores from baseline to week 52 by baseline calcification group. Symbols are: (■) sevelamer; (▨) calcium.

creased risk of cardiovascular events and mortality in both non-uremic and uremic patients [24–34]. Like in the non-uremic patient, calcification in ESRD occurs in the arterial intima in association with atherosclerotic plaques [35]. However, medial calcification can also occur and probably increases arterial stiffness and ventricular afterload [36]. Increased arterial stiffness in turn has been associated with increased cardiovascular mortality in ESRD [33, 34].

In observational studies, cardiovascular calcification in ESRD has been variably associated with age, dialysis vintage, race, diabetes, serum phosphorus, calcium, HDL cholesterol and triglyceride concentrations, markers of inflammation, and higher doses of calcium salts used as phosphate binders [8, 11, 36–38]. However, to our knowledge this is the first study in patients with ESRD in which the progression of calcification over time has been influenced by any means.

A possible mechanism explaining the observed treatment effects may be ongoing calcium loading related to oral calcium ingestion. This would be consistent with the findings of Goodman et al and Guérin et al, who reported an association of the dose of oral calcium and the risk of vascular calcification [11, 36]. Notably, the serum calcium may not reflect the total body calcium load, and excess calcium may be particularly prone to deposit in the tissues when the serum phosphorus is high and when the intact PTH is low, the latter reflecting a state of low bone turnover [12]. Other factors unrelated to calcium, such as the favorable effect of sevelamer on LDL cholesterol, also may have contributed to the study's findings. In a cross sectional analysis of these study subjects, we found serum phosphorous, calcium, and intact PTH to be related to coronary and aortic calcification, while total, LDL, and HDL cholesterol were not [8]. Callister et al demonstrated that HMG Co-A reductase inhibitors reduce or arrest the progression of coronary artery calcification in persons with normal renal function [20]. Whether statins would reduce coronary and aortic calcification in persons with ESRD is unknown.

Limitations of the study include the relatively brief period of observation (1 year), the absence of subjects on peritoneal dialysis, and the inability of EBT to distinguish between intimal (atherosclerotic) and medial calcification, although both carry a negative prognosis for cardiovascular events. While both treatments were able to achieve excellent control of serum phosphorus and calcium-phosphorus product, the study failed to achieve the end point for which it was powered (a 10 mg^2/dL^2 difference in end-of-study calcium-phosphorus product between study groups). Nevertheless, the calcium-phosphorus product was marginally lower in the sevelamer group and the serum calcium and intact PTH levels were more likely within target ranges. Finally, we cannot determine the exact mechanism of the relative protection afforded by sevelamer. Additional studies will be required to determine whether reduced calcium intake, fewer episodes of hypercalcemia, improved control of intact PTH, or other metabolic effects (such as, lipids) are responsible for the benefit. At present, it is difficult to ascribe the progression in calcification to vitamin D per se, since usage was increased in the sevelamer-treated subjects who experienced less calcification over time.

In summary, herein we provide evidence that treatment with sevelamer results in fewer episodes of hypercalcemia, improved control of PTH and attenuation of the progression of coronary artery and aortic calcification relative to calcium salts. It remains to be demonstrated whether attenuation of coronary artery and aortic calcification will translate into a reduction in the burden of cardiovascular disease in this vulnerable population.

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