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Original Investigation

Effect of Sevelamer and Calcium-Based Phosphate Binders on Coronary Artery Calcification and Accumulation of Circulating Advanced Glycation End Products in Hemodialysis Patients

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Background: Some trials have indicated that coronary artery calcification progresses more slowly in sevelamer-treated dialysis patients than in those using calcium-based binders. Effects of phosphate binders on circulating advanced glycation end products (AGEs) are unknown.

Study Design: Randomized trial with parallel-group design.

Setting & Participants: 183 adult (aged >20 years) patients on maintenance hemodialysis therapy at 12 dialysis facilities with a mean vintage of 118 ± 89 (median, 108) months. Dialysate calcium concentration was 2.5 mEq/L, and dietary calcium was not controlled.

Intervention: Patients were randomly assigned to 12 months of treatment with sevelamer (n = 91) or calcium carbonate (n = 92).

Outcomes & Measurements: Primary outcome measures were change from baseline in coronary artery calcification score (CACS) determined at study entry and completion using multislice computed tomography and the proportion of patients with a ≥15% increase in CACS. Blood parameters were determined at study entry and 2-week intervals, and levels of plasma pentosidine, a representative AGE, were determined at study entry, 6 months, and study completion.

Results: 79 (86.8%) and 84 (91.3%) patients in the sevelamer and calcium-carbonate arms completed the treatment, respectively. Both binders were associated with an increase in mean CACS: 81.8 (95% CI, 42.9-120.6) and 194.0 (139.7-248.4), respectively ($P < 0.001$ for both). After adjustment for baseline values, the increase in the sevelamer group was 112.3 (45.8-178) less ($P < 0.001$). Percentages of patients with a ≥15% increase in CACS were 35% of the sevelamer group and 59% of the calcium-carbonate group ($P = 0.002$). Plasma pentosidine levels increased with sevelamer treatment ($P < 0.001$). Sevelamer use was associated with decreased risk of a ≥15% increase in CACS regardless of baseline blood parameters, pentosidine level, and CACS.

Limitations: Treatment duration was relatively short, some sevelamer-treated patients (7 of 79) received calcium carbonate, and washout could not be performed.

Conclusions: The data suggest that sevelamer treatment slowed the increase in CACS and suppressed AGE accumulation.

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INDEX WORDS: Advanced glycation end products; coronary artery calcification; hemodialysis; low-density lipoprotein (LDL) cholesterol; pentosidine; sevelamer hydrochloride.

Coronary artery calcification occurs often in dialysis patients[1,2] and is predictive of cardiovascular morbidity and mortality in patients with end-stage renal disease.[3-7] Disturbed mineral metabolism assumes particular importance in vascular calcification in patients with end-stage renal disease.[8-11] Increased levels of serum phosphorus and calcium and calcium-phosphorus product in dialysis patients are associated independently with increased risk of arterial calcification[12,13] and cardiovascular mortality.[13-17] In vitro, exposure to high concentrations of phosphate, calcium, or both causes calcification of human smooth

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muscle cells[18,19] and rat aortic rings.[20] However, dietary restriction and dialysis are ineffective in controlling hyperphosphatemia, and most dialysis patients require phosphate-binder therapy.

Calcium-based phosphate binders have been the first-choice binder for dialysis patients. However, use of calcium-based phosphate binders has been questioned because calcium intake is higher in dialysis patients with coronary artery calcification than in those without,[2] and calcium-based phosphate-binder dose correlates with the severity of arterial calcification.[7,21] An option is to decrease dialysate calcium concentrations; however, adequate dialysate calcium concentrations presently are a subject of debate.[22,23] Sevelamer, a nonabsorbed mineral-free phosphate binder, decreases serum phosphorus and parathyroid hormone (PTH) levels in dialysis patients[24,25] and has decelerated the progression of coronary artery calcification[26-31] and improved mortality.[32] These effects of sevelamer have been attributed to its ability to improve key parameters, including low-density lipoprotein (LDL) cholesterol and PTH.[26-32]

Advanced glycation end products (AGEs) are a group of heterogeneous compounds formed through nonenzymatic oxidative and nonoxidative reactions between proteins and reactive carbonyl compounds derived from carbohydrates and lipids.[33] AGE levels and oxidative stress are both increased in uremic patients and have been related to cardiovascular disease.[34-36] Recently, evidence was provided that an increase in levels of plasma pentosidine, an AGE, is associated with the progression of coronary artery calcification in dialysis patients.[37,38]

The present randomized trial examined the effects of sevelamer and calcium carbonate on the progression of coronary artery calcification and plasma pentosidine concentrations in hemodialysis (HD) patients.

METHODS

Patients

Adult (aged >20 years) patients undergoing maintenance HD therapy at 12 participating dialysis facilities in Japan were enrolled. Exclusion criteria were serious gastrointestinal disease (dysphagia, active untreated gastroparesis, severe motility disorder, intestinal surgery, and markedly irregular bowel function), alcohol or drug dependence or abuse, active malignancy vasculitis, or poorly controlled diabetes or hypertension deemed by the investigator to interfere with appropriate and safe study execution.

Written informed consent was obtained from all patients before study-related procedures were performed. The study was approved by the institutional review board at each participating organization and conducted in compliance with the Declaration of Helsinki.

Study Design and Procedures

We based target sample-size calculation on data from Chertow et al[26]; namely, mean ± standard deviation coronary artery calcification score (CACS) of 151 ± 471 and –46 ± 692 after 52 weeks of treatment with calcium carbonate and sevelamer, respectively. A 2-group t test with 2-sided α error rate of 5%, 80% power, and common standard deviation of 471 estimated that 91 patients per group would allow detection of a significant difference in absolute change from baseline CACS between the sevelamer and calcium-carbonate groups.

Patients were randomly assigned at the coordinating center between April 1, 2004, and December 30, 2005, in a 1:1 fashion to open-label treatment with sevelamer hydrochloride or calcium carbonate. Investigators were informed of patient allocation using concealed envelopes. The study was completed on December 30, 2006. Sevelamer hydrochloride (Renagel, 250-mg tablets; Chugai Pharmaceutical Co Ltd [www.chugai-pharm.co.jp] or Phosblock, 250-mg tablets, Kyowa Hakko Kirin Co Ltd. [www.kyowa-kirin.co.jp]) was prescribed in the sevelamer arm. When serum phosphorus level could not be controlled to <6.5 mg/dL in the sevelamer arm, 9 g/d of sevelamer with up to 1.5 g/d of precipitated calcium carbonate was allowed. In the calcium-carbonate arm, only calcium carbonate was used. Study duration was 12 months. Multislice computed tomography (CT) was performed at study entry and completion.

Investigators were instructed to control serum calcium, phosphorus, PTH, and dyslipidemia every 2 weeks. Although this study predated publication of the National Kidney Foundation's KDOQI (Kidney Disease Outcomes Quality Initiative) clinical practice guideline for bone disease and metabolism in chronic kidney disease,[39] clinical practice included target values <10.2 mg/dL for serum calcium, <6.5 mg/dL for serum phosphorus, <65 mg^2/dL^2 for calcium-phosphorus product, and 150-300 pg/mL for PTH. Investigators were free to modify the dose of phosphate binders. In general, when serum calcium level was >10.5 mg/mL, either the calcium carbonate dose was decreased or vitamin D_3 dose was decreased or discontinued; when serum phosphorus level was >6.5 mg/dL, phosphate-binder doses were increased. During the trial, dialysate calcium concentration was 2.5 mEq/L, dietary calcium intake was not controlled, no estimate of patient adherence (pill count) was performed, and no patient received calcimimetics. Investigators and clinicians were blinded to results of multislice CT. Baseline medical conditions were based on clinical diagnoses and assessed using chart review.

Laboratory Measurements

Biochemical parameters were determined at baseline and 2-week intervals. Serum glucose, creatinine, urea, phosphorus, calcium, LDL and high-density lipoprotein cholesterol, and triglycerides were measured using an Hitachi Model 7700 (Hitachi Electronics Co Ltd, www.hitachi.co.jp). PTH was determined using an Elecsys PTH analyzer (Roche Diagnosis, www.roche.com).

Pentosidine Measurement by High-Performance Liquid Chromatography

Plasma pentosidine concentration was determined at study entry, 6 months into treatment, and at study completion. Fresh heparinized plasma samples were obtained before dialysis. Pentosidine concentrations were determined using reverse-phase high-performance liquid chromatography as described previously[40,41] with synthetic pentosidine as a standard.

Imaging Procedure

All CT was performed at the Tokai University Hospital on 1 CT scanner by 2 radiologists who were blinded to patient information. CT was performed using a 64-slice multislice CT scanner (Somatom Cardiac Sensation 64; Siemens Medical Solutions, www.siemens.com). The CT protocol consisted of electrocardiogram-

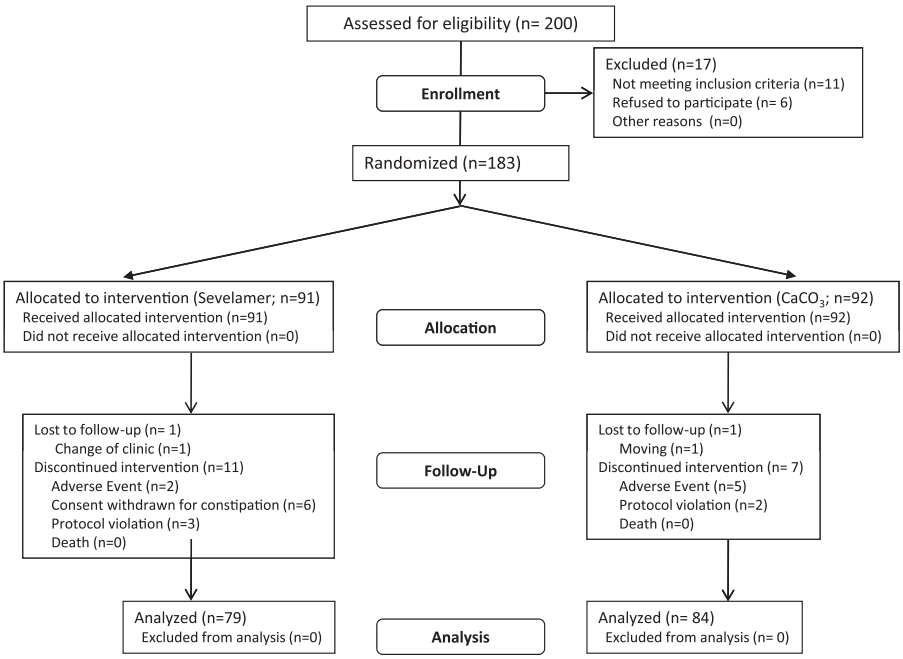

Figure 1. Patient disposition. A total of 200 hemodialysis patients initially were screened; 17 were excluded on the basis of the exclusion criteria, and 183 patients were randomly assigned to 12-month treatment with either sevelamer hydrochloride (n = 91) or calcium carbonate ($CaCO_3$; n = 92). Of those, 163 patients (79 patients in the sevelamer arm and 84 patients in the calcium-carbonate arm) completed the study.

gated acquisition of the entire heart, with the patient scanned in the supine position in the cranio-caudal direction and after deep inspiration. Acquisition parameters were collimation of 64×0.6 mm with z-flying focal spot for the simultaneous acquisition of 64 overlapping 0.6-mm slices, rotation time of 0.33 seconds, pitch of 0.3, tube voltage of 120 kV, tube-current time product of 200 mA, and slice thickness of 3.0 mm. Calcium scoring was performed by the 2 radiologists according to Agatston scoring[42] on the reconstructed image sets using commercially available software (syngo Ca Scoring; Siemens Medical Solutions) using the standard lower threshold of 130 HU.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and compared using Student *t* test or Pearson χ^2 test. A last-value-carried-forward approach was used for biochemical parameters. The difference between groups in proportions of patients with a ≥15% increase in CACS was analyzed using χ^2 test. Differences in the mean change in each variable were evaluated using analysis of covariance. Logistic regression was used to examine the relationships between risk of a ≥15% increase in CACS and calcium carbonate treatment compared with sevelamer treatment. Odds ratios also were adjusted for each variable. All statistical analyses followed the intent-to-treat principle.

Changes in calcification were evaluated as absolute change in CACS (final value minus baseline value) and relative change in CACS (proportion of patients with a ≥15% increase in CACS). These 2 outcome measures were used for analyses because the former more heavily weighs patients with extensive baseline calcification and the latter carries the risk of more heavily weighing those with less extensive baseline calcification.

All probability values are 2 tailed. $P < 0.05$ is considered significant. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc, www.spss.com) and R, version 2.10.1 (www.r-project.com).

RESULTS

Patients

Two hundred patients were screened; 17 were excluded on the basis of the established criteria, and 183 patients were randomly assigned to sevelamer (n = 91) or calcium-carbonate therapy (n = 92; Fig 1). Seventy-nine (86.8%) and 84 (91.3%) participants in the sevelamer and calcium-carbonate arms completed the 12 months of treatment, respectively. Of sevelamer-

Table 1. Baseline Characteristics of Study Participants

	Sevelamer	Calcium Carbonate	*P*
No. of participants	91	92	
Men/women	52/39	47/45	0.5
Age (y)	59 ± 12	57 ± 12	0.3
HD vintage (mo)	105 ± 84	119 ± 92	0.3
Primary cause of CKD (%)			
Diabetes	23	19	0.5
Chronic glomerular nephritis	59	57	0.9
Others	18	24	0.3
Smoking (%)	17	22	0.5
Hypertension (%)	55	59	0.7
Coronary artery disease (%)	9	5	0.2
Vitamin D_3 medication (%)	60	68	0.3
Statin medication (%)	8	11	0.6
Phosphate-binder use before study entry (%)			
Sevelamer	39	26	0.1
Calcium carbonate	25	40	0.1
Sevelamer + calcium carbonate	32	29	0.6
Other combinations	3	4	0.7

Note: Unless otherwise indicated, continuous variables expressed as mean ± standard deviation. Differences between groups were analyzed using *t* test for continuous variables and χ^2 test for categorical variables.

Abbreviations: CKD, chronic kidney disease; HD, hemodialysis.

Table 2. Biochemical Parameters and Coronary Artery Calcification During the Study

Variable	Sevelamer (n = 91)				Calcium Carbonate (n = 92)					
	Baseline	Final	Mean Change (95% CI)	*P*	Baseline	Final	Mean Change (95% CI)	*P*	Difference in Mean Change (95% CI)	*P*[a]
Albumin (g/dL)	4.03 ± 0.42	3.92 ± 0.37	−0.10 (−0.17 to −0.04)	0.001	4.03 ± 0.42	3.91 ± 0.40	−0.12 (−0.20 to −0.05)	0.002	0.02 (−0.08 to 0.12)	0.7
Calcium corrected (mg/dL)	9.79 ± 0.79	9.61 ± 0.60	−0.18 (−0.33 to −0.03)	0.02	9.71 ± 0.63	9.85 ± 0.79	0.14 (−0.003 to 0.28)	0.06	−0.32 (−0.52 to −0.12)	0.002
Phosphorus (mg/dL)	5.65 ± 0.56	5.15 ± 0.83	−0.50 (−0.69 to −0.31)	<0.001	5.75 ± 0.76	5.14 ± 0.94	−0.61 (−0.81 to −0.41)	<0.001	0.11 (−0.17 to 0.38)	0.7
Ca × P (mg^2/dL^2)	55.33 ± 7.10	49.50 ± 8.71	−5.83 (−7.73 to −3.92)	<0.001	55.78 ± 7.8	50.56 ± 9.8	−5.21 (−7.23 to −3.20)	<0.001	−0.62 (−3.37 to 2.14)	0.5
Intact PTH (pg/mL)	235.6 ± 169.9	233.9 ± 196.4	−1.7 (−44.5 to 41.2)	0.9	214.9 ± 137.3	237.5 ± 231.8	22.6 (−16.0 to 61.1)	0.2	−24.2 (−38.9 to 42.2)	0.5
LDL-C (mg/dL)	92.1 ± 25.6	72.9 ± 27.7	−19.2 (−24.6 to −13.8)	<0.001	97.2 ± 33.2	98.9 ± 33.1	1.6 (−3.5 to 6.8)	0.5	−20.8 (−28.2 to −13.4)	<0.001
HDL-C (mg/dL)	50.8 ± 14.4	50.4 ± 18.2	−0.4 (−2.6 to 1.9)	0.7	51.2 ± 17.6	51.0 ± 17.7	−0.2 (−3.1 to 2.7)	0.9	−0.2 (−3.8 to 3.5)	0.9
Pentosidine (nmol/mL)	1.861 ± 0.761	1.882 ± 0.860	0.022 (−0.072 to 0.116)	0.6	1.845 ± 0.907	2.121 ± 0.930	0.276 (0.167 to 0.385)	<0.001	−0.254 (−0.396 to −0.112)	<0.001
WBC (/μL)	5,373 ± 1,557	5,295 ± 1,508	−78 (−322 to 166)	0.5	5,548 ± 2,070	5,421 ± 1,704	−127 (−370 to 116)	0.3	49 (−293 to 391)	0.9
CACS	879 ± 1,334	961 ± 1,438	81.8 (42.9 to 120.6)	<0.001	872 ± 1,186	1,066 ± 1,380	194.0 (139.7 to 248.4)	<0.001	−112.3 (−178.8 to −45.8)	<0.001

Note: Continuous variables are expressed as mean ± standard deviation and compared using paired *t* test. Difference in mean change represents the difference between the sevelamer and calcium-carbonate groups in the mean value of change from baseline. The difference between groups was analyzed using ANCOVA after controlling for baseline values, and the obtained *P* values are presented in the far right column. Conversion factors for units: albumin in g/dL to g/L, ×10; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; LDL-C and HDL-C in mg/dL to mmol/L, ×0.02586; no conversion necessary for PTH in pg/mL and ng/L and pentosidine in nmol/L and mmol/L.

Abbreviations: ANCOVA, analysis of covariance; CACS, coronary artery calcification score; Ca × P, calcium-phosphorus product; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone; WBC, white blood cell count.

[a]ANCOVA.

treated participants, 72 received sevelamer alone and 7 received sevelamer and calcium carbonate. All participants in the calcium-carbonate arm received calcium carbonate only. Adverse events were constipation (n = 2) in the sevelamer arm and persistent increases in serum calcium levels (>11 mg/dL; n = 5) in the calcium-carbonate arm.

The 2 groups were similar in baseline characteristics (Table 1). Coronary artery disease at study entry included previous myocardial infarction, history of coronary angioplasty and/or stent placement, angina pectoris, evidence of coronary atherosclerotic disease, stroke, transient ischemic attack, and claudication. Phosphate-binder use before study entry included monotherapy with sevelamer or calcium carbonate, their combination, and other phosphate-binder combinations, such as calcium carbonate and calcium acetate.

Coronary Artery Calcification

At baseline, 10 (11.6%) and 8 (9.7%) participants in the sevelamer and calcium-carbonate arms had no detectable coronary artery calcification, respectively. During the 12-month treatment, absolute values for CACS increased significantly in both groups ($P < 0.001$; Table 2). Analysis of covariance after adjusting for baseline values showed that the mean change in CACS was significantly smaller for the sevelamer group ($P < 0.001$; Table 2). The proportion of participants with a ≥15% increase in CACS also was significantly smaller for the sevelamer group ($P = 0.002$; Table 3; Fig 2), with a ≥15% increase in CACS in 35% of the sevelamer group and 59% of the calcium-carbonate group.

Biochemical Parameters

Baseline biochemical parameters were not different between the groups at study entry (Table 2). During treatment, serum albumin levels decreased significantly in both groups ($P = 0.001$ for the sevelamer and $P = 0.002$ for the calcium-carbonate groups). Serum calcium levels showed no significant change in either group (Table 2), whereas values at study completion were significantly higher for the calcium-carbonate group ($P = 0.002$; Table 2; Fig 3). Serum phosphorus and calcium-phosphorus product values decreased from baseline in both groups ($P < 0.001$; Table 2) and were indistinguishable at study completion between groups (Table 2; Fig 3). PTH and high-density lipoprotein cholesterol levels were unchanged in both groups. LDL cholesterol levels decreased significantly in only the sevelamer group ($P < 0.001$) and were significantly lower for the sevelamer group at study completion ($P < 0.001$; Table 2). Plasma pentosidine levels increased in only the calcium carbonate group ($P < 0.001$; Table 2; Fig 4), and analysis of covariance after adjusting for baseline values showed that plasma pentosidine levels were significantly higher in the sevelamer group at completion of treatment ($P < 0.001$).

During the course of the study, suppression of PTH (<150 pg/mL) occurred at similar frequencies (38.0% and 40.5% in the sevelamer and calcium-carbonate groups, respectively; not significant). Increases in LDL cholesterol levels (>120 mg/dL) were more frequent in the calcium-carbonate group (20.2% vs 15.2%; $P = 0.001$).

Table 3. Treatment Effect on CAC Progression in Subgroups Defined by Baseline Variables

	No.	OR (95% CI) for ≥15% Increase in CACS	P
Intervention effect			
Calcium carbonate	92	1.00 (reference)	
Sevelamer	91	0.38 (0.21-0.69)	0.002
Interaction between intervention and each variable			
Sex	183	NA	0.5
Age (y)	183	NA	0.3
HD vintage (mo)	183	NA	0.3
Diabetes mellitus	183	NA	0.3
Baseline Ca × P (mg^2/dL^2)	183	NA	0.7
Baseline LDL cholesterol	183	NA	0.5
Baseline pentosidine	183	NA	0.1
Baseline CACS	183	NA	0.8

Note: ORs for a ≥15% increase from baseline CACS were determined for the sevelamer and calcium-carbonate groups, and that for the sevelamer group is presented using as reference the OR for the calcium-carbonate group. Interaction between intervention and each variable was determined, and *P* value is presented for each variable.

Abbreviations: CAC, coronary artery calcification; CACS, coronary artery calcification score; Ca × P, calcium-phosphorus product; CI, confidence interval; HD, hemodialysis; LDL, low-density lipoprotein; NA, not applicable; OR, odds ratio.

Treatment Effect Interacted With Each Variable on CACS Progression

The treatment effect on the risk of a ≥15% increase in CACS was analyzed using logistic regression. Compared with calcium carbonate, sevelamer therapy was associated with decreased risk of a ≥15% increase in CACS (Table 3). We also evaluated effect modification using cross-product terms (interaction terms) in the model to test the relationship between intervention and each variable (sex, age, HD vintage, presence or absence of diabetes mellitus, baseline LDL cholesterol level, baseline pentosidine level, baseline CACS, or baseline calcium-phosphorus product). There were no statistically significant interactions (Table 3).

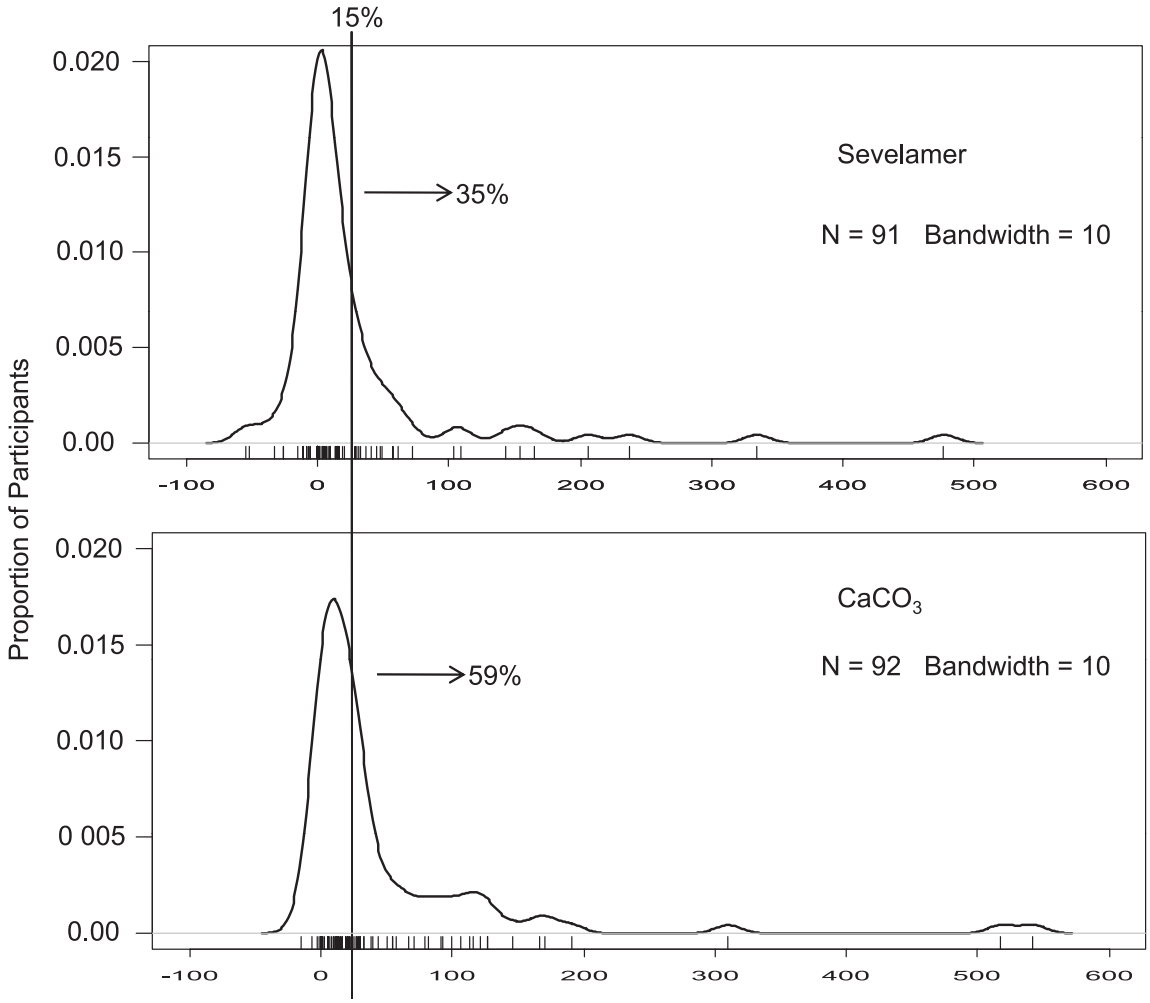

Figure 2. Distribution of participants according to percentage of increase from baseline coronary artery calcification score (CACS). The vertical line represents a 15% increase in CACS. The percentage of participants with a ≥15% increase in CACS is indicated for each group. Abbreviation: $CaCO_3$, calcium carbonate.

DISCUSSION

This randomized trial showed that sevelamer and calcium carbonate were equipotent in decreasing serum phosphorus levels in HD patients, whereas sevelamer resulted in a smaller increase in CACS. Compared with calcium carbonate, sevelamer was associated with decreased risk of progression of coronary artery calcification regardless of sex, age, HD vintage, CACS, and levels of serum calcium and phosphorus, LDL cholesterol, and plasma pentosidine at baseline.

For the study duration of 12 months, the increases of 211 (95% confidence interval, 153-270) and 90 (95% confidence interval, 45-134) in CACS with calcium carbonate and sevelamer, respectively, are similar to the corresponding values of 484 and 37 in a 21-month trial,[30] 37 and 0 in a 52-week trial,[26] and 42 and 0 in an 18-month trial.[29] It deserves mention that dialysis vintages of the present participants, 107 ± 86 and 119 ± 94 months for the sevelamer and calcium-carbonate arms, respectively, are longer than the 68 ± 64 and 55 ± 64 months in Asmus et al,[30] 69 ± 65 and 58 ± 66 months in Braun et al,[28] and median vintage of 3.6 and 2.9 years in Chertow et al.[26] Thus, our trial extends the previously described beneficial effect of sevelamer on coronary artery calcification to HD patients with a relatively longer vintage.

Sevelamer and calcium-carbonate therapy decreased serum phosphorus levels, with no significant change in PTH levels. Serum calcium levels showed a statistically insignificant increase and decrease with calcium carbonate and sevelamer, respectively, resulting in a significant difference between groups at study completion. Sevelamer was associated with decreased risk of progression of coronary artery calcification regardless of baseline serum calcium concentration. Seminal in warning against calcium-based phosphate binder–associated calcium intake were reports that

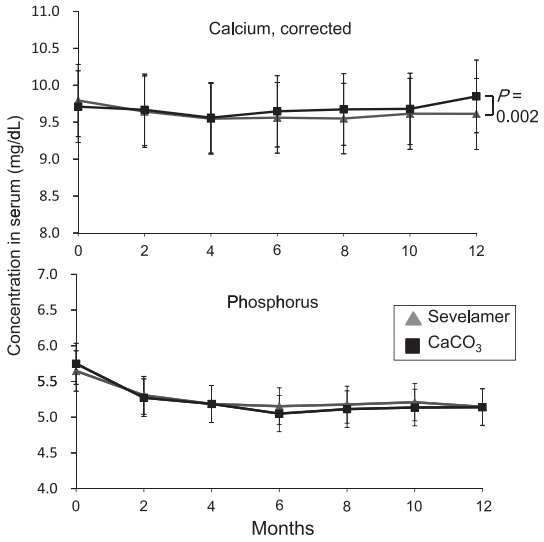

Figure 3. Changes in serum calcium and phosphorus concentrations during treatment. Serum calcium and phosphorus concentrations were determined at study entry and every 2 weeks thereafter during treatment. Values are mean ± standard deviation. Conversion factors for units: phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/mL to mmol/L, ×0.2495. Abbreviation: $CaCO_3$, calcium carbonate.

dialysis patients with coronary artery calcification had higher calcium intake than those without,[2] and calcium-based phosphate-binder dose correlated positively with severity of arterial calcification.[7,21] Calcium-based phosphate binders were more likely than sevelamer to cause low PTH level episodes, hypercalcemia,[26,29,43] and decreased trabecular bone density.[30] Our trial had more withdrawals for increased serum calcium levels in the calcium-carbonate arm, indicating the occurrence of calcium loading. However, in the present patients who completed the study without hypercalcemic events, serum calcium levels had no influence on the effect of sevelamer on the progression of coronary artery calcification. Moreover, both binders resulted in similar incidences of low PTH levels and no significant changes in PTH levels. Thus, given that dialysate concentration was the same and dietary calcium intake was not controlled in the present trial, calcium loading with calcium carbonate had a minor role in the difference observed in the effect on coronary artery calcification, except when so extreme to have precipitated hypercalcemia.

Only sevelamer decreased LDL cholesterol levels, whereas calcium carbonate resulted in more frequent increases in LDL cholesterol levels (>120 mg/dL). Sevelamer's effect on the risk of progression of coronary artery calcification was not affected by baseline LDL cholesterol level. Decreases in LDL cholesterol levels commonly occur with sevelamer use[26,29,43,44] and are explained because sevelamer shares the cationic character of bile acid sequestrants[45,46] and has a cooperative high-capacity bile acid–binding ability.[47] The potential of lipid-lowering therapy on vascular calcification was suggested first by the report that statins decreased the volume of calcified plaques in coronary arteries.[48] Lipid-lowering therapy attenuated the progression of coronary artery calcification in patients with LDL cholesterol levels >130 mg/dL[49] and hypercholesterolemic postmenopausal women.[50] However, a recent trial showed that halving LDL cholesterol levels using statins had no effect on the progression of coronary artery calcification.[51] In the trials of sevelamer, the associations between coronary artery calcification and LDL cholesterol level were unsubstantiated,[26] not significant,[4,43] or inconclusive.[29] The benefit of lipid-lowering therapy in general was documented when participants had mean LDL cholesterol levels ≥120,[48] >130,[49] or 175.3 ± 32.4 mg/dL.[50] It is possible that the number of patients with baseline LDL cholesterol levels ≥120 mg/dL in the present study was too small to assess the clinical significance of the LDL cholesterol-lowering effect of sevelamer.

Plasma pentosidine levels increased in only the calcium-carbonate group and were significantly higher in the calcium-carbonate group at study completion. Sevelamer therapy was associated with decreased risk of progression of coronary artery calcification regardless of baseline plasma pentosidine concentration. Pentosidine is a representative AGE often used as a marker for AGEs.[52,53] Initially believed to occur only under a high carbohydrate milieu, pentosidine and other AGEs are present in nondiabetic uremic patients in concentrations higher than those in diabetic patients.[40,54-58] Formation of pentosidine and N^{ϵ}(carboxyl-methyl)lysine, an AGE structure, in uremia is driven by accumulating reactive carbonyl compounds,[53,59] which are generated not only from carbohydrates but also from polyunsaturated fatty acids

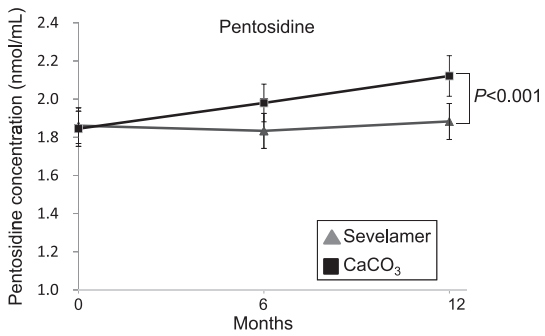

Figure 4. Changes in plasma pentosidine concentrations during treatment. Plasma pentosidine concentrations were determined at study entry, 6 months into the treatment, and study completion, and the mean of each determination is presented. No conversion necessary for pentosidine in nmol/mL and mmol/L. Abbreviation: $CaCO_3$, calcium carbonate.

through peroxidation[60] and modify proteins to form advanced lipoxidation end products.[53] Levels of these products also are increased in uremia.[53,61-63] A link was presented for AGEs and vascular calcification when increased plasma pentosidine levels were correlated with severity of abdominal aorta calcification in HD patients.[37] Taki et al[38] determined levels of circulating pentosidine, N^{ϵ}(carboxyl-methyl)lysine, malondialdehyde, and lipid peroxides along with traditional cardiovascular risk factors and calcium overload in HD patients and concluded that AGEs and oxidative stress were associated with coronary artery calcification independent of previously described risk factors. An 18-year follow-up also showed a significant correlation between increased circulating AGE levels and increased cardiovascular and coronary disease mortality in nondiabetic women.[64] Thus, the present prospective trial provided further evidence for the association between AGE accumulation and progression of coronary artery calcification. However, analysis after controlling for pentosidine level change from baseline as a covariate produced $P = 0.661$ for pentosidine level and $P = 0.001$ for intervention, indicating that the effect of the intervention is not mediated by the change in pentosidine levels. It is possible that calcium-based phosphate binder–associated calcium loading entails AGE accumulation, resulting in enhanced coronary artery calcification.

Multiple lines of evidence indicate that AGEs and oxidative stress are involved in the pathogenesis of cardiovascular disease.[34,65-67] Notably, atherogenesis and vascular calcification were enhanced by uremia in apolipoprotein E–deficient mice[68-70] and attenuated by oral sevelamer therapy, with decreases in serum phosphorus and PTH levels and oxidative damage, whereas levels of serum total cholesterol, calcium, and uremic toxins were unaffected,[71] suggesting a relationship between AGEs and the effect of sevelamer on vascular calcification in uremia. However, because the contribution of dietary AGEs to their plasma levels has been documented,[72-74] we cannot deny the possibility that sevelamer decreased appetite and dietary AGE intake, resulting in decreased plasma pentosidine levels.

Limitations of the present study were that treatment duration was relatively short, treatment was open label, some sevelamer-treated participants (7 of 79) also received calcium carbonate, and statistical power was 80%. Washout could not be performed because participants were well informed of the risk of hyperphosphatemia and were unwilling to discontinue phosphate-binder therapy.

In conclusion, our findings extended the beneficial effect of sevelamer to HD patients with relatively long vintage and suggested a relationship between the effect of sevelamer on the progression of coronary artery calcification and suppression of AGE accumulation.

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