Dialysis

A 1-Year Randomized Trial of Calcium Acetate Versus Sevelamer on Progression of Coronary Artery Calcification in Hemodialysis Patients With Comparable Lipid Control: The Calcium Acetate Renagel Evaluation-2 (CARE-2) Study

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Background: Previous clinical trials showed that progression of coronary artery calcification (CAC) may be slower in hemodialysis patients treated with sevelamer than those treated with calcium-based phosphate binders. Because sevelamer decreases low-density lipoprotein cholesterol (LDL-C) levels, we hypothesized that intensive lowering of LDL-C levels with atorvastatin in hemodialysis patients treated with calcium acetate would result in CAC progression rates similar to those in sevelamer-treated patients.

Study Design: Randomized, controlled, open-label, noninferiority trial with an upper bound for the noninferiority margin of 1.8.

Setting & Participants: 203 prevalent hemodialysis patients at 26 dialysis centers with serum phosphorus levels greater than 5.5 mg/dL, LDL-C levels greater than 80 mg/dL, and baseline CAC scores of 30 to 7,000 units assessed by means of electron-beam computed tomography.

Interventions: 103 patients were randomly assigned to calcium acetate, and 100 patients to sevelamer for 12 months to achieve phosphorus levels of 3.5 to 5.5 mg/dL. Atorvastatin was added to achieve serum LDL-C levels less than 70 mg/dL in both groups.

Outcomes & Measurements: The primary end point was change in CAC score assessed by means of electron-beam computed tomography.

Results: After 12 months, mean serum LDL-C levels decreased to 68.8 $\pm$ 22.0 mg/dL in the calcium-acetate group and 62.4 $\pm$ 23.0 mg/dL in the sevelamer group ($P = 0.3$). Geometric mean increases in CAC scores were 35% in the calcium-acetate group and 39% in the sevelamer group, with a covariate-adjusted calcium acetate–sevelamer ratio of 0.994 (95% confidence interval, 0.851 to 1.161).

Limitations: Treatment assignment was not blinded. The 1.8 a priori margin is large, CAC is a surrogate outcome, duration of treatment was short, and dropout rate was high.

Conclusions: With intensive lowering of LDL-C levels for 1 year, hemodialysis patients treated with either calcium acetate or sevelamer experienced similar progression of CAC.

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INDEX WORDS: Cardiovascular disease; hyperphosphatemia; dialysis; vascular calcification; secondary hyperparathyroidism; electron-beam computed tomography (EBCT); low-density lipoprotein; statins; atorvastatin; cholesterol; dyslipidemia.

Editorial, p. 877

Patients undergoing maintenance hemodialysis (HD) have a high mortality rate, mainly from cardiovascular disease.[1] Factors that contribute to this risk include traditional risk factors for atherosclerotic coronary artery disease[2,3] and uremia-related disordered mineral metabolism, particularly hyperphosphatemia.[4,5] An important feature of cardiac disease in HD patients is accelerated cardiovas-

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cular calcification. Morphological examination of coronary arteries from HD patients showed heavily calcified atheromatous plaques.[6] Also, studies using electron-beam computed tomography (EBCT), a sensitive technique for quantification of coronary artery calcium,[7-11] showed a high prevalence of coronary artery calcification (CAC) in HD patients, even in young adults.[12,13]

Cardiovascular calcification may contribute to increased risk of death from myocardial infarction, fatal arrhythmia, and congestive heart failure.[14,15] Thus, interventions designed to slow or reverse the calcification process may lead to improved patient outcomes. Currently, there is no effective treatment for cardiovascular calcification in HD patients.[16] Two previous clinical trials showed that progression of CAC was slower in HD patients treated with sevelamer for hyperphosphatemia compared with calcium-based phosphate binder (CBPB)-treated patients.[17,18] Although the beneficial effect of sevelamer was attributed mainly to its lack of calcium content, sevelamer decreases serum low-density lipoprotein cholesterol (LDL-C) levels in dialysis patients[19] and allegedly has pleiotropic actions that may affect the atherosclerotic process independent of its cholesterol-lowering effects.[20,21] HD patients have accelerated atherosclerosis.[2,22-24] Moreover, the extent of coronary artery disease in HD patients with atherosclerosis correlated with CAC scores.[24] Thus, it is conceivable that the beneficial effect of sevelamer on CAC in HD patients could be related, at least in part, to its LDL-C–lowering and pleiotropic effects. Use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), an established treatment for patients with atherosclerotic coronary artery disease, may decrease the progression of CAC.[25] Some studies of the general population,[26-28] but not others,[29-31] showed that decreasing LDL-C levels with statins may retard or even halt the progression of CAC. There are no studies that specifically examined the effect of these agents on coronary calcification in HD patients. A recent study of the effect of atorvastatin in HD patients with diabetes showed no significant decrease in patient mortality,[32] but CAC was not measured in that study. The aim of this prospective randomized clinical trial was to test the hypothesis that progression of calcification would be similar in HD patients treated with calcium-containing or calcium-free phosphate binders when LDL-C was decreased to a target level less than 70 mg/dL (<1.81 mmol/L).

METHODS

Patients

This prospective, randomized, open-label, parallel-group study was conducted in 26 centers in the United States. The study protocol and informed consent form were reviewed and approved by the institutional review boards of each participating center and registered as study number NCT00211939 at www.clinicaltrials.gov. All subjects gave their written informed consent. Eligibility criteria included patients with end-stage renal disease 18 years or older who were receiving thrice-weekly HD for 3 months to 5 years. Exclusion criteria included any condition that could restrict survival of participants for the duration of the study or interfere with their ability to strictly follow the study protocol. Also excluded were patients with parathyroid hormone (PTH) levels greater than 1,000 pg/mL (ng/L), calciphylaxis, recent history of hypercalcemia (serum calcium > 11.5 mg/dL [>2.87 mmol/L]), planned living donor renal transplantation or anticipated transplantation within 1 year, and a history of allergy or intolerance to study drugs.

Study Design and Randomization

The study included a washout period of up to 6 weeks, followed by 52 weeks of treatment. During washout, all phosphate binders, calcium supplements, lipid-lowering agents, and vitamin D analogues were discontinued. To be randomly assigned, patients had to have serum phosphorus levels greater than 5.5 mg/dL (>1.78 mmol/L), LDL-C levels greater than 80 mg/dL (>2.07 mmol/L), and baseline EBCT score (interpreted locally at the study site) of 30 to 7,000 units inclusive. Patients were randomly assigned in a 1:1 ratio to 2 treatment strategies: (1) calcium acetate (PhosLo, 667-mg capsules; Fresenius Medical Care North America, Waltham, MA), or (2) sevelamer hydrochloride (Renagel, 800-mg tablets; Genzyme Corp, Cambridge, MA). Randomization was stratified by center using computerized lists for each site, prepared by using permuted blocks of 4 to attain balance within strata. Lists for each site were maintained in the pharmacy binder at the study clinic.

Interventions

Atorvastatin (Lipitor; 20-mg tablets; Pfizer, New York, NY) was given to calcium acetate–treated patients at randomization, but was added to sevelamer-treated patients at week 8 only if their LDL-C levels were not less than 70 mg/dL (<1.81 mmol/L). The starting dose of atorvastatin in both treatment groups was 20 mg/d, but subsequently was increased to achieve the LDL-C goal of less than 70 mg/dL (<1.81 mmol/L).

Initial phosphate-binder dose was based on serum phosphorus level and manufacturers' package inserts and subsequently titrated at the time of measurement of serum phosphorus to achieve a phosphorus level of 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L). Thereafter, subjects with PTH levels greater than 300 pg/mL (ng/L) were administered intrave-

nous paricalcitol or doxercalciferol at doses titrated to achieve a PTH level of 150 to 300 pg/mL (ng/L). If adjusted serum calcium level exceeded 10.2 mg/dL (2.54 mmol/L), vitamin D therapy initially was discontinued for 1 week, but if hypercalcemia persisted, calcium acetate dose was decreased by 1 gelcap per meal. Dialysate calcium level was maintained at 2.5 mEq/L (1.25 mmol/L) throughout the study period.

Serum phosphorus and calcium were measured every 2 weeks for 2 months, then at monthly intervals. Intact PTH, total cholesterol, LDL-C, high-density lipoprotein cholesterol, and triglycerides were measured at monthly intervals. All laboratory work was performed at Spectra Laboratories, Rockleigh, NJ. Calcium and phosphorus were measured using colorimetric assays on the Olympus 5400 analyzer (Olympus America Inc, Melville, NY). Intact PTH and homocysteine were assayed by using a chemiluminescent assay on the Bayer Advia Centaur (Bayer HealthCare LLC, Diagnostic Division, Tarrytown, NY). Cholesterol assays were performed using enzymatic methods on an Olympus analyzer.

EBCT Imaging Protocol

EBCT studies were performed at baseline and days 180 and 360 using an Imatron C-150XL or C-300 Ultrafast computed tomographic scanner (GE-Imatron, South San Francisco, CA) in the high-resolution volume mode with 100-ms exposure time, as previously described.[33] Electrocardiographic triggering was used so that each image was obtained at the same point in diastole, corresponding to 40% of the RR interval. At least 30 consecutive images were obtained at 3-mm intervals. Coronary calcium was defined as plaque of at least 3 contiguous pixels (area = 1.02 mm^2) with density greater than 130 Hounsfield units. Reproducibility of computed tomography was determined by 2 sequential scans in 18 randomly selected subjects. For CAC, inter-reader variability for Agatston scores was 3.9%, interscan variability was 5.0%, and intrareader variability was 4.5%.

Calcium score was calculated by multiplying lesion area by a density factor derived from the maximal Hounsfield unit within this area, as described by Agatston et al.[34] Total calcium score was determined by summing individual lesion scores from each of 4 anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries). Other areas of calcification with a minimal density of 130 Hounsfield units within the borders of the aorta, mitral valve, and aortic valves also were computed. At each time, a pair of scans was obtained and calcium scores were averaged.

Eligibility for randomization was based on preliminary reading of CAC scores by local cardiologists. However, all scans subsequently were forwarded to a single experienced cardiologist who was blinded to treatment assignment, identifying information, and temporal relationship of the scans and who interpreted all studies on a commercially available software package (Neo Imagery Technologies, City of Industry, CA). Fourteen of 203 randomly assigned patients initially classified as having a CAC score of 30 or greater subsequently were reclassified by the study cardiologist as having zero scores (5 patients) or scores of 1 to 29 units (9 patients).

Outcome Measures

The primary efficacy end point of the study was the ratio of CAC score at 52 weeks to score at baseline. Secondary outcomes included aorta, mitral, and aortic valve calcification scores and serum phosphorus and calcium, calcium-phosphorus product, PTH, total cholesterol, LDL-C, high-density lipoprotein cholesterol, and triglyceride levels.

Statistical Methods

The protocol was designed as a noninferiority trial to show that calcium acetate is not associated with greater progression of CAC than sevelamer when LDL-C level is decreased to less than 70 mg/dL (<1.81 mmol/L). An a priori specification considered calcium acetate to be noninferior if the day-360–screening ratio of geometric mean (GM) CAC scores in calcium acetate–treated patients did not exceed 1.8-fold the ratio in sevelamer-treated patients. A demonstration of noninferiority required that the upper bound of the 95% confidence interval (CI) for the calcium acetate–sevelamer ratio of the 2 ratios not exceed 1.8. The GM was computed from the arithmetic mean of logarithms of calcification scores excluding zero values. The GM was used in this trial because it is less sensitive than the arithmetic mean to the impact of very large calcification scores. Logarithmically transformed calcification scores were used as outcomes in regression models because they have an approximately Gaussian distribution. Although aorta, mitral, and aortic valve EBCT calcification scores also were calculated and compared, all of the study's type I error rate of 0.05 was "spent" in testing the primary hypothesis about CAC score. Analysis was based on the intention-to-treat principle and included subjects with baseline EBCT scores outside the 30- and 7,000-unit range regardless of treatment adherence. However, subjects without day-360 CAC score were not included in the primary day-360 CAC score–based analysis.

Sample size calculation showed that with a factor of 1.8 as the upper margin, 83 subjects per arm with screening and day-360 data (or 93 per arm allowing for attrition up to 10%) were needed for a test with type I error rate of 5% and power of 80%. A linear mixed-effects regression model (SAS/STAT PROC MIXED; SAS Institute, Cary, NC) was used to test the primary hypothesis with the log-transformed day-360–screening ratio of calcification score as the outcome and treatment (calcium acetate versus sevelamer), log-transformed baseline calcification score, baseline PTH level, and demographic variables (age, sex, race, and body weight) as covariates.

Additional Post Hoc Analyses

Tests of superiority were performed for 6- and 12-month values of the primary CAC outcome. By means of Wilcoxon rank-sum test and Fisher exact test, calcium acetate and sevelamer were compared regarding percentage of median change from baseline and percentage of patients with at least a 15% increase in CAC, respectively.

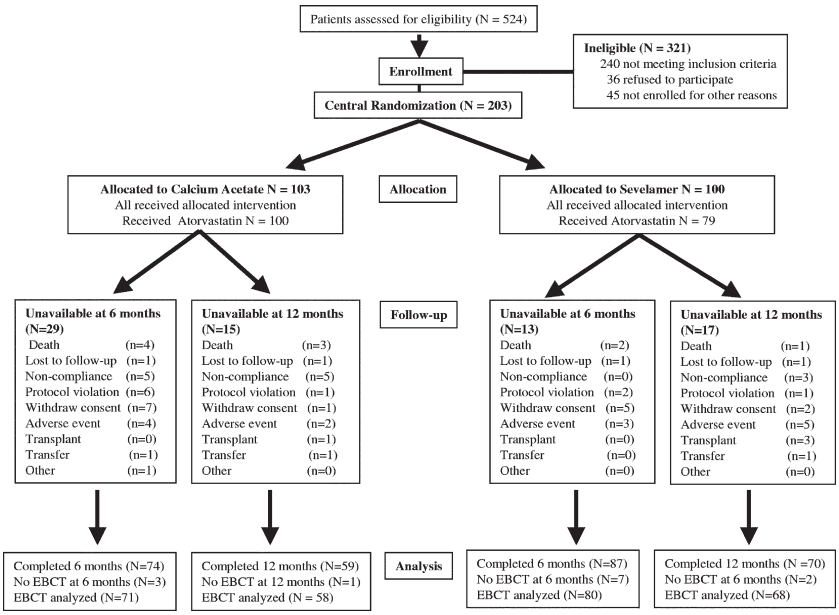

Figure 1. Patient disposition. Abbreviation: EBCT, electron-beam computed tomography.

Assessing the Impact of Missing Values

Of 103 subjects in the calcium-acetate arm, 55 provided nonzero day-360–baseline ratios; in the sevelamer arm, these counts were 100 and 67 (attrition of 46.6% and 33%, respectively). The method of multiple imputation[35] was used in a sensitivity analysis to examine the impact of missing total EBCT scores on the comparison of calcium acetate to sevelamer. Each missing EBCT value was imputed 5 times by using a log-linear regression plus random error with the same predictors as in the primary analysis model plus the patient's previous nonmissing total EBCT scores. Analyses of the 5 complete data sets were pooled to reflect their consensus and the differences among the 5 sets of regression coefficients. An additional sensitivity analysis set zero calcification scores to 1 (so their logarithm was 0). A "pessimistic" analysis of missing values imputed missing day-360 CAC scores as twice their last observed value for calcium acetate, but equal to their last value for sevelamer.

Statistical analyses were performed using SAS software, version 8.2. A 2-sided P of 0.05 was considered significant, and no corrections were used for multiple comparisons.

RESULTS

Recruitment

Between January 6, 2005, and November 11, 2005, a total of 203 patients were randomly assigned to treatment with calcium acetate plus atorvastatin or sevelamer plus atorvastatin. Figure 1 shows in detail the flow of patients from recruitment through randomization, allocation, follow-up, and analysis. The 2 groups were well matched at baseline (Table 1). At baseline, calcification of the aorta was present in 85.7% of patients, whereas that of mitral and aortic valves, in 54.7% and 39.9%, respectively. Fifty-five subjects had both mitral and aortic valve calcification (27%). Median CAC scores at baseline were 468 (25th and 75th percentiles, 150 and 1,458) and 439 units (25th and 75th percentiles, 138 and 1,030) for the calcium-acetate and sevelamer groups, respectively. Baseline CAC scores from 15 subjects were outside the 30- to 7,000-U range, but were still included in the intention-to-treat analysis. Of these subjects, 5 had a zero score, 9 had scores of 18 to 29, and 1 had a score higher than 7,000. Mean durations of follow-up were 265 $\pm$ 128 days in the calcium-acetate group and 300 $\pm$ 107 days in the sevelamer group (median, 355 and 357 days, respectively).

Outcomes

Table 2 lists laboratory characteristics of the 2 groups at randomization and study completion. One hundred calcium-acetate–treated patients (97.1%) received atorvastatin with an average daily dose of 32.7 $\pm$ 13.4 mg. In comparison, 79 sevelamer-treated subjects

Table 1. Baseline Characteristics of Randomized Study Subjects

	Calcium Acetate (N = 103)	Sevelamer (N = 100)	*P*
Age (y)	58.5 ± 12.8	60.3 ± 12.1	0.3
Women (%)	42.7	54.0	0.1
Blacks (%)	34.0	39.0	0.5
Body mass index (kg/m^2)	30.0 ± 6.0	30.1 ± 7.0	0.9
Dialysis vintage (y)	1.9 ± 1.1	1.8 ± 1.1	0.6
Cause of end-stage renal disease (%)			0.9
Diabetes	57.3	57.0	
Hypertension	31.1	31.0	
Glomerulonephritis	4.9	3.0	
Others	6.8	9.0	
Current smoking (%)	20.4	19.0	0.8
Albumin (g/dL)	3.9 ± 0.4	4.0 ± 0.3	0.5
Phosphorus (mg/dL)	6.5 ± 1.9	6.6 ± 1.5	0.6
Adjusted calcium (mg/dL)	8.8 ± 0.8	8.8 ± 0.7	0.7
Ca × P product (mg^2/dL^2)	57.5 ± 17.2	58.2 ± 13.3	0.7
Intact PTH (pg/mL)	465.7 ± 358.4	509.0 ±328.9	0.4
Cholesterol			
Total (mg/dL)	168.4 ± 40.6	169.5 ± 36.2	0.9
LDL (mg/dL)	112.0 ± 28.2	108.0 ± 23.6	0.3
HDL (mg/dL)	40.0 ± 9.4	42.9 ± 13.3	0.1
Triglycerides (mg/dL)	173.3 ± 120.2	179.2 ± 104.0	0.7
C-Reactive protein (mg/L)	9.1 ± 9.9	10.6 ± 14.9	0.4
Homocysteine (μmol/L)	31.4 ± 20.2	29.8 ± 10.8	0.5

Note: Values expressed as mean ± SD or percent. To convert serum calcium in mg/dL to mmol/L, multiply by 0.2495; serum phosphorus in mg/dL to mmol/L, multiply by 0.3229; cholesterol in mg/dL to mmol/L, multiply by 0.0259; triglycerides in mg/dL to mmol/L, multiply by 0.0113; albumin in g/dL to g/L, multiply by 10. PTH levels expressed in pg/mL and ng/L are equivalent.

Abbreviations: Ca × P, calcium-phosphorus; PTH, parathyroid hormone; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

(79%) received atorvastatin at an average daily dose of 28.0 ± 12.3 (P = 0.016). Figure 2 shows changes in total cholesterol, high-density lipoprotein cholesterol, and LDL-C levels and percentages of patients achieving goal LDL-C target level. After 1 year of treatment, LDL-C levels decreased from 112.0 ± 28.2 mg/dL (2.9 ± 0.73 mmol/L) to 68.8 ± 22.0 mg/dL (1.78 ± 0.57 mmol/L) in the calcium-acetate group and 108 ± 23.6 mg/dL (2.79 ± 0.61 mmol/L) to 62.4 ± 23.0 mg/dL (1.61 ± 0.59 mmol/dL) in the sevelamer group (P = 0.3; Fig 2C and D).

Forty-four patients (42.7%) in the calcium-acetate arm and 30 (30.0%) in the sevelamer arm dropped out of the study before 1 year. There were no significant differences between study arms in baseline characteristics of patients who dropped out or between these patients and the study population as a whole. For dropouts, the overall distribution of cited reasons for dropping out did not differ significantly between study arms (P = 0.6).

Primary Outcome: Effect of Phosphate Binders and Atorvastatin on CAC Progression

Table 3 lists mean and median values for CAC outcomes at 3 times: baseline, 6 months, and 12 months. Median baseline CAC scores did not differ significantly between treatment groups. There was a highly significant within-group increase in CAC scores during the study period in both treatment groups. However, these increases did not differ significantly between treatment arms in either absolute or relative terms.

The GM day-360–screening CAC score ratios were 1.35 (95% CI, 1.19 to 1.53) for calcium acetate and 1.39 (95% CI, 1.25 to 1.56) for sevelamer, with a covariate-adjusted ratio of ratios of 0.994 (95% CI, 0.85 to 1.16). Given that the upper bound of the CI was much less than the 1.8 margin, the noninferiority of calcium acetate

Table 2. Laboratory Values at Baseline and Study Completion

Variable	Calcium Acetate		Sevelamer	
	Baseline (N = 103)	Final (N = 59)	Baseline (N = 100)	Final (N = 70)
Phosphorus (mg/dL)	6.5 ± 1.9	5.0 ± 1.6	6.6 ± 1.5	5.4 ± 1.8
Adjusted calcium (mg/dL)	8.8 ± 0.8	9.4 ± 0.7	8.8 ± 0.7	9.0 ± 0.7*
Ca × P product (mg^2/dL^2)	57.5 ± 17.2	46.0 ± 14.7	58.2 ± 13.3	48.0 ± 15.4
PTH (pg/mL)	465.7 ± 358.4	316.0 ± 212.0	509.0 ± 328.9	434.0 ± 359.0*
Bicarbonate (mEq/L)	23.5 ± 4.4	23.1 ± 3.9	22.9 ± 3.8	21.6 ± 4.3
Total cholesterol (mg/dL)	168.4 ± 40.6	134.0 ± 32.3	169.5 ± 36.2	123.0 ± 30.6*
LDL cholesterol (mg/dL)	112.0 ± 28.2	68.8 ± 22.3	108.0 ± 23.6	62.4 ± 23.0
HDL cholesterol (mg/dL)	40.0 ± 9.4	38.4 ± 8.7	42.9 ± 13.3	38.8 ± 11.3
Triglycerides (mg/dL)	173.3 ± 120.2	157.0 ± 124	179.2 ± 104.0	149.0 ± 69.8
Serum albumin (g/dL)	3.9 ± 0.4	3.9 ± 0.3	4.0 ± 0.3	3.9 ± 0.3
Alkaline phosphatase (U/L)	88.9 ± 39.3	95.1 ± 36.2	93.9 ± 46.5	124.0 ± 71.6
Bone-specific alkaline phosphatase (U/L)	19.0 ± 12.2	18.8 ± 11.6	19.7 ± 10.7	27.2 ± 18.1
C-Reactive protein (mg/L)	9.1 ± 9.9	10.1 ± 13.9	10.6 ± 14.9	10.8 ± 26.0
Homocysteine (mg/dL)	31.4 ± 20.2	28.9 ± 9.8	29.8 ± 10.8	29.1 ± 13.5

Note: Values expressed as mean ± SD. To convert serum calcium in mg/dL to mmol/L, multiply by 0.2495; serum phosphorus in mg/dL to mmol/L, multiply by 0.3229; cholesterol in mg/dL to mmol/L, multiply by 0.0259; triglycerides in mg/dL to mmol/L, multiply by 0.0113; albumin in g/dL to g/L, multiply by 10. PTH levels in pg/mL and ng/L are equivalent.

Abbreviations: Ca × P, calcium-phosphorus; PTH, parathyroid hormone; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

*$P < 0.05$.

was shown. Alternative regression models for the CAC outcome yielded virtually identical results (Table 4).

Sensitivity Analyses

A total of 74 patients did not have day-360 EBCT scans; 44 in the calcium-acetate arm and 30 in the sevelamer arm. Moreover, 1 patient in the calcium-acetate arm and 2 patients in the sevelamer arm did not have day-360 EBCT scans, although they were seen at the visit. A multiple imputation sensitivity analysis was performed to examine the impact of missing values. The analysis yielded an estimated ratio (day-360–baseline ratios) of 0.993 (95% CI, 0.81 to 1.21), nearly identical to the 0.994 obtained by omitting subjects with missing CAC data. The 1.21 upper 95% confidence bound for the ratio of GM also was much less than the 1.8 margin. Two additional sensitivity analyses were conducted to examine the impact of missing and zero values for CAC scores. In the pessimistic analysis described, the model-based ratio of ratios was 1.363; upper 95% bound, 1.560. In the second sensitivity analysis, zero values for the CAC score (5 at baseline, 4 at day 360) were replaced by 1. The model-based ratio of ratios was 0.994; upper 95% bound, 1.161, nearly identical to results based on excluding zeros.

Post Hoc Tests of Superiority

At 6 months, median percentages of change in CAC scores from baseline were 20% in the calcium-acetate group and 14% in the sevelamer group ($P = 0.5$). At day 360, these median changes were 29% in the calcium-acetate group and 30% in sevelamer group ($P = 0.9$; Table 3; Fig 3). The proportion of patients with a greater than 15% increase in CAC scores, as previously suggested for a meaningful change in calcification score,[18,26] also did not differ significantly between calcium acetate and sevelamer: 54% versus 47% at 6 months ($P = 0.4$) and 64% versus 57% at 12 months ($P = 0.5$; Fig 4).

Secondary Calcification Outcomes

For unadjusted aortic valve scores, day-360–baseline GM ratios were 1.61 for calcium acetate and 1.43 for sevelamer. However, this variable had a baseline imbalance between the 2 treatment groups (day-0 GM aortic valve scores, 64 and 137 for calcium acetate and sevelamer; $P = 0.02$). Adjusting for this imbalance, the second and third models for the aortic valve calcium

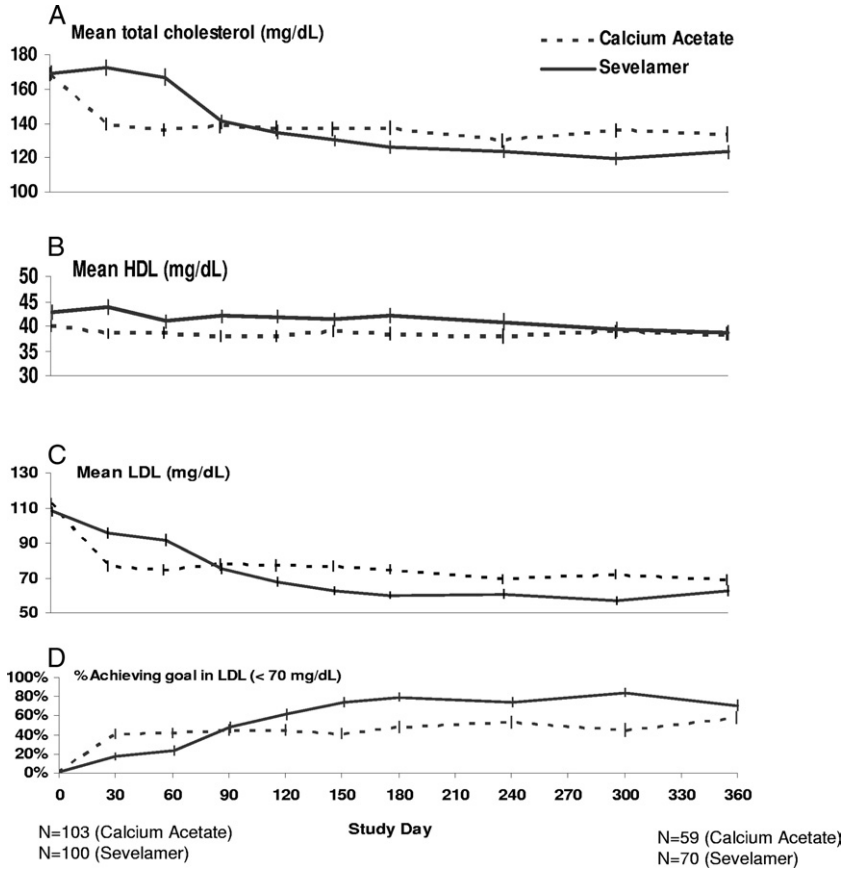

Figure 2. Mean serum lipid parameters by treatment group from baseline to end of study. Mean serum (A) total cholesterol, (B) high-density lipoprotein (HDL), and (C) low-density lipoprotein (LDL) cholesterol levels. (D) Proportion of patients who achieved the goal LDL level of less than 70 mg/dL. To convert cholesterol in mg/dL to mmol/L, multiply by 0.0256.

score yielded an adjusted ratio of ratios of 0.714 (95% CI, 0.47 to 1.09; Table 4).

For the mitral valve, day-360–baseline ratios were 1.51 for calcium acetate and 1.78 for sevelamer, with 0.840 for the adjusted ratio of ratios (95% CI, 0.55 to 1.27). For the aorta, day-360–baseline GM ratios were 1.40 for calcium acetate and 1.66 for sevelamer, with a 0.920 adjusted ratio of ratios (95% CI, 0.74 to 1.15). Except for aortic valve scores, the 3 regression models for each outcome consistently supported the assertion that calcium acetate and sevelamer had similar effects on progression of cardiovascular calcification, with ratio of ratios (calcium-acetate ratio to sevelamer ratio) less than 1 and upper 95% bounds of the ratio of ratios much less than the a priori margin of 1.8 (Table 4). Figure 5 summarizes analyses of the primary outcomes. The ratios of ratios were less than 1.0 for all measured calcification sites with no upper 95% CI more than 1.27. This yields robust support for the assertion that calcium acetate and sevelamer have similar effects on progression of cardiovascular calcification.

Other Secondary Outcomes

Calcium acetate and sevelamer were effective in controlling serum phosphorus and calcium-phosphorus product values to the goals recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI; Table 2; Fig 6A). Mean daily dose of calcium acetate in the last week of the study was 5.5 g (1.375 g of elemental calcium), whereas that of sevelamer was 7.3 g. Serum calcium levels were significantly greater in the calcium acetate–treated group (Table 2; Fig 6B), but calcium-phosphorus product was not significantly different (Fig 6C). The inci-

Table 3. CAC Scores at Baseline, Month 6, and Month 12 (intention-to-treat population)

	Calcium Acetate	Sevelamer	Wilcoxon Rank-Sum Test *P**
Baseline			
No. of patients	103	100	
Mean ± SD	1,098 ± 1,440	969 ± 1,386	
Median	468	439	0.6
6 Months			
No. of patients	71	68	
Mean ± SD	1,197 ± 1,413	996 ± 1,419	
Median	644	447	0.2
Absolute increase			
Mean ± SD	109 ± 374	97 ± 211	
Median	79	54	0.6
Wilcoxon signed rank test† *P*	<0.0001	<0.0001	
Percent increase			
Mean ± SD	71 ± 365	24 ± 39	
Median	20	14	0.5
12 Months			
No. of patients	58	68	
Mean ± SD	1,297 ± 1,487	1,116 ± 1,569	
Median	691	527	0.3
Absolute increase			
Mean ± SD	228 ± 355	227 ± 485	
Median	126	96	0.4
Wilcoxon signed rank test† *P*	<0.0001	<0.0001	
Percent increase			
Mean ± SD	52 ± 92	57 ± 86	
Median	29	30	0.9

Note: Absolute change was calculated for all subjects. Percentage of increase was calculated in only subjects with an electron-beam computed tomographic baseline CAC score greater than zero.

Abbreviation: CAC, coronary artery calcification.

*Between-group, Wilcoxon rank-sum test.

†Within-group, Wilcoxon signed rank test.

dence of hypercalcemia, defined as an adjusted calcium level greater than 10.2 mg/dL (>2.54 mmol/L) on 1 or more study visits, was observed in 31% of calcium-acetate- and 19% of sevelamer-treated patients ($P = 0.05$). However, persistent hypercalcemia, defined as adjusted serum calcium level greater than 10.2 mg/dL (>2.54 mmol/L) for 3 consecutive study time points, developed in 2.9% and 3.0% of the calcium-acetate and sevelamer groups, respectively. Persistent hypocalcemia (adjusted serum calcium < 8.5 mg/dL [<2.12 mmol/L]) was recorded in

Table 4. Summary of Primary and Secondary Noninferiority Testing: Calcium Acetate to Sevelamer Ratio of Day-360 to Screening Ratio in EBCT Calcification Scores

	Adjusted Ratio: Calcium Acetate to Sevelamer		
Cardiac Structure	Model Has Treatment Term Only	Treatment and Baseline Calcium Score Terms Only	Treatment, Baseline, & Other Covariates*
Coronary artery	0.95 (0.82–1.11)	0.99 (0.85–1.16)	0.99 (0.85–1.16)
Aortic valve	1.20 (0.75–1.94)	0.79 (0.50–1.24)	0.71 (0.47–1.09)
Mitral valve	0.85 (0.55–1.32)	0.80 (0.53–1.19)	0.84 (0.55–1.27)
Total aorta	0.84 (0.65–1.09)	0.86 (0.69–1.08)	0.92 (0.74–1.15)

Note: Values expressed as geometric mean (95% confidence interval).

Abbreviation: EBCT, electron-beam computed tomography.

*Other covariates: age, sex, race, body weight, parathyroid hormone level, and log-transformed baseline coronary artery calcification score.

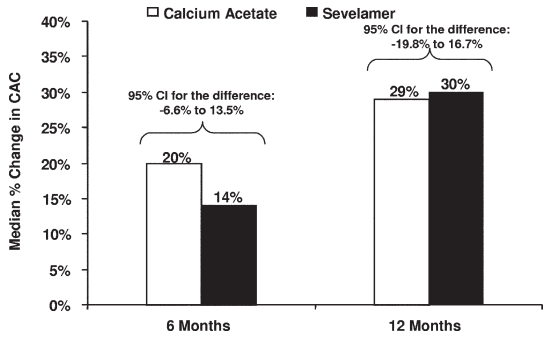

Figure 3. Median percentage of change in coronary artery calcium (CAC) scores from baseline to months 6 and 12 in patients with scores of 30 or higher at baseline and 95% confidence interval (CI) for the between-group difference (calcium acetate to sevelamer) in median percentage of change.

13.6% and 21% in the 2 groups, respectively ($P = 0.06$).

PTH levels decreased from 464 ± 360 pg/mL (ng/L) to 316 ± 212 pg/mL (ng/L) in calcium-acetate patients and 503 ± 327 pg/mL (ng/L) to 434 ± 359 pg/mL (ng/L) in sevelamer-treated patients (Table 2; Fig 6D). Proportions of patients who received vitamin D therapy were 79.6% for the calcium-acetate group and 88.0% for the sevelamer group ($P = 0.1$). Mean weekly doses of paricalcitol were 12.6 ± 7.7 and 15.6 ± 11.2 μg in the calcium-acetate and sevelamer groups, respectively ($P = 0.09$). For doxercalciferol, mean weekly doses were 8.5 ± 5.0 μg for calcium acetate and 11.5 ± 6.3 μg for sevelamer ($P = 0.02$). Four patients (1 in the calcium-acetate group, 3 in the sevelamer group) were inadvertently treated with cinacalcet.

Adverse Events

There were similar rates of treatment-related adverse events in the 2 treatment groups, and these were consistent with the adverse-event profile of these drugs (Table 5). Specifically, adverse events related to the use of atorvastatin in dialysis patients were not different from those reported in other large-scale trials with this drug, such as the recently published trial in diabetic hemodialysis patients.[32]

DISCUSSION

To our knowledge, our prospective randomized controlled study is the first clinical trial specifically designed to examine the effects of concurrent use of calcium load and LDL-C–lowering on progression of CAC in HD patients. We show that progression of CAC is similar in HD patients treated with calcium acetate or sevelamer when LDL-C level is decreased to less than 70 mg/dL (<1.81 mmol/L). GM rates of CAC progression were nearly identical in the 2 treatment groups.

Based on our results, we conclude that control of hyperphosphatemia in HD patients with calcium acetate during a 12-month period does not contribute to progression of CAC compared with sevelamer. However, it is more difficult to conclude that intensive lowering of LDL-C levels influenced the rate of progression of calcification in these patients because, despite excellent cholesterol level control in both treatment groups, there was significant within-group progression of calcification, indicating that other factors are driving the progression of calcification. Given the multifactorial pathogenesis of calcification, it probably is unrealistic to expect that cholesterol lowering alone will prevent or reverse severe cardiovascular calcification in HD patients.[16,36] Sixty percent of sevelamer-treated patients and 93% of CBPB-treated patients in the Renagel in New Dialysis (RIND) trial showed a true increase in CAC scores at 18 months.[18] In that study, median percentages of increase in CAC scores were 38% and 52% in patients randomly assigned to sevelamer and CBPB, respectively.[18] This progression likely was caused by several

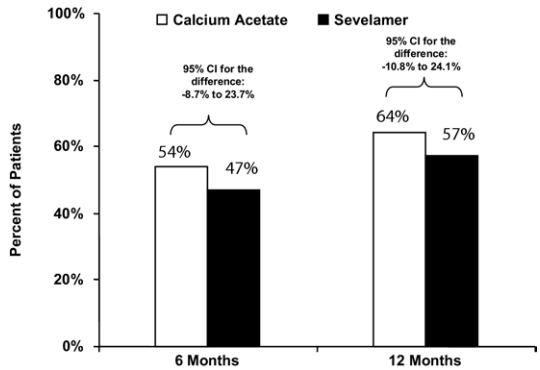

Figure 4. Proportion of subjects with progression of coronary artery calcium scores at months 6 and 12. Progression defined as greater than 15% increase in coronary artery calcium score from baseline and 95% confidence interval (CI) for the between-group difference (calcium acetate to sevelamer) in the proportion.

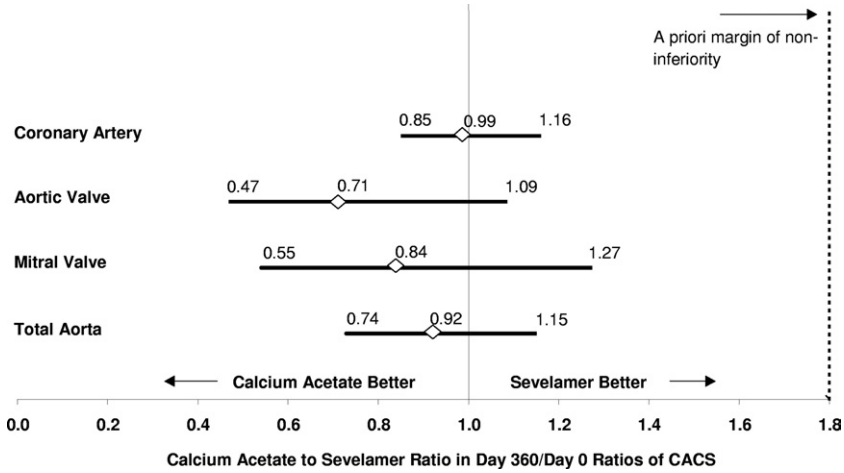

Figure 5. Summary of primary and secondary efficacy testing of noninferiority hypotheses. Estimated ratio of ratios of day-360 to screening electron-beam computed tomography calcium scores and 95% confidence bounds. Analyses adjusted for age, sex, race, body weight, parathyroid hormone level, and log-transformed baseline coronary artery calcification (CAC) score (CACS).

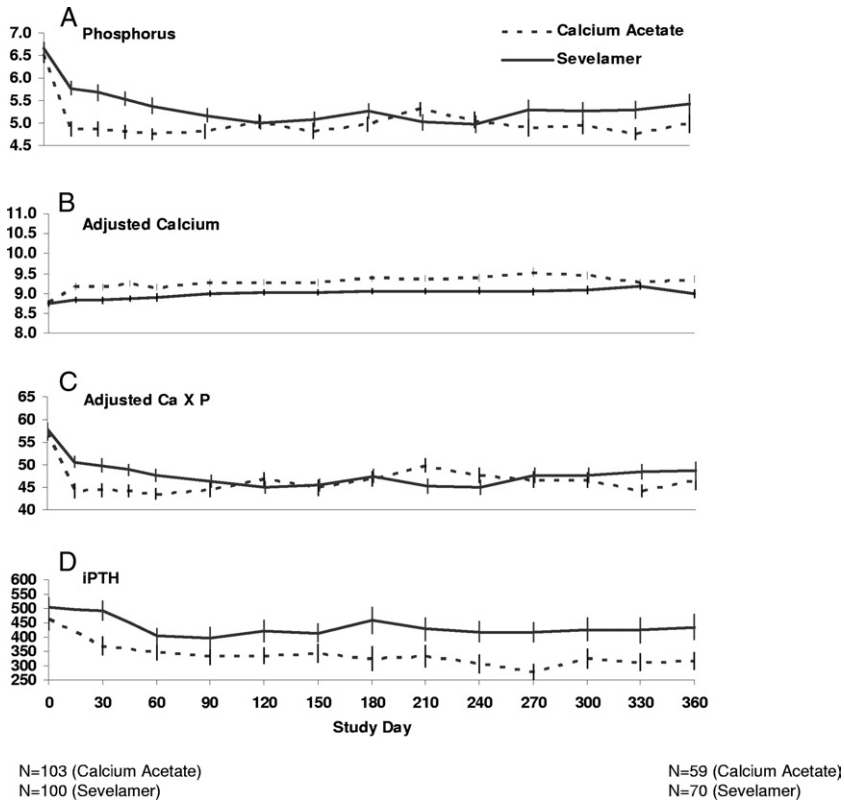

Figure 6. Mean (A) serum phosphorus (milligrams per deciliter), (B) adjusted serum calcium (milligrams per deciliter), (C) adjusted serum calcium-phosphorus (Ca × P) product (milligrams squared per deciliter squared), and (D) intact parathyroid hormone (iPTH; picograms per milliliter) values by treatment group from baseline to end of study. To convert calcium in mg/dL to mmol/L, multiply by 0.25; phosphorus in mg/dL to mmol/L, multiply by 0.32; calcium in mg/dL to mmol/L, multiply by 0.25. iPTH levels expressed in pg/mL and ng/L are equivalent.

Table 5. Summary of Treatment-Related Adverse Events

Organ System	Calcium Acetate	Sevelamer	*P*
Gastrointestinal disorders			
Abdominal pain	4 (4)	8 (8)	0.3
Constipation	5 (5)	10 (10)	0.2
Diarrhea	16 (16)	16 (16)	1.0
Gastroesophageal reflux disease	5 (5)	6 (6)	0.8
Nausea	18 (17)	17 (17)	1.0
Vomiting	18 (17)	18 (18)	1.0
General			
Asthenia	11 (11)	4 (4)	0.1
Fatigue	9 (9)	4 (4)	0.3
Malaise	10 (10)	7 (7)	0.6
Pruritus	5 (5)	11 (11)	0.1
Musculoskeletal disorders			
Arthralgia	8 (8)	12 (12)	0.4
Back pain	10 (10)	10 (10)	1.0
Muscle spasms	12 (12)	19 (19)	0.2
Myalgia	7 (7)	4 (4)	0.5
Other			
Persistent hypercalcemia	3 (2.9)	3 (3.0)	0.3
Persistent hypocalcemia	14 (13.6)	21 (21.0)	0.1

Note: Values expressed as number (percent).

uremia-related factors, such as the uremic milieu: high serum phosphorus, calcium and PTH levels; vitamin D, chronic inflammation, oxidative stress, and others.[36,37] In this regard, oversuppression of PTH frequently is implicated in the heavy burden of cardiovascular calcification in HD patients.[17,18] However, only 11% of calcium-acetate- and 9% of sevelamer-treated patients had PTH levels less than 150 pg/mL (ng/L) at the end of our study.

Our results clearly differ from those of the Treat to Goal and RIND Studies.[17,18] In the Treat to Goal Study, Chertow et al[17] reported that median percentage of increase in CAC score was 25% in prevalent HD patients treated with CBPB compared with a 6% increment in the sevelamer group. However, in their sevelamer-treated patients, plasma LDL-C levels decreased from 102 to 65 mg/dL (2.64 to 1.68 mmol/L) during the study period, but did not change in patients treated with CBPB.[17] Similarly, in patients new to HD with evidence of CAC at baseline, Block et al[18] showed that use of CBPB resulted in more rapid progression of CAC than use of sevelamer. Likewise, LDL-C levels were 25% lower in their sevelamer-treated patients.[18] Despite that, in patients in the RIND Study with baseline CAC scores of 30 or higher, there was no significant difference in rates of progression of CAC between sevelamer-treated and CBPB-treated patients at any point up to 18 months of follow-up.[18] That we did not observe a difference in rates of progression of CAC between calcium-acetate- and sevelamer-treated patients similar to the reported difference in the mentioned trials suggests that decreasing LDL-C levels must have had a role in retarding the progression of calcification. However, definitive conclusions about the role of LDL-C lowering in the progression of CAC must await other studies that include a calcium-acetate arm not treated with statin.

Several factors may have influenced the rate of CAC progression in our patients. First, the degree of decrease in LDL-C levels in calcium-acetate-treated patients was similar to that achieved in sevelamer-treated patients in the Treat to Goal and RIND trials. Second, the contribution of both traditional and uremia-related risk factors to progression of calcification may explain the lack of a greater effect of decreasing LDL-C levels on attenuation of calcification in our study, as well as in other trials.[17,18] Third, the duration of intensive lowering of LDL-C levels in this study was relatively short; therefore, it is conceivable that maintaining LDL-C at levels achieved in this study for a longer period may uncover a greater effect on slowing the rate of CAC progression. This long-term effect of cholesterol was highlighted by Hoeg et al,[38] who reported in a group of homozygous hyperlipidemic patients that CAC scores correlated significantly with cholesterol-year product.

The beneficial effects of statins on the progression of cardiovascular calcification may be caused by its LDL-C–lowering effect. However, statins also protect vascular smooth muscle cells from phosphate-induced calcification by inhibiting their apoptosis.[39] Moreover, statins may affect minimally oxidized LDL-C, shown by Parhami et al[40] and Proudfoot et al[41] to have a strong dose-dependent effect on transdifferentiation of vascular smooth muscle cells into osteoblast-like cells capable of calcification. Finally, statins have pleiotropic effects that may affect calcification, such as improving endothelial function, enhancing the stability of atherosclerotic plaques, and decreasing oxidative stress and inflammation.[42]

Interestingly, sevelamer also was reported to have similar pleiotropic effects.[20]

It frequently is stated that CBPBs may result in oversuppression of PTH, which in turn may lead to impaired bone buffering of calcium. In our study, PTH levels less than 150 pg/mL (ng/L) were observed in only 11% of calcium-acetate- and 9% of sevelamer-treated patients at study end. Conversely, patients in the Treat to Goal and RIND Studies had mean baseline PTH levels that were almost half the baseline levels in our study[17,18] and thus may have predisposed them to oversuppression of PTH. Although sevelamer is a non–calcium-containing binder, 30% of sevelamer-treated patients in the Treat to Goal Study and 18% in the RIND Study had PTH levels less than 150 pg/mL (ng/L), much greater than the 9% observed in our study. Moreover, although coinvestigators in these 2 trials were free to control PTH levels according to their own clinic protocols, our study protocol provided uniform guidance for control of PTH levels, including stopping intravenous vitamin D therapy for PTH levels less than 150 pg/mL (ng/L). Thus, oversuppression of PTH probably did not have a major role in the progression of CAC in our study.

There are a number of important limitations to our study. First, treatment assignment was not blinded. Second, the 1.8 a priori margin is large. However, a study with a meaningfully smaller margin would have required a much larger sample size and increased cost. Based on the study's data, the actual upper confidence bound for the fold ratio was 1.16. Thus, after the protocol development phase of the study, the large margin of 1.8 had no quantitative effect and also had no qualitative impact regarding conclusions about the relative efficacy of calcium acetate and sevelamer. Third, during the course of the trial, a high dropout rate was encountered (Fig 1). This could have influenced our results. However, several analyses were conducted specifically to assess the impact of missing data and were described in the section entitled Sensitivity Analyses. These included the use of multiple imputation, a standard statistical method for dealing with missing observations, and an additional pessimistic analysis of missing values that imputed missing day-360 CAC scores as twice their last observed value for calcium-acetate recipients, but equal to their last value for sevelamer recipients. Qualitative and quantitative results of these 2 sensitivity analyses were similar to results of primary analyses that omitted missing values. Thus, based on these exploratory analyses, we can conclude that although there were substantial proportions of missing values, these had no material impact on the study's findings about the relative effects of calcium acetate and sevelamer on progression of calcification. It is important to note that the dropout rate in our study is similar to that encountered in the Treat to Goal Study.[17] Moreover, the overall distribution of cited reasons for dropping out of the study did not differ significantly between study arms ($P = 0.6$), and there were no significant differences in frequencies of individual reasons for dropping out.

Fourth, the study duration of 12 months is relatively short. With longer follow-up, a difference in CAC progression between the 2 treatment groups possibly could have been observed. Alternatively, longer duration of treatment with atorvastatin may have shown a lower rate of CAC progression in both groups. Fifth, mean PTH levels generally were greater than the KDOQI-recommended level of 150 to 300 pg/mL (ng/L). Thus, it could be argued that high PTH levels, particularly in sevelamer-treated patients, may have contributed to the progression of CAC in these patients. However, the effect of increased PTH level on CAC progression still is not well established. Finally, the study was not powered to examine the effect of intensive lowering of LDL-C on such meaningful cardiovascular end points as myocardial infarction, stroke, amputation, or death from cardiovascular events. In this regard, the Dialysis Clinical Outcomes Revisited (DCOR) Study, which randomly assigned 2,103 patients, did not show a significant difference in the primary end point of all-cause mortality or the secondary end point of cardiovascular mortality in CBPB- and sevelamer-treated HD patients.[43] Moreover, in a much smaller observational study, Block et al[44] claimed lower mortality with sevelamer versus CBPB during the extension phase, but not during the randomized phase of the RIND Study. Results of this study were questioned because there was no significant difference in mortality during the randomized phase or the almost 18 months after the end of randomization.[45] Finally, it may be argued that use of a single drug, such as sevelamer, for

control of both serum phosphorus and LDL-C levels to the recommended goals is better for adherence. However, we believe nephrologists should decide for themselves whether they can achieve these same goals by using the more cost-effective combination of calcium acetate and statin therapy.

In conclusion, our data suggest that intensive LDL-C–lowering therapy with atorvastatin is associated with similar progression of CAC in HD patients treated with either calcium acetate or sevelamer. The study indicates that calcium absorption from use of calcium acetate as a phosphate binder does not contribute to the progression of CAC.

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