

# Valvular Calcification in Hemodialysis Patients Randomized to Calcium-Based Phosphorus Binders or Sevelamer

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**Background and aim of the study:** Valvular calcification is common in patients with end-stage renal disease, and is associated with an unfavorable prognosis. It was hypothesized that sevelamer, a non-calcium-based phosphorus binder, might attenuate the progression of valvular calcification.

**Methods:** Two hundred subjects on maintenance hemodialysis received either sevelamer or calcium-based phosphorus binders. To assess the extent of calcification, 186 subjects underwent baseline electron beam tomography (EBT) of the coronary arteries, aorta and mitral and aortic valves, and 132 had follow up EBT scans at week 52. Changes in valvular calcification and combined valvular/vascular calcification were monitored and compared.

**Results:** At baseline, mitral valve calcification was seen in 46% of subjects, aortic valve calcification in 33%. Most subjects with zero values at baseline failed to progress over one year. Aortic valve calcification was significantly increased in calcium-treated subjects. Changes in mitral valve calcification, and combined mitral + aortic valve calcification were less in sevelamer-treated than in calcium-treated sub-

jects, but not significantly so. When combining valvular and vascular calcification, the median (10%, 90%) change in sevelamer-treated subjects was significantly lower than in calcium-treated subjects (6, -5084 to 1180 versus 81, -1150 to 2944,  $p = 0.04$ ). The effect of sevelamer remained significant after adjustment for baseline calcification and the time-averaged calcium-phosphorus product, and was independent of the calcium preparation (acetate versus carbonate), geographic region (US versus Europe), LDL- or HDL-cholesterol, C-reactive protein and statin use. Significantly more sevelamer-treated subjects experienced an arrest (45 versus 28%,  $p = 0.047$ ) or regression (26 versus 10%,  $p = 0.02$ ) in total valvular and vascular calcification.

**Conclusion:** Sevelamer arrested the progression of valvular and vascular calcification in almost 50% of hemodialysis subjects. Sevelamer treatment, plus intensive control of calcium and phosphorus levels, may attenuate progression of, or achieve regression in, cardiac valvular calcification.

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Persons with end-stage renal disease (ESRD) are frequently burdened with calcific valvular heart disease, the prevalence of which is estimated to be between 24% and 78% (1-6). In turn, calcific valvular heart disease contributes to the strikingly high incidence of valvular dysfunction, left ventricular hypertrophy, left ventricular dysfunction, atrial and ventricular arrhythmias and death in ESRD (7-10). Disorders of mineral metabolism, including hyperphosphatemia, hypercalcemia and secondary hyperparathyroidism, are common and severe in ESRD, and are associated with

mortality and significant morbidity (11-13). Recent observations in clinical and basic science have focused on the effects of phosphorus, calcium and parathyroid hormone (PTH) on vascular calcification, and the potential role of disorders of mineral metabolism in cardiovascular disease (14-17). Of interest, several studies have shown that the treatment of hyperphosphatemia with calcium-based phosphate binders may increase the risk of vascular calcification (18,19), though whether calcium contributes to progressive valvular calcification is unclear.

Sevelamer is a non-calcium-, non-aluminum-containing hydrogel used to control hyperphosphatemia in ESRD (20,21). Sevelamer is resistant to digestive degradation, and is not absorbed from the gastrointestinal tract. A randomized clinical trial was recently completed which compared the effects of sevelamer

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with those of calcium-based phosphorus binders on biochemical parameters of mineral metabolism and cardiovascular calcification, by use of electron beam tomography (EBT) (22). In the present study, the effects of sevelamer and calcium-based phosphorus binders on mitral and aortic valvular calcification were examined. In addition, the effects of these materials on the total burden of cardiovascular and valvular calcification (coronary artery, aorta, mitral and aortic valves), and the likelihood of arrest or regression of calcification over time, were explored.

## Clinical material and methods

### Subjects

The study subjects were all adult (age  $\geq 19$  years) maintenance hemodialysis patients who were enrolled at 15 participating dialysis units (seven in the USA, seven in Germany, and one in Austria). Exclusion criteria included serious gastrointestinal disease (including dysphagia, active untreated gastroparesis, severe motility disorder, major intestinal surgery, markedly irregular bowel function), ethanol or drug dependence or abuse, active malignancy, HIV infection, vasculitis, and very poorly controlled diabetes mellitus or hypertension (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

#### *Washout (run-in) phase*

After screening, subjects underwent a two-week washout period during which all phosphate binders were withheld (weeks -2 to 0). Subjects who developed hyperphosphatemia (serum phosphorus level  $>5.5$  mg/dl) during the washout period were eligible for randomization.

#### *Randomization*

Subjects were randomized (computer-generated) in a 1:1 ratio to receive either sevelamer or calcium, and stratified by clinical site and the diagnosis of diabetes mellitus at screening.

#### *Treatment phase*

Subjects were randomized to receive either sevelamer (Renagel® 800 mg tablets; GelTex Pharmaceuticals, Inc., Waltham, MA, USA) or calcium-based binders. Among subjects randomized to calcium treatment, those in the USA received calcium acetate (PhosLo® 667 mg tablets; Braintree Pharmaceuticals, Inc., Braintree, MA, USA), while those in Europe

received 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 study protocol. 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 phosphorus and calcium concentrations in the target ranges of 3.0-5.0 mg/dl and 8.5-10.5 mg/dl, respectively. Serum calcium was adjusted for the serum albumin concentration using the formula: adjusted Ca = total measured calcium +  $0.8 \times (4.0 - \text{albumin g/dl})$ . Treating physicians could prescribe aluminum hydroxide as a rescue binder if the calcium-phosphorus product exceeded  $72 \text{ mg}^2/\text{dl}^2$ . After 12 weeks, the dose of phosphate binder, vitamin D, and the dialysate calcium concentration could be titrated every four weeks to achieve serum phosphorus and calcium levels in the aforementioned target ranges. The target range for intact PTH (150-300 pg/ml) was selected a priori based on published evidence (23).

Serum phosphorus and calcium were monitored weekly during the titration phase and monthly thereafter. Intact PTH was drawn at screening, baseline, 12 weeks, and monthly thereafter. Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and homocysteine were measured at baseline, and at 12, 24 and 52 weeks; C-reactive protein (CRP) at baseline and 52 weeks. All blood samples were analyzed by Quest Diagnostics (Van Nuys, CA, USA; Heston, Middlesex, UK). LDL levels were calculated according to the Friedewald formula on non-fasting samples (24,25).

#### *Imaging procedure*

Subjects underwent an EBT imaging procedure at day 0, and again at 26 and 52 weeks. Details of the methods and reliability of EBT imaging have been published elsewhere (22). Briefly, all areas of calcification with a minimal radiological attenuation of 130 Hounsfield units within the borders of the coronary arteries, thoracic aorta, mitral valve and aortic valve were computed. The traditional calcium score originally described by Agatston et al. (26) was used to quantify the extent of calcification. The Agatston score is obtained by multiplying the area of a calcified focus by a weighted attenuation coefficient based on peak density measured inside the calcified focus. The median inter-scan variability for the Agatston score is 8-10% (27,28). Scans were considered of acceptable research quality only if the images were free from artifacts due to motion, respiration or asynchronous electrocardiographic triggering.

### Statistical analysis

Continuous variables were expressed as mean  $\pm$  SD or median with 10%, 90% range. Within-group comparisons were made with the Wilcoxon signed rank test. Between-group comparisons were made with Student's *t*-test or the Wilcoxon rank sum test, where appropriate. Categorical variables were compared with Fisher's Exact test. Relationships among demographic, historical and baseline laboratory data and baseline mitral and aortic valvular calcification were described with the Spearman rank-based correlation coefficient. Laboratory values obtained after washout were averaged over the time of study participation to provide a best estimate of exposure for longitudinal analyses. Changes in calcification of the mitral valve, aortic valve, the sum of both valves, and the overall sum of coronary arteries, aorta, and mitral and aortic valves were calculated by subtracting scores obtained on the baseline scan from those obtained on the 52-week EBT scan. The proportion of subjects who experienced an arrest or regression of calcification (zero or negative change in calcification score) over the 52-week study period was also calculated. Finally, in order to evaluate independent effects of binder assignment, baseline calcification and other factors, a multivariable linear regression was performed using the change in total vascular and valvular calcification as the dependent variable. The change in overall calcification was normally distributed permitting valid interpretation of linear regression results. A backward variable selection was used, with a *p*-value criterion of 0.05. Selected variables were re-entered to evaluate for residual confounding. Adjusted means were calculated using least squares regression. Model fit was assessed using Mallow's Cp. Two-tailed *p*-values <0.05 were considered to be statistically significant. Analyses were conducted using SAS 8.02 (SAS Institute, Cary, NC, USA).

### Results

#### Baseline characteristics of study subjects

The mean age of study subjects was  $56.5 \pm 14.9$  years. Among patients, 70 (35%) were female, 40 (20%) were black, and 65 (33%) had diabetes mellitus. There were no significant differences in demographic factors by binder assignment. The median dialysis vintage (time since initiation of dialysis) was slightly longer (43 versus 35 months) in subjects randomized to sevelamer, but the difference was not significant (*p* = 0.23). In total, 186 (93%) of the enrolled subjects underwent a baseline EBT scan. Baseline median (10%, 90% range) calcification scores and the fraction of zero scores by binder assignment are shown in Table I. At baseline, median scores tended to be higher, and there were fewer zero scores among subjects randomized to sevelamer, although the differences were not statistically significant.

Mitral valve calcification was generally more extensive than aortic calcification. Among the 186 subjects with baseline EBT scans, 76 (41%) had zero scores on both mitral and aortic valves, 76 (41%) had mitral valve score > aortic valve score, and 34 (18%) had aortic valve score > mitral valve score. A transverse computed tomographic section of the heart of a 56-year-old man on chronic dialysis with heavily calcified mitral and aortic valves and right coronary artery is shown in Figure 1. Mitral and aortic valve calcification scores were directly correlated (*r* = 0.33, *p* <0.0001), although less strongly so than coronary artery and aortic calcification scores (*r* = 0.64, *p* <0.0001).

#### Correlates of baseline valvular calcification

Baseline mitral valve calcification was directly correlated with age (*r* = 0.28, *p* = 0.007) and baseline CRP (*r* = 0.25, *p* = 0.03). Baseline aortic valve calcification was directly correlated with age (*r* = 0.37, *p* = 0.0003). The

Table I: Baseline calcification scores by binder assignment.

Tissue	Sevelamer (n = 92)	Calcium (n = 94)	<i>p</i> -value*
Coronary arteries	683 (0, 4167)	600 (0, 2788)	0.51
(% zero)	18	16	
Aorta	746 (0, 11538)	367 (0, 9620)	0.39
(% zero)	18	22	
Mitral valve	4 (0, 4851)	0 (0, 2353)	0.41
(% zero)	50	57	
Aortic valve	0, (0, 294)	0 (0, 199)	0.11
(% zero)	59	70	
Both valves	56 (0, 6046)	25 (0, 2353)	0.37
(% zero)	36	46	

Values are median, 10%, 90% range.

\**p*-value by Wilcoxon rank sum test.

combined valvular calcification score was directly correlated with age ( $r = 0.33$ ,  $p = 0.001$ ) and dialysis vintage ( $r = 0.22$ ,  $p = 0.03$ ).

### Changes in valvular calcification

A total of 132 subjects (71%) completed the 52-week study period. The mean and median (10%, 90%) changes in mitral valve, aortic valve, combined valvular and total calcification by binder assignment are shown in Table II. The distributions were left-shifted for sevelamer-treated subjects, but the vast majority of subjects with no visible valvular calcification at baseline remained zero when re-scanned at 52 weeks (mitral valve 71/71, aortic valve 84/87). Hence, the power to identify treatment-related differences was reduced. Aortic valve calcification was significantly increased in calcium-treated subjects ( $p = 0.04$ ). The corresponding increase in mitral valve calcification was not significant. There was a trend toward less calcification with sevelamer among subjects with non-zero scores of the mitral valve at baseline ( $n = 61$ , median change 19 (-2500, 691) versus 55 (-868, 1838),  $p = 0.24$ ), although the difference was not statistically significant.

### Total burden of valvular and vascular calcification

To calculate an integrated burden of cardiovascular calcification, the calcification scores of the coronary arteries, thoracic aorta and mitral and aortic valves were summed. Comparing median changes from baseline to week 52, there was significantly more progression of cardiovascular calcification among subjects treated with

calcium-based binders (Table II). The proportion of subjects who experienced an arrest (no change) or regression (negative change) in total calcific cardiovascular disease burden by binder assignment was also examined. The fraction of subjects who showed an arrest in progression of total calcification was 45% versus 28% ( $p = 0.047$ ) in the sevelamer and calcium-treated groups, respectively. The fraction of subjects who experienced regression in calcification was 26% versus 10% ( $p = 0.02$ ) in the corresponding groups.

### Multivariable analysis

In addition to treatment assignment and baseline calcification score, age, gender, race, presence of diabetes, dialysis vintage, geographic region (US versus Europe), time-averaged calcium-phosphorus product, PTH, LDL-cholesterol, HDL-cholesterol and CRP concentrations and hexamethyl-glutaryl-CoA reductase inhibitor ('statin') use were included as candidate variables in a multivariable linear regression analysis. The change in total cardiovascular calcification was significantly related to treatment assignment ( $p = 0.046$ ), baseline calcification score ( $p < 0.0001$ ) and calcium-phosphorus product ( $p = 0.006$ ). The model explained 43% of the variation and was well fitted (Mallow's  $C_p = 4.0$ ). The adjusted mean change in total calcification score was -905 in sevelamer-treated subjects, and +190 in calcium-

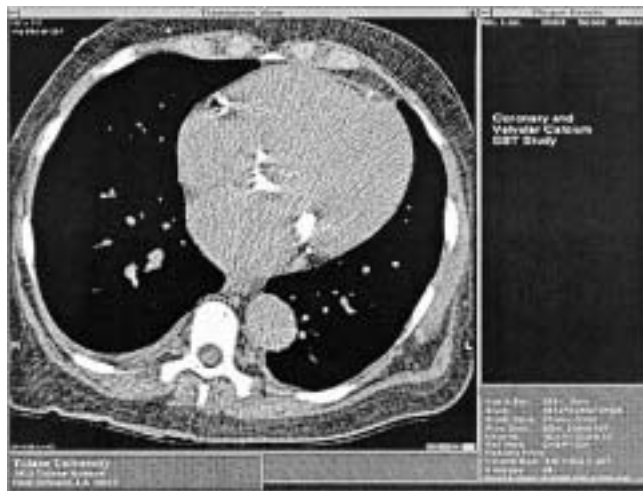


Figure 1: Thoracic transverse computed tomography section of a 56-year-old man undergoing maintenance hemodialysis. Note the heavy calcification of aortic valve (AoV), mitral valve (MV) and portion of the right coronary artery (RCA). The computer software highlights in yellow all tissues with a radiological density above 130 Hounsfield units for easier visualization.

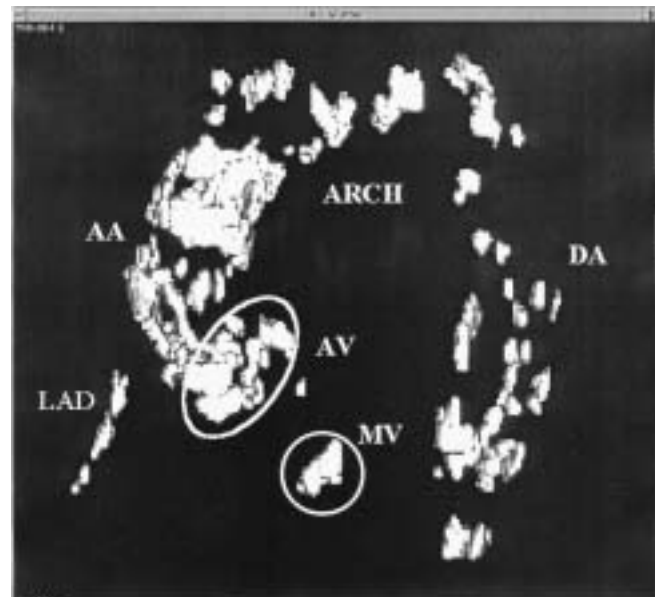


Figure 2: Three-dimensional volume rendering image of a 70-year-old man undergoing maintenance hemodialysis.

Here, the soft tissues are removed such that only the calcified portion of the cardiovascular system is visible. The heavily calcified aortic valve (AV) and mitral valve (MV) are both surrounded by a yellow circle. The ascending aorta (AA), aortic arch (ARCH), descending aorta (DA) and left anterior descending coronary artery (LAD) are also very heavily calcified.

treated subjects. Independent of treatment assignment, a relative time-averaged decrease in calcium-phosphorus product of  $10 \text{ mg}^2/\text{dl}^2$  was associated with an adjusted mean change in calcification score of -802. In other words, both binder choice and the degree of metabolic control influenced the change in calcification over time. Moreover, the change in calcification was independent of calcium preparation (acetate versus carbonate), geographic region (US versus Europe), PTH, LDL- or HDL-cholesterol, CRP, statin use and other factors.

## Discussion

The results of the present study were derived from a carefully conducted clinical trial, and confirm and extend previously the results of earlier studies of valvular calcification in ESRD (1-10). As expected, there was a direct correlation between age and the severity of valvular calcification. The direct correlation between mitral valvular calcification and CRP, while provocative, has been previously described (29). More striking were the longitudinal, multivariable results. By incorporating changes at multiple sites (coronary arteries, thoracic aorta, mitral and aortic valves) there were appropriate data structures and sufficient variability and power to conduct multivariable linear regression. These analyses suggested that patient characteristics (baseline calcification), therapeutic choices

(calcium- versus non-calcium-based binder) and target laboratory surrogates (calcium-phosphorus product) independently influenced the risk of progressive cardiovascular calcification.

Calcific valvular heart disease contributes to adverse clinical manifestations frequently seen in patients with ESRD, including left ventricular hypertrophy, left ventricular dysfunction, atrial and ventricular arrhythmias, endocarditis, heart failure and sudden death (7-10). Valvular heart disease can also worsen other more subtle, dialysis-related complications (30,31). For instance, aortic stenosis may exacerbate dialysis-related hypotension, rendering ultrafiltration more difficult, and ultimately lead to unremitting volume overload. Mitral stenosis or regurgitation may contribute to pulmonary hypertension, a condition which is often present in conjunction with biventricular failure, volume overload, and chronic pulmonary emboli associated with indwelling central venous catheters (32,33). Pulmonary hypertension may also be exacerbated by subclinical pulmonary emboli associated with procedures aimed at 'declotting' thrombosed arteriovenous fistulae or grafts, or associated vessels requiring transluminal angioplasty.

Several studies have estimated the prevalence and clinical correlates of valvular calcification among patients with ESRD. Braun et al. (4) initially reported on 49 maintenance hemodialysis patients, and identified calcification of the mitral valve in 59% of cases and

Table II: Changes in vascular and valvular calcification scores and percentage demonstrating non-progression and regression by binder assignment after 52 weeks follow up.

Tissue	Sevelamer (n = 62)	Calcium (n = 70)	p-value*
Coronary arteries	-46 ± 692 0 (-685, 413)	151 ± 471 37 (-106, 827) §	0.04
Aorta	-532 ± 1706 0 (-2021, 629)	185 ± 3100 75 (-933, 2316) §§	0.01
Mitral valve	-655 ± 3415 0 (-329, 130)	98 ± 710 0 (-125, 508)	0.75
Aortic valve	24 ± 210 0 (-33, 52)	24 ± 113 0 (-1, 73) †	0.57
Both valves	-631 ± 3470 0 (-329, 445)	122 ± 720 0 (-197, 614)	0.39
Total vascular and valvular	-1209 ± 4602 6 (-5084, 1180)	458 ± 3182 81 (-1150, 2944) †	0.04
No progression of total calcification burden	45%	28%	0.047
Regression of total calcification burden	26%	10%	0.02

Values are mean ± SD, and median, 10%, 90% range.

\*p-value by Wilcoxon rank sum test.

†p = 0.04; ‡p = 0.0007; §p = 0.0002; §§p = 0.0007 by Wilcoxon signed rank test.

aortic valve in 55%. These authors used EBT, which is a more sensitive method of detecting valvular calcification than echocardiography-based techniques (34-36). Ribeiro et al. (5) used transthoracic echocardiography (TTE) to compare the prevalence of valvular calcification in 92 hemodialysis patients and 92 age- and gender-matched controls. Mitral and aortic calcification were present in 45% and 52% of hemodialysis patients, compared with 10% and 4% of controls, respectively. Age and calcium-phosphorus product were directly related to mitral calcification, while aortic calcification was associated with age and arterial hypertension (the latter possibly the result of, rather than the cause of, valvular disease). Wang et al. (29) also used TTE to evaluate valvular calcification in 137 Chinese patients on ambulatory peritoneal dialysis. Forty-four (32%) had calcification of either or both mitral and aortic valves. Valvular calcification was independently associated with age, diabetes, calcium-phosphorus product, and the concentrations of serum albumin and CRP. Other studies using a variety of detection methods have shown prevalence estimates ranging from 24% to 78% (1-3,6-10).

Valvular calcification may have serious consequences in persons with ESRD. More recently, Wang et al. (15) described a cohort of 192 ambulatory peritoneal dialysis patients of whom 62 (32%) had valvular calcification who were carefully followed for a mean of 18 months (range <1 to 34 months). One-year survival was 70% with, and 93% without, valvular calcification. Adjusting for the effects of age, gender, diabetes, dialysis vintage, CRP, and the presence of atherosclerotic coronary artery disease, valvular calcification was associated with 2.5-fold and 5.4-fold increases in all-cause and cardiovascular mortality hazards, respectively. Moreover, there was a graded increase in risk with the number of valves calcified - with unadjusted one-year mortality rates of 15, 40 and 57% for patients with zero, one or two calcified valves. While there were numerous causes of death, sudden death (presumably due to ventricular arrhythmia) was responsible for seven out of 27 (26%) deaths among patients with valvular calcification.

Risk factors for atherosclerosis have been implicated in the development of mitral and aortic sclerosis and calcification in non-uremic individuals (37,38). Valvular calcification in persons with normal kidney function is associated with a high risk of cardiovascular events (39). Nonetheless, the prevalence and extent of vascular and valvular calcification observed in dialysis patients are so severe that they cannot be attributed to diabetes, hypertension, dyslipidemia and inflammation alone (as these factors are not unique to persons with advanced chronic kidney disease). Rather, disorders of mineral metabolism, including

hyperphosphatemia, secondary hyperparathyroidism and hypercalcemia resulting from therapy with calcium-based phosphorus binders and vitamin D, are likely implicated. Targets for metabolic control may have been too lax in past years. While traditional targets for the calcium-phosphorus product were  $<72 \text{ mg}^2/\text{dl}^2$ , and have been modified more recently to  $<55 \text{ mg}^2/\text{dl}^2$ , Rufino et al. (40) - using receiver operating characteristic (ROC) curves - suggested that a calcium-phosphorus product  $<43 \text{ mg}^2/\text{dl}^2$  might further reduce the risk of valvular calcification in hemodialysis patients.

In non-uremic individuals, the calcification of native and bioprosthetic valves seemingly proceeds through active processes of mineralization involving mediators of bone metabolism, and several traditional risk factors for atherosclerosis seem to contribute to this process (37,38,41-43). Whether similar mechanisms are involved in the calcification of valves in patients with ESRD remains to be determined (29). Slowing of valvular calcification has been attained in non-uremic subjects with use of statins (44) and inhibitors of angiotensin-converting enzyme (45). Although sevelamer is known to reduce total and LDL-cholesterol in hemodialysis patients (21,22), changes in lipid parameters did not appear to be the mechanism by which sevelamer treatment resulted in a slowing of calcification in the present study. Rather, the absence of calcium loading and subsequent metabolic effects were more likely to be operative.

### Study limitations

Several limitations to the present study were recognized. First, the sample size was relatively small, and the power to detect changes in mitral and aortic valvular calcification over time was limited. However, when pooling the effects of sevelamer and calcium on multiple sites of cardiovascular calcification, independent effects were found of binder assignment, even after adjusting for the effects of baseline calcification and metabolic control. The subjects were clinical trial participants and, as such, may not be fully representative of the overall dialysis population, although the inclusion criteria were broad. Metabolic targets (phosphorus, calcium, PTH) were more rigorous than are undertaken by most individuals in clinical practice; therefore, the frequency and severity of progressive calcification relative to all hemodialysis patients may have been underestimated. Finally, 54 (29%) subjects dropped out of the study before the 52-week follow up EBT, due to adverse events, transplantation and other factors. Although the number of drop-outs was not unexpected (given the severity of underlying diseases), it further reduced the power to detect changes in valvular calcification over time.

*In summary*, in a randomized clinical trial comparing

calcium- and non-calcium-based phosphorus binders in subjects receiving maintenance hemodialysis, a high prevalence of mitral and aortic valvular calcification was found. Valvular calcification was associated with advanced age, longer dialysis vintage, and higher levels of CRP. Most subjects without calcification at baseline failed to progress. Among subjects with valvular calcification at baseline, more tended to progress on calcium-based phosphorus binders than sevelamer. When pooling changes in coronary arteries, thoracic aorta, mitral and aortic valves, subjects randomized to sevelamer experienced slower progression of calcification. In order to attenuate progression or achieve regression in cardiovascular calcification in dialysis, sevelamer treatment plus intensive control of calcium and phosphorus concentrations appear to be advisable strategies.

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