Determinants of progressive vascular calcification in haemodialysis patients

Glenn M. Chertow¹, Paolo Raggi², Scott Chasan-Taber³, Juergen Bommer⁴, Herwig Holzer⁵ and Steven K. Burke⁶

¹Divisions of Nephrology, Moffitt-Long Hospitals and UCSF-Mt. Zion Medical Center, Department of Medicine, University of California San Francisco, San Francisco, ²Division of Cardiology, Department of Medicine, Tulane University, New Orleans, ³Pioneer BioDiligence, Amherst, Massachusetts, USA, ⁴Universitätsklinikum Heidelberg, Heidelberg, Germany, ⁵Universitätsklinikum Graz, Graz, Austria and ⁶Genzyme Drug Discovery and Development, Waltham, Massachusetts, USA

Abstract

Background. We determined recently that targeted treatment with calcium-based phosphate binders (calcium acetate and carbonate) led to progressive coronary artery and aortic calcification by electron beam tomography (EBT), while treatment with the non-calcium-containing phosphate binder, sevelamer, did not. Aside from the provision of calcium, we hypothesized that other factors might be related to the likelihood of progressive calcification in both or either treatment groups.

Methods. We explored potential determinants of progressive vascular calcification in 150 randomized study subjects who underwent EBT at baseline and at least once during follow-up (week 26 or 52).

Results. Among calcium-treated subjects, higher time-averaged concentrations of calcium, phosphorus and the calcium-phosphorus product were associated with more pronounced increases in EBT scores; no such associations were demonstrated in sevelamer-treated subjects. The relation between parathyroid hormone (PTH) and the progression of calcification was more complex. Lower PTH was associated with more extensive calcification in calcium-treated subjects, whereas higher PTH was associated with calcification in sevelamer-treated subjects. Serum albumin was inversely correlated with progression in aortic calcification. Sevelamer was associated with favourable effects on lipids, although the link between these effects and the observed attenuation in vascular calcification remains to be elucidated.

Conclusion. Calcium-based phosphate binders are associated with progressive coronary artery and aortic calcification, especially when mineral metabolism is not well controlled. Calcium may directly or indirectly (via PTH) adversely influence the balance of skeletal and extraskeletal calcification in haemodialysis patients.

Keywords: calcium; ESRD; haemodialysis; PTH; sevelamer

Introduction

The very high rates of cardiovascular mortality and morbidity in persons with end-stage renal disease (ESRD) are only partly explained by the high prevalence of risk factors for atherosclerosis found in these individuals [1,2]. Recent observations indicate that the common disorders of mineral metabolism seen in this patient population may contribute to the high incidence of cardiovascular events [3–6]. Hyperphosphataemia, hypercalcaemia and secondary hyperparathyroidism, as well as treatments used to control these abnormalities have been implicated in the development of vascular and visceral calcifications [7,8]. In addition, epidemiological evidence has linked the severity of vascular calcification to the dose of oral calcium used for phosphorus binding [5,9] and preliminary observations have shown rapid progression of cardiovascular calcification in dialysis patients treated with calcium salts [9,10].

In a recent randomized clinical trial we compared the effects of calcium salts (acetate and carbonate) and sevelamer, a non-absorbable hydrogel, on the serum concentrations of phosphorus, calcium and parathyroid...
hormone (PTH) and on coronary artery and aortic calcification using sequential electron beam tomography (EBT) imaging [11]. Subjects treated with calcium salts experienced significant progression of vascular calcification, while sevelamer-treated subjects demonstrated no substantial change and—in a substantial number—regression in the extent of calcification. Hence, an important question that should be addressed is whether there were any factors within each randomization group associated with progressive vascular calcification. We hypothesized that progressive vascular calcification would be more prominent among subjects who had relative hyperphosphataemia, relative hypercalcaemia and low or high levels of intact PTH.

We were also interested in analysing the role of lipids and mediators of inflammation in this process given the substantial involvement of these factors in atherosclerosis inception and progression [12,13].

Subjects and methods

Subjects

Subjects were adult (age ≥19 years) maintenance haemodialysis patients enrolled at 15 participating dialysis units: seven in the US, seven in Germany and one in Austria. Individuals with the following medical conditions were excluded from participation: 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 extremely poorly controlled diabetes mellitus or hypertension. Two hundred and fifty-two subjects were randomized to calcium (n = 101) or sevelamer (n = 99). One hundred and fifty (75%) subjects underwent two or more EBT scans and comprised the analytic sample. Of the 150, 18 had an EBT scan at week 26 and no week 52 EBT scan. For subjects who had scans at all three time points, the change in calcification was calculated by subtracting the baseline score from the week 52 score. 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 2-week washout period in which all phosphate binders were withheld (weeks −2 to 0). Subjects who developed hyperphosphataemia [serum phosphorous >1.38 mmol/l (>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 sevelamer (Renagel® 800 mg tablets, GelTex Pharmaceuticals, Inc., Waltham, MA) or calcium-based binders. Subjects randomized to calcium in the US received calcium acetate (PhosLo® 667 mg tablets, Braintree Pharmaceuticals, Inc., Braintree, MA). Subjects randomized to calcium in Europe received calcium carbonate (Sertuerner® 500 mg tablets, Sertuerner Arzneimittel GmbH, Guetersloh, Germany). Because of the size, appearance and taste of the tablets, neither the subjects nor the investigators were blinded. 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 3 weeks to achieve serum phosphorous and calcium concentrations in the target ranges of 0.97–1.61 mmol/l (3.0–5.0 mg/dl) and 2.13–2.63 mmol/l (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 × (4.0 – albumin g/dl). After 12 weeks, the dose of phosphate binder, vitamin D analogues and the dialysate calcium concentration could be titrated every 4 weeks to achieve serum phosphorous and calcium levels in the aforementioned target ranges. Subjects could use aluminum as a rescue binder if the calcium-phosphorus product exceeded 5.81 mmol²/l² (72 mg²/dl²). The target range for intact PTH was 150–300 ng/l [14–16].

Serum phosphorous and calcium were drawn weekly during the titration phase and monthly thereafter. Intact PTH was drawn at screening, baseline, 12 weeks and monthly thereafter. Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, homocysteine, 25-hydroxy- and 1,25 dihydroxy vitamin D₃ were drawn at baseline, 12, 24 and 52 weeks. C-reactive protein was drawn at baseline and 52 weeks. All blood samples were analysed at Quest Diagnostics, Van Nuys, CA, USA and Heston, Middlesex, UK. LDL was calculated according to the Friedewald formula on nonfasting samples [17,18].

Imaging procedure

Subjects underwent an EBT imaging procedure at day 0 and at 26 and 52 weeks. Details of the methods and reliability of EBT imaging have been published elsewhere [19]. Briefly, all areas of calcification with a minimal density of 130 Hounsefield 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. [20] was calculated. The Agatston score is obtained by multiplying the area of a calcified focus by a weighted density coefficient based on peak density measured inside the calcified focus. The median inter-scan variability for the Agatston score is 8–10% [19,21]. 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 ± standard deviation or median ± interquartile range, and compared with Student’s t-test or the Wilcoxon rank sum test, where appropriate. Categorical variables were compared with Fisher’s Exact test. Laboratory values obtained after washout were averaged over the time of study participation to
provide a best estimate of exposure. The change in coronary artery and aortic calcification was calculated by subtracting the baseline score from that of the last EBT scan (26 or 52 weeks). Non-parametric inference testing was employed due to the non-normal distribution of calcification scores and to ensure conservative probability value estimates. In contrast to the parent study where the focus was on between-group effects, here we focused on within-group effects, in an effort to explore the mechanism(s) of progressive vascular calcification. We stratified all of the EBT calcium score analyses by assigned treatment group (i.e. sevelamer or calcium). To evaluate the importance of calcium and phosphorus control, we compared subjects above and below the following values: mean serum calcium 2.38 mmol/l (9.5 mg/dl), phosphorus 1.78 mmol/l (5.5 mg/dl) and calcium-phosphorus product 4.44 mmol²/l² (55 mg²/dl²). These values correspond to the upper limit of the target range outlined by the National Kidney Foundation (NKF) Kidney Disease Quality Initiative (K/DOQI) Clinical Practice Guidelines on Bone Metabolism and Disease [22]. For analyses of intact PTH, we compared subjects whose mean intact PTH values were inside vs outside the target range (150–300 pg/dl). Other laboratory studies (e.g. LDL cholesterol, HDL cholesterol, homocysteine, 1,25 dihydroxy vitamin D₃) were dichotomized above and below overall median values. In companion analyses, the change in calcification score was modelled as a continuous variable, with laboratory variables added individually to a core model that included group assignment, baseline calcification score (an important predictor of change in calcium score) and the time between the first and final EBT. Finally, Spearman rank correlation coefficients between laboratory variables and the change in calcification score were computed, and intergroup (calcium vs sevelamer) correlations compared to evaluate for potential determinant × treatment interactions. Two-tailed P-values <0.05 were considered significant. Analyses were conducted using SAS 8.02 (SAS Institute, Cary, NC, USA).

**Results**

Baseline characteristics of study subjects are shown in Table 1. The groups were well balanced by randomization. Coronary and aortic calcification tended to be higher at baseline in the subjects randomized to sevelamer, although the differences were not statistically significant.

**Time-averaged laboratory tests associated with mineral metabolism**

Mean serum calcium was higher (2.43 ± 0.14 vs 2.34 ± 0.13 mmol/l, \( P = 0.0002 \)) and median PTH lower [143, interquartile range 89–252 vs 251 (177–338) ng/l, \( P < 0.0001 \)] in calcium-treated subjects compared with sevelamer-treated subjects. There were no significant

| Table 1. Baseline characteristics of study subjects with repeat EBT |
|-----------------|-----------------|-----------------|
| Age (years) (mean±SD) | 56.4±13.5 | 57.3±15.5 | 0.54 |
| Female [n (%)] | 24 (35%) | 27 (33%) | 0.86 |
| Race | | | |
| Black | 14 (20%) | 18 (22%) | 0.87 |
| White | 48 (70%) | 57 (70%) | |
| Other | 7 (10%) | 6 (7%) | |
| US-based [n (%)] | 36 (52%) | 41 (51%) | 0.87 |
| Diabetes [n (%)] | 25 (36%) | 25 (31%) | 0.49 |
| Vintage (months) [median (IQR)] | 39 (20–72) | 33 (14–56) | 0.15 |
| Body mass index (kg/m²) (mean±SD) | 26.2±4.1 | 26.1±4.5 | 0.73 |
| Primary cause of ESRD [n (%)] | | | |
| Hypertension | 10 (14%) | 12 (15%) | 0.58 |
| Glomerulonephritis | 19 (28%) | 18 (26%) | 14 (17%) |
| Diabetes | 7 (10%) | 17 (25%) | 22 (27%) |
| Polycystic kidney disease | | 10 (12%) | |
| Other | 23 (28%) | | |
| Systolic blood pressure (mm Hg) (mean±SD) | 135±20 | 142±23 | 0.08 |
| Diastolic blood pressure (mm Hg) (mean±SD) | 76±11 | 77±11 | 0.45 |
| Coronary artery Agatston’s score [median (IQR)] | 665 (79–2250) | 578 (76–1294) | 0.30 |
| Aortic Agatston’s score [median (IQR)] | 668 (25–3662) | 360 (4–4030) | 0.61 |
| Phosphate binder [n (%)] | | | |
| Calcium carbonate | 28 (41%) | 36 (44%) | 0.69 |
| Calcium acetate | 24 (35%) | 30 (37%) | |
| Calcium + aluminum | 8 (12%) | 10 (12%) | |
| Sevelamer | 1 (1%) | 1 (1%) | |
| Other combinations | 8 (12%) | 4 (5%) | |
| Vitamin D usage [n (%)] | 35 (51%) | 49 (60%) | 0.25 |
| Dialysate calcium concentration (mEq/l) | | | |
| ≤2.5 | 31 (44%) | 36 (45%) | 0.92 |
| 3.0 | 21 (30%) | 23 (28%) | |
| >3.0 | 17 (25%) | 22 (27%) | |

Note: n = 150 subjects with two or more EBT scans (of 200 subjects initially enrolled in study).
differences in mean serum phosphorus (1.73 ± 0.33 vs 1.73 ± 0.29 mmol/l, \( P = 0.94 \)), median 25 hydroxy-
[34 (23–61) vs 30 (18–47) ng/l, \( P = 0.09 \)] or median 1,25
dihydroxy vitamin D3 [21 (16–31) vs 23 (18–31) ng/l,
\( P = 0.38 \)].

**Calcification by serum calcium, phosphorus and
calcium-phosphorus product**

Higher concentrations of calcium, phosphorus and
calcium-phosphorus product were associated with more
prominent progression of calcification in calcium-
treated subjects (median changes shown in Figures
1–3). Corresponding mean changes in coronary calcifi-
cation score were for 58 and 224 for calcium < 2.38 and
\( \geq 2.38 \) mmol/l, 97 and 270 for phosphorus < 1.78 and
\( \geq 1.78 \) mmol/l, and 137 and 223 for calcium-phosphorus
product < 4.44 and \( \geq 4.44 \) mmol\(^2\)/l\(^2\), respectively. Cor-
responding mean changes in aortic calcification scores
were 206 and 389 for calcium < 2.38 and \( \geq 2.38 \) mmol/l,
10 and 808 for phosphorus < 1.78 and \( \geq 1.78 \) mmol/l,
and 87 and 803 for calcium-phosphorus product < 4.44
and \( \geq 4.44 \) mmol\(^2\)/l\(^2\), respectively.

Among sevelamer-treated subjects, mean changes in
calcification were negative and widely variable (overall
mean \( \pm \) SD change in coronary calcification \(-86 \pm 714\)
and change in aortic calcification \(-483 \pm 1632\)). The
degree of relative hypercalcaemia, hyperphosphata-
aemia and elevation of the calcium-phosphorus pro-
duct did not significantly affect the median changes in
coronary artery or aortic calcification when subjects
were treated with sevelamer (Figures 1–3).

![Fig. 1: Median changes in calcification scores of coronary arteries and aorta for subjects randomized to calcium and sevelamer and with
time-averaged serum calcium concentrations <9.5 mg/dl and
\( \geq 9.5 \) mg/dl. For calcium-treated subjects, \( n = 28 \) below and \( n = 53 \) at or above
9.5 mg/dl. For sevelamer-treated subjects, \( n = 45 \) below and \( n = 24 \) at or above 9.5 mg/dl.](image1)

![Fig. 2: Median changes in calcification scores of coronary arteries and aorta for subjects randomized to calcium and sevelamer and with
time-averaged serum phosphorus concentrations <5.5 mg/dl and
\( \geq 5.5 \) mg/dl. For calcium-treated subjects, \( n = 49 \) below and \( n = 32 \) at or above
5.5 mg/dl. For sevelamer-treated subjects, \( n = 44 \) below and \( n = 25 \) at or above 5.5 mg/dl.](image2)
Calcification by PTH

There were no significant differences in the progression of coronary artery calcification among calcium-treated subjects stratified by intact PTH. Subjects who were above or below target values tended to experience more extensive progression in aortic calcification [e.g. mean (median) aortic calcium score 753 (104) vs 545 (35), \( P = 0.11 \)]. Among sevelamer-treated subjects, median changes in calcification were zero whether or not subjects were within or above or below the intact PTH target. It is worth noting that relative to calcium-treated subjects, the power to identify determinants of progressive calcification in sevelamer-treated subjects was lower (as fewer subjects progressed).

Calcification by vitamin D and dialysate calcium

While the frequency and dose of vitamin D decreased in calcium-treated subjects and increased in sevelamer-treated subjects over the course of the study, there was no association between vitamin D use (or measured levels) and progressive calcification. End-of-study dialysate calcium concentrations were known in 90% of subjects; it was assumed to have been unchanged in those with missing data. In response to hypercalcemia and/or unintended suppression of PTH, dialysate calcium was lowered more frequently in calcium-treated compared with sevelamer-treated subjects (26 vs 8%, \( P = 0.01 \)). Among calcium-treated subjects whose dialysate calcium was lowered, the median change was –0.5 mEq/l.

Calcification by lipids and pro-inflammatory factors

Mean LDL cholesterol (1.69 ± 0.54 vs 2.63 ± 0.93 mmol/l, \( P < 0.0001 \)) and mean apolipoprotein B (0.62 ± 0.14 vs 0.83 ± 0.28 g/l, \( P < 0.0001 \)) were significantly lower in sevelamer-treated compared with calcium-treated subjects. There were no significant differences in mean HDL cholesterol, apolipoprotein A, homocysteine, leukocyte count or C-reactive protein concentrations among sevelamer-treated and calcium-treated subjects. There were no associations among any of the lipid or pro-inflammatory mediators and progressive calcification in calcium- or sevelamer-treated subjects.

Correlation analyses

Non-parametric testing with the Spearman rank-based correlation coefficients confirmed the results of the primary analyses. In calcium-treated subjects, the change in coronary calcification was directly correlated with serum phosphorus (\( r = 0.22, P = 0.04 \)) and calcium-phosphorus product (\( r = 0.26, P = 0.02 \)); the change in aortic calcification was directly correlated with serum calcium (\( r = 0.28, P = 0.01 \)). In sevelamer-treated subjects, none of the corresponding correlations were significant. When considering the overall study sample, the relations among serum calcium and change in aortic calcification \( (P = 0.03) \) and PTH and change in aortic calcification \( (P = 0.03) \) were dependent on sevelamer vs calcium therapy. In other words, among calcium-treated subjects, the higher the serum calcium concentration, the more extensive the aortic calcification. This relation did not hold in sevelamer-treated subjects. When considering PTH, lower values were associated with more extensive calcification in calcium-treated subjects, whereas higher values were associated with more extensive calcification in sevelamer-treated subjects. These results should also be interpreted cautiously, as the analyses cannot provide simultaneous

![Fig. 3. Median changes in calcification scores of coronary arteries and aorta for subjects randomized to calcium and sevelamer and with time-averaged calcium-phosphorus product <55 mg²/dl² and ≥55 mg²/dl². For calcium-treated subjects, \( n = 54 \) below and \( n = 27 \) at or above 55 mg²/dl². For sevelamer-treated subjects, \( n = 50 \) below and \( n = 19 \) at or above 55 mg²/dl².](image-url)
adjustment for calcium, 1,25 dihydroxy vitamin D₃, age, race and other factors associated with PTH.

Regression analyses

The baseline calcification was strongly predictive of change in calcification ($P<0.0001$) as expected. Of the many laboratory values tested, the mean serum albumin was inversely correlated with the change in calcification, significantly so in the aorta (estimated change in calcification score of 184 per g/l decrease in serum albumin, $P=0.02$). Using the regression techniques, we could demonstrate no other independent associations among laboratory variables and vascular calcification. Finally, the regression analyses should also be cautiously interpreted, as the data were not normally distributed. There were extensive ‘tails’ at both extremes and negative changes in calcification prohibited log or square root transformation. The power to demonstrate significant independent associations with multivariable regression was thereby reduced.

Discussion

Herein we explored within-group determinants of vascular calcification from a clinical trial comparing sevelamer with calcium salts. The main study results were published recently [11]. Briefly, while both agents provided excellent phosphorus control, calcium-treated subjects were more likely to experience hypercalcaemia (corrected serum calcium $\geq 2.63$ mmol/l, equivalent to $\geq 10.5$ mg/dl) and intact PTH concentrations below the target range of 150–300 ng/l. In addition, there was progressive coronary artery and aortic calcification among calcium-treated subjects, and no progression (on average) in sevelamer-treated subjects, despite the latter group having somewhat more severe calcification at baseline.

The exact mechanism(s) for the benefit of sevelamer are unknown. Others and we have shown previously a direct correlation between the severity of vascular calcification and the presence of elevated concentrations of calcium and phosphorus [3,5]. The results presented herein also suggest the importance of tight control of calcium and phosphorus, at least among subjects given calcium-based phosphate binders. The absence of an association in sevelamer-treated subjects could reflect a relative paucity of substrate (i.e. calcium for deposition) or altered bone dynamics with a propensity toward bone mineralization rather than visceral calcification. A beta error associated with the relatively small sample size and limited number of persons treated with sevelamer who experienced progression could also have masked these associations. Based on the data, one cannot implicate vitamin D or the dialysate calcium. Vitamin D and dialysate calcium concentrations were significantly increased in sevelamer-treated subjects relative to those treated with calcium-based phosphate binders. While vitamin D and higher concentrations of dialysate calcium can indirectly and directly, respectively, increase the net influx of calcium, these effects were dominated by the differences in oral calcium intake between the two treatment groups. On average, study subjects treated with calcium acetate and carbonate, respectively, ingested $\sim 1.2$ and $1.5$ g/day of non-dietary elemental calcium [11]. The study results would support the K/DOQI recommendation that no more than $1.5$ g of calcium-based phosphate binders be ingested per day [22]. One might argue that even lower doses should be used, particularly in the presence of vitamin D, as the average dose of calcium salts was associated with progressive calcification. Moreover, while hypercalcaemia may reflect only the ‘tip of the iceberg’ with regard to calcification risk, our findings also validate the K/DOQI guidelines for maintenance of serum calcium concentration at or below 2.58 mmol/l (9.5 mg/dl) [22]. Efforts to increase serum calcium to 2.5 mmol/l (10.0 mg/dl) or above to control PTH should probably be abandoned in favour of other strategies.

Sevelamer resulted in favourable changes in the lipid profile. While we did not observe an association between changes in lipid levels and changes in coronary artery or aortic calcification, here too we may have had insufficient power to detect an effect. Other studies have shown a link between the degree of LDL lowering and change in coronary artery calcification [23]. Extrapolating from the totality of evidence in non-uraemic individuals, it would be wise to correct dyslipidaemia in haemodialysis patients, given the exceptionally high risk of cardiovascular death in the ESRD population [24].

The mechanisms linking abnormal mineral metabolism and vascular calcification are not fully understood. Nevertheless, recent evidence suggests that vascular calcification is a complex and highly active process. Giachelli et al. [25] reported that human aortic smooth muscle cells cultured in media containing higher than normal phosphate concentrations exhibited dose-dependent increases in calcium deposition. The phosphate-induced calcification observed in cell culture was linked to enhanced expression of the osteogenic markers osteocalcin and Cbfa-1 [26]. Moe et al. [27] confirmed the role of Cbfa-1 and osteopontin in vascular calcification based on examination of sections of human inferior epigastric artery obtained from uraemic individuals. Deficiencies of circulating inhibitors of calcification, such as fetuin A (alpha2-Heremans Schmid glycoprotein) and matrix Gla protein also appear to modulate vascular calcification in ESRD [28,29].

There are several important limitations to this study. The within-group sample sizes were relatively small and the power to detect associations with multivariable regression analysis was limited. Power was further limited by infrequent testing for some of the potential determinants of progressive calcification, such as C-reactive protein and cholesterol subfractions. However, it is worth emphasizing that neither C-reactive protein, LDL, nor HDL cholesterol
concentrations were associated with the extent of calcification at baseline [3]. Independent effects of correlated factors such as hypercalcaemia and low levels of PTH on progressive calcification could not be explored. Skeletal and extraskeletal calcification may be inversely related according to the experimental data of Price et al. [30]. Therefore, low levels of PTH (with low bone turnover) may be in part responsible for accelerated vascular calcification, with higher serum calcium concentrations only indirectly responsible. The results may not be fully generalizable to general nephrology practice, where most patients do not receive the same attention given to clinical trial participants, and protocols for provision of vitamin D analogues and other therapies may be less stringently followed. Finally, fetuin A, matrix Gla protein and other potential modulators of calcification were not measured; the importance of these factors was not anticipated at the time the trial was designed.

In summary, we determined that relative hyperphosphataemia, hypercalcaemia and elevations in the calcium-phosphorus product were associated with accelerated coronary artery and aortic calcification in haemodialysis patients given calcium salts as phosphate binders. No other predictors of progressive calcification were consistently identified. Sevelamer was associated with favourable effects on lipids, although the link between these effects and the observed attenuation in vascular calcification remains to be elucidated. Exogenous calcium loading and/or unintended suppression of PTH may contribute to progressive calcific vascular disease in haemodialysis patients.

Conflict of interest statement. Dr Burke is an employee of Genzyme, Inc. Dr Chasan-Taber was hired by Genzyme, Inc. to direct statistical analysis of the parent study. For the analyses presented in this manuscript, Dr Chertow was given all data elements and conducted the statistical analyses independently. While Dr Burke contributed to the study design and implementation, neither he nor any employee or contractor of Genzyme, Inc. materially influenced the content of the manuscript, which was left to the authors/investigators. The investigators received research funding from Genzyme, Inc. to conduct the study. Drs Chertow and Raggi serve on an Advisory Board for Genzyme, Inc. The investigators do not own stock or have any other financial interest in Genzyme, Inc.

References


1495


Received for publication: 15.10.03
Accepted in revised form: 17.12.03