The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer

D Russo[1], I Miranda[1], C Ruocco[1], Y Battaglia[1], E Buonanno[1], S Manzi[1], L Russo[1], A Scafarto[1] and VE Andreucci[1]

[1]*Department of Nephrology. University 'Federico II', Naples, Italy*

Coronary artery calcification is more prevalent in dialysis patients than in patients without kidney disease and this is associated with high serum phosphorus. In this study, we evaluate the effect of calcium carbonate or sevelamer treatments on the progression of calcification in 90 predialysis patients. Inclusion criteria were stable serum calcium, phosphorus, parathyroid hormone, and a similar baseline total calcium score (TCS). These patients were not treated by phosphate binder, vitamin D, or statin. They were given low-phosphorus diets without or with daily calcium carbonate or sevelamer throughout the study that averaged 2 years. Baseline demographic or clinical characteristics along with biochemical parameters were not different among the three groups. The TCS significantly increased in patients on the low-phosphorus diet alone, to a lesser extent in calcium carbonate-treated patients, and not at all in sevelamer-treated patients. The progression of coronary calcification paralleled that of the calcium score. Our study shows that sevelamer treatment should not be restricted to dialysis patients; however, a larger study should be undertaken to confirm these results.

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Correspondence: *D Russo, Via G Marconi, 80, 80024 Cardito. Napoli, Italy. E-mail: domenicorusso51@hotmail.com*

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In patients on dialysis, the prevalence of vascular calcification is greater than in age- and sex-matched individuals without kidney disease;[1] for instance, coronary artery calcification (CAC) is more frequent in these patients than in individuals with established coronary artery disease but with normal kidney function.[1,2] This finding together with the very high rate of cardiovascular events sustains the opinion that the presence of vascular calcification is the strongest predictor of cardiovascular morbidity and mortality in patients on dialysis.[3] Very recently, the severity of CAC at the time of entry in the hemodialysis has been confirmed as an important predictor of long-term survival.[4]

A harmful characteristic of CACs is its progression over the time that is regarded as further predictor of cardiac events. Among the several pathogenetic factors contributing to formation and progression of CAC, the serum concentration of phosphorus plays a major role.[5–7] The relationship between concentration of phosphorus, CAC, and cardiovascular events is likely more complex than previously thought.[7–9] Phosphorus may accelerate the development and progression of CAC through both passive precipitation and cell-mediated process, the latter being more important than the former.[7] Association between higher phosphate levels and mortality risk has been reported among predialysis patients with absolute serum phosphate levels in the high–normal range but not among patients with lower serum phosphate levels; it has been hypothesized that phosphorus might contribute to mortality by increasing vascular calcifications.[8] In addition, severe CACs were found in predialysis patients despite the fact that majority of them had concentration of serum phosphorus within the normal range.[9] Not only hyperphosphatemia but even its treatment may promote the calcification process and enhance the progression of CAC. The use of calcium-based phosphate binders is, in fact, strongly associated with development and progression of CAC due to the large amount of calcium ingested and the consequent hypercalcemia. Thus, therapeutic approaches such as limiting the use of calcium-based phosphate binders and implementing the use of sevelamer, a non-calcium-based phosphate binder, have been undertaken

to modify the development or progression of CAC. Sevelamer halted or significantly reduced the progression of CAC in prevalent and incident patients on dialysis.[2,10] However, there is no unanimous agreement on abandoning the calcium-based phosphate binders for the treatment of hyperphosphatemia; the trials forming the case against calcium are regarded as flawed,[11] and the cost–benefit analysis indicates that in absence of hypercalcemia, calcium acetate should remain the treatment of choice for hyperphosphatemia in hemodialysis patients.[12]

We have demonstrated that both prevalence and progression of CAC are greater in pre-dialysis patients than in subjects with normal renal function.[13] In addition, although derangement of mineral metabolism does not predict the prevalence of CAC, values of serum phosphorus at the upper limit of normal range are associated with faster progression of CAC.[13,14]

On the basis of the previous observations and lack of data on phosphate binders and progression of CAC in pre-dialysis patients, we have undertaken this study to assess the efficacy of calcium carbonate and sevelamer in reducing the progression of CAC in pre-dialysis patients.

RESULTS

Study design and final number of patients available for analysis are reported in Figure 1. At the start of the study, 90 patients were randomly assigned to one of the following regimens: low-phosphate diet alone (controls; $n=30$), low-phosphate diet + calcium carbonate ($n=30$), low-phosphate diet + sevelamer ($n=30$). Six patients were lost during the follow-up: one was assigned to low-phosphate diet suffered acute myocardial infarction, two assigned to calcium carbonate withdrew their consent, three assigned to sevelamer could not bear the cost of the drug any longer. All dropped-out patients had baseline CAC. Thus, 84 patients completed the study.

Baseline demographic and clinical characteristics of patients who completed the study are reported in Table 1. There was no statistically significant difference among the groups apart from higher body mass index and shorter duration of hypertension in patients assigned to sevelamer.

Baseline (initial) and end of the study (final) biochemical variables are reported in Table 2. Initial values were not significantly different across the groups. On the contrary, significant changes were observed in some final values. For instance, glomerular filtration rate and serum concentration of calcium, alkaline phosphatase, and fibrinogen were significantly changed in the sevelamer group. Phosphaturia increased in controls. As expected, there was a significant decrease in urinary phosphorus excretion with both binders and particularly with sevelamer. Absolute mean serum concentration of lipids did not change. However, in sevelamer groups, median concentration of total cholesterol decreased by 7% (from 170 to 158 mg/dl), triglycerides by 18% (from 107 to 88 mg/dl), and low-density lipoprotein cholesterol by 11% (from 106 to 94 mg/dl); median values remained unchanged in the other two groups.

At the end of the study, there were no statistically significant differences in systolic, diastolic, mean blood pressure, and pulse pressure across the groups.

Mean absolute and annualized absolute changes of total calcium score (TCS) are reported in Figure 2 and 3. The final TCS was significantly greater than the initial TCS in controls (369 ± 115 (mean $\pm$ s.e.) vs 547 ± 175; $P<0.001$) and in calcium-treated subjects (340 ± 38 vs 473 ± 69; $P<0.001$); in contrast, the final TCS was not significantly different from the initial TCS among subjects receiving sevelamer (415 ± 153 vs 453 ± 127; NS). Annualized progression of TCS was 205 ± 82 in controls, 178 ± 40 in calcium carbonate patients, and 36 ± 32 in sevelamer patients. No significant between-group change was found in mean absolute and annualized absolute values of TCS.

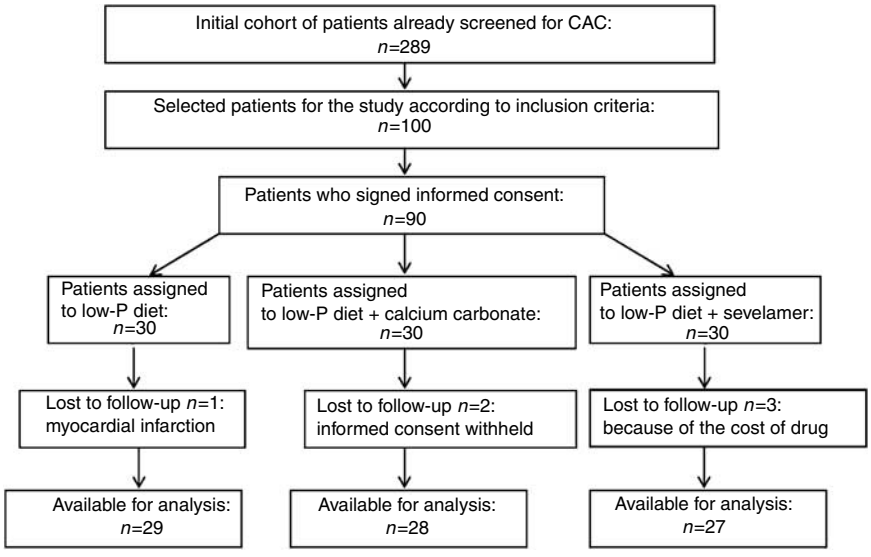

Figure 1 | Study design.

Table 1 | Baseline demographic clinical characteristics of patients

	Controls (*n*=29)	Calcium carbonate (*n*=28)	Sevelamer (*n*=27)
Gender (M/F)	25/4	23/5	24/3
Age (years)	54.4 (13.7)	55.2 (12.0)	54.4 (12.9)
Body mass index (kg/m^2)	24.8 (2.3)	24.5 (2.9)	26.1 (4.1)*
Traditional risk factor (*n*)	5.3 (1.4)	5.3 (1.2)	5.6 (1.4)
Systolic blood pressure (mm Hg)	134.4 (13.9)	136.8 (7.6)	135.5 (9.7)
Diastolic blood pressure (mm Hg)	82.2 (5.6)	84.8 (5)	80.5 (3.7)
Mean blood pressure (mm Hg)	99.4 (7.9)	102 (3.7)	98.8 (3.9)
Pulse pressure (mm Hg)	51.4 (9.7)	52.0 (10.2)	55.0 (10.7)
Duration HTN (months)	90 (89)	133 (73)*	60 (52)
Antihypertensive drugs (*n*)	2.1 (0.6)	2.3 (0.7)	2.5 (1.1)
Calcium channel blockers use (%)	44	48	45
Without CAC (*n*)	5	5	5

CAC, coronary artery calcification; F, female; HTN, hypertension; M, male.
Numbers are mean s.d.
*$P<0.01$ vs other groups.

Table 2 | Initial and final biochemical variables

	Controls		Calcium		Sevelamer	
Variables	Initial	Final	Initial	Final	Initial	Final
GFR (ml/min)	33.4 (20.2)	33.6 (25.0)	26.2 (8.3)	25.9 (5.3)	26.3 (15.6)	24.1* (14.7)
PTH (pg/ml)	140.7 (73.2)	146.9 (77.4)	172.1 (73.8)	176.1 (54.8)	136.5 (101.7)	134.9 (72.7)
Serum calcium (mg/dl)	9.2 (0.6)	9.3 (0.5)	9.0 (0.7)	9.1 (0.8)	9.2 (0.2)	9.0* (0.3)
Serum phosphorus (mg/dl)	3.9 (0.7)	3.9 (0.9)	4.6 (1.5)	4.7 (1.5)	4.5 (0.7)	4.8 (0.9)
Calcium $\times$ *P* product (mg^2 $\times$ dl^2)	35.8 (7.0)	36.0 (7.8)	42.3 (8.0)	40.3 (11.8)	41.7 (6.9)	43.1 (8.4)
Alkaline phosphatase (mg/dl)	113.7 (62.2)	85.1* (25.1)	148.0 (83.2)	143.0 (93.2)	134.2 (67.1)	103.4** (47.6)
Total serum proteins (mg/dl)	7.2 (0.8)	7.5 (0.8)	6.9 (1.0)	7.2 (1.2)	7.2 (0.7)	7.2 (0.7)
Serum albumin (mg/dl)	3.9 (0.52)	4.2 (0.5)	3.8 (0.7)	3.9 (0.8)	3.9 (0.4)	4.2 (0.2)
Carbonate (mEq/l)	23.4 (3.8)	24.3 (3.5)	21.6 (5.3)	23.2 (4.2)	22.3 (3.1)	21.2 (2.3)
Homocysteine (μmol/l)	29.8 (18.7)	27.2 (14.6)	38.0 (14.5)	38.0 (14.5)	31.5 (10.5)	33.5 (19.7)
Fibrinogen (mg/dl)	342.6 (124.5)	385.5 (99.5)	401.3 (96.7)	397.3 (85.7)	424 (222)	332** (57)
Total cholesterol (mg/dl)	189.0 (36.3)	188.6 (38.8)	184.9 (32.5)	184.0 (23.5)	173.0 (50.5)	181.3 (53.1)
Triglycerides (mg/dl)	137.7 (101.8)	131.9 (94.4)	119.2 (50.3)	139.2 (50.3)	141.4 (92.3)	131.6 (109.7)
HDL cholesterol (mg/dl)	59.8 (44.1)	48.9 (13.1)	46.8 (10.2)	46.7 (10.2)	48.8 (10.7)	49.9 (11.8)
LDL cholesterol (mg/dl)	115.9 (32.1)	118.0 (47.5)	121.0 (47.4)	101.0 (33.2)	113.9 (55.1)	107.3 (39.1)
C-reactive protein (mg/dl)	0.98 (2.38)	0.34 (0.08)	1.1 (2.7)	0.33 (0.09)	0.50 (0.27)	0.73 (0.99)
Phosphorus intake (mg/day)	682 (480)	788 (470)	694 (492)	658 (478)	690 (398)	784 (385)
Phosphaturia (mg/24 h)	367 (389)	514* (285)	496 (125)	413* (126)	490 (128)	410** (130)

GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone.
Numbers are mean and s.d.
*$P<0.05$, **$P<0.01$ vs own initial.

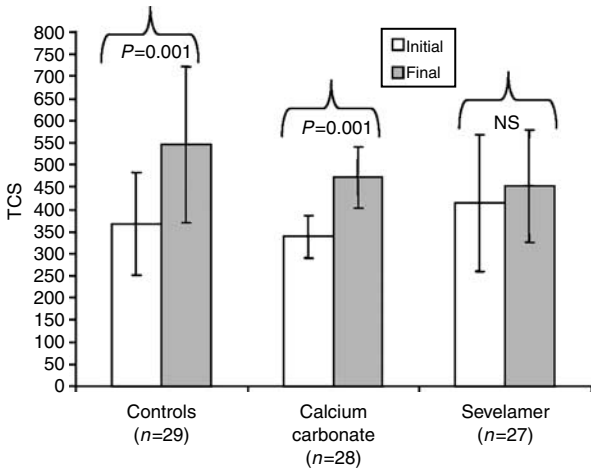

Figure 2 | Initial (white bars) and final (dark bars) absolute TCS in controls (*n* = 29) and in patients assigned to calcium carbonate (*n* = 28) and sevelamer (*n* = 27). Numbers are mean and s.e.

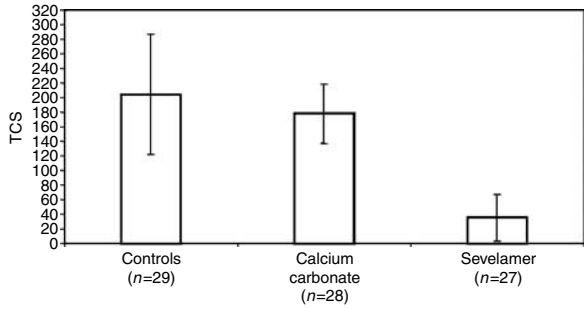

Figure 3 | Annualized progression of TCS in controls (*n* = 29) and in patients assigned to calcium carbonate (*n* = 28) and sevelamer (*n* = 27). Numbers are mean and s.e.

Fifteen patients without baseline CAC remained 'not calcified' at the end of the study.

DISCUSSION

In a recent study, we have demonstrated progression of CAC in pre-dialysis patients by an extent nearly similar to that reported in patients on dialysis and in subjects with symptomatic coronary artery disease.[14] In addition, our study has shown that higher serum concentration of phosphorus was significantly associated to greater progression of CAC, despite that the majority of patients had normal serum concentration of ion. Finally, fatal and not fatal cardiac events were more frequent in patients whose CAC progressed. These findings motivated the present study, which aimed to evaluate whether the administration of two distinctive phosphate binders, calcium carbonate and sevelamer, could modify the progression of CAC in pre-dialysis patients.

Some relevant findings were attained in this study. First, treatment with calcium carbonate in pre-dialysis patients did not enhance the progression of CAC as it has been observed in patients on dialysis. Second, sevelamer reduced progression of CAC in a more consistent manner than calcium carbonate. Third, progression was observed only in patients with CAC, whereas those without baseline CAC remained 'non-calcified' at the end of the study.

It is worth noting that high-risk patients were enrolled; in fact, several traditional risk factors were associated with high baseline calcium score. Apart from traditional risk factors, high calcium score is regarded as a strong predictor of cardiovascular events in patients on dialysis.[4,10,15,16]

Without treatment with phosphate binders CAC progressed more severely. This finding is clinically relevant. A similar rate of progression in non-uremic individuals has been associated with very high risk for myocardial infarction.[17,18] Therefore, a potential association between progression of CAC and cardiac outcome should be taken into account for pre-dialysis patients.

All available studies comparing the effects of sevelamer and calcium-based phosphate binders on progression of calcification have been undertaken in patients on dialysis with deranged mineral metabolism. Thus, the achievement of lower or normal serum concentration of phosphorus, calcium, parathyroid hormone (PTH), and calcium $\times$ phosphorus product has been regarded as crucial determinant for slowing down the progression of calcification. In this study, patients without baseline alteration of mineral metabolism were studied. Nevertheless, given that progression of CAC was reduced only in patients treated with phosphorus binders, we can hypothesize that serum phosphorus might have been involved despite that its serum concentration remained within normal range. This hypothesis seems supported by two studies in patients not yet on dialysis. In the first study,[8] increased mortality risk was not observed among people with lower serum phosphate levels whereas an association between phosphate and mortality risk was found among people with serum phosphate levels in high–normal range. Serum phosphorus of 3.5 mg/dl was associated with a significantly increased risk for death, and mortality risk increased linearly with each subsequent 0.5 mg/dl rise of serum phosphorus level. Vascular calcifications were claimed as the potential determinant of the increased mortality risk. In the second study,[9] a significant correlation was found between severe CAC and phosphorus despite that the majority of patients had normal serum concentration of the ion.

It is commonly recognized that development and progression of CAC in patients on dialysis is dependent on hyperphosphatemia on the one hand and on calcium ingested as phosphate binder on the other hand. To our knowledge, no clinical studies have evaluated the development and progression of CAC in untreated and treated patients on dialysis with calcium-based phosphate binders. Likewise, no study has been carried out in pre-dialysis patients. In this study, CAC progressed by a minor extent in patients treated with calcium carbonate than in controls. Therefore, in pre-dialysis patients, the progression of CAC should not be unequivocally ascribed to the calcium ingested as phosphate binder as it occurs in patients on dialysis. Otherwise, the progression of CAC should have been greater in patients treated with calcium carbonate than in controls, because a significant progression has been reported in patients on dialysis with doses of elemental calcium as small as 1.1 g/day.[10] It is likely that exogenous calcium load from phosphate binder may have fewer effects on the calcification process, since the function of renal tubuli is not completely lost in CKD patients.

It is worth noting that baseline levels of serum phosphorus and TCS were higher (although not significantly different) in patients assigned to sevelamer than in controls; nonetheless, sevelamer patients did not experience significant progression of CAC and three of them had regression of the process. It has been reported that progression is more severe when baseline plaque burden is greater.[10] The least severe progression of CAC with sevelamer is in keeping with that found by others in prevalent and incident patients on dialysis.[2,10] Calcium scores were, in fact, significantly lower in patients treated with sevelamer compared to patients treated with calcium-based phosphate binders, despite a similar control of mineral metabolism. Fewer episodes of hypercalcemia and favorable effects on lipid profile were potential determinants of the greater efficacy of sevelamer in slowing down the progression of coronary and cardiac valve calcification.[2,10] In fact, hypercalcemic episodes were less frequent in sevelamer subjects even if an increase in serum calcium was observed.[10,19] On the contrary, in this study, a small but significant decrease in final serum calcium (9.2 ± 0.2 vs 9.0 ± 0.2 mg/dl; $P < 0.05$) was observed in patients assigned to sevelamer; this decrease was, in our opinion, of minimal clinical significance. In the same way, final calcium was not increased in patients assigned to calcium carbonate. Both the findings may be likely due to the fact that in our patients the renal function was not completely lost and that they were not treated with vitamin D.

Sevelamer is the unique phosphate binder that consistently decreases low-density lipoprotein cholesterol and increases high-density lipoprotein cholesterol in patients on dialysis.[2,10,19] We cannot determine whether the greater reduction of progression was due to the effect of sevelamer on lipids. In fact, no significant differences were found in the markers of lipid metabolism at the end of the study. Nevertheless, sevelamer decreased the absolute concentration of cholesterol and, by a greater extent, the median value of low-density lipoprotein cholesterol; likewise, it increased high-density lipoprotein cholesterol. More marked effects on lipid profile observed in patients on dialysis may be due to larger prescribed doses of sevelamer.[2,10]

Markers of inflammation have been associated with mortality and coronary calcification in patients on dialysis because they may activate arterial calcium deposition.[20–22] Distinctive effects of sevelamer on inflammation are regarded as capable of slowing down the progression of CAC.[10,19] In this study, patients assigned to sevelamer showed no changes in the concentration of C-reactive protein and homocysteine but showed a significant decrease in fibrinogen. In a previous study, the markers of inflammation were not predictive factors of either prevalence or progression of CAC in pre-dialysis patients.[13,14]

Clinical studies have shown that sevelamer reduces plasma concentration of bicarbonate, worsening metabolic acidosis in patients on dialysis.[10,12,23] In this study, the reduction of carbonate in patients assigned to sevelamer was negligible, likely due to, on the one hand, to a small amount of the binder, and on the other hand, to still preserved renal function. However, acid–base balance should be closely monitored during treatment with higher doses of sevelamer.

The duration of hypertension was shorter in patients treated with sevelamer than in other groups; however, this difference had, in our opinion, no relevant implication as the duration of hypertension was not a predictive factor of progression in previous larger studies in pre-dialysis patients.[13,14]

A further relevant finding of this study is that patients without baseline CAC remained free from CAC at the end of the study despite similar 'uremic' environment and exogenous promoting factors. Persisting 'non-calcified' patients were, in fact, found in all groups. This finding might suggest that use of phosphate binders is not required in pre-dialysis patients without CAC, the progression being a natural process that occurs only in the presence of CAC. It should be of clinical relevance to identify demographic, biochemical, and/or genetic characteristics that protect pre-dialysis patients against development of CAC. The 'non-calcified' status is, however, not permanent; in fact, CAC has not been found in 47% of pre-dialysis patients, in 36% of those entering dialysis treatment, and in 11 and 7% of those on hemodialysis for an average of 39 and 65 months, respectively.[2,3,13,16] These data may indicate that distinctive pathogenetic factors are involved in the process leading to development and progression of CAC among pre-dialysis patients and those on dialysis.

LIMITATIONS

Main limitation of this study is the small number of patients. This was mainly due to the fact that prescription of sevelamer is authorized only for patients on dialysis.

The dosing of binders was not adjusted to reach a targeted serum concentration of phosphorus. Nonetheless, calcium carbonate and sevelamer were clearly effective in reducing CAC progression.

Owing to small cohort of patients, on the one hand, and to a large variation in the values of TCS, on the other hand, no significant between-group change was found. No significant between-group difference has been reported in a recent larger study evaluating the effects of sevelamer on progression of CAC in incident patients on dialysis.[2]

The exclusion of patients with diabetes might have made the study not representative of 'the real-life'. But patients with diabetes would have influenced the results since diabetes '*per se*' accelerates the progression of CAC.

CONCLUSIONS

Progression of CAC is severe in pre-dialysis patients not treated with phosphate binders. Treatment with calcium carbonate appears to be safe in pre-dialysis patients given that the binder does not worsen the progression of CAC as it does in patients on dialysis. The progression of CAC may be more markedly hampered by sevelamer. Nevertheless, the relatively small number of patients does not allow drawing a definitive conclusion on both issues. Larger prospective study should be undertaken in pre-dialysis patients to confirm these results. In this case, the use of sevelamer should be not restricted to patients on dialysis. Finally, it would be clinically relevant to identify demographic, biochemical, and/or genetic characteristics that protect some pre-dialysis patients against the development of CAC.

MATERIALS AND METHODS

From a cohort of 289 outpatients with stage 3–5 of chronic kidney disease not yet on dialysis and previously screened for the presence of CAC with spiral computed tomography (CT), we selected 100 patients. Exclusion criteria were age <18 years, symptomatic coronary disease, past myocardial infarction, previous coronary surgery/angioplasty or stroke, progressive renal disease, and arrhythmia (to avoid motion artifacts during CT scans). Diabetic patients (e.g., those regularly using insulin and hypoglycemic drugs) were excluded because progression of CAC is greater and independent of mineral metabolism and renal function.[2,24] The inclusion criteria were constant low dietary phosphate intake; stable serum concentration of phosphorus, calcium, calcium $\times$ phosphorus product, and PTH in the prior 6 months; no previous therapy with aluminum- or calcium-based phosphate binders, vitamin D sterols, and statins; comparable mean baseline TCS at CT scan.

Before the enrollment, patients were informed about the therapeutic interventions, purpose and nature of the study, and that the use of sevelamer in predialysis patients had not been approved as yet by FDA or by the Health Department of our country.

Of the initial cohort, 90 patients accepted to participate in the study and signed written informed consent. Among these patients,

there were some without baseline CAC ($n=15$) to establish the efficacy of the planned therapeutic interventions in preventing the development of plaque.

Protocol of the study was approved by the Internal Review Board.

Lacking references on sevelamer in predialysis patients, a pilot study had been performed in 20 volunteers with stable stage 3–5 of chronic kidney disease not yet on dialysis to establish the dose that had phosphate-binding capacity and that less likely could cause hypophosphatemia or oversuppression of PTH (data not presented). In this pilot study, sevelamer was administered at increasing doses from 0.8 to 2.4 g/day. The phosphate-binding capacity was evaluated by comparing changes from baseline in urine phosphorus excretion, measured as mean daily urine phosphorus content. The lowest dose of binder did not affect serum concentration of phosphorus and PTH, and did not reduce 24 h urinary phosphate excretion. On the contrary, the highest dose reduced phosphaturia, and caused hypophosphatemia and oversuppression of PTH in 60% of participants.

In this study, sevelamer was administered at the daily dose of 1600 mg. The administered dose of calcium carbonate was 2 g/day, equivalent to 1600 mg of sevelamer as counseled by the producer when patients are shifting from calcium acetate to sevelamer.

Patients were randomly assigned to low-phosphate diet alone and to receive either calcium carbonate or sevelamer by the co-author (YB), who was unaware of their baseline demographic and clinical characteristics and biochemistry.

Serum concentrations of calcium, phosphorus, PTH (i-PTH), homocysteine, C-reactive protein, triglycerides, total cholesterol, high-density lipoprotein cholesterol were measured; low-density lipoprotein cholesterol was calculated using the Friedewald equation. Glomerular filtration rate was measured as 24-h measured creatinine clearance. The biochemical measurements were obtained at baseline and every 3 months during the observation period; the on-treatment measurements were averaged for statistical analysis and are reported.

Data were collected to determine in each subject the sum of 'traditional' risk factors such as age, gender, family history of premature cardiovascular disease, hypertension, high total cholesterol, low high-density lipoprotein cholesterol, hypertension, smoking, and obesity.

CACs were assessed by multislice spiral CT (GE Medical Systems, Milano, Italy). CT scans were performed at the entry (initial) and at the end of the study (final). CT evaluation was carried out in an institution external to authors' university. Both initial and final scans were analyzed by radiologists who were unaware of both treatment allocation and previous CT reading.

Collection and scoring of CT images were performed as described elsewhere.[13] CT images were reconstructed with a standard algorithm, prospective gating, 512×512 matrix, SFOV 50 cm, DFOV 25 cm. Prospective gating does not require manual analysis and reduces variability of coronary calcium scores, being less dependent on the operator. The system was synchronized (Millennia 3500 CT-P) with the cardiac cycle to trigger scanning during the R to R interval. All pixels with intensity value above the threshold of 130 Hounsfield Units were counted; calcification was then assigned to one of the coronary arteries. CT images were transferred to workstation (Advantage work station; ADV 4.0), and scored. Scores were summed to obtain the TCS.

The progression of CAC was measured both as an absolute increase of TCS from the first to the second CT scan and as annualized absolute change (computed as second TCS−first TCS/days of follow-up $\times$ 365).[25]

The observation period lasted 24 ± 4.2 (mean $\pm$ s.d.) months.

PTH was assayed by a chemiluminescent immunometric method (Diagnostic Products Corporation, Los Angeles, CA, USA) and hsC-reactive protein by an immunoturbidimetric method.

Variables lacking normal distribution were analyzed by non-parametric tests. Progression of CAC was evaluated between groups and the within group by the Kruskall–Wallis test or the Wilcoxon signed ranks test, when appropriate. Continuous variables were compared with Student's *t*-test. Categorical variables were compared with Fisher's exact test.

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