

Ten-Year Experience with Sevelamer and Calcium Salts as Phosphate Binders

Paolo Raggi,* Slobodan Vukicevic,[†] Rosa Maria Moysés,[‡] Katherine Wesseling,[§] and David M. Spiegel^{||}

*Division of Cardiology and Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; [†]School of Medicine, University of Zagreb, Zagreb, Croatia; [‡]Division of Nephrology, Universidade de São Paulo, São Paulo, Brazil; [§]Department of Pediatric Nephrology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California; and ^{||}Department of Medicine and Division of Nephrology, University of Colorado Denver, Denver, Colorado

Most patients with chronic kidney disease experience abnormalities in serum calcium, phosphorus, parathyroid hormone, and vitamin D metabolism. These can lead to vascular calcification (VC), which has been associated with increased risk for cardiovascular disease and mortality. Although hyperphosphatemia is believed to be a risk factor for mortality and VC, no randomized trial was ever designed to demonstrate that lowering phosphate reduces mortality. Nonetheless, binders have been used extensively, and the preponderance of evidence shows that sevelamer slows the development of VC whereas calcium salts do not. Four studies have demonstrated a slower progression of VC with sevelamer than with calcium-containing binders, although a fifth study showed nonsuperiority. Conversely, the results on mortality with sevelamer have been variable, and data on calcium-based binders are nonexistent. Improved survival with sevelamer was demonstrated in a small randomized clinical trial, whereas a larger randomized trial failed to show a benefit. In addition, preclinical models of renal failure and preliminary clinical data on hemodialysis patients suggest a potential benefit for bone with sevelamer. Meanwhile, several randomized and observational studies suggested no improvement in bone density and fracture rate, and a few noted an increase in total and cardiovascular mortality in the general population given calcium supplements. Although additional studies are needed, there are at least indications that sevelamer may improve vascular and bone health and, perhaps, mortality in hemodialysis patients, whereas data on calcium-based binders are lacking.

Clin J Am Soc Nephrol 5: S31–S40, 2010. doi: 10.2215/CJN.05880809

Most patients with chronic kidney disease (CKD) experience abnormalities in calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism. Hyperphosphatemia that results from declining kidney function is a hallmark of advanced CKD and is associated with abnormal mineral and bone metabolism. In cross-sectional studies, each 1-mg/dl rise in serum phosphorus was associated with a 23% increased risk of death (1). Hyperphosphatemia is also correlated with increased risk of soft tissue and vascular calcification (VC), which may contribute to higher morbidity and mortality (2). Despite the absence of prospective studies to confirm these cross-sectional data, reducing serum phosphorus levels has been at the center of nephrologists' efforts for treatment of dialysis patients for several decades and is now being considered for patients with earlier stage CKD (3).

In randomized clinical trials, calcium-based phosphate binders and sevelamer have shown the same phosphorus-reducing ability (4–7). Laboratory experiments, however, have raised some concern regarding the risk of hypercalcemia as an inducer of VC (8,9). Similarly, in clinical studies that demonstrated

progression of VC, episodes of hypercalcemia were significantly more frequent among users of calcium-based binders (4,6). In addition to controlling hyperphosphatemia, potentially beneficial effects of sevelamer include its influence on biomarkers such as C-reactive protein (CRP), uric acid, and LDL cholesterol (10–12), as well as bone density (13), structure (14), and remodeling (15,16).

This review summarizes studies of calcium salts and sevelamer for treatment of hyperphosphatemia as it may affect CKD and mineral and bone disorders (CKD-MBD). CKD-MBD describes a clinical syndrome that is characterized by a systemic disorder manifested by one or more abnormalities in laboratory parameters, bone histomorphometry, and/or VC or other soft tissue calcification (17). The effects of calcium phosphate binders and sevelamer are discussed in four areas: Biomarkers, VC, bone homeostasis, and mortality.

Effects of Phosphate Binders on Biomarkers

A biomarker is a surrogate indicator of a biologic state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In theory, if a treatment alters a biomarker that has a direct connection to improved health, then it could serve as a surrogate end

Correspondence: Dr. Paolo Raggi, Department of Medicine and Radiology, Emory University School of Medicine, 1365 Clifton Road NE, Atlanta, GA 30322. Phone: 404-778-5414; Fax: 404-778-3540; E-mail: praggi@emory.edu

point for evaluating clinical benefit. In CKD, multiple surrogate biomarkers have been used to investigate disease progression. These include classical risk factors for cardiovascular disease, such as total cholesterol, LDL cholesterol, and apolipoprotein B (4,10,11), and markers of inflammation such as β 2-microglobulin and CRP (10). Since its introduction on the market, significant reductions in total cholesterol and LDL cholesterol have been described with sevelamer, which is likely due to inhibition of cholesterol absorption from the intestine (18). These resin-like activities have not been associated with altered drug absorption (19,20).

The acute-phase reactant CRP is often elevated in CKD and has been associated with overall and cardiovascular death in hemodialysis (HD) patients (19,20). Some studies have demonstrated a reduction in serum CRP and in apolipoprotein B after sevelamer treatment, suggesting another potentially beneficial effect of this drug (10,11). These effects were not demonstrated with the administration of calcium salts.

A relatively new biomarker is fetuin-A, a negative acute-phase reactant that is involved in bone remodeling in the fetus and demonstrates a powerful inhibitory function of deposition of calcium-phosphate crystals *in vitro* (21). Decreased serum levels of fetuin-A have been associated with a worse cardiovascular calcification status (22,23). In HD patients, lower fetuin-A serum levels correlated with increased mortality in some (24–26) but not all (27) studies. In a trial of patients with stage 4 CKD and without diabetes, significantly increased concentrations of serum fetuin-A were noted after short-term treatment with sevelamer but not with calcium acetate (28).

Because observational studies have demonstrated the association of serum levels of calcium, phosphorus, and PTH with increased mortality in patients with CKD, to a large extent, these, too, could be considered biomarkers (1,21,29). In three randomized trials (4–6) and other studies (6,30), sevelamer was found to be equivalent to calcium-based binders with respect to phosphorus-lowering ability without causing clinical hypocalcemia. In a head-to-head comparison, the PTH-lowering effect of calcium carbonate and sevelamer was found to be equivalent (31); however, it should be noted that serum phosphorus level is a poor indicator of phosphorus retention, because phosphorus levels increase relatively late in CKD. For this reason, attention has recently been focused on fibroblast growth factor 23 (FGF-23). This inhibitor of tubular phosphate reabsorption

seems to increase early as kidney function deteriorates. Indeed, FGF-23 levels were found to be inversely correlated with GFR and were predictive of disease progression in a cohort of patients with mild to moderate CKD (32).

In HD patients, FGF-23 levels correlate modestly with coronary artery calcium (CAC) score as measured by multislice computed tomography (CT; $R = 0.36$, $P < 0.05$) (33). In a cross-sectional study of HD patients, higher serum FGF-23 and phosphorus levels were associated with increased mortality (Table 1) (34). Because of these findings, serum FGF-23 levels have become of interest as a possible marker of response to phosphate binder therapy.

A prospective randomized trial evaluated whether 6 wk of sevelamer or calcium acetate treatment decreases serum FGF-23 levels in patients with stage 3 or 4 CKD (33). Absolute and relative changes in FGF-23 levels were threefold greater with sevelamer than with calcium acetate in the presence of equivalent phosphate control ($P = 0.0466$). Similarly, in a study of 46 HD patients, those treated with both sevelamer and calcium carbonate had a statistically significant decrease in serum FGF-23 levels after 4 wk of therapy, whereas no change was seen with calcium carbonate alone (35). Future trials will clarify whether these effects will result in a favorable outcome with sevelamer phosphate-binding therapy. An important consideration to be made when evaluating biomarkers in CKD is that, in these patients, there are large (nearly 50%) within-subject variations relative to the total variation in measurements (36).

Effects of Phosphate Binders on VC

It is well established that patients with advanced CKD are at increased risk for VC, which is a significant predictor of morbidity and mortality (37,38). The prevalence of coronary calcification has been estimated at 40% for patients with stage 4 CKD (39), approximately 60% for incident HD patients (40), and approximately 80% for prevalent HD patients (4). Proposed regulators of VC in humans include phosphorus, pyrophosphate, FGF-23/Klotho, bone morphogenetic protein 7, calcium, vitamin D, aldosterone, TNF- α , oxidized LDL, and PTH, among others. Numerous studies have reported an association between increased serum phosphorus levels and greater prevalence of VC and valvular calcification in patients with moderate to severe CKD (41–43). It is therefore conceivable that phosphorus-lowering therapies may reduce VC and decrease

Table 1. Association of FGF-23 levels and survival in patients who had CKD and underwent dialysis (34)

| Phosphate Level (mg/dl) | cFGF-23 Level (Median [IQR]) | | P | OR for Death (95% CI) |
|-------------------------|------------------------------|---------------------|--------|-----------------------|
| | Deceased (n = 200) | Alive (n = 200) | | |
| All levels | 2260 (1196 to 5296) | 1406 (989 to 2741) | <0.001 | 1.5 (1.2 to 1.8) |
| <3.5 | 1790 (1175 to 3941) | 1148 (927 to 2169) | 0.008 | 1.8 (1.2 to 2.8) |
| 3.5 to 4.4 | 2049 (1109 to 4865) | 1131 (893 to 1629) | 0.003 | 1.8 (1.2 to 2.7) |
| 4.5 to 5.5 | 2207 (1186 to 5238) | 1499 (1044 to 2262) | 0.02 | 1.8 (1.1 to 3.0) |
| >5.5 | 3541 (1871 to 10,491) | 2686 (1527 to 6210) | 0.29 | 1.1 (0.7 to 1.6) |

cFGF-23, C-terminal FGF-23; IQR, interquartile range; OR, odds ratio.

mortality. Although no randomized trials have been performed, a recent prospective cohort study that analyzed more than 10,000 incident HD patients found that treatment with phosphate binders was associated with improved survival (as measured by 1-yr all-cause mortality), independent of baseline and follow-up serum phosphorus levels (44).

The effect of various phosphate binders on VC and arterial stiffness has been the subject of some debate. Several clinical studies suggested that the risk for VC and/or increased arterial stiffness is greater with calcium-based binders as compared with sevelamer, as discussed herein (2,5,6,22,40–43,45–47). A high cumulative dosage of calcium may also contribute to VC. For example, in children who underwent dialysis, the risk for VC was shown to be associated with the cumulative dosage of ingested calcium (41). The avoidance of excessive calcium intake in the pediatric population, therefore, should be balanced with adequate calcium nutrition.

Five studies have evaluated the effects of various binders on VC: Four of HD patients and one in the predialysis setting (Table 2) (4–6,22,48). The Renegel in New Dialysis (RIND) was a prospective, randomized study that compared the effect of sevelamer and calcium-based binders on the progression of VC in 129 adult incident HD patients (6). The CAC score was assessed by CT at baseline and every 6 mo for up to 18 mo. At baseline, a similar proportion of patients in each treatment arm had no detectable CAC (37 and 31%, respectively).

Although the CAC score increased significantly in each arm at the end of study, the absolute median increase was 11-fold greater with calcium-based binders than with sevelamer ($P = 0.01$). As confirmatory evidence of the risk that is inherent with CAC, greater baseline CAC scores were a predictor of all-cause mortality after 4.5 yr of follow-up ($P = 0.002$) (40).

In the Treat-to-Goal (TTG) study, 200 adult patients who were on maintenance HD were randomly assigned to receive a calcium-based binder or sevelamer for 52 wk (4). After the first 12 wk, the dosages of binder, vitamin D, and dialysate calcium concentration were titrated to achieve target levels of serum calcium (<10.5 mg/dl), phosphorus (3.5 to 5.5 mg/dl), and intact PTH (iPTH; 150 to 300 pg/ml). At baseline, CAC was present in 83% of patients and aorta calcification in 80%. The median percentage change in CAC score from baseline was significantly greater with calcium-based binders than with sevelamer at both 26 wk (14 *versus* 0%; $P = 0.002$) and 52 wk (25 *versus* 6%; $P = 0.04$; Figure 1). Calcium-treated patients had more frequent suppression of iPTH below the target range compared with the sevelamer group (57 *versus* 30%, respectively; $P = 0.001$).

The Calcium Acetate Renegel Evaluation 2 (CARE-2) study was a noninferiority trial designed to compare the effects of calcium acetate and sevelamer on progression of CAC (5). Prevalent HD patients with hyperphosphatemia ($N = 203$) were randomly assigned to calcium acetate or sevelamer for 12 mo to achieve target phosphorus levels of 3.5 to 5.5 mg/dl. To control for LDL cholesterol lowering by sevelamer (49,50), atorvastatin was administered to the calcium acetate-treated patients to reduce LDL cholesterol levels to <70 mg/dl and to sevelamer-treated patients whose LDL cholesterol failed to

reach this level. It is interesting that 97% of the calcium-treated patients and 79% of the sevelamer-treated patients received atorvastatin. After 12 mo, the decrease in mean serum phosphorus level was comparable in both treatment arms. Significant ($P < 0.05$) between-group differences existed in change from baseline values for adjusted calcium, PTH, and total cholesterol. The mean increase in CAC score was 35% with calcium acetate and 39% with sevelamer (NS). The authors concluded that sevelamer was noninferior to calcium acetate with respect to CAC progression. There were limitations in this study, including the very frequent use of statins in sevelamer-treated patients; a significant difference in end-of-study PTH levels, with the sevelamer-treated patients having a high PTH level compared with studies that demonstrated slowing of CAC with this drug; a large *a priori* margin (1.8) by which noninferiority was determined; and a high dropout rate (42.7% calcium acetate *versus* 30.0% sevelamer). Because PTH control seems to be responsible for slowing of VC in animal experiments (51–54) as well as human studies (55,56), it is possible that the lack of inhibition of CAC progression observed with sevelamer was due to insufficient control of PTH. It has also been suggested that patients in CARE-2 may have been at higher risk for VC than those in the TTG study because of differences in baseline characteristics such as higher incidence of diabetic neuropathy, greater prevalence of smokers, and higher iPTH levels (57). It should also be noted that atorvastatin has been described to increase CAC progression in randomized trials of patients without uremia (58–60), and it was used in almost 80% of the patients who were assigned to sevelamer treatment as well as 97% of the calcium-treated patients (59,60).

The Phosphate Binder Impact on Bone Remodeling and Coronary Calcification (BRiC) study randomly assigned 101 Brazilian patients who were on maintenance HD to sevelamer or calcium acetate and compared the effects of treatment on CAC and bone histology (48). After 12 mo of therapy, no significant difference was observed in CAC progression or bone remodeling between these two groups. Although all patients were treated with a 1.75 mmol/L dialysate calcium concentration at the start of the study, during the trial patients in the sevelamer group were treated with higher dialysate calcium concentrations than those who received calcium acetate, thereby potentially mitigating any differences between treatment groups.

Russo *et al.* (22) investigated whether differences in CAC score progression could be detected in predialysis patients. In that observational study, 90 patients who had never received a phosphate binder, vitamin D, or statin therapy were treated with a low-phosphorus diet, calcium carbonate, or sevelamer for 2 yr. The annual progression in total CAC score was greatest in the group on the low-phosphorus diet, intermediate in those who were treated with calcium carbonate, and least in the sevelamer arm (Figure 2). These results suggest that phosphate binders could be beneficial in predialysis patients; nonetheless, these preliminary findings require confirmation in randomized studies.

In summary, results from some CKD clinical trials and animal models suggest that the use of calcium-based phosphate binders may accelerate VC. Although the clinical studies have

Table 2. Studies analyzing effect of calcium-based phosphate binders and sevelamer on VC in patients with CKD

| Reference | Study | Patient Population | N | No. Available for VC Analysis ^a | | Study Design | Results |
|----------------------------|--------|----------------------|-----|--|--------------------|---|--|
| | | | | Calcium | Sevelamer | | |
| Block <i>et al.</i> (6) | RIND | Incident HD | 129 | 55 | 54 | Randomly assigned to calcium-based phosphate binder or sevelamer | Calcium-based binders resulted in faster and larger increases in CACS <i>versus</i> sevelamer ($P = 0.056$ at 12 mo; $P = 0.015$ at 18 mo) Median increase in CACS was 11 times greater with calcium than with sevelamer ($P = 0.01$) |
| Chertow <i>et al.</i> (4) | TTG | Prevalent HD | 200 | 75 | 66 | Randomly assigned to calcium-based phosphate binder or sevelamer for 52 wk | Calcium-based binders associated with greater median percentage change in CACS from baseline than sevelamer at 26 wk ($P = 0.002$) and 52 wk ($P = 0.04$) |
| Qunibi <i>et al.</i> (5) | CARE-2 | Prevalent HD | 203 | 71/58 ^b | 68/68 ^b | Randomly assigned to calcium acetate + atorvastatin or sevelamer ± atorvastatin ^c for 52 wk | Calcium-treated patients had more suppression of iPTH below target range of 15 to 300 pg/ml <i>versus</i> sevelamer group (57 <i>versus</i> 30%; $P = 0.001$) Sevelamer judged to be noninferior to calcium acetate; mean increase in CACS 35% with calcium acetate <i>versus</i> 39% with sevelamer |
| Barreto <i>et al.</i> (48) | BRiC | Prevalent HD | 101 | 18 | 11 | Randomly assigned to calcium acetate or sevelamer | No significant difference in CAC progression or bone remodeling rate At follow-up, significantly higher levels of iPTH, BAP, and deoxypyridinoline and lower LDL cholesterol level with sevelamer |
| Russo <i>et al.</i> (22) | N/A | Predialysis patients | 90 | 29/28 ^d | 27 | Patients maintained on low-phosphorus diet and treated with calcium carbonate or sevelamer (no previous phosphate binder, vitamin D, or statin therapy) | Annual progression in TCS: low-phosphate diet > calcium carbonate > sevelamer Increase in absolute TCS from baseline significant with low-phosphorus diet ($P = 0.001$) and calcium carbonate ($P = 0.001$), NS with sevelamer |

BAP, bone-specific alkaline phosphatase; CACS, coronary artery calcium score; N/A, not available; TCS, total calcium score

^aVC assessed by electron-beam CT scans.

^bNumber of patients available for VC assessment at 6 and 12 mo.

^cAtorvastatin administered to sevelamer-treated patients at week 8 only when LDL cholesterol levels were <70 mg/dl.

^dTwenty-nine patients were assigned to a low-phosphorus diet, 28 to a low-phosphorus diet plus calcium carbonate, and 27 to a low-phosphorus diet plus sevelamer.

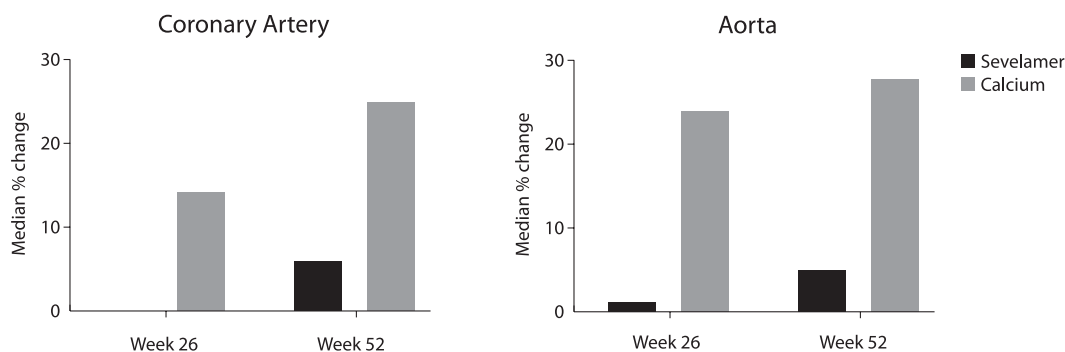


Figure 1. Change in coronary artery and aortic calcification in TTG study (4).

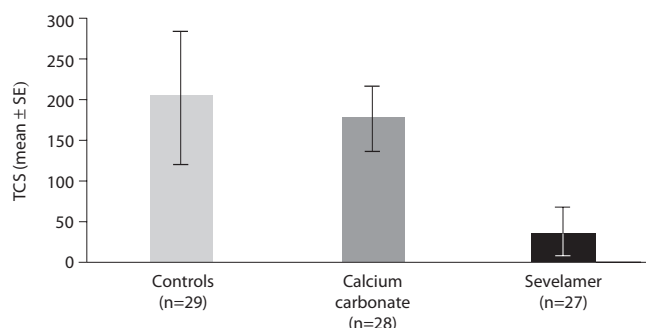


Figure 2. Annual progression of coronary artery calcification in predialysis patients. Treatment consisted of low-phosphorus diet only (controls) or in combination with calcium carbonate or sevelamer. Data are means \pm SEM. TCS, total calcium score (22).

given inconsistent results, differences in study design, study population, dialysate calcium bath concentration, and level of PTH control may account for some of these differences. Furthermore, statistical probability suggests that when several small clinical trials are performed, the null hypothesis will not be rejected in some cases even when true differences exist.

Effects of Phosphate Binders on Bone

The effects of calcium and phosphorus on bone have been widely studied. Calcium is known to play a key role in enhancing peak bone mass in young, healthy individuals, and calcium supplementation may help to prevent osteoporosis in older men and women; however, because most studies of calcium for osteoporosis prevention have also included vitamin D, the contribution of each in reducing fracture risk is unclear. In adult patients with CKD, no data exist demonstrating that exogenous calcium (as supplements or binders) reduces the risk for osteoporotic fracture or increases bone mineral density (see accompanying article by Seeman).

Current data suggest that non-calcium-containing binders and sevelamer may have differential effects on bone. Indeed, different effects on bone turnover, mineralization, and volume have been attributed to sevelamer hydrochloride and lanthanum carbonate compared with calcium-based binders. How these effects might translate into bone strength or growth remains to be elucidated.

In adult patients with stage 5 CKD, low bone turnover (adynamic bone disease) is a common histologic lesion. Children with stage 5 CKD primarily display lesions of high bone turnover (osteitis fibrosa and mixed uremic osteodystrophy), although both high and low bone turnover may occur in either patient population (61). High-turnover bone disease can be associated with deformities, fractures, and growth failure, whereas low-turnover bone disease has been associated with hypercalcemia, VC (in adults), and aggravation of growth failure (in children). Some data suggest that treatment with sevelamer may differentially alter bone histology compared with calcium-based binders and thus could favorably affect these renal-associated bone diseases.

Mathew *et al.* (15) developed an LDL receptor-deficient murine model of VC that is exacerbated by CKD and is associated with adynamic bone disorder. When such animals undergo subtotal kidney ablation and are fed a high-fat/high-cholesterol diet, the vascular disease mimics the CKD-induced VC that complicates the metabolic syndrome, with hypertension, obesity, severe atherosclerotic plaque formation, insulin resistance, early type 2 diabetes, and adynamic bone disease. In this model, treatment with sevelamer decreased serum cholesterol and phosphorus levels. As measured by bone histomorphometry, sevelamer treatment normalized rates of bone formation, mineralization parameters, and trabecular bone volume. In this model of murine metabolic syndrome with CKD, sevelamer reduced VC, possibly in part by reducing hyperphosphatemia and promoting bone formation rate (BFR). These results are supported by other data demonstrating that sevelamer could prevent renal osteodystrophy in a rat model of chronic kidney failure (62).

In patients, the relative effects of sevelamer on bone turnover are less clear; however, two clinical trials have evaluated the effects of 1 yr of therapy with sevelamer *versus* calcium carbonate in adult HD patients, 60% of whom had low-turnover bone disease (14,48). In each study, baseline PTH levels were equivalent, and no differences were observed in bone turnover regardless of phosphate binder therapy. It is interesting that, although final rates of bone turnover did not differ between groups in either study, Ferreira *et al.* (14) did note that BFR increased from baseline in patients who were treated with sevelamer whereas it remained unchanged in those who received calcium carbonate. These findings raise the possibility

that sevelamer may increase BFR during the treatment of adynamic bone disease, an effect that might be more obvious given a larger, more homogeneous sample size. Similarly, lanthanum carbonate has been shown to result in higher bone turnover after at least 1 yr of treatment when compared with calcium-based therapy; this may translate into improvements in bone volume after 2 yr of treatment (63,64).

In contrast to patients with underlying adynamic bone disease, current data suggest that sevelamer does not further increase bone turnover in patients with underlying high-turnover renal osteodystrophy. In a trial of pediatric patients with secondary hyperparathyroidism (sHPT) and osteitis fibrosa, both sevelamer and calcium carbonate, when used in conjunction with vitamin D sterols, were similarly effective in controlling serum phosphorus concentrations, reducing serum PTH values, and suppressing BFR (65). Patients who received sevelamer required higher dosages of vitamin D or its active metabolites to maintain PTH levels within target ranges (14,65). Despite the increased dosages of vitamin D sterols, serum calcium levels were maintained in the lower end of the normal range in sevelamer-treated patients in contrast to increasing calcium concentrations in the calcium carbonate group. Thus, during the treatment of sHPT, sevelamer may not cause further increases in BFR. If PTH levels are maintained within appropriate target ranges, however, then bone turnover can be controlled to a similar degree with sevelamer or calcium carbonate. Studies on the effects of lanthanum in pediatric patients or in adults with only sHPT have not been performed.

In addition to disorders of bone turnover, alterations in bone mineralization may occur in renal osteodystrophy. In pediatric patients with sHPT, treatment with calcium carbonate resulted in greater improvements in mineralization than did sevelamer (65); however, mineralization did not normalize in any patient, despite ingestion of up to 2.6 g/d elemental calcium in patients who were treated with calcium carbonate. In that study, pediatric patients who were treated with sevelamer ingested a smaller dose of calcium than recommended by the Institute of Medicine Dietary Reference Intakes (66), suggesting that, at least in children, insufficient calcium intake may exacerbate the mineralization defect. This may not be as significant a problem in adults, who seem to have a lower prevalence of defective mineralization (63). Although preclinical data suggest that lanthanum carbonate may exacerbate mineralization defects in rodents (67,68), clinical trials have not confirmed this effect in humans (63,69).

Non-calcium-, non-metal-based phosphate binders have been shown to improve bone volume in preclinical models and clinical studies. The beneficial effects of sevelamer on bone volume and strength were seen in a non-CKD model of osteoporosis that involved aged ovariectomized rats (70). Treatment with sevelamer raised the total-body bone mineral density in the femur, tibia, and lumbar spine and also increased the BFR, cortical thickness, and bone volume, resulting in improved bone biomechanical properties. Although many of the clinical trials conducted to date were not designed to demonstrate effects on bone strength and were thus underpowered for this purpose, they do support the benefits suggested by preclinical

data. For example, a *post hoc* analysis was conducted of a randomized clinical trial in which 111 HD patients were treated for 1 yr with a calcium-based phosphate binder or sevelamer (13). Patients who received a calcium-based binder showed a decrease in thoracic vertebral trabecular bone density compared with sevelamer therapy ($-7%$ versus $5%$, respectively; $P = 0.01$) and indicated a trend toward decreased vertebral cortical bone density despite increases in serum calcium levels. Moreover, Ferreira *et al.* (14) demonstrated a decrease in cancellous bone trabecular separation during therapy only in patients who received sevelamer, suggesting that sevelamer may improve trabecular bone structure and density.

Impact of Phosphate Binders on Mortality

A few studies addressed the important question of whether a mortality difference is associated with the use of calcium-based binders and sevelamer (6,7,71). Two studies of incident HD patients (one prospective and randomized and one retrospective) showed a survival advantage with sevelamer. In the RIND study described previously, all-cause mortality was a predefined secondary end point (6). After 4 yr, the mortality rate was higher in calcium-treated patients (10.6 per 100 patient-years; 95% confidence interval [CI] 6.3 to 14.9) than sevelamer-treated patients (5.3 per 100 patient-years; 95% CI 2.2 to 8.5; $P = 0.05$). Multivariate analysis demonstrated improved survival for those in the sevelamer group, after adjustment for confounding variables (hazard ratio [HR] 3.1; 95% CI 1.23 to 7.61; $P = 0.02$; Figure 3). The strengths of the RIND trial were the enrollment of incident HD patients, long-term follow-up (median 44 mo), and excellent patient retention (127 of the original 129 patients submitted to CT imaging); limitations included the small sample size and randomized binder treatment limited to the initial 18 mo. Using Veterans Health Administration databases, a retrospective cohort study was performed in 1377 incident HD patients who received sevelamer or a calcium-based binder (71). At baseline, patients who received sevelamer were younger than those who were treated with a calcium-based binder (mean age 59.6 versus 63.0 yr, respectively; $P < 0.001$) and had fewer comorbidities. After correction for differ-

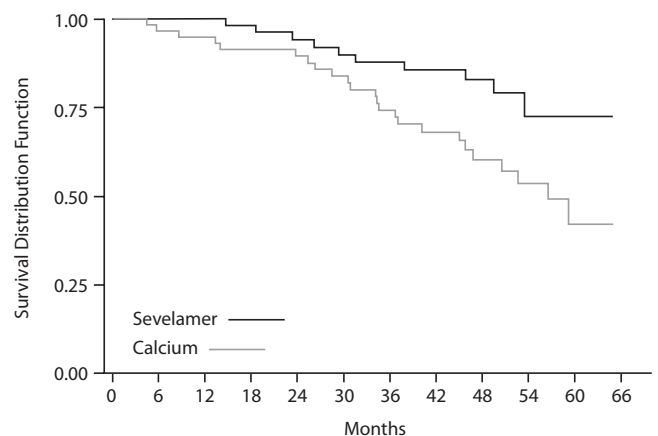


Figure 3. Adjusted survival in RIND study of sevelamer and calcium-based phosphate binders in patients with CKD (6).

ences across treatment groups, the adjusted HR for death was 0.67 (95% CI 0.54 to 0.84), indicating a survival advantage of treatment with sevelamer compared with calcium carbonate.

The effect of sevelamer and calcium-based binders on the survival of prevalent HD patients was evaluated in the multicenter, randomized Dialysis Clinical Outcomes Revisited (DCOR) study (72). In patients who were treated for up to 2 yr, no statistically significant difference was seen in all-cause mortality between the two treatment arms (HR 0.93; 95% CI 0.79 to 1.10; $P = 0.40$). In prespecified analyses, however, mortality for patients who were aged ≥ 65 yr (44% of the study population) was lower when treated with sevelamer than with calcium based binders (HR 0.77; 95% CI 0.61 to 0.96; $P = 0.02$). Despite the large study size, DCOR presented several limitations. Many patients were lost to follow-up or terminated the study early, with approximately half of all enrolled patients discontinuing prematurely (many because of investigators' decision). Practice patterns varied widely and follow-up was short (mean 20 mo). Furthermore, prevalent rather than incident HD patients were enrolled, which may have introduced a survival selection bias. A predefined intention-to-treat analysis of Centers for Medicare and Medicaid Services mortality data was also conducted to assess morbidity and mortality in HD (7). No significant differences were seen in all-cause mortality, cardiovascular mortality, first hospitalization, cause-specific multiple hospitalizations, first morbidity, or multiple morbidity rates. However, multiple all-cause hospitalizations and the number of hospital days were significantly lower in the sevelamer group, which we speculate may accrue substantial cost savings over prolonged treatment periods. In summary, although as suggested in the recent publication of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (73) and two meta-analyses (74,75), currently "there is no robust statistically significant difference (between calcium and sevelamer) for mortality," in the opinion of the authors, the evidence so far accumulated is reassuring and provides an important signal as to the advantage of sevelamer over calcium salts for phosphate binding.

Conclusions

Our understanding of bone and mineral disorders in CKD has evolved significantly in recent years, changing the approach to therapy. The link between bone metabolism and cardiovascular disorders has been strengthened and, although incompletely understood, has led to the notion of a common pathophysiologic pathway summarized in the new definition of CKD-MBD. Calcium-based binders and sevelamer are equally effective for treatment of hyperphosphatemia; however, calcium excess accumulated through the use of binders, supplements, and dialysate can lead to hypercalcemia, contribute to VC, and potentially affect bone histology and mortality. Achieving calcium balance and minimizing the concomitant risks of calcium excess is therefore a rational approach for patients with advanced stages of CKD. Indeed, the recent KDIGO guidelines (73) advise restriction and/or avoidance of calcium intake in the presence of proven cardiovascular calcification, persistent hypercalcemia, and hyperparathyroidism as well as adynamic bone disease.

Several studies have indicated and KDIGO recently agreed that the use of sevelamer is associated with a lower incidence of hypercalcemia and VC compared with calcium-based binders and does not increase the risk for hypocalcemia. Preclinical and clinical studies suggested that differential effects on bone structure and function may result from the use of sevelamer or calcium salts. Data from some studies suggested a better survival with sevelamer than with calcium-based binders, although additional prospective, randomized studies are needed to confirm these findings. Other pleiotropic effects of sevelamer have not been observed with calcium-based agents, but, to date, these have not been shown to affect outcome. In summary, selection of phosphate binders in CKD-MBD should not be based solely on reduction in serum phosphorus levels but on the overall potential beneficial effects on mineral homeostasis, bone histomorphometry, vasculature biology, and mortality.

Acknowledgments

This work was supported by Genzyme Corporation. Writing and editorial assistance was provided by Larry Rosenberg, PhD, of Envision Scientific Solutions, which was funded by Genzyme Corporation.

Disclosures

P.R. has served on an advisory board for and received research grants from Genzyme. S.V. has served on a scientific advisory committee for Pfizer. R.M.M. has received research grants from and consulted for Genzyme and received research grants from Fresenius Medical Care. K.W. has received honoraria from Genzyme. D.M.S. has served on advisory boards for Amgen, Abbott, and Genzyme; has consulted for Amgen; and has received grant support from Amgen, Nephro-Tech, and Genentech.

References

1. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL: Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 16: 520–528, 2005
2. Moe SM, Chen NX: Mechanisms of vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 19: 213–216, 2008
3. Isakova T, Gutiérrez OM, Wolf M: A blueprint for randomized trials targeting phosphorus metabolism in chronic kidney disease. *Kidney Int* 76: 705–716, 2009
4. Chertow GM, Burke SK, Raggi P: Treat to Goal Working Group: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 62: 245–252, 2002
5. Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, Budoff M: 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. *Am J Kidney Dis* 51: 952–965, 2008
6. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, Raggi P: Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int* 68: 1815–1824, 2005
7. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, Ling BN, Chasan-Taber S, Dillon MA, Blair AT,

- Burke SK: Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 72: 1130–1137, 2007
8. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnen-Dechent W, Weissberg PL, Shanahan CM: Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: A potential mechanism for accelerated vascular calcification in ESRD. *J Am Soc Nephrol* 15: 2857–2867, 2004
 9. Yang H, Curinga G, Giachelli CM: Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization in vitro. *Kidney Int* 66: 2293–2299, 2004
 10. Ferramosca E, Burke S, Chasan-Taber S, Ratti C, Chertow GM, Raggi P: Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients. *Am Heart J* 149: 820–825, 2005
 11. Shantouf R, Budoff MJ, Ahmadi N, Tiano J, Flores F, Kalantar-Zadeh K: Effects of sevelamer and calcium-based phosphate binders on lipid and inflammatory markers in hemodialysis patients. *Am J Nephrol* 28: 275–279, 2008
 12. Garg JP, Chasan-Taber S, Blair A, Plone M, Bommer J, Raggi P, Chertow GM: Effects of sevelamer and calcium-based phosphate binders on uric acid concentrations in patients undergoing hemodialysis: A randomized clinical trial. *Arthritis Rheum* 52: 290–295, 2005
 13. Raggi P, James G, Burke SK, Bommer J, Chasan-Taber S, Holzer H, Braun J, Chertow GM: Decrease in thoracic vertebral bone attenuation with calcium-based phosphate binders in hemodialysis. *J Bone Miner Res* 20: 764–772, 2005
 14. Ferreira A, Frazao JM, Monier-Faugere MC, Gil C, Galvao J, Oliveira C, Baldaia J, Rodrigues I, Santos C, Ribeiro S, Hoenger RM, Duggal A, Malluche HH: Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. *J Am Soc Nephrol* 19: 405–412, 2008
 15. Mathew S, Lund RJ, Strebeck F, Tustison KS, Geurs T, Hruska KA: Reversal of the adynamic bone disorder and decreased vascular calcification in chronic kidney disease by sevelamer carbonate therapy. *J Am Soc Nephrol* 18: 122–130, 2007
 16. Asmus HG, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, Neumayer HH, Raggi P, Bommer J: Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. *Nephrol Dial Transplant* 20: 1653–1661, 2005
 17. Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G; Kidney Disease: Improving Global Outcomes (KDIGO): Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 69: 1945–1953, 2006
 18. Wilkes BM, Reiner D, Kern M, Burke S: Simultaneous lowering of serum phosphate and LDL-cholesterol by sevelamer hydrochloride (RenaGel) in dialysis patients. *Clin Nephrol* 50: 381–386, 1998
 19. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 55: 648–658, 1999
 20. Wanner C, Metzger T: C-reactive protein a marker for all-cause and cardiovascular mortality in haemodialysis patients. *Nephrol Dial Transplant* 17[Suppl 8]: 29–32, discussion 39–40, 2002
 21. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 15: 2208–2218, 2004
 22. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, Russo L, Scafarto A, Andreucci VE: The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int* 72: 1255–1261, 2007
 23. Cozzolino M, Galassi A, Biondi ML, Turri O, Papagni S, Mongelli N, Civita L, Gallieni M, Brancaccio D: Serum fetuin-A levels link inflammation and cardiovascular calcification in hemodialysis patients. *Am J Nephrol* 26: 423–429, 2006
 24. Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Bohm R, Metzger T, Wanner C, Jahnen-Dechent W, Floege J: Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: A cross-sectional study. *Lancet* 361: 827–833, 2003
 25. Stenvinkel P, Wang K, Qureshi AR, Axelsson J, Pecoits-Filho R, Gao P, Barany P, Lindholm B, Jogestrand T, Heimbürger O, Holmes C, Schalling M, Nordfors L: Low fetuin-A levels are associated with cardiovascular death: Impact of variations in the gene encoding fetuin. *Kidney Int* 67: 2383–2392, 2005
 26. Hermans MM, Brandenburg V, Ketteler M, Kooman JP, van der Sande FM, Boeschoten EW, Leunissen KM, Krediet RT, Dekker FW: Association of serum fetuin-A levels with mortality in dialysis patients. *Kidney Int* 72: 202–207, 2007
 27. Ix JH, Shlipak MG, Sarnak MJ, Beck GJ, Greene T, Wang X, Kusek JW, Collins AJ, Levey AS, Menon V: Fetuin-A is not associated with mortality in chronic kidney disease. *Kidney Int* 72: 1394–1399, 2007
 28. Caglar K, Yilmaz MI, Saglam M, Cakir E, Acikel C, Eyileten T, Yenicesu M, Oguz Y, Vural A, Carrero JJ, Axelsson J, Lindholm B, Stenvinkel P: Short-term treatment with sevelamer increases serum fetuin-a concentration and improves endothelial dysfunction in chronic kidney disease stage 4 patients. *Clin J Am Soc Nephrol* 3: 61–68, 2008
 29. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD: Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 70: 771–780, 2006
 30. Russo D, Corrao S, Miranda I, Ruocco C, Manzi S, Elefante R, Brancaccio D, Cozzolino M, Biondi ML, Andreucci VE: Progression of coronary artery calcification in predialysis patients. *Am J Nephrol* 27: 152–158, 2007
 31. Sadek T, Mazouz H, Bahloul H, Oprisiu R, El Esper N, El Esper I, Boitte F, Brazier M, Moriniere P, Fournier A: Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: An open-label, randomized study. *Nephrol Dial Transplant* 18: 582–588, 2003
 32. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Linggenhel A, Ritz E, Kronenberg F, Kuen E, König P, Kraatz G, Mann JF, Müller GA, Kohler H, Riegler P: Fibroblast growth factor 23 (FGF23) predicts progression of chronic

- kidney disease: The Mild to Moderate Kidney Disease (MMKD) Study. *J Am Soc Nephrol* 18: 2600–2608, 2007
33. Oliveira RB, Cancela ALE, Gracioli FG, Dos Reis LM, Draibe SA, Cuppari L, Carvalho AB, Jorgetti V, Canziani ME, Moyses RMA: Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? *Clin J Am Soc Nephrol* November 12, 2009 [epub ahead of print]
 34. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Juppner H, Wolf M: Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 359: 584–592, 2008
 35. Koiwa F, Kazama JJ, Tokumoto A, Onoda N, Kato H, Okada T, Nii-Kono T, Fukagawa M, Shigematsu T: Sevelamer hydrochloride and calcium bicarbonate reduce serum fibroblast growth factor 23 levels in dialysis patients. *Ther Apher Dial* 9: 336–339, 2005
 36. LaClair R, O'Neal K, Ofner S, Sosa MJ, Labarrere CA, Moe SM: Precision of biomarkers to define chronic inflammation in CKD. *Am J Nephrol* 28: 808–812, 2008
 37. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM: Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 38: 938–942, 2001
 38. Rodriguez-Garcia M, Gomez-Alonso C, Naves-Diaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andia JB: Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. *Nephrol Dial Transplant* 24: 239–246, 2009
 39. Russo D, Palmiero G, De Blasio AP, Balletta MM, Andreucci VE: Coronary artery calcification in patients with CRF not undergoing dialysis. *Am J Kidney Dis* 44: 1024–1030, 2004
 40. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM: Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 71: 438–441, 2007
 41. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342: 1478–1483, 2000
 42. Guerin AP, London GM, Marchais SJ, Metivier F: Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 15: 1014–1021, 2000
 43. Adeney KL, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS, Kestenbaum BR: Association of serum phosphate with vascular and valvular calcification in moderate CKD. *J Am Soc Nephrol* 20: 381–387, 2009
 44. Isakova T, Gutierrez OM, Chang Y, Shah A, Tamez H, Smith K, Thadhani R, Wolf M: Phosphorus binders and survival on hemodialysis. *J Am Soc Nephrol* 20: 388–396, 2009
 45. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H: Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 18: 1731–1740, 2003
 46. Litwin M, Wuhl E, Jourdan C, Trelewicz J, Niemirska A, Fahr K, Jobs K, Grenda R, Wawer ZT, Rajszyz P, Troger J, Mehls O, Schaefer F: Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. *J Am Soc Nephrol* 16: 1494–1500, 2005
 47. Braun J, Asmus HG, Holzer H, Brunkhorst R, Krause R, Schulz W, Neumayer HH, Raggi P, Bommer J: Long-term comparison of a calcium-free phosphate binder and calcium carbonate–phosphorus metabolism and cardiovascular calcification. *Clin Nephrol* 62: 104–115, 2004
 48. Barreto DV, Barreto Fde C, de Carvalho AB, Cuppari L, Draibe SA, Dalboni MA, Moyses RM, Neves KR, Jorgetti V, Miname M, Santos RD, Canziani ME: Phosphate binder impact on bone remodeling and coronary calcification: Results from the BRiC study. *Nephron Clin Pract* 110: c273–c283, 2008
 49. Burke SK, Dillon MA, Hemken DE, Rezabek MS, Balwit JM: Meta-analysis of the effect of sevelamer on phosphorus, calcium, PTH, and serum lipids in dialysis patients. *Adv Ren Replace Ther* 10: 133–145, 2003
 50. Nikolov IG, Joki N, Maizel J, Lacour B, Druke TB, Massy ZA: Pleiotropic effects of the non-calcium phosphate binder sevelamer. *Kidney Int Suppl* S16–S23, 2006
 51. Kawata T, Nagano N, Obi M, Miyata S, Koyama C, Kobayashi N, Wakita S, Wada M: Cinacalcet suppresses calcification of the aorta and heart in uremic rats. *Kidney Int* 74: 1270–1277, 2008
 52. Lopez I, Aguilera-Tejero E, Mendoza FJ, Almaden Y, Perez J, Martin D, Rodriguez M: Calcimimetic R-568 decreases extraosseous calcifications in uremic rats treated with calcitriol. *J Am Soc Nephrol* 17: 795–804, 2006
 53. Moe SM, Seifert MF, Chen NX, Sinderson RM, Chen X, Duan D, Henley C, Martin D, Gattone VH 2nd: R-568 reduces ectopic calcification in a rat model of chronic kidney disease-mineral bone disorder (CKD-MBD). *Nephrol Dial Transplant* 24: 2371–2377, 2009
 54. Joki N, Nikolov IG, Caudrillier A, Mentaverri R, Massy ZA, Druke TB: Effects of calcimimetic on vascular calcification and atherosclerosis in uremic mice. *Bone* 45: S30–S34, 2009
 55. Bleyer AJ, Burkart J, Piazza M, Russell G, Rohr M, Carr JJ: Changes in cardiovascular calcification after parathyroidectomy in patients with ESRD. *Am J Kidney Dis* 46: 464–469, 2005
 56. Sharma J, Khan A, Bailey J, Milas M, Casarella W, Dodson T, Raggi P, Weber C: Successful near-total parathyroidectomy inhibits long-term coronary calcification progression in patients undergoing hemodialysis. *J Am Soc Nephrol* 19: SA-PO2719, 2008
 57. Floege J: Calcium-containing phosphate binders in dialysis patients with cardiovascular calcifications: Should we CARE-2 avoid them? *Nephrol Dial Transplant* 23: 3050–3052, 2008
 58. Raggi P, Davidson M, Callister TQ, Welty FK, Bachmann GA, Hecht H, Rumberger JA: Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation* 112: 563–571, 2005
 59. Schmermund A, Achenbach S, Budde T, Buziashvili Y, Förster A, Friedrich G, Henein M, Kerkhoff G, Knollmann F, Kukharchuk V, Lahiri A, Leischik R, Moshage W, Scharlt M, Siffert W, Steinhagen-Thiessen E, Sinitsyn V, Vogt A, Wiedeking B, Erbel R: Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months:

- A multicenter, randomized, double-blind trial. *Circulation* 113: 427–437, 2006
60. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD: Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: The St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* 46: 166–172, 2005
 61. Wesseling K, Bakkaloglu S, Salusky I: Chronic kidney disease mineral and bone disorder in children. *Pediatr Nephrol* 23: 195–207, 2008
 62. Katsumata K, Kusano K, Hirata M, Tsunemi K, Nagano N, Burke SK, Fukushima N: Sevelamer hydrochloride prevents ectopic calcification and renal osteodystrophy in chronic renal failure rats. *Kidney Int* 64: 441–450, 2003
 63. Malluche HH, Siami GA, Swanepoel C, Wang GH, Mawad H, Confer S, Smith M, Pratt RD, Monier-Faugere MC, SPD405-307 Lanthanum Carbonate Study Group: Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. *Clin Nephrol* 70: 284–295, 2008
 64. Freemont AJ, Hoyland JA, Denton J: The effects of lanthanum carbonate and calcium carbonate on bone abnormalities in patients with end-stage renal disease. *Clin Nephrol* 64: 428–437, 2005
 65. Salusky IB, Goodman WG, Sahney S, Gales B, Perilloux A, Wang HJ, Elashoff RM, Juppner H: Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. *J Am Soc Nephrol* 16: 2501–2508, 2005
 66. Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*, Washington, DC, National Academy Press, 1997
 67. Huang J, Zhang TL, Xu SJ, Li RC, Wang K, Zhang J, Xie YN: Effects of lanthanum on composition, crystal size, and lattice structure of femur bone mineral of Wistar rats. *Calcif Tissue Int* 78: 241–247, 2006
 68. Behets GJ, Dams G, Vercauteren SR, Damment SJ, Bouillon R, De Broe ME, D'Haese PC: Does the phosphate binder lanthanum carbonate affect bone in rats with chronic renal failure? *J Am Soc Nephrol* 15: 2219–2228, 2004
 69. Freemont T, Malluche HH: Utilization of bone histomorphometry in renal osteodystrophy: Demonstration of a new approach using data from a prospective study of lanthanum carbonate. *Clin Nephrol* 63: 138–145, 2005
 70. Sampath TK, Simic P, Moreno S, Bukanov N, Draca N, Kufner V, Tikvica A, Blair A, Semenski D, Brncic M, Burke SK, Vukicevic S: Sevelamer restores bone volume and improves bone microarchitecture and strength in aged ovariectomized rats. *Endocrinology* 149: 6092–6102, 2008
 71. Borzecki AM, Lee A, Wang SW, Brenner L, Kazis LE: Survival in end stage renal disease: Calcium carbonate vs. sevelamer. *J Clin Pharm Ther* 32: 617–624, 2007
 72. St Peter WL, Liu J, Weinhandl E, Fan Q: A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: A secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. *Am J Kidney Dis* 51: 445–454, 2008
 73. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 113: S1–S130, 2009
 74. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX: Chronic kidney disease and mortality risk: A systematic review. *J Am Soc Nephrol* 17: 2034–2047, 2006
 75. Navaneethan SD, Palmer SC, Craig JC, Elder GJ, Strippoli GF: Benefits and harms of phosphate binders in CKD: A systematic review of randomized controlled trials. *Am J Kidney Dis* 54: 619–637, 2009