Sevelamer carbonate appears to be a promising new agent in the control of serum phosphorus levels in subjects with chronic kidney disease. It contains the same active moiety as sevelamer hydrochloride, but has carbonate instead of chloride as the counterion. This substitution has resulted in a statistically significant improvement in serum bicarbonate levels in chronic kidney disease patients receiving chronic dialysis, and may support, in the future, the treatment of hyperphosphatemia in chronic kidney disease patients not yet on dialysis. It also offers the potential for improved gastrointestinal tolerability and the prospect of alternative formulations, such as a powder. However, most of the proposed benefits of sevelamer carbonate are extrapolated from the studies completed with sevelamer hydrochloride. Hence, the determination of an added benefit from sevelamer carbonate compared with sevelamer hydrochloride and other phosphorus binders will require direct comparison.

An emerging body of evidence associating hyperphosphatemia in chronic kidney disease (CKD) patients with increased all-cause mortality, cardiovascular mortality, vascular calcification and valvular calcification has raised the question of whether reducing phosphorus levels could result in improved survival [1–6]. The recommendations of the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guideline for Bone Metabolism and Disease in CKD emphasize strict control of serum phosphorus. Recommendations include a target serum phosphorus level of 3.5–5.5 mg/dl for those with CKD stage 5 and less than 4.6 mg/dl in CKD stages 3 and 4 [7]. Achieving these target levels, particularly in CKD stage 5, is challenging, and typically requires the administration of a binder to reduce the intestinal absorption of dietary phosphorus.

Available phosphorus binding agents include aluminum salts, calcium salts, magnesium salts, lanthanum salts and sevelamer, a metal-free ion-exchange resin. Unfortunately, all of these agents are associated with significant side effects, and the most appropriate management of mineral and bone metabolism remains highly controversial. One area of debate is the preferential use of calcium-based phosphorus binders versus non-calcium-based phosphorus binders not only in controlling serum phosphorus, but also in modulating vascular calcification and overall mortality rate.

Sevelamer hydrochloride
Sevelamer hydrochloride (Renagel®) was the first non-aluminum, non-calcium-based (metal free) phosphate binder developed for the management of hyperphosphatemia in end-stage renal disease (ESRD). Multiple studies have demonstrated its effectiveness in lowering serum phosphorus levels [8–16], as well as attenuating vascular calcification in prevalent dialysis patients, incident dialysis patients and pre-dialysis patients. One of these studies was the ‘Treat to Goal’ study, a prospective, randomized year-long study of 200 chronic hemodialysis patients comparing sevelamer hydrochloride with a calcium-based binder [13]. Subjects underwent electron-beam computed tomography (EBT) at baseline, 26 and 52 weeks to measure coronary artery and aortic calcification. This study found similar serum phosphate levels after 1 year of therapy for both the sevelamer hydrochloride group and the calcium-based binder group (5.1 ± 1.2 and 5.1 ± 1.4 mg/dl, respectively; p = 0.33). A decreased serum calcium concentration was seen in the sevelamer hydrochloride group versus the calcium-based binder group (9.5 ± 0.6 vs 9.7 ± 0.7 mg/dl; p = 0.002). Over the entire study period, 43% of subjects treated with calcium binders, compared with 17% of those treated with sevelamer hydrochloride, had at least one episode of hypercalcemia (p = 0.0005). Those treated with sevelamer hydrochloride had a statistically significant lowering of both total cholesterol (181 ± 36 to 141 ± 28 mg/dl) and
low-density lipoprotein (LDL) cholesterol (102 ± 30 to 65 ± 21 mg/dl) from baseline to follow-up when compared with those treated with a calcium-based binder, who had no change (p < 0.0001 for change from baseline across treatment groups). Serum bicarbonate levels were higher in the calcium-treated patients compared with the sevelamer hydrochloride-treated patients (22.1 ± 4.4 vs 19.2 mEq/l; p = 0.0003). In addition, at both weeks 26 and 52 there was significant progression of both coronary artery and aortic calcification in those treated with calcium compared with those treated with sevelamer hydrochloride. Furthermore, in a post-hoc analysis of thoracic vertebral bone attenuation of subjects in this study, there was a significant decrease in trabecular bone attenuation in those treated with calcium-based binders compared with no significant change in those treated with sevelamer hydrochloride (between-group differences p = 0.01) [17].

Another study, the Calcium Acetate Renagel Evaluation (CARE) Study, compared the efficacy of calcium acetate and sevelamer hydrochloride in controlling serum phosphorus levels in patients on maintenance hemodialysis [16]. This was an 8-week prospective, randomized study of 100 hemodialysis patients, which found lower serum phosphate levels (1.08 mg/dl difference; p < 0.0006) and lower calcium phosphate product levels (6.1 mg²/dl² difference; p < 0.0001) in the calcium acetate-treated group compared with the sevelamer hydrochloride-treated group. The calcium acetate-treated group (PhosLo® 667 mg capsules) received an average daily dose of 10.7 ± 7.5 capsules (7.1 ± 5.0 g/day) compared with the sevelamer hydrochloride-treated group (Renagel 403 mg capsules), who received an average daily dose of 17.2 ± 9.0 capsules (6.9 ± 3.6 g/day). This study was limited by its short-term nature, but did demonstrate the superior ability of calcium acetate to lower serum phosphate and calcium phosphate product levels when similar amounts of binder were used per day.

In addition, a study performed in subjects new to hemodialysis examined the relationship between phosphate binder assignment and progression of coronary artery calcification. The Renagel in New Dialysis (RIND) study was an 18-month prospective trial of 129 patients randomized to treatment with calcium-based binders or sevelamer hydrochloride [18]. Subjects underwent EBT imaging to assess coronary artery calcification at baseline, 6, 12 and 18 months. Both treatment groups demonstrated similar control of serum phosphorus levels over the study period; the calcium-based binder group had an average serum phosphorus level of 5.1 ± 0.8 mg/dl, with an average dose of elemental calcium of 2.3 g/day, and the sevelamer hydrochloride group had an average serum phosphorus level of 5.2 ± 0.9 mg/dl, with an average sevelamer hydrochloride dose of 8 g/day. However, those in the calcium-based binder group were more likely to experience hypercalcemic episodes and had a higher mean corrected calcium level (9.6 ± 0.5 vs 9.1 ± 0.5 mg/dl; p ≤ 0.05), lower intact parathyroid hormone level (243 ± 136 vs 298 ± 152 pg/ml; p = 0.05), a higher total cholesterol level (160 ± 32 vs 134 ± 52 mg/dl; p = 0.003), and higher LDL cholesterol (81 ± 26 vs 60 ± 34 mg/dl; p = 0.0003) when compared with the sevelamer hydrochloride-treated group. More importantly, those subjects treated with calcium-based phosphate binders demonstrated a more rapid and severe progression of coronary artery calcification when compared with those treated with sevelamer hydrochloride. Furthermore, those treated with sevelamer hydrochloride were more likely to demonstrate stabilization or regression in coronary artery calcification scores at both 12 months (p = 0.003) and 18 months (p = 0.01) compared with those treated with calcium-based binders.

A recent study reported the progression of coronary artery calcification in a cohort of subjects with CKD not on dialysis (mean estimated glomerular filtration rate [GFR]: 25–35 ml/min). This was a randomized trial of 90 non-diabetic predialysis subjects assigned to one of three groups: low-phosphorus diet alone (control group), low-phosphorus diet plus calcium carbonate (fixed dose of 2 g/day), or low-phosphorus diet plus sevelamer hydrochloride (fixed dose of 1.6 g/day) [19]. Coronary artery calcium scores were assessed by multislice spiral computed tomography at baseline and at end of study (24 ± 4.2 months). Mean GFR at the start of the study for the entire cohort was 33.2 ± 20.2 ml/min and at completion of the study was 33.6 ± 25.0 ml/min. In both binder groups there was decreased phosphaturia from approximately 490 to 410 mg/24 h compared with an increase in phosphaturia seen in the diet-controlled-only group from 367 to 514 mg/24 h. In the sevelamer hydrochloride-treated group there was a statistically significant lowering of serum calcium (p < 0.05), alkaline phosphatase (p < 0.01) and fibrinogen (p < 0.01) levels, which was not seen in the calcium carbonate-treated
group. Mean lipid levels were not changed in any of the groups. In both the control and the calcium carbonate groups, the total calcium score significantly increased from baseline to end of study (369 ± 115 to 547 ± 175 [mean ± standard error]; p < 0.001 for control vs 340 ± 38 to 473 ± 69; p < 0.001 for calcium carbonate). However, in the sevelamer group there was no significant change in total calcium score from baseline to follow-up (415 ± 153 to 453 ± 127; p = not significant).

Additionally, the Dialysis Clinical Outcomes Revisited (DCOR) trial examined the effects of sevelamer hydrochloride and calcium-based phosphate binders on mortality in prevalent hemodialysis patients [20]. It was a multicenter, open-labeled, parallel-design trial of 2103 patients randomized to treatment with sevelamer hydrochloride or to a calcium-based binder for a median follow-up time of 19.6 versus 18.5 months, respectively. There were 267 deaths in the sevelamer hydrochloride-treated group versus 275 deaths in the calcium-based binder group. The primary end point showed a nonsignificant 7% reduction in all-cause mortality with sevelamer relative to the calcium-binder group (p = 0.40). Unfortunately, this study had a nearly 51% drop-out rate and an intention-to-treat analysis was not performed, limiting further interpretation of these data.

All-cause mortality was also assessed as a pre-specified secondary end point of the RIND study [21]. A total of 34 deaths occurred at a median follow-up of 44 months: 23 in the calcium-based binder group and 11 in the sevelamer hydrochloride group. Baseline coronary artery calcification score was found to be a significant predictor of all-cause mortality. In a univariate analysis, the sevelamer hydrochloride-treated group had a borderline statistically significant lower mortality (5.3/100 patient-years; 95% CI: 2.2–8.5) when compared with those in the calcium-based binder group (10.6/100 patient-years; 95% CI: 6.3–14.9; p = 0.05). Multivariate analysis adjusting for age, race, gender, presence of baseline atherosclerotic cardiovascular disease, baseline coronary artery calcification, and diabetic status demonstrated a greater risk of death for patients treated with calcium-containing phosphate binders (hazard ratio: 3.1; 95% CI: 1.23–7.61; p = 0.016). These findings were also demonstrated in a subsequent study by Sigrist et al., where vascular calcification and mortality were assessed over a 2-year follow-up in a cohort of 134 patients: 46 with CKD stage 4, 60 with CKD stage 5 on hemodialysis, and 46 with CKD stage 5 on peritoneal dialysis [22]. Progressive calcification was seen in 57% of patients, and both change in coronary artery calcium score and calcium intake from phosphate binders were associated with reduced survival in a Cox proportional hazard analysis.

Given these aggregate study results, sevelamer hydrochloride offers several advantages when compared with calcium-based phosphorus binders. These benefits include fewer hypercalcemic episodes, avoidance of an excessive calcium load, an ability to lower total cholesterol and LDL cholesterol, an anti-inflammatory effect, the ability to reduce uric acid levels and a favorable effect on vascular calcification and bone mineral attenuation [8–13,16,17,19–27]. Its potential drawbacks are gastrointestinal side effects, lowering of serum bicarbonate, pill burden and cost [16,18,20,28,29].

Sevelamer carbonate
Sevelamer carbonate (Renvela®) was developed as an alternative to sevelamer hydrochloride in an effort to improve the buffering capacity of sevelamer hydrochloride. It was approved by the US FDA for the control of serum phosphorus in patients with CKD on dialysis in October 2007, and became available in the USA for prescription in March 2008. Regulatory review within the European Union is underway. The chemical structure of sevelamer carbonate is a poly (allylamine-co-N,N’-diallyl-1,3-diamino-2-hydroxypropane) carbonate salt [30]. It contains multiple amine groups separated by a carbon from the polymer backbone. The active moiety, the anion-exchange resin, in sevelamer carbonate is identical to that of sevelamer hydrochloride. However, the counterion in sevelamer carbonate is carbonate, which replaces the chloride in sevelamer hydrochloride (Figure 1) [30,31]. Sevelamer carbonate lowers serum phosphorus levels by binding phosphorus in the gastrointestinal tract through the ionic and hydrogen bonding of phosphate molecules with the amine groups. Although absorption studies have not been performed with sevelamer carbonate in patients with kidney failure, a mass balance study in 16 healthy volunteers using 14C-sevelamer hydrochloride demonstrated that sevelamer hydrochloride was not systemically absorbed [32]. Similarly, drug-interaction studies have only been performed with sevelamer hydrochloride and not with sevelamer carbonate. In these studies, sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of digoxin, warfarin, enalapril, metoprolol or iron, but was found to decrease the bioavailability of ciprofloxacin by approximately 50% [33–36].
Sevelamer carbonate has equivalent dosing and administration as sevelamer hydrochloride and is available in a single dosage form of 800 mg. Sevelamer carbonate provides 144 mg of potential bicarbonate per 800 mg tablet. Similar to sevelamer hydrochloride, sevelamer carbonate has not been studied in patients with dysphagia or severe gastrointestinal motility disorders, patients who have undergone major gastrointestinal tract surgery, or patients receiving anti-arrhythmic or anti-seizure medication, and its use is contraindicated in patients with hypophosphatemia or bowel obstruction [30,31].

Clinical studies with sevelamer carbonate
To date, the results of only one randomized trial with sevelamer carbonate are available. This trial was a multicenter, randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis examining the safety, tolerability and efficacy of sevelamer carbonate [37]. This study took place in the USA and enrolled 79 chronic hemodialysis patients who had been receiving sevelamer hydrochloride for at least 5 weeks with historically reasonably well-controlled serum phosphorus levels (3.5–6.5 mg/dl). These patients were randomly assigned to either sevelamer carbonate or sevelamer hydrochloride for an 8-week period, followed by an 8-week cross-over period to the alternative binder. The mean daily dose of medication used in both therapies was 6.0 ± 2.8 g/day. The compliance rates were similar with both sevelamer carbonate (85%) and sevelamer hydrochloride (86%). Phosphorus control in the sevelamer carbonate-treated patients (4.6 ± 0.9 mg/dl) was equivalent to that in the sevelamer hydrochloride-treated patients (4.7 ± 0.9 mg/dl) (Table 1). Equivalency in controlling serum phosphate levels was demonstrated by a geometric least-square mean ratio (sevelamer carbonate:sevelamer hydrochloride) of 0.99 with a 90% confidence interval of 0.95–1.03. This study demonstrated a higher serum bicarbonate level in the sevelamer carbonate-treated group (22.4 ± 3.7 mEq/l) compared with the sevelamer hydrochloride-treated group (21.2 ± 3.8 mEq/l), with a mean change of 1.3 ± 4.1 versus -0.3 ± 3.6 mEq/l, respectively (p < 0.001). No single gastrointestinal side effect was statistically different between the two groups; however, the total number of gastrointestinal adverse events was significantly lower in the sevelamer carbonate group compared with the sevelamer hydrochloride-treated group (25 vs 45 events, or 20.5 vs 35.9% of patients, p = 0.007). The most common gastrointestinal events seen in patients treated with sevelamer carbonate were nausea (9.6%), vomiting (8.2%) and diarrhea (2.7%).

Other studies using sevelamer carbonate have been conducted and await publication. One such study performed in the UK was a randomized, multicenter, open-label, cross-over study of 31 hemodialysis patients comparing the efficacy...
of the powder form of sevelamer carbonate with the tablet form of sevelamer hydrochloride [38]. Another study was performed in 46 CKD patients not on chronic dialysis, evaluating the efficacy and tolerability of sevelamer carbonate tablets in a multicenter, single-arm, open-label, dose-titration study [39]. The results of these studies may provide more options for dosing, and in doing so may help patients better adhere to their prescribed phosphate-binder therapy. These results might also be used as a basis to expand the current FDA approval of sevelamer carbonate for treatment of hyperphosphatemia in ESRD to also include CKD subjects not receiving chronic dialysis.

Conclusion & future perspective

The management of abnormalities in mineral and bone metabolism in patients with CKD presents an immense ongoing challenge. Phosphorus control, one component of this challenge, has significant room for improvement, as evidenced by data from the International Dialysis and Practice Patterns Study, which suggests that fewer than 50% of dialysis patients meet the target value for serum phosphorus [40]. As such, sevelamer carbonate appears to be a promising agent in the control of phosphorus in subjects with CKD. However, most of the proposed benefits of this new agent are extrapolated from the studies completed with sevelamer hydrochloride. Hence, the determination of an added benefit from sevelamer carbonate compared with sevelamer hydrochloride and other phosphorus binders will require direct comparison.

This new phosphorus-binding agent offers the potential for improved gastrointestinal tolerability and the prospect for alternative formulations, such as a powder, both of which could improve adherence to binder therapy. By a simple change in the accompanying counterion, the buffering capacity of sevelamer hydrochloride was improved and has resulted in a statistically significant improvement in serum bicarbonate levels in subjects with CKD on hemodialysis. However, it remains to be seen if this statistical significance translates into improvements of clinical outcomes.

An improvement in serum bicarbonate offers many possible benefits. Chronic metabolic acidosis in the setting of CKD has been associated with numerous adverse clinical consequences, including increased efflux of calcium and phosphorus from the bone, impaired growth when it occurs in children, enhanced skeletal muscle catabolism and diminished albumin synthesis, leading to muscle wasting and muscle weakness [41–45]. Moreover, correction of metabolic acidosis has been shown to diminish the stimulus for hyperparathyroidism, decrease protein degradation rates, increase serum albumin levels, improve subjective global assessment scores and reduce hospital admissions and length of stay [46–52].

In clinical practice, assessment of serum bicarbonate is subject to measurement error, and the long-term effects of correcting acidemia on clinical outcomes are not known. Data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) has correlated predialysis serum bicarbonate levels with survival in an analysis of 7000 patients on hemodialysis [53]. The lowest mortality risk was associated with midweek predialysis bicarbonate levels of 20.1–21.0 mEq/l, with an observed increased mortality level for levels of 17 mEq/l or less and 27 mEq/l or greater. The lowest risk for hospitalization was seen with bicarbonate levels of 21.1–22.0 mEq/l. In accordance with these data, the current NKF K/DOQI guidelines recommend maintenance of serum bicarbonate levels at 22 mEq/l or greater [54].

In subjects with CKD, the impact of metabolic acidosis on vascular calcification, which is considered by some to be a strong predictor of cardiovascular morbidity and mortality in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sevelamer carbonate</th>
<th>Sevelamer hydrochloride</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphorus</td>
<td>4.6 ± 0.9 mg/dl</td>
<td>4.7 ± 0.9 mg/dl</td>
<td>NS</td>
</tr>
<tr>
<td>Number of gastrointestinal events</td>
<td>25 (20.5% of patients)</td>
<td>45 (35.9% of patients)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum bicarbonate change</td>
<td>1.3 ± 4.1 mEq/l</td>
<td>-0.3 ± 3.6 mEq/l</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>144.0 ± 33.9 mg/dl</td>
<td>139.0 ± 33.6 mg/dl</td>
<td>0.009</td>
</tr>
<tr>
<td>Low-density-lipoprotein cholesterol</td>
<td>59.5 ± 24.9 mg/dl</td>
<td>56.0 ± 23.3 mg/dl</td>
<td>0.035</td>
</tr>
</tbody>
</table>

NS: Not significant.
patients on chronic dialysis [4,19], is not established. Recently, Mendoza et al. demonstrated that the development of extracellular mineralization was prevented in uremic rats by experimentally induced metabolic acidosis [55]. The effects of metabolic acidosis on bone (demineralization) and vasculature (inhibition of mineralization) emphasizes the need for a more comprehensive understanding of the optimal level of serum bicarbonate in order to provide the most favorable environment for both. Furthermore, the premise that improvements in surrogate outcome measures (laboratory parameters of mineral and bone metabolism, progression of vascular calcification and serum bicarbonate levels) will translate into clinically meaningful benefits remains unproven. How best to prioritize and manage the metabolic derangements seen in CKD patients in order to maintain both bone and vascular health is not known, and will likely be the focus of much research for years to come.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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**Executive summary**

- Current recommendations for serum phosphorus levels in patients with kidney disease on dialysis are often only attainable with the administration of oral phosphate binders to reduce intestinal absorption of dietary phosphorus.
- When compared with calcium-containing phosphorus binders, sevelamer hydrochloride offers several advantages: fewer episodes of hypercalcemia, avoidance of an excessive calcium load, an anti-inflammatory effect, a lipid-lowering effect, the ability to reduce uric acid, a favorable effect on vascular calcification and bone mineral attenuation, and, potentially, a reduction in mortality rate.
- Sevelamer carbonate has been developed as an alternative to sevelamer hydrochloride in an effort to improve its gastrointestinal tolerability and buffering capacity, as well as to provide alternative formulations, such as a powder.
- Sevelamer carbonate and sevelamer hydrochloride contain identical active moieties with the same dosing and administration. However, the counterion differs between the two compounds, with sevelamer carbonate containing carbonate.
- In a study of patients with chronic kidney disease (CKD) on dialysis, treatment with sevelamer carbonate or sevelamer hydrochloride resulted in similar levels of serum phosphorus.
- A statistically significant improvement in serum bicarbonate levels in patients with CKD on dialysis was seen in those treated with sevelamer carbonate compared with those treated with sevelamer hydrochloride. However, it remains to be seen if this statistical significance translates into improvements in clinical outcomes.
- Studies on the efficacy and tolerability of sevelamer carbonate use in patients with CKD not receiving chronic dialysis, as well as the efficacy of the powder form versus the tablet form of sevelamer carbonate, await publication and ultimate US FDA approval.
- The determination of an added benefit from the use of sevelamer carbonate compared with sevelamer hydrochloride, as well as other phosphorus binders, will require direct comparison.

**Bibliography**

Papers of special note have been highlighted as of interest (*) or of considerable interest (**) to readers.


Sevelamer carbonate in the management of hyperphosphatemia – DRUG EVALUATION


Randomized, controlled trial comparing sevelamer hydrochloride and sevelamer carbonate in dialysis patients, which demonstrated equivalency in serum phosphate reduction between the two agents.


