Sevelamer Versus Calcium-Based Binders for Treatment of Hyperphosphatemia in CKD: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background and objectives People with CKD stages 3–5 and on dialysis (5D) have dramatically increased mortality, which has been associated with hyperphosphatemia in many studies. Oral phosphate binders are commonly prescribed to lower serum phosphate. We conducted an updated meta-analysis of the noncalcium–based binder (non-CBB) sevelamer versus CBBs in CKD stages 3–5D.

Design, setting, participants, & measurements Randomized, controlled trials comparing sevelamer with CBBs were identified through MEDLINE and the Cochrane Central Register of Controlled Trials. Patient-level outcomes included all-cause mortality, cardiovascular events and mortality, hospitalization, and adverse effects. Intermediate outcomes included vascular calcification and bone changes. Biochemical outcomes included serum phosphate, calcium, parathyroid hormone, lipids, and hypercalcemia. We conducted and reported this review according to Cochrane guidelines.

Results We included 25 studies to March 31, 2015 with 4770 participants (88% on hemodialysis). Patients receiving sevelamer had lower all-cause mortality (risk ratio [RR], 0.54; 95% confidence interval [95% CI], 0.32 to 0.93), no statistically significant difference in cardiovascular mortality (n=2712; RR, 0.33; 95% CI, 0.07 to 1.64), and an increase in combined gastrointestinal events of borderline statistical significance (n=384; RR, 1.42; 95% CI, 0.97 to 2.08). For biochemical outcomes, patients receiving sevelamer had lower total serum cholesterol (mean difference [MD], −20.2 mg/dl; 95% CI, −25.9 to −14.5 mg/dl), LDL-cholesterol (MD, −21.6 mg/dl; 95% CI, −27.9 to −15.4 mg/dl), and calcium (MD, −0.4 mg/dl; 95% CI, −0.6 to −0.2 mg/dl) and a reduced risk of hypercalcemia (RR, 0.30; 95% CI, 0.19 to 0.48). End of treatment intact parathyroid hormone was significantly higher for sevelamer (MD, 32.9 pg/ml; 95% CI, 0.1 to 65.7 pg/ml). Serum phosphate values showed no significant differences.

Conclusions Patients with CKD stages 3–5D using sevelamer have lower all-cause mortality compared with those using CBBs. Because of a lack of placebo-controlled studies, questions remain regarding phosphate binder benefits for patients with CKD stages 3–5 and not on dialysis.

Introduction

Patients with CKD are at increased risk of CKD-mineral and bone disorder (MBD), laboratory features of which include abnormalities of serum calcium (Ca), phosphate, and parathyroid hormone (PTH) (1). Patient-level consequences include increased risks of vascular calcification, cardiovascular (CV) disease and CV events, metabolic bone disease, fracture, and mortality.

Hyperphosphatemia, in particular, is associated with many patient-level risks and generally occurs late in the evolution of CKD as adaptive responses fail to maintain mineral homeostasis (2). Abnormal values of Klotho, fibroblast growth factor (FGF-23), 1,25-dihydroxyvitamin-D, PTH, and other mineral regulators and inflammatory markers generally precede the development of hyperphosphatemia and are also independently associated with higher mortality (2). Oral phosphate binder use has been associated with improved outcomes and survival (1,3,4), with calcium-based binders (CBBs) being most widely used. However, because of concerns for the sequelae of positive Ca balance (5–7), Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend restricting CBBs for patients with known vascular calcification, persistently low PTH, low/adynamic bone turnover, and persistent/recurrent hypercalcemia (1). KDIGO also recommends restricting calcitriol/analogs in hypercalcemia and using dialysate with 2.5–3.0 mEq/L (1.25–1.50 mmol/L) ionized Ca to maintain near–neutral Ca balance (1).

The non–CBBs sevelamer hydrochloride, sevelamer carbonate, and lanthanum carbonate are also approved in many countries to manage hyperphosphatemia. A Cochrane systematic review and meta-analysis to March of 2010 regarded data as insufficient to establish
superiority of non-CBB agents over CBBs for mortality (8). However, using data to 2012, Jamal et al. (9) reported significantly lower all-cause mortality with non-CBBs than CBBs and called for research to compare mortality among non-CBBs (9).

Several subsequent studies have evaluated the efficacy and safety of sevelamer in patients with CKD, but none has compared lanthanum with CBBs or sevelamer for patient outcomes. Consequently, this systematic review and meta-analysis evaluate efficacy and safety of sevelamer versus CBBs.

Materials and Methods

This analysis updates the sevelamer versus CBB component of the 2011 Cochrane (8) systematic review and meta-analysis, comparing efficacy of sevelamer versus CBBs (Ca salts, Ca acetate, Ca carbonate, and Ca keto-glutarate) on patient level, intermediate, and biochemical end points. Cochrane methods and quality of reporting guidelines were followed (10).

Inclusion Criteria

Eligible studies were published randomized, controlled trials (RCTs) and quasi-RCTs (using predictable methods for treatment allocation) >8 weeks in duration enrolling adults with CKD stages 3-5 and on dialysis (eGFR≤59 ml/min per 1.73 m² or on dialysis). In RCTs, the first phase was included where possible. Post-transplantation studies were excluded along with single-arm or observational studies and abstracts.

Search Strategy

Search strategies and terms, adapted from the 2011 Cochrane search sets (8) and RCT-enriching search methods (11), are provided in Supplemental Table 1. Studies published from March of 2009 to March 31, 2015 were searched in PubMed and the Cochrane Central Register of Controlled Trials with no limits on language or publication status. Congresses and journals were also hand searched (Supplemental Table 2).

Two reviewers (D. Rubinger (D.R.), personal communication and L.P.) independently screened potentially relevant titles, abstracts, and full texts of potentially relevant studies. Discrepant opinions on study inclusion were resolved by consensus with a third opinion (L.M.B.). We attempted to ascertain publication intentions from recent abstracts’ authors.

Data Extraction

Data from the meta-analysis by Navaneethan et al. (8) and studies published March 2009 to March 2015 were extracted by an author (L.P.) and contributor (D.R.) and into standardized data collection forms and imported into Review Manager software v5.2 (Cochrane Collaboration, Copenhagen, Denmark) (10).

Extracted patient-level outcomes comprised all-cause and CV mortality, CV events, hospitalization (incidence and duration), fracture at any site, calciphylaxis, health-related quality of life, and incidence and nature of treatment-related adverse effects. Intermediate outcomes comprised vascular, valvular, or soft tissue calcification; percentage change in bone mineral density (BMD) (g/cm²); Z or T-scores (assessed by dual-energy x-ray absorptiometry or quantitative computerized tomography); and changes to bone histomorphometry. Biochemical outcomes included values of serum Ca, phosphorus (P), and Ca × P product; PTH (intact parathyroid hormone [iPTH] or PTH 1–84); alkaline phosphatase and bicarbonate. Differences in total cholesterol, LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) were assessed along with the incidence of hypercalcemia (serum Ca level >11.0 mg/dl or as defined by study investigators) and when available, values of 1,25-dihydroxyvitamin D, fetuin A, and FGF-23.

Errors in the 2011 data extraction by Navaneethan et al. (8) were corrected (Supplemental Table 3). Where one study generated multiple publications, the most complete dataset was used and supplemented with data from other publications. Graphic data in source studies that could not be imputed statistically by standard methods were extracted from figures using digital graph reader software. Outcomes with incomplete data were excluded from analysis.

Quality Assessment

Study quality was assessed independently by two reviewers (D.R. and L.P.) using the Cochrane Renal Group checklist to score risk of bias on the basis of randomization, allocation concealment, intent to treat analysis, follow-up completeness, and masking (10).

Statistical Analyses

Dichotomous data were analyzed using risk ratios (RRs) and 95% confidence intervals (95% CIs), and estimates were pooled using a random effects model. Continuous data were analyzed using mean difference (MDs) and 95% CIs.

Heterogeneity was assessed graphically by forest plots and statistically by heterogeneity $\chi^2$ (Cochran Q) and $I^2$ statistics (12). Publication bias was tested by funnel plot for primary outcomes of all-cause mortality and serum P; asymmetry was tested using R statistical software (13). L’Abbé plots and influence analyses were also evaluated.

Results

Search Results

The 2011 Cochrane review (8) included 24 publications (14–35) of 19 studies comparing sevelamer versus CBBs; removal of abstracts (E. Kinugasa and S. Koshikawa S, unpublished data; M. Gallieni, et al., unpublished data) yielded 17 eligible studies ($n=3557$). Electronic searches from March of 2009 to March of 2015 identified 1807 potentially relevant reports (Figure 1). Of these, 1770 were excluded after title and abstract review. Full text was reviewed on 37 reports; ten publications (36–45) reporting eight new studies ($n=1213$) were eligible. Combining these eight with the 2011 Cochrane study set by Navaneethan et al. (8) yielded a final set of 25 studies ($n=4770$).

Study Characteristics

Table 1 details characteristics of included studies, which fell into three groups: comparisons of sevelamer (any form) with Ca acetate (ten studies; $n=949$) (14,16,19,22,26,33,38,39,41,45), comparisons of sevelamer (any form) with Ca carbonate (12 studies; $n=1409$) (17,18,20,21,23–25,34,37,42–44), and comparisons of
sevelamer (any form) with Ca salts (CBB combinations; three studies, \( n = 2412 \)) (27,29,35).

Most studies (22 of 25) enrolled patients on dialysis (14,16–22,24–27,29,33–35,37,39,40,43–45); 12% (three of 25) enrolled patients with CKD stages 3–5 (23,38,42). Most studies enrolled patients with hyperphosphatemia, although four (including one nondialysis study) included patients who were normophosphatemic. Participant
<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Follow-Up, mo</th>
<th>Enrolled Patient Population</th>
<th>Intervention, Starting Dose (Mean Study End Dose)</th>
<th>Comparator, Starting Dose (Mean Study End Dose); Expressed as Elemental Ca</th>
<th>Cointervention</th>
<th>Included End Points</th>
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<tr>
<td>45</td>
<td>140</td>
<td>Parallel RCT</td>
<td>6</td>
<td>Stable HD three times per wk for at least 3 mo</td>
<td>SEV HCl, 810 mg three times per d (NR)</td>
<td>Ca acetate, 169 mg three per d (NR)</td>
<td>NA</td>
<td>Serum P, serum Ca, serum iPTH</td>
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<tr>
<td>16</td>
<td>80</td>
<td>Crossover RCT</td>
<td>4</td>
<td>HD; stable dose of Ca or aluminum-based binders for 1 mo; serum P &gt; 6 mg/dl during washout</td>
<td>SEV HCl, two to four capsules three times per d to achieve serum P 2.5–5.5 mg/dl (NR)</td>
<td>Ca acetate 169 mg, three to nine per d to achieve serum P 2.5–5.5 mg/dl (NR)</td>
<td>Vitamin D</td>
<td>Serum P, serum Ca, Ca × P product, iPTH, lipid profile</td>
</tr>
<tr>
<td>27,28</td>
<td>109, 127</td>
<td>Parallel RCT stratified by diabetes mellitus</td>
<td>18</td>
<td>New to HD</td>
<td>SEV HCl, NR (8 g/d)</td>
<td>Ca carbonate or/plus Ca acetate, NR (2300 mg/d)</td>
<td>Vitamin D</td>
<td>CAC score (27); all-cause mortality, progression of CAC score (28)</td>
</tr>
<tr>
<td>38</td>
<td>106</td>
<td>Parallel RCT</td>
<td>9</td>
<td>Patients with moderate to advanced CKD: eGFR=20–45 ml/min per 1.73 m² with serum P ≥3.5 and &lt;6.0 mg/dl</td>
<td>SEV carbonate, 800 mg per meal, adjusted to maximum dose of 3200 mg (NR)</td>
<td>Ca acetate, 169 mg, 3–12 per day (NR) lanthanum carbonate, 500 mg per meal, adjusted to maximum dose of 1500 mg (NR) placebo</td>
<td>Vitamin D</td>
<td>Serum P (primary end point), serum P,PTH, FGF-23, 1,25 (OH)₂D, urine P, fractional excretion of P, change in coronary artery, thoracic, and abdominal aortic Ca volume scores, change in lumbar BMD</td>
</tr>
<tr>
<td>14,15,36</td>
<td>101, 31, 72</td>
<td>Parallel RCT</td>
<td>12</td>
<td>Maintenance HD</td>
<td>SEV HCl, adjusted up to 12 g/d (NR)</td>
<td>Ca acetate, 169 mg, up to 12 per d (NR)</td>
<td>Vitamin D</td>
<td>Serum P, serum ionized Ca, iPTH, bone biopsy histomorphometry, vascular calcification (14); serum P, Ca, iPTH, Ca × P, albumin, total cholesterol, inflammatory markers (15); bone turnover and histomorphometry, serum FGF-23, P, ionized Ca, iPTH, coronary Ca score, bone alkaline phosphatase (36)</td>
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<td>22</td>
<td>98</td>
<td>Parallel RCT</td>
<td>2</td>
<td>HD ≥3 mo; stable doses of phosphate binder and vitamin D for ≥1 mo</td>
<td>SEV HCl, two to four capsules (403 mg) three times per d to achieve serum P &lt;5.5 mg/dl (NR)</td>
<td>Ca acetate, 169 mg, 6–12 per d to achieve serum P &lt; 5.5 mg/dl (NR)</td>
<td>Vitamin D</td>
<td>Serum P, Ca, Ca × P, iPTH</td>
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<tr>
<td>Ref.</td>
<td>No. of Patients</td>
<td>Study Design</td>
<td>Follow-Up, mo</td>
<td>Enrolled Patient Population</td>
<td>Intervention, Starting Dose (Mean Study End Dose)</td>
<td>Comparator, Starting Dose (Mean Study End Dose); Expressed as Elemental Ca</td>
<td>Cointervention</td>
<td>Included End Points</td>
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<td>33</td>
<td>203</td>
<td>Parallel RCT</td>
<td>12</td>
<td>HD 3 mo to 5 yr</td>
<td>SEV HCl, to achieve serum P of 3.5–5.5 mg/dl and LDL&lt;70.0 mg/dl (NR)</td>
<td>Ca acetate, to achieve serum P of 3.5–5.5 mg/dl and LDL&lt;70.0 mg/dl (NR)</td>
<td>Vitamin D</td>
<td>Change in CAC score by EBCT</td>
</tr>
<tr>
<td>37</td>
<td>15</td>
<td>Crossover RCT</td>
<td>2</td>
<td>PD with type 2 diabetes mellitus and serum P ≥3.5 mg/dl</td>
<td>SEV HCl, NR (NR)</td>
<td>Ca carbonate, NR (NR)</td>
<td>NA</td>
<td>Endothelial function, endothelial function biomarkers, proinflammatory cytokines, serum Ca, P, and lipids</td>
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<td>25</td>
<td>71</td>
<td>Parallel RCT</td>
<td>3</td>
<td>HD≥3 mo; stable CBB or aluminum-based binder use for ≥1 mo before</td>
<td>SEV HCl, two to four capsules (465 mg) three times per d to achieve serum P of 2.5–5.5 mg/dl (NR)</td>
<td>SEV HCl (two to four capsules [465 mg] three times per d) + Ca carbonate to 900 mg/d to achieve serum P of 2.5–5.5 mg/dl (NR)</td>
<td>Vitamin D</td>
<td>Serum P, iPTH (primary end points); Ca, Ca × P, lipid profile</td>
</tr>
<tr>
<td>29–32</td>
<td>200, 72, 108, 111</td>
<td>Parallel RCT</td>
<td>12</td>
<td>Patients on HD</td>
<td>SEV HCl, to achieve serum P of 3.0–5.0 mg/dl and serum Ca of 8.5–10.5 mg/dl (6.5 g/d)</td>
<td>Ca acetate to 1165 mg per carbonate to 1560 mg to achieve serum P of 3.0–5.0 mg/dl and serum Ca of 8.5–10.5 mg/dl</td>
<td>Vitamin D</td>
<td>Serum P, Ca, iPTH, lipid profile A (29); hypercalcemic episodes, Ca × P, serum iPTH, CAC and aortic calcification score increases, trabecular and cortical BMD (30); changes in CAC score, changes in lipids and inflammatory markers (31); serum P, Ca, Ca × P, iPTH, changes in bone attenuation, bone turnover markers, changes in bone attenuation, bone turnover markers (32)</td>
</tr>
<tr>
<td>Ref.</td>
<td>No. of Patients</td>
<td>Study Design</td>
<td>Follow-Up, mo</td>
<td>Enrolled Patient Population</td>
<td>Intervention, Starting Dose (Mean Study End Dose)</td>
<td>Comparator, Starting Dose (Mean Study End Dose); Expressed as Elemental Ca</td>
<td>Cointervention</td>
<td>Included End Points</td>
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<td>35</td>
<td>2103</td>
<td>Parallel RCT</td>
<td>Mean ± SD: 20.3 ± 13.9 (SEV); 19.6 ± 13.6 (Ca)</td>
<td>Dialysis &gt;3 mo, requiring phosphate binder therapy</td>
<td>SEV HCl, NR (6.9 g/d)</td>
<td>Ca acetate, NR (1342 mg/d) Ca carbonate, NR (1960 mg/d)</td>
<td>NA</td>
<td>All-cause mortality, cause-specific mortality, MI, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, cerebrovascular accident, ischemic brain damage/anoxic encephalopathy, hospitalization</td>
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<td>21</td>
<td>16</td>
<td>Parallel RCT with crossover</td>
<td>6</td>
<td>Men on maintenance HD for 6–10 mo before screening with serum P &gt;5.5 mg/dl during washout</td>
<td>SEV HCl, 800-mg tablets, two to three capsules three times per d to achieve P 5.5 mg/dl and Ca 8.5–10.5 mg/dl (NR)</td>
<td>Ca carbonate, 250 mg/d to achieve P of 5.5 mg/dl and Ca of 8.5–10.5 mg/dl (NR)</td>
<td>NA</td>
<td>Time courses of concentrations of plasma bicarbonate, serum albumin, iPTH</td>
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<tr>
<td>42</td>
<td>212</td>
<td>Parallel open-label RCT</td>
<td>36</td>
<td>Stages 3–4 CKD with 6 mo follow-up before enrollment</td>
<td>SEV HCl, 1600 mg/d (2184 mg/d)</td>
<td>Ca carbonate, 800 mg/d (1180 mg/d)</td>
<td>Vitamin D</td>
<td>All-cause mortality (primary end point); composite of all-cause mortality and dialysis inception, dialysis inception, serum P, Ca, iPTH, lipids, plasma profile, CAC score</td>
</tr>
<tr>
<td>17</td>
<td>143</td>
<td>Parallel RCT</td>
<td>3.25</td>
<td>Stable PD for &gt;8 wk with serum P &gt;5.5 mg/dl and normal serum Ca 8.4–10.4 mg/dl</td>
<td>SEV HCl, 1600 mg three times per d titrated to achieve serum P 3.0–5.5 mg/dl (5.8 g/d)</td>
<td>Ca carbonate, 538 mg, to nine per d titrated to achieve serum P of 3.0–5.5 mg/dl (4.5 g/d)</td>
<td>Vitamin D</td>
<td>Changes in serum P (primary end point); changes in Ca, iPTH, lipids, plasma biomarkers (secondary end points)</td>
</tr>
<tr>
<td>34</td>
<td>91</td>
<td>Parallel RCT</td>
<td>12.5</td>
<td>HD three times per wk with stable serum P &lt;8.1 mg/dl for &gt;1 mo before enrollment</td>
<td>SEV HCl, to achieve serum P 3.2–5.0 mg/dl and maintain serum Ca &lt;10.4 mg/dl (NR)</td>
<td>Ca carbonate to achieve serum P of 3.2–5.0 mg/dl and maintain serum Ca &lt;10.4 mg/dl (NR)</td>
<td>Vitamin D</td>
<td>Changes in serum biochemical and bone mineralization parameters</td>
</tr>
<tr>
<td>26</td>
<td>40</td>
<td>Parallel RCT</td>
<td>8.5</td>
<td>HD three times per wk; stable dose of CBBS and vitamin D for ≥1 mo</td>
<td>SEV HCL, two to four capsules (403 mg) three times per d (4.09 g/d)</td>
<td>Ca acetate, 169 mg, 1–12 per d (988 mg/d)</td>
<td>Vitamin D</td>
<td>Serum P, Ca, iPTH, lipid profile, alkaline phosphatase</td>
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<tr>
<td>Ref.</td>
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<td>Follow-Up, mo</td>
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<td>Intervention, Starting Dose (Mean Study End Dose)</td>
<td>Comparator, Starting Dose (Mean Study End Dose); Expressed as Elemental Ca</td>
<td>Cointervention</td>
<td>Included End Points</td>
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<tr>
<td>43</td>
<td>163</td>
<td>Parallel open-label RCT</td>
<td>12</td>
<td>HD</td>
<td>SEV HCl, NR (NR)</td>
<td>Ca carbonate, NR (NR)</td>
<td>Vitamin D</td>
<td>Change in CAC score (primary end point); change in serum P, Ca, glucose, creatinine, urea, lipid profile, PTH, plasma pentosidine</td>
</tr>
<tr>
<td>18</td>
<td>86</td>
<td>Parallel RCT</td>
<td>3</td>
<td>HD</td>
<td>SEV HCl, 6 g/d (6 g/d)</td>
<td>SEV HCl, 3 g/d (3 g/d) + Ca carbonate, 1200 mg/d (1200 mg/d) Ca carbonate 1200 mg/d</td>
<td>Vitamin D</td>
<td>Serum-corrected Ca, P, bicarbonate, iPTH</td>
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<tr>
<td>39,40</td>
<td>52, 52</td>
<td>Parallel open-label RCT</td>
<td>2</td>
<td>Stable HD &gt;3 mo; on phosphate binders &gt;1 mo before screening, with serum P &gt; 5.5 mg/d</td>
<td>SEV HCl, one to three 800-mg tablets three times per d depending on serum P (NR)</td>
<td>Ca acetate, 169 mg, three to nine per d depending on serum P (NR)</td>
<td>Vitamin D</td>
<td>Serum P, Ca, Ca × P, iPTH, alkaline phosphatase, AEs (39); serum P, Ca, cholesterol, uric acid, plasma reactive oxygen species, AEs (40)</td>
</tr>
<tr>
<td>19</td>
<td>70</td>
<td>Parallel RCT</td>
<td>2</td>
<td>HD ≥3 mo with serum P &gt; 6.0 mg/d during washout; stable CBB dosage ≥1 mo</td>
<td>SEV HCl, one to three 800-mg tablets three times per d depending on serum P (NR)</td>
<td>Ca acetate, 169 mg, three to nine per d depending on serum P (NR)</td>
<td>Vitamin D</td>
<td>Changes in serum P, Ca, Ca × P, iPTH, alkaline phosphatase</td>
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<tr>
<td>44</td>
<td>466</td>
<td>Parallel open-label RCT</td>
<td>24</td>
<td>New to HD</td>
<td>SEV, to achieve serum P of 2.7–5.5 mg/d (NR)</td>
<td>Ca carbonate, to achieve serum P of 2.7–5.5 mg/d (NR)</td>
<td>Vitamin D</td>
<td>CV mortality (primary end point); all-cause mortality, non-CV mortality, CAC scores</td>
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<td>41</td>
<td>59</td>
<td>Parallel open-label RCT</td>
<td>3</td>
<td>CKD stage 5D on maintenance HD ≥3 mo</td>
<td>SEV HCl, 1600 mg three times per d (1600 mg three times per d)</td>
<td>Ca acetate, 127 mg three per d (127 mg three per d)</td>
<td>NA</td>
<td>Serum IL-6, inflammatory profile, LPS, sCD14, P, Ca, iPTH, Ca × P product</td>
</tr>
<tr>
<td>23</td>
<td>84</td>
<td>Parallel RCT</td>
<td>24 ≤4.2</td>
<td>CKD stages 3–5 and not 5D; no previous aluminum-based binder or CBB therapy</td>
<td>SEV HCl, 1600 mg/d (1600 mg/d); low-phosphate diet</td>
<td>Ca carbonate, 800 mg/d (800 mg); low-phosphate diet</td>
<td>NA</td>
<td>Changes in total Ca score, progression of CAC, changes in biochemical variables</td>
</tr>
</tbody>
</table>
numbers ranged from 15 to 2103, with <100 in 14 studies. Study durations ranged from 2 to 36 months, with 80% (20 of 25) <18 months. Most studies included cotreatment with calcitriol or analogs, but no study included information on calciferol use. Hypercalcemia definitions varied (serum Ca >10 to >11 mg/dL).

**Study Quality**

Quality varied widely (Supplemental Figure 1). Risk of allocation bias was high in one study, low in nine studies, and unclear in the remaining 15 studies. Interventions were masked to participants and investigators in two studies, and outcome assessors were masked in six studies. Twenty-three studies were open label; eight studies underwent intent to treat analysis.

Publication bias was assessed by funnel plots for all-cause mortality (Supplemental Figure 2) and serum phosphate (not shown). Both plots were symmetrical, indicating that outcomes were unlikely to be affected by publication bias. The Egger linear regression test for publication bias (13) was not significant for all-cause mortality ($P=0.18$) or serum phosphate ($P=0.18$).

**Patient-Level Outcomes**

**All-Cause Mortality.** Compared with CBBs, sevelamer significantly lowered all-cause mortality in patients with CKD stages 3–5 and on dialysis (13 studies; $n=3799$; RR, 0.54; 95% CI, 0.32 to 0.93) (Figure 2) (14,16,18,20,22,26,27,29,33–35,42,44). Heterogeneity was significant ($\chi^2=45.11$; $I^2=82$%). All-cause mortality differed significantly between sevelamer and Ca carbonate (five studies; $n=847$; RR, 0.35; 95% CI, 0.22 to 0.56) (18,20,34,42,44) but not between sevelamer and Ca acetate (five studies; $n=522$; RR, 0.43; 95% CI, 0.13 to 1.38) (14,16,22,26,33) or Ca salts (three studies; $n=2430$; RR, 0.85; 95% CI, 0.57 to 1.27) (27,29,35), with no significant heterogeneity in these subgroup analyses. Only three of 13 studies reported causes of death. All nine deaths in the study by Barreto et al. (14) were CV related, although exact causes were not specified. Sadek et al. (20) attributed four deaths in their study to sudden death ($n=2$), septicemia ($n=1$), and colon cancer ($n=1$). Among 542 deaths reported in the Dialysis Clinical Outcomes Revisited (DCOR) Study (35), 289 reflected CV causes, 88 were from infection, and 165 were from other causes; no additional details were provided.

Methodology and baseline characteristics of included studies were scrutinized to explain differences in all-cause mortality; heterogeneity was explored through a series of subgroup analyses. Results of the subgroup analyses are presented in Supplemental Figures 3 and 4 and Table 2. In a subgroup analysis that included only patients on dialysis (12 studies; $n=3587$), the RR for all-cause mortality was similar to that of the primary analysis (0.54), but the 95% CI of 0.29 to 1.01 failed to achieve statistical significance (14,16,18,20,22,26,27,29,33–35,44). Significant heterogeneity was observed ($\chi^2=43.66$; $P=84$%; $I^2=90$%).

Omitting studies where all-cause mortality was not a prespecified outcome abrogated significant differences between sevelamer and CBBs (four studies; $n=2908$; RR, 0.53; 95% CI, 0.26 to 1.09) (27,35,42,44). Mortality on sevelamer was significantly lower in studies ≥1 year in duration (eight studies; $n=3503$; RR, 0.53; 95% CI, 0.29 to 0.95) (14,27,29,33–35,42,44) and ≥2 years in duration (two
studies; n = 678; RR, 0.37; 95% CI, 0.20 to 0.68) (42,44) and studies with 100 participants (seven studies; n = 3412; RR, 0.53; 95% CI, 0.29 to 0.95) (14,27,29,33,35,42,44). Sevelamer recipients on dialysis, 3 months had significantly lower mortality than similar participants receiving CBBs; no significant differences occurred in other analyzed groups (not on dialysis, 3 months to 3 years on dialysis, and > 3 years on dialysis). Sevelamer recipients with known vascular calcification had significantly lower mortality than similar patients on CBBs. Significant differences between sevelamer and CBBs were no longer observed in subgroup analyses of studies that reported mean baseline serum phosphate levels > 5.5 mg/dl, studies that included a washout period, studies reporting losses to follow-up > 20%, and studies determined to be at low risk of bias because of the reporting of intent to treat analysis. No mortality data were reported for peritoneal dialysis.

CV Mortality. Meta-analysis of four studies showed no significant difference in CV mortality between sevelamer and CBBs (n = 2712; RR, 0.33; 95% CI, 0.07 to 1.64) (14,20,35,44). Heterogeneity was highly significant ($\chi^2=41.81; P=93\%$; $P<0.001$). Contributing studies that reported data on CV deaths per total group and follow-up duration are as indicated: phosphate binder Impact on Bone Remodeling and Coronary Calcification (BRiC) (14): sevelamer, one of 52; CBB, eight of 49 (12 months); Reduce Cardiovascular Calcifications to Reduce QT Interval in Dialysis (INDEPENDENT-HD) Trial (44): sevelamer, nine of 232; CBB, 79 of 234 (>36 months); Sadek et al. (20): sevelamer, one of 21; CBB, one of 21 (5 months); and DCOR Study (35): sevelamer, 142 of 1053; CBB, 147 of 1050 (20 months).

Hospitalization. Two hemodialysis studies reported the numbers and lengths of hospitalizations (29,35). Measurement scales differed, precluding formal meta-analysis. Hospitalization parameters did not differ between sevelamer and CBBs in the work by Chertow et al. (29) (n = 200) and the full DCOR Study population (35) (n = 2103).

Calciphylaxis and Health–Related Quality of Life. There were no evaluable results for these outcomes.

Adverse Events

Sevelamer and CBBs did not differ significantly in incidence of nausea and/or vomiting (two studies; n = 255; RR, 0.64; 95% CI, 0.12 to 3.45) (33,39), constipation (five studies; n = 554; RR, 1.70; 95% CI, 0.69 to 4.15) (18,33,38,39,43), diarrhea (two studies; n = 255; RR, 1.03;
95% CI, 0.55 to 1.91) (33,39), or abdominal bloating (one study; n=56; RR, 2.33; 95% CI, 0.49 to 11.01) (18). Combined gastrointestinal adverse events occurred more often with sevelamer (four studies; n=384; RR, 1.42; 95% CI, 0.97 to 2.08) (16,17,19,34).

Intermediate Outcomes

Vascular Calcification. Twelve publications on nine studies reported effects of sevelamer and CBBs on vascular calcification (14,23,27,29–33,38,42–44). In six studies (nine publications), CBB recipients showed more rapid and/or severe increases in coronary artery calcification measures than sevelamer recipients (23,27,29–32,42–44). In the remaining three studies, calcification progression did not differ (14,33,38). Calcification scoring differences precluded meta-analysis.

Bone Outcomes. Four studies reported BMD change by dual-energy x-ray absorptiometry or quantitative computerized tomography and/or histomorphometry (14,32,34,38). Measures were inconsistent, precluding meta-analysis. Treatment with Ca was reported to increase (38) or decrease BMD (32). For bone histomorphometry,
differences in remodeling did not differ in BRIIC (14), but in a study with a 60% baseline prevalence of adynamic bone disease (34), improved bone formation rate/bone surface and trabecular architecture was reported for patients on dialysis receiving sevelamer versus Ca carbonate.

**Biochemical End Points**

**Serum Phosphate.** A meta-analysis of 23 studies (n=4010) showed no significant difference in end of treatment serum phosphate between sevelamer and CBBs (MD, 0.1 mg/dl; 95% CI, −0.1 to 0.2 mg/dl; heterogeneity: $\chi^2=109.14; P=80\%$; $P<0.001$) or between sevelamer and Ca acetate, carbonate, or salts (14,16,24,26,27,29,33,34,37–39,41–45). (Supplemental Figure 5).

**Serum Calcium.** In a meta-analysis of 22 studies (n=3933), end of treatment serum Ca was significantly lower with sevelamer versus CBBs (MD, −0.4 mg/dl; 95% CI, −0.6 to −0.2 mg/dl) with significant heterogeneity ($\chi^2=243.02; P=91\%; P<0.001$) (16–24,26,27,29,33–35,37,38,41–45). CBB-specific analyses showed no significant heterogeneity ($\chi^2=0.88; P=0\%; P=0.64$) and similar results.

**Hypercalcemia.** The risk of hypercalcemia decreased significantly with sevelamer versus CBBs (RR, 0.30; 95% CI, 0.19 to 0.48) with significant heterogeneity ($\chi^2=34.56; P=62\%; P=0.001$), in a meta-analysis of 15 studies (n=1537) (16,17,19–22,24,26,27,29,33,38,42,43). CBB-specific analyses were similar to the overall comparison without significant heterogeneity ($\chi^2=4.72; P=57.6\%; P=0.09$).

**Ca × P Product.** End of treatment serum Ca × P product did not differ significantly between sevelamer and CBBs (16 studies; n=2971; MD, 1.0 mg²/dl²; 95% CI, −0.5 to 2.6 mg²/dl²; heterogeneity: $\chi^2=27.90; P=46\%; P=0.02$) (16,17,19–22,24,26,27,29,33,37,39,41,43).

**Serum iPTH.** End of treatment iPTH was higher for patients treated with sevelamer compared with CBBs (18 studies; n=1835; MD, 32.9 pg/ml; 95% CI, 0.1 to 65.7 pg/ml) (14,16,18,20,21–24,26,27,29,33,37,39,41,43–45). Heterogeneity was significant ($\chi^2=107.75; P=86\%; P=0.001$). PTH (1–84) was not assessed in any included studies.

**Serum Bicarbonate.** Meta-analysis of seven studies (n=457) showed that sevelamer recipients had significantly lower serum bicarbonate levels than CBB recipients (MD, −1.5 mg/dl; 95% CI, −2.3 to −0.7 mg/dl; heterogeneity: $\chi^2=15.12; P=60\%; P=0.02$) (20–23,33,34,38). Six of these studies used sevelamer hydrochloride; only one (40) used sevelamer carbonate.

**Serum Alkaline Phosphatase.** Alkaline phosphatase levels showed no significant difference between sevelamer and CBB users in a meta-analysis of seven studies (n=352; MD, −8.4 μL/L; 95% CI, −34.0 to 17.2 μL/L; heterogeneity: $\chi^2=12.71; P=53\%; P=0.05$) (14,16,18,19,23,24,26).

**Total Cholesterol.** End of treatment total cholesterol was significantly lower for sevelamer versus CBB recipients (MD, −20.2 mg/dl; 95% CI, −25.9 to −14.5 mg/dl; heterogeneity: $\chi^2=31.69; P=59\%; P=0.003$) in a meta-analysis of 14 studies (n=2039) (14,16,18,20,23,24,26,27,29,34,35,37,39,42).

**LDL-C.** End of treatment LDL-C was significantly lower with sevelamer versus CBBs on the basis of 12 studies (n=1171; MD, −21.6 mg/dl; 95% CI, −27.9 to −15.4 mg/dl; heterogeneity: $\chi^2=43.16; P=75\%; P<0.001$) (14,16,20,23,29,33,34,37–39,42,43). Individual CBB results resembled the overall comparison.

**HDL-C.** End of treatment HDL-C did not differ significantly between sevelamer and CBBs in a meta-analysis of nine studies including 847 participants (MD, 1.5 mg/dl; 95% CI, −0.4 to 3.5 mg/dl) without significant heterogeneity ($\chi^2=15.08; P=47\%; P=0.06$) (14,16,20,23,29,33,34,37,43).

**1,25-Dihydroxyvitamin D.** Values of 1,25-dihydroxyvitamin D were assessed in one predialysis study (38) and one dialysis study (16) (in which low values would be expected). In the predialysis study (38), 1,25-dihydroxyvitamin D was 24.7±10.3 pg/ml at baseline and 26.8±12.3 pg/ml at month 9 on sevelamer and decreased significantly on CBBs (38). In the dialysis study (16), treatment groups did not differ significantly.

**Serum Fetuin-A.** No included studies examined change in serum fetuin-A levels.

**FGF-23.** Block et al. (38) reported significantly decreased intact FGF-23 with sevelamer (median decrease =24 pg/ml; P=0.002 versus placebo) in patients with estimated GFR 20–45 ml/min per 1.73 m², whereas Ca acetate increased intact FGF-23 (median increase =28 pg/ml; P=0.03 versus placebo). C-terminal FGF-23 did not differ significantly between groups.

**Discussion**

This meta-analysis, combining 25 studies and 4770 participants, shows a 46% reduction in all-cause mortality risk for sevelamer. Sevelamer was also associated with lower serum Ca, higher iPTH, lower total and LDL-C, a reduced risk of hypercalcemia versus CBBs, and a marginally increased risk of combined gastrointestinal adverse events. In contrast to the earlier Cochrane review (8), sevelamer and CBBs did not differ significantly for end of study serum phosphate. Serum bicarbonate values were lower with sevelamer (hydrochloride and carbonate coanalyzed), likely reflecting the lower buffering capacity of sevelamer hydrochloride than Ca carbonate (46,47).

The mechanisms responsible for sevelamer’s mortality benefit remain unclear. By CKD stages 3 and 4, patients have reduced natural inhibitors of calcification and increased oxidative stress, and the addition of CBBs leads to positive Ca balance (6) that may contribute to the initiation or progression of coronary artery calcification (42), vascular stiffness, reduced subendocardial perfusion, conduction abnormalities, and CV risk (48). In this analysis, CBB recipients were at increased risk of hypercalcemia, indicating that homeostatic adaptations were exceeded. However, we were unable to determine whether effects of sevelamer on total cholesterol, LDL-C, FGF-23, fetuin-A, inflammatory markers, or glycoxidative markers influenced any outcome.

In this meta-analysis, the RR for mortality was significantly reduced for sevelamer recipients who were new to dialysis, patients with vascular calcification at baseline, and those with baseline iPTH ≥300 pg/ml. Although these results are in accord with current KDIGO cautions on Ca use in patients with CKD-MBD, such subgroup analyses should be interpreted circumspectly. Study characteristics also influenced outcomes, with mortality lower for patients treated with sevelamer in studies of ≥100 participants, ≥1-year duration, ≥20% loss to follow-up, and a low risk of intention-to-treat bias. Despite a nonsignificant reduction in mortality detected in patients with CKD
stages 3–5 and not on dialysis treated with sevelamer versus CBBs, proof is lacking for an advantage of any phosphate binder over placebo in the predialysis setting (49).

A limitation of this meta-analysis is significant interstudy heterogeneity, which is illustrated by differences in the baseline characteristics of enrollees to the DORC Study (35) and INDEPENDENT-HD Trial (44). INDEPENDENT-HD (44) Trial participants were older and incident to dialysis, and 29% had diabetes. However, DORC (35) Study participants had a mean dialysis duration of 3.2 ± 3.3 years, and 50% had diabetes. Loss to follow-up was 49% in the DORC Study (44) and <15% in the INDEPENDENT-HD Trial (44). The INDEPENDENT-HD (44) Trial also reported a remarkable nine-fold reduction in all-cause CV mortality for patients allocated to sevelamer. It remains speculative whether factors other than phosphate binder allocation influenced this outcome, including lower baseline coronary artery calcification scores, better end of study serum phosphate, and higher baseline weight in those assigned to sevelamer. Nevertheless, some similarities are also apparent. In the DORC Study (35), mortality was significantly lower in patients receiving sevelamer aged 65 years or older and those receiving sevelamer for ≥24 months.

Additional limitations include scant outcome data for CV mortality, vascular calcification, hospitalization, bone outcomes, and health-related quality of life. Also, risks associated with maximal per protocol or end of study doses may differ from risks of low- or moderate-dose therapy. Effective management of hyperphosphatemia in CKD requires a multifaceted approach, of which dietary phosphate restriction and phosphate binders are important components (50). The recent non-CBBs versus CBBs analysis by Jamal et al. (9) and this meta-analysis showing lower mortality with sevelamer shift that paradigm and suggest a need to re-evaluate the recommendations of international guidelines for the management of hyperphosphatemia in CKD-MBD.

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