The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis

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Abstract

Background. The effects of calcium compared with non-calcium-based phosphate binders on mortality, cardiovascular events and vascular calcification in patients with chronic kidney disease (CKD) are unknown.

Methods. To address this question, we conducted a systematic review. We electronically searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL. We identified 160 potential studies and included 8 randomized trials. Eligible studies, determined by consensus using predefined criteria, were reviewed, and data were extracted onto a standard form.

Results. There was a trend towards a decrease in all-cause mortality among non-calcium-based versus calcium-based phosphate binders [relative risk (RR) 0.68; 95% CI 0.41–1.11] based upon eight randomized controlled trials and 2873 subjects. Two trials reported on cardiovascular events with a RR of 0.85 (95% CI 0.35–2.03) in patients receiving calcium-based versus non-calcium-based binders. Coronary artery calcification was reported in five trials involving 469 patients; the difference in the change in the calcium score from baseline to follow-up among subjects taking non-calcium-based binders versus calcium-based binders was -76.35 (95% CI -158.25–5.55).

Conclusion. Despite the trends observed, we did not find a statistically significant difference in cardiovascular mortality and coronary artery calcification in patients receiving calcium-based phosphate binders compared to non-calcium-based phosphate binders. However, the data are limited by the small number of studies and the confidence intervals do not exclude a potentially important beneficial effect. Therefore, further randomized trials are required.

Keywords: chronic kidney disease; meta-analysis; phosphate binders; systematic review; vascular calcification

Introduction

Two-thirds of all deaths in patients with end-stage renal disease (ESRD) are due to cardiovascular disease. Death from vascular disease occurs prematurely in patients with ESRD; data from the US Renal Data System demonstrate that 30-year-old dialysis patients suffer from a 500-fold elevated mortality risk compared with an age-matched general population [1].

A significant risk factor for cardiovascular disease in patients with ESRD is accelerated vascular calcification [2,3]. While the pathogenesis of arterial calcification has not yet been fully elucidated, it is likely to involve a transformation of vascular smooth muscle cells into bone-forming, osteoblast-like cells. Two factors that accelerate this transformation are elevated serum calcium and elevated serum phosphate, raising the concern that calcium-based phosphate binders, used very commonly in patients with ESRD, may accelerate arterial calcification, arterial stiffening and perhaps ultimately worsen patient outcomes.

There are an abundance of observational studies in humans with ESRD that show an association between elevations in serum calcium, phosphate and calcium phosphate product with overall and cardiovascular mortality [4–11]. Clinical trials concerning the use of calcium- or non-calcium-based phosphate binders, vascular morbidity and mortality have been inconclusive. Most studies involve small numbers of patients and evaluate intermediate outcomes such as serum levels of calcium and phosphorus, vascular compliance and vascular calcification. Individually, and even considered together, none have had sufficient power to evaluate mortality or cardiovascular events. Indeed, a recent systematic review [12] that examined the clinical efficacy and safety of the non-calcium-based binder sevelamer in dialysis patients demonstrated that compared with calcium-based phosphate binders, the use of sevelamer was associated with slightly lower serum calcium,
slightly higher serum phosphate and no difference in the calcium phosphate cross-product but there was no difference in all-cause mortality or cardiovascular mortality. This lack of difference in mortality outcomes may be related to power—there were five randomized controlled trials with 2429 participants that reported on mortality and three randomized trials with 2102 subjects that reported on cardiovascular events. To assess the impact of more recent publications on our ability to determine the effect of calcium-based versus non-calcium-based phosphate binders on all-cause mortality among patients with chronic kidney disease (CKD), we performed a systematic review and meta-analysis.

Subjects and methods

Search strategy
An experienced medical librarian developed and conducted a computerized search of the electronic databases MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (1980 to August 2008) and CINAHL (1982 to August 2008). Keywords included kidney disease, phosphate binders, calcium, dialysis, phosphate levels, cardiovascular events and mortality. In addition, one investigator hand searched cited references of published reviews of phosphate binders in CKD. We did not restrict the searches or inclusion criteria to any specific language. We did not search for abstracts nor did we include unpublished studies. We made no contact with authors. The complete search strategy is available online as an appendix.

Inclusion criteria
We included published completed studies that enrolled men and/or women, regardless of menopausal status, with CKD, regardless of the stage of CKD or type of dialysis. We included all randomized and nonrandomized trials that compared outcomes among subjects taking calcium-based binders to subjects taking non-calcium-based binders (sevelamer or lanthanum).

Our primary outcome was all-cause mortality reported in randomized controlled trials. We also abstracted data on secondary outcomes that included cardiovascular events (fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, and sudden death), fractures, vascular calcification, and vascular compliance.

We followed a standard Cochrane protocol for study selection and data abstraction [13,14]. All authors reviewed abstracts and identified potential manuscripts for retrieval independently. Study eligibility was determined by consensus, based on previously determined inclusion criteria. Eligible studies were reviewed independently by two authors who assessed study characteristics, clinical relevance and if appropriate extracted study data. We used consensus and a third reviewer, if necessary, to resolve disagreements. We extracted the following information from the studies included onto standardized forms: number of subjects included (pooled and by treatment assignment), number of subjects excluded, number of subjects observed, total lost to follow-up and the reasons for loss to follow-up, population characteristics (age, weight, gender, and for women, menopausal status), stage of CKD, duration of CKD, diabetes, use of cardiac medications at randomization, use of bisphosphonates, smoking status, presence of hypertension and laboratory results at randomization. We also abstracted data on trial characteristics (inclusion and exclusion criteria), type of study (for RCTs we recorded: independent randomization centre, blindness, random allocation, adequate allocation concealment, intention to treat and withdrawal/drop out rate) and trial intervention. With regard to outcomes, we recorded which of our primary or secondary outcomes were assessed. Our data abstraction form is available on request.

Subjects taking non-calcium-based binders included calcium carbonate and calcium acetate (Table 1).

We appraised study quality using the Cochrane Risk of Bias Tool [15]: two reviewers independently rated each study on the six domains (low, unclear or high bias for sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias) and then compared assessments. Any discrepancies were resolved by consensus. As dictated by the tool, low risk of bias is when all domains are rated low and means that bias is unlikely to seriously alter the results. Unclear risk indicates unclear risk for at least one domain and infers that there may be bias that raises some doubts about the results. Studies are rated at high risk for bias when at least one domain is rated high risk and infers that the bias seriously weakens confidence in the results.

Reviewers were not blinded to authors, institution or journal of publication. The use of non-blinded reviewers is accepted in meta-analyses and has not been found to bias results [16].

Statistical analysis
Studies were combined using the DerSimonian and Laird random effects model [17]. Dichotomous outcomes (e.g. all-cause mortality) were combined using risk ratios (RR), although odds ratios (OR) were examined in sensitivity analyses. Continuous outcomes (e.g. vascular calcification) were pooled using the weighted mean difference (WMD). We assessed heterogeneity among studies using the I-squared statistic, judging values of <25% to be minimal, <50% to be moderate and >50% to be substantial.

Publication bias was assessed using the weighted regression [18]. We conducted secondary analyses of the primary outcome measure by including a nonrandomized trial [19] that reported on mortality among those treated with calcium and non-calcium-based binders and by removal of the Block [20] manuscript due to the methodological limitations of this study [21]. We double-checked the data entry for all analyses.

Results
A total of 158 trials were identified via literature search and screened for retrieval. Of these, 101 were excluded, most for not comparing the agents of interest or not being trials. A total of 57 trials were retrieved for more detailed evaluation, with 44 excluded, mostly for reasons of not comparing the phosphate binders of interest or not providing details on any outcomes of interest. We excluded one trial from our primary analysis because it did not utilize a randomized design [19]. A total of 12 trials met our inclusion criteria for the meta-analysis [20,22–32]; however, four were withdrawn from the analysis for total mortality [29–32] and three from the analysis for cardiovascular events [29,31,32] because they did not include unique patients (i.e. used the same dataset as another reported trial).

As such, a total of eight trials were included in our review (Figure 1) [20,22–28]. The selected eight trials included a total of 2873 patients, 1434 receiving sevelamer (the only non-calcium-based phosphate binder noted in the trials meeting the inclusion criteria) and 1439 receiving calcium-based phosphate binders. Trials ranged in size from 42 to 2103, with a duration of follow-up between 5 and 44 months. All but one trial enrolled patients receiving haemodialysis; one study included predialysis patients [24]. No patients were receiving peritoneal dialysis. The calcium-based phosphate binders included calcium carbonate and calcium acetate (Table 1).

The study quality, as assessed by the Cochrane Risk of Bias Tool, is shown in Table 1. Three studies [24,27,28] were rated as high risk—due to inadequate sequence generation, allocation concealment and/or blinding. Two studies [22,29] were rated as unclear because of failure to indicate sequence generation, allocation concealment and/or of blinding and three studies were at low risk of bias [20,25,26].

The results are shown in Figures 2–4. The primary outcome, all-cause mortality, which was based upon eight randomized controlled trials and 2873 patients, is shown in Figure 2a. There was a non-significant reduction in
all-cause mortality of 32% [relative risk (RR) 0.68; 95% confidence interval (CI) 0.41–1.11], in favour of non-calcium-based phosphate binders. Expressed as an odds ratio, the impact of sevelamer on all-cause mortality was 0.75 (95% CI: 0.55–1.01). An a priori specified sub-analysis including the eight randomized and one nonrandomized trial showed a RR of 0.81 (95% CI: 0.65–1.02) (Figure 2b). Removal of the study by Block et al. 2007 resulted in a RR of 0.71 (95% CI: 0.38–1.31) [20]. The I-squared statistic was consistent with moderate heterogeneity for the primary analysis (47.8%) and remained substantially unchanged in the subgroup analyses, 43.2% and 38.6%, respectively.

Only two trials reported information on cardiovascular events, RR of 0.85 (95% CI 0.35–2.03), in favour of sevelamer (Figure 3) [23,29]. Only one trial reported the endpoint of sudden cardiac death RR 1.00 (95% CI 0.07–14.95, results not shown) [23]. Coronary artery calcification was reported in five randomized controlled trials, involving 238 patients receiving sevelamer and 231 patients receiving calcium-based phosphate binders (Figure 4) [20,22,24–26]. The key design features of the six trials reporting on coronary artery calcification are outlined in Table 2. All of these trials used the Agatston score to rate coronary artery calcification, and all scans were read by an assessor blinded to

Table 1. Characteristics of randomized trials included

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Design</th>
<th>Patients</th>
<th>Age (mean, years)</th>
<th>Sex (% female)</th>
<th>Non-Ca-based phosphate binder (n)</th>
<th>Ca-based phosphate binder (n)</th>
<th>Follow-up duration (months)</th>
<th>Risk of bias score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chertow (2002)</td>
<td>RCT</td>
<td>HD</td>
<td>57</td>
<td>35</td>
<td>S (99)</td>
<td>CA or CC (101)</td>
<td>12</td>
<td>Unclear</td>
</tr>
<tr>
<td>Sadek (2003)</td>
<td>RCT</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>S (15)</td>
<td>CC (16)</td>
<td>5</td>
<td>Unclear</td>
</tr>
<tr>
<td>Block (2007)</td>
<td>RCT</td>
<td>HD</td>
<td>58</td>
<td>37</td>
<td>S (54)</td>
<td>CA or CC (55)</td>
<td>18, 44*</td>
<td>Low</td>
</tr>
<tr>
<td>Russo (2007)</td>
<td>RCT</td>
<td>PreD</td>
<td>55</td>
<td>17</td>
<td>S (27)</td>
<td>CC (28)</td>
<td>24</td>
<td>High</td>
</tr>
<tr>
<td>Barreto (2008)</td>
<td>RCT</td>
<td>HD</td>
<td>47</td>
<td>32</td>
<td>S (52)</td>
<td>CA (49)</td>
<td>12</td>
<td>Low</td>
</tr>
<tr>
<td>Qunibi (2008)</td>
<td>RCT</td>
<td>HD</td>
<td>59</td>
<td>49</td>
<td>S (100)</td>
<td>CA (103)</td>
<td>12</td>
<td>Low</td>
</tr>
<tr>
<td>Suki (2008)</td>
<td>RCT</td>
<td>HD</td>
<td>60</td>
<td>46</td>
<td>S (1053)</td>
<td>CA or CC (1050)</td>
<td>20</td>
<td>High</td>
</tr>
<tr>
<td>Takei (2008)</td>
<td>RCT</td>
<td>HD</td>
<td>54</td>
<td>52</td>
<td>S (22)</td>
<td>CC (20)</td>
<td>24</td>
<td>High</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; RR, retrospective review; HD, hemodialysis; PreD, pre-dialysis; S, sevelamer; CA, calcium acetate; CC, calcium carbonate.

*18-month follow-up in the original study; 44 months median follow-up in the long-term outcome substudy.
Calcium binders and mortality

Fig. 2. (a) All-cause mortality by a phosphate binder of randomized trials. (b) All-cause mortality by a phosphate binder of randomized and non-randomized trials. (c) All-cause mortality by a phosphate binder of randomized trials excluding Block 2007.

treatment assignment; however, many of these trials had a high loss of patients to follow-up. The data are grouped by duration of follow-up at 6, 12, 18 and 24 months, and also by the longest follow-up duration for each study. Overall, the difference in the change in the calcium score from baseline to follow-up among subjects taking sevelamer compared to those taking calcium-based phosphate binders was −76.35 (95% CI −158.25–5.55). None of the trials reported on fractures or vascular compliance. To assess for the potential of publication bias, we examined a funnel plot using all-cause
Fig. 3. Cardiovascular events by a phosphate binder.

Fig. 4. Coronary artery calcification by a phosphate binder.

Table 2. Key design characteristics of studies reporting coronary calcification

<table>
<thead>
<tr>
<th>Study</th>
<th>Ca-based</th>
<th>Non-Ca-based</th>
<th>Reproducibility check</th>
<th>Technique</th>
<th>Slice thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chertow (2002)</td>
<td>24/94 (26%)</td>
<td>30/92 (33%)</td>
<td>None</td>
<td>EBCT C-150</td>
<td>3</td>
</tr>
<tr>
<td>Braun (2004)</td>
<td>13/59 (22%)</td>
<td>19/55 (35%)</td>
<td>None</td>
<td>EBCT C-150</td>
<td>3</td>
</tr>
<tr>
<td>Block (2007)</td>
<td>20/75 (27%)</td>
<td>19/73 (26%)</td>
<td>None</td>
<td>EBCT C-150</td>
<td>3</td>
</tr>
<tr>
<td>Qunibi (2008)</td>
<td>45/103 (44%)</td>
<td>32/100 (32%)</td>
<td>Yes</td>
<td>EBCT C-150 or C-300</td>
<td>3</td>
</tr>
<tr>
<td>Barreto (2008)</td>
<td>19/49 (39%)</td>
<td>11/52 (21%)</td>
<td>None</td>
<td>16-slice MsCT</td>
<td>3</td>
</tr>
<tr>
<td>Russo (2007)</td>
<td>2/30 (7%)</td>
<td>3/30 (10%)</td>
<td>None</td>
<td>Spiral CT</td>
<td>n/s</td>
</tr>
</tbody>
</table>

EBCT, electron beam computed axial tomography; MsCT, multislice computed axial tomography.

aAll trials used the Agatston score to score coronary calcification and all scans were read by a blinded assessor.
mortality as an outcome. Our plot was asymmetrical (not shown) and the bias value was $-1.25$ ($P = 0.07$).

**Discussion**

We found no statistically significant differences in all-cause mortality, cardiovascular mortality or vascular events among those randomized to receive calcium-based binders compared to those randomized to sevelamer. Our conclusions are limited due to an insufficient quantity and quality of trials. Indeed, we observed a trend favouring sevelamer for all outcomes and the 95% CI did not exclude a clinically important benefit. It is important to report this trend as it highlights the need for further studies to definitively determine the effects of calcium-based versus non-calcium-based binders on mortality in this high-risk population.

Most studies did not report on specific causes of mortality. However, 5 out of 10 reported on the coronary artery calcification score as an outcome in our meta-analysis; all of these studies were randomized and the maximum follow-up time ranged from 12 [20,22,25,26] to 24 [24] months. We found that compared to subjects randomized to calcium-based phosphate binders, those randomized to sevelamer had a trend towards a lower coronary artery calcification score at trial completion consistent with slowing in the progression of coronary artery calcification. Coronary calcification has been shown to be a valid surrogate outcome in non-ESRD cardiovascular research [33], and at least two prospective studies in ESRD show concordant results, such that higher vascular calcification scores predict higher mortality rates [2,20]. That said, direct data to support the concept that vascular calcification is a surrogate for death in patients with ESRD are lacking. While the clinical significance of the observed decrease in CACS is not conclusively known, the observation may be consistent with the concept that sevelamer may decrease mortality by decreasing the risk of cardiovascular events [34]. Only two studies reported specifically on cardiovascular events and while there was a trend towards a decreased risk of cardiovascular events in subjects randomized to sevelamer, the CIs were wide, therefore limiting our ability to draw any definitive conclusions.

That said, in vitro models have demonstrated that both elevated calcium and elevated phosphate increase atherosclerotic calcification and observational studies have demonstrated an increased risk of death in patients with renal disease given calcium supplementation [35]. These data are consistent with the hypothesis that calcium supplementation may increase atherosclerotic vascular disease and increase the risk of cardiovascular events. These data are further supported from studies in non-dialysis patients that demonstrate that increased calcium supplementation increases the risk of cardiovascular disease.

Our systematic review has several strengths and limitations. We conducted a broad search using standard Cochrane protocols. Further, while a number of the studies did have a high loss to follow-up, the dropout was not different between treatment groups and the studies were of a reasonable quality otherwise. Our funnel plot analyses did not demonstrate statistical evidence of publication bias; however, the small number of studies limits our power to draw definitive conclusions. Additional limitations include the fact that most of the studies included had a high or unclear risk of bias, and data on mortality and cause of death were limited to a few studies with few events resulting in insufficient power to make definitive conclusions about the causal relationship between calcium-based binders and death from cardiovascular disease. Similarly, the high loss to follow-up limited our assessment of secondary outcomes such as vascular calcification. None of the studies systematically assessed adverse events, and there was a moderate degree of heterogeneity between studies. Finally, we note that for cardiovascular outcomes including all-cause mortality, the follow-up was relatively short. As such, it seems likely that our estimates of the impact of non-calcium-based phosphate binders may be underestimated.

Cardiovascular events are an important cause of morbidity and mortality in patients with CKD and we describe a trend towards both a decrease in cardiovascular mortality and all measures of coronary artery calcification; however, we do not know if the decrease in mortality associated with sevelamer is due to an associated decrease in cholesterol, a decrease in coronary artery calcification, other pleiotropic effects of sevelamer or even an increase in mortality associated with calcium-based phosphate binders. We did not have sufficient data to examine these important clinical questions.

Clearly, future studies are needed in order to make definitive conclusions about the best type of phosphate binder for use in patients on haemodialysis as well as research on the mechanism by which non-calcium-based phosphate binders reduce mortality or, alternatively, how calcium-based binders increase mortality. In addition, research is needed to determine the effects of phosphate binders on survival in patients with earlier stages of CKD.

To help address some of these research needs, we have formed a collaborative review group to conduct an ongoing cumulative meta-analysis. Interested trialists can contact the corresponding author to provide individual patient data and join the group.

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Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

References


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