Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis

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CRD summary
This review concluded that non-calcium-based phosphate binders were associated with a decreased risk of all-cause mortality compared with calcium-based phosphate binders in patients with chronic kidney disease. This was a generally well-conducted review but the conclusions seem overly strong.

Authors' objectives
To update a prior meta-analysis that compared the effect of calcium-based and non-calcium-based phosphate binders on mortality in patients with chronic kidney disease.

Searching
A prior meta-analysis was the source of studies up to August 2008 (see Other Publications of Related Interest). PubMed, EMBASE, IPA, Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL were searched from August 2008 to October 2012. Search terms were reported in the paper and the full search strategy was available as an online appendix. There were no language restrictions. References of relevant reviews were searched. Abstracts and unpublished studies were excluded.

Study selection
Randomised and non-randomised studies that compared outcomes of calcium-based and non-calcium-based phosphate binders in patients with any stage of chronic kidney disease were eligible for inclusion. The primary outcome was all-cause mortality; secondary outcomes were cardiovascular events, vascular calcification, fractures and vascular compliance.

Where reported, mean age of study participants ranged from 47 to 68 years, up to half of the participants were female, 14.1% to 60.6% of the patients had diabetes and mean duration of dialysis ranged from 2.9 to 118 months. Most patients on non-calcium-based regimens received sevelamer; lanthanum was also used. Patients on a calcium-based regimen received calcium acetate and/or calcium carbonate. Most patients were receiving haemodialysis.

All reviewers independently selected abstracts for retrieval and two reviewers independently assessed full papers for inclusion; disagreements were resolved by discussion or referral to a third reviewer at the full-paper stage.

Assessment of study quality
Study quality was assessed by two independent reviewers using the Cochrane risk of bias tool; disagreements were resolved by discussion. Studies were considered at a low risk of bias occurs when all six domains were rated low.

Data extraction
Data were extracted by two independent reviewers to calculate relative risks (RR) for binary outcomes and mean differences for continuous outcomes, each with 95% confidence intervals (CI). Disagreements were resolved by discussion or referral to a third reviewer. Study authors were contacted to clarify data where necessary.

Methods of synthesis
Pooled relative risks or mean differences and 95% CI were calculated using a DerSimonian and Laird random-effects model. Heterogeneity was assessed using the I² statistic. The primary analysis included only randomised controlled trials (RCTs); non-randomised studies were included in a secondary analysis of all-cause mortality. Subgroup analyses investigated duration of follow-up, dialysis status and type of non-calcium-based phosphate binder. Odds ratios were calculated as a sensitivity analysis. Publication bias was investigated using a funnel plot, Egger's test and Duval's trim-and-fill method.

Results of the review
Eighteen studies (7,564 patients, range 31 to 2,103) were included in the review; 10 were included in the previous review and eight were new. Fourteen studies were RCTs, two were observational studies, one was a retrospective cohort study and one was a cross-sectional study. Follow-up ranged from zero (in a cross-sectional study) to 44 months. Risk of bias was considered to be low in five studies, high in six studies and unclear in three studies; the risk of bias tool was considered not applicable in four studies. Only one RCT was blinded.

Patients who received non-calcium-based phosphate binders had a statistically significant reduction of 22% in all-cause mortality compared with calcium-based phosphate binders (RR 0.78, 95% CI 0.61 to 0.98; I²=43%; 11 RCTs; 4,622 patients); results were similar in three non-RCTs (RR 0.89, 0.78 to 1.00; I²=0%). Results of subgroup analyses were reported.

Patients who received non-calcium-based phosphate binders had a statistically significant reduction in vascular calcification (mean difference in Agatston score -95.26, 95% CI -146.68 to -43.84; seven RCTs; I²=0%). No studies reported on fractures or vascular compliance.

There was some evidence of publication bias but the trim-and-fill method did not add new studies to the analysis.

**Authors’ conclusions**
Non-calcium-based phosphate binders were associated with a decreased risk of all-cause mortality compared with calcium-based phosphate binders in patients with chronic kidney disease.

**CRD commentary**
The review addressed a clear question supported by reproducible inclusion criteria. Several relevant sources were searched. There were no language restrictions. Unpublished studies were not included and this risked publication bias. Each stage of the review was conducted in duplicate which reduced risks of error and bias. Appropriate criteria were used to assess the quality of the RCTs; the quality of the non-RCTs was not assessed. The authors stated that RCTs were considered at a low risk of bias when all six domains were rated low on the Cochrane risk of bias tool; only one RCT reported blinding so it was unclear how five trials were rated as low risk of bias.

Methods of synthesis seemed appropriate. The two largest RCTs reported non-significant results but these trials were at a high risk of bias. It was unclear which domain these two RCTs failed so the importance of the bias and its potential impact on the results of those RCTs was uncertain and made the results of the meta-analysis difficult to assess.

This was a generally well-conducted review. The authors’ conclusion may be overly strong because RCTs with zero events in both arms were not considered in the pooled results (were these included the pooled estimate would have moved towards the line of no effect and the result would likely have become non-significant). Also the pooled results were affected by small studies with imprecise results.

**Implications of the review for practice and research**

**Practice:** The authors did not state implications for practice.

**Research:** The authors stated that further studies were needed to unequivocally show the effects of calcium-based versus non-calcium-based phosphate binders on mortality, to identify causes of mortality and to assess whether mortality differed by type of non-calcium-based phosphate binder. The authors stated that the mechanism of the benefits of non-calcium-based phosphate binders seems to be a slower progression of vascular calcification and the mechanism needed to be confirmed by studies of cardiovascular outcomes.

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