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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CRD summary
The review assessed the effects of calcium-based versus non-calcium-based phosphate binders on mortality, cardiovascular events and vascular calcification in patients with chronic kidney disease. Although no significant differences were found, the results did not exclude an important beneficial effect of non-calcium-based phosphate binders. The authors' conclusions are appropriately conservative given the quality of the included studies.

Authors' objectives
To assess the effects of calcium-based versus non-calcium-based phosphate binders on mortality, cardiovascular events and vascular calcification in patients with chronic kidney disease.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) (1980 to August 2008) and CINAHL (1982 to August 2008) were searched; full details of the search strategy were available in an online appendix. Bibliographies of published reviews were handsearched. Only published studies were eligible for inclusion. No language restrictions were applied.

Study selection
Randomised and non-randomised controlled trials that compared the effectiveness of calcium-based versus non-calcium-based phosphate binders were eligible for inclusion. Outcome inclusion criteria were not specified. The primary outcome was defined as all-cause mortality in randomised controlled trials (RCTs). Secondary outcomes were mortality, cardiovascular events (fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, sudden death), fractures, vascular calcification and vascular compliance in patients with chronic kidney disease.

In the included studies, where stated, participants had a mean age of 47 to 60 years and 17% to 52% were female. All studies except one study included patients on haemodialysis (one included pre-dialysis patients). No patients were on peritoneal dialysis. Follow-up ranged from five to 24 months; one study had an extended follow-up in a subsample of participants to 44 months. The non-calcium phosphate binder in all studies was sevelamer. The calcium-based binders used were calcium acetate and calcium carbonate.

All five reviewers independently reviewed the results of the search according to predefined selection criteria; discrepancies were resolved by consensus.

Assessment of study quality
Two reviewers independently reviewed each study according to the Cochrane Risk of Bias tool to rate studies on the basis of the domains of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. The overall risk of bias for each study was rated as low (all domains low risk), unclear (unclear for at least one domain) or high (high for at least one domain). Discrepancies were resolved by consensus. The reviewers were not blind to the study authors, institution or journal of publication.

Data extraction
Relative risks, odds ratios and mean differences for intervention and control groups were extracted.

Two reviewers independently extracted the data; disagreements were resolved by consensus and discussion with a third reviewer.

Methods of synthesis
Studies were combined in a meta-analysis using DerSimonian and Laird random-effects models to calculate pooled
relative risks and weighted mean differences (WMD). Heterogeneity was tested for using $X^2$ and $I^2$. Publication bias was assessed using a funnel plot and weighted regression.

Sensitivity analyses were conducted by including a non-randomised study, by excluding one trial due to methodological problems and by analysing odds ratios instead of relative risks.

**Results of the review**

Eight RCTs (2,873 participants) and one non-randomised study (1,377 participants) were included in the review. Validity assessment of the RCTs rated three studies as high risk, three as low risk and two as unclear.

**All cause mortality**: Based on the RCTs only, there was no significant difference in mortality between non calcium-based and calcium-based binders. There was some evidence of statistical heterogeneity ($p=0.09; I^2=47.8\%$). Inclusion of the non-randomised study and exclusion of one RCT did not substantially alter these results.

**Cardiovascular events**: Two trials showed no significant difference in cardiovascular events between non calcium-based and calcium-based binders. There was no evidence of statistical heterogeneity.

**Coronary artery calcification**: There was no evidence of any difference in coronary artery calcification between treatment and control groups either overall or at any specific time point (six, 12, 18 or 24 months follow-up).

The funnel plot was asymmetrical and there was a suggestion of publication bias ($p=0.07$).

**Authors’ conclusions**

Although no significant differences between the study groups was found, the results did not exclude an important beneficial effect; further RCTs were required.

**CRD commentary**

The review addressed a clear research question. Participant, intervention and study design criteria were all well defined. Outcome inclusion criteria were not specified. The search strategy appeared comprehensive for published studies; unpublished studies were not eligible for inclusion and the authors found a suggestion of publication bias. Attempts were made to limit errors and bias in the study selection, review and data abstraction processes.

The validity assessment was performed using an appropriate tool, but individual items for each study were not reported. The meta-analysis was appropriate, although no attempt was made to investigate the suggestion of statistical heterogeneity.

The quality of the included studies was mixed and the authors’ conclusions are appropriately conservative in the light of this.

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

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

**Research**: The authors stated that further RCTs were required as results were consistent with a clinically important benefit in favour of calcium-based binders. They recommended further research on the effects of phosphate binders on survival in patients with earlier stage chronic kidney disease.

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