Phosphate binders for preventing and treating bone disease in chronic kidney disease patients (Review)

Navaneethan SD, Palmer SC, Vecchio M, Craig JC, Elder GJ, Strippoli GFM

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 2

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Sankar D Navaneethan[1], Suetonia C Palmer[2], Mariacristina Vecchio[3], Jonathan C Craig[4], Grahame J Elder[5], Giovanni FM Strippoli[6]

[1]Department of Nephrology and Hypertension, Glickman Urological and Kidney institute, Cleveland Clinic, Cleveland, OH, USA. [2]Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand. [3]Clinical Pharmacology and Epidemiology, Mario Negri Sud Consortium, Santa Maria Imbaro, Italy. [4]a) Cochrane Renal Group, Centre for Kidney Research, The Children's Hospital at Westmead, b) Sydney School of Public Health, The University of Sydney, Sydney, Australia. [5]a) Department of Renal Medicine, Westmead Hospital, b) Osteoporosis and Bone Biology Program, Garvan Institute of Medical Research, Darlinghurst, Australia. [6]a) Mario Negri Sud Consortium, Santa Maria Imbaro (Ch), Italy, b) Sydney School of Public Health, University of Sydney, Australia, c) Diaverum Medical-Scientific Office, Lund, Sweden

Contact address: Sankar D Navaneethan, Department of Nephrology and Hypertension, Glickman Urological and Kidney institute, Cleveland Clinic, Cleveland, OH, 44195, USA. navanes@ccf.org. sankardass@hotmail.com.

Editorial group: Cochrane Renal Group.
Publication status and date: New, published in Issue 2, 2011.
Review content assessed as up-to-date: 1 March 2010.

Citation: Navaneethan SD, Palmer SC, Vecchio M, Craig JC, Elder GJ, Strippoli GFM. Phosphate binders for preventing and treating bone disease in chronic kidney disease patients. *Cochrane Database of Systematic Reviews* 2011, Issue 2. Art. No.: CD006023. DOI: 10.1002/14651858.CD006023.pub2.

ABSTRACT

Background

Phosphate binders are widely used to lower serum phosphorus levels in people with chronic kidney disease (CKD) but their impact in CKD remains controversial.

Objectives

To review the effects of various phosphate binders on biochemical and patient-level end-points in CKD stages 3 to 5D.

Search strategy

In March 2010 we searched MEDLINE, EMBASE, the Cochrane Renal Group's Specialised Register and CENTRAL for relevant studies.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs that assessed the effects of various phosphate binders in adults with CKD.

Data collection and analysis

Two authors independently reviewed search results and extracted data. Results were expressed as mean differences (MD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes with 95% confidence intervals (CI) using a random-effects model.

Main results

Sixty studies (7631 participants) were included. There was no significant reduction in all-cause mortality (10 studies, 3079 participants: RR 0.73, 95% CI 0.46 to 1.16), or serum calcium by phosphorus (Ca x P) product with sevelamer hydrochloride compared to calcium-based agents. There was a significant reduction in serum phosphorus (16 studies, 3126 participants: MD 0.23 mg/dL, 95% CI 0.04 to 0.42) and parathyroid hormone (PTH) (12 studies, 2551 participants; MD 56 pg/mL, 95% CI 26 to 84) but a significant increase in the risk of hypercalcaemia (12 studies, 1144 participants: RR 0.45, 95% CI 0.35 to 0.59) with calcium-based agents compared to sevelamer hydrochloride. There was a significant increase in the risk of adverse gastrointestinal events with sevelamer hydrochloride in comparison to calcium salts (5 studies, 498 participants: RR 1.58, 95% CI 1.11 to 2.25). Compared with calcium-based agents, lanthanum significantly reduced serum calcium (2 studies, 122 participants: MD -0.30 mg/dL, 95% CI -0.64 to -0.25) and the Ca x P product, but not serum phosphorus levels. The effects of calcium acetate on biochemical end-points were similar to those of calcium carbonate. The phosphorus lowering effects of novel agents such as ferric citrate, colestilan and niacinamide were only reported in a few studies.

Authors' conclusions

Available phosphate-binding agents have been shown to reduce phosphorus levels in comparison to placebo. However, there are insufficient data to establish the comparative superiority of novel non-calcium binding agents over calcium-containing phosphate binders for patient-level outcomes such as all-cause mortality and cardiovascular end-points in CKD.

PLAIN LANGUAGE SUMMARY

Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

People with chronic kidney disease (CKD) develop impaired excretion of the dietary phosphorus. This results in a condition known as mineral and bone disorder in chronic kidney disease (CKD-MBD). CKD-MBD is characterized by high bone turnover, increased musculoskeletal morbidity including bone pain and muscle weakness, and vascular calcification which may contribute to the high incidence of cardiovascular disease and associated deaths. Several agents such as phosphate binders, vitamin D compounds, and calcimimetics are widely used to slow the development and progression of CKD-MBD complications.

Several phosphate binders, including aluminium and calcium-containing agents, have been widely used since 1970. The use of newer non-calcium or aluminium-based agents, such as sevelamer hydrochloride compounds and lanthanum carbonate is increasing although the cost is greater than the older phosphate binders. The avoidance of calcium-based binding agents to lower phosphorus in CKD theoretically reduces the risk of vascular calcification and cardiovascular disease. The balance between calcium-free phosphate binders reducing clinical events in CKD versus their cost remains controversial. Recently released KDIGO guidelines recommend restricting the use of calcium-based binders in people with persistent or recurrent hypercalcaemia or arterial calcification, or both.

We identified 60 studies, enrolling 7631 participants comparing phosphate binders to placebo or other phosphate binders. There was no significant reduction in all-cause mortality (10 studies, 3079 participants) or serum calcium by phosphorus product with sevelamer hydrochloride compared to calcium-based agents. There was a significant reduction in phosphorus (16 studies, 3126 participants) and parathyroid hormone (12 studies, 2551 participants) levels, but a significant increase in the risk of hypercalcaemia (12 studies, 1144 participants) with calcium salts compared to sevelamer hydrochloride. There was a significant increase in the risk of adverse gastrointestinal events with sevelamer hydrochloride compared to calcium salts (5 studies, 498 participants). Compared with calcium-based agents, lanthanum significantly reduced serum calcium (2 studies, 122 participants) and the calcium by phosphorous product, but not serum phosphorus levels. The effects of calcium acetate on biochemical end-points were similar to those of calcium carbonate. The phosphorus lowering effects of novel agents such as ferric citrate, colestilan and niacinamide were only reported in a few studies.

Available phosphate-binding agents have been shown to reduce phosphorus levels in comparison to placebo. However, there are insufficient data to establish the comparative superiority of novel non-calcium binding agents over calcium-containing phosphate binders for patient-level outcomes such as all-cause mortality and cardiovascular end-points in CKD.

BACKGROUND

People with chronic kidney disease (CKD) develop impaired excretion of the dietary phosphorus load (Hurska 2008). This further leads to high parathyroid hormone (PTH) levels (Cozzolino 2005; Hurska 2008; Silver 2005) mediated by a rise in fibroblast growth factor 23 (FGF23) levels that reduce calcitriol levels (Gutierrez 2005) by both inhibiting calcitriol production and increasing calcitriol catabolism. The resulting mineral and bone disorder in CKD (CKD-MBD) is characterized by high bone turnover, exaggerated marrow fibrosis, and increased musculoskeletal morbidity including bone pain and muscle weakness. Epidemiological data have increasingly demonstrated an association between elevated serum phosphorus, PTH, and calcium caused by CKD and increased morbidity, mortality, hospitalisation, reduced quality of life and increased costs of care (Block 1998; Block 2004; Tentori 2008).

Over the past few decades, cardiovascular disease has accounted for over half of the deaths in people receiving dialysis (USRDS 2009). The development of vascular calcification in the media of arterial vessels, associated with an increased serum calcium by phosphorus (Ca x P) product, is advocated as a major contributing factor (Guerin 2001; Stevens 2004) to this increased mortality. Several agents such as phosphate binders, vitamin D compounds, and calcimimetics are widely used to retard the development and progression of CKD-MBD complications that include both renal osteodystrophy and vascular calcification.

Several phosphate binders, including aluminium and calcium-containing agents, have been widely used since 1970. Non-calcium or aluminium-based agents such as sevelamer hydrochloride compounds and lanthanum carbonate have recently become available. The use of sevelamer hydrochloride and lanthanum compounds is increasing in nephrology practice, although they incur greater cost than the older phosphate binders (St Peter 2008; St Peter 2009; USRDS 2009). The avoidance of calcium-based binding agents to lower phosphorus in CKD theoretically reduces the risk of an elevated serum Ca x P product, and consequently the risk of vascular calcification and cardiovascular disease. For control of hyperphosphataemia, the National Kidney Foundation Kidney Disease Outcomes Quality Initiatives (NKF-KDOQI) recommends the use of calcium-based binders in CKD stages 3 and 4 (glomerular filtration rate (GFR) 30 to 59 mL/min/1.73m² and 15 to 29 mL/min/1.73m², respectively), and both calcium-based and calcium and aluminium-free binders in CKD stages 5 and 5D (GFR < 15 mL/min/1.73m² and dialysis) (K/DOQI 2003). The utility of calcium-free phosphate binders in reducing clinical events in CKD, balanced against their cost, remains controversial (Salusky 2006; St Peter 2009). Recently released KDIGO guidelines recommend restricting the use of calcium-based binders in people with persistent or recurrent hypercalcaemia or arterial calcification, or both (KDIGO 2009).

OBJECTIVES

The aim of this review was to assess the benefits and harms of various phosphate binders in people with CKD with particular reference to biochemical end-points, musculoskeletal and cardiovascular morbidity, hospitalisation, and mortality. In particular we aimed to:

1. Evaluate the serum phosphorus lowering effect of aluminium salts, calcium salts, sevelamer hydrochloride, lanthanum carbonate, iron salts and magnesium-based phosphate binders.

2. Assess the impact of phosphate binders on biochemical end-points such as PTH, serum calcium, phosphorus, and Ca x P product. In addition, the influences of these drugs were assessed in relation to lipid profile, tissue calcification, and common symptoms such as pruritis and bone or muscle pain.

3. Assess the impact of these agents on bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DEXA) or quantitative computerised tomography (QCT), and on bone turnover and mineralization based on histomorphometry and fracture events.

4. Assess other clinical end-points such as incidence of cardiovascular events, number of hospital admissions, and all-cause mortality.

5. Assess the impact of various phosphate binders on vascular calcification events.

6. Characterise the adverse events and their incidence for individual phosphate binders.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth, or other predictable methods) of phosphate binders used for the control of hyperphosphataemia and CKD-MBD of any stage. Studies of phosphate binders, alone or in combination with other (non-randomised) co-interventions (for example vitamin D compounds) were included. The first phase of randomised cross-over studies was included. There were no language restrictions.

Types of participants

Inclusion criteria

People with CKD in stage 3, 4, 5 and 5D as defined by the K/DOQI guidelines (stage 3: GFR 30-59 mL/min; stage 4: GFR 15-29 mL/min; stage 5: GFR < 15 mL/min; stage 5D: on dialysis) and older than 18 years (K/DOQI 2003).

Exclusion criteria

Studies of participants with a kidney transplant were excluded as these studies are the subject of a separate review (Palmer 2007).

Types of interventions

Studies greater than eight weeks duration of phosphate binders such as aluminium hydroxide, calcium acetate, calcium carbonate, calcium ketoglutarate, sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, and magnesium carbonate compared with placebo or to other phosphate binder were included. Comparisons were categorised as:

1. Calcium salts versus other calcium salts or placebo or other agents.
2. Sevelamer versus calcium salts or placebo or other agents.
3. Lanthanum carbonate versus calcium salts or placebo or other agents.
4. Miscellaneous agents versus placebo or other agents.

Types of outcome measures

1. All-cause mortality, cardiovascular mortality, cardiovascular events, hospitalisation (incidence or duration of hospitalisation), or fracture (incidence of fracture at any site; vertebral compression fractures; fracture of femur, hip, and any long bones identified by radiographic studies).
2. Incidence and nature of treatment-related adverse effects including gastrointestinal (gastritis, diarrhoea, constipation, abdominal bloating), electrolyte imbalance (hypomagnesaemia, hyperkalaemia), accumulation of drug deposits as demonstrated by bone biopsies or anaemia.
3. Hypercalcaemia (defined as serum calcium level > 10.2 mg/dL or as defined by the study investigators)
4. Hyperphosphataemia.
5. Serum phosphorus (mg/dL), serum calcium (mg/dL), Ca x P product (mg^2/dL^2), PTH (intact (iPTH), or PTH (1-84)); alkaline phosphatase (IU/L), serum bicarbonate (mEq/L).
6. Total serum cholesterol (mg/dL).
7. Vascular calcification, soft tissue or valvular calcification, or incidence of calciphylaxis.
8. Bone mineral density assessed by DEXA or QCT (change in BMD using Z-scores or per cent change (g/cm^2) at the lumbar spine, femoral neck, or radius).
9. Bone turnover and mineralisation based on histomorphometry and histology.

Search methods for identification of studies

Relevant studies were obtained from the following sources.

Electronic searches

1. The Cochrane Renal Group's specialised register using keywords relevant to this review. The register is populated using the following strategies:

i) Screening of weekly Ovid MEDLINE AutoAlerts using a search strategy covering the scope of the Group (see the Renal Group's module under Specialised Register at http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/RENAL/frame.html) plus the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008).

ii) Quarterly searches of NEW records in the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* using a search strategy covering the scope of the Group.

iii) Records handsearched by the Renal Group. The Renal Group has undertaken extensive handsearching of renal-related journals and conference proceedings, therefore we did not specifically search conference proceedings for this review. For a full list of journals and conference proceedings handsearched by the Renal Group use the link to its module (Renal Group 2010).

2. MEDLINE (from 1966) using the optimally sensitive strategy developed for The Cochrane Collaboration to identify RCTs (Lefebvre 2008) with a specific search strategy developed with input from the Trial Search Coordinator.
3. EMBASE (from 1980) using a search strategy adapted from that developed for The Cochrane Collaboration to identify RCTs (Lefebvre 2008) together with a specific search strategy developed with input from the Trial Search Coordinator.

See Appendix 1 for search terms used.
Date of search: March 2010

Searching other resources

Reference lists of nephrology textbooks, review articles, and relevant studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may have been relevant to the review. The titles

and abstracts were screened independently by two authors, who discarded studies that were not applicable. Studies and reviews that might have included relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Data were extracted on the characteristics of participants, interventions, comparisons, and the outcomes listed above. Authors were contacted if data relating to mortality, phosphorus, calcium, PTH, or Ca x P product were not available or not reported in the published reports. Discrepancies between the assessments of the two data extractors were resolved by discussion with an arbitrator

Assessment of risk of bias in included studies

The quality of studies to be included was assessed independently by two authors, without blinding to authorship or journal, using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by discussion with a third author. The quality items assessed were allocation concealment; blinding of investigators, participants, outcome assessors, and data analysis; intention-to-treat analysis and completeness to follow-up (see Appendix 2).

Measures of treatment effect

Dichotomous data were analysed using the risk ratio (RR) and its 95% confidence interval (CI). Where continuous measurements of outcomes were used, the mean difference (MD) and its 95% CI were computed.

Dealing with missing data

Any further information (relating to serum phosphorus, calcium, PTH, and mortality) required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review.

Assessment of heterogeneity

Heterogeneity across included studies was analysed by visual analysis of the forest plot and formally using the heterogeneity Chi² and I² statistic (Higgins 2003).

Assessment of reporting biases

We had planned to examine for publication bias using a funnel plot, however there were insufficient studies for any of the comparison groups (Higgins 2008).

Data synthesis

Risk estimates from individual studies were pooled using the Der Simonian-Laird random-effects model (Dersimonian 1986).

Subgroup analysis and investigation of heterogeneity

Sources of heterogeneity that were explored in the subgroup analyses were: older versus newer phosphate binding agents; baseline serum PTH levels; baseline serum phosphorus levels; type of calcium assay used in the study; use of washout of phosphate binder; study duration; quality items including allocation concealment, blinding, use of intention-to-treat analysis; number of participants lost to follow-up; and number of study participants.

RESULTS

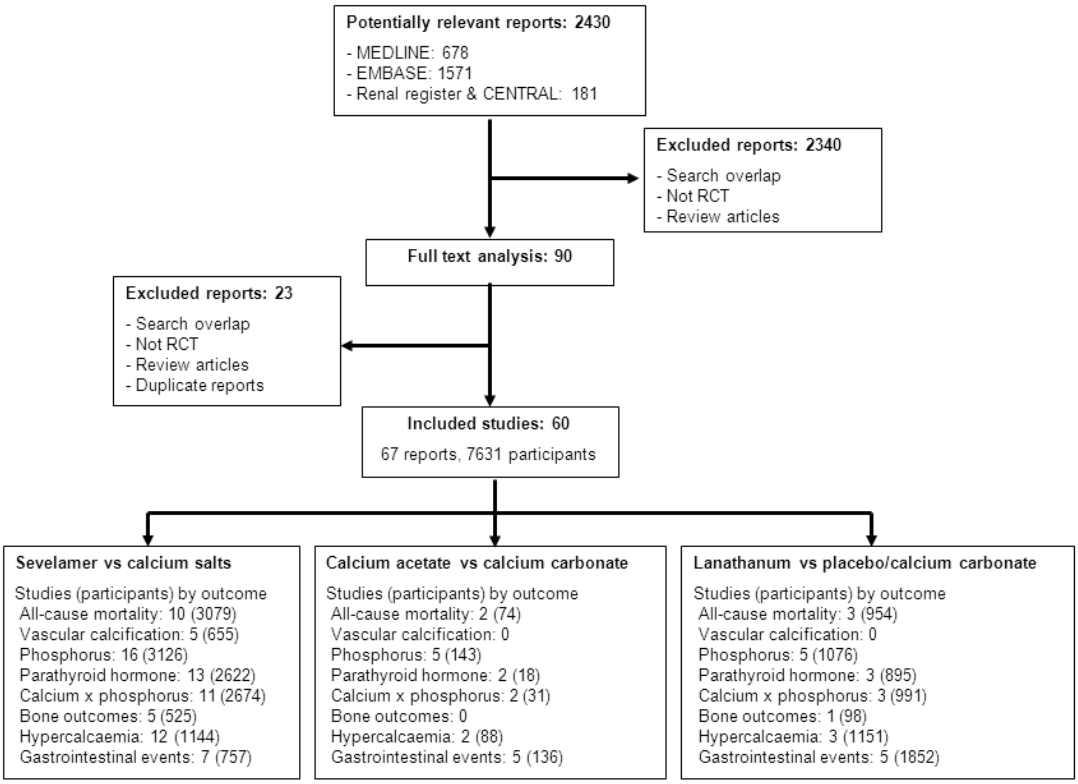
Description of studies

See: Characteristics of included studies.

Results of the search

The combined search of *The Cochrane Library*, MEDLINE, and EMBASE identified 2381 citations, of which 2298 were excluded after title and abstract review (Figure 1). Full-text assessment of 90 potentially relevant articles identified 60 eligible studies reported in 67 publications and enrolling 7631 participants (Al-Baaj 2005; Almirall 1994; BRiC Study 2008 (two reports); Birck 1999; Bleyer 1999; Block 2005 (two reports); Borrego 2000; Bro 1998; Caravaca 1992; CARE Study 2004; CARE-2 Study 2008; Cheng 2008; Chertow 1997; Chertow 1999; Chertow 2002 (four reports); Chiang 2005; DCOR Study 2007; De Santo 2006; Deuber 2003a; D'Haese 2003; Emmett 1991; Evenepoel 2009; Fan 2009; Ferreira 2008; d'Almeida Filho 2000; Finn 2004 (two reports); Fischer 2006; Gallieni 2005; Hervas 2003; Hutchison 2005 (two reports); Itoh 2008; Ittel 1991; Janssen 1996; Jespersen 1991; Joy 2003; Kinugasa 2001; Koiwa 2005a; Kurihara 2005; Liu 2006; Malluche 2008; McIntyre 2009; FORESEE Study 2008; Pflanz 1994; Phelps 2002; Ring 1993; Roxe 1989; Rudnicki 1994; Russo 2007; Sadek 2003; Saif 2007; Salusky 1991; Schaefer 1991; Shaheen 2004; Shigematsu 2008; Spasovski 2006; Spiegel 2007; Sprague 2009a; Sprague 2009b; Tzanakis 2008; Yang 2002). Authors of eight studies responded to requests for additional data or clarification of study methods.

Figure 1. Flow chart showing study selection procedure



Included studies

Characteristics of the participants and the interventions of the included studies are detailed in the Characteristics of included studies.

Four different groups of studies were identified.

- Any calcium salt versus another calcium salt, placebo, or different doses of the same calcium salt (13 studies, 501 participants):
  - Eight studies (371 participants) compared calcium acetate to calcium carbonate (Almirall 1994; Borrego 2000; Caravaca 1992; Emmett 1991; d'Almeida Filho 2000; Pflanz 1994; Ring 1993; Saif 2007).
  - Two studies (47 participants) compared calcium ketoglutarate to calcium carbonate (Birck 1999; Bro 1998).
  - One study (18 participants) compared calcium salts to placebo (Rudnicki 1994).
  - Two studies (65 participants) compared different doses of calcium acetate (Phelps 2002; Schaefer 1991).

- Sevelamer hydrochloride versus calcium salts or placebo (21 studies, 4045 participants):
  - Six studies (546 participants) compared sevelamer hydrochloride with calcium acetate (BRiC Study 2008; Bleyer 1999; Evenepoel 2009; Koiwa 2005a; Liu 2006; Sadek 2003).
  - Seven studies (703 participants) compared sevelamer hydrochloride with calcium carbonate (De Santo 2006; Ferreira 2008; Gallieni 2005; Kinugasa 2001; CARE Study 2004; Russo 2007; Shaheen 2004).
  - Two studies (157 participants) compared sevelamer hydrochloride directly with sevelamer hydrochloride and calcium carbonate (Chertow 1999; Hervas 2003).
  - Three studies (2369 participants) compared sevelamer hydrochloride to calcium acetate, calcium carbonate, or both (Block 2005; Chertow 2002; DCOR Study 2007).
  - One study (203 participants) compared sevelamer hydrochloride plus atorvastatin to calcium acetate plus atorvastatin (CARE-2 Study 2008).
  - One study (31 participants) compared sevelamer carbonate powder to sevelamer hydrochloride tablets (Fan 2009).
  - One study (36 participants) compared sevelamer hydrochloride to placebo (Chertow 1997).

- Studies evaluating lanthanum carbonate (12 studies, 2541 participants):
  - Four studies (1181 participants) compared lanthanum carbonate to calcium carbonate (D'Haese 2003; Hutchison 2005; Shigematsu 2008; Spasovski 2006).
  - Five studies (454 participants) compared lanthanum carbonate to placebo or different doses of lanthanum carbonate (Al-Baaj 2005; Chiang 2005; Finn 2004; Joy 2003; Sprague 2009a).
  - Three studies (906 participants) compared lanthanum carbonate to sevelamer hydrochloride and calcium salts (Malluche 2008; FORESEE Study 2008; Sprague 2009b).

- Other agents (14 studies, 544 participants):
  - Four studies (105 participants) compared aluminium and calcium salts (Ittel 1991; Janssen 1996; Jespersen 1991; Salusky 1991);
  - One study (30 participants) compared aluminium hydroxide and sucralfate (Roxe 1989).
  - One study (55 participants) compared ferric citrate to calcium carbonate in haemodialysis patients (Yang 2002).
  - One study (46 participants) compared MCI-196 (colestilan) to placebo (Kurihara 2005).
  - One study (24 participants) compared once daily sevelamer hydrochloride to thrice daily sevelamer hydrochloride (Fischer 2006);
  - One study (33 participants) compared niacinamide to placebo (Cheng 2008).
  - One study (30 participants) compared magnesium carbonate plus calcium carbonate to calcium acetate (Spiegel 2007).
  - One study (62 participants) compared sevelamer hydrochloride plus calcium carbonate to colestimide plus calcium carbonate (Itoh 2008).
  - One study (63 participants) compared iron-magnesium hydroxycarbonate to placebo (McIntyre 2009).
  - One study (46 participants) compared magnesium carbonate to calcium carbonate (Tzanakis 2008).
  - One study (50 participants) compared calcium carbonate to calcium acetate plus magnesium carbonate (Deuber 2003a).

Four studies included people with CKD stages 3 and 4 (Borrego 2000; Phelps 2002; Russo 2007; Sprague 2009a) and the rest enrolled haemodialysis patients. The majority of studies were of short duration (1 to 18 months of treatment administration) except for the Dialysis Clinical Outcomes Revisited (DCOR) study (DCOR Study 2007), which analysed the efficacy of phosphate binders to reduce serum phosphorus, where 42% of participants had a follow-up of more than 24 months. The number of participants ranged from 10 to 2100 with 27/60 (45%) of studies enrolling fewer than 100 participants. Most studies co-administered vitamin D compounds and the route of administration of these agents (IV or oral) varied among the studies. The assays used to measure PTH also differed in the included studies. Most studies defined hypercalcaemia as serum calcium > 10.2 mg/dL, some used > 10.5 mg/dL and others used > 11.0 mg/dL as the cut-off.

Risk of bias in included studies

Reported study quality was variable.

- Allocation concealment was adequate in 11/60 (18%) studies and unclear in other studies.
- Participants and investigators were blinded in 10/60 (17%) studies and outcome assessors were blinded in none of the studies.
- Only 13/60 (22%) studies were analysed on an intention-to-treat basis.
- The number of participants lost to follow-up ranged from 0% to 31% but did not differ between the treatment and control groups of the studies.

See Characteristics of included studies - risk of bias tables.

Effects of interventions

Vascular calcification and bone outcomes

Vascular calcification

Five studies reported the effects of sevelamer hydrochloride and calcium salts on vascular calcification (BRiC Study 2008; Block 2005; Chertow 2002; Qunibi 2008; Russo 2007) (Table 1). Chertow 2002 reported slower progression of coronary, aortic, and heart valve calcification (measured by electron beam computed tomography) with the use of sevelamer hydrochloride in comparison to calcium acetate, using the Agatston scoring system. Similarly, Block 2005 showed decreased progression of coronary artery calcification with sevelamer hydrochloride compared to calcium salts in incident haemodialysis patients. By contrast, Qunibi 2008 compared sevelamer hydrochloride plus atorvastatin to calcium acetate plus atorvastatin and reported similar coronary artery calcification progression in both groups. BRiC Study 2008 recorded coronary artery calcium scores in 101 dialysis patients (using a modified Agatston scoring system) and reported no difference in coronary artery calcification progression between the sevelamer hydrochloride and calcium groups (P = 0.59). The included studies used different scoring systems to assess vascular calcification and thus could not be pooled.

Bone outcomes

Lanthanum carbonate reduced the number of participants developing low turnover bone disease when compared to calcium carbonate (Spasovski 2006), and resulted in an improvement of bone volume in comparison to standard phosphate binder therapy (Malluche 2008) (Table 1). Aluminium-like effects on bone were not noted in follow-up studies that assessed the safety of lanthanum carbonate (Spasovski 2006). Based upon electron beam computer tomography results, BRiC Study 2008 reported a significant reduction in trabecular bone attenuation with sevelamer hydrochloride, and a trend towards reduction in cortical bone attenuation (P = 0.05) in thoracic vertebrae, compared to calcium salts. In Schaefer 1991, enrolling 101 dialysis patients, there was no difference in bone remodelling between sevelamer hydrochloride and calcium groups at the end of one-year follow-up. Ferreira 2008 reported increased bone formation and improved trabecular architecture but with no significant change in bone turnover or mineralization with sevelamer hydrochloride in comparison to calcium salts. A formal meta-analysis could not be performed for incidence of fracture.

Patient-centred end-points (all-cause mortality, hospitalisation, adverse events)

Calcium salts versus placebo

All-cause mortality

No deaths were reported in one short-term study comparing calcium acetate to placebo (18 participants) (Rudnicki 1994).

Hospitalisation

This outcome was not reported.

Hypercalcaemia

No hypercalcaemic events were reported in either the calcium acetate or placebo groups (1 study, 18 participants) (Rudnicki 1994).

Other adverse events

Gastrointestinal side effects were not reported in either the calcium acetate or placebo groups (1 study, 18 participants) (Rudnicki 1994).

Calcium acetate versus calcium carbonate

All-cause mortality

There was no significant reduction in the risk of all-cause mortality with calcium acetate in comparison to calcium carbonate (Analysis 2.1 (2 studies, 74 participants): RR 1.13, 95% CI 0.07 to 17.30) (Almirall 1994; Caravaca 1992).

Hospitalisation

This outcome was not reported.

Hypercalcaemia

There was no significant difference in the incidence of hypercalcaemia between calcium acetate and calcium carbonate (Analysis 2.2 (2 studies, 88 participants): RR 1.08, 95% CI 0.11 to 10.99). Significant heterogeneity was identified (Chi^2 = 2.46, I^2 = 59%) (Caravaca 1992; Pflanz 1994).

Other adverse events

There was no significant difference in the occurrence of gastritis between calcium acetate and calcium carbonate (Analysis 2.3.1 (1 study, 30 participants): RR 1.25, 95% CI 0.41 to 3.77) (d'Almeida Filho 2000).

There was no significant difference in the occurrence of diarrhoea events between calcium acetate and calcium carbonate (Analysis 2.3.2 (2 studies, 53 participants): RR 1.65, 95% CI 0.22 to 12.56). No significant heterogeneity was identified (Chi^2 = 0.32, I^2 = 0%) (d'Almeida Filho 2000; Pflanz 1994).

Similarly there was no significant difference in the occurrence of constipation events between calcium acetate and calcium carbonate (Analysis 2.3.3 (2 studies, 53 participants): RR 1.16, 95% CI 0.38 to 3.52). No significant heterogeneity was identified (Chi^2 = 0.50, I^2 = 0%) (d'Almeida Filho 2000; Pflanz 1994).

Calcium load

We planned to assess the daily calcium load with various calcium-based phosphate binders. However, studies did not report calcium intake in a consistent manner that could be pooled in a meta-analysis.

Calcium ketoglutarate versus other calcium salts

All-cause mortality

There were no deaths reported in two short-term studies comparing calcium ketoglutarate to other calcium salts (47 participants) (Birck 1999; Bro 1998).

Hospitalisation

This outcome was not reported.

Hypercalcaemia

This outcome was not reported.

Other adverse events

There was no significant difference in the occurrence of gastrointestinal events between calcium ketoglutarate and other calcium salts (Analysis 3.2 (1 study, 17 participants): RR 5.00, 95% CI 0.65 to 38.42) (Bro 1998).

Sevelamer hydrochloride versus placebo

All-cause mortality

There were no deaths reported in one short-term study comparing sevelamer hydrochloride to placebo (36 participants) (Chertow 1997).

Hospitalisation

This outcome was not reported.

Hypercalcaemia

This outcome was not reported.

Other adverse events

There was no significant difference in the occurrence of gastritis between sevelamer hydrochloride and placebo (Analysis 4.2.1 (1 study, 36 participants): RR 1.00, 95% CI 0.10 to 9.96) (Chertow 1997).

There was no significant difference in the occurrence of diarrhoea events between sevelamer hydrochloride and placebo (Analysis 4.2.2 (1 study, 36 participants): RR 0.17, 95%CI 0.01 to 3.96) (Chertow 1997).

Sevelamer hydrochloride versus calcium salts

All-cause mortality

There was no significant reduction in the risk of all-cause mortality with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.1 (10 studies, 3079 participants): RR 0.73, 95% CI 0.46 to 1.16). No significant heterogeneity was identified (Chi^2 = 8.81, I^2 = 43%) (BRiC Study 2008; Bleyer 1999; Block 2005; CARE Study 2004; CARE-2 Study 2008; Chertow 2002; DCOR Study 2007; Ferreira 2008; Hervas 2003; Koiwa 2005a).

Hospitalisation

There was no difference in the number hospitalised in 52 weeks between sevelamer hydrochloride and calcium salts (P = 0.23) (Chertow 2002). There was no statistically significant difference in the number of days hospitalised/patient-year between sevelamer hydrochloride and calcium salts (P = 0.09) (DCOR Study 2007).

Hypercalcaemia

There was a significant reduction in the incidence of hypercalcaemia with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.2 (12 studies, 1144 participants): RR 0.45, 95% CI 0.35 to 0.59No significant heterogeneity was identified (Chi^2 = 9.05, I^2 = 0%) (Bleyer 1999; Block 2005; CARE Study 2004; CARE-2 Study 2008; Chertow 2002; De Santo 2006; Evenepoel 2009; Gallieni 2005; Hervas 2003; Liu 2006; Sadek 2003; Shaheen 2004).

Other adverse events

There was no significant increase in the occurrence of nausea with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.3.1 (1 study, 203 participants): RR 1.03, 95% CI 0.57 to 1.86) (CARE-2 Study 2008).

There was no significant increase in the occurrence of diarrhoea events with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.3.2 (1 study, 203 participants): RR 1.03, 95% CI 0.55 to 1.95) (CARE-2 Study 2008).

Similarly there was no significant increase in the occurrence of abdominal bloating events with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.3.3 (1 study, 56 participants): RR 2.33, CI 0.49 to 11.01) (Koiwa 2005a).

There was a significant increase in the occurrence of constipation with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.3.4 (2 studies, 259 participants): RR 2.63, 95% CI 1.29 to 5.35). No significant heterogeneity was identified (Chi^2 = 0.40, I^2 = 0%) (CARE-2 Study 2008; Koiwa 2005a).

Among studies that reported combined gastrointestinal events there was a higher number of gastrointestinal events with sevelamer hydrochloride compared to calcium salts (Analysis 5.3.5 (5 studies, 498 participants): RR 1.58, 95% CI 1.11 to 2.25) (Bleyer 1999; Evenepoel 2009; Ferreira 2008; Gallieni 2005; Liu 2006).

Lanthanum carbonate versus placebo

All-cause mortality

There were no deaths reported in two studies comparing lanthanum carbonate with placebo, with no deaths reported in two studies (154 participants) (Chiang 2005; Joy 2003).

Hospitalisation

This outcome was not reported.

Hypercalcaemia

This outcome was not reported.

Other adverse events

There was no significant difference in gastrointestinal toxicity with lanthanum carbonate in comparison to placebo (Analysis 6.2.4 (2 studies, 154 participants): RR 1.05, 95% CI 0.45 to 2.45). No significant heterogeneity was identified (Chi^2 = 0.30, I^2 = 0%) (Chiang 2005; Joy 2003).

Lanthanum carbonate versus calcium carbonate

All-cause mortality

There were no deaths reported in the two studies comparing lanthanum carbonate with calcium carbonate (351 participants) (D'Haese 2003; Shigematsu 2008).

Hospitalisation

This outcome was not reported.

Hypercalcaemia

There was a significant reduction in hypercalcaemic events with lanthanum carbonate compared with calcium carbonate (Analysis 7.2 (2 studies, 351 participants): RR 0.17, 95% CI 0.09 to 0.31). No significant heterogeneity was identified (Chi^2 = 0.36, I^2 = 0%) (D'Haese 2003; Shigematsu 2008).

Other adverse events

There was no significant difference in gastrointestinal toxicity with lanthanum carbonate in comparison to calcium carbonate (Analysis 7.2.4 (1 study, 98 participants): RR 1.04, 95% CI 0.70 to 1.55) (D'Haese 2003).

Other comparisons

All-cause mortality

There were no deaths reported in four short-term studies comparing aluminium salts to other agents (Ittel 1991; Janssen 1996; Jespersen 1991; Roxe 1989). Similarly, one short-term study comparing ferric citrate and calcium carbonate (Yang 2002) and single studies comparing niacinamide to placebo (Cheng 2008), magnesium carbonate to calcium acetate (Spiegel 2007), lanthanum carbonate to placebo (Sprague 2009a) and sevelamer carbonate powder to sevelamer hydrochloride (Fan 2009) did not report any deaths. One patient in the placebo group died while no deaths were reported in the iron-magnesium group in McIntyre 2009.

Biochemical and other surrogate end-points

Calcium salts versus placebo

Phosphorus

There were significantly lower phosphorus levels with calcium salts in comparison to placebo (Analysis 1.3 (1 study, 18 participants): MD -0.82 mg/dL, 95% CI -1.24 to -0.40) (Rudnicki 1994).

Calcium

There were significantly higher calcium levels with calcium salts in comparison to placebo (Analysis 1.4 (1 study, 18 participants): MD 0.52 mg/dL, 95% CI 0.13 to 0.91) (Rudnicki 1994).

Other outcomes

Relevant data were not available from the included studies to conduct meta-analyses for iPTH, Ca x P product, alkaline phosphatase, serum bicarbonate, total cholesterol or total calcium intake.

Calcium acetate versus calcium carbonate

Phosphorus

There was no significant difference in phosphorus levels with calcium acetate in comparison to calcium carbonate (Analysis 2.4 (5 studies, 143 participants): MD -0.19 mg/dL, 95%CI -0.61 to 0.24). No significant heterogeneity was identified (Chi^2 = 2.13, I^2 = 0%) (Almirall 1994; Borrego 2000; Caravaca 1992; d'Almeida Filho 2000; Pflanz 1994).

Calcium

There was no significant difference in calcium levels with calcium acetate in comparison to calcium carbonate (Analysis 2.5 (5 studies, 143 participants): MD -0.09 mg/dL, 95% CI -0.35 to 0.17). No significant heterogeneity was identified (Chi^2 = 5.00, I^2 = 20%) (Almirall 1994; Borrego 2000; Caravaca 1992; d'Almeida Filho 2000; Pflanz 1994).

Ca x P product

There was no significant difference in Ca x P product with calcium acetate in comparison to calcium carbonate (Analysis 2.6 (2 studies, 31 participants): MD -4.92 mg^2/dL^2, 95% CI -10.03 to 0.19). Significant heterogeneity was identified (Chi^2 = 3.26, I^2 = 69%) (Almirall 1994; Pflanz 1994).

PTH

There was no significant difference in PTH levels with calcium acetate in comparison to calcium carbonate (Analysis 2.7 (1 study, 16 participants): MD -52.00 pg/mL, 95% CI -211.02 to 107.02) (Borrego 2000).

Serum bicarbonate

There was no significant difference in serum bicarbonate levels with calcium acetate in comparison to calcium carbonate (Analysis 2.8 (2 studies, 53 participants): MD 0.21 mEq/L, 95% CI -1.32 to 1.74). No significant heterogeneity was identified (Chi^2 = 1.24, I^2 = 19%) (d'Almeida Filho 2000; Pflanz 1994).

Serum alkaline phosphatase

There was no significant difference in serum alkaline phosphatase levels with calcium acetate in comparison to calcium carbonate (Analysis 2.9): 4 studies, 74 participants; MD 1.42 IU/L, 95% CI -8.99 to 11.82). No significant heterogeneity was identified (Chi^2 = 0.37, I^2 = 0%) (Almirall 1994; Borrego 2000; Janssen 1996; Pflanz 1994).

Total cholesterol

Relevant data were not available to conduct a meta-analyses for this outcome.

Calcium ketoglutarate versus other calcium salts

Phosphorus

There was no significant difference in phosphorus levels with calcium ketoglutarate in comparison to other calcium salts (Analysis 3.3 (2 studies, 48 participants): MD -0.10 mg/dL, 95% CI -0.32 to 0.12). No significant heterogeneity was identified (Chi^2 = 0.02, I^2 = 0%) (Birck 1999; Bro 1998).

Calcium

There were significantly lower ionised calcium levels with calcium ketoglutarate in comparison to other calcium salts (Analysis 3.4 (1 study, 20 participants): MD -0.40 mg/dL, 95% CI -0.49 to -0.31) (Bro 1998).

Ca x P product

There was a significant decrease in Ca x P product with calcium ketoglutarate in comparison to other calcium salts (Analysis 3.5 (1 study, 20 participants): MD -4.50 mg^2/dL^2, 95% CI -5.65 to -3.35) (Bro 1998).

PTH

There was no significant difference in PTH levels with calcium ketoglutarate in comparison to other calcium salts (Analysis 3.6 (1 study, 20 participants): MD -35.00 pg/mL; 95% CI -155.07 to 85.07) (Bro 1998).

Serum bicarbonate

There was a significantly higher serum bicarbonate levels with calcium ketoglutarate in comparison to other calcium salts (Analysis 3.7 (2 studies, 62 participants): MD 1.66 mEq/L, 95% CI 1.03 to 2.29). No significant heterogeneity was identified (Chi^2 = 0.13, I^2 = 0%) (Birck 1999; Bro 1998).

Other outcomes

Relevant data were not available to conduct a meta-analysis for the outcomes alkaline phosphatase and total cholesterol.

Sevelamer hydrochloride versus placebo

Phosphorus

There were significantly lower serum phosphorus levels with sevelamer hydrochloride in comparison to placebo (Analysis 4.3 (1 study, 36 participants): MD -1.80 mg/dL, 95% CI -3.32 to -0.28) (Chertow 1997).

Calcium

There was no significant difference in calcium levels with sevelamer hydrochloride in comparison to placebo (Analysis 4.4 (1 study, 36 participants): MD -0.10 mg/dL, 95% CI -0.52 to 0.32) (Chertow 1997).

Serum bicarbonate

There was no significant difference in serum bicarbonate levels with sevelamer hydrochloride in comparison to placebo (Analysis 4.5 (1 study, 36 participants): MD -0.50 mEq/L, 95% CI -2.53 to 1.53) (Chertow 1997).

Total cholesterol

There were significantly lower total cholesterol levels with sevelamer hydrochloride in comparison to placebo (Analysis 4.6 (1 study, 36 participants): -28.00 mg/dL, 95% CI -51.58 to -4.42) (Chertow 1997).

Other outcomes

Relevant data were not available to conduct meta-analyses for iPTH, Ca x P product and alkaline phosphatase.

Sevelamer versus calcium salts

Phosphorus

There were significantly higher phosphorus levels with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.4 (16 studies, 3126 participants): MD 0.23 mg/dL, 95% CI 0.04 to 0.42). Significant heterogeneity was identified (Chi^2 = 32.32, I^2 = 57%) (Bleyer 1999; Block 2005; CARE Study 2004; CARE-2 Study 2008; Chertow 2002; DCOR Study 2007; Gallieni 2005; Evenepoel 2009; Ferreira 2008; Hervas 2003; Kinugasa 2001; Koiwa 2005a; Russo 2007; Sadek 2003; Shaheen 2004).

Calcium

There were significantly lower calcium levels with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.5 (15 studies, 3039 participants): MD -0.34 mg/dL, 95% CI -0.45 to -0.24). Significant heterogeneity was identified (Chi^2 = 29.13, I^2 = 55%) (BRiC Study 2008; Bleyer 1999; Block 2005; CARE Study 2004; CARE-2 Study 2008; Chertow 2002; DCOR Study 2007; Evenepoel 2009; Ferreira 2008; Gallieni 2005; Hervas 2003; Kinugasa 2001; Koiwa 2005a; Russo 2007; Sadek 2003; Shaheen 2004).

Ca x P product

There was no significant difference in Ca x P product levels with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.6 (11 studies, 2674 participants): MD 0.86 mg^2/dL^2, 95% CI -0.69 to 2.40). Significant heterogeneity was identified (Chi^2 = 15.02, I^2 = 33%) (Bleyer 1999; Block 2005; CARE Study 2004; CARE-2 Study 2008; Chertow 2002; DCOR Study 2007; Evenepoel 2009; Gallieni 2005; Hervas 2003; Russo 2007; Shaheen 2004).

PTH

There were significantly higher PTH levels with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.7 (12 studies, 1009 participants): MD 59.74 pg/mL, 95% CI 27.47 to 92.02). No significant heterogeneity was identified (Chi^2 = 10.16, I^2 = 21%) (BRiC Study 2008; Bleyer 1999; Block 2005; CARE Study 2004; CARE-2 Study 2008; Chertow 2002; De Santo 2006; Hervas 2003; Kinugasa 2001; Koiwa 2005a; Sadek 2003; Shaheen 2004).

Serum bicarbonate

There were significantly lower serum bicarbonate levels with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.8 (5 studies, 381 participants): MD -1.43 mEq/L, 95% CI -2.07 to -0.79). No significant heterogeneity was identified (Chi^2 = 1.75, I^2 = 0%) (CARE Study 2004; CARE-2 Study 2008; Ferreira 2008; Russo 2007; Sadek 2003).

Serum alkaline phosphatase

There was no significant difference in serum alkaline phosphatase levels with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.9 (4 studies, 187 participants): MD 10.13 IU/L, 95% CI -11.28 to 31.53). No significant heterogeneity was identified (Chi^2 = 1.59, I^2 = 0%) (BRiC Study 2008; Bleyer 1999; Hervas 2003; Koiwa 2005a).

Total cholesterol

There were significantly lower total cholesterol levels with sevelamer hydrochloride in comparison to calcium salts (Analysis 5.10 (10 studies, 1705 participants): MD -19.16 mg/dL, 95% CI -27.42 to -10.90). Significant heterogeneity was identified (Chi^2 = 24.82, I^2 = 64%) (BRiC Study 2008; Bleyer 1999; Block 2005; Chertow 2002; DCOR Study 2007; Ferreira 2008; Hervas 2003; Koiwa 2005a; Russo 2007; Sadek 2003).

Lanthanum carbonate versus placebo

Phosphorus

There were significantly lower phosphorus levels with lanthanum carbonate in comparison to placebo (Analysis 6.3 (2 studies, 154 participants): MD -2.01 mg/dL, 95% CI -2.52 to -1.50). No significant heterogeneity was identified (Chi^2 = 0.13, I^2 = 0%) (Chiang 2005; Joy 2003).

Calcium

There were significantly higher calcium levels with lanthanum carbonate in comparison to placebo (Analysis 6.4 (1 study, 93 participants): MD 0.35 mg/dL, 95% CI 0.04 to 0.66) (Chiang 2005).

Ca x P product

There was a significantly lower Ca x P product with lanthanum carbonate in comparison to placebo (Analysis 6.5 (1 study, 93 participants): MD -14.20 mg^2/dL^2, 95% CI -21.03 to -7.37) (Chiang 2005).

PTH

There were significantly lower PTH levels with lanthanum carbonate in comparison to placebo (Analysis 6.6 (1 study, 93 participants): MD -83.00 pg/mL, 95% CI -154.63 to -11.37) (Chiang 2005).

Other outcomes

Relevant data were not available to conduct meta-analyses for the outcomes serum alkaline phosphatase, serum bicarbonate and total cholesterol.

Lanthanum carbonate versus calcium carbonate

Phosphorus

There was no significant difference in serum phosphorus levels with lanthanum carbonate in comparison to calcium carbonate (Analysis 7.4 (2 studies, 122 participants): MD 0.22 mg/dL, 95% CI -0.32 to 0.75). No significant heterogeneity was identified (Chi^2 = 1.19, I^2 = 16%) (D'Haese 2003; Spasovski 2006).

Calcium

There were significantly lower calcium levels with lanthanum carbonate in comparison to calcium carbonate (Analysis 7.5 (2 studies, 122 participants): MD -0.30 mg/dL, 95% CI -0.57 to -0.03). No significant heterogeneity was identified (Chi^2 = 0.92, I^2 = 0%) (D'Haese 2003; Spasovski 2006).

Ca x P product

There was a significantly lower Ca x P product with lanthanum carbonate in comparison with calcium carbonate (Analysis 7.6 (1 study, 98 participants): MD -6.01 mg^2/dL^2, 95% CI -9.66 to -2.36) (D'Haese 2003).

PTH

There was no significant difference in PTH levels with lanthanum carbonate in comparison to calcium carbonate (Analysis 7.7 (2 study, 364 participants; MD 100.91 pg/mL, 95% CI -75.30 to 277.12) (D'Haese 2003, Spasovski 2006).

Other outcomes

Relevant data were not available to conduct meta-analyses for the outcomes serum bicarbonate and total cholesterol.

Other agents

Serum calcium, phosphorus and PTH

Studies comparing miscellaneous agents reported outcomes in different ways (e.g. end of treatment values of various biochemical

end-points, mean change in biochemical end-points) and sufficient data were not available to meta-analyse. Therefore, these data were tabulated (Table 2; Table 3; Table 4).

Investigation for sources of heterogeneity by subgroup analysis

Since heterogeneity was observed in many analyses, we explored the potential sources of heterogeneity using subgroup analysis (Table 5). This was possible for studies comparing either sevelamer hydrochloride or lanthanum carbonate to calcium salts, while other treatment comparisons contained too few studies to undertake subgroup analyses. Some covariates including measures of study quality (blinding and intention-to-treat analysis), patient characteristics (baseline PTH concentration), and study characteristics (study duration) were significant effect modifiers on some outcomes. However, data were often insufficient to allow definitive conclusions to be drawn.

DISCUSSION

Summary of main results

Several RCTs have examined the impact of various phosphate binders in people with CKD. All phosphate binders reduced serum phosphorus levels when compared with placebo, however use of newer agents such as lanthanum carbonate and sevelamer hydrochloride did not result in consistently superior biochemical outcomes compared with calcium-based therapies. These studies have not demonstrated that phosphate binders compared with placebo, or calcium salts compared with non-calcium or aluminium-containing agents, reduce all-cause or cardiovascular mortality. Rather, in studies comparing calcium salts to sevelamer hydrochloride, calcium salts were superior to sevelamer hydrochloride for reducing serum phosphorus. Compared with calcium salts, sevelamer hydrochloride and lanthanum carbonate were associated with significantly lower rates of treatment-related hypercalcaemia, which may result in reduced vascular calcification. The differential effect on serum levels of calcium and phosphorus resulted in increased PTH suppression by calcium treatment compared with sevelamer hydrochloride or lanthanum. The efficacy of available phosphate-binding agents on the surrogate outcomes of bone mineral density or histomorphometry and vascular calcification were variable and only reported in few studies and reliable conclusions could not be drawn through meta-analysis.

Sevelamer hydrochloride was associated with lower serum calcium, higher phosphorus, and higher PTH levels when compared to calcium salts. This may be due to non-compliance (secondary to increased gastrointestinal events and pill burden) resulting in less phosphorus reduction with sevelamer hydrochloride, or it may be because sevelamer hydrochloride is less effective at the relative doses used. Sevelamer hydrochloride treatment resulted in lower serum calcium levels, which might have contributed to the higher PTH levels noted. The DCOR Study 2007, which was the largest study (2103 participants) conducted at present, reported no difference in the risk of all-cause mortality between sevelamer hydrochloride and calcium salts except for a subgroup analysis in people older than 65 years who completed a two-year follow-up. Because of its size, DCOR Study 2007 was very influential and contributed 46% of the weight in our all-cause mortality analysis. Exclusion of this study resulted in a similar but smaller risk of all-cause mortality (RR 0.59, 95% CI 0.35 to 1.01 versus RR 0.75, 95% CI 0.48 to 1.16). Given the limitations of the analysis by DCOR Study 2007, we also conducted a sensitivity analysis using data from St Peter 2008, who used the centre for Medicare and Medicaid services claims data to reassess the DCOR study results. The risk of all-cause mortality was unchanged (RR 0.75, 95% CI 0.56 to 1.33) using these data.

The occurrence, progression, and prognostic importance of vascular calcification remain important questions in CKD and the influence of calcium-based binders on the progression of vascular calcification is a matter of intense debate (Bushinsky 2006; Friedman 2006; Moe 2006; Silver 2007). Two studies in the current analysis reported a higher rate of progression of vascular calcification with calcium salts compared with sevelamer hydrochloride (Block 2005; CARE Study 2004), while another showed no difference in calcium scores between sevelamer hydrochloride and calcium salts (BRiC Study 2008). The possibility that the cholesterol lowering effect of sevelamer hydrochloride may con-

tribute to this effect (rather than hypercalcaemia from calcium salts) cannot be excluded based on the recently published CARE-2 Study 2008. While vascular calcification is associated with an increased risk of mortality in haemodialysis patients, the impact of reducing vascular calcification on survival outcomes has not been demonstrated in RCTS in CKD and non-CKD populations (McCullough 2009; Silver 2007). As the recent negative results of the AURORA study (analysing the beneficial effects of statins in dialysis patients) have shown, even a universally accepted surrogate end-point like LDL cholesterol may not predict patient-centred end-points such as mortality in a different setting; in dialysis patients the causal pathway to cardiovascular endpoints and death may be different (Fellstrom 2009; Strippoli 2009). A surrogate end-point must be validated and tested in specific settings prior to validating assumptions that modifying the surrogate marker will impact upon clinical outcomes.

Sevelamer hydrochloride has not been well studied in CKD stages 3 to 5 (not requiring dialysis) except for a single study (Russo 2007). Therefore, this systematic review can only inform the therapeutic use of sevelamer hydrochloride and calcium salts in dialysis patients and only for surrogate biochemical end-points. It is still uncertain whether sevelamer hydrochloride reduces hypercalcaemia and cardiovascular disease in stage 3 to 5 CKD compared with calcium-based agents. Calcium salts are recommended in pre-dialysis patients by various international guideline agencies for the control of hyperphosphataemia (Elder 2006; K/DOQI 2003). Our review confirms that calcium carbonate and calcium acetate are equally effective in reducing phosphorus and PTH levels, with a similar incidence of hypercalcaemia and gastrointestinal adverse events; we identified only two studies conducted in pre-dialysis patients (Borrego 2000; Phelps 2002). Included studies did not separately report net elemental calcium intake for calcium acetate and calcium carbonate. This precluded us from pooling the data to assess the daily calcium load associated with these agents. Thus, the lack of a higher incidence of hypercalcaemia with calcium carbonate compared to calcium acetate should be interpreted with caution. As few studies are available, no strong RCT evidence exists (regarding outcomes of mortality and morbidity) for the use of calcium-based phosphate binders in earlier stages of CKD.

Few studies have analysed the use of lanthanum carbonate, alone or in conjunction with calcium salts, for phosphate binding in CKD. Lanthanum carbonate has been compared to placebo and calcium carbonate in dialysis patients. Available data confirm its efficacy in reducing phosphorus levels, similar to calcium carbonate, with a reduced incidence of hypercalcaemia. Accumulation of lanthanum in bone was assessed in Spasovski 2006 by bone biopsy at the end of two years of treatment and no evidence of aluminium-like toxicity was observed.

In CKD, fibroblast growth factor-23 (FGF-23) levels rise in parallel with declining renal function before a significant increase in serum phosphorus concentration is detected. Results from preliminary animal and human studies suggest that phosphate binders reduce serum FGF-23 levels (Koiwa 2005b; Nagano 2006). However, this has not been examined in well-conducted prospective studies and the impact of this reduction in FGF-23 levels is unknown.

Agreements and disagreements with other studies or reviews

A previous meta-analysis (including 17 prospective and retrospective studies comparing sevelamer hydrochloride to placebo) showed that sevelamer hydrochloride compared with placebo or no treatment improved biochemical end-points (serum phosphorus, Ca x P product, PTH, and lipids) without increased serum calcium levels. However, data on survival, hospitalisation, and vascular calcification were not included (Burke 2003). The inclusion of both observational studies and RCTs in that review decreased the strength of its conclusions through potential for bias and unknown confounding. A second systematic review of seven RCTs (746 participants) concluded that sevelamer hydrochloride had similar effects on phosphorus and Ca x P product with a lower incidence of hypercalcaemia (Manns 2004). Similar to the previous analysis, that review focused only on the effects of sevelamer hydrochloride and included some but not all available studies. Another analysis by Tonelli 2007 (an update of their previous review; Manns 2004) analysed the benefits of sevelamer hydrochloride in comparison to calcium alone and included 10 studies. This review did not assess the role of other phosphate binders and did not explore the risk of vascular calcification (Palmer 2007). A more recent analysis by Jamal 2009 compared calcium salts and non-calcium salts and noted a decrement in coronary calcification with no difference in mortality rates. Similar to previous reviews, other types of phosphate binders were not included.

Strengths and limitations

Our systematic review has a number of strengths and some weaknesses. It is based upon prior publication of a prospectively designed peer-reviewed protocol (Navaneethan 2006) and a systematic search of medical databases, data extraction, analysis, and study quality assessment by two independent review authors with supervision by a third experienced investigator. The key findings are limited by the lack of long-term studies analysing the efficacy of phosphate binders on mortality and musculoskeletal morbidity. Most included studies enrolled few people (except for the large DCOR Study 2007) and all were powered to observe differences in surrogate end-points rather than patient-focused outcomes. This attention to surrogate rather than patient-level end-points in CKD is not new and should be superseded by a focus on major patient-level end-points in future studies (Hutchinson 2009; Strippoli 2005; Strippoli 2007). The strength of conclusions drawn from this review is also limited by suboptimal reporting of study methods, to determine study quality and significant heterogeneity observed for many outcomes. Further, many studies were sponsored by different pharmaceutical companies. We could

not conduct subgroup analysis to explore the potential impacts due to the small number of studies.

The primary advantage for more recently developed phosphate binders (lanthanum carbonate and sevelamer hydrochloride) is a reduction in hypercalcaemia in dialysis patients. Further, newer agents may cause less PTH inhibition, which may offer additional benefits in low bone turnover states. However, such benefits have not been established so far. Existing studies using patient-focused end-points in pre-dialysis patients are inadequate to inform clinical recommendations for any phosphate binder, required before advocating that newer agents are superior to existing, lower cost interventions. Full adoption of sevelamer hydrochloride and lanthanum by government drug reimbursement agencies in place of calcium salts would lead to a large increase in healthcare expenditure (Manns 2007; St Peter 2009; Taylor 2008). This can only be justified by presenting evidence for improved clinical outcomes with these agents compared with calcium salts; current evidence suggests similar phosphate-binding effects but more potent effects on PTH with calcium salts. Additionally, it should be remembered that, to date, no clinical study has shown a survival advantage for calcium salts either, when compared with placebo or other agents.

AUTHORS' CONCLUSIONS

Implications for practice

Our review supports the conclusion that the novel phosphate binders such as sevelamer hydrochloride and lanthanum carbonate are not superior to calcium salts for the control of phosphorus levels in dialysis patients and their impact on morbidity and mortality is unknown. The primary advantage of more recently developed phosphate binders (lanthanum carbonate and sevelamer hydrochloride) is a reduction in hypercalcaemia. Data for patient-focused end-points in dialysis patients are inadequate to inform clinical recommendations for any phosphate binder.

Implications for research

Further research using a RCT design is required to assess the effect of surrogate biochemical end-points (phosphorus, calcium, PTH, FGF-23) on mortality and morbidity in CKD. These might include studies of:

1. direct comparisons between sevelamer compounds, calcium salts, and lanthanum carbonate in people with CKD with primary outcomes of all-cause and cardiovascular mortality, fractures, hospitalisation, and parathyroidectomy;

2. any phosphate binder used to control hyperphosphataemia in CKD stage 3 and 4; or

3. efficacy of combination therapy (such as sevelamer hydrochloride with or without calcium salts) on both surrogate and patient-level end-points.

ACKNOWLEDGEMENTS

We thank Narelle Willis (Managing Editor, Cochrane Renal Group), Ruth Mitchell (Trials Search Coordinator, Cochrane Renal Group) and the Cochrane Renal Group for assistance with preparation of this study. We also thank Dr Pooja Chaukiyal (PC) who contributed to the protocol development stage. We thank all the authors who provided additional details of their studies.

REFERENCES

References to studies included in this review

Al-Baaj 2005 *{published data only}*
Al-Baaj F, Speake M, Hutchinson J. Control of serum phosphate by oral lanthanum carbonate in patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis in a short-term, placebo-controlled study. *Nephrology Dialysis Transplantation* 2005;**20**(4):775–85. [MEDLINE: 15703206]

Almirall 1994 *{published data only}*
* Almirall J, Veciana L, Llibre J. Calcium acetate versus calcium carbonate for the control of serum phosphorus in haemodialysis patients. *American Journal of Nephrology* 1994;**14**(3):192–6. [MEDLINE: 7977479]

Birck 1999 *{published data only}*
Birck R, Zimmermann E, Wassmer S, Nowack R, van der Woude FJ. Calcium ketoglutarate versus calcium acetate for treatment of hyperphosphataemia in patients on maintenance haemodialysis: a cross-over study. *Nephrology Dialysis Transplantation* 1999;**14**(6):1475–9. [MEDLINE: 10383011]

Bleyer 1999 *{published data only}*
Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, et al.A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in haemodialysis patients. *American Journal of Kidney Diseases* 1999;**33**(4):694–701. [MEDLINE: 10196011]

Block 2005 *{published data only}*
Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident haemodialysis patients. *Kidney International* 2007;**71**(5):438–41. [MEDLINE: 17200680]
Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh

J, Dreisbach A, et al.Effects of sevelamer and calcium on coronary artery calcification in patients new to haemodialysis. *Kidney International* 2005;**68**(4):1815–24. [MEDLINE: 16164659]

Borrego 2000 *{published data only}*
Borrego J, Perez del Barrio P, Serrano P, Garcia Cortes MJ, Sanchez Perales MC, Borrego FJ, et al.A comparison of phosphorus-chelating effect of calcium carbonate versus calcium acetate before dialysis. *Nefrologia* 2000;**20**(4): 348–54. [MEDLINE: 11039260]

BRiC Study 2008 *{published data only}*
Barreto DV, Barreto FC, de Carvalho AB, Cuppari L, Draibe SA, Dalboni MA, et al.Phosphate binder impact on bone remodeling and coronary calcification - results from the BRiC study. *Nephron* 2008;**110**(4):c273–83. [MEDLINE: 19001830]
Peres AT, Dalboni MA, Canziani ME, Manfredi SR, Carvalho JT, Batista MC, et al.Effect of phosphate binders on oxidative stress and inflammation markers in hemodialysis patients. *Hemodialysis International* 2009;**13** (3):271–7. [CENTRAL: CN–00747277]

Bro 1998 *{published data only}*
Bro S, Rasmussen RA, Handberg J, Olgaard K, Feld-Rasmussen B. Randomized crossover study comparing the phosphate-binding efficacy of calcium ketoglutarate versus calcium carbonate in patients on chronic haemodialysis. *American Journal of Kidney Diseases* 1998;**31**(2):257–62. [MEDLINE: 9469496]

Caravaca 1992 *{published data only}*
Caravaca F, Santos I, Cubero JJ, Esparrago JF, Arrobas M, Pizarro JL, et al.Calcium acetate versus calcium carbonate as phosphate binders in haemodialysis patients. *Nephron* 1992;**60**(4):423–7. [MEDLINE: 1584317]

CARE Study 2004 *{published data only}*
Qunibi WY, Hootkins RE, McDowell LL, Meyer MS, Simon M, Garza RO, et al.Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study). *Kidney International* 2004;**65** (5):1914–26. [MEDLINE: 15086935]

CARE-2 Study 2008 *{published data only}*
Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, et al.A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in haemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. *American Journal of Kidney Diseases* 2008;**51**(6): 952–65. [MEDLINE: 18423809]

Cheng 2008 *{published data only}*
Cheng SC, Young DO, Huang Y, Delmez JA, Coyne DW. A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in haemodialysis patients. *Clinical Journal of the American Society of Nephrology: CJASN* 2008;**3**(4):1131–8. [MEDLINE: 18385391]

Chertow 1997 *{published data only}*
Chertow GM, Burke SK, Lazarus MJ, Stenzel KH, Wombolt D, Goldberg D, et al.Poly(allylamine hydrochloride) (RenaGel): A noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *American Journal of Kidney Diseases* 1997;**29**(1):66–71. [MEDLINE: 9002531]

Chertow 1999 *{published data only}*
Chertow GM, Dillon M, Burke SK, Steg M, Bleyer AJ, Garrett BN, et al.A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in haemodialysis patients. *Clinical Nephrology* 1999;**51**(1):18–26. [MEDLINE: 9988142]

Chertow 2002 *{published data only}*
Asmus HG, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, et al.Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. *Nephrology Dialysis Transplantation* 2005;**20** (8):1653–61. [MEDLINE: 15930018]
* Chertow GM, Burke SK, Raggi P, Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in haemodialysis patients. *Kidney International* 2002;**62**(1):245–52. [MEDLINE: 12081584]
Ferramosca E, Burke S, Chasan-Taber S, Ratti C, Chertow GM, Raggi P. Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients. *American Heart Journal* 2005;**149** (5):820–5. [MEDLINE: 15894962]
Raggi P, James G, Burke SK, Bommer S, Chasan-Taber S, Holzer H, et al.Decrease in thoracic vertebral bone attenuation with calcium-based phosphate binders in hemodialysis. *Journal of Bone & Mineral Research* 2005;**20** (5):764–72. [MEDLINE: 15824849]

Chiang 2005 *{published data only}*
Chiang SS, Chen JB, Yang WC. Lanthanum carbonate (Fosrenol) efficacy and tolerability in the treatment of hyperphosphatemic patients with end-stage renal disease. *Clinical Nephrology* 2005;**63**(6):461–70. [MEDLINE: 15960148]

d'Almeida Filho 2000 *{published data only}*
d'Almeida Filho EJ, da Cruz EA, Hoette M, Ruzany F, Keen LN, Lugon JR. Calcium acetate versus calcium carbonate in the control of hyperphosphatemia in hemodialysis patients. *Revista Paulista de Medicina [Sao Paulo Medical Journal]* 2000;**118**(6):179–84. [MEDLINE: 11120549]

D'Haese 2003 *{published data only}*
D'Haese PC, Spasovski GB, Sikole A, Hutchinson A, Freemont TJ, Sulkova S, et al.A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. *Kidney International - Supplement* 2003, (85):73–8. [MEDLINE: 12753271]
Wilson R. Spica Consultants Ltd. Personal communication 2005.

DCOR Study 2007 *{published data only}*

Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, et al.Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney International* 2007;**72**(9):1130–7. [MEDLINE: 17728707]

De Santo 2006 *{published data only}*

De Santo NG, Frangiosa A, Anastasio P, Marino A, Correale G, Perna A, et al.Sevelamer worsens metabolic acidosis in hemodialysis patients. *Journal of Nephrology* 2006;**19 Suppl 9**:S108–14. [MEDLINE: 16736432]

Deuber 2003a *{published data only}*

Deuber HJ. Effective reduction of serum phosphate by a calcium and magnesium containing phosphate binder without induction of hypermagnesemia [abstract]. *Nephrology Dialysis Transplantation* 2003;**18 Suppl 4**: 680–1. [CENTRAL: CN–00445085]

Emmett 1991 *{published data only}*

Emmett M, Sirmon MD, Kirkpatrick GW, Nolan C, Schmitt GW, Cleveland MB. Calcium acetate control of serum phosphorus in hemodialysis patients. *American Journal of Kidney Diseases* 1991;**17**(5):544–50. [MEDLINE: 2024656]

Evenepoel 2009 *{published data only}*

Evenepoel P, Selgas R, Caputo F, Foggensteiner L, Heaf JG, Ortiz A, et al.Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. *Nephrology Dialysis Transplantation* 2009;**24**(1):278–85. [MEDLINE: 18820280]

Fan 2009 *{published data only}*

Fan S, Ross C, Mitra S, Kalra P, Heaton J, Hunter J, et al.A randomized, crossover design study of sevelamer carbonate powder and sevelamer hydrochloride tablets in chronic kidney disease patients on haemodialysis. *Nephrology Dialysis Transplantation* 2009;**24**(12):3794–9. [MEDLINE: 19666658]

Ferreira 2008 *{published data only}*

Ferreira A, Frazão JM, Monier-Faugere MC, Gil C, Galvao J, Oliveira C, et al.Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in haemodialysis patients. *Journal of the American Society of Nephrology* 2008; **19**(2):405–12. [MEDLINE: 18199805]

Finn 2004 *{published data only}*

Altmann P, Barnett ME, Finn WF, SPD405-307 Lanthanum Carbonate Study Group. Cognitive function in Stage 5 chronic kidney disease patients on haemodialysis: no adverse effects of lanthanum carbonate compared with standard phosphate-binder therapy. *Kidney International.* 2007;**71**(3):252–9. [MEDLINE: 17035945]

* Finn WF, Joy MS, Hladik G, Lanthanum Study Group. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis. *Clinical Nephrology* 2004;**62**(3): 193–201. [MEDLINE: 15481851]

Fischer 2006 *{published data only}*

Fischer D, Cline K, Plone MA, Dillon M, Burke SK, Blair AT. Results of a randomized crossover study comparing once daily and thrice-daily sevelamer dosing. *American Journal of Kidney Diseases* 2006;**48**(3):437–44. [MEDLINE: 16931217]

FORESEE Study 2008 *{published data only}*

Mehrotra R, Martin KJ, Fishbane S, Sprague SM, Zeig S, Anger M, Fosrenol Overview Research Evaluation Study for Early Experience Study Group. Higher strength lanthanum carbonate provides serum phosphorus control with a low tablet burden and is preferred by patients and physicians: a multicenter study. *Clinical Journal of the American Society of Nephrology: CJASN* 2008;**3**(5):1437–45. [MEDLINE: 18579668]

Gallieni 2005 *{published data only}*

Gallieni M, Cicchetti T, Salvadori M, Sorba G, Stalteri A, Tarchini R, et al.Comparison of sevelamer HCL and calcium carbonate in the treatment of hyperphosphatemia in dialysis patients: a randomized clinical trial - Calcium Carbonate Sevelamer Evaluation (CaCSE) study [abstract]. *Journal of the American Society of Nephrology* 2005;**16**:746A. [CENTRAL: CN–00583853]

Hervas 2003 *{published data only}*

Hervas JG, Prados D, Cerezo S. Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: a comparison with calcium acetate. *Kidney International - Supplement* 2003, (85):69–72. [MEDLINE: 12753270]

Hutchison 2005 *{published data only}*

* Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R, et al.Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: A 6-month, randomized, comparative trial versus Calcium carbonate. *Nephron* 2005;**100**(1):c8–19. [MEDLINE: 15809508]

Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R, et al.Long-term efficacy and tolerability of lanthanum carbonate: results from a 3-year study. *Nephron* 2006;**102**(2):c61–71. [MEDLINE: 16224198]

Itoh 2008 *{published data only}*

Itoh K, Tanaka M, Hashiguchi J, Funakoshi S, Nakano H, Kubo H, et al.Comparison of sevelamer hydrochloride with colestimide, administered alone or in combination with calcium carbonate, in patients on hemodialysis. *Therapeutic Apheresis & Dialysis* 2008;**12**(2):126–32. [MEDLINE: 18387160]

Ittel 1991 *{published data only}*

Ittel TH, Schfer C, Schmitt H, Gladziwa U, Sieberth HG. Calcium carbonate as a phosphate binder in dialysis patients: evaluation of an enteric-coated preparation and effect of additional Aluminium hydroxide on hyperaluminaemia. *Klinische Wochenschrift* 1991;**69**(2):59–67. [MEDLINE: 2027271]

Janssen 1996 *{published data only}*

Janssen MJ, van der Kuy A, ter Wee PM, van Boven WP. Aluminum hydroxide, calcium carbonate and calcium acetate in chronic intermittent hemodialysis patients. *Clinical Nephrology* 1996;**45**(2):111–9. [MEDLINE: 8846523]

Jespersen 1991 *{published data only}*

Jespersen B, Jensen JD, Nielsen HK, Lauridsen IN, Andersen MJ, Poulsen JH, et al.Comparison of calcium carbonate and aluminium hydroxide as phosphate binders on biochemical bone markers, PTH(1-84), and bone mineral content in dialysis patients. *Nephology Dialysis Transplantation* 1991;**6**(2):98–104. [MEDLINE: 1857534]

Joy 2003 *{published data only}*

Joy MS, Finn WF, LAM-302 Study Group. Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. *American Journal of Kidney Diseases* 2003;**42**(1):96–107. [MEDLINE: 12830461]

Kinugasa 2001 *{published data only}*

Kinugasa E, Koshikawa S, PB-94 Study Group. Effects of PB-94 (sevelamer hydrochloride), a phosphate binder, on the treatment of hyperphosphatemia in hemodialysis patients - a randomized, open label, dose titration study of PB-94 versus caltan® tablet 500 (calcium carbonate) [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):755A. [CENTRAL: CN–00626049]

Koiwa 2005a *{published data only}*

Koiwa F, Onoda N, Kato H, Tokumoto A, Okada T, Fukagawa M, et al.Prospective randomized multicenter trial of sevelamer hydrochloride and calcium carbonate for the treatment of hyperphosphatemia in hemodialysis patients in Japan. *Therapeutic Apheresis & Dialysis* 2005;**9**(4):340–6. [MEDLINE: 16076379]

Kurihara 2005 *{published data only}*

Kurihara S, Tsuruta Y, Akizawa T. Effect of MCI-196 (colestilan) as a phosphate binder on hyperphosphataemia in haemodialysis patients: a double-blind, placebo-controlled, short-term trial. *Nephrology Dialysis Transplantation* 2005; **20**(2):424–30. [MEDLINE: 15673691]

Liu 2006 *{published data only}*

Liu YL, Lin HH, Yu CC, Kuo HL, Yang YF, Chou CY, et al.A comparison of sevelamer hydrochloride with calcium acetate on biomarkers of bone turnover in hemodialysis patients. *Renal Failure* 2006;**28**(8):701–7. [MEDLINE: 17162430]

Malluche 2008 *{published data only}*

Malluche HH, Siami GA, Swanepoel C, Wang GH, Mawad H, Confer S, et al.Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. *Clinical Nephrology* 2008;**70**(4):284–95. [MEDLINE: 18826853]

McIntyre 2009 *{published data only}*

McIntyre CW, Pai P, Warwick G, Wilkie M, Toft AJ, Hutchison AJ. Iron-magnesium hydroxycarbonate (Fermagate): a novel non-calcium-containing phosphate binder for the treatment of hyperphosphatemia in chronic hemodialysis patients. *Clinical Journal of the American Society of Nephrology: CJASN* 2009;**4**(2):401–9. [MEDLINE: 19158369]

Pflanz 1994 *{published data only}*

Pflanz S, Henderson IS, McElduff N, Jones MC. Calcium acetate versus calcium carbonate as phosphate-binding agents in chronic haemodialysis. *Nephrology Dialysis Transplantation* 1994;**9**(8):1121–4. [MEDLINE: 7800211]

Phelps 2002 *{published data only}*

Phelps KR, Stern M, Slingerland A, Heravi M, Strogatz DS, Haqqie SS. Metabolic and skeletal effects of low and high doses of calcium acetate in patients with preterminal chronic renal failure. *American Journal of Nephrology* 2002; **22**(5-6):445–54. [MEDLINE: 12381942]

Ring 1993 *{published data only}*

Ring T, Nielsen C, Andersen SP, Behrens JK, Sodemann B, Kornerup HJ. Calcium acetate versus calcium carbonate as phosphorus binders in patients on chronic haemodialysis: a controlled study. *Nephrology Dialysis Transplantation* 1993; **8**(4):341–6. [MEDLINE: 8390009]

Roxe 1989 *{published data only}*

Roxe DM, Mistovich M, Barch DH. Phosphate-binding effects of sucralfate in patients with chronic renal failure. *American Journal of Kidney Diseases* 1989;**13**(3):194–9. [MEDLINE: 2919600]

Rudnicki 1994 *{published data only}*

Rudnicki M, Hyldstrup L, Petersen LJ, Hojsted J, Tranbol I. Effect of oral calcium on noninvasive indices of bone formation and bone mass in hemodialysis patients: a randomized double-blind placebo-controlled study. *Mineral & Electrolyte Metabolism* 1994;**20**(3):130–4. [MEDLINE: 7816001]

Russo 2007 *{published data only}*

Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al.The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney International* 2007;**72**(10):1255–61. [MEDLINE: 17805238]

Sadek 2003 *{published data only}*

Sadek T, Mazouz H, Bahlou H, Oprisiu R, El Esper N, El Esper I, et al.Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients An open-label, randomized study. *Nephrology Dialysis Transplantation* 2003;**18**(3): 582–9. [MEDLINE: 12584283]

Saif 2007 *{published data only}*

Saif I, Halim A, Altaf A, Saif M, Khalid M, Ahmad D, et al.Comparison of calcium acetate with calcium carbonate as phosphate binder in patients on maintenance haemodialysis. *Journal of Ayub Medical College, Abbottabad: JAMC* 2007; **19**(4):26–8. [MEDLINE: 18693591]

Salusky 1991 *{published data only}*

Salusky IB, Foley J, Nelson P, Goodman WG. Aluminum accumulation during treatment with aluminum hydroxide and dialysis in children and young adults with chronic renal disease. *New England Journal of Medicine* 1991;**324**(8): 527–31. [MEDLINE: 1992306]

Schaefer 1991 *{published data only}*

Schaefer K, Scheer J, Asmus G, Umlauf E, Hagemann J, von Herrath D. The treatment of uraemic hyperphosphataemia with calcium acetate and calcium carbonate: a comparative study. *Nephrology Dialysis Transplantation* 1991;**6**(3):170–5. [MEDLINE: 1866045]

Shaheen 2004 *{published data only}*

Shaheen A, Akeel NM, Badawi LS, Souqiyyeh MZ. Efficacy and safety of sevelamer: comparison with calcium carbonate in the treatment of hyperphosphatemia in hemodialysis patients. *Saudi Medical Journal* 2004;**25**(6):785–91. [MEDLINE: 15195212]

Shigematsu 2008 *{published data only}*

Shigematsu T, Lanthanum Carbonate Group. Multicenter prospective randomized, double-blind comparative study between lanthanum carbonate and calcium carbonate as phosphate binders in Japanese hemodialysis patients with hyperphosphatemia. *Clinical Nephrology* 2008;**70**(5): 404–10. [MEDLINE: 19000540]

Spasovski 2006 *{published data only}*

Spasovski GB, Sikole A, Gelev S, Masin-Spasovska J, Freemont T, Webster I, et al.Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. *Nephrology Dialysis Transplantation* 2006;**21**(8):2217–24. [MEDLINE: 16595583]

Spiegel 2007 *{published data only}*

Spiegel DM, Farmer B, Smits G, Chonchol M. Magnesium carbonate is an effective phosphate binder for chronic hemodialysis patients: a pilot study. *Journal of Renal Nutrition* 2007;**17**(6):416–22. [MEDLINE: 17971314]

Sprague 2009a *{published data only}*

Sprague SM, Abboud H, Qui P, Dauphin M, Zhang P, Finn W. Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial. *Clinical Journal of the American Society of Nephrology: CJASN* 2009;**4**(1):178–85. [MEDLINE: 19056618]

Sprague 2009b *{published data only}*

Sprague SM, Ross EA, Nath SD, Zhang P, Pratt RD, Krause R. Lanthanum carbonate vs sevelamer hydrochloride for the reduction of serum phosphorus in hemodialysis patients: a crossover study. *Clinical Nephrology* 2009;**72**(4):252–8. [MEDLINE: 19825330]

Tzanakis 2008 *{published data only}*

Tzanakis IP, Papadaki AN, Wei M, Kagia S, Spadidakis VV, Kallivretakis NE, et al.Magnesium carbonate for phosphate control in patients on hemodialysis. A randomized controlled trial. *International Urology & Nephrology* 2008; **40**(1):193–201. [MEDLINE: 18193489]

Yang 2002 *{published data only}*

Yang WC, Yang CS, Hou CC, Wu TH, Young EW, Hsu CH. An open-label, crossover study of a new phosphate-binding agent in haemodialysis patients: ferric citrate. *Nephrology Dialysis Transplantation* 2002;**17**(2):265–70. [MEDLINE: 11812877]

Additional references

Block 1998

Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic haemodialysis patients: a national study. *American Journal of Kidney Diseases* 1998;**31**(4):607–17. [MEDLINE: 9531176]

Block 2004

Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance haemodialysis. *Journal of the American Society of Nephrology* 2004;**15**(8):2208–18. [MEDLINE: 15284307]

Burke 2003

Burke SK, Dillon MA, Hemken DE, Rezabek MS, Balwit JM. Meta-analysis of the effect of sevelamer on phosphorus, calcium, PTH, and serum lipids in dialysis patients. *Advances in Renal Replacement Therapy* 2003;**10**(2):133–45. [MEDLINE: 12879374]

Bushinsky 2006

Bushinsky DA. Phosphate binders: hold the calcium? . *Clinical Journal of the American Society of Nephrology: CJASN* 2006;**1**(4):695–6. [MEDLINE: 17699274]

Cozzolino 2005

Cozzolino M, Brancaccio D, Gallieni M, Slatopolsky E. Pathogenesis of vascular calcification in chronic kidney disease. *Kidney International* 2005;**68**(2):429–36. [MEDLINE: 16014020]

Dersimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88. [MEDLINE: 3802833]

Elder 2006

Elder G, Faull R, Branley P, Hawley C. Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone.. *Nephrology* 2006;**11 Suppl 1**:230–61. [MEDLINE: 16684078]

Fellstrom 2009

Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al.Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *New England Journal of Medicine* 2009;**360**(14):1395–407. [MEDLINE: 19332456]

Friedman 2006

Friedman EA. Calcium-based phosphate binders are appropriate in chronic renal failure. *Clinical Journal of the American Society of Nephrology: CJASN* 2006;**1**(4):704–809. [MEDLINE: 17699276]

Guerin 2001

Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;**103**(7):987–92. [MEDLINE: 11181474]

Gutierrez 2005

Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, et al.Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *Journal of the American Society of Nephrology* 2005;**16**(7):2205–15. [MEDLINE: 15917335]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60. [MEDLINE: 12958120]

Higgins 2008

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration. 2008. Available from www.cochrane-handbook.org.

Hurska 2008

Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of chronic kidney disease. *Kidney International* 2008;**74**(2):148–57. [MEDLINE: 18449174]

Hutchinson 2009

Hutchinson AJ. Oral phosphate binders. *Kidney International* 2009;**75**(9):906–14. [MEDLINE: 19279554]

Jamal 2009

Jamal SA, Fitchett D, Lok CE, Mendelssohn DC, Tsuyuki RT. The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis. *Nephrology Dialysis Transplantation* 2009;**24**(10):3168–74. [MEDLINE: 19622572]

K/DOQI 2003

National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *American Journal of Kidney Diseases* 2003;**42** (4 Suppl 3):70–7. [MEDLINE: 14520607]

KDIGO 2009

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney International - Supplement* 209;**76**(113):S1–130. [MEDLINE: 19644521]

Koiwa 2005b

Koiwa F, Kazama JJ, Tokumoto A, Onoda N, Kato H, Okada T, et al.Sevelamer hydrochloride and calcium bicarbonate reduce serum fibroblast growth factor 23 levels in dialysis patients. *Therapeutic Apheresis & Dialysis* 2005;**9** (4):336–9. [MEDLINE: 16076378]

Lefebvre 2008

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (updated February 2008). The Cochrane Collaboration. Available from www.cochrane-handbook.org.

Manns 2004

Manns B, Stevens L, Miskulin D, Owen WF Jr, Winkelmayer WC, Tonelli M. A systematic review of sevelamer in ESRD and an analysis of its potential economic impact in Canada and the United States. *Kidney International* 2004;**66**(3):1239–47. [MEDLINE: 15327423]

Manns 2007

Manns B, Klarenbach S, Lee H, Culleton B, Shrive F, Tonelli M. Economic evaluation of sevelamer in patients with end-stage renal disease. *Nephrology Dialysis Transplantation* 2007;**22**(10):2867–78. [MEDLINE: 17595182]

McCullough 2009

McCullough PA, Chinnaiyan M. Annual progression of coronary calcification in trials of preventive therapies: a systematic review. *Archives of Internal Medicine* 2009;**169** (22):2064–70. [MEDLINE: 20008688]

Moe 2006

Moe SM, Chertown G. The case against calcium-based phosphate binders. *Clinical Journal of the American Society of Nephrology: CJASN* 2006;**1**(4):697–703. [MEDLINE: 17699275]

Nagano 2006

Nagano N, Miyata S, Abe M, Kobayashi N, Wakita S, Yamashita T, et al.Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats. *Kidney International* 2006;**69**(3):531–7. [MEDLINE: 16395276]

Palmer 2007

Palmer SC, McGregor DO, Strippoli GFM. Interventions for preventing bone disease in kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD005015.pub3]

Qunibi 2008

Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, et al.A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in haemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. *American Journal of Kidney Diseases* 2008;**51**(6): 952–8. [MEDLINE: 18423809]

Renal Group 2010

Willis NS, Mitchell R, Higgins GY, Webster AC, Craig JC. Cochrane Renal Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2010, Issue 12. Art. No.: RENAL (accessed December 2010).

Salusky 2006

Salusky IB. A new era in phosphate binder therapy: what are the options?. *Kidney International - Supplement* 2006;**70** (105):10–5. [MEDLINE: 17136110]

Silver 2005
Silver J, Levi R. Cellular and molecular mechanisms of secondary hyperparathyroidism. *Clinical Nephrology* 2005; **63**(2):119–26. [MEDLINE: 15730054]

Silver 2007
Silver J. The details bedevil DCOR. *Kidney International* 2007;**72**(9):1041–3. [MEDLINE: 17943149]

St Peter 2008
St Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. *American Journal of Kidney Diseases* 2008;**51**(3):445–54. [MEDLINE: 18295060]

St Peter 2009
St Peter W, Fan Q, Weinhandl E, Liu J. Economic evaluation of sevelamer versus calcium-based phosphate binders in hemodialysis patients: a secondary analysis using centers for Medicare & Medicaid services data. *Clinical Journal of the American Society of Nephrology: CJASN* 2009; **4**(12):1954–61. [MEDLINE: 19833904]

Stevens 2004
Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. *Journal of the American Society of Nephrology* 2004;**15**(3):770–9. [MEDLINE: 14978180]

Strippoli 2005
Strippoli GF, Craig JC. Hypothesis versus association: the optimal hemoglobin target debate. *American Journal of Kidney Diseases* 2005;**46**(5):970–3. [MEDLINE: 16253741]

Strippoli 2007
Strippoli GF, Tognoni G, Navaneethan SD, Nicolucci A, Craig JC. Haemoglobin targets: we were wrong, time to move on. *Lancet* 2007;**369**(9559):346–50. [MEDLINE: 17276756]

Strippoli 2009
Strippoli GF, Craig JC. Sunset for statins after AURORA? . *New England Journal of Medicine* 2009;**360**(14):1455–7. [MEDLINE: 19332454]

Taylor 2008
Taylor MJ, Elgazzar HA, Chaplin S, Goldsmith D, Molony DA. An economic evaluation of sevelamer in patients new to dialysis. *Current Medical Research & Opinion* 2008;**24** (2):601–8. [MEDLINE: 18205996]

Tentori 2008
Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *American Journal of Kidney Diseases* 2008;**52**(3):519–30. [MEDLINE: 18514987]

Tonelli 2007
Tonelli M, Wiebe N, Culleton B, Lee H, Klarenbach S, Shrive F, et al.Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrology Dialysis Transplantation* 2007;**22**(10):2856–66. [MEDLINE: 17906326]

USRDS 2009
United States Renal Data System (USRDS). Costs of ESRD. http://www.usrds.org/2009/pdf/V2˙11˙09.pdf (accessed October 2010).

References to other published versions of this review

Navaneethan 2006
Navaneethan SD, Palmer SC, Vecchio M, Craig JC, Elder G, Strippoli GFM. Phosphate binders for preventing and treating bone disease in chronic kidney disease patients. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD006023]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al-Baaj 2005

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 23

Participants	Inclusion criteria
	• Country: USA
	• Setting: multicentre
	• >18 years; HD or CAPD for > 6 months, including those who had undergone a kidney transplant
	• Number
	  ○ lanthanum: 17
	  ○ placebo: 19
	• Mean age (± SD)
	  ○ lanthanum: 57 years (± 17)
	  ○ placebo: 53.3 years (± 16)
	• Sex (M/F)
	  ○ lanthanum: 10/7
	  ○ placebo: 10/9
	Exclusion criteria
	• Hypercalcaemia; severe hyperparathyroidism; serum phosphorus > 3 mg/dL after the washout phase; other clinically significant abnormal laboratory values; positive pregnancy test; significant GI disorder (including known active peptic ulcer, Crohn's disease, ulcerative colitis, irritable bowel syndrome and past or present malignancies); unstable dietary habits; life-threatening malignancy or HIV-status; history of drug or alcohol abuse

Interventions	Lanthanum group • 375 to 2250 mg/d Placebo group • Placebo Co-interventions • Oral or IV vitamin D analogues
Outcomes	• Serum calcium • Serum phosphorus • iPTH
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS

Al-Baaj 2005 (*Continued*)

Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	Low risk	Yes
Blinding of data analysers?	Low risk	Yes
Intention to treat?	High risk	No

Almirall 1994

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 24 weeks • Lost to follow-up: 3
Participants	Inclusion criteria • Country: Spain • Setting: hospital • Chronic HD for 54 ± 38 months (3 times/week) • Number: 7/10 completed study • Age: NS • Sex (M/F): NS Exclusion criteria: NS
Interventions	Calcium acetate group • 3.8 g/d Calcium carbonate group • 4 g/d Co-interventions: Oral calcitriol
Outcomes	• Serum calcium • Serum phosphorus • Ca x P product • iPTH
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)

Almirall 1994 (*Continued*)

Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Birck 1999

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 24 weeks • Lost to follow-up: 4
Participants	Inclusion criteria • Country: Germany • Setting: multicentre • HD for at least 12 months; hyperphosphataemia after withdrawal of phosphate-binding agents; known adherence to therapy; iPTH smaller than the 10-fold upper normal level • Number: 28 • Mean age (range): 61 years (37 to 87) • Sex (M/F): 18/10 Exclusion criteria: NS
Interventions	Group 1 • Calcium ketoglutarate and then calcium carbonate to achieve serum phosphorus < 5.3 mg/dL Group 2 • Calcium carbonate and then calcium ketoglutarate to achieve serum phosphorus < 5.3 mg/dL Co-interventions: none
Outcomes	• Serum calcium • Serum phosphorus • iPTH
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)

Birck 1999 (*Continued*)

Blinding of participants?	Unclear risk	No
Blinding of investigators?	Unclear risk	No
Blinding of outcome assessors?	Unclear risk	No
Blinding of data analysers?	Unclear risk	No
Intention to treat?	Unclear risk	No

Bleyer 1999

Methods	• Study design: crossover RCT • Time frame: July 1996 to February 1997 • Follow-up period: 16 weeks • Lost to follow-up: 4
Participants	Inclusion criteria • Country: USA • Setting: multicentre • > 18 years; HD patients on stable doses of calcium or aluminium-based phosphate binders and on stable doses or no calcitriol for 1 month • Number: 80 • Mean age (± SD): 54.5 years (± 15) • Sex: 53% male Exclusion criteria: NS
Interventions	Sevelamer group • Sevelamer hydrochloride 2 to 4 capsules 3 times/day to achieve serum phosphorus 2.5 to 5.5 mg/dL Calcium group • Calcium acetate 1 to 3 capsules 3 times/day to achieve serum phosphorus 2.5 to 5.5 mg/dL Co-interventions: Calcitriol
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH • Lipid profile
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS

Bleyer 1999 (*Continued*)

Allocation concealment?	High risk	No (C)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

Block 2005

Methods	• Study design: parallel RCT, stratified by DM • Time frame: NS • Follow-up period: 18 months • Lost to follow-up: 39

Participants	Inclusion criteria
	• Country: USA
	• Setting: multicentre
	• >18 years; new to HD patients
	• Number
	  ○ calcium: 55
	  ○ sevelamer: 54
	• Mean age (± SD)
	  ○ calcium: 59 years (± 15)
	  ○ sevelamer: 57 years (± 15)
	• Sex (M/F)
	  ○ calcium: 36/9
	  ○ sevelamer: 31/22
	Exclusion criteria
	• Prior history of dialysis; kidney transplant; coronary artery bypass surgery; weight > 300 pounds; current atrial fibrillation or atrial flutter

Interventions	Calcium group • Calcium-containing phosphate binders Sevelamer group • Sevelamer hydrochloride Co-interventions: NS

Outcomes	• Outcomes for Block 2005
	  ○ CAC score
	• Outcomes for **Block 2007**
	  ○ All-cause mortality
	  ○ Progression of CAC score

Block 2005 (*Continued*)

Notes	• "Investigators were free to alter phosphate binder dose and, within the calcium treatment arm, to alternate between various types of calcium containing phosphate binders at their discretion. Patients randomised to sevelamer were allowed to take calcium as a nightly supplement at the discretion of the investigator."
	• "The dialysate calcium concentration was maintained at 2.5 mEq/L throughout the study period. No estimate of patient adherence (pill count) was performed, and no patient received calcimimetic agents during the course of the clinical trial."
	• **Block 2007**
	  ○ This was a follow-up study
	  ○ Follow-up period: 44 months
	• Study supported by Genzyme Corp.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"randomisation to treatment was computer generated in blocks of 10"
Allocation concealment?	Low risk	"assigned by the coordinating centre using concealed envelopes"
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No (except the EBCT results)
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Borrego 2000

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 24 months • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: Brazil
	• Setting: hospital
	• CKD with CrCl < 21 mL/min; serum phosphorus > 5 mg/dL
	• Number
	  ○ calcium carbonate: 14
	  ○ calcium acetate: 14
	• Age (range)

Borrego 2000 (*Continued*)

	○ calcium carbonate: 55 years (23 to 76) ○ calcium acetate: 63 years (23 to 90) • Sex (M/F) ○ calcium carbonate: 5/9 ○ calcium acetate: 7/7 Exclusion criteria • DKD; treatment with vitamin D analogues; serum calcium > 10.5 mg/dL
Interventions	Calcium carbonate group • 2.5 g/day Calcium acetate group • 1g/day Co-interventions: NS
Outcomes	• Serum phosphorus • Serum calcium • iPTH • CrCl
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	Unclear (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

BRiC Study 2008

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 12 months • Lost to follow-up: 30

BRiC Study 2008 (*Continued*)

Participants	Inclusion criteria
	• Country: Brazil
	• Setting: multicentre
	• On maintenance HD for at least 3 months
	• Number
	  ○ calcium: 49
	  ○ sevelamer: 52
	• Mean age (± SD)
	  ○ calcium: 47 years (± 14)
	  ○ sevelamer: 47 years (± 13)
	• Sex (M/F)
	  ○ calcium: 21/9
	  ○ sevelamer: 27/14
	Exclusion criteria
	• GI disease; ethanol or drug abuse; active malignancy; HIV infection; chronic inflammatory disease; current use of steroids; severe hyperparathyroidism; body weight > 100 kg; continuous use of antiarrhythmic or seizure drugs; pregnancy or breast-feeding; previous myocardial revascularization; uncontrolled DM or hypertension

Interventions	Calcium group • Calcium acetate adjusted monthly up to 2.028 mg of elemental calcium daily Sevelamer group • Sevelamer hydrochloride adjusted monthly up to 12 mg daily Co-interventions: No

Outcomes	• Outcomes reported in BRiC Study 2008
	  ○ Serum phosphorus
	  ○ Serum i-Ca level
	  ○ iPTH
	  ○ Histomorphometric data from bone biopsies
	  ○ Vascular calcification
	• Outcomes reported in **Peres 2009**
	  ○ Serum phosphorus
	  ○ Serum calcium
	  ○ iPTH
	  ○ Ca x P product
	  ○ Serum albumin
	  ○ Total cholesterol
	  ○ Markers of inflammation: CRP, TNF-alpha, IL-10

Notes	• Data about age and sex are reported for 30 and 41 participants (calcium acetate and sevelamer respectively) • **Peres 2009** ○ This is a substudy. Data relating to total cholesterol only was used for analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

BRiC Study 2008 (*Continued*)

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	Yes (A)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Bro 1998

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 12 weeks • Lost to follow-up: 9
Participants	Inclusion criteria • Country: Denmark • Setting: hospital • >18 years; HD treatment for at least 1 month; stable protein and energy intake; treatment with a dialysate calcium concentration of 1.25 mmol/L; stable dosage of alfacalcidol for the last 2 months • Number: 19 enrolled, 10 completed study • Median age (range): 54 years (25 to 80) • Sex(M/F): 12/7 (completed study: NS) Exclusion criteria • Pregnancy or lactation; mental retardation or dementia; psychiatric illness; recent infection or surgical trauma within 3 months; insufficient dialysis (Kt/V < 1.2); malignancies; immobilization; prior parathyroidectomy and tertiary hyperparathyroidism
Interventions	Group 1 • Calcium ketoglutarate and then calcium carbonate to achieve serum phosphorus < 5.3 mg/dL Group 2 • Calcium carbonate and then calcium ketoglutarate to achieve serum phosphorus < 5.3 mg/dL Co-interventions • Oral alfacalcidol
Outcomes	• Serum phosphorus • Serum calcium • iPTH

Bro 1998 (*Continued*)

Notes	Study received financial support from the Danish Kidney Foundation and Leo Pharmaceuticals, Ballerup, Denmark. Calcium ketoglutarate was kindly provided by Gambro Medicoteknik A/S, Vallensbaek, Denmark

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Caravaca 1992

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 16 weeks • Lost to follow-up: 14

Participants	Inclusion criteria
	• Country: Spain
	• Setting: hospital
	• Chronic HD treatment for 2 to 175 months; CrCl < 1 mL/min; treatment with aluminium hydroxide
	• Number
	  ○ calcium acetate: 31
	  ○ calcium carbonate: 35
	• Mean age (± SD)
	  ○ calcium acetate: 51 years (± 10)
	  ○ calcium carbonate: 45 years (± 16)
	• Sex (M/F)
	  ○ calcium acetate: 20/11
	  ○ calcium carbonate: 17/16
	Exclusion criteria: NS

Interventions	Calcium acetate group • 6.5 g/day

Caravaca 1992 (*Continued*)

	Calcium carbonate group • 3.75 g/day Co-interventions: No
Outcomes	• Serum phosphorus • Serum calcium • iPTH
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

CARE Study 2004

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 8 • Lost to follow-up: 2
Participants	Inclusion criteria • Country: USA • Setting: multicentre (6 outpatient clinics at 2 centres) • HD for at least 3 months; receiving a stable dose of phosphate binder and IV vitamin D for at least 1 month • Number ○ sevelamer: 50 ○ calcium): 48 • Mean age (± SD) ○ sevelamer: 52.3 years (± 14.7) ○ calcium: 53.9 years (± 13.3) • Sex (M/F) ○ sevelamer: 28/22

CARE Study 2004 (*Continued*)

	○ calcium: 28/20 Exclusion criteria • iPTH > 1000 pg/mL; history of previous parathyroidectomy
Interventions	Sevelamer group • Sevelamer hydrochloride: 2 to 4 capsules (403 mg) 3 times/day to achieve serum phosphorus < 5.5 mg/dL Calcium group • Calcium acetate: 2 to 4 capsules (667 mg) 3 times/day to achieve serum phosphorus < 5.5 mg/dL Co-interventions • IV vitamin D analogues
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

CARE-2 Study 2008

Methods	• Study design: parallel RCT • Time frame: January 2005 to November 2005 • Follow-up period: 52 weeks • Lost to follow-up: 2
Participants	Inclusion criteria • Country: USA • Setting: 26 dialysis centres

CARE-2 Study 2008 (*Continued*)

	• ESKD; ≥18 years; HD for 3 months to 5 years
	• Number
	  ○ calcium: 103
	  ○ sevelamer: 100
	• Mean age (± SD)
	  ○ calcium: 58.5 years (± 12.8)
	  ○ sevelamer: 60.3 years (± 12.1)
	• Sex (M/F)
	  ○ calcium: 61/42
	  ○ sevelamer: 46/54
	Exclusion criteria
	• Condition that could restrict survival of participants for the duration of the study or interfere with their ability to follow the study

Interventions	Calcium group • Calcium acetate to achieve a phosphorus level of 3.5 to 5.5 mg/dL and LDL < 70 Sevelamer group • Sevelamer hydrochloride to achieve a phosphorus level of 3.5 to 5.5 mg/dL and LDL < 70 Co-interventions: No
Outcomes	• Change in CAC score assessed by means of electron-beam computed tomography
Notes	This study was supported by a grant from Fresenius Medical Care North America, Waltham, MA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"randomisation was stratified by centre using computerized lists for each site, prepared by using permuted blocks of 4 to attain balance within strata"
Allocation concealment?	Low risk	Yes (A)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Cheng 2008

Methods	• Study design: placebo-controlled, crossover RCT • Time frame: February 2006 to December 2006 • Follow-up period: 16 weeks • Lost to follow-up: 0
Participants	• Inclusion criteria • Country: USA • Setting: 2 dialysis units • ≥18 years; capacity for informed consent; long term HD > 90 days; stable dosage of phosphorus binders during the previous 2-week period; serum phosphorus level > 5.0 mg/dL • Number: 33 • Age: 52.6 years • Sex (M/F): 23/10 Exclusion criteria • Pregnancy; history of liver disease; active peptic ulcer disease; treatment with carbamazepine; niacin therapy; more than one missed HD session in the past 30 days
Interventions	Niacinamide • 250 mg twice daily increased to 500 mg twice daily at week 3 and 750 mg twice daily at week 5 Placebo • 250 mg twice daily increased to 500 mg twice daily at week 3 and 750 mg twice daily at week 5 Co-interventions • Phosphorus binders, vitamin D, paracalcitol, cinacalcet
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH • Uric acid levels
Notes	One author "received support for this study through the Amgen Fellowship Support Stipend during the 2006 to 2007 academic year"

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	"Research pharmacist also randomly assigned patients"
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	"provided blinded bottles to the research staff for distribution"
Blinding of investigators?	Low risk	"provided blinded bottles to the research staff for distribution"

Cheng 2008 (*Continued*)

Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Chertow 1997

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: USA
	• Setting: multicentre
	• > 18 years; thrice weekly HD for at least 3 months; administration of calcium-based phosphate binders with or without vitamin D or vitamin D metabolite replacement therapy at stable doses for at least 1 month before screening
	• Number
	  ○ sevelamer: 24
	  ○ placebo: 12
	• Mean age (± SD)
	  ○ sevelamer: 58.8 years (± 17.1)
	  ○ placebo: 53.7 years (± 13.9)
	• Sex (M/F)
	  ○ sevelamer: 13/11
	  ○ placebo: 10/2
	Exclusion criteria
	• Unstable medical condition; including poorly controlled DM or hypertension, or any GI abnormality

Interventions	Sevelamer group • Sevelamer hydrochloride: mean 7.2 capsules/day Placebo group • Placebo Co-interventions • IV or oral vitamin D analogues
Outcomes	• Serum phosphorus • Serum calcium • Lipid profile
Notes	Supported by a grant from GelTex Pharmaceuticals, Inc
Risk of bias	

Chertow 1997 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	2:1 randomisation, method not described
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

Chertow 1999

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 12 weeks • Lost to follow-up: 16
Participants	Inclusion criteria • Country: USA • Setting: multicentre • > 18 years; thrice weekly HD for at least three months; regular administration of calcium- and/or aluminium-based phosphate binders, with or without vitamin D metabolite replacement therapy at stable doses for at least one month before screening • Number ○ sevelamer: 35 ○ sevelamer + calcium: 36 • Mean age (± SD) ○ sevelamer: 55.9 years (± 14.1) ○ sevelamer + calcium: 60.7 years (± 15.0) • Sex(M/F) ○ sevelamer: 10/25 ○ sevelamer + calcium: 14/22 Exclusion criteria • Total parathyroidectomy; serious GI disease (including dysphagia, vomiting, motility disorder, major intestinal surgery, markedly irregular bowel function); ethanol or drug dependence or abuse; active malignancy; HIV infection; vasculitis; poorly controlled DM or hypertension
Interventions	Sevelamer group • Sevelamer hydrochloride 2 to 4 capsules (465 mg) 3 times/day to achieve serum phosphorus 2.5 to 5.5 mg/dL Sevelamer + calcium carbonate group • Sevelamer hydrochloride 2 to 4 capsules (465 mg) 3 times/day + calcium carbonate 900 mg/

Chertow 1999 (*Continued*)

	day to achieve serum phosphorus 2.5 to 5.5 mg/dL Co-interventions • IV or oral vitamin D analogues
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH • Lipid profile
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

Chertow 2002

Methods	• Study design: parallel RCT • Time frame: May 1999 to January 2001 • Follow-up period: 52 weeks • Lost to follow-up: NS

Participants	Inclusion criteria
	• Countries: USA, Germany, Austria
	• Setting: Dialysis centres; USA (15), Germany (7), Austria (1)
	• < 19 years; HD patients
	• Number
	  ○ sevelamer: 99
	  ○ calcium: 101
	• Mean age (± SD)
	  ○ sevelamer: 57 years (± 14)
	  ○ calcium: 56 years (± 16)
	• Sex (M/F)

	○ sevelamer: 36/63 ○ calcium: 34/67 Exclusion criteria • Serious GI disease (dysphagia, active untreated gastroparesis, severe motility disorder, major intestinal surgery, markedly irregular bowel function); ethanol or drug dependence or abuse; active malignancy; HIV infection; vasculitis; poorly controlled DM or hypertension
Interventions	Sevelamer group • Sevelamer hydrochloride, dose to achieve serum phosphorus of 3 to 5 mg/dL and serum calcium 8.5 to 10.5 mg/dL Calcium group • Calcium acetate/carbonate, dose to achieve serum phosphorus level of 3 to 5 mg/dL and serum calcium level of 8.5 to 10.5mg/dL Co-interventions • IV or oral vitamin D analogues
Outcomes	• Outcomes reported in Chertow 2002 ○ Serum phosphorus, calcium, iPTH, lipid profile ○ Cardiovascular calcification ○ Changes in calcification score • Outcomes reported in **Asmus 2005** (N = 72) ○ Hypercalcaemic episodes ○ Ca x P product ○ iPTH serum concentration ○ Increases in CAC score ○ Increases in aortic calcification score ○ Trabecular bone density ○ Cortical bone density • Outcomes reported in **Ferramosca 2005** (N = 108) ○ Changes in CAC score ○ Changes in lipids and markers of inflammation • Outcomes reported in **Raggi 2005** (N = 111) ○ Serum phosphorus, calcium, iPTH, Ca x P product ○ Changes in bone attenuation ○ Markers of bone turnover ○ Change in coronary artery and aortic calcification
Notes	• **Asmus 2005** ○ 114 participants were randomised, but data about allocation, age, and sex are reported for only 72 participants ○ This was a secondary analysis ○ Follow-up period: 24 months • **Ferramosca 2005** ○ This was a secondary analysis • **Raggi 2005** ○ This was a secondary analysis
Risk of bias	

Chertow 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomised 1:1, stratified by site and DM using a computer generated randomisation sequence (SAS 6.12 (Cary, NC, USA))
Allocation concealment?	Low risk	Yes (A)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Chiang 2005

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 4 weeks • Lost to follow-up: 31

Participants	Inclusion criteria
	• Country: Taiwan
	• Setting: multicentre
	• > 20 years; HD 3 times/week for a minimum of 2 consecutive months
	• Number
	  ○ lanthanum: 30
	  ○ placebo: 31
	• Mean age (± SD)
	  ○ lanthanum: 53.6 years (± 11.2)
	  ○ placebo: 51.7 years (± 9.4)
	• Sex (M/F)
	  ○ lanthanum: 16/14
	  ○ placebo: 14/17
	Exclusion criteria
	• GI surgery or disorder such as Crohn's disease or peptic ulcers; hyperparathyroidism

Interventions	Lanthanum group • Lanthanum 375 to 3000 mg/day Placebo group • Placebo Co-interventions: No

Chiang 2005 (*Continued*)

Outcomes	• Serum phosphorus • iPTH • Serum calcium • Ca x P product
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	1:1 randomisation, method not mentioned
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

d'Almeida Filho 2000

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 4 weeks • Lost to follow-up: 29
Participants	Inclusion criteria • Country: Brazil • Setting: private hospital dialysis centre • HD, 3 times/week (Ca dialysate 3.5 mEq/L) • Number: 52 enrolled, 23 completed study • Age: NS • Sex (M/F): NS Exclusion criteria • Parathyroidectomy
Interventions	Group 1 • Calcium acetate 5.6 g/day and then calcium carbonate 6.2 g/day Group 2 • Calcium carbonate 6.2 g/day and then calcium acetate 5.6 g/day Co-interventions: No

d'Almeida Filho 2000 (*Continued*)

Outcomes	• Serum phosphorus • Serum calcium • Kt/V • Serum bicarbonate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

D'Haese 2003

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 1 year • Lost to follow-up: 30

Participants	Inclusion criteria
	• Countries: Belgium, Czech Republic, Italy, Macedonia, Poland, Portugal, South Africa, Tenerife, Yugoslavia, UK, USA
	• Setting: international multicentre study (18 centres)
	• > 18 years; HD or CAPD within 12 weeks; people who had been diagnosed with CKD and were scheduled to begin dialysis
	• Number
	  ○ lanthanum: 49 enrolled, 34 completed study
	  ○ calcium: 49 enrolled; 34 completed study
	• Mean age (± SD): 55 years (± 14.3)
	• Sex (M/F): 59/39
	Exclusion criteria
	• Hypocalcaemia or concurrent illness

D'Haese 2003 (*Continued*)

Interventions	Lanthanum group • Lanthanum up to 3750 mg/day Calcium group • Calcium carbonate up to 9000 mg/day Co-interventions • Oral or IV vitamin D analogues
Outcomes	• Serum calcium • Serum phosphorus • iPTH • Markers of bone turnover
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

DCOR Study 2007

Methods	• Study design: parallel RCT • Time frame: March 2001 to December 2004 • Follow-up period: 20.3 ± 13.9 months (sevelamer); 19.6 ± 13.6 months (calcium) • Lost to follow-up: 207

Participants	Inclusion criteria
	• Country: USA
	• Setting: 75 Fresenius dialysis centres
	• > 18 years; patients on dialysis for more than 3 months required phosphate binders therapy
	• Number
	  ○ calcium: 1050
	  ○ sevelamer: 1053
	• Mean age (± SD)

DCOR Study 2007 (*Continued*)

	○ calcium: 60.1 years (± 15.2) ○ sevelamer: 59.9 years (± 14.3) • Sex (M/F) ○ calcium: 569/481 ○ sevelamer: 574/479 Exclusion criteria • Dysphagia/swallowing disorders; severe GI motility disorders; bowel obstruction
Interventions	Calcium group • Calcium-based binders: calcium acetate (mean 5.3 g); calcium carbonate (mean 4.9 g) Sevelamer group • Sevelamer hydrochloride 6.9 g daily (mean) Co-interventions: No
Outcomes	• All-cause mortality • Cause-specific mortality: myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary oedema, cerebrovascular accident, ischaemic brain damage/anoxic encephalopathy • Hospitalisation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"randomisation was executed in blocks assuring a 1:1 ratio between treatment groups within strata defined by race (black and non-black), sex, diabetic status, and by age (< 55 and ≥ 55 years). Institutional balancing was used to assure comparable number of subjects between treatment groups within a site."
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

De Santo 2006

Methods	• Study design: parallel RCT with crossover to second treatment at 24 weeks • Time frame: NS • Follow-up period: 24 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: Italy
	• Setting: hospital
	• Excellent albumin levels and blood pressure; stable haemodynamic condition
	• Number
	  ○ calcium: 8
	  ○ sevelamer: 8
	• Age range: 36 to 50 years
	• Sex (M/F): All male
	Exclusion criteria
	• DM; severe osteitis fibrosa; use of corticosteroids; phosphorus levels < 5.5 mg/dL; not requiring phosphate binders; iPTH > 400 pg/mL; non-compliant; ethanol or drugs dependence; HIV infection; vasculitis; active malignancy; severe GI disease

Interventions	Calcium group • Calcium carbonate to achieve a phosphorus level of 5.5 mg/dL and calcium concentrations in the range of 8.5 to 10.5 mg/dL for 24 weeks Sevelamer group • Sevelamer hydrochloride: based on manufacturer's instructions Co-interventions • After 24 weeks participants were crossed to the other treatment • Vitamin D
Outcomes	• Time course of plasma bicarbonate concentration • Time course of serum albumin concentration • Time course of iPTH concentration
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No

De Santo 2006 (*Continued*)

Intention to treat?	High risk	No

Deuber 2003a

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 30 months • Lost to follow-up: NS

Participants	Inclusion criteria
	• Country: Germany
	• Setting: dialysis centre
	• HD for at least 15 ± 6 months; had been on a constant doses of calcium carbonate for 12 months
	• Number
	  ○ calcium carbonate: 27
	  ○ calcium acetate: 23
	• Mean age (± SD): 62 years (± 11.7)
	• Sex (M/F): 23/27
	Exclusion criteria: NS

Interventions	Calcium carbonate group • 500 mg calcium carbonate/tablet Calcium acetate + magnesium carbonate group • 435 mg calcium acetate + 235 mg magnesium carbonate/tablet Co-interventions: NS
Outcomes	• Serum phosphorus • Serum calcium • Serum magnesium • iPTH
Notes	Conference abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Unclear risk	NS
Blinding of investigators?	Unclear risk	NS
Blinding of outcome assessors?	Unclear risk	NS

Deuber 2003a (*Continued*)

Blinding of data analysers?	Unclear risk	NS
Intention to treat?	Unclear risk	NS

Emmett 1991

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 12 weeks • Lost to follow-up: 16
Participants	Inclusion criteria • Country: USA • Setting: 4 centres in Texas • HD 3 times/week; treatment with phosphorus-binding drugs to reduce serum phosphorus • Number: 69 • Age: 55.5 years • Sex (M/F): 38/31 Exclusion criteria • Pregnant (or intending to become pregnant); mentally unstable; unable to comply with the study protocol; persistent hypercalcaemia (> 11 mg/dL)
Interventions	Calcium group • Calcium acetate: dose to achieve serum phosphorus of 4.5 to 5.5 mg/dL Placebo group • Placebo Co-interventions • Oral or IV vitamin D analogues
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product
Notes	Study supported by a grant from Baintree Laboratories, Baintree MA, and the Renal Research and Education Fund, Baylor University Medical centre, Dallas TX

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	Yes (A)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes

Emmett 1991 (*Continued*)

Blinding of outcome assessors?	Low risk	Yes
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Evenepoel 2009

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 13 weeks • Lost to follow-up: 0 (39 dropped out)
Participants	Inclusion criteria • Country: Belgium, Denmark, France, Italy, Spain, Netherlands • Setting: multicentre (15 sites) • > 18 years; stable PD for > 8 weeks; serum phosphorus > 5.5 mg/dL and serum calcium within the normal range (8.4 to 10.4 mg/dL); compliant with dialysis and phosphate binder therapy • Number ○ sevelamer: 97 ○ calcium: 46 • Mean age (± SD) ○ sevelamer: 54.6 years (± 15.7) ○ calcium: 54.1 years (± 15.8) • Sex (M/F) ○ sevelamer: 65/32 ○ calcium: 28/18 Exclusion criteria • History of peritonitis, dysphagia, bowel obstruction or severe GI motility disorder; unstable concurrent clinical condition; use of anti-arrhythmic or anti seizure medications for the control of these disorders; alcohol or drug abuse; hypersensitivity to sevelamer or hydrochloride
Interventions	Sevelamer group • Sevelamer hydrochloride: starting dose 1600 mg, 3 times/day titrated as necessary to achieve a target serum phosphorus of 3.0 to 5.5 mg/dL Calcium group • Calcium carbonate: starting dose 538 mg, 3 times/day titrated as necessary to achieve a target serum phosphorus of 3.0 to 5.5 mg/dL Co-interventions: No
Outcomes	• Changes in serum phosphorus, calcium, iPTH • Changes in lipids and plasma biomarkers
Notes	P.E. has received speakers' honoraria from Genzyme Corporation. A.O. has received an honorarium from Genzyme Corporation. A.K., S.C. and A.D. are employees of Genzyme Corporation

Evenepoel 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"patients were stratified (anuric or non-anuric) at each treatment site and were randomised to sevelamer hydrochloride or calcium acetate in a 2:1 ratio in order to maximize sevelamer hydrochloride data generation" - method of randomisation not mentioned
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	Low risk	Yes
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Fan 2009

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: UK
	• Setting: multicentre
	• HD for 3 months or more; ≥18 years; maintained on sevelamer hydrochloride alone or in combination with other binders; serum phosphorus level ≥1.76 mmol/L after phosphate binders washout; iPTH ≤ 800 ng/L; serum calcium level within the normal range
	• Number
	  ○ powder: 17
	  ○ tablets: 14
	• Mean age (± SD): 52.9 years ± (13.2)
	• Sex (M/F): 21/10
	Exclusion criteria
	• Severe GI motility disorder; poorly controlled DM; hypertension; any other clinically significant unstable medical condition

Interventions	Powder group • Sevelamer carbonate powder: dose was individualized based on the participants' most recent

Fan 2009 (*Continued*)

	carbonate dose during the run-in period given 3 times/day with meals for weeks 1 to 4 • Sevelamer hydrochloride tablets: 3 times/day with meals for weeks 5 to 8 Tablet group • Sevelamer hydrochloride tablets: dose was individualized based on the participants' most recent hydrochloride dose during the run-in period given 3 times/day with meals for weeks 1 to 4 • Sevelamer carbonate powder: 3 times/day with meals for weeks 5 to 8 Co-interventions: No
Outcomes	• Serum phosphorus • Ca x P product • Serum bicarbonate • Serum calcium • iPTH • Safety of medications
Notes	"Stanley Fan has received speaker's honoraria from Genzyme Corporation and the department has received educational and research grants. Jeremy Heaton, John Hunter and Melissa Plone are employees of Genzyme Corporation"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"patients were randomised in a 1:1 fashion to one of two treatment sequences" method of randomisation not mentioned
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	Unclear risk	NS
Blinding of data analysers?	Unclear risk	NS
Intention to treat?	Low risk	Yes

Ferreira 2008

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 54 weeks • Lost to follow-up: 0
Participants	Inclusion criteria • Country: Portugal

Ferreira 2008 (*Continued*)

	• Setting: multicentre (16 centres)
	• > 18 years; HD 3 times/week (> 3 months); stable serum phosphorus < 8.1 mg/dL for > 1 month before screening and who were receiving treatment with a phosphate binder
	• Number
	  ○ calcium: 47
	  ○ sevelamer: 44
	• Mean age (± SD)
	  ○ calcium: 53.9 years (± 13.7)
	  ○ sevelamer: 55.5 years (± 15.4)
	• Sex (M/F)
	  ○ calcium: 18/17
	  ○ sevelamer: 22/11
	Exclusion criteria
	• Use of aluminium-based binders in the previous year; treatment with medication that are known to affect bone metabolism; tetracycline allergy; alcohol or drug abuse; any significant concurrent clinical condition

Interventions	Calcium group • Calcium carbonate to achieve serum phosphorus of 3.2 to 5.0mg/dL and to maintain serum calcium at <10.4 mg/dL Sevelamer group • Sevelamer hydrochloride to achieve serum phosphorus of 3.2 to 5.0 mg/dL and to maintain serum calcium at < 10.4 mg/dL Co-interventions: No
Outcomes	• Changes in serum biochemical parameters • Changes in parameters of bone mineralization
Notes	• This study was supported by Genzyme Corp. A.F. is a member of a speaker bureau for Genzyme Corp. and an advisor for Abbott; J.M.F. is a consultant for Genzyme Portugal and Amgen Portugal; R.M.H. and A.D. are employees of Genzyme Corp. • Data about age and sex are reported for 33 and 35 participants (sevelamer and calcium respectively)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"randomly assigned to treatment with either sevelamer or calcium in a 1:1 manner. randomisation was performed centrally by an independent study coordinator"
Allocation concealment?	Low risk	Yes (A)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No

Ferreira 2008 (*Continued*)

Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Unclear risk	Yes

Finn 2004

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 6 months • Lost to follow-up: 53

Participants	Inclusion criteria
	• Country: USA
	• Setting: multicentre
	• > 18 years; HD 3 times/week for a minimum of 6 months
	• Number
	  ○ group 1: 27
	  ○ group 2: 29
	  ○ group 3: 30
	  ○ group 4: 26
	  ○ placebo: 32
	• Age:
	  ○ group 1: 53.6 years
	  ○ group 2: 57.5 years
	  ○ group 3: 59.4 years
	  ○ group 4: 54.0 years
	  ○ placebo: 56.8 years
	• Sex (M/F)
	  ○ group 1: 14/13
	  ○ group 2: 19/10
	  ○ group 3: 17/13
	  ○ group 4: 16/10
	  ○ placebo: 13/19
	Exclusion criteria
	• Significant hypercalcaemia; severe hyperparathyroidism; clinically significant abnormal laboratory values; significant GI disease

Interventions	Group 1 • Lanthanum 225 mg/day Group 2 • Lanthanum 675 mg/day Group 3 • Lanthanum 1350 mg/day Group 4 • Lanthanum 2250 mg/day Placebo group

Finn 2004 (*Continued*)

	• Placebo Co-interventions • Oral or IV vitamin D analogues
Outcomes	• Outcomes reported in Finn 2004 ○ Serum phosphorus ○ Serum calcium ○ Ca x P product ○ iPTH • Outcomes reported in **Altmann 2007** ○ Differences in cognitive function
Notes	• **Altmann 2007** ○ This is a secondary analysis ○ This study was funded by Shire Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

Fischer 2006

Methods	• Study design: crossover RCT • Time frame: August 2003 to May 2004 • Follow-up period: 8 months • Lost to follow-up: 0
Participants	Inclusion criteria • Country: USA • Setting: 2 nephrology centres • Life expectancy of at least 12 months; HD 3 times/week for 3 months or longer; maintained on sevelamer in a daily dose $\leq$ 9600 mg as their only phosphate binder; serum phosphorus concentrations at last 2 measurements between 3.0 and 6.5 mg/dL • Number: 21

Fischer 2006 (*Continued*)

	• Age: 63.4 years • Sex (M/F): 13/5 Exclusion criteria • Active bowel obstruction; dysphagia; swallowing disorders; significant GI disease; methanol or drug abuse; need for antiarrhythmic or anti seizure medication to control these condition; poorly controlled DM or hypertension; active vasculitis or active malignancy other than basal cell carcinoma; immunodeficiency virus infection
Interventions	Once per day • Sevelamer hydrochloride standard dose once/day for 4 weeks Three times per day • Sevelamer hydrochloride standard dose 3 times/day for 4 weeks Co-interventions • Vitamin D
Outcomes	• Serum phosphorus level • Serum calcium corrected for albumin level • Ca x P product • iPTH • Albumin • Total, LDL, HDL and non-HDL cholesterol • Triglyceride levels
Notes	This clinical study (GTC-68-209) was funded by Genzyme Corp. Potential conflicts of interest: M.A.P., M.D., S.K.B., and A.T.B are employed by Genzyme Corp, the sponsor of the clinical trial reported in this article

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"patients then were assigned randomly (based on computer generated random numbers)... randomisation was stratified by site to ensure equal allocation of patients within sites"
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Unclear risk	No
Blinding of investigators?	Unclear risk	No
Blinding of outcome assessors?	Unclear risk	No
Blinding of data analysers?	Unclear risk	No
Intention to treat?	Unclear risk	No

FORESEE Study 2008

Methods	• Study design: quasi-RCT • Time frame: NS • Follow-up period: 6 months • Lost to follow-up: 56

Participants	Inclusion criteria
	• Country: USA
	• Setting: multicentre
	• >18 years old; HD 3 times/week
	• Number
	  ○ cohort A: 215
	  ○ cohort B: 142
	• Mean age (range)
	  ○ cohort A: 56.7 years (27 to 89)
	  ○ cohort B: 51.6 years (19 to 87)
	• Sex (M/F)
	  ○ cohort A: 125/90
	  ○ cohort B: 85/57
	Exclusion criteria
	• Phosphorus < 5.5 mg/dL, PTH > 800 pg/mL

Interventions	Initial washout and open-label titration phase • Washout period followed by open label titration of 1500 mg/day, 2250 mg/d and 3000 mg/d to achieve target phosphorus level 3.5 to 5.5 mg/dL Cohort A • In participants who achieved target level, an open label treatment up to 3000 mg/d was adopted Cohort B • In participants who did not reach target, an double blind forced dose titration was followed (forced titration to 3000 mg, 3750 mg or 4500 mg/day)
Outcomes	• Serum phosphorus • Serum calcium • iPTH • Ca x P product • Serum albumin • Side effects (GI)
Notes	This study was funded by Shire Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS; double-dummy, double-blind, forced-dosage titration
Allocation concealment?	Unclear risk	NS

FORESEE Study 2008 (*Continued*)

Blinding of participants?	Unclear risk	No
Blinding of investigators?	Unclear risk	No
Blinding of outcome assessors?	Unclear risk	No
Blinding of data analysers?	Unclear risk	No
Intention to treat?	Unclear risk	Yes

Gallieni 2005

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 12 weeks • Lost to follow-up: NS
Participants	Inclusion criteria • Country: Italy • Setting: NS • HD; previously treated with calcium carbonate; phosphorus level at study entry 5.5 to 8.0 mg/dL • Number: 115 • Age: NS • Sex (M/F): NS Exclusion criteria: NS
Interventions	Sevelamer group • Sevelamer hydrochloride to decrease serum phosphorus level below 5 mg/dL (if phosphorus levels > 5 mg/dL, binder dose could be increased by 1 to 5 capsules/day) Calcium group • Calcium carbonate to decrease serum phosphorus level below 5 mg/dL (if phosphorus levels > 5 mg/dL, binder dose could be increased by 1 to 5 capsules/day) Co-interventions: NS
Outcomes	• Serum calcium • Serum phosphorus • Ca x P product • Serum bicarbonate • Total and LDL cholesterol • Total adverse events • GI side effects • Hypercalcaemia
Notes	• Conference abstract • Dompé Biotec (MG); Honoraria: Genzyme (MG)

Risk of bias

Gallieni 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

Hervas 2003

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 34 weeks • Lost to follow-up: 10
Participants	Inclusion criteria • Country: Spain • Setting: University • > 18 years; HD 3 times/week; calcium-based phosphate binders and vitamin D therapy at stable doses for at least one month • Number: 51 randomised, 40 completed study • Mean age (± SD): 60.4 years (± 15.1) • Sex (M/F): 40% female Exclusion criteria • Unstable medical condition including poorly controlled DM; hypertension or any GI abnormality
Interventions	Sevelamer group • Sevelamer hydrochloride 2 to 4 capsules (403 mg) 3 times/day Calcium group • Calcium acetate 1 to 4 capsules (500 mg) 3 times/day Co-interventions • IV or oral vitamin D analogues
Outcomes	• Serum phosphorus • Serum calcium • Alkaline phosphatase • iPTH • Lipid profile

Hervas 2003 (*Continued*)

Notes	Supported in part by grants of Sociedad Espanola de Dialisisy Transplante (SEDYT)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Hutchison 2005

Methods	• Study design: parallel RCT • Time frame: September 1998 to October 1999 • Follow-up period: 6 months initially with a 6 month and 2 year open-label study extension • Lost to follow-up: NS

Participants	Inclusion criteria
	• Countries: UK, Germany, The Netherlands, Belgium
	• Setting: multicentre (67 centres)
	• >18 years; HD 3 times/week for at least 3 consecutive months (including those who had previously undergone kidney transplantation)
	• Number
	  ○ lanthanum: 510
	  ○ calcium: 257
	• Mean age (± SD)
	  ○ lanthanum: 57.0 years (± 14.3)
	  ○ calcium: 58.4 years (± 13.3)
	• Sex (M/F)
	  ○ lanthanum: 341/169
	  ○ calcium: 164/113
	Exclusion criteria
	• Hypercalcaemia, severe hyperparathyroidism or other clinically significant abnormal laboratory values; lactating females or those with a positive screening pregnancy test; HIV-positive, known hepatitis B or C, or other significant concurrent liver disorder; life-threatening malignancy, multiple myeloma or a history of epilepsy; drug or alcohol abuse within 2 years; treatment with an investigational drug 30 days prior to screening; those who, in the opinion of

Hutchison 2005 (*Continued*)

	the investigators, would not comply with the study requirements
Interventions	Lanthanum group • Lanthanum doses to achieve serum phosphorus < 5.5 mg/dL Calcium group • Calcium carbonate doses to achieve serum phosphorus < 5.5 mg/dL Co-interventions • Oral or IV vitamin D analogues
Outcomes	• Outcomes reported in **Hutchinson 2005** ○ Serum calcium ○ Ca x P product ○ iPTH and vitamin D • Outcomes reported in **Hutchinson 2006** ○ Serum calcium ○ Ca x P product ○ iPTH and vitamin D
Notes	• **Hutchinson 2006** ○ Extension study performed in Germany, Belgium and Netherlands ○ Follow-up period 3 years

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Randomised 2:1, method not described
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	Yes

Itoh 2008

Methods	Study design: parallel RCT Time frame: NS Follow-up period: 8 weeks Lost to follow-up: 35/62 dropped out

Participants	Inclusion criteria
	• Country: Japan
	• Setting: multicentre (4 institutions)
	• HD patients with hyperphosphataemia
	• Number
	  ○ sevelamer: 31 enrolled, 13 completed study
	  ○ colestimide: 31 enrolled, 14 completed study
	• Mean age (± SD)
	  ○ sevelamer: 55.9 years (± 9.8)
	  ○ colestimide: 57.5 years (± 14.7)
	• Sex (M/F)
	  ○ sevelamer: 11/2
	  ○ colestimide: 11/3
	Exclusion criteria: NS

Interventions	Sevelamer group • Sevelamer hydrochloride 3.0 g/day for 8 weeks Colestimide group • Colestimide 3.0 g/day for 8 weeks Co-interventions • $CaCO_3$ 3.0 g/day for weeks 5 to 8
Outcomes	• Serum calcium • Serum phosphorus • Ca x P product • iPTH • Serum alkaline phosphatase
Notes	"During the study period, 35 of the 62 subjects (56.5%) dropped out, almost all because of gastrointestinal problems, such as the onset or exacerbation of constipation, abdominal bloating, nausea or abdominal pain" "The authors acknowledge the support of the Kirin Brewery Pharmacological Fund for this study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No

Itoh 2008 (*Continued*)

Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Ittel 1991

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 8 months • Lost to follow-up: 10
Participants	Inclusion criteria • Country: Germany • Setting: hospital • Previous compliance with medication regimen; acceptable control of serum phosphorus with a moderate dose (< 5 g) of aluminium hydroxide; HD for at least 12 months • Number: 21 • Age: NS • Sex (M/F): NS Exclusion criteria: NS
Interventions	Group 1 • Calcium carbonate gastric-coated preparation and the calcium carbonate enteric coated capsules Group 2 • Calcium carbonate enteric-coated capsules and the calcium carbonate gastric-coated preparation Co-interventions • Aluminium hydroxide
Outcomes	• Serum calcium
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes

Ittel 1991 (*Continued*)

Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Janssen 1996

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 12 months • Lost to follow-up: 16

Participants	Inclusion criteria
	• Country: Netherlands
	• Setting: Multicentre
	• Regular HD
	• Number
	  ○ aluminium: 15
	  ○ calcium acetate: 18
	  ○ calcium carbonate: 20
	• Mean age (± SD)
	  ○ aluminium: 62 years (± 4)
	  ○ calcium acetate: 51 years (± 4)
	  ○ calcium carbonate: 58 years (± 4)
	• Sex(M/F)
	  ○ aluminium: 5/10
	  ○ calcium acetate: 11/7
	  ○ calcium carbonate: 7/13
	Exclusion criteria: NS

Interventions	Aluminium group • Aluminium doses to achieve serum phosphorus < 5.0 mg/dL and serum calcium 8.8 to 11.0 mg/dL Calcium acetate group • Calcium acetate doses to achieve serum phosphorus < 5.0 mg/dL and serum calcium 8.8 to 11.0 mg/dL Calcium carbonate group • Calcium carbonate doses to achieve serum phosphorus < 5.0 mg/dL and serum calcium 8.8 to 11.0 mg/dL Co-interventions • 1-alpha-hydroxyvitamin D3
Outcomes	• Serum calcium • Serum phosphorus • iPTH
Notes	

Janssen 1996 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Jespersen 1991

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 12 months • Lost to follow-up: 3

Participants	Inclusion criteria
	• Country: Denmark
	• Setting: University
	• Chronic HD; >18 years; serum phosphorus > 2 mmol/L without treatment with a phosphate binder to maintain serum phosphorus < 2 mmol/L; serum calcium < 2.6 mmol/L
	• Number
	  ○ aluminium: 5
	  ○ calcium: 6
	• Age (range)
	  ○ aluminium: 41 years (22 to 69)
	  ○ calcium: 49 years (27 to 65)
	• Sex (M/F)
	  ○ aluminium: 2/3
	  ○ calcium: 4/2
	Exclusion criteria
	• Previous parathyroidectomy; ongoing treatment with 1,25(OH2)D3; glucocorticoid treatment

Interventions	Aluminium group • Aluminium hydroxide 33 to 66 mg/kg/day and then calcium carbonate 83 to 166 mg/kg/day Calcium group • Calcium carbonate 83 to 166 mg/kg/day and then aluminium hydroxide 33 to 66 mg/kg/day

Jespersen 1991 (*Continued*)

	Co-interventions: No
Outcomes	• Serum calcium • Serum phosphorus • Effect on bone turnover and hyperparathyroidism • Bone mineral content and extraskeletal calcification • Serum aluminium
Notes	This study was supported by grants from the Danish Medical Research Council and Livens Kemiske Fabrik (Leo Pharmaceuticals), Ballerup, Denmark

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Joy 2003

Methods	• Study design: parallel RCT • Time frame: October 1999 to July 2000 • Follow-up period: 16 weeks • Lost to follow-up: 44

Participants	Inclusion criteria
	• Country: USA
	• Setting: multicentre (14 sites)
	• HD 3 times/week for at least 2 months; > 18 years
	• Number
	  ○ lanthanum: 49
	  ○ placebo: 44
	• Mean age (± SD)
	  ○ lanthanum: 60.2 years (± 13.3)
	  ○ placebo: 60.2 years (± 13.3)
	• Sex (M/F)
	  ○ lanthanum: 65.3% male

Joy 2003 (*Continued*)

	○ placebo: 65.9% male Exclusion criteria • Pregnant or lactating or who were not using appropriate birth control; significant hypercalcaemia or hypocalcaemia, clinically significant abnormal laboratory values, severe hyperparathyroidism; uncontrolled concurrent illness, significant GI disorders, any life-threatening malignancy or current multiple myeloma, or any exposure to other investigational drugs within 30 days prior to the start of the study
Interventions	Lanthanum group • Lanthanum carbonate dose to achieve serum phosphorus < 5.9 mg/dL Placebo group • Matched placebo Co-interventions • Oral or IV vitamin D analogues
Outcomes	• Serum calcium • Ca x P product • iPTH
Notes	"Study supported by Shire Pharmaceutical Development Inc."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	1:1 randomisation; method not mentioned
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

Kinugasa 2001

Methods	• Study design: parallel open-label RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: NS

Kinugasa 2001 (*Continued*)

Participants	Inclusion criteria
	• Country: Japan
	• Setting: Hospital
	• Number
	  ○ calcium: 115
	  ○ sevelamer: 115
	• Age: NS
	• Sex (M/F): NS
	Exclusion criteria: NS

Interventions	Calcium group • Calcium carbonate mean dose 4.7 g/day (range 1.3 to 7.7) Sevelamer group • Sevelamer hydrochloride mean dose 2.8 g/day (range 1.0 to 5.0) Co-interventions: NS
Outcomes	• Serum phosphorus • Serum calcium • iPTH
Notes	Conference abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Unclear risk	NS

Koiwa 2005a

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 12 weeks • Lost to follow-up: 24

Participants	Inclusion criteria
	• Country: Japan
	• Setting: multicentre (9 centres)
	• Not restricted on the basis of aetiology of kidney failure, age, sex, or duration of dialysis, but doctors at each institution decided if patients were suitable for the study.
	• Number (86 enrolled, 62 completed study)
	  ○ sevelamer: 29
	  ○ sevelamer+calcium: 30
	  ○ calcium: 27
	• Mean age (± SD): 57.1 years (± 10.6)
	• Sex (M/F): 39/23
	Exclusion criteria: NS

Interventions	Observation and first non-randomised study periods (all participants) • Calcium carbonate: 3 g/day for weeks 1 to 4 • Sevelamer hydrochloride: 3 g/day for weeks 5 to 8 Sevelamer group • Sevelamer hydrochloride: 6 g/day for weeks 9 to 12 Sevelamer + calcium group • Sevelamer hydrochloride (3 g/day) + calcium carbonate (3 g/day) for weeks 9 to 12 Calcium group • Calcium carbonate (3 g/day) for weeks 9 to 12 Co-interventions: No
Outcomes	• Serum corrected calcium • Serum phosphorus • Serum bicarbonate • iPTH
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Patients were registered with the secretariat and comprised the study group (ROD 21). The patients were randomly allocated to three groups by the secretariat and notified by fax or email
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No

Koiwa 2005a (*Continued*)

Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Kurihara 2005

Methods	• Study design: parallel RCT • Time frame: July 2002 to January 2003 • Follow-up period: 2 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: Japan
	• Setting: multicentre (2)
	• HD, > 20 years; on HD therapy 3 times/week continuously for 3 months; stable dosage of vitamin D (if used) and calcium concentration (3.0 mEq/L) for 1 month
	• Number
	  ○ MCI-196: 21
	  ○ placebo: 12
	• Mean age (± SD)
	  ○ MCI-196: 53.0 years (±10.9)
	  ○ placebo: 58.4 years (± 9.8)
	• Sex (M/F)
	  ○ MCI-196: 18/3
	  ○ placebo: 10/2
	Exclusion criteria: NS

Interventions	MCI-196 group • MCI-196: 2 g (4 tablets) 3 times/day with meals Placebo group • Placebo 3 times/day with meals Co-interventions: No
Outcomes	• Effectiveness and safety of short term administration of MCI-196
Notes	This work was supported by Mitsubishi Pharma Corporation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	2:1 randomisation, method not mentioned

Kurihara 2005 (*Continued*)

Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	Unclear risk	No
Blinding of data analysers?	Unclear risk	No
Intention to treat?	Unclear risk	No

Liu 2006

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 0
Participants	Inclusion criteria • Country: Taiwan • Setting: hospital • Hyperphosphataemia (serum phosphorus level > 6.0 mg/dL) during the 2-week washout period; age ≥ 20 years; HD 3 times/week for at least 3 months; stable doses of calcium-based phosphate binders for at least 1 month if this therapy was given; stable doses of vitamin D replacement for at least 1 month if this therapy was given • Number ○ sevelamer: 37 ○ calcium: 33 • Mean age (± SD) ○ sevelamer: 47.6 years (± 11.9) ○ calcium: 50.4 years (± 10.9) • Sex (M/F) ○ sevelamer: 21/16 ○ calcium: 17/16 Exclusion criteria • Adjusted serum calcium level > 11 mg/dL during the washout period; Hb < 8.0 g/dL; ALT or AST ≥ 3 times the upper limit of normal
Interventions	Sevelamer group • Starting dosage of sevelamer hydrochloride depended on the degree of hyperphosphataemia. ○ > 6.0 to 7.5 mg/dL: 2 tablets, 3 times/day ○ ≥ 7.5 to < 9.0 mg/dL: 3 tablets, 3 times/day ○ ≥ 9.0 mg/dL: 4 tablets, 3 times/day • The dose was titrated every 2 weeks as necessary to achieve a serum phosphorus level of 3.5 to 6.0 mg/dL. The largest daily dose of sevelamer was 12 g. Calcium group • Starting dosage of calcium acetate depended on the degree of hyperphosphataemia.

Liu 2006 (*Continued*)

	○ >6.0 to 7.5 mg/dL: 1 tablet, 3 times/day ○ ≥7.5 to < 9.0 mg/dL: 2 tablets, 3 times/day ○ ≥ 9.0 mg/dL: 3 tablets, 3 times/day • The dose was titrated every 2 weeks as necessary to achieve a serum phosphorus level of 3.5 to 6.0 mg/dL. The largest daily dose of calcium acetate was 12 g. Co-interventions: NS
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH • ALP
Notes	Chugai Pharma Taiwan Ltd. provided the sevelamer hydrochloride tablets for this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

Malluche 2008

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 2 years • Lost to follow-up: 4
Participants	Inclusion criteria • Country: USA, Puerto Rico, Poland, South Africa • Setting: multicentre • >18 years; HD 3 times/week • Number ○ standard phosphate binder: 103 ○ lanthanum: 108 • Mean age (± SD)

	○ standard phosphate binder: 50.6 years (±13.9) ○ lanthanum: 48.5 years (± 13.4) • Sex (M/F) ○ standard phosphate binder: 37/11 ○ lanthanum: 37/14 Exclusion criteria • Abnormal laboratory values at screening or screening calcium level < 7.9 mg/dL; prior GI surgery, GI disorders, GI bleeding within last 6 months, GI malignancy; elevated serum transaminases; HIV-positive status; malignancy; pregnancy or lactation, women of reproductive ages who did not agree to use effective birth control methods; allergy to tetracycline; use of cyclosporin; corticosteroid therapy; parathyroid surgery within 6 months; failed transplant within 2 months before bone biopsy
Interventions	Standard phosphate binder group • Standard phosphate binder to achieve target phosphorus levels of 5.9 mg/dL Lanthanum group • Lanthanum carbonate to achieve target phosphorus levels of 5.9 mg/dL (maximum dose 3 mg/day) Co-interventions: No
Outcomes	• Serum phosphorus • Serum calcium • Serum PTH • Changes in bone turnover • Bone volume • Bone lanthanum content
Notes	Data about age and sex are reported for 51 and 48 participants (lanthanum carbonate and standard phosphate binder respectively)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

McIntyre 2009

Methods	• Study design: parallel, 3-arm RCT • Time frame: February 2004 to May 2005 • Follow-up period: 5 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: UK
	• Setting: multicentre (5 centres)
	• >18 years; HD 3 times/week for at least 3 months
	• Number
	  ○ fermagate-1g: 21
	  ○ fermagate-2g: 21
	  ○ placebo: 21
	• Mean age (± SD)
	  ○ fermagate-1g: 60.6 years (± 15.2)
	  ○ fermagate-2g: 58.1 years (± 14.0)
	  ○ placebo: 58.6 years (± 13.8)
	• Sex (M/F)
	  ○ fermagate-1g: 16/5
	  ○ fermagate-2g: 13/8
	  ○ placebo: 16/5
	Exclusion criteria
	• History of haemochromatosis; serum ferritin concentration ≥1000 ng/mL; clinically significant GI motility disorder; dysphagia or swallowing disorder; Hb < 10 g/dL

Interventions	Fermagate-1g group • Fermagate 1 g, 3 times/day Fermagate-2g group • Fermagate: 2 g, 3 times/day Placebo group • Matching placebo Co-interventions • Vitamin D supplements was to remain unchanged during the study period
Outcomes	• Serum phosphorus • Adverse events and serious adverse events • Death • Serum magnesium • Serum calcium • Other haematology and biochemistry parameters
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

McIntyre 2009 (*Continued*)

Adequate sequence generation?	Low risk	"A randomisation schedule was generated, each treatment packed accordingly in a block size of six (two sets of each treatment per block) and sent to the site. A unique randomisation number was indicated on the label of each drug pack and sequentially dispensed to new patients at each centre."
Allocation concealment?	Low risk	Adequate
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	Low risk	Yes
Blinding of data analysers?	High risk	No
Intention to treat?	Low risk	Yes

Pflanz 1994

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 6 weeks • Lost to follow-up: 8
Participants	Inclusion criteria • Country: UK • Setting: hospital • HD (4 hour dialysis treatment 3 times/week) whose usual phosphate binding therapy consisted of calcium carbonate in a total daily dose of between 2.5 and 5.0 g • Number: 31 • Mean age (range): 59.5 years (23 to 79) • Sex (M/F): 21/10 Exclusion criteria • Other doses or on other phosphate binders
Interventions	Calcium acetate group • Calcium acetate: 2 g, 3 times/day Calcium carbonate group • Calcium carbonate: 2g, 3 times/day Co-interventions: No
Outcomes	• Serum calcium • Serum phosphorus • Ca x P product

Pflanz 1994 (*Continued*)

	• iPTH
Notes	Financial support from Tayside Health Board Research Committee

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Phelps 2002

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 2

Participants	Inclusion criteria
	• Country: USA
	• Setting: multicentre
	• Men >18 years; CrCl 10 to 70 mL/min; iPTH > 65 pg/mL; 1,25 dihydroxyvitamin D > 15 ng/mL; F-thyroxine 0.77 to 1.61 ng/mL; TSH 0.35 to 5.5 µIU/mL
	• Number
	  ○ calcium-2g: 8
	  ○ calcium-6g: 10
	• Mean age (± SD)
	  ○ calcium-2g: 71.3 years (± 8.6)
	  ○ calcium-6g: 69.4 years (± 7.3)
	• Sex (M/F): 100% male
	Exclusion criteria
	• Current corticosteroid ingestion; any allograft; any disorder other than CKD associated with bone loss

Interventions	Calcium-2g group • Calcium acetate 2 g/day Calcium-6g group

Phelps 2002 (*Continued*)

	• Calcium acetate 6 g/day Co-interventions: No
Outcomes	• iPTH • Changes in the ratio of phosphorus to creatinine excreted • Changes in serum calcium, phosphorus and 1,25 dihydroxyvitamin D • Changes in BMD at sites in lumbar spine and femur
Notes	Financial support from the National Kidney Foundation of Northeast New York

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	Low risk	Yes
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Ring 1993

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 3 weeks • Lost to follow-up: 0
Participants	• Country: Denmark • Setting: Hospital • Chronic HD, 4 hours 3 times/week or 4 hours 2 times/week; treatment with calcium carbonate as the only phosphorus binder for at least 1 month; no vitamin D • Number: 21 enrolled, 15 analysed • Age range: 19 to 75 years • Sex(M/F): 9/6 Exclusion criteria: NS
Interventions	Calcium acetate group • 3.8 g/day Calcium carbonate group • 4 g/day

Ring 1993 (*Continued*)

	Co-interventions: No
Outcomes	• Serum phosphorus • Serum calcium • iPTH
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"Using random numbers patients were assigned to receive either calcium acetate or calcium carbonate as the first drug and then crossed over to the other in the last period."
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Roxe 1989

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 2
Participants	Inclusion criteria • Country: USA • Setting: University • 18 to 70 years; HD 3 times/week • Number: 27 randomised, 21 analysed • Age: NS • Sex (M/F): 6/15 Exclusion criteria • Treatment with phenytoin, cardiac glycosides or calcium carbonate; chronic anticoagulation

Roxe 1989 (*Continued*)

Interventions	Aluminium group • Aluminium hydroxide 3 g/day and then sucralfate 6 g/day to achieve serum phosphorus < 4.5 mg/dL Sucralfate group • Sucralfate 6 g/day and then aluminium hydroxide 3 g/day to achieve serum phosphorus < 4.5 mg/dL Co-interventions: No
Outcomes	• Serum phosphorus • Serum aluminium
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Rudnicki 1994

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 24 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: Denmark
	• Setting: hospital
	• HD 3 times/week (6 months to 10 years); iPTH above the normal range and serum ionised calcium within or below it
	• Number
	  ○ calcium: 9
	  ○ placebo: 9
	• Mean age (range): 55 years (31 to 70)

Rudnicki 1994 (*Continued*)

	• Sex (M/F): 13/5 Exclusion criteria: NS
Interventions	Calcium group • Calcium carbonate 2 g/day for 6 months Placebo group • Placebo for 6 months Co-interventions • Oral vitamin D analogues
Outcomes	• Bone markers
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"randomised by a computer-generated list to receive in a double-blind manner..."
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	"in a double-blind manner"
Blinding of investigators?	Low risk	"in a double-blind manner"
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Russo 2007

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 24 ± 4.2 months • Lost to follow-up: 6
Participants	Inclusion criteria • Country: Italy • Setting: NS • Constant low dietary phosphorus intake; stable serum concentration of phosphorus, calcium, Ca x P product, PTH; no previous therapy with aluminium or calcium based phosphate binders, vitamin D sterols, statins; comparable mean baseline total calcium score at CT scan • Number ○ low phosphate diet: 30 randomised, 29 analysed

	○ sevelamer: 30 randomised, 27 analysed ○ calcium carbonate: 30 randomised, 28 analysed • Mean age (± SD) ○ low phosphate diet: 54.4 years (± 3.7) ○ sevelamer: 55.2 years (± 12.0) ○ calcium carbonate: 54.4 years (± 12.9) • Sex (M/F) ○ low phosphate diet: 25/4 ○ sevelamer: 23/5 ○ calcium carbonate: 24/3 Exclusion criteria • < 18 years; symptomatic coronary disease, past myocardial infarction, previous coronary surgery/angioplasty, stroke, arrhythmia; progressive kidney disease; diabetes
Interventions	Low phosphate diet • Not described Sevelamer group • Sevelamer hydrochloride:1600 mg/day • Low phosphate diet Calcium carbonate group • Calcium carbonate: 2 g/day • Low phosphate diet Co-interventions: No
Outcomes	• Changes in total calcium score • Progression of CAC • Changes in biochemical variables
Notes	Data about age and sex are reported for 29, 28 and 27 participants (controls, calcium carbonate and sevelamer respectively) This is an unsupported study. No funding was provided by the Government, corporations, or manufacturers of the drugs evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	participants were randomly assigned to low-phosphate diet alone and to receive either calcium carbonate or sevelamer by the coauthor (YB), who was unaware of their baseline demographic and clinical characteristics and biochemistry
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No

Russo 2007 (*Continued*)

Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Sadek 2003

Methods	• Study design: parallel RCT • Time frame: November 2000 to April 2001 • Follow-up period: 5 months • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: France
	• Setting: Hospital
	• HD 3 times/week
	• Number
	  ○ sevelamer: 21
	  ○ calcium: 21
	• Age: NS
	• Sex (M/F): NS
	Exclusion criteria: NS

Interventions	Sevelamer group • Initial dose: 1.2 g at lunch and dinner • Dose progressively increased to 4.4 g/d Calcium group • Continued their pre-existing treatment with calcium carbonate Co-interventions: No
Outcomes	• Serum calcium • Serum phosphorus • Serum PTH • 25-OH vitamin D • Triglycerides, LDL, HDL, total cholesterol
Notes	The result were analysed in only 16 participants of the calcium carbonate group and 15 of the sevelamer group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"patients were randomised into two groups with stratification for PTH"
Allocation concealment?	Unclear risk	NS (B)

Sadek 2003 (*Continued*)

Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Saif 2007

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 12 weeks • Lost to follow-up: 23
Participants	Inclusion criteria • Country: Pakistan • Setting: HD centre • ESKD, on maintenance HD for at least 3 months • Number: 64 randomised, 41 analysed • Mean age (± SD): 42.6 years (± 15.7) • Sex(M/F): 24/17 Exclusion criteria • Previous parathyroidectomy and advanced malignancy/metastasis
Interventions	Calcium acetate group • Calcium acetate: 4.002 g/day • After crossover: 5.625 g/day calcium carbonate Calcium carbonate group • Calcium carbonate: 5.625g/day • After crossover: 4.002 g/day calcium acetate
Outcomes	• Serum urea • SCr • Calcium • Albumin • Phosphate
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS

Saif 2007 (*Continued*)

Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Unclear risk	NS
Blinding of investigators?	Unclear risk	NS
Blinding of outcome assessors?	Unclear risk	NS
Blinding of data analysers?	Unclear risk	NS
Intention to treat?	Unclear risk	No

Salusky 1991

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 13 months • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: US
	• Setting: Hospital
	• Chronic PD
	• Number
	  ○ aluminium: 10 randomised, 7 analysed
	  ○ calcium: 12 randomised, 10 analysed
	• Mean age (± SD)
	  ○ aluminium: 14.1 years (3.7)
	  ○ calcium: 15.5 years (3.7)
	• Sex (M/F)
	  ○ aluminium: 3/4
	  ○ calcium: 2/8
	Exclusion criteria: NS

Interventions	Aluminium group • Aluminium hydroxide: adjusted according to serum phosphorus levels, maximal daily dose was limited to 30 mg/kg Calcium • Calcium carbonate: adjusted according to serum phosphorus levels, dose range 2.5 to 12 g Co-intervention • Oral calcitriol
Outcomes	• Serum calcium • Serum phosphorus • iPTH
Notes	

Salusky 1991 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Schaefer 1991

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 7 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: Germany
	• Setting: Hospital
	• Chronic HD (for at least 40 months)
	• Number: 47
	  ○ group 1: 12
	  ○ group 2: 12
	  ○ group 3: 10
	  ○ group 4: 13
	• Mean age: 62.5 years
	• Sex (M/F): 21/26
	Exclusion criteria: NS

Interventions	Group 1 • Calcium acetate: oral 6 g/day Group 2 • Calcium acetate: oral 6 g/day • Calcitriol: 4 µg twice/week Group 3 • Calcium acetate: 6 g/day • Calcitriol: 0.5 µg twice/week Group 4

Schaefer 1991 (*Continued*)

	• Aluminium hydroxide: given aluminium hydroxide by way of phosphate-reducing medication exclusively during the first study period and the second study period • Calcitriol: 4 µg twice/week Co-interventions: NS
Outcomes	• Serum calcium • Serum phosphorus • iPTH
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Shaheen 2004

Methods	• Study design: crossover RCT • Time frame: March 2003 to June 2003 • Follow-up period: 8 weeks • Lost to follow-up: 3
Participants	Inclusion criteria • Country: Kingdom of Saudi Arabia • Setting: Hospital • 15 to 75 years; chronic HD (2 or 3 times/week) for at least 3 months and optimally dialysed as judged by usual dialysis and serum chemistry parameters; current phosphorus: 5.5 mg/dL • Number: 20 • Mean age (± SD): 42.7 years (± 9.9) • Sex (M/F): 12/8 Exclusion criteria • Serious GI disease including dysphasia, vomiting, motility disorder, major intestinal surgery or markedly irregular bowel function; alcohol abuse or drug dependence; clinically relevant liver disease, uncontrolled diabetes or uncontrolled hypertension, malignancy, human

Shaheen 2004 (*Continued*)

	immunodeficiency virus infection, active vasculitis or illness at the time of entry to the study
Interventions	Sevelamer group • Sevelamer hydrochloride: 800 mg tablets orally 3 times/day post meals Calcium group • Calcium carbonate (Caltrate 600): 1500 mg tablet 3 times/day post meals
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH levels • Lipid profile
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Shigematsu 2008

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 0
Participants	Inclusion criteria • Country: Japan • Setting: Multicentre • > 20 years; on maintenance HD with hyperphosphataemia; serum phosphate levels > 5.6 mg/dL at 1 week after the initiation of the washout period • Number ○ lanthanum: 126

Shigematsu 2008 (*Continued*)

	○ calcium: 132 • Mean age (± SD) ○ lanthanum: 58.8 years (± 10.5) ○ calcium: 56.1 years (± 11.5) • Sex (M/F) ○ lanthanum: 87/39 ○ calcium: 87/45 Exclusion criteria • Serum phosphate levels > 10 mg/dL at the start of the washout period or 11.0 mg/dL during the washout period; corrected serum calcium level of < 7.0 mg/dL; iPTH > 1 pg/mL at the start of the washout period
Interventions	Lanthanum group • Lanthanum carbonate: starting dose 750 mg/day Calcium group • Calcium carbonate: starting dose 1500 mg/day Co-interventions: No
Outcomes	• Change in serum phosphate levels • Serum calcium • iPTH • Serum phosphorus
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	Unclear risk	NS
Blinding of data analysers?	Unclear risk	NS
Intention to treat?	Low risk	Yes

Spasovski 2006

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 3 years • Lost to follow-up: 1

Participants	Inclusion criteria
	• Country: Macedonia
	• Setting: Dialysis centre
	• Dialysis patients who had required oral phosphate binders to control serum phosphorus levels
	• Number
	  ○ lanthanum: 12
	  ○ calcium: 12
	• Mean age (± SD)
	  ○ lanthanum: 55 years (± 10)
	  ○ calcium: 57 years (± 10)
	• Sex (M/F)
	  ○ lanthanum: 7/5
	  ○ calcium: 7/5
	Exclusion criteria
	• Any significant GI problem; history of treatment with corticosteroids or bisphosphonates; hypocalcaemia at screening

Interventions	Lanthanum group • Lanthanum carbonate: to achieve optimal control of serum phosphorus levels (< 1.8 mmol/L) (maximum dose of 3000 mg/day) Calcium group • Calcium carbonate: to achieve optimal control of serum phosphorus levels (< 1.8 mmol/L) (maximum dose of 4000 mg/day) Co-interventions: No
Outcomes	• Biochemical parameters • Lanthanum level in plasma and bone • Safety and efficacy of treatments
Notes	• Treatment period was 1 year • During the other 2 years all participants were switched to calcium carbonate

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No

Spasovski 2006 (*Continued*)

Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	No

Spiegel 2007

Methods	• Study design: parallel, open-label RCT • Time frame: NS • Follow-up period: 12 weeks • Lost to follow-up: NS

Participants	Inclusion criteria
	• Country: USA
	• > 18 years; chronic HD for at least 3 months; receiving phosphate binders before entry into the study; serum calcium of 8.0 to 10.2 mg/dL and serum phosphorus of 3.0 to 6.9 mg/dL
	• Number
	  ○ magnesium: 20
	  ○ calcium: 10
	• Mean age (± SD)
	  ○ magnesium: 55.5 years (± 12.6)
	  ○ calcium: 55.9 years (± 12.0)
	• Sex (M/F)
	  ○ magnesium: 12/8
	  ○ calcium: 4/6
	Exclusion criteria
	• Frequent diarrhoea; declined to give informed consent

Interventions	Magnesium group • Magnesium carbonate: to achieve the target phosphorus of < 5.5 mg/dL Calcium group • Calcium acetate: to achieve the target phosphorus of < 5.5 mg/dL Co-interventions: No
Outcomes	• Serum phosphorus • Serum magnesium • Serum calcium • iPTH • Serum bicarbonate
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Spiegel 2007 (*Continued*)

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No
Intention to treat?	High risk	no

Sprague 2009a

Methods	• Study design: parallel RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: USA
	• Setting: multicentre (28 dialysis centres)
	• ≥18 years; eGFR 15 to 59 mL/min/1.73 m² at screening; undergoing physician care for CKD for > 2 months; not expected to begin dialysis for ≥ 4 months
	• Number
	  ○ lanthanum: 78
	  ○ placebo: 41
	• Mean age (± SD)
	  ○ lanthanum: 61.8 years (± 12.9)
	  ○ placebo: 63.0 years (± 12.7)
	• Sex (M/F)
	  ○ lanthanum: 40/38
	  ○ placebo: 21/20
	Exclusion criteria
	• Requirement for treatment with cinacalcet HCl or compounds containing phosphorus, aluminium, magnesium or calcium; AKI within 12 weeks of screening; rapidly progression of glomerulonephritis; significant GI surgery or disorders; evidence of clinically significant liver disease; pregnant or lactating women; women on reproductive potential who did not agree to use effective contraception

Interventions	Lanthanum group • Lanthanum carbonate: 750 mg/day to a maximum of 3000 mg/day to achieve a target serum phosphorus level of < 4.0 mg/dL Placebo group • Matching placebo

Sprague 2009a (*Continued*)

	Co-interventions • Participants receiving vitamin D or calcium supplements before screening could continue treatment during the study. Treatments could not be initiated during the study, and the dose could not be increased, but it could be decreased if a patient experienced hypercalcaemia
Outcomes	• Change in serum phosphorus • Change in Ca x P product • Change in iPTH levels • Safety and tolerability of treatment
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Randomised 2:1, method not described
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	Low risk	Yes
Blinding of investigators?	Low risk	Yes
Blinding of outcome assessors?	Unclear risk	NS
Blinding of data analysers?	Unclear risk	NS
Intention to treat?	High risk	No

Sprague 2009b

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 0

Participants	Inclusion criteria
	• Country: USA, Puerto Rico, Germany, UK
	• ≥18 years; CKD stage 5; undergoing stable HD 2 to 3 times/week for at least 2 months before screening
	• Number
	  ○ lanthanum: 95
	  ○ sevelamer: 86
	• Mean age (± SD): 55.5 years (± 13.1)
	• Sex (M/F): 102/79
	Exclusion criteria
	• Previously received treatment with lanthanum carbonate or sevelamer; iPTH levels > 600

Sprague 2009b (*Continued*)

	pg/mL
Interventions	Lanthanum group • Lanthanum carbonate: 2250 mg/day. After the first week, dose was increased to 3000 mg/day Sevelamer group • Sevelamer hydrochloride: 4800 mg/day. After the first week, dose was increased to 6400 mg/day Co-interventions: No
Outcomes	• Serum phosphorus • Serum calcium • PTH levels • Safety and tolerability of treatments
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	Unclear risk	NS
Blinding of data analysers?	Unclear risk	NS
Intention to treat?	Low risk	Yes

Tzanakis 2008

Methods	• Study design: quasi-RCT • Time frame: NS • Follow-up period: 6 months • Lost to follow-up: 1 (who moved to another hospital)

Participants	Inclusion criteria
	• Country: Greece
	• Setting: Dialysis unit
	• Stable ESKD, on maintenance HD
	• Number
	  ○ magnesium: 26
	  ○ calcium: 25

	• Mean age (± SD)
	  ○ magnesium: 63.2 years (± 12.2)
	  ○ calcium: 65.3 years (± 11.7)
	• Sex (M/F): NS
	Exclusion criteria
	• < 18 years; HD < 6 months; psychiatric or other disorders leading to non-compliance; unlikeliness to continue HD for more than 6 months in the same facility; critical illness at the time of recruitment; previous parathyroidectomy; severe hyperparathyroidism (iPTH > 500 pg/mL); normal serum phosphorus (< 5.5 mg/dL) without phosphate binders; diseases resulting in diarrhoea; lack of informed consent

Interventions	Magnesium group • Magnesium carbonate: 750 mg/day Calcium group • Calcium carbonate: 1260 mg/day Co-interventions: None
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH levels
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	High risk	4 participants did not agree to consume magnesium carbonate and they were allocated to the calcium carbonate group
Blinding of participants?	Unclear risk	NS
Blinding of investigators?	Unclear risk	NS
Blinding of outcome assessors?	Unclear risk	NS
Blinding of data analysers?	Unclear risk	NS
Intention to treat?	Unclear risk	No

Yang 2002

Methods	• Study design: crossover RCT • Time frame: NS • Follow-up period: 8 weeks • Lost to follow-up: 9
Participants	Inclusion criteria • Country: USA • Setting: Multicentre • HD; concentration of calcium in the dialysate was 2.5 mEq/L; predictable compliance with their medical regimen; serum iron or ferritin level within or below the normal range; serum calcium of 8 to 10 mg/dL • Number: 54 randomised, 45 analysed • Mean age: 52.5 ± 11.8 years • Sex (M/F): 22/23 Exclusion criteria • < 18 years; pregnancy; active GI bleeding; use of calcitriol; tertiary hyperparathyroidism; immediate post-operative parathyroidectomy (within the first 3 months or serum calcium < 7 mg/dL); severe congestive heart failure; anorexia and cachexia; DM with gastroparesis and malignancy
Interventions	Group 1 • Ferric citrate: 1g, 3 times/day Group 2 • Calcium carbonate: 1g, 3 times/day Co-interventions: No
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH levels
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS (B)
Blinding of participants?	High risk	No
Blinding of investigators?	High risk	No
Blinding of outcome assessors?	High risk	No
Blinding of data analysers?	High risk	No

Yang 2002 (*Continued*)

Intention to treat?	High risk	No

AKI - acute kidney injury; ALP - alkaline phosphatase; AST - aspartate aminotransferase; Ca x P product - calcium by phosphorus; CAC - coronary artery calcium/calcification; CAPD - continuous ambulatory peritoneal dialysis; CKD - chronic kidney disease; CrCl - creatinine clearance; DKD - diabetic kidney disease; DM - diabetes mellitus; ESKD - end-stage kidney disease; GI - gastrointestinal; Hb - haemoglobin; HD - haemodialysis; iPTH - intact parathyroid hormone; ITT - intention to treat; NS - not stated; PD - peritoneal dialysis

DATA AND ANALYSES

Comparison 1. Calcium salts versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Hypercalcaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Serum phosphorus	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 2. Calcium acetate versus calcium carbonate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Hypercalcaemia	2	88	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.11, 10.99]
3 Adverse gastrointestinal events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Gastritis	1	30	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.41, 3.77]
3.2 Diarrhoea	2	53	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.22, 12.56]
3.3 Constipation	2	53	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.38, 3.52]
3.4 Abdominal bloating	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.5 Combined	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Serum phosphorus	5	143	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.61, 0.24]
5 Serum calcium	5	143	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.35, 0.17]
6 Serum calcium x phosphorus product	2	31	Mean Difference (IV, Random, 95% CI)	-4.92 [-10.03, 0.19]
7 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Serum bicarbonate	2	53	Mean Difference (IV, Random, 95% CI)	0.21 [-1.32, 1.74]
9 Serum alkaline phosphatase	4	74	Mean Difference (IV, Random, 95% CI)	1.42 [-8.99, 11.82]

Comparison 3. Calcium ketoglutarate versus other calcium salts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse gastrointestinal events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Gastritis	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Diarrhoea	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Gastroparesis	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Combined	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Serum phosphorus	2	48	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.32, 0.12]

4 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Total calcium	0		Mean Difference (IV, Random, 95% CI)	Not estimable
4.2 Ionised calcium	1		Mean Difference (IV, Random, 95% CI)	Not estimable
5 Serum calcium x phosphorus product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Serum bicarbonate	2	62	Mean Difference (IV, Random, 95% CI)	1.66 [1.03, 2.29]

Comparison 4. Sevelamer versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse gastrointestinal events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Gastritis	1	36	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.10, 9.96]
2.2 Diarrhoea	1	36	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 3.96]
2.3 Gastroparesis	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Serum phosphorus	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Total calcium	1		Mean Difference (IV, Random, 95% CI)	Not estimable
4.2 Ionised calcium	0		Mean Difference (IV, Random, 95% CI)	Not estimable
5 Serum bicarbonate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Serum total cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 5. Sevelamer versus calcium salts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	10	3079	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.46, 1.16]
1.1 Sevelamer versus calcium acetate	6	613	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.13, 1.38]
1.2 Sevelamer versus calcium carbonate	1	36	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	2430	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.57, 1.27]
2 Hypercalcaemia	12	1144	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.35, 0.59]
2.1 Sevelamer versus calcium acetate	6	634	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.27, 0.66]
2.2 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	2	309	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.26, 0.72]
2.3 Sevelamer versus calcium carbonate	4	201	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.14, 0.78]
3 Gastrointestinal adverse events	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

3.1 Nausea/vomiting	1	203	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.57, 1.86]
3.2 Diarrhoea	1	203	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.55, 1.95]
3.3 Abdominal bloating	1	56	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.49, 11.01]
3.4 Constipation	2	259	Risk Ratio (M-H, Random, 95% CI)	2.63 [1.29, 5.35]
3.5 Combined	5	498	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.11, 2.25]
4 Serum phosphorus	16	3126	Mean Difference (IV, Random, 95% CI)	0.23 [0.04, 0.42]
4.1 Sevelamer versus calcium acetate	7	612	Mean Difference (IV, Random, 95% CI)	0.25 [-0.20, 0.71]
4.2 Sevelamer versus calcium carbonate	6	519	Mean Difference (IV, Random, 95% CI)	0.46 [0.17, 0.74]
4.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	1995	Mean Difference (IV, Random, 95% CI)	0.09 [-0.02, 0.20]
5 Serum calcium	15	3039	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.45, -0.24]
5.1 Sevelamer versus calcium acetate	6	541	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.53, -0.20]
5.2 Sevelamer versus calcium carbonate	6	519	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.74, 0.01]
5.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	1979	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.46, -0.23]
6 Serum calcium x phosphorus product	11	2674	Mean Difference (IV, Random, 95% CI)	0.86 [-0.69, 2.40]
6.1 Sevelamer versus calcium acetate	5	486	Mean Difference (IV, Random, 95% CI)	2.56 [-0.72, 5.84]
6.2 Sevelamer versus calcium carbonate	3	209	Mean Difference (IV, Random, 95% CI)	3.09 [0.15, 6.02]
6.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	1979	Mean Difference (IV, Random, 95% CI)	-0.37 [-1.42, 0.69]
7 Serum iPTH	12	1080	Mean Difference (IV, Random, 95% CI)	59.74 [27.47, 92.02]
7.1 Sevelamer versus calcium acetate	5	418	Mean Difference (IV, Random, 95% CI)	89.91 [12.37, 167.44]
7.2 Sevelamer versus calcium carbonate	5	353	Mean Difference (IV, Random, 95% CI)	46.95 [-2.39, 96.29]
7.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	2	309	Mean Difference (IV, Random, 95% CI)	55.00 [0.82, 109.18]
8 Serum bicarbonate	5	381	Mean Difference (IV, Random, 95% CI)	-1.43 [-2.07, -0.79]
8.1 Sevelamer versus calcium acetate	2	227	Mean Difference (IV, Random, 95% CI)	-1.63 [-2.47, -0.79]
8.2 Sevelamer versus calcium carbonate	3	154	Mean Difference (IV, Random, 95% CI)	-1.17 [-2.15, -0.18]
9 Serum alkaline phosphatase	4	187	Mean Difference (IV, Random, 95% CI)	10.13 [-11.28, 31.53]
9.1 Sevelamer versus calcium acetate	3	151	Mean Difference (IV, Random, 95% CI)	14.40 [-8.38, 37.18]
9.2 Sevelamer versus calcium carbonate	1	36	Mean Difference (IV, Random, 95% CI)	-22.0 [-84.47, 40.47]
10 Serum total cholesterol	10	1705	Mean Difference (IV, Random, 95% CI)	-19.16 [-27.42, -10.90]

10.1 Sevelamer versus calcium acetate	3	151	Mean Difference (IV, Random, 95% CI)	-14.29 [-27.61, -0.98]
10.2 Sevelamer versus calcium carbonate	4	190	Mean Difference (IV, Random, 95% CI)	-14.06 [-25.14, -2.99]
10.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	1364	Mean Difference (IV, Random, 95% CI)	-27.09 [-44.59, -9.60]
11 Serum 1, 25 dihydroxyvitamin D	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 Sevelamer versus calcium acetate	1		Mean Difference (IV, Random, 95% CI)	Not estimable

Comparison 6. Lanthanum carbonate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	154	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Adverse gastrointestinal events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Gastritis	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Diarrhoea	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Gastroparesis	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Combined	2	154	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.45, 2.45]
3 Serum phosphorus	2	154	Mean Difference (IV, Random, 95% CI)	-2.01 [-2.52, -1.50]
4 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Total calcium	1		Mean Difference (IV, Random, 95% CI)	Not estimable
4.2 Ionised calcium	0		Mean Difference (IV, Random, 95% CI)	Not estimable
5 Serum calcium x phosphorus product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 7. Lanthanum carbonate versus calcium salts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	351	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Hypercalcaemia	2	351	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.09, 0.31]
3 Adverse gastrointestinal events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Gastritis	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2 Diarrhoea	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Constipation	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 Combined	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Serum phosphorus	2	122	Mean Difference (IV, Random, 95% CI)	0.22 [-0.32, 0.75]
5 Serum calcium	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Total calcium	2	122	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.57, -0.03]
5.2 Ionised calcium	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

6 Serum calcium x phosphorus product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Serum iPTH	2	364	Mean Difference (IV, Random, 95% CI)	100.91 [-75.30, 277.12]
8 Serum alkaline phosphatase	2	824	Mean Difference (IV, Random, 95% CI)	29.01 [2.28, 55.74]

Analysis 1.1. Comparison 1 Calcium salts versus placebo, Outcome 1 All-cause mortality.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 1 Calcium salts versus placebo

Outcome: 1 All-cause mortality

Study or subgroup	Calcium salts n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Rudnicki 1994	0/9	0/9		0.0 [0.0, 0.0]

Analysis 1.2. Comparison 1 Calcium salts versus placebo, Outcome 2 Hypercalcaemia.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 1 Calcium salts versus placebo

Outcome: 2 Hypercalcaemia

Study or subgroup	Calcium salts n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Rudnicki 1994	0/9	0/9		0.0 [0.0, 0.0]

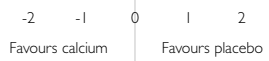
Analysis 1.3. Comparison 1 Calcium salts versus placebo, Outcome 3 Serum phosphorus.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 1 Calcium salts versus placebo

Outcome: 3 Serum phosphorus

Study or subgroup	Calcium salts N	Mean(SD)[mg/dL]	Placebo N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Rudnicki 1994	9	5.21 (0.53)	9	6.03 (0.37)		-0.82 [-1.24, -0.40]



Analysis 1.4. Comparison 1 Calcium salts versus placebo, Outcome 4 Serum calcium.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 1 Calcium salts versus placebo

Outcome: 4 Serum calcium

Study or subgroup	Calcium salts N	Mean(SD)[mg/dL]	Placebo N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Rudnicki 1994	9	5.04 (0.36)	9	4.52 (0.48)		0.52 [0.13, 0.91]

Analysis 2.1. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 1 All-cause mortality.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 1 All-cause mortality

Study or subgroup	Calcium acetate n/N	Calcium carbonate n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Almirall 1994	0/4	0/4		0.0 [0.0, 0.0]
Caravaca 1992	1/31	1/35		1.13 [0.07, 17.30]

Analysis 2.2. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 2 Hypercalcaemia.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 2 Hypercalcaemia

Study or subgroup	Calcium acetate n/N	Calcium carbonate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Caravaca 1992	4/30	10/35		65.7 %	0.47 [0.16, 1.34]
Pflanz 1994	2/11	0/12		34.3 %	5.42 [0.29, 101.77]
Total (95% CI)	**41**	**47**		**100.0 %**	**1.08 [0.11, 10.99]**

Total events: 6 (Calcium acetate), 10 (Calcium carbonate)

Heterogeneity: $Tau^2 = 1.84$; $Chi^2 = 2.46$, df = 1 (P = 0.12); $I^2 = 59\%$

Test for overall effect: Z = 0.07 (P = 0.95)

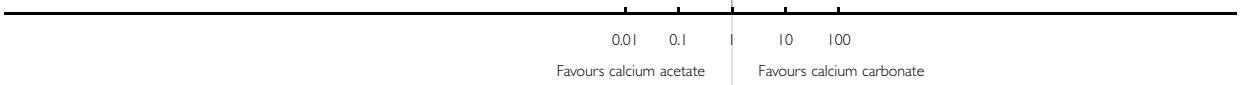
Analysis 2.3. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 3 Adverse gastrointestinal events.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 3 Adverse gastrointestinal events

Study or subgroup	Calcium acetate n/N	Calcium carbonate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Gastritis					
d'Almeida Filho 2000	5/15	4/15		100.0 %	1.25 [0.41, 3.77]
Subtotal (95% CI)	**15**	**15**		**100.0 %**	**1.25 [0.41, 3.77]**
Total events: 5 (Calcium acetate), 4 (Calcium carbonate)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.40 (P = 0.69)					
2 Diarrhoea					
d'Almeida Filho 2000	1/15	1/15		57.3 %	1.00 [0.07, 14.55]
Pflanz 1994	1/11	0/12		42.7 %	3.25 [0.15, 72.36]
Subtotal (95% CI)	**26**	**27**		**100.0 %**	**1.65 [0.22, 12.56]**
Total events: 2 (Calcium acetate), 1 (Calcium carbonate)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 0.49 (P = 0.63)					
3 Constipation					
d'Almeida Filho 2000	4/15	4/15		87.2 %	1.00 [0.31, 3.28]
Pflanz 1994	1/11	0/12		12.8 %	3.25 [0.15, 72.36]
Subtotal (95% CI)	**26**	**27**		**100.0 %**	**1.16 [0.38, 3.52]**
Total events: 5 (Calcium acetate), 4 (Calcium carbonate)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 0.27 (P = 0.79)					
4 Abdominal bloating					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Calcium acetate), 0 (Calcium carbonate)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 Combined					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Calcium acetate), 0 (Calcium carbonate)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 2.4. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 4 Serum phosphorus.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

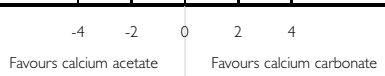
Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 4 Serum phosphorus

Study or subgroup	Calcium acetate N	Mean(SD)[mg/dL]	Calcium carbonate N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Almirall 1994	4	4.79 (0.6)	4	4.94 (0.8)		18.7 %	-0.15 [-1.13, 0.83]
Borrego 2000	7	4.8 (0.9)	9	4.6 (0.9)		22.7 %	0.20 [-0.69, 1.09]
Caravaca 1992	31	5.57 (1.54)	35	5.97 (1.48)		33.6 %	-0.40 [-1.13, 0.33]
d'Almeida Filho 2000	15	4.6 (1.32)	15	4.57 (1.57)		16.7 %	0.03 [-1.01, 1.07]
Pflanz 1994	11	4.67 (2.01)	12	5.57 (1.54)		8.3 %	-0.90 [-2.37, 0.57]
Total (95% CI)	**68**		**75**			**100.0 %**	**-0.19 [-0.61, 0.24]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.13$, df = 4 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 0.86 (P = 0.39)



Analysis 2.5. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 5 Serum calcium.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

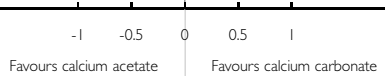
Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 5 Serum calcium

Study or subgroup	Calcium acetate N	Mean(SD)[mg/dL]	Calcium carbonate N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Almirall 1994	4	10.36 (0.5)	4	10.2 (0.5)		12.5 %	0.16 [-0.53, 0.85]
Borrego 2000	7	9.5 (0.7)	9	9.8 (0.7)		12.5 %	-0.30 [-0.99, 0.39]
Caravaca 1992	31	9.88 (0.68)	35	10.2 (0.88)		32.4 %	-0.32 [-0.70, 0.06]
d'Almeida Filho 2000	15	9.73 (0.62)	15	9.91 (0.79)		20.9 %	-0.18 [-0.69, 0.33]
Pflanz 1994	11	9.6 (0.68)	12	9.28 (0.52)		21.6 %	0.32 [-0.18, 0.82]
Total (95% CI)	**68**		**75**			**100.0 %**	**-0.09 [-0.35, 0.17]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.00$, df = 4 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 0.67 (P = 0.50)



Analysis 2.6. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 6 Serum calcium x phosphorus product.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 6 Serum calcium x phosphorus product

Study or subgroup	Calcium acetate N	Mean(SD)[mg²/dL²]	Calcium carbonate N	Mean(SD)[mg²/dL²]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Almirall 1994	4	49.7 (2.9)	4	51.1 (5.2)		35.5 %	-1.40 [-7.23, 4.43]
Pflanz 1994	11	44.83 (1.42)	12	51.68 (0.8)		64.5 %	-6.85 [-7.80, -5.90]
Total (95% CI)	**15**		**16**			**100.0 %**	**-4.92 [-10.03, 0.19]**

Heterogeneity: Tau² = 10.30; Chi² = 3.26, df = 1 (P = 0.07); I² =69%

Test for overall effect: Z = 1.89 (P = 0.059)

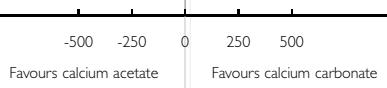
Analysis 2.7. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 7 Serum iPTH.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 7 Serum iPTH

Study or subgroup	Calcium acetate N	Mean(SD)[pg/mL]	Calcium carbonate N	Mean(SD)[pg/mL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Borrego 2000	7	244 (84)	9	296 (224)		-52.00 [-211.02, 107.02]

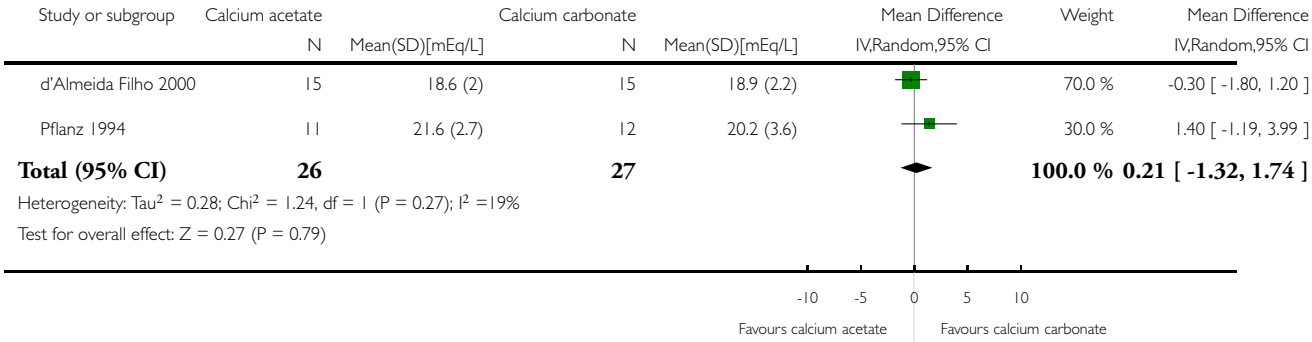


Analysis 2.8. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 8 Serum bicarbonate.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 8 Serum bicarbonate

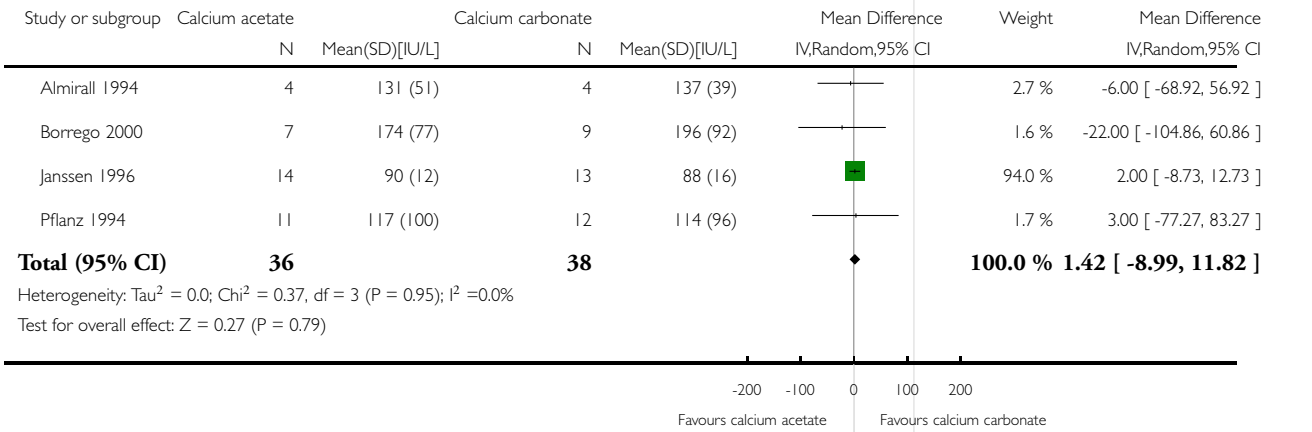


Analysis 2.9. Comparison 2 Calcium acetate versus calcium carbonate, Outcome 9 Serum alkaline phosphatase.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 2 Calcium acetate versus calcium carbonate

Outcome: 9 Serum alkaline phosphatase



Analysis 3.1. Comparison 3 Calcium ketoglutarate versus other calcium salts, Outcome 1 All-cause mortality.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 3 Calcium ketoglutarate versus other calcium salts

Outcome: 1 All-cause mortality

Study or subgroup	Calcium ketoglutarate n/N	Other calcium salts n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Birck 1999	0/14	0/14		0.0 [0.0, 0.0]
Bro 1998	0/17	0/17		0.0 [0.0, 0.0]

Analysis 3.2. Comparison 3 Calcium ketoglutarate versus other calcium salts, Outcome 2 Adverse gastrointestinal events.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 3 Calcium ketoglutarate versus other calcium salts

Outcome: 2 Adverse gastrointestinal events

Study or subgroup	Calcium ketoglutarate n/N	Other calcium salts n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Gastritis				
2 Diarrhoea				
3 Gastroparesis				
4 Combined				
Bro 1998	5/17	1/17		5.00 [0.65, 38.42]

Analysis 3.3. Comparison 3 Calcium ketoglutarate versus other calcium salts, Outcome 3 Serum phosphorus.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

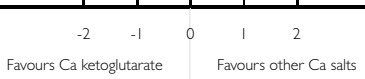
Comparison: 3 Calcium ketoglutarate versus other calcium salts

Outcome: 3 Serum phosphorus

Study or subgroup	Calcium ketoglutarate N	Mean(SD)[mg/dL]	Other calcium salts N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Birck 1999	14	6 (1.95)	14	6 (1.85)		2.5 %	0.0 [-1.41, 1.41]
Bro 1998	10	4.5 (0.3)	10	4.6 (0.2)		97.5 %	-0.10 [-0.32, 0.12]
Total (95% CI)	**24**		**24**			**100.0 %**	**-0.10 [-0.32, 0.12]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 0.87 (P = 0.39)



Analysis 3.4. Comparison 3 Calcium ketoglutarate versus other calcium salts, Outcome 4 Serum calcium.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 3 Calcium ketoglutarate versus other calcium salts

Outcome: 4 Serum calcium

Study or subgroup	Calcium ketoglutarate N	Mean(SD)[mg/dL]	Other calcium salts N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Total calcium						
2 Ionised calcium						
Bro 1998	10	4.8 (0.1)	10	5.2 (0.1)		-0.40 [-0.49, -0.31]

Analysis 3.5. Comparison 3 Calcium ketoglutarate versus other calcium salts, Outcome 5 Serum calcium x phosphorus product.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 3 Calcium ketoglutarate versus other calcium salts

Outcome: 5 Serum calcium x phosphorus product

Study or subgroup	Calcium ketoglutarate N	Mean(SD)[mg^2/dL^2]	Other calcium salts N	Mean(SD)[mg^2/dL^2]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Bro 1998	10	21.8 (1.5)	10	26.3 (1.1)		-4.50 [-5.65, -3.35]

Analysis 3.6. Comparison 3 Calcium ketoglutarate versus other calcium salts, Outcome 6 Serum iPTH.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 3 Calcium ketoglutarate versus other calcium salts

Outcome: 6 Serum iPTH

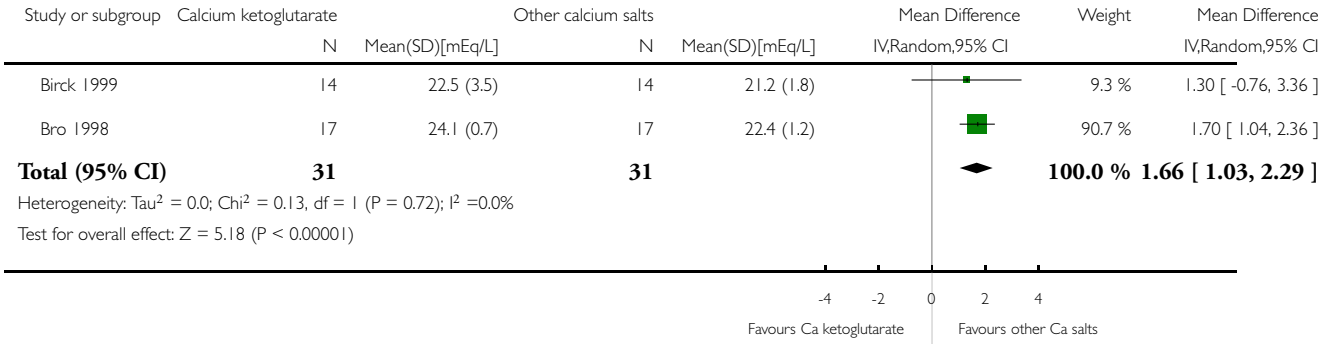
Study or subgroup	Calcium ketoglutarate N	Mean(SD)[pg/mL]	Other calcium salts N	Mean(SD)[pg/mL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Bro 1998	10	266 (125)	10	301 (148)		-35.00 [-155.07, 85.07]

Analysis 3.7. Comparison 3 Calcium ketoglutarate versus other calcium salts, Outcome 7 Serum bicarbonate.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 3 Calcium ketoglutarate versus other calcium salts

Outcome: 7 Serum bicarbonate



Analysis 4.1. Comparison 4 Sevelamer versus placebo, Outcome 1 All-cause mortality.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 4 Sevelamer versus placebo

Outcome: 1 All-cause mortality

Analysis 4.2. Comparison 4 Sevelamer versus placebo, Outcome 2 Adverse gastrointestinal events.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 4 Sevelamer versus placebo

Outcome: 2 Adverse gastrointestinal events

Study or subgroup	Sevelamer n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Gastritis					
Chertow 1997	2/24	1/12		100.0 %	1.00 [0.10, 9.96]
Subtotal (95% CI)	**24**	**12**		**100.0 %**	**1.00 [0.10, 9.96]**
Total events: 2 (Sevelamer), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Diarrhoea					
Chertow 1997	0/24	1/12		100.0 %	0.17 [0.01, 3.96]
Subtotal (95% CI)	**24**	**12**		**100.0 %**	**0.17 [0.01, 3.96]**
Total events: 0 (Sevelamer), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
3 Gastroparesis					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Sevelamer), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 4.3. Comparison 4 Sevelamer versus placebo, Outcome 3 Serum phosphorus.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 4 Sevelamer versus placebo

Outcome: 3 Serum phosphorus

Study or subgroup	Sevelamer N	Mean(SD)[mg/dL]	Placebo N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Chertow 1997	24	5.4 (1.7)	12	7.2 (2.4)		-1.80 [-3.32, -0.28]

Analysis 4.4. Comparison 4 Sevelamer versus placebo, Outcome 4 Serum calcium.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 4 Sevelamer versus placebo

Outcome: 4 Serum calcium

Study or subgroup	Sevelamer N	Mean(SD)[mg/dL]	Placebo N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Total calcium						
Chertow 1997	24	9.3 (0.6)	12	9.4 (0.6)		-0.10 [-0.52, 0.32]
2 Ionised calcium						

Analysis 4.5. Comparison 4 Sevelamer versus placebo, Outcome 5 Serum bicarbonate.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 4 Sevelamer versus placebo

Outcome: 5 Serum bicarbonate

Study or subgroup	Sevelamer N	Mean(SD)[mEq/L]	Placebo N	Mean(SD)[mEq/L]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Chertow 1997	24	20.4 (4.1)	12	20.9 (2.1)		-0.50 [-2.53, 1.53]

Analysis 4.6. Comparison 4 Sevelamer versus placebo, Outcome 6 Serum total cholesterol.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 4 Sevelamer versus placebo

Outcome: 6 Serum total cholesterol

Study or subgroup	Sevelamer N	Mean(SD)[mg/dL]	Placebo N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Chertow 1997	24	149 (32)	12	177 (35)		-28.00 [-51.58, -4.42]

Analysis 5.1. Comparison 5 Sevelamer versus calcium salts, Outcome 1 All-cause mortality.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 1 All-cause mortality

Study or subgroup	Sevelamer n/N	Calcium salts n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Sevelamer versus calcium acetate				
Bleyer 1999	0/40	0/40		0.0 [0.0, 0.0]
BRiC Study 2008	1/52	8/49		0.12 [0.02, 0.91]
CARE Study 2004	0/50	0/48		0.0 [0.0, 0.0]
CARE-2 Study 2008	3/100	7/103		0.44 [0.12, 1.66]
Ferreira 2008	0/44	0/47		0.0 [0.0, 0.0]
Hervas 2003	2/18	2/22		1.22 [0.19, 7.84]
Subtotal (95% CI)	**304**	**309**		**0.43 [0.13, 1.38]**
Total events: 6 (Sevelamer), 17 (Calcium salts)				
Heterogeneity: Tau² = 0.34; Chi² = 2.87, df = 2 (P = 0.24); I² =30%				
Test for overall effect: Z = 1.42 (P = 0.15)				
2 Sevelamer versus calcium carbonate				
Koiwa 2005a	0/16	0/20		0.0 [0.0, 0.0]
Subtotal (95% CI)	**16**	**20**		**0.0 [0.0, 0.0]**

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Sevelamer n/N	Calcium salts n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total events: 0 (Sevelamer), 0 (Calcium salts)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)				
Block 2005	11/60	23/67		0.53 [0.28, 1.00]
Chertow 2002	6/99	5/101		1.22 [0.39, 3.88]
DCOR Study 2007	267/1053	275/1050		0.97 [0.84, 1.12]
Subtotal (95% CI)	**1212**	**1218**		**0.85 [0.57, 1.27]**
Total events: 284 (Sevelamer), 303 (Calcium salts)				
Heterogeneity: Tau² = 0.06; Chi² = 3.47, df = 2 (P = 0.18); I² =42%				
Test for overall effect: Z = 0.79 (P = 0.43)				
Total (95% CI)	**1532**	**1547**		**0.73 [0.46, 1.16]**
Total events: 290 (Sevelamer), 320 (Calcium salts)				
Heterogeneity: Tau² = 0.12; Chi² = 8.81, df = 5 (P = 0.12); I² =43%				
Test for overall effect: Z = 1.32 (P = 0.19)				

Analysis 5.2. Comparison 5 Sevelamer versus calcium salts, Outcome 2 Hypercalcaemia.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 2 Hypercalcaemia

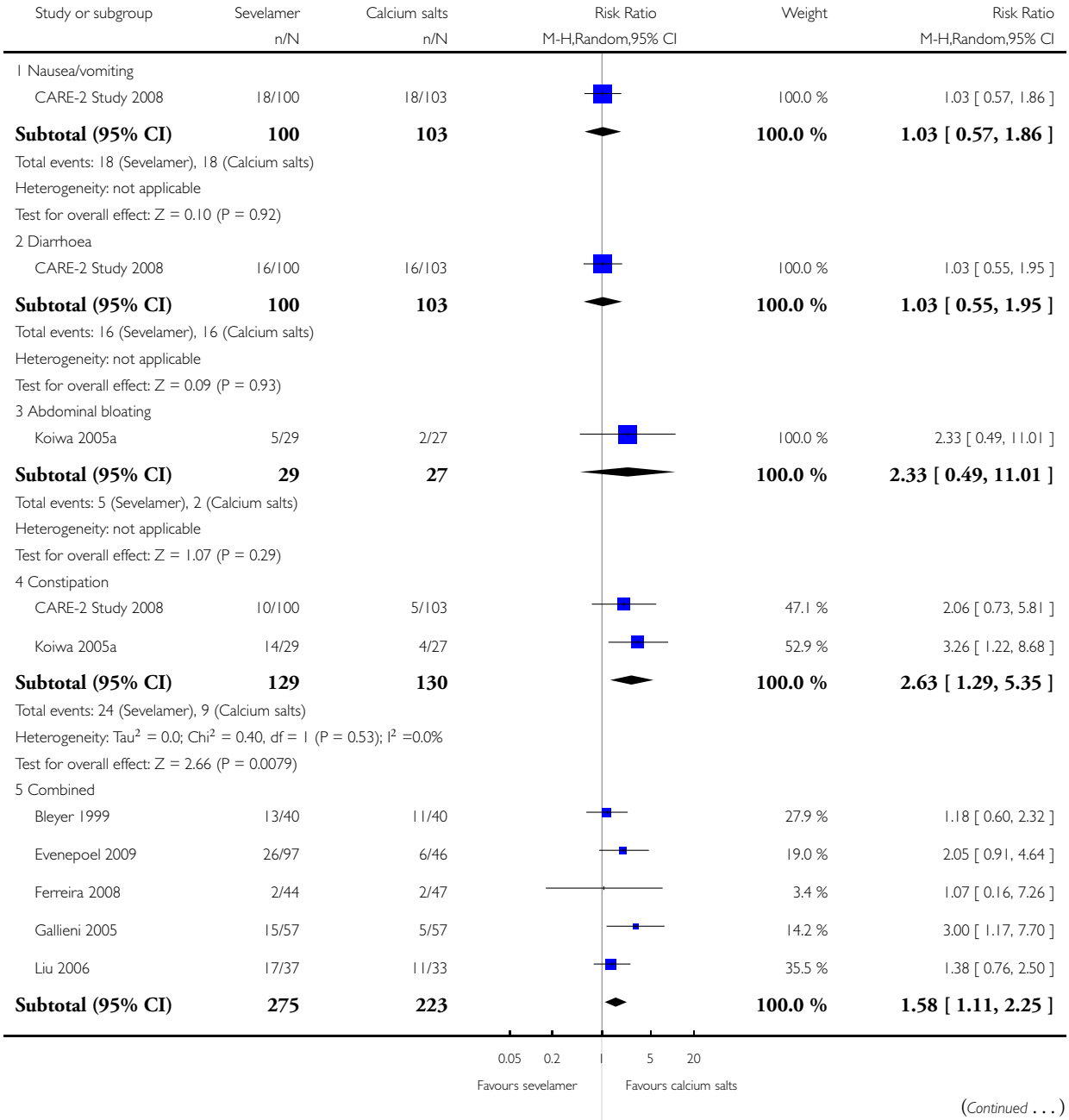
Study or subgroup	Sevelamer n/N	Calcium salts n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Sevelamer versus calcium acetate				
Bleyer 1999	2/40	9/40		0.22 [0.05, 0.96]
CARE Study 2004	3/50	8/48		0.36 [0.10, 1.28]
CARE-2 Study 2008	19/100	31/103		0.63 [0.38, 1.04]
Evenepoel 2009	2/97	8/46		0.12 [0.03, 0.54]
Hervas 2003	9/20	15/20		0.60 [0.35, 1.04]
Liu 2006	5/37	15/33		0.30 [0.12, 0.73]
Subtotal (95% CI)	**344**	**290**		**0.43 [0.27, 0.66]**
Total events: 40 (Sevelamer), 86 (Calcium salts)				
Heterogeneity: Tau^2 = 0.10; Chi^2 = 7.82, df = 5 (P = 0.17); I^2 =36%				
Test for overall effect: Z = 3.79 (P = 0.00015)				
2 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)				
Block 2005	12/54	30/55		0.41 [0.23, 0.71]
Chertow 2002	3/99	5/101		0.61 [0.15, 2.49]
Subtotal (95% CI)	**153**	**156**		**0.43 [0.26, 0.72]**
Total events: 15 (Sevelamer), 35 (Calcium salts)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.28, df = 1 (P = 0.60); I^2 =0.0%				
Test for overall effect: Z = 3.21 (P = 0.0013)				
3 Sevelamer versus calcium carbonate				
De Santo 2006	0/8	0/8		0.0 [0.0, 0.0]
Gallieni 2005	2/57	4/57		0.50 [0.10, 2.62]
Sadek 2003	1/15	3/16		0.36 [0.04, 3.05]
Shaheen 2004	3/20	11/20		0.27 [0.09, 0.83]
Subtotal (95% CI)	**100**	**101**		**0.33 [0.14, 0.78]**
Total events: 6 (Sevelamer), 18 (Calcium salts)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.36, df = 2 (P = 0.84); I^2 =0.0%				
Test for overall effect: Z = 2.53 (P = 0.011)				
Total (95% CI)	**597**	**547**		**0.45 [0.35, 0.59]**
Total events: 61 (Sevelamer), 139 (Calcium salts)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 9.05, df = 10 (P = 0.53); I^2 =0.0%				
Test for overall effect: Z = 6.03 (P < 0.00001)				

Analysis 5.3. Comparison 5 Sevelamer versus calcium salts, Outcome 3 Gastrointestinal adverse events.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 3 Gastrointestinal adverse events



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Sevelamer n/N	Calcium salts n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 73 (Sevelamer), 35 (Calcium salts)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.34$, df = 4 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.51 (P = 0.012)					

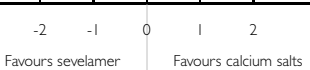
Analysis 5.4. Comparison 5 Sevelamer versus calcium salts, Outcome 4 Serum phosphorus.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 4 Serum phosphorus

Study or subgroup	Sevelamer N	Mean(SD)[mg/dL]	Calcium salts N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Sevelamer versus calcium acetate						
Bleyer 1999	40	6.4 (1.7)	40	5.9 (1.7)		0.50 [-0.25, 1.25]
BRiC Study 2008	41	5.29 (0.92)	30	5.78 (0.92)		-0.49 [-0.92, -0.06]
CARE Study 2004	50	6.8 (1.6)	48	5.5 (1.5)		1.30 [0.69, 1.91]
CARE-2 Study 2008	70	5.4 (1.8)	59	5 (1.6)		0.40 [-0.19, 0.99]
Evenepoel 2009	95	5.91 (1.25)	44	5.77 (1.61)		0.14 [-0.40, 0.68]
Hervas 2003	18	5.8 (1.01)	22	5.9 (1.5)		-0.10 [-0.88, 0.68]
Russo 2007	27	4.8 (0.9)	28	4.7 (1.5)		0.10 [-0.55, 0.75]
Subtotal (95% CI)	**341**		**271**			**0.25 [-0.20, 0.71]**
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 23.79$, df = 6 (P = 0.00057); $I^2 = 75\%$						
Test for overall effect: Z = 1.08 (P = 0.28)						
2 Sevelamer versus calcium carbonate						
Ferreira 2008	33	5.4 (1.4)	35	5.3 (1.9)		0.10 [-0.69, 0.89]
Gallieni 2005	57	5.25 (1.2)	57	4.82 (1.04)		0.43 [0.02, 0.84]
Kinugasa 2001	115	5.62 (0)	115	5.59 (0)		0.0 [0.0, 0.0]
Koiwa 2005a	16	6.1 (1.5)	20	6 (1.5)		0.10 [-0.89, 1.09]
Sadek 2003	15	5.71 (1.08)	16	5.09 (1.58)		0.62 [-0.33, 1.57]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Sevelamer N	Mean(SD)[mg/dL]	Calcium salts N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Shaheen 2004	20	5.7 (1.2)	20	4.9 (0.7)		0.80 [0.19, 1.41]
Subtotal (95% CI)	**256**		**263**			**0.46 [0.17, 0.74]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.64, df = 4 (P = 0.62); I^2 =0.0%						
Test for overall effect: Z = 3.15 (P = 0.0016)						
3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)						
Block 2005	54	5.2 (0.9)	55	5.1 (0.8)		0.10 [-0.22, 0.42]
Chertow 2002	99	5.1 (1.2)	101	5.1 (1.4)		0.0 [-0.36, 0.36]
DCOR Study 2007	843	5.8 (1.3)	843	5.7 (1.3)		0.10 [-0.02, 0.22]
Subtotal (95% CI)	**996**		**999**			**0.09 [-0.02, 0.20]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.27, df = 2 (P = 0.87); I^2 =0.0%						
Test for overall effect: Z = 1.61 (P = 0.11)						
Total (95% CI)	**1593**		**1533**			**0.23 [0.04, 0.42]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 32.32, df = 14 (P = 0.004); I^2 =57%						
Test for overall effect: Z = 2.35 (P = 0.019)						

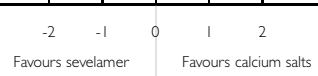
Analysis 5.5. Comparison 5 Sevelamer versus calcium salts, Outcome 5 Serum calcium.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 5 Serum calcium

Study or subgroup	Sevelamer N	Mean(SD)[mg/dL]	Calcium salts N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Sevelamer versus calcium acetate						
Bleyer 1999	40	9.3 (0.6)	40	9.7 (0.8)		-0.40 [-0.71, -0.09]
CARE Study 2004	50	8.9 (0.5)	48	9.5 (0.7)		-0.60 [-0.84, -0.36]
CARE-2 Study 2008	70	9 (0.7)	59	9.4 (0.7)		-0.40 [-0.64, -0.16]
Evenepoel 2009	95	9.59 (0.56)	44	10 (0.99)		-0.41 [-0.72, -0.10]
Hervas 2003	18	10.22 (0.77)	22	10.18 (0.9)		0.04 [-0.48, 0.56]
Russo 2007	27	9 (0.3)	28	9.1 (0.8)		-0.10 [-0.42, 0.22]
Subtotal (95% CI)	**300**		**241**			**-0.36 [-0.53, -0.20]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.78$, df = 5 (P = 0.12); $I^2 = 43\%$						
Test for overall effect: Z = 4.28 (P = 0.000019)						
2 Sevelamer versus calcium carbonate						
Ferreira 2008	33	9.1 (1.1)	35	9.3 (0.7)		-0.20 [-0.64, 0.24]
Gallieni 2005	57	9.4 (0.9)	57	9.6 (1.2)		-0.20 [-0.59, 0.19]
Kinugasa 2001	115	9.13 (0)	115	9.65 (0)		0.0 [0.0, 0.0]
Koiwa 2005a	16	8.7 (0.7)	20	9.7 (0.8)		-1.00 [-1.49, -0.51]
Sadek 2003	15	9.64 (0.4)	16	9.6 (0.4)		0.04 [-0.24, 0.32]
Shaheen 2004	20	9.3 (0.8)	20	10 (1.4)		-0.70 [-1.41, 0.01]
Subtotal (95% CI)	**256**		**263**			**-0.36 [-0.74, 0.01]**
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 14.72$, df = 4 (P = 0.01); $I^2 = 73\%$						
Test for overall effect: Z = 1.92 (P = 0.055)						
3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)						
Block 2005	54	9.1 (0.5)	55	9.6 (0.5)		-0.50 [-0.69, -0.31]
Chertow 2002	99	9.4 (0.7)	101	9.7 (0.7)		-0.30 [-0.49, -0.11]
DCOR Study 2007	835	9.2 (0.7)	835	9.5 (0.7)		-0.30 [-0.37, -0.23]
Subtotal (95% CI)	**988**		**991**			**-0.35 [-0.46, -0.23]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.91$, df = 2 (P = 0.14); $I^2 = 49\%$						
Test for overall effect: Z = 5.91 (P < 0.00001)						
Total (95% CI)	**1544**		**1495**			**-0.34 [-0.45, -0.24]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 29.13$, df = 13 (P = 0.01); $I^2 = 55\%$						
Test for overall effect: Z = 6.40 (P < 0.00001)						



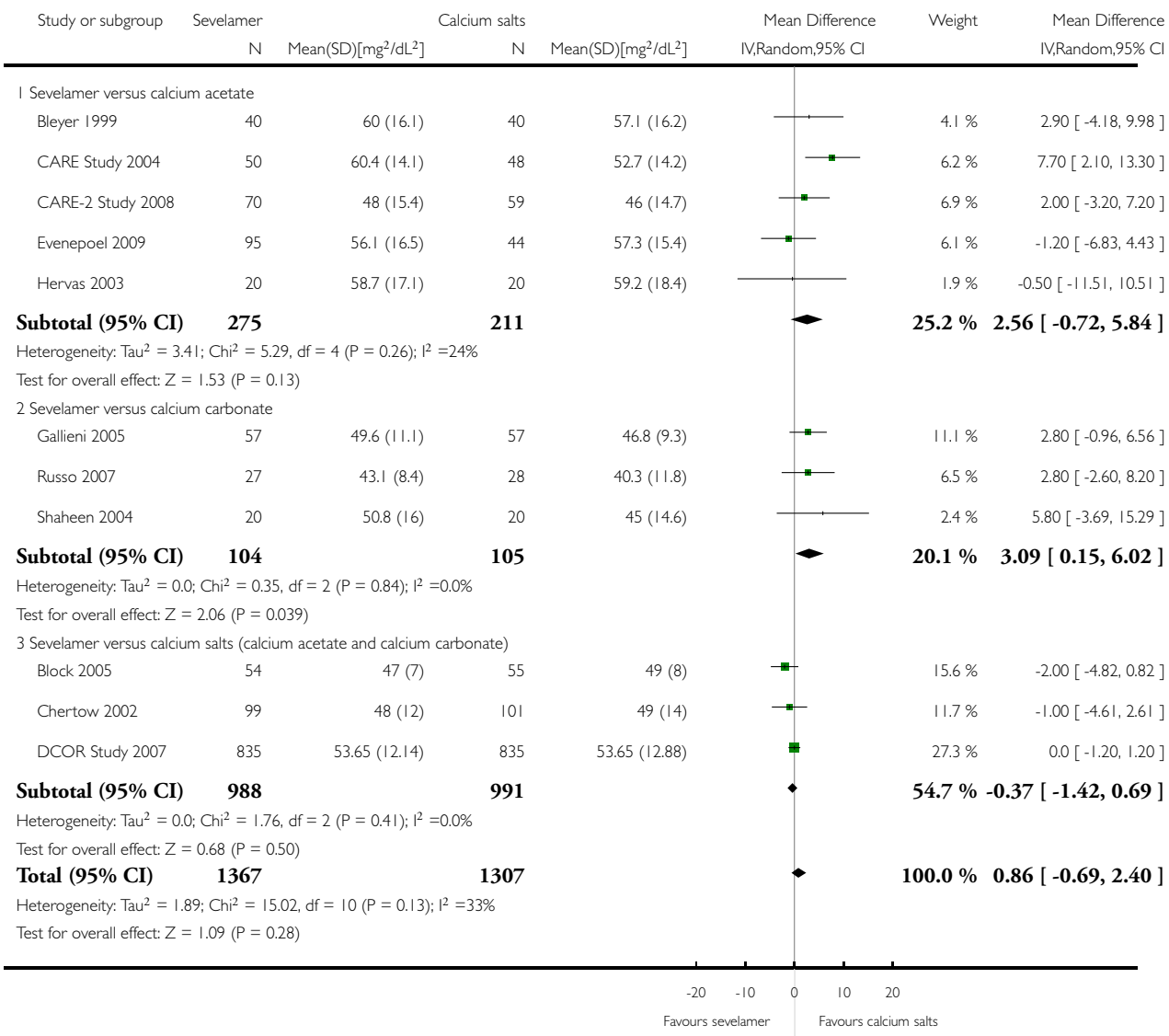
Analysis 5.6. Comparison 5 Sevelamer versus calcium salts, Outcome 6 Serum calcium x phosphorus product.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 6 Serum calcium x phosphorus product

Study or subgroup	Sevelamer N	Mean(SD)[mg²/dL²]	Calcium salts N	Mean(SD)[mg²/dL²]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Sevelamer versus calcium acetate							
Bleyer 1999	40	60 (16.1)	40	57.1 (16.2)		4.1 %	2.90 [-4.18, 9.98]
CARE Study 2004	50	60.4 (14.1)	48	52.7 (14.2)		6.2 %	7.70 [2.10, 13.30]
CARE-2 Study 2008	70	48 (15.4)	59	46 (14.7)		6.9 %	2.00 [-3.20, 7.20]
Evenepoel 2009	95	56.1 (16.5)	44	57.3 (15.4)		6.1 %	-1.20 [-6.83, 4.43]
Hervas 2003	20	58.7 (17.1)	20	59.2 (18.4)		1.9 %	-0.50 [-11.51, 10.51]
Subtotal (95% CI)	**275**		**211**			**25.2 %**	**2.56 [-0.72, 5.84]**
Heterogeneity: Tau² = 3.41; Chi² = 5.29, df = 4 (P = 0.26); I² =24%							
Test for overall effect: Z = 1.53 (P = 0.13)							
2 Sevelamer versus calcium carbonate							
Gallieni 2005	57	49.6 (11.1)	57	46.8 (9.3)		11.1 %	2.80 [-0.96, 6.56]
Russo 2007	27	43.1 (8.4)	28	40.3 (11.8)		6.5 %	2.80 [-2.60, 8.20]
Shaheen 2004	20	50.8 (16)	20	45 (14.6)		2.4 %	5.80 [-3.69, 15.29]
Subtotal (95% CI)	**104**		**105**			**20.1 %**	**3.09 [0.15, 6.02]**
Heterogeneity: Tau² = 0.0; Chi² = 0.35, df = 2 (P = 0.84); I² =0.0%							
Test for overall effect: Z = 2.06 (P = 0.039)							
3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)							
Block 2005	54	47 (7)	55	49 (8)		15.6 %	-2.00 [-4.82, 0.82]
Chertow 2002	99	48 (12)	101	49 (14)		11.7 %	-1.00 [-4.61, 2.61]
DCOR Study 2007	835	53.65 (12.14)	835	53.65 (12.88)		27.3 %	0.0 [-1.20, 1.20]
Subtotal (95% CI)	**988**		**991**			**54.7 %**	**-0.37 [-1.42, 0.69]**
Heterogeneity: Tau² = 0.0; Chi² = 1.76, df = 2 (P = 0.41); I² =0.0%							
Test for overall effect: Z = 0.68 (P = 0.50)							
Total (95% CI)	**1367**		**1307**			**100.0 %**	**0.86 [-0.69, 2.40]**
Heterogeneity: Tau² = 1.89; Chi² = 15.02, df = 10 (P = 0.13); I² =33%							
Test for overall effect: Z = 1.09 (P = 0.28)							



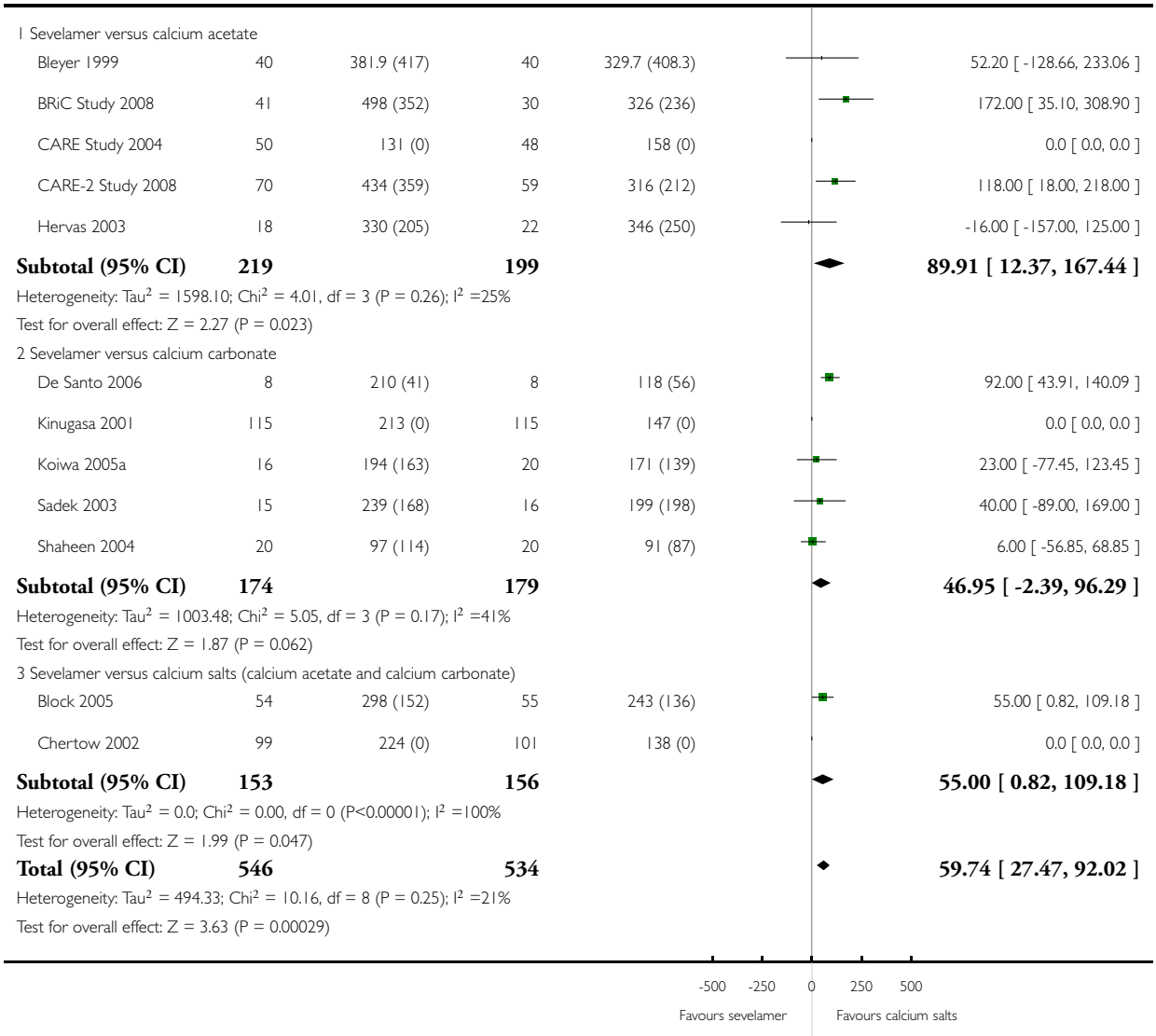
Analysis 5.7. Comparison 5 Sevelamer versus calcium salts, Outcome 7 Serum iPTH.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 7 Serum iPTH

Study or subgroup	Sevelamer N	Mean(SD)[pg/mL]	Calcium salts N	Mean(SD)[pg/mL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Sevelamer versus calcium acetate						
Bleyer 1999	40	381.9 (417)	40	329.7 (408.3)		52.20 [-128.66, 233.06]
BRiC Study 2008	41	498 (352)	30	326 (236)		172.00 [35.10, 308.90]
CARE Study 2004	50	131 (0)	48	158 (0)		0.0 [0.0, 0.0]
CARE-2 Study 2008	70	434 (359)	59	316 (212)		118.00 [18.00, 218.00]
Hervas 2003	18	330 (205)	22	346 (250)		-16.00 [-157.00, 125.00]
Subtotal (95% CI)	**219**		**199**			**89.91 [12.37, 167.44]**
Heterogeneity: Tau^2 = 1598.10; Chi^2 = 4.01, df = 3 (P = 0.26); I^2 =25%						
Test for overall effect: Z = 2.27 (P = 0.023)						
2 Sevelamer versus calcium carbonate						
De Santo 2006	8	210 (41)	8	118 (56)		92.00 [43.91, 140.09]
Kinugasa 2001	115	213 (0)	115	147 (0)		0.0 [0.0, 0.0]
Koiwa 2005a	16	194 (163)	20	171 (139)		23.00 [-77.45, 123.45]
Sadek 2003	15	239 (168)	16	199 (198)		40.00 [-89.00, 169.00]
Shaheen 2004	20	97 (114)	20	91 (87)		6.00 [-56.85, 68.85]
Subtotal (95% CI)	**174**		**179**			**46.95 [-2.39, 96.29]**
Heterogeneity: Tau^2 = 1003.48; Chi^2 = 5.05, df = 3 (P = 0.17); I^2 =41%						
Test for overall effect: Z = 1.87 (P = 0.062)						
3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)						
Block 2005	54	298 (152)	55	243 (136)		55.00 [0.82, 109.18]
Chertow 2002	99	224 (0)	101	138 (0)		0.0 [0.0, 0.0]
Subtotal (95% CI)	**153**		**156**			**55.00 [0.82, 109.18]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 0 (P<0.00001); I^2 =100%						
Test for overall effect: Z = 1.99 (P = 0.047)						
Total (95% CI)	**546**		**534**			**59.74 [27.47, 92.02]**
Heterogeneity: Tau^2 = 494.33; Chi^2 = 10.16, df = 8 (P = 0.25); I^2 =21%						
Test for overall effect: Z = 3.63 (P = 0.00029)						



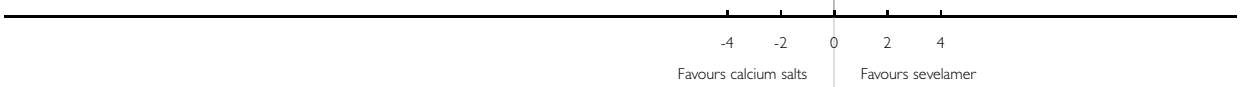
Analysis 5.8. Comparison 5 Sevelamer versus calcium salts, Outcome 8 Serum bicarbonate.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 8 Serum bicarbonate

Study or subgroup	Sevelamer N	Mean(SD)[mEq/L]	Calcium salts N	Mean(SD)[mEq/L]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Sevelamer versus calcium acetate							
CARE Study 2004	50	19.3 (2.7)	48	21 (2.6)		37.3 %	-1.70 [-2.75, -0.65]
CARE-2 Study 2008	70	21.6 (4.3)	59	23.1 (3.9)		20.5 %	-1.50 [-2.92, -0.08]
Subtotal (95% CI)	**120**		**107**			**57.8 %**	**-1.63 [-2.47, -0.79]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.79 (P = 0.00015)							
2 Sevelamer versus calcium carbonate							
Ferreira 2008	33	20.4 (3.3)	35	21.2 (4.1)		13.2 %	-0.80 [-2.56, 0.96]
Russo 2007	27	21.2 (2.3)	28	23.2 (4.2)		12.9 %	-2.00 [-3.78, -0.22]
Sadek 2003	15	22.2 (1.9)	16	23 (2.6)		16.1 %	-0.80 [-2.40, 0.80]
Subtotal (95% CI)	**75**		**79**			**42.2 %**	**-1.17 [-2.15, -0.18]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.21$, df = 2 (P = 0.55); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.32 (P = 0.020)							
Total (95% CI)	**195**		**186**			**100.0 %**	**-1.43 [-2.07, -0.79]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.75$, df = 4 (P = 0.78); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.39 (P = 0.000011)							

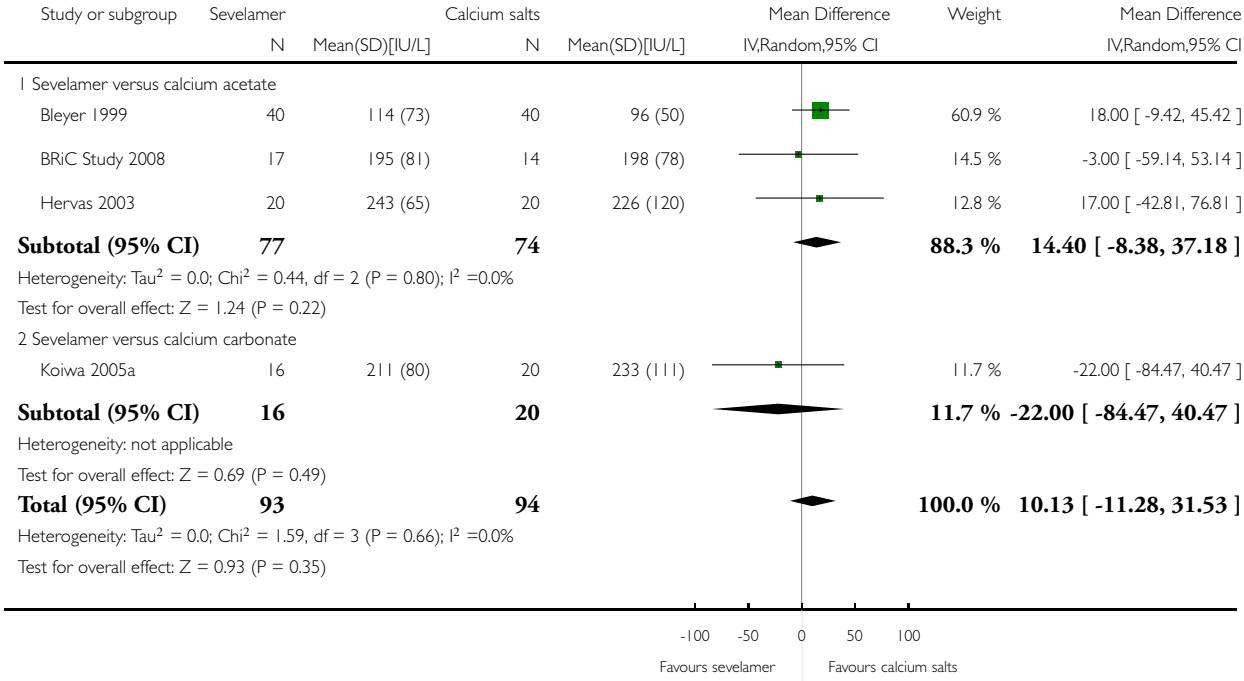


Analysis 5.9. Comparison 5 Sevelamer versus calcium salts, Outcome 9 Serum alkaline phosphatase.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 9 Serum alkaline phosphatase



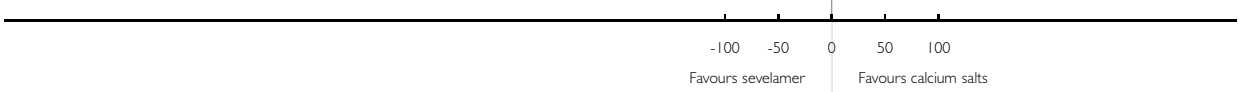
Analysis 5.10. Comparison 5 Sevelamer versus calcium salts, Outcome 10 Serum total cholesterol.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 10 Serum total cholesterol

Study or subgroup	Sevelamer N	Mean(SD)[mg/dL]	Calcium salts N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Sevelamer versus calcium acetate							
Bleyer 1999	40	146.8 (42.8)	40	169.9 (51.4)		8.7 %	-23.10 [-43.83, -2.37]
BRiC Study 2008	17	139 (40)	14	141 (26)		7.5 %	-2.00 [-25.39, 21.39]
Hervas 2003	18	154.62 (49.79)	22	170.25 (28.91)		6.6 %	-15.63 [-41.61, 10.35]
Subtotal (95% CI)	**75**		**76**			**22.8 %**	**-14.29 [-27.61, -0.98]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.76, df = 2 (P = 0.41); I^2 =0.0%							
Test for overall effect: Z = 2.10 (P = 0.035)							
2 Sevelamer versus calcium carbonate							
Ferreira 2008	33	140 (34)	35	166 (41)		10.1 %	-26.00 [-43.86, -8.14]
Koiwa 2005a	16	156 (30)	20	171 (18)		10.7 %	-15.00 [-31.68, 1.68]
Russo 2007	27	181.3 (53.1)	28	184 (23.5)		8.2 %	-2.70 [-24.54, 19.14]
Sadek 2003	15	180 (44)	16	180 (48)		4.9 %	0.0 [-32.39, 32.39]
Subtotal (95% CI)	**91**		**99**			**33.8 %**	**-14.06 [-25.14, -2.99]**
Heterogeneity: Tau^2 = 18.35; Chi^2 = 3.49, df = 3 (P = 0.32); I^2 =14%							
Test for overall effect: Z = 2.49 (P = 0.013)							
3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)							
Block 2005	54	134 (52)	55	160 (32)		11.0 %	-26.00 [-42.24, -9.76]
Chertow 2002	99	141 (28)	101	182 (49)		14.2 %	-41.00 [-52.03, -29.97]
DCOR Study 2007	526	150.8 (34.8)	529	166.4 (36)		18.1 %	-15.60 [-19.87, -11.33]
Subtotal (95% CI)	**679**		**685**			**43.4 %**	**-27.09 [-44.59, -9.60]**
Heterogeneity: Tau^2 = 206.91; Chi^2 = 18.39, df = 2 (P = 0.00010); I^2 =89%							
Test for overall effect: Z = 3.03 (P = 0.0024)							
Total (95% CI)	**845**		**860**			**100.0 %**	**-19.16 [-27.42, -10.90]**
Heterogeneity: Tau^2 = 93.11; Chi^2 = 24.82, df = 9 (P = 0.003); I^2 =64%							
Test for overall effect: Z = 4.55 (P < 0.00001)							



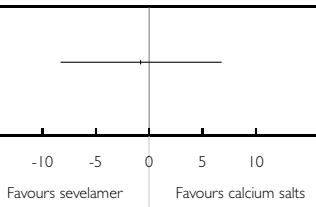
Analysis 5.11. Comparison 5 Sevelamer versus calcium salts, Outcome 11 Serum 1, 25 dihydroxyvitamin D.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 5 Sevelamer versus calcium salts

Outcome: 11 Serum 1, 25 dihydroxyvitamin D

Study or subgroup	Sevelamer N	Mean(SD)	Calcium salts N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Sevelamer versus calcium acetate						
Bleyer 1999	40	22.4 (18.3)	40	23.16 (16.3)		-0.76 [-8.35, 6.83]



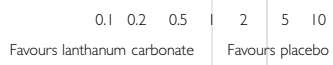
Analysis 6.1. Comparison 6 Lanthanum carbonate versus placebo, Outcome 1 All-cause mortality.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 6 Lanthanum carbonate versus placebo

Outcome: 1 All-cause mortality

Study or subgroup	Lanthanum carbonate n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Chiang 2005	0/30	0/31		0.0 [0.0, 0.0]
Joy 2003	0/49	0/44		0.0 [0.0, 0.0]
Total (95% CI)	**79**	**75**		**0.0 [0.0, 0.0]**
Total events: 0 (Lanthanum carbonate), 0 (Placebo)				
Heterogeneity: Tau^2 = ï½; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				



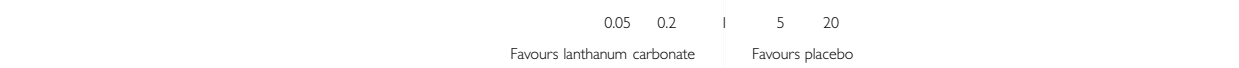
Analysis 6.2. Comparison 6 Lanthanum carbonate versus placebo, Outcome 2 Adverse gastrointestinal events.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 6 Lanthanum carbonate versus placebo

Outcome: 2 Adverse gastrointestinal events

Study or subgroup	Lanthanum carbonate n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Gastritis					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Lanthanum carbonate), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Diarrhoea					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Lanthanum carbonate), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Gastroparesis					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Lanthanum carbonate), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Combined					
Chiang 2005	2/30	3/31		24.5 %	0.69 [0.12, 3.84]
Joy 2003	8/49	6/44		75.5 %	1.20 [0.45, 3.18]
Subtotal (95% CI)	**79**	**75**		**100.0 %**	**1.05 [0.45, 2.45]**
Total events: 10 (Lanthanum carbonate), 9 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 1 (P = 0.58); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.10 (P = 0.92)					



Analysis 6.3. Comparison 6 Lanthanum carbonate versus placebo, Outcome 3 Serum phosphorus.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

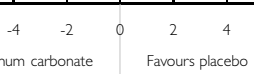
Comparison: 6 Lanthanum carbonate versus placebo

Outcome: 3 Serum phosphorus

Study or subgroup	Lanthanum carbonate N	Mean(SD)[mg/dL]	Placebo N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chiang 2005	30	5.1 (1.5)	31	7.2 (1.3)		52.5 %	-2.10 [-2.81, -1.39]
Joy 2003	49	5.94 (1.65)	44	7.85 (1.96)		47.5 %	-1.91 [-2.65, -1.17]
Total (95% CI)	**79**		**75**			**100.0 %**	**-2.01 [-2.52, -1.50]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 7.71 (P < 0.00001)



Analysis 6.4. Comparison 6 Lanthanum carbonate versus placebo, Outcome 4 Serum calcium.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 6 Lanthanum carbonate versus placebo

Outcome: 4 Serum calcium

Study or subgroup	Lanthanum carbonate N	Mean(SD)[mg/dL]	Placebo N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Total calcium						
Joy 2003	49	8.83 (0.68)	44	8.48 (0.81)		0.35 [0.04, 0.66]
2 Ionised calcium						

Analysis 6.5. Comparison 6 Lanthanum carbonate versus placebo, Outcome 5 Serum calcium x phosphorus product.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 6 Lanthanum carbonate versus placebo

Outcome: 5 Serum calcium x phosphorus product

Study or subgroup	Lanthanum carbonate N	Mean(SD)[mg^2/dL^2]	Placebo N	Mean(SD)[mg^2/dL^2]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Joy 2003	49	52.4 (14.9)	44	66.6 (18.3)		-14.20 [-21.03, -7.37]

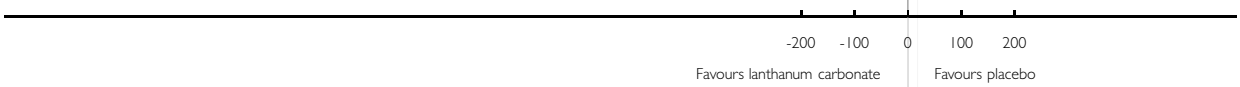
Analysis 6.6. Comparison 6 Lanthanum carbonate versus placebo, Outcome 6 Serum iPTH.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 6 Lanthanum carbonate versus placebo

Outcome: 6 Serum iPTH

Study or subgroup	Lanthanum carbonate N	Mean(SD)[pg/mL]	Placebo N	Mean(SD)[pg/mL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Joy 2003	49	209 (152)	44	292 (195)		-83.00 [-154.63, -11.37]



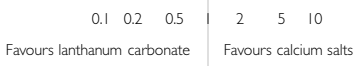
Analysis 7.1. Comparison 7 Lanthanum carbonate versus calcium salts, Outcome 1 All-cause mortality.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 7 Lanthanum carbonate versus calcium salts

Outcome: 1 All-cause mortality

Study or subgroup	Lanthanum carbonate n/N	Calcium salts n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
D'Haese 2003	0/49	0/49		0.0 [0.0, 0.0]
Shigematsu 2008	0/123	0/130		0.0 [0.0, 0.0]
Total (95% CI)	**172**	**179**		**0.0 [0.0, 0.0]**
Total events: 0 (Lanthanum carbonate), 0 (Calcium salts)				
Heterogeneity: Tau² = ï½; Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				



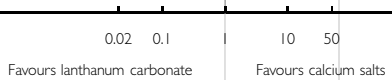
Analysis 7.2. Comparison 7 Lanthanum carbonate versus calcium salts, Outcome 2 Hypercalcaemia.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 7 Lanthanum carbonate versus calcium salts

Outcome: 2 Hypercalcaemia

Study or subgroup	Lanthanum carbonate n/N	Calcium salts n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
D'Haese 2003	3/49	24/49		31.4 %	0.13 [0.04, 0.39]
Shigematsu 2008	7/123	39/130		68.6 %	0.19 [0.09, 0.41]
Total (95% CI)	**172**	**179**		**100.0 %**	**0.17 [0.09, 0.31]**
Total events: 10 (Lanthanum carbonate), 63 (Calcium salts)					
Heterogeneity: Tau² = 0.0; Chi² = 0.36, df = 1 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 5.54 (P < 0.00001)					



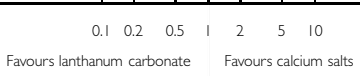
Analysis 7.3. Comparison 7 Lanthanum carbonate versus calcium salts, Outcome 3 Adverse gastrointestinal events.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 7 Lanthanum carbonate versus calcium salts

Outcome: 3 Adverse gastrointestinal events

Study or subgroup	Lanthanum carbonate n/N	Calcium salts n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Gastritis				
2 Diarrhoea				
3 Constipation				
4 Combined				
D'Haese 2003	25/49	24/49		1.04 [0.70, 1.55]



Analysis 7.4. Comparison 7 Lanthanum carbonate versus calcium salts, Outcome 4 Serum phosphorus.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 7 Lanthanum carbonate versus calcium salts

Outcome: 4 Serum phosphorus

Study or subgroup	Lanthanum carbonate N	Mean(SD)[mg/dL]	Calcium salts N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
D'Haese 2003	49	5.59 (1.46)	49	5.15 (1.68)		59.9 %	0.44 [-0.18, 1.06]
Spasovski 2006	12	4.8 (0.77)	12	4.92 (1.17)		40.1 %	-0.12 [-0.91, 0.67]
Total (95% CI)	**61**		**61**			**100.0 %**	**0.22 [-0.32, 0.75]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.19$, df = 1 (P = 0.28); $I^2 = 16\%$

Test for overall effect: Z = 0.79 (P = 0.43)

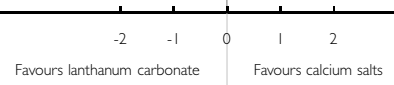
Analysis 7.5. Comparison 7 Lanthanum carbonate versus calcium salts, Outcome 5 Serum calcium.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 7 Lanthanum carbonate versus calcium salts

Outcome: 5 Serum calcium

Study or subgroup	Lanthanum carbonate N	Mean(SD)[mg/dL]	Calcium salts N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Total calcium							
D'Haese 2003	49	9.32 (0.64)	49	9.56 (0.84)		83.9 %	-0.24 [-0.54, 0.06]
Spasovski 2006	12	8.72 (0.76)	12	9.32 (0.92)		16.1 %	-0.60 [-1.28, 0.08]
Subtotal (95% CI)	**61**		**61**			**100.0 %**	**-0.30 [-0.57, -0.03]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.92$, df = 1 (P = 0.34); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.16 (P = 0.031)							
2 Ionised calcium							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							



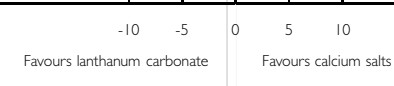
Analysis 7.6. Comparison 7 Lanthanum carbonate versus calcium salts, Outcome 6 Serum calcium x phosphorus product.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 7 Lanthanum carbonate versus calcium salts

Outcome: 6 Serum calcium x phosphorus product

Study or subgroup	Lanthanum carbonate N	Mean(SD)[mg^2/dL^2]	Calcium salts N	Mean(SD)[mg^2/dL^2]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
D'Haese 2003	49	52.09 (9.8)	49	58.1 (8.6)		-6.01 [-9.66, -2.36]

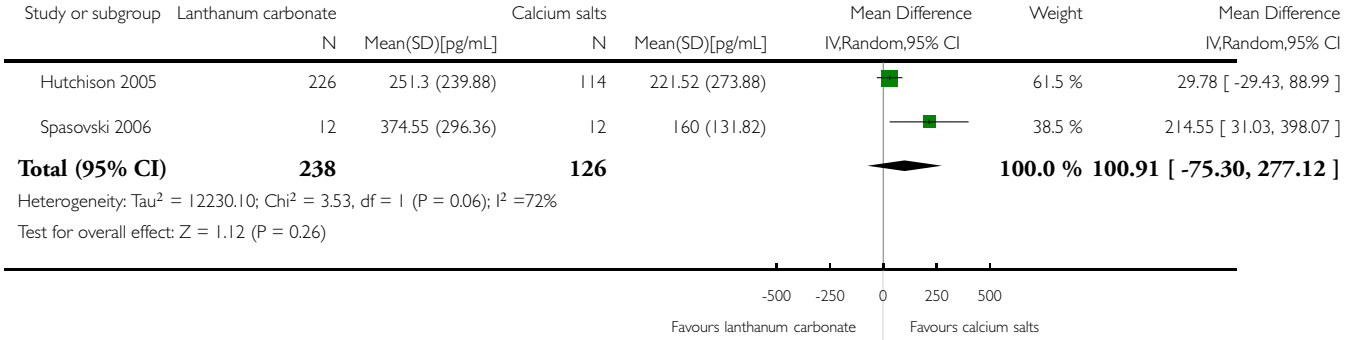


Analysis 7.7. Comparison 7 Lanthanum carbonate versus calcium salts, Outcome 7 Serum iPTH.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 7 Lanthanum carbonate versus calcium salts

Outcome: 7 Serum iPTH

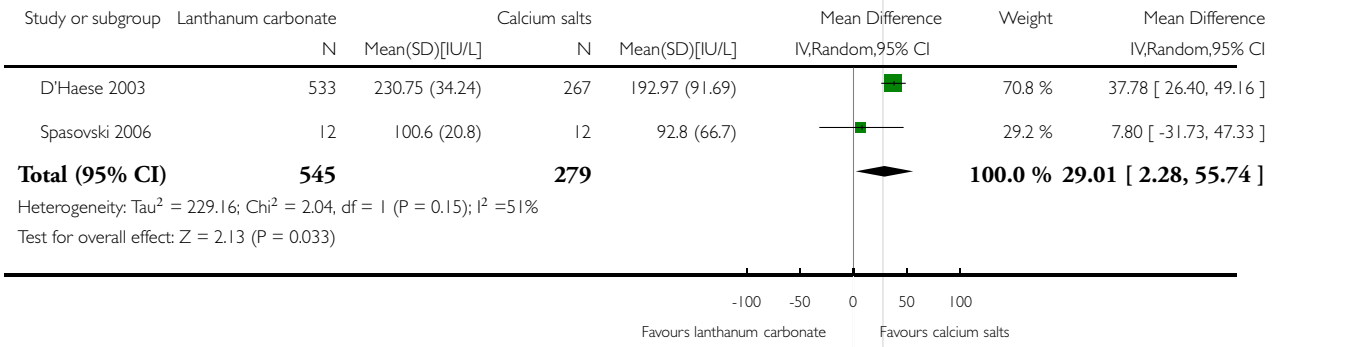


Analysis 7.8. Comparison 7 Lanthanum carbonate versus calcium salts, Outcome 8 Serum alkaline phosphatase.

Review: Phosphate binders for preventing and treating bone disease in chronic kidney disease patients

Comparison: 7 Lanthanum carbonate versus calcium salts

Outcome: 8 Serum alkaline phosphatase



ADDITIONAL TABLES

Table 1. Characteristics and key results of studies analysing the effects of various phosphate binders on bone densitometry, bone histomorphometry and vascular calcification

Study, year	Comparisons	Study duration (months)	Number of participants	Outcomes analysed	Key findings
BRiC Study 2008	Sevelamer versus calcium acetate	12	101	CAC scores using electron beam computer tomography Bone histomorphometry	CAC progression and bone remodelling did not differ between the two groups
Block 2005	Sevelamer versus calcium carbonate plus calcium acetate	18	129	CAC scores using electron beam computer tomography	Calcium-containing phosphate binders increased coronary artery calcium scores compared with sevelamer (P = 0.01)
Chertow 2002	Sevelamer versus calcium acetate	12	132	Vascular calcification scores[$] (Agatston scores) using electron beam computer tomography	Coronary, aortic and valvular calcification progressed in calcium-treated participants but no significant progression was noted in the sevelamer treated group
CARE-2 Study 2008	Sevelamer plus atorvastatin versus calcium acetate plus atorvastatin	12	203	Vascular calcification scores (Agatston scores) using electron beam computer tomography	Coronary calcification scores was similar in both groups
Raggi 2005*	Sevelamer versus calcium acetate	12	111	Thoracic vertebral bone attenuation using electron beam computed tomography	Trabecular bone attenuation decreased significantly in sevelamer-treated participants (P < 0.05) Cortical bone attenuation did not decrease significantly with sevelamer (P = 0.05)
Russo 2007	Sevelamer versus calcium carbon-	24	90	CAC scores using electron beam com-	Sevelamer reduced the progression of

Table 1. Characteristics and key results of studies analysing the effects of various phosphate binders on bone densitometry, bone histomorphometry and vascular calcification (*Continued*)

	ate versus low-phosphorus diet			puter tomography	CAC while calcium carbonate did not increase or reduce the progression on CAC
D'Haese 2003	Lanthanum carbonate versus placebo	12	98	Bone histomorphometry analysing	The prevalence of renal osteodystrophy decreased from 36% to 18% in the lanthanum carbonate group and increased from 43% to 53% in calcium carbonate-treated participants Bone lanthanum levels were higher in lanthanum carbonate- treated participants than calcium carbonate-treated participants
Phelps 2002	Calcium acetate 2 g/day versus calcium acetate 6 g/day	18	24	BMD at lumbar spine, femoral neck and greater trochanter using DEXA	No significant difference between treatment groups
Ferreira 2008	Sevelamer versus calcium carbonate	12	91	Mineralization lag time, changes in bone turnover, development of osteomalacia, adynamic bone disease	Bone formation and trabecular architecture increased with sevelamer with no changes in bone turnover or mineralization
Malluche 2008	Lanthanum carbonate versus standard phosphate binder therapy	24	211	Bone histomorphometry analysing changes in bone turnover, mineralization, bone volume and lanthanum content in bone	Participants on lanthanum carbonate had an improvement in bone turn over and bone volume

[$] Agatston score was obtained by multiplying the area of calcified focus by a weighted density coefficient based on the peak density of the calcification noted in the electron beam computed tomography

*Substudy of Chertow 2002

CAC - coronary artery calcium/calcification

Table 2. Serum phosphorus data from miscellaneous studies not included in the meta-analysis

Study	Comparison	Phosphorus (mg/dL)		Comment
		Treatment group	Control group	
Cheng 2008	Niacinamide versus placebo	-0.79	+ 0.13	A significant decrease in serum phosphorus levels was noted only in the niacinamide group
Fan 2009	Sevelamer carbonate powder versus sevelamer hydrochloride	5.0 ± 1.5	5.2 ± 1.1	Both agents reduced serum phosphorus and no significant difference between two groups was noted
Itoh 2008	Sevelamer hydrochloride and calcium carbonate versus colestimide and calcium carbonate	5.63 ± 1.93	5.11 ± 1.31	Both agents reduced serum phosphorus and no significant difference between two groups was noted
McIntyre 2009	Iron-magnesium hydroxycarbonate 1 g versus 2 g versus placebo	1 g: -1.4 2 g: -2.1	NR	Significant decrease in phosphorus levels were noted in both groups
Tzanakis 2008	Magnesium carbonate versus calcium carbonate	5.12 ± 0.70	5.28 ± 0.74	Significant decrease in phosphorus levels were noted in both groups
Yang 2002	Ferric citrate versus calcium carbonate	5.7 ± 1.6	5.2 ± 1.5	Both agents reduced serum phosphorus and no significant difference between two groups was noted

NR - not reported

Table 3. Serum calcium data from miscellaneous studies not included in the meta-analysis

Study	Comparison	Calcium (mg/dL)		Comment
		Treatment group	Control group	
Cheng 2008	Niacinamide versus placebo	9.52 ± 0.76	9.45 ± 0.70	No significant difference in serum calcium levels was noted between the groups
Fan 2009	Sevelamer carbonate powder versus sevelamer hydrochloride	9.1 ± 0.8	9.1 ± 0.9	No significant difference in serum calcium levels was noted between the groups

Table 3. Serum calcium data from miscellaneous studies not included in the meta-analysis (*Continued*)

Itoh 2008	Sevelamer hydrochloride and calcium carbonate versus colestimide and calcium carbonate	8.68 ± 0.62	8.84 ± 0.45	No significant difference in serum calcium levels was noted between the groups
Tzanakis 2008	Magnesium carbonate versus calcium carbonate	8.97 ± 0.57	9.72 ± 0.42	A significant increase in calcium levels from baseline was reported in calcium group
Yang 2002	Ferric citrate versus calcium carbonate	9.0 ± 1.0	9.5 ± 0.7	A significant increase in calcium levels from baseline was reported in calcium group

Table 4. Serum parathyroid hormone (PTH) data from miscellaneous studies not included in the meta-analysis

Study	Comparison	PTH values (pg/mL)		Comment
		treatment group	Control group	
Cheng 2008	Niacinamide versus placebo	296 ± 195	280 ± 222	No significant difference between the two groups was noted
Fan 2009	Sevelamer carbonate powder versus sevelamer hydrochloride	390	408	No significant difference between the two groups was noted
Itoh 2008	Sevelamer hydrochloride and calcium carbonate versus colestimide and calcium carbonate	161.6 ± 118.4	91.4 ± 62.8	No significant difference between the two groups was noted
Spiegel 2007	Magnesium carbonate versus calcium acetate	322 ± 416	373 ± 326	No significant difference between the two groups was noted
Tzanakis 2008	Magnesium carbonate versus calcium carbonate	251 ± 118	212 ± 198	No significant difference between the two groups was noted
Yang 2002	Ferric citrate versus calcium carbonate	240 ± 184	228 ± 160	No significant difference between the two groups was noted

Table 5. Subgroup analyses to explore the reasons for heterogeneity in studies comparing newer agents with older phosphate binding agents

Variables	All-cause mortality		Treatment-related hypercalcaemia		PTH (pg/mL)		Phosphorus (mg/dL)	
	RR (95% CI); N'	P[2]	RR (95% CI); N	P	MD (95% CI); N	P	MD (95% CI); N	P

Table 5. Subgroup analyses to explore the reasons for heterogeneity in studies comparing newer agents with older phosphate binding agents (*Continued*)

Older versus newer agents								
Calcium carbonate versus sevelamer and lanthanum	0.75 (0.39 to 1.44); 4	0.82	0.45 (0.28 to 0.73); 5	0.11	51.72 (17.66 to 85.78); 5	0.82	0.09 (-0.06 to 0.25) ; 10	0.15
Calcium acetate versus sevelamer and lanthanum	0.64 (0.21 to 1.94); 2		0.20 (0.07 to 0.50); 6		62.02 (-21.97 to 146.03); 3		0.41 (0.00 to 0.82) ; 6	
Baseline PTH								
< 150	-	0.61	0.02 (0.00 to 0.08); 1	**< 0.001**	-	0.22	0.10 (-0.13 to 0.33) ; 1	0.49
150 to 300	0.44 (0.04 to 4.3); 2		0.30 (0.16 to 0.56); 5		42.53 (8.26 to 76.81); 8		0.11 (-0.19 to 0.43) ; 7	
> 300	0.81 (0.48 to 1.37); 4		0.42 (0.16 to 0.54); 5		118.00 (8.18 to 218.0); 1		0.31 (0.02 to 0.60) ; 8	
Type of calcium assay								
Corrected calcium	0.56 (0.29 to 1.07); 4	**0.04**	0.25 (0.11 to 0.55); 7	0.71	57.89 (24.55 to 91.24); 8	0.38	0.13 (-0.11 to 0.37) ; 9	0.42
Absolute calcium	1.12 (0.96 to 1.29); 2		0.31 (0.14 to 0.68); 4		26.58 (-10.70 to 63.86); 3		0.28 (0.01 to 0.54) ; 7	
Ionised calcium			-		-		-	
Washout of phosphate binder								
Yes	0.75 (0.44 to 1.27); 5	NA	0.27 (0.15 to 0.48); 10	0.82	58.16 (27.43 to 88.89); 9	0.24	0.18 (0.01 to 0.36) ; 14	0.75
No	-		0.36 (0.04 to 3.05); 1		29.42 (-49.84 to 108.7); 2		0.36 (-0.32 to 1.05) ; 2	
Study duration								
< 6 months	-	0.23	0.24 (0.13 to 0.46); 5	**0.01**	17.61 (-29.91 to 65.12); 6	0.61	0.48 (0.11 to 0.85) ; 7	**0.008**

Table 5. Subgroup analyses to explore the reasons for heterogeneity in studies comparing newer agents with older phosphate binding agents (*Continued*)

6 to 12 months	0.43 (0.14 to 1.27); 3		0.62 (0.42 to 0.89); 2		59.17 (-38.19 to 156.54); 2		-0.30 (-0.65 to 0.03); 3	
> 12 months	0.90 (0.53 to 1.53); 3		0.16 (0.04 to 0.62); 4		49.95 (11.66 to 88.25); 4		0.11(0.01 to 0.21); 6	
Allocation concealment								
Adequate	0.57 (0.31 to 1.03); 2	0.47	0.41 (0.24 to 0.68); 5	0.26	49.95 (11.66 to 88.25); 4	0.27	0.19 (-0.02 to 0.40) ; 7	0.97
Unclear	0.79 (0.39 to 1.62); 4		0.21 (0.07 to 0.60); 6		67.29 (28.73 to 105.86); 6		0.19 (-0.03,0.43); 9	
Blinding								
Yes	-	NA	0.36 (0.10 to 1.28); 1	0.69	-	NA	1.30 (0.68 to 1.91) ; 1	**< 0.001**
No	0.88 (0.58 to 1.35); 5		0.27 (0.15 to 0.47); 10		47.95 (23.78 to 72.13); 11		0.11 (-0.01 to 0.23) ; 15	
Intention to treat analysis								
Yes	0.67 (0.35 to 1.26): 5	0.37	0.49 (0.37 to 0.66); 6	**0.03**	-	NA	0.22 (0.01 to 0.45) ; 7	0.74
No	1.22 (0.38 to 1.34); 1		0.15 (0.04 to 0.44); 5		54.78 (25.90 to 83.66); 8		0.16 (-0.13 to 0.46) ; 9	
Lost to follow-up (%)								
0	-		-		-		-	
1 to 10	-	0.37	0.21 (0.10 to 0.43); 3	0.07	30.76 (-7.04 to 68.56); 3	0.52	0.49 (-0.01 to 0.99) ; 5	0.26
10 to 20	1.22 (0.38, 3.88); 1		0.15 (0.02 to 1.26); 3		6.00 (-56.85 to 68.85); 2		0.18 (-0.10 to 0.47) ; 4	
> 20	0.67 (0.35 to 1.26); 5		0.49 (0.33 to 0.72); 5		58.32 (15.72 to 100.92); 4		0.05 (-0.13 to 0.25) ; 7	
Number of participants								
1 to 20	-	0.74	0.27 (0.08 to 0.83); 1	0.97	51.48 (-32.66 to 135.6); 2	0.71	0.80 (0.19 to 1.41) ; 1	**0.05**

Table 5. Subgroup analyses to explore the reasons for heterogeneity in studies comparing newer agents with older phosphate binding agents (*Continued*)

20 to 50	-		0.35 (0.04 to 0.62); 1		40.00 (89.00 to 169.0); 1		0.20 (-0.52 to 0.92) ; 2	
50 to 100	1.00 (0.15 to 6.42); 1		0.31 (0.14 to 0.68); 4		27.08 (-7.23 to 61.40); 5		0.44 (0.00 to 0.88) ; 6	
> 100	0.72 (0.40 to 1.30); 5		0.24 (0.09 to 0.62); 5		71.91 (17.19 to 126.62); 4		0.06 (-0.01 to 0.19) ; 7	
Baseline phosphorus								
< 5.5 mg/dL	0.53 (0.28 to 1.00); 1	0.61	0.41 (0.23 to 0.70); 1	0.1	55.00 (0.82 to 109.18); 1	0.19	0.10 (-0.22 to 0.42) ; 1	0.52
5.5 to 7.0 mg/dL	0.57 (0.18 to 1.79); 2		0.61 (0.38 to 1.00); 2		88.72 (9.69 to 167.25); 1		0.30 (-0.13 to 0.72) ; 6	
7.0 to 8.0 mg/dL	1.22 (0.38 to 3.88); 1		0.31 (0.12 to 0.76); 5		92.00 (43.91 to 140.90); 4		0.63 (-0.65 to 1.90) ; 5	
> 8.0 mg/dL	1.00 (0.15 to 6.42); 1		0.42 (0.22 to 0.79); 3		6.92 (-47.80 to 61.63); 3		0.52 (-0.09 to 1.14) ; 4	

Some data are not estimable because no study with the variable of interest reported outcome or because studies in that group reported no events in both treatment and control arms. To convert parathyroid hormone pg/mL to pmol/L, multiply by 0.11. To convert calcium mg/dL to mmol/L, multiply by 0.25. To convert phosphorus mg/dL to mmol/L, multiply by 0.323.

[1]N - number of studies

[2]P value for interaction, calculated by analysing each category compared to first (referent) category for categorical variables; $P < 0.05$ was considered statistically significant.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. KIDNEY DISEASES 2. KIDNEY FAILURE CHRONIC 3. KIDNEY FAILURE 4. RENAL REPLACEMENT THERAPY

(*Continued*)

	5. RENAL DIALYSIS 6. HEMOFILTRATION 7. ((chronic next kidney) or (chronic next renal)) 8. (ckd or ckf or crd or crf or eskd or esrd or eskf or esrf) 9. (predialysis or dialysis) 10. (haemodialysis or haemodialysis) 11. (capd or ccpd or apd) 12. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11) 13. BONE DISEASES 14. RENAL OSTEODYSTROPHY 15. (bone next disease*) 16. (bone* and (atroph* or formation or deform* or destruct* or necrosis or resorption or metabol* or turnover or demineral* or decalcif* or density)) 17. (#13 or #14 or #15 or #16) 18. (#12 and #17) 19. aluminium HYDROXIDE 20. CALCIUM CARBONATE 21. CALCIUM GLUCONATE 22. POLYAMINES 23. ANION EXCHANGE RESINS 24. ((phosphate next buffer*) or (phosphate next binder*)) 25. ((aluminium next carbonate*) or (aluminium next carbonate*)) 26. (calcium next acetate*) 27. (calcium next ketoglutarate*) 28. sevelamer 29. (lanthanum next carbonate*) 30. (magnesium next carbonate*) 31. ((aluminium next hydroxide*) or (aluminium next hydroxide*)) 32. colestimide 33. phoslo 34. renagel 35. fosrenol 36. (#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35) 37. (#18 and #36)
MEDLINE	1. Kidney Diseases/ 2. Kidney Failure, Chronic/ 3. Kidney Failure/ 4. renal replacement therapy/ or exp renal dialysis/ or exp hemofiltration/ 5. (chronic kidney or chronic renal).tw. 6. (CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF).tw. 7. (predialysis or dialysis).tw. 8. (haemodialysis or haemodialysis).tw. 9. (CAPD or CCPD or APD).tw. 10. or/1-9 11. exp Bone Diseases/ 12. Renal Osteodystrophy/ 13. bone disease$.tw.

(*Continued*)

	14. (bone$ and (atroph$ or formation or deform$ or destruct$ or necrosis or resorption or metabol$ or turnover or demineral$ or decalcif$ or density)).tw. 15. (osteo$ or hyperparathyroid$ or hyperphosphat$).tw. 16. or/11-15 17. and/10,16 18. aluminium Hydroxide/ 19. Calcium Carbonate/ 20. Calcium Gluconate/ 21. Polyamines/ 22. Anion Exchange Resins/ 23. (phosphate buffer$ or phosphate bind$).tw. 24. alumin?um carbonate$.tw. 25. calcium acetate$.tw. 26. calcium ketoglutarate$.tw. 27. sevelamer.tw. 28. lanthanum carbonate$.tw. 29. magnesium carbonate$.tw. 30. alumin?um hydroxide$.tw. 31. colestimide.tw. 32. phoslo.tw. 33. renagel.tw. 34. fosrenol.tw. 35. or/18-34 36. and/17,35
EMBASE	1. Kidney Disease/ 2. Kidney Failure/ 3. Chronic Kidney Failure/ 4. exp haemodialysis/ 5. (haemodialysis or haemodialysis).tw. 6. dialysis.tw. 7. (CAPD or CCPD or APD).tw. 8. predialysis.tw. 9. (chronic renal or chronic kidney).tw. 10. (CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF).tw. 11. or/1-10 12. exp Bone Disease/ 13. bone disease$.tw. 14. (bone$ and (atroph$ or formation or deform$ or destruct$ or necrosis or resorption or metabol$ or turnover or demineral$ or decalcif$ or density)).tw. 15. (osteo$ or hyperparathyroid$ or hyperphosphat$).tw. 16. or/12-15 17. aluminium Hydroxide/ 18. Calcium Carbonate/ 19. Gluconate Calcium/ 20. Polyamine/ 21. Anion Exchange Resin/ 22. Sevelamer/ 23. Lanthanum Carbonate/

(*Continued*)

	24. Magnesium Carbonate/ 25. aluminium Carbonate/ 26. Calcium Acetate/ 27. Phosphate Binding Agent/ 28. aluminium Hydroxide/ 29. Colestilan/ 30. (phosphate buffer$ or phosphate bind$).tw. 31. alumin?um carbonate$.tw. 32. calcium acetate$.tw. 33. calcium ketoglutarate$.tw. 34. sevelamer.tw. 35. colestimide.tw. 36. phoslo.tw. 37. renagel.tw. 38. fosrenol.tw. 39. lanthanum carbonate$.tw. 40. magnesium carbonate$.tw. 41. alumin?um hydroxide$.tw. 42. or/17-41 43. and/11,16,42

Appendix 2. Quality checklist

Allocation concealment

- Adequate (A): randomisation method described that would not allow investigator or participant to know or influence intervention group before eligible participant entered the study
- Unclear (B): randomisation stated but no information on method used was available
- Inadequate (C): the method of randomisation used such as alternate medical record numbers or unsealed envelopes; information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes, No, not stated
- Blinding of participants: Yes, No, not stated
- Blinding of outcome assessor: Yes, No, not stated
- Blinding of data analysis: Yes, No, not stated

The above are considered not blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment

Intention-to-treat analysis

- Yes: specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: not stated but confirmed on study assessment
- No: not reported and lack of intention-to-treat analysis confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study, or were not included because of protocol violation)
- No: stated but not confirmed upon study assessment

- Not stated

Completeness of follow-up

Percentage of participants excluded or lost to follow-up

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 2, 2011

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review: SN, SP, MV, JC, GE, SP
- Screening of titles and abstracts: SN, SCP, MV
- Assessment for inclusion: SN, SCP, MV, GFMS
- Quality assessment: SN, SCP, MV, GFMS
- Data extraction: SN, SCP, MV, GFMS
- Data entry into RevMan: SN, MV
- Data analysis: SN
- Disagreement resolution: GFMS

DECLARATIONS OF INTEREST

- A/Prof Grahame Elder has been a member of the advisory boards of Amgen, Shire and Genzyme Australia and has been a speaker at scientific meetings arranged by all of the above and also by Abbott Australia.

- Sankar D Navaneethan, Suetonia C Palmer, Mariacristina Vecchio, Jonathan C Craig, Giovanni FM Strippoli: Nothing to declare

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- SDN is supported by Multidisciplinary Clinical Research Career Development Program CTSA KL2 Grant #: RR024990, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Diseases, Metabolic [*drug therapy; prevention & control]; Calcium [blood]; Calcium Compounds [adverse effects; *therapeutic use]; Chelating Agents [adverse effects; *therapeutic use]; Chronic Disease; Hypercalcemia [chemically induced]; Kidney Diseases [blood; *complications]; Parathyroid Hormone [blood]; Phosphorus [*blood]; Polyamines [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans