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

Review information

Authors

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

[1]Department of Nephrology and Hypertension, Glickman Urological and Kidney institute, Cleveland Clinic, Cleveland, OH, USA

[2]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[3]Clinical Pharmacology and Epidemiology, Mario Negri Sud Consortium, S. Maria Imbaro, Italy

[4]Centre for Kidney Research, The Children's Hospital at Westmead, School of Public Health, The University of Sydney, Westmead, Australia

[5]Bone and Mineral Program, Garvan Institute of Medical Research, Darlinghurst, Australia

[6]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia

Citation example: 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 . Art. No.: CD006023. DOI: 10.1002/14651858.CD006023 .

Contact person

Sankar D Navaneethan

Department of Nephrology and Hypertension
Glickman Urological and Kidney institute, Cleveland Clinic
Cleveland
OH
44195
USA

E-mail: navanes@ccf.org
E-mail 2: sankardass@hotmail.com

Dates

Assessed as Up-to-date:	Not provided
Date of Search:	Not provided
Next Stage Expected:	14 August 2005
Protocol First Published:	Issue 2 , 2006
Review First Published:	Not specified
Last Citation Issue:	Issue 2 , 2006

What's new

Date	Event	Description
2 September 2008	Amended	Converted to new review format.

History

Date	Event	Description

Abstract

Background

Phosphate binders are widely used to lower serum phosphorus levels in patients with chronic kidney disease (CKD).

Objectives

We aimed to systematically review the effects of currently available phosphate binders on biochemical and patient-level end-points in CKD.

Search strategy

MEDLINE (1966-April 2009), EMBASE (1980-April 2009), and the Cochrane Renal Group Specialised Register and

the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant trials.

Selection criteria

Randomized or quasi randomized controlled trials that assessed the effects of various phosphate binders in adult patients with CKD (both predialysis and dialysis patients).

Data collection and analysis

Two reviewers independently reviewed search results and extracted data. Results were expressed as weighted mean differences (WMD) for continuous outcomes and as a relative risk (RR) for categorical outcomes with 95% confidence intervals (CI) using a random effects model.

Main results

Fifty one trials (6733 patients) were included. There was no significant reduction in all-cause mortality (10 RCTs, 3079 patients, relative risk [RR] 0.73, 95% confidence interval [CI] 0.46 to 1.16), hospitalization or end of treatment serum calcium by phosphorus product (Ca × P) with sevelamer compared to calcium-based agents. There was a significant reduction in the end of treatment phosphorus (15 trials, 3012 patients, WMD 0.21 mg/dl, 95%CI 0.01 to 0.41) and parathyroid hormone (PTH) levels (12 trials, 2551 patients, WMD 55.57 pg/ml, 95%CI 26.69 to 84.45) with calcium salts compared to sevelamer and a significant reduction in the risk of hypercalcemia (RR 0.47, 95% CI 0.36 to 0.62) with sevelamer when compared to calcium-based agents. There was a significant increase in the risk of gastrointestinal adverse events with sevelamer in comparison to calcium salts. Compared with calcium-based agents, lanthanum significantly reduced end of treatment serum calcium (2 trials, 122 patients, WMD -0.30 mg/dl, 95%CI -0.64 to -0.25) and the Ca × P product but with similar end of treatment phosphorus levels. The effects of calcium acetate on biochemical end-points were similar to those of calcium carbonate. Existing data are insufficient to conclude for a differential impact of any phosphate binder on cardiovascular mortality or other patient-level outcomes.

Authors' conclusions

Currently, there are insufficient data to establish the comparative superiority of non-calcium binding agents over calcium-containing phosphate binders for the important patient-level outcomes such as all-cause mortality and cardiovascular end-points. Future clinical trials should examine differential effects of phosphate binding agents on these end-points and the mineral homeostasis pathway.

Plain language summary

Background

The incidence of chronic kidney disease (CKD) is increasing worldwide with about $23 billion (6.6% of Medicare budget) spent on the care of patients with end-stage kidney disease (ESKD) in 2006 in the United States alone (USRDS 2008). Worsening kidney function results in impaired clearance of the dietary phosphorus load (Hruska 2008) which directly and indirectly increase parathyroid hormone (PTH) secretion (Hruska 2008; Cozzolino 2005; Silver 2005). Secondary hyperparathyroidism (SHPT) is characterized by high bone turnover, exaggerated marrow fibrosis and increased musculoskeletal morbidity. Recently, epidemiological data have shifted the focus of altered mineral metabolism in CKD from renal bone disease to a broader recognition that hyperphosphatemia is associated with increased morbidity, mortality, hospitalization, reduced quality of life and increased costs of care (Block 1998; Tentori 2008; Block 2004).

Cardiovascular disease accounts for over half of deaths in dialysis patients (USRDS 2008) and the development of vascular calcification of the arterial media has been advocated as a major contributing factor (Guerin 2001; Stevens 2004). Since abnormalities of mineral metabolism involve a paradigm incorporating bone disease as well as vascular and soft tissue calcification that have potential effects on fracture, cardiovascular outcomes and mortality, the concept of CKD-mineral and bone disorder (CKD-MBD) has been introduced. This condition is the target of several interventions including phosphate binders, vitamin D analogues and calcimimetics that all may suppress the development or progression of CKD-MBD (Coladonato 2005; Fadem 2007).

Phosphate binders containing aluminum and calcium have been widely used since 1970 and the non-calcium or aluminum-based agents, sevelamer hydrochloride and lanthanum carbonate have more recently become available. Their use is increasing in current practice and although they are and remain more expensive, the potential reduction in the risk of vascular calcifications and toxicity advocates for a broader adoption. For control of hyperphosphatemia, 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] 30-59 ml/min/1.73m^2 and 15-29 ml/min/1.73m^2 respectively) and both calcium-based and calcium and aluminum-free binders in CKD stages 5 and 5D (GFR<15 ml/min/1.73m^2 and dialysis) (K-DOQI 2003). The relative merits of available phosphate-binding agents remain controversial (Salusky 2006). We have conducted a systematic review of the benefits and harms of phosphate binders to determine whether, compared with calcium salts or placebo, newer agents deliver improved biochemical and patient-level outcomes, with particular reference to musculoskeletal and cardiovascular morbidity, hospitalization and mortality.

Objectives

1. The efficacy of the available aluminium salts, calcium salts, sevelamer hydrochloride, lanthanum carbonate, iron salts and magnesium-based phosphate binders in treatment of hyperphosphataemia.
2. To assess their impact on the development of SHPT or low bone turnover based on surrogate markers (PTH, bone specific alkaline phosphatase, osteocalcin or other bone turnover markers) and the serum calcium, phosphate, the calcium by phosphate product, PTH levels. In addition, the influence of these drugs would be assessed in relation to lipid profile, tissue calcification and common symptoms such as pruritis and bone or muscle pain.
3. To study the impact of these agents on BMD assessed by dual-energy X-ray absorptiometry (DXA) or quantitative computerised tomography (QCT) and on bone turnover and mineralization based on histomorphometry and fracture rates.
4. To assess other patient-based 'hard' endpoints such as incidence of cardiovascular events, number of hospital admissions and all-cause mortality rates.
5. To assess the impact of various phosphate binders on vascular calcification rates.
6. To assess the incidence and nature of side effects with various phosphate binders.

Methods

Criteria for considering studies for this review

Types of studies

All 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 secondary hyperparathyroidism in CKD patients, alone or in combination with other (non randomised) co interventions (e.g. vitamin D analogues) were included. The first period of randomised cross-over studies were included. There was no language restrictions.

Types of participants

Inclusion criteria

CKD patients in stage 3, 4, and 5 as defined by NKF/K-DOQI guidelines (stage 3: GFR 30-59 mL/min; stage 4: GFR 16-29 mL/min; stage 5: GFR < 15 mL/min) greater than 18 years of age.

Exclusion criteria

Studies that included transplant patients as the occurrence of bone disease may be affected other factors such as use of steroids.

Types of interventions

The use of any phosphate binders (aluminium hydroxide, calcium acetate, calcium carbonate, calcium ketoglutarate, sevelamer hydrochloride, lanthanum carbonate, magnesium carbonate) with or without vitamin D analogues compared to a placebo, or to a different phosphate binder or dose given for at least eight weeks. Comparisons considered for inclusion were:

1. Any phosphate binder with or without vitamin D (25(OH) D) versus placebo.
2. Phosphate binder versus other phosphate binder with or without vitamin D co-intervention.
3. Different doses of the same phosphate binder with or without vitamin D therapy co-intervention.
4. Combination therapy with different phosphate binders versus placebo with or without vitamin D co-intervention.

Types of outcome measures

Primary outcome measure

1. The efficacy of the available aluminium salts, calcium salts, sevelamer, lanthanum carbonate and magnesium based phosphate binders in the prevention and treatment of hyperphosphataemia (serum phosphorous level in mg/dL or mmol/L).
2. To assess the impact of treatment with these drugs on the development of/impact on:
   a. Serum calcium (in mg/dL or mmol/L), phosphate (mg/dL or mmol/L), the calcium by phosphate product (mmol2/L2 or mg2/dL2), PTH (intact-PTH or PTH (1-84) in pmol/L and pg/mL).
   b. The effect of these agents on lipid parameters (in mg/dL or mmol/L).
   c. The incidence of vascular calcification (as measured by electron beam tomography, ultrasound or other techniques), other soft tissue or valvular calcification and calciphylaxis as reported in the studies.
3. To study the impact of these agents on BMD assessed by DXA or QCT (assessed as change in BMD using Z scores or percent change in g/cm2 at the lumbar spine, femoral neck and radius when reported).
4. To assess 'hard' patient-based endpoints, including:
   a. Bone turnover and mineralization based on histomorphometry and histology.
   b. Fracture (incidence of fracture at any site, vertebral compression fractures, fracture of femur, hip and any long bones identified by radiographic studies.).
   c. Cardiovascular events.

d. Hospital admission (measured as number of patients who are hospitalised or mean number of days of hospitalisation).
e. Cardiovascular, vascular, fracture-related and all-cause mortality.

5. Incidence and nature of adverse effects, including gastrointestinal (gastritis, diarrhoea, constipation, abdominal bloating), electrolyte imbalance (hypermagnesaemia, hyperkalaemia), accumulation of drugs as demonstrated by bone biopsies (especially for aluminium hydroxide and lanthanum carbonate), and worsening anaemia.

Search methods for identification of studies

Relevant trials were obtained from the following sources:-

1) The Cochrane Renal Groups Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, (most recent) which will be searched using the following terms:-
#1. KIDNEY DISEASES
#2. KIDNEY FAILURE CHRONIC
#3. KIDNEY FAILURE
#4. RENAL REPLACEMENT THERAPY
#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. (hemodialysis 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. ALUMINUM HYDROXIDE
#20. CALCIUM CARBONATE
#21. CALCIUM GLUCONATE
#22. POLYAMINES
#23. ANION EXCHANGE RESINS
#24. ((phosphate next buffer*) or (phosphate next binder*))
#25. ((aluminum 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. ((aluminum 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)

CENTRAL and the Renal Groups Specialised Register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (http://www.cochrane.us/masterlist.asp). Therefore we will not specifically search conference proceedings.

2) MEDLINE (1966 to most recent) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific search strategy developed with input from the Trial Search Coordinator.
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. (hemodialysis or haemodialysis).tw.
9. (CAPD or CCPD or APD).tw.
10. or/1-9
11. exp Bone Diseases/
12. Renal Osteodystrophy/
13. bone disease$.tw.
14. (bone$ 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$).tw.
16. or/11-15
17. and/10,16
18. Aluminum Hydroxide/
19. Calcium Carbonate/
20. Calcium Gluconate/
21. Polyamines/
22. Anion Exchange Resins/
23. (phosphate buffer$ 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

3) EMBASE (1980 to most recent) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a specific search strategy developed with input from the Trial Search Coordinator.
1. Kidney Disease/
2. Kidney Failure/
3. Chronic Kidney Failure/
4. exp hemodialysis/
5. (hemodialysis 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$).tw.
16. or/12-15
17. Aluminum Hydroxide/
18. Calcium Carbonate/
19. Gluconate Calcium/
20. Polyamine/
21. Anion Exchange Resin/
22. Sevelamer/
23. Lanthanum Carbonate/
24. Magnesium Carbonate/
25. Aluminum Carbonate/
26. Calcium Acetate/
27. Phosphate Binding Agent/
28. Aluminum Hydroxide/
29. Colestilan/
30. (phosphate buffer$ 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

4) Reference lists of nephrology textbooks, review articles and relevant trials.
5) Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.

Data collection and analysis

Included and excluded studies

The review was undertaken by six authors (SN, SCP, MV, JC, GE and GFMS). The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened independently by (SN) and (PC), who discarded studies that were not applicable, however studies and reviews that might include relevant data or information on trials were retained initially. Reviewers (SN), (SCP) independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Data extraction was carried out by the same reviewers independently using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one trial exists, only the publication with the most complete data was included. Any further information required from the original author were requested by written correspondence and any relevant information obtained in this manner was included in the review. Disagreements were resolved in consultation with GS, GE and JC who also provided methodological assistance through the review process.

Study quality

The quality of studies to be included were assessed independently by (SN), and (SCP) without blinding to authorship or journal using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by discussion with GS. The quality items assessed are allocation concealment, intention-to-treat analysis, completeness to follow-up and blinding of investigators, participants, outcome assessors and data analysis.

Quality checklist

Allocation concealment

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

- 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 to follow-up

Per cent of participants excluded or lost to follow-up.

Statistical assessment

We followed the Cochrane methodology for conduct and reporting of this systematic review. Two authors independently assessed each trial and data were extracted on the characteristics of participants, interventions, comparisons and the following outcomes, when reported in the trials: all-cause mortality, cardiovascular mortality, non-fatal cardiovascular events, vascular calcification by any imaging modality, end of treatment PTH concentration (intact PTH and PTH 1-84 as reported in the studies), serum calcium (mg/dl), serum phosphorus (mg/dl), serum calcium by phosphorus product (Ca × P, mg^2/dl^2), alkaline phosphatase (IU/l), serum bicarbonate (mEq/L), total cholesterol (mg/dl), bone mineral density, bone mineral content, bone histomorphometry, occurrence of hypercalcemia (defined as serum calcium level >10.2 mg/dl or as defined by the study investigators) and treatment-related toxicity (gastrointestinal side effects). Authors were contacted if data related to mortality, phosphorus, calcium, PTH, or Ca × P were not available or not reported in the published reports.

The quality of RCTs was assessed using a checklist that included allocation concealment, blinding of participants, investigators, outcome assessors and data analysts, use of intention-to-treat analyses, and completeness of follow-up (Schulz 1995). Discrepancies between the two data extractors (SN, SCP) were resolved by discussion with an arbitrator (GFMS). Dichotomous data were analyzed using the relative risk (RR) measure and its 95% confidence intervals (CI). Risk estimates from individual trials were pooled using the Der Simonian-Laird random effects model (Dersimonian 1986). Where continuous measurements of outcomes were used, the weighted mean difference (WMD) and its CI were computed using the end of treatment values. Heterogeneity across included trials was analyzed by visual analysis of the forest plot and formally using the heterogeneity $?^2$ (Cochran Q) statistic, the I^2 statistics. Subgroup analyses were performed as applicable based on a pre-defined study protocol and were reported when significant (Higgins 2003). Sources of heterogeneity to be explored in the subgroup analyses were the following: older *versus* newer phosphate binding agents; baseline PTH levels; baseline 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 patients lost to follow up; and number of trial participants. Analyses were performed using Revman 5 (©2007, The Cochrane Collaboration, UK), and Comprehensive Meta-analysis (Biostat, USA).

Results

Description of studies

The combined search of MEDLINE, EMBASE and the Cochrane Library identified 2381 citations, of which 2298 were excluded after title and abstract review (Figure 1). Full-text assessment of 83 potentially relevant articles identified 51 eligible trials reported in 57 publications and enrolling 6733 patients (Figure 1)(Almirall 1994, Bro 1998, Birck 1999, Borrego 2000, Caravaca 1992, Emmett 1991, d'Almeida Filho 2000, Phelps 2002, Pflanz 1994, Ring 1993, Rudnicki 1994, Schaefer 1991, Barreto 2008, Bleyer 1999, Block 2005, CARE-2 2008, Chertow 1999, Chertow 2002, D-CORE 2007, DeSanto 2006, Evenepoel 2009, Ferreira 2008, Kingusa 2001, Koiwa 2005, Hervas 2003, Sadek 2003, Qunibi 2004, Russo 2007, Shaheen 2004, Chertow 1997, D'Haese 2003, Hutchison 2005, Shigematsu 2008 , Spasovski 2006, Al-Baaj 2005, Chiang 2005, Finn 2004, Joy 2003, Malluche 2008, Mehrotra 2008, Block 2007, Asmus 2005, Raggi 2005, Hutchison 2006, Altmann 2007, Ferramosca 2005, Ittel 1991, Janssen 1996, Jespersen 1991, Roxe 1989, Salusky 1991, Wu-Chang 2002, Kurihara 2005, Fischer 2006, Itoh 2008, Cheng 2008, Spiegel 2007). Authors of 19 trials were contacted for additional information and clarification relating to study methods and additional unreported data, with eight responding.

Trial Characteristics

Characteristics of the participants and the interventions of the included trials are detailed in Table 1. Four different groups of trials were identified. The first group of trials compared any calcium salt with another calcium salt or placebo (Almirall 1994, Bro 1998, Birck 1999, Borrego 2000, Caravaca 1992, Emmett 1991, d'Almeida Filho 2000, Phelps 2002, Pflanz 1994, Ring 1993, Rudnicki 1994, Schaefer 1991). Seven trials (307 patients) compared calcium acetate to calcium carbonate (Almirall 1994,Borrego 2000, Caravaca 1992, Emmett 1991, d'Almeida Filho 2000,Pflanz 1994, Ring 1993), two trials (47 patients) compared calcium ketoglutarate to calcium carbonate (Bro 1998, Birck 1999). One trial (18 patients) compared calcium acetate to placebo (Rudnicki 1994) and two trials (65 patients) compared different doses of calcium acetate (Phelps 2002,Schaefer 1991). Two studies included patients with CKD stages 3 and 4 (Borrego 2000,Phelps 2002) and the rest enrolled hemodialysis patients. Concomitant vitamin D analogues (intravenous or oral) were administered in most of these studies.

The second group compared the efficacy of sevelamer hydrochloride against calcium salts or placebo (Barreto 2008, Bleyer 1999, Block 2005, CARE-2 2008, Chertow 1999, Chertow 2002, D-COR 2007, DeSanto 2006, Evenepoel 2009, Ferreira 2008, Kinugasa 2001, Koiwa 2005, Hervas 2003, Sadek 2003, Qunibi 2004, Russo 2007, Shaheen 2004, Chertow 1997). Five trials (476 patients) compared sevelamer with calcium acetate (Barreto 2008, Bleyer 1999, Evenepoel 2009, Koiwa 2005, Sadek 2003), 6 trials (589 patients) compared sevelamer with calcium carbonate (DeSanto 2006, Ferreira 2008, Kinugasa 2001, Qunibi 2004, Russo 2007, Shaheen 2004), 2 trials (157 patients) compared sevelamer directly with sevelamer and calcium carbonate (Chertow 1999, Hervas 2003), three trials (2369 patients) compared sevelamer to calcium acetate and calcium carbonate (Block 2005, Chertow 2002, D-COR 2007), one trial compared sevelamer plus atorvastatin to calcium acetate plus atorvastatin

(CARE-2 2008) and one trial (36 patients) compared sevelamer to placebo (Chertow 1997). All these trials were performed in patients on hemodialysis and oral or intravenous vitamin D compounds were used as co-intervention in most patients. The third group of trials (10 trials, 2239 patients) compared lanthanum carbonate to calcium carbonate (4 studies, 1181 patients)(D'Haese 2003, Hutchison 2005, Shigematsu 2008, Spasovski 2006) lanthanum carbonate to placebo (4 studies, 333 patients) (Al-Baaj 2005, Chiang 2005, Finn 2004, Joy 2003), different doses of lanthanum carbonate, and lanthanum carbonate to standard phosphate binders (sevelamer and calcium salts) in dialysis patients (Malluche 2008, Mehrotra 2008).

Fourth group of studies compared other agents (Ittel 1991, Janssen 1996, Jespersen 1991, Roxe 1989, Salusky 1991, Wu-Chang 2002, Kurihara 2005, Fischer 2006, Itoh 2008, Cheng 2008, Spiegel 2007). Four studies compared aluminium and calcium salts (Ittel 1991, Janssen 1996, Jespersen 1991, Salusky 1991), while one study compared aluminium hydroxide and sucralfate (Roxe 1989) and one study compared a novel agent, ferric citrate to calcium carbonate in hemodialysis patients (Wu-Chang 2002). One study compared MCI-196 (Colestilan) to placebo (Kurihara 2005) and another study compared once daily sevelamer to thrice daily sevelamer hydrochloride (Fischer 2006). Cheng et al compared niacinamide to placebo (Cheng 2008) while Spiegel et al compared magnesium carbonate plus calcium carbonate to calcium acetate (Spiegel 2007). One study compared sevelamer plus calcium carbonate to colestimide plus calcium carbonate (Itoh 2008).

The majority of trials included in this review were of short duration (1-18 months of treatment administration) except for the Dialysis Clinical Outcomes Revisited (DCOR) trial (D-COR 2007) that analyzed the efficacy of phosphate binders to reduce serum phosphorus, where 42% of patients had a follow-up of more than 24 months. The number of participants ranged from 10 to 2100 with 27 of 40 (67%) of trials enrolling fewer than 100 participants. Co-administration of vitamin D analogues and the route of administration of these agents varied among the studies. Assays used to measure PTH also differed in the included studies. Most studies defined hypercalcemia as a serum calcium >10.2 mg/dl while some used >10.5 mg/dl and some >11.0 mg/dl as a cut-off to define hypercalcemia.

Risk of bias in included studies

By current methodological standards for reporting, trial quality was variable. Allocation concealment was adequate in 11 out of 51 (21%) trials and unclear in other trials. Participants and investigators were blinded in 8 of 51 (16%) trials and outcome assessors were blinded in none of the trials. Only 11 of the 51 (21%) trials were analyzed on an intention-to-treat basis. The number of patients lost to follow-up ranged from 0% to 31%, but did not differ between the treatment and control groups of the trials.

Effects of interventions

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

Calcium salts versus placebo

All cause mortality

There was no death reported in one short-term trial (n=72) that compared calcium acetate to placebo.

Hypercalcemia

There was no significant difference in the incidence of hypercalcemia between calcium acetate and placebo (1 trial, 72 patients, RR 11.00, 95%CI 0.63 to 191.88).

Other adverse events

Gastrointstinal side effects were not reported in both groups during the study period.

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 (2 trials, 74 patients, RR 1.13, 95%CI 0.07 to 17.30).

Hypercalcemia

There was no significant difference in the incidence of hypercalcemia between calcium acetate and calcium carbonate (2 trials, 88 patients, RR 1.08, 95%CI 0.11 to 10.99) but with significant heterogeneity between the two studies (heterogeneity χ^2=2.46, I^2=59%).

Other adverse events

There was no significant difference in the occurrence of gastrits between calcium acetate and calcium carbonate (1 trials, 30 patients, RR 1.25, 95% CI 0.41 to 3.77).

There was no significant difference in the occurrence of diarrhea events between calcium acetate and calcium carbonate (2 trials, 53 patients, RR 1.65, 95%CI 0.22 to 12.56) with no significant heterogeneity between the included studies (heterogeneity χ^2=0.32, I^2=0%).

Similarly there was no significant difference in the occurrence of constipation events between calcium acetate and calcium carbonate (2 trials, 53 patients, RR 1.16, 95% CI 0.38 to 3.52) with no significant heterogeneity

between the included studies (heterogeneity χ^2=0.50, I^2=0%).

Calcium ketoglutarate versus other calcium salts

All cause mortality

There was no death reported in one short-term trial (n=34) that compared calcium acetate to placebo.

Other adverse events

There was no significant difference in the occurrence of gastrointestinal events between calcium ketoglutarate and other calcium salts (1 trial, 34 patients, RR 5.00, 95%CI 0.65 to 38.42).

Sevelamer versus placebo

All cause mortality

There was no death reported in one short-term trial (n=36) that compared sevelamer to placebo.

Other adverse events

There was no significant difference in the occurrence of gastrits between sevelamer and placebo (1 trial, 36 patients, RR 1.00, 95%CI 0.10 to 9.96).

There was no significant difference in the occurrence of diarrhea events between sevelamer and placebo (1 trial, 36 patients, RR 0.17, 95%CI 0.01 to 3.96).

Sevelamer versus calcium salts

All cause mortality

There was no significant reduction in the risk of all-cause mortality with sevelamer in comparison to calcium salts (10 trials, 3079 patients, RR 0.73, 95%CI 0.46 to 1.16) with no significant heterogeneity between the included studies (heterogeneity χ^2=8.81, I^2=43%) (Figure 1).

Hospitalisation

There was no difference in the number of patients hospitalised in 52 weeks between sevelamer and calcium salts (p=0.23)(Chertow 2002). and did not find any There was not statistically significant difference in the number of days hospitalised per patient-year between sevelamer and calcium salts (p=0.09)(Suki 2007).

Hypercalcemia

There was significant reduction in the incidence of hypercalcemia with Sevelamer in comparison to calcium salts (10 trials, 960 patients, RR 0.47, 95% CI 0.36 to 0.62) with no significant heterogeneity between the included studies (heterogeneity χ^2=8.10, I^2=1%) (Figure 2).

Other adverse events

There was no significant increase in the occurrence of nausea with sevelamer in comparison to calcium salts (1 trial, 203 patients, RR 1.03, CI 0.57 to 1.86).

There was no significant increase in the occurrence of diarrhea events with sevelamer in comparison to calcium salts (1 trial, 203 patients, RR 1.03, CI 0.55 to 1.95).

Similarly there was no significant increase in the occurrence of abdominal bloating events with sevelamer in comparison to calcium salts (1 trial, 56 patients, RR 2.33, CI 0.49 to 11.01).

There was significant increase in the occurrence of constipation with sevelamer in comparison to calcium salts (2 trials, 259 patients, RR 2.63, CI 1.29 to 5.35) with no significant heterogeneity between the included studies (heterogeneity χ^2=0.40, I^2=0%).

Lanthanum carbonate versus placebo

All cause mortality

There was no effect on all-cause mortality with lanthanum carbonate compared with placebo with no deaths reported in included trials.

Other adverse events

There was no significant difference in gastrointestinal toxicity with lanthanum carbonate in comparison to placebo (2 trials, 154 patients, RR 1.05, 95%CI 0.45 to 2.45) with no significant heterogeneity between the included studies (heterogeneity χ^2=0.30, I^2=0%).

Lanthanum carbonate versus calcium carbonate

All cause mortality

There was no effect on all-cause mortality with lanthanum carbonate compared with calcium carbonate with no deaths reported in included trials.

Hypercalcemia

There was significant reduction in hypercalcemic events with lanthanum carbonate compared with calcium carbonate (2 trials, 351 patients, RR 0.17, 95% CI 0.09 to 0.31) with no significant heterogeneity between the included studies (heterogeneity χ^2=0.36, I^2=0%).

Other adverse events

There was no significant difference in gastrointestinal toxicity with lanthanum carbonate in comparison to calcium carbonate (1 trial, 98 patients, RR 1.04, 95%CI, 0.70 to 1.55).

Other comparisons

All cause mortality

There was no deaths reported in 4 short-term trials that compared aluminum salts to other agents (Ittle 1991, Roxe 1989, Jannsen 1996,Jespersen 1991). Similarly, another one short-term trial that compared ferric citrate and calcium carbonate (Yang 2002), another that comapred Niacinamide to placebo (Cheng 2008), another that compared magnesium carbonate to calcium acetate (Speigel 2007) did not report any deaths in both arms of the study.

Biochemical and other surrogate end-points

Calcium salts versus placebo

Phosphorus

There was a significant difference between treatment groups for serum phosphorus (2 trials, 90 patients, WMD -1.41 mg/dl, 95%CI -2.52 to -0.29) with significant heterogeneity between the included studies (heterogeneity χ^2 =24.80, I^2=96%).

Calcium

There was a significant difference between treatment groups for calcium levels (1 trial, 72 patients, WMD 0.60 mg/dl, 95%CI 0.53 to 0.67).

IPTH, Ca x P product, alkaline phosphatase, serum bicarbonate, total cholesterol

Relevant data was not available from the included studies to conduct a meta-analyses for these outcomes.

Calcium acetate versus calcium carbonate

Calcium

There was no significant difference between treatment groups for calcium levels (5 trials, 143 patients, WMD -0.09 mg/dl, 95%CI -0.35 to 0.17) with no significant heterogeneity between the included studies (heterogeneity χ^2=5.0, I^2=20%).

Phosphorus

There was no significant difference between treatment groups for serum phosphorus (5 trials, 143 patients, WMD -0.19 mg/dl, 95%CI -0.61 to 0.24) with no significant heterogeneity between the included studies (heterogeneity χ^2=2.13, I^2=0%).

Ca x P product

There was no significant difference between treatment groups for Ca x P (2 trials, 31 patients, WMD -4.92 mg^2/dL^2, 95%CI -10.03 to 0.19) with significant heterogeneity between the included studies (heterogeneity χ^2=3.26, I^2=69.7%).

PTH, alkaline phosphatase, serum bicarbonate, total cholesterol

Relevant data was not available from the included studies to conduct a meta-analyses for these outcomes.

Calcium ketoglutarate versus other calcium salts

Calcium

There was no significant difference between treatment groups for ionized calcium levels (1 trials, 20 patients, WMD -0.40 mg/dl, 95%CI -0.49 to -0.31).

Phosphorus

There was no significant difference between treatment groups for serum phosphorus (2 trials, 48 patients, WMD -0.10 mg/dl, 95%CI -0.32 to 0.12) with no significant heterogeneity between the included studies (heterogeneity χ^2=0.02, I^2=0%).

Ca x P product

There was a significant difference between treatment groups for Ca x P (1 trials, 20 patients, WMD -4.50 mg^2/dL^2 , 95%CI -5.65 to -3.35).

PTH

There was no significant difference between treatment groups for treatment intact PTH (1 trial, 20 patients, WMD −35.00 pg/ml, 95%CI −155.07 to 85.07).

Serum bicarbonate

There was a significant difference between treatment groups for bicarbonate (2 trials, 62 patients, WMD 1.66 mEq/L, 95%CI 1.03 to 2.29) with no significant heterogeneity between the included studies (heterogeneity chi-square=0.13, I^2=0%).

Alkaline phosphatase, total cholesterol

Relevant data was not available from the included studies to conduct a meta-analyses for these outcomes.

Sevelamer versus placebo

Calcium

There was no significant difference between treatment groups for serum calcium levels (1 trial, 36 patients, WMD −0.10 mg/dl, 95%CI −0.52 to 0.32).

Phosphorus

There was a significant difference between treatment groups for phosphorus levels (1 trial, 36 patients, WMD −1.80 mg/dl, 95%CI −3.32 to −0.28).

Serum bicarbonate

There was no significant difference between treatment groups for bicarbonate (1 trial, 36 patients, WMD −0.50 mEq/L, 95%CI −2.53 to 1.53).

IPTH, Ca x P product, alkaline phosphatase, total cholesterol

Relevant data was not available from the included studies to conduct a meta-analyses for these outcomes.

Sevelamer versus calcium salts

Phosphorus

There was significant difference between treatment groups for serum phosphorus (15 trials, 3012 patients, WMD 0.21 mg/dl, 95%CI 0.01 to 0.41) with significant heterogeneity between the included studies (heterogeneity χ^2 =26.10, I^2=66%).

Calcium

There was significant difference between treatment groups for calcium levels (14 trials, 2915 patients, WMD −0.35 mg/dl, 95%CI −0.46 to −0.24) with significant heterogeneity between the included studies (heterogeneity χ^2 =28.72, I^2=58%).

PTH

There was significant difference between treatment groups for treatment intact PTH (12 trials, 2551 patients, WMD 55.57 pg/ml, 95%CI 26.69 to 84.45) with no significant heterogeneity between the included studies (heterogeneity χ^2=7.54, I^2=7%).

Ca x P product

There was no significant difference between treatment groups for Ca x P product (10 trials, 2560 patients, WMD 0.61 mg^2/dL^2, 95%CI −1.02 to 2.24) with significant heterogeneity between the included studies (heterogeneity χ^2 =13.24, I^2=32%).

Serum alkaline phosphatase

There was no significant difference for alkaline phosphatase between treatment groups (3 trials, 156 patients, WMD 12.36 IU/L, 95%CI −10.79 to 35.51) with no significant heterogeneity between the included studies (heterogeneity χ^2=1.35, I^2=0%) .

Serum bicarbonate

There was significant difference between sevelamer and calcium salts for bicarbonate (5 trials, 381 patients, WMD −1.43 mEq/L, 95%CI −2.07 to −0.79) with no significant heterogeneity between the included studies (heterogeneity chi-square=1.75, I^2=0%).

Total cholesterol

There was significant difference between treatment groups for total cholesterol levels (9 trials, 1674 patients, WMD −20.55 mg/dl, 95%CI −29.15 to −11.96) with significant heterogeneity between the included studies (heterogeneity χ^2=22.89, I^2=65%) (Table 3).

Vascular calcification

Five studies reported the effects of sevelamer and calcium salts on vascular calcification (32,34-36,42) (Table 4). One study reported slower progression of coronary, aortic and heart valve calcification (measured by electron beam computed tomography) with the use of sevelamer in comparison to calcium acetate (37) using the Agatston scoring system. Similarly, another study showed decreased progression of coronary artery calcification with sevelamer compared to calcium salts in incident hemodialysis patients (34) (Table 4). By contrast, a third study compared sevelamer plus atorvastatin to calcium acetate plus atorvastatin and reported similar coronary artery calcification progression in both groups (35). There was also a study which reported coronary artery calcium scores in 101 dialysis patients (using a modified Agatston scoring system) and reported no differences in coronary artery calcification progression between sevelamer and calcium groups (p=0.59) (32). Included studies used different scoring systems to assess vascular calcification and thus could not be pooled.

Bone outcomes

Lanthanum carbonate reduced the number of patients developing low turnover bone disease in comparison to calcium carbonate (53) and resulted in an improvement of bone volume in comparison to standard phosphate binder therapy (58) (Table 4). Aluminum-like effects on bone were not noted in follow up studies that assessed the safety of lanthanum carbonate (53). Based upon on electron beam computer tomography results, one study reported a significant reduction in trabecular bone attenuation and a trend towards reduction in cortical bone attenuation (p=0.05) in thoracic vertebrae with sevelamer compared to calcium salts (62). In another study enrolling 101 dialysis patients, there was no difference in the bone remodelling between sevelamer and calcium groups at the end of 1-year follow up (31). Another study reported increased bone formation and improved trabecular architecture but with no significant change in bone turn-over or mineralization with sevelamer in comparison to calcium salts (41). A formal meta-analysis could not be performed for incidence of fracture due to insufficient data.

Lanthanum carbonate versus placebo

Phosphorus

There was significant difference between treatment groups for serum phosphorus (2 trials, 154 patients, WMD -2.01 mg/dl, 95%CI -2.52 to -1.50) with no significant heterogeneity between the included studies (heterogeneity χ^2=0.13, I^2=0%).

Calcium

There was significant difference between treatment groups for calcium levels (1 trial, 93 patients, WMD 0.35 mg/dl, 95%CI 0.04 to 0.66).

PTH

There was significant difference between treatment groups for PTH levels (1 trial, 93 patients, WMD -83.0 pg/ml, 95%CI -154.63 to -11.37).

Ca x P product

There was significant difference between treatment groups for Lanthanum Ca x P (1 trial, 93 patients, WMD -14.20 mg^2/dL^2, 95%CI -21.03 to -7.37).

Other outcomes

Lanthanum carbonate reduced the number of patients developing low bone turnover bone in comparison to placebo (table 2).

Serum alkaline phosphatase, serum bicarbonate, total cholesterol

Relevant data was not available from the included studies to conduct a meta-analyses for these outcomes.

Lanthanum carbonate versus calcium carbonate

Phosphorus

There was no significant difference between treatment groups for serum phosphorus (2 trials, 122 patients, WMD 0.22 mg/dl, 95%CI -0.32 to 0.75) with no significant heterogeneity between the included studies (heterogeneity χ^2=1.19, I^2=16%).

Calcium

There was significant difference between treatment groups for calcium levels (2 trials, 122 patients, WMD -0.30 mg/dl, 95%CI -0.64 to -0.25) with no significant heterogeneity between the included studies (heterogeneity χ^2 =0.92, I^2=0%).

PTH

There was no significant difference between treatment groups for PTH levels (1 trial, 800 patients, WMD 29.78 pg/ml, 95%CI 8.87 to 68.43).

Ca x P product

There was significant difference between treatment groups for Ca x P levels (1 trial, 98 patients, WMD -6.01 mg /dL^2, 95%CI -9.66 to -2.36).

Serum alkaline phosphatase, serum bicarbonate, total cholesterol

Relevant data was not available from the included studies to conduct a meta-analyses for these outcomes.

Other agents

Phosphorus

There was a significant difference between niacinamide and placebo for serum phosphorus (1 trial, -0.79 mg d/l, 95% CI -0.12 to -1.46 mg/dl).In one cross-over study, there was a signifcant decrease in phosphorus with both calcium carbonate and ferric citrate. Four studies compared aluminum salts to other agents but sufficient data was not available in the reported studies to conduct a meta-analysis.

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 (Additional table). This was possible for trials comparing either sevelamer hydrochloride or lanthanum carbonate to calcium salts, while other treatment comparisons contained too few trials. Some covariates including measures of trial 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

Our systematic review has identified a large number of RCTs that examine phosphate binders in people with CKD. These trials have not demonstrated that phosphate binders compared with placebo or calcium salts compared with non-calcium or aluminum-containing agents reduce all-cause or cardiovascular mortality. As expected, all phosphate binders reduced serum phosphorus levels when compared with placebo, however newer agents (lanthanum carbonate and sevelamer) did not result in consistently superior biochemical outcomes compared with calcium-based therapies. Rather, in direct comparisons ('head to head' studies), calcium salts were superior to sevelamer for reduction of serum phosphorus. Compared with calcium salts, sevelamer and lanthanum carbonate were associated with significantly lower rates of less treatment-related hypercalcemia, which may result in reduced vascular calcification. The differential effect on levels of serum calcium and phosphorus resulted in increased PTH suppression by treatment with calcium compared with sevelamer or lanthanum. The efficacy of available phosphate binding agents on the surrogate outcomes of bone mineral density or histomorphometry and vascular calcification have been reported heterogeneously in few studies and reliable conclusions could not be drawn through meta-analysis.

Sevelamer was associated with lower serum calcium, higher phosphorus, and higher PTH levels at the end of treatment period when compared to calcium salts. This may be due to noncompliance (secondary to increased gastrointestinal events and pill burden) resulting in lower phophorus reduction with sevelamer, or because it is less effective at the relative doses used. Sevelamer resulted in a lower end of treatment serum calcium levels which might have contributed to the higher PTH levels noted. The DCOR study, which is the largest trial (n=2103) conducted at present, reported no difference in the risk of all-cause mortality between sevelamer and calcium salts (Suki 2007) except for a subgroup analysis in patients older than 65 years who completed a 2-year follow-up. Because of the size of this study, DCOR 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 for all-cause mortality (RR 0.59, CI 0.35 to 1.01 *versus* RR 0.75, CI 0.48 to 1.16). Given the limitations of the analysis by Suki *et al*, we also conducted a sensitivity analysis using data from St.Peters *et al* , who used the Center for Medicare and Medicaid services claims data to reassess the DCOR trial results (St. Peters 2008). The risk of all-cause mortality was unchanged (RR 0.75, 95% 0.56 to 1.33) using these data.

The occurrence, progression and prognostic importance of vascular calcification remain an important question in CKD and the influence of calcium-based binders on the progression of vascular calcification is a matter of intense debate (Moe 2006, Friedman 2006, Bushinsky 2006, Silver 2007). Two studies in the current analysis reported a higher rate of progression of vascular calcification with calcium salts compared with sevelamer (Block 2005, Qunibi 2008) while one study showed no difference in calcium scores between sevelamer and calcium salts (Barreto 2008). The possibility that the cholesterol-lowering effect of sevelamer may contribute to this effect (rather than hypercalcemia from calcium salts) cannot be excluded based on the recently published CARE-2 study (Qunibi 2008). While vascular calcification is associated with an increased risk of mortality in hemodialysis patients, the impact of reducing vascular calcification on survival outcomes has not been demonstrated in randomized, intervention trials (Silver 2007). As the recent negative results of the AURORA study (analyzing the beneficial effects of statins in dialysis patients) have shown, even a universally accepted surrogate endpoint, like LDL cholesterol, may not predict patient-centered end- points such as mortality in a different setting, like dialysis where the causal pathway to cardiovascular endpoints and death may be different (Strippoli 2009, Fellström 2009). A surrogate end-point must be validated and tested in specific settings prior to validating assumptions that modifying the surrogate marker will reduce clinical outcomes.

Sevelamer has not been well studied in CKD stages 3 to 5 (not requiring dialysis) except for a single study (Qunibi 2004). Therefore, this systematic review can only inform the therapeutic use of sevelamer and calcium

salts in dialysis patients and only for surrogate biochemical end-points; it is still uncertain whether sevelamer reduces hypercalcemia and cardiovascular disease in stage 3-5 CKD compared with calcium-based agents. Calcium salts are recommended in predialysis patients for the control of hyperphosphatemia by various international guideline agencies (K-DOQUI 2003, Elder 2006). Our review confirms that calcium carbonate and calcium acetate are equally effective in reducing phosphorus and PTH levels with a similar incidence of hypercalcemia and gastrointestinal adverse events; we identified only two studies conducted in predialysis patients (Borrego 2000, Phelps 2002). As few studies are available, there is currently no strong RCT evidence exists (for the outcomes of mortality and morbidity) for the use of calcium-based phosphate binders in earlier stages of CKD.

Few studies have analyzed 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 and available data confirm their efficacy in reducing phosphorus levels that is similar to calcium carbonate, with a reduced incidence of hypercalcemia. Accumulation of lanthanum in bone has been assessed in one study by bone biopsy at the end of two years of treatment and no evidence of aluminum-like toxicity was observed (Spasovski 2006).

To the best of our knowledge, this is the first comprehensive systematic review of RCTs that has assessed the benefits and harms of all phosphate-binding agents in CKD. A previous meta-analysis (including 17 prospective and retrospective studies comparing sevelamer hydrochloride to placebo) showed that sevelamer compared with placebo or no treatment improved biochemical end-points (serum phosphorus, Ca × P, PTH and lipids) without increased serum calcium levels. However, data on survival, hospitalization, and vascular calcification were not included (Burke 2003). The inclusion of both observational studies and RCTs in that review decreased the strengths of its conclusions through potential for bias and unknown confounding. A second systematic review of 7 RCTs (746 patients) concluded that sevelamer had similar effects on phosphorus and Ca × P levels with a lower incidence of hypercalcemia (Manns 2004). Similar to the previous analysis, that review focused only on the effects of sevelamer and included some, but not all available trials. A more recent analysis by Tonelli et al (an update of their own previous review) analyzed the benefits of sevelamer in comparison to calcium alone and included 10 trials (Manns 2004, Tonelli 2007). This review did not assess the role of other phosphate binders and did not explore the risk of vascular calcification (Palmer 2007).

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 trial quality assessment by two independent reviewers with supervision by a third experienced investigator. The key findings are limited by the lack of long-term studies analyzing the efficacy of phosphate binders on mortality and musculoskeletal morbidity. Most included studies enrolled few patients (except for the large DCOR trial) 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 focus on major patient-level end-points in future trials (Strippoli 2007, Strippoli 2005, Hutchinson 2009). The strength of conclusions drawn from this review is also limited by suboptimal reporting of study methods to determine trial quality and significant heterogeneity observed for many outcomes.

The primary advantage for more recently developed phosphate binders (lanthanum carbonate and sevelamer) is a reduction in hypercalcemia in dialysis patients. Existing trials using patient-focused end-points in predialysis patients are inadequate to inform clinical recommendations for any phosphate binder and are required before advocating that newer agents are superior to existing, lower cost interventions. Full adoption of sevelamer and lanthanum by government drug reimbursement agencies in place of calcium salts would lead to a large increase in health care expenditure (Taylor 2008, Manns 2007). This can only be justified by presenting evidence for improved clinical outcomes of these agents compared with calcium salts. Additionally it should be remembered that, to date, no clinical trial has shown a survival advantage for calcium salts either (when compared with placebo or other agents).

Authors' conclusions

Implications for practice

Our review supports that the novel phosphate binders such as sevelamer 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 are unknown. The primary advantage for more recently developed phosphate binders (lanthanum carbonate and sevelamer) is a reduction in hypercalcaemia. Data for patient-focussed end points in dialysis patients are inadequate to inform clinical recommendations for any phosphate binder.

Implications for research

Further research using a randomized, controlled trial design is required to assess the effect of surrogate biochemical end-points (phosphorus, calcium, PTH) on mortality and morbidity in CKD. These might include trials of (1) direct comparisons between sevelamer, calcium salts and lanthanum carbonate in CKD with primary outcomes of all-cause and cardiovascular mortality, fractures, hospitalization and parathyroidectomy; (2) any phosphate binder to control hyperphosphatemia in CKD stage 3 and 4; or (3) efficacy of combination therapy (such as sevelamer with or without calcium salts) on both surrogate and patient-level end-points.

Acknowledgements

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

Contributions of authors

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

Declarations of interest

None known

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

Al-Baaj 2003

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: YES -Data analysis: YES Intention to treat: NO Follow-up period: 8 weeks Loss to follow-up: 23
Participants	INCLUSION CRITERIA: -Age>18 years -Hemodialysis or CAPD for >6 months, including patients who had undergone renal transplantation EXCLUSION CRITERIA: -Hypercalcemia -Severe hyperparathyroidism -Serum phosphate >3mg/dl after the washout phase -Other clinically significant abnormal laboratory values -Positive pregnancy test -Significant gastrointestinal disorder(including known active peptic ulcer, Crohn's disease, ulcerative colitis, irritable bowel syndrome and past or present malignancies) -Unstable dietary habits -Life-threatiening malignancy or HIV-status -History of drug or alcohol abuse LANTANUM GROUP Number: 17 Age: 57 (17) Sex (M/F): 10/7 PLACEBO GROUP Number: 19 Age: 53.3 (16) Sex(M/F):10/9
Interventions	LANTANUM GROUP:375-2250mg/day GROUP CO-INTERVENTIONS: Oral or IV vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Serum calcium; 2)Serum phosphate; 3)PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Almirall 1994

Methods	Country: Spain Setting/Design Hospital: Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 24 weeks Loss to follow-up: 3
Participants	INCLUSION CRITERIA: -Chronic hemodialysis for 54 +/- 38 months(three times a week) EXCLUSION CRITERIA: Not specified CALCIUM ACETATE GROUP Number: NA Age: NA Sex (M/F): NA CALCIUM CARBONATE GROUP Number: NA Age: NA Sex(M/F): NA
Interventions	CALCIUM ACETATE GROUP: 3.8g/day CALCIUM CARBONATE GROUP : 4g/day CO-INTERVENTIONS: Oral Calcitriol
Outcomes	STUDY OUTCOMES: 1)Serum calcium; 2)Serum phosphorus; 3)Ca xP product; 4)PTHI
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Altmann 2007

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 24 months Loss to follow-up: NS
Participants	INCLUSION CRITERIA: -Patients who received hemodialysis 3 times per week for stage 5CKD for at least 2 months before enrolment -Patients >18 years old EXCLUSION CRITERIA: -abnormality in laboratory values -patients receiving psychotropic drugs -pregnancy -gastrointestinal disease; -active malignancy or current multiple myeloma; -HIV infection; -levels of transaminases more than 3 timesupper limit of normal LANTHANUM CARBONATE GROUP Number: 179 Age: 54.4±15.6 Sex (M/F): 58/42 STANDARD THERAPY GROUP Number: 181 Age: 56.5±14.1 Sex(M/F): 60/40
Interventions	LANTHANUM CARBONATE GROUP: 750 or 1500mg/day at the discetion of the investigator. Dose could be titrated up to 3000 or down to 375mg/day STANDARD THERAPY GROUP : At the discretion of the investigator CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) Differences in cognitive function
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B-Unclear

Asmus 2005

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 24 months Loss to follow-up: NS
Participants	INCLUSION CRITERIA: - Patients on hemodialysis - -Patients >19 years old EXCLUSION CRITERIA: - gastrointestinal disease; -ethanol or drug abuse; -active malignancy; -human immunodeficiency virus infection; -vasculitis and uncontrolled diabetes mellitus or hypertension CALCIUM CARBONATE GROUP Number: 41 Age: 60±14 Sex (M/F): 25/16 SEVELAMER GROUP Number: 31 Age: 54±14 Sex(M/F): 25/6
Interventions	CALCIUM ACETATE GROUP : Sertuerner to achive a serum calcim level <2.6mmol/l SEVELAMER GROUP : Renagel to achive a serum phosphorus level in the target range of 1.0-1.6mmol/l CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) Hypercalcaemic episodes 2) Ca X Phosphorous serum level 3) iPTH serum concentration 4)Increases in coronary artery calcification score 5)Increases in aortic calcification score 6)Trabecular bone density 7)Cortical bone density
Notes	114 patients were randomized , but data about allocation , age, and sex are reported for only 72 patients

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B-Unclear

Barreto 2008

Methods	Country: Brazil Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 12 months Loss to follow-up: 30
Participants	INCLUSION CRITERIA: - Patients on maintenance hemodialysis for at least 3 months EXCLUSION CRITERIA: - gastrointestinal disease; ethanol or drug abuse; active malignancy; human immunodeficiency virus infection; chronic inflammatory disease; current use of steroids; severe hyperparathyroidism; body weight >100Kg, continuous use of antiarrhythmic or seizure drugs, pregnancy or breast-feeding; previous myocardial revascularization; uncontrolled diabetes mellitus or hypertension CALCIUM ACETATE GROUP Number: 49 Age: 47±14 Sex (M/F): 21/9 SEVELAMER GROUP Number: 52 Age: 47±13 Sex(M/F): 27/14
Interventions	CALCIUM ACETATE GROUP : adjusted monthly up to 2.028 mg of elemental calcium daily SEVELAMER GROUP : adjusted monthly up to 12mg daily CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) Phosphorus concentration level 2) i-Ca serum level 3) iPTH serum concentration 4)Histomorphometric data from bone biopsies
Notes	Ps: data about age and sex are reported for 30 and 41 patients (calcium acetate and sevelamer respectively)

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate

Birck 1999

Methods	Country: Germany Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 24 weeks Loss to follow-up: 4
Participants	INCLUSION CRITERIA: -Haemodialysis for at least 12 months -hyperphosphatemia after withdrawal of phosphate binding agents -Known adherence to therapy -PTHi smaller than the ten-fold upper normal level EXCLUSION CRITERIA: Not specified GROUP 1: Number: 14 Age: NA Sex (M/F):NA GROUP 2: Number: 14 Age: NA Sex(M/F): NA
Interventions	GROUP 1:Calcium ketoglutarate and than calcium carbonate to achieve serum phosphorus < 5.3mg/dl GROUP 2: Calcium carbonate and than calcium ketoglutarate to achieve serum phosphorus < 5.3mg/dl CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum calcium; 2)Serum phosphate; 3)PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bleyer 1999

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: YES Follow-up period: 16 Loss to follow-up: 4
Participants	INCLUSION CRITERIA: -Age >18 ys -HD patients on stable doses of calcium or aluminum-based phosphate binders and on stable doses or no calcitriol for 1 months EXCLUSION CRITERIA: Not stated SEVELAMER GROUP Number: NA Age: NA Sex: NA CALCIUM ACETATE GROUP Number: NA Age: NA Sex(M/F): NA
Interventions	SEVELAMER GROUP: 2 to 4 cp x3/day to achieve serum phosporus 2.5-5.5mg/dl CALCIUM ACETATE GROUP : 1 to 3 cp x3/day to achieve serum phosporus 2.5-5.5mg/dl CO-INTERVENTIONS: Calcitriol
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2)Serum calcium; 3) Serum calcium x phosphorus; 4)PTHi levels; 5)Lipid profile
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	No	C - Inadequate

Block 2005

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: No(except the EBCT results) -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 18 months Loss to follow-up: 39
Participants	INCLUSION CRITERIA: -Age >18 years -New to hemodialysis patients EXCLUSION CRITERIA: -Prior histoty of dialysis, kidney transplant, coronary artery bypass surgery, weight greater than 300 pounds or current atrial fibrillation or atrial flutter CALCIUM GROUP Number: 55 Age: 59 (15) Sex (M/F): 36/9 SEVELAMER GROUP Number: 54 Age: 57 (15) Sex(M/F): 31/22
Interventions	CALCIUM GROUP: NA SEVELAMER GROUP : NA CO-INTERVENTIONS: NA
Outcomes	STUDY OUTCOMES: 1)Coronary artery calcium score
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate

Block 2007

Methods	Country: USA Setting/Design:Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 44 months Loss to follow-up: 0
Participants	INCLUSION CRITERIA: - New hemodialysis patients EXCLUSION CRITERIA: -Not stated CALCIUM SALTS GROUP Number: 67 Age: 58±14.8 Sex (M/F): 64/3 SEVELAMER GROUP Number: 60 Age: 56±14.8 Sex(M/F):58/2
Interventions	CALCIUM SALTS GROUP : Not stated SEVELAMER GROUP : Not stated CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) All-cause mortality 2) Progression of CAC
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	C - Unclear

Borrego 2000

Methods	Country: Brazil Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: No -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 24 months Loss to follow-up: 0
Participants	INCLUSION CRITERIA: -IRC with ClCr <21ml/min -S phosphorus >5mg/dl EXCLUSION CRITERIA: -Diabetic nephropathy -Treatment with vitamin D analogues -SCa >10.5mg/dl CALCIUM CARBONATE GROUP Number: 14 Age: 55 (23-76) Sex (M/F): 5/9 CALCIUM ACETATE GROUP Number: 14 Age: 63 (23-90) Sex(M/F): 7/7
Interventions	CALCIUM CARBONATE GROUP: 2.5g/day CALCIUM ACETATE GROUP : 1g/day CO-INTERVENTIONS: NA
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2)Serum calcium; 3)PTHi; 4)ClCr
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bro 1998

Methods	Country: Denmark Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 12 weeks Loss to follow-up: 9
Participants	INCLUSION CRITERIA: -Age >18 years -Hemodialysis 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 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 GROUP 1: Number: NA Age: NA Sex(M/F): NA GROUP 2: Number: NA Age: NA Sex(M/F): NA
Interventions	GROUP 1:Doses calcium ketoglutarate and then calcium carbonate to achieve serum phosphorus <5.3mg/dl GROUP 2: Doses calciumcarbonate and then calcium ketoglutarate to achieve serum phosphorus <5.3mg/dl CO-INTERVENTIONS: Oral alfacalcidiol
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2)Serum calcium; 3)PTHi;
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Caravaca 1992

Methods	Country: Spain Setting/Design: Hospiatl Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 16 weeks Loss to follow-up: 14
Participants	INCLUSION CRITERIA: -Chronic hemodialysis treatment for 2-175 months -ClCr <1ml/min -treatment with aluminum hydroxide EXCLUSION CRITERIA: Not specified CALCIUM ACETATE GROUP Number: 31 Age: 51 (10) Sex (M/F): 20/11 CALCIUM CARBONATE GROUP Number: 35 Age: 45 (16) Sex(M/F):19/16
Interventions	CALCIUM ACETATE GROUP: 6.5 g/day CALCIUM CARBONATE GROUP : 3.75g/day CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2) Serum calcium; 3)PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

CARE-2 2008

Methods	Country: USA Setting/Design: dialysis centers Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 52 weeks Loss to follow-up: 2
Participants	INCLUSION CRITERIA: -end-stage renal disease -18 years or older patients -Hd for 3 months to 5 years EXCLUSION CRITERIA: -Condition that could restrict survival of participants foor the duration of the study or interfere with their ability to follow the study CALCIUM ACETATE GROUP Number: 103 Age: 58.5 (12.8) Sex (M/F): 61/42 SEVELAMER GROUP Number: 100 Age: 60.3 (12.1) Sex(M/F):46/54
Interventions	CALCIUM ACETATE GROUP:to achive a phosphorus level of 3.5 to 5.5 mg/dL and LDL<70 SEVELAMER GROUP : to achive a phosphorus level of 3.5 to 5.5 mg/dL and LDL<70 CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Change in CAC score assessed by means of electron-beam computed tomography
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate

Cheng 2008

Methods	Country: USA Setting/Design: Randomized, double-blind, cross-over, placebo-controlled trial Time frame: NA Randomisation method: Blinding -Participants: Yes -Investigators: Yes -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 16 weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: -18 years or older patients -capacity for informed consent -long term Hd >90d -stable dosage of phosphorus binders during the previous 2-wk period -serum phosphorus level >5.0mg/dl 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 d NIACINAMIDE GROUP Number: 33 Age: NA Sex (M/F): 23/10 PLACEBO GROUP Number: 33 Age: NA Sex(M/F):23/10
Interventions	NIACINAMIDE GROUP:250 mg twice daily increased to 500 mg twice daily at week 3 and 750mg twice daily at week 5 PLACEBO GROUP :250 mg twice daily increased to 500 mg twice daily at week 3 and 750mg twice daily at week 5 CO-INTERVENTIONS: Phosphorus binders, vitamin D, paracalcitol, cinacalcet
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus 2)Serum calcium 3)Ca X P 4)iPTH 5)Uric acid levels
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	

Chertow 1997

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: YES Follow-up period: 8 weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: -Age >18 years -Thrice-weekly hemodialysis 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 EXCLUSION CRITERIA: -Unstable medical condition, including poorly controlled diabetes mellitus or hypertension, or any gastrointestinal abnormality SEVELAMER GROUP Number: 24 Age: 58.8 (17.1) Sex(M/F):13/11 PLACEBO GROUP Number: 12 Age: 53.7 (13.9) Sex(M/F):10/2
Interventions	SEVELAMER GROUP: mean 7.2 cp/day PLACEBO GROUP CO-INTERVENTIONS: IV or oral vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2) Serum calcium; 3)Lipid profile
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Chertow 1999

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: YES Follow-up period: 12 weeks Loss to follow-up: 16
Participants	INCLUSION CRITERIA: -Age >18 years -Thrice weekly hemodialysis for at least three months -Regualr adminidtration of calcium- and/or aluminum-based phosphate binders, wth or without vitamin D metabolite replacement therapy at stable doses for at least one month before screening EXCLUSION CRITERIA: -Total parathyroidectomy -serious gastrointestnal disease(including dysphagia, vomiting, motility disorder, major intestinal surgery, markedly irregular bowel function) -Ethanol or drug dependence or abuse -active malignancy -HIV infection -VAculitis -Poorly controlled diabetes mellitus or hypertension SEVELAMER GROUP Number: 35 Age: 55.9 (14.1) Sex(M/F):10/25 SEVELAMER + CALCIUM CARBONATE GROUP Number: 6 Age: 60.7 (15.0) Sex(M/F): 14/22
Interventions	SEVELAMER GROUP: 2-4 x3/day to achieve serum phosphate 2.5-5.5mg/dl SEVELAMER + CALCIUM CARBONATE GROUP : 2-4 cp(465mg))x3/die + 900mg/day to achieve serum phosphate 2.5-5.5mg/dl CO-INTERVENTIONS: IV or oral vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2) Serum calcium;3)Calcium x phosphate product; 4)PTHi: 5)Lipid profile
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Chertow 2002

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: No -Data analysis: NO Intention to treat: NO Follow-up period: 52 weeks Loss to follow-up: NA
Participants	INCLUSION CRITERIA: -Age <19 years -Hemodialysis patients EXCLUSION CRITERIA: -serious gastrointestinal disease (dysphagia, active untreated gastroparesis, severe motitlity disorder, major intestinal surgery, markedly irregular bowel function) -Ethanolol or drug dependence or abuse -Active malignancy -HIV infection -Vasculitis -Diabetes mellitus or hypertension SEVELAMER GROUP Number: 99 Age: 57 (14) Sex (M/F): 36/63 CALCIUM GROUP Number:101 Age: 56(16) Sex(M/F): 34/67
Interventions	SEVELAMER GROUP: Dose to achieve serum phosphorus of 3-5mg/dl and calcium 8.5-10.5mg/dl CALCIUM GROUP : Dose to achieve serum phosphorus of 3-5mg/dl and calcium 8.5-10.5mg/dl CO-INTERVENTIONS: IV or oral vitamin D analogues
Outcomes	STUDY OUTCOMES:1)Serum phosphorus, calcium, PTHi, Lipid profile; 2)Cardiovascular calcification; 3)Changes in calcification score
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate

Chiang 2005

Methods	Country: Taiwan Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: YES Follow-up period: 4 weeks Loss to follow-up: 31
Participants	INCLUSION CRITERIA: -Age >20 -Hemodialysis three times a week for a minimun of two consecutive months EXCLUSION CRITERIA: -GI surgery or disorder such as Crohn's disease or peptic ulcers -Hyperparathyroidism LANTHANUM GROUP Number: 30 Age: 53.6 (11.2) Sex (M/F): 16/14 PLACEBO GROUP Number: 31 Age: 51.7 (9.4) Sex(M/F): 14/17
Interventions	LANTHANUM GROUP: 375-3000mg/day PLACEBO GROUP CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2)PTHi; 3)Serum calcium; 4)Ca x P
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

D'Haese 2003

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: No -Outcome assessors: No -Data analysis: NO Intention to treat: YES Follow-up period: 1 year Loss to follow-up: 30
Participants	INCLUSION CRITERIA: -Age >18 years -Hemodialysis or CAPD within 12 weeks -Patients who had been diagnosed with chronic renal failure and were scheduled to begin dialysis EXCLUSION CRITERIA: -Hypocalcemia or cocurrent illness LANTHANUM GROUP Number: 49 Age: NA Sex (M/F): NA CALCIUM CARBONATE GROUP Number: 49 Age: NA Sex(M/F): NA
Interventions	LANTHANUM GROUP: up to 3750mg/day CALCIUM CARBONATE GROUP : up to 9000mg/day CO-INTERVENTIONS: Oral or IV vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Serum calcium; 2) Serum phosphate; 3)PTHi; 4)Markers of bone turnover
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

DCOR 2007

Methods	Country: USA Setting/Design: Dialisys centers Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: YES Follow-up period: 20.3±13.9 (sevelamer) 19.6±13.6 (calcium) Loss to follow-up: 207
Participants	INCLUSION CRITERIA: -Age >18 -Patients in dialisys for more than 3 months required phosphate binders therapy EXCLUSION CRITERIA: -Dysphagia -swallowing disorders -severe gastrointestinal motility disorders -bowel obstruction CALCIUM-BASED BINDERS GROUP Number: 1050 Age: 60.1±15.2 Sex (M/F): 569/481 SEVELAMER GROUP Number: 1053 Age: 59.9±14.3 Sex(M/F):574/479
Interventions	CALCIUM -BASED BINDERS GROUP : 5.3g (mean for calcium acetate); 4.9g (mean for calcium carbonate) SEVELAMER GROUP : 6.9g daily (mean) CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)All-cause mortality 2)Cause specific mortality (myocardial infarction, pericardits, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, cerebrovascular accident, ischemic brain demage/anoxic encephalopathy. 3) Hospitalizations
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - unclear

DeSanto 2006

Methods	Country: Italy Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 24 weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: -excellent albumin levels -excellent blood pressure -stable hemodyanamic condition EXCLUSION CRITERIA: -DM -Severe osteitis fibrosa -use of corticosteroids -phosphate levels <5.5mg/dL -patients requiring no phosphate binders -patients with intact PTH>400pg/mL -patients no- compliant -patients with ethanol or drugs dependence -HIV infection -vasculitis -active malignancy -severe gastrointestinal disease CALCIUM CARBONATE GROUP Number: 8 Age: 36-50 Sex (M/F): 8/0 SEVELAMER GROUP Number: 8 Age: 35-50 Sex(M/F): 8/0 COINTERVENTION: vitamin D
Interventions	CALCIUM CARBONATE :to achive a phosphorus level of 5.5 mg/dL and calcium concentrations in the range of 8.5-10.5 mg/dL. SEVELAMER : based on manufacturer's instructions CO-INTERVENTIONS: after 24 weeks patients were crossed to the other treatment
Outcomes	STUDY OUTCOMES: 1)Time course of plasma bicarbonate concentration 2) Time course of serum albumin concentration 3)Time course of iPTH concentration
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B-unclear

Emmett 1991

Methods	Country: Texas Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: YES -Data analysis: NO Intention to treat: NO Follow-up period: 12 weeks Loss to follow-up: 16
Participants	INCLUSION CRITERIA: -Hemodialysis three times a week -Treatment with phosphorus-binding drugs to reduce serun phosphorus EXCLUSION CRITERIA: -Patients pregnant(or intented to become pregnant), mentally unstable, unable to comply with the study protocol -Persistent hypercalcemia (>11mg/100ml) CALCIUM ACETATE or PLACEBO GROUP Number: 69 Age: 55.5 Sex (M/F): 38/31
Interventions	CALCIUM ACETATE GROUP:Dosse to achieve serum phosphorus of 4.5-5.5mg/dl PLACEBO GROUP CO-INTERVENTIONS:Oral or IV vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Serum Phosphorus; 2)serum calcium; 3)Calcium x phosphorus product
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate

Evenepoel 2009

Methods	Country: Belgium, Denmark, France, Italy, Spain, Netherlands Setting/Design: Multicentre Time frame: NA Randomization method: Blinding -Participants: No -Investigators: No -Outcome assessors: Yes -Data analysis: No Intention to treat: No Follow-up period: 13 weeks Loss to follow-up: 0 (39 drop out)
Participants	INCLUSION CRITERIA: - Age>18, stable PD for >8 weeks -Serum phosphorus>5.5mg/dl and serum calcium within the normal range (8.4-10.4mg/dl) -Patients compliant with dialysis and phosphate binder therapy EXCLUSION CRITERIA: -History of peritonitis, dysphagia, bowel obstruction or severe gastrointestinal 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 SEVELAMER GROUP Number: 97 Age: 54.6±15.7 Sex (M/F): 65/32 CALCIUM ACETATE GROUP Number: 46 Age: 54.1±15.8 Sex(M/F): 28/18
Interventions	LANTHANUM CARBONATE GROUP: starting dose 1600mg TID titrated as necessary to achieve a target serum phosphorus of 3.0-5.5mg/dl CALCIUM CARBONATE GROUP : starting dose 538mg TID titrated as necessary to achieve a target serum phosphorus of 3.0-5.5mg/dl CO-INTERVENTIONS: No
Outcomes	STUDY OUTCOMES: 1) Changes in serum phosphorus, calcium, iPTH 2) Changes in lipids and plasma biomarkers
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ferramosca 2005

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomization method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: Loss to follow-up:
Participants	INCLUSION CRITERIA: -Patients undergoing maintenance hemodialysis EXCLUSION CRITERIA: NS SEVELAMER GROUP Number: 54 Age: 58±15 Sex (M/F): 32/22 CALCIUM ACETATE GROUP Number: 54 Age: 54±17 Sex(M/F): 38/16
Interventions	SEVELAMER GROUP: Renagel 800mg CALCIUM CARBONATE GROUP : PhosLo 667mg CO-INTERVENTIONS: No
Outcomes	STUDY OUTCOMES: 1) Changes in coronary calcification score 2) Changes in lipids and markers of inflammation
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B- Unclear

Ferreira 2008

Methods	Country: Portugal Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: Yes Follow-up period: 54 weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: - Age>18 on hemodialysis 3 times/wk (>3 mo) - Patients with Stable serum phosphorus < 8.1mg/dL for >1mo before screening and who were receiving treatment with a phosphate binder EXCLUSION CRITERIA: - use of aluminum-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 CALCIUM BASED BINDERS GROUP Number: 47 Age: 53.9±13.7 Sex (M/F): 18/17 SEVELAMER GROUP Number: 44 Age:55.5 ±15.4 Sex(M/F): 22/11
Interventions	CALCIUM GROUP : To achieve serum phosphorus of 3.2 to 5.0mg/dl and to maintain serum calcium at<10.4mg/dl SEVELAMER GROUP : To achieve serum phosphorus of 3.2 to 5.0mg/dl and to maintain serum calcium at<10.4mg/dl CO-INTERVENTIONS: No
Outcomes	STUDY OUTCOMES: 1) Changes in serum biochemical parameters 2) Changes in parameters of bone mineralization
Notes	Ps: data about age and sex are reported for 33 and 35 patients (sevelamer and calcium respectively)

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate

Filho 2000

Methods	Country: Brazil Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 4weeks Loss to follow-up: 29
Participants	INCLUSION CRITERIA: -Hemodialysis patients three times a week(Ca dialysate 3.5mEq/l) EXCLUSION CRITERIA: -Parathyroidectomized patients GROUP 1 Number: NA Age: NA Sex(M/F): NA GROUP 2 Number: NA Age: NA Sex(M/F): NA
Interventions	GROUP 1: Calcium acetate 5.6g/day and than calcium carbonate 6.2g/day GROUP 2 : Calcium carbonate 6.2g/day and than calcium acetate 5.6 g/day CO-INTERVENTIONS: No
Outcomes	STUDY OUTCOMES: 1)Serum Phosphorus; 2)Serum calcium; 3)Kt/V; 4)Serum Bicarbonate
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Finn 2004

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: YES Follow-up period: 6 months Loss to follow-up: 53
Participants	INCLUSION CRITERIA: -Age >18 years -Hemodialysis 3 times weekly for a minimun of 6 months EXCLUSION CRITERIA: -Significant hypercalcemia -Severe hyperparathyroidism -Clinically significant abnormal laboratory values .-Significant gastrointestinal diseae LANTHANUM GROUP 1 Number: 27 Age: 53.6 Sex (M/F):14/13 LANTHANUM GROUP 2 Number: 29 Age: 57.5 Sex(M/F):19/10 LANTHANUM GROUP 3 Number: 30 Age: 59.4 Sex(M/F):17/13 LANTHANUM GROUP 4: Number: 26 Age: 54.0 Sex(M/F): 16/10 PLACEBO GROUP Number: 32 Age: 56.8 Sex(M/F): 13/19
Interventions	LANTHANUM GROUP 1: 225mg/day LANTHANUM GROUP 2: 675mg/day LANTHANUM GROUP 3: 1350mg/day LANTHANUM GROUP 4:2250mg/day PLACEBO GROUP CO-INTERVENTIONS: Oral or IV vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2)Serum calcium; 3)Ca x P; 4) PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Fischer 2006

Methods	Country: USA Setting/Design: randomized, crossover, open-label study Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 8 months Loss to follow-up: 0
Participants	INCLUSION CRITERIA: -life expectancy of at least 12 months -Hemodialysis 3 times weekly for 3 months or longer -patients manteined on sevelamer in a daily dose of 9600mg or less as their only phosphate binder -serum phosphorus concentrations at last 2 measurements between 3.0 and 6.5mg/dL EXCLUSION CRITERIA: -active bowel obstruction -dysphagia -swallowing disorders -significant gastrointestinal diseae -etanol or drug abuse -need for antiarrhythmic or antiseizure medication to control these condition -poorly controlled DM or Htn -active vasculite or active malignancy other than basal cell carcinoma -immunodeficiency virus infection SEVELAMER DOSED ONCE DAILY Number: 21 Age: 63.4 Sex (M/F):13/5 SEVELAMER DOSED THRICE DAILY Number: 21 Age: 63.4 Sex(M/F):13/5
Interventions	SEVELAMER DOSED ONCE DAILY:standard dose once daily followed by standard thrice-daily dose SEVELAMER DOSED THRICE DAILY:standard dose thrice daily followed by standard once-daily dose CO-INTERVENTIONS: vitamin D
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus level; 2)Serum calcium corrected for albumin level; 3)Ca x P; 4) PTHi 5)albumin 6)total, LDL, HDLand non-HDL colesterol 7)triglyceride levels
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B-unclear

Hervas 2003

Methods	Country: SPAIN Setting/Design: Universuty Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 34 weeks Loss to follow-up: 10
Participants	INCLUSION CRITERIA: -Age > 18 years -Hemodialysis three times per weeks -Calcium-based phosphate binders and vitamin D therapy at stable doses for at least one month EXCLUSION CRITERIA: -Unstable medical condition including poorly controlled diabetes mellitus, hypertension or any gastrointestinal abnormality SEVELAMER GROUP Number: NA Age: NA Sex (M/F): NA CALCIUM ACETATE GROUP Number: NA Age: NA Sex(M/F): NA
Interventions	GROUP: 2-4 cp (403mg) x3/day CALCIUM ACETATE GROUP : 1-4cp (500mg) x3/day CO-INTERVENTIONS: IV or oral vitamin analogues
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus2)Serum calcium; 3)Fosfatasi alcalina; 4)PTHi; 5)Lipid profile
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hutchinson 2005

Methods	Country: UK Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: YES Follow-up period: 6 month Loss to follow-up: NA
Participants	INCLUSION CRITERIA: -Age >18 years -Hemodialysis 3 times a week for at least 3 consecutive months(including patients who had previously undergone renal transplantation) EXCLUSION CRITERIA: -Hypercalcemia, svere hyperparathyroidism or other clinically significant abnormal laboratory values -Lacting females or those with a positive screening pregnancy test -Patients who were HIV-positive, known hepatitis B e C, or other significant concurrent liver disorder -Patients with a life-threatening malignancy, multiple myeloma or a history of epilepsy -Drug or alcohol abuse within 2 yeas -Treatment with an investigational drug 30 days prior to screening -Patients who, in the opinion of the investigators, would not comply with the study requirements LANTHANUM GROUP Number: 510 Age: 57.0 (14.3) Sex (M/F):341/169 CALCIUM CARBONATE GROUP Number: 257 Age: 58.4 (13.3) Sex(M/F): 164/113
Interventions	LANTHANUM GROUP: Doses to achieve serum phosphorus < 5.5 mg/dl CALCIUM CARBONATE GROUP : Doses to achieve serum phosphorus < 5.5 mg/dl CO-INTERVENTIONS: Oral or IV vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Serum calcium; 2)Ca x P; 3)PTHi and vitaminD
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hutchison 2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	

Itoh 2008

Methods	Country: Japan Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 8 weeks Loss to follow-up: NA
Participants	INCLUSION CRITERIA: -Hemodialysis patients with hyperphosphatemia EXCLUSION CRITERIA: -NS SEVELAMER GROUP Number: 31 Age: 57.6 Sex (M/F): 23/8 COLESTIMIDE GROUP Number: 31 Age: 59.6 Sex(M/F):20/11
Interventions	SEVELAMER GROUP: 3.0 g/day COLESTIMIDE GROUP: 3.0 g/day CO-INTERVENTIONS: CaCO3 3.0 g/day
Outcomes	STUDY OUTCOMES: 1)Serum Ca concentration 2)Serum Pi concentration 3)Ca x P product 4)PTH levels 5)Serum Alkaline phosphatase
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B- Unclear

Ittel 1991

Methods	Country: Germany Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 8 months Loss to follow-up: 10
Participants	INCLUSION CRITERIA: -Previous compliance with medication regimen -Acceptable control of serum phosphate with a moderate dose(<5g) of aluminium hydroxide -Hemodialysis for at least 12 months EXCLUSION CRITERIA: Not specified GROUP 1 Number: NA Age: NA Sex (M/F): NA GROUP 2 Number: NA Age: NA Sex(M/F): NA
Interventions	GROUP 1: CaCO3-gastric-coated preparation and the CaCO3-enteric coated capsules GROUP 2: CaCO3-enteric coated capsusles and the CaCO3-gastric-coated preparation CO-INTERVENTIONS: Aluminium hydroxide
Outcomes	STUDY OUTCOMES: 1)
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	D - Not used

Janssen 1996

Methods	Country: The Netherlands Setting/Design:Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: No Follow-up period: 12 months Loss to follow-up: 16
Participants	INCLUSION CRITERIA: -Regualar hemodialysis EXCLUSION CRITERIA: Not specified ALUMINUM GROUP Number: 15 Age: 62 (4) Sex(M/F): 5/10 CALCIUM ACETATE GROUP Number: 18 Age: 51 (4) Sex(M/F): 11/7 CALCIUM CARBONATE GROUP Number: 20 Age: 58 (4) Sex(M/F): 7/13
Interventions	ALUMINUM GROUP: Doses to achieve serum phosphorus <5.0mg/dl and serum calcium 8.8-11.0mg/dl CALCCIUM ACETATE GROUP : Doses to achieve serum phosphorus <5.0mg/dl and serum calcium 8.8-11.0mg/dl CALCIUM CARBONATE GROUP: Doses to achieve serum phosphorus <5.0mg/dl and serum calcium 8.8-11.0mg/dl CO-INTERVENTIONS: 1 alfa OH vit D3
Outcomes	STUDY OUTCOMES:1)Serum calcium and phosphorus;2)PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jespersen 1991

Methods	Country: Denmark Setting/Design: University Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 12 months Loss to follow-up: 3
Participants	INCLUSION CRITERIA: -Chronic hemodialysis -Age: Age >18 years -Serum phosphorus greater than 2 mmol/l without treatment with a phosphate binder to maintain serum phosphorus below 2 mmol/l -Serum calcium <2.6mmol/l EXCLUSION CRITERIA: -Previous parathyroidectomy -Ongoing treatment with 1,25(OH2)D3 -Glucocorticoid treatment GROUP 1 Number: 5 Age: 41 (22-69) sex (M/F): 2/3 GROUP 2 Number: 6 Age: 49 (27-65) Sex(M/F): 4/2
Interventions	GROUP 1: Aluminum hydroxide 33-66mg/Kg/day and then Calcium carbonate 83-166mg/Kg/day GROUP 2: Calcium carbonate 83-166mg/Kg/day and then Aluminum hydroxide 33-66mg/Kg/dayCO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum calcium and phosphorus; 2)Effect on bone turnover and hyperparathyroidism; 3)Bone mineral content and extraskeletal calcification; 4)serum aluminium
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Joy 2003

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: NO -Data analysis: NO Intention to treat: YES Follow-up period: 16 weeks Loss to follow-up: 44
Participants	INCLUSION CRITERIA: -Hemodialysis 3 times per week for at least 2 months -Age> 18 years EXCLUSION CRITERIA: -Preganant or lactating or who were not using appropriate birth control -Significant hypercalcemia or hypocalcemia, clinically significant abnormal laboratory values, severe hyperparathyroidism -Uncontrolled concurrent illness, significant gastrointestinal 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 LANTANUM CARBONATE GROUP Number: 49 Age: 60.2 (13.3) Sex(M/F): 31/18 PLACEBO GROUP Number: 44 Age: 60.2 (13.3) Sex(M/F): 16 CALCIUM CARBONATE GROUP Number: 27 Age: NA Sex(M/F): NA
Interventions	LANTANUM CARBONATO GROUP: Dose to achieve serum phosphorus < 5.9mg/dl PLACEBO GROUP CO-INTERVENTIONS:Oral or IV vitaminD analogues
Outcomes	STUDY OUTCOMES: 1)Serum calcium; 2) Ca x P; 3) PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kingusa 2001

Methods	Country: Japan Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: NA Follow-up period: 8 weeks Loss to follow-up: NA
Participants	INCLUSION CRITERIA: - Not stated EXCLUSION CRITERIA: - Not stated CALCIUM CARBONATE GROUP Number: 115 Age: NA Sex (M/F): NA SEVELAMER GROUP Number: 115 Age: NA Sex(M/F): NA
Interventions	CALCIUM CARBONATEGROUP : mean doses=4.7g ranging from 1.3 to 7.7 g/day SEVELAMER GROUP : mean doses= 2.8g/day ranging from 1.0 to 5.0 g/day CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) Changes in P levels 2) Final Ca levels 3)Final i-PTH levels
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B-unclear

Koiwa 2005

Methods	Country: Japan Setting/Design: Muticentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: No -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period:12 weeks Loss to follow-up: 24
Participants	INCLUSION CRITERIA: Not restricted on the basis of etiology of renal failure, age, sex, or duration of dialysis, but doctors at each institution decided if patients were suitable for the study. EXCLUSION CRITERIA: NOt specified SEVELAMER GROUP Number: 29 Age: NA Sex (M/F): NA SECELAMER+CALCIUM CARBONATE GROUP Number: 30 Age: NA Sex(M/F): NA CALCIUM CARBONATE GROUP Number: 27 Age: NA Sex(M/F): NA
Interventions	onate 3g/day for the first 4 weeks) SEVELAMER + CALCIUM CARBONATE GROUP : 3g/day +3g/day (Calcium carbonate 3g/day for the first 4 weeks) CALCIUMA CARBONATE GROUP: 3g/day for the final 4 weeks (Calcium carbonate 3g/day for the first 4 weeks) CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum corrected calcium ; 2)Serum phosphorus; 3)Seum bicarbonate; 4)PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kurihara 2005

Methods	Country: Japan Setting/Design:Multicentre Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 2 weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: - HD patients older than 20 -Patients on hemodialysis therapy three times a week continuously for ?3 months -Stable dosage of vitamin D (if used) and calcium concentration (3.0mEq/L)for ?1 month EXCLUSION CRITERIA: -Not stated MCI-196 GROUP Number: 21 Age: 53.0±10.9 Sex (M/F): 18/3 PLACEBO GROUP Number: 12 Age: 58.4±9.8 Sex(M/F): 10/2
Interventions	MCI-196 GROUP : 6a day PLACEBO GROUP : 6g a day CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) effectiveness and safety of short term administration of MCI-196
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - unclear

Malluche 2008

Methods	Country: USA, Puerto Rico, Poland, South Africa Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 2 years Loss to follow-up: 4
Participants	INCLUSION CRITERIA: - patients >18 years old and received hemodialysis 3 times weekly EXCLUSION CRITERIA: - Abnormal laboratory values at screening or screening calcium level < 7.9mg/dl, prior gastrointestinal(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 cyclosporine, corticosteroid therapy, parathyroid surgery within 6 months, failed transplant within 2 months before bone biopsy. STANDARD PHOSPHATE-BINDER GROUP Number: 103 Age: 50.6±13.9 Sex (M/F): 37/11 LANTHANUM CARBONATE GROUP Number: 108 Age: 48.5±13.4 Sex(M/F): 37/14
Interventions	STANDARD PHOSPHATE-BINDER GROUP : to achieve target phosphorus levels of 5.9mg/dl LANTHANUM CARBONATE GROUP: to achieve target phosphorus levels of 5.9mg/dl (maximum dose=3mg/day) CO-INTERVENTIONS: No
Outcomes	STUDY OUTCOMES: 1) Serum level of phosphorus 2) Serum level of calcium 3) Serum level of PTH 4) Changes in bone turnover 5) Bone volume 6) Bone lanthanum content
Notes	Ps: data about age and sex are reported for 51 and 48 patients (lanthanum carbonate and standard phosphate binder respectively)

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Mehrotra 2008

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: ITT Follow-up period: 6 MONTHS Loss to follow-up: N=56
Participants	INCLUSION CRITERIA: - patients >18 years old and received hemodialysis 3 times weekly EXCLUSION CRITERIA: EXCLUSION CRITERIA: Patients with phosphorus <5.5 mg/dl, PTH >800pg/ml. COHORT A (upto 2000 mg of lanthanum carbonate) Number: 215 Age: 56.7 (27-89) Sex (M/F): 125/90 COHORT B (Forced titration to 3000 mg, 3750 mg or 4500 mg/d) Number: 142 Age: 51.6 (19-87) Sex(M/F): 85/57
Interventions	Patients had a washout period followed by open label titration of 1500 mg/day, 2250 mg/d and 3000 mg/d to acheive target phosphorus level 3.5-5.5 mg/dl. In people who acheived target level, an open label treatment upto 3000 mg/d was adopted. In patients who did not reach target, an double blind forced dose titration was followed.
Outcomes	STUDY OUTCOMES: 1) Serum level of phosphorus 2) Serum level of calcium 3) Serum level of PTH 4) Ca X P 5) Albumin level 6) Side effects (GI)
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	

Pflanz 1994

Methods	Country: UK Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 6 weeks Loss to follow-up: 8
Participants	INCLUSION CRITERIA: -Hemodialysis patients(4h dialysis treatment three times per week) whose usual phosphate-binding therapy consisted of calcium carbonate in atotal daily dose of between 2.5 and 5.0g EXCLUSION CRITERIA: -Other doses or on other phosphate binders CALCIUM ACETATE GROUP Number:NA Age: NA Sex(M/F): NA CALCIUM CARBONATE GROUP Number: NA Age: NA Sex(M/F): NA
Interventions	CALCIUM ACETATE GROUP: 2 g x3/day CALCIUM CARBONATE GROUP : 2g x3/day CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum calcium; 2)Serum phosphorus; 3)Calcium x phosphorus product; 4)PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Phelps 2002

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: No -Outcome assessors: YES -Data analysis: NO Intention to treat: NO Follow-up period: 8 weeks Loss to follow-up: 2
Participants	INCLUSION CRITERIA: -Men >18 years -Cl Cr 10-70 ml/min -PTHi >65pg/ml -25-OHD>15ng/ml -F-Thyroxine 0.77-1.61 ng/ml -TSH 0.35-5.5 microU/ml EXCLUSION CRITERIA: -Current corticosteroid ingestion -Any allograft -any disorder other than chronic renal failure associated with bone loss GROUP 1 Number: 8 Age: 71.3 (8.6) Sex (M/F): all M GROUP 2 Number: 10 Age: 69.4 (7.3) Sex(M/F): All M
Interventions	GROUP 1: Calcium acetate 2g/day GROUP 2 : Calcium acetate 6g/day CO-INTERVENTIONS:NO
Outcomes	STUDY OUTCOMES: 1)PTHi;2)Changes in the ratio of phosphorus to creatinine excreted; 3)Changes in serum calcium, phosphorus and 1,25 OHD; 4) Changes in BMD at sites in lumbar spine and femur
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Qunibi 2004

Methods	Country: USA Setting/Design: Multicenter Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 8 Loss to follow-up: 2
Participants	INCLUSION CRITERIA: -Hemodialysis for at least 3 months, receveing a stable dose of phosphate binder and i.v. vitamin D for at least one month EXCLUSION CRITERIA: -PTHi>1000pg/ml -History of previous parathyroidectomy SEVELAMER GROUP Number: 50 Age: 52.3 (14.7) Sex(M/F): 28/22 CALCIUM ACETATE GROUP Number: 48 Age: 53.9 (13.3) Sex(M/F): 28/20
Interventions	SEVELAMER GROUP: 2-4 cp(403mg) x3/day to achieve serum phosphorus <5.5mg/dl CALCIUM ACETATEGROUP : 2-4 cp(667mg) x3/day to achieve serum phosphorus <5.5mg/dl CO-INTERVENTIONS: IV vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus2)Serum calcium; 3)Calcium-phosphate product; 4)PTHi;
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Raggi 2005

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: No -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 52 weks Loss to follow-up: NA
Participants	INCLUSION CRITERIA: -Hemodialysis patients EXCLUSION CRITERIA: Not stated SEVELAMER GROUP Number: 51 Age: 56 (13) sex (M/F): 17/34 CALCIUM GROUP Number: 60 Age: 58 (15) Sex(M/F): 20/40
Interventions	SEVELAMER GROUP: Dose to achieve serum phosphorus between 3 and 5 mg/dl, serum calcium between 8.5 and 10.5 mg/dl and PTHi between 150 and 300 pg/ml GROUP : Dose to achieve serum phosphorus between 3 and 5 mg/dl, serum calcium between 8.5 and 10.5 mg/dl and PTHi between 150 and 300 pg/ml CO-INTERVENTIONS: NA
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus, calcium, PTHi, Calcium xphosphorus; 2)Changes in bone attenuation; 3)Markers of bone turnover; 4)Change in coronary artery and aortic calcifiaction
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate

Ring 1993

Methods	Country: Denmark Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 3weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: -Chronic haemodialysis 4h three times or 4 h twice a week TReatment with calcium carbonate as the only phosphorus binber for at least 1 month/ No vitamin D EXCLUSION CRITERIA: Not specified CALCIUM ACETATE GROUP Number: NA Age: NA Sex(M/F): NA CALCIUM CARBONATE GROUP Number: NA Age: NA Sex(M/F): NA
Interventions	CALCIUM ACETATE GROUP: 3.8 g/day CALCIUM CARBONATE GROUP : 4 g/day CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum phosphate; 2)Serum calcium; 3)PTHi;
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Roxe 1989

Methods	Country: USA Setting/Design: University Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 8 weeeks Loss to follow-up:2
Participants	INCLUSION CRITERIA: -Age: 18-70 years -Hemodialysis three times eacg week EXCLUSION CRITERIA: -Treatment with phenytoin, cardiac glycosides or calcium carbonate -Chronic anticoagulation GROUP 1 Number: NA Age: NA Sex (M/F):NA GROUP 2 Number: NA Age: NA Sex(M/F): NA CALCIUM CARBONATE GROUP Number: 27 Age: NA Sex(M/F): NA
Interventions	GROUP 1: Aluminium hydroxide 3g/day and then sucralfate 6g/day to achieve serum phosphorus < 4.5mg/dl GROUP 2 : Sucralfate 6g/day and then Aluminium hydroxide 3g/day to achieve serum phosphorus < 4.5mg/dl CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum phosphate; 2)Serum aluminum
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rudnicki 1994

Methods	Country: Denmark Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: YES -Investigators: YES -Outcome assessors: NO -Data analysis: NO Intention to treat: No Follow-up period: 24 weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: -Hemodialysis for three times a week (6months-10 years) -PTHi above the normal range and serum ionized calcium within or below it EXCLUSION CRITERIA: Not specified CALCIUM CARBONATE GROUP Number: 9 Age: NA Sex(M/F):NA PLACEBO GROUP Number: 9 Age: NA Sex(M/F): NA
Interventions	CALCIUM GROUP: 2g/day PLACEBO GROUP CO-INTERVENTIONS: Oral vitamin D analogues
Outcomes	STUDY OUTCOMES: 1)Bone markers
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Russo 2007

Methods	Country: Italy Setting/Design: Time frame: NA Randomisation method: Blinding -Participants: No -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: No Follow-up period: 24±4.2 months Loss to follow-up: 6
Participants	INCLUSION CRITERIA: - Constant low dietary phosphate intake - Stable serum concentration of phosphorus, calcium, calcium x phosphorus product, PTH -No previous therapy with aluminum or calcium based phosphate binders, vitamin D sterols, statins -Comparable mean baseline total calcium score (TCS) at CT scan EXCLUSION CRITERIA: - Age < 18 -Symptomatic coronary disease, past myocardial infarction, previous coronary surgery/angioplasty, stroke, arrhythmia -Progressive renal disease -Diabetes LOW PHOSPHORUS DIET GROUP Number: 30 Age: 54.41±3.7 Sex (M/F): 25/4 SEVELAMER(+low P diet) GROUP Number: 30 Age: 55.2±12.0 Sex(M/F): 23/5 CALCIUM CARBONATE (+low P diet) GROUP Number: 30 Age: 54.4±12.9 Sex(M/F): 24/3
Interventions	SEVELAMER(+low P diet) GROUP : 1600mg daily CALCIUM CARBONATE (+low P diet) GROUP : 2g daily CO-INTERVENTIONS: No
Outcomes	STUDY OUTCOMES: 1) Changes in TCS 2) Progression of CACs 3)Changes in biochemical variables Ps: data about age and sex are reported for 29, 28 and 27 patients (controls, calcium carbonate and sevelamer espectively)
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sadek 2003

Methods	Country: France Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 5 months Loss to follow-up: 0
Participants	INCLUSION CRITERIA: - Not stated EXCLUSION CRITERIA: - Not stated SEVELAMER GROUP Number: 21 Age: NA Sex (M/F):NA CALCIUM CARBONATE GROUP Number: 21 Age: NA Sex(M/F):NA
Interventions	SEVELAMER GROUP : CALCIUM CARBONATE GROUP CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) Serum calcium 2) Serum phosphate 3) Serum PTH 4) 25-OH vitamin D 5)Triglycerides, LDL, HDL, total cholesterol
Notes	The result were analyzed in only 16 patients of the CaCO3 group and 15 of the sevelamer group

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Saluski 1991

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	

Schaefer 1991

Methods	Country: Germany Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: No -Outcome assessors: No -Data analysis: No Intention to treat: NO Follow-up period: 7 weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: -Chronic haemodialysis patients (for at least 40 months) EXCLUSION CRITERIA: Not specified GROUP 1 Number: 12 Age: NA Sex: NA GROUP 2 Number: 12 Age: NA Sex(M/F): NA GROUP 3 Number: 10 Age: NA Sex: NA GROUP 4 Number: 13 Age: NA Sex: NA
Interventions	GROUP1: Calcium acetate 6g/day GROUP 2 : Calcium acetate(6g/day)+calcitriol(4mcg/2x wk) GRUPPO 3: Calcium acetate(6g/day)+calcitriol(0.5mcg/2X wk) GRUPPO 4: Aluminium Hydroxide+ Calcitriol(4mcg/2X wk) CO-INTERVENTIONS:
Outcomes	STUDY OUTCOMES: 1)Serum calcium; 2)Serum phosphorus; 3)PTHi
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Shaheen 2004

Methods	Country: Kingdom of Saudi Arabia Setting/Design: Hospital Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: No Intention to treat: NO Follow-up period: 8 weeks Loss to follow-up: 3
Participants	INCLUSION CRITERIA: -Age: 15-75 years -Chronic hemodialysis(2 or 3 times weekly) for at least 3 months and optimally dialyzed as judged by usual dialysis and serum chemistry parameters Current phosphorus: 5.5mg/dl EXCLUSION CRITERIA: -Serious gastrointestinal 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 immunodeficiency virus infection, active vasculitis or illness at the time of entry to the study SEVEALMER GROUP: Number: 20 Age: 42.7(9.9) Sex(M/F): 12/8 PLACEBO GROUP Number: 20 Age: 42.7 (9.9) Sex(M/F): 12/8
Interventions	IA: -Age <18 years -Pregnancy -Active GI bleeding -Use of calcitriol -Tertiary hyperparathyroidism -Immediate post-operative parathyroidectomy(within the first 3 months
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2)Serum calcium; 3) Serum calcium x phosphorus; 4)PTHi levels; 5)Lipid profile
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	D - Not used

Shigmetsu 2008

Methods	Country: Japan Setting/Design: Multicentre Time frame: NA Randomization method: Blinding -Participants: Yes -Investigators: Yes -Outcome assessors: Ns -Data analysis: Ns Intention to treat: yes Follow-up period: 8 weeks Loss to follow-up: 0
Participants	INCLUSION CRITERIA: - Age >20 -Patients in maintenance HD with hyperphosphatemia - PSPL> 5.6mg/dl at 1 week after the initiation of the washout period EXCLUSION CRITERIA: - PSPL>10mg/dl at the staret of the washout period or =11.0mg/dl during the washout period -Corrected serum calcium level of<7.0mg/dl -Serum intact PTH of>1pg/ml at the start of the washout period LANTHANUM CARBONATE GROUP Number: 126 Age: 58.8±10.5 Sex (M/F): 87/39 CALCIUM CARBONATE GROUP Number: 132 Age: 56.1±11.5 Sex(M/F): 87/45
Interventions	LANTHANUM CARBONATE GROUP: starting dose of 750mg/day CALCIUM CARBONATE GROUP : starting dose of 1500mg/day CO-INTERVENTIONS: No
Outcomes	STUDY OUTCOMES: 1) Changes in PSPL 2)Serum calcium levels 3)PTH levels 4)Serum phosphate level
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Spasovski 2006

Methods	Country: Macedonia Setting/Design: Dialysis centre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 3 years Loss to follow-up: 1
Participants	INCLUSION CRITERIA: - Dialysis patients who had required oral phosphate binders to control serum phosphorus levels EXCLUSION CRITERIA: -Patients with any significant gastrointestinal problem -Patients with history of treatment with corticosteroids or bisphosphonates -Patients with hypocalcaemia at screening LANTHANUM CARBONATE GROUP Number: 12 Age: 55±10 Sex (M/F): 7/5 CALCIUM CARBONATE GROUP Number: 12 Age: 57 ±10 Sex(M/F): 7/5
Interventions	LANTHANUM CARBONATE GROUP : to achive optimal control of serum phosphorus levels (<1.8mmol/l) (maximum dose of 3000mg/day) CALCIUM CARBONATE GROUP : to achive optimal control of serum phosphorus levels (<1.8mmol/l) (maximum dose of 4000mg/day) CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) Biochemical parameters 2)Lanthanum level in plasma and bone 3)Safety and efficacy of treatments
Notes	Treatment period of this trial is one year. During the other two years all patients are switched to calcio carbonate.

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - unclear

Spiegel 2007

Methods	Country: USA Setting/Design: Prospective, randomized, open-label trial Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 12 weeks Loss to follow-up: NA
Participants	INCLUSION CRITERIA: - patients >18 years of age on chronic hemodialysis for at least 3 months -patients receiving phosphate binders before entry into the study -patiens with serum calcium of 8.0 to 10.2 mg dL and serum phosphorus of 3.0 to 6.9 mg/dL EXCLUSION CRITERIA: -Patients with frequent diarrhea -Patients declined to give informed consent MAGNESIUM CARBONATE GROUP Number: 20 Age: 55.5±12.6 Sex (M/F): 12/8 CALCIUM ACETATE GROUP Number: 10 Age: 55.9 ±12.0 Sex(M/F): 4/6
Interventions	MAGNESIUM CARBONATE GROUP : to achive the target phosphorus of <5.5 mg/dL CALCIUM ACETATE GROUP : to achive the target phosphorus of <5.5 mg/dL CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1) Serum phosphorus 2) Serum magnesium 3) Serum calcium 4) iPTH 5) Serum bicarbonate concentration
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B-unclear

Wu-Chang 2002

Methods	Country: USA Setting/Design: Multicentre Time frame: NA Randomisation method: Blinding -Participants: NO -Investigators: NO -Outcome assessors: NO -Data analysis: NO Intention to treat: NO Follow-up period: 8 weeks Loss to follow-up: 9
Participants	INCLUSION CRITERIA: -Hemodialysis patients -Concentration of calcium in the dialysate was 2.5mEq/l -Predictable compliance with their medical regimen -Serum iron or ferritin level wiyhin or below the normal range -Serum calcium of 8-10 mg/dl EXCLUSION CRITERIA: -Age <18 years -Pregnancy -Active GI bleeding -Use of calcitriol -Tertiary hyperparathyroidism -Immediate post-operative parathyroidectomy(within the first 3 months or serum calcium below 7 mg/dl) -Severe congestive heart failure -Anorexia and cachexia -Diabetes mellitus with gastroparesis and malignancy GROUP 1 Number: NA Age: NA Sex (M/F): NA GROUP 2 Number: NA Age: NA Sex(M/F): NA
Interventions	GROUP 1: Ferric citrate 1g x3/day and then Calcium carbonate 1 g x3/day GROUP 2 : Calcium carbonate 1g x3/day and then Ferric citrate 1 g x3/day CO-INTERVENTIONS: NO
Outcomes	STUDY OUTCOMES: 1)Serum phosphorus; 2)Serum calcium; 3) Serum calcium x phosphorus; 4)PTHi levels;
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B - Unclear

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Al-Baaj 2003

Al-Baaj F, Speake M, Hutchinson J. Control of serum phosphate by oral lanthanum carbonate in patients undergoing haemodialysis and continuos ambulatory peritoneal dialysis in a short-term, placebo-controlled study. Nephrol Dial Transplant 2005.

Almirall 1994

* Almirall J, Veciana L, Llibre J.. Calcium Acetate versus CAìalcium Carbonate for the control of serum phosphorus in hemodialysis patients. Am J Nephrol 1994.

Altmann 2007

Altmann P, Barnett ME, Finn WF; SPD405-307 Lanthanum Carbonate Study Group. Cognitive function in Stage 5 chronic kidney disease patients on hemodialysis: no adverse effects of lanthanum carbonate compared with standard phosphate-binder therapy. Kidney Int. 2007;71:252-259.

Asmus 2005

Asmus HG, Braun J, Krause R.. Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. Nephrol Dial Transplant 2005;20(1653-1661).

Barreto 2008

Barreto DV, Barreto Fde C, de Carvalho ABNephron Clin Pract. 2008;110:c273-83.. Phosphate binder impact on bone remodeling and coronary calcification?results from the BRiC study..

Birck 1999

Birck R, Zimmermann E, Wassmer S, Rainer N and Fokko J. van der Woude. Calcium ketoglutarate versus calcium acetate for treatment of hyperphosphatemia in patients on maintance haemodialysis: a cross-over study. Nephrol Dial Transplant 1999.

Bleyer 1999

Bleyer AJ, Burke SK, Dillon M, Garrett B, et al.. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. American Journal of Kidney Disease 1999.

Block 2005

Block GA, Spiegel DM, Ehrlich J, Mehta R et al.. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney International 2005.

Block 2007

Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of cornoary calcification and phosphate binder choice in incident hemodialysis patients.. Kidney Int. 2007;71:438-411..

Borrego 2000

Borrego J, Perez del Barrio P, serrano P, Garcia cortes MJ et al. Comparation of the binder phosphorus effect og calcium carbonate vs calcium acetate during chronic renal failure before dialysis. Nefrologia 2000.

Bro 1998

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 hemodialysis. Anerican Journal of Kidney Diseases 1998.

Caravaca 1992

Caravaca F, santos I, Cubero JJ, Esparrago JF, et al. Calcium acetate versus Calcium carbonate as phosphate binders in hemodialysis patients. Nephron 1992.

CARE-2 2008

Qunibi W, Moustafa M, Muenz LR, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. Am J Kidney Dis. 2008;51:952-965..

Cheng 2008

Cheng SC, Young DO, Huang Y, Delmez JA, Coyne DW.. A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in hemodialysis patients.. Clin J Am Soc Nephrol. 2008 Jul;3(4):1131-8.

Chertow 1997

Chertow GM, Burke SK, Lazarus MJ et al.. Poly(allylamine hydrochloride)(RenaGel): A noncalcemic phosphate binder for yhr treatment of hyperphosphatemia in chronic renal failure. American Journal of kidney Disease 1997.

Chertow 1999

Chertow GM, Dillon M, Burke SK, Steg M, Bleyer AJ, et al.. A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemntal calcium. Clinical Nephrology 1999.

Chertow 2002

Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients.. Kidney Int. 2002;62(245-252).

Chiang 2005

Chiang SS, Chen JB, Yang WC Lanthanum carbonate (Fosrenol) efficacy and tolerability in the treatment of hyperphosphatemic patients with end-stage renal disease.. Lanthanum carbonate (Fosrenol) efficacy and tolerability in the treatment of hyperphosphatemic patients with end-stage renal disease.. Clin Nephrol 2005;63(461-470).

D'Haese 2003

D'Haese P, Spasovski GB, Sikole A, Hutchinson A, et al. A multicenter study on the effects of lanthanum carbonate(Fosrenol) and calcium carbonate on renal bone disease in dyalisis patients. Kidney International 2003.

DCOR 2007

Suki W, Zabaneh R, Cngiano J, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients.. Kidney Int 2007;72:1130-1137.

DeSanto 2006

DeSanto NG, Frangiosa A, Anastasio P, et al. Sevelamer worsens metabolic acidosis in hemodialysis patients. J Nephrol 2006;199((Suppl 9)):108-114.

Emmett 1991

Emmett M, Sirmon MD, Kirkpatrick GW, Nolan C et al.. Calcium Acetate control of serum phosphorus in hemodialysis patients. American Journal of Kidney Disease 1991.

Evenepoel 2009

Evenepoel P, Selgas R, Caputo F, et al. Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. Nephrol Dial Transplant 2009;24:278-85.

Ferramosca 2005

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. Am Heart J 2005;149:820-825.

Ferreira 2008

Ferreira A, Frazão JM, Monier-Faugere MC, et al. Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. J Am Soc Nephrol 2008;19(405-12).

Filho 2000

Filho E, Sampaio da Cruz E, Hoette M, Ruzany F, et al.. Calcium acetate versus calcium carbonate in the control of hyperphosphatemia in hemodialysis patients. Medical Journal 2000.

Finn 2004

Finn WF, Joy MS, Hladik G and the Lanthanum Study Group. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receveing hemodialysis. Clinical Nephrology 2004.

Fischer 2006

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. Am J Kidney Dis 2006;48:437-44.

Hervas 2003

Hervas JG, Prados D, Cerezo S. Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: A comparison with calcium acetate. Kidney International 2003.

Hutchinson 2005

Hutchinson AJ, Maes B, Vanwalleghem J et al.. Efficacy, tolerability, and safety of Lanthanum carbonate in hyperphosphatemia: A 6-month, randomized, comparative trial versus Calcium carbonate. Nephron Clin Pract 2005.

Hutchison 2006

Hutchison AJ, Maes B, Vanwalleghem J, et al. Long-term efficacy and tolerability of lanthanum carbonate: results from a 3-year study.. Nephron Clin Pract. 2006;102:61-71.

Itoh 2008

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.. Ther Apher Dial. 2008 Apr;12(2):126-32.

Ittel 1991

Ittel TH. Schfer C, Schmitt H, et al.. Calcium carbonate as a Phosphate binde in dialysis patients: Evaluation of an enteric-coated preparation and effect of additional Aluminium hydroxide on hyperaluminaemia. Klin Wochenschr 1991.

Janssen 1996

Janssen MJA, van Der Kuy A, Ter Wee PM and van Bowen WPL. Aluminum hydroxide, calcium carbonate and calcium acetate in chronic intermittent hemodialysis patients. Clinical Nephrology 1996.

Jespersen 1991

Jespersen B, Jensen JD, Nielsen HK, Lauridsen IN, et al. Comparison of Calcium Carbonate and Aluminium Hydroxide as Phosphate binders on biochemical bone markers, PTH(1-84), and bone mineral content in dyalisis patients. Nephol Dial Transplant 1991.

Joy 2003

Joy MS, Finn WF, on behalf of the LAM-302 Study Group. Randomized, Double-blind, placebo-controlled, dose-tritation. phaseIII study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. American Journal of Kdney Diseases 2003.

Kingusa 2001

Kingusa E, Koshikawa S. 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). J Am Soc Nephrol 2001;12:755A.

Koiwa 2005

Koiwa F, Onoda N, Kato H, Tokumoto A, Okada T et al.. Prospective randomized multicenter trial of Sevelamer Hydrocjloride and Calcium Carbonate fot the treatment of hyperphosphatemia in hemodialysis patients in Japan. Therapeutic Apheresis and Dialysis 2005.

Kurihara 2005

Kurihara S, Tsuruta Y, Akizawa T.. Effect of MCI-196 (colestilan) as a phosphate binder on hyperphosphataemia in hemodialysis patients: a double-blind, placebo-controlled, short-term trial. Nephrol Dial Transplant 2005 Feb;20(2):424-30.

Malluche 2008

Malluche HH, Siami GA, Swanepoel C et al. Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. Clin Nephrol 2008;70:284-95.

Mehrotra 2008

Mehrotra R, Martin KJ, Fishbane S, et al. Higher strength lanthanum carbonate provides serum phosphorus control with a low tablet burden and is preferred by patients and physicians: a multicenter study.. Clin J Am Soc Nephrol 2008;3:1437-45.

Pflanz 1994

Pfanz S, Henderson IS, McElduff N, Jones MC. Calcium acetate versus calcium carbonate as phosphate-binding agents in chronic haemodialysis. Nephrol Dial Transplant 1994.

Phelps 2002

Phelps KR, Stern M, Slingerland A, et al.. Metabolic and skeletal effects of low and high doses of calcium acetate in patients with preterminal chronic renal failure. Am J Nephrol 2002.

Qunibi 2004

Qunibi WY, Hootkins RE, McDowell LL, Meyer MS, et al. Treatmnet of hyperphosphatemia in hemodialysis patients: The Calcium Acetate REnagel Evaluation(CARE Study). Kidney International 2004.

Raggi 2005

Raggi P, James G, Burke S, Bommer S, Chasan-Taber S, Holzer H, Braun J, Chertow G. Decrease in thoracic vertebral bone attenuation with calcium-based phosphate binders in hemodialysis. Journal of bone and mineral

research 2005.

Ring 1993

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. Nephrol Dial Transplant 1993.

Roxe 1989

Roxe DM, Mistovich M, Barch DH. Phosphate-binding effects of sucralfate in patients with chronic renal failure. American Journal of Kidney Disease 1989.

Rudnicki 1994

Rudnicki M, Hyldstrup L, Petersen L, Hojsted J, Tranbol I. Effect of oral Calcium indices of bone formation and bone mass in hemodialysis patients: A randomized double-blind placebo-controlled study. Miner Electrolyte Metab 1994.

Russo 2007

Russo D, Miranda I, Ruocco C, et al The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer.. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int 2007;72:1255-61.

Sadek 2003

Sadek T, Mazouz H, Bahlou H, et al. Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients An open-label, randomized study.. Nephrol Dial Transplant 2003;18:582-589.

Saluski 1991

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.. N Engl J Med. 1991 Feb;21(324(8)):527-31.

Schaefer 1991

Schaefer K, Scheer J, Asmus G, Umlauf E, Hagemann J, von Herrath D. The treatment of uraemic hyperphoshatemia with calcium acetate and calcium carbonate: A comparative study. Nephrol Dial Transplant 1991.

Shaheen 2004

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 Med J 2004.

Shigmetsu 2008

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.. Clin Nephrol 2008;70:404-10.

Spasovski 2006

Spasovski GB, Sikole A, Gelev S, 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. Nephrol Dial Transplant 2006;21:2217-2224.

Spiegel 2007

Spiegel DM, Farmer B, Smits G, Chonchol M.. Magnesium carbonate is an effective phosphate binder for chronic hemodialysis patients: a pilot study.. J Ren Nutr. 2007 Nov;17(6):416-22.

Wu-Chang 2002

Wu-Chang Y, Yang C, Hou C, Wu T, et al.. An open-label, crossover study of anew phosphate-binding agent in haemodialysis patients: ferric citrate. Nephrol Dial Transplantation 2002.

Excluded studies

Studies awaiting classification

Ongoing studies

Other references

Additional references

Barreto 2008

Barreto DV, Barreto Fde C, de Carvalho AB, et al. Phosphate binder impact on bone remodeling and coronary calcification? Results from the BRiC study. Nephron Clin Pract. 2008;110:c273-83..

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 hemodialysis 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 hemodialysis. Journal of the Amercian Society of Nephrology 2004;15(8):2208-18. [MEDLINE: 15284307]

Block 2005

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 hemodialysis. Kidney International 2005;68(4):1815-24. [MEDLINE: 16164659]

Borrego 2000

Borrego J, Perez del Barrio P, serrano P, Garcia cortes MJ et al. Comparation of the binder phosphorus effect og calcium carbonate vs calcium acetate during chronic renal failure before dialysis. Nefrologia 2000.

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? Clin J Am Soc Nephrol 2006;1:695-696.

Coladonato 2005

Coladonato JA. Control of hyperphosphatemia among patients with ESRD. J Am Soc Nephrol 2005;16(Suppl 2):107-114.

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;7:177-188.

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 (Carlton) 2006;11(Suppl 1):S230-261..

Fadem 2007

Fadem SZ, Moe SM. Management of chronic kidney disease mineral-bone disorder. Adv Chronic Kidney Dis 2007;14:44-43.

Fellstrom 2009

Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395-407..

Friedman 2006

Friedman EA:. Calcium-based phosphate binders are appropriate in chronic renal failure.. Clin J Am Soc Nephrol 2006;1:704-809.

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]

Higgins 2003

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

Hurska 2008

Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of chronic kidney disease. Kidney Int 2008;74:148-157.

Hutchinson 2009

Hutchinson AJ. Oral phosphate binders. Kidney Int. 2009;75:906-914.

K-DOQI 2003

K-DOQI 2003.. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease patients.. Am J Kidney Dis 2003;42:70-77.

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. Nephrol Dial Transplant 2007;22:2867-2878.

Moe 2006

Moe SM, Chertown G. The case against calcium-based phosphate binders. Clin J Am Soc Nephrol 2006;1:697-703.

Navaneethan 2006

Navaneethan SD, Chaukiyal P, Strippoli GF, Palmer S, Craig J, Elder G:. Phosphate binders for preventing and treating bone and cardiovascular disease in chronic kidney disease patients. (Protocol). The Cochrane Database of Systematic Reviews 2006;(2):Art No.:CD006023.

Palmer 2007

Palmer SC, Craig JC, Strippoli GF. Sevelamer: a promising but unproven drug. Nephrol Dial Transplant. 2007;22:2742-2745.

Phelps 2002

Phelps KR, Stern M, Slingerland A, et al.. Metabolic and skeletal effects of low and high doses of calcium acetate in patients with preterminal chronic renal failure. Am J Nephrol 2002.

Quinibi 2004

Qunibi WY, Hootkins RE, McDowell LL, Meyer MS, et al. Treatmnet of hyperphosphatemia in hemodialysis patients: The Calcium Acetate REnagel Evaluation(CARE Study). Kidney International 2004.

Quinibi 2008

Qunibi W, Moustafa M, Muenz LR, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. Am J Kidney Dis. 2008;51.

Salusky 2006

Salusky IB. A new era in phosphate binder therapy: what are the options? Kidney Int Suppl 2006;70(Suppl 105):10-15.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-412.

Silver 2005

Silver J, Levi R. Cellular and molecular mechanisms of secondary hyperparathyroidism.. Clin Nephrol 2005;63:119-126.

Silver 2007

Silver J .. The details bedevil DCOR. Kidney Int. 2007;72:1041-1043.

Spasovski 2006

Spasovski GB, Sikole A, Gelev S, 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. Nephrol Dial Transplant 2006;21:2217-2224. [MEDLINE: 12748350]

St Peters 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. Am J Kidney Dis 2008;51:445-54.

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 Amercian Society of Nephrology 2004;15(3):770-9. [MEDLINE: 14978180]

Strippoli 2005

Strippoli GF, Craig JC: Hypothesis versus association: the optimal hemoglobin target debate.. Am J Kidney Dis 2005;46:970-973.

Strippoli 2007

Strippoli GF, Tognoni G, Navaneethan SD, Nicolucci A, Craig JC . Lancet. 2007;369:346-350. Haemoglobin targets: we were wrong, time to move on. Lancet 2007;369:346-350.

Strippoli 2009

Strippoli GF, Craig JC. Sunset for statins after AURORA? N Engl J Med 2009;360(14):1455-7..

Taylor 2008

Taylor MJ, Elgazzar HA, Chaplin S, Goldsmith D, Molony DA. An economic evaluation of sevelamer in patients new to dialysis. Curr Med Res Opin 2008;24:601-608.

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).. Am J Kidney Dis 2008;52:519-530.

Tonelli 2007

Tonelli M, Wiebe N, Culleton B, et al. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. Nephrol Dial Transplant. 2007;22:2856-2866.

USRDS 2008

United States Renal Data System (USRDS) 2008. http://www.usrds.org/2008/pdf/V2_11_2008.pdf. Last accessed April 16, 2009..

Other published versions of this review

Classification pending references

Data and analyses

1 Calcium salts versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 All cause mortality	1	72	Risk Ratio (M-H , Random , 95% CI)	Not estimable
1.2 Hypercalcemic events	1	72	Risk Ratio (M-H , Random , 95% CI)	11.00 [0.63, 191.88]
1.3 Serum calcium	1	72	Mean Difference (IV , Random , 95% CI)	0.60 [0.53, 0.67]
1.3.1 Total calcium	1	72	Mean Difference (IV , Random , 95% CI)	0.60 [0.53, 0.67]
1.4 Phosporus	2	90	Mean Difference (IV , Random , 95% CI)	-1.41 [-2.52, -0.29]

2 Calcium Acetate versus Calcium carbonate

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 All cause mortality rates	2	74	Risk Ratio (M-H , Random , 95% CI)	1.13 [0.07, 17.30]
2.2 Hypercalcemic events	2	88	Risk Ratio (M-H , Random , 95% CI)	1.08 [0.11, 10.99]

2.3 Gastrointestinal adverse events	2	136	Risk Ratio (M-H , Random , 95% CI)	1.26 [0.61, 2.60]
2.3.1 Gastritis	1	30	Risk Ratio (M-H , Random , 95% CI)	1.25 [0.41, 3.77]
2.3.2 Diarrhea	2	53	Risk Ratio (M-H , Random , 95% CI)	1.65 [0.22, 12.56]
2.3.3 Abdominal bloating	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
2.3.4 Constipation	2	53	Risk Ratio (M-H , Random , 95% CI)	1.16 [0.38, 3.52]
2.3.5 Combined	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
2.4 Serum Calcium	5	143	Mean Difference (IV , Random , 95% CI)	-0.09 [-0.35, 0.17]
2.5 Serum Phosporous	5	143	Mean Difference (IV , Random , 95% CI)	-0.19 [-0.61, 0.24]
2.6 I PTH	1	16	Mean Difference (IV , Random , 95% CI)	-52.00 [-211.02, 107.02]
2.7 Ca X P	2	31	Mean Difference (IV , Random , 95% CI)	-4.92 [-10.03, 0.19]
2.8 Serum alkaline phosphatase	4	74	Mean Difference (IV , Random , 95% CI)	1.42 [-8.99, 11.82]
2.9 Serum bicarbonate	2	53	Mean Difference (IV , Random , 95% CI)	0.21 [-1.32, 1.74]

3 Calcium ketoglutarate versus other calcium salts

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 All cause mortality	1	34	Risk Ratio (M-H , Random , 95% CI)	Not estimable
3.2 Gastrointestinal toxicity	1	34	Risk Ratio (M-H , Random , 95% CI)	5.00 [0.65, 38.42]
3.2.1 Gastritis	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
3.2.2 Diarrhea	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
3.2.3 Gastroparesis	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
3.2.4 Combined	1	34	Risk Ratio (M-H , Random , 95% CI)	5.00 [0.65, 38.42]
3.3 Serum calcium	1	20	Mean Difference (IV , Random , 95% CI)	-0.40 [-0.49, -0.31]
3.3.1 Total calcium	0	0	Mean Difference (IV , Random , 95% CI)	Not estimable
3.3.2 Ionised calcium	1	20	Mean Difference (IV , Random , 95% CI)	-0.40 [-0.49, -0.31]
3.4 Phosporus	2	48	Mean Difference (IV , Random , 95% CI)	-0.10 [-0.32, 0.12]
3.5 Intact PTH	1	20	Mean Difference (IV , Random , 95% CI)	-35.00 [-155.07, 85.07]
3.6 Calcium X Phosporus	1	20	Mean Difference (IV , Random , 95% CI)	-4.50 [-5.65, -3.35]
3.7 Serum bicarbonate	2	62	Mean Difference (IV , Random , 95% CI)	1.66 [1.03, 2.29]

4 Sevelamer versus Placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 All cause mortality	1	36	Risk Ratio (M-H , Random , 95% CI)	Not estimable

4.2 Gastrointestinal toxicity	1	72	Risk Ratio (M-H , Random , 95% CI)	0.54 [0.08, 3.45]
4.2.1 Gastritis	1	36	Risk Ratio (M-H , Random , 95% CI)	1.00 [0.10, 9.96]
4.2.2 Diarrhea	1	36	Risk Ratio (M-H , Random , 95% CI)	0.17 [0.01, 3.96]
4.2.3 Gastroparesis	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
4.3 Serum calcium	1	36	Mean Difference (IV , Random , 95% CI)	-0.10 [-0.52, 0.32]
4.3.1 Total calcium	1	36	Mean Difference (IV , Random , 95% CI)	-0.10 [-0.52, 0.32]
4.3.2 Ionised calcium	0	0	Mean Difference (IV , Random , 95% CI)	Not estimable
4.4 Phosporus	1	36	Mean Difference (IV , Random , 95% CI)	-1.80 [-3.32, -0.28]
4.5 Serum bicarbonate	1	36	Mean Difference (IV , Random , 95% CI)	-0.50 [-2.53, 1.53]
4.6 Total cholesterol	1	36	Mean Difference (IV , Random , 95% CI)	-28.00 [-51.58, -4.42]

5 Sevelamer versus Calcium Salts

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 All cause mortality rates	10	3079	Risk Ratio (M-H , Random , 95% CI)	0.73 [0.46, 1.16]
5.1.1 Sevelamer versus calcium acetate	6	613	Risk Ratio (M-H , Random , 95% CI)	0.43 [0.13, 1.38]
5.1.2 Sevelamer versus calcium carbonate	1	36	Risk Ratio (M-H , Random , 95% CI)	Not estimable
5.1.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	2430	Risk Ratio (M-H , Random , 95% CI)	0.85 [0.57, 1.27]
5.3 Hypercalcemic events	10	960	Risk Ratio (M-H , Random , 95% CI)	0.47 [0.36, 0.62]
5.3.1 Sevelamer versus calcium acetate	5	564	Risk Ratio (M-H , Random , 95% CI)	0.45 [0.27, 0.74]
5.3.2 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	2	309	Risk Ratio (M-H , Random , 95% CI)	0.43 [0.26, 0.72]
5.3.3 Sevelamer versus calcium carbonate	3	87	Risk Ratio (M-H , Random , 95% CI)	0.29 [0.11, 0.78]
5.4 Gatrointestinal adverse events	5	1035	Risk Ratio (M-H , Random , 95% CI)	1.39 [1.04, 1.87]
5.4.1 Nausea vomiting	1	203	Risk Ratio (M-H , Random , 95% CI)	1.03 [0.57, 1.86]
5.4.2 Diarrhea	1	203	Risk Ratio (M-H , Random , 95% CI)	1.03 [0.55, 1.95]
5.4.3 Abdominal bloating	1	56	Risk Ratio (M-H , Random , 95% CI)	2.33 [0.49, 11.01]
5.4.4 Constipation	2	259	Risk Ratio (M-H , Random , 95% CI)	2.63 [1.29, 5.35]
5.4.5 Combined	3	314	Risk Ratio (M-H , Random , 95% CI)	1.45 [0.88, 2.39]

5.6 Calcium	14	2925	Mean Difference (IV , Random , 95% CI)	−0.35 [−0.46, −0.24]
5.6.1 Sevelamer versus calcium acetate	6	541	Mean Difference (IV , Random , 95% CI)	−0.36 [−0.53, −0.20]
5.6.2 Sevelamer versus calcium carbonate	5	405	Mean Difference (IV , Random , 95% CI)	−0.43 [−0.93, 0.07]
5.6.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	1979	Mean Difference (IV , Random , 95% CI)	−0.35 [−0.46, −0.23]
5.7 Serum Phosporous	15	3012	Mean Difference (IV , Random , 95% CI)	0.21 [0.01, 0.41]
5.7.1 Sevelamer versus calcium acetate	7	612	Mean Difference (IV , Random , 95% CI)	0.25 [−0.20, 0.71]
5.7.2 Sevelamer versus calcium carbonate	5	405	Mean Difference (IV , Random , 95% CI)	0.48 [0.09, 0.88]
5.7.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	1995	Mean Difference (IV , Random , 95% CI)	0.09 [−0.02, 0.20]
5.8 I PTH	12	1080	Mean Difference (IV , Random , 95% CI)	55.57 [26.69, 84.45]
5.8.1 Sevelamer versus calcium acetate	5	418	Mean Difference (IV , Random , 95% CI)	65.93 [−16.80, 148.66]
5.8.2 Sevelamer versus calcium carbonate	5	353	Mean Difference (IV , Random , 95% CI)	46.95 [−2.39, 96.29]
5.8.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	2	309	Mean Difference (IV , Random , 95% CI)	55.00 [0.82, 109.18]
5.9 Ca X P	10	2560	Mean Difference (IV , Random , 95% CI)	0.61 [−1.02, 2.24]
5.9.1 Sevelamer versus calcium acetate	5	486	Mean Difference (IV , Random , 95% CI)	2.56 [−0.72, 5.84]
5.9.2 Sevelamer versus calcium carbonate	2	95	Mean Difference (IV , Random , 95% CI)	3.53 [−1.16, 8.23]
5.9.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	1979	Mean Difference (IV , Random , 95% CI)	−0.37 [−1.42, 0.69]
5.10 1, 25 (OH)2 D2	1	80	Mean Difference (IV , Random , 95% CI)	−0.76 [−8.35, 6.83]
5.10.1 Sevelamer versus calcium acetate	1	80	Mean Difference (IV , Random , 95% CI)	−0.76 [−8.35, 6.83]
5.11 Serum alkaline phosphatase	3	156	Mean Difference (IV , Random , 95% CI)	12.36 [−10.79, 35.51]
5.11.1 Sevelamer versus calcium acetate	2	120	Mean Difference (IV , Random , 95% CI)	17.83 [−7.10, 42.75]
5.11.2 Sevelamer versus calcium carbonate	1	36	Mean Difference (IV , Random , 95% CI)	−22.00 [−84.47, 40.47]
5.12 Serum bicarbonate	5	381	Mean Difference (IV , Random , 95% CI)	−1.43 [−2.07, −0.79]
5.12.1 Sevelamer versus calcium acetate	2	227	Mean Difference (IV , Random , 95% CI)	−1.63 [−2.47, −0.79]
5.12.2 Sevelamer versus calcium carbonate	3	154	Mean Difference (IV , Random , 95% CI)	−1.17 [−2.15, −0.18]
5.13 Total cholesterol	9	1674	Mean Difference (IV , Random , 95% CI)	−20.55 [−29.15, −11.96]
5.13.1 Sevelamer versus calcium acetate	2	120	Mean Difference (IV , Random , 95% CI)	−20.19 [−36.40, −3.99]
5.13.2 Sevelamer versus calcium carbonate	4	190	Mean Difference (IV , Random , 95% CI)	−14.06 [−25.14, −2.99]
5.13.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)	3	1364	Mean Difference (IV , Random , 95% CI)	−27.09 [−44.59, −9.60]

6 Lanthanum carbonate versus placebo

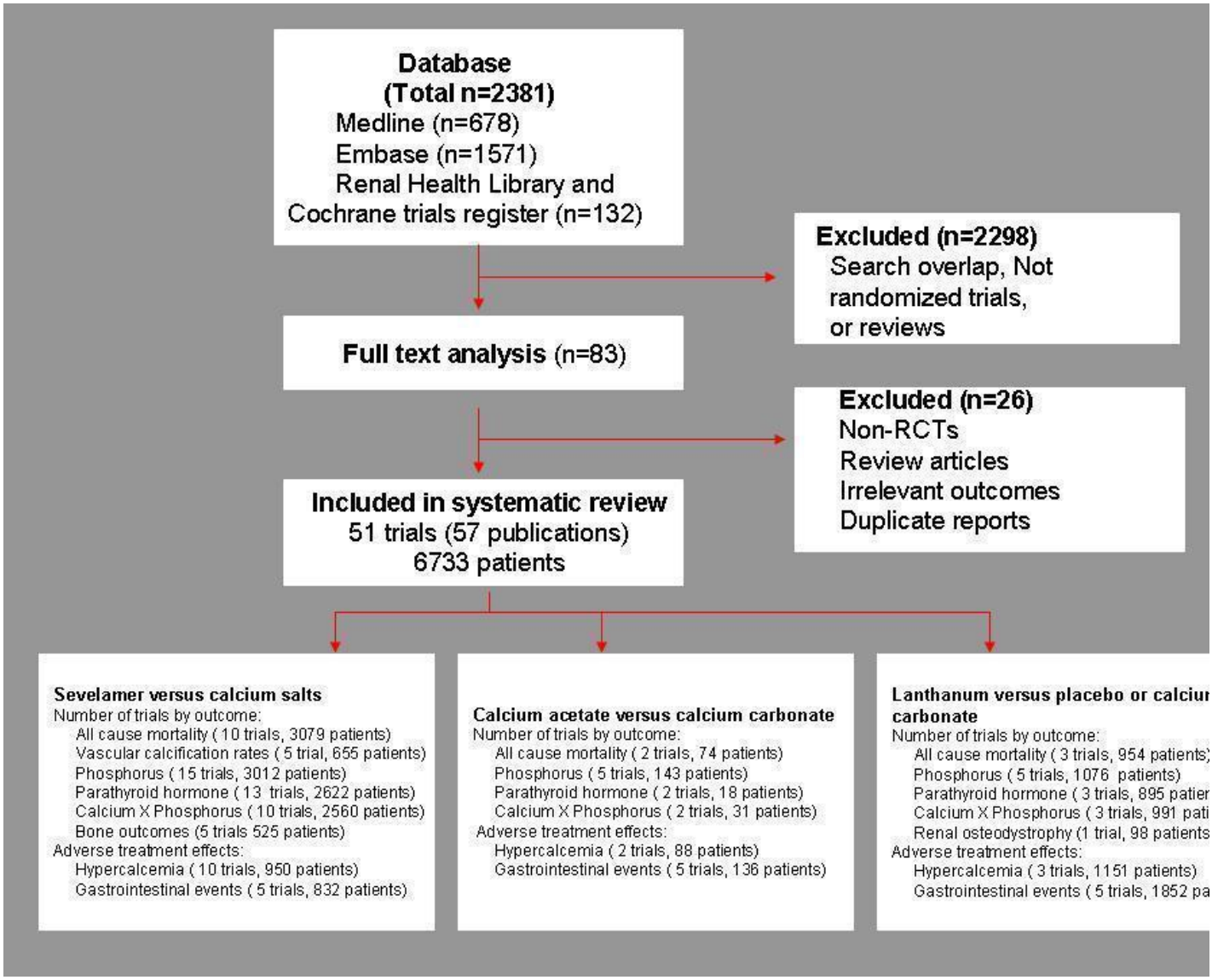
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 All cause mortality	2	154	Risk Ratio (M-H , Random , 95% CI)	Not estimable
6.2 Gastrointestinal toxicity	2	154	Risk Ratio (M-H , Random , 95% CI)	1.05 [0.45, 2.45]
6.2.1 Gastritis	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
6.2.2 Diarrhea	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
6.2.3 Gastroparesis	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
6.2.4 Combined	2	154	Risk Ratio (M-H , Random , 95% CI)	1.05 [0.45, 2.45]
6.3 Serum calcium	1	93	Mean Difference (IV , Random , 95% CI)	0.35 [0.04, 0.66]
6.3.1 Total calcium	1	93	Mean Difference (IV , Random , 95% CI)	0.35 [0.04, 0.66]
6.3.2 Ionised calcium	0	0	Mean Difference (IV , Random , 95% CI)	Not estimable
6.4 Phosporus	2	154	Mean Difference (IV , Random , 95% CI)	-2.01 [-2.52, -1.50]
6.5 Intact PTH	1	93	Mean Difference (IV , Random , 95% CI)	-83.00 [-154.63, -11.37]
6.6 Calcium X Phosporus	1	93	Mean Difference (IV , Random , 95% CI)	-14.20 [-21.03, -7.37]

7 Lanthanum carbonate versus Calcium salts

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Hypercalcemic events	2	351	Risk Ratio (M-H , Random , 95% CI)	0.17 [0.09, 0.31]
7.2 Gastrointestinal toxicity	1	98	Risk Ratio (M-H , Random , 95% CI)	1.04 [0.70, 1.55]
7.2.1 Gastritis	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
7.2.2 Diarrhea	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
7.2.3 Constipation	0	0	Risk Ratio (M-H , Random , 95% CI)	Not estimable
7.2.4 combined	1	98	Risk Ratio (M-H , Random , 95% CI)	1.04 [0.70, 1.55]
7.3 Serum calcium	2	122	Mean Difference (IV , Random , 95% CI)	-0.30 [-0.57, -0.03]
7.3.1 Total calcium	2	122	Mean Difference (IV , Random , 95% CI)	-0.30 [-0.57, -0.03]
7.3.2 Ionised calcium	0	0	Mean Difference (IV , Random , 95% CI)	Not estimable
7.4 Phosporus	2	122	Mean Difference (IV , Random , 95% CI)	0.22 [-0.32, 0.75]
7.5 Intact PTH	1	800	Mean Difference (IV , Random , 95% CI)	29.78 [-8.87, 68.43]
7.6 Calcium X Phosporus	1	98	Mean Difference (IV , Random , 95% CI)	-6.01 [-9.66, -2.36]
7.7 1, 25(OH)2 D2	1	24	Mean Difference (IV , Fixed , 95% CI)	-0.80 [-27.16, 25.56]
7.8 Serum alkaline phosphatase	2	824	Mean Difference (IV , Random , 95% CI)	29.01 [2.28, 55.74]

Figures

Figure 1



Caption

Literature search flow diagram

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Feedback

Appendices