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Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD) (Review)

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[Intervention Review]

Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD)

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ABSTRACT

Background

Phosphate binders are used to reduce positive phosphate balance and to lower serum phosphate levels for people with chronic kidney disease (CKD) with the aim to prevent progression of chronic kidney disease-mineral and bone disorder (CKD-MBD). This is an update of a review first published in 2011.

Objectives

The aim of this review was to assess the benefits and harms of phosphate binders for people with CKD with particular reference to relevant biochemical end-points, musculoskeletal and cardiovascular morbidity, hospitalisation, and death.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 12 July 2018 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We included randomised controlled trials (RCTs) or quasi-RCTs of adults with CKD of any GFR category comparing a phosphate binder to another phosphate binder, placebo or usual care to lower serum phosphate. Outcomes included all-cause and cardiovascular death, myocardial infarction, stroke, adverse events, vascular calcification and bone fracture, and surrogates for such outcomes including serum phosphate, parathyroid hormone (PTH), and FGF23.

Data collection and analysis

Two authors independently selected studies for inclusion and extracted study data. We applied the Cochrane 'Risk of Bias' tool and used the GRADE process to assess evidence certainty. We estimated treatment effects using random-effects meta-analysis. Results were expressed

as risk ratios (RR) for dichotomous outcomes together with 95% confidence intervals (CI) or mean differences (MD) or standardised MD (SMD) for continuous outcomes.

Main results

We included 104 studies involving 13,744 adults. Sixty-nine new studies were added to this 2018 update.

Most placebo or usual care controlled studies were among participants with CKD G2 to G5 not requiring dialysis (15/25 studies involving 1467 participants) while most head to head studies involved participants with CKD G5D treated with dialysis (74/81 studies involving 10,364 participants). Overall, seven studies compared sevelamer with placebo or usual care (667 participants), seven compared lanthanum to placebo or usual care (515 participants), three compared iron to placebo or usual care (422 participants), and four compared calcium to placebo or usual care (278 participants). Thirty studies compared sevelamer to calcium (5424 participants), and fourteen studies compared lanthanum to calcium (1690 participants). No study compared iron-based binders to calcium. The remaining studies evaluated comparisons between sevelamer (hydrochloride or carbonate), sevelamer plus calcium, lanthanum, iron (ferric citrate, sucroferric oxyhydroxide, stabilised polynuclear iron(III)-oxyhydroxide), calcium (acetate, ketoglutarate, carbonate), bixalomer, colestilan, magnesium (carbonate), magnesium plus calcium, aluminium hydroxide, sucralfate, the inhibitor of phosphate absorption nicotinamide, placebo, or usual care without binder. In 82 studies, treatment was evaluated among adults with CKD G5D treated with haemodialysis or peritoneal dialysis, while in 22 studies, treatment was evaluated among participants with CKD G2 to G5. The duration of study follow-up ranged from 8 weeks to 36 months (median 3.7 months). The sample size ranged from 8 to 2103 participants (median 69). The mean age ranged between 42.6 and 68.9 years.

Random sequence generation and allocation concealment were low risk in 25 and 15 studies, respectively. Twenty-seven studies reported low risk methods for blinding of participants, investigators, and outcome assessors. Thirty-one studies were at low risk of attrition bias and 69 studies were at low risk of selective reporting bias.

In CKD G2 to G5, compared with placebo or usual care, sevelamer, lanthanum, iron and calcium-based phosphate binders had uncertain or inestimable effects on death (all causes), cardiovascular death, myocardial infarction, stroke, fracture, or coronary artery calcification. Sevelamer may lead to constipation (RR 6.92, CI 2.24 to 21.4; *low certainty*) and lanthanum (RR 2.98, CI 1.21 to 7.30, *moderate certainty*) and iron-based binders (RR 2.66, CI 1.15 to 6.12, *moderate certainty*) probably increased constipation compared with placebo or usual care. Lanthanum may result in vomiting (RR 3.72, CI 1.36 to 10.18, *low certainty*). Iron-based binders probably result in diarrhoea (RR 2.81, CI 1.18 to 6.68, *high certainty*), while the risks of other adverse events for all binders were uncertain.

In CKD G5D sevelamer may lead to lower death (all causes) (RR 0.53, CI 0.30 to 0.91, *low certainty*) and induce less hypercalcaemia (RR 0.30, CI 0.20 to 0.43, *low certainty*) when compared with calcium-based binders, and has uncertain or inestimable effects on cardiovascular death, myocardial infarction, stroke, fracture, or coronary artery calcification. The finding of lower death with sevelamer compared with calcium was present when the analysis was restricted to studies at low risk of bias (RR 0.50, CI 0.32 to 0.77). In absolute terms, sevelamer may lower risk of death (all causes) from 210 per 1000 to 105 per 1000 over a follow-up of up to 36 months, compared to calcium-based binders. Compared with calcium-based binders, lanthanum had uncertain effects with respect to all-cause or cardiovascular death, myocardial infarction, stroke, fracture, or coronary artery calcification and probably had reduced risks of treatment-related hypercalcaemia (RR 0.16, CI 0.06 to 0.43, *low certainty*). There were no head-to-head studies of iron-based binders compared with calcium. The paucity of placebo-controlled studies in CKD G5D has led to uncertainty about the effects of phosphate binders on patient-important outcomes compared with placebo.

It is uncertain whether the effects of binders on clinically-relevant outcomes were different for patients who were and were not treated with dialysis in subgroup analyses.

Authors' conclusions

In studies of adults with CKD G5D treated with dialysis, sevelamer may lower death (all causes) compared to calcium-based binders and incur less treatment-related hypercalcaemia, while we found no clinically important benefits of any phosphate binder on cardiovascular death, myocardial infarction, stroke, fracture or coronary artery calcification. The effects of binders on patient-important outcomes compared to placebo are uncertain. In patients with CKD G2 to G5, the effects of sevelamer, lanthanum, and iron-based phosphate binders on cardiovascular, vascular calcification, and bone outcomes compared to placebo or usual care, are also uncertain and they may incur constipation, while iron-based binders may lead to diarrhoea.

PLAIN LANGUAGE SUMMARY

Phosphate binders to prevent complications of chronic kidney disease

What is the issue?

People with chronic kidney disease (CKD) have a reduction in their capacity to remove phosphate from the body via the kidneys, so that phosphate levels in the blood and in body tissues increase as kidney function decreases. This may lead to the development of deposits comprised of calcium plus phosphate in blood vessels and other tissues, together with damage to the skeleton, worsening of kidney failure and an increased risk of cardiovascular disease, bone pain, fractures, and death.

Phosphate binders are often prescribed with meals to people with kidney disease, with the intention of reducing the absorption of dietary phosphate from the gastrointestinal tract.

What did we do?

This review asked whether phosphate binders influence damage to blood vessels and soft tissues, skeletal changes, kidney function, and risks of cardiovascular disease, bone pain, fractures, and death that accompany worsening kidney failure. We included all clinical studies in which people with CKD were given different phosphate binders (by random chance) for at least eight weeks. We also checked the quality of the information in the studies to learn how certain we could be about the results.

What did we find?

We identified 104 studies of phosphate binders that included 13,744 people. Some studies gave treatment for only eight weeks while some studies treated participants for three years. People in the studies had a range of kidney function, and many were on dialysis. Overall we could not be certain of a number of important outcomes because many of the clinical studies we included had important flaws in their design.

Sevelamer treatment may have decreased death for those patients given this medication when taken instead of calcium. The phosphate binders probably caused constipation, but we could not be very certain about the risks of other side-effects. We were not very certain whether phosphate binders reduced heart complications, stroke, bone pain, or calcification of blood vessels.

Conclusions

Overall, we are not very sure whether specific phosphate binders are beneficial to patients with CKD. There is a possibility that sevelamer may prevent death compared to calcium-based binders, but we don't know whether this may be caused by an increased risk of calcium-based binders, a lower risk with sevelamer treatment, or the possibility that both may be true. Patients need to know that it is not certain whether phosphate binders help to prevent complications of kidney disease, but sevelamer may be preferred to calcium binders.

We did not find differences in the effects of treatment for patients on dialysis and those not on dialysis, although most studies evaluating treatment with calcium-based binders were among dialysis patients and those comparing binders with placebo were among people not treated with dialysis.

Summary of findings for the main comparison. Summary of findings: Sevelamer versus placebo/usual care

Sevelamer versus placebo or usual care for preventing and treating bone disease in people chronic kidney disease (CKD)

Patient or population: people with CKD

Setting: most studies involved people with CKD not requiring dialysis

Intervention: sevelamer versus placebo or usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Sevelamer				
Death (all causes) Follow-up: 3 to 24 months (median 10 months)	Low risk population		**RR 2.16** (0.20 to 22.8)	248 (3)	⊕⊖⊖⊖ **very low[1,5]**	A single study reported 1 or more events. The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
	8 per 1000	**17 per 1000** (2 to 183)				
Cardiovascular death	No data observations	Not estimable	No studies	No studies	Not estimable	--
Hypercalcaemia Follow-up: 9 months	18 per 1000	33 per 1000	RR 1.90 (0.12 to 29.32)	42 (1)	⊕⊖⊖⊖ **very low[6]**	A single study reported 1 event in each group
Nausea Follow-up: 2 to 9 months (median 3 months)	**30 per 1000**	**38 per 1000** (2 to 673)	**RR 1.27** (0.07 to 22.42)	370 (3)	⊕⊖⊖⊖ **very low[1,5]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Vomiting Follow-up: 2.8 to 9 months	**10 per 1000**	**22 per 1000** (3 to 173)	**RR 2.09** (0.26 to 16.57)	165 (2)	⊕⊖⊖⊖ **very low[1,5]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Constipation	**10 per 1000**	**71 per 1000**	**RR 6.92**	430 (4)	⊕⊕⊖⊖	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for pa-

Follow-up: 2 to 9 months (median 3 months)		(23 to 218)	(2.24 to 21.38)		**low[1,3]**	tients treated with dialysis (GFR 5D) is very low
Serum phosphate level Follow-up: 2 to 10 months (median 3 months)	The mean serum phosphate level in the placebo group was **4.48 mg/dL**	The mean serum phosphate level in the sevelamer group was **0.28 mg/dL lower** (0.39 higher to 0.94 lower)	--	483 (5)	⊕⊖⊖⊖ **very low[1,2,3]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Coronary artery calcification score Follow-up: 24 months (both studies)	The mean coronary artery calcium score in the placebo group was **945**	The mean coronary artery calcium score in the sevelamer group was **70 lower** (362 lower to 222 higher)	--	115 (2)	⊕⊖⊖⊖ **very low[1,5]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

The assumed risk is the event rate per annum in the control arm of included studies
[1] Evidence certainty was downgraded by one level due to study limitations. Most studies had unclear risks for random sequence generation and allocation concealment and were not blinded (participants or investigators)
[2] Evidence certainty was downgraded by one level due to moderate or substantial between-study heterogeneity
[3] Evidence certainty was downgraded by one level due to imprecision
[4] Evidence certainty was downgraded by one level due to publication bias
[5] Evidence certainty was downgraded by two levels due to severe imprecision
[6] Data came from only one study

Summary of findings 2. Summary of findings: Lanthanum versus placebo/usual care

Lanthanum versus placebo or usual care for preventing and treating bone disease in people chronic kidney disease (CKD)

Patient or population: people with CKD

Setting: most studies involved people with CKD not requiring dialysis

Intervention: lanthanum versus placebo or usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or standard care	Lanthanum				
Death (all causes) Follow-up: 1.8 to 12 months (median 3 months)	Low risk population 0 per 1000	0 per 1000	**RR 1.63** (0.07 to 37.12)	214 (3)	⊕⊖⊖⊖ **very low[1,5,6]**	A single death was reported among three studies. The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Cardiovascular death	No data observations	Not estimable	No studies	No studies	Not estimable	--
Nausea Follow-up: 1.8 to 12 months (median 2 months)	**23 per 1000**	**87 per 1000** (32 to 237)	**RR 3.72** (1.36 to 10.18)	383 (4)	⊕⊕⊖⊖ **low[1,3]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Vomiting Follow-up: 1.8 to 9 months (median 3 months)	**32 per 1000**	**89 per 1000** (13 to 601)	**RR 2.76** (0.41 to 18.63)	261 (3)	⊕⊖⊖⊖ **very low[1,5]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Constipation Follow-up: 1.8 to 9 months (median 3 months)	**35 per 1000**	**104 per 1000** (42 to 255)	**RR 2.98** (1.21 to 7.30)	299 (4)	⊕⊕⊕⊖ **moderate[1]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Serum phosphate level Follow-up: 1.8 to 12 months (median 3 months)	The mean serum phosphate level in the placebo group was **4.7 mg/dL**	The mean serum phosphate level in the lanthanum group was **0.48 mg/dL lower** (0.05 to 0.90 lower)	--	171 (4)	⊕⊕⊖⊖ **low[1,2]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low

Coronary artery calcification score Follow-up: 12 months	The mean coronary artery calcification score in the placebo group was **23 mm^3**	The mean coronary artery calcification score in the lanthanum group was**3 mm^3 higher** (9.86 lower to 15.86 higher)	--	38 (1)	⊕⊖⊖⊖ **very low**[6]	A single study reported this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

The assumed risk is the event rate per annum in the control arm of included studies
[1] Evidence certainty was downgraded by one level due to study limitations. Most studies had unclear risks for random sequence generation and allocation concealment and were not blinded (participants or investigators)
[2] Evidence certainty was downgraded by one level due to moderate or substantial between-study heterogeneity
[3] Evidence certainty was downgraded by one level due to imprecision
[4] Evidence certainty was downgraded by one level due to publication bias
[5] Evidence certainty was downgraded by two levels due to severe imprecision
[6] Data came from only one study

Summary of findings 3. Summary of findings: Iron versus placebo/usual care

Iron versus placebo or usual care for preventing and treating bone disease in people chronic kidney disease (CKD)

Patient or population: people with CKD

Setting: dialysis (1 study) and CKD (2 studies)

Intervention: iron versus placebo or usual care

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo or standard care	**Iron**				

Death (all causes) Follow-up: 2.75 to 3 months	**19 per 1000**	**10 per 1000** (1 to 89)	**RR 0.52** (0.06 to 4.65)	239 (2)	⊕⊕⊖⊖ **low[1,3]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Cardiovascular death	No data observations	Not estimable	No studies	No studies	Not estimable	--
Hypercalcaemia	No data observations	Not estimable	No studies	No studies	Not estimable	--
Nausea	**68 per 1000**	**67 per 1000** (20 to 221)	**RR 0.99** (0.30 to 3.27)	149 (1)	⊕⊖⊖⊖ **very low[6]**	A single study reported this outcome
Vomiting	No data observations	Not estimable	Not estimable	No studies	Not estimable	--
Constipation Follow-up: 1.8 to 3 months (median 2.75 months)	**43 per 1000**	**114 per 1000** (49 to 262)	**RR 2.66** (1.15 to 6.12)	422 (3)	⊕⊕⊕⊖ **moderate[1]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Serum phosphate level Follow-up: 1.8 to 3 months (median 2.75 months)	The mean serum phosphate level in the placebo group was **5.8 mg/dL**	The mean serum phosphate in the iron group was **1.33 mg/dL lower** (0.41 to 2.25 lower)	--	422 (3)	⊕⊕⊖⊖ **low[1,2]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Coronary artery calcification score	No data observations	Not estimable	Not estimable	No studies	Not estimable	--

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

The assumed risk is the event rate per annum in the control arm of included studies

[1] Evidence certainty was downgraded by one level due to study limitations. Most studies had unclear risks for random sequence generation and allocation concealment and were not blinded (participants or investigators)
[2] Evidence certainty was downgraded by one level due to moderate or substantial between-study heterogeneity
[3] Evidence certainty was downgraded by one level due to imprecision
[4] Evidence certainty was downgraded by one level due to publication bias
[5] Evidence certainty was downgraded by two levels due to severe imprecision
[6] Data came from only one study

Summary of findings 4. Summary of findings: Calcium versus placebo/usual care

Calcium versus placebo or usual care for preventing and treating bone disease in people chronic kidney disease (CKD)

Patient or population: people with CKD

Setting: Most studies involved people with CKD not requiring dialysis

Intervention: calcium versus placebo or usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Calcium				
Death (all causes)	**47 per 1000**	**22 per 1000** (2 to 203)	**RR 0.46** (0.05 to 4.32)	110 (1)	⊕⊝⊝⊝ **very low[6]**	A single study reported this outcome
Cardiovascular death	No data observations	Not estimable	Not estimable	No studies	Not estimable	--
Hypercalcaemia Follow-up: 3 to 9 months	**8 per 1000**	**56 per 1000** (13 to 248)	**RR 7.28** (1.64 to 32.2)	215 (3)	⊕⊕⊝⊝ **low[1,3]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Nausea Follow-up: 3 to 9 months	**66 per 1000**	**38 per 1000** (10 to 144)	**RR 0.58** (0.15 to 2.18)	197 (2)	⊕⊕⊝⊝ **low[1,3]**	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Vomiting	No data observations	Not estimable	Not estimable	No studies	Not estimable	--

Constipation Follow-up: 3 to 9 months	**66 per 1000**	**161 per 1000** Not estimable	**RR 2.44** (0.32 to 18.4)	197 (2)	⊕⊖⊖⊖ **very low**[1,5]	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Serum phosphate level Follow-up: 5.5 to 24 months (median 9 months)	The mean serum phosphate level in the placebo group was **5.0 mg/dL**	The mean serum phosphate level in the calcium group was **0.18 mg/dL lower** (0.95 higher to 1.30 lower)	--	151 (3)	⊕⊖⊖⊖ **very low**[1,2,3]	The studies were predominantly in CKD G2 to G5. Therefore, the evidence certainty for patients treated with dialysis (GFR 5D) is very low
Coronary artery calcification score	The mean coronary artery calcification score in the placebo group was **473**	The mean coronary artery calcification score in the calcium group was **74 lower** (443 lower to 295 higher)	--	60 (1)	⊕⊖⊖⊖ **very low**[6]	A single study reported this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

The assumed risk is the event rate per annum in the control arm of included studies
[1] Evidence certainty was downgraded by one level due to study limitations. Most studies had unclear risks for random sequence generation and allocation concealment and were not blinded (participants or investigators)
[2] Evidence certainty was downgraded by one level due to moderate or substantial between-study heterogeneity
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[5] Evidence certainty was downgraded by two levels due to severe imprecision
[6] Data came from only one study

Summary of findings 5. Summary of findings: Sevelamer versus calcium

Sevelamer versus calcium for preventing and treating bone disease people with in chronic kidney disease (CKD)

Patient or population: people with CKD

Setting: most studies involved people treated with dialysis

Intervention: sevelamer versus calcium

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Calcium	Sevelamer				
Death (all causes) Follow-up: 1.8 to 36 months (median 5.5 months)	Low risk population (CKD G2 to G5)		**RR 0.53** (0.30 to 0.91)	3688 (16)	⊕⊕⊖⊖ **low**[1,2]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
	124 per 1000	**79 per 1000** (27 to 227)				
	High risk population (CKD G5D)					
	210 per 1000	**105 per 1000** (55 to 199)				
Cardiovascular death Follow-up: 3 to 36 months (median 12 months)	Low risk population (CKD G2 to G5)		**RR 0.45** (0.11 to 1.77)	2829 (6)	⊕⊖⊖⊖ **very low**[1,2,3]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
	92 per 1000	**34 per 1000** (1 to 1000)				
	High risk population (CKD G5D)					
	132 per 1000	**112 per 1000** (11 to 177)				
Hypercalcaemia Follow-up: 1.8 to 36 months (median 5.5 months)	**139 per 1000**	**42 per 1000** (28 to 60)	**RR 0.30** (0.20 to 0.43)	4084 (19)	⊕⊖⊖⊖ **very low**[1,2,4]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
Nausea Follow-up: 2 to 12 months (median 9 months)	**125 per 1000**	**123 per 1000** (70 to 214)	**RR 0.98** (0.56 to 1.71)	365 (4)	⊕⊕⊖⊖ **low**[1,3]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low

Vomiting Follow-up: 9 to 12 months	**158 per 1000**	**150 per 1000** (85 to 267)	**RR 0.95** (0.54 to 1.69)	263 (2)	⊕⊕⊖⊖ **low**[1,3]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
Constipation Follow-up: 2 to 20 months (median 12 months)	**13 per 1000**	**17 per 1000** (9 to 33)	**RR 1.35** (0.71 to 2.57)	2652 (6)	⊕⊕⊖⊖ **low**[1,3]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
Serum phosphate level Follow-up: 1.8 to 36 months (median 5.5 months)	The mean serum phosphate level in the calcium group was **5.39 mg/dL**	The mean serum phosphate level in the sevelamer group was **0.06 mg/dL higher** (0.11 lower to 0.23 higher)	--	4360 (23)	⊕⊖⊖⊖ **very low**[1,2,3]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
Coronary artery calcium score Follow-up: 12-24 months (median 12 months)	The mean coronary artery calcium score in the calcium group was **923**	The mean coronary artery calcium score in the sevelamer group was **25 lower** (76 lower to 26 higher)	--	517 (4)	⊕⊕⊖⊖ **low**[1,3]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

The assumed risk is the median incidence of the event in the control arm of included studies. Where there was a wide range of reported incidence (for example, Death (all causes) ranged from 10 per 1000 to 340 per 1000), two levels of risk (high and low) were generated for calculation of absolute risks

[1] Evidence certainty was downgraded by one level due to study limitations. Most studies had unclear risks for random sequence generation and allocation concealment and were not blinded (participants or investigators)

[2] Evidence certainty was downgraded by one level due to moderate or substantial between-study heterogeneity

[3] Evidence certainty was downgraded by one level due to imprecision

[4] Evidence certainty was downgraded by one level due to publication bias

Summary of findings 6. Summary of findings - Lanthanum versus calcium

Lanthanum versus calcium for preventing and treating bone disease people with in chronic kidney disease (CKD)

Patient or population: patients with CKD

Setting: most studies involved people treated with dialysis

Intervention: lanthanum versus calcium

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Calcium	Lanthanum				
Death (all causes) Follow-up: 1.8 to 18 months (median 6 months)	High risk population (CKD G5D)		**RR 0.76** (0.18 to 3.11)	505 (6)	⊕⊕⊖⊖ **low**[1,3]	The studies were in CKD G5D
	15 per 1000	**12 per 1000** (3 to 48)				
Cardiovascular death	No data observations	Not estimable	No studies	No studies	Not estimable	--
Hypercalcaemia Follow-up: 1.8 to 12 months (median 6 months)	**240 per 1000**	**38 per 1000** (14 to 103)	**RR 0.16** (0.06 to 0.43)	1347 (8)	⊕⊕⊖⊖ **low**[1,2]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
Nausea Follow-up: 1.8 to 12 months (median 6 months)	**88 per 1000**	**145 per 1000** (84 to 254)	**RR 1.65** (0.95 to 2.89)	1191 (5)	⊕⊕⊖⊖ **low**[1,3]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
Vomiting Follow-up: 1.8 to 6 months	**78 per 1000**	**301 per 1000** (37 to 1000)	**RR 3.88** (0.48 to 31.7)	1058 (2)	⊕⊖⊖⊖ **very low**[1,3,5]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
Constipation	**67 per 1000**	**53 per 1000** (33 to 84)	**RR 0.79** (0.50 to 1.26)	1213 (5)	⊕⊕⊖⊖ **low**[1,3]	The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low

Follow-up: 1.8 to 18 months (median 6 months)						
Serum phosphate level Follow-up: 3 to 12 months (median 6 months)	The mean serum phosphate level in the calcium group was **5.39 mg/dL**	The mean serum phosphate level in the lanthanum group was **0.01 mg/dL lower** (0.42 higher to 0.43 lower)	--	400 (9)	⊕⊖⊖⊖ **very low[1,2,3]**	It was not possible to assess for publication bias due to substantial between-study heterogeneity. The studies were predominantly in CKD G5D Therefore, the evidence certainty for patients with CKD G2 to G5 is very low
Coronary artery calcium score Follow-up: 6 months	The mean coronary artery calcium score in the calcium group was **1640**	The mean coronary artery calcium score in the lanthanum group was **57** lower (1308 lower to 5 higher)	--	42 (1)	⊕⊖⊖⊖ **very low[6]**	A single study reported 1 or more events

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

The assumed risk is the event rate per annum in the control arm of the control arm of included studies. Where there was a wide range of reported incidence (for example, Death (all causes) ranged from 10 per 1000 to 340 per 1000), two levels of risk (high and low) were generated for calculation of absolute risks.
[1] Evidence certainty was downgraded by one level due to study limitations. Most studies had unclear risks for random sequence generation and allocation concealment and were not blinded (participants or investigators)
[2] Evidence certainty was downgraded by one level due to moderate or substantial between-study heterogeneity
[3] Evidence certainty was downgraded by one level due to imprecision
[4] Evidence certainty was downgraded by one level due to publication bias
[5] Evidence certainty was downgraded by two levels due to severe imprecision
[6] Data came from only one study

BACKGROUND

Description of the condition

People with chronic kidney disease (CKD) develop impaired excretion of their dietary phosphate load (Hruska 2008) leading to positive phosphate balance. Hyperphosphataemia leads to a rise in fibroblast growth factor-23 (FGF23) levels that provide a compensatory increase of renal phosphate excretion and inhibit 1,25 dihydroxy-vitamin D production and increase its catabolism (Gutiérrez 2005). However, in the presence of further reductions in kidney function, these initial homeostatic responses fail and further increases in serum phosphate and reductions in serum 1,25-dihydroxy-vitamin D contribute to an increase in parathyroid hormone (PTH), the actions of which will initially restore calcium and phosphate values toward their normal ranges (Cozzolino 2005; Hruska 2008; Silver 2005). With progression of CKD, these homeostatic responses fail and result in increased risks for hypocalcaemia and hyperphosphataemia that increase PTH release via the calcium-sensing receptor on parathyroid cells. Prolonged low serum calcium levels lead to stabilisation of mRNA encoding PTH. Reduced 1,25 dihydroxy-vitamin D levels allow increased transcription of the PTH gene (Kumar 2011). Abnormal serum levels of PTH are observed in 10% of people with a glomerular filtration rate (GFR) above 80 mL/min and in 80% of people with a GFR below 20 mL/min (Levin 2007). Serum levels of calcium and phosphate tend to be within the normal range with a GFR above 40 mL/min and tend to remain stable until the GFR is below 20 mL/min (Levin 2007).

Together, these changes may contribute to the development of a cluster of inter-related conditions described as chronic kidney disease-mineral and bone disorder (CKD-MBD). This systemic disorder manifests in a number of ways. In bone, there are alterations of bone turnover, mineralization, and volume that may be accompanied by marrow fibrosis. These changes can cause altered bone growth and strength, leading to bone pain. In the cardiovascular system, excess vascular and other soft-tissue calcification leads to occlusive arterial disease and cardiac valvular abnormalities.

Commonly measured laboratory abnormalities that accompany the development of CKD-MBD include values of serum calcium, phosphate, vitamin D metabolites, PTH, markers of bone turnover, and FGF23. Epidemiological data have increasingly demonstrated an association between abnormal values of serum phosphate, PTH, calcium, and FGF23 caused by CKD and increased cardiovascular events and death, hospitalisation, reduced quality of life, and increased costs of care (Block 1998; Block 2004; Gutiérrez 2008; Tentori 2008).

Description of the intervention

Over the past few decades, cardiovascular disease has accounted for over half of the deaths in people receiving dialysis (USRDS 2009). The development of CKD-MBD causing vascular calcification in the media of arterial vessels and soft tissues is recognised as a major contributing factor (Guerin 2001; Stevens 2004) to this increased death.

Several agents such as phosphate binders, vitamin D compounds, and calcimimetics are widely used to retard the development and progression of CKD-MBD complications by acting to reduce dietary phosphate absorption and uptake, treat hyperphosphataemia and hypocalcaemia, increase low 1,25 dihydroxy-vitamin D levels, and attenuate PTH secretion.

How the intervention might work

Several phosphate binders, including aluminium- and calcium-based agents, have been widely used since 1970. Non-calcium and non-aluminium-based agents, such as sevelamer hydrochloride and lanthanum carbonate, subsequently became available, and more recently, iron-based compounds have been developed. The use of sevelamer, lanthanum, and iron-based compounds is increasing in nephrology practice, although they incur greater cost than the older phosphate binders (St Peter 2008; St Peter 2009; USRDS 2009).

The avoidance of calcium-based agents in CKD theoretically avoids the risks associated with positive calcium balance and the consequent acceleration of vascular calcification and cardiovascular events. For control of hyperphosphataemia, the 2003 National Kidney Foundation Kidney Disease Outcomes Quality Initiatives (NKF-KDOQI) recommended calcium-based binders in CKD stages 3 and 4 (glomerular filtration rate (GFR) 30 to 59 mL/min/1.73 m^2 and 15 to 29 mL/min/1.73 m^2, respectively), and both calcium-based and calcium- and aluminium-free binders in CKD stages 5 and 5D (GFR < 15 mL/min/1.73 m^2 and dialysis) (K/DOQI 2003). However, more recently, the Kidney Disease: Improving Global Outcomes (KDIGO) 2017 update suggests that for patients with CKD G3a-G5D, elevated phosphate levels should be lowered toward the normal range rather than normalised, while avoiding hypercalcaemia for adult patients (KDIGO 2017). The 2017 KDIGO update suggested restricting the dose of calcium-based phosphate binders and tolerance of mild and asymptomatic hypocalcaemia, in order to avoid exogenous calcium loading. These guidelines offered a more conservative approach to the use of phosphate binders in patients with CKD G3a to G4, due to insufficient evidence that targeting normal range serum phosphate values improved clinical outcomes, and based upon the safety and side effects of the therapeutic interventions.

Why it is important to do this review

The utility of calcium-free phosphate binders in reducing clinical events in CKD, balanced against their cost and potential harms has been controversial (Salusky 2006; St Peter 2009). The KDIGO guidelines of 2009 recommended restricting the use of calcium-based binders in people with persistent or recurrent hypercalcaemia or arterial calcification, or both (KDIGO 2009) and that phosphate binders might be used in patients with CKD G3-5 and on dialysis (CKD G5D) to achieve improvements in serum phosphate levels toward the normal range. However, citing new trial evidence, the KDIGO 2017 guidelines suggest that phosphate binders have an insufficient evidence base for efficacy and safety among patients with CKD G3a to G5 not on dialysis and that phosphate binders be limited to patients with "progressive or persistent" hyperphosphataemia (KDIGO 2017). The 2017 KDIGO guidelines have suggested that not all phosphate binders are interchangeable, and that excess exposure to calcium, as calcium-based binders, may be harmful across all GFR categories, however there has remained some uncertainty about the evidence that calcium-free agents are superior to calcium-based agents for prevention of adverse clinical outcomes.

In addition, non-calcium binders may increase healthcare costs. Subsidisation of non-calcium based phosphate binders in Australia led to increased medication costs from AUD 12.85 per patient per week to AUD 59.85 per patient per week (an additional AUD 2444 per patient per years) (Gray 2011). Medicare costs for phosphate binders among dialysis patients in the US were in excess of USD 1.5 billion in 2015 (St. Peter 2018).

Current guidelines suggest the restriction of calcium-based phosphate binders for patients treated with dialysis, and a more tolerant approach to higher phosphate levels among patients with CKD G3a to 5 not requiring dialysis, likely to lead to less phosphate binder use for these patients. Because of these factors and the emergence of new studies since the 2011 Cochrane review, we have updated the evidence to address the use of phosphate binder for patients with CKD.

OBJECTIVES

The aim of this review was to assess the benefits and harms of phosphate binders for people with CKD with particular reference to relevant biochemical end-points, musculoskeletal and cardiovascular morbidity, hospitalisation, and death.

In particular we aimed to evaluate the effects of aluminium-, calcium-, sevelamer-, lanthanum-, iron-, bixalomer-, colestilan-, and magnesium-based phosphate binders, and nicotinamide, on:

1. Relevant biochemical end-points: serum PTH, calcium, phosphate and FGF23
2. Symptoms: pruritis and bone pain
3. Bone structure and function: bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DEXA) or quantitative computerised tomography (QCT), bone turnover and mineralisation based on biochemical bone turnover markers, turnover and volume based on histomorphometry, and fracture events
4. Clinical outcomes: cardiovascular events, number of hospital admissions, and cardiovascular and death (all causes)
5. Vascular calcification
6. Adverse events

We also aimed to identify whether treatment efficacy differed based on GFR categories (CKD G5D and CKD G2 to G5) and whether individual phosphate binders within each class had different effects.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

Inclusion criteria

Adults with CKD (any category) including G2 to G5 (GFR 15 to 90 mL/min) and G5D (dialysis) (KDIGO 2012).

Exclusion criteria

Studies of participants with a kidney transplant (CKD 5T) were excluded as these studies have been reviewed in a separate Cochrane review (Palmer 2007) that is currently being updated. Studies evaluating treatment in children were excluded as these have been evaluated in a separate Cochrane review (Hahn 2015).

Types of interventions

We included studies with follow-up of at least eight weeks evaluating phosphate binders (including: sevelamer-, lanthanum-, calcium-, iron-, bixalomer-, colestilan- (colestimide), magnesium-, and aluminium- based binders) and nicotinamide (nicotinic acid), compared with another phosphate binder or placebo or usual care without phosphate binder.

Types of outcome measures

Primary outcomes

Death (all causes)

Secondary outcomes

1. Cardiovascular death
2. Hospitalisation
3. Nonfatal myocardial infarction
4. Nonfatal stroke
5. Fracture (incidence of fracture at any site; vertebral compression fractures; fracture of femur, hip, and any long bones identified by radiographic studies)
6. Pruritus
7. Calciphylaxis
8. Adverse effects: including gastrointestinal (nausea, diarrhoea, constipation, abdominal bloating, abdominal pain), electrolyte imbalance (hyperkalaemia)
9. Hypercalcaemia (defined as serum calcium level > 10.2 mg/dL (2.6 mmol/L) or as defined by the study investigators)
10. Serum phosphate (mg/dL), serum calcium (mg/dL), calcium-by-phosphate product (mg^2/dL^2), PTH (intact (iPTH), or PTH (1-84)); alkaline phosphatase (IU/L), serum bicarbonate (mEq/L), fibroblast growth factor 23 (FGF23), fetuin-A, and Klotho (any form)
11. Vascular calcification, soft tissue or valvular calcification
12. Bone mineral density assessed by dual energy X-ray absorptiometry (DXA) or quantitative computed tomography (QCT) (change in bone mineral density using Z-scores, T-scores, or g/cm^2 (DXA) or g/cm^3 (QCT) at the lumbar spine, femoral neck, or radius)
13. Estimated GFR (eGFR); end-stage kidney disease (ESKD) (defined as eGFR < 15 mL/min/1.73 m^2, or commencing dialysis, or as defined by investigators).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 12 July 2018 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the *Specialised Register* section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

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

Data extraction and management

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

Assessment of risk of bias in included studies

The following items were assessed independently by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

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

Dealing with missing data

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

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

We had planned to examine for publication bias using evidence of asymmetry in a funnel plot in the absence of between-study statistical heterogeneity (Higgins 201).

Data synthesis

Risk estimates from individual studies were pooled using the inverse variance random-effects model.

Subgroup analysis and investigation of heterogeneity

Sources of heterogeneity that were explored in the subgroup analyses for the primary outcome (death (all causes)) were: age (older than 60 years and 60 years or younger), CKD stage (stages 1-4 and stage 5D), baseline serum phosphate (above or below 4.5 mg/dL (1.5 mmol/L)), study duration (above and below 12 months), and methodological quality (low risk of bias for allocation concealment and high or unclear risk of bias). We did not complete planned subgroup analyses for older versus newer agents as most binder types are well-established. We have also not included subgroup analysis based on number of participants. We have now included subgroup analyses based on age and CKD category, which were not pre-defined in the previous protocol for this review.

'Summary of findings' tables

The main results are presented in the 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We present the following outcomes in the 'Summary of findings' tables.

- Death (all causes)
- Cardiovascular death
- Hypercalcaemia
- Nausea
- Vomiting
- Constipation
- Serum phosphate
- Vascular calcification

RESULTS

Description of studies

Results of the search

Search results are shown in Figure 1. For this 2018 review update, we identified 404 new reports. Sixty-nine new studies in 138 reports were eligible (Characteristics of included studies). Ninety-two additional reports of 20 studies included in the 2011 review were identified in the updated search and added to the review. Our search identified three studies that have not yet been completed (COMBINE 2014; IMPROVE-CKD 2012; LANDMARK 2017) according to details held within the www.ClinicalTrials.gov registry. Three studies were identified as completed without published results and have been categorised as "Awaiting Classification" (NCT00317694; NCT00560300; NCT01968759). These three studies are reported as completed within www.ClinicalTrials.gov, but no results have been published or were available directly from the investigators. Twenty-three studies in 24 reports were removed from the 2011 review during the update process as the studies did not have eight weeks follow-up or longer (Al-Baaj 2005; Chertow 1997; Chiang 2005; d'Almeida Filho 2000; Emmett 1991; Fan 2009; Joy 2003; Koiwa 2005a; Kurihara 2005; Finn 2004; McIntyre 2009; Pflanz 1994; Ring 1993; Schaefer 1991; Sprague 2009b; Yang 2002), included non-randomised patients (Borrego 2000), did not evaluate an eligible intervention (Fischer 2006; FORESEE 2008; Ittel 1991; Phelps 2002), evaluated treatment in children (Salusky 1991), or were a secondary publication of an existing excluded study.

Figure 1. Flow diagram.

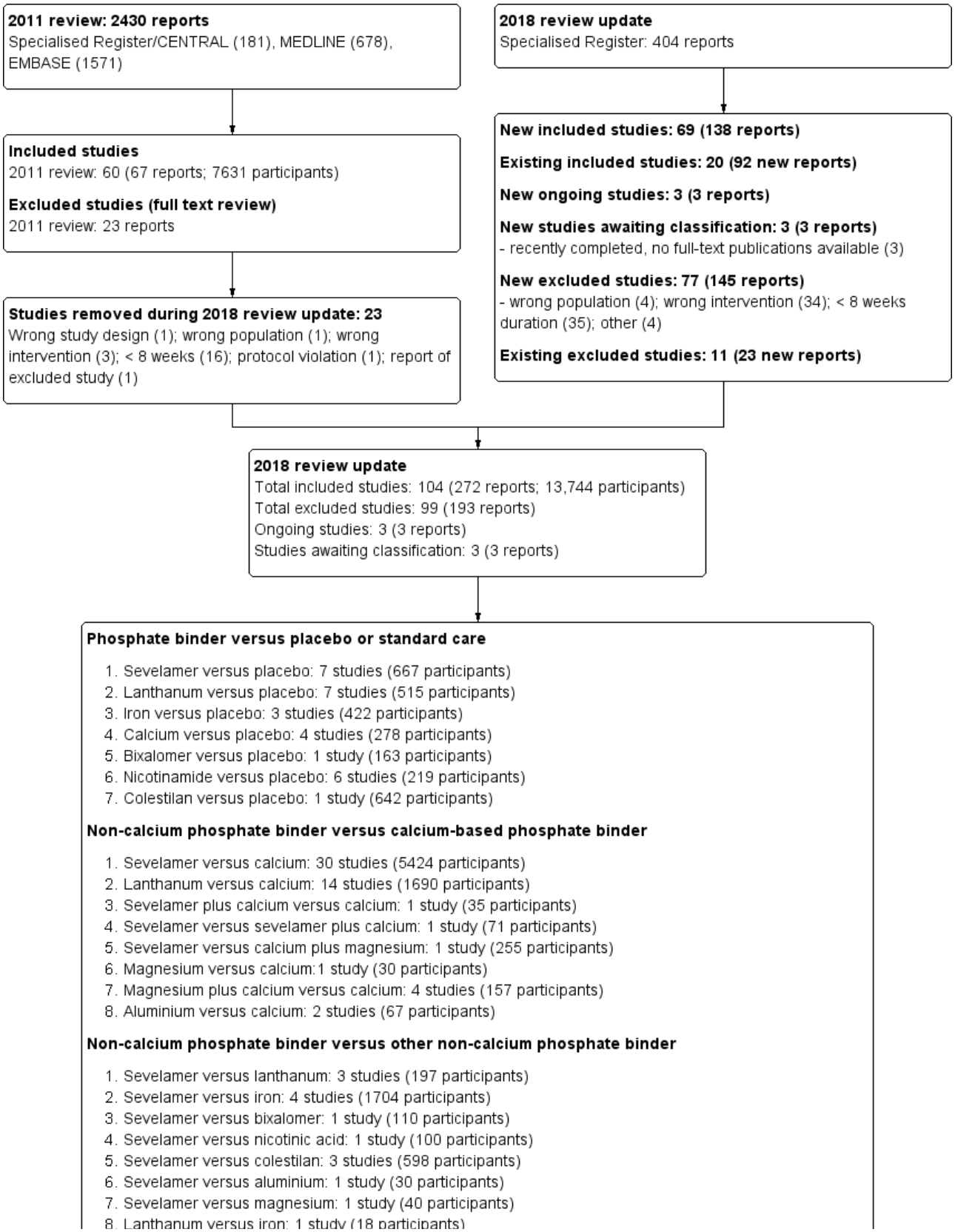


Figure 1. (Continued)

7. Sevelamer versus magnesium: 1 study (40 participants)
8. Lanthanum versus iron: 1 study (18 participants)
9. Aluminium versus sucralfate: 1 study (27 participants)

Phosphate binder class

1. Sevelamer carbonate versus sevelamer hydrochloride: 2 studies (296 participants)
2. Calcium carbonate or ketoglutarate versus calcium acetate or carbonate: 10 studies (320 participants)
3. Ferric citric hydrate versus sucroferric oxyhydroxide: 1 study (43 participants)

This 2018 review update therefore includes 104 studies (272 reports) involving 13,744 adult participants.

Included studies

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

Study design, setting, and characteristics

Study duration varied from 8 weeks to 36 months (median 3.7 months). Twenty studies were a cross-over study design in which participants were administered each of the study interventions sequentially with or without a washout period.

Studies were conducted in twenty-nine different countries or regions including Australia (SLO-NIACIN 2013; Toussaint 2009), Belgium (Tielmans 1990), Brazil (BRiC 2005; Lemos 2013), China (Chen 2014; Song 2014; Wang 2015b; Zhao 2014), Denmark (Bro 1998; Jespersen 1991; Rudnicki 1994), Egypt (Allam 2012) multiple European countries (CALMAG 2010; Evenepoel 2009; Hutchison 2005), France (Liabeuf 2017; NICOREN 2017; PREFECT 2014; Sadek 2003), Germany (Birck 1999; Deuber 2004), Greece (Katopodis 2006; Tzanakis 2014), Iran (Shahbazian 2011), Italy (De Santo 2006; Gallieni 2005; INDEPENDENT-CKD 2012; INDEPENDENT-HD 2009; Riccio 2018; Russo 2007), Japan (Akizawa 2000; Akizawa 2014a; Akizawa 2016; Fujii 2017; Fujimori 2017; Itoh 2008; Kakuta 2011; Kasai 2012; Matsushima 2017; Ohtake 2013; Shibata 2007; Shigematsu 2008; Takahara 2014; Wada 2014; Yokoyama 2014; Yokoyama 2014a), Japan and Taiwan (Chen 2011b; Toida 2012), Republic of Korea (Ko 2010; Lee 2013), Macedonia (Spasovski 2006), multinational (D'Haese 2003; Floege 2014; Locatelli 2013; Locatelli 2014; NCT00542815), Pakistan (Ahmed 2014; Saif 2007), Poland (Zwiech 2011), Portugal (Ferreira 2008), Saudi Arabia (Shaheen 2004), Spain (Almirall 1994; Caravaca 1992; Foraster 1998; Hervas 2003; Navarro-Gonzalez 2011; Soriano 2013), Taiwan (Lee 2015b; Lin 2010; Lin 2014a; Liu 2006), Thailand (Aramwit 2012), The Netherlands (Janssen 1995; Janssen 1996), Turkey (Caglar 2008; Sezer 2010), the USA (Bleyer 1999; Block 2005; Block 2009; Block 2015; CARE-2 2008; CARE 2004; Cheng 2008; Chennasamudram 2013; Chertow 1999; DCOR 2007; Delmez 1996; Delmez 2007; Fishbane 2010; Greenberg 1994; Isakova 2013; Qunibi 2011; Roxe 1989; Seifert 2013; Spiegel 2007; Sprague 2009a; Vlassara 2012; Young 2009a), and the USA and Europe (Chertow 2002). Forty-six studies received at least some funding from companies that manufacture phosphate binders, while 41 studies provided no specific details about funding sources.

Study participants

The 104 studies included 13,744 randomised participants. Most studies involved participants with CKD G5D ((83 studies). Of these, 73 were among participants treated with haemodialysis, two involved participants treated with haemodialysis or peritoneal dialysis, and eight involved participants treated with peritoneal dialysis. Twenty studies involved participants with CKD G2 to G5 not requiring dialysis. In one study, the GFR category of CKD was not reported. The sample size varied from eight participants (De Santo 2006) to 2013 participants (DCOR 2007). The median number of participants was 69. The inclusion criteria included specific serum phosphate levels in 40 studies; the requirement for a phosphate binder in 26 studies; and was not specified in the remaining 38 studies. The mean study age ranged from 42.6 years (Saif 2007) to 68.9 years (Wang 2015b), with a median of 57.2 years.

Interventions

Details of interventions in each study are presented in the Characteristics of included studies. Twenty-eight studies compared a phosphate binder with placebo or usual care (not including phosphate binder), 49 studies compared a calcium-free binder with a calcium-based binder, 16 studies compared a calcium-free binder with a second calcium-free binder class, and 14 studies compared two different drugs within the same binder class. In 77 studies, the phosphate binder was titrated to specific levels of serum phosphate, while in 25 studies, a fixed dose of phosphate binder was used. Specific approaches to phosphate binder therapy were not reported in two studies. Most placebo or usual care controlled studies were among participants with CKD G2 to G5 not requiring dialysis (15/25 studies involving 1467 participants) while most head to head studies involved participants with CKD G5D treated with dialysis (74/81 studies involving 10,364 participants).

Phosphate binder versus placebo or usual care

Sevelamer versus placebo or usual care (677 participants)

Sevelamer hydrochloride or carbonate was compared with placebo or usual care in seven studies involving 667 participants (Block 2009; Chen 2014; CRIB-PHOS 2011; Liabeuf 2017; Lemos 2013; Riccio 2018; Russo 2007). Six of the seven studies involved participants with CKD G2 to G5 not requiring dialysis. Treatment duration and follow-up ranged between 2 and 24 months with a median of 3 months.

Lanthanum versus placebo or usual care (515 participants)

Lanthanum carbonate was compared with placebo or usual care in seven studies involving 515 participants (Block 2009; Isakova 2013; PREFECT 2014; Seifert 2013; Sprague 2009a; Takahara 2014; Wang 2015b). Six of the seven studies evaluated therapy for participants

with CKD G2 to G5 not requiring dialysis. Treatment and follow-up ranged between 3 and 12 months with a median of 3 months.

Iron versus placebo or usual care (422 participants)

An iron-based binder (ferric citrate, previously designated as JTT-751) was compared with placebo or usual care in three studies involving 422 participants (Block 2015; Lee 2015b; Yokoyama 2014). Two of the three studies involved adults with CKD G2 to G5 not requiring dialysis. Treatment and follow-up ranged between 1.8 and 3 months with a median of 2.75 months.

Calcium versus placebo or usual care (278 participants)

Calcium carbonate was compared with placebo in four studies (Block 2009; Qunibi 2011; Rudnicki 1994; Russo 2007) involving 278 participants. Three of the four studies evaluated treatment in patients with CKD G2 to G5 not requiring dialysis. Treatment and follow-up ranged between 3 and 9 months with a median of 7 months.

Bixalomer versus placebo or usual care (163 participants)

Bixalomer is a non-calcium, metal-free non-absorbable polymer which has been compared with placebo for 3 months among 163 participants with CKD G2 to G5 not requiring dialysis (Akizawa 2016).

Nicotinamide versus placebo or usual care (219 participants)

Nicotinamide (also known as nicotinic acid), while not a phosphate binder, inhibits active phosphate absorption from the gut. Nicotinamide was compared with placebo or usual care in six studies involving 219 participants (Allam 2012; Aramwit 2012; Cheng 2008; Shahbazian 2011; SLO-NIACIN 2013; Young 2009a). All studies involved participants with CKD G5D. Treatment and follow-up ranged between 1.8 and 3.7 months with a median of 2.4 months.

Colestilan versus placebo or usual care (642 participants)

Colestilan (also known as colestimide) was compared with placebo for three months in a single study involving 642 haemodialysis patients (Locatelli 2013).

Non-calcium phosphate binder versus calcium phosphate binder

Sevelamer versus calcium (5424 participants)

Thirty studies (5424 participants) compared sevelamer hydrochloride or sevelamer carbonate with calcium carbonate or acetate (Ahmed 2014; Akizawa 2000; Bleyer 1999; Block 2005; Block 2009; BRiC 2005; Caglar 2008; CARE-2 2008; CARE 2004; Chennasamudram 2013; Chertow 2002; DCOR 2007; De Santo 2006; Evenepoel 2009; Ferreira 2008; Gallieni 2005; Hervas 2003; INDEPENDENT-CKD 2012; INDEPENDENT-HD 2009; Kakuta 2011; Lin 2010; Lin 2014a; Liu 2006; Navarro-Gonzalez 2011; Russo 2007; Sadek 2003; Sezer 2010; Shaheen 2004; Vlassara 2012; Zhao 2014). The duration of treatment ranged between 1.8 and 24 months with a median of 5.5 months. Nearly all studies (25) involved participants with CKD G5D treated with haemodialysis (24 studies) or peritoneal dialysis (1 study).

Lanthanum versus calcium (1690 participants)

Fourteen studies (1690 participants) compared lanthanum carbonate with calcium carbonate or acetate (Block 2009; D'Haese 2003; Fujii 2017; Hutchison 2005; Ko 2010; Lee 2013; Ohtake 2013; Shigematsu 2008; Song 2014; Soriano 2013; Spasovski 2006; Toida 2012; Toussaint 2009; Wada 2014). The duration of treatment ranged between 1.8 and 18 months with a median of 6 months. All but three studies involved participants with CKD G5D treated with haemodialysis (9 studies) or peritoneal dialysis (3 studies).

Sevelamer plus calcium versus calcium (35 participants)

Sevelamer hydrochloride plus calcium carbonate was compared with calcium carbonate for 36 months in 35 patients with CKD G5D treatment with haemodialysis (Shibata 2007).

Sevelamer versus calcium plus magnesium (255 participants)

Sevelamer hydrochloride was compared with calcium acetate plus magnesium carbonate for six months in 255 participants with CKD G5D treated with haemodialysis (CALMAG 2010).

Sevelamer versus sevelamer plus calcium (71 participants)

Sevelamer hydrochloride was compared with sevelamer hydrochloride plus calcium for 2.8 months in one study of 71 patients with CKD 5D treated with haemodialysis (Chertow 1999).

Magnesium versus calcium (30 participants)

Spiegel 2007 evaluated magnesium carbonate versus calcium carbonate treatment for 2.8 months among 30 dialysis patients.

Magnesium plus calcium versus magnesium (157 participants)

Combined magnesium and calcium therapy was compared with calcium alone in four studies (157 participants) (Deuber 2004; Evsanaa 2015; Spiegel 2007; Tzanakis 2014). All studies involved participants with CKD 5D treated with long-term haemodialysis or peritoneal dialysis. Follow-up ranged from three months to 30 months, with a median of 7.5 months.

Aluminium versus calcium (67 participants)

Aluminium hydroxide was compared with calcium carbonate or acetate over 6 to 12 months among 67 haemodialysis patients (Janssen 1996; Jespersen 1991).

Non-calcium phosphate binder versus non-calcium phosphate binder

Sevelamer versus lanthanum (197 participants)

Sevelamer hydrochloride or carbonate was compared with lanthanum carbonate in three studies (Block 2009; Kasai 2012; Pratt 2007) involving 197 participants. Two of the three studies involved participants with CKD 5D treated with haemodialysis. Follow-up ranged from 2 months to 12 months.

Sevelamer versus iron (1704 participants)

Sevelamer hydrochloride or carbonate was compared with iron-based binders (SBR759 (iron (III) starch/saccharose complex); sucroferric oxyhydroxide; ferric citrate) in four studies involving 1704 participants (Chen 2011b; Floege 2014; Koiwa 2017; Yokoyama 2014a). Three of the four studies involved participants with CKD G5D. Follow-up ranged between 3 and 6 months, with a median of 3 months.

Sevelamer versus bixalomer (110 participants)

Akizawa 2014a evaluated sevelamer hydrochloride versus bixalomer over three months in 110 participants with CKD G5D treated with haemodialysis.

Sevelamer versus nicotinamide (100 participants)

Sevelamer hydrochloride was compared with nicotinamide for six months in one study (NICOREN 2017) involving 100 participants with CKD G5D treated with haemodialysis.

Sevelamer versus colestilan (598 participants)

Sevelamer was compared with colestilan in three studies involving 598 participants (Itoh 2008; Locatelli 2014; NCT00542815). All participants had CKD G5D treated with haemodialysis or peritoneal dialysis. Treatment and follow-up continued for 1.9 to 12 months.

Sevelamer versus aluminium (30 participants)

Sevelamer hydrochloride was compared with aluminium hydroxide during treatment over 16 months in 30 participants with CKD G5D treated with peritoneal dialysis (Katopodis 2006).

Sevelamer versus magnesium (40 participants)

Zwiech 2011 compared sevelamer hydrochloride with magnesium carbonate during treatment of 3 months in 40 participants with CKD G5D treated with haemodialysis.

Lanthanum versus iron (18 participants)

Fujimori 2017 evaluated lanthanum carbonate versus ferric citrate for 3 months in 18 participants with CKD G5D treated with haemodialysis.

Aluminium versus sucralfate (27 participants)

Aluminium hydroxide was compared with sucralfate (not used in current clinical care) for 1.8 months in 27 participants with CKD G5D treated with haemodialysis (Roxe 1989).

Phosphate binder class

Sevelamer hydrochloride versus sevelamer carbonate (296 participants)

Sevelamer hydrochloride was compared with sevelamer carbonate in two studies involving 296 participants with CKD G5D treated with haemodialysis (Delmez 2007; Fishbane 2010). Treatment and follow-up was for 5.5 and 12 months, respectively.

Calcium-based binder versus calcium-based binder (320 participants)

Calcium carbonate was compared with calcium acetate in eight studies (209 participants) (Almirall 1994; Caravaca 1992; Foraster 1998; Greenberg 1994; Janssen 1995; Janssen 1996; Tielmans 1990). Calcium ketoglutarate was compared with calcium acetate or carbonate in two studies involving 47 participants (Birck 1999; Bro 1998). All studies involved participants with CKD G5D treated with haemodialysis. Treatment and follow-up ranged between 2 and 12 months with a median of 3 months.

Ferric citrate versus sucroferric oxyhydroxide (43 participants)

Ferric citrate was compared with sucroferric oxyhydroxide during three months of treatment among 43 participants with CKD G5D treated with haemodialysis (Matsushima 2017).

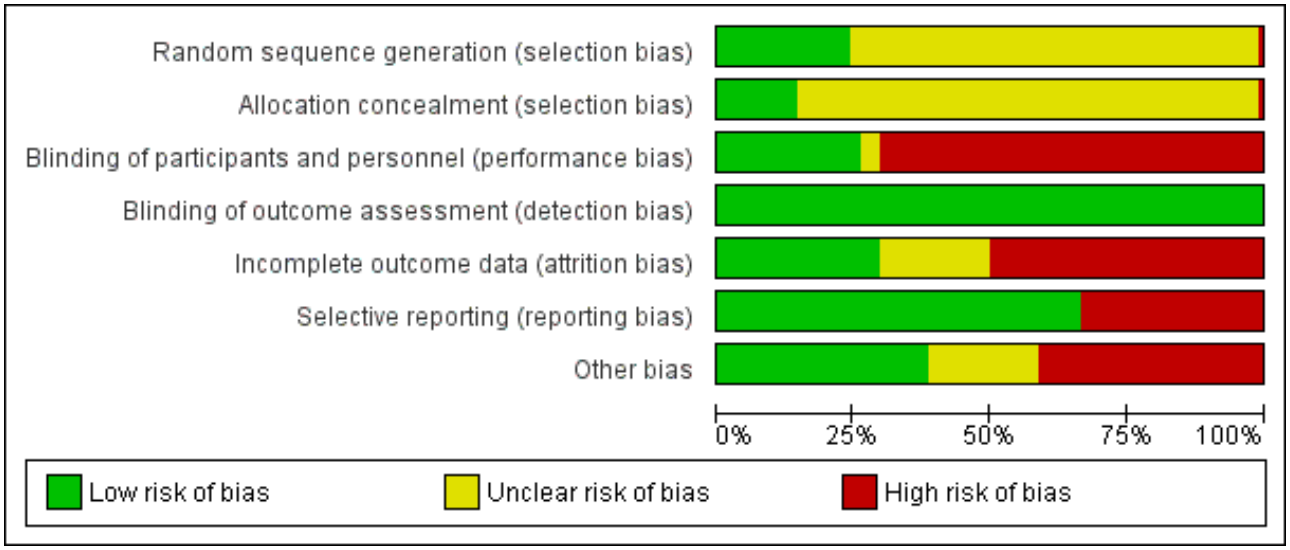
Excluded studies

In total, we excluded 99 studies (in 193 reports) as studies were not RCTs, were studies involving children, did not evaluate two different phosphate binders, or had follow-up of less than eight weeks (Characteristics of excluded studies).

Risk of bias in included studies

The risk of bias for studies overall are summarised in Figure 2 and the risk of bias in each individual study is reported in Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Methods for generating the random sequence were deemed to be at low risk of bias in 25 studies (Block 2005; Block 2009; Block 2015; BRiC 2005; CARE-2 2008; Chertow 2002; Floege 2014; Liabeuf 2017; Greenberg 1994; INDEPENDENT-CKD 2012; Katopodis 2006; Koiwa 2017; Lemos 2013; Locatelli 2013; Locatelli 2014; Navarro-Gonzalez 2011; Ohtake 2013; Riccio 2018; Rudnicki 1994; Seifert

2013; SLO-NIACIN 2013; Song 2014; Toida 2012; Toussaint 2009; Tzanakis 2014). The sequence did not appear to be random in one study, in which treatment group may have been based on serum phosphate levels (Fujii 2017). In the remaining 78 studies, the method for generating the random sequence was unclear.

Allocation concealment was adjudicated as low risk of bias in 15 studies (Block 2005; Block 2009; Block 2015; BRiC 2005; Floege 2014; Liabeuf 2017; Greenberg 1994; INDEPENDENT-CKD 2012; Kakuta 2011; Koiwa 2017; NICOREN 2017; PREFECT 2014; Riccio 2018; Riccio 2018; Russo 2007; Toussaint 2009). The method to conceal allocation was deemed to be high risk in one study in which some participants could choose their treatment group (Tzanakis 2014). The risk of bias for allocation concealment was unclear in the remaining 88 studies.

Blinding

Twenty-seven studies were blinded and considered to be at low risk of bias for performance bias (Akizawa 2016; Block 2009; Block 2015; CARE 2004; Chen 2014; Cheng 2008; CRIB-PHOS 2011; Evsanaa 2015; Liabeuf 2017; Isakova 2013; Lee 2015b; Locatelli 2013; PREFECT 2014; Qunibi 2011; Riccio 2018; Rudnicki 1994; Seifert 2013; Shahbazian 2011; Shigematsu 2008; SLO-NIACIN 2013; Sprague 2009a; Takahara 2014; Tielmans 1990; Toussaint 2009; Tzanakis 2014; Yokoyama 2014; Young 2009a). Blinding was unclear in four studies (Almirall 1994; Aramwit 2012; Matsushima 2017; Sezer 2010). The remaining 73 studies were not blinded and were considered at high risk of performance bias.

As most studies were based on laboratory assessment or patient-centred outcomes including death, all studies were considered at low risk of bias for blinding of outcome assessment.

Incomplete outcome data

Thirty-one studies met criteria for low risk of attrition bias (Almirall 1994; Aramwit 2012; Bleyer 1999; Block 2015; Caglar 2008; Chen 2011b; Chen 2014; Cheng 2008; CRIB-PHOS 2011; Delmez 2007; Evsanaa 2015; Hervas 2003; INDEPENDENT-HD 2009; Isakova 2013; Kasai 2012; Liu 2006; Navarro-Gonzalez 2011; Riccio 2018; Rudnicki 1994; Russo 2007; Sezer 2010; Shahbazian 2011; Shaheen 2004; Shigematsu 2008; SLO-NIACIN 2013; Spasovski 2006; Tzanakis 2014; Wada 2014; Wang 2015b; Young 2009a; Zhao 2014). Fifty-two studies were considered at high risk of attrition bias when there was differential loss to follow-up between treatment groups, high attrition rates (> 10%), or when adverse events were substantially higher in one or both treatment groups (Akizawa 2014a; Akizawa 2016; Allam 2012; Birck 1999; Block 2005; Block 2009; BRiC 2005; Bro 1998; CALMAG 2010; Caravaca 1992; CARE 2004; CARE-2 2008; D'Haese 2003; DCOR 2007; Evenepoel 2009; Ferreira 2008; Fishbane 2010; Floege 2014; Fujimori 2017; Hutchison 2005; INDEPENDENT-CKD 2012; Itoh 2008; Janssen 1995; Janssen 1996; Jespersen 1991; Kakuta 2011; Koiwa 2017; Lee 2013; Lee 2015b; Lemos 2013; Liabeuf 2017; Lin 2010; Lin 2014a; Locatelli 2013; Locatelli 2014; NCT00542815; NICOREN 2017; Ohtake 2013; PREFECT 2014; Qunibi 2011; Roxe 1989; Sadek 2003; Saif 2007; Seifert 2013; Seifert 2013; Sprague 2009a; Takahara 2014; Toida 2012; Toussaint 2009; Vlassara 2012; Yokoyama 2014; Yokoyama 2014a). In the remaining 21 studies, attrition bias was considered unclear. Loss to follow-up was commonly due to death, transplantation, withdrawal of consent, protocol violation, or adverse events.

Selective reporting

Sixty-nine studies reported expected and clinically-relevant outcomes and were deemed to be at low risk of bias (Akizawa 2000; Akizawa 2014a; Akizawa 2016; Allam 2012; Aramwit 2012; Bleyer 1999; Block 2005; Block 2009; Block 2015; BRiC 2005; Bro 1998; CALMAG 2010; CARE-2 2008; CARE 2004; Chen 2011b; Chen 2014; CRIB-PHOS 2011; DCOR 2007; Delmez 2007; Evenepoel 2009; Fishbane 2010; Floege 2014; Gallieni 2005; Hutchison 2005; INDEPENDENT-CKD 2012; INDEPENDENT-HD 2009; Isakova 2013; Janssen 1995; Janssen 1996; Kakuta 2011; Kasai 2012; Katopodis 2006; Ko 2010; Koiwa 2017; Lee 2013; Lee 2015b; Lemos 2013; Liabeuf 2017; Lin 2010; Lin 2014a; Liu 2006; Locatelli 2013; Locatelli 2014; Matsushima 2017; NCT00542815; NICOREN 2017; Ohtake 2013; Pratt 2007; PREFECT 2014; Qunibi 2011; Riccio 2018; Sadek 2003; Seifert 2013; Sezer 2010; Shahbazian 2011; Shigematsu 2008; SLO-NIACIN 2013; Spasovski 2006; Sprague 2009a; Takahara 2014; Tielmans 1990; Toida 2012; Toussaint 2009; Tzanakis 2014; Vlassara 2012; Wada 2014; Yokoyama 2014; Yokoyama 2014a; Zhao 2014). The remaining 35 studies did not report patient-centred outcomes of death or adverse events.

Other potential sources of bias

Forty studies appeared to be free from other sources of bias (Allam 2012; Block 2005; Block 2009; Block 2015; BRiC 2005; Caglar 2008; CALMAG 2010; Caravaca 1992; CARE-2 2008; Chertow 1999; Chertow 2002; CRIB-PHOS 2011; Deuber 2004; Floege 2014; Hutchison 2005; INDEPENDENT-CKD 2012; INDEPENDENT-HD 2009; Isakova 2013; Itoh 2008; Kakuta 2011; Lemos 2013; Liabeuf 2017; Lin 2010; Locatelli 2013; Locatelli 2014; Riccio 2018; Russo 2007; Seifert 2013; Shahbazian 2011; Song 2014; Soriano 2013; Spiegel 2007; Toida 2012; Toussaint 2009; Tzanakis 2014; Vlassara 2012; Wada 2014; Wang 2015b; Yokoyama 2014a; Zhao 2014). Forty-three studies had other sources of bias (Ahmed 2014; Akizawa 2014a; Akizawa 2016; Almirall 1994; Aramwit 2012; Birck 1999; Bleyer 1999; Bro 1998; CARE 2004; Chen 2011b; Chen 2014; Cheng 2008; Chennasamudram 2013; DCOR 2007; Delmez 1996; Delmez 2007; De Santo 2006; Evenepoel 2009; Evsanaa 2015; Ferreira 2008; Fishbane 2010; Greenberg 1994; Hervas 2003; Jespersen 1991; Ko 2010; Koiwa 2017; Lin 2014a; Liu 2006; Navarro-Gonzalez 2011; NICOREN 2017; Ohtake 2013; PREFECT 2014; Qunibi 2011; Roxe 1989; Rudnicki 1994; Sadek 2003; Shaheen 2004; Shigematsu 2008; SLO-NIACIN 2013; Spasovski 2006; Sprague 2009a; Takahara 2014; Young 2009a). It was unclear whether the remaining 21 studies had other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: Sevelamer versus placebo/usual care; **Summary of findings 2** Summary of findings: Lanthanum versus placebo/usual care; **Summary of findings 3** Summary of findings: Iron versus placebo/usual care; **Summary of findings 4** Summary of findings: Calcium versus placebo/usual care; **Summary of findings 5** Summary of findings: Sevelamer versus calcium; **Summary of findings 6** Summary of findings - Lanthanum versus calcium

Sevelamer versus placebo or usual care

The major outcomes for the comparison of sevelamer with placebo or usual care are shown in the Summary of findings for the main comparison. Evidence was generally restricted to people with CKD G2 to G5 not requiring dialysis.

No study was designed to evaluate death or cardiovascular events. In the three studies comparing sevelamer with placebo or usual care, deaths were reported as reasons for drop-out from study follow-up. A single study reported one or more deaths during a median of 10 months (Lemos 2013). In very low certainty evidence, sevelamer had uncertain effects on death (all causes) (RR 2.16, 95% CI 0.20 to 22.84) (Analysis 1.1). No studies reported whether deaths due to cardiovascular events occurred. Two studies each reported one participant experiencing a myocardial infarction (Liabeuf 2017; Russo 2007), while a third posted zero events on a studies registry web site (Block 2009). Whether sevelamer prevents myocardial infarction is uncertain due to very low certainty evidence (Analysis 1.2 RR 1.00, 95% CI 0.11 to 9.35). A single study reported one stroke event in the sevelamer group on www.ClinicalTrials.gov (Block 2009) (Analysis 1.3). One study reported no difference in the number of patients requiring hospitalisation during follow-up (CRIB-PHOS 2011) (Analysis 1.4).

Block 2009 reported two fracture events in the control group (Analysis 1.5) and one participant experienced pruritus during follow-up in the control group (Analysis 1.6).

With respect to adverse events, nausea was reported in three studies (370 participants) in a meta-analysis marked by substantial heterogeneity. In very low certainty evidence, sevelamer had uncertain risks of nausea (Analysis 1.7: RR 1.27, 95% CI 0.07 to 22.42; I^2 = 71%). In low- or very-low certainty evidence, sevelamer had uncertain risks of vomiting (Analysis 1.8 (2 studies, 165 participants): RR 2.09, 95% CI 0.26 to 16.57; I^2 = 0%), abdominal pain (Analysis 1.9 (3 studies, 370 participants): RR 0.38, 95% CI 0.13 to 1.14; I^2 = 0%), and diarrhoea (Analysis 1.11 (2 studies, 1965 participants): RR 2.02, 95% CI 0.13 to 31.62; I^2 = 66%). Liabeuf 2017 reported no difference in abdominal bloating between the two groups (Analysis 1.12). Compared with placebo or usual care, sevelamer may lead to an increased risk of constipation (Analysis 1.10 (4 studies, 430 participants): RR 6.92, 95% CI 2.24 to 21.38; I^2 = 0%; *low certainty evidence*).

Two studies reported ESKD; Riccio 2018 reported no events during treatment while Lemos 2013 reported 12 events (7 in the sevelamer group and 5 in the placebo group). In very low certainty evidence, sevelamer had uncertain effects on the need for renal replacement therapy (Analysis 1.13 (2 studies, 139 participants): RR 1.51, 95% CI 0.52 to 4.36; I^2 = 0%).

At 24 months, the mean coronary artery calcium score measured by multislice computed tomography was 434 with placebo or usual care and 70 points lower (362 lower to 222 higher) with sevelamer (Analysis 1.14 (2 studies, 155 participants): MD -70.19, 95% CI -362.44 to 222.06; I^2 = 0%; *very low certainty evidence*).

With respect to biochemical responses to therapy, at a median of 3 months the mean serum phosphate level was 0.28 mg/dL (0.09 mmol/L) lower (0.94 mg/dL lower to 0.39 mg/dL higher (-0.30 to 0.13 mmol/L) with sevelamer (Analysis 1.15) in an analysis characterised by substantial heterogeneity (I^2 = 95%) (leading to *very low certainty*). Compared with placebo or usual care, sevelamer did not have clinically important effects on serum calcium (MD 0.03 mg/dL (0.0085 mmol/L), 95% CI -0.08 to 0.14 (0.02 to 0.04 mmol/L); I^2 = 72%) (Analysis 1.16). The impact of treatment on hypercalcaemia (Analysis 1.17) was uncertain. Sevelamer had uncertain effects on the serum calcium-by-phosphate product (MD 2.66 mg^2/dL^2, 95% CI -5.52 to 10.84; I^2 = 98%) (Analysis 1.18), serum iPTH (MD -6.55 pg/mL (0.74 pmol/L), 95% CI -21.16 to 8.07 (-2.41 to 0.92 pmol/L); I^2 = 0%) (Analysis 1.19), serum alkaline phosphatase (Analysis 1.20), serum bicarbonate (MD 0.12 mEq/L, 95% CI -1.30 to 1.54; I^2 = 82%) (Analysis 1.21), eGFR (MD -0.45 mL/min, 95% CI -4.74 to 3.85; I^2 = 45%) (Analysis 1.22), and bone mineral density measured at the hip or spine (Analysis 1.23; Analysis 1.24). Serum FGF23 levels were not reported in a format that was extractable for meta-analysis. CRIB-PHOS 2011 reported no difference in Klotho levels between the two groups (Analysis 1.25).

Lanthanum versus placebo or usual care

The major outcomes for the comparison of lanthanum with placebo or usual care are shown in the Summary of findings 2.

None of the seven studies were designed to measure death or cardiovascular events. Studies generally involved people with CKD G2 to G5 not requiring dialysis.

Three studies reported death as either a reason for study drop-out or as an adverse event. PREFECT 2014 reported a single death in the lanthanum group. Compared with placebo or usual care, it was uncertain whether lanthanum made any difference to the risk of death (all causes) (Analysis 2.1 (3 studies, 214 participants): RR 1.63, 95% CI 0.07 to 37.12; I^2 = 100%) after a median study follow-up of 3 months. No study reported cardiovascular deaths. Three studies reported myocardial infarction as an adverse treatment event, with only two events reported in the lanthanum group. Lanthanum had very uncertain effects on myocardial infarction (Analysis 2.2 (3 studies, 239 participants): RR 1.61, 95% CI 0.17 to 14.97; I^2 = 0%). There were no reports of stroke in Block 2009 (Analysis 2.3), Isakova 2013 reported no difference in hospitalisation events (Analysis 2.4), and Block 2009 reported no difference in fractures (Analysis 2.5).

Lanthanum treatment had uncertain effects on the risk of pruritus measured as a discrete outcome (Analysis 2.6 (3 studies, 345 participants): RR 1.09, 95% CI 0.14 to 8.45; I^2 = 37%) or as a continuous pruritus score (Wang 2015b) (Analysis 2.7).

Adverse events were measured over a median of two to three months. In low or moderate certainty evidence, lanthanum may have led to nausea (Analysis 2.8 (4 studies, 383 participants): RR 3.72, 95% CI 1.36 to 10.18; I^2 = 0%) and probably leads to an increased risk of constipation (RR 2.98, 95% CI 1.21 to 7.30) (Analysis 2.11). Lanthanum had uncertain risks of abdominal pain (RR 0.23, 95% CI 0.03 to 1.96) (Analysis 2.10) and diarrhoea (RR 0.68, 95% CI 0.13 to 3.68; I^2 = 71%) (Analysis 2.12).

Single studies reported no difference in treatment effects of lanthanum on ESKD (Analysis 2.13), coronary artery calcification (Analysis 2.14), or vascular calcification (Analysis 2.15).

After a median of 3 months, the average serum phosphate level was 0.48 mg/dL (0.16 mmol/L) lower (0.05 lower to 0.90 mg/dL lower (-0.02 to 0.29), *low certainty*) (Analysis 3.8). Lanthanum did not lead to clinically-important effects on serum calcium (MD 0.03 mg/dL (0.008 mmol/L), 95% CI -0.18 to 0.23 mg/dL (-0.04 to 0.06 mmol/L)) (Analysis 2.17), and the risk of hypercalcaemia were uncertain in one study (Analysis 2.18). The effects of sevelamer were uncertain for the outcomes of serum calcium by phosphate product (2 studies, 194 participants: MD -4.36 mg^2/dL^2, 95% CI -9.96 to 1.24; I^2 = 77%) (Analysis 2.19), serum iPTH (4 studies, 253

participants: MD 10.07 pg/mL (1.15 pmol/L), 95% CI -10.69 to 30.83 pg/mL (-1.22 to 3.52 pmol/L); I^2 = 61%) (Analysis 2.20), eGFR (2 studies, 128 participants: MD 0.13 mL/min, 95% CI -1.80 to 2.07; I^2 = 0%) (Analysis 2.21), bone mineral density at the lumbar spine measured as a Z-score (Analysis 2.22), and serum FGF23 levels (2 studies, 50 participants: SMD 0.32, 95% CI -0.81 to 1.45; I^2 = 73%) (Analysis 2.23).

Iron versus placebo or usual care

The major outcomes for the comparison of iron with placebo or usual care are shown in the Summary of findings 3.

In the three studies comparing iron-based binders with placebo or usual care, one involved dialysis patients and two involved patients with CKD G2 to G5 not requiring dialysis. The studies were not designed to measure the effects of treatment on death or cardiovascular events. Death (all causes) was reported in two studies. At 2.75 to 3 months, iron-based binders had uncertain effects on death (all causes) (2 studies, 239 participants: RR 0.52, 95% CI 0.06 to 4.65; I^2 = 0%; *very low certainty evidence*) (Analysis 3.1). Cardiovascular death, myocardial infarction, and stroke were not reported. Block 2015 reported no differences in the risks of fracture (Analysis 3.2), pruritus (Analysis 3.3), or nausea (Analysis 3.4). Outcome data for vascular calcification and bone-related outcomes could not be extracted for analysis.

Iron-based binders had clinically uncertain risks for abdominal pain (2 studies, 332 participants: RR 1.20, 95% CI 0.34 to 4.27) (Analysis 3.7), while probably increasing the risk of constipation (3 studies, 422 participants: RR 2.66, 95% CI 1.15 to 6.12; I^2 = 0%; *moderate certainty evidence*) (Analysis 3.5) and diarrhoea (3 studies, 422 participants: RR 2.81, 95% CI 1.18 to 6.68; I^2 = 25%) (Analysis 3.6).

Iron-based binders lowered serum phosphate levels (3 studies, 301 participants: MD -1.33 mg/dL (-0.43 mmol/L), 95% CI -2.25 to -0.41 mg/dL (-0.73 to -0.13 mmol/L); I^2 = 91%) in an analysis possessing substantial between-study heterogeneity (Analysis 3.8). Iron-based binder therapy may be associated with higher serum calcium levels (3 studies, 301 participants: MD 0.21 mg/dL (0.05 mmol/L), 95% CI 0.09 to 0.33 mg/dL (0.02 to 0.08 mmol/L); I^2 = 0%) (Analysis 3.9) while singles studies reported uncertain effects on serum calcium-by-phosphate product (Analysis 3.10), alkaline phosphatase (Analysis 3.11), and serum bicarbonate (Analysis 3.12). Iron-based binders had uncertain effects on eGFR (2 studies, 239 participants: MD -0.67 mL/min, 95% CI -2.97 to 1.64; I^2 = 0%) (Analysis 3.13). Outcome data for serum FGF23 levels could not be extracted for analysis.

Calcium versus placebo or usual care

The major outcomes for the comparison of calcium-based binders compared with usual care are shown in the Summary of findings 4.

Evidence was generally restricted to people with CKD G2 to G5 not requiring dialysis. Meta-analyses involved two studies (or three for biochemical outcomes). As a result, evidence certainty was either low, very low, or absent. No study was specifically designed to measure death or cardiovascular complications. Treatment endpoints were measured during nine months of therapy.

Qunibi 2011 reported no difference in the number of deaths between calcium and placebo (Analysis 4.1). Death due to cardiovascular events was not reported by any study. It is uncertain whether calcium-based binders make any difference to the risk of myocardial infarction (2 studies, 147 participants: RR 1.36, 95% CI 0.09 to 21.71; I^2 = 35%) (Analysis 4.2). Two studies reported stroke; there were no reports of stoke in Block 2009, while Qunibi 2011 reported one stroke in the calcium group. The summary estimate for stroke was extremely imprecise (Analysis 4.3). Block 2009 reported two fractures in the placebo group (Analysis 4.4). The effect of calcium-based binders on pruritus was very uncertain in two studies (2 studies, 197 participants: RR 1.19, 95% CI 0.29 to 4.81; I^2 = 0%) (Analysis 4.5).

In low- or very low-certainty evidence, calcium-based binders had uncertain risks on adverse events including nausea (2 studies, 197 participants: RR 0.58, 95% CI 0.15 to 2.18; I^2 = 0%) (Analysis 4.6), abdominal pain (2 studies, 197 participants: RR 0.66, 95% CI 0.13 to 3.34; I^2 = 0%) (Analysis 4.8), constipation (2 studies, 197 participants: RR 2.44, 95% CI 0.32 to 18.42; I^2 = 53%) (Analysis 4.9), and diarrhoea (2 studies, 197 participants: RR 0.94, 95% CI 0.39 to 2.28; I^2 = 0%) (Analysis 4.10). Block 2009 reported one vomiting event in the placebo group (Analysis 4.7).

Russo 2007 reported no differences between the two groups in coronary artery calcium score at 2 years (Analysis 4.11).

In very low certainty evidence, calcium-based binders had uncertain effects on serum phosphate (3 studies, 151 participants: MD -0.18 mg/dL (-0.06 mmol/L), 95% CI -1.30 to 0.95 mg/dL (-0.42 to 0.31 mmol/L); I^2 = 85%) (Analysis 4.12) and serum calcium (3 studies, 151 participants: MD 0.33 mg/dL (0.08 mmol/L), 95% CI -0.26 to 0.92 (-0.07 to 0.23 mmol/L); I^2 = 85%) (Analysis 4.13) in meta-analyses with by substantial heterogeneity. Hypercalcaemia was reported as an adverse event in three studies after 12 weeks, 3 months, and 9 months of treatment. There was no uniform definition of hypercalcaemia. In low certainty evidence, calcium-based binders may increase the risk of hypercalcaemia (3 studies, 215 participants: RR 7.28, 95% CI 1.64 to 32.29; I^2 = 0%)) (Analysis 4.14).

Calcium-based binders had uncertain effects on serum iPTH (2 studies, 133 participants: MD -80.15 pg/mL (-9.14 pmol/L), 95% CI -305.46 to 145.16 pg/mL (-34.8 to 16.5 pmol/L); I^2 = 94%) (Analysis 4.16) and alkaline phosphatase (2 studies, 78 participants: MD 34.86 IU/L, 95% CI -21.47 to 91.20; I^2 = 60%) (Analysis 4.17). Calcium binders may lead to a small clinical reduction in serum bicarbonate (2 studies 138 participants: MD -1.85 mEq/L, 95% CI -3.12 to -0.59) (Analysis 4.18). Russo 2007 reported no differences between calcium and placebo in serum calcium-by-phosphate product or eGFR (Analysis 4.15; Analysis 4.19). Outcome data for serum FGF23 levels could not be extracted for analysis.

Bixalomer versus placebo or usual care

Akizawa 2016 evaluated bixalomer versus placebo for 12 weeks among people with an eGFR < 60 mL/min per 1.73 m^2. This study reported no differences in death (Analysis 5.1), ESKD (Analysis 5.2), nausea (Analysis 5.3), abdominal pain (Analysis 5.4), constipation (Analysis 5.5), and diarrhoea (Analysis 5.6).

Nicotinamide versus placebo or usual care

Four studies evaluated nicotinamide or placebo or usual care in patients with CKD G5D treated with dialysis. Studies were between 1.8 and 3 months in duration. The studies were not designed to measure the effects of treatment on death or cardiovascular events. SLO-NIACIN 2013 reported one death as a study drop-out (Analysis 6.1). There were no reported cardiovascular deaths. Young 2009a reported no differences in the risk of pruritus (Analysis 6.2).

Constipation was reported in one study at 2.75 months (Aramwit 2012) (Analysis 6.3). It was very uncertain whether nicotinamide increased risks of diarrhoea (RR 1.61, 95% CI 0.06 to 40.36) (Analysis 6.4).

There was no evidence that nicotinamide had clinically-important effects on serum phosphate (3 studies, 98 participants: MD -0.56 mg/dL (-0.18 mmol/L), 95% CI -1.24 to 0.12 mg/dL (-0.40 to 0.04 mmol/L); I^2 = 61%), in an analysis with moderate heterogeneity (Analysis 6.5). Nicotinamide had uncertain effects on serum calcium (3 studies, 98 participants: MD 0.07 mg/dL (0.02 mmol/L), 95% CI -0.30 to 0.44 mg/dL (-0.06 to 0.11 mmol/L); I^2 = 0%) (Analysis 6.6), and may lower serum calcium-by-phosphate product (2 studies, 74 participants: MD -7.81 mg^2/dL^2, 95% CI -13.36 to -2.25) (Analysis 6.8). Allam 2012 reported on difference in serum PTH (Analysis 6.7).

Colestilan versus placebo or usual care

Data from a single placebo-controlled, multiple fixed-dose study in patients treated with dialysis was available (Locatelli 2013). This study reported no differences between colestilan and placebo in death (Analysis 7.1), abdominal pain (Analysis 7.3), diarrhoea (Analysis 7.4), and constipation (Analysis 7.5). Locatelli 2013 reported more nausea in the placebo group (Analysis 7.2).

Sevelamer versus calcium

The major outcomes for the comparison of sevelamer with calcium are shown in the Summary of findings 5.

Studies comparing sevelamer with calcium were dominated by those evaluating therapy in participants with CKD G5D treated with dialysis. Death (all causes) was reported in sixteen studies. Of these, zero events were reported in four studies (Bleyer 1999; CARE 2004; Ferreira 2008; Kakuta 2011), deaths were reported as reasons for drop-out from study follow-up in six studies (BRiC 2005; CARE-2 2008; Hervas 2003; Lin 2014a; Sadek 2003; Vlassara 2012), and were reported as adverse events in two studies (Chertow 2002; Sezer 2010). In four studies, all-cause or cause-specific death was a pre-specified primary or secondary outcome (Block 2005; DCOR 2007; INDEPENDENT-CKD 2012; INDEPENDENT-HD 2009). In low certainty evidence downgraded for study limitations and evidence of important statistical heterogeneity, sevelamer may reduce death (all causes) compared with calcium-based binders (16 studies, 4266 participants: RR 0.53, 95% CI 0.30 to 0.91; I^2 = 78%) (Analysis 8.1). It was not possible to evaluate for presence of publication bias due to the important statistical heterogeneity.

In very low certainty evidence, whether sevelamer made any difference to cardiovascular death was uncertain (6 studies, 2904 participants: RR 0.45, 95% CI 0.11 to 1.77; I^2 = 73%) (Analysis 8.2), with important statistical heterogeneity in the analysis. Myocardial infarction (2 studies, 177 participants: RR 1.02, 95% CI 0.11 to 9.59; I^2 = 0%) (Analysis 8.3) and stroke (2 studies, 102 participants: RR 3.00, 95% CI 0.32 to 27.90; I^2 = 0%) (Analysis 8.4) were reported for a single patient in each of two studies leading to a very imprecise risk estimates. Two studies reported hospitalisation, with the evidence dominated by a single study with a large number of reported events in both groups (2 studies, 242 participants: RR 0.78, 95% CI 0.56 to 1.08; I^2 = 0%) (Analysis 8.5). Block 2009 reported no differences in fracture events between the two groups (Analysis 8.6).

In low certainty evidence involving studies with a median follow-up of 5.5 months, sevelamer may have similar risks of nausea compared with calcium (4 studies, 365 participants: RR 0.98, 95% CI 0.56 to 1.71; I^2 = 0%) (Analysis 8.7). Based on two studies in low certainty evidence, there was no clinical difference in the risk of vomiting between sevelamer and calcium (2 studies, 263 participants: RR 0.95, 95% CI 0.54 to 1.69; I^2 = 0%) (Analysis 8.8). There was no evidence of important differences in treatments for the risk of abdominal pain (4 studies, 363 participants: RR 1.77, 95% CI 0.68 to 4.63; I^2 = 0%) (Analysis 8.9), constipation (6 studies, 2652 participants: RR 1.35, 95% CI 0.71 to 2.57; I^2 = 2%) (Analysis 8.10), diarrhoea (3 studies, 315 participants: RR 0.98, 95% CI 0.55 to 1.75; I^2 = 0%) (Analysis 8.11), or abdominal bloating (2 studies, 112 participants: RR 4.85, 95% CI 0.87 to 27.03; I^2 = 0%) (Analysis 8.12).

In very low certainty evidence with important statistical heterogeneity in the analysis, sevelamer may result in markedly less hypercalcaemia compared with calcium-based binders (19 studies, 4084 participants: RR 0.30, 95% CI 0.20 to 0.43; I^2 = 49%) (Analysis 8.13). DCOR 2007 reported no difference in the comparative effect of sevelamer and calcium on calciphylaxis (Analysis 8.14). There was no evidence that the coronary artery calcium score at 12 or 24 months was different for sevelamer or calcium use (4 studies, 517 participants: MD -24.89, 95% CI -75.66 to 25.88; I^2 = 0%) (Analysis 8.15).

Among twenty-three studies involving 4360 participants, the mean serum phosphate at end of treatment was clinically similar between treatment groups (MD 0.06 mg/dL (0.02 mmol/L), 95% CI -0.11 to 0.23 mg/dL (-0.04 to 0.07 mmol/L); I^2 = 78%) (Analysis 8.16), although there was important statistical heterogeneity between the studies. Sevelamer may provide a small clinical impact on serum calcium compared with a calcium-based binder (22 studies, 4313: MD -0.38 mg/dL (-0.10 mmol/L), 95% CI -0.54 to -0.21 mg/dL (-0.14 to -0.05 mmol/L); I^2 = 92%), in an analysis showing substantial statistical heterogeneity (Analysis 8.17). Sevelamer may have similar clinical effects on the serum calcium-by-phosphate product (13 studies, 2983 participants: MD 0.36 mg^2/dL^2, 95% CI -0.57 to 1.28; I^2 = 25%) (Analysis 8.18), while sevelamer was possibly associated with a clinically increased serum iPTH levels (16 studies, 1420 participants: MD 44.24 pg/mL (5.04 pmol/L), 95% CI 10.93 to 77.55 (1.24 to 8.84 pmol/L); I^2 = 71%) (Analysis 8.19). Calcium-based treatment may decrease serum alkaline phosphatase compared to placebo (7 studies, 611 participants: MD 17.64 IU/L, 95% CI -0.16 to 35.43; I^2 = 68%) although the confidence interval included the possibility of no difference (Analysis 8.20). Sevelamer use may result in lower serum bicarbonate levels (7 studies, 695 participants: MD -1.57 mEq/L, 95% CI -2.15 to -1.00; I^2 = 24%) (Analysis 8.21). Russo 2007 reported no difference in eGFR between the groups at the end of treatment (Analysis 8.22). Lin 2014a reported no differences between the groups for serum FGF23 (Analysis 8.23) and soluble Klotho levels (Analysis 8.24).

Lanthanum versus calcium

The major outcomes for the comparison of lanthanum with calcium are shown in the Summary of findings 6.

Nearly all studies evaluated therapy in patients with CKD G5D treated with peritoneal dialysis or haemodialysis. None of the studies were designed to evaluate treatment effects on death or cardiovascular endpoints. Death (all causes) was reported in six studies. Of these, zero events were reported in two studies (D'Haese 2003; Shigematsu 2008), and seven events were reported among the remaining four studies (Ohtake 2013; Spasovski 2006; Toussaint 2009; Wada 2014) at between 6 and 18 months of therapy. In low certainty evidence, the effect of lanthanum treatment on death (all causes) was uncertain (6 studies, 5050 participants: RR 0.76, 95% CI 0.18 to 3.11; I^2 = 0%) (Analysis 9.1). Endpoints for cardiovascular death, myocardial infarction, and stroke were not reported in any of the studies. Based on two studies, there was no evidence of a clinically-important effect of lanthanum on hospitalisation (2 studies, 88 participants: RR 0.80, 95% CI 0.34 to 1.93; I^2 = 0%) (Analysis 9.2). Block 2009 reported not differences between lanthanum and calcium for fracture (Analysis 9.3) and pruritus (Analysis 9.4). Ohtake 2013 reported no difference between the two treatments on coronary artery calcium score (Analysis 9.11).

Evidence for treatment adverse effects was low- or very low-certainty. Lanthanum may lead to nausea (5 studies, 1191 participants: RR 1.65, 95% CI 0.95 to 2.89; I^2 = 20%), although the estimate included the possibility of no difference (Analysis 9.5). Lanthanum had uncertain effects on vomiting (2 studies, 1058 participants: RR 3.88, 95% CI 0.48 to 31.74; I^2 = 77%) with important statistical heterogeneity in the analysis (Analysis 9.6). There was no evidence of different effects for lanthanum and calcium on abdominal pain (2 studies, 137 participants: RR 0.24, 95% CI 0.03 to 1.94; I^2 = 0%) (Analysis 9.7), constipation (5 studies, 1213 participants: RR 0.79, 95% CI 0.50 to 1.26; I^2 = 0%) (Analysis 9.8), or diarrhoea (2 studies, 858 participants: RR 2.44, 95% CI 0.34 to 17.35; I^2 = 56%) (Analysis 9.9). Shigematsu 2008 reported no differences in abdominal bloating between the two groups (Analysis 9.10).

In very low certainty evidence with important statistical heterogeneity in the analysis, lanthanum may result in markedly less hypercalcaemia compared with calcium-based binders (8 studies, 1347 participants: RR 0.16, 95% CI 0.06 to 0.43; I^2 = 59%) (Analysis 9.12).

Lanthanum and calcium-based binders had clinically similar effects on serum phosphate (9 studies, 400 participants: MD -0.02 mg/dL (0.006 mmol/L), 95% CI -0.45 to 0.41 (-0.15 to 0.13 pmol/L); I^2 = 76%), in an analysis with marked statistical heterogeneity (Analysis 9.13). Lanthanum treatment may have a small clinical effect on serum calcium levels, although the estimated effect included the possibility of no difference (8 studies, 350 participants: MD -0.28 mg/dL (-0.07 mmol/L), 95% CI -0.59 to 0.02 mg/dL (-0.15 to 0.005 mmol/L); I^2 = 81%), in an analysis with important statistical heterogeneity (Analysis 9.14). Lanthanum may have reduced the serum calcium-by-phosphate product (5 studies, 1007 participants: MD -2.67 mg^2/dL^2, 95% CI -5.01 to -0.34; I^2 = 26%) (Analysis 9.15). There was no evidence of clinical differences in end of treatment serum PTH (8 studies, 597 participants: MD 33.78 pg/mL(3.85 pmol/L), 95% CI -9.03 to 76.60 pg/mL (-1.03 to 8.73 pmol/L); I^2 = 73%) (Analysis 9.16) or serum alkaline phosphatase (3 studies, 856 participants: MD 20.03 IU/L, 95% CI -3.69 to 43.75; I^2 = 88%) (Analysis 9.17). Soriano 2013 reported a higher eGFR at the end of treatment with lanthanum (Analysis 9.18). Lanthanum had uncertain effects on serum FGF23 levels compared with calcium-based binders (2 studies, 116 participants: SMD -0.85, 95% CI -2.33 to 0.63; I^2 = 90%) (Analysis 9.19).

Iron versus calcium

No studies were identified that provided a head-to-head comparison of iron- versus calcium-based binders.

Magnesium versus calcium

Spiegel 2007 reported no differences in hospitalisation (Analysis 10.1), constipation (Analysis 10.2), and diarrhoea (Analysis 10.3) between magnesium and calcium-based binders.

Aluminium versus calcium

Two studies evaluated aluminium compared with calcium (Janssen 1996; Jespersen 1991), however data could not be extracted from Jespersen 1991. Janssen 1996 reported lower serum alkaline phosphatase with calcium-based binders (Analysis 11.1).

Magnesium plus calcium versus calcium

Combined magnesium and calcium-based binders were compared with calcium alone in four studies (Delmez 1996; Deuber 2004; Evsanaa 2015; Tzanakis 2014). The studies were not designed to evaluate death or cardiovascular endpoints. Tzanakis 2014 reported no difference between the two groups for death as a reason for drop-out from the study during follow-up (Analysis 12.1).

The clinical effects of magnesium plus calcium compared with calcium alone on serum phosphate levels (2 studies, 109 participants: MD -1.26 mg/dL (-0.41 mmol/L), 95% CI -3.52 to 1.00 mg/dL (-1.14 to 0.32 mmol/L), I^2 = 93%) (Analysis 12.2) and serum calcium levels (2 studies, 109 participants: MD -0.92 mg/dL (-0.23 mmol/L), 95% CI -2.39 to 0.55 mg/dL (-0.60 to 0.14 mmol/L); I^2 = 96%) (Analysis 12.3) were uncertain in analyses with important statistical heterogeneity. Tzanakis 2014 reported no differences in serum calcium-by-phosphate product (Analysis 12.4) or iPTH (Analysis 12.5) between the two groups.

Sevelamer versus lanthanum

Clinical endpoints for the comparison of sevelamer versus lanthanum were reported in two groups of a four-arm study (Block 2009). Block 2009 reported no difference between the two groups for myocardial infarction (Analysis 13.1), stroke (Analysis 13.2), fracture (Analysis 13.3), pruritis (Analysis 13.4), nausea (Analysis 13.5), vomiting (Analysis 13.6), abdominal pain (Analysis 13.7), constipation (Analysis 13.8), diarrhoea (Analysis 13.9), abdominal bloating (Analysis 13.10), and hypercalcaemia (Analysis 13.11). Data from two other studies could not be extracted for meta-analysis (Kasai 2012; Pratt 2007).

Sevelamer versus iron

Sevelamer was compared with iron-based binders in four studies that reported outcomes during three to six months of follow-up (Chen 2011b; Floege 2014; Koiwa 2017; Yokoyama 2014). In three of the four studies, participants were treated with haemodialysis or peritoneal dialysis. The studies were not designed to evaluate death or cardiovascular endpoints. Deaths were reported as a

reason for drop-out from follow-up or as an adverse event in two studies. In very-low certainty evidence, sevelamer had uncertain effects on the risk of death (all causes) (4 studies, 1683 participants: RR 1.07, 95% CI 0.38 to 2.98; I^2 = 0%) (Analysis 14.1). Chen 2011b reported no differences between the groups for the risk of cardiovascular death (Analysis 14.2), myocardial infarction (Analysis 14.3), and fractures (Analysis 14.4).

Compared with iron-based binders, the risk of nausea (2 studies, 1257 participants: RR 3.86, 95% CI 0.33 to 44.86; I^2 = 68%) (Analysis 14.5), abdominal pain (2 studies, 431 participants: RR 0.42, 95% CI 0.02 to 9.01; I^2 = 79%) (Analysis 14.6), constipation (4 studies, 1699 participants: RR 4.96, 95% CI 1.96 to 12.55; I^2 = 71%) (Analysis 14.7), and diarrhoea (4 studies, 1699 participants: RR 0.28, 95% CI 0.15 to 0.54; I^2 = 51%) (Analysis 14.8) with sevelamer was uncertain in analyses with important statistical heterogeneity.

Based on two studies, whether sevelamer had different effects on serum phosphate levels compared with iron-based binders was uncertain in an analysis within substantial statistical heterogeneity (2 studies, 417 participants: MD 0.19 mg/dL (0.06 mmol/L), 95% CI -0.06 to 0.43 mg/dL (-0.02 to 0.14 mmol/L); I^2 = 28%) (Analysis 14.9). Sevelamer may slightly decrease serum calcium (2 studies, 417 participants: MD -0.16 mg/dL (-0.04 mmol/L, 95% CI -0.29 to -0.04 mg/dL (-0.07 to -0.01 mmol/L); I^2 = 0%) compared with iron (Analysis 14.10). Yokoyama 2014a reported serum bicarbonate levels were lower in the sevelamer group (Analysis 14.11).

Sevelamer versus bixalomer

Akizawa 2014a reported no differences between sevelamer and bixalomer for death (Analysis 15.1), fracture (Analysis 15.2), pruritis (Analysis 15.3), nausea (Analysis 15.4), vomiting (Analysis 15.5), abdominal pain (Analysis 15.6), constipation (Analysis 15.7), abdominal bloating (Analysis 15.8), serum phosphate (Analysis 15.9), serum calcium (Analysis 15.10), and serum calcium-by-phosphate product (Analysis 15.11). Akizawa 2014a reported serum iPTH (Analysis 15.12) and serum bicarbonate (Analysis 15.13) were lower in the sevelamer group.

Sevelamer versus nicotinamide

NICOREN 2017 reported no differences between sevelamer and nicotinamide for death (Analysis 16.1), stroke (Analysis 16.2), vomiting (Analysis 16.3), serum calcium (Analysis 16.4), serum iPTH (Analysis 16.5), and serum alkaline phosphatase Analysis 16.6).

Sevelamer versus colestilan

Clinical outcomes for the comparison of sevelamer versus colestilan were reported in three studies (Itoh 2008; Locatelli 2014; NCT00542815). In moderate certainty evidence, sevelamer may reduce death (all causes) compared with colestilan (2 studies, 536 participants: RR 0.30, 95% CI 0.10 to 0.96; I^2 = 0%) during follow-up ranging from 1.9 to 12 months (Analysis 17.1). NCT00542815 reported no differences between sevelamer and colestilan for cardiovascular death (Analysis 17.2), myocardial infarction (Analysis 17.3), stroke (Analysis 17.4), pruritis (Analysis 17.5), nausea (Analysis 17.6), vomiting (Analysis 17.7), abdominal pain (Analysis 17.8), constipation (Analysis 17.9), and diarrhoea (Analysis 17.10). Itoh 2008 reported no differences between the groups for serum phosphate (Analysis 17.11), serum calcium (Analysis 17.12), and serum calcium-by-phosphate product (Analysis 17.13). Itoh 2008 reported serum iPTH (Analysis 17.14) and serum alkaline phosphatase (Analysis 17.15) were lower in the sevelamer group.

Sevelamer versus aluminium

Katopodis 2006 reported no differences between sevelamer and aluminium for nausea (Analysis 18.1), constipation (Analysis 18.2), serum phosphate (Analysis 18.3), serum calcium (Analysis 18.4), and serum iPTH (Analysis 18.5).

Sevelamer versus magnesium

Zwiech 2011 reported serum phosphate (Analysis 19.1) and serum calcium-by-phosphate product (Analysis 19.3) were lower with magnesium; serum calcium (Analysis 19.2) was lower with sevelamer; and there was no difference between the groups for iPTH (Analysis 19.4).

Sevelamer versus sevelamer plus calcium

Chertow 1999 reported no differences between sevelamer and combination sevelamer plus calcium-based binders for hypercalcaemia (Analysis 20.1) and serum calcium-by-phosphate product (Analysis 20.2).

Sevelamer versus calcium plus magnesium

CALMAG 2010 reported no differences between sevelamer and combination calcium plus magnesium for serum phosphate (Analysis 21.1), serum calcium (Analysis 21.2), and serum iPTH (Analysis 21.3). Serum alkaline phosphate was reported to be lower with calcium plus magnesium (Analysis 21.4), and serum bicarbonate was reported to be lower with sevelamer (Analysis 21.5).

Lanthanum versus iron

Fujimori 2017 compared lanthanum to ferric citrate however data could not be extracted.

Sevelamer hydrochloride versus sevelamer carbonate

Fishbane 2010 reported no differences between sevelamer hydrochloride and sevelamer carbonate for death (Analysis 22.1), nausea (Analysis 22.2), vomiting (Analysis 22.3), constipation (Analysis 22.4), and diarrhoea (Analysis 22.5).

Calcium acetate versus calcium carbonate

Data for the comparison of calcium acetate compared with calcium carbonate were reported in four studies (Almirall 1994; Caravaca 1992; Foraster 1998; Janssen 1996). The studies were not designed to evaluate death or cardiovascular endpoints. It was uncertain whether calcium acetate prevents death because the certainty of the evidence was very low (2 studies, 74 participants: RR 1.13, 95% CI 0.07 to 17.30; I^2 = 0%) (Analysis 23.1). Calcium acetate may lower the risk of hypercalcaemia compared with calcium carbonate (2 studies, 92 participants: RR 0.66, 95% CI 0.45 to 0.97; I^2 = 0%) (Analysis 23.2). Adverse events for the treatment comparison could not be extracted for meta-analysis.

Calcium acetate may make little or no difference to serum phosphate levels (3 studies, 98 participants: MD -0.24 mg/dL (-0.08 mmol/L), 95% CI -0.74 to 0.26 mg/dL (-0.24 to 0.08 mmol/L); I^2 = 0%) (Analysis 23.3), serum calcium (3 studies, 98 participants: MD -0.21 mg/dL (-0.05 mmol/L), 95% CI -0.45 to 0.04 mg/dL (-0.11 to 0.01

mmol/L); I^2 = 0%) (Analysis 23.4), or serum alkaline phosphatase (2 studies, 35 participants: MD 1.77 IU/L, 95% CI -8.80 to 12.35; I^2 = 0%) (Analysis 23.7). Almirall 1994 reported no difference between the groups for calcium-by-phosphate product (Analysis 23.5) and Foraster 1998 reported no difference in serum iPTH (Analysis 23.6).

Investigation for sources of heterogeneity

Subgroup analysis

We pre-planned subgroup analysis by age (greater or less than 60 years old), CKD GFR categories (G2 to G5 or G5D), baseline serum phosphate level (above or below 4.5 mg/dL (1.5 mmol/L)), study duration (above and below 12 months), and methodological quality (low risk of bias for allocation concealment and high or unclear risk of bias). There was no evidence of different treatment effects based on these factors (Analysis 24.1; Analysis 24.2; Analysis 24.3; Analysis 24.4; Analysis 24.5). Subgroup analyses based on different serum phosphate levels at baseline were not possible. Subgroup analyses based on CKD GFR category were limited in statistical power as placebo or usual care controlled studies primarily involved participants with CKD G2 to G5, and those comparing calcium-free with calcium-based binders involved participants with GFR G5D.

Sensitivity analysis

Due to the low certainty of the comparison of sevelamer versus calcium on death (all causes) because of study limitations and evidence of important statistical heterogeneity, we did a sensitivity analysis restricting the comparison to studies with a low risk of selection bias. Limiting analysis to include the six studies at low risk of bias for this treatment comparison (Block 2005; BRiC 2005; CARE 2004; Chertow 2002; INDEPENDENT-CKD 2012; Kakuta 2011) resulted in evidence of decreased death (all causes) with sevelamer compared with calcium-based binders in an analysis without evidence of important statistical heterogeneity (RR 0.58, 95% CI 0.36 to 0.94; I^2 = 7%; *high certainty evidence*).

DISCUSSION

Summary of main results

In this updated review, 69 new studies have been added to the 2011 Cochrane review and 23 were removed to provide a total of 104 studies involving 13,744 adults. Studies comparing phosphate binders (sevelamer, lanthanum, calcium, and ferric citrate) to placebo or usual care without binder administration were largely limited to adult patients with CKD G2 to G5 not requiring dialysis (15/25 studies involving 1467 participants), Head-to-head studies including those comparing non-calcium- and calcium-based binders were predominantly conducted among participants with CKD G5D treated with dialysis (74/81 studies involving 10,364 participants).

Overall, the superiority of phosphate binders to placebo has not been demonstrated across the range of GFR categories. The addition of new studies has led to the updated conclusion that sevelamer may decrease death (all causes) in studies involving people with CKD G5D when compared with calcium-based binders. When restricted to higher quality studies, high certainty evidence suggested that sevelamer lead to lower death (all causes) when compared to calcium-based binders. Despite over one hundred studies eligible for this review, only three were designed to examine non-fatal cardiovascular events and all-cause and cardiovascular death as primary or important secondary outcomes. Currently, the evidence for effects of phosphate binders on cardiovascular events and cardiovascular death is uncertain due to a paucity of data. The effects of treatment on fracture and rare outcomes such as calciphylaxis were very uncertain because of a lack of studies reporting these outcomes.

Phosphate binders versus placebo or usual care

Placebo- or usual care-controlled studies predominantly involved participants who had moderate CKD (CKD G2 to G5 not requiring dialysis) and were of short duration (generally three months or less). These studies generally involved few participants, with nearly all involving < 200 adults. All but two placebo-controlled studies had been published since 2008.

No placebo-controlled study was designed to evaluate treatment effects on death (all causes) or individual major cardiovascular outcomes, such as stroke or myocardial infarction. Based on a limited number of short-term studies, whether phosphate binders prevented all-cause or cardiovascular death in adults with CKD G2 to G5 was uncertain. There is currently no high-certainty evidence that phosphate binders prevent myocardial infarction or stroke when compared with placebo or usual care. Sevelamer may incur nausea while lanthanum may lead to nausea and constipation, and iron-based binders may lead to diarrhoea or constipation.

We were uncertain whether phosphate binders impacted on coronary artery calcium scores, fracture risk, or calciphylaxis when compared to placebo in adults with CKD G2 to 5, although the follow-up duration was very short. Not unexpectedly, calcium-based binders incurred substantially increased risks of hypercalcaemia.

Non-calcium-based binders versus calcium-based binders

Unlike placebo-controlled studies which were conducted in the setting of CKD G2 to 5, active comparator studies evaluating treatment against calcium-based binders were generally conducted among adults with CKD G5D treated with dialysis. Studies involved generally few participants with the median sample size of 70 adults. Follow-up ranged between 1.8 and 36 months, with a median of 6 months. Three studies were designed to evaluate all-cause or cause-specific death as a pre-specified primary or secondary outcome.

In low certainty evidence, sevelamer may prevent death (all causes) when compared with calcium-based binders. This finding was robust when evaluated in an analyses restricted to higher quality studies, leading to higher certainty in the result. It is unclear from this observation whether sevelamer leads to lower death, calcium-binders cause excess death, or both these observations are true.

It was uncertain whether lanthanum decreased death (all causes) compared with calcium-based binders, and comparative data for iron-based binders were absent. There was no evidence that non-calcium phosphate binders improved fracture, pruritus, calciphylaxis, or coronary artery calcification. Sevelamer and lanthanum may have similar risks of nausea, vomiting or constipation compared with calcium-based binders. Not unexpectedly, sevelamer and lanthanum may incur less hypercalcaemia than calcium-based binders. There was no evidence that non-calcium and calcium-based binders had different effects on serum phosphate levels.

Non-calcium-based binder versus non-calcium-based binder

Head-to-head studies of sevelamer, lanthanum, iron, and other non-calcium phosphate binders were extremely limited. No available studies were designed to evaluate death or cardiovascular events. The effects of treatment on other outcomes were obscured by the paucity of data including for adverse treatment events.

Overall, there was insufficient evidence to conduct subgroup analyses based on CKD GFR category and to assess individual phosphate binder agents within drug classes.

Overall completeness and applicability of evidence

This review included evidence from 104 RCTs from 29 different countries or global regions, to evaluate the effects of phosphate binders versus placebo or usual care or other phosphate binder. In general, placebo- and usual care studies were more recently published and involved adults with CKD who do not require dialysis therapy. Active comparator studies were mostly conducted among dialysis patients. Therefore, there is a paucity of placebo-controlled studies in the dialysis setting.

In general, study follow-up was short and very few studies were designed to evaluate death endpoints, specifically for lanthanum and iron-based binders compared with calcium-based agents for dialysis patients. An ongoing study (LANDMARK 2017) of lanthanum carbonate compared with calcium carbonate has completed recruitment of 2309 participants treated with haemodialysis and is due to report in July 2018. The primary outcome of the LANDMARK 2017 is survival free from a composite of cardiovascular death and nonfatal cardiovascular events, and may provide new information relevant to death outcomes for phosphate binders in CKD G5D. A further placebo-controlled study of lanthanum among 278 participants with an eGFR between 15 to 44 mL/ min/1.73m^2 is due to complete follow-up in December 2018 (IMPROVE-CKD 2012) with the primary outcome of arterial compliance. This may provide additional data for surrogate outcomes in CKD G2 to G5 not requiring dialysis.

A key limitation in the evidence is the lack of standardisation of outcome reporting in the available studies. As a result, many outcomes, such as cardiovascular events, hospitalisation, itch, calciphylaxis, and fracture were reported in few studies. For many of these outcomes, the data were available on the study registry database rather than reporting within primary journal publication. In future phosphate binder studies, standardisation of outcome reporting, as prioritised by the Standardised Outcomes in Nephrology (SONG) by patients, caregivers and health professionals may assist to improve the evidence base. In the haemodialysis setting, this would include the compulsory reporting of endpoints for fatigue, cardiovascular disease, vascular access, and death (SONG-HD). Based on SONG-HD, additional core outcomes for studies of phosphate binders might include mobility, pain, hospitalisation, bone health, calcium, itching, nausea/vomiting, serum phosphate levels, restless legs syndrome, and financial impact.

Complications from phosphate binders reported in the included studies were principally gastrointestinal adverse events. However, as the event rates in available studies were often low, we could not be certain whether there were between-group differences for many of the adverse outcomes. Potential adverse events such as severe bowel complications, or fractures related to suppressed bone turnover (from calcium-based binders) and microfracture accumulation are not well understood based on existing studies.

Based on epidemiological data, there is evidence that higher serum phosphate levels are consistently associated with death for people with CKD (Block 1998; Block 2004; Palmer 2011). This evidence generates the biological plausibility for use of phosphate binders to improve clinical outcomes, and generates the ongoing clinical equipoise needed for the further conduct of RCTs with sufficient power to detect patient-level outcomes. Based on the data in this review, evidence for outcomes such as death, cardiovascular events, fracture, pain, and health-related quality of life are required to support decision-making for phosphate binder uses in CKD G2 to G5, and data for cardiovascular events and skeletal symptoms would assist decision-making for patients with CKD 5D, particularly for regimens restricting the use of calcium-based binders and less stringent serum phosphate control.

Quality of the evidence

The overall certainty of the evidence for most outcomes was low or very low, meaning that future research is likely to have an important impact on our knowledge of the benefits and harms of phosphate binders according to the GRADE approach (GRADE 2008). Key methodological limitations included attrition from follow-up due to events that may have been related to the clinical outcomes of interest, differences between treatment groups, or relatively larger proportions of randomised participants. Methods for random sequence generation and allocation concealment were insufficiently reported in most studies, preventing judgement of the risks of bias for these parameters. Empirical evidence suggests that treatment effects may be exaggerated when allocation concealment and blinding are not reported within studies, although this is particularly relevant for subjective outcomes including symptoms and adverse events (Wood 2008). Study limitations led to the downgrading of all evidence by one level (from high to moderate). Minimisation of selection and detection bias in future research studies would increase the certainty of treatment benefits and harms.

The relative impact of sevelamer and calcium-based binders on death was downgraded due to important statistical heterogeneity (I^2 = 74%), leading to low certainty in the evidence. This heterogeneity could not be explained by pre-specified subgroup analyses including subgroups based on age, stage of CKD, duration or follow-up or study risk of bias. When this analysis was restricted to the six studies (1053 participants) at low risk of bias for random sequence generation or allocation concealment, we found that there was moderate-to-high certainty of lower death with sevelamer compared with calcium-based binders (RR 0.55, 95% CI 0.36 to 0.82; I^2 = 4%). This meta-analysis that was restricted to lower risk studies provided a similar magnitude of effect as the full meta-analysis of all available studies, and had no important statistical heterogeneity.

Evidence for adverse events was frequently low or very low certainty, due to substantial imprecision in treatment estimates and study limitations including selective reporting of outcomes.

Potential biases in the review process

This review was carried out using standard Cochrane methods. Each step was completed independently by at least two authors

including selection of studies, data management, and risk of bias assessment, thus reducing the risks of errors in identification of eligible studies and adjudication of evidence certainty. A highly sensitive search of the Cochrane Kidney Transplant Specialised Registry was completed without language restriction in November 2017, with a final search undertaken in just prior to publication in July 2018. The Registry contains hand-searched literature and conference proceedings, maximising the inclusion of grey literature in this review. Most studies did not report key outcomes in a format available for meta-analysis. This potentially introduced bias in our review and may have been a source of publication bias. We identified three studies (NCT00317694; NCT00560300; NCT01968759) that had completed based on study registry information but for which we could not obtain results despite attempted contact with investigators. These studies may be a potential source of bias. Formal assessment for publication bias through visualisation of asymmetry in funnel plots was precluded for many treatments and outcomes because of few studies.

Agreements and disagreements with other studies or reviews

Numerous systematic reviews with meta-analysis of RCTs investigating phosphate binders in CKD have been published including our own (Palmer 2016), and others (Bravo-Soto 2017; Burke 2003; Habbous 2017; Jamal 2009; Jamal 2013; Manns 2004; Patel 2016; Sekercioglu 2016; Sekercioglu 2017; Tonelli 2007; Wang 2015; Zhang 2010). Most existing reviews have focused on the comparison between calcium-based and non-calcium-based phosphate binders because of the concern that excess exogenous calcium may accelerate vascular calcification and cardiovascular complications and calciphylaxis, and due to emerging evidence of higher death with calcium-based treatments (Jamal 2009). Essentially the current Cochrane review is consistent with the findings of earlier reviews that have identified lower death for sevelamer treatment compared with calcium-based binders although few existing analyses have incorporated judgement of evidence certainty. The reported relative risk for death (all causes) with sevelamer compared with calcium-based phosphate binders have ranged between 0.54 and 0.78. In the review by Bravo-Soto 2017 including studies available in existing systematic reviews, the authors used the GRADE process. They downgraded evidence certainty for death by three grades to very low due to risks of bias (two downgrades) and inconsistency between studies.

The present Cochrane review update is consistent with existing systematic reviews demonstrating there is little or no evidence for beneficial treatment effects on cardiovascular death for non-calcium versus calcium-based binders, a marked reduction in risks of hypercalcaemia with non-calcium binders, and variable hazards of gastrointestinal adverse effects with specific agents.

A previous review has focused on the available evidence with respect to coronary artery calcification (Zhang 2010). The findings of that review are broadly consistent with ours that it is not possible to establish whether or not specific phosphate binders alter progression of coronary artery calcification scores.

Notably in our and other reviews, robust long-term study data for lanthanum or iron-based binders compared with either placebo or calcium-based binders on death outcomes and adverse events are lacking.

The findings of this updated review are consistent with the Kidney Disease Improving Global Outcomes (KDIGO) 2017 Clinical Practice Guideline Update for the evaluation, prevention and treatment of CKD-MBD (KDIGO 2017) that suggest that the dose of calcium-based phosphate binders is restricted among adult patients receiving phosphate-lowering treatment. This updated guideline removes the more restrictive qualifier present in the earlier 2009 KDIGO guideline that calcium-based phosphate-binders be avoided in patients with hypercalcaemia, known arterial calcification, adynamic bone disease, or low serum PTH levels (KDIGO 2009), and is updated based on the additional death data available from three new studies (Block 2009; INDEPENDENT-CKD 2012; INDEPENDENT-HD 2009). It should be noted that current evidence does not allow us to discern whether the increased possible hazard for death with calcium-based binders compared with sevelamer is caused by calcium-containing medications. A placebo-controlled study of calcium-based phosphate binders could address this question but such a study is unlikely to be conducted.

AUTHORS' CONCLUSIONS

Implications for practice

The superiority of phosphate binders over placebo has not been demonstrated across the range of GFR categories. The current evidence for phosphate binders supports the use of sevelamer compared with calcium-based agents based on lower death (all causes) with sevelamer for adults with CKD G5D. Whether this finding is due to avoidance of calcium loading from calcium-based binders, or a direct beneficial effect of sevelamer on lowering phosphate balance or both is not known. It is not possible to definitively establish whether this possible benefit of sevelamer on death (all causes) when compared with calcium-based binders extends to other non-calcium-based binders including lanthanum and iron-based binders as studies for these agents have not evaluated death and cardiovascular outcomes. However, the LANDMARK 2017 is near to reporting. The impact of sevelamer or other non-calcium-based binders on cardiovascular events and death, bone symptoms, or vascular calcification is uncertain. There is very limited evidence for phosphate binders compared with placebo or usual care in the dialysis setting. As such, the superiority of phosphate-binding therapies over placebo has not been demonstrated across the range of CKD GFR categories.

For patients with CKD G2 to G5 not requiring dialysis, there is very limited evidence for phosphate binders compared with placebo or usual care. The impact of phosphate binder therapy on cardiovascular complications and bone and skeletal symptoms is uncertain for this group of patients.

Overall, there are very few data for the comparative effects of individual phosphate binders including iron-based binders and sevelamer hydrochloride versus sevelamer bicarbonate.

Patients across the range of GFR categories should be informed about the low- to very-low certainty evidence for use of phosphate binders with respect to death and cardiovascular outcomes and of the potential for phosphate binders to cause harm. Patients in CKD GFR categories G2 to G5 not treated with dialysis may reasonably choose not to receive or limit phosphate binder therapy based on the lack of clear evidence for improved clinical outcomes and potential side-effects. Patients who are on

dialysis should be informed of the balance between the potential benefits and adverse effects of phosphate binders, including possible differences in these benefits and adverse events between binder classes as well as the lack of evidence of phosphate binders compared with placebo. Patients treated with dialysis may reasonably wish to avoid or to limit calcium-based binders due to the potential for higher treatment-related death and may reasonably choose not to receive or limit phosphate binder therapy due to the low or very low certainty evidence.

Implications for research

Based on limitations in existing studies and a paucity of evidence for specific clinical questions, further research is likely to change the estimated effects of different phosphate binders in CKD and increase our certainty in the evidence.

Current research does not provide high-quality evidence for the long-term benefits of lanthanum or iron-based binders compared with either placebo or calcium-based treatment. The LANDMARK 2017 comparing lanthanum carbonate versus calcium carbonate among >2300 patients is due to report and may offer higher certainty for the effects of lanthanum carbonate for people with ESKD treated with dialysis. It will be important to update this Cochrane review when the LANDMARK study results are reported. A similar study of an iron-based binder such as ferric citrate or sucroferric oxyhydroxide compared with a calcium-based binder or placebo and designed to evaluate death and cardiovascular events would inform contemporary clinical decision-making.

The present body of evidence for phosphate binders includes over 100 studies involving over 13,000 patients. Despite this, evidence for the use of phosphate binders is low or very low certainty because of the dominance of small studies, the short duration of follow-up for many studies, and the incomplete reporting of core outcomes that are most relevant to clinical care. Future phosphate binder studies should be designed to evaluate patient-centred core outcomes based on SONG-HD together with systematic reporting of adverse events and specific outcomes related to CKD-MBD, such as bone pain, inability to participate in life and work, health-related quality of life, and impaired mobility. It would be very informative if future studies could incorporate cost-effectiveness analyses as part of the study design.

Studies comparing non-calcium phosphate binders with calcium binders are principally in patients treated with dialysis. Future large-scale placebo-controlled studies of sevelamer, lanthanum, or iron-based binders particularly involving patients treated with dialysis are critical to informing clinical across the range of CKD GFR categories would inform clinical care.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ahmed 2014

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 24 weeks
Participants	• Country: Pakistan • Setting: single centre • Inclusion criteria: 18 to 80 years; HD; serum phosphorus > 4 mg/dL; serum calcium < 10.4 mg/dL; iPTH > 25 pg/ml • Number (analysed/randomised): treatment group 1 (not reported/70); treatment group 2 (not reported/70) • Mean age ± SD (years): treatment group 1 (44.9); treatment group 2 (41.9) (SD not reported) • Sex (M/F): treatment group 1 (37/33); treatment group 2 (41/29) • Exclusion criteria: malignant involvement of bone; tertiary hyperparathyroidism; salt-wasting nephropathy
Interventions	Treatment group 1 • Sevelamer hydrochloride: 800 mg, 3 times/d for 24 weeks Treatment group 2 • Calcium acetate: 667 mg, 3 times/d for 24 weeks Cointerventions • HD 3 times/wk • Dialysis calcium: 1.25 mmol/L
Outcomes	• Serum calcium • Serum phosphate • Serum iPTH
Notes	• Funding sources were not reported • There was no reported registration of the study within a trials registry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement. "Randomly divided into two groups"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators aware of treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not mentioned. Outcomes were laboratory measures and unlikely to be influenced by lack of blinding

Ahmed 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal/lost to follow-up was not reported
Selective reporting (reporting bias)	High risk	Only laboratory measures were reported. Patient-level outcomes including adverse events were not reported
Other bias	High risk	Differences in mean baseline values of serum calcium and iPTH between treatment groups

Akizawa 2000

Methods	• Study design: parallel, open-label RCT • Time frame: not reported • Follow-up period: 8 weeks
Participants	• Country: Japan • Setting: not reported • Inclusion criteria: HD • Number (analysed/randomised): treatment group 1 (not reported/115); treatment group 2 (not reported/115) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride: mean dose 2.8 g/d (range 1.0 to 5.0). Dose titrated according to investigator discretion Treatment group 2 • Calcium carbonate mean dose 4.7 g/d (range 1.3 to 7.7). Dose titrated according to investigator discretion Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum calcium • Serum iPTH • Major adverse events including gastrointestinal disorders, constipation, hypercalcaemia
Notes	• Funding sources: not reported • Study registration not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement

Akizawa 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory events which were unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Akizawa 2014a

Methods	• Study design: parallel RCT • Time frame: January 2010 to June 2010 • Duration of follow-up: 3 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: aged ≥ 20 years and < 75 years; CKD requiring treatment with HD 3 times/wk for at least 12 weeks before the washout period; stable dialysis treatment; hyperphosphataemia requiring phosphorus-lowering medications; no change to dose of phosphorus-lowering medications such as phosphate binders; stable dose of cinacalcet and active vitamin D preparations. • Number (analysed/randomised): treatment group 1 (48/55); treatment group 2 (46/55) • Mean age ± SD (years): treatment group 1 (60.2 ± 10.44); treatment group 2 (60.6 ± 7.96) • Sex (M/F): treatment group 1 (31/19); treatment group 2 (36/18) • Exclusion criteria: history of gastrectomy or bowel resection (except for polypectomy or appendectomy); dysphagia or bowel obstruction; gastrointestinal tract bleeding; severe chronic constipation or diarrhoea; parathyroid intervention (parathyroidectomy, percutaneous ethanol injection therapy, etc.) within 24 weeks (168 days) before starting the washout period; and patients with no oral intake or severe dietary restriction
Interventions	Treatment group 1 • Sevelamer hydrochloride: started at 3.0 or 6.0 g/d and adjusted to maximum of 9.0 g/d depending on the serum phosphate level Treatment group 2 • Bixalomer: started at 1.5 g/d and adjusted to maximum of 7.5 g/d depending on the serum phosphate level
Outcomes	• Serum phosphate • Serum target phosphate level between 3.5 to 6.0 mg/dL • Serum corrected calcium

Akizawa 2014a *(Continued)*

- Serum Ca x P product
- Serum iPTH
- Serious adverse events and adverse events
- Serum cholesterol levels
- Serum bicarbonate levels

Notes	• The study was funded by Astellas Pharma. Some authors were employees of the funding company • Study registration: www.ClinicalTrials.gov NCT01057407 • It was unclear whether the data management and analysis was conducted independently of the funding body.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators aware of treatment assignment. Lack of blinding could affect patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment reported. Most outcomes were objective (laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	9/55 in bixalomer group (adverse events (3); lack of efficacy (1); withdrawal of consent (3); other reasons (2)) did not complete study follow-up 7/55 in sevelamer group (adverse events (6); withdrawal of consent (1)) did not complete study follow-up
Selective reporting (reporting bias)	Low risk	All expected laboratory measures were reported. Adverse events were reported systematically
Other bias	High risk	Study was funded and authored by Astellas Pharma

Akizawa 2016

Methods	• Study design: parallel RCT • Duration of follow-up: 3 months • Time frame: October 2012 to May 2014
Participants	• Country: Japan • Setting: multicentre • Discontinued therapy: 32/163 randomised participants • Inclusion criteria: ≥ 20 years, could give informed consent, and were unlikely to need dialysis after preliminary registration and 6 months after study treatment started • Number (analysed/randomised): treatment group (80/81); control group (81/82) • Mean age ± SD: treatment group (62.9 ± 10.9); control group (65.5 ± 8.2)

Akizawa 2016 *(Continued)*

- Sex (M): treatment group (47.5%); control group (48%)
- Exclusion criteria: hypocalcaemia (serum albumin corrected calcium < 7.0 mg/dL) during the pre-investigational period; history of gastrectomy or enterectomy (excluding polypectomy and appendectomy), or concurrent dysphagia, ileus, and/or haemorrhagic gastrointestinal lesions; persistent, severe constipation or diarrhoea; history of parathyroid intervention (parathyroidectomy or percutaneous ethanol injection therapy) within 6 months before or during the pre-investigational period; uncontrolled hypertension within 16 weeks before preliminary registration, or on the start day or 2 weeks after the start day of the pre-investigational period; having severe cerebrovascular or heart conditions concurrently or within 12 weeks before the start of the pre investigational period, or require hospitalisation during the pre-investigational period; hepatic impairment or diseases, serious drug allergy, malignancy, or previous kidney transplant; fasting or extreme dietary restriction; lactating, pregnant, or planning to be pregnant during the study; already received bixalomer medication or involved in other clinical studies within 12 weeks before informed consent

Interventions	Treatment group • Bixalomer: started at 1.5 g/d and adjusted to maximum of 7.5 g/d depending on the serum phosphate level. Control group • Placebo Co-interventions • Activated vitamin D or calcitonin
Outcomes	• Serum phosphorus • Achieving serum phosphorus target • Serum corrected calcium • Urinary phosphorus excretion • Adverse events • Serious adverse events • Death (all causes) • Cardiovascular death
Notes	• The study was funded by Astellas Pharma • Some authors were employees of the funding company • The study publication had medical writing assistance funded by the sponsor. • It was unclear whether data management and analysis was conducted independently of the study sponsor • Study registration: www.ClinicalTrials.gov NCT01742585

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The treatment allocation table was managed by the registration centre and drugs were allocated by drug number at the study site
Allocation concealment (selection bias)	Unclear risk	Assignment of study drugs was blinded using numbers registered at each study site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All drugs had indistinguishable appearance and packaging

Akizawa 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was mentioned. Most outcomes were objective (death or laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	15/66 participants assigned to bixalomer (adverse events (9); prohibited therapies (1), initiation of dialysis (3); other (1)) did not complete study 18/62 participants assigned to placebo (eligibility problems (1); adverse events (5); consent withdrawal (2); lack of efficacy (1); prohibited medication (1); initiation of dialysis (8)) did not complete study
Selective reporting (reporting bias)	Low risk	All expected laboratory measures were reported. Death (all causes), adverse events, and cardiovascular death were reported
Other bias	High risk	Study funded and authored by Astellas Pharma

Allam 2012

Methods	• Study design: parallel RCT • Follow-up period: 3 months • Time frame: August to December 2010
Participants	• Country: Egypt • Setting: multicentre (2 sites) • Inclusion criteria: regular HD > 3 months; stable dosage of calcium carbonate during previous 2 weeks; age > 21 years; serum phosphorus level ≥1.62 mmol/L (5 mg/dL) • Number (analysed/randomised): treatment group (26/30); control group (30/30) • Mean age ± SD (years): treatment group (51.63 ± 8.10); control group (50.2 ± 9.87) • Sex (M/F): treatment group (24/6); control group (22/8) • Exclusion criteria: pregnancy; liver disease; active peptic ulcer disease; treatment with carbamazepine; niacin therapy; non-adherence
Interventions	Treatment group • Nicotinamide: titrated to 1000 mg/d Control group • No treatment Co-interventions • Calcium carbonate
Outcomes	• Serum phosphorus • Serum calcium • Serum iPTH • Serum Ca x P product • Adverse events: GI disturbance, flushing, rash, and blurred vision, hepatotoxicity, thrombocytopaenia, uricaemia • Lipid profile
Notes	• Funding sources not described • Study registration not reported

Allam 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators aware of treatment assignment. Lack of blinding could affect patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Most outcomes were objective (laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	4/30 participants assigned to nicotinamide were withdrawn (due to adverse events) 0/30 participants assigned to control group were withdrawn
Selective reporting (reporting bias)	Low risk	All expected laboratory measures were measured. Adverse events were measured
Other bias	Low risk	The study appeared to be free of other sources of bias

Almirall 1994

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 24 weeks
Participants	• Country: Spain • Setting: single hospital • Inclusion criteria: long-term HD for 54 ± 38 months (3 times/wk) • Number (analysed/randomised): 7/10 • Mean age ± SD: 53 ± 13 years • Sex (M/F): 3/7 • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium carbonate: initial dosage of 4 g/d Treatment group 2 • Calcium acetate: initial dosage of 3.8 g/d Co-interventions • Oral calcitriol
Outcomes	• Serum calcium

Almirall 1994 *(Continued)*

	• Serum phosphorus • Ca x P product • iPTH • Hypercalcaemia • ALP • Adverse events
Notes	• Funding sources not reported • Study registration not required as published before 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and investigators aware of treatment assignment. Lack of blinding could affect patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Most outcomes were objective (laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/10 participants did not complete study (kidney transplant (1); adverse events due to calcium (1); changed address and treatment centre (1))
Selective reporting (reporting bias)	High risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses
Other bias	High risk	Doses of calcium were not comparable between groups. There was no washout interval between the two treatment periods. Data were not analysed using methods appropriate for cross-over study design

Aramwit 2012

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 2.75 months
Participants	• Country: Thailand • Setting: multicentre • Inclusion criteria: HD; serum phosphorus > 5.5 mg/dL; 23-74 years; dialysed for at least 6 months; Kt/V > 1.2; naive to nicotinamide treatment; iPTH > 800 pg/dL • Number (analysed/randomised): treatment group (not reported/14); control group (not reported/14) • Mean age ± SD (years): treatment group (45.52 ± 11.46); control group (49.39 ± 10.85) • Sex (M/F): treatment group (10/4); control group (10/4)

Aramwit 2012 *(Continued)*

	• Exclusion criteria: uncontrolled DM; abnormal liver function tests or chronic liver disease; chronic infection; malignancy; autoimmune disease; gout; recent GI haemorrhage
Interventions	Treatment group • Nicotinamide: initial dose 375 mg once/d and dose gradually increased once a week to 500, 750, and 1000 mg per day or the maximum dose tolerated Control group • Placebo Co-interventions • Aspirin for hot flushes; standard phosphate binding therapy; dietary advice. No dose adjustments were made to vitamin D derivatives, lipid-lowering agents, or phosphate binding drugs
Outcomes	• Serum phosphorus levels • Serum Ca x P product • Serum lipid levels • Death (all causes) • Adverse events
Notes	• Funding from the Graduate School, Chulalongkorn University • Study registration was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	study described as double-blinded, but the methods for participant and investigator blinding were not described. Lack of blinding may have affected patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Most outcomes were objective (death or laboratory measures) and unlikely to be influenced by lack of blinding Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/14 withdrawn from nicotinic acid treatment due to adverse events
Selective reporting (reporting bias)	Low risk	All expected laboratory measures were reported. Death (all causes) and adverse events were reported
Other bias	High risk	Baseline imbalance in serum PTH levels

Birck 1999

Methods	• Study design: cross-over RCT

Birck 1999 *(Continued)*

	• Time frame: not reported • Follow-up period: 24 weeks
Participants	• Country: Germany • Setting: multicentre • Inclusion criteria: HD for at least 12 months; hyperphosphataemia after withdrawal of phosphate-binding agents; known adherence to therapy; iPTH <10-fold upper normal level • Number (analysed/randomised): (not reported/28) • Mean age (range): 61 years (37 to 87) • Sex (M/F): 18/10 • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium ketoglutarate: to achieve serum phosphorus < 5.3 mg/dL Treatment group 2 • Calcium carbonate: to achieve serum phosphorus < 5.3 mg/dL Co-interventions • None reported
Outcomes	• Death (all causes) • Cardiovascular death • Serum calcium • Serum phosphorus • Serum iPTH • Serum calcitriol, albumin, bicarbonate • Hypercalcaemia
Notes	• Funding sources not reported • Study registration not required as published before 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators aware of treatment assignment. Lack of blinding may have affected patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was mentioned. Most outcomes were objective (death or laboratory measures) and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	4/30 participants withdrew from the study and were not included in analyses (severe intercurrent illness, kidney transplant; lost to follow up; death due to

Birck 1999 *(Continued)*

		MI). Unclear which treatment phase of the study was associated with patient drop-out
Selective reporting (reporting bias)	High risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. All expected laboratory measures were recorded. Death outcomes were recorded
Other bias	High risk	Data were not analysed using methods appropriate for cross-over study design

Bleyer 1999

Methods	• Study design: cross-over RCT • Time frame: July 1996 to February 1997 • Follow-up period: 16 weeks
Participants	• Country: USA • Setting: multicentre • Inclusion criteria: > 18 years; HD patients on stable doses of calcium or aluminium-based phosphate binders and on stable doses or no calcitriol for 1 month • Number (analysed/randomised): 80/83 • Mean age ± SD: 54.5 ± 15 years • Sex: 53% male • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride: 2 to 4 capsules 3 times/d to achieve serum phosphorus 2.5 to 5.5 mg/dL Treatment group 2 • Calcium acetate: 1 to 3 capsules 3 times/d to achieve serum phosphorus 2.5 to 5.5 mg/dL Co-interventions: Calcitriol
Outcomes	• Serum phosphorus • Serum calcium • Serum Ca x P product • Plasma iPTH • Lipid profile • Adverse events and serious adverse events
Notes	• Supported by a grant from GelTex Pharmaceuticals • Study registration not required as published before 2005 • Employees of GelTex Pharmaceuticals were listed as authors • It was unclear whether data management and analyses were conducted independently of funding body.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement

Bleyer 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators aware of treatment assignment. Lack of blinding could have affected patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was mentioned. Most outcomes were objective (death or laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	80/83 participants completed both treatment sequences
Selective reporting (reporting bias)	Low risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. Key laboratory measures reported. Adverse events reported
Other bias	High risk	Data were not analysed using methods appropriate for cross-over study design. Smaller doses of control therapy (calcium acetate) than intervention were used. Baseline characteristics for each treatment group were not provided; funded by GelTex

Block 2005

Methods	• Study design: parallel RCT, stratified by presence of DM • Time frame: September 2000 to December 2002 (enrolment) • Follow-up period: 18 months
Participants	• Country: USA • Setting: multicentre (5 sites) • Inclusion criteria: > 18 years; incident HD • Number (analysed/randomised): treatment group 1 (54/73); treatment group 2 (55/75) • Mean age ± SD (years): treatment group 1 (59 ± 15); treatment group 2 (57 ± 15) • Sex (% men): treatment group 1 (59); treatment group 2 (67) • Exclusion criteria: prior history of dialysis; kidney transplant; coronary artery bypass surgery; weight > 300 pounds; current atrial fibrillation or atrial flutter
Interventions	Treatment group 1 • Sevelamer hydrochloride: investigators were instructed to control parameters of mineral metabolism (calcium, phosphorus, Ca x P product , iPTH), and dyslipidaemia per their clinic routine. No study specific management protocols were provided. Treatment group 2 • Calcium-containing phosphate binders. Investigators were instructed to control parameters of mineral metabolism (calcium, phosphorus, Ca x P product, iPTH) and dyslipidaemia per their clinic routine. No study specific management protocols were provided Co-interventions • Dialysate calcium 2.5 mEq/L

Block 2005 *(Continued)*

	• Investigators were free to alter phosphate binder dose and, within the calcium treatment arm, to alternate between various types of calcium containing phosphate binders at their discretion • Patients randomised to sevelamer were allowed to take calcium as a nightly supplement at the discretion of the investigator
Outcomes	• Death (all causes) • Adverse events • Serum phosphorus • Serum iPTH • Serum calcium • Hypercalcaemia • CACS
Notes	• Study supported by Genzyme Corp • Study registration was not required at the time of publication • The design, conduct, analysis, and publication of the study was solely the responsibility of the Principal Investigators. Data were maintained and analysed solely by the authors. There were no restrictions on the publication of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation to treatment was computer generated in blocks of 10"
Allocation concealment (selection bias)	Low risk	"Assigned by the coordinating centre using concealed envelopes". Not stated whether envelopes were sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants received open label sevelamer or calcium containing phosphate binders. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was mentioned. Most outcomes were objective (death or laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding. CACS scans were read by a single experienced investigator (P.R.) who was blinded to all other patient data
Incomplete outcome data (attrition bias) All outcomes	High risk	19/73 participants allocated to sevelamer were not included in analysis (11 did not have CT at baseline; adverse event (1); transplanted (2); death (1); other (2); transferred to peritoneal dialysis (2)) 20/75 participants allocated to calcium were not included in analysis (8 did not have baseline CT; adverse event (1); transplanted (3); death (1); other (4); lost to follow-up (1); transfer to PD (2))
Selective reporting (reporting bias)	Low risk	Key laboratory measures, adverse events, and death reported
Other bias	Low risk	The study appeared to be free from other sources of bias

Block 2009

Methods	• Study design: parallel RCT • Time frame: February 2009 to September 2010 (enrolment) • Follow-up period: 9 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: eGFR 20 to 45 ml/min per 1.73 m^2; serum phosphorus ≥ 3.5 to < 6.0 mg/dL (1.13 to 1.94 mmol/L); willingness to avoid intentional change in diet • Number (analysed/randomised): treatment group 1 (25/30); treatment group 2 (18/30); treatment group 3 (22/30); control group (41/58) • Mean age ± SD (years): treatment group 1 (66 ± 12); treatment group 2 (70 ± 10); treatment group 3 (68 ± 12); control group (65 ± 12) • Sex (% men): treatment group 1 (50); treatment group 2 (54); treatment group 3 (47); Control group (49) • Exclusion criteria: phosphate binding medication; use of active vitamin D treatment or cinacalcet; iPTH ≥ 500 pg/mL (57 pmol/L); uncontrolled hyperlipidaemia
Interventions	Treatment group 1 • Lanthanum carbonate: 1 or 2 units (500 mg) per meal based on screening serum phosphorus below or above 4.5 mg/dL. Increased study medication at each visit if the serum phosphorus remained >3.5 mg/dL to a maximum dose of 1500 mg per meal Treatment group 2 • Sevelamer carbonate: 1 or 2 units (800 mg) per meal based on screening serum phosphorus below or above 4.5 mg/dL. Increased study medication at each visit if the serum phosphorus remained >3.5 mg/dL to a maximum dose of 3200 mg per meal Treatment group 3 • Calcium acetate: 1 or 2 units (667 mg) per meal based on screening serum phosphorus below or above 4.5 mg/dL. Increased study medication at each visit if the serum phosphorus remained > 3.5 mg/dL to a maximum dose of 2668 mg per meal Control group • Placebo Co-interventions • Not reported
Outcomes	• Serum phosphorus (change from baseline) • Serum PTH • FGF23 • Serum 1,25 dihydroxy-vitamin D • Urine phosphorus • Fractional excretion of phosphorus • Coronary artery, thoracic and abdominal aorta calcium volume scores • Lumbar bone mineral density • Adverse events and serious adverse events
Notes	• Funding for this investigator-initiated study was provided by Shire, Inc., Fresenius NA, Genzyme, Inc., Denver Nephrologists, PC, Novartis, Inc., and Davita, Inc. • Funding entities had no role in the design, conduct, analysis, interpretation, or preparation of the manuscript. Each funding entity was permitted to review the manuscript for verification that no proprietary or confidential information was included

Block 2009 *(Continued)*

- Study registration: www.ClinicalTrials.gov NCT00785629

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent statistician performed randomisation using SAS
Allocation concealment (selection bias)	Low risk	Sealed envelopes were opened at the study centre by a staff member not involved in the conduct of the study. Not stated whether opaque or sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study medication was released by a single unblinded staff member in bottles identified by a unique identification number. The study was double-blinded with active drug and matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All clinical personnel, data analysts, and participants remained blinded to study treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	5/30 participants assigned to sevelamer did not complete study (consent withdrawn (1); non-adherence (2); adverse event (1); other (1)) 12/30 participants assigned to lanthanum did not complete study (not treated (2); consent withdrawn (2); non-adherence (4); adverse event (1); other (3)) 8/30 participants assigned to calcium did not complete study (non-adherence (1); adverse event (2); other (2); drug expiration (3)) 17/58 participants assigned to placebo did not complete study (not treated (1); consent withdrawn (2); non-adherence (5); adverse events (4); other (2); renal replacement (1); drug expiration (2)
Selective reporting (reporting bias)	Low risk	Key laboratory measures reported; vascular calcification reported; adverse events reported
Other bias	Low risk	The study appeared to be free from other sources of bias

Block 2015

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 2.75 months
Participants	• Country: USA • Setting: multicentre • Inclusion criteria: eGFR <60 mL/min/1.73 m^2, serum phosphate level ≥ 4.0 to 6.0 mg/dL, serum ferritin level ≤3 00 ng/mL, TSAT≤ 30%, Hb 9.0 to 12.0 g/dL • Number (analysed/randomised): treatment group (72/75); control group (69/74) • Mean age ± SD (years): treatment group (66 ± 12); control group (64 ± 14) • Sex (% men): treatment group (31.9) control group (37.7) • Exclusion criteria: ESA within 4 weeks or IV iron within 8 weeks of screening; any known cause of anaemia other than iron deficiency or CKD; symptomatic GI bleeding, or inflammatory bowel disease

Block 2015 *(Continued)*

Interventions	Treatment group • Ferric citrate: commenced at 1000 mg 3 times/d (210 mg of ferric iron) and adjusted according to serum phosphorus levels. Control group • Placebo: commenced at one caplet 3 times/d and adjusted according to serum phosphorus levels. Co-interventions • Not reported
Outcomes	• eGFR • TSAT • Serum phosphate • Hb • Serum ferritin • Urinary phosphate • Serum FGF23 • Treatment emergent adverse effects • Serious adverse effects • Death (all causes)
Notes	• Support for the conduct of this study was provided by Keryx Biopharmaceuticals Inc, which contributed to the study design, data acquisition, and data analysis. Support for medical writing/editing was provided by Keryx Biopharmaceuticals Inc • Drs Block, Fishbane, and Chertow had final decision-making responsibility for the primary and secondary outcomes of the study and in determining the inclusion of data in the manuscript. Drs Block and Chertow had final decision-making authority on the content of the manuscript • Study registration: www.ClinicalTrials.gov; study number NCT01736397

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned patients by a centralised interactive voice-response system with allocation generated by an independent biostatistician
Allocation concealment (selection bias)	Low risk	Randomly assigned patients by a centralised interactive voice-response system with allocation generated by an independent biostatistician
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Keryx Biopharmaceuticals Inc provided active drug and matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Most outcomes were objective (death or laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All except 1 participant were included in safety analysis 14/75 participants assigned to ferric citrate discontinued intervention (treatment failure (1); withdrew consent (6); adverse events (6); other(1))

Block 2015 *(Continued)*

		24/74 participants assigned to placebo discontinued intervention (treatment failures (11); withdrew consent (5); lost to follow-up (1); adverse events (3); other (4))
Selective reporting (reporting bias)	Low risk	All the review's key outcomes were recorded
Other bias	Low risk	The study appeared to free from other sources of bias

BRiC 2005

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 months
Participants	• Country: Brazil • Setting: multicentre (4 sites) • Inclusion criteria: maintenance HD for at least 3 months, > 18 years, iPTH levels < 1000 pg/mL • Number (analysed/randomised): treatment group 1 (41/52); treatment group 2 (30/49) • Mean age ± SD (years): treatment group 1 (47 ± 13); treatment group 2 (47 ± 14) • Sex (M/F): treatment group 1 (27/14); treatment group 2 (21/9) • Exclusion criteria: GI disease; ethanol or drug abuse; active malignancy; HIV infection; chronic inflammatory disease; current use of steroids; severe hyperparathyroidism; body weight > 100 kg; continuous use of antiarrhythmic or seizure drugs; pregnancy or breast-feeding; previous myocardial revascularization; uncontrolled diabetes or hypertension
Interventions	Treatment group 1 • Sevelamer hydrochloride: adjusted monthly up to 12 mg/d Treatment group 2 • Calcium acetate: adjusted monthly up to 2.028 mg of elemental calcium/d Co-interventions: calcium dialysate concentration; vitamin D treatment.
Outcomes	• Serum phosphorus • Serum ionised calcium • Serum iPTH • Serum Ca x P product • Serum albumin • Histomorphometric data from bone biopsies • Vascular calcification • Total cholesterol • CRP, TNF-alpha, IL-10 • Death (all causes)
Notes	• Study registration not reported as published before this requirement was encouraged for all studies published • The funding source was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

BRiC 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Treatment was assigned by the coordinating centre using concealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Coronary artery scores were assessed by an outcome assessor who was blinded to treatment allocation. No blinding of outcome assessment for other outcomes was reported. Most outcomes were objective (death or laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	11/52 participants allocated to sevelamer did not complete follow-up (parathyroidectomy (transplanted (6); death (1); other (3)) 19/49 participants allocated to calcium did not complete follow-up (parathyroidectomy (1); transplanted (6); death (8); other (4))
Selective reporting (reporting bias)	Low risk	Key laboratory measures were reported; adverse events were not reported; death was reported.
Other bias	Low risk	The study appeared to be free from other sources of bias

Bro 1998

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 12 weeks
Participants	• Country: Denmark • Setting: single centre • Inclusion criteria: age > 18 years; HD treatment for at least 1 month; stable protein and energy intake; treatment with a dialysate calcium concentration of 1.25 mmol/L; stable dosage of alfacalcidol for the last 2 months • Number (analysed/randomised): (10/19) • Median age (range): 54 years (25 to 80) • Sex (M/F): 12/7 • Exclusion criteria: pregnancy or lactation; intellectual impairment or dementia; psychiatric illness; recent infection or surgical trauma within 3 months; insufficient dialysis (Kt/V < 1.2); malignancies; immobilisation; prior parathyroidectomy and tertiary hyperparathyroidism
Interventions	Treatment group 1 • Calcium ketoglutarate: to achieve serum phosphorus < 5.3 mg/dL. The starting dose was 4 g 3 times/d administered as equal amounts to be taken with meals. Maximum dose was 12 g 3 times/d. Only in cases of combined hyperphosphataemia (plasma phosphate > 6.2 mg/dL) and hypercalcaemia (plasma ionised calcium > 5.4 mg/dL), was the main phosphate binder temporarily supplemented with or replaced by aluminium aminoacetate Treatment group 2

Bro 1998 *(Continued)*

	• Calcium carbonate: to achieve serum phosphorus < 5.3 mg/dL. The starting dose of calcium carbonate was identical to the pre study dose. Only in cases of combined hyperphosphataemia (plasma phosphate > 6.2 mg/dL) and hypercalcaemia (plasma ionised calcium > 5.4 mg/dL), was the main phosphate binder temporarily supplemented with or replaced by aluminium aminoacetate Co-interventions • Oral alfacalcidol
Outcomes	• Serum phosphorus • Serum calcium • Plasma PTH • Plasma albumin; bicarbonate; creatinine; urea • Treatment intolerance (nausea, vomiting, diarrhoea) • Adverse events
Notes	• Study received financial support from the Danish Kidney Foundation and Leo Pharmaceuticals, Ballerup, Denmark. Calcium ketoglutarate was provided by Gambro Medicoteknik A/S, Vallensbaek, Denmark. It was not clear whether the study design, conduct, data management and analysis were independent of the funding bodies • Study registration was not required at the time of publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators aware of treatment assignment. Lack of blinding likely to influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Most outcomes were objective (laboratory measures) and unlikely to be influenced by lack of blinding. Adverse event reporting may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	10/19 participants who were randomised to treatment were not included in analysis; 5/17 patients who started calcium ketoglutarate treatment showed immediate intolerance to ketoglutarate 12 g/d and were withdrawn from the study within 1 to 2 weeks
Selective reporting (reporting bias)	Low risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses Key laboratory measures and adverse events were collected
Other bias	High risk	The content of elemental calcium was lower in the group assigned to calcium ketoglutarate at the commencement of therapy. Statistical analysis was not specifically appropriate for a cross-over study design. The baseline characteristics for each treatment group were not provided

Caglar 2008

Methods	• Study design: parallel RCT • Time frame: 2005 to 2006 • Follow-up period: 2 months
Participants	• Country: Turkey • Setting: outpatient clinic of a tertiary referral nephrology centre • Inclusion criteria: CKD stage 4; > 18 years; serum phosphorus > 1.78 mmol/L (> 5.5 mg/dL) • Number (analysed/randomised): treatment group 1 (25/25); treatment group 2 (25/25) • Mean age ± SD (years): treatment group 1 (43.1 ± 12.6); treatment group 2 (43.6 ± 13.6) • Sex (M/F): treatment group 1 (12/13); treatment group (13/12) • Exclusion criteria: diabetes; hypercalcaemia (> 2.75 mmol/L (11 mg/dL)); history of coronary artery disease; smokers; prescription of statins or renin-angiotensin blockers
Interventions	Treatment group 1 • Sevelamer hydrochloride: starting dose 1600 mg 3 times/d Treatment group 2 • Calcium acetate: starting dose 1000 mg 3 times/d Co-interventions • Patients were not given calcitriol during the study period
Outcomes	• Fetuin-A • High-sensitivity CRP • Ca x P product • Flow-mediated dilation • Insulin • Homeostasis model assessment • Serum calcium • Serum phosphorus
Notes	• Funded in part by an unconditional grant to the Karolinska Institutet from Baxter Healthcare • Study registration: www.ClinicalTrials.gov NCT00486772

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators aware of treatment assignment. Lack of blinding likely to influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment of flow mediated dilatation was conducted by investigators who were unaware of treatment allocation. Blinding of outcome assessment for other outcomes was not reported. Most outcomes were objective (laboratory measures) and unlikely to be influenced by lack of blinding

Caglar 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in analyses
Selective reporting (reporting bias)	High risk	All key laboratory measures were reported. Adverse events and other patient-level outcomes were not reported
Other bias	Low risk	The study appeared to be free from other sources of bias

CALMAG 2010

Methods	• Study design: parallel RCT • Time frame: November 2007 to March 2009 • Follow-up period: 6 months
Participants	• Country: Germany, Poland, Portugal, Romania, Spain • Setting: multicentre (36 sites) • Inclusion criteria: 18 to 85 years; stable without serious illness; treated with 4 to 6 h HD or online haemodiafiltration 3 times/wk for at least 3 months; not taking any magnesium or calcium containing supplement; serum phosphorus ≥ 1.78 mmol/L (5.5 mg/dL); serum calcium ≤ 2.6 mmol/L (≤ 10.4 mg/dL) and serum magnesium ≤ 1.5 mmol/L (≤ 3.65 mg/dL) • Number (analysed/randomised): treatment group 1 (99/129); treatment group 2 (105/126) • Mean age ± SD (years): treatment group 1 (55.9 ± 11.75); treatment group 2 (59.2 ± 13.72) • Sex (M/F): treatment group 1 (51/48); treatment group 2 (56/49) • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride: 800 mg (starting dose of study drugs was at least four tablets per day. Thereafter, following each laboratory result and depending on individual dietary intake, the dose was increased by one to three tablets per day (i.e. one to two tablets per meal) in order to reduce serum phosphorus levels below 1.78 mmol/L (5.5 mg/dL) in the absence of hypercalcaemia or hypermagnesaemia. Treatment group 2 • Calcium acetate: 435 mg containing 110 mg elemental calcium combined with magnesium carbonate 235 mg containing 60 mg elemental magnesium (OsvaRen®). Starting dose of study drugs was at least four tablets per day. Thereafter, following each laboratory result and depending on individual dietary intake, the dose was increased by one to three tablets per day (i.e. one to two tablets per meal) in order to reduce serum phosphorus levels below 1.78 mmol/L (5.5 mg/dL) in the absence of hypercalcaemia or hypermagnesaemia. Co-interventions • None reported
Outcomes	• Serum phosphorus • Serum calcium • Serum magnesium • iPTH • ALP • Lipid levels • GI quality of life index • Safety parameters (adverse events/serious adverse events)

CALMAG 2010 *(Continued)*

Notes	• This study was supported by Fresenius Medical Care Deutschland GmbH, Germany. It was not clear whether the study design, conduct, data management and analysis were independent of the funding body • The study was registered at the European clinical study database: EudraCT No.: 2006-002589-20.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study medication was packed in opaque blister strips and only administered by the study nurse whereby the investigator and other site staff was masked to study medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary efficacy parameter (serum phosphorus) was determined in a central laboratory blinded to treatment allocation as were all other persons involved in the study. GI quality of life index was completed by personnel who were unaware of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	34/129 participants allocated to sevelamer did not complete intervention (lack of efficacy data (5); withdrawal of consent (14); adverse event (9); transplantation (7); other (4)) 18/126 participants allocated to calcium/magnesium not included in analyses (lack of efficacy data (3); withdrawal of consent (7); adverse event (3); transplantation (6); other (2))
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were collected
Other bias	Low risk	The study appeared to be free from other sources of bias

Caravaca 1992

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 16 weeks
Participants	• Country: Spain • Setting: single centre • Inclusion criteria: chronic HD treatment for 2 to 175 months; CrCl < 1 mL/min; treatment with aluminium hydroxide • Number (analysed/randomised): treatment group 1 (35/40); treatment group 2 (31/40) • Mean age ± SD (years): treatment group 1 (45 ± 16); treatment group 2 (51 ± 10) • Sex (M/F): treatment group 1 (17/16); treatment group 2 (20/11) • Exclusion criteria: changes in vascular access; non-adherence
Interventions	Treatment group 1

Caravaca 1992 *(Continued)*

	• Calcium carbonate: 3.75 g/d titrated to achieve predialysis serum phosphorus levels of 1.40 to 1.77 mmol/L Treatment group 2 • Calcium acetate: 6.5 g/d titrated to achieve predialysis serum phosphorus levels of 1.40 to 1.77 mmol/L Co-interventions • None reported
Outcomes	• Serum phosphorus • Serum calcium • iPTH level • Protein catabolic rate
Notes	• No funding source reported • Study registration not reported as study published before late 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Outcome measures were laboratory measurements and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	5/40 participants allocated to calcium carbonate were not included in analyses 9/40 participants allocated to calcium acetate were not included in analyses Seven patients did not tolerate calcium acetate due to adverse events Two patients did not tolerate calcium carbonate.
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded. Adverse events (other than GI events) and death were not reported
Other bias	Low risk	The study appeared to be free from other sources of bias

CARE 2004

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 8 weeks

CARE 2004 *(Continued)*

Participants	• Country: USA • Setting: multicentre (6 outpatient clinics at 2 centres) • Inclusion criteria: HD for at least 3 months; receiving a stable dose of phosphate binder and IV vitamin D for at least 1 month • Number (analysed/randomised): treatment group 1 (45/50); treatment group 2 (46/48) • Mean age ± SD (years) treatment group 1 (52.3 ± 14.7); treatment group 2 (53.9 ± 13.3) • Sex (M/F): treatment group 1 (28/22); treatment group 2 (28/20) • Exclusion criteria: iPTH > 1000 pg/mL; history of previous parathyroidectomy
Interventions	Treatment group 1 • Sevelamer hydrochloride: 2 to 4 capsules (403 mg) 3 times/d to achieve serum phosphorus < 5.5 mg/dL Treatment group 2 • Calcium acetate: 2 to 4 capsules (667 mg) 3 times/d to achieve serum phosphorus < 5.5 mg/dL Co-intervention • IV vitamin D analogues
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH • Adverse events • Serum bicarbonate • Hypercalcaemia • Hypocalcaemia
Notes	• This study was sponsored by grants from Braintree Laboratories, Braintree, Massachusetts, and Nabi Biopharmaceuticals, Boca Raton, Florida. It was not clear whether the study design, conduct, data management and analysis were independent of the funding bodies • Study registration was not required at the time this study was published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study blinding was maintained by packaging calcium acetate in hard gelatin capsules identical to the sevelamer hydrochloride capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Outcomes were predominantly laboratory measures and unlikely to be affected by outcome assessment. Adverse events were possibly influenced by an awareness of treatment allocation
Incomplete outcome data (attrition bias)	High risk	5/50 participants allocated to sevelamer not included in analyses 2/48 participants allocated to calcium not included in analyses

CARE 2004 *(Continued)*

All outcomes		Reasons for withdrawal not provided
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	High risk	Imbalance in baseline characteristics

CARE-2 2008

Methods	• Study design: parallel RCT • Time frame: January 2005 to November 2005 • Follow-up period: 52 weeks
Participants	• Country: USA • Setting: multicentre (26 sites) • Inclusion criteria: ESKD; age ≥ 18 years; HD for 3 months to 5 years • Number (analysed/randomised): treatment group 1 (70/100); treatment group 2 (59/103) • Mean age ± SD (years): treatment group 1 (58.5 ± 12.8); treatment group 2 (60.3 ± 12.1) • Sex (M/F): treatment group 1 (46/54); treatment group 2 (61/42) • Exclusion criteria: condition that could restrict survival of participants for the duration of the study or interfere with their ability to follow the study
Interventions	Treatment group 1 • Sevelamer hydrochloride: to achieve a phosphorus level of 3.5 to 5.5 mg/dL and LDL < 70 Treatment group 2 • Calcium acetate: to achieve a phosphorus level of 3.5 to 5.5 mg/dL and LDL < 70 Co-interventions • None reported
Outcomes	• Serum phosphorus • Serum calcium • Death (all causes) • Adverse events • Change in CACS assessed by means of electron-beam CT • Cardiac valvular calcification • Ca x P product • Hypercalcaemia • Serum PTH
Notes	• This study was supported by a grant from Fresenius Medical Care North America, Waltham, MA. Employees of companies that were involved in development of the investigational drug were authors. It was not clear whether the study design, conduct, data management and analysis were independent of the funding bodies • Study registration: www.ClinicalTrials.gov NCT00211939

Risk of bias

Bias	Authors' judgement	Support for judgement

CARE-2 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was stratified by centre using computerised lists for each site
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessments for coronary artery calcification were forwarded to a single experienced cardiologist who was blinded to treatment assignment, identifying information, and temporal relationship of the scans. Blinding of other outcomes was not reported. Outcome measures were objective (laboratory and radiological) and were unlikely to be influenced by study blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	17/100 participants allocated to sevelamer were unavailable at 12 months (death (1); lost to follow-up (1); non-adherence (3); protocol violation (1); withdraw consent (2); adverse event (5); transplant (3); transfer (1)) 15/103 participants allocated to calcium were unavailable at 12 months (death (1); lost to follow-up (1); non-adherence (5); protocol violation (1); withdrawal consent (1); adverse event (2); transplant (1); transfer (1))
Selective reporting (reporting bias)	Low risk	All the review's key outcomes were recorded
Other bias	Low risk	The study appeared to be free from other sources of bias

Chen 2011b

Methods	• Study design: parallel RCT • Follow-up period: 3 months • Time frame: not reported
Participants	• Country: Japan and Taiwan • Setting: multicentre • Inclusion criteria: CKD; patients aged ≥ 18 years; long-term HD 3 times/wk for longer than 3 months; stable on oral phosphate binders • Number analysed/randomised: treatment group 1 (67/68); treatment group 2 (134/135) • Mean age ± SD (years): treatment group 1 (59.6 ± 11.3); treatment group 2 (58.1 ± 11.1) • Sex (M/F): treatment group 1 (38/29); treatment group 2 (76/58) • Exclusion criteria: haemochromatosis; unstable GI motility disorder; history of major GI tract surgery; other clinically unstable medical condition
Interventions	Treatment group 1 • Sevelamer hydrochloride: dosed 3 times/d with meals. Starting doses/d were 2.4 or 4.8 g. Daily doses were up-titrated every 2 weeks by 2.4 g to reach K/DOQI recommended target serum phosphate concentration ≤ 1.7 mmol/L at 72 h post-HD. Down-titration was permitted to maintain serum phosphate ≥ 1.1 mmol/L or in case of adverse events Treatment group 2

Chen 2011b *(Continued)*

	• SBR759: dosed 3 times/d with meals. Starting doses/d were 3.0 or 4.5 g. Daily doses were up-titrated every 2 weeks by 3 g for SBR759 to reach K/DOQI recommended target serum phosphate concentration ≤ 1.7 mmol/L at 72 h post-HD. Down-titration was permitted to maintain serum phosphate ≥ 1.1 mmol/L or in case of adverse events Co-interventions • None reported
Outcomes	• Death (all causes) • Serum phosphorus • Serum calcium • Serum iPTH • Adverse events • Fracture • Serum iron, total iron-binding capacity, ferritin, percent transferrin saturation
Notes	• This study was supported by Novartis Pharma AG, Switzerland. Several employees of the funding body were authors of the study publication. It was not clear whether the study design, conduct, data management and analysis were independent of the funding body • Study registration: www.ClinicalTrials.gov NCT00704678

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported, however most outcomes were objective laboratory or death measures
Incomplete outcome data (attrition bias) All outcomes	Low risk	14/68 participants allocated to sevelamer did not complete study (adverse events (9); abnormal laboratory values (2); withdrawal consent (3)) 16/135 participants allocated to SBR759 did not complete study (adverse events (5); consent withdrawal (10); protocol violation (1))
Selective reporting (reporting bias)	Low risk	All key laboratory outcomes, death, and adverse events were measured
Other bias	High risk	Funded by Novartis

Chen 2014

Methods	• Study design: parallel RCT • Time frame: March to September 2010

Chen 2014 *(Continued)*

	• Follow-up period: 2 months
Participants	• Country: China • Setting: multicentre (18 sites) • Inclusion criteria: patients aged ≥18 years receiving maintenance HD for 30 days or longer; serum phosphorus level > 1.78 mmol/L (> 5.51 mg/dL) after phosphate binder withdrawal and an iPTH ≤ 114 pmol/L (1000 pg/mL) at screening • Number analysed/randomised: treatment group (128/135); control group (68/70) • Mean age ± SD (years): treatment group (48.4 ± 13.1); control group (49.5 ± 12.3) • Sex (M/F): treatment group (84/51); control group (40/30) • Exclusion criteria: severe GI motility disorder; poorly controlled DM; uncontrolled hypertension or any other clinically significant unstable medical condition
Interventions	Treatment group • Sevelamer carbonate: 800 mg tablet 3 times/d with meals Control group • Placebo Co-interventions • None reported
Outcomes	• Serum phosphorus • Serum total and LDL cholesterol • Serum corrected calcium phosphorus product • Serum bicarbonate • Adverse events
Notes	• This study was funded by Genzyme Corporation. Several employees of the funding body were authors of the study publication. It was not clear whether the study design, conduct, data management and analysis were independent of the funding body • The authors acknowledge proofreading and graphical support for this manuscript provided by Envision Scientific Solutions, whose services were funded by Sanofi • Study registration was not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Outcomes were primarily laboratory measures and unlikely to be influenced by lack of blinding

Chen 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	7/135 participants allocated to sevelamer did not complete study (adverse events (4); preference to withdraw (3)) 2/70 participants allocated to placebo did not complete study (adverse event (1); consent withdrawal (1))
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	High risk	Funded and authored by Genzyme

Cheng 2008

Methods	• Study design: placebo-controlled, cross-over RCT • Time frame: February 2006 to December 2006 • Follow-up period: 16 weeks
Participants	• Country: USA • Setting: Singe centre, 2 sites • Inclusion criteria: ≥ 18 years; capacity for informed consent; long term HD > 90 days; stable dosage of phosphorus binders during the previous 2-week period; serum phosphorus level > 5.0 mg/dL • Number analysed/randomised: 33/33 • Age: 52.6 years • Sex (M/F): 23/10 • Exclusion criteria: pregnancy; history of liver disease; active peptic ulcer disease; treatment with carbamazepine; niacin therapy; more than one missed HD session in the past 30 days
Interventions	Treatment group • Niacinamide: 250 mg twice/d increased to 500 mg twice/d at week 3 and 750 mg twice/d at week 5 Control group • Placebo Co-interventions • Phosphorus binders, vitamin D, paricalcitol, cinacalcet
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • Serum PTH • Uric acid levels
Notes	• One author "received support for this study through the Amgen Fellowship Support Stipend during the 2006 to 2007 academic year" • Study registration: www.ClinicalTrials.gov NCT00316472

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement

Cheng 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules containing 250 mg of niacinamide or placebo were manufactured by a research pharmacist; double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Outcomes were laboratory measures that were unlikely to be influenced by any lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants completed the study
Selective reporting (reporting bias)	High risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. No patient-centred outcomes including adverse events were provided
Other bias	High risk	The study analyses were not conducted appropriately for the cross-over study design

Chennasamudram 2013

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 4 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: type 2 diabetes; treated with PD; serum phosphate levels ≥ 5.5 mmol/L • Number analysed/randomised: not reported/15 • Mean age ± SD: 54 ± 9 years • Sex (men): 53.3% • Exclusion criteria: PTH > 1,000 mmol/L, calciphylaxis, a history of hypercalcaemia within the past three months or a history of allergy/intolerance to sevelamer
Interventions	Treatment group 1 • Sevelamer hydrochloride: initial dose of two capsules of 800 mg each, 3 times/d (4.8 g/d). The dosage was adjusted every two weeks if needed to maintain a serum phosphate level < 5.5 mmol/L Treatment group 2 • Calcium carbonate: initiated at a dose of 1,000 mg, 3 times/d. The dosage was adjusted every two weeks if needed to maintain a serum phosphate level < 5.5 mmol/L Co-interventions: none reported.
Outcomes	• Flow mediated dilatation • Endothelin-1 • Plasminogen activator inhibitor

Chennasamudram 2013 *(Continued)*

- Serum soluble vascular adhesion molecule-1 and soluble intercellular adhesion molecule 1; pro-inflammatory cytokines interleukin-6 and interleukin-1; TNF-a; CRP and endothelial cell injury marker and cluster of differentiation-146 (CD146)
- Serum albumin, calcium, phosphate and lipids

Notes	• The study was sponsored by Sanofi, Inc., Cambridge, MA. It was not clear whether the study design, conduct, data management and analysis were independent of the funding body • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Outcomes were predominantly objective laboratory or clinical measures and were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants who completed study follow-up and were included in analyses was not reported
Selective reporting (reporting bias)	High risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. No patient-centred outcomes including adverse events were provided
Other bias	High risk	The study analyses were not conducted appropriately for the cross-over study design. The baseline characteristics for each treatment group were not reported in sufficient detail to determine whether they were balanced

Chertow 1999

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 weeks
Participants	• Country: USA • Setting: multicentre (number of sites not reported) • Inclusion criteria: > 18 years; HD 3 time/wk for at least 3 months; regular administration of calcium- and/or aluminium-based phosphate binders, with or without vitamin D metabolite replacement therapy at stable doses for at least one month before screening • Number analysed/randomised: treatment group 1 (35/35); treatment group 2 (36/36) • Mean age ± SD (years): treatment group 1 (55.9 ± 14.1); treatment group 2 (60.7 ± 15.0) • Sex(M/F): treatment group 1 (10/25); treatment group 2 (14/22)

Chertow 1999 *(Continued)*

	• Exclusion criteria: total parathyroidectomy; serious GI disease (including dysphagia, vomiting, motility disorder, major intestinal surgery, markedly irregular bowel function); ethanol or drug dependence or abuse; active malignancy; HIV infection; vasculitis; poorly controlled diabetes or hypertension
Interventions	Treatment group 1 • Sevelamer hydrochloride: 2 to 4 capsules (465 mg) 3 times/d to achieve serum phosphorus 2.5 to 5.5 mg/dL Treatment group 2 • Sevelamer hydrochloride: 2 to 4 capsules (465 mg) 3 times/d + calcium carbonate 900 mg/d to achieve serum phosphorus 2.5 to 5.5 mg/dL Co-interventions • IV or oral vitamin D analogues
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH • Lipid profile
Notes	• Study funding from GelTex Pharmaceuticals. It was not clear whether the study design, conduct, data management and analysis were independent of the funding body • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported. Outcomes were predominantly objective laboratory or clinical measures and were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported in sufficient detail to permit judgement
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded. No patient-centred outcomes including adverse events were provided
Other bias	Low risk	The study appeared to be free from other sources of bias

Chertow 2002

Methods	• Study design: parallel RCT • Time frame: May 1999 to January 2001 • Follow-up period: 52 weeks
Participants	• Countries: USA, Germany, Austria • Setting: multicentre; USA (15), Germany (7), Austria (1) • Inclusion criteria: > 19 years; HD patients • Number analysed/randomised: treatment group 1 (unclear/99); treatment group 2 (unclear/101) • Mean age ± SD (years): treatment group 1 (57 ± 14); treatment group 2 (56 ± 16) • Sex (M/F): treatment group 1 (36/63); treatment group 2 (34/67) • Exclusion criteria: serious GI disease (dysphagia, active untreated gastroparesis, severe motility disorder, major intestinal surgery, markedly irregular bowel function); ethanol or drug dependence or abuse; active malignancy; HIV infection; vasculitis; poorly controlled diabetes or hypertension
Interventions	Treatment group 1 • Sevelamer hydrochloride: dose to achieve serum phosphorus of 3 to 5 mg/dL and serum calcium 8.5 to 10.5 mg/dL Treatment group 2 • Calcium acetate/carbonate: dose to achieve serum phosphorus level of 3 to 5 mg/dL and serum calcium level of 8.5 to 10.5mg/dL Co-interventions • Aluminium as a rescue binder, vitamin D, dialysate calcium
Outcomes	• Serum phosphorus, calcium, iPTH, lipid profile • Ca x P product • Cardiovascular calcification • CACS • Aortic calcification score • Hypercalcaemia • Trabecular bone density • Cortical bone density • Changes in bone attenuation • Markers of bone turnover
Notes	• This study was supported by Genzyme Corporation. Employees of the funding body were authors of the study publication. It was not clear whether the study design, conduct, data management and analysis were independent of the funding body • Study registration not required.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule was computer generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Open label. Lack of blinding may have influenced patient management

Chertow 2002 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment of CACSs was blinded. The blinding of other outcome measures was not reported. Outcomes were predominantly objective laboratory or clinical measures and were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported in sufficient detail to permit judgement
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded. No patient-centred outcomes including adverse events were provided
Other bias	Low risk	The study appeared to be free from other sources of bias

CRIB-PHOS 2011

Methods	• Study design: parallel RCT • Time frame: 2009 to 2011 • Follow-up period: 10 months
Participants	• Country: UK • Setting: single centre • Inclusion criteria: 18 to 80 years; stage 3 CKD (eGFR 30 to 59 mL/min/1.73 m^2); total cholesterol < 212 mg/dL; resting BP < 140/90 mmHg • Number analysed/randomised: treatment group (54/55); control group (50/53) • Mean age ± SD (years): treatment group (55 ± 13); control group (55 ± 14) • Sex (M/F): treatment group (32/23); control group (28/26) • Exclusion criteria: existing or previous treatment with the last year with a phosphate binder or vitamin D compound; serum phosphorus > 1.81 mmol/L (> 5.6 mg/dL) or < 0.81 mmol/L (< 2.5 mg/dL); PTH > 9.1 pmol/L (> 80 pg/mL); DM; pregnancy; history of GI pathology
Interventions	Treatment group 1 • Sevelamer carbonate: 1600 mg sevelamer carbonate with meals during a 4-week open-label run-in phase. This dose was reduced to 800 mg with meals only if persistent adverse effects or hypophosphataemia occurred. Those who tolerated sevelamer then underwent 1:1 randomisation to continue another 36 weeks of treatment of sevelamer with meals Treatment group 2 • Placebo Co-interventions • Treatment with vitamin D analogues and other phosphate binders was not permitted during study enrolment • Regular medications unrelated to mineral metabolism that were taken at study entry were continued; no changes were made to regular medications during the study period
Outcomes	• Left ventricular mass • Serum FGF23 • Arterial stiffness • Aortic distensability • Bone density • eGFR

CRIB-PHOS 2011 *(Continued)*

- Plasma 25-dihydroxyvitamin D
- 24-hour urine phosphate excretion
- Serum phosphate
- Serum calcium
- Serum PTH
- Hypophosphataemia
- Death (all causes)

Notes	• The study was investigator led and funded by an unrestricted grant from Genzyme Corporation. Genzyme Corporation provided the study drug sevelamer carbonate and matching placebo. Genzyme Corporation had no role in study design or data analysis and interpretation • Study registration: www.ClinicalTrials.gov NCT00806481; Current Controlled Trials ISRCTN35254279

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcomes were predominantly objective laboratory or clinical measures and were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/55 allocated to sevelamer were withdrawn (hypophosphataemia (3); withdrew consent (1); intolerance (1)) 7/54 allocated to placebo were withdrawn (hypophosphataemia (1); withdrew consent (5); intolerance (1))
Selective reporting (reporting bias)	Low risk	Key laboratory measures and death were reported
Other bias	Low risk	The study appeared to be free from other sources of bias

D'Haese 2003

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 1 year
Participants	• Countries: Belgium, Czech Republic, Italy, Macedonia, Poland, Portugal, South Africa, Tenerife, Yugoslavia, UK, USA • Setting: international multicentre study (18 sites) • Inclusion criteria: > 18 years; HD or PD within 12 weeks; people who had been diagnosed with CKD and were scheduled to begin dialysis • Number analysed/randomised: treatment group 1 (34/49); treatment group 2 (34/49)

D'Haese 2003 *(Continued)*

	• Mean age ± SD: 55 ± 14.3 years • Sex (M/F): 59/39 • Exclusion criteria: hypocalcaemia or concurrent illness
Interventions	Treatment group 1 • Lanthanum: titrated up to 3750 mg/d Treatment group 2 • Calcium carbonate: titrated up to 9000 mg/d Co-interventions • Oral or IV vitamin D analogues
Outcomes	• Serum calcium • Serum phosphorus • iPTH • Markers of bone turnover
Notes	• Funding sources not reported • Study registration not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding likely to influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcomes were predominantly objective laboratory or clinical measures and were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal due to adverse events was lanthanum 24% and calcium 22%
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded. Patient-centred outcomes including cause-specific adverse events and death were not reported
Other bias	Unclear risk	Insufficient information to permit judgement. The baseline characteristics for each treatment group were not provided to assess for balance

DCOR 2007

Methods	• Study design: parallel RCT

DCOR 2007 *(Continued)*

	• Time frame: March 2001 to December 2004 • Follow-up period: 20.3 ± 13.9 months (treatment group 1); 19.6 ± 13.6 months (treatment group 2)
Participants	• Country: USA • Setting: 75 Fresenius dialysis centres within the United States • Inclusion criteria: age >18 years; patients on HD for more than 3 months required phosphate binders therapy • Number analysed/randomised: treatment group 1 (551/1053); treatment group 2 (517/1050) • Mean age ± SD (years): treatment group 1 (59.9 ± 14.3); treatment group 2 (60.1 ± 15.2) • Sex (M/F): treatment group 1 (574/479); treatment group 2 (569/481) • Exclusion criteria: dysphagia/swallowing disorders; severe GI motility disorders; bowel obstruction
Interventions	Treatment group 1 • Sevelamer hydrochloride: 6.9 g daily (mean) Treatment group 2 • Calcium-based binders: calcium acetate (mean 5.3 g); calcium carbonate (mean 4.9 g) Co-interventions • not reported
Outcomes	• Death (all causes) • Cause-specific death: MI, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary oedema, cerebrovascular accident, ischaemic brain damage/anoxic encephalopathy • Hospitalisation
Notes	• Genzyme Corporation funded this study and wrote the protocol. It was not clear whether the funding agency had a role in study design, conduct, analysis, or manuscript for publication. Averion Inc (Southborough, MA, USA) monitored data collection and provided data management and statistical analysis. The primary author (Suki) reviewed all statistical analyses and authored this paper in collaboration with the other authors • Study registration: www.ClinicalTrials.gov NCT00324571

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcomes were predominantly objective measures and were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias)	High risk	502/1053 allocated to sevelamer not included in analyses 533/1050 allocated to placebo not included in analyses

DCOR 2007 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Key patient-centred outcomes reported
Other bias	High risk	Many sites (number not specified) participated in the study until 31 December 2003. This was the originally planned study end date. A more extended follow-up period was deemed inappropriate because of the anticipated crossover to the alternate therapy in those who terminated early, especially in those terminating due to adverse events or investigator decisions. There was a single pre-specified interim analysis at which a P-value of 0.006 was required to stop the study and a P-value of 0.048 was required to achieve statistical significance at the end of the study based on the O'Brien and Fleming sequential testing procedure. A Data Monitoring Committee (DMC) conducted the interim analysis in two stages 1 year after the last patient enrolled. First, the DMC conducted a blinded analysis of aggregated death data. The aggregate death rate was 13.6 per 100 patient-years, substantially lower than the anticipated 17.8 per 100 patient-years. The DMC recommendation to extend the treatment by a year, to retain the original power of the study, was followed. Second, the DMC conducted an unblinded analysis on the primary end point data. The death difference was not significant (stopping rule: P<0.006). Results of this second analysis were not shared with the investigators, Genzyme, or anyone else involved with the study

De Santo 2006

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 24 weeks
Participants	• Country: Italy • Setting: hospital • Inclusion criteria: 35 to 50 years; HD 6 to 10 months; urine volume < 50 mL/d, stable haemodynamic status, reached Hb target • Number analysed/randomised: (not reported/8) • Age range: 36 to 50 years • Sex (M/F): All male • Exclusion criteria: DM; severe osteitis fibrosa; use of corticosteroids; phosphorus levels < 5.5 mg/dL; not requiring phosphate binders; iPTH > 400 pg/mL; non-compliant; ethanol or drugs dependence; HIV infection; vasculitis; active malignancy; severe GI disease
Interventions	Treatment group 1 • Sevelamer hydrochloride: starting at 1600 mg 3 times/d for serum phosphorus in the range 6.0 to 7.5 mg/dL, 2400 mg 3 times/d for serum phosphorus > 7.5 mg/dL. The phosphate binder was titrated every 2 weeks to achieve serum phosphorus < 5.5 mg/dL and calcium concentrations in the range 8.5 to 10.5 mg/dL Treatment group 2 • Calcium carbonate: 625 mg/half tablet to achieve a phosphorus level of 5.5 mg/dL and calcium concentrations in the range of 8.5 to 10.5 mg/dL for 24 weeks Co-interventions • Dialysis calcium concentration 1.25 mmol/L, vitamin D

De Santo 2006 *(Continued)*

Outcomes	• Plasma bicarbonate • Serum albumin • iPTH • Serum calcium • Serum phosphorus
Notes	• Supported by MIUR and ASI • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measures predominantly laboratory measures that were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about attrition to permit judgement
Selective reporting (reporting bias)	High risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. Key laboratory measures reported. Patient centred outcomes including adverse events not reported
Other bias	High risk	The study analysis was not appropriate for the cross-over study design. There was not reported wash-out phase between treatment periods. Baseline characteristics for each group were not reported in sufficient detail to assess balance

Delmez 1996

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 2.5 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: treatment of kidney failure with HD for more than 6 months, PTH > 8.0 ng/mL, and good dietary and medical compliance as assessed by the dietary, nursing • Number analysed/randomised: (not reported/15) • Mean age ± SD 58 ± 4 years • Sex (males): 40%

Delmez 1996 *(Continued)*

- Exclusion criteria: not reported

Interventions	Treatment group 1 • At the start of the run-in phase, participants were switched from generic calcium carbonate to a single calcium carbonate formulation. The amounts of calcium carbonate prescribed were adjusted weekly to attain target serum calcium levels between 9.5 and 10.5 mg/dL and phosphate levels < 6 mg/dL. If the target levels were attained for four consecutive weeks, participants were randomised to a phase where they each received half the amount of calcium carbonate Treatment group 2 • At the start of the run-in phase, participants were switched from generic calcium carbonate to a single calcium carbonate formulation. The amounts of calcium carbonate prescribed were adjusted weekly to attain target serum calcium levels between 9.5 and 10.5 mg/dL and phosphate levels < 6 mg/dL. If the target levels were attained for four consecutive weeks, participants were randomised to a phase where they each received half the amount of calcium carbonate and magnesium carbonate. The initial dose of magnesium was 750 mg/d (214 mg elemental Mg), which was titrated weekly as necessary for four to eight weeks to attain the target phosphate of less than 6 mg/dL Co-interventions • Not reported
Outcomes	• Serum calcium • Serum phosphate • PTH
Notes	• This study was supported in part, by U.S. Public Health Service NTADDK grants DK49240, DK-09976, DK-07126 and RR-00036 • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	High risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. No patient-centred outcomes including adverse events were provided

Delmez 1996 *(Continued)*

Other bias	High risk	The study analysis methods were not appropriate for the cross-over study design. Baseline characteristics for each group were not reported in sufficient detail to assess balance

Delmez 2007

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 12 months
Participants	• Country: USA • Setting: multicentre (13 sites) • Inclusion criteria: HD 3 times/wk for 3 months or longer, were maintained on sevelamer hydrochloride as their primary phosphate binder with a total daily dose of 13.6 g, with or without vitamin D analogue and/or lipid-lowering therapy at stable doses and had historically well-controlled serum phosphorus (3.5 to 6.5 mg/dL), calcium (normal range) and iPTH (600 pg/mL) • Number analysed/randomised: 74/79 • Mean age ± SD: 58.10 ± 12.30 years • Sex (males): 51% • Exclusion criteria: dysphagia, swallowing disorders or severe GI motility disorders; need for antidysrhythmic or anti-seizure medications; or any clinically significant unstable medical condition
Interventions	Treatment group 1 • Eligible patients entered a 5-week run-in period when sevelamer hydrochloride was prescribed to all patients to assure a stable sevelamer hydrochloride dose. There was one opportunity during the run-in period to titrate the sevelamer hydrochloride dose, cinacalcet dose, vitamin D analogue therapy and HD prescription, if necessary. Sevelamer carbonate was prescribed at a fixed dose. The starting dose was individualised based on the prescribed daily dose during the run-in period Treatment group 2 • Eligible patients entered a 5-week run-in period when sevelamer carbonate was prescribed to all patients to assure a stable sevelamer hydrochloride dose. There was one opportunity during the run-in period to titrate the sevelamer hydrochloride dose, cinacalcet dose, vitamin D analogue therapy and HD prescription, if necessary. Sevelamer hydrochloride was prescribed at a fixed dose. The starting dose was individualised based on the prescribed daily dose during the run-in period Co-interventions • None reported
Outcomes	• Serum phosphorus • Serum lipids • Serum bicarbonate • Adverse events • Death (all causes)
Notes	• This clinical study (GD3-163-201) was funded by Genzyme Corporation. The role of the funder in study design, conduct, analysis, and publication was not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Delmez 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were death and laboratory measures and unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/39 patients allocated to sevelamer hydrochloride not included in analyses (adverse event (4)) 1/40 patients allocated to sevelamer carbonate not included in analyses (never received study medication (1))
Selective reporting (reporting bias)	Low risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. Key death outcomes and laboratory measures were reported
Other bias	High risk	The study analysis methods were not appropriate for the cross-over study design. Baseline characteristics for each group were not reported in sufficient detail to assess balance

Deuber 2004

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 30 months
Participants	• Country: Germany • Setting: not reported • Inclusion criteria: long-term HD; treated with calcium carbonate for 12 months; HD for at least 15 months • Number analysed/randomised: treatment group 1 (25/25); treatment group 2 (25/25) • Mean age ± SD (years): treatment group 1 (64.1 ± 8.8); treatment group 2 (60.1 ± 15.4) • Sex (M/F): treatment group 1 (14/11); treatment group 2 (14/11) • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium carbonate. dose adjustment of was based on the progression made of the laboratory parameters iPTH, calcium and phosphate Treatment group 2 • Calcium acetate + magnesium carbonate: dose adjustment of was based on the progression made of the laboratory parameters iPTH, calcium and phosphate Co-interventions

Deuber 2004 *(Continued)*

	• Not reported
Outcomes	• Serum phosphorus • Serum calcium • Serum magnesium • Serum PTH
Notes	• Funding not reported • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about outcome assessment to permit judgement
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded. Patient-centred outcomes not reported
Other bias	Low risk	The study appeared to be free from other sources of bias

Evenepoel 2009

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 13 weeks
Participants	• Country: Belgium, Denmark, France, Italy, Spain, Netherlands • Setting: multicentre (15 sites) • Inclusion criteria: > 18 years; stable PD for > 8 weeks; serum phosphorus > 5.5 mg/dL and serum calcium within the normal range (8.4 to 10.4 mg/dL); compliant with dialysis and phosphate binder therapy • Number analysed/randomised: treatment group 1 (74/97); treatment group 2 (30/46) • Mean age ± SD (years): treatment group 1 (54.6 ± 15.7); treatment group 2 (54.1 ± 15.8) • Sex (M/F): treatment group 1 (65/32); treatment group (28/18) • Exclusion criteria: history of peritonitis, dysphagia, bowel obstruction or severe GI motility disorder; unstable concurrent clinical condition; use of anti-arrhythmic or anti-seizure medications for the control of these disorders; alcohol or drug abuse; hypersensitivity to sevelamer or hydrochloride

Evenepoel 2009 *(Continued)*

Interventions	Treatment group 1 • Sevelamer hydrochloride: starting dose 1600 mg, 3 times/d titrated as necessary to achieve a target serum phosphorus of 3.0 to 5.5 mg/dL Treatment group 2 • Calcium carbonate: starting dose 538 mg, 3 times/d titrated as necessary to achieve a target serum phosphorus of 3.0 to 5.5 mg/dL Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum calcium • iPTH • Serum lipids and plasma biomarkers • Adverse events • Serum bicarbonate • Hypercalcaemia • Death (all causes)
Notes	• This study was supported by Genzyme Corporation. The role of the funder in study design, conduct, analysis, and publication was not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were death and laboratory measures and unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	16/46 participants randomised to calcium acetate not included in analyses 23/97 participants randomised to sevelamer hydrochloride not included in analyses Adverse events were the main reason for premature withdrawal from the study (18% of sevelamer hydrochloride-treated patients and 28% of calcium acetate-treated patients). Four patients had no post-baseline efficacy assessment and so the ITT population consisted of 139 patients (sevelamer hydrochloride (95); calcium acetate (44)). Thirty-six patients were excluded from the PP analysis, which consisted of 103 patients (sevelamer hydrochloride (72); calcium acetate (31)). The main reasons for exclusion from the PP population were poor compliance (sevelamer hydrochlo-

Evenepoel 2009 *(Continued)*

		ride (15, 16%); calcium acetate (10, 22%)) and duration on treatment of < 3 weeks (sevelamer hydrochloride (7, 7%); calcium acetate (3, 7%)). Other reasons were proscribed medication usage, inadequate washout duration and randomised treatment not used
Selective reporting (reporting bias)	Low risk	Death (all causes), adverse events, and key laboratory measures were recorded
Other bias	High risk	Imbalance in baseline characteristics

Evsanaa 2015

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 3 months
Participants	• Country: not reported • Setting: single centre • Inclusion criteria: consenting PD patients; >18 years; serum phosphate > 1.8 mmol/L on 2 occasions; calcium carbonate was only phosphate binder • Number analysed/randomised: 17/20 • Mean age ± SD: 51 ± 22 years • Sex (% men): 35 • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium carbonate: same dose as before study enrolment. The dose was halved if calcium levels > 1.40 mmol/L or if diarrhoea or constipation developed and was deemed drug related. The treating clinic physician prescribed calcium carbonate targeting a serum phosphate < 1.80 mmol/L Treatment group 2 • Calcium magnesium carbonate: 100 mg calcium, 85 mg magnesium per tablet. The dose was halved if calcium levels > 1.40 mmol/L or if diarrhoea or constipation developed and was deemed drug related. The treating clinic physician prescribed calcium carbonate targeting a serum phosphate < 1.80 mmol/L Co-interventions • No changes were made in PD prescription (standard solutions were used, magnesium concentration 0.34 mmol/L, calcium concentration 1.3 mmol/L). All laxatives were discontinued at study enrolment
Outcomes	• Serum phosphate • Serum calcium • Serum magnesium • Serum PTH • Adverse events • Death (all causes)
Notes	• Funding sources not reported • Study registration not reported
Risk of bias	

Evsanaa 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigator blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were death and laboratory measures and unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	17/20 patients completed the study (transplant (1); died (1); intolerance of medication (1))
Selective reporting (reporting bias)	High risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. Key patient-centred outcomes and laboratory measures reported
Other bias	High risk	The analysis methods were not appropriate for the cross-over study design. Baseline characteristics for each study group were not reported in sufficient detail to assess for balance

Ferreira 2008

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 54 weeks
Participants	• Country: Portugal • Setting: multicentre (16 sites) • Inclusion criteria: > 18 years; HD 3 times/wk (> 3 months); stable serum phosphorus < 8.1 mg/dL for > 1 month before screening and who were receiving treatment with a phosphate binder • Number analysed/randomised: treatment group 1 (33/44); treatment group 2 (35/47) • Mean age ± SD (years): treatment group 1 (55.5 ± 15.4); treatment group 2 (53.9 ± 13.7) • Sex (M/F): treatment group 1 (22/11); treatment group 2 (18/17) • Exclusion criteria: use of aluminium-based binders in the previous year; treatment with medication that are known to affect bone metabolism; tetracycline allergy; alcohol or drug abuse; any significant concurrent clinical condition
Interventions	Treatment group 1 • Sevelamer hydrochloride: to achieve serum phosphorus of 3.2 to 5.0 mg/dL and to maintain serum calcium at < 10.4 mg/dL Treatment group 2 • Calcium carbonate: to achieve serum phosphorus of 3.2 to 5.0mg/dL and to maintain serum calcium at <10.4 mg/dL

Ferreira 2008 *(Continued)*

	Co-interventions • None reported
Outcomes	• Serum biochemical parameters • Bone turnover and mineralization
Notes	• This study was supported by Genzyme Corp. Employees of Genzyme were authors • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lack of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory-based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	11/44 participants allocated to sevelamer not included in analyses (adverse event (2); withdrew consent (2); kidney transplant (4); other (2)) 12/47 participants allocated to calcium not included in analyses (adverse even (2); non-adherence (1; withdrew consent (1); kidney transplant (8); other (2))
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	High risk	Imbalance in baseline characteristics. Differential use of co-interventions

Fishbane 2010

Methods	• Study design: parallel RCT • Time frame: January to September 2006 • Follow-up period: 24 weeks
Participants	• Country: USA • Setting: multicentre (29 sites) • Inclusion criteria: serum phosphorus level > 5.5 mg/dL after phosphate binder therapy withdrawal and iPTH ≤ 800 pg/mL; receiving maintenance HD for ≥ 3 months. • Number analysed/randomised: treatment group 1 (62/73); treatment group 2 (93/144) • Mean age ± SD (years): treatment group 1 (59.0 ± 13.8); treatment group 2 (56.7 ± 14.2) • Sex (M/F): treatment group 1 (42/30); treatment group 2 (79/62) • Exclusion criteria: severe GI motility disorder; poorly controlled DM; hypertension; other clinically significant unstable medical condition

Fishbane 2010 *(Continued)*

Interventions	Treatment group 1 • Sevelamer carbonate: powder was provided packaged in 2.4 g sachets. The starting dose was 4.8 g/d of sevelamer carbonate powder. Patients were to return to the clinic every 2 weeks for the first 8 weeks on treatment (weeks 2, 4, 6, and 8) and every 4 weeks thereafter (weeks 12, 16, 20, and 24) for laboratory assessments. The dose was to be titrated up or down in increments of 2.4 g/d (i.e., one 2.4 g powder sachet once daily) as needed at each visit by the investigator to reach a target serum phosphorus level ≥ 3.5 and ≤ 5.5 mg/dL Treatment group 2: • Sevelamer hydrochloride: was provided as 800 mg tablets. The starting dose was 4.8 g/d of sevelamer hydrochloride tablets. Patients were to return to the clinic every 2 weeks for the first 8 weeks on treatment (weeks 2, 4, 6, and 8) and every 4 weeks thereafter (weeks 12, 16, 20, and 24) for laboratory assessments. The dose was to be titrated up or down in increments of 2.4 g/d (one 800-mg tablet 3 times/d) as needed at each visit by the investigator to reach a target serum phosphorus level ≥ 3.5 and ≤ 5.5 mg/dL Co-interventions • None reported
Outcomes	• Death (all causes) • Serum phosphorus • Serum calcium-phosphorus • Serum calcium • Serum lipid levels • Adverse events • Serum bicarbonate • Serum chloride
Notes	• There was no specific funding for this study. Employees of Genzyme, a manufacturer of the interventions, were authors of the study publication. It is unclear what role Genzyme Corp had in study design, conduct, analysis, and publication • Study registration: www.ClinicalTrials.gov NCT00324376

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lacking of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were death or laboratory-based and unlikely to be influenced by lack of blinding. Adverse events may have been influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	11/73 participants allocated to sevelamer hydrochloride not included in analyses (adverse event (4); withdrew consent (2); death (2); lost-to follow-up (1); other (2))

Fishbane 2010 *(Continued)*

		51/144 participants allocated to sevelamer carbonate not included in analyses (adverse event (18); withdrew consent (18); did not adhere to protocol (4); death (1); lost to follow-up (1); other (9))
Selective reporting (reporting bias)	Low risk	Key biochemical outcomes were measured, together with death and adverse events
Other bias	High risk	Study funded and authored by Genzyme

Floege 2014

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 6 months
Participants	• Country: Europe, USA, Russia, Ukraine, and South Africa • Setting: international multicentre (174 sites) • Inclusion criteria: ≥ 18 years; hyperphosphataemia; treated with stable doses of phosphate binders for ≥1 month; long-term HD 3 times/wk (Kt/V ≥ 1.2) or PD (Kt/V ≥ 1.7) for at least 3 months; serum phosphorus concentration ≥ 1.94 mmol/L (6.0 mg/dL) • Number analysed/randomised: treatment group 1 (293/348); treatment group 2 (515/710) • Mean age ± SD (years): treatment group 1 (56 ± 15); treatment group 2 (56 ± 13) • Sex (males): treatment group 1 (63.1%); treatment group 2 (55.2%) • Exclusion criteria: iPTH > 88 pmol/L (800 pg/mL) or if parathyroidectomy planned or expected; significant GI or hepatic disorder or major GI surgery; serum ferritin > 4494 pmol/L (> 2000 µg/L); patients on PD with a history of peritonitis in the past 3 months or ≥ 3 episodes in the past 12 months; non-calcium-based phosphate binders with hypercalcaemia (total serum calcium > 2.60 mmol/L (> 10.4 mg/dL)), or patients with hypocalcaemia (total serum calcium <1.9 mmol/L (> 7.6 mmol/L)) at screening
Interventions	Treatment group 1 • Sevelamer carbonate: starting dose 4800 mg/d taken 3 times/d (divided). The study comprised an 8 week dose titration during which doses could be titrated for efficacy and tolerability. The permitted dose titration was 2.4 g/d (three tablets), maximum dose 14.4 g/d Treatment group 2 • PA21: commenced at 1.0 g/d (two doses divided). The study comprised an 8 week dose titration during which doses could be titrated for efficacy and tolerability. The permitted dose titration was 500 mg/d; maximum dose 3.0 g/d Co-interventions • concomitant medications that have a direct influence on serum phosphorus concentrations (e.g., vitamin D, vitamin D analogs, and calcimimetics) remained unchanged as far as possible, in accordance with local clinical practice
Outcomes	• Serum phosphorus • Serum $1,25(OH)_2$ D • Death (all causes) • Serum iPTH • Adverse events • Iron parameters • CRP

Floege 2014 *(Continued)*

Notes	• Sponsored by Vifor Pharma. The role of the funder in study design, conduct, analysis and publication was not reported. The authors acknowledge editorial assistance from AXON Communications • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice response system
Allocation concealment (selection bias)	Low risk	Interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Lacking of blinding may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory based and death. Knowledge of treatment allocation may have influenced interpretation of adverse event reporting
Incomplete outcome data (attrition bias) All outcomes	High risk	56/349 participants assigned to sevelamer not included in analyses (death (5); adverse event (21); hyperphosphataemia (0); withdraw consent (15); investigator or sponsor decision (5); kidney transplant (7); other (3)) 195/710 participants assigned to PA21 not included in analyses (death (9); adverse event (94); hyperphosphataemia (12); withdrew consent (32); investigator or sponsor decision (10); kidney transplant (16; other (22))
Selective reporting (reporting bias)	Low risk	Key biochemical outcomes were measured, together with death and adverse events
Other bias	Low risk	The study appeared to have no other sources of bias

Foraster 1998

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 3 months
Participants	• Country: Spain • Setting: single centre • Inclusion criteria: long-term HD; serum calcium between 2.6 and 2.9 mmol/L • Number analysed/randomised: not reported/24 • Mean age ± SD (years): treatment group 1 (60.8 ± 11.2); treatment group 2 (61.2 ± 11.6) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium carbonate: same dose as taken before entry into the study Treatment group 2:

Foraster 1998 *(Continued)*

	• Calcium acetate: at equivalent dose Co-interventions • Dialysate calcium; calcitriol
Outcomes	• Serum calcium • Serum phosphorus • Serum iPTH
Notes	• Funding sources not reported • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation likely to influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Unclear risk	Insufficient information to permit judgement

Fujii 2017

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 18 months
Participants	• Country: Japan • Setting: multicentre • Inclusion criteria: not reported • Number analysed/randomised: not reported/108 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Fujii 2017 *(Continued)*

Interventions	Treatment group 1 • Lanthanum carbonate: description of dosing not provided Treatment group 2 • Calcium carbonate: description of dosing not provided Co-interventions • Not reported
Outcomes	• Serum calcium • Serum phosphorus • Serum iPTH • CACS • Echocardiography • FGF23
Notes	• Funding sources not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Insufficient information about sequence generation to permit judgement. Described as randomised study. Patients were divided into groups based on the treatment of hyperphosphataemia. Unclear whether study design was randomised controlled study
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. Patient management may have been influenced by knowledge of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory based and unlikely to be influenced by knowledge of treatment allocation. Imaging analysis of echocardiography and coronary artery calcification may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Unclear risk	Insufficient information to permit judgement

Fujimori 2017

Methods	• Study design: parallel RCT

Fujimori 2017 *(Continued)*

	• Time frame: not reported • Follow-up period: 3 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: patients on HD with inorganic phosphate> 6.0 mg/dL • Number: treatment group 1 (4/9); treatment group 2 (9/9) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Lanthanum carbonate: 250 mg after each meal Treatment group 2 • Ferric citrate: 250 mg after each mean for the first month, then 500 mg
Outcomes	• Serum calcium • Serum phosphorus • Serum iPTH • Hb, ferritin, transferrin • FGF23
Notes	• Funding sources not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	4/9 participants allocated to ferric citrate were not included in analysis (overshoot of Hb (4); GI effects (1)) All participants allocated to lanthanum carbonate were included in analysis
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Unclear risk	Insufficient information to permit judgement

Gallieni 2005

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 weeks
Participants	• Country: Italy • Setting: not reported • Inclusion criteria: HD; previously treated with calcium carbonate; phosphorus level at study entry 5.5 to 8.0 mg/dL • Number analysed/randomised: not reported/115 • Age: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride: to decrease serum phosphorus level below 5 mg/dL (if phosphorus levels > 5 mg/dL, binder dose could be increased by 1 to 5 capsules/d) Treatment group 2 • Calcium carbonate: to decrease serum phosphorus level below 5 mg/dL (if phosphorus levels > 5 mg/dL, binder dose could be increased by 1 to 5 capsules/d) Co-interventions • Not reported
Outcomes	• Serum calcium • Serum phosphorus • Ca x P product • Serum bicarbonate • Total and LDL cholesterol • Total adverse events • GI side effects • Hypercalcaemia
Notes	• Funding not reported • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management

Gallieni 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Key biochemical measures were reported. Adverse events were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Greenberg 1994

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 9 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: CAPD patients • Number analysed/randomised: not reported/11 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium carbonate: starting with 1 g elemental calcium. Adjustments in phosphate binder every 2 to 4 weeks based on calcium, phosphorus, and PTH levels Treatment group 2 • Calcium acetate: starting with 1 g elemental calcium. Adjustments in phosphate binder every 2 to 4 weeks based on calcium, phosphorus, and PTH levels
Outcomes	• Serum calcium • Serum phosphorus • Serum Ca x P product
Notes	• Funding not reported • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Low risk	Insufficient information about allocation concealment to permit judgement

Greenberg 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	High risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. No reporting of adverse events or other patient-centred outcomes
Other bias	High risk	Analytical approach not appropriate for study cross-over design

Hervas 2003

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 34 weeks
Participants	• Country: Spain • Setting: single centre • Inclusion criteria: > 18 years; HD 3 times/wk; calcium-based phosphate binders and vitamin D therapy at stable doses for at least one month • Number analysed/randomised: 41/51 • Mean age ± SD: 60.4 ± 15.1 years • Sex (males): 60% • Exclusion criteria: unstable medical condition including poorly controlled diabetes; hypertension or any GI abnormality
Interventions	Treatment group 1 • Sevelamer hydrochloride capsules: 403 mg; the beginning medication dose was determined by the initial level of phosphorus and ranged from 2 to 4 capsules with meals. Doses could be increased by 1 capsule per meal every 4 weeks Treatment group 2 • Calcium acetate: 500 mg; the beginning medication dose was determined by the initial level of phosphorus and ranged from 1 to 4 tablets with meals. Doses could be increased by 1 tablet per meal every 4 weeks Co-interventions • IV or oral vitamin D analogues
Outcomes	• Serum phosphorus • Serum calcium • ALP • iPTH

Hervas 2003 *(Continued)*

	• Lipid profile
Notes	• Supported in part by grants of Sociedad Espanola de Dialisisy Transplante (SEDYT) • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/51 participants allocated to treatment were not included in analysis (death (4); kidney transplant (2); adverse event (1); lack of adherence (4))
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded; number of patients in each group not reported
Other bias	High risk	The baseline characteristics for each treatment group were not reported in sufficient detail to assess for balance

Hutchison 2005

Methods	• Study design: parallel RCT • Time frame: September 1998 to October 1999 • Follow-up period: 6 months initially with a 6 month and 2 year open-label study extension
Participants	• Countries: UK, Germany, The Netherlands, Belgium • Setting: multicentre (67 sites) • Inclusion criteria: > 18 years; HD 3 times/wk for at least 3 consecutive months (including those who had previously undergone kidney transplantation) • Number analysed/randomised: treatment group 1 (510/533); treatment group 2 (257/267) • Mean age ± SD (years): treatment group 1 (57.0 ± 14.3); treatment group 2 (58.4± 13.3) • Sex (M/F): treatment group 1 (341/169); treatment group 2 (164/113) • Exclusion criteria: hypercalcaemia, severe hyperparathyroidism or other clinically significant abnormal laboratory values; lactating females or those with a positive screening pregnancy test; HIV-positive, known hepatitis B or C, or other significant concurrent liver disorder; life-threatening malignancy, multiple myeloma or a history of epilepsy; drug or alcohol abuse within 2 years; treatment with an investigational drug 30 days prior to screening; those who, in the opinion of the investigators, would not comply with the study requirements
Interventions	Treatment group 1

Hutchison 2005 *(Continued)*

	• Lanthanum: doses to achieve serum phosphorus < 5.5 mg/dL treatment group 2 • Calcium carbonate: doses to achieve serum phosphorus < 5.5 mg/dL Co-interventions • Oral or IV vitamin D analogues
Outcomes	• Serum phosphorus • Serum Ca x P product • Serum PTH • Serum vitamin D • Hypercalcaemia • Adverse events • GI adverse events • Plasma lanthanum
Notes	• Funding source not reported • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and unlikely to have been influenced by knowledge of treatment allocation. Adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	23/533 participants allocated to lanthanum not included in analyses 10/267 participants allocated to calcium not included in analyses Efficacy data for 33 patients from a single centre were not included due to unreliability of data. 54.2% of participants who commenced titration with lanthanum carbonate completed titration and maintenance phase. 57.7% of patients receiving calcium carbonate treatment progressed to and completed maintenance phase
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

INDEPENDENT-CKD 2012

Methods	Study design: parallel RCT Follow-up period: 24 months Time frame: Enrolment began in November 2005
Participants	• Country: Italy • Setting: multicentre (12 sites) • Inclusion criteria: ≥ 18 years; having 6 months of follow-up before enrolment and having stage 3-4 CKD • Number analysed/randomised: treatment group 1 (107/121); treatment group 2 (105/118) • Mean age ± SD(years): treatment group 1 (57.4 ± 12); treatment group 2 (58.5 ± 12.4) • Sex (men): treatment group 1 (61%); treatment group 2 (61) • Exclusion criteria: heart failure; coronary bypass; coronary artery disease; angioplasty; stroke; arrhythmia; liver dysfunction; nephrotic syndrome; fast progression of kidney function (defined as 24 h measured CrCl loss ≥ 12 ml/min/year)
Interventions	Treatment group 1 • Sevelamer hydrochloride: commenced at 1600 mg/d. Increased to maintain serum phosphorus between 2.7 and 4.6 mg/dL for patients with stage 3-4 CKD and between 3.5 and 5.5 mg/dL for patients with stage 5 CKD Treatment group 2 • Calcium carbonate: commenced at 2000 mg/d. Increased to maintain serum phosphorus between 2.7 and 4.6 mg/dL for patients with stage 3-4 CKD and between 3.5 and 5.5 mg/dL for patients with stage 5 CKD
Outcomes	• Death (all causes) • Dialysis inception • Composite endpoint of death and dialysis inception • Serum phosphorus, calcium, iPTH, lipids, CRP • Hypercalcaemia
Notes	• Funding sources not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A single simple randomisation list was generated by computer
Allocation concealment (selection bias)	Low risk	Allocation was concealed with the use of numbered, opaque sealed envelopes that were opened in sequence by the administrative personnel of the coordinating centre not involved in patient care. All participating centres followed the same procedure via a phone call to the coordinating centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Two readers unaware of phosphate binder assignments read the CT scans. Blinding of outcome assessment for other outcomes was not reported. Out-

INDEPENDENT-CKD 2012 *(Continued)*

		come measures were laboratory measures and death and were unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	14/121 participants allocated to sevelamer not included in analysis (lost to follow-up (3); poor quality basal scan (4); change of clinic (4)) 13/118 participants allocated to calcium not included in analysis (lost to follow-up (4); poor quality basal scan (3); withdrawal of consent (1); change of clinic (5))
Selective reporting (reporting bias)	Low risk	Key death and patient-centred outcomes reported. Key laboratory outcomes reported
Other bias	Low risk	The study appeared to be free of other sources of bias

INDEPENDENT-HD 2009

Methods	• Study design: parallel RCT • Time frame: enrolment January 2007 to September 2008 • Follow-up period: 36 months
Participants	• Country: Italy • Setting: multicentre (18 sites) • Inclusion criteria: > 18 years; CKD treated with dialysis < 120 days • Number analysed/randomised: treatment group 1 (232/232); treatment group 2 (234/234) • Mean age ± SD (years): treatment group 1 (66.6 ± 14.1); treatment group 2 (64.6 ± 15.4) • Sex (men): treatment group 1 (50%); treatment group 2 (48%) • Exclusion criteria: > 75 years; history of cardiac arrhythmia (reported history of cardiac arrhythmia; evidence of arrhythmias on an ECG; or presence of a pacemaker); syndrome of congenital prolongation of the QT segment interval, corrected QT interval longer than 440 milliseconds or increased QT dispersion; history of coronary artery bypass; liver dysfunction (elevation of liver enzyme levels > 2-fold higher than the upper limits of the normal range); hypothyroidism; use of drugs known to prolong the QT interval
Interventions	Treatment group 1 • Sevelamer hydrochloride: adjusted to achieve a serum phosphorus level of 2.7 to 5.5 mg/dL Treatment group 2 • Calcium-containing phosphate binders: adjusted to achieve a serum phosphorus level of 2.7 to 5.5 mg/dL Co-interventions • aluminium hydroxide; BP control; anaemia targets; acidosis targets; treatment to maintain serum calcium and PTH within target range
Outcomes	• Death (all causes) • Cardiovascular death • Non-cardiovascular death • Serum phosphorus, calcium, iPTH
Notes	• All costs connected to the INDEPENDENT Study were covered by the Italian National Health Care System through the local ASLs (Azienda Sanitaria Locale) • Study registration: www.ClinicalTrials.gov NCT00710788

INDEPENDENT-HD 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	To maintain allocation concealment, randomisation was performed centrally
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and death and were unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	33/232 participants allocated to sevelamer did not complete follow-up (poor quality CT scan (6); consent withdrawal (8); change of clinic (19)) 36/234 participants allocated to calcium did not complete follow-up (poor quality CT scan (7); consent withdrawal (11); change of clinic (18))
Selective reporting (reporting bias)	Low risk	Key death and patient-centred outcomes reported. Key laboratory outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias. Because a lower than expected overall death rate was observed in the total study population without consideration of group allocation after 12 months of study, an 8-month extension of the recruitment phase was obtained

Isakova 2013

Methods	• Study design: parallel RCT • Time frame: July 2009 and November 2011 • Follow-up period: 3 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: 18 years or older; eGFR 15 to 59 mL/min/1.73 m^2; normal phosphate levels (0.8 to 1.5 mmol/L (2.5 to 4.6 mg/dL)) • Number analysed/randomised: treatment group (19/22); control group (20/21) • Mean age ± SD (years): treatment group (55.4 ± 0.3); control group (55.4 ± 10.3) • Sex (M/F): treatment group (13/19); control group (12/20) • Exclusion criteria: Hyperphosphataemia (phosphate > 1.5 mmol/L (4.5 mg/dL); advancing CKD; primary hyper- or hypoparathyroidism or prior parathyroidectomy; malabsorption; malnutrition (serum albumin < 3.0 mg/dL); liver disease (ALT or AST > 100 U/L), cholestasis (direct bilirubin > 1.0 mg/dL), or anaemia (HCT < 27%); had received prior counselling by a nutritionist within 6 months; were taking phosphate binders; were hospitalised within the previous 4 weeks; were pregnant or breastfeeding mothers; or were unable to provide written informed consent
Interventions	Treatment group

Isakova 2013 *(Continued)*

	• Lanthanum carbonate: fixed dose of 1000 mg 3 times/d (with or without specific dietary phosphorus content) Control group • Placebo: fixed dose (with or without specific dietary phosphorus content) Co-interventions • Not reported
Outcomes	• Serum phosphorus, PTH, calcium • FGF23 • ECG • Hypophosphataemia • GI adverse effects • Hospitalisation
Notes	• This study was supported by a grant from Shire Pharmaceuticals and by grants from the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases. The role of Shire Pharmaceuticals in study design, conduct, analysis and publication was not reported • Study registered: ww.ClinicalTrials.gov NCT00843349

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement. Randomisation was conducted by a research pharmacist
Allocation concealment (selection bias)	Unclear risk	Treatment allocation was conducted by a research pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The phosphate binder intervention was double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and hospitalisation and were unlikely to have been influenced by knowledge of treatment allocation. Adverse event reporting may have been influenced by lack of blinding; however; participants and investigators were unaware of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/22 participants allocated to lanthanum were not included in analysis 1/21 participants allocated to placebo were not included in analysis
Selective reporting (reporting bias)	Low risk	Key adverse events and laboratory measures were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Itoh 2008

Methods	• Study design: parallel RCT

Itoh 2008 *(Continued)*

	• Time frame: not reported • Follow-up period: 8 weeks
Participants	• Country: Japan • Setting: multicentre (4 sites) • Inclusion criteria: HD patients with hyperphosphataemia • Number analysed/randomised: treatment group 1 (13/31); treatment group 2 (14/31) • Mean age ± SD (years): treatment group 1 (55.9 ± 9.8); treatment group 2 (57.5 ± 14.7) • Sex (M/F): treatment group 1 (11/2); treatment group 2 (11/3) • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride: 3.0 g/d for 8 weeks Treatment group 2 • Colestimide: 3.0 g/d for 8 weeks Co-interventions • Calcium carbonate 3.0 g/d for weeks 5 to 8
Outcomes	• Serum calcium • Serum phosphorus • Ca x P product • iPTH • Serum ALP
Notes	• "The authors acknowledge the support of the Kirin Brewery Pharmacological Fund for this study" • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory based and unlikely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	35/62 participants withdrew from the study due primarily to GI side-effects; 18 participants dropped out from the sevelamer group and 17 dropped out from the colestimide group
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded

Itoh 2008 *(Continued)*

Other bias	Low risk	The study appeared to be free of other sources of bias

Janssen 1995

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 months
Participants	• Country: The Netherlands • Setting: not reported • Inclusion criteria: regular HD • Number analysed/randomised: treatment group 1 (9/17); treatment group 2 (11/17) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium carbonate: before meals adjusted to serum phosphorus (≤1.6 mg/dL) and calcium levels. Treatment group 2 • Calcium acetate: before meals adjusted to serum phosphorus (≤1.6 mg/dL) and calcium levels. Co-interventions • If necessary, patients received adjuvant aluminium hydroxide • In patients with the target serum phosphate level and a serum calcium level < 2.20 mmol/L, 1-a-hydroxyvitamin D3 (Etalpha®) was added
Outcomes	• Death (all causes) • Serum phosphorus • Serum calcium • Serum PTH • Serum ALP • Hb/HCT
Notes	• Funding not reported • Study registration not required.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management

Janssen 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory based or death and were unlikely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	8/17 participants allocated to calcium carbonate not completed follow-up 6/16 participants allocated to calcium acetate not completed follow-up The reasons for loss to follow up in each treatment group was not reported
Selective reporting (reporting bias)	Low risk	Key laboratory measures and death were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Janssen 1996

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 months
Participants	• Country: The Netherlands • Setting: not reported • Inclusion criteria: regular HD • Number analysed/randomised: treatment group 1 (13/20); treatment group 2 (14/18); treatment group 3 (10/15) • Mean age ± SD (years): treatment group 1 (58 ± 4); treatment group 2 (51 ± 4); treatment group 3 (62 ± 4) • Sex(M/F): treatment group 1 (7/13); treatment group 2 (11/7); treatment group 3 (5/10) • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium carbonate: to achieve serum phosphorus < 5.0 mg/dL and serum calcium 8.8 to 11.0 mg/dL Treatment group 2 • Calcium acetate: to achieve serum phosphorus < 5.0 mg/dL and serum calcium 8.8 to 11.0 mg/dL Treatment group 3 • Aluminium hydroxide: to achieve serum phosphorus < 5.0 mg/dL and serum calcium 8.8 to 11.0 mg/dL Co-interventions • 1-alpha-hydroxyvitamin D_3
Outcomes	• Death (all causes) • Serum calcium • Serum phosphorus • iPTH • Hypercalcaemia • Serum aluminium
Notes	• Study funding sources not reported • Study registration not required

Janssen 1996 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory based or death and were unlikely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	7/20 participants allocated to calcium carbonate did not complete follow-up (death (2); change in dialysis therapy (1); hypercalcaemia (1); medication resistance (2); transplantation (1)) 4/18 participants allocated to calcium acetate did not complete follow-up (change in dialysis treatment (1); other (3)) 5/15 participants allocated to aluminium hydroxide did not complete follow-up (death (2); hypercalcaemia (1); side effects (1); other (1))
Selective reporting (reporting bias)	Low risk	Key laboratory measures and death were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Jespersen 1991

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 6 months
Participants	• Country: Denmark • Setting: single centre • Inclusion criteria: long-term HD; > 18 years; serum phosphorus > 2 mmol/L without treatment with a phosphate binder to maintain serum phosphorus < 2 mmol/L; serum calcium < 2.6 mmol/L • Number analysed/randomised: 11/14 • Age, range (years): treatment group 1 (49, 27 to 65); treatment group 2(41, 22 to 69) • Sex (M/F): treatment group 1 (4/2); treatment group 2 (2/3) • Exclusion criteria: previous parathyroidectomy; ongoing treatment with 1,25(OH2)D_3; glucocorticoid treatment
Interventions	Treatment group 1 • Calcium carbonate: 83 to 166 mg/kg/d Treatment group 2

Jespersen 1991 *(Continued)*

	• Aluminium hydroxide: 33 to 66 mg/kg/d Co-interventions • Ergocalciferol; protein restriction; dialysate calcium
Outcomes	• Serum calcium • Serum phosphorus • Effect on bone turnover and hyperparathyroidism • Bone mineral content and extraskeletal calcification • Serum aluminium
Notes	• This study was supported by grants from the Danish Medical Research Council and Livens Kemiske Fabrik (Leo Pharmaceuticals), Ballerup, Denmark • Study registration not required.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory based and were unlikely to be influenced by knowledge of treatment assignment. Interpretation of bone histomorphometry may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	3/14 did not complete follow-up
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded. Data were not available for the first period of treatment
Other bias	High risk	Data analysis was not appropriate for cross-over study design

Kakuta 2011

Methods	• Study design: parallel RCT • Time frame: random allocation between April 2004 and December 2005; study completed on December 2006 • Follow-up period: 12 months
Participants	• Country: Japan • Setting: multicentre (12 sites) • Inclusion criteria: > 20 years; long-term HD

Kakuta 2011 *(Continued)*

- Number analysed/randomised: treatment group 1 (79/91); treatment group 2 (84/92)
- Mean age ± SD (years): treatment group 1 (59 ± 12); treatment group 2 (57 ± 12)
- Sex (M/F): treatment group 1 (53/39); treatment group 2 (47/45)
- Exclusion criteria: serious GI disease (dysphagia, active untreated gastroparesis, severe motility disorder; intestinal surgery, and markedly irregular bowel function); alcohol or drug dependence or abuse; active malignancy; vasculitis; poorly controlled diabetes or hypertension

Interventions	Treatment group 1 • Sevelamer hydrochloride: when serum phosphorus could not be controlled < 6.5 mg/dL, 9 g/d of sevelamer and up to 1.5 g/d of calcium carbonate was allowed. Investigators were instructed to control serum calcium, phosphorus, PTH, and dyslipidaemia every 2 weeks Treatment group 2 • Calcium carbonate: when serum phosphorus could not be controlled < 6.5 mg/dL, up to 1.5 g/d of calcium carbonate was allowed. Investigators were instructed to control serum calcium, phosphorus, PTH, and dyslipidaemia every 2 weeks Co-interventions • Investigators were free to modify the dose of phosphate binders. In general, when serum calcium level was 10.5 mg/mL, either the calcium carbonate dose was decreased or vitamin D3 dose was decreased or discontinued; when serum phosphorus level was 6.5 mg/dL, phosphate-binder doses were increased. • During the study, dialysate calcium concentration was 2.5 mEq/L, dietary calcium intake was not controlled, no estimate of patient adherence(pill count) was performed, and no patient received calcimimetics
Outcomes	• CACS • Serum phosphorus • Serum calcium • Serum PTH • Serum calcium-phosphorus product • Suppression of serum PTH • Death (all causes)
Notes	• Funded in part by grants from the Japan Dialysis Outcomes Research Group • Study registration: www.umin.ac.jp/ctr/; study number: UMIN000002150.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Low risk	Investigators were informed of patient allocation using concealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment of CACS was blinded. Blinding of other outcomes was not reported. Outcome measures were laboratory based or death and were unlikely to be influenced by knowledge of treatment assignment

Kakuta 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	12/91 participants allocated to sevelamer were not included in analysis (change of clinic (1); adverse event (2); consent withdrawn due to constipation (6); protocol violation (3)) 8/92 participants allocated to calcium were not included in analysis (change of clinic (1); adverse event (5); protocol violation (2))
Selective reporting (reporting bias)	Low risk	Key measures of laboratory outcomes, death, and vascular calcification were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Kasai 2012

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 12 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: ≥ 18 years; HD for at least 3 months • Number analysed/randomised: 41/42 • Mean age ± SD: 60.9 ± 11.9 years • Sex (men): 57.1% • Exclusion criteria: primary hyperparathyroidism; severe secondary hyperparathyroidism; active infectious diseases; malignancies; poor control of inter-dialytic weight gain
Interventions	Treatment group 1 • Sevelamer hydrochloride: dose adjusted every 2 weeks for a total daily dose of 750 to 9000 mg to maintain the serum phosphorus within a target range. If the serum phosphate level fell below or increased above the target range, the dose was increased or decreased by a daily dose of 750 mg Treatment group 2 • Lanthanum carbonate: adjusted every 2 weeks for a total daily dose of 375 to 2250 mg to maintain the serum phosphorus within a target range. If the serum phosphate level fell below or increased above the target range, the dose was increased or decreased by a daily dose of 375 mg Co-interventions • The doses of vitamin D, calcium-containing phosphate binders, cinacalcet hydrochloride, and other drugs depended on the individual patient's condition and were maintained throughout the study
Outcomes	• Death (all causes) • Adverse events • Serious adverse events • Serum phosphorus, calcium, Ca x P product, iPTH, ALP, bone ALP
Notes	• Funding sources not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Kasai 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were death and laboratory events which were unlikely to be influenced by knowledge of treatment allocation. Adverse events may have been influenced by knowledge of treatment outcome. Study described as blinded-endpoint study design
Incomplete outcome data (attrition bias) All outcomes	Low risk	42/42 participants included in safety analysis. Two patients discontinued the study; one died and the other withdrew due to an adverse event
Selective reporting (reporting bias)	Low risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. Key laboratory outcomes and death were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Katopodis 2006

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 8 weeks
Participants	• Country: Greece • Setting: multicentre (2 sites) • Inclusion criteria: CAPD patients in stable condition for the previous 6 months • Number analyses/randomised: treatment group 1 (not reported/15); treatment group 2 (not reported/15) • Mean age ± SD (years): treatment group 1 (59.9 ± 14.3); treatment group 2 (56.7 ± 19.2) • Sex (men): treatment group 1 53.3%; treatment group 2 (66.7%) • Exclusion criteria: unstable medical condition; severe anaemia (Hb < 9 g/dL); heart failure (dyspnoea on exertion and rest and left ventricular ejection fraction < 45%); liver dysfunction; DM; bowel dysfunction; chronic hepatitis; intestinal surgery; cancer; current use of anti-arrhythmic or anti-seizure drugs
Interventions	Treatment group 1 • Sevelamer hydrochloride: 403 mg of poly-allylamine hydrochloride starting at two capsules with each meal if serum phosphorus was > 6.0 and < 7.5 mg/dL, 3 capsules with each meal if phosphorus ≥ 7.5 and < 9.0 mg/dL and 4 capsules with each meal if phosphorus ≥ 9.0 mg/dL Treatment group 2 • Aluminium hydroxide: 475 mg starting at two capsules with each meal if serum phosphorus was > 6.0 and < 7.5 mg/dL, 3 capsules with each meal if phosphorus ≥ 7.5 and < 9.0 mg/dL and 4 capsules with each meal if phosphorus ≥ 9.0 mg/dL

Katopodis 2006 *(Continued)*

	Co-interventions • Not reported
Outcomes	• Serum phosphorus, calcium, magnesium • iPTH • ALP • Lipid parameters • Adverse events
Notes	• Funding sources not reported • Study registration not required.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures laboratory events which were unlikely to be influenced by knowledge of treatment allocation. Adverse events may have been influenced by knowledge of treatment outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Cross-over study and no separate results available for first part of the study so results could not be included in meta-analyses. Key laboratory measures and adverse events were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Ko 2010

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 6 months
Participants	• Country: Republic of Korea • Setting: single centre • Inclusion criteria: >18 years, HD, serum phosphorus > 5.6 mg/dL • Number analysed/randomised: treatment group 1 (not reported/12); treatment group 2 (not reported/11) • Mean age ± SD (years): treatment group 1 (52.7 ± 10.8); treatment group 2 (49.4 ± 16.1)

Ko 2010 *(Continued)*

- Sex (men): treatment group 1 (50%); treatment group 2 (45.5%)
- Exclusion criteria: iPTH concentration ≥ 1000 pg/mL and hyperparathyroidism, abnormal serum test results; history of tumour; HbA1c > 9.5%, chronic liver disease; heart failure at terminal stage (NYHA III or higher, severe weight loss (last 4 weeks of weight loss more than 10%), serious infection

Interventions	Treatment group 1 • Lanthanum carbonate: 1500 to 3000 mg/d Treatment group 2 • Calcium carbonate: 2000 mg/d Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum calcium • Serum Ca x P product • Bone ALP, osteocalcin • Adverse events (hypercalcaemia, GI events, skin lesions)
Notes	• Funding sources not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory events which were unlikely to be influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	High risk	Imbalance in baseline characteristics

Koiwa 2017

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 3 months
Participants	• Country: Japan • Setting: Dialysis facilities • Inclusion criteria: patients with CKD undergoing stable maintenance HD 3 times/wk, for 12 weeks or more, before the initiation of the washout period, and with planned continued HD during the treatment period; patients with no change in their phosphate binder agent dose, for 4 weeks or more before the initiation of the washout period; patients whose predialysis serum phosphorus concentration was > 1.94 mmol/L and ≤ 3.23 mmol/L at week 1; patients with no change, at least 4 weeks before the initiation of the washout period, in the dose of any vitamin D receptor activator, calcimimetic, or osteoporosis drug that they may have been receiving; patients considered able to discontinue their current therapy for hyperphosphataemia for the 3-week washout period; ≥ 20 years at the time their consent was obtained, regardless of sex • Number analysed/randomised: treatment group 1 (87/105); treatment group 2 (94/108) • Mean age ± SD (years): treatment group 1 (60.8 ± 12); treatment group 2 (61 ± 11.7) • Sex (men): treatment group 1 (57.6%); treatment group 2 (75%) • Exclusion criteria: corrected serum calcium concentration ≤ 1.8 8mmol/L or > 2.75mmol/L at week 1; iPTH > 800 ng/L at the beginning of the washout period; history of haemochromatosis, or any other iron accumulation disorder, or whose serum ferritin was > 1797.60 pmol/L or TSAT > 50% at the beginning of the washout period; severe GI disorders based on the investigator's diagnosis; history of a severe digestive tract procedure based on the investigator's diagnosis
Interventions	Treatment group 1 • Sevelamer: orally administered at 1000 mg/dose or 2000 mg/dose if the serum phosphorus concentration before dialysis at week 1 was < 2.58 mmol/L or ≥ 2.58 mmol/L, respectively. Sevelamer was administered 3 times/d, immediately before every meal. During week 2 to week 8, based on the serum phosphorus concentration from the previous week, the investigator decided to maintain, increase, or decrease the dose of each drug using the following criteria for dose adjustment. If the serum phosphorus concentration at the beginning of the previous week was > 1.94 mmol/L, the dose of sevelamer was increased by 750 or 1500 mg/d; if it was 1.13 to 1.94 mmol/L, sevelamer doses were maintained; and if it was < 1.13mmol/L, the dose of sevelamer was reduced by 750 or 1500 mg/d. The maximum allowed dose of sevelamer was 3000 mg/dose 3 times/d (9000 mg/d). The dose was maintained from week 8 to week 12. Treatment group 2 • PA21: orally administered at 250 mg/dose 3 times/d (750 mg/d) immediately before every meal; During week 2 to week 8, based on the serum phosphorus concentration from the previous week, the investigator decided to maintain, increase, or decrease the dose of each drug using the following criteria for dose adjustment. If the serum phosphorus concentration at the beginning of the previous week was > 1.94 mmol/L, the dose of PA21 was increased by 750 mg/d; if it was 1.13 to 1.94 mmol/L, PA21 dose were maintained; and if it was < 1.13 mmol/L, the dose of PA21 was reduced by 750 mg/d. The maximum allowed dose of PA21 was 1000 mg/dose 3 times/d (3000 mg/d). The dose was maintained from week 8 to week 12 Co-interventions • Concomitant use of the following drugs was prohibited during the study period: other phosphate binders, drugs with a phosphate binding action: oral iron agents, drugs having an effect on serum phosphorus concentrations and any study drugs other than PA21 • Use of IV iron was permitted if the investigator considered it necessary • The use of vitamin D receptor activators and calcimimetics was allowed as long as the participants were receiving it for 4 weeks or more before the start of the observation period and the dose was not changed through the study period. Any patient not using vitamin D receptor activators or calcimimetics at the study start was not allowed to begin using them during the study period

Koiwa 2017 *(Continued)*

	• Pre-specified diet therapies were not to be changed during the study (observation and treatment) periods
Outcomes	• Serum phosphorus • Corrected serum calcium • Serum iPTH • Safety outcomes included adverse events, adverse drug reactions, transferrin saturation, ferritin, Hb and bicarbonate levels
Notes	• This study was funded by Kissei Pharmaceutical Co, Ltd. Akira Terao was a statistical advisor for this clinical study and has received consulting fees from Kissei Pharmaceutical Co, Ltd. Dr. Michelle Belanger of Edanz Group Ltd. for provided medical writing assistance. The role of the funder in study design, analysis, conduct and publication was not reported • Study registration: www.ClinicalTrials.gov NCT01850602

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive web response system
Allocation concealment (selection bias)	Low risk	Interactive web response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory events which were unlikely to be influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	18/105 discontinued therapy in the sevelamer group (adverse event (10); calcium decrease (3); other (5)) 14/108 discontinued therapy in the PA21 group (adverse event (7); calcium decrease (2); ferritin decrease (1); other (6))
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	High risk	Imbalance in baseline characteristics

Lee 2013

Methods	• Study design: parallel RCT • Time frame: June 2008 to May 2009 • Follow-up period: 6 months
Participants	• Country: Republic of Korea • Setting: single centre • Inclusion criteria: ≥ 18 years; PD for at least 6 months; serum phosphorus > 5.6 mg/dL

Lee 2013 *(Continued)*

- Number analysed/randomised: treatment group 1 (20/34); treatment group 2 (30/37)
- Mean age ± SD (years): treatment group 1 (48.25 ± 11.06); treatment group 2 (51.80 ± 11.62)
- Sex (M/F): treatment group 1 (11/9); treatment group 2 (11/19)
- Exclusion criteria: Serum iPTH > 1000 pg/mL (114 pmol/L); serum calcium < 1.88 mmol/L (7.5 mg/dL); HbA1c ≥ 9.5%; chronic liver disease; sepsis; malignancy; oral immunosuppressant use; cardiac failure (> NYHA III); non-adherence

Interventions	Treatment group 1 • Lanthanum carbonate: initial dose was 1,500 mg/d. The dose was adjusted by the clinician after each laboratory examination to maintain a serum phosphate level between 3.5 and 5.5 mg/dL Treatment group 2 • Calcium carbonate: initial dose was 3 g/d. The dose was adjusted by the clinician after each laboratory examination to maintain a serum phosphate level between 3.5 and 5.5 mg/dL Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum calcium • Serum calcium x phosphorus product • iPTH level • Adverse events
Notes	• Study funding not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory events which were unlikely to be influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	22 patients dropped out (10 patients due to GI trouble, such as nausea, vomiting, constipation, and abdominal discomfort) in the lanthanum carbonate group 3 patients in the lanthanum carbonate group and 5 patients in the calcium carbonate group due to noncompliance 1 patient in the lanthanum carbonate group and 2 patients in the calcium carbonate group for other reasons)

Lee 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Lee 2015b

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 8 weeks
Participants	• Country: Taiwan • Setting: multicentre (5 sites) • Inclusion criteria: ≥18 years; had been receiving HD 3 time/wk for at least 3 months, were on a stable dose (change ≤ 25 %) of a phosphate-binding agent for at least 1 month prior to study entry; URR > 65 % within the 4 weeks prior to screening, HCT > 20 %, and a serum calcium level of 8 to 10.5 mg/dL • Number analysed/randomised: treatment group 1 (66/72); treatment group 2 (72/75); control group (28/36) • Mean age ± SD (years): treatment group 1 (56.4 ± 10.5); treatment group 2 (53.4 ± 11.7); control group (53.0 ± 11.8) • Sex (M/F): treatment group 1 (41/31); treatment group 2 (47/28); control group (25/11) • Exclusion criteria: pregnancy; lactating; GI abnormality; tertiary hyperparathyroidism; congestive heart failure; DM with clinically relevant gastroparesis; unstable medical or psychiatric condition; clinically significant abnormality on screening ECG; active malignancy other than basal cell or squamous cell carcinoma; serum ferritin (800 ng/mL; history of iron allergy or haemochromatosis; or treatment with an investigational agent within 30 days of enrolment).
Interventions	Treatment group 1 • Ferric citrate 6 g/d: participants with serum phosphorus levels of ≥ 9 mg/dL at 2 consecutive measurements after randomisation were withdrawn from the study, and instructed to resume their pre-study medications. Subjects with TSAT ≥ 55% were also withdrawn from the study Treatment group 2 • Ferric citrate 4 g/d: participants with serum phosphorus levels of ≥ 9 mg/dL at 2 consecutive measurements after randomisation were withdrawn from the study, and instructed to resume their pre-study medications. Subjects with TSAT ≥ 55% were also withdrawn from the study Treatment group 3 • Placebo: participants with serum phosphorus levels of ≥ 9 mg/dL at 2 consecutive measurements after randomisation were withdrawn from the study, and instructed to resume their pre-study medications. Subjects with TSAT ≥ 55% were also withdrawn from the study Co-interventions • From the start of washout to the end of the study, all phosphate binding agents and other medications that could have potentially affected serum phosphorus or calcium concentrations were prohibited. Medications containing minimal amounts of aluminium, calcium, phosphorus, or magnesium, or used at a dose that would not interfere with phosphorus or calcium absorption, were allowed • From the start of washout until the end of the study, no iron-containing medications, and no oral or IV iron therapy was allowed • Vitamin D analogs were permitted during the study; however, the use and dose had to remain constant throughout the study. All patients were required to maintain their dialysis treatment at 3 times/wk throughout the study

Lee 2015b *(Continued)*

Outcomes	• Serum phosphorus • Serum Ca x P product • Adverse events • Serious adverse events • Changes in haematological and biochemical laboratory parameters
Notes	• Panion & BF Biotech Inc. was the sponsor of the study. The role of the funder in study design, conduct, analysis and interpretation was not reported • Study registration: www.ClinicalTrials.gov NCT01503736

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory events which were unlikely to be influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	18/72 assigned to ferric citrate 6 g/d did not complete study (adverse event (7); withdrawal (8); TSAT > 55% (3)) 9/75 assigned to ferric citrate 4 g/d did not complete study (adverse event (2); voluntary withdrawal (3); hyperphosphataemia (1); TSAT > 55% (3)) 24/36 assigned to placebo did not complete study (adverse event (3); voluntary withdrawal (17); hyperphosphataemia (1); TSAT > 55% (2); other (1))
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Lemos 2013

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 24 months
Participants	• Country: Brazil • Setting: single centre • Inclusion criteria: older than 18 years, nephrology care >3 months • Number analysed/randomised: treatment group (26/38); control group (29/41) • Age (SD): treatment group (58.2 ± 9.7); control group (57.4 ± 12.7)

Lemos 2013 *(Continued)*

- Sex (M/F): treatment group (17/9); control group (20/9)
- Exclusion criteria: chronic inflammatory diseases; active malignancy; HIV; viral hepatitis, chronic steroids

Interventions	Treatment group • Sevelamer: 2400 mg daily Control group • No treatment Co-interventions • Calcium carbonate; calcitriol; aspirin; epoetin; iron supplements
Outcomes	• Serum phosphorus • Serum lipids • Coronary artery calcium score • Death (all causes) • Dialysis
Notes	• Genzyme Corporation provided the funding for FGF23. The investigators were solely responsible for the design, conduct, analysis, and publication of the study. There was no restriction for publication, and all data were maintained and analysed solely by the authors • This study was registered at The Brazilian Clinical Trials Registry (REBEC - Registro Brasileiro de Ensaios Clinicos, RBR-6pngwz)., which is part of the International Clinical study Registry Platform of the World Health Organization (ICTRP/WHO: U1111-1122-6205)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The CACS images were scored by a single radiologist blinded to clinical and biochemical aspects of the patient. Blinding of outcome assessment for other outcomes was not reported. Outcome measures were laboratory measure, death and dialysis and were unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	12/38 allocated to sevelamer did not complete study (dialysis (7); death (2); no CT imaging (2); other (1)) 12/41 allocated to control did not complete study (dialysis (5); death (1); without CT (3); other (3))
Selective reporting (reporting bias)	Low risk	Key death, vascular calcification, and laboratory outcomes were reported

Lemos 2013 *(Continued)*

Other bias	Low risk	The study appeared to be free of other sources of bias

Liabeuf 2017

Methods	• Study design: parallel RCT • Time frame: October 2010 to April 2013 • Follow-up: 12 weeks
Participants	• Country: France • Setting: 15 hospital centres in France • Inclusion criteria: >18 years; no concomitant treatment with phosphate binders; CKD patients not on dialysis stage 3b or 4, GFR between 15 and 45 ml/min/1.73m^2, using simplified MDRD formula; levels of C-terminal FGF23 > 120 RU/mL and fasting phosphataemia > 1.0 mmol/L; able to comply with the study procedures during all the study period; willing to abstain from taking any following medication during all the study period: antacid and phosphate binders with aluminium, magnesium, calcium or lanthanum; treatment for hyperparathyroid; active vitamin D and calcimimetic; native vitamin D; childbearing potential must have a reliable contraceptive methods during all the study period (hormonal, barrier methods or intrauterine device); no participation in any clinical study using an investigational product or device during the 30 days preceding the first protocol visit • Number analysed/randomised: treatment group (31/39); control group (33/39) • Mean age ± SD (years): treatment group (63 ± 13); control group (63 ± 14) • Sex (men): treatment group (69%); control group (72%) • Exclusion criteria: predisposition with or presence of intestinal or ileus obstruction or severe GI motility disorder(like severe constipation); antecedent of major GI surgery; abusive consumption of alcohol and drug (excluding tobacco) according the investigator; arrhythmia treated by antiarrhythmic agent or epileptic treated by anticonvulsant; antecedent of kidney transplantation; antecedent of parathyroidectomy; fasting phosphataemia > 1.78 mmol/L or serum 25(OH)D3 < 20 ng/mL (< 50 nmol/L); pregnancy or breastfeeding
Interventions	Treatment group 1 • Sevelamer carbonate: 800 mg, 2 tablets 3 times/d taken with meals Treatment group 2 • Placebo Co-interventions • Not reported
Outcomes	• iPTH • Serum calcitriol • Serum phosphorus, calcium, intact FGF23, 25(OH)D_3, bone specific ALP, osteocalcin, collagen crosslink • Urine phosphate • Urine calcium, creatinine, urea • Urine and serum biomarkers • Adverse events
Notes	• Sanofi Genzyme provided financial assistance, drugs, and placebo. The role of the funder in study conduct, design, analysis and interpretation was not reported • Study registration: NCT01220843

Liabeuf 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized randomisation was performed by the clinical research unit at Amiens University Hospital. A data manager configured an interactive web response system (running Ennov Clinical software V6.2; Ennov SA, Paris, France) to randomise patients using a minimization algorithm
Allocation concealment (selection bias)	Low risk	Interactive web response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were unlikely to be influence by knowledge of treatment allocation as they were laboratory measures. Adverse events were unlikely to be influenced by knowledge of treatment allocation as participants and investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	8/39 participants allocated to sevelamer did not complete follow-up (adverse event (4); patient request (4)) 6/39 participants allocated to placebo did not complete follow-up (patient request (4); other (2))
Selective reporting (reporting bias)	Low risk	All key laboratory measures and adverse events were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Lin 2010

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 2 months
Participants	• Country: Taiwan • Setting: single centre • Inclusion criteria: > 18 years; receiving stable regular HD for at least 3 months; phosphate binders (either calcium carbonate, calcium acetate, aluminium salts, or sevelamer) for at least 1 month; serum phosphorus > 1.78 mmol/L (5.5 mg/dL) and ≤ 2.75 mmol/L (8.5 mg/dL) developed again after the 2-week washout period; stable vitamin D replacement therapy for at least 3 months prior to screening • Number analysed/randomised: treatment group 1 (23/26); treatment group 2 (20/26) • Mean age ± SD (years): treatment group 1 (58.5 ± 10.3); treatment group 2 (56 ± 13.6) • Sex (M/F): treatment group 1 (18/8); treatment group 2 (12/14) • Exclusion criteria: severe hypercalcaemia (adjusted serum calcium > 2.75 mmol/L (11 mg/dL)); uncontrolled BP; poor heart function (NYHA stage > 3); abnormal liver function (ALT or AST level over 3 times the upper limit of normal value); GI motility disorder, or malignancy during the washout period
Interventions	Treatment group 1

Lin 2010 *(Continued)*

	• Sevelamer hydrochloride: 800 mg with meals 3 times/d, according to the level of hyperphosphataemia after the washout period: one tablet 3 times/d if the level was > 5.5 mg/dL and ≤ 6.5 mg/dL, two tablets 3 times/d if > 6.5 mg/dL and ≤ 7.5 mg/dL and three tablets if > 7.5 mg/dL and ≤ 8.5 mg/dL. At each subsequent 2-week interval, the dosage was titrated gradually to achieve the target level of serum phosphorus (3.5 mg/dL to 5.5 mg/dL) and decreased or increased by one tablet if serum phosphorus was < 3.5 mg/dL or > 5.5 mg/dL, accordingly Treatment group 2 • Calcium carbonate: 677 mg with meals 3 times/d, according to the level of hyperphosphataemia after the washout period: one tablet 3 times/d if the level was > 5.5 mg/dL and ≤ 6.5 mg/dL, two tablets 3 times/d if > 6.5 mg/dL and ≤ 7.5 mg/dL and three tablets if > 7.5 mg/dL and ≤ 8.5 mg/dL. At each subsequent 2-week interval, the dosage was titrated gradually to achieve the target level of serum phosphorus (3.5 mg/dL to 5.5 mg/dL) and decreased or increased by one tablet if serum phosphorus was < 3.5 mg/dL or > 5.5 mg/dL, accordingly Co-interventions • If patients were on vitamin D replacement therapy, the dosage must have been stable for at least 3 months prior to screening
Outcomes	• Adverse events • Serum phosphorus • Serum calcium • Serum Ca x P product • Serum iPTH
Notes	• This study was financially supported by the Improving Dialysis Quality Research Funds, Ta-Tung Kidney Foundation • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and were unlikely to be influenced by knowledge of treatment allocation. Knowledge of treatment allocation may have influenced reporting of adverse events
Incomplete outcome data (attrition bias) All outcomes	High risk	3/26 allocated to sevelamer did not complete follow-up (tarry stool (1); upper GI bleeding (1); severe itch (1)) 6/26 allocated to calcium did not complete follow-up (constipation (4); GI upset (1); nausea (1))
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported

Lin 2010 *(Continued)*

Other bias	Low risk	The study appeared to be free of other sources of bias

Lin 2014a

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 months
Participants	• Country: Taiwan • Setting: multicentre • Inclusion criteria: ESKD patients ≥ 45 years with anuria attending routine HD sessions 3 times/wk for at least 3 months with adequate dialysis dose (KT/V > 1.2) • Number analysed/randomised: treatment group 1 (23/36); treatment group 2 (27/39) • Mean age ± SD (years): treatment group 1 (59.61 ± 8.16); treatment group 2 (56.96 ± 7.72) • Sex (M/F): treatment group 1 (11/23); treatment group 2 (18/27) • Exclusion criteria: hypercalcaemia; ALT or AST > 3 times upper normal limit or iPTH > 1000 pg/mL before screening; clinical inflammatory or infectious diseases, GI bleeding or any other cause of hospital admission within 3 months before enrolment; thyroid disease, parathyroidectomy, swallowing disorders, gastrectomy or intestinal resection; osteoporosis and concurrently receiving related medications
Interventions	Treatment group 1 • Sevelamer hydrochloride: 800 mg tablets. The starting dose of the medications was based on the baseline serum phosphate level; one tablet 3 times/d (1.78 < phosphate < 2.10 mmol/L), 2 tablets (2.10 ≤ phosphate < 2.42 mmol/L), or 3 tablets (phosphate ≥ 2.42 mmol/L) given with meals and dose was titrated according to a fixed algorithm: increase 1 tablet per meal (if phosphate > 1.78 mmol/L), no change (1.13 ≤ phosphate ≤ 1.78 mmol/L), or decrease one tablet per meal (if phosphate < 1.13 mmol/L). The largest daily dose was 12 tablets. Treatment group 2 • Calcium carbonate: 500 mg tablets. The starting dose of the medications was based on the baseline serum phosphate level. one tablet 3 times/d (1.78 < phosphate < 2.10 mmol/L), two tablets (2.10 ≤ phosphate < 2.42 mmol/L), or three tablets (phosphate ≥ 2.42 mmol/L) given with meals and dose was titrated according to a fixed algorithm: increase 1 tablet per meal (if phosphate > 1.78 mmol/L), no change (1.13 ≤ phosphate ≤ 1.78 mmol/L), or decrease one tablet per meal (if phosphate < 1.13 mmol/L). If the serum total calcium level rose above 2.62 mmol/L, the investigator reduced the calcium carbonate dosage by one tablet per meal to bring the serum calcium below 2.62 mmol/L. The largest daily dose was 12 tablets Co-interventions • All patients maintained their regular dialysis schedule, dietary habits and prescribed medication for dyslipidaemia (statin), hypertension (antihypertension drugs) and hyperparathyroidism (vitamin D, by KDOQI guideline) throughout the study period by the physicians in the three centres • Magnesium-containing drugs, vitamin D analogs and calcimimetics were not prescribed to the patients
Outcomes	• Death (all causes) • Serum phosphorus • Serum calcium • Serum iPTH • ALP • Highly-sensitive CRP • s-Klotho

Lin 2014a *(Continued)*

	• HCT • Serum albumin • LDL cholesterol • FGF23 • Adverse events
Notes	• Sevelamer used in this study was sponsored by Chugai Pharma Taiwan. This study is supported in part by Taiwan Department of Health Clinical study and Research centre of Excellence (DOH102-TD-B-111-004), and is also supported by a grant from China Medical University Hospital, Taiwan (DMR-101-015) • Study registration: www.ClinicalTrials.gov NCT01755078

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomisation schedule was generated using a validated system that automates the random assignment of treatment groups to randomised numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and death and were unlikely to be influenced by knowledge of treatment allocation. Knowledge of treatment allocation may have influenced reporting of adverse events
Incomplete outcome data (attrition bias) All outcomes	High risk	13/36 participants allocated to sevelamer did not complete study (GI upset (8); sepsis (1); transplant (1); loss of follow-up (1); consent withdrawal (1); gastric cancer (1)) 12/39 participants allocated to calcium carbonate did not complete study (GI upset (7); pneumonia (1); transplant (1); consent withdrawal (3))
Selective reporting (reporting bias)	Low risk	Key death, adverse events, and laboratory measures were reported
Other bias	High risk	There was imbalance between study groups for serum phosphorus levels and ALP levels

Liu 2006

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 8 weeks
Participants	• Country: Taiwan • Setting: single centre • Inclusion criteria: hyperphosphataemia (serum phosphorus level > 6.0 mg/dL) during the 2-weCk washout period; age ≥ 20 years; HD 3 times/wk for at least 3 months; stable doses of calcium-based

Liu 2006 *(Continued)*

	phosphate binders for at least 1 month if this therapy was given; stable doses of vitamin D replacement for at least 1 month if this therapy was given • Number analysed/randomised: treatment group 1 37/37; treatment group 2 (30/33) • Mean age ± SD (years): treatment group 1 (47.6 ± 11.9); treatment group 2 (50.4 ± 10.9) • Sex (M/F); treatment group 1 (21/16); treatment group (17/16) • Exclusion criteria: adjusted serum calcium level > 11 mg/dL during the washout period; Hb < 8.0 g/dL; ALT or AST ≥ 3 times the upper limit of normal
Interventions	Treatment group 1 • sevelamer hydrochloride: starting dosage of depended on the degree of hyperphosphataemia; > 6.0 to 7.5 mg/dL: 2 tablets, 3 times/d; ≥ 7.5 to < 9.0 mg/dL: 3 tablets, 3 times/d; ≥ 9.0 mg/dL: 4 tablets, 3 times/d. The dose was titrated every 2 weeks as necessary to achieve a serum phosphorus level of 3.5 to 6.0 mg/dL. The largest daily dose of sevelamer was 12 g Treatment group 2 • calcium acetate: starting dosage of depended on the degree of hyperphosphataemia; >6.0 to 7.5 mg/dL: 1 tablet, 3 times/d; ≥7.5 to < 9.0 mg/dL: 2 tablets, 3 times/d; ≥ 9.0 mg/dL: 3 tablets, 3 times/d. The dose was titrated every 2 weeks as necessary to achieve a serum phosphorus level of 3.5 to 6.0 mg/dL. The largest daily dose of calcium acetate was 12 g Co-interventions • Patients were prohibited from consuming antacids containing aluminium or magnesium during the study • For patients on vitamin D replacement therapy, the investigator maintained the original dose recorded at the start of the study unless significant hypercalcaemia developed. In this situation, vitamin D was reduced or stopped according to the level of hypercalcaemia • Patients maintained their regular dialysis schedule and normal dietary habits throughout the study
Outcomes	• Serum phosphorus • Serum calcium • Serum Ca x P product • Serum iPTH • Serum ALP • GI adverse events • Adverse events
Notes	• Chugai Pharma Taiwan Ltd. provided the sevelamer hydrochloride tablets for this study • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management

Liu 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and death and were unlikely to be influenced by knowledge of treatment allocation. Knowledge of treatment allocation may have influenced reporting of adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	63/73 participants completed the study. The most common reason for discontinuation was withdrawal of consent. In the sevelamer hydrochloride group, four patients discontinued due to consent withdrawal, investigator judgment, or violation of the protocol. In calcium acetate group, six patients discontinued due to consent withdrawal or adverse event. Three patients who did not have post-baseline efficacy data were excluded from the efficacy analysis. Therefore the intent-to-treat population comprised 70 patients: 37 in the sevelamer hydrochloride group and 33 in the calcium acetate group
Selective reporting (reporting bias)	Low risk	Key adverse events and laboratory measures were reported
Other bias	High risk	The doses of the control medication (calcium acetate) were lower than the intervention

Locatelli 2013

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 3 months
Participants	• Country: Hungary, Italy, Poland, Serbia, Macedonia, Ukraine, Russia, Malaysia • Setting: multicentre (100 sites) • Inclusion criteria: ≥18 years; CKD stage 5; hyperphosphataemia and dyslipidaemia; serum phosphorus ≥ 1.94 mmol/L (6.0 mg/dL) and serum LDL cholesterol level ≥ 1.82 mmol/L (70 mg/dL) after washout of phosphate binders and lipid-lowering drugs; 3 times/wk HD, daily APD or CAPD; baseline dialysis fractional clearance of urea (Kt/V) value (single pool) ≥1.2 for those on HD or a weekly Kt/V value ≥1.8 for those on PD, a calcium dialysate content of 1.00 to 1.75 mmol/L (2 to 3.5 mEq/L) and to be on a stabilised phosphate diet • Number analysed/randomised: treatment group (328/510); control group (82/132) • Mean age ± SD: 49.1 ± 12.65 years • Sex (M/F): 340/299 • Exclusion criteria: PTH persistently > 1000 pg/mL; serum LDL > 4.94 mmol/L (190 mg/dL); serum triglycerides > 6.76 mmol/L (600 mg/dL); serum albumin < 30.0 g/L; significant GI abnormalities or liver dysfunction, including liver function test values three times above normal; receive drugs that could affect phosphorus or lipid levels, other than study medication
Interventions	Treatment group 1 • Colestilan: 3, 6, 9, 12, 15 g daily. Study medication was split into 3 daily doses, taken with meals. Patients in the 3 lower dose groups and the corresponding placebo group all took 9 tablets per day, comprising active and/or placebo tablets. Patients in the 12 and 15 g groups, and the corresponding placebo groups, received 12 or 15 tablets. The two high-dose groups were handled separately to the lower dose groups because of the potential impact on treatment compliance of such a large number of tablets per day, and to avoid subjecting all patients to such a regimen. Treatment group 2 • Placebo Co-interventions

Locatelli 2013 *(Continued)*

	• Not reported
Outcomes	• Death (all causes) • Adverse events • Serum phosphorus • Serum calcium • Serum PTH • Lipids • Serum uric acid • CRP • HbA1C • Vitamin B12, A, E, K • Folic acid
Notes	• The study was funded by Mitsubishi Pharma Europe Ltd. Editorial assistance was provided by K. Croom, with financial support from Mitsubishi Pharma Europe Ltd. The role of the funder in study design, conduct, analysis, and interpretation was not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed according to a computer-generated central randomisation code, which was designed within countries to ensure that each site enrolled approximately equal numbers of patients in each treatment group
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and death and were unlikely to be influenced by knowledge of treatment allocation. Knowledge of treatment allocation may have influenced reporting of adverse events
Incomplete outcome data (attrition bias) All outcomes	High risk	139/510 participants allocated to colestilan withdrew from treatment (death (4); adverse events (36); withdrawn consent (49); high phosphate (70); low phosphate (4); investigator request (2); other (13); protocol violation (1)) 50/132 participants allocated to placebo withdrew from treatment death (2); adverse event (4); withdrawal consent (7); high phosphate (30); protocol violation (4); other (3))
Selective reporting (reporting bias)	Low risk	Key death, adverse events and laboratory measures were reported
Other bias	Low risk	The study appeared to be free from other sources of bias

Locatelli 2014

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 weeks
Participants	• Country: Australia, Austria, Czech Republic, France, Germany, Hungary, Italy, Poland, South Africa, Spain, UK • Setting: multicentre (69 sites) • Inclusion criteria: ≥ 18 years; CKD 5D; PD or HD; stable phosphate control using phosphate-binding medication for at least 1 month prior to screening, and to have a serum phosphorus level < 2.42 mmol/L (7.5 mg/dL) at screening; calcium dialysate content had to be between 2 and 3.5 mEq/L and to remain constant throughout the study; serum phosphorus had to be ≥ 1.94 mmol/L (6.0 mg/dL) and at least 15% greater than at screening, after both 2 and 3 weeks of phosphate binder washout, or ≥ 2.58 mmol/L (8.0 mg/dL) and at least 15% greater than at screening after 1 week of washout • Number analysed/randomised: treatment group 1 (139/171); treatment group 2 (105/165) • Mean age ± SD (years): treatment group 1 (59.5 ± 13.8); treatment group 2 (56.4 ± 14.7) • Sex (M/F): treatment group 1 (108/54); treatment group 2 (97/72) • Exclusion criteria: clinically significant medical co-morbidities which could substantially compromise patient safety or interfere with study procedures; serum albumin level < 30.0 g/L; iPTH levels consistently/frequently > 1000 pg/mL; BMI ≤ 16.0 or ≥ 40.0 kg/m^2; a history of significant GI abnormalities including motility problems or major GI surgery; biliary obstruction or proven liver dysfunction or liver function tests 3 times the upper limit of normal for at least two of aminotransferase, AST and gamma-glutamyl transferase
Interventions	Treatment group 1 • Sevelamer: starting dose was 2.4 g/d (i.e. 3 tablets) if serum phosphorus was ≤ 2.42 mmol/L (7.5 mg/dL) or 4.8 g/d (i.e. 6 tablets) if serum phosphorus was > 2.42 mmol/L (7.5 mg/dL), with titration up or down between 2.4 and 12 g/d Treatment group 2 • Colestilan: starting dose was 6 g/d (i.e. 6 tablets, 2 tablets 3 times/d). Titration up or down was allowed every 3 weeks within the range 3 to 15 g/d (using 3 g increments) with the aim of achieving and maintaining serum phosphorus levels between 1.13 mmol/L (3.5 mg/dL) and 1.78 mmol/L (5.5 mg/dL) Co-interventions • Not reported
Outcomes	• Death (all causes) • Serum phosphorus • Serum calcium • Serum Ca x P product • Lipid levels • HbA1c • Adverse events
Notes	• The study was funded by Mitsubishi Pharma Europe Ltd. Editorial assistance was provided by K. Croom, with financial support from Mitsubishi Pharma Europe Ltd. The role of the funder in the study design, conduct, analysis, and interpretation was not reported • Study registration: EudraCT database (2006-003323-37); www.ClinicalTrials.gov NCT00416520

Risk of bias

Bias	Authors' judgement	Support for judgement

Locatelli 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Patients were randomised according to a centrally generated randomisation code
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and death and were unlikely to be influenced by knowledge of treatment allocation. Knowledge of treatment allocation may have influenced reporting of adverse events
Incomplete outcome data (attrition bias) All outcomes	High risk	32/171 participants allocated to sevelamer withdrew from study (adverse events (10); death (1); consent withdrawn (5); protocol violation (3); high serum phosphate (1); randomised in error (3); other (9)) 60/165 participants allocated to colestilan withdrew from study (adverse events (28); death (2); consent withdrawn (16); protocol violation (3); high serum phosphate (8); other (3))
Selective reporting (reporting bias)	Low risk	Key death, adverse events and laboratory measures were reported
Other bias	Low risk	Study did not appear to have other sources of bias

Matsushima 2017

Methods	• Study design: parallel RCT • Time frame: June and December 2016 • Follow-up period: 6 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: chronic HD • Number analysed/randomised: 43/not reported • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Ferric citrate hydrate: 1500 mg/d Treatment group 2 • Sucroferric oxyhydroxide: 750 mg/d Co-interventions • Not reported
Outcomes	• Serum phosphorus

Matsushima 2017 *(Continued)*

- Hb levels
- Transferrin saturation
- iPTH
- Serum calcium
- Adverse events

Notes	• Study funding not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about blinding to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were laboratory measures and were unlikely to be influenced by knowledge of treatment allocation. Knowledge of treatment allocation may have influenced reporting of adverse events
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Key adverse events and laboratory measures were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Navarro-Gonzalez 2011

Methods	• Study design: parallel RCT • Time frame: • Follow-up period: 3 months
Participants	• Country: Spain • Setting: single centre • Inclusion criteria: stable adult patients with CKD stage 5D on long-term HD for at least 3 months; men and women; ≥ 18 years; requiring therapy with phosphate binder; not receiving vitamin D or calcimimetics • Number analysed/randomised: treatment group 1 (30/33); treatment group (29/32) • Mean age ± SD (years): treatment group 1 (59.6 ± 16.9); treatment group (62.8 ± 14.1) • Sex (M/F): treatment group (15/15); treatment group (14/15)

Navarro-Gonzalez 2011 *(Continued)*

	• Exclusion criteria: severe GI disease; current smoking habit; alcohol dependence or drug abuse; history of immunological or tumour disease; inflammatory or infectious episode in the previous month; hepatitis B, C or HIV; previous transplantation; immunotherapy or immunosuppressive treatment
Interventions	Treatment group 1 • Sevelamer hydrochloride: 1600 mg 3 times/d Treatment group 2 • Calcium acetate: 500 mg 3 times/d Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum Ca x P product • Serum PTH • Serum inflammatory markers
Notes	• This study was supported in part by FUNCIS and ACINEF. The role of the funder in the study design, conduct, analysis, and interpretation was not reported • Study registered at the European clinical study database (EudraCT 2005–004052-12).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a computer-generated series of random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All laboratory parameters were determined blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/33 participants allocated to sevelamer withdrew from study 3/32 participants allocated to calcium withdrew from study
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	High risk	The dose of the comparator (calcium acetate) was lower than the dose of sevelamer at baseline

NCT00542815

Methods	• Study design: parallel RCT

NCT00542815 *(Continued)*

- Time-frame: November 2007 to August 2010
- Follow-up: 52 weeks

Participants	• Country: Austria, France, Germany, Hungary, Italy, Macedonia, Malaysia, Poland, Russia, Serbia, South Africa, Spain, Ukraine, UK • Setting: multicentre (115 sites) • Inclusion criteria: clinically stable HD or PD treatment; stable phosphate control; stabilised phosphorus diet; female subjects of child-bearing potential must have a negative serum pregnancy test; male subjects must agree to use appropriate contraception; completed one of the MCI-196 PIII studies • Number analysed/randomised: treatment group 1 (92/124); treatment group 2 (44/76) • Age (SD): not reported • Sex (M/F): treatment group 1 (71/53); treatment group 2 (51/25) • Exclusion criteria: current clinically significant medical comorbidities, which may substantially compromise subject safety, or expose them to undue risk, or interfere significantly with study procedures and which, in the opinion of the Investigator, makes the subject unsuitable for inclusion in the study; BMI ≤ 16.0 kg/m^2 or ≥ 40.0 kg/m^2; current or a history of significant GI motility problems; positive test for HIV 1 and 2 antibodies; history of substance or alcohol abuse within the last year; seizure disorders; history of drug or other allergy; temporary catheter with active signs of inflammation or infection; the subject has participated in a clinical study with any experimental medication (with the exception of MCI-196 PIII studies) in the last 30days or experimental biological product within the 90 days prior to signing of informed consent form
Interventions	Treatment group 1 • Colestimide: 3g to 15 g/d (3 times/d) 40 weeks of flexible dose Treatment group 2 • Sevelamer: approved dosing recommendations for 12 weeks Co-interventions • None reported
Outcomes	• Serum phosphorus • Serum LDL cholesterol • Death (all causes) • MI • Stroke • Adverse events
Notes	• Funding sources: Mitsubishi Tanabe Pharma Corporation. The role of the funder in the study design, conduct, analysis, and interpretation was not reported • Study registration: www.ClinicalTrials.gov NCT00542815. Results obtained from www.ClinicalTrials.gov website

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement

NCT00542815 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were death and biochemical parameters and were unlikely to be influenced by knowledge of treatment allocation. Cardiovascular event reporting may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	32/124 participants allocated to sevelamer did not complete study (adverse event (9); death (3); protocol violation (2); withdrawal by subject (8); other reasons (10)) 32/76 participants allocated to colestimide did not complete study (adverse events (6); death (7); lack of efficacy (2); physician decision (1); protocol violation (1); withdrawal (5); other reasons (10))
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	Unclear risk	Insufficient information to permit judgement

NICOREN 2017

Methods	• Study design: parallel RCT • Time frame: January 2010 to July 2014 • Follow-up period: 6 months
Participants	• Country: France • Setting: multicentre (18 sites) • Inclusion criteria: ≥ 18 years; serum phosphorus levels ≥ 1.6 mmol/L, serum total calcium levels ≤ 2.37 mmol/L during washout period. serum iPTH between 60 and 800 pg/mL, serum aluminium levels < 0.5 µmol/L, serum 25-OH vitamin D levels between 30 and 60 ng/mL, serum albumin levels > 30 g/L and platelet count > 150 000/mm^3 • Number analysed/randomised: treatment group 2 (46/51); treatment group 2 (27/49) • Mean age ± SD (years): treatment group 1 (65 ± 13); treatment group 2 (65 ± 14) • Sex (M/F): treatment group 1 (31/51); treatment group 2 (32/65) • Exclusion criteria: abnormal liver function; autoimmune disease; ongoing chemotherapy and body weight loss > 3 kg in the previous 3 months or > 6 kg in the previous 6 months
Interventions	Treatment group 1 • Sevelamer hydrochloride: initiated at 3.2 g/d; 4-week dose titration period during which the drug was titrated according to efficacy and tolerability (3.2 to 9.6 g/d) Treatment group 2 • Nicotinamide: initiated at 0.5 g/d; 4-week dose titration period during which the drug was titrated according to efficacy and tolerability (0.5 to 2.0 g/d) Co-interventions • To ensure that changes in serum phosphate levels during the study were due to the study medication and not result of significant changes in dietary phosphate intake, nutritional counselling was given to all patients to limit the intake of diet rich in phosphorus, which included moderate protein intake (~1.2 g/kg/d)

NICOREN 2017 *(Continued)*

	• Patients were asked not to change their use of concomitant medications with a possible direct influence on serum phosphorus levels such as vitamin D and calcium binders, as far as possible in accordance with local clinical practice • No patient was treated with active vitamin D sterols or calcimimetics during the study period
Outcomes	• Death (all causes) • Serum phosphorus • Adverse events • Serious adverse events • Serum calcium • Serum lipids • FGF23 levels • Alpha-Klotho levels
Notes	• This study was funded by an inter-regional grant (PHRC IR08: 2008-004673-17). The role of the funding body in study design, conduct, analysis, interpretation and publication was not reported • Study registration: ClinicalTrials.gov NCT01011699

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about generation of the random sequence to permit judgement
Allocation concealment (selection bias)	Low risk	Randomised to treatment via an interactive system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Outcome measures were death and biochemical parameters and were unlikely to be influenced by knowledge of treatment allocation. Adverse event reporting may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	5/51 participants allocated to sevelamer withdrawn from study (death (1); transplant (1); gastro-intestinal side-effects (2); other (1)) 22/49 participants allocated to nicotinamide withdrawn from study (death (2); transplant (3); gastro-intestinal side-effects (7); thrombocytopaenia (4); non-adherence (2); low serum phosphorus (1); other (3))
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	High risk	Due to technical and financial problems, the study was stopped early. This decision was taken by the steering committee

Ohtake 2013

Methods	• Study design: parallel RCT • Time frame: September 2009

Ohtake 2013 *(Continued)*

	• Follow-up period: 6 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: outpatients; treated with HD; using calcium carbonate as phosphate binder • Number analysed/randomised: treatment group 1 (19/26); treatment group 2 (23/26) • Mean age ± SD: 67.8 ± 6.3 years • Sex (M/F): 25/42 • Exclusion criteria: pregnancy; malignancy; severe GI disease; liver disease; endocrine disease and arrhythmia
Interventions	Treatment group 1 • Lanthanum carbonate: mean dose 1430.6 mg/d Treatment group 2 • Calcium carbonate: mean dose 3000 mg/d Co-interventions • The calcium, phosphate, and iPTH levels were modulated by medication according to routine clinical practice in our dialysis centre. The type of vitamin D used in our study was 1,25-(OH) D_3, that is, calcitriol. To address calcium, phosphate, and iPTH control, phosphate was prioritised and was controlled by a phosphate binder. Then, if serum calcium was below 8.4 mg/dL (lower normal limit), vitamin D was newly added or increased to increase calcium absorption from the GI tract. If serum calcium was higher than 10.4 mg/dL (upper normal limit), vitamin D dosage was decreased. Cinacalcet was added or increased as needed to maintain the levels of iPTH within their target range
Outcomes	• Death (all causes) • Cardiovascular events • Adverse events • Serum phosphorus • Serum calcium • Serum PTH • Serum albumin • CRP • CACS
Notes	• No funding sources • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management

Ohtake 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	CACSs blinded. Other outcome measures of death and laboratory measures were unlikely to be influenced by treatment assignment. Reporting of cardiovascular events and adverse events may have been influenced by treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	7/26 assigned to lanthanum did not complete study (adverse events (7)) 3/26 assigned to calcium did not complete study (arrhythmia (2); death (1))
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	High risk	Imbalance in baseline characteristics and co-intervention with vitamin D agents

Pratt 2007

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 2 months
Participants	• Country: not reported • Setting: not reported • Inclusion criteria: CKD stage 5 treated with HD • Number analysed/randomised: treatment group 1 (27/27); treatment group 2 (27/27) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride: dose adjustments were permitted to control serum phosphate levels to a target range of 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L). Treatment group 2 • Lanthanum carbonate: dose adjustments were permitted to control serum phosphate levels to a target range of 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L). Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum calcium • Serum Ca x P product • Serum iPTH • Adverse events
Notes	• Study funding not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Pratt 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures were unlikely to be influenced by treatment assignment. Reporting of adverse events may have been influenced by treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	Unclear risk	Insufficient information to permit judgement

PREFECT 2014

Methods	• Study design: parallel RCT • Time frame: November 2010 to May 2012 • Follow-up period: 3 months
Participants	• Country: France • Setting: single centre • Inclusion criteria: Men and non-pregnant, non-lactating women ≥ 18 years with CKD stage 3; serum phosphate levels within the normal range (0.808 to 1.55 mmol/L), an eGFR 30 to 59 mL/min/1.73 m^2, cFGF23 levels ≥ 50.0 RU/mL and 25-hydroxy-vitamin D levels ≥ 20 ng/mL • Number analysed/randomised: treatment group (17/23); control group (12/12) • Mean age ± SD (years): treatment group (66 ± 13.9); control group (69.4 ± 13.2) • Sex (men): treatment group (56.5%); control group (41.7%) • Exclusion criteria: vitamin D supplements or compounds containing calcium, phosphate, aluminium or magnesium; AKI; rapidly progressing glomerulonephritis; cirrhosis or other clinically significant liver disease; HIV infection; life-threatening malignancy or multiple myeloma; or any clinically significant illness that would, in the opinion of the investigator, impair their ability to give informed consent or to take part in or complete the study
Interventions	Treatment group 1 • Lanthanum carbonate: 1000 mg, 3 times/d Treatment group 2 • Placebo Co-interventions • Not reported

PREFECT 2014 *(Continued)*

Outcomes	• Death (all causes) • Serum FGF23 • Serum and urinary phosphate • Serum total calcium • Serum Ca x P product • Urinary calcium • iPTH • 1,25 dihydroxy-vitamin D_3 • Adverse events • Major cardiovascular events
Notes	• This study was funded by Shire Development LLC. Rosalind Morley PhD, an employee of PharmaGenesis™ London, was funded by Shire to provide writing support for this publication. Several authors were employees of Shire and owned stock in Shire at time of publication. The role of Shire in study design, conduct, analysis, and interpretation was not reported • Study registered: www.ClinicalTrials.gov NCT01128179.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Treatment was assigned by a randomisation schedule
Allocation concealment (selection bias)	Low risk	Patients were assigned to treatment in the form of code-break envelopes held at the investigational site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Other outcome measures of death and laboratory measures were unlikely to be influenced by treatment assignment. Reporting of cardiovascular events and adverse events may have been influenced by treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	6/23 participants allocated to sevelamer were not included in analyses (protocol violation (1); death (1); non-adherence (2); prohibited medication (1); low serum FGF23 (1)) 0/12 participants allocated to placebo were not included in the analyses
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	High risk	Imbalance in baseline characteristics

Qunibi 2011

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 6 months

Qunibi 2011 *(Continued)*

Participants	• Country: USA • Setting: multicentre (34 sites) • Inclusion criteria: men and women with CKD with a GFR < 30 mL/min/1.73 m^2 not treated with dialysis; elevated serum phosphorus before or after washout > 1.45 mmol/L (4.5 mg/dL) • Number analysed/randomised: treatment group (37/46); control group (41/64) • Mean age ± SD (years): treatment group (63.2 ± 11.7); control group (62.2 ±14.2) • Sex (M/F): treatment group (23/23); control group (35/29) • Exclusion criteria: history of medications non-adherence, GI motility disorders, or any other conditions that rendered them clinically unstable
Interventions	Treatment group 1 • Calcium carbonate: 667 mg capsules; patients with serum phosphorus levels between 4.5 and 5.0 mg/dL received an initial dose of 1 gel cap per meal; those with phosphorus levels between 5.1 and 6.0 mg/dL started with 2 gel caps per meal and those with phosphorus levels > 6.0 mg/dL were administered a starting dose of 3 gel caps per meal. Study participants returned for follow-up visits every 2 weeks. During these visits, the dose was titrated up to a maximum of 15 gel caps per day. If, after 3 months of treatment, the serum phosphorus level remained > 5.5 mg/dL or the iPTH was still > 110 pg/mL despite maximum daily dose of 15 gel caps, the study protocol required that such participants be withdrawn from the study for failure to control Treatment group 2 • Placebo Co-interventions • Usual diet • During the washout period, all phosphate binders, calcium supplements, and vitamin D analogues were discontinued if previously taken
Outcomes	• Serum phosphorus • Serum calcium • Serum PTH • Serum bicarbonate • Serum albumin • Death (all causes) • Adverse events • Cardiac disorders
Notes	• This study was supported by a grant from Fresenius Medical Care North America, Waltham, MA. Authors were employees of the funder. The role of the funder in study design, conduct, analysis, interpretation, and publication was not reported • Study registration: www.ClinicalTrials.gov NCT00211978

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement

Qunibi 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Other outcome measures of death and laboratory measures were unlikely to be influenced by treatment assignment. Reporting of cardiovascular events and adverse events may have been influenced by treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	18/46 participants allocated to calcium acetate did not complete study 44/64 participants allocated to placebo did not complete study
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	High risk	Study was funded and authored by Fresenius

Riccio 2018

Methods	• Study design: parallel RCT • Time-frame: June 2014 to May 2015 • Follow-up: 3 months
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: > 18 years, CKD stage 3-5 • Number analysed/randomised: treatment group (30/35); control group (30/34) • Age (SD): treatment group (56.9 ± 15.2); control group (54.7 ± 18.3) • Sex (M/F): treatment group (14/16); control group (15/15) • Exclusion criteria: existing or previous treatment within the last 1 year with a phosphate binder; hyperphosphataemia (> 5.6 mg/dL); hypophosphataemia (< 2.5 mg/dL); malnutrition, malignant neoplasms, current history of GI and/or endocrine diseases
Interventions	Treatment group 1 • Sevelamer: 800 mg, 3 times/d; drug dosage was adjusted according to phosphate plasma levels at 4-week intervals: was reduced to 800 mg (1 tablet daily) if persistent adverse effects or hypophosphataemia ensued, or was increased to 2400 mg (3 tablets daily) when hyperphosphataemia occurred despite treatment Treatment group 2 • Placebo Co-interventions • Concomitant pharmacological and non-pharmacological therapies were prescribed to each patient to achieve the therapeutic targets in keeping with Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for CKD stages 3–5. In particular, all the patients were prescribed a personalised diet to limit the intake of salt (below 6g NaCl/d) and protein (from 0.7 to 1.0 g/kg/d according to residual kidney function) • Dietary prescription was integrated with nutritional questionnaires by a dedicated dietitian during the clinical visits (at 4-week intervals) to grossly evaluate the stability of tyrosine and phenylalanine ingestion

Riccio 2018 *(Continued)*

Outcomes	• Serum p-creol levels • eGFR • Serum lipids • Serum phosphorus • Serum calcium • Serum PTH • Serum highly-sensitive CRP • Serum bicarbonate • Urinary protein • BP • Adverse events • Death (all causes)
Notes	• Funding sources: Federico II University. The role of the funding body in study design, conduct, interpretation, analysis or publication was not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes opened in sequence by administrative staff personnel not involved in patients care
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Other outcome measures of death and laboratory measures were unlikely to be influenced by treatment assignment. Reporting of adverse events may have been influenced by treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/30 participants allocated to sevelamer did not complete study (withdrew consent (1); low phosphate (3); drug intolerance (1) 4/30 participants allocated to placebo did not complete study (withdrew consent (1); low phosphate (2); drug intolerance (1)
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free of other sources of bias

Roxe 1989

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 8 weeks

Roxe 1989 *(Continued)*

Participants	• Country: USA • Setting: single centre • Inclusion criteria: 18 to 70 years; HD 3 times/wk • Number analysed/randomised: 21/27 • Age: not reported • Sex (M/F): 6/15 • Exclusion criteria: treatment with phenytoin, cardiac glycosides or calcium carbonate; chronic anticoagulation
Interventions	Treatment group 1 • Aluminium hydroxide: 3 g/d to achieve serum phosphorus < 4.5 mg/dL Treatment group 2 • Sucralfate: 6 g/d to achieve serum phosphorus < 4.5 mg/dL Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum aluminium
Notes	• Supported by Marion Laboratories • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures were unlikely to be influenced by treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	6/27 participants not included in analyses
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded. Data were not available for the first period of treatment
Other bias	High risk	Statistical approach did not account for cross-over study design. Baseline participant characteristics were not reported in sufficient detail to assess for balance between treatment groups

Rudnicki 1994

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 24 weeks
Participants	• Country: Denmark • Setting: single centre • Inclusion criteria: maintenance HD 3 times/wk (6 months to 10 years); iPTH above the normal range and serum ionised calcium within or below it • Number analysed/randomised: treatment group (9/10); control group (9/10) • Mean age (range): 55 years (31 to 70) • Sex (M/F): 13/5 • Exclusion criteria: not reported
Interventions	Treatment group • Calcium carbonate 2 g/d for 6 months Control group • Placebo for 6 months Co-interventions • Aluminium-containing phosphate binders.
Outcomes	• Serum phosphate • Serum calcium • Serum iPTH • Serum ALP • Bone markers
Notes	• Funding not reported • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures were unlikely to be influenced by treatment assignment
Incomplete outcome data (attrition bias)	Low risk	2/20 randomised participants did not complete study

Rudnicki 1994 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	High risk	Imbalance in baseline serum phosphorus

Russo 2007

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 24 ± 4.2 months
Participants	• Country: Italy • Setting: not reported • Inclusion criteria: advanced CKD not requiring dialysis; low dietary phosphorus intake; stable serum concentration of phosphorus, calcium, calcium by phosphorus product, PTH; no previous therapy with aluminium or calcium-based phosphate binders, vitamin D sterols, statins; comparable mean baseline total calcium score at CT scan • Number analysed/randomised: treatment group 1 (27/30); treatment group 2 (28/30); control group (29/30) • Mean age ± SD (years): treatment group 1 (55.2 ± 12.0); treatment group 2 (54.4 ±12.9); control group (54.4 ± 13.7) • Sex (M/F): treatment group 1 (23/5); treatment group 2 (24/3); control group (25/4) • Exclusion criteria: < 18 years; symptomatic coronary disease; past MI; previous coronary surgery/angioplasty; stroke; arrhythmia; progressive kidney disease; diabetes
Interventions	Treatment group 1 • Sevelamer hydrochloride: 1600 mg/d Treatment group 2 • Calcium carbonate: 2 g/d Control group • Low phosphate diet Co-interventions • Low phosphate diet
Outcomes	• Total calcium score • Coronary artery calcification • Biochemical variables
Notes	• This is an unsupported study • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement

Russo 2007 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomised by co-author not aware of clinical or baseline characteristics
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	CT evaluation was carried out in an institution external to authors' university. Both initial and final scans were analysed by radiologists who were unaware of both treatment allocation and previous CT reading. Laboratory measures were unlikely to be influenced by treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/30 participants allocated to sevelamer did not complete study (due to cost of drug) 2/30 participants allocated to calcium carbonate did not complete study (lost to follow-up (2); informed consent (1)) 1/30 participants allocated to control did not complete study (MI (1)
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free of other sources of bias

Sadek 2003

Methods	• Study design: parallel RCT • Time frame: November 2000 to April 2001 • Follow-up period: 5 months
Participants	• Country: France • Setting: single centre • Inclusion criteria: HD 3 times/wk for 4 hours; usual serum PTH levels < 400 pg/mL, while using calcium carbonate as only phosphate binder • Number analysed/randomised: treatment group 1 (15/21); treatment group 2 (16/21) • Age: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride: initial dose: 1.2 g at lunch and dinner; dose progressively increased to 4.4 g/d. Treatment group 2 • Continued their pre-existing treatment with calcium carbonate Co-interventions

Sadek 2003 *(Continued)*

	• Each month, if the values of serum corrected calcium decreased below 2.30 mmol/L, the following measures were taken in the sevelamer group
	  * (i) if serum phosphate was >1.70 mmol/L, alphacalcidol was not given —instead, the dialysate calcium concentration was increased by 0.25 mmol/L; and
	  * (ii) if serum phosphate was ≤1.70 mmol/L, an oral bolus of alphacalcidol was given at the end of each dialysis session at an increasing dose starting from 0.25 mg. Otherwise, no other change in the dialysis treatment was introduced
	• The dialysate concentrations of bicarbonate and magnesium were, respectively, 39 and 0.50 mmol/L, while dialysate calcium varied
	• Patients who were on statins for dyslipidaemia did not change their dose

Outcomes	• Death (all causes) • Cardiovascular death • Cardiovascular events • Serum calcium • Serum phosphorus • Hypercalcaemia • Serum PTH • 25-OH vitamin D • Triglycerides, LDL, HDL, total cholesterol • Serum bicarbonate
Notes	• Funding not reported • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Other outcome measures of death and laboratory measures were unlikely to be influenced by treatment assignment. Reporting of adverse events may have been influenced by treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	6/21 participants allocated to sevelamer not included in analysis (intolerance (5); sudden death (1)) 5/21 participants allocated to calcium not included in analysis (transplant (1); deaths (3); stroke (1))
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	High risk	Imbalance in use of vitamin D agents as co-interventions

Saif 2007

Methods	• Study design: cross-over RCT • Time frame; not reported • Follow-up period: 8 weeks
Participants	• Country: Pakistan • Setting: single centre • Inclusion criteria: ESKD, on maintenance HD for at least 3 months • Number analysed/randomised: 41/64 • Mean age ± SD: 42.6 ± 15.7 years • Sex (M/F): 24/17 • Exclusion criteria: previous parathyroidectomy; advanced malignancy/metastasis
Interventions	Treatment group 1 • Calcium carbonate: 5.625 mg/d Treatment group 2 • Calcium acetate: 4.002 g/d Co-interventions • Not reported
Outcomes	• Serum urea • Serum creatinine • Serum calcium • Serum albumin • Serum phosphorus
Notes	• Funding sources not reported • Study registration not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	23/64 participants not included in analysis

Saif 2007 *(Continued)*

Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Unclear risk	Insufficient information to permit judgement

Seifert 2013

Methods	• Study design: parallel RCT • Time frame: January to December 2010 • Follow-up period: 12 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: > 18 years, stage 3 CKD (eGFR 30 to 59 mL/min/1.73 m^2) using the MDRD equation • Number analysed/randomised: treatment group (16/19); control group (19/19) • Mean age ± SD (years): treatment group (62 ± 11); control group (61 ± 13) • Sex (M/F): treatment group (9/10); control group (14/5) • Exclusion criteria: pregnancy; bone disease; MI; congestive heart failure; diastolic dysfunction; severe hypertension
Interventions	Treatment group • Lanthanum carbonate: 1000 mg with meals Control group • Placebo Co-interventions • Not reported
Outcomes	• Serum phosphorus • Urinary phosphorus excretion • iPTH • Serum calcium • Serum creatinine • FGF23 level • BP • Pulse wave velocity • Vascular calcification • Carotid intima-media thickness • Left ventricular ejection fraction • CACS • Death (all causes)
Notes	• The lanthanum carbonate and matched placebo were provided by Shire U.S. Pharmaceuticals Inc. The role of Shire in the study design, analysis, interpretation, and publication was not reported. The study was funded by Shire U.S. Pharmaceuticals Inc., and by NIH grants DK070790, DK 089137 (K.A.H.), KL2RR024994, and UL1 RR024992 (Washington University) • Study registration not reported

Risk of bias

Seifert 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation and double-blind strategy was designed and maintained by research pharmacist and statistician
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cardiac measurements blinded, otherwise outcome assessment blinding not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Three participants (assigned to lanthanum) withdrew from the study
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free of other sources of bias

Sezer 2010

Methods	• Study design: parallel RCT • Time frame: November 2007 to November 2009 • Follow-up period: 2 years
Participants	• Country: Turkey • Setting: single centre • Inclusion criteria: HD treatment with serum phosphorus > 5.5 mg/dL • Number analysed/randomised: 126/126 • Mean age ± SD: 54.4 ± 14.9 years • Sex (men): 58% • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride Treatment group 2 • Calcium acetate Co-interventions • None reported
Outcomes	• Death (all causes) • Serum phosphorus • Hypercalcaemia

Sezer 2010 *(Continued)*

	• Serum potassium • Serum lipids • Serum homocysteine
Notes	• Funding sources not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about blinding to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures and death outcomes unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants evaluated for death
Selective reporting (reporting bias)	Low risk	Key laboratory measures and death were reported
Other bias	Unclear risk	Insufficient information to permit judgement as the study was published as a conference proceeding only

Shahbazian 2011

Methods	• Study design: parallel RCT • Time frame: January to March 2010 • Follow-up period: 2 months
Participants	• Country: Iran • Setting: multicentre (2 sites) • Inclusion criteria: > 18 years; fasting serum phosphorus > 5 mg/dL; HD for more than 2 months; constant dosage of phosphate binders during past 2 weeks • Number analysed/randomised: treatment group (24/24); control group (24/24) • Mean age ± SD (years): treatment group (53.92 ± 11.07); control group (54.08 ± 16.59) • Sex (males): treatment group (58.3%; control group (58.3) • Exclusion criteria: history of hepatic disease or significant disturbance in liver tests; active peptic ulcer; recent treatment with niacin or nicotinamide; non-cooperation; malignancy; absence from HD sessions
Interventions	Treatment group 1

Shahbazian 2011 *(Continued)*

	• Nicotinamide: 500 to 1000 mg/d Treatment group 2 • Placebo Co-interventions • Usual doses of calcium carbonate
Outcomes	• Serum phosphorus • Serum Ca x P • Serum HDL • Serum fasting blood sugar • Platelet count • Adverse drug effects
Notes	• The study was granted by Ahvaz Jundishapur University of Medical Sciences. The role of the funding body in study design, conduct, analysis, interpretation or publication was not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. Placebo and immediate release nicotinamide tablets (500 mg) were prepared by consultant pharmacist of the study at the industrial laboratory of pharmacy faculty of the university using nicotinamide powder purchased from Saveh Novin Kavosh Company
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation. Adverse event reporting may have been influenced by awareness of treatment allocation, although patients unaware of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/24 allocated to nicotinamide did not adhere to study follow-up 5/24 participants assigned to placebo did not adhere to study follow-up
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Shaheen 2004

Methods	• Study design: cross-over RCT • Time frame: March 2003 to June 2003 • Follow-up period: 8 weeks

Shaheen 2004 *(Continued)*

Participants	• Country: Kingdom of Saudi Arabia • Setting: single centre • Inclusion criteria: 15 to 75 years; long-term HD (2 or 3 times/wk) for at least 3 months and optimally dialysed as judged by usual dialysis and serum chemistry parameters; current phosphorus 5.5 mg/dL • Number analysed/randomised: 17/20 • Mean age ± SD: 42.7 ± 9.9 years • Sex (M/F): 12/8 • Exclusion criteria: serious GI disease including dysphasia, vomiting, motility disorder, major intestinal surgery or markedly irregular bowel function; alcohol abuse or drug dependence; clinically relevant liver disease; uncontrolled diabetes or uncontrolled hypertension; malignancy; HIV infection; active vasculitis; illness at the time of entry to the study
Interventions	Treatment group 1 • Sevelamer hydrochloride: 800 mg tablets 3 times/d post meals. The dose of medication was adjusted in order to reach control of phosphorus between 0.8 to 1.8 mmol/L using an increment or decrement in dose every 2o weeks by adding one tablet 3 times/d Treatment group 2 • Calcium carbonate (Caltrate 600): 1500 mg tablet 3 times/d post meals. The dose of medication was adjusted in order to reach control of phosphorus between 0.8 to 1.8 mmol/L using an increment or decrement in dose every 2 weeks by adding one tablet 3 times/d. Co-interventions • Dialysis calcium 1.75 mmol/L
Outcomes	• Serum phosphorus • Serum calcium • Ca x P product • iPTH levels • Lipid profile
Notes	• Funding sources not reported • Study registration not required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias)	Low risk	1/20 participants did not complete sevelamer treatment phase; 2/20 participants did not complete calcium phase

Shaheen 2004 *(Continued)*

All outcomes

Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	High risk	The statistical analysis methods did not account for the cross-over study design. Baseline characteristics for each study group were not provided for assessment of any imbalance

Shibata 2007

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 36 months
Participants	• Country: Japan • Setting: not reported • Inclusion criteria: HD; treatment with calcium carbonate as phosphate binder • Number analysed/randomised: not reported/35 • Mean age ± SD (years): not reported • Sex (men %): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Sevelamer hydrochloride: mean 2600 mg/d • Calcium carbonate: mean 1000 mg/d Treatment group 2 • Calcium carbonate: mean 1700 mg/d Cointerventions • Not reported
Outcomes	• Pulse wave velocity • Serum phosphorus, calcium • Ca x P product • Serum lipids
Notes	• Funding sources not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement

Shibata 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation. Measurement of pulse wave velocity may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Unclear risk	Insufficient information to permit judgement. The study was reported as a conference proceeding only

Shigematsu 2008

Methods	• Study design: parallel RCT • Time frame: January 2005 to May 2005 • Follow-up period: 8 weeks
Participants	• Country: Japan • Setting: multicentre (14 sites) • Inclusion criteria: > 20 years; on maintenance HD with hyperphosphataemia; serum phosphate levels > 5.6 mg/dL at 1 week after the initiation of the washout period • Number analysed/randomised: treatment group 1 (126/126); treatment group 2 (131/132) • Mean age ± SD (years): treatment group 1 (58.8 ± 10.5); treatment group 2 (56.1 ± 11.5) • Sex (M/F): treatment group 1 (87/39); treatment group 2 (87/45) • Exclusion criteria: serum phosphate levels > 10 mg/dL at the start of the washout period or 11.0 mg/dL during the washout period; corrected serum calcium level of < 7.0 mg/dL; iPTH > 1 pg/mL at the start of the washout period
Interventions	Treatment group 1 • Lanthanum carbonate: starting dose 750 mg/d; doses titrated every two weeks according to serum phosphorus (aim between 3.5 and 5.5 mg/dL and tolerability to higher and lower doses Treatment group 2 • Calcium carbonate: starting dose 1500 mg/d; doses titrated every two weeks according to serum phosphorus (aim between 3.5 and 5.5 mg/dL and tolerability to higher and lower doses Co-interventions • Vitamin D could be co-administered • Dialysate calcium 3.0 mEq/L
Outcomes	• Serum calcium • iPTH • Serum phosphorus • Adverse events

Shigematsu 2008 *(Continued)*

	• Serious adverse events
Notes	• Research supported by Bayer Yahukin. The role of the funder in study design, conduct, analysis, interpretation and publication not reported • Study registration not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	14/256 patients were excluded from efficacy analysis as their treatment period was less than 2 weeks' duration due either to discontinuation or to missing efficacy measurements at given study visits
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were measured
Other bias	High risk	Imbalance in baseline characteristics

SLO-NIACIN 2013

Methods	• Study design: cross-over RCT • Time frame: recruitment June 2012 to July 2012. Last study follow-up October 2012 • Follow-up period: 2 months
Participants	• Country: Australia • Setting: single hospital dialysis unit • Inclusion criteria: > 18 years; serum phosphate > 1.8 mmol/L • Number analysed/randomised: treatment group (14/17); control group (15/16) • Median age (IQR): 60 years (52 to 71) • Sex (M/F): 19/14 • Exclusion criteria: < 18 years; current pregnancy; likelihood of receiving a kidney transplant within 20 weeks of commencing study (currently active on deceased donor list or suitable live donor already found); known allergy to niacin; concurrent enrolment in another study of experimental medication
Interventions	Treatment group • Nicotinamide: 500 mg

SLO-NIACIN 2013 *(Continued)*

	Control group • Placebo Co-interventions • Usual phosphate binders and cinacalcet and vitamin D analogues (no dose adjustments were allowed)
Outcomes	• Death (all causes) • Adverse events • Serum phosphorus • Serum calcium
Notes	• Funding from co-authors not otherwise specified • The study was registered with the Australia and New Zealand clinical trials registry (12611000500954)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The computer generated randomisation sequence was also determined offsite by the company which had manufactured the placebo
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. The study medication was packed offsite in identical containers by the company which had manufactured the placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Results were analysed in blinded fashion by an offsite investigator who had no contact with the study patients
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/17 participants allocated to nicotinamide did not complete study follow-up (death (1); side effects (2)) 1/15 participants allocated to placebo did not complete follow-up (side effects (1))
Selective reporting (reporting bias)	Low risk	Death, adverse events, and laboratory measures were reported
Other bias	High risk	The study analysis did not account for the cross-over study design

Song 2014

Methods	• Study design: parallel RCT • Time frame: March to June 2013 • Follow-up period: 3 months
Participants	• Country: China • Setting: single centre • Inclusion criteria: ≥ 18 years; CAPD 6 months or longer; iPTH 34 to 57 pmol/L (300 to 500 pg/mL) • Number analysed/randomised: treatment group 1 (20); treatment group 2 (20)

Song 2014 *(Continued)*

	• Mean age ± SD (years): treatment group 1 (51.35 ± 13.01); treatment group 2 (56.80 ± 13.11) • Sex (M/F): 17/23 • Exclusion criteria: primary hyperparathyroidism; Ca x P product < 4.52 mmol/L; renal tubular acidosis; calcium above 2.6 mmol/L (10.4 mg/dL); phosphorus > 1.45 mmol/L (4.49 mg/dL); GI disorders and other diseases
Interventions	Treatment group 1 • Lanthanum carbonate: 500 mg 3 times/d Treatment group 2 • Calcium carbonate: 750 mg twice/d Co-interventions • Calcitriol
Outcomes	• Serum phosphorus, calcium • PTH
Notes	• Funding sources not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blinded. Knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free from other sources of bias

Soriano 2013

Methods	• Study design: parallel RCT • Time frame: not reported

Soriano 2013 *(Continued)*

	• Follow-up period: 4 months
Participants	• Country: Spain • Setting: single centre • Inclusion criteria: clinically stable CKD 4-5 non-dialysis patients followed for more than 6 months in an outpatient clinic; serum phosphorus > 1.3 mmol/L (4 mg/dL); serum calcium < 2.38 mmol/L (9.5 mg/dL); 25(OH)D levels > 30 ng/mL; serum albumin > 3 g/dL • Number analysed/randomised: treatment group 1 (not reported/16); treatment group (not reported/16) • Median age, IQR (years): treatment group 1 (58.4, 46 to 83); treatment group 2 (62.3, 30 to 84) • Sex (M/F): treatment group 1 (11/5); treatment group 2 (10/6) • Exclusion criteria: nephrotic syndrome; systemic or autoimmune disease; neoplasia; liver disease; and those on phosphate binders; anticonvulsant therapy or vitamin D receptor activators
Interventions	Treatment group 1 • Lanthanum carbonate: maximum 3000 mg/d; dose of phosphate binders was adjusted to maintain serum phosphate < 4.5 mg/dL Treatment group 2 • Calcium carbonate: maximum 2500 mg/d; dose of phosphate binders was adjusted to maintain serum phosphate < 4.5 mg/dL
Outcomes	• Serum phosphorus, calcium, PTH • FGF23 • 25-hydroxy-vitamin D • Serum creatinine
Notes	• This study was supported by grants from Fondo de Investigacion Sanitaria, Instituto de Salud Carlos III, Junta de Andalucia, and Fundacion Nefrologica. The role of the funding body in study design, conduct, analysis, interpretation, and outcome was not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement

Soriano 2013 *(Continued)*

Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free of other sources of bias

Spasovski 2006

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 1 year
Participants	• Country: Macedonia • Setting: single centre • Inclusion criteria: dialysis patients who had required oral phosphate binders to control serum phosphorus levels • Number analysed/randomised: treatment group 1 (9/12); treatment group 2 (10/12) • Mean age ± SD (years): treatment group 1 (55 ± 10); treatment group 2 (57 ± 10) • Sex (M/F): treatment group 1 (7/5); treatment group 2 (7/5) • Exclusion criteria: any significant GI problem; history of treatment with corticosteroids or bisphosphonates; hypocalcaemia at screening
Interventions	Treatment group 1 • Lanthanum carbonate: to achieve optimal control of serum phosphorus levels (< 1.8 mmol/L) (maximum dose of 3000 mg/d) Treatment group 2 • Calcium carbonate: to achieve optimal control of serum phosphorus levels (< 1.8 mmol/L) (maximum dose of 4000 mg/d) Co-interventions • The use of erythropoietin, vitamin D and calcium was monitored closely throughout the study
Outcomes	• Serum phosphorus • Serum calcium • Serum iPTH • 25-hydroxy-vitamin D_3 • 1,25 di-hydroxy-vitamin D3 • Liver enzymes • Adverse events • Lanthanum level in plasma and bone
Notes	• Treatment period was 1 year. During the other 2 years all participants were switched to calcium carbonate. Funding from Shire Pharmaceutical Development. The role of the funding body in study design, conduct, analysis, interpretation, and publication was not reported. Employees of Shire were authors of the publication • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Spasovski 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/12 participants allocated to lanthanum did not complete follow-up 2/12 participants allocated to calcium did not complete follow-up
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	High risk	Study funded and authored by Shire

Spiegel 2007

Methods	• Study design: parallel, open-label RCT • Time frame: not reported • Follow-up period: 12 weeks
Participants	• Country: USA • Setting: University health sciences centre • Inclusion criteria: age > 18 years; HD for at least 3 months; receiving phosphate binders before entry into the study; serum calcium of 8.0 to 10.2 mg/dL and serum phosphorus of 3.0 to 6.9 mg/dL • Number analysed/randomised: treatment group 1 (17/20); treatment group 2 (8/10) • Mean age ± SD (years): treatment group 1 (55.5 ± 12.6); treatment group (55.9 ± 12.0) • Sex (M/F): treatment group 1 (12/8); treatment group 2 (4/6) • Exclusion criteria: frequent diarrhoea; declined to give informed consent
Interventions	Treatment group 1 • Magnesium carbonate: to achieve the target phosphorus of < 5.5 mg/dL Treatment group 2 • Calcium acetate: to achieve the target phosphorus of < 5.5 mg/dL Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum magnesium • Serum calcium • iPTH

Spiegel 2007 *(Continued)*

	• Serum bicarbonate
Notes	• This study was supported by a grant from Nephro-Tech, Inc. All aspects of the study design, conduct, and analysis, including ownership of the data, are under the sole authority of the authors, with no restrictions on publication • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	3/20 participants allocated to magnesium carbonate did not complete study (diarrhoea (3)) 2/10 participants allocated to calcium did not complete study (adverse events (2))
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free from other sources of bias

Sprague 2009a

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 8 weeks
Participants	• Country: USA • Setting: multicentre (28 sites) • Inclusion criteria: ≥ 18 years; eGFR 15 to 59 mL/min/1.73 m^2 at screening; undergoing physician care for CKD for > 2 months; not expected to begin dialysis for ≥ 4 months • Number analysed/randomised: treatment group (43/80); control group (28/41) • Mean age ± SD (years): treatment group (61.8 ± 12.9); control group (63.0 ± 12.7) • Sex (M/F): treatment group (40/38); control group (21/20) • Exclusion criteria: requirement for treatment with cinacalcet HCl or compounds containing phosphorus, aluminium, magnesium or calcium; acute kidney injury within 12 weeks of screening; rapidly progression of glomerulonephritis; significant GI surgery or disorders; evidence of clinically significant liver disease; pregnant or lactating women; women on reproductive potential who did not agree to use effective contraception

Sprague 2009a *(Continued)*

Interventions	Lanthanum group • Lanthanum carbonate: 750 mg/d to a maximum of 3000 mg/d to achieve a target serum phosphorus level of < 4.0 mg/dL Placebo group • Matching placebo Co-interventions • Participants receiving vitamin D or calcium supplements before screening could continue treatment during the study. Treatments could not be initiated during the study, and the dose could not be increased, but it could be decreased if a patient experienced hypercalcaemia
Outcomes	• Serum phosphorus • Serum calcium-by phosphorus product • Serum iPTH • Safety and tolerability of treatment
Notes	• This study was funded by Shire Pharmaceuticals. Employees of Shire Pharmaceuticals were authors. Shire Pharmaceuticals also provided assistance with analysis and interpretation of the data • Study registration: www.Clinicaltrials.gov NCT00234702

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	37/80 participants allocated to lanthanum did not complete study follow-up 13/43 participants allocated to placebo did not complete study follow-up
Selective reporting (reporting bias)	Low risk	Data for the end of the first period of the cross-over were not available. Key laboratory measures and adverse events were reported.
Other bias	High risk	Study funded and authored by Shire

Takahara 2014

Methods	• Study design: parallel RCT

Takahara 2014 *(Continued)*

- Time frame: June 2010 to November 2011
- Follow-up period: 8 weeks

Participants	• Country: Japan • Setting: multicentre (40 sites) • Inclusion criteria: ≥ 20 years; eGFR (eGFR) < 60 mL/min/1.73 m^2 (stage 3–5 CKD) not on dialysis; CKD treatment history > 2 months; not indicated for dialysis within 4 months; diet therapy ≥ 1 month before the run-in period; serum phosphate level: 5.6 – 11.0 mg/dL at week –4 or –2 • Number analysed/randomised: treatment group (76/88); control group (43/55) • Mean age ± SD (years): treatment group (61.3 ± 11.4); control group (62.1 ± 12.8) • Sex (M/F): treatment group (39/47); control group (28/27) • Exclusion criteria: hypocalcaemia or hypercalcaemia (corrected serum calcium level of < 7.0 mg/dL or ≥ 11.0 mg/dL) at week –2; significant kidney disease, including rapidly progressing glomerulonephritis, hydronephrosis, transplanted kidney; AKI within 3 months before the run-in period; significant GI disorders including acute peptic ulcer (excluding chronic gastritis), Crohn's Disease, ulcerative colitis, bowel obstruction, and malignant tumour; cirrhosis or other clinically significant liver diseases; life-threatening malignancy or current multiple myeloma; positive human immunodeficiency virus reaction; known or suspected intolerance or hypersensitivity to the study drug(s); alcoholism or drug abuse; pregnant or lactating females; other conditions considered ineligible
Interventions	Treatment group 1 • Lanthanum carbonate: starting dose 750 mg/d which was up-titrated to 2250 mg/d depending on the serum phosphate level (target level 2.7 to 4.6 mg/dL) and tolerability; the dose was adjusted every 2 weeks by 750 mg/d at the discretion of the investigator or sub-investigator Treatment group 2 • Placebo Co-interventions • The following concomitant substances were prohibited during the study period: other phosphate binders; serum phosphate level affecting drugs like niceritrol, colestimide, and cinacalcet; phosphate-containing compounds; and phosphate-binding dietary substances like calcium acetate and egg shell derived calcium
Outcomes	• Serum phosphate • Serum Ca x P product • Serum iPTH • Urinary phosphate • Adverse events • Death (all causes)
Notes	• This research was a phase III clinical study and funded by Bayer Yakuhin, Ltd; first author employee of Bayer Yakuhin • Study registered Clinical Trials.gov Identifier: NCT01110629

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement

Takahara 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. Placebo tablets were indistinguishable from lanthanum carbonate tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures and reporting of death unlikely to have been influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	12/88 participants allocated to lanthanum did not complete study follow-up 12/55 participants allocated to placebo did not complete study follow-up
Selective reporting (reporting bias)	Low risk	Key laboratory measures and death (all causes) reported
Other bias	High risk	Study funded and authored by Bayer Yakuhin

Tielmans 1990

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 6 months
Participants	• Country: Belgium • Setting: single centre • Inclusion criteria: HD patients with serum phosphorus level ≥ 6.0 mg/d • Number analysed/randomised: not reported/12 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Calcium carbonate: 2.5 g/d divided into 3 doses with meals Treatment group 2 • Calcium acetate: 4.2 g/d divided into 3 doses with meals Co-interventions • Not reported
Outcomes	• Serum phosphorus • Serum calcium • Serum ALP • Serum aluminium levels • Hypercalcaemia • Adverse events
Notes	• Funding sources not reported • Study registration not required

Tielmans 1990 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about study attrition to permit judgement
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events reported
Other bias	Unclear risk	The statistical analysis did not account for the cross-over study design

Toida 2012

Methods	• Study design: cross-over RCT • Time frame: not reported • Follow-up period: 3 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: on maintenance HD therapy for longer than 3 months • Number analysed/randomised: treatment group 1 (20/25); treatment group 2 (22/25) • Mean age ± SD (years): treatment group 1 (65.2 ± 13.8); treatment group 2 (65.9 ± 8.9) • Sex (men): treatment group 1 (60%); treatment group 2 (60%) • Exclusion criteria: significant medical disorder which may affect the completion of any aspect of the protocol existed, as determined by the investigator; cancer or suspected cancer; inflammatory disorders; contraindications listed in the package insert of lanthanum; pregnancy; possible pregnancy; or breast-feeding
Interventions	Treatment group 1 • Lanthanum carbonate: initiated at 750 mg/d (one tablet of 250 mg was taken with meals). The doses could be changed to maintain serum levels of phosphorus, calcium and iPTH Treatment group 2 • Calcium carbonate: initiated at 1500 mg/d (one tablet of 500 mg was taken with meals). The doses could be changed to maintain serum levels of phosphorus, calcium and iPTH

Toida 2012 *(Continued)*

	Co-interventions • HD 3 times a week with bicarbonate dialysate containing calcium 2.5 mEq/L • Vitamin D analogues
Outcomes	• Serum phosphorus • Adverse events • Serum corrected calcium • Serum Ca x P product • Serum iPTH • Serum bone ALP • FGF23 • Bone markers
Notes	• Funding not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation process was computer generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open-label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	5/25 participants allocated to lanthanum did not complete study follow-up (adverse event (2); lung cancer (1); protocol violation (1) 1/25 participants allocated to calcium did not complete study follow-up (early haemorrhage (1))
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events reported. Data for the end of the first period of the cross-over were not available
Other bias	Low risk	The study appeared to be free from other sources of bias

Toussaint 2009

Methods	• Study design: parallel RCT • Time frame: June 2007 to March 2008 • Follow-up period: 18 months
Participants	• Country: Australia • Setting: single centre

Toussaint 2009 *(Continued)*

- Inclusion criteria: aged 18 to 80 years; established on HD for at least 3 months; serum phosphorus ≥1.6 mmol/L during 1 week washout period
- Number analysed/randomised: treatment group 1 (17/22); treatment group 2 (13/23)
- Mean age ± SD (years): treatment group 1 (56 ± 15.2); treatment group 2 (58.8 ± 14.9)
- Sex (men): treatment group 1 (54.6%); treatment group 2 (73.9%)
- Exclusion criteria: absolute or relative contraindication to lanthanum carbonate including pregnancy; active peptic ulcer disease; ulcerative colitis and Crohn's disease; extended hours or nocturnal HD; scheduled to have parathyroidectomy or living kidney transplant within 6 months; life expectancy < 3 months

Interventions	Treatment group 1 • Lanthanum carbonate: 750 mg 3 times/d orally with meals. Dose titrations initially every 2 weeks by investigators for the first 6 weeks to achieve normalisation of serum phosphate levels Treatment group 2 • Calcium carbonate: 600 mg elemental calcium 3 times/d orally with meals. Dose titrations initially every 2 weeks by investigators for the first 6 weeks to achieve normalisation of serum phosphate levels Co-interventions • During the study, other non-study phosphate binders (e.g. aluminium-based) and vitamin D analogues and supplements were adjusted by the treating physicians as per usual care for best management of CKD-MBD • For treating clinicians, target levels for serum markers of CKD-MBD were those recommended by the Caring for Australasians with Renal Impairment Guidelines • Dialysate calcium concentrations were 1.3 mmol/L for all HD patients and were unchanged throughout the study period
Outcomes	• Vascular calcification • Bone mineral density • Serum phosphate • Serum calcium • Serum Ca x P product • Serum iPTH • Hospitalisation • Cardiovascular events • Death (all causes) • Adverse events
Notes	• Shire PharmaceuticalsTM provided financial support and provision of lanthanum carbonate for this study. The role of the funder in study design, conduct, analysis, interpretation and publication was not reported • Australian Clinical Trials Registry No. ACTRN12607000046404

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed envelopes with dispensing of medications by pharmacist

Toussaint 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open label; knowledge of treatment assignment may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	8/22 participants allocated to lanthanum did not complete study follow-up (adverse event (3); refusal to follow up (1); transplanted (1); death (1) 11/23 participants allocated to calcium did not complete study follow-up (commenced sevelamer (1); refused follow up (3); transplanted (5); death (2))
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free from other sources of bias

Tzanakis 2014

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up duration: 12 months
Participants	• Country: Greece • Setting: single centre • Inclusion criteria: > 18 years, stable on HD for more than 3 months • Number analysed/randomised: treatment group 1 (32/36); treatment group 2 (27/36) • Mean age ± SD (years): treatment group 1 (66.71 ± 12.03); treatment group 2 (68.56 ± 11.58) • Sex (M/F): treatment group 1 (20/12); treatment group 2 (17/10) • Exclusion criteria: malignancy; severe hyperparathyroidism (iPTH > 600 pg/mL), parathyroidectomy, anatomical or functional bowel disorder
Interventions	Treatment group 1 • Magnesium carbonate: 235 mg plus calcium acetate 435 mg commencing three tablets/d. The dose was adjusted according to serum phosphate values weekly for the first month, and then monthly. The dose was increased by one or two tablets per meal as required to achieve the serum phosphate target < 5.5 mg/dL Treatment group 2 • Calcium acetate: 600 mg commencing three tablets/d. The dose was adjusted according to serum phosphate values weekly for the first month, and then monthly. The dose was increased by one or two tablets per meal as required to achieve the serum phosphate target < 5.5 mg/dL Co-interventions • All patients were in the same HD schedule: standard bicarbonate HD using a low flux polysulfone membrane • In both groups, calcium and magnesium concentrations in the dialysate bath were 1.50 and 0.48 mmol/L, respectively
Outcomes	• Death (all causes)

Tzanakis 2014 *(Continued)*

	• Cause-specific death • Serum phosphorus, calcium • Ca x P product • PTH • Vascular calcifications
Notes	• Funding not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients' randomisation in the two groups was performed by using a statistical table of random numbers
Allocation concealment (selection bias)	High risk	Four patients did not agree to consume magnesium carbonate but did agree to participate by taking their standard binder of calcium carbonate; we allocated these patients to the calcium carbonate group, whereas the remainder of the patients were randomly allocated with a ratio 1:1 to either the calcium carbonate (21 randomly assigned patients plus 4 = 25 patients) or to the magnesium carbonate (26) group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The radiographs were evaluated at the beginning and at the end of the study by the same experienced radiologist who was absolutely blind to any data regarding the treatment regimens. Other outcome measures (death and laboratory measures) were unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/36 participants allocated to magnesium did not complete study follow-up (non-adherence (1); adverse events (2)) 4/36 participants allocated to calcium did not complete study follow-up (transplant (2); death due to pneumonia (1); stroke (1))
Selective reporting (reporting bias)	Low risk	Review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free from other sources of bias

Vlassara 2012

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 3 months
Participants	• Country: USA • Setting: multicentre (2 sites)

Vlassara 2012 *(Continued)*

- Inclusion criteria: type 2 diabetes treated with one or more diabetes medications; HbA1c > 6.5%, with albuminuria (> 200 mg urinary albumin/g creatinine; albumin/creatinine ratio, and stages 2–4 diabetic kidney disease
- Number analysed/randomised: treatment group 1 (44/57); treatment group 2 (47/60)
- Mean age ± SD (years): treatment group 1 (63.5 ± 10.2); treatment group 2 (63.2 ± 9.6)
- Sex (men): treatment group (51%); treatment group 2 (62%)
- Exclusion criteria: hypophosphataemia (< 2.4 mg/dL); hyperphosphataemia (> 4.5 mg/dL); hypercalcaemia (> 10.5 mg/dL); biopsy-proven kidney disease other than diabetic kidney disease; significant GI disorders

Interventions	Treatment group 1 • Sevelamer carbonate: 1600 mg 3 times/d with meals Treatment group 2 • Calcium carbonate: 1200 mg 3 times/d with meals Co-interventions • Most patients received insulin, metformin (48%), other oral antidiabetic drugs, statins, aspirin, and one or more antihypertensive drugs • Daily multivitamin supplements, containing 400 IU cholecalciferol (Nature's Bounty Inc, Bohemia, NY), were provided
Outcomes	• Advanced glycosylation end products • Cytokines • HbA1C • eGFR • Albuminuria • Adverse events • Serum calcium, phosphorus, and FGF23
Notes	• This independent investigator-initiated study was funded by a contract (to provide drugs, laboratory tests, and support for study staff) between G.E.S. and H.V. and Genzyme Corporation, a Sanofi Company • Study registration: www.ClinicalTrials.gov NCT01493050

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blinded. Knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory personnel were blinded

Vlassara 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	13/57 participants allocated to sevelamer did not complete study follow-up 13/60 participants allocated to calcium did not complete follow-up
Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	Low risk	The study appeared to be free from other sources of bias

Wada 2014

Methods	• Study design: parallel RCT • Time frame: September to November 2010 • Follow-up period: 12 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: > 20 years; type 2 diabetes with stable glycaemic control; HD treatment • Number analysed/randomised: treatment group 1 (19/21); treatment group 2 (22/22) • Mean age ± SD (years): treatment group 1 (65.57 ± 10.24); treatment group 2 (65.77 ± 8.47) • Sex (M/F): treatment group 1 (16/5); treatment group 2 (19/3) • Exclusion criteria: significant GI disorders; high risk of bleeding; elevated serum transaminases (AST or ALT); hypocalcaemia; severe cardiovascular complications; poorly controlled DM; hypertension
Interventions	Treatment group 1 • Lanthanum carbonate: 250 and 500 mg tablets 3 times/d orally with meals. Dose titrations occurred every 2 weeks for the first 6 weeks to achieve normalisation of both serum phosphate (4.5 to 5.5 mg/dL) and calcium levels (8.5 to 10.5 mg/dL) Treatment group 2 • Calcium carbonate: 500 mg tablets 3 times/d orally with meals. Dose titrations occurred every 2 weeks for the first 6 weeks to achieve normalisation of both serum phosphate (4.5 to 5.5 mg/dL) and calcium levels (8.5 to 10.5 mg/dL) Co-interventions • Calcitriol was adjusted by the investigator as per usual care for the best management of the patient • Cinacalcet and aluminium- or magnesium-based phosphate binders were not used
Outcomes	• Death (all causes) • Serum phosphorus • Serum calcium • Vascular calcification
Notes	• Funding not reported • University Hospital Medical Information Network Clinical study Registry ID: 000 004 633.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement

Wada 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/22 participant allocated to lanthanum did not complete study 1/22 participant allocated to calcium did not complete study
Selective reporting (reporting bias)	Low risk	Key laboratory measures, vascular calcification, and death events were reported
Other bias	Low risk	The study appeared to be free from other sources of bias

Wang 2015b

Methods	• Study design: parallel RCT • Time frame: 2010 to 2014 • Follow-up period: 3 months
Participants	• Country: China • Setting: single centre • Inclusion criteria: conventional HD therapy; skin itching and hyperphosphataemia (serum phosphorus > 1.78 mmol/L) • Number analysed/randomised: treatment group (28/not reported); control group (26/not reported) • Mean age ± SD (years): treatment group (68.87 ± 9.62); control group (69.93 ± 10.86) • Sex (M/F): treatment group (16/12); control group (15/11) • Exclusion criteria: serum calcium level > 2.60 or < 2.10 mmol/L; severe hyperparathyroidism (iPTH > 1000 pg/mL); previous history of GI surgery, active peptic ulcer, inflammatory bowel disease, or GI bleeding within 6 months; serum transaminases or bilirubin levels > 2.5-fold the upper normal limit; severe heart failure (grade Ⅲ–Ⅳ); an HIV-positive status, a known allergy to lanthanum, a fatal malignancy, or exposure to other experimental drugs within 30 days before screening or who were pregnant or lactating
Interventions	Treatment group • Lanthanum carbonate: 500 mg 3 times/d with food Control group • Standard care Co-interventions • Symptomatic treatment with a control diet (phosphorus intake 800 to 1000 mg/d) • Conventional antihypertensive drugs • Conventional active vitamin D, iron, and erythropoietin injection

Wang 2015b *(Continued)*

Outcomes	• Serum phosphorus • Serum calcium • Serum Ca x P product • Vascular calcification
Notes	• Study funding source not reported • Study registration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Two experienced and blinded radiologists reviewed and scored the images for vascular calcification, and the two scores were averaged. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/27 participants allocated to lanthanum carbonate withdrew from the study due to adverse events
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded
Other bias	Low risk	The study appeared to be free from other sources of bias

Yokoyama 2014

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 3 months
Participants	• Country: Japan • Setting: multicentre (36 sites) • Inclusion criteria: ≥ 20 years; non-dialysis CKD stages 3 to 5; serum phosphorus ≥ 1.62 mmol/L (5.0 mg/dL) and < 2.58 (8.0 mg/dL); receiving treatment with phosphate-lowering drug or vitamin D preparation; constant dosage ≥ 4 weeks before initial screening date • Number analysed/randomised: treatment group (46/60); control group (23/30) • Mean age ± SD (years): treatment group (65.3 ± 10.2); control group (64.6 ± 13.5) • Sex (M/F): treatment group (33/24); control group (17/12) • Exclusion criteria: scheduled for dialysis or kidney transplantation ≤ 4 months after initial screening date; AKI
Interventions	Treatment group

Yokoyama 2014 *(Continued)*

	• Ferric citrate: starting dose 1.5 g daily administered 3 times/d after a meal. The dose was increased to 3.0 g daily at week 2. At week 4, the dose was adjusted between 1.5 and 6.0 g daily according to the target range of serum phosphate 2.5-4.5 mg/dL. When serum phosphate exceeded 4.5 mg/dL, the dose was increased by two tablets per dose, and when serum phosphate fell below 2.5 mg/dL, the dose was reduced by two tablets per dose. Decisions to change the dosage were made on weeks 4, 6, and 8. Thereafter, the dose was maintained, except in certain cases, such as when adverse events occurred Control group • Placebo Co-interventions • The doses of vitamin D preparations were kept constant • IV iron preparations as iron replacement therapy for renal anaemia were permitted • No change in prescribed diet was allowed during the study
Outcomes	• Serum phosphorus • Serum calcium • Serum Ca x P product • Urinary phosphate excretion • Intact serum PTH • Serum iron and ferritin • FGF23 • Adverse events
Notes	• Financial support for this study was provided by JapanTobacco, Inc. The role of the funder in the study design, conduct, analysis, interpretation, and publication was not reported • This study was registered with the Japan Pharmaceutical Information centre as CTI-111435

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. The investigational products, JTT-751 tablets containing 250 mg JTT-751 as an anhydride and placebo tablets, were indistinguishable in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment was not reported. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation. Adverse event reporting may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	14/60 participants allocated to iron did not complete study (adverse events (5); worsening of underlying disease (1); phosphate low (1); patient request (4); ineligible patient (2); investigator decision (1)) 7/30 participants allocated to placebo did not complete study (adverse event (1); worsening of underlying disease (1); patient request (4); investigator decision (1))

Yokoyama 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	Key laboratory measures and adverse events were reported
Other bias	Unclear risk	The study appeared to be free from other sources of bias. The baseline characteristics were not reported for each study arm to enable assessment for any imbalance

Yokoyama 2014a

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 3 months
Participants	• Country: Japan • Setting: multicentre (number of sites not reported) • Inclusion criteria: age≥20 years of age; HD 3 times/wk for ≥12 weeks before the initial screening date; patients taking a constant dose of phosphate binders for 4 weeks prior to the initial screening date; patients who had discontinued phosphate binders with serum phosphorus concentrations ≥ 1.97 mmol/L (6.1 mg/dL) and < 3.23 mmol/L (10.0 mg/dL); patients taking constant doses of vitamin D preparations, calcitonin preparations or cinacalcet for 4 weeks prior to the initial screening date • Number analysed/randomised: treatment group 1 (110/114); treatment group 2 (115/116) • Mean age ± SD (years): treatment group 1 (61.4 ± 9.5); treatment group 2 (60.2 ± 10.7) • Sex (M/F): treatment group 1 (72/38); treatment group 2 (73/42) • Exclusion criteria: GI disease including acute peptic ulcers, chronic ulcerative colitis, regional enteritis, intestinal obstruction or dysphagia; history of gastrectomy or enterectomy; marked constipation or severe GI motility disorders; haemochromatosis or serum ferritin concentration > 500 ng/mL or TSAT > 50% on initial screening date; corrected serum calcium concentration < 2.00 mmol/L (8.0 mg/dL) or > 2.75 mmol/L (11.0 mg/dL) at 1 week after the initial screening date; parathyroidectomy or percutaneous ethanol injection therapy within 24 weeks before the initial screening date; history of severe heart disease, hepatic dysfunction or hepatic cirrhosis
Interventions	Treatment group 1 • Sevelamer hydrochloride: starting dose 3.0 and 6.0 g daily if serum phosphorus < 2.58 mmol/ and ≥ 2.58 mmol/L respectively at 1 week after initial screening administered orally 3 times/d immediately after each meal. The dose was adjusted within the range of 3.0 to 9.0 g/d. Dose titration criteria were established with reference to the target control range of serum phosphate recommended in guidelines (3.5 to 6.0 mg/dL (1.13 to 1.94 mmol/L)). Decisions for dose changes were made on Weeks 2, 4, 6 and 8. For sevelamer, the dose was increased by 1 or 2 tablets/dose if serum phosphate was ≥ 1.97 mmol/L (6.1 mg/dL) and decreased by 1 or 2 tablets/dose if serum phosphate was < 1.13 mmol/L (3.5 mg/dL), with these doses being maintained after this time Treatment group 2 • Ferric citrate: starting dose 1.5 g/d administered orally 3 times/d immediately after each meal. The dose was adjusted within the range of 1.5 to 6.0 g/d. The dose was adjusted within the range of 3.0 to 9.0 g/d. Dose titration criteria were established with reference to the target control range of serum phosphate recommended in guidelines (3.5 to 6.0 mg/dL (1.13 to 1.94 mmol/L)). Decisions for dose changes were made on Weeks 2, 4, 6 and 8. For JTT-751, the dose was increased by 2 tablets/dose if serum phosphate was ≥ 1.97 mmol/L (6.1 mg/dL) and decreased by 2 tablets/dose if serum phosphate was < 1.13 mmol/L (3.5 mg/dL) Cointerventions • During the study, concomitant use of drugs with phosphate binding properties (e.g. magnesium- or aluminium-containing antacids, sucralfate) and other drugs that may affect phosphate absorption (e.g. niceritrol and colestimide) was prohibited. Dosages of vitamin D derivatives, calcitonin prepara-

Yokoyama 2014a *(Continued)*

	tions, and cinacalcet were kept constant, except when they were changed to correct or prevent adverse events. Concurrent use of IV iron preparations was permitted when the investigator considered that iron-replacement therapy was necessary to treat ESRD-associated anaemia
Outcomes	• Death (all causes) • Adverse events • Serum phosphorus • Serum calcium • Serum iPTH • Iron-related parameters • Dialysis adequacy • ESA dosing.
Notes	• The study was sponsored by Japan Tobacco, Inc. The role of the funder in the study design, conduct, analysis, interpretation was not reported • Study registration: CTI-111433 (The Japan Pharmaceutical Information centre at www.ClinicalTrials.jp)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment allocation may have influenced patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reporting of blinding of outcomes not provided in sufficient detail to permit judgement. Laboratory measures and death outcomes unlikely to have been influenced by knowledge of treatment allocation. Adverse event reporting may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	17/114 participants allocated to sevelamer did not complete study follow-up (adverse events (3); high phosphate (1); patient request (9); investigator decision (2)) 14/116 participants allocated to iron did not complete follow-up (adverse events (6); patient request (6); ineligible patients (2))
Selective reporting (reporting bias)	Low risk	Key laboratory measures, adverse events and death (all causes) events reported
Other bias	Low risk	The study appeared to be free from other sources of bias

Young 2009a

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 8 weeks

Young 2009a *(Continued)*

Participants	• Country: USA • Setting: single centre • Inclusion criteria: > 18 years; duration PD > 3 months; stable phosphate binder dose; plasma phosphorus > 4.9 mg/dL • Number analysed/randomised: treatment group (7/8); control group (7/9) • Mean age ± SD (years): treatment group (51.1 ± 10.3); control group (55.7 ± 11.8) • Sex (M/F): treatment group (5/2); control group (7/0) • Exclusion criteria: pregnancy; known liver disease; active peptic ulcer disease; treatment with carbamazepine; current medication including niacin or niacinamide; planned surgical procedure with 4 months; facility care
Interventions	Treatment group 1 • Niacinamide: study medication or placebo was started at 250 mg twice/d, increased to 500 mg twice/d after 2 weeks and to 750 mg twice/d after 4 weeks, and continued until study completion Treatment group 2 • Placebo Co-interventions • Active vitamin D and cinacalcet doses were required to remain stable
Outcomes	• Plasma phosphorus • Ca x P product • High-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides
Notes	• This study was supported by a grant from the National Kidney Foundation of Eastern Missouri and Metro East, Inc., and a Nephrology Fellowship Stipend support from Amgen • Study registration: www.ClinicalTrials.gov NCT00508885

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	The research pharmacist who prepared the study medication and placebo capsules also performed patient randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. Niacinamide (250 mg per capsule) and placebo were packaged as identically appearing capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reporting of blinding of outcomes not provided in sufficient detail to permit judgement. Laboratory measures unlikely to have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/8 participants allocated to niacinamide did not complete study follow-up 2/9 participants allocated to placebo did not complete study follow-up
Selective reporting (reporting bias)	High risk	Not all the review's pre-specified outcomes were recorded

Young 2009a *(Continued)*

Other bias	High risk	Imbalance in baseline biochemical characteristics

Zhao 2014

Methods	• Study design: parallel RCT • Time frame: July to November 2013 • Follow-up period: 8 weeks
Participants	• Country: China • Setting: single centre • Inclusion criteria: ESKD treated with dialysis; serum phosphorus ≥ 5.5 mg/dL; 18 to 70 years; serum PTH ≤ 1000 pg/mL; serum calcium ≤ 9.48 mg/dL; stable diet • Number analysed/randomised: treatment group 1 (30/34); treatment group 2 (30/34) • Mean age ± SD (years): treatment group 1 (51.3 ± 9.4); treatment group 2 (50.9 ± 9.2) • Sex (M/F): treatment group 1 (20/14); treatment group 2 (18/16) • Exclusion criteria: Severe GI motility disorder; uncontrolled diabetes or hypertension; pregnancy
Interventions	Treatment group 1 • Sevelamer carbonate: starting 800 mg daily administered 3 times/d at mealtime Treatment group 2 • Calcium acetate: starting 667 mg daily administered 3 times/d at mealtime (the maximum calcium content is no more than 1500 mg)
Outcomes	• Serum phosphorus • Ca x P product • Corrected serum calcium • Blood iPTH • Blood LDL cholesterol • Blood bicarbonate levels • Safety assessment mainly includes life index, haematology, and blood Indicators, as well as the occurrence of adverse reactions
Notes	• Funding not reported • Study registration not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may influence patient management

Zhao 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reporting of blinding of outcomes not provided in sufficient detail to permit judgement. Laboratory measures unlikely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/34 participants allocated to sevelamer did not complete study follow-up 4/34 participants allocated to calcium did not complete study follow-up
Selective reporting (reporting bias)	Low risk	Key laboratory and adverse events measures were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Zwiech 2011

Methods	• Study design: parallel RCT • Time-frame: not reported • Follow-up period: 12 weeks
Participants	• Country: Poland • Setting: single centre • Inclusion criteria: dialysis for at least 6 months; abnormal calcium and phosphate levels; no severe comorbidities • Number analysed/randomised: treatment group 1 (10); treatment group 2 (30) • Mean age ± SD (years): treatment group 1 (57.0 ± 15.6); treatment group 2 (58.1 ± 12.8) • Sex (M/F): treatment group 1 (5/5); treatment group 2 (17/13) • Exclusion criteria: iPTH < 150 pg/mL or > 800 pg/mL; parathyroidectomy; normal levels of calcium and phosphorus
Interventions	Treatment group 1 • Sevelamer hydrochloride: 800 mg, 2 tablets 3 times/d Treatment group 2 • Magnesium carbonate: 1 g 3 times/d
Outcomes	• Serum phosphorus • Serum calcium
Notes	• Funding sources not reported • Study registration not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about random sequence generation to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about allocation concealment to permit judgement

Zwiech 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label; knowledge of treatment assignment may influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reporting of blinding of outcomes not provided in sufficient detail to permit judgement. Laboratory measures unlikely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described in sufficient detail to permit judgement
Selective reporting (reporting bias)	High risk	Important clinical outcomes not available
Other bias	Unclear risk	Insufficient information to permit judgement

AKI - acute kidney injury; ALP - alkaline phosphatase; ALT - alanine aminotransferase; APD - automated peritoneal dialysis; ASP - aspartate aminotransferase; BMI - body mass index; BP - blood pressure; ESA - erythropoiesis-stimulating agent; C x P - calcium by phosphorous; CACS - coronary artery calcification score; CAPD - continuous ambulatory peritoneal dialysis; CKD - chronic kidney disease; CrCl - creatinine clearance; CRP - C-reactive protein; CT - computed tomography; DM - diabetes mellitus; ECG - electrocardiograph; eGFR - estimated glomerular filtration rate; FGF- fibroblast growth factor; GI - gastrointestinal; Hb - haemoglobin; HbA1c - haemoglobin A1c (glycated); HCT - haematocrit; HD - haemodialysis; HIV - human immunodeficiency virus; iPTH - intact parathyroid hormone; IV - intravenous; LDL - low-density lipoprotein; MDRD - Modification of Diet in Renal Disease; MI - myocardial infarction; NYHA - New York Heart Association; PD - peritoneal dialysis; PTH - parathyroid hormone; RCT - randomised controlled trial; SD - standard deviation; TNF - tumour necrosis factor; TSAT - transferrin saturation; URR - urea reduction ratio

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

Study	Reason for exclusion
Abraham 2012a	Treatment duration/study follow up was less than 8 weeks
Ahmadi 2012	Treatment duration/study follow up was less than 8 weeks
Akizawa 2014	Treatment duration/study follow up was less than 8 weeks
Akizawa 2014b	Treatment duration/study follow up was less than 8 weeks
Al-Baaj 2005	Treatment duration/study follow up was less than 8 weeks
Babarykin 2004	Wrong intervention: calcium-enriched bread was used as treatment (not pharmacological phosphate binder)
Bigi 2003	Wrong intervention: evaluating the effects of cheto-analogues on calcium-phosphate metabolism
Bleskestad 2012	Treatment duration/study follow up was less than 8 weeks
Block 2013	Treatment duration/study follow up was less than 8 weeks
Borrego 2000	Study design: not clearly stated as randomised allocation to treatment
Chertow 1997	Treatment duration/study follow up was less than 8 weeks

Study	Reason for exclusion
Chiang 2005	Treatment duration/study follow up was less than 8 weeks
Chiang 2007	Treatment duration/study follow up was less than 8 weeks
Chow 2007	Wrong intervention: comparing two different dose approaches to sevelamer treatment
d'Almeida Filho 2000	Treatment duration/study follow up was less than 8 weeks
Dwyer 2013	Treatment duration/study follow up was less than 8 weeks
El Borolossy 2016	Wrong population: study evaluating therapy in children
Emmett 1991	Treatment duration/study follow up was less than 8 weeks
Fabrizi 1996	Wrong intervention: evaluating different dialysate calcium levels
Fan 2009	Treatment duration/study follow up was less than 8 weeks
Finn 2004	Treatment duration/study follow up was less than 8 weeks
Fischer 2006	Wrong intervention: comparing two different dose approaches to sevelamer treatment
FORESEE 2008	Wrong intervention: not comparing two different phosphate binders
Friedrich 2006	Treatment duration/study follow up was less than 8 weeks
Fukagawa 2014	Treatment duration/study follow up was less than 8 weeks
Hertel 2015	Treatment duration/study follow up was less than 8 weeks
Hill 2013	Treatment duration/study follow up was less than 8 weeks
How 2011	Wrong intervention: valuating effect of lanthanum carbonate on oral absorption of ciprofloxacin. Participants were randomised to ciprofloxacin or ciprofloxacin plus lanthanum carbonate.
Ibrahim 2013	Treatment duration/study follow up was less than 8 weeks
Isakova 2011	Treatment duration/study follow up was less than 8 weeks
Ittel 1991	Wrong intervention: comparing two different formulations of calcium carbonate
Joy 1999	Treatment duration/study follow up was less than 8 weeks
Joy 2003	Treatment duration/study follow up was less than 8 weeks
Kalil 2012	Wrong intervention: evaluating lanthanum carbonate versus non-lanthanum carbonate containing phosphate binders (but comparator intervention not specified)
Koiwa 2005	Treatment duration/study follow up was less than 8 weeks
Koiwa 2005a	Treatment duration/study follow up was less than 8 weeks
Koiwa 2017a	Treatment duration/study follow up was less than 8 weeks
Koontz 2012	Wrong intervention: comparing lanthanum with non-lanthanum binders.

Study	Reason for exclusion
Kurihara 2005	Treatment duration/study follow up was less than 8 weeks
Lee 2013b	Wrong intervention: comparing calcitriol versus calcitriol with calcium carbonate
Locatelli 2010a	Treatment duration/study follow up was less than 8 weeks
Mai 1989	Treatment duration/study follow up was less than 8 weeks
Mak 1985	Study evaluating therapy in children
Matuszkiewicz 2004	Wrong intervention: participants were either randomised to salmon calcitonin or control. Non-randomised intervention included phosphate binders
McIntyre 2009	Treatment duration/study follow up was less than 8 weeks
Messana 1999	Treatment duration/study follow up was less than 8 weeks
Moustafa 2014	Treatment duration/study follow up was less than 8 weeks
Mouzo 2004	Wrong intervention: participants received sevelamer at different doses based on meal size. Administration was randomly allocated to occur on dialysis or away from dialysis. Treatment duration/study follow up was less than 8 weeks.
NCT00018135	Treatment duration/study follow up was less than 8 weeks
NCT00364000	Study was abandoned due to limited financial resources. Study first posted on www.ClinicalTrials.gov on August 15, 2006. Last update posted: December 22, 2017
NCT00436683	This was a commercially sponsored study. The sponsor, Ineos, decided to close its medical division before the study could be completed and it was therefore abandoned. The data were owned by the company and were never made available for publication
NCT00660530	Wrong intervention: comparing different formulations of lanthanum carbonate
NCT00745589	Wrong intervention: comparing different doses of sevelamer hydrochloride.
NCT01427907	Treatment duration/study follow up was less than 8 weeks
NCT01748396	Wrong intervention: participants were randomised to calcitriol with or without calcium carbonate
NCT02027662	Wrong intervention: treatment duration/study follow up was less than 8 weeks
NCT02492620	Wrong intervention: comparing ferric citrate versus non-ferric citrate binder
NCT02684643	Wrong intervention: comparing two different individualised treatment plans for phosphate lowering
NCT02688764	Wrong intervention: comparing nicotinamide with usual phosphate binder
NCT03163576	Wrong intervention: comparing nicotinamide with usual phosphate binder
NCT03305471	Treatment duration/study follow up was less than 8 weeks
Nishi 2005	Wrong intervention: participants were randomised to oral vitamin D sterol, calcitriol, alfacalcidol, with or without calcium carbonate

Study	Reason for exclusion
Oliveira 2010	Treatment duration/study follow up was less than 8 weeks
OPTIMA 2008	Wrong intervention: participants were randomly allocated to receive cinacalcet or standard care in an algorithm which included vitamin D therapy
Ouellet 2010	Wrong intervention: participants were randomly allocated to either sevelamer and calcium carbonate taken together or separately
Pai 2008a	Treatment duration/study follow up was less than 8 weeks
Pflanz 1994	Treatment duration/study follow up was less than 8 weeks
Phelps 2002	Wrong intervention: participants were randomly allocated to higher and lower dose of calcium acetate
Phelps 2014	Treatment duration/study follow up was less than 8 weeks
Przedlacki 2005	Wrong intervention: evaluating calcitriol versus placebo
Ring 1993	Treatment duration/study follow up was less than 8 weeks
Rudnicki 1993	Wrong intervention: participants assigned to oral elemental calcium supplementation or placebo (calcium not administered as phosphate binder)
Ruff 2008	Wrong intervention: pharmacokinetic study of interaction between sevelamer and warfarin
Salusky 1991	Study evaluating therapy in children
Salusky 2005	Study evaluating therapy in children
Scaria 2009	Treatment duration/study follow up was less than 8 weeks
Schaefer 1990	Wrong intervention: treatment with calcium acetate and calcitriol
Schaefer 1991	Treatment duration/study follow up was less than 8 weeks
Sechet 1998	Treatment duration/study follow up was less than 8 weeks
Sechet 1999	Wrong intervention: participants treated with omeprazole and calcium carbonate
Seferi 2012	Treatment duration/study follow up was less than 8 weeks
Shigematsu 2001	Wrong intervention: participants treated with combination therapy (vitamin D plus calcium) versus vitamin D therapy alone
Shigematsu 2008a	Treatment duration/study follow up was less than 8 weeks
Shimoda 1996	Wrong intervention: participants randomly allocated to niceritrol (vitamin D analogue)
Sigrist 2013	Wrong intervention: participants randomly allocated to different dietary phosphate content
SPD405-307 2004	Wrong intervention: participants were not randomised to two different specific phosphate binders. Participants were randomly allocated to lanthanum carbonate versus standard therapy (calcium/aluminium salts or sevelamer)

Study	Reason for exclusion
Sprague 2009b	Treatment duration/study follow up was less than 8 weeks
SUMMER 2011	Nested cross-sectional analyses within the "Sevelamer hydrochloride and ultrasound-measured femoral and carotid intima media thickness progression in end-stage renal disease (SUMMER) clinical trial". The primary report of the SUMMER study not identified
Tzanakis 2008	Protocol violation: some patients (4) elected to continue their specific phosphate binder and were allocated to that treatment group rather than random allocation
Tzanno-Martins 2014	Wrong intervention: comparing two different tablet forms of sevelamer
Umanath 2013	Wrong intervention: study did not compare two different specific phosphate binders
van den Bergh 1994	Treatment duration/study follow up was less than 8 weeks
Vemuri 2006	Interim analysis of a subgroup of participants within a previous RCT of lanthanum versus previous phosphate binder therapy
Wei 2014	Wrong intervention: participants randomised to calcitonin (not a phosphate binder) and calcium carbonate versus lanthanum carbonate
Wesseling 2004	Study evaluating therapy in children
Wuthrich 2013	Treatment duration/study follow up was less than 8 weeks
Xu 2013	Treatment duration/study follow up was less than 8 weeks
Yang 2002	Treatment duration/study follow up was less than 8 weeks
Yokoyama 2012	Treatment duration/study follow up was less than 8 weeks

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00317694

Methods	Study design: parallel RCT Time-frame: March 2006 to June 2007 Follow-up: not reported
Participants	Country: USA and UK Setting: multicentre Inclusion criteria: male or female subjects on active HD, aged 18 years or over; on a stable HD regimen (3 times/wk) for at least 3 months and be unlikely to change their dialysis prescription during the study period; on a stable dose of a phosphate binder for at least 1 month prior to screening; willing to abstain from taking any phosphate binder or oral magnesium, aluminium or iron-containing products and preparations, other than the study medication; willing to avoid any intentional changes in diet such as fasting, dieting or overeating; willing to maintain their usual type and dose of Vitamin D supplementation. Exclusion criteria: participation in any other clinical study using an investigational product or device within the previous 4 months; significant history of alcohol, drug or solvent abuse in the opinion of the investigator; any disease or condition, physical or psychological, which in the opinion of

NCT00317694 *(Continued)*

	the investigator would compromise the safety of the subject or increase the likelihood of the subject being withdrawn; clinically significant laboratory findings (for this subject population) in the opinion of the investigator; any malignancy requiring treatment within 5 years of screening with the exception of basal cell carcinoma and Bowen's disease; history of a motility disorder of the intestines, including, but not limited to, gastroparesis, ileus, pseudo-obstruction, megacolon, or mechanical obstruction; significant illness in the 4 weeks before screening; taking medication prescribed for seizures; history of haemochromatosis; history of high serum ferritin concentration of ≥ 1000ng/mL (excluding transient, treatment-induced ferritin elevation); history of dysphagia or swallowing disorders that might limit the subject's ability to swallow study medication in the opinion of the investigator; female subjects who are lactating or pregnant; women of childbearing potential (pre-menopausal and not surgically sterilised) unless they are using a reliable contraceptive method, that is, barrier methods, hormones or intrauterine device; current Hb concentration of < 10.00 g/dL; allergy to the investigational product or its constituents. Number randomised: 111
Interventions	Treatment group 1 • Magnesium iron hydroxycarbonate: 500 mg Treatment group 2 • Placebo • Co-interventions None reported
Outcomes	• Achievement of controlled serum phosphate levels • Serum phosphate • Serum calcium • Serum calcium-by-phosphate product • Serum PTH • Serum magnesium • Adverse events • Safety laboratory parameters • Bowel habit
Notes	Study start date: March 2006 Primary completion date: June 2007 Last update posted to www.ClinicalTrials.gov: August 10, 2009. A search of the literature has not identified any study results. Study results have not been posted on www.ClinicalTrials.gov. Principal investigator: Simon Roe, Nottingham Renal and Transplant unit, Nottingham City Hospital. Funding sources: Ineos Healthcare Limited. Principal investigator was contacted by email (10 April 2018) to request an update on the study status and results. No reply was received. As the study was completed nearly 10 years ago, it is unlikely the results will be published.

NCT00560300

Methods	Study design: factorial RCT

NCT00560300 *(Continued)*

	Time-frame: November 2000 to November 2006 Follow-up: 8 months
Participants	Country: not reported Setting: not reported Inclusion criteria: age 2 to 21 years; stable ESKD treated with continuous cycling peritoneal dialysis; biochemical evidence of secondary hyperparathyroidism (PTH>400 pg/mL) with bone biopsy evidence of high turnover bone disease. Exclusion criteria: history of parathyroidectomy; growth hormone; prednisone, or other immunosuppressant medication within the past year; recent history of medication non-compliance.
Interventions	Treatment group 1 • Doxercalciferol + sevelamer Treatment group 2 • Doxercalciferol + calcium carbonate Treatment group 3 • Calcitriol + calcium carbonate Treatment group 4 • Calcitriol + sevelamer Cointerventions: none
Outcomes	• Bone formation rate • Bone histomorphometric parameters other than bone formation rate, biochemical parameters (phosphate, calcium, PTH, ALP, FGF23, vitamin D dose)
Notes	Study start date: November 2000 Study completion date: November 2006 Principal Investigator: Isidro Salusky, University of California Los Angeles Last update posted to www.ClinicalTrials.gov: January 2010 Funding sources: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Principal Investigator was contacted by email (10 April 2018) to request an update on the study status and results. No reply was received. As the study was completed >10 years ago, it is unlikely the results will be published.

NCT01968759

Methods	Study design: cross-over RCT Time-frame: October 2013 to October 2015 Follow-up: 3 months
Participants	Country: Italy Setting: multicentre

NCT01968759 *(Continued)*

	Inclusion criteria: age > 18 years; eGFR (GFR) by simplified MDRD formula > 15 mL/min/1.73m^2; 24-h urinary protein excretion rate ≥ 0.5 g/24hour; no concomitant treatment with phosphate binders; written informed consent. Exclusion criteria: serum phosphate level < 2.5 or > 5.5 mg/dL; patients with serum PTH levels >250 pg/mL without stable vitamin D (calcitriol or paricalcitol) or calcimimetic therapy from at least three months; serum calcium level < 7.5 or >10.5 mg/dL; history of congestive heart failure, MI, cerebrovascular accident within the last 6 months; cancer and any severe systemic disease or clinical condition that may jeopardize data interpretation or completion of the study; presence of, or predisposition to, intestinal or ileus obstruction or severe GI motility disorder (like severe constipation); previous major GI surgery; previous kidney transplantation; previous parathyroidectomy; concomitant treatment with antacid and phosphate binders with aluminium, magnesium, calcium or lanthanum; pregnancy or breastfeeding; childbearing potential without reliable contraceptive methods during the whole study period; participation in any clinical study using an investigational product or device during the 30 days preceding the first protocol visit; alcohol or drug (excluding tobacco) abuse; inability to comply with the study procedures during the whole study period, legal incapacity.
Interventions	Treatment group 1 • Sevelamer carbonate: 800 mg 3 times/d with meals Treatment group 2 • Standard care Co-interventions • none reported
Outcomes	• 24-h urinary protein excretion • BP • Glomerular filtration rate
Notes	Study start date: October 2013 Study completion date: October 2015 Principal Investigator: not reported. Last update posted to www.ClinicalTrials.gov: October 2015 Funding sources: Mario Negri Institute for Pharmacological Research No results posted. Unable to contact Principal Investigator.

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

COMBINE 2014

Trial name or title	The COMBINE Study: the CKD Optimal Management With BInders and NicotinamidE
Methods	Study design: parallel RCT Time frame: March 2015 to June 2018 follow-up: 12 months
Participants	Country: USA

COMBINE 2014 *(Continued)*

	Setting: 5 centres Inclusion criteria • Patients with eGFR (eGFR) 20-45 mL/min/1.73m^2 • Age 18-85 years • Serum phosphate ≥ 2.8 mg/dL • Platelet count ≥ 125,000/mm^3 • Able to provide consent • Able to travel to study visits • Able to eat at least two meals a day • In the opinion of the site investigator, willing and able to follow the study treatment regimen and comply with the site investigator's recommendations. Exclusion Criteria: • History of allergic reaction to nicotinamide, niacin (excluding flushing), multivitamin preparations, or lanthanum carbonate • Liver disease, defined as known cirrhosis by imaging or physician diagnosis, documented alcohol use > 14 drinks/wk, or AST, ALT, ALP, or total bilirubin concentrations > 2 times the upper limit of the local laboratory reference range • Creatine kinase (CK) concentrations > 2 times the upper limit of the local laboratory reference range • Major haemorrhagic event within the past six months requiring in-patient admission • Blood or platelet transfusion within the past six months • Secondary hyperparathyroidism (PTH > 5 times the upper limit of normal range for the laboratory) or currently taking cinacalcet (Sensipar) • Current, clinically significant malabsorption, as determined at the discretion of the site investigator • Anaemia (screening Hg < 9.0 g/dL) • Serum albumin < 2.5 mg/dL • Anticipated initiation of dialysis or kidney transplantation within 12 months as assessed by and at the discretion of the site investigator. • Use of immunosuppressive medications (stable oral steroids ≤ 10 mg of prednisone/d or inhaled steroids are exempted) • In the opinion of the site investigator, active abuse of alcohol or drugs • Recent (within the last 14 days) initiation or change in dose of treatment with 1,25 (OH)2 vitamin D or active vitamin D analogues (paricalcitol or hectorol). Patients on stable doses of these agents initiated more than 14 days prior to screening are eligible to participate. • Current or recent treatment (within the last 14 days) with phosphate binder or niacin/nicotinamide > 100 mg/d • Current participation in another clinical study or other interventional research • Currently taking investigational drugs • Institutionalised individuals, including prisoners and nursing home residents • Malignancy requiring therapy within 2 years (basal or squamous cell skin carcinoma and localized prostate cancer are exempted)
Interventions	Treatment group 1 • One nicotinamide 750 mg capsule by mouth twice/d (1500 mg) for 12 months. Two lanthanum carbonate 500 mg capsules by mouth with each meal (3000 mg) for 12 months. Treatment group 2 • Two lanthanum carbonate 500 mg capsules by mouth with each meal (3000 mg) for 12 months. One Placebo (for nicotinamide) 750 mg capsule by mouth twice/d (1500 mg) for 12 months. Treatment group 3

COMBINE 2014 *(Continued)*

	• One nicotinamide 750 mg capsule by mouth twice/d (1500 mg) for 12 months. Two Placebo (for lanthanum carbonate) 500 mg capsules by mouth with each meal (3000 mg) for 12 months. Treatment group 4 • One placebo (for nicotinamide) 750 mg capsule by mouth twice/d (1500 mg) for 12 months. Two placebo (for lanthanum carbonate) 500 mg capsules by mouth with each meal (3000 mg) for 12 months.
Outcomes	Primary outcomes • Since this is a pilot study, the primary outcome measure is feasibility. • The clinical outcome measure is change from baseline to 12 months in serum phosphate and FGF23 levels Secondary: • Bone and mineral metabolism markers • Change from baseline in surrogate measures of cardiovascular disease (CVD) risk over 12 months • Change from baseline in surrogate measures of CKD progression and inflammation, by changes in intra-renal oxygenation and fibrosis over 12 months
Starting date	March 2015 (estimated completion date June 2018)
Contact information	Principal investigator: Jennifer Gassman, Data Coordinating centre, Cleveland Clinic. Email gassmaj@ccf.org
Notes	Funding sources: National Institute of Diabetes and Digestive and Kidney Diseases. study registration: www.ClinicalTrials.gov NCT02258074

IMPROVE-CKD 2012

Trial name or title	IMPROVE: IMpact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease
Methods	Study design: parallel RCT Time frame: Recruitment end date 31 December 2016. Follow-up end date December 2018 follow-up: 24 months
Participants	Country: Australia and New Zealand Setting: 11 hospitals in Australia and 1 hospital in New Zealand Number randomised: 278 (target for randomisation 488) Inclusion criteria • Patients with CKD (CKD) stages 3b-4 (eGFR between 15-44 mL/ min/1.73m^2) • serum phosphate level greater than 1.00 mmol/L on at least 1 occasion over the previous 6 months • minimum age 18 years. Exclusion criteria • history of psychological illness or condition which interferes with their ability to understand or comply with the requirements of the study • kidney transplantation • recent (within 1 month) hospitalisation or cardiovascular event • pregnancy or breast feeding

IMPROVE-CKD 2012 *(Continued)*

	• medical conditions that impact on phosphate metabolism (apart from CKD), e.g. primary hyperparathyroidism or hypoparathyroidism • previous subtotal parathyroidectomy • GI malabsorption disorders such as Crohn's disease, ulcerative colitis, celiac disease or severe liver dysfunction; • malnutrition, defined as serum albumin < 30g/L • presence of atrial fibrillation • inability to obtain a pulse wave velocity
Interventions	Treatment group 1 • Lanthanum carbonate: 500 mg 3 times daily Treatment group 2 • Matched placebo: 3 times daily
Outcomes	• Primary * Arterial compliance (measured by pulse wave velocity) as a surrogate marker of cardiovascular morbidity and death • Secondary * Serum phosphate * Serum calcium * Serum calcium phosphate product * Serum PTH levels * kidney function measured by eGFR and % change * Bone mineral density, measured by CT of the lumbar spine * Aortic calcification (measured with CT)
Starting date	November 2011
Contact information	nigel.toussaint@monash.edu
Notes	Funding sources: SHIRE; NHMRC; Australasian Kidney Trials Network. study registration: ACTRN12610000650099

LANDMARK 2017

Trial name or title	Outcome study of lanthanum carbonate compared with calcium carbonate on cardiovascular mortality and morbidity in patients with chronic kidney disease on hemodialysis (CKD5D) (LANDMARK study)
Methods	Study design: parallel RCT
Participants	Country: Japan Setting: not reported Inclusion criteria • HD patients with hyperphosphataemia who require phosphate binders • HD for more than 3 months • patients who have at least one calcification risk factor (elderly > 65 years, postmenopausal woman, type 2 diabetes mellitus) • intact-PTH ≥ 240 pg/mL • life expectancy > 1 years

LANDMARK 2017 *(Continued)*

	Exclusion criteria • contraindications to lanthanum carbonate and calcium carbonate • swallowing disorders • severe GI disorders • history of obstructed bowels • history of IHD/stroke within 6 months before randomisation • NYHA classification Ⅲ–Ⅳ • severe liver dysfunction (AST or ALT greater than 3 times the upper limit of institution) • require treatment of arrhythmia • severe malnutrition • malignancy of any type within the last five years • PD patients • pregnant or possibly pregnant women or women on lactation and planned to get pregnant within study term • ineligible patients according to the investigator's judgment
Interventions	Treatment group 1 • Lanthanum carbonate: oral administration after meals 3 times/d in total daily dose of 750 to 2250 mg Treatment group 2 • Calcium carbonate: oral administration after meals 3 times/d in total daily dose of 3.0 g
Outcomes	Primary • Cardiovascular event free survival time. Cardiovascular event consisting of * death due to cardiovascular diseases including sudden cardiac death (ICD-10 codes R96.0/96.1), * nonfatal MI, * nonfatal cerebral stroke including transient Ischaemic attack * unstable angina, * hospitalisation for heart failure, * hospitalisation for ventricular arrhythmia Secondary • Overall survival • Secondary hyperparathyroidism free survival • Hip fracture free survival • Quality of life questionnaire (KDQOL-SF, v1.3) • Bone mineral density (DEXA)
Starting date	December 2011
Contact information	Principal investigator: Tadao Akizawa, MD, PhD, Showa University; Division of Nephrology, Department of Medicine, Showa University School of Medicine, Sinagawa-ku, Tokyo, Japan Hiroaki Ogata, Phone: +81-45-949-7000, Email: pj.ca.u-awohs.dem@hatago
Notes	Funding sources: Translational Research Informatics centre, Kobe, Hyogo, Japan. study registration: www.ClinicalTrials.gov (NCT01578200) and umin.ac.jp (UMIN000006815).

DATA AND ANALYSES

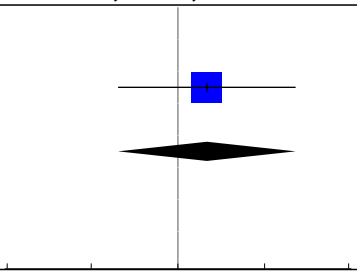
Comparison 1. Sevelamer versus placebo or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	3	248	Risk Ratio (IV, Random, 95% CI)	2.16 [0.20, 22.84]
2 Myocardial infarction	3	205	Risk Ratio (IV, Random, 95% CI)	1.00 [0.11, 9.35]
3 Stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Hospitalisation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Pruritus	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Nausea	3	370	Risk Ratio (IV, Random, 95% CI)	1.27 [0.07, 22.42]
8 Vomiting	2	165	Risk Ratio (IV, Random, 95% CI)	2.09 [0.26, 16.57]
9 Abdominal pain	3	370	Risk Ratio (IV, Random, 95% CI)	0.38 [0.13, 1.14]
10 Constipation	4	430	Risk Ratio (IV, Random, 95% CI)	6.92 [2.24, 21.38]
11 Diarrhoea	2	165	Risk Ratio (IV, Random, 95% CI)	2.02 [0.13, 31.62]
12 Abdominal bloating	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
13 End-stage kidney disease	2	139	Risk Ratio (IV, Random, 95% CI)	1.51 [0.52, 4.36]
14 Coronary artery calcium score	2	115	Mean Difference (IV, Random, 95% CI)	-70.19 [-362.44, 222.06]
15 Serum phosphate	5	483	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.94, 0.39]
16 Serum calcium	5	366	Mean Difference (IV, Random, 95% CI)	0.03 [-0.08, 0.14]
17 Hypercalcaemia	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
18 Serum calcium-by-phosphate product	2	265	Mean Difference (IV, Random, 95% CI)	-4.23 [-26.52, 18.05]
19 Serum iPTH	2	120	Mean Difference (IV, Random, 95% CI)	-6.55 [-21.16, 8.07]
20 Serum alkaline phosphatase	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
21 Serum bicarbonate	6	571	Mean Difference (IV, Random, 95% CI)	0.12 [-1.30, 1.54]
22 eGFR	4	306	Mean Difference (IV, Random, 95% CI)	-0.45 [-4.74, 3.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Bone mineral density: lumbar spine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
24 Bone mineral density: hip	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
25 Klotho	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

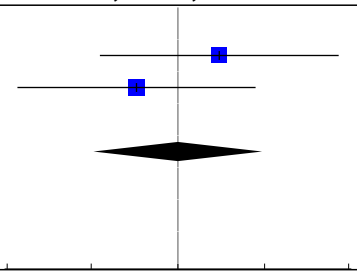
Analysis 1.1. Comparison 1 Sevelamer versus placebo or usual care, Outcome 1 Death (all causes).

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Riccio 2018	0/30	0/30			Not estimable
CRIB-PHOS 2011	0/55	0/54			Not estimable
Lemos 2013	2/38	1/41		100%	2.16[0.2,22.84]
Total (95% CI)	**123**	**125**		**100%**	**2.16[0.2,22.84]**
Total events: 2 (Sevelamer), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					



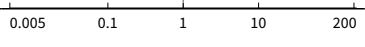
Analysis 1.2. Comparison 1 Sevelamer versus placebo or usual care, Outcome 2 Myocardial infarction.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Block 2009	0/30	0/37			Not estimable
Liabeuf 2017	1/39	0/39		49.86%	3[0.13,71.46]
Russo 2007	0/30	1/30		50.14%	0.33[0.01,7.87]
Total (95% CI)	**99**	**106**		**100%**	**1[0.11,9.35]**
Total events: 1 (Sevelamer), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.93, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=0(P=1)					



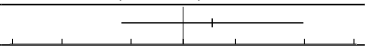
Analysis 1.3. Comparison 1 Sevelamer versus placebo or usual care, Outcome 3 Stroke.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	1/30	0/57		5.61[0.24,133.73]



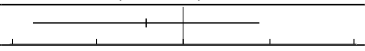
Analysis 1.4. Comparison 1 Sevelamer versus placebo or usual care, Outcome 4 Hospitalisation.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
CRIB-PHOS 2011	6/55	4/54		1.47[0.44,4.93]



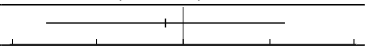
Analysis 1.5. Comparison 1 Sevelamer versus placebo or usual care, Outcome 5 Fracture.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	0/30	2/57		0.37[0.02,7.55]



Analysis 1.6. Comparison 1 Sevelamer versus placebo or usual care, Outcome 6 Pruritus.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	0/30	1/57		0.62[0.03,14.86]

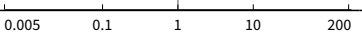


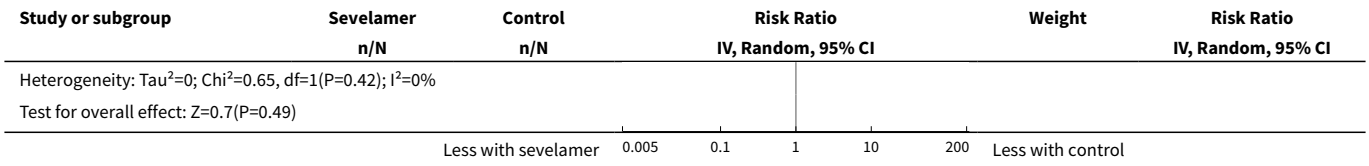
Analysis 1.7. Comparison 1 Sevelamer versus placebo or usual care, Outcome 7 Nausea.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Liabeuf 2017	2/39	0/39		31.2%	5[0.25,100.89]
Chen 2014	0/135	4/70		31.89%	0.06[0,1.06]
Block 2009	3/30	1/57		36.92%	5.7[0.62,52.46]
Total (95% CI)	**204**	**166**		**100%**	**1.27[0.07,22.42]**
Total events: 5 (Sevelamer), 5 (Control)					
Heterogeneity: Tau^2=4.54; Chi^2=6.81, df=2(P=0.03); I^2=70.63%					
Test for overall effect: Z=0.16(P=0.87)					

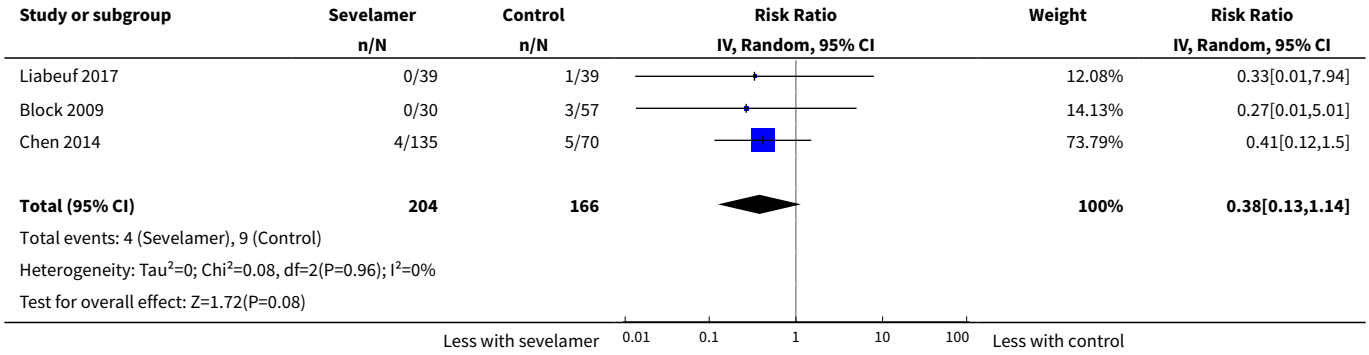
Analysis 1.8. Comparison 1 Sevelamer versus placebo or usual care, Outcome 8 Vomiting.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Block 2009	1/30	0/57		42.68%	5.61[0.24,133.73]
Liabeuf 2017	1/39	1/39		57.32%	1[0.06,15.43]
Total (95% CI)	**69**	**96**		**100%**	**2.09[0.26,16.57]**
Total events: 2 (Sevelamer), 1 (Control)					

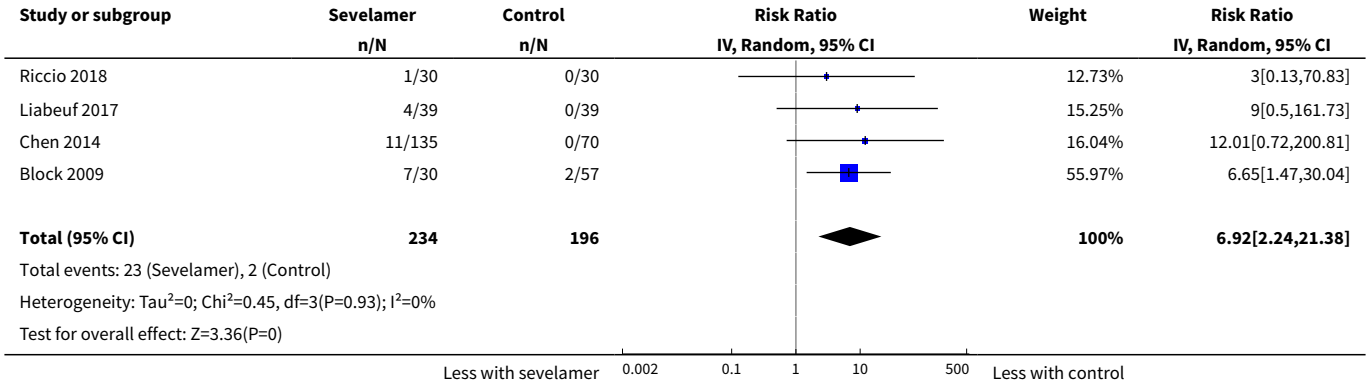




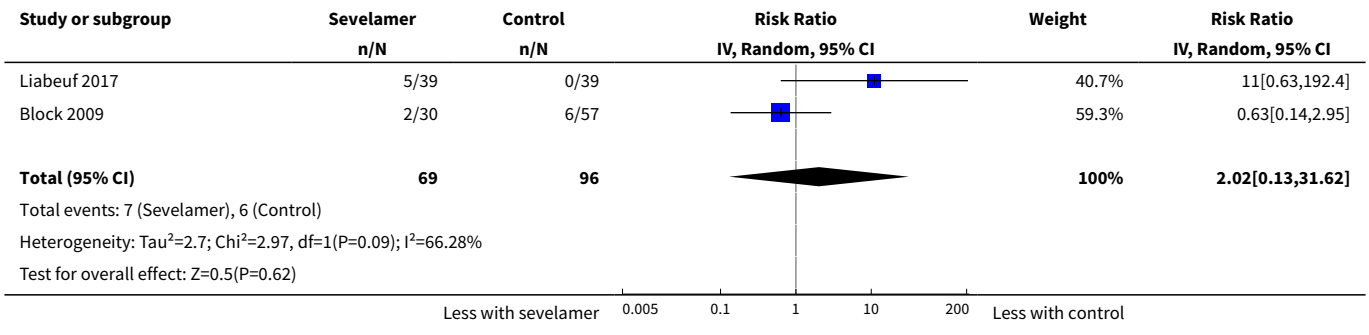
Analysis 1.9. Comparison 1 Sevelamer versus placebo or usual care, Outcome 9 Abdominal pain.



Analysis 1.10. Comparison 1 Sevelamer versus placebo or usual care, Outcome 10 Constipation.

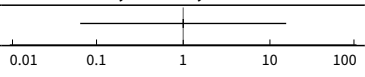


Analysis 1.11. Comparison 1 Sevelamer versus placebo or usual care, Outcome 11 Diarrhoea.



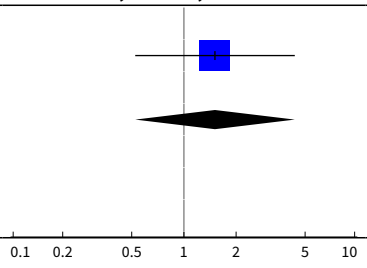
Analysis 1.12. Comparison 1 Sevelamer versus placebo or usual care, Outcome 12 Abdominal bloating.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Liabeuf 2017	1/39	1/39		1[0.06,15.43]



Analysis 1.13. Comparison 1 Sevelamer versus placebo or usual care, Outcome 13 End-stage kidney disease.

Study or subgroup	Sevelamer n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Riccio 2018	0/30	0/30			Not estimable
Lemos 2013	7/38	5/41		100%	1.51[0.52,4.36]
Total (95% CI)	**68**	**71**		**100%**	**1.51[0.52,4.36]**
Total events: 7 (Sevelamer), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.76(P=0.45)					

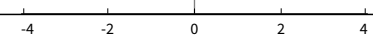


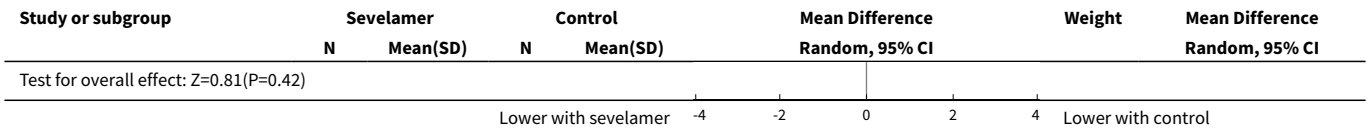
Analysis 1.14. Comparison 1 Sevelamer versus placebo or usual care, Outcome 14 Coronary artery calcium score.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Russo 2007	30	453 (695)	30	547 (959)		47.55%	-94[-517.81,329.81]
Lemos 2013	26	413.8 (570.6)	29	462.4 (930.7)		52.45%	-48.6[-452.14,354.94]
Total ***	**56**		**59**			**100%**	**-70.19[-362.44,222.06]**
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.88); I²=0%							
Test for overall effect: Z=0.47(P=0.64)							

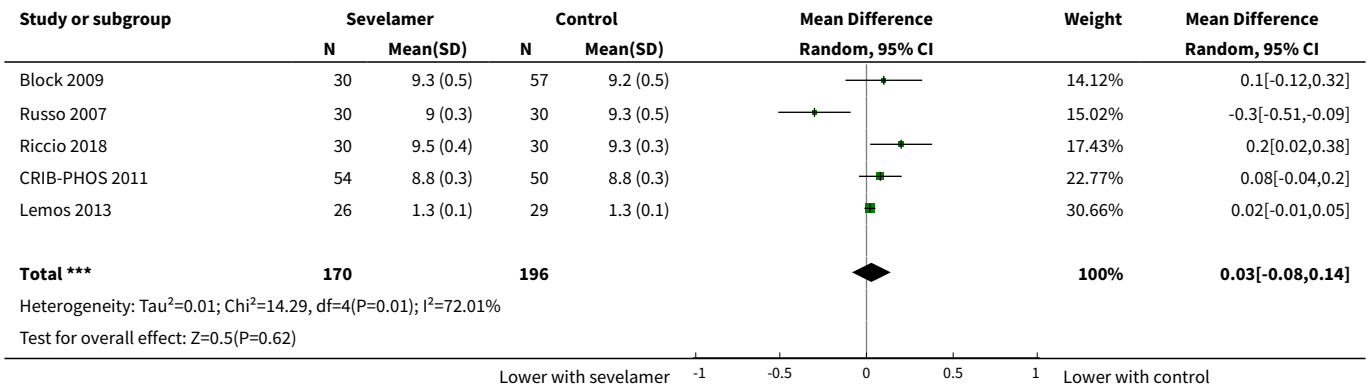
Analysis 1.15. Comparison 1 Sevelamer versus placebo or usual care, Outcome 15 Serum phosphate.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Chen 2014	134	5.8 (1.6)	70	7.6 (1.7)		19.21%	-1.78[-2.26,-1.3]
Russo 2007	30	4.8 (0.9)	30	3.9 (0.9)		19.41%	0.9[0.44,1.36]
Lemos 2013	26	3.5 (0.7)	29	3.3 (0.6)		20.18%	0.2[-0.15,0.55]
Riccio 2018	30	3.7 (0.5)	30	4.3 (0.7)		20.44%	-0.58[-0.88,-0.28]
CRIB-PHOS 2011	54	3.2 (0.7)	50	3.3 (0.5)		20.77%	-0.15[-0.39,0.09]
Total ***	**274**		**209**			**100%**	**-0.28[-0.94,0.39]**
Heterogeneity: Tau²=0.54; Chi²=75, df=4(P<0.0001); I²=94.67%							

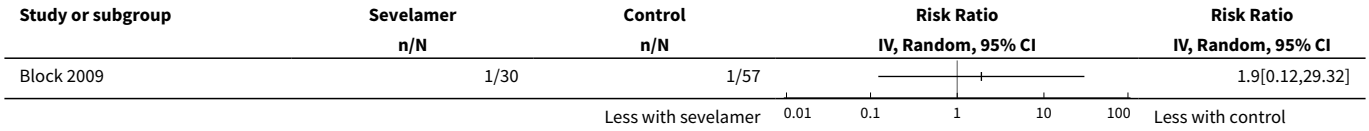




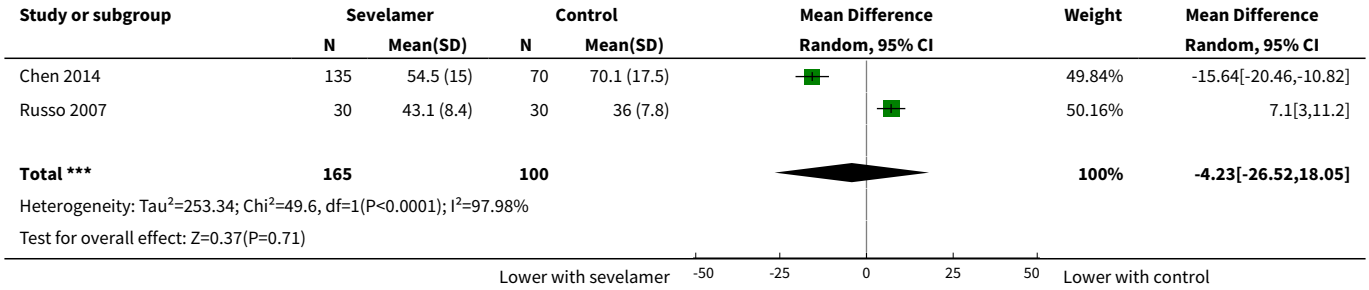
Analysis 1.16. Comparison 1 Sevelamer versus placebo or usual care, Outcome 16 Serum calcium.



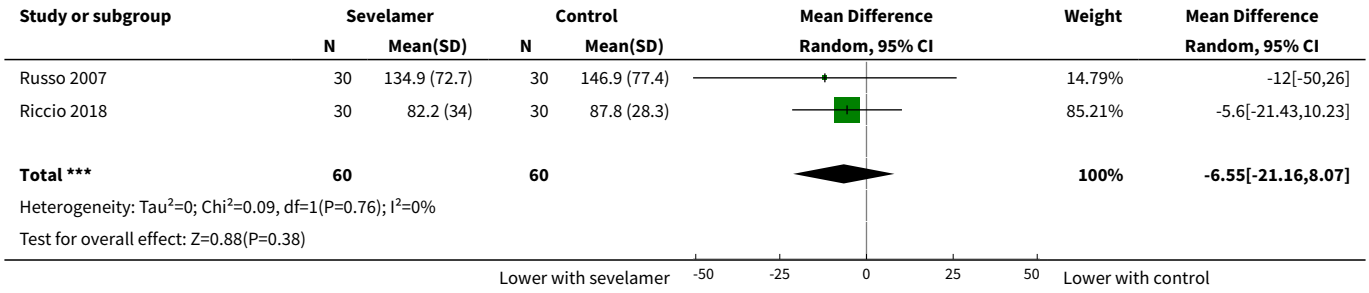
Analysis 1.17. Comparison 1 Sevelamer versus placebo or usual care, Outcome 17 Hypercalcaemia.



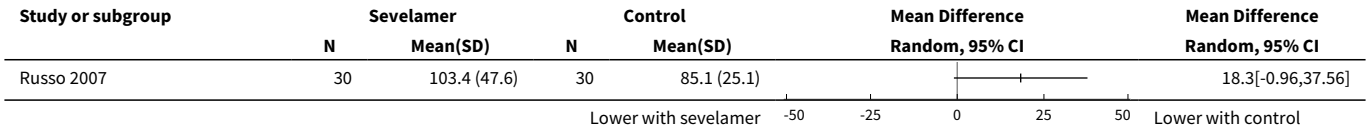
Analysis 1.18. Comparison 1 Sevelamer versus placebo or usual care, Outcome 18 Serum calcium-by-phosphate product.



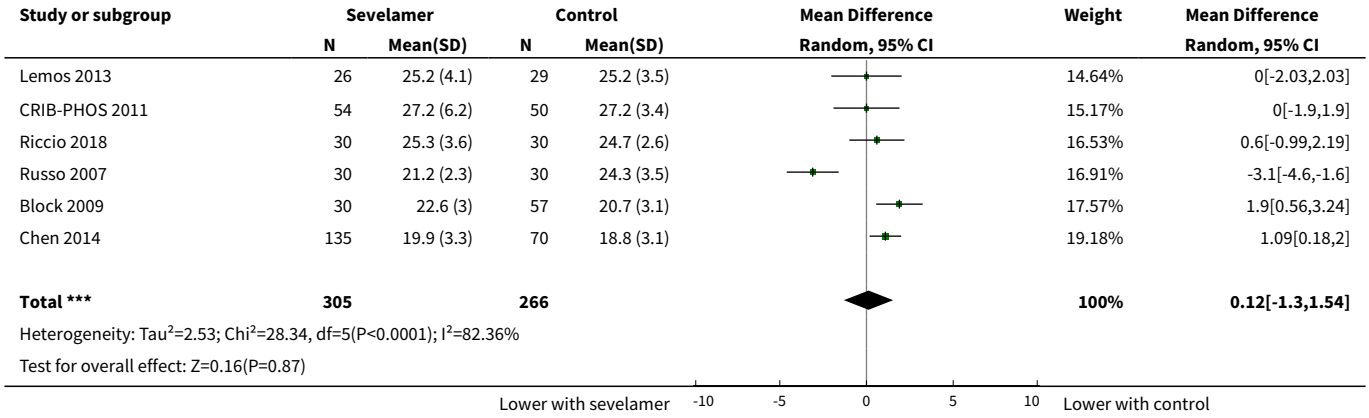
Analysis 1.19. Comparison 1 Sevelamer versus placebo or usual care, Outcome 19 Serum iPTH.



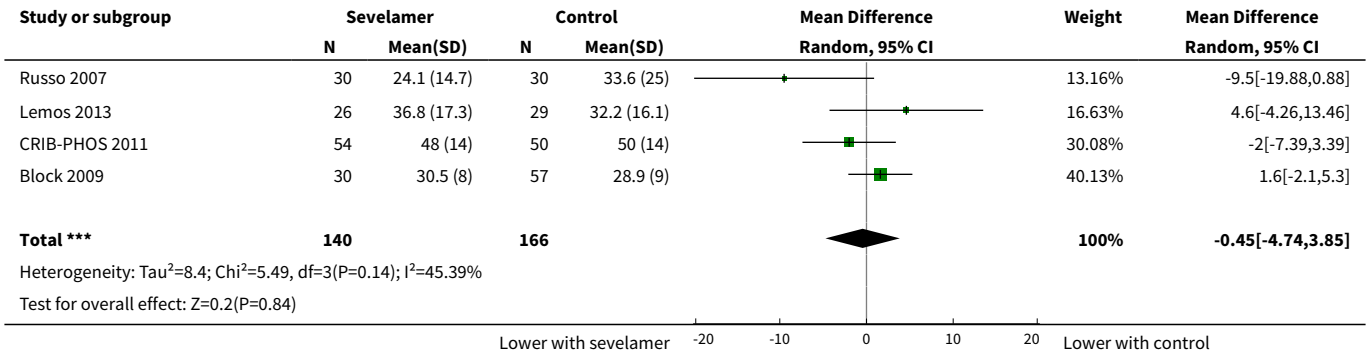
Analysis 1.20. Comparison 1 Sevelamer versus placebo or usual care, Outcome 20 Serum alkaline phosphatase.



Analysis 1.21. Comparison 1 Sevelamer versus placebo or usual care, Outcome 21 Serum bicarbonate.

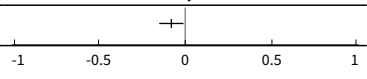


Analysis 1.22. Comparison 1 Sevelamer versus placebo or usual care, Outcome 22 eGFR.



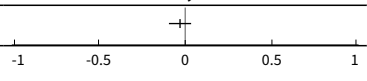
Analysis 1.23. Comparison 1 Sevelamer versus placebo or usual care, Outcome 23 Bone mineral density: lumbar spine.

Study or subgroup	Sevelamer		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
CRIB-PHOS 2011	54	1.1 (0.2)	50	1.1 (0.2)		-0.08[-0.15,-0.01]



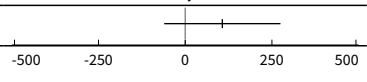
Analysis 1.24. Comparison 1 Sevelamer versus placebo or usual care, Outcome 24 Bone mineral density: hip.

Study or subgroup	Sevelamer		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
CRIB-PHOS 2011	54	1 (0.2)	50	1 (0.2)		-0.03[-0.09,0.03]



Analysis 1.25. Comparison 1 Sevelamer versus placebo or usual care, Outcome 25 Klotho.

Study or subgroup	Sevelamer		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
CRIB-PHOS 2011	54	980 (533)	50	873 (320)		107[-60.56,274.56]



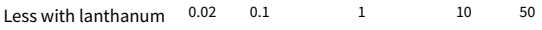
Comparison 2. Lanthanum versus placebo or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	3	214	Risk Ratio (IV, Random, 95% CI)	1.63 [0.07, 37.12]
2 Myocardial infarction	3	239	Risk Ratio (IV, Random, 95% CI)	1.61 [0.17, 14.97]
3 Stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Hospitalisation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Pruritus	3	345	Risk Ratio (IV, Random, 95% CI)	1.09 [0.14, 8.45]
7 Pruritus	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Nausea	4	383	Risk Ratio (IV, Random, 95% CI)	3.72 [1.36, 10.18]
9 Vomiting	3	261	Risk Ratio (IV, Random, 95% CI)	2.76 [0.41, 18.63]
10 Abdominal pain	2	120	Risk Ratio (IV, Random, 95% CI)	0.23 [0.03, 1.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Constipation	4	299	Risk Ratio (IV, Random, 95% CI)	2.98 [1.21, 7.30]
12 Diarrhoea	3	261	Risk Ratio (IV, Random, 95% CI)	0.68 [0.13, 3.68]
13 End-stage kidney disease	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
14 Coronary artery calcification score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15 Vascular calcification score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16 Serum phosphate	4	271	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.90, -0.05]
17 Serum calcium	2	91	Mean Difference (IV, Random, 95% CI)	0.03 [-0.18, 0.23]
18 Hypercalcaemia	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
19 Serum calcium-by-phosphate product	2	194	Mean Difference (IV, Random, 95% CI)	-4.36 [-9.96, 1.24]
20 Serum iPTH	4	253	Mean Difference (IV, Random, 95% CI)	10.07 [-10.69, 30.83]
21 eGFR	2	128	Mean Difference (IV, Random, 95% CI)	0.13 [-1.80, 2.07]
22 Bone mineral density: lumbar spine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
23 Serum FGF23	2	50	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-0.81, 1.45]

Analysis 2.1. Comparison 2 Lanthanum versus placebo or usual care, Outcome 1 Death (all causes).

Study or subgroup	Lanthanum carbonate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Seifert 2013	0/19	0/19			Not estimable
Takahara 2014	0/86	0/55			Not estimable
PREFECT 2014	1/23	0/12		100%	1.63[0.07,37.12]
Total (95% CI)	**128**	**86**		**100%**	**1.63[0.07,37.12]**
Total events: 1 (Lanthanum carbonate), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.3(P=0.76)					

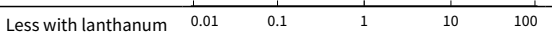


Analysis 2.2. Comparison 2 Lanthanum versus placebo or usual care, Outcome 2 Myocardial infarction.

Study or subgroup	Lanthanum carbonate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Block 2009	0/28	0/57			Not estimable
Sprague 2009a	1/78	0/41		49.21%	1.59[0.07,38.3]
PREFECT 2014	1/23	0/12		50.79%	1.63[0.07,37.12]
Total (95% CI)	**129**	**110**		**100%**	**1.61[0.17,14.97]**
Total events: 2 (Lanthanum carbonate), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.42(P=0.68)					

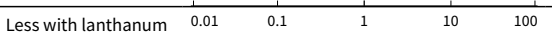
Analysis 2.3. Comparison 2 Lanthanum versus placebo or usual care, Outcome 3 Stroke.

Study or subgroup	Lanthanum carbonate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	0/28	0/59		Not estimable



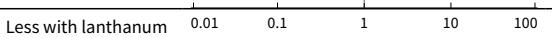
Analysis 2.4. Comparison 2 Lanthanum versus placebo or usual care, Outcome 4 Hospitalisation.

Study or subgroup	Lanthanum carbonate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Isakova 2013	2/19	1/20		2.11[0.21,21.36]



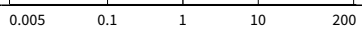
Analysis 2.5. Comparison 2 Lanthanum versus placebo or usual care, Outcome 5 Fracture.

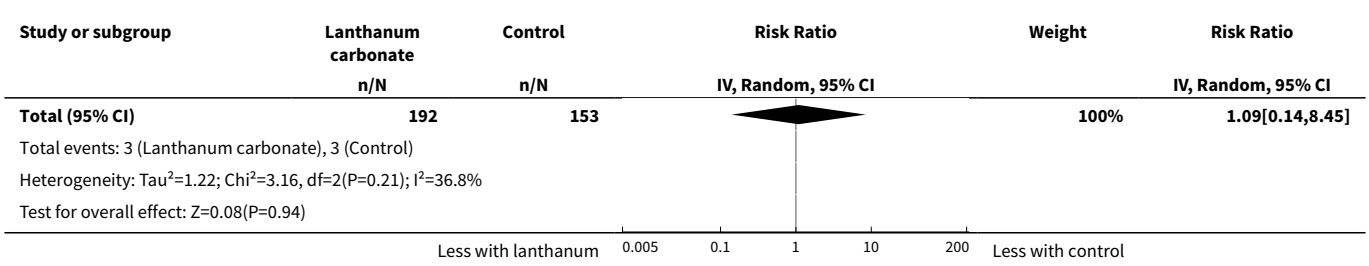
Study or subgroup	Lanthanum carbonate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	1/28	2/57		1.02[0.1,10.75]



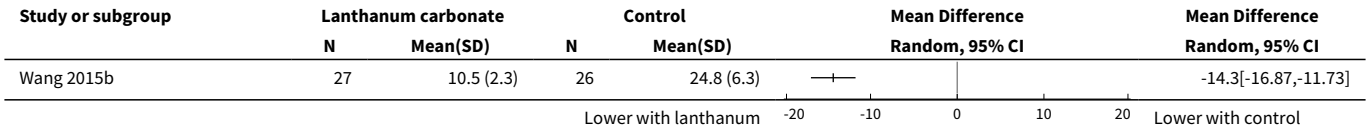
Analysis 2.6. Comparison 2 Lanthanum versus placebo or usual care, Outcome 6 Pruritus.

Study or subgroup	Lanthanum carbonate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Sprague 2009a	1/78	0/41		28.44%	1.59[0.07,38.3]
Takahara 2014	0/86	2/55		30.49%	0.13[0.01,2.63]
Block 2009	2/28	1/57		41.07%	4.07[0.39,43.01]

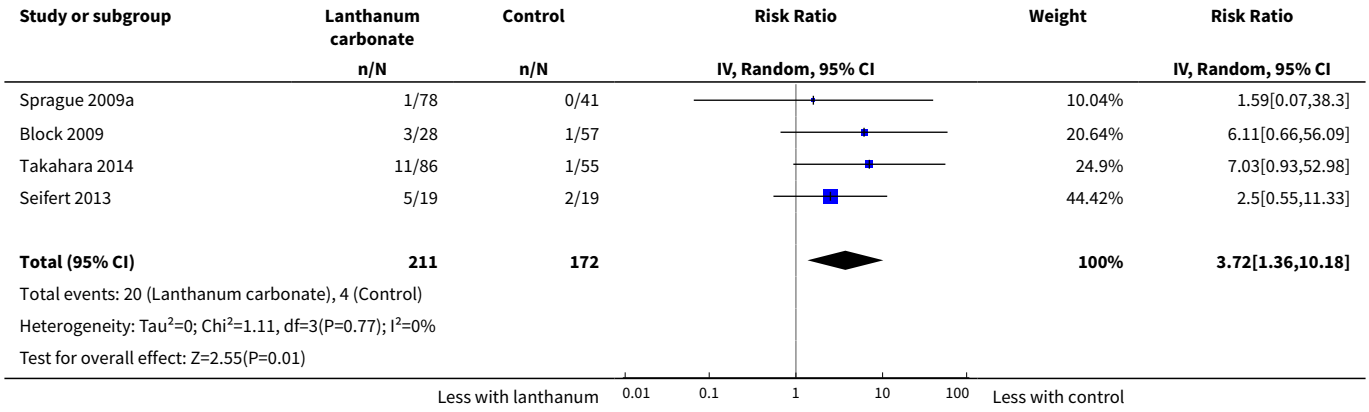




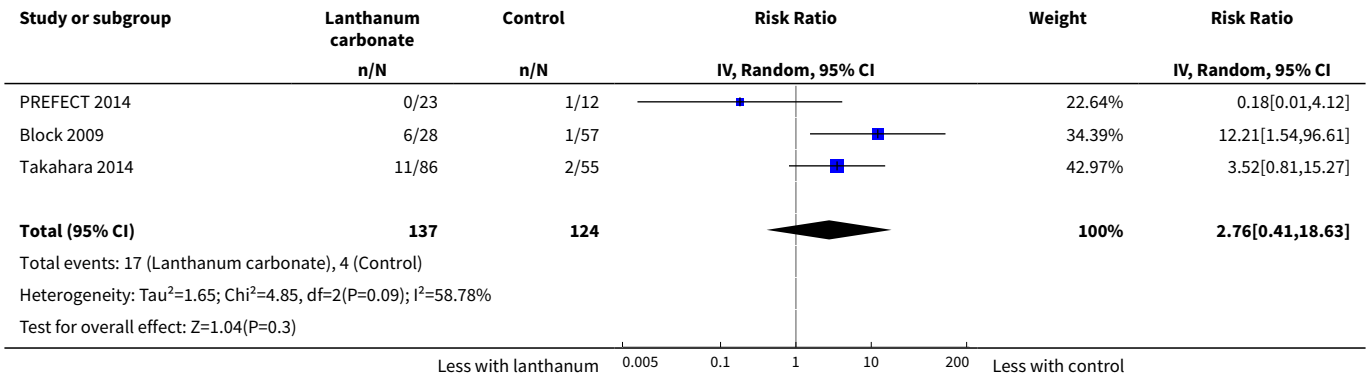
Analysis 2.7. Comparison 2 Lanthanum versus placebo or usual care, Outcome 7 Pruritus.



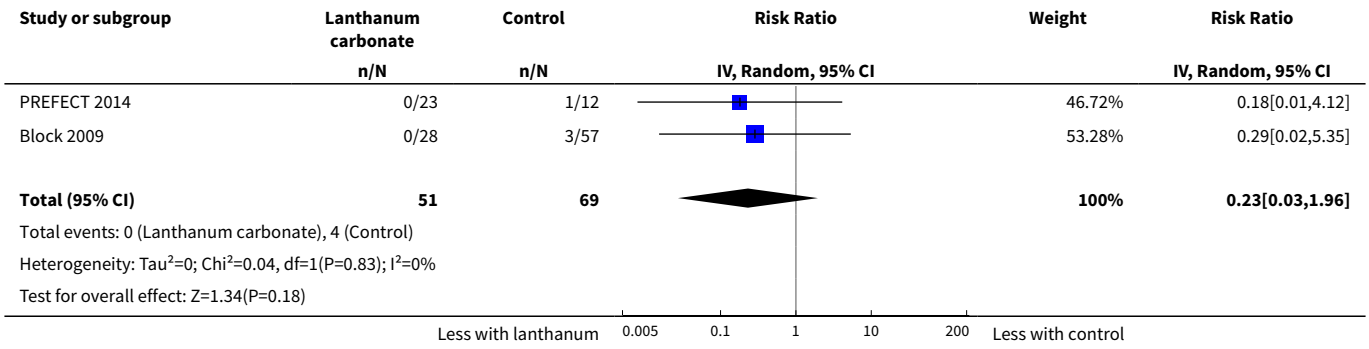
Analysis 2.8. Comparison 2 Lanthanum versus placebo or usual care, Outcome 8 Nausea.



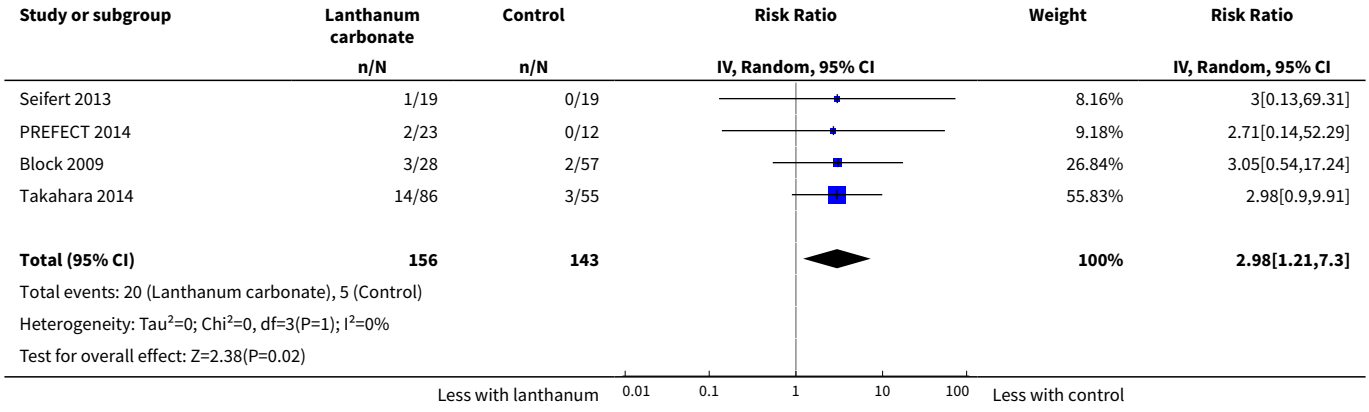
Analysis 2.9. Comparison 2 Lanthanum versus placebo or usual care, Outcome 9 Vomiting.



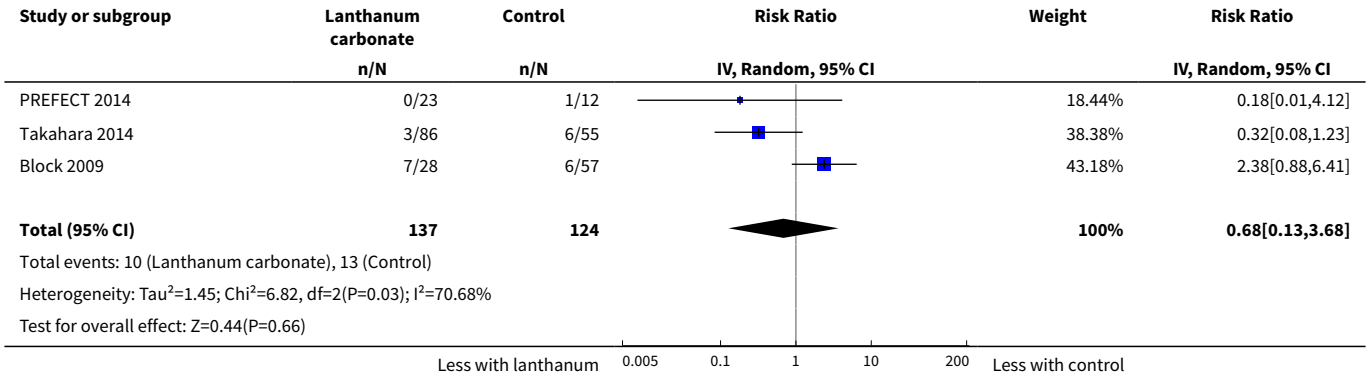
Analysis 2.10. Comparison 2 Lanthanum versus placebo or usual care, Outcome 10 Abdominal pain.



Analysis 2.11. Comparison 2 Lanthanum versus placebo or usual care, Outcome 11 Constipation.

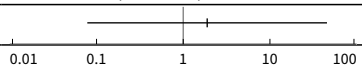


Analysis 2.12. Comparison 2 Lanthanum versus placebo or usual care, Outcome 12 Diarrhoea.



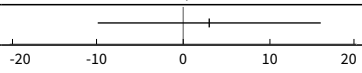
Analysis 2.13. Comparison 2 Lanthanum versus placebo or usual care, Outcome 13 End-stage kidney disease.

Study or subgroup	Lanthanum carbonate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Takahara 2014	1/88	0/55		1.89[0.08,45.53]



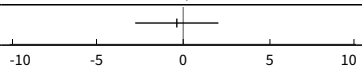
Analysis 2.14. Comparison 2 Lanthanum versus placebo or usual care, Outcome 14 Coronary artery calcification score.

Study or subgroup	Lanthanum carbonate N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Seifert 2013	19	23 (23)	19	20 (17)		3[-9.86,15.86]



Analysis 2.15. Comparison 2 Lanthanum versus placebo or usual care, Outcome 15 Vascular calcification score.

Study or subgroup	Lanthanum carbonate N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Wang 2015b	27	14.4 (4.8)	26	14.8 (4.1)		-0.37[-2.77,2.03]

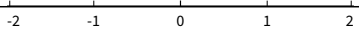


Analysis 2.16. Comparison 2 Lanthanum versus placebo or usual care, Outcome 16 Serum phosphate.

Study or subgroup	Lanthanum carbonate N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Isakova 2013	19	3.3 (0.7)	20	3.6 (0.8)		22.44%	-0.3[-0.77,0.17]
Takahara 2014	86	5.1 (1.4)	55	6.1 (1.1)		24.02%	-0.96[-1.37,-0.55]
Seifert 2013	19	3.3 (0.5)	19	3.2 (0.7)		24.62%	0.1[-0.29,0.49]
Wang 2015b	27	5.3 (0.5)	26	6 (0.2)		28.92%	-0.7[-0.9,-0.5]
Total ***	**151**		**120**			**100%**	**-0.48[-0.9,-0.05]**

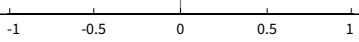
Heterogeneity: Tau^2=0.16; Chi^2=17.93, df=3(P=0); I^2=83.27%

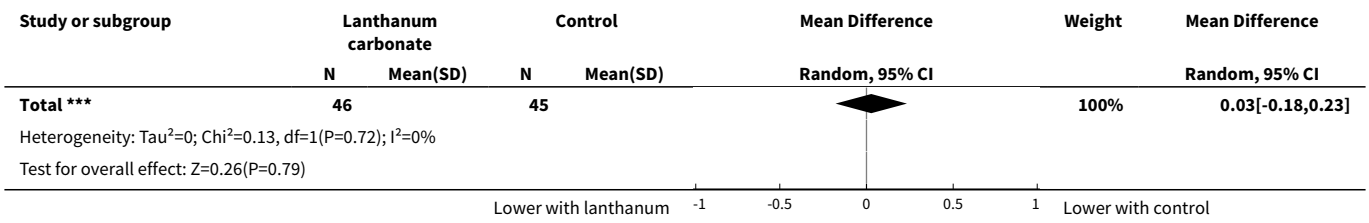
Test for overall effect: Z=2.18(P=0.03)



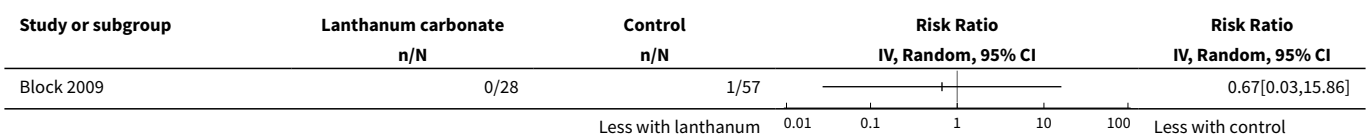
Analysis 2.17. Comparison 2 Lanthanum versus placebo or usual care, Outcome 17 Serum calcium.

Study or subgroup	Lanthanum carbonate N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Wang 2015b	27	9.4 (0.6)	26	9.3 (0.7)		34.36%	0.08[-0.27,0.43]
Seifert 2013	19	9.5 (0.4)	19	9.5 (0.4)		65.64%	0[-0.25,0.25]

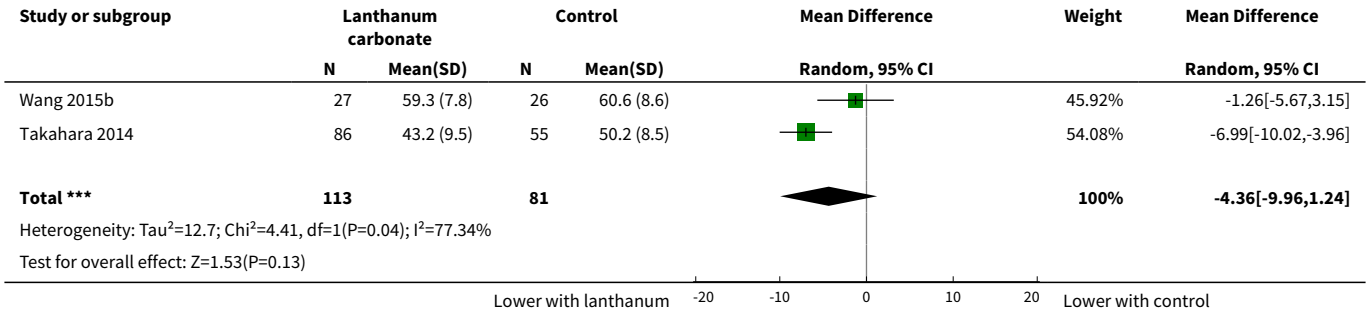




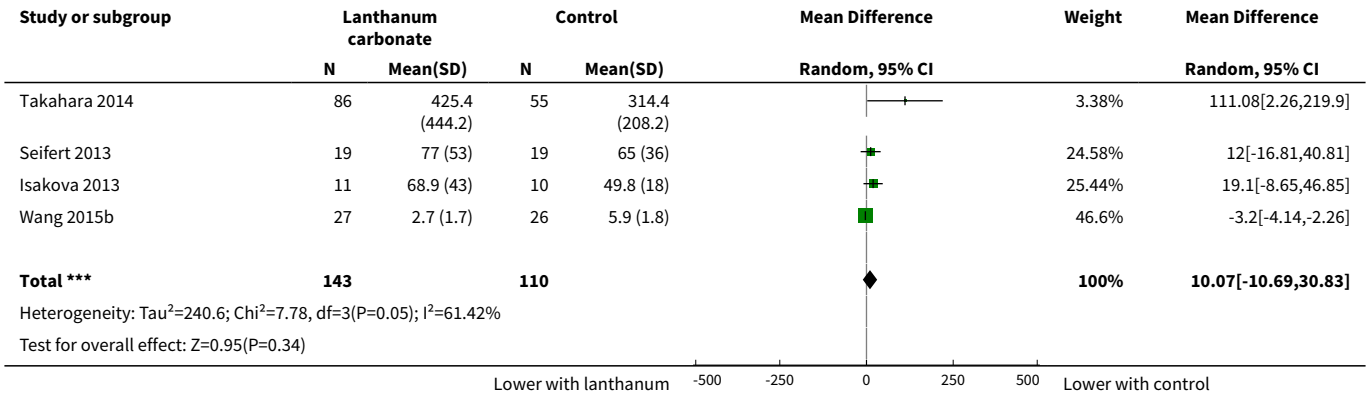
Analysis 2.18. Comparison 2 Lanthanum versus placebo or usual care, Outcome 18 Hypercalcaemia.



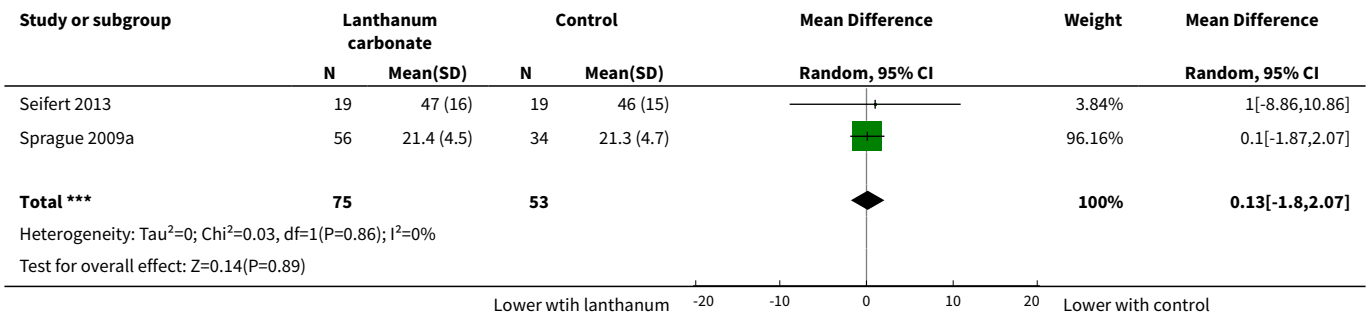
Analysis 2.19. Comparison 2 Lanthanum versus placebo or usual care, Outcome 19 Serum calcium-by-phosphate product.



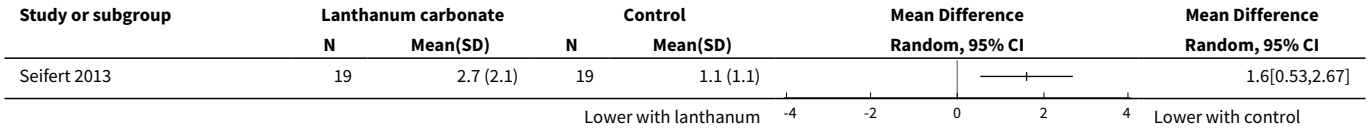
Analysis 2.20. Comparison 2 Lanthanum versus placebo or usual care, Outcome 20 Serum iPTH.



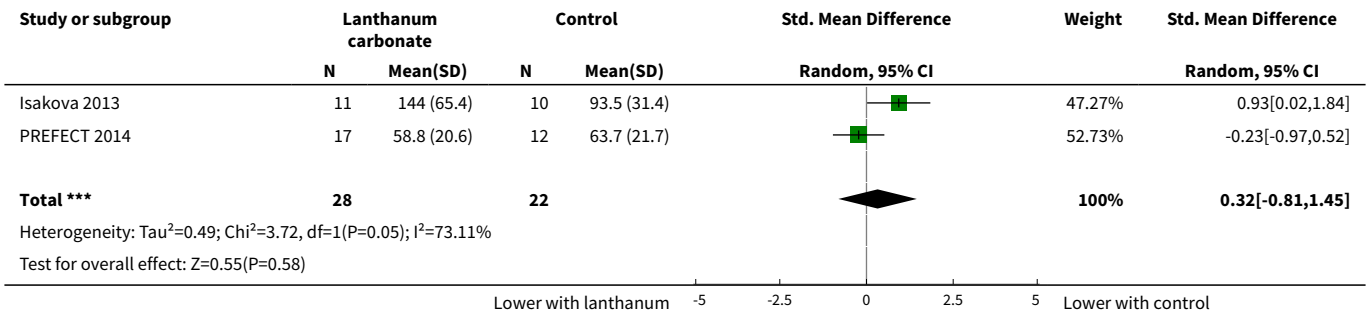
Analysis 2.21. Comparison 2 Lanthanum versus placebo or usual care, Outcome 21 eGFR.



Analysis 2.22. Comparison 2 Lanthanum versus placebo or usual care, Outcome 22 Bone mineral density: lumbar spine.



Analysis 2.23. Comparison 2 Lanthanum versus placebo or usual care, Outcome 23 Serum FGF23.



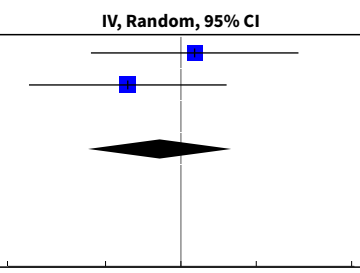
Comparison 3. Iron versus placebo or usual care

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death (all causes)	2	239	Risk Ratio (IV, Random, 95% CI)	0.52 [0.06, 4.65]
2 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Pruritus	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Constipation	3	422	Risk Ratio (IV, Random, 95% CI)	2.66 [1.15, 6.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Diarrhoea	3	422	Risk Ratio (IV, Random, 95% CI)	2.81 [1.18, 6.68]
7 Abdominal pain	2	332	Risk Ratio (IV, Random, 95% CI)	1.20 [0.34, 4.27]
8 Serum phosphate	3	301	Mean Difference (IV, Random, 95% CI)	-1.33 [-2.25, -0.41]
9 Serum calcium	3	301	Mean Difference (IV, Random, 95% CI)	0.21 [0.09, 0.33]
10 Serum calcium-by-phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Serum alkaline phosphatase	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Serum bicarbonate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13 eGFR	2	239	Mean Difference (IV, Random, 95% CI)	-0.67 [-2.97, 1.64]

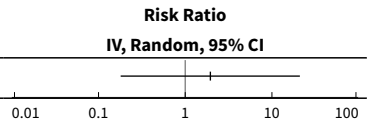
Analysis 3.1. Comparison 3 Iron versus placebo or usual care, Outcome 1 Death (all causes).

Study or subgroup	Iron n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Yokoyama 2014	1/60	0/30		47.55%	1.52[0.06,36.34]
Block 2015	0/75	2/74		52.45%	0.2[0.01,4.04]
Total (95% CI)	**135**	**104**		**100%**	**0.52[0.06,4.65]**
Total events: 1 (Iron), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.84, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=0.58(P=0.56)					



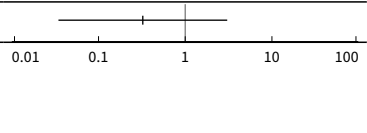
Analysis 3.2. Comparison 3 Iron versus placebo or usual care, Outcome 2 Fracture.

Study or subgroup	Iron n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2015	2/75	1/73		1.95[0.18,21.01]

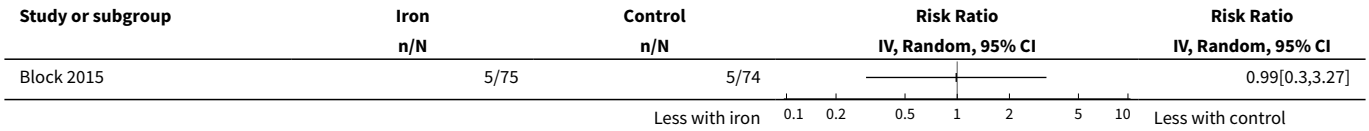


Analysis 3.3. Comparison 3 Iron versus placebo or usual care, Outcome 3 Pruritus.

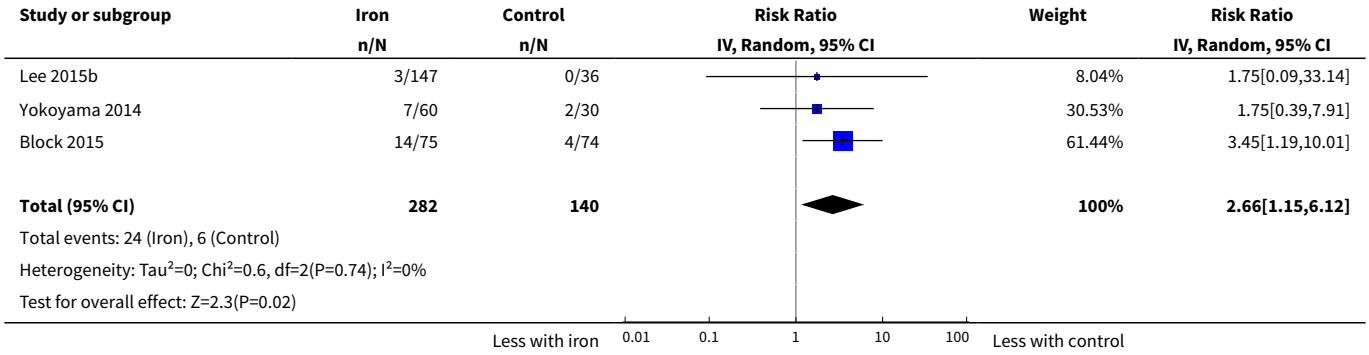
Study or subgroup	Iron n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2015	1/75	3/73		0.32[0.03,3.05]



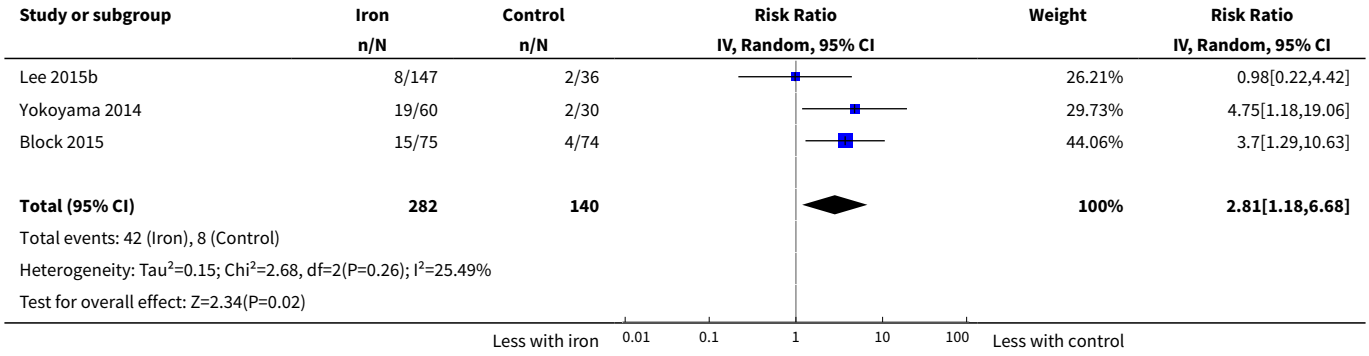
Analysis 3.4. Comparison 3 Iron versus placebo or usual care, Outcome 4 Nausea.



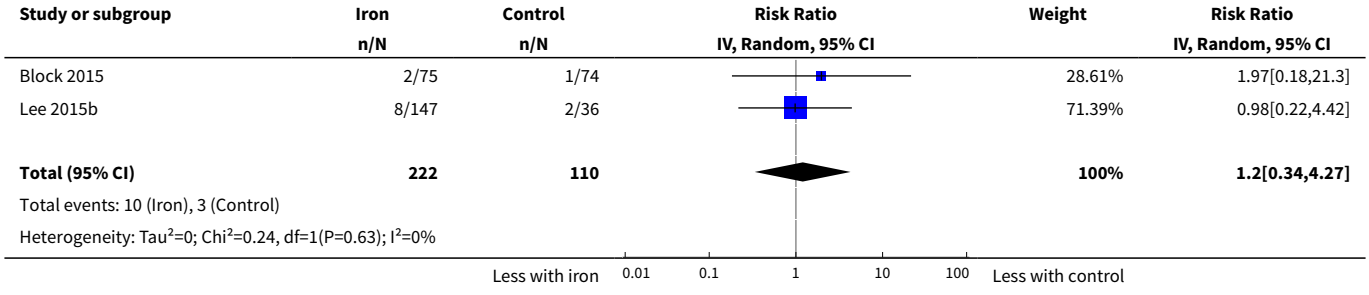
Analysis 3.5. Comparison 3 Iron versus placebo or usual care, Outcome 5 Constipation.

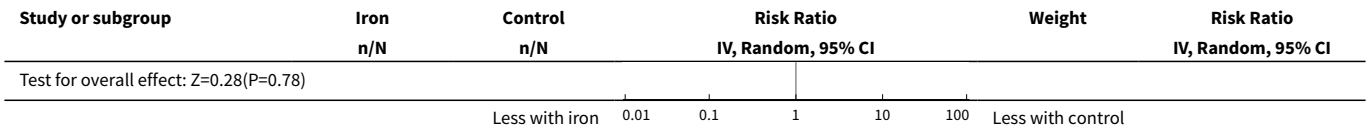


Analysis 3.6. Comparison 3 Iron versus placebo or usual care, Outcome 6 Diarrhoea.

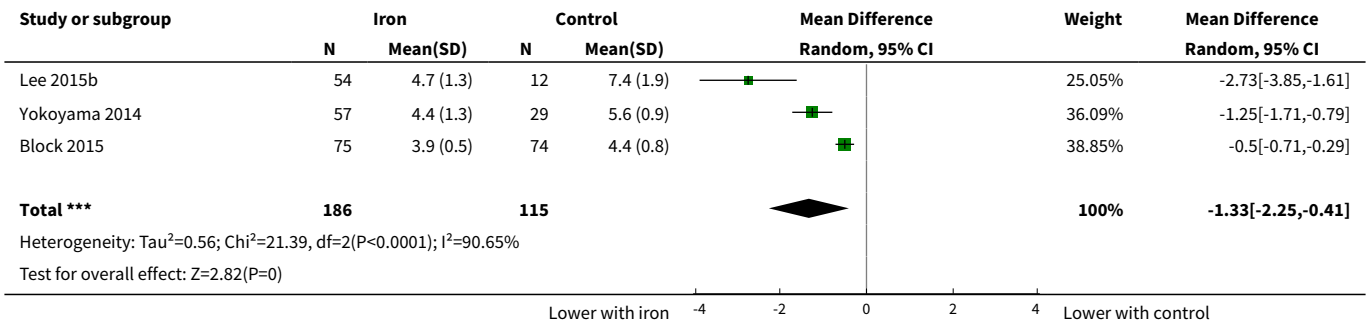


Analysis 3.7. Comparison 3 Iron versus placebo or usual care, Outcome 7 Abdominal pain.

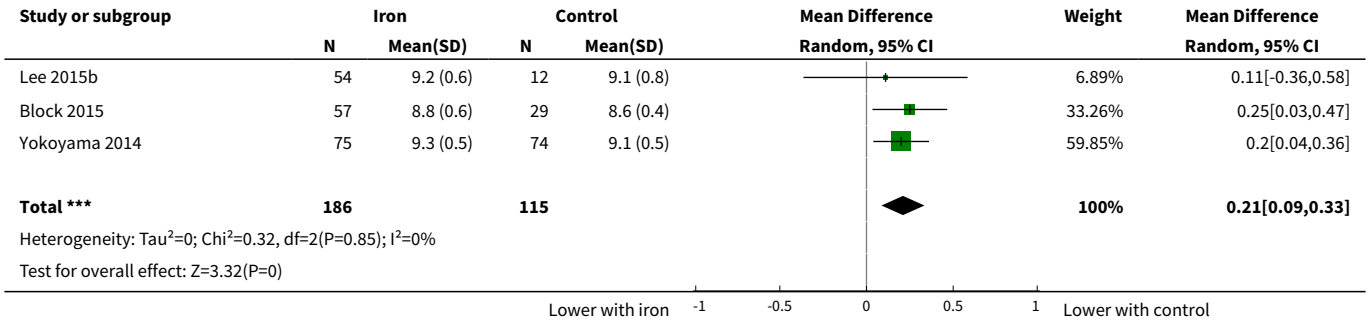




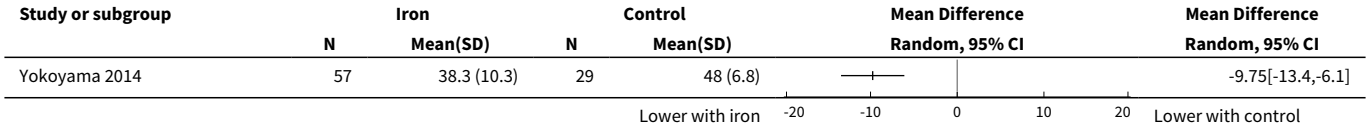
Analysis 3.8. Comparison 3 Iron versus placebo or usual care, Outcome 8 Serum phosphate.



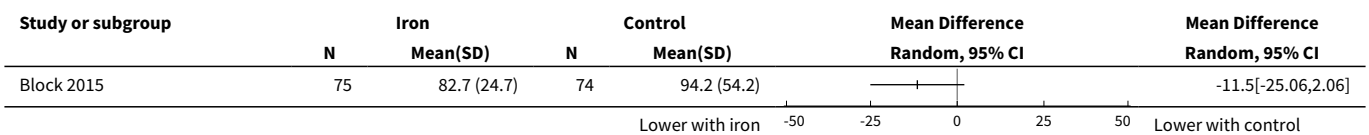
Analysis 3.9. Comparison 3 Iron versus placebo or usual care, Outcome 9 Serum calcium.



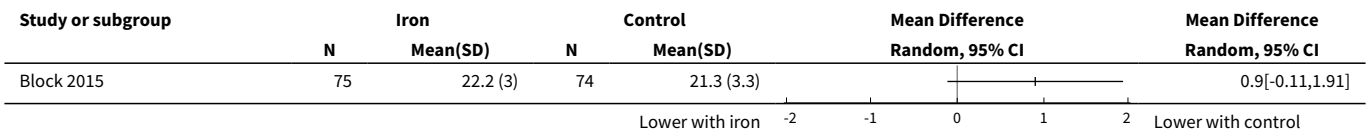
Analysis 3.10. Comparison 3 Iron versus placebo or usual care, Outcome 10 Serum calcium-by-phosphate product.



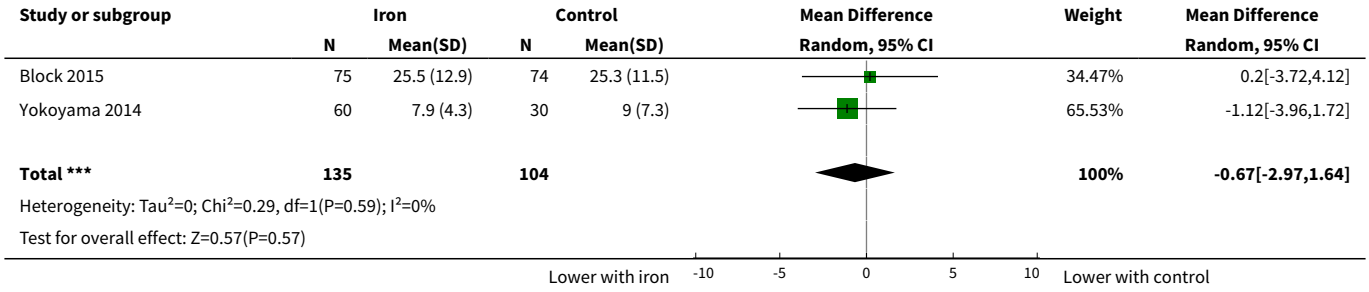
Analysis 3.11. Comparison 3 Iron versus placebo or usual care, Outcome 11 Serum alkaline phosphatase.



Analysis 3.12. Comparison 3 Iron versus placebo or usual care, Outcome 12 Serum bicarbonate.



Analysis 3.13. Comparison 3 Iron versus placebo or usual care, Outcome 13 eGFR.



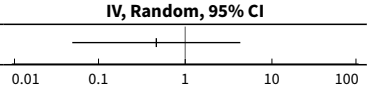
Comparison 4. Calcium versus placebo or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Myocardial infarction	2	147	Risk Ratio (IV, Random, 95% CI)	1.36 [0.09, 21.71]
3 Stroke	2	197	Risk Ratio (IV, Random, 95% CI)	4.15 [0.17, 99.62]
4 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Pruritus	2	197	Risk Ratio (IV, Random, 95% CI)	1.19 [0.29, 4.81]
6 Nausea	2	197	Risk Ratio (IV, Random, 95% CI)	0.58 [0.15, 2.18]
7 Vomiting	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Abdominal pain	2	197	Risk Ratio (IV, Random, 95% CI)	0.66 [0.13, 3.34]
9 Constipation	2	197	Risk Ratio (IV, Random, 95% CI)	2.44 [0.32, 18.42]
10 Diarrhoea	2	197	Risk Ratio (IV, Random, 95% CI)	0.94 [0.39, 2.28]
11 Coronary artery calcification score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Serum phosphate	3	151	Mean Difference (IV, Random, 95% CI)	-0.18 [-1.30, 0.95]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
13 Serum calcium	3	151	Mean Difference (IV, Random, 95% CI)	0.33 [-0.26, 0.92]
14 Hypercalcaemia	3	215	Risk Ratio (IV, Random, 95% CI)	7.28 [1.64, 32.29]
15 Serum calcium-by-phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16 Serum iPTH	2	133	Mean Difference (IV, Random, 95% CI)	-80.15 [-305.46, 145.16]
17 Serum alkaline phosphatase	2	78	Mean Difference (IV, Random, 95% CI)	34.86 [-21.47, 91.20]
18 Serum bicarbonate	2	138	Mean Difference (IV, Random, 95% CI)	-1.85 [-3.12, -0.59]
19 eGFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

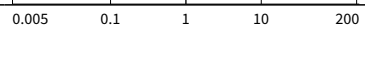
Analysis 4.1. Comparison 4 Calcium versus placebo or usual care, Outcome 1 Death (all causes).

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Qunibi 2011	1/46	3/64		0.46[0.05,4.32]



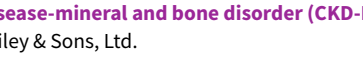
Analysis 4.2. Comparison 4 Calcium versus placebo or usual care, Outcome 2 Myocardial infarction.

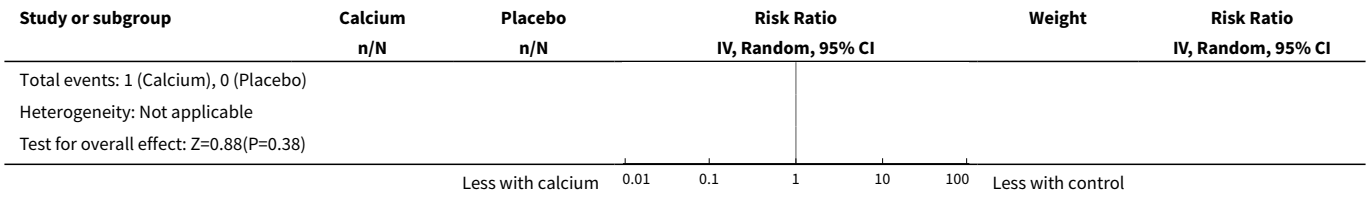
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Block 2009	1/30	0/57		49.91%	5.61[0.24,133.73]
Russo 2007	0/30	1/30		50.09%	0.33[0.01,7.87]
Total (95% CI)	**60**	**87**		**100%**	**1.36[0.09,21.71]**
Total events: 1 (Calcium), 1 (Placebo)					
Heterogeneity: Tau^2=1.38; Chi^2=1.53, df=1(P=0.22); I^2=34.54%					
Test for overall effect: Z=0.22(P=0.83)					



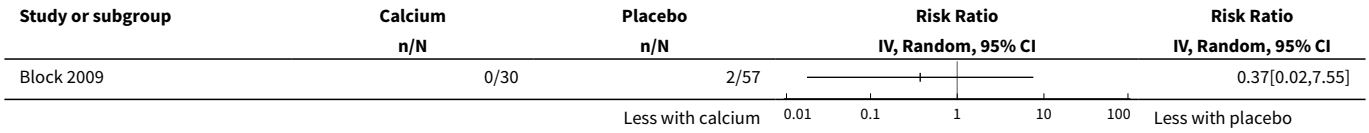
Analysis 4.3. Comparison 4 Calcium versus placebo or usual care, Outcome 3 Stroke.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Block 2009	0/30	0/57			Not estimable
Qunibi 2011	1/46	0/64		100%	4.15[0.17,99.62]
Total (95% CI)	**76**	**121**		**100%**	**4.15[0.17,99.62]**

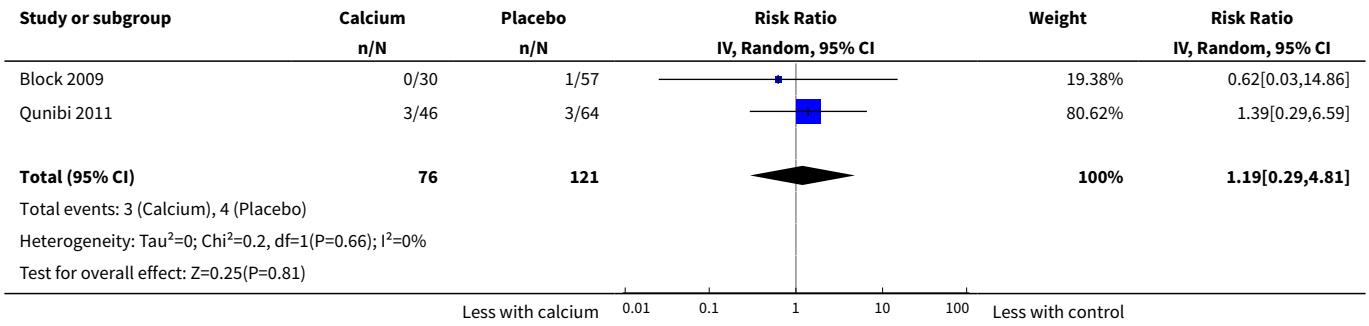




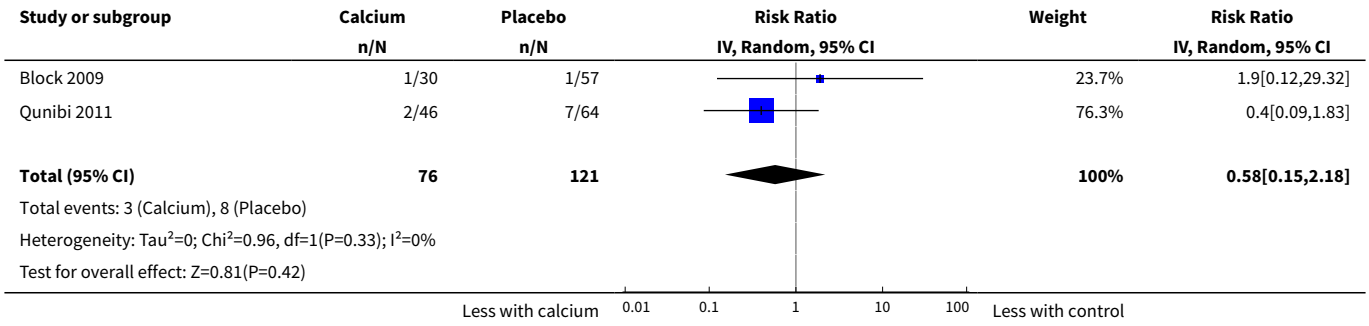
Analysis 4.4. Comparison 4 Calcium versus placebo or usual care, Outcome 4 Fracture.



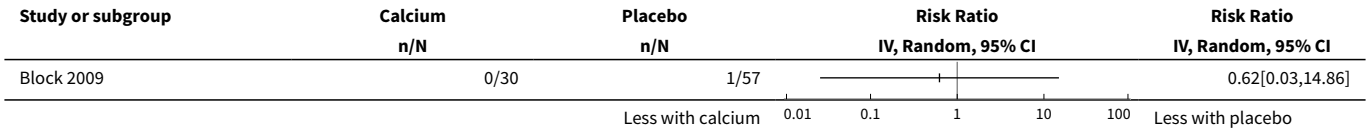
Analysis 4.5. Comparison 4 Calcium versus placebo or usual care, Outcome 5 Pruritus.



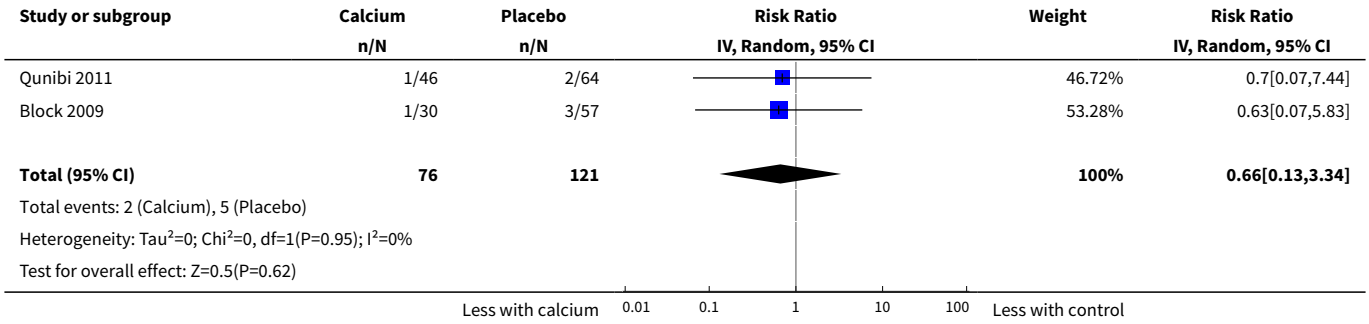
Analysis 4.6. Comparison 4 Calcium versus placebo or usual care, Outcome 6 Nausea.



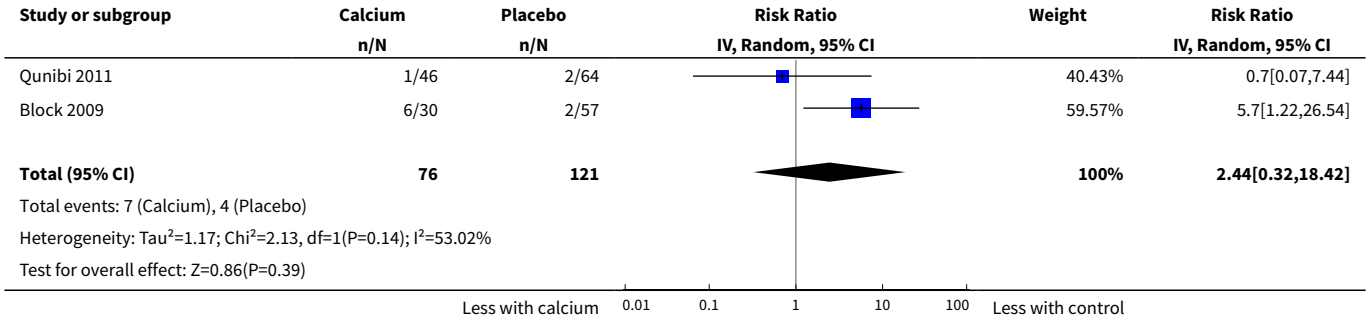
Analysis 4.7. Comparison 4 Calcium versus placebo or usual care, Outcome 7 Vomiting.



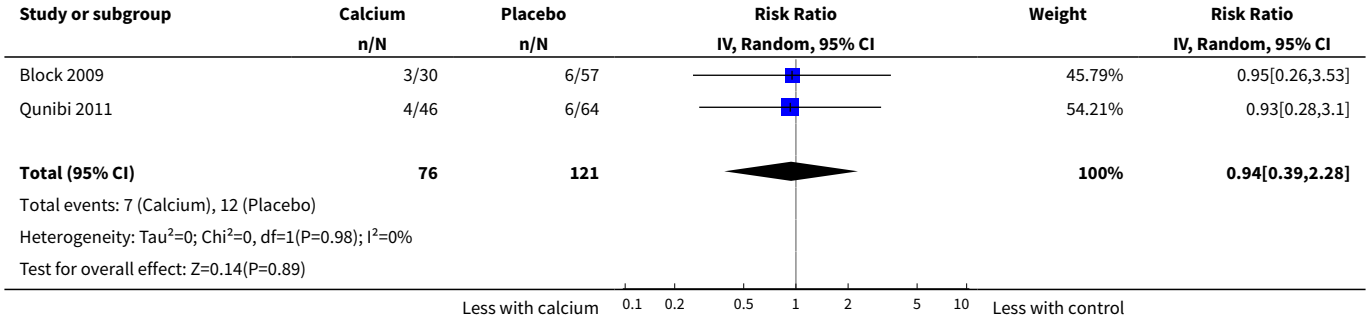
Analysis 4.8. Comparison 4 Calcium versus placebo or usual care, Outcome 8 Abdominal pain.



Analysis 4.9. Comparison 4 Calcium versus placebo or usual care, Outcome 9 Constipation.

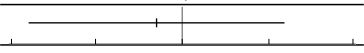


Analysis 4.10. Comparison 4 Calcium versus placebo or usual care, Outcome 10 Diarrhoea.



Analysis 4.11. Comparison 4 Calcium versus placebo or usual care, Outcome 11 Coronary artery calcification score.

Study or subgroup	Calcium N	Calcium Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Russo 2007	30	473 (378)	30	547 (959)		-74[-442.86,294.86]



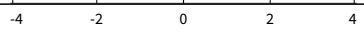
Lower with calcium — Lower with control

Analysis 4.12. Comparison 4 Calcium versus placebo or usual care, Outcome 12 Serum phosphate.

Study or subgroup	Calcium N	Calcium Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Rudnicki 1994	9	5.2 (1.6)	9	6 (1.1)		27.12%	-0.78[-2.03,0.47]
Russo 2007	30	4.7 (1.5)	30	3.9 (0.9)		36.27%	0.8[0.17,1.43]
Qunibi 2011	37	4.4 (1.2)	36	5.1 (1.4)		36.61%	-0.7[-1.3,-0.1]
Total ***	**76**		**75**			**100%**	**-0.18[-1.3,0.95]**

Heterogeneity: Tau^2=0.81; Chi^2=12.91, df=2(P=0); I^2=84.5%

Test for overall effect: Z=0.31(P=0.76)



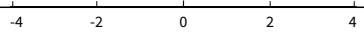
Lower with calcium — Lower with control

Analysis 4.13. Comparison 4 Calcium versus placebo or usual care, Outcome 13 Serum calcium.

Study or subgroup	Calcium N	Calcium Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Rudnicki 1994	9	5 (0.4)	9	4.5 (0.6)		31.17%	0.52[0.04,1]
Qunibi 2011	37	9.5 (0.8)	36	8.8 (0.8)		34.06%	0.7[0.33,1.07]
Russo 2007	30	9.1 (0.8)	30	9.3 (0.5)		34.77%	-0.2[-0.54,0.14]
Total ***	**76**		**75**			**100%**	**0.33[-0.26,0.92]**

Heterogeneity: Tau^2=0.23; Chi^2=13.76, df=2(P=0); I^2=85.46%

Test for overall effect: Z=1.1(P=0.27)



Lower with calcium — Lower with placebo

Analysis 4.14. Comparison 4 Calcium versus placebo or usual care, Outcome 14 Hypercalcaemia.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Qunibi 2011	1/46	0/64		21.98%	4.15[0.17,99.62]
Rudnicki 1994	3/9	0/9		27.72%	7[0.41,118.69]
Block 2009	5/30	1/57		50.3%	9.5[1.16,77.66]
Total (95% CI)	**85**	**130**		**100%**	**7.28[1.64,32.29]**

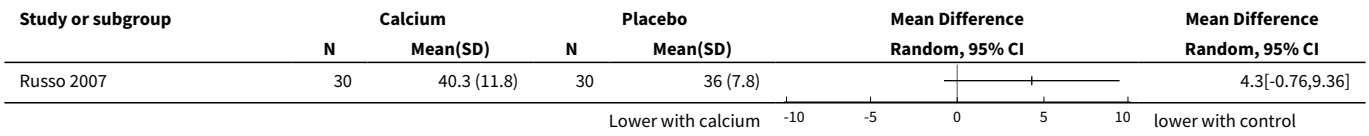
Total events: 9 (Calcium), 1 (Placebo)

Heterogeneity: Tau^2=0; Chi^2=0.18, df=2(P=0.91); I^2=0%

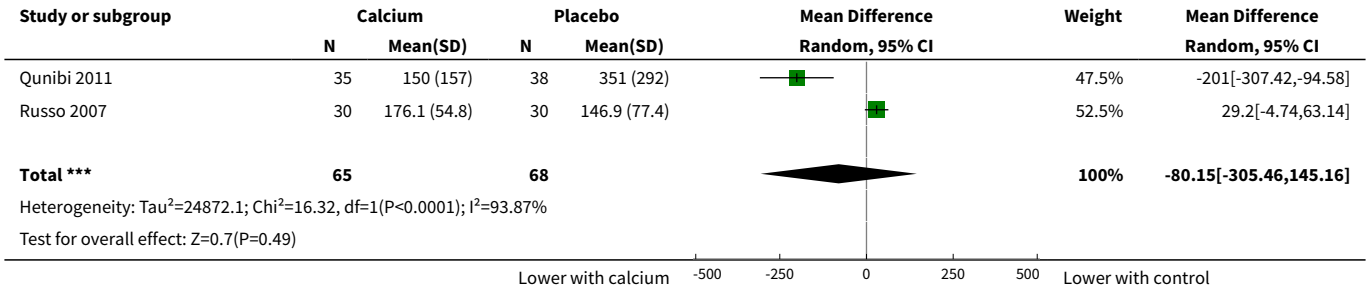
Test for overall effect: Z=2.61(P=0.01)

Less with calcium — Less with control

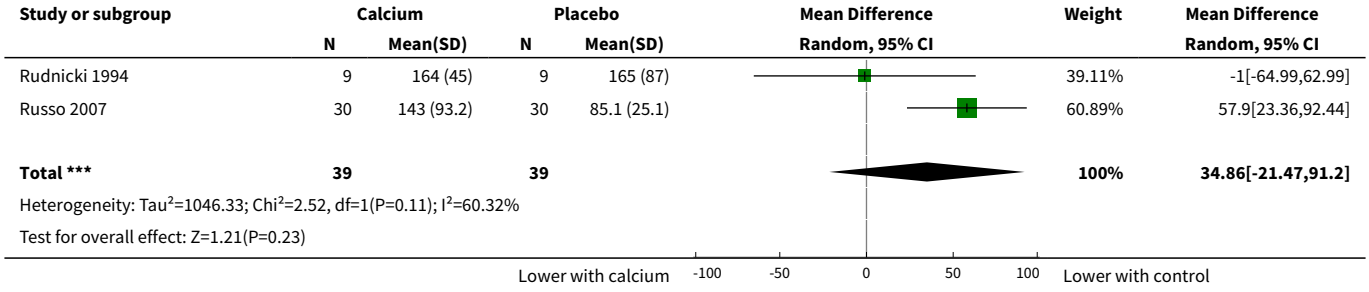
Analysis 4.15. Comparison 4 Calcium versus placebo or usual care, Outcome 15 Serum calcium-by-phosphate product.



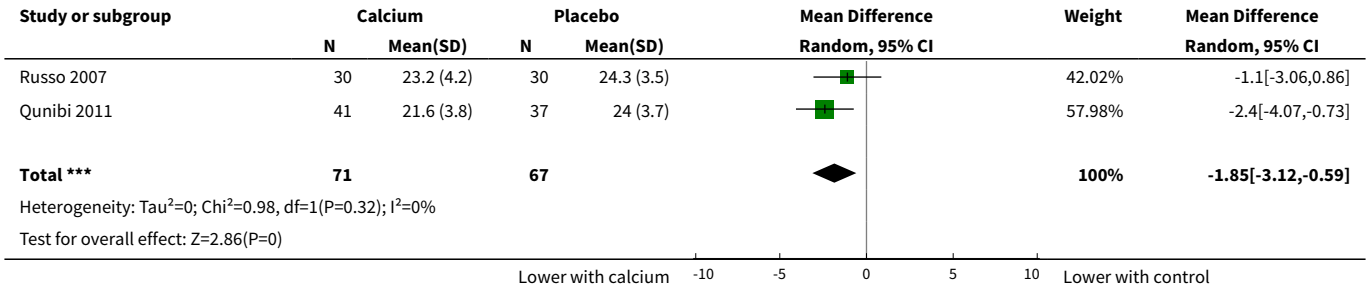
Analysis 4.16. Comparison 4 Calcium versus placebo or usual care, Outcome 16 Serum iPTH.



Analysis 4.17. Comparison 4 Calcium versus placebo or usual care, Outcome 17 Serum alkaline phosphatase.



Analysis 4.18. Comparison 4 Calcium versus placebo or usual care, Outcome 18 Serum bicarbonate.



Analysis 4.19. Comparison 4 Calcium versus placebo or usual care, Outcome 19 eGFR.

Study or subgroup	Calcium N	Calcium Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Russo 2007	30	25.9 (5.3)	30	33.6 (25)		-7.7[-16.84,1.44]

Lower with calcium -50 -25 0 25 50 Lower with control

Comparison 5. Bixalomer versus placebo or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 End-stage kidney disease	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Abdominal pain	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Diarrhoea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Bixalomer versus placebo or usual care, Outcome 1 Death (all causes).

Study or subgroup	Bixalomer n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2016	1/80	0/81		3.04[0.13,73.46]

Less with bixalomer 0.01 0.1 1 10 100 Less with placebo

Analysis 5.2. Comparison 5 Bixalomer versus placebo or usual care, Outcome 2 End-stage kidney disease.

Study or subgroup	Bixalomer n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2016	3/81	8/82		0.38[0.1,1.38]

Less with bixalomer 0.1 0.2 0.5 1 2 5 10 Less with control

Analysis 5.3. Comparison 5 Bixalomer versus placebo or usual care, Outcome 3 Nausea.

Study or subgroup	Bixalomer n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2016	2/80	2/82		1.02[0.15,7.1]

Less with bixalomer 0.1 0.2 0.5 1 2 5 10 Less with control

Analysis 5.4. Comparison 5 Bixalomer versus placebo or usual care, Outcome 4 Abdominal pain.

Study or subgroup	Bixalomer n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2016	2/80	0/82		5.12[0.25,105.08]

Less with bixalomer 0.005 0.1 1 10 200 Less with control

Analysis 5.5. Comparison 5 Bixalomer versus placebo or usual care, Outcome 5 Constipation.

Study or subgroup	Bixalomer n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2016	13/80	8/82		1.67[0.73,3.8]

Less with bixalomer 0.1 0.2 0.5 1 2 5 10 Less with control

Analysis 5.6. Comparison 5 Bixalomer versus placebo or usual care, Outcome 6 Diarrhoea.

Study or subgroup	Bixalomer n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2016	1/80	3/82		0.34[0.04,3.22]

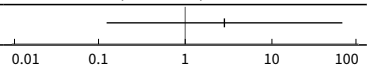
Less with bixalomer 0.01 0.1 1 10 100 Less with control

Comparison 6. Nicotinamide versus placebo or usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Pruritus	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Diarrhoea	2	73	Risk Ratio (IV, Random, 95% CI)	1.61 [0.06, 40.36]
5 Serum phosphate	3	98	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.24, 0.12]
6 Serum calcium	3	98	Mean Difference (IV, Random, 95% CI)	0.07 [-0.30, 0.44]
7 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Serum calcium-by-phosphate product	2	74	Mean Difference (IV, Random, 95% CI)	-7.81 [-13.36, -2.25]

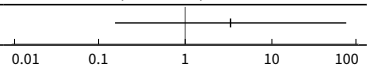
Analysis 6.1. Comparison 6 Nicotinamide versus placebo or usual care, Outcome 1 Death (all causes).

Study or subgroup	Nicotinamide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
SLO-NIACIN 2013	1/17	0/16		2.83[0.12,64.89]



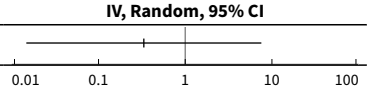
Analysis 6.2. Comparison 6 Nicotinamide versus placebo or usual care, Outcome 2 Pruritus.

Study or subgroup	Nicotinamide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Young 2009a	1/8	0/9		3.33[0.15,71.9]



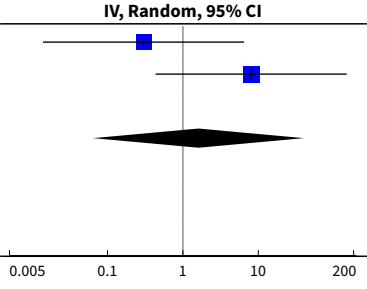
Analysis 6.3. Comparison 6 Nicotinamide versus placebo or usual care, Outcome 3 Constipation.

Study or subgroup	Nicotinamide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Aramwit 2012	0/14	1/14		0.33[0.01,7.55]



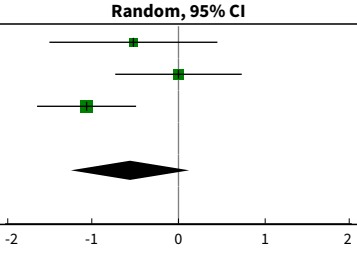
Analysis 6.4. Comparison 6 Nicotinamide versus placebo or usual care, Outcome 4 Diarrhoea.

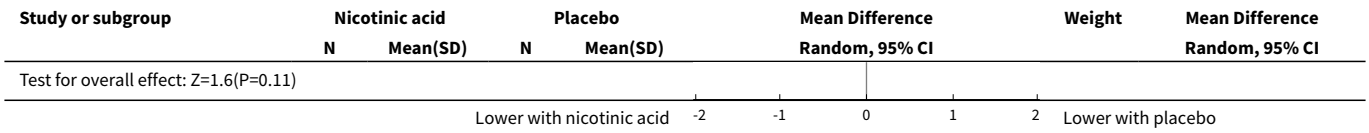
Study or subgroup	Nicotinamide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Young 2009a	0/9	1/8		48.89%	0.3[0.01,6.47]
Allam 2012	3/26	0/30		51.11%	8.04[0.43,148.71]
Total (95% CI)	**35**	**38**		**100%**	**1.61[0.06,40.36]**
Total events: 3 (Nicotinamide), 1 (Control)					
Heterogeneity: Tau^2=3.07; Chi^2=2.31, df=1(P=0.13); I^2=56.79%					
Test for overall effect: Z=0.29(P=0.77)					



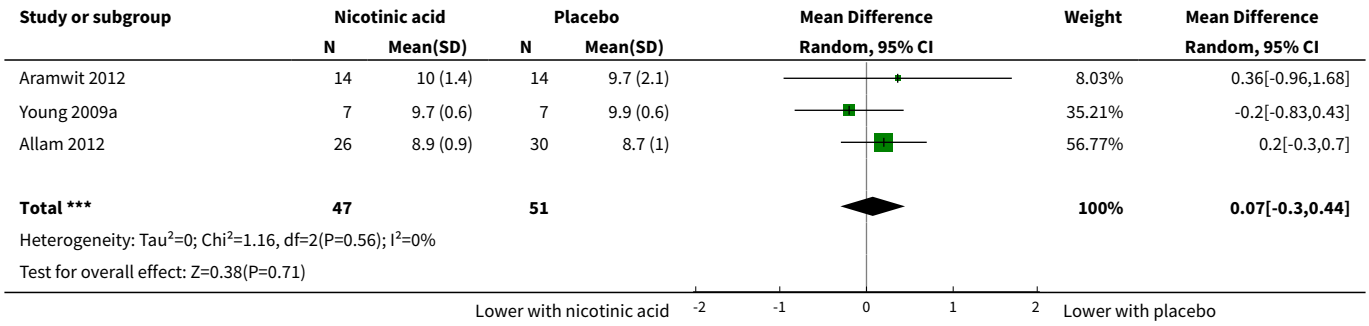
Analysis 6.5. Comparison 6 Nicotinamide versus placebo or usual care, Outcome 5 Serum phosphate.

Study or subgroup	Nicotinic acid N	Nicotinic acid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Aramwit 2012	14	5.7 (1.2)	14	6.2 (1.4)		26.18%	-0.52[-1.49,0.45]
Young 2009a	7	5.2 (0.4)	7	5.2 (0.9)		33.92%	0[-0.73,0.73]
Allam 2012	26	5.5 (1.3)	30	6.5 (0.8)		39.9%	-1.06[-1.63,-0.49]
Total ***	**47**		**51**			**100%**	**-0.56[-1.24,0.12]**
Heterogeneity: Tau^2=0.22; Chi^2=5.09, df=2(P=0.08); I^2=60.72%							

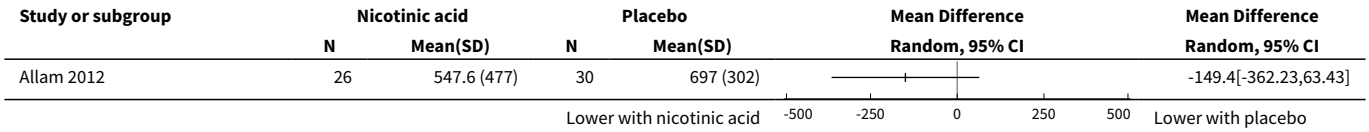




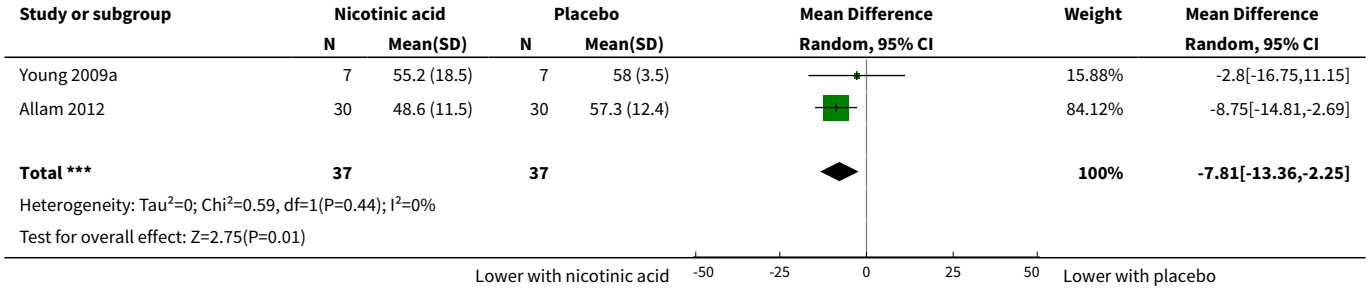
Analysis 6.6. Comparison 6 Nicotinamide versus placebo or usual care, Outcome 6 Serum calcium.



Analysis 6.7. Comparison 6 Nicotinamide versus placebo or usual care, Outcome 7 Serum iPTH.



Analysis 6.8. Comparison 6 Nicotinamide versus placebo or usual care, Outcome 8 Serum calcium-by-phosphate product.



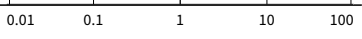
Comparison 7. Colestilan versus placebo or usual care

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Abdominal pain	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Diarrhoea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

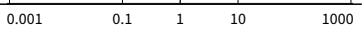
Analysis 7.1. Comparison 7 Colestilan versus placebo or usual care, Outcome 1 Death (all causes).

Study or subgroup	Colestilan n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Locatelli 2013	4/510	2/132		0.52[0.1,2.8]



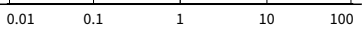
Analysis 7.2. Comparison 7 Colestilan versus placebo or usual care, Outcome 2 Nausea.

Study or subgroup	Colestilan n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Locatelli 2013	0/132	65/507		0.03[0,0.47]



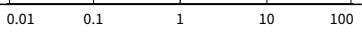
Analysis 7.3. Comparison 7 Colestilan versus placebo or usual care, Outcome 3 Abdominal pain.

Study or subgroup	Colestilan n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Locatelli 2013	2/132	13/507		0.59[0.14,2.59]



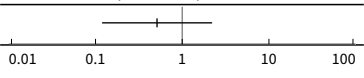
Analysis 7.4. Comparison 7 Colestilan versus placebo or usual care, Outcome 4 Diarrhoea.

Study or subgroup	Colestilan n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Locatelli 2013	7/132	25/507		1.08[0.48,2.43]



Analysis 7.5. Comparison 7 Colestilan versus placebo or usual care, Outcome 5 Constipation.

Study or subgroup	Colestilan n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Locatelli 2013	2/132	15/507		0.51[0.12,2.21]



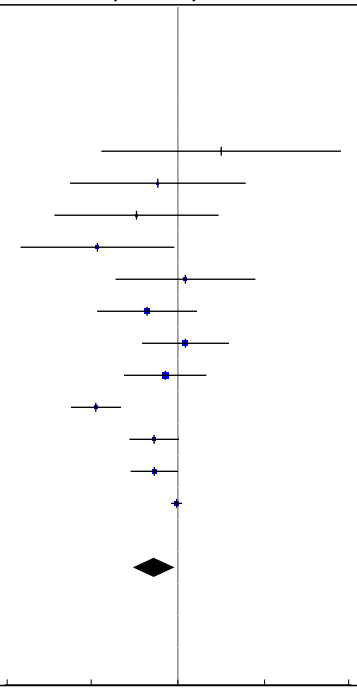
Comparison 8. Sevelamer versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	16	4266	Risk Ratio (IV, Random, 95% CI)	0.53 [0.30, 0.91]
2 Cardiovascular death	6	2904	Risk Ratio (IV, Random, 95% CI)	0.45 [0.11, 1.77]
3 Myocardial infarction	2	177	Risk Ratio (IV, Random, 95% CI)	1.02 [0.11, 9.59]
4 Stroke	2	102	Risk Ratio (IV, Random, 95% CI)	3.0 [0.32, 27.90]
5 Hospitalisation	2	242	Risk Ratio (IV, Random, 95% CI)	0.78 [0.56, 1.08]
6 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Nausea	4	365	Risk Ratio (IV, Random, 95% CI)	0.98 [0.56, 1.71]
8 Vomiting	2	263	Risk Ratio (IV, Random, 95% CI)	0.95 [0.54, 1.69]
9 Abdominal pain	4	363	Risk Ratio (IV, Random, 95% CI)	1.77 [0.68, 4.63]
10 Constipation	6	2652	Risk Ratio (IV, Random, 95% CI)	1.35 [0.71, 2.57]
11 Diarrhoea	3	315	Risk Ratio (IV, Random, 95% CI)	0.98 [0.55, 1.75]
12 Abdominal bloating	2	112	Risk Ratio (IV, Random, 95% CI)	4.85 [0.87, 27.03]
13 Hypercalcaemia	19	4084	Risk Ratio (IV, Random, 95% CI)	0.30 [0.20, 0.43]
14 Calciphylaxis	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
15 Coronary artery calcium score	4	517	Mean Difference (IV, Random, 95% CI)	-24.89 [-75.66, 25.88]
16 Serum phosphate	23	4360	Mean Difference (IV, Random, 95% CI)	0.06 [-0.11, 0.23]
17 Serum calcium	22	4313	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.54, -0.21]
18 Serum calcium-by-phosphate product	13	2983	Mean Difference (IV, Random, 95% CI)	0.36 [-0.57, 1.28]
19 Serum iPTH	16	1420	Mean Difference (IV, Random, 95% CI)	44.24 [10.93, 77.55]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
20 Serum alkaline phosphatase	7	611	Mean Difference (IV, Random, 95% CI)	17.64 [-0.16, 35.43]
21 Serum bicarbonate	7	695	Mean Difference (IV, Random, 95% CI)	-1.57 [-2.15, 1.00]
22 eGFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
23 Serum FGF23	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
24 Soluble Klotho	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

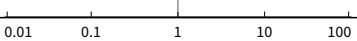
Analysis 8.1. Comparison 8 Sevelamer versus calcium, Outcome 1 Death (all causes).

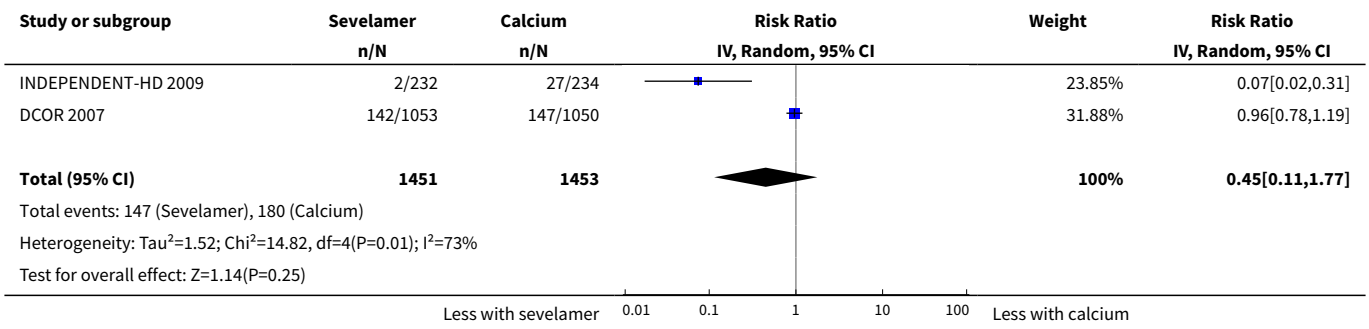
Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Bleyer 1999	0/40	0/40			Not estimable
Ferreira 2008	0/44	0/47			Not estimable
CARE 2004	0/50	0/48			Not estimable
Kakuta 2011	0/91	0/92			Not estimable
Vlassara 2012	1/57	0/60		2.52%	3.16[0.13,75.9]
Lin 2014a	1/23	2/27		4.08%	0.59[0.06,6.06]
Sadek 2003	1/21	3/21		4.5%	0.33[0.04,2.95]
BRiC 2005	1/52	8/49		4.92%	0.12[0.02,0.91]
Hervas 2003	2/18	2/22		5.56%	1.22[0.19,7.84]
CARE-2 2008	3/100	7/103		8.05%	0.44[0.12,1.66]
Chertow 2002	6/99	5/101		9.05%	1.22[0.39,3.88]
Sezer 2010	5/63	7/63		9.43%	0.71[0.24,2.13]
INDEPENDENT-HD 2009	9/232	80/234		12.27%	0.11[0.06,0.22]
INDEPENDENT-CKD 2012	12/121	22/118		12.33%	0.53[0.28,1.03]
Block 2005	11/60	23/67		12.51%	0.53[0.28,1]
DCOR 2007	267/1053	275/1050		14.76%	0.97[0.84,1.12]
Total (95% CI)	**2124**	**2142**		**100%**	**0.53[0.3,0.91]**
Total events: 319 (Sevelamer), 434 (Calcium)					
Heterogeneity: Tau²=0.54; Chi²=48.9, df=11(P<0.0001); I²=77.51%					
Test for overall effect: Z=2.28(P=0.02)					



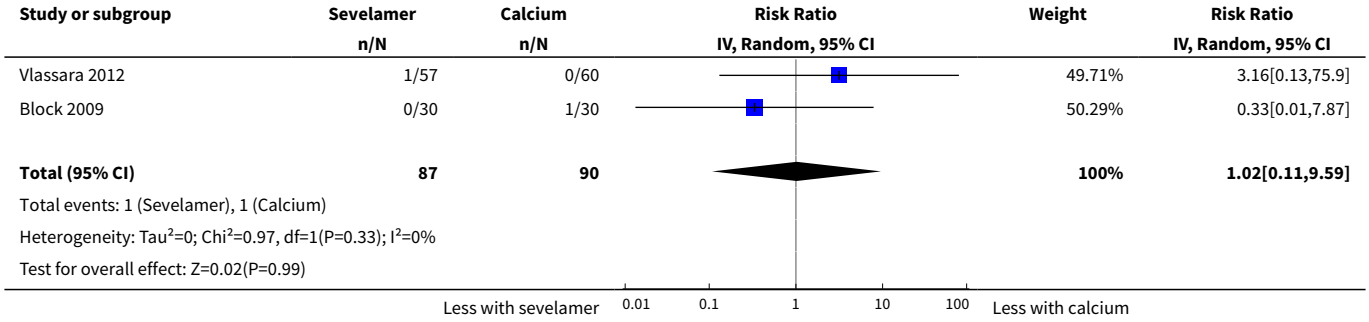
Analysis 8.2. Comparison 8 Sevelamer versus calcium, Outcome 2 Cardiovascular death.

Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lin 2014a	0/36	0/39			Not estimable
Vlassara 2012	1/57	0/60		11.77%	3.16[0.13,75.9]
Sadek 2003	1/21	1/21		14.27%	1[0.07,14.95]
BRiC 2005	1/52	5/49		18.23%	0.19[0.02,1.56]

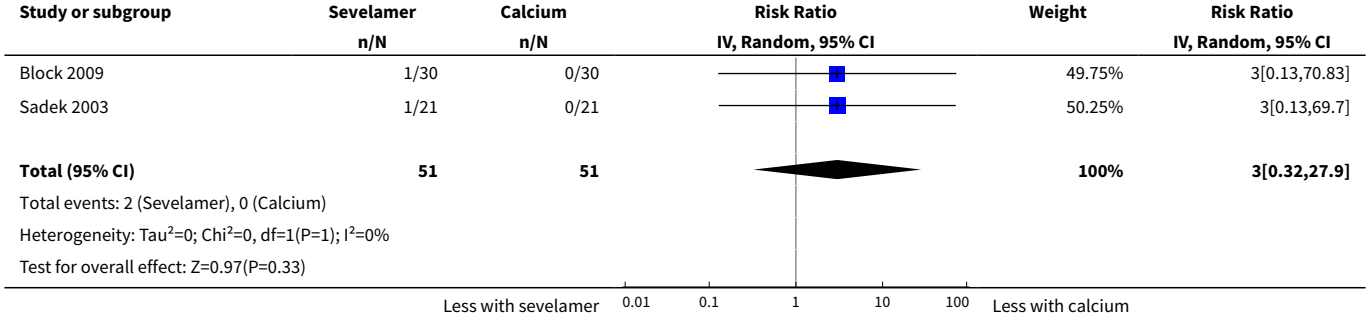




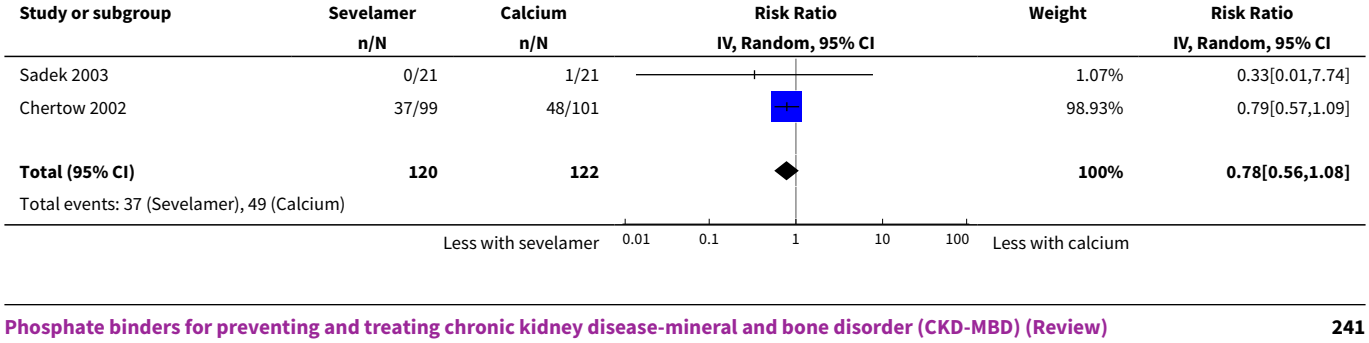
Analysis 8.3. Comparison 8 Sevelamer versus calcium, Outcome 3 Myocardial infarction.



Analysis 8.4. Comparison 8 Sevelamer versus calcium, Outcome 4 Stroke.



Analysis 8.5. Comparison 8 Sevelamer versus calcium, Outcome 5 Hospitalisation.



Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.28, df=1(P=0.59); I²=0%					
Test for overall effect: Z=1.5(P=0.13)					

Analysis 8.6. Comparison 8 Sevelamer versus calcium, Outcome 6 Fracture.

Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	2/30	1/30		2[0.19,20.9]

Analysis 8.7. Comparison 8 Sevelamer versus calcium, Outcome 7 Nausea.

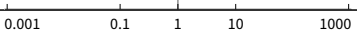
Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lin 2010	0/26	3/26		3.67%	0.14[0.01,2.63]
Caglar 2008	1/25	1/25		4.23%	1[0.07,15.12]
Block 2009	3/30	1/30		6.41%	3[0.33,27.23]
CARE-2 2008	17/100	18/103		85.7%	0.97[0.53,1.78]
Total (95% CI)	**181**	**184**		**100%**	**0.98[0.56,1.71]**
Total events: 21 (Sevelamer), 23 (Calcium)					
Heterogeneity: Tau²=0; Chi²=2.67, df=3(P=0.45); I²=0%					
Test for overall effect: Z=0.09(P=0.93)					

Analysis 8.8. Comparison 8 Sevelamer versus calcium, Outcome 8 Vomiting.

Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Block 2009	1/30	3/30		6.73%	0.33[0.04,3.03]
CARE-2 2008	18/100	18/103		93.27%	1.03[0.57,1.86]
Total (95% CI)	**130**	**133**		**100%**	**0.95[0.54,1.69]**
Total events: 19 (Sevelamer), 21 (Calcium)					
Heterogeneity: Tau²=0; Chi²=0.94, df=1(P=0.33); I²=0%					
Test for overall effect: Z=0.16(P=0.87)					

Analysis 8.9. Comparison 8 Sevelamer versus calcium, Outcome 9 Abdominal pain.

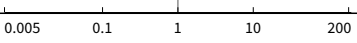
Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Block 2009	0/30	1/30		9.26%	0.33[0.01,7.87]
Lin 2014a	2/23	0/27		10.37%	5.83[0.29,115.65]
Caglar 2008	1/25	1/25		12.55%	1[0.07,15.12]
CARE-2 2008	8/100	4/103		67.82%	2.06[0.64,6.63]
Total (95% CI)	**178**	**185**		**100%**	**1.77[0.68,4.63]**
Total events: 11 (Sevelamer), 6 (Calcium)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=3(P=0.59); I^2=0%					
Test for overall effect: Z=1.16(P=0.24)					



Less with sevelamer — Less with calcium

Analysis 8.10. Comparison 8 Sevelamer versus calcium, Outcome 10 Constipation.

Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
DCOR 2007	1/1053	0/1050		4.05%	2.99[0.12,73.35]
Kakuta 2011	2/91	0/93		4.54%	5.11[0.25,104.97]
Lin 2010	0/26	4/26		5.02%	0.11[0.01,1.96]
Lin 2014a	1/23	2/27		7.57%	0.59[0.06,6.06]
CARE-2 2008	10/100	5/103		36.75%	2.06[0.73,5.81]
Block 2009	7/30	6/30		42.07%	1.17[0.44,3.06]
Total (95% CI)	**1323**	**1329**		**100%**	**1.35[0.71,2.57]**
Total events: 21 (Sevelamer), 17 (Calcium)					
Heterogeneity: Tau^2=0.02; Chi^2=5.1, df=5(P=0.4); I^2=1.94%					
Test for overall effect: Z=0.9(P=0.37)					



Less with sevelamer — Less with calcium

Analysis 8.11. Comparison 8 Sevelamer versus calcium, Outcome 11 Diarrhoea.

Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lin 2010	1/26	1/26		4.59%	1[0.07,15.15]
Block 2009	2/30	3/30		11.52%	0.67[0.12,3.71]
CARE-2 2008	16/100	16/103		83.89%	1.03[0.55,1.95]
Total (95% CI)	**156**	**159**		**100%**	**0.98[0.55,1.75]**
Total events: 19 (Sevelamer), 20 (Calcium)					
Heterogeneity: Tau^2=0; Chi^2=0.22, df=2(P=0.9); I^2=0%					
Test for overall effect: Z=0.07(P=0.94)					

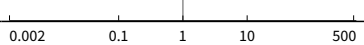
Less with sevelamer — Less with calcium

Analysis 8.12. Comparison 8 Sevelamer versus calcium, Outcome 12 Abdominal bloating.

Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Block 2009	3/30	0/30		34.56%	7[0.38,129.93]
Lin 2010	4/26	1/26		65.44%	4[0.48,33.42]
Total (95% CI)	**56**	**56**		**100%**	**4.85[0.87,27.03]**
Total events: 7 (Sevelamer), 1 (Calcium)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%					
Test for overall effect: Z=1.8(P=0.07)					

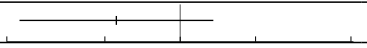
Analysis 8.13. Comparison 8 Sevelamer versus calcium, Outcome 13 Hypercalcaemia.

Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
De Santo 2006	0/8	0/8			Not estimable
DCOR 2007	0/1053	1/1050		1.25%	0.33[0.01,8.15]
Kakuta 2011	0/91	5/92		1.52%	0.09[0.01,1.64]
Caglar 2008	0/47	8/53		1.57%	0.07[0,1.12]
Lin 2010	1/26	3/26		2.42%	0.33[0.04,3]
Sadek 2003	1/15	3/16		2.51%	0.36[0.04,3.05]
Block 2009	1/30	5/30		2.64%	0.2[0.02,1.61]
Gallieni 2005	2/57	4/57		3.77%	0.5[0.1,2.62]
Evenepoel 2009	2/97	8/46		4.32%	0.12[0.03,0.54]
Bleyer 1999	2/40	9/40		4.48%	0.22[0.05,0.96]
Chertow 2002	3/99	5/101		4.76%	0.61[0.15,2.49]
CARE 2004	3/50	8/48		5.44%	0.36[0.1,1.28]
Shaheen 2004	3/20	11/20		6.32%	0.27[0.09,0.83]
Liu 2006	5/37	15/33		7.88%	0.3[0.12,0.73]
INDEPENDENT-CKD 2012	6/107	82/105		8.81%	0.07[0.03,0.16]
Akizawa 2000	7/115	38/115		8.99%	0.18[0.09,0.4]
Block 2005	12/54	30/55		10.92%	0.41[0.23,0.71]
Hervas 2003	9/20	15/20		10.99%	0.6[0.35,1.04]
CARE-2 2008	19/100	31/103		11.42%	0.63[0.38,1.04]
Total (95% CI)	**2066**	**2018**		**100%**	**0.3[0.2,0.43]**
Total events: 76 (Sevelamer), 281 (Calcium)					
Heterogeneity: Tau^2=0.26; Chi^2=33.64, df=17(P=0.01); I^2=49.47%					
Test for overall effect: Z=6.38(P<0.0001)					



Analysis 8.14. Comparison 8 Sevelamer versus calcium, Outcome 14 Calciphylaxis.

Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
DCOR 2007	0/1053	3/1050		0.14[0.01,2.75]

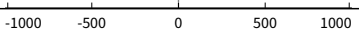


Analysis 8.15. Comparison 8 Sevelamer versus calcium, Outcome 15 Coronary artery calcium score.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
BRiC 2005	41	646 (973)	30	857 (1559)		0.64%	-211[-843.39,421.39]
CARE-2 2008	100	1116 (1569)	103	1297 (1487)		1.46%	-181[-601.75,239.75]
Kakuta 2011	91	961 (1438)	92	1066 (1380)		1.55%	-105[-513.42,303.42]
Russo 2007	30	453 (127)	30	473 (69)		96.35%	-20[-71.72,31.72]
Total ***	**262**		**255**			**100%**	**-24.89[-75.66,25.88]**

Heterogeneity: Tau²=0; Chi²=1.04, df=3(P=0.79); I²=0%

Test for overall effect: Z=0.96(P=0.34)



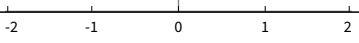
Lower with sevelamer — 1lower with calcium

Analysis 8.16. Comparison 8 Sevelamer versus calcium, Outcome 16 Serum phosphate.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Sadek 2003	15	5.7 (1.1)	16	5.1 (1.6)		2.23%	0.62[-0.33,1.57]
Ferreira 2008	33	5.4 (1.4)	35	5.3 (1.9)		2.79%	0.1[-0.69,0.89]
Hervas 2003	18	5.8 (1)	22	5.9 (1.5)		2.83%	-0.1[-0.88,0.68]
Bleyer 1999	40	6.4 (1.7)	40	5.9 (1.7)		2.98%	0.5[-0.25,1.25]
Lin 2014a	23	6.6 (1.1)	27	7.4 (1.3)		3.36%	-0.8[-1.47,-0.13]
Russo 2007	27	4.8 (0.9)	28	4.7 (1.5)		3.43%	0.1[-0.55,0.75]
CARE 2004	50	6.8 (1.6)	48	5.5 (1.5)		3.62%	1.3[0.69,1.91]
Shaheen 2004	20	5.7 (1.2)	20	4.9 (0.7)		3.65%	0.8[0.19,1.41]
CARE-2 2008	70	5.4 (1.8)	59	5 (1.6)		3.77%	0.4[-0.19,0.99]
Evenepoel 2009	95	5.9 (1.3)	44	5.8 (1.6)		4.05%	0.14[-0.4,0.68]
Zhao 2014	30	5.9 (1.1)	30	6 (1.1)		4.09%	-0.13[-0.66,0.4]
CALMAG 2010	99	5.5 (1.9)	105	5.3 (1.5)		4.47%	0.2[-0.27,0.67]
Sezer 2010	63	6.1 (1.6)	63	5.7 (1)		4.48%	0.4[-0.07,0.87]
Navarro-Gonzalez 2011	30	4.9 (1)	29	4.7 (0.7)		4.65%	0.2[-0.24,0.64]
BRiC 2005	41	5.3 (0.9)	30	5.8 (0.9)		4.69%	-0.49[-0.92,-0.06]
Gallieni 2005	57	5.3 (1.2)	57	4.8 (1)		4.82%	0.43[0.02,0.84]
Chertow 2002	99	5.1 (1.2)	101	5.1 (1.4)		5.14%	0[-0.36,0.36]
Block 2005	54	5.2 (0.9)	55	5.1 (0.8)		5.4%	0.1[-0.22,0.42]
INDEPENDENT-CKD 2012	107	4.2 (1.3)	105	4.7 (1)		5.47%	-0.56[-0.87,-0.25]
Kakuta 2011	91	5.2 (0.8)	92	5.1 (0.9)		5.78%	0.01[-0.25,0.27]
Ahmed 2014	70	5 (0.7)	70	5.2 (0.8)		5.86%	-0.27[-0.51,-0.03]
INDEPENDENT-HD 2009	232	4.2 (1.2)	234	4.8 (1.1)		6.04%	-0.6[-0.81,-0.39]
DCOR 2007	843	5.8 (1.3)	843	5.7 (1.3)		6.4%	0.1[-0.02,0.22]
Total ***	**2207**		**2153**			**100%**	**0.06[-0.11,0.23]**

Heterogeneity: Tau²=0.12; Chi²=99.87, df=22(P<0.0001); I²=77.97%

Test for overall effect: Z=0.68(P=0.49)



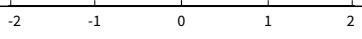
Lower with sevelamer — Lower with calcium

Analysis 8.17. Comparison 8 Sevelamer versus calcium, Outcome 17 Serum calcium.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Shaheen 2004	20	9.3 (0.8)	20	10 (1.4)		2.67%	-0.7[-1.41,0.01]
Hervas 2003	18	10.2 (0.8)	22	10.2 (0.9)		3.48%	0.04[-0.48,0.56]
Lin 2014a	23	9.6 (0.8)	27	10.2 (0.9)		3.73%	-0.56[-1.03,-0.09]
Ferreira 2008	33	9.1 (1.1)	35	9.3 (0.7)		3.85%	-0.2[-0.64,0.24]
Gallieni 2005	57	9.4 (0.9)	57	9.6 (1.2)		4.11%	-0.2[-0.59,0.19]
Russo 2007	27	9 (0.3)	28	9.1 (0.8)		4.46%	-0.1[-0.42,0.22]
Evenepoel 2009	95	9.6 (0.6)	44	10 (1)		4.47%	-0.41[-0.72,-0.1]
Bleyer 1999	40	9.3 (0.6)	40	9.7 (0.8)		4.49%	-0.4[-0.71,-0.09]
Sadek 2003	15	9.6 (0.4)	16	9.6 (0.4)		4.62%	0.04[-0.24,0.32]
Navarro-Gonzalez 2011	30	9.1 (0.5)	29	9.3 (0.5)		4.74%	-0.2[-0.46,0.06]
Sezer 2010	63	1.3 (1)	63	1.3 (0.1)		4.77%	0[-0.25,0.25]
CARE-2 2008	70	9 (0.7)	59	9.4 (0.7)		4.79%	-0.4[-0.64,-0.16]
CARE 2004	50	8.9 (0.5)	48	9.5 (0.7)		4.79%	-0.6[-0.84,-0.36]
Ahmed 2014	70	8.4 (0.8)	70	8.6 (0.7)		4.83%	-0.24[-0.47,-0.01]
INDEPENDENT-CKD 2012	107	8.5 (0.7)	105	9.6 (1)		4.83%	-1.1[-1.33,-0.87]
Zhao 2014	30	9 (0.4)	30	9.3 (0.4)		4.91%	-0.32[-0.53,-0.11]
Kakuta 2011	91	9.6 (0.6)	92	9.9 (0.8)		4.95%	-0.24[-0.44,-0.04]
Chertow 2002	99	9.4 (0.7)	101	9.7 (0.7)		4.98%	-0.3[-0.49,-0.11]
Block 2005	54	9.1 (0.5)	55	9.6 (0.5)		5%	-0.5[-0.69,-0.31]
CALMAG 2010	122	8.8 (0.6)	122	8.9 (0.6)		5.1%	-0.12[-0.28,0.04]
INDEPENDENT-HD 2009	232	8.2 (0.5)	234	9.6 (1.1)		5.11%	-1.4[-1.55,-1.25]
DCOR 2007	835	9.2 (0.7)	835	9.5 (0.7)		5.31%	-0.3[-0.37,-0.23]
Total ***	**2181**		**2132**			**100%**	**-0.38[-0.54,-0.21]**

Heterogeneity: Tau^2=0.13; Chi^2=255.57, df=21(P<0.0001); I^2=91.78%

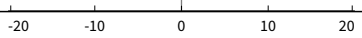
Test for overall effect: Z=4.52(P<0.0001)



Analysis 8.18. Comparison 8 Sevelamer versus calcium, Outcome 18 Serum calcium-by-phosphate product.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hervas 2003	20	58.7 (17.1)	20	59.2 (18.4)		0.7%	-0.5[-11.51,10.51]
Shaheen 2004	20	50.8 (16)	20	45 (14.6)		0.93%	5.8[-3.69,15.29]
Bleyer 1999	40	60 (16.1)	40	57.1 (16.2)		1.65%	2.9[-4.18,9.98]
Evenepoel 2009	95	56.1 (16.5)	44	57.3 (15.4)		2.54%	-1.2[-6.83,4.43]
CARE 2004	50	60.4 (14.1)	48	52.7 (14.2)		2.56%	7.7[2.1,13.3]
Russo 2007	27	43.1 (8.4)	28	40.3 (11.8)		2.75%	2.8[-2.6,8.2]
CARE-2 2008	70	48 (15.4)	59	46 (14.7)		2.94%	2[-3.2,7.2]
Gallieni 2005	57	49.6 (11.1)	57	46.8 (9.3)		5.29%	2.8[-0.96,6.56]
Chertow 2002	99	48 (12)	101	49 (14)		5.67%	-1[-4.61,2.61]
Block 2005	54	47 (7)	55	49 (8)		8.53%	-2[-4.82,0.82]
Kakuta 2011	91	49.5 (8.7)	92	50.6 (9.8)		9.21%	-1.06[-3.75,1.63]
DCOR 2007	835	53.7 (12.1)	835	53.7 (12.9)		24.1%	0[-1.2,1.2]
Sezer 2010	63	7.8 (2.5)	63	7.4 (1.2)		33.14%	0.4[-0.28,1.08]
Total ***	**1521**		**1462**			**100%**	**0.36[-0.57,1.28]**

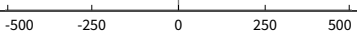
Heterogeneity: Tau^2=0.55; Chi^2=16.09, df=12(P=0.19); I^2=25.4%



Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.75(P=0.45)							

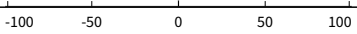
Analysis 8.19. Comparison 8 Sevelamer versus calcium, Outcome 19 Serum iPTH.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lin 2014a	23	329.6 (319.8)	27	165.2 (405.6)		2.17%	164.4[-36.82,365.62]
Bleyer 1999	40	381.9 (417)	40	329.7 (408.3)		2.56%	52.2[-128.66,233.06]
Hervas 2003	18	330 (205)	22	346 (250)		3.63%	-16[-157,125]
BRiC 2005	41	498 (352)	30	326 (236)		3.77%	172[35.1,308.9]
Sadek 2003	15	239 (168)	16	199 (198)		4.06%	40[-89,169]
CARE-2 2008	70	434 (359)	59	316 (212)		5.37%	118[18,218]
Sezer 2010	63	385.5 (298.4)	63	321.5 (199.7)		5.99%	64[-24.66,152.66]
Ahmed 2014	70	543.4 (269.1)	70	388.1 (157.5)		6.94%	155.21[82.18,228.24]
CALMAG 2010	112	385 (226)	118	337 (266)		7.54%	48[-15.68,111.68]
Shaheen 2004	20	97 (114)	20	91 (87)		7.6%	6[-56.85,68.85]
Kakuta 2011	91	233.9 (196.4)	92	237.5 (231.8)		7.64%	-3.6[-65.82,58.62]
Navarro-Gonzalez 2011	30	196 (94)	30	217 (136)		7.84%	-21[-80.16,38.16]
Block 2005	54	298 (152)	55	243 (136)		8.16%	55[0.82,109.18]
De Santo 2006	8	210 (41)	8	118 (56)		8.55%	92[43.91,140.09]
Zhao 2014	30	368.8 (94.7)	30	366.4 (80.1)		8.79%	2.41[-41.96,46.78]
Russo 2007	27	134.9 (72.7)	28	176.1 (54.8)		9.39%	-41.2[-75.32,-7.08]
Total * **	**712**		**708**			**100%**	**44.24[10.93,77.55]**
Heterogeneity: Tau^2=2774.1; Chi^2=51.09, df=15(P<0.0001); I^2=70.64%							
Test for overall effect: Z=2.6(P=0.01)							



Analysis 8.20. Comparison 8 Sevelamer versus calcium, Outcome 20 Serum alkaline phosphatase.

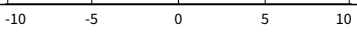
Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hervas 2003	20	243 (65)	20	226 (120)		6.5%	17[-42.81,76.81]
BRiC 2005	17	195 (81)	14	198 (78)		7.13%	-3[-59.14,53.14]
Russo 2007	30	103.4 (47.6)	30	143 (93.2)		11.75%	-39.6[-77.05,-2.15]
Bleyer 1999	40	114 (73)	40	96 (50)		15.49%	18[-9.42,45.42]
Lin 2014a	23	112.4 (43.2)	27	64.4 (23.1)		18.84%	48.02[28.32,67.72]
CARE-2 2008	70	124 (71.6)	59	95.1 (36.2)		19.08%	28.9[9.75,48.05]
CALMAG 2010	105	125.9 (53.5)	116	106.8 (53.8)		21.21%	19.09[4.93,33.25]
Total * **	**305**		**306**			**100%**	**17.64[-0.16,35.43]**
Heterogeneity: Tau^2=336.58; Chi^2=18.58, df=6(P=0); I^2=67.71%							



Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=1.94(P=0.05)							

Analysis 8.21. Comparison 8 Sevelamer versus calcium, Outcome 21 Serum bicarbonate.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Russo 2007	27	21.2 (2.3)	28	23.2 (4.2)		8.9%	-2[-3.78,-0.22]
Ferreira 2008	33	20.4 (3.3)	35	21.2 (4.1)		9.05%	-0.8[-2.56,0.96]
Sadek 2003	15	22.2 (1.9)	16	23 (2.6)		10.7%	-0.8[-2.4,0.8]
CARE-2 2008	70	21.6 (4.3)	59	23.1 (3.9)		12.98%	-1.5[-2.92,-0.08]
Chertow 2002	99	19.2 (4.3)	101	22.1 (4.4)		16.57%	-2.9[-4.11,-1.69]
CARE 2004	50	19.3 (2.7)	48	21 (2.6)		20.12%	-1.7[-2.75,-0.65]
Gallieni 2005	57	20.8 (2.6)	57	21.8 (2.8)		21.67%	-1[-1.99,-0.01]
Total ***	**351**		**344**			**100%**	**-1.57[-2.15,-1]**
Heterogeneity: Tau^2=0.14; Chi^2=7.86, df=6(P=0.25); I^2=23.67%							
Test for overall effect: Z=5.35(P<0.0001)							



Analysis 8.22. Comparison 8 Sevelamer versus calcium, Outcome 22 eGFR.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Russo 2007	27	24.1 (14.7)	28	25.9 (5.3)		-1.8[-7.68,4.08]

Analysis 8.23. Comparison 8 Sevelamer versus calcium, Outcome 23 Serum FGF23.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Lin 2014a	23	795.6 (1098.4)	27	1449.2 (3507.1)		-653.63[-2050.59,743.33]

Analysis 8.24. Comparison 8 Sevelamer versus calcium, Outcome 24 Soluble Klotho.

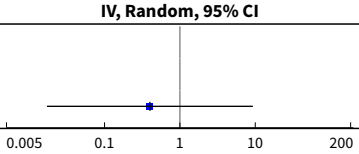
Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Lin 2014a	23	252.9 (517.8)	27	188.6 (252.4)		64.37[-167.67,296.41]

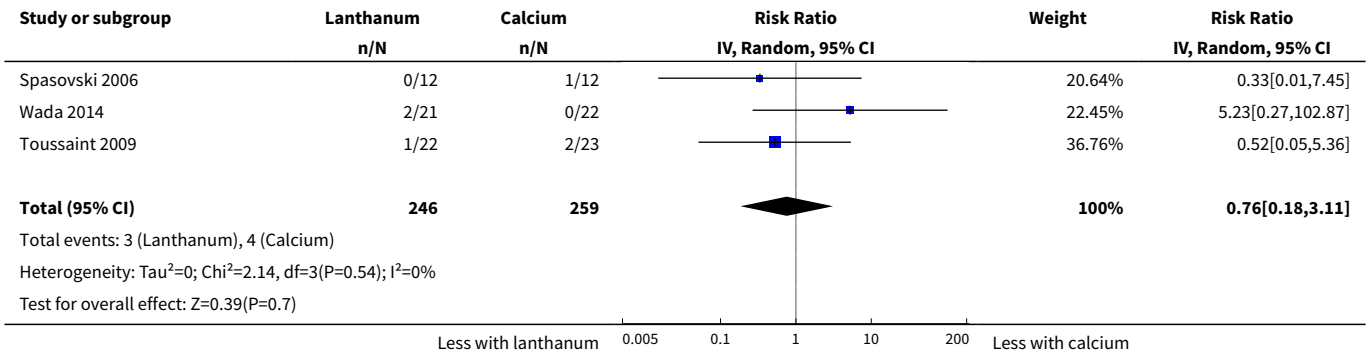
Comparison 9. Lanthanum versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	6	505	Risk Ratio (IV, Random, 95% CI)	0.76 [0.18, 3.11]
2 Hospitalisation	2	88	Risk Ratio (IV, Random, 95% CI)	0.80 [0.34, 1.93]
3 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Pruritus	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Nausea	5	1191	Risk Ratio (IV, Random, 95% CI)	1.65 [0.95, 2.89]
6 Vomiting	2	1058	Risk Ratio (IV, Random, 95% CI)	3.88 [0.48, 31.74]
7 Abdominal pain	2	137	Risk Ratio (IV, Random, 95% CI)	0.24 [0.03, 1.94]
8 Constipation	5	1213	Risk Ratio (IV, Random, 95% CI)	0.79 [0.50, 1.26]
9 Diarrhoea	2	858	Risk Ratio (IV, Random, 95% CI)	2.44 [0.34, 17.35]
10 Abdominal bloating	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
11 Coronary artery calcium score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Hypercalcaemia	8	1347	Risk Ratio (IV, Random, 95% CI)	0.16 [0.06, 0.43]
13 Serum phosphate	9	400	Mean Difference (IV, Random, 95% CI)	0.01 [-0.42, 0.43]
14 Serum calcium	8	350	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.59, 0.02]
15 Serum calcium-by-phosphate product	5	1007	Mean Difference (IV, Random, 95% CI)	-2.67 [-5.01, -0.34]
16 Serum iPTH	8	597	Mean Difference (IV, Random, 95% CI)	33.78 [-9.03, 76.60]
17 Serum alkaline phosphatase	3	856	Mean Difference (IV, Random, 95% CI)	20.03 [-3.69, 43.75]
18 eGFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
19 Serum FGF23	2	116	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-2.33, 0.63]

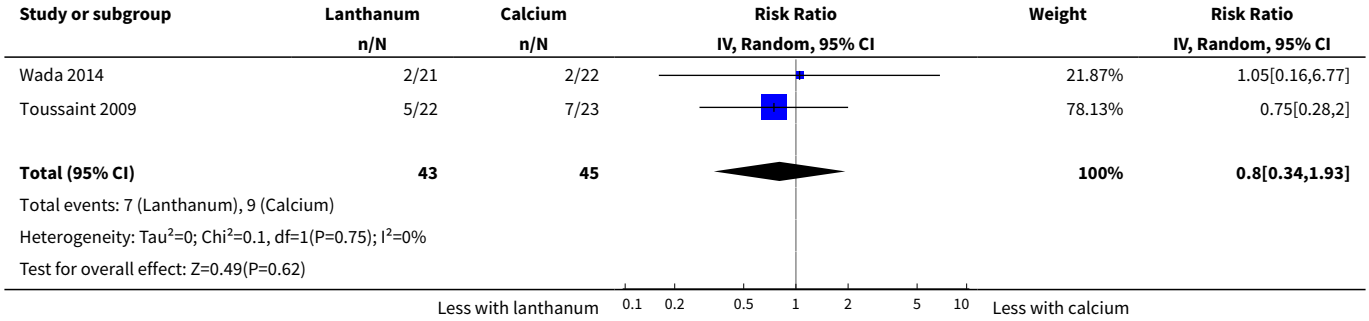
Analysis 9.1. Comparison 9 Lanthanum versus calcium, Outcome 1 Death (all causes).

Study or subgroup	Lanthanum n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Shigematsu 2008	0/123	0/130			Not estimable
D'Haese 2003	0/49	0/49			Not estimable
Ohtake 2013	0/19	1/23		20.15%	0.4[0.02,9.29]

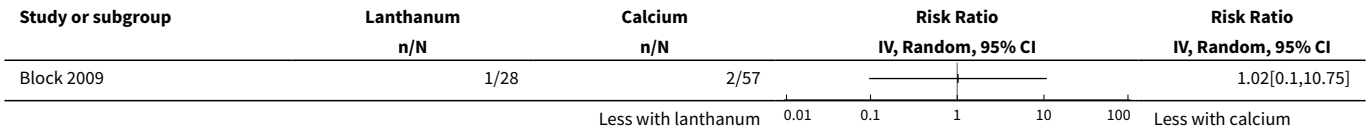




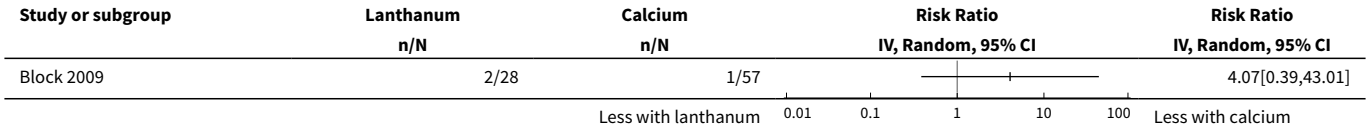
Analysis 9.2. Comparison 9 Lanthanum versus calcium, Outcome 2 Hospitalisation.



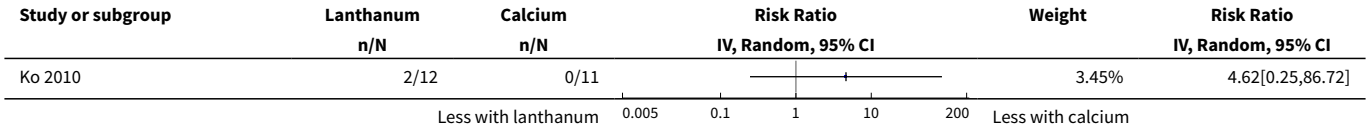
Analysis 9.3. Comparison 9 Lanthanum versus calcium, Outcome 3 Fracture.

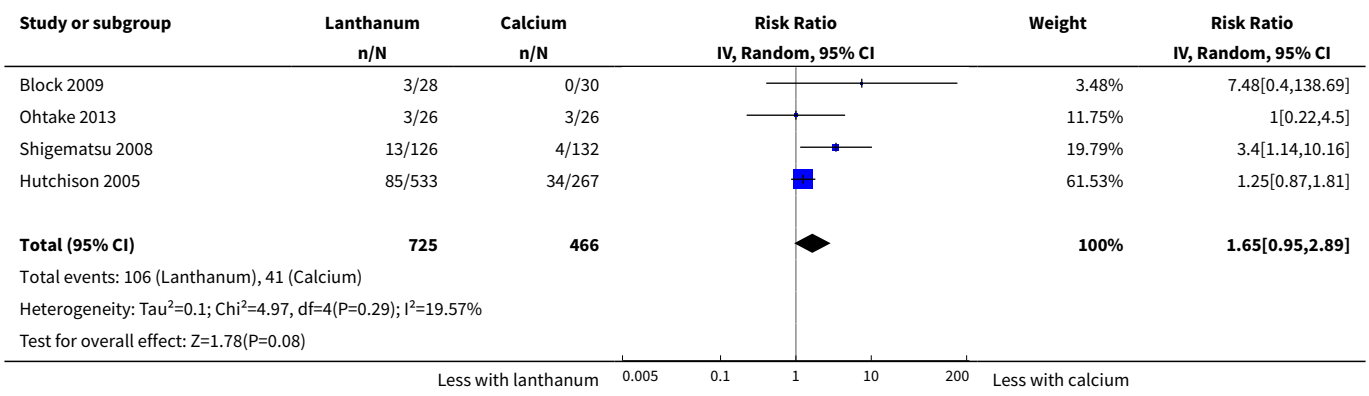


Analysis 9.4. Comparison 9 Lanthanum versus calcium, Outcome 4 Pruritus.

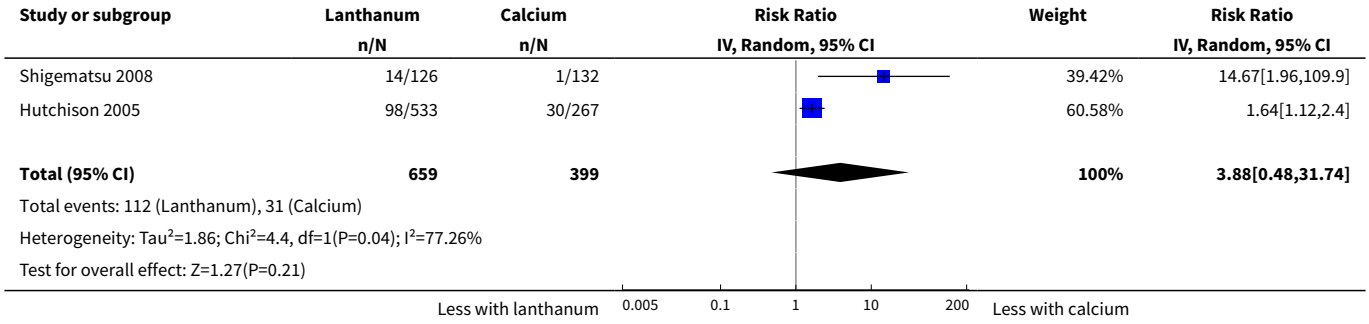


Analysis 9.5. Comparison 9 Lanthanum versus calcium, Outcome 5 Nausea.

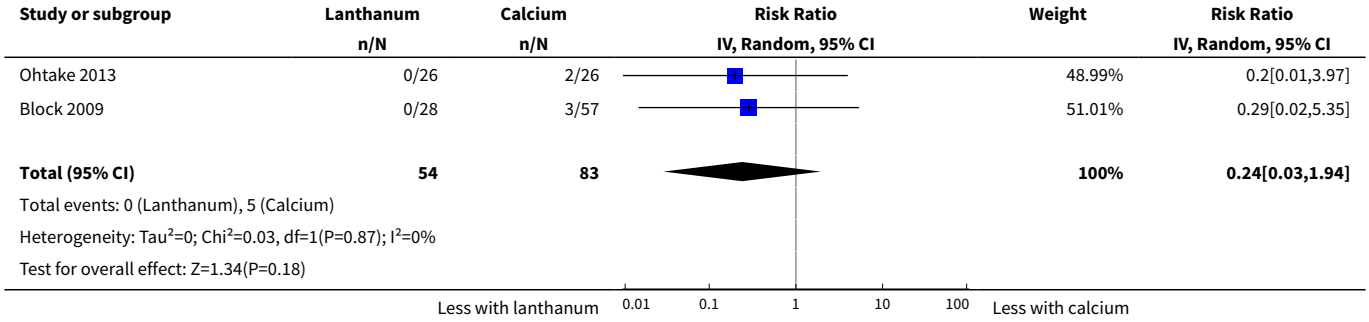




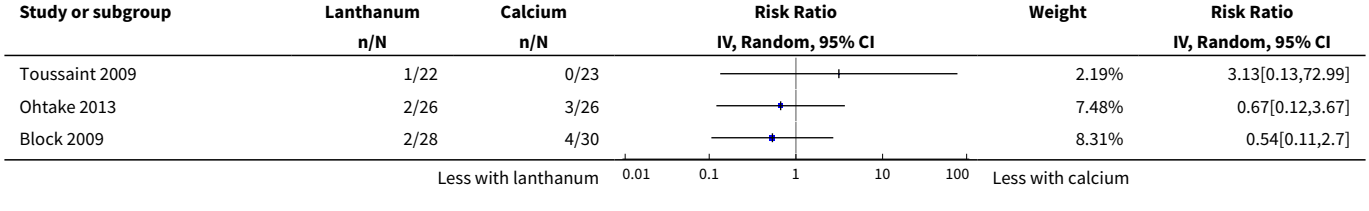
Analysis 9.6. Comparison 9 Lanthanum versus calcium, Outcome 6 Vomiting.

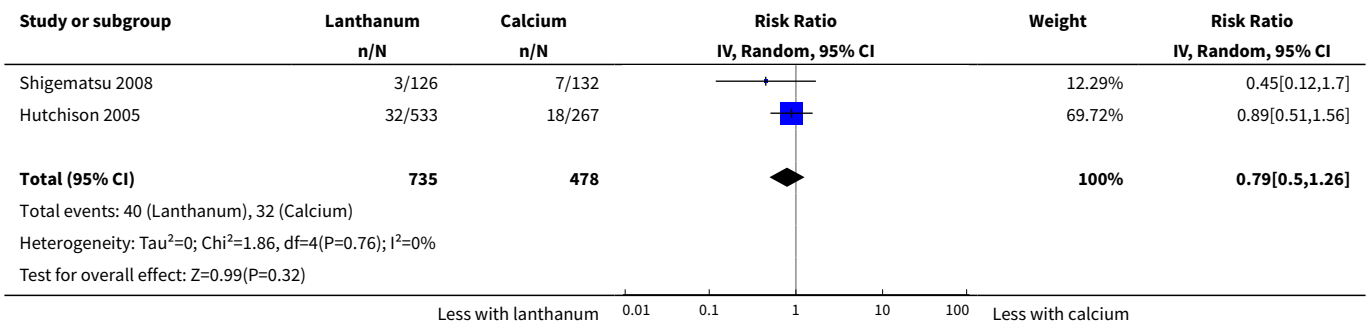


Analysis 9.7. Comparison 9 Lanthanum versus calcium, Outcome 7 Abdominal pain.

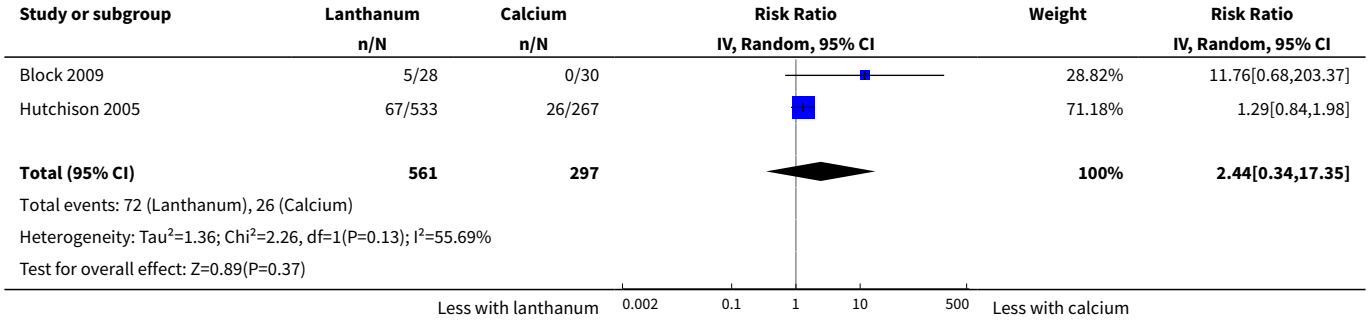


Analysis 9.8. Comparison 9 Lanthanum versus calcium, Outcome 8 Constipation.

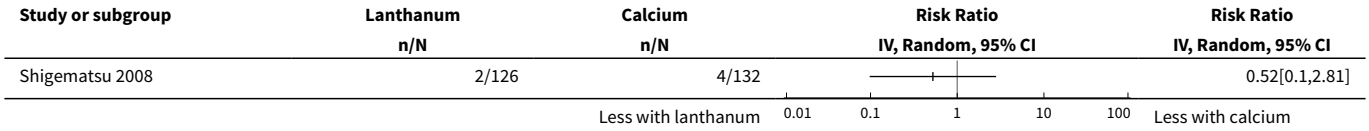




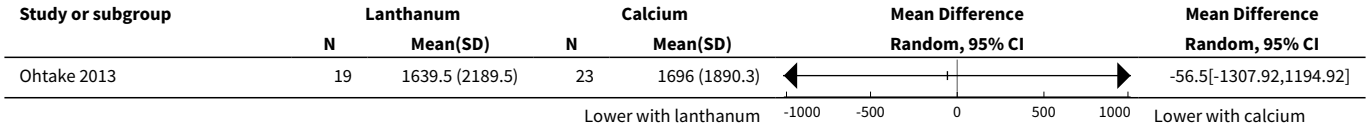
Analysis 9.9. Comparison 9 Lanthanum versus calcium, Outcome 9 Diarrhoea.



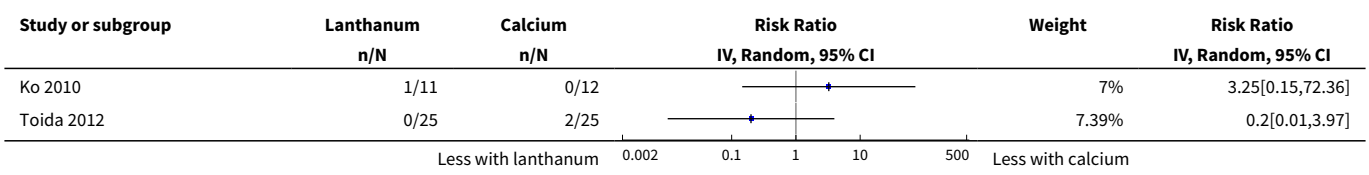
Analysis 9.10. Comparison 9 Lanthanum versus calcium, Outcome 10 Abdominal bloating.

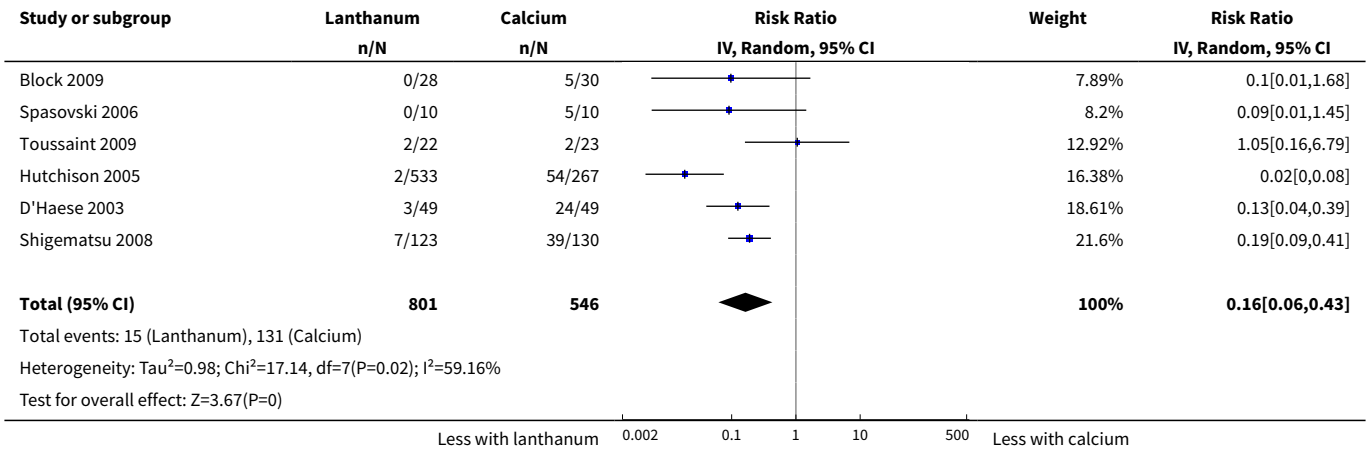


Analysis 9.11. Comparison 9 Lanthanum versus calcium, Outcome 11 Coronary artery calcium score.

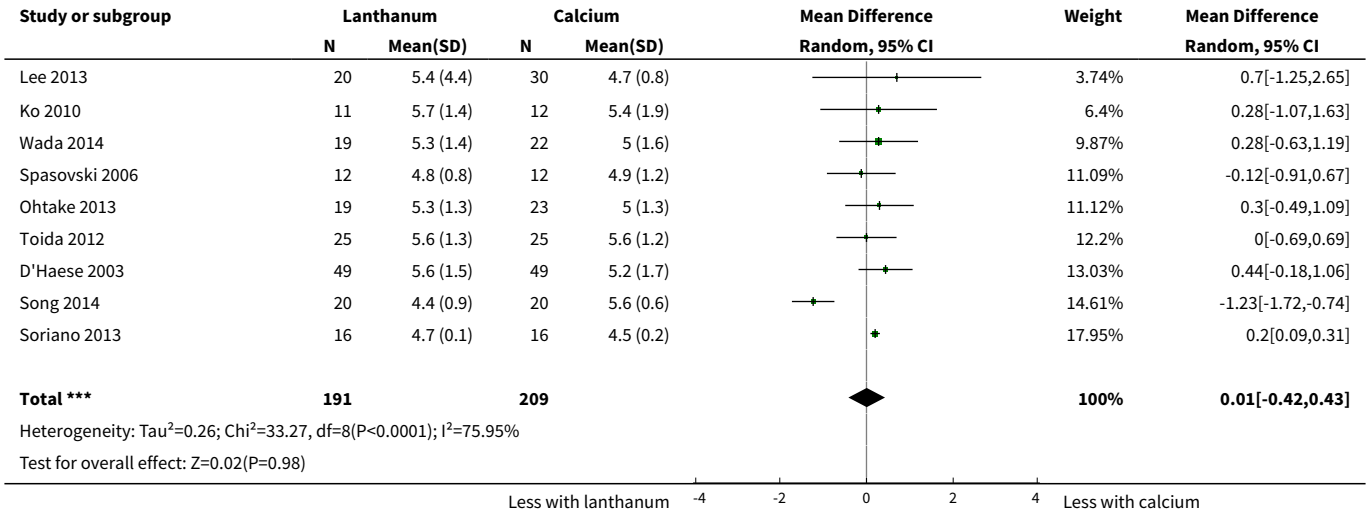


Analysis 9.12. Comparison 9 Lanthanum versus calcium, Outcome 12 Hypercalcaemia.

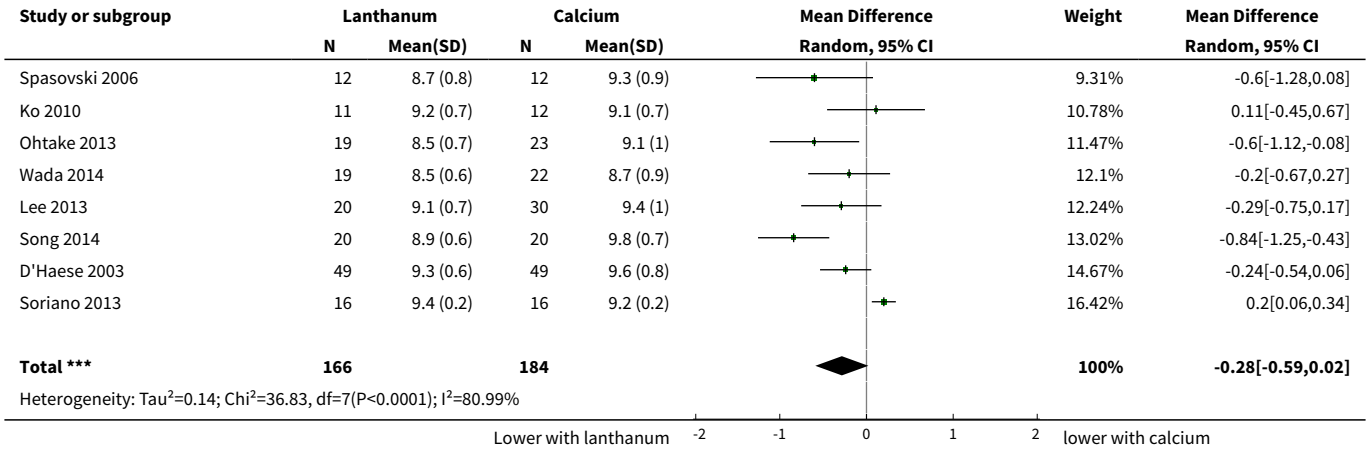


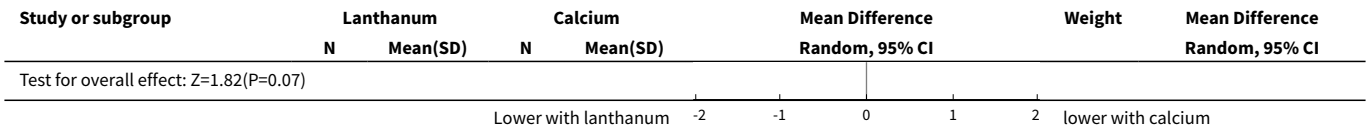


Analysis 9.13. Comparison 9 Lanthanum versus calcium, Outcome 13 Serum phosphate.

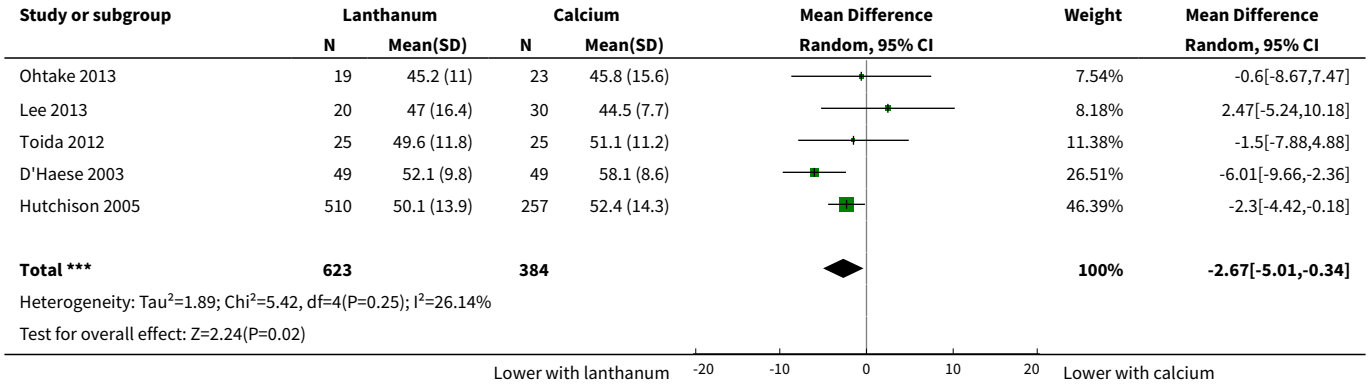


Analysis 9.14. Comparison 9 Lanthanum versus calcium, Outcome 14 Serum calcium.

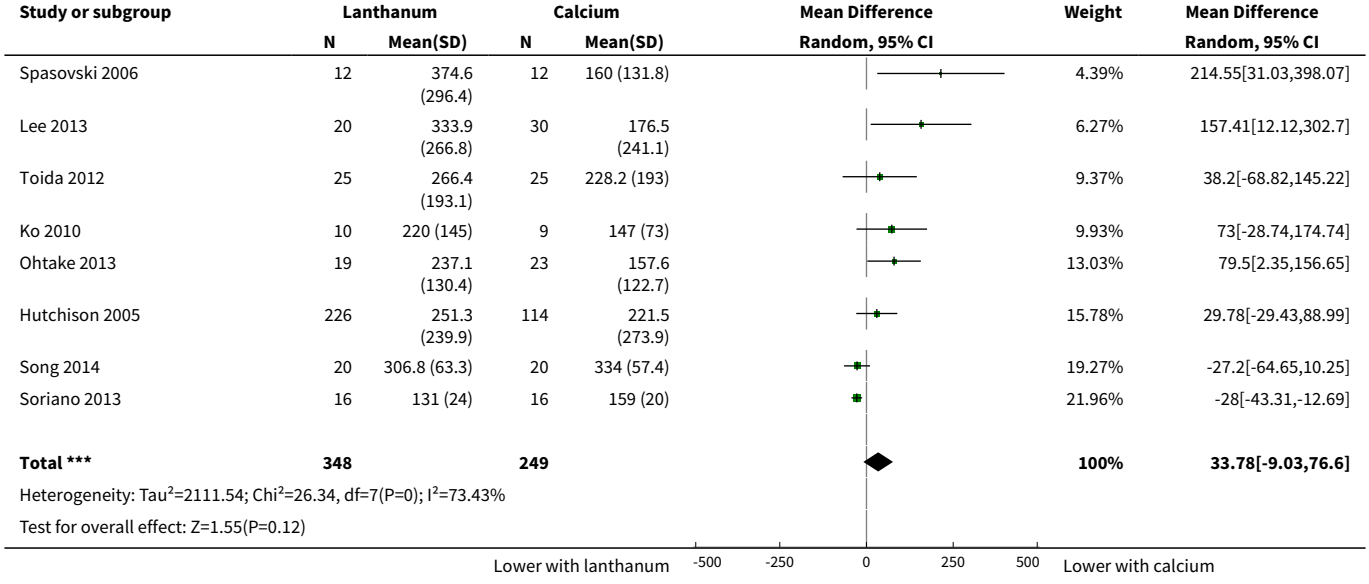




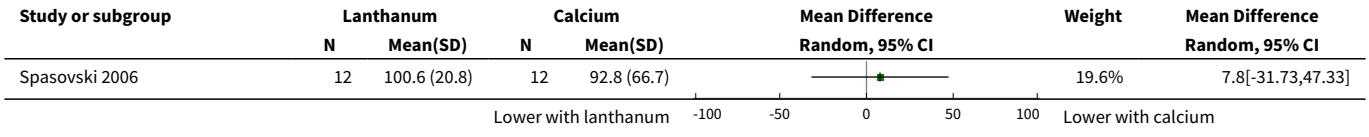
Analysis 9.15. Comparison 9 Lanthanum versus calcium, Outcome 15 Serum calcium-by-phosphate product.

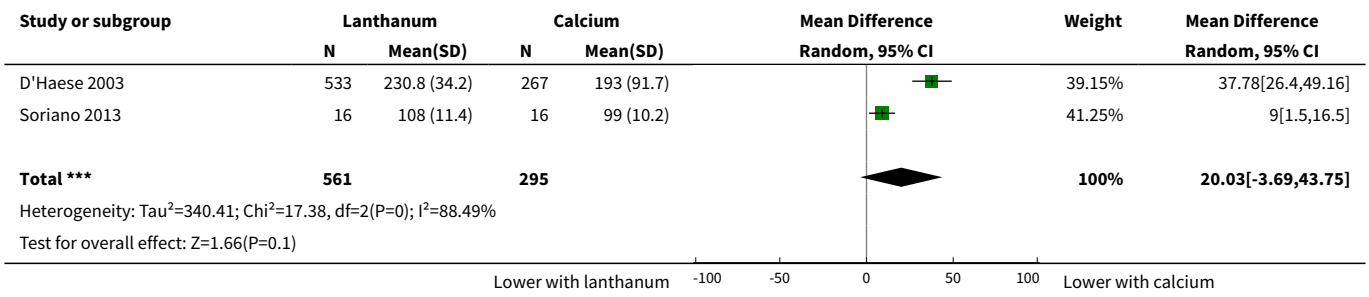


Analysis 9.16. Comparison 9 Lanthanum versus calcium, Outcome 16 Serum iPTH.

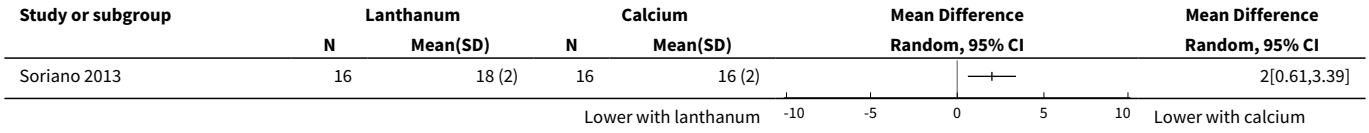


Analysis 9.17. Comparison 9 Lanthanum versus calcium, Outcome 17 Serum alkaline phosphatase.

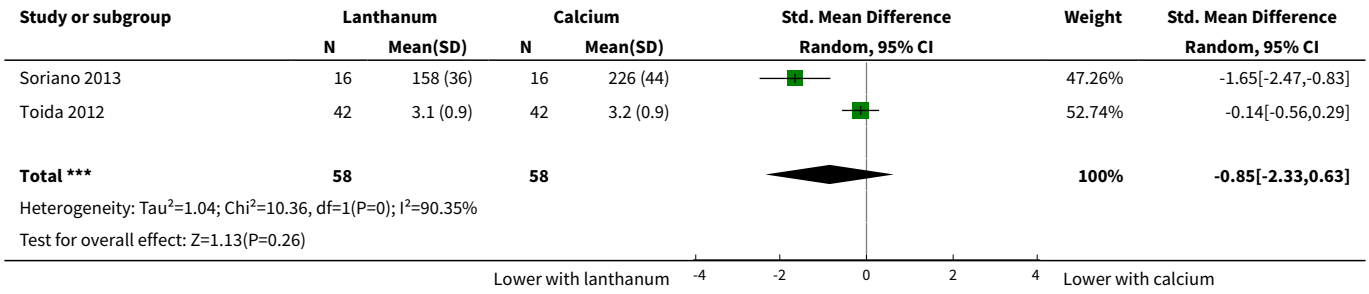




Analysis 9.18. Comparison 9 Lanthanum versus calcium, Outcome 18 eGFR.



Analysis 9.19. Comparison 9 Lanthanum versus calcium, Outcome 19 Serum FGF23.



Comparison 10. Magnesium versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospitalisation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Diarrhoea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10 Magnesium versus calcium, Outcome 1 Hospitalisation.

Study or subgroup	Magnesium n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Spiegel 2007	0/20	1/10		0.17[0.01,3.94]

Less with magnesium — 0.005 — 0.1 — 1 — 10 — 200 — Less with control

Analysis 10.2. Comparison 10 Magnesium versus calcium, Outcome 2 Constipation.

Study or subgroup	Magnesium n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Spiegel 2007	0/20	1/10		0.17[0.01,3.94]

Less with magnesium — 0.005 — 0.1 — 1 — 10 — 200 — Less with control

Analysis 10.3. Comparison 10 Magnesium versus calcium, Outcome 3 Diarrhoea.

Study or subgroup	Magnesium n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Spiegel 2007	3/20	0/10		3.67[0.21,64.8]

Less with magnesium — 0.01 — 0.1 — 1 — 10 — 100 — Less with control

Comparison 11. Aluminium versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum alkaline phosphatase	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 11.1. Comparison 11 Aluminium versus calcium, Outcome 1 Serum alkaline phosphatase.

Study or subgroup	Aluminium N	Aluminium Mean(SD)	Calcium N	Calcium Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Janssen 1996	10	131 (50)	14	82 (11)		49[17.48,80.52]

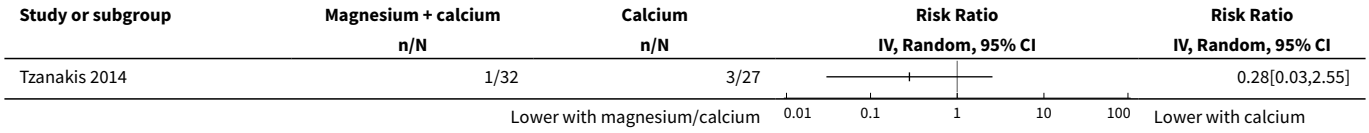
Lower with aluminium — -100 — -50 — 0 — 50 — 100 — Lower with calcium

Comparison 12. Magnesium plus calcium versus calcium

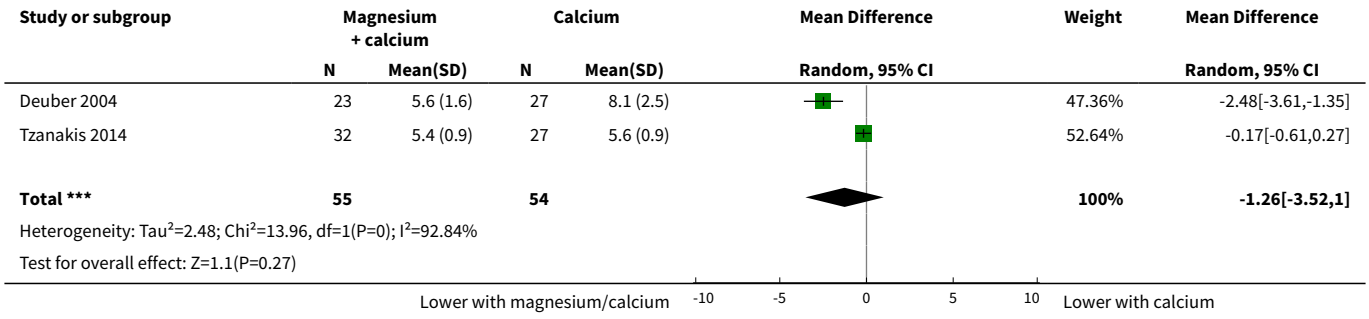
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Serum phosphate	2	109	Mean Difference (IV, Random, 95% CI)	-1.26 [-3.52, 1.00]
3 Serum calcium	2	109	Mean Difference (IV, Random, 95% CI)	-0.92 [-2.39, 0.55]
4 Serum calcium-by-phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

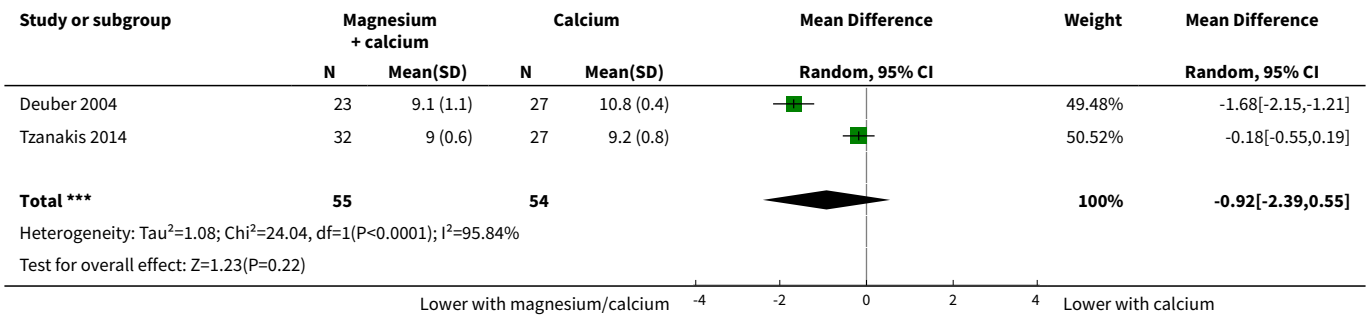
Analysis 12.1. Comparison 12 Magnesium plus calcium versus calcium, Outcome 1 Death (all causes).



Analysis 12.2. Comparison 12 Magnesium plus calcium versus calcium, Outcome 2 Serum phosphate.

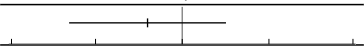


Analysis 12.3. Comparison 12 Magnesium plus calcium versus calcium, Outcome 3 Serum calcium.



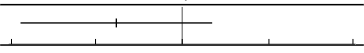
Analysis 12.4. Comparison 12 Magnesium plus calcium versus calcium, Outcome 4 Serum calcium-by-phosphate product.

Study or subgroup	Magnesium + calcium		Calcium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Tzanakis 2014	32	49 (9.2)	27	51 (8.5)		-2[-6.52,2.52]



Analysis 12.5. Comparison 12 Magnesium plus calcium versus calcium, Outcome 5 Serum iPTH.

Study or subgroup	Magnesium + calcium		Calcium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Tzanakis 2014	32	178 (96)	27	216 (117)		-38[-93.26,17.26]



Comparison 13. Sevelamer versus lanthanum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Pruritus	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Vomiting	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Abdominal pain	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
9 Diarrhoea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
10 Abdominal bloating	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
11 Hypercalcaemia	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13 Sevelamer versus lanthanum, Outcome 1 Myocardial infarction.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	0/30	0/28		Not estimable

Less with sevelamer 0.01 0.1 1 10 100 Less with lanthanum

Analysis 13.2. Comparison 13 Sevelamer versus lanthanum, Outcome 2 Stroke.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	1/30	0/28		2.81[0.12,66.17]

Less with sevelamer 0.01 0.1 1 10 100 Less with lanthanum

Analysis 13.3. Comparison 13 Sevelamer versus lanthanum, Outcome 3 Fracture.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	2/30	1/28		1.87[0.18,19.47]

Less with sevelamer 0.01 0.1 1 10 100 Less with lanthanum

Analysis 13.4. Comparison 13 Sevelamer versus lanthanum, Outcome 4 Pruritus.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	0/30	2/28		0.19[0.01,3.73]

Less with sevelamer 0.005 0.1 1 10 200 Less with lanthanum

Analysis 13.5. Comparison 13 Sevelamer versus lanthanum, Outcome 5 Nausea.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	3/30	3/28		0.93[0.21,4.25]

Less with sevelamer 0.1 0.2 0.5 1 2 5 10 Less with lanthanum

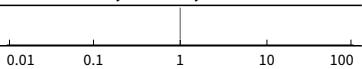
Analysis 13.6. Comparison 13 Sevelamer versus lanthanum, Outcome 6 Vomiting.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	1/30	6/28		0.16[0.02,1.21]

Less with sevelamer 0.01 0.1 1 10 100 Less with lanthanum

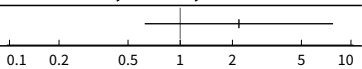
Analysis 13.7. Comparison 13 Sevelamer versus lanthanum, Outcome 7 Abdominal pain.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	0/30	0/28		Not estimable



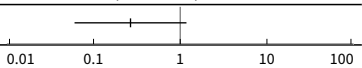
Analysis 13.8. Comparison 13 Sevelamer versus lanthanum, Outcome 8 Constipation.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	7/30	3/28		2.18[0.62,7.61]



Analysis 13.9. Comparison 13 Sevelamer versus lanthanum, Outcome 9 Diarrhoea.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	2/30	7/28		0.27[0.06,1.18]



Analysis 13.10. Comparison 13 Sevelamer versus lanthanum, Outcome 10 Abdominal bloating.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	3/30	1/28		2.8[0.31,25.37]

Analysis 13.11. Comparison 13 Sevelamer versus lanthanum, Outcome 11 Hypercalcaemia.

Study or subgroup	Sevelamer n/N	Lanthanum n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Block 2009	1/30	0/28		2.81[0.12,66.17]

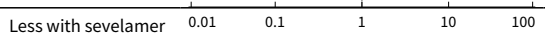
Comparison 14. Sevelamer versus iron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	4	1683	Risk Ratio (IV, Random, 95% CI)	1.07 [0.38, 2.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Cardiovascular death	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Nausea	2	1257	Risk Ratio (IV, Random, 95% CI)	3.86 [0.33, 44.86]
6 Abdominal pain	2	431	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 9.01]
7 Constipation	4	1699	Risk Ratio (IV, Random, 95% CI)	4.96 [1.96, 12.55]
8 Diarrhoea	4	1699	Risk Ratio (IV, Random, 95% CI)	0.28 [0.15, 0.54]
9 Serum phosphate	2	417	Mean Difference (IV, Random, 95% CI)	0.19 [-0.06, 0.43]
10 Serum calcium	2	417	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.29, -0.04]
11 Serum bicarbonate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

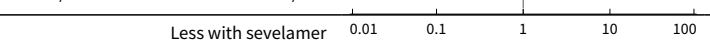
Analysis 14.1. Comparison 14 Sevelamer versus iron, Outcome 1 Death (all causes).

Study or subgroup	Sevelamer n/N	Iron n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Yokoyama 2014a	0/114	0/116			Not estimable
Koiwa 2017	0/92	0/100			Not estimable
Floege 2014	0/68	1/134		10.4%	0.65[0.03,15.8]
Chen 2011b	5/349	9/710		89.6%	1.13[0.38,3.35]
Total (95% CI)	**623**	**1060**		**100%**	**1.07[0.38,2.98]**
Total events: 5 (Sevelamer), 10 (Iron)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%					
Test for overall effect: Z=0.12(P=0.9)					



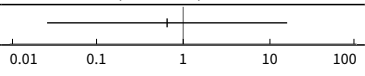
Analysis 14.2. Comparison 14 Sevelamer versus iron, Outcome 2 Cardiovascular death.

Study or subgroup	Sevelamer n/N	Iron n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chen 2011b	0/67	1/134		0.66[0.03,16.03]



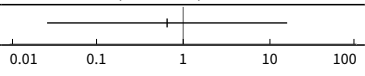
Analysis 14.3. Comparison 14 Sevelamer versus iron, Outcome 3 Myocardial infarction.

Study or subgroup	Sevelamer n/N	Iron n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chen 2011b	0/68	1/134		0.65[0.03,15.8]



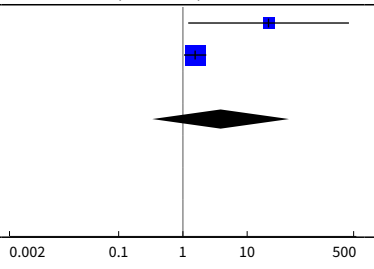
Analysis 14.4. Comparison 14 Sevelamer versus iron, Outcome 4 Fracture.

Study or subgroup	Sevelamer n/N	Iron n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chen 2011b	0/68	1/134		0.65[0.03,15.8]



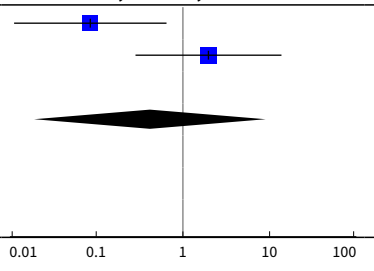
Analysis 14.5. Comparison 14 Sevelamer versus iron, Outcome 5 Nausea.

Study or subgroup	Sevelamer n/N	Iron n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Chen 2011b	5/68	0/134		34.67%	21.52[1.21,383.58]
Floege 2014	39/348	51/707		65.33%	1.55[1.04,2.31]
Total (95% CI)	**416**	**841**		**100%**	**3.86[0.33,44.86]**
Total events: 44 (Sevelamer), 51 (Iron)					
Heterogeneity: Tau^2=2.35; Chi^2=3.14, df=1(P=0.08); I^2=68.14%					
Test for overall effect: Z=1.08(P=0.28)					



Analysis 14.6. Comparison 14 Sevelamer versus iron, Outcome 6 Abdominal pain.

Study or subgroup	Sevelamer n/N	Iron n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Yokoyama 2014a	1/113	12/116		49.55%	0.09[0.01,0.65]
Chen 2011b	2/68	2/134		50.45%	1.97[0.28,13.69]
Total (95% CI)	**181**	**250**		**100%**	**0.42[0.02,9.01]**
Total events: 3 (Sevelamer), 14 (Iron)					
Heterogeneity: Tau^2=3.9; Chi^2=4.82, df=1(P=0.03); I^2=79.23%					
Test for overall effect: Z=0.56(P=0.58)					



Analysis 14.7. Comparison 14 Sevelamer versus iron, Outcome 7 Constipation.

Study or subgroup	Sevelamer n/N	Iron n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Koiwa 2017	19/105	2/108		19.57%	9.77[2.33,40.92]
Yokoyama 2014a	21/113	3/116		22.98%	7.19[2.2,23.42]
Chen 2011b	15/68	4/134		24.73%	7.39[2.55,21.41]
Floege 2014	25/348	27/707		32.72%	1.88[1.11,3.19]
Total (95% CI)	**634**	**1065**		**100%**	**4.96[1.96,12.55]**
Total events: 80 (Sevelamer), 36 (Iron)					
Heterogeneity: Tau^2=0.61; Chi^2=10.39, df=3(P=0.02); I^2=71.13%					
Test for overall effect: Z=3.38(P=0)					

Less with sevelamer — Less with iron

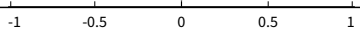
Analysis 14.8. Comparison 14 Sevelamer versus iron, Outcome 8 Diarrhoea.

Study or subgroup	Sevelamer n/N	Iron n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Yokoyama 2014a	1/113	12/116		8.67%	0.09[0.01,0.65]
Koiwa 2017	3/105	27/108		19.66%	0.11[0.04,0.37]
Chen 2011b	6/68	24/134		27.85%	0.49[0.21,1.15]
Floege 2014	26/348	142/707		43.82%	0.37[0.25,0.55]
Total (95% CI)	**634**	**1065**		**100%**	**0.28[0.15,0.54]**
Total events: 36 (Sevelamer), 205 (Iron)					
Heterogeneity: Tau^2=0.21; Chi^2=6.1, df=3(P=0.11); I^2=50.82%					
Test for overall effect: Z=3.82(P=0)					

Less with sevelamer — Less with iron

Analysis 14.9. Comparison 14 Sevelamer versus iron, Outcome 9 Serum phosphate.

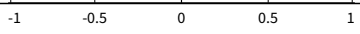
Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Iron N	Iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Yokoyama 2014a	110	5.4 (1.1)	115	5.3 (1.2)		48.66%	0.06[-0.24,0.36]
Koiwa 2017	92	5.3 (1)	100	5 (1)		51.34%	0.31[0.02,0.6]
Total ***	**202**		**215**			**100%**	**0.19[-0.06,0.43]**
Heterogeneity: Tau^2=0.01; Chi^2=1.39, df=1(P=0.24); I^2=27.83%							
Test for overall effect: Z=1.51(P=0.13)							



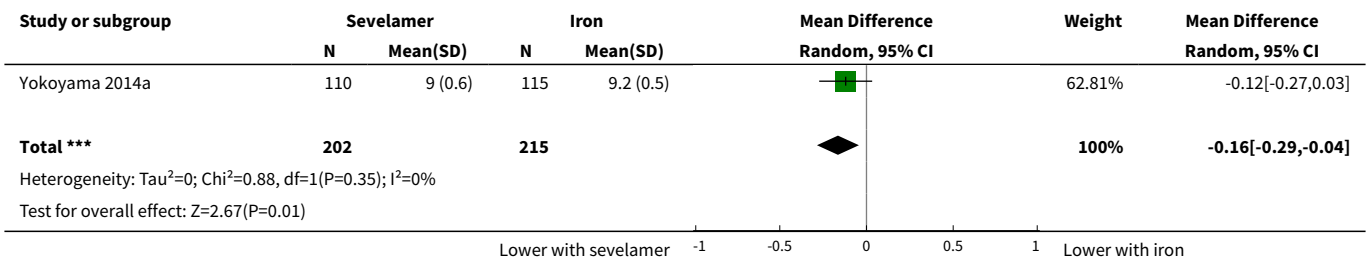
Less with sevelamer — Less with iron

Analysis 14.10. Comparison 14 Sevelamer versus iron, Outcome 10 Serum calcium.

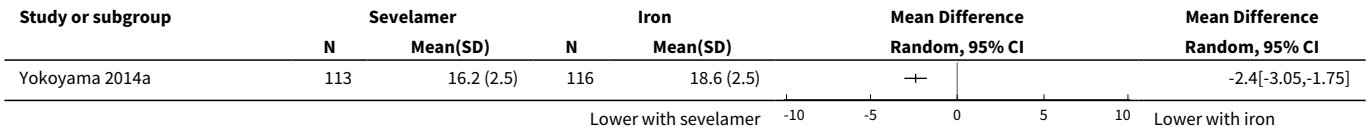
Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Iron N	Iron Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Koiwa 2017	92	8.9 (0.7)	100	9.2 (0.7)		37.19%	-0.24[-0.44,-0.04]



Lower with sevelamer — Lower with iron



Analysis 14.11. Comparison 14 Sevelamer versus iron, Outcome 11 Serum bicarbonate.



Comparison 15. Sevelamer versus bixalomer

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Pruritus	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Vomiting	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Abdominal pain	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Abdominal bloating	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
9 Serum phosphate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Serum calcium-by-phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13 Serum bicarbonate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 15.1. Comparison 15 Sevelamer versus bixalomer, Outcome 1 Death (all causes).

Study or subgroup	Sevelamer n/N	Bixalomer n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2014a	0/55	0/55		Not estimable

Less with sevelamer 0.01 0.1 1 10 100 Less with bixalomer

Analysis 15.2. Comparison 15 Sevelamer versus bixalomer, Outcome 2 Fracture.

Study or subgroup	Sevelamer n/N	Bixalomer n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2014a	0/55	1/55		0.33[0.01,8.01]

Less with sevelamer 0.01 0.1 1 10 100 Less with bixalomer

Analysis 15.3. Comparison 15 Sevelamer versus bixalomer, Outcome 3 Pruritus.

Study or subgroup	Sevelamer n/N	Bixalomer n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2014a	1/55	0/55		3[0.12,72.08]

Less with sevelamer 0.01 0.1 1 10 100 Less with bixalomer

Analysis 15.4. Comparison 15 Sevelamer versus bixalomer, Outcome 4 Nausea.

Study or subgroup	Sevelamer n/N	Bixalomer n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2014a	1/55	1/55		1[0.06,15.59]

Favours sevelamer 0.01 0.1 1 10 100 Favours bixalomer

Analysis 15.5. Comparison 15 Sevelamer versus bixalomer, Outcome 5 Vomiting.

Study or subgroup	Sevelamer n/N	Bixalomer n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2014a	2/55	0/55		5[0.25,101.81]

Less with sevelamer 0.002 0.1 1 10 500 Less with bixalomer

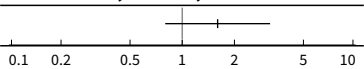
Analysis 15.6. Comparison 15 Sevelamer versus bixalomer, Outcome 6 Abdominal pain.

Study or subgroup	Sevelamer n/N	Bixalomer n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2014a	1/55	1/55		1[0.06,15.59]

Less with sevelamer 0.01 0.1 1 10 100 Less with iron

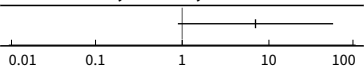
Analysis 15.7. Comparison 15 Sevelamer versus bixalomer, Outcome 7 Constipation.

Study or subgroup	Sevelamer n/N	Bixalomer n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2014a	16/55	10/55		1.6[0.8,3.21]



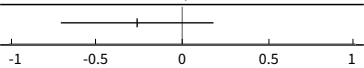
Analysis 15.8. Comparison 15 Sevelamer versus bixalomer, Outcome 8 Abdominal bloating.

Study or subgroup	Sevelamer n/N	Bixalomer n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Akizawa 2014a	7/55	1/55		7[0.89,55.01]



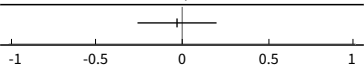
Analysis 15.9. Comparison 15 Sevelamer versus bixalomer, Outcome 9 Serum phosphate.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Bixalomer N	Bixalomer Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Akizawa 2014a	50	5.6 (1)	54	5.8 (1.2)		-0.26[-0.7,0.18]



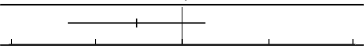
Analysis 15.10. Comparison 15 Sevelamer versus bixalomer, Outcome 10 Serum calcium.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Bixalomer N	Bixalomer Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Akizawa 2014a	50	8.9 (0.5)	54	8.9 (0.6)		-0.03[-0.26,0.2]



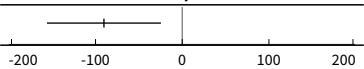
Analysis 15.11. Comparison 15 Sevelamer versus bixalomer, Outcome 11 Serum calcium-by-phosphate product.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Bixalomer N	Bixalomer Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Akizawa 2014a	50	49.3 (9.1)	54	51.9 (11.5)		-2.63[-6.6,1.34]



Analysis 15.12. Comparison 15 Sevelamer versus bixalomer, Outcome 12 Serum iPTH.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Bixalomer N	Bixalomer Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Akizawa 2014a	50	209.8 (129.4)	54	300.1 (206.4)		-90.3[-156,-24.6]



Analysis 15.13. Comparison 15 Sevelamer versus bixalomer, Outcome 13 Serum bicarbonate.

Study or subgroup	Sevelamer		Bixalomer		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Akizawa 2014a	55	18.8 (2.7)	44	21.1 (2.2)		-2.29[-3.26,-1.32]

Lower with sevelamer -4 -2 0 2 4 Lower with bixalomer

Comparison 16. Sevelamer versus nicotinamide

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Vomiting	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Serum alkaline phosphatase	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 16.1. Comparison 16 Sevelamer versus nicotinamide, Outcome 1 Death (all causes).

Study or subgroup	Sevelamer	Nicotinic acid	Risk Ratio	Risk Ratio
	n/N	n/N	IV, Random, 95% CI	IV, Random, 95% CI
NICOREN 2017	1/51	2/49		0.48[0.04,5.13]

Less with sevelamer 0.01 0.1 1 10 100 Less with nicotinic acid

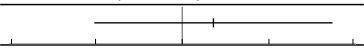
Analysis 16.2. Comparison 16 Sevelamer versus nicotinamide, Outcome 2 Stroke.

Study or subgroup	Sevelamer	Nicotinamide	Risk Ratio	Risk Ratio
	n/N	n/N	IV, Random, 95% CI	IV, Random, 95% CI
NICOREN 2017	0/51	1/49		0.32[0.01,7.68]

Less with sevelamer 0.01 0.1 1 10 100 Less with nicotinamide

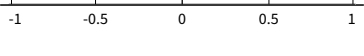
Analysis 16.3. Comparison 16 Sevelamer versus nicotinamide, Outcome 3 Vomiting.

Study or subgroup	Sevelamer n/N	Nicotinamide n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NICOREN 2017	1/37	0/28		2.29[0.1,54.18]



Analysis 16.4. Comparison 16 Sevelamer versus nicotinamide, Outcome 4 Serum calcium.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Nicotinamide N	Nicotinamide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
NICOREN 2017	46	9.2 (0.8)	27	9.2 (0.8)		0[-0.38,0.38]



Analysis 16.5. Comparison 16 Sevelamer versus nicotinamide, Outcome 5 Serum iPTH.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Nicotinamide N	Nicotinamide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
NICOREN 2017	46	321 (221)	27	305 (206)		16[-84.58,116.58]

Analysis 16.6. Comparison 16 Sevelamer versus nicotinamide, Outcome 6 Serum alkaline phosphatase.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Nicotinamide N	Nicotinamide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
NICOREN 2017	46	82.4 (50)	27	71.6 (45)		10.8[-11.49,33.09]

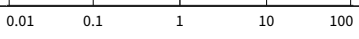
Comparison 17. Sevelamer versus colestilan

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	2	536	Risk Ratio (IV, Random, 95% CI)	0.30 [0.10, 0.96]
2 Cardiovascular death	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Pruritus	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Vomiting	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Abdominal pain	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
9 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
10 Diarrhoea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
11 Serum phosphate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13 Serum calcium-by-phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15 Serum alkaline phosphatase	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 17.1. Comparison 17 Sevelamer versus colestilan, Outcome 1 Death (all causes).

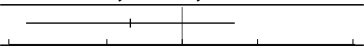
Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Locatelli 2014	1/171	2/165		23.42%	0.48[0.04,5.27]
NCT00542815	3/124	7/76		76.58%	0.26[0.07,0.99]
Total (95% CI)	**295**	**241**		**100%**	**0.3[0.1,0.96]**
Total events: 4 (Sevelamer), 9 (Colestilan)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					



Less with sevelamer — Less with colestilan

Analysis 17.2. Comparison 17 Sevelamer versus colestilan, Outcome 2 Cardiovascular death.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	0/124	1/76		0.21[0.01,4.98]



Less with sevelamer — Less with colestilan

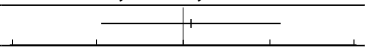
Analysis 17.3. Comparison 17 Sevelamer versus colestilan, Outcome 3 Myocardial infarction.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	1/124	0/76		1.85[0.08,44.79]

Favours sevelamer — Favours colestilan

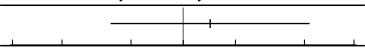
Analysis 17.4. Comparison 17 Sevelamer versus colestilan, Outcome 4 Stroke.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	2/124	1/76		1.23[0.11,13.29]



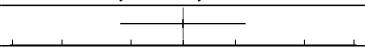
Analysis 17.5. Comparison 17 Sevelamer versus colestilan, Outcome 5 Pruritus.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	7/124	3/76		1.43[0.38,5.36]



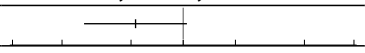
Analysis 17.6. Comparison 17 Sevelamer versus colestilan, Outcome 6 Nausea.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	13/124	8/76		1[0.43,2.29]



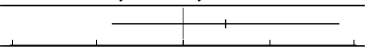
Analysis 17.7. Comparison 17 Sevelamer versus colestilan, Outcome 7 Vomiting.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	13/124	15/76		0.53[0.27,1.05]



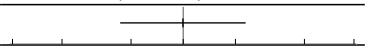
Analysis 17.8. Comparison 17 Sevelamer versus colestilan, Outcome 8 Abdominal pain.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	2/124	0/76		3.08[0.15,63.31]



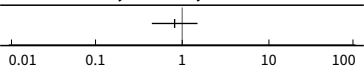
Analysis 17.9. Comparison 17 Sevelamer versus colestilan, Outcome 9 Constipation.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	13/124	8/76		1[0.43,2.29]



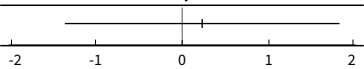
Analysis 17.10. Comparison 17 Sevelamer versus colestilan, Outcome 10 Diarrhoea.

Study or subgroup	Sevelamer n/N	Colestilan n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NCT00542815	20/124	15/76		0.82[0.45,1.5]



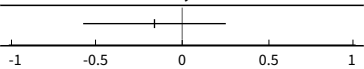
Analysis 17.11. Comparison 17 Sevelamer versus colestilan, Outcome 11 Serum phosphate.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Colestilan N	Colestilan Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Itoh 2008	13	6.7 (2.2)	14	6.5 (2)		0.23[-1.35,1.81]



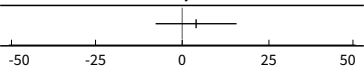
Analysis 17.12. Comparison 17 Sevelamer versus colestilan, Outcome 12 Serum calcium.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Colestilan N	Colestilan Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Itoh 2008	13	8.7 (0.6)	14	8.8 (0.5)		-0.16[-0.57,0.25]



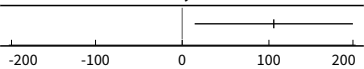
Analysis 17.13. Comparison 17 Sevelamer versus colestilan, Outcome 13 Serum calcium-by-phosphate product.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Colestilan N	Colestilan Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Itoh 2008	13	50.6 (17.7)	14	46.6 (12.6)		4[-7.67,15.67]



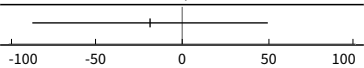
Analysis 17.14. Comparison 17 Sevelamer versus colestilan, Outcome 14 Serum iPTH.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Colestilan N	Colestilan Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Itoh 2008	13	228.7 (139.1)	14	123.1 (97.5)		105.6[14.35,196.85]



Analysis 17.15. Comparison 17 Sevelamer versus colestilan, Outcome 15 Serum alkaline phosphatase.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Colestilan N	Colestilan Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Itoh 2008	13	231.3 (99.5)	14	249.9 (78.4)		-18.55[-86.45,49.35]



Comparison 18. Sevelamer versus aluminium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Serum phosphate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18 Sevelamer versus aluminium, Outcome 1 Nausea.

Study or subgroup	Sevelamer n/N	Aluminium n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Katopodis 2006	0/15	1/15		0.33[0.01,7.58]
		Less with sevelamer	0.01 0.1 1 10 100	Less with aluminium

Analysis 18.2. Comparison 18 Sevelamer versus aluminium, Outcome 2 Constipation.

Study or subgroup	Sevelamer n/N	Aluminium n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Katopodis 2006	2/15	0/15		5[0.26,96.13]
		Less with sevelamer	0.01 0.1 1 10 100	Less with aluminium

Analysis 18.3. Comparison 18 Sevelamer versus aluminium, Outcome 3 Serum phosphate.

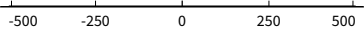
Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Aluminium N	Aluminium Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Katopodis 2006	15	6.3 (1.3)	15	5.9 (1.1)		0.37[-0.48,1.22]
				Lower with sevelamer	-2 -1 0 1 2	Lower with aluminium

Analysis 18.4. Comparison 18 Sevelamer versus aluminium, Outcome 4 Serum calcium.

Study or subgroup	Sevelamer N	Sevelamer Mean(SD)	Aluminium N	Aluminium Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Katopodis 2006	15	9.4 (0.6)	15	9.4 (0.6)		0[-0.43,0.43]
				Lower with sevelamer	-1 -0.5 0 0.5 1	Lower with aluminium

Analysis 18.5. Comparison 18 Sevelamer versus aluminium, Outcome 5 Serum iPTH.

Study or subgroup	Sevelamer		Aluminium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Katopodis 2006	15	318.6 (245.8)	15	374 (225.2)		-55.4[-224.1,113.3]



Lower with sevelamer — lower with aluminium

Comparison 19. Sevelamer versus magnesium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum phosphate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Serum calcium-by-phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 19.1. Comparison 19 Sevelamer versus magnesium, Outcome 1 Serum phosphate.

Study or subgroup	Sevelamer		Magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Zwiech 2011	10	6.2 (0.9)	30	5 (1.2)		1.2[0.5,1.9]

Lower with sevelamer — Lower with magnesium

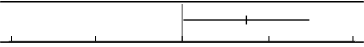
Analysis 19.2. Comparison 19 Sevelamer versus magnesium, Outcome 2 Serum calcium.

Study or subgroup	Sevelamer		Magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Zwiech 2011	10	8 (0.4)	30	9.2 (0.4)		-1.2[-1.49,-0.91]

Lower with sevelamer — Lower with magnesium

Analysis 19.3. Comparison 19 Sevelamer versus magnesium, Outcome 3 Serum calcium-by-phosphate product.

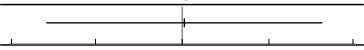
Study or subgroup	Sevelamer		Magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Zwiech 2011	10	50.8 (8.7)	30	43.4 (13.6)		7.4[0.14,14.66]



Lower with sevelamer — Lower with magnesium

Analysis 19.4. Comparison 19 Sevelamer versus magnesium, Outcome 4 Serum iPTH.

Study or subgroup	Sevelamer		Magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Zwiech 2011	10	445.6 (222.3)	30	443.2 (223.1)		2.4[-156.84,161.64]



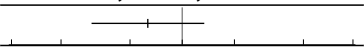
Lower with sevelamer — Lower with magnesium

Comparison 20. Sevelamer versus sevelamer + calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypercalcaemia	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Serum calcium-by-phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 20.1. Comparison 20 Sevelamer versus sevelamer + calcium, Outcome 1 Hypercalcaemia.

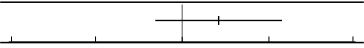
Study or subgroup	Sevelamer	Sevelamer + calcium	Risk Ratio	Risk Ratio
	n/N	n/N	IV, Random, 95% CI	IV, Random, 95% CI
Chertow 1999	8/35	13/36		0.63[0.3,1.34]



Less with sevelamer — Less with sevelamer/calcium

Analysis 20.2. Comparison 20 Sevelamer versus sevelamer + calcium, Outcome 2 Serum calcium-by-phosphate product.

Study or subgroup	Sevelamer		Sevelamer plus calcium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Chertow 1999	35	60.1 (17.3)	36	55.9 (13.9)		4.2[-3.11,11.51]



Lower with sevelamer — Lower with sevelamer/calcium

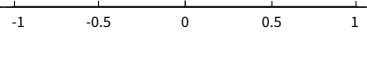
Comparison 21. Sevelamer versus calcium + magnesium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum phosphate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Serum calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Serum alkaline phosphatase	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Serum bicarbonate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

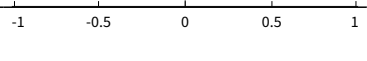
Analysis 21.1. Comparison 21 Sevelamer versus calcium + magnesium, Outcome 1 Serum phosphate.

Study or subgroup	Sevelamer		Calcium plus magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
CALMAG 2010	99	5.5 (1.9)	105	5.3 (1.5)		0.2[-0.27,0.67]



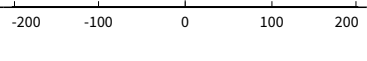
Analysis 21.2. Comparison 21 Sevelamer versus calcium + magnesium, Outcome 2 Serum calcium.

Study or subgroup	Sevelamer		Calcium plus magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
CALMAG 2010	122	8.8 (0.6)	122	8.9 (0.6)		-0.12[-0.28,0.04]



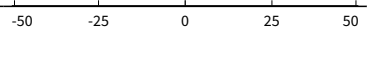
Analysis 21.3. Comparison 21 Sevelamer versus calcium + magnesium, Outcome 3 Serum iPTH.

Study or subgroup	Sevelamer		Calcium plus magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
CALMAG 2010	112	384.7 (226.3)	118	337.2 (266.4)		47.47[-16.3,111.24]



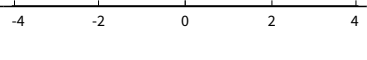
Analysis 21.4. Comparison 21 Sevelamer versus calcium + magnesium, Outcome 4 Serum alkaline phosphatase.

Study or subgroup	Sevelamer		Calcium plus magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
CALMAG 2010	105	125.9 (53.5)	116	106.8 (53.8)		19.09[4.93,33.25]



Analysis 21.5. Comparison 21 Sevelamer versus calcium + magnesium, Outcome 5 Serum bicarbonate.

Study or subgroup	Sevelamer		Calcium plus magnesium		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
CALMAG 2010	114	21.1 (4.1)	117	22.5 (3.3)		-1.41[-2.37,-0.45]



Comparison 22. Sevelamer hydrochloride versus sevelamer carbonate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Vomiting	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Constipation	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Diarrhoea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

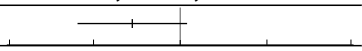
Analysis 22.1. Comparison 22 Sevelamer hydrochloride versus sevelamer carbonate, Outcome 1 Death (all causes).

Study or subgroup	Sevelamer hydrochloride n/N	Sevelamer carbonate n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Fishbane 2010	2/73	1/144		3.95[0.36,42.79]

Less with hydrochloride — Less with carbonate

Analysis 22.2. Comparison 22 Sevelamer hydrochloride versus sevelamer carbonate, Outcome 2 Nausea.

Study or subgroup	Sevelamer hydrochloride n/N	Sevelamer carbonate n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Fishbane 2010	2/72	14/141		0.28[0.07,1.2]



Less with hydrochloride — Less with carbonate

Analysis 22.3. Comparison 22 Sevelamer hydrochloride versus sevelamer carbonate, Outcome 3 Vomiting.

Study or subgroup	Sevelamer hydrochloride n/N	Sevelamer carbonate n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Fishbane 2010	1/72	8/141		0.24[0.03,1.92]

Less with hydrochloride — Less with carbonate

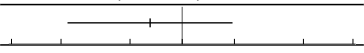
Analysis 22.4. Comparison 22 Sevelamer hydrochloride versus sevelamer carbonate, Outcome 4 Constipation.

Study or subgroup	Sevelamer hydrochloride n/N	Sevelamer carbonate n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Fishbane 2010	4/72	1/141		7.83[0.89,68.8]

Less with hydrochloride — Less with carbonate

Analysis 22.5. Comparison 22 Sevelamer hydrochloride versus sevelamer carbonate, Outcome 5 Diarrhoea.

Study or subgroup	Sevelamer hydrochloride n/N	Sevelamer carbonate n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Fishbane 2010	4/72	12/141		0.65[0.22,1.95]



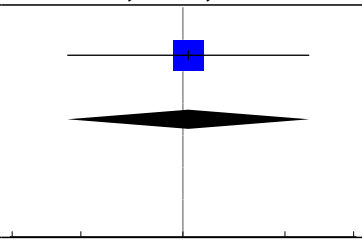
Less with hydrochloride — Less with carbonate

Comparison 23. Calcium acetate versus calcium carbonate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	2	74	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.07, 17.30]
2 Hypercalcaemia	2	92	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.45, 0.97]
3 Serum phosphate	3	98	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.74, 0.26]
4 Serum calcium	3	98	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.04]
5 Serum calcium-by-phosphate product	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Serum iPTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Serum alkaline phosphatase	2	35	Mean Difference (IV, Random, 95% CI)	1.77 [-8.80, 12.35]

Analysis 23.1. Comparison 23 Calcium acetate versus calcium carbonate, Outcome 1 Death (all causes).

Study or subgroup	Calcium acetate n/N	Calcium carbonate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Almirall 1994	0/4	0/4			Not estimable
Caravaca 1992	1/31	1/35		100%	1.13[0.07,17.3]
Total (95% CI)	**35**	**39**		**100%**	**1.13[0.07,17.3]**
Total events: 1 (Calcium acetate), 1 (Calcium carbonate)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.09(P=0.93)					

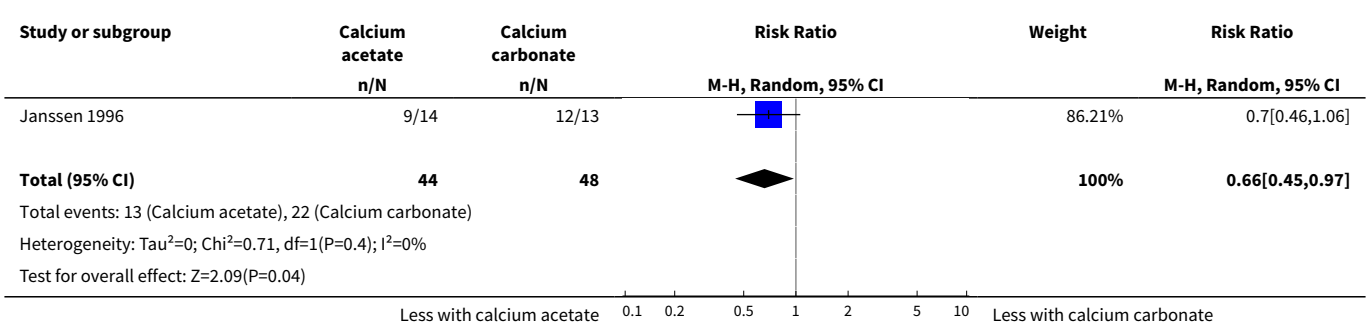


Less with calcium acetate — Less with calcium carbonate

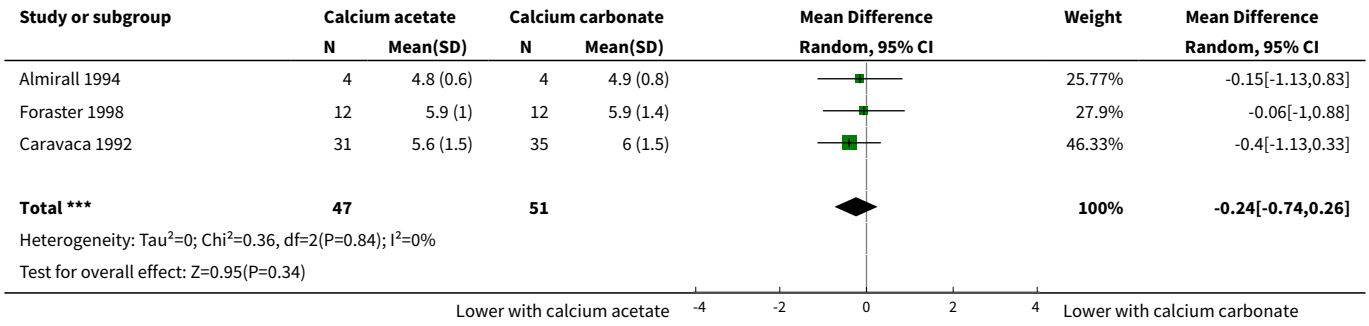
Analysis 23.2. Comparison 23 Calcium acetate versus calcium carbonate, Outcome 2 Hypercalcaemia.

Study or subgroup	Calcium acetate n/N	Calcium carbonate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Caravaca 1992	4/30	10/35		13.79%	0.47[0.16,1.34]

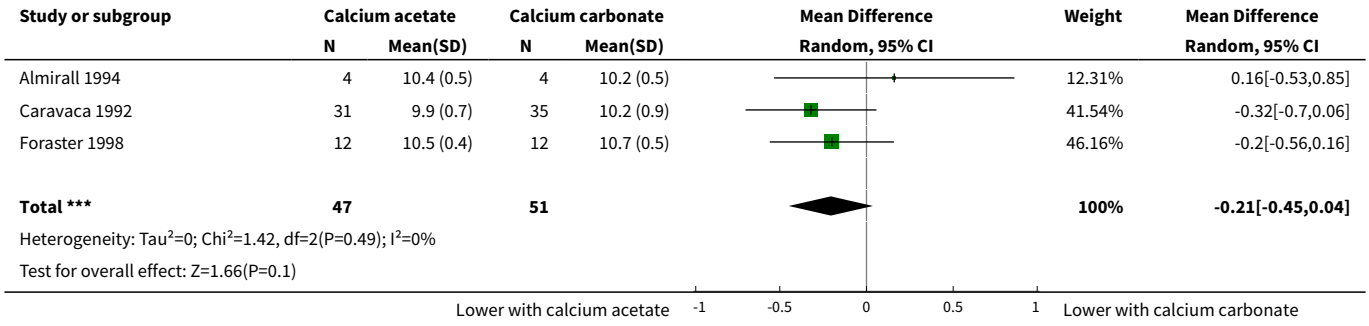
Less with calcium acetate — Less with calcium carbonate



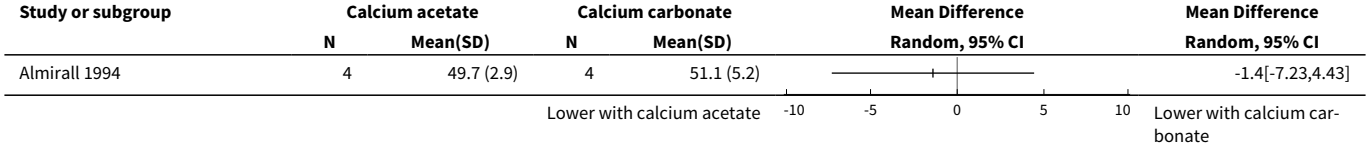
Analysis 23.3. Comparison 23 Calcium acetate versus calcium carbonate, Outcome 3 Serum phosphate.



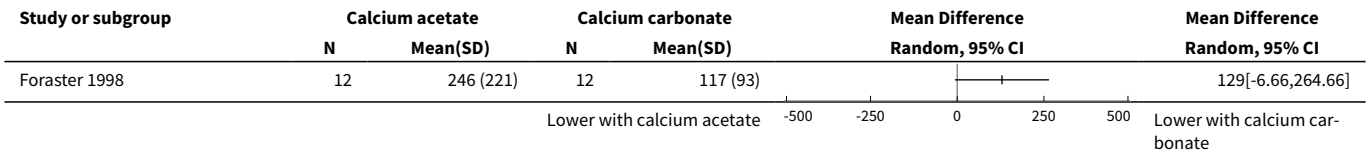
Analysis 23.4. Comparison 23 Calcium acetate versus calcium carbonate, Outcome 4 Serum calcium.



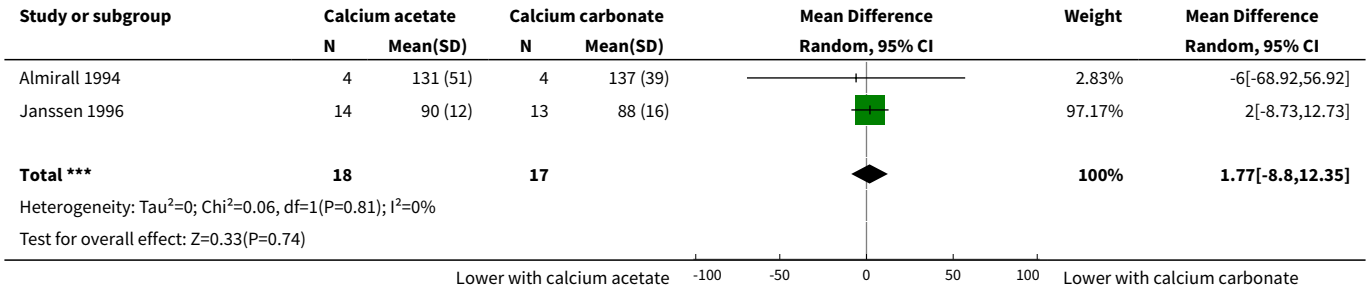
Analysis 23.5. Comparison 23 Calcium acetate versus calcium carbonate, Outcome 5 Serum calcium-by-phosphate product.



Analysis 23.6. Comparison 23 Calcium acetate versus calcium carbonate, Outcome 6 Serum iPTH.



Analysis 23.7. Comparison 23 Calcium acetate versus calcium carbonate, Outcome 7 Serum alkaline phosphatase.

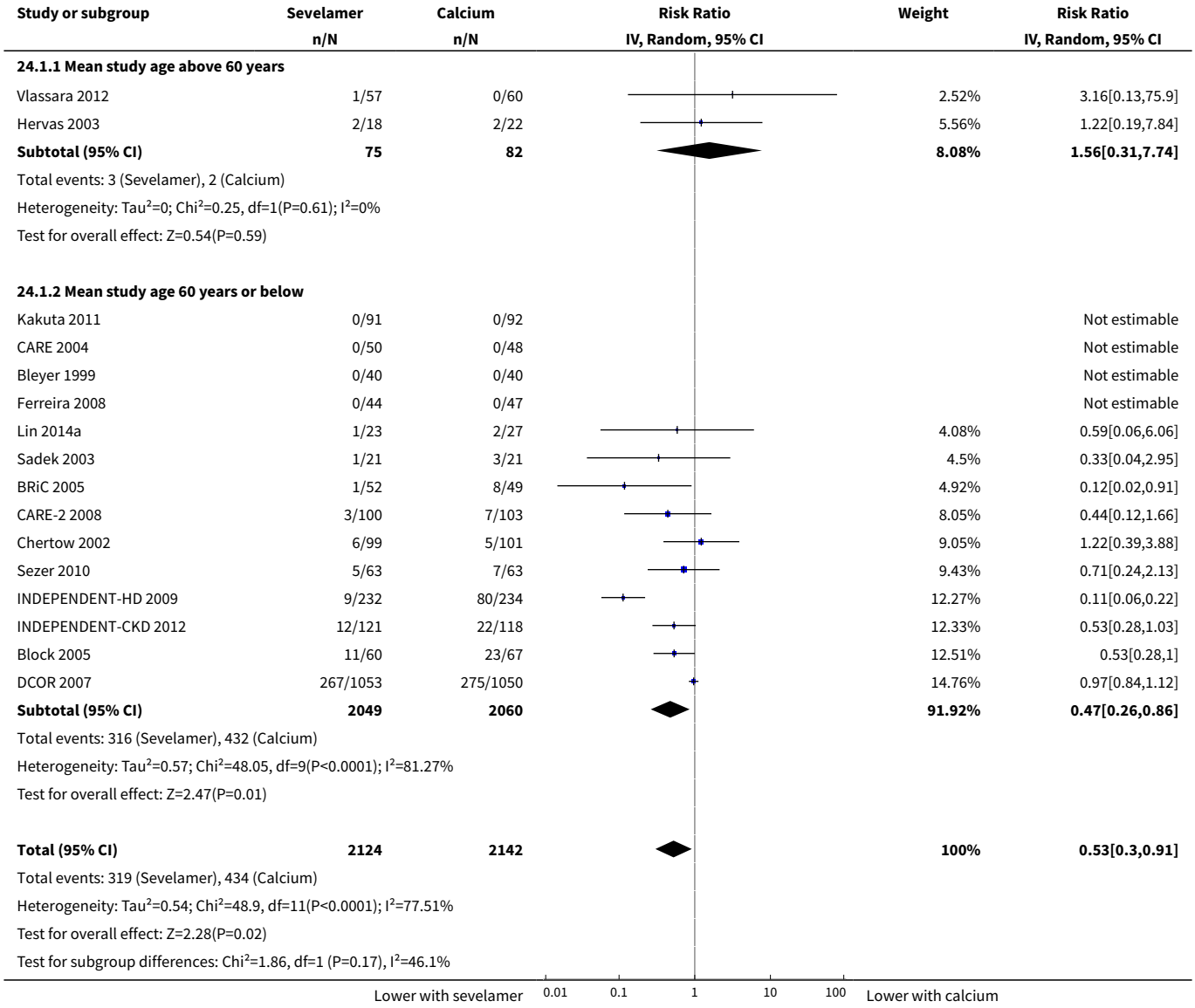


Comparison 24. Subgroup: sevelamer versus calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes): age	16	4266	Risk Ratio (IV, Random, 95% CI)	0.53 [0.30, 0.91]
1.1 Mean study age above 60 years	2	157	Risk Ratio (IV, Random, 95% CI)	1.56 [0.31, 7.74]
1.2 Mean study age 60 years or below	14	4109	Risk Ratio (IV, Random, 95% CI)	0.47 [0.26, 0.86]
2 Death (all causes): CKD GFR category	16	4266	Risk Ratio (IV, Random, 95% CI)	0.53 [0.30, 0.91]
2.1 Stage 2-5	2	356	Risk Ratio (IV, Random, 95% CI)	0.64 [0.22, 1.84]
2.2 Stage 5D	14	3910	Risk Ratio (IV, Random, 95% CI)	0.50 [0.26, 0.95]
3 Cardiovascular death: CKD GFR category	6	2904	Risk Ratio (IV, Random, 95% CI)	0.45 [0.11, 1.77]
3.1 Stage 2 to 5	2	583	Risk Ratio (IV, Random, 95% CI)	0.37 [0.01, 13.78]
3.2 Stage 5D	4	2321	Risk Ratio (IV, Random, 95% CI)	0.85 [0.46, 1.57]
4 Death (all causes): study duration	16	4393	Risk Ratio (IV, Random, 95% CI)	0.53 [0.32, 0.86]
4.1 Less than 12 months	6	504	Risk Ratio (IV, Random, 95% CI)	0.59 [0.34, 1.04]

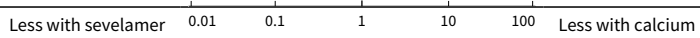
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Equal to or longer than 12 months	11	3889	Risk Ratio (IV, Random, 95% CI)	0.48 [0.26, 0.89]
5 Death (all causes): random sequence generation and allocation concealment	16	4669	Risk Ratio (IV, Random, 95% CI)	0.55 [0.34, 0.90]
5.1 Low risk	6	1053	Risk Ratio (IV, Random, 95% CI)	0.55 [0.36, 0.82]
5.2 Unclear/high risk	12	3616	Risk Ratio (IV, Random, 95% CI)	0.60 [0.27, 1.30]

Analysis 24.1. Comparison 24 Subgroup: sevelamer versus calcium, Outcome 1 Death (all causes): age.



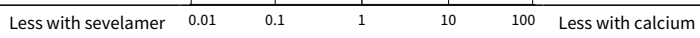
Analysis 24.2. Comparison 24 Subgroup: sevelamer versus calcium, Outcome 2 Death (all causes): CKD GFR category.

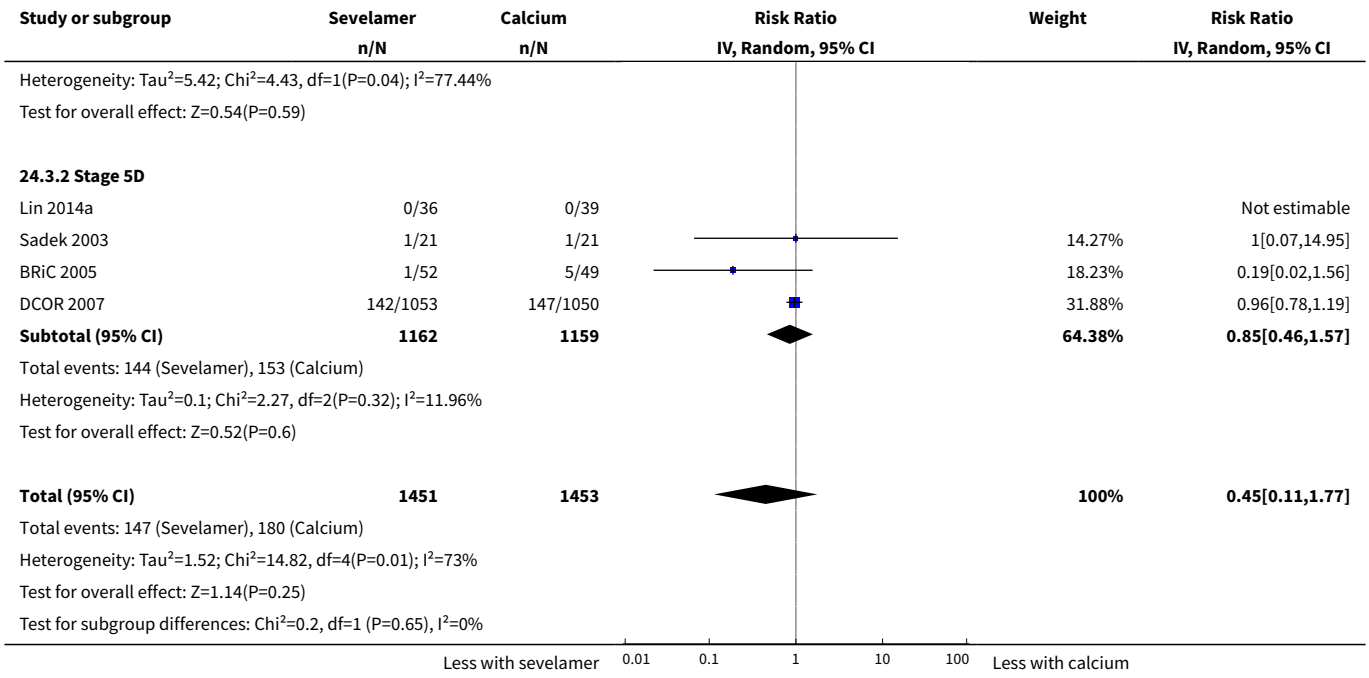
Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
24.2.1 Stage 2-5					
Vlassara 2012	1/57	0/60		2.52%	3.16[0.13,75.9]
INDEPENDENT-CKD 2012	12/121	22/118		12.33%	0.53[0.28,1.03]
Subtotal (95% CI)	**178**	**178**		**14.85%**	**0.64[0.22,1.84]**
Total events: 13 (Sevelamer), 22 (Calcium)					
Heterogeneity: Tau^2=0.21; Chi^2=1.15, df=1(P=0.28); I^2=13.39%					
Test for overall effect: Z=0.83(P=0.41)					
24.2.2 Stage 5D					
Kakuta 2011	0/91	0/92			Not estimable
Bleyer 1999	0/40	0/40			Not estimable
Ferreira 2008	0/44	0/47			Not estimable
CARE 2004	0/50	0/48			Not estimable
Lin 2014a	1/23	2/27		4.08%	0.59[0.06,6.06]
Sadek 2003	1/21	3/21		4.5%	0.33[0.04,2.95]
BRiC 2005	1/52	8/49		4.92%	0.12[0.02,0.91]
Hervas 2003	2/18	2/22		5.56%	1.22[0.19,7.84]
CARE-2 2008	3/100	7/103		8.05%	0.44[0.12,1.66]
Chertow 2002	6/99	5/101		9.05%	1.22[0.39,3.88]
Sezer 2010	5/63	7/63		9.43%	0.71[0.24,2.13]
INDEPENDENT-HD 2009	9/232	80/234		12.27%	0.11[0.06,0.22]
Block 2005	11/60	23/67		12.51%	0.53[0.28,1]
DCOR 2007	267/1053	275/1050		14.76%	0.97[0.84,1.12]
Subtotal (95% CI)	**1946**	**1964**		**85.15%**	**0.5[0.26,0.95]**
Total events: 306 (Sevelamer), 412 (Calcium)					
Heterogeneity: Tau^2=0.68; Chi^2=46.4, df=9(P<0.0001); I^2=80.6%					
Test for overall effect: Z=2.12(P=0.03)					
Total (95% CI)	**2124**	**2142**		**100%**	**0.53[0.3,0.91]**
Total events: 319 (Sevelamer), 434 (Calcium)					
Heterogeneity: Tau^2=0.54; Chi^2=48.9, df=11(P<0.0001); I^2=77.51%					
Test for overall effect: Z=2.28(P=0.02)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%					



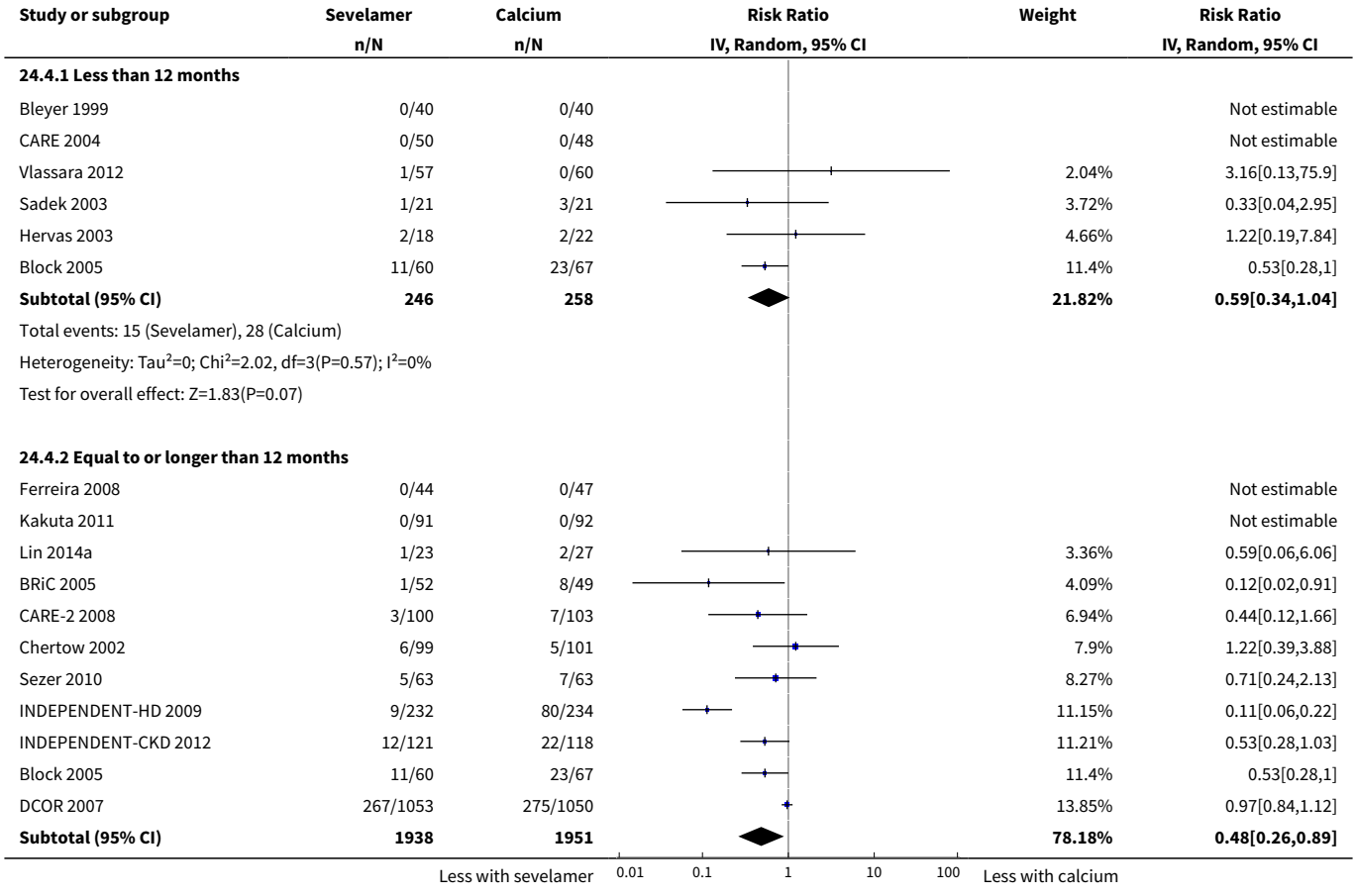
Analysis 24.3. Comparison 24 Subgroup: sevelamer versus calcium, Outcome 3 Cardiovascular death: CKD GFR category.

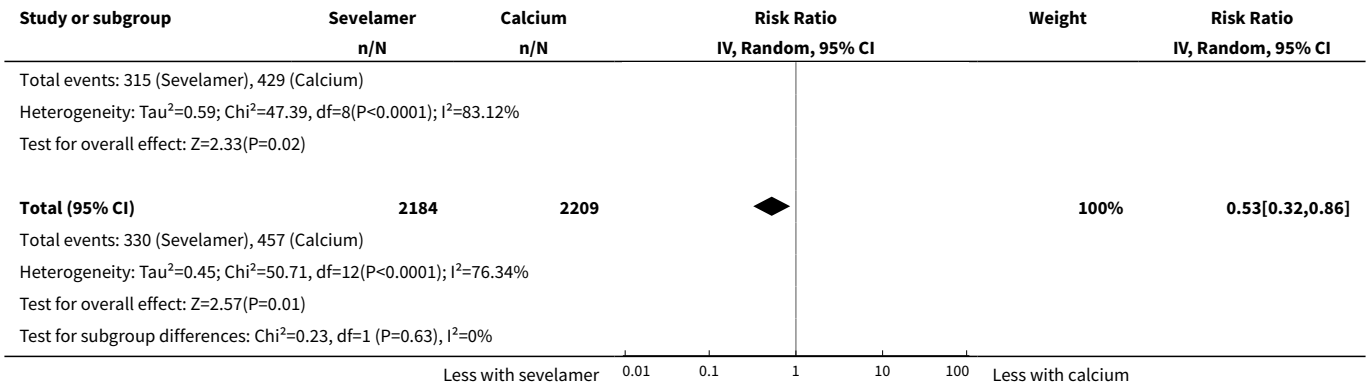
Study or subgroup	Sevelamer n/N	Calcium n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
24.3.1 Stage 2 to 5					
Vlassara 2012	1/57	0/60		11.77%	3.16[0.13,75.9]
INDEPENDENT-HD 2009	2/232	27/234		23.85%	0.07[0.02,0.31]
Subtotal (95% CI)	**289**	**294**		**35.62%**	**0.37[0.01,13.78]**
Total events: 3 (Sevelamer), 27 (Calcium)					



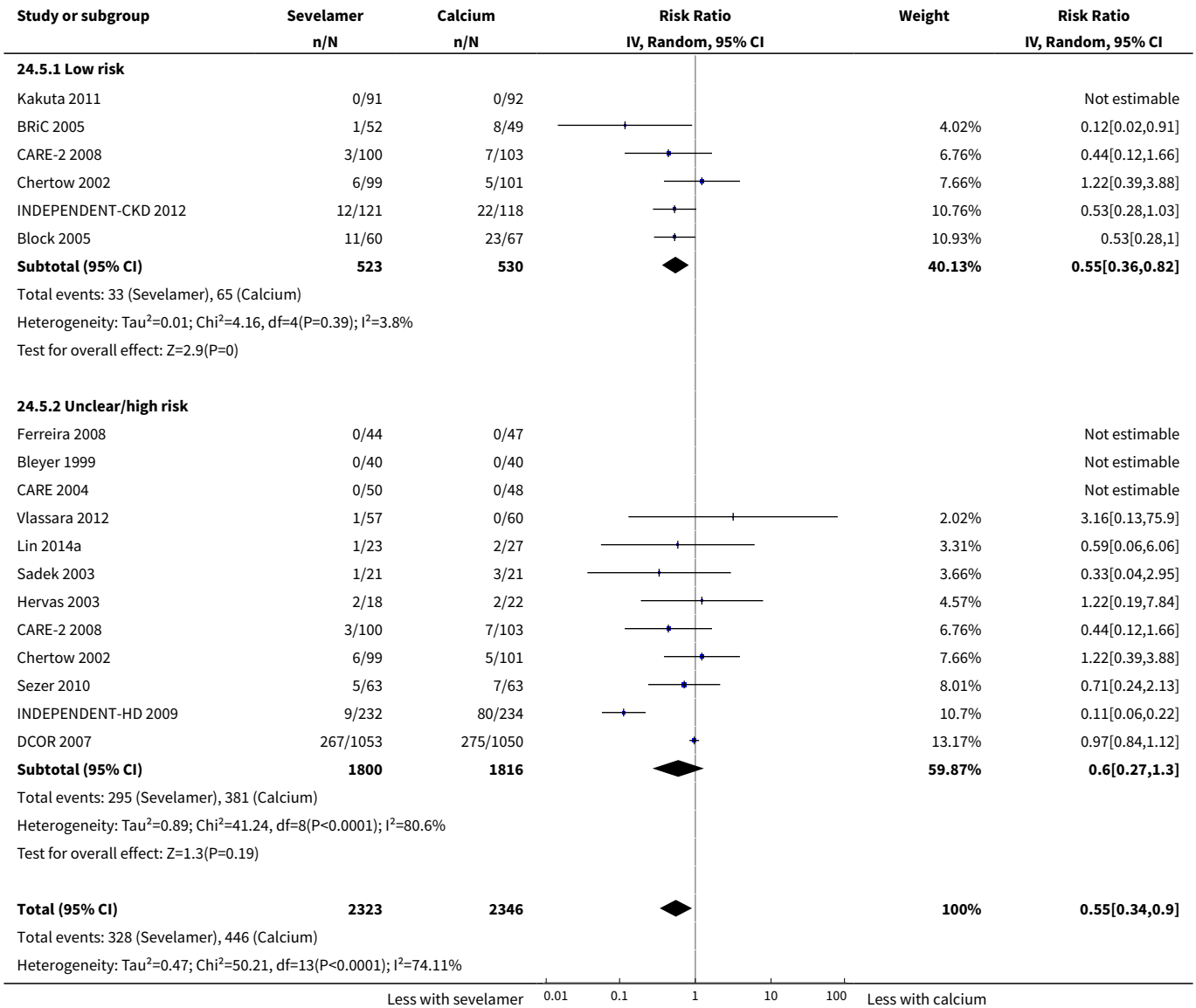


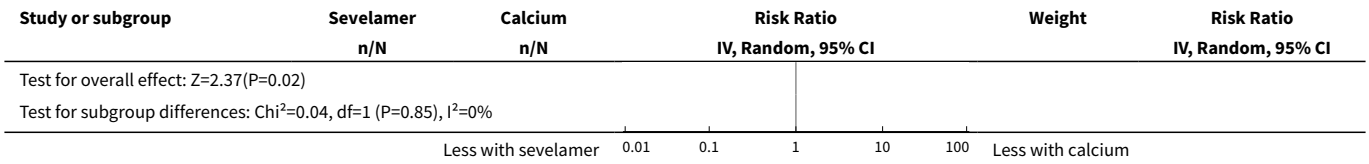
Analysis 24.4. Comparison 24 Subgroup: sevelamer versus calcium, Outcome 4 Death (all causes): study duration.





Analysis 24.5. Comparison 24 Subgroup: sevelamer versus calcium, Outcome 5 Death (all causes): random sequence generation and allocation concealment.





APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	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.(haemodialysis or haemodialysis) 11.(capd or ccpd or apd) 12.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11) 13.BONE DISEASES 14.RENAL OSTEODYSTROPHY 15.(bone next disease*) 16.(bone* and (atroph* or formation or deform* or destruct* or necrosis or resorption or metabol* or turnover or demineral* or decalcif* or density)) 17.(#13 or #14 or #15 or #16) 18.(#12 and #17) 19.aluminium HYDROXIDE 20.CALCIUM CARBONATE 21.CALCIUM GLUCONATE 22.POLYAMINES 23.ANION EXCHANGE RESINS 24.((phosphate next buffer*) or (phosphate next binder*)) 25.((aluminium next carbonate*) or (aluminium next carbonate*)) 26.(calcium next acetate*) 27.(calcium next ketoglutarate*) 28.sevelamer 29.(lanthanum next carbonate*) 30.(magnesium next carbonate*) 31.((aluminium next hydroxide*) or (aluminium next hydroxide*)) 32.colestimide 33.phoslo 34.renagel 35.fosrenol

(Continued)

	36.(#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35) 37.(#18 and #36)
MEDLINE	1. Kidney Diseases/ 2. Kidney Failure, Chronic/ 3. Kidney Failure/ 4. renal replacement therapy/ or exp renal dialysis/ or exp hemofiltration/ 5. (chronic kidney or chronic renal).tw. 6. (CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF).tw. 7. (predialysis or dialysis).tw. 8. (haemodialysis or haemodialysis).tw. 9. (CAPD or CCPD or APD).tw. 10.or/1-9 11.exp Bone Diseases/ 12.Renal Osteodystrophy/ 13.bone disease$.tw. 14.(bone$ and (atroph$ or formation or deform$ or destruct$ or necrosis or resorption or metabol$ or turnover or demineral$ or decalcif$ or density)).tw. 15.(osteo$ or hyperparathyroid$ or hyperphosphat$).tw. 16.or/11-15 17.and/10,16 18.aluminium Hydroxide/ 19.Calcium Carbonate/ 20.Calcium Gluconate/ 21.Polyamines/ 22.Anion Exchange Resins/ 23.(phosphate buffer$ or phosphate bind$).tw. 24.alumin?um carbonate$.tw. 25.calcium acetate$.tw. 26.calcium ketoglutarate$.tw. 27.sevelamer.tw. 28.lanthanum carbonate$.tw. 29.magnesium carbonate$.tw. 30.alumin?um hydroxide$.tw. 31.colestimide.tw. 32.phoslo.tw. 33.renagel.tw. 34.fosrenol.tw. 35.or/18-34 36.and/17,35
EMBASE	1. Kidney Disease/ 2. Kidney Failure/ 3. Chronic Kidney Failure/ 4. exp haemodialysis/ 5. (haemodialysis or haemodialysis).tw. 6. dialysis.tw. 7. (CAPD or CCPD or APD).tw. 8. predialysis.tw. 9. (chronic renal or chronic kidney).tw. 10.(CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF).tw.

(Continued)

11.or/1-10
12.exp Bone Disease/
13.bone disease$.tw.
14.(bone$ and (atroph$ or formation or deform$ or destruct$ or necrosis or resorption or metabol$ or turnover or demineral$ or decalcif$ or density)).tw.
15.(osteo$ or hyperparathyroid$ or hyperphosphat$).tw.
16.or/12-15
17.aluminium Hydroxide/
18.Calcium Carbonate/
19.Gluconate Calcium/
20.Polyamine/
21.Anion Exchange Resin/
22.Sevelamer/
23.Lanthanum Carbonate/
24.Magnesium Carbonate/
25.aluminium Carbonate/
26.Calcium Acetate/
27.Phosphate Binding Agent/
28.aluminium Hydroxide/
29.Colestilan/
30.(phosphate buffer$ or phosphate bind$).tw.
31.alumin?um carbonate$.tw.
32.calcium acetate$.tw.
33.calcium ketoglutarate$.tw.
34.sevelamer.tw.
35.colestimide.tw.
36.phoslo.tw.
37.renagel.tw.
38.fosrenol.tw.
39.lanthanum carbonate$.tw.
40.magnesium carbonate$.tw.
41.alumin?um hydroxide$.tw.
42.or/17-41
43.and/11,16,42

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.

(Continued)

Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

(Continued)

	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
12 July 2018	New citation required and conclusions have changed	New studies included
12 July 2018	New search has been performed	Review updated. Conclusions changed.

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review: SN, SCP, MR, PN, JCC, GJE, GFMS
- Screening of titles and abstracts: SCP, MR, PN
- Assessment for inclusion: SCP, MR, PN
- Quality assessment: SCP, MR, PN
- Data extraction: SCP, MR
- Data entry into RevMan: SCP, MR
- Data analysis: SCP, MR
- Disagreement resolution: GFMS

DECLARATIONS OF INTEREST

- Nothing to declare

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the process of this review update, we identified 21 studies that were included in the 2011 review but did not meet the study review criteria (Al-Baaj 2005; Borrego 2000; Chertow 1997; Chiang 2005; d'Almeida Filho 2000; Emmett 1991; Fan 2009; Fischer 2006; FORESEE 2008; Ittel 1991; Joy 2003; Koiwa 2005a; Kurihara 2005; McIntyre 2009; Pflanz 1994; Phelps 2002; Ring 1993; Salusky 1991; Schaefer 1991; Sprague 2009b; Tzanakis 2008). The reasons for exclusion are reported in the Characteristics of excluded studies table. We reassigned the study "Deuber 2003a" in the 2011 review as a secondary publication of Deuber 2004. We identified secondary publications of "Finn 2004" of the 2011 review as secondary publications of Finn 2004 and SPD405-307 2004. We identified the study "Malluche 2008" as a publication of the SPD405-307 2004.

We added kidney function outcomes to the 2018 update including eGFR and ESKD. We have included Summary of Findings tables for the comparisons of: sevelamer versus placebo or usual care; lanthanum versus placebo or usual care; iron versus placebo or usual care; sevelamer versus calcium; and lanthanum versus calcium. Additional surrogate markers of CKD-MBD including fibroblast growth factor 23 (FGF23), fetuin-A, and Klotho have been added to the 2018 review update.

We changed subgroup analyses, adding age and CKD stage and deleting older/newer agents and number of participants.

INDEX TERMS

Medical Subject Headings (MeSH)

Calcium [blood]; Calcium Compounds [adverse effects] [*therapeutic use]; Cause of Death; Chelating Agents [adverse effects] [*therapeutic use]; Chronic Disease; Chronic Kidney Disease-Mineral and Bone Disorder [blood] [*drug therapy] [*prevention & control]; Disease Progression; Hypercalcemia [chemically induced]; Iron Compounds [adverse effects] [therapeutic use]; Lanthanum [adverse effects] [therapeutic use]; Parathyroid Hormone [blood]; Phosphorus [*blood]; Polyamines [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Renal Dialysis [statistics & numerical data]; Sevelamer [therapeutic use]

MeSH check words

Adult; Aged; Humans; Middle Aged