National Institute for Health and Care Excellence

Draft

Chronic kidney disease

[L] Evidence reviews for the use of phosphate binders

NICE guideline <number>

Evidence reviews underpinning recommendations 1.11.5 – 1.11.17 and the research recommendations on phosphate binders in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by the NICE Guideline Updates Team

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Use of phosphate binders for people with stage 4 or 5 CKD who are not on dialysis

1.1 Review question

RQ5.1 For people with stage 4 or 5 CKD who are not on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?

1.1.1 Introduction

As kidney dysfunction advances, there is a higher risk of mortality and some co-morbidities become more severe. Hyperphosphataemia is one example of this and occurs because of insufficient filtering of phosphate from the blood by poorly functioning kidneys. This means that a certain amount of the phosphate does not leave the body in the urine, instead remaining in the blood at abnormally elevated levels. High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to the development of secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism increases morbidity and mortality and may lead to renal bone disease, with people experiencing bone and muscular pain, increased incidence of fracture, abnormalities of bone and joint morphology, and vascular and soft tissue calcification. Standard management of hyperphosphataemia includes the use of phosphate binders.

The NICE guideline on chronic kidney disease (stage 4 or 5): management of hyperphosphataemia (NICE guideline CG157) was reviewed in 2017 as part of NICE's routine surveillance programme to determine whether new evidence was available that could alter the current recommendations. The surveillance report identified that sevelamer carbonate (a type of phosphate binder) is available at considerably reduced cost to sevelamer hydrochloride as a generic version. However, sevelamer is still significantly more expensive than other phosphate binders such as calcium-based binders. There is therefore a potential need to revise the health economic modelling in CG157, and to consider sevelamer carbonate which was not included in the original guideline. As a result, the decision was made to update this part of the guideline.

The aim of this review is to compare phosphate binders, calcium and non-calcium based, to determine the most effective treatments for hyperphosphataemia in people with stage 4 or 5 CKD who are not on dialysis. This review identified studies that fulfilled the conditions specified in Table 1. For full details of the review protocol, see Appendix A.

1.1.2 Summary of the protocol

Table 1: PICO table for the use of phosphate binders for people with stage 4 or 5 CKD who are not on dialysis

Population	**Inclusion:** Adults, children and young people with stage 4 or 5 chronic kidney disease who are not on dialysis **Exclusion:** Pregnant women
Intervention	Calcium and non-calcium based phosphate binders: • Lanthanum carbonate • Ferric carboxymaltose • Sevelamer hydrochloride

	• Sevelamer carbonate • Aluminium hydroxide • Magnesium carbonate • Calcium carbonate • Calcium acetate • Sucroferric oxyhydroxide • Calcium acetate/magnesium carbonate (Osvaren)
Comparator	• Placebo • other phosphate binding treatment (or combinations) from the list above
Outcomes	Over the duration of follow up of the study: • Overall and cardiovascular related mortality and morbidity • Serum phosphate • Adverse effects (#, bone density, Ectopic calcification (inc PAD) Cardiovascular calcification scores, Parathyroidectomy) • Patient concordance (author defined) • Serum calcium • QoL (validated QoL measures)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods in Appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The following methods were specific for this review:

1. For pairwise analysis, 3-arm RCTs were analysed according to the Cochrane methods splitting the 'shared' group into two or more groups with smaller sample size (for example, control group for Russo 2007), and include two or more (reasonably independent) comparisons (for example, 2 independent interventions for Russo 2007). For dichotomous outcomes, both the number of events and the total number of patients would be divided up (if number of events was 1, this could not be divided). For continuous outcomes, only the total number of participants would be divided up and the means and standard deviations left unchanged.
2. The network meta-analysis (NMA) models for a dichotomous outcome were based on models from the NICE Decision Support Unit (DSU) technical support document 2 (models 1c and 1d for probabilities of events [logit link; odds ratio scale]; 3a and 3b for rates of events over time [cloglog link; hazard ratio scale]). The NMA models for a [pcontinuous outcome were based on models from the NICE DSU technical support document 2 (models 5a and 5b). The models are shown in Appendix P.
3. The cloglog models generate results in the form of HRs. To enable comparisons between the pairwise direct data and NMA outputs to be made, approximate HRs and their variances were calculated from event data, using the methods described by Watkins et al. (2018).
4. Results were reported as the posterior median and 95% credible interval from the NMA fixed effect models. Random effect models could not be fit with uninformative priors because there was very little data to estimate the heterogeneity term (there were very few contrasts with multiple trials and/or multiple loops in the available networks).
5. Where the data for the NMA for a dichotomous outcome (for example discontinuation due to adverse events) included RCTs with 0 events in both arms, these RCTs were not included as part of the analysis because RCTs with 0 events in both arms do not contribute evidence on the relative treatment effects in pairwise meta-analysis or NMA.

6. Inconsistency checking of the NMA was carried out (see Appendix P).

We would like to acknowledge the Technical Support Unit, at University of Bristol, particularly Nicky Welton, Hugo Pedder, Tony Ades, and Caitlin Daly, for providing advice, models, and quality assurance for the network meta-analyses included in this review.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A single systematic search was carried out for the 2 review questions in this evidence review to identify randomised controlled trials (RCTs) and systematic reviews of RCTs, which found 575 references (see Appendix C). Evidence included in the original guideline and evidence from systematic reviews and network meta-analyses were also reviewed to identify primary studies. In total, 632 references were identified for screening at title and abstract level. Of these, 501 were excluded based on their titles and abstracts and 131 references (20 systematic reviews and 111 RCTs) were ordered for screening based on their full texts.

Of the 131 references screened at full text, 75 RCTs published in 87 references were included for the 2 review questions based on their relevance to the review protocols (Appendix A). Of the 87 included references, 7 presented data and met the inclusion criteria for the review on the use of phosphate binders for adults with stage 4 or 5 CKD who are not on dialysis. There were no references for children and young people.

The clinical evidence study selection is presented as a PRISMA diagram in Appendix D.

See 1.1.12 References – included studies for a list of references for included studies.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 47 references for this review question, these were screened on title and abstract. Eight references were ordered for full text screening. None of these references were included based on their relevance to the review protocol (Appendix A).

1.1.4.2 Excluded studies

See Appendix M for a list of excluded studies with reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Clinical studies on adults with stage 4 or 5 CKD who are not on dialysis

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
Qunibi et al. (2011) N=110	Calcium Acetate versus Placebo	USA	None	84 days	From 0.87 to 1.45	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Compliance Proportion with hypercalcaemia
Russo et al. (2007)	Control-low phosphate diet	Italy	None	728 days	Not reported	Serum Ca (mmol/L)

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
N=90	only versus Calcium Carbonate and low phosphate diet versus Sevelamer and low phosphate diet					Serum Phosphate (mmol/L) Coronary arterial calcification
Soriano et al. (2013) N=32	Calcium Carbonate versus Lanthanum carbonate	Spain	None	121	1.45	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Sprague et al. (2009) N=121	Lanthanum versus Placebo	USA	None	56 days	Up to 1.49	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Nausea & Vomiting
Takahara et al. (2014) N=141	Lanthanum carbonate versus Placebo	Japan	None	56 days	From 0.87 to 1.48	Serum Phosphate (mmol/L) Constipation Nausea Vomiting Renal failure chronic Renal impairment Azotemia Hyperkalemia
Yilmaz et al. (2012) N=100	Sevelamer hydrochloride versus Calcium acetate	Turkey	None	56 days	Up to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Yokoyama et al. (2014a) N=86	Ferric citrate hydrate versus Placebo	Japan	None	84 days	From 0.8 to 1.45	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Nausea Abdominal discomfort Abdominal distension Duodenal ulcer

1 See Appendix E for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Serum phosphate levels 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Calcium acetate	Calcium Carbonate	-0.07 (-0.31, 0.17)	Low	Could not differentiate
Ferric citrate	Calcium Carbonate	-0.28 (-0.49, -0.07)	Low	Effect favours ferric citrate
Lanthanum carbonate	Calcium Carbonate	-0.03 (-0.16, 0.10)	Low	Could not differentiate
Placebo	Calcium Carbonate	0.16 (0.01, 0.32)	Low	Effect favours calcium carbonate
Sevelamer hydrochloride	Calcium Carbonate	-0.10 (-0.38, 0.18)	Low	Could not differentiate
Ferric citrate	Calcium acetate	-0.21 (-0.44, 0.02)	Low	Could not differentiate
Lanthanum carbonate	Calcium acetate	0.04 (-0.16, 0.24)	Low	Could not differentiate
Placebo	Calcium acetate	0.23 (0.05, 0.41)	Low	Effect favours calcium acetate
Sevelamer hydrochloride	Calcium acetate	-0.03 (-0.17, 0.11)	Low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.24 (0.09, 0.40)	Low	Effect favours ferric citrate
Placebo	Ferric citrate	0.44 (0.30, 0.58)	Low	Effect favours ferric citrate
Sevelamer hydrochloride	Ferric citrate	0.17 (-0.09, 0.45)	Low	Could not differentiate
Placebo	Lanthanum carbonate	0.19 (0.11, 0.27)	Low	Effect favours lanthanum carbonate
Sevelamer hydrochloride	Lanthanum carbonate	-0.07 (-0.31, 0.17)	Low	Could not differentiate
Sevelamer hydrochloride	Placebo	-0.26 (-0.49, -0.03)	Low	Effect favours sevelamer hydrochloride

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was +/- 0.12.

Table 4: Proportion of adults with stage 4 or 5 CKD who are not on dialysis achieving phosphate control

Treatment 1	Treatment 2	Effect size Odds ratio (95% CIr)	Quality	Interpretation of effect[a]
Calcium acetate	Placebo	2.59 (1.05, 6.60)	Low	Effect favours calcium acetate
Ferric citrate	Placebo	30.30 (7.13, 255.00)	Low	Effect favours ferric citrate

Treatment 1	Treatment 2	Effect size Odds ratio (95% CIr)	Quality	Interpretation of effect[a]
Lanthanum carbonate	Placebo	3.38 (1.80, 6.78)	Low	Effect favours lanthanum carbonate
Ferric citrate	Calcium acetate	11.88 (2.07, 114.20)	Low	Effect favours ferric citrate
Lanthanum carbonate	Calcium acetate	1.31 (0.43, 4.03)	Low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.11 (0.01, 0.56)	Low	Effect favours ferric citrate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 5: Serum calcium levels 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Calcium acetate	Calcium Carbonate	0.09 (-0.08, 0.25)	Low	Could not differentiate
Ferric citrate	Calcium Carbonate	-0.02 (-0.17, 0.12)	Low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	-0.03 (-0.16, 0.10)	Low	Could not differentiate
Placebo	Calcium Carbonate	-0.08 (-0.21, 0.06)	Low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	0.04 (-0.15, 0.22)	Low	Could not differentiate
Ferric citrate	Calcium acetate	-0.11 (-0.22, -0.01)	Low	Effect favours ferric citrate
Lanthanum carbonate	Calcium acetate	-0.12 (-0.22, -0.01)	Low	Effect favours lanthanum carbonate
Placebo	Calcium acetate	-0.17 (-0.26, -0.07)	Low	Effect favours placebo
Sevelamer hydrochloride	Calcium acetate	-0.05 (-0.13, 0.03)	Low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.00 (-0.07, 0.06)	Low	No meaningful difference
Placebo	Ferric citrate	-0.06 (-0.10, -0.01)	Low	There is an effect which favours placebo, but it is less than the defined MID
Sevelamer hydrochloride	Ferric citrate	0.06 (-0.07, 0.20)	Low	Could not differentiate
Placebo	Lanthanum carbonate	-0.05 (-0.09, -0.01)	Low	There is an effect which favours placebo, but it is less than the defined MID

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Sevelamer hydrochloride	Lanthanum carbonate	0.07 (-0.06, 0.20)	Low	Could not differentiate
Sevelamer hydrochloride	Placebo	0.12 (0.00, 0.24)	Low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was +/- 0.09.

Table 6: Adverse events (constipation) in adults with stage 4 or 5 CKD who are not on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Ferric citrate	Placebo	2.11 (0.48, 16.78)	Low	Could not differentiate
Lanthanum carbonate	Placebo	3.53 (1.11, 15.38)	Low	Effect favours placebo
Lanthanum carbonate	Ferric citrate	1.68 (0.16, 13.60)	Low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 7: Adverse events (diarrhoea) in adults with stage 4 or 5 CKD who are not on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)		Quality	Interpretation of effect[a]
Ferric citrate	Placebo	2.46 (0.56, 19.03)		Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 8: Adverse events (nausea/vomiting) in adults with stage 4 or 5 CKD who are not on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Ferric citrate	Placebo	0.20 (0.01, 2.56)	Very low	Could not differentiate
Lanthanum carbonate	Placebo	1.85 (0.78, 5.17)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	9.54 (0.62, 336.20)	Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 9: Discontinuation due to adverse events in adults with stage 4 or 5 CKD who are not on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Calcium acetate	Placebo	0.64 (0.08, 3.46)	Low	Could not differentiate
Ferric citrate	Placebo	4.29 (0.61, 103.20)	Low	Could not differentiate
Lanthanum carbonate	Placebo	0.42 (0.16, 1.03)	Low	Could not differentiate
Sevelamer hydrochloride	Placebo	0.69 (0.00, 587.00)	Low	Could not differentiate
Ferric citrate	Calcium acetate	7.38 (0.49, 292.00)	Low	Could not differentiate
Lanthanum carbonate	Calcium acetate	0.66 (0.09, 6.37)	Low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	1.14 (0.00, 828.70)	Low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.10 (0.00, 0.84)	Low	Effect favours lanthanum carbonate
Sevelamer hydrochloride	Ferric citrate	0.14 (0.00, 166.40)	Low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	1.67 (0.00, 1569.00)	Low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

See Appendix I for full GRADE tables.

1.1.7 Economic evidence

A single search was carried out for the 2 review questions in this evidence review, using the same terms as the clinical search but with a health economic study filter (Appendix B). The search returned a total of 363 records, 334 of which were excluded based on title and abstract. We brought forward the 6 articles that were included in the previous iteration of the guideline and de-duplicated these against the remaining 29 from the search, leaving 33 full-text articles as potentially relevant to 1 or both review questions.

11 of these CUAs related to the population with CKD 4 or 5 not on dialysis (3 of which include both the pre-dialysis and on dialysis populations). Selective exclusions – that is, exclusion of studies when more directly relevant alternatives have been found – were discussed for any pairwise comparison for which multiple studies were available, in order to present the committee with a comprehensible amount of evidence.

- For the comparison of sevelamer hydrochloride versus calcium-based binders a Malaysian study by Goh et al. (2018) and a study from Singapore by Nguyen et al. (2016) were selectively excluded as 2 more applicable cost–utility analyses were available: 1 from the UK (Thompson et al., 2013) and 1 from Canada (Habbous et al., 2018; prioritised because the Canadian population bares a closer resemblance to the UK than Malaysia or Singapore).
- For the comparison of lanthanum carbonate versus calcium-based binders, a study in the Spanish population (Gros et al., 2015) was excluded because a UK study comparing the same binders was available (Vegter et al., 2011).

After exclusion based on the PICO and the selective exclusions, this left a total of 3 economic evaluations relating to people with stage 4 or 5 CKD who are not on dialysis in the synthesis.

1.1.7.1 Included studies

The included studies are summarised in evidence profiles, below; full evidence tables are provided in Appendix K.

1.1.7.2 Excluded studies

Details of excluded studies (including those that were selectively excluded as described above) are provided in Appendix M.

1.1.8 Summary of included economic evidence

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Cost (£)[a]	Effects (QALYs)	ICER (£/QALY)	
Habbous et al. (2018) Cost-Effectiveness of First-Line Sevelamer and Lanthanum versus Calcium-Based Binders for Hyperphosphatemia of Chronic Kidney Disease	Potentially serious [b]	Partially applicable [c]	Sevelamer hydrochloride vs lanthanum carbonate vs calcium-based binders Modelled cost-utility analysis, Canadian public payer perspective Dialysis costs included in base case	Sevelamer hydrochloride vs calcium-based binders			Sevelamer hydrochloride vs calcium-based binders: when dialysis costs excluded >70% probability sevelamer has an ICER better than $50K/QALY in CAD2015 (~=£25K/QALY in GBP2018)
				£96,039	1.59	£60,402	
				Lanthanum carbonate vs calcium-based binders			
				£65,765	0.98	Extendedly dominated	
Thompson et al. (2013) Economic evaluation of sevelamer for the treatment of hyperphosphatemia in chronic kidney disease patients not on dialysis in the United Kingdom	Potentially serious [d]	Partially applicable [e]	Sevelamer vs calcium carbonate Modelled cost-utility analysis, UK NHS perspective Dialysis costs included in base case	£39,854	1.56	£25,526	Sevelamer cost-effective in 93% of simulations (at a threshold of £30,000/QALY) Excluding dialysis costs led to a decreased cost per QALY
Vegter et al. (2011) Cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in chronic kidney disease before and during dialysis	Potentially serious [f]	Partially applicable [g]	Lanthanum carbonate (second-line after therapy failure with calcium-based binders) vs calcium-based binders alone	-£381	0.044	Lanthanum carbonate dominates	Calcium-based binders alone are favoured if dialysis costs are included

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Cost (£)[a]	Effects (QALYs)	ICER (£/QALY)	
			Modelled cost-utility analysis, UK NHS perspective Dialysis costs excluded in base case				

Key: CAD, Canadian dollars; GBP, British pound sterling; ICER, incremental cost-effectiveness ratio; OSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; USD, United States Dollars.

a. Costs were uprated to 2017/18 values using the Hospital and Community Health Service (HCHS) pay and prices inflator from the Unit Costs of Health and Social Care 2018 (Curtis and Burns, 2018). Where applicable, costs were converted from other currencies to GBP using purchasing power parities from the OECD (OECD, 2019).

b. Effects of PO4 and Ca on fractures, non-fatal CV events, and hyperparathyroidism were not modelled.

c. CKD stages undefined. Lumped calcium-based binders. It is unclear if the Canadian healthcare system was sufficiently similar to the NHS context. Other interventions not included.

d. Effects of PO4 and/or Ca on fractures, non-fatal CV events, and hyperparathyroidism were not modelled.

e. Modelled CKD stage 3 & 4. Also, other interventions relevant to the review were not included.

f. The effects of lowering PO4 on non-fatal cardiovascular events, fractures, hospitalisation and parathyroidectomy were not included. Also, effects of calcium were not modelled. Additionally, the majority of people treated with lanthanum were phosphate-binder naive, and so the trial was not truly reflective of lanthanum as second-line.

g. US trial data.

1

1.1.9 Economic model

Although the economic model developed for people with stage 5 CKD who are on dialysis (see below) was also theoretically capable of simulating people with stage 4 or 5 CKD who are not on dialysis, insufficient effectiveness data were available to estimate the relative benefits and harms of different phosphate binders, in this population.

1.1.10 The committee's discussion and interpretation of the evidence

The joint discussion section for the use of phosphate binders for people with stage 4 or 5 CKD who are not on dialysis and stage 5 CKD who are on dialysis is below in the review for the use of phosphate binders for people with stage 5 CKD who are on dialysis.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.11.5 – 1.11.16 and 1.11.8 – 1.11.17 and the research recommendations on phosphate binders (see Appendix N for further details about the research recommendation).

1.1.12 References – included studies

1.1.12.1 Effectiveness

Qunibi W., Winkelmayer W.C., Solomon R. et al. (2011) A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease. BMC Nephrology 12(1): 9

Russo, D., Miranda, I., Ruocco, C. et al. (2007) The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney International 72(10): 1255-1261

Soriano, Sagrario, Ojeda, Raquel, Rodriguez, Mencarnacion et al. (2013) The effect of phosphate binders, calcium and lanthanum carbonate on FGF23 levels in chronic kidney disease patients. Clinical nephrology 80(1): 17-22

Sprague, S. M., Abboud, H., Qiu, P. et al. (2009) Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial. Clinical Journal of The American Society of Nephrology: CJASN 4(1): 178-185

Takahara, Yuki, Matsuda, Yoshimi, Takahashi, Shunichi et al. (2014) Efficacy and safety of lanthanum carbonate in pre-dialysis CKD patients with hyperphosphatemia: a randomized trial. Clinical nephrology 82(3): 181-90

Yilmaz, Mahmut Ilker, Sonmez, Alper, Saglam, Mutlu et al. (2012) Comparison of calcium acetate and sevelamer on vascular function and fibroblast growth factor 23 in CKD patients: a randomized clinical trial. American journal of kidney diseases : the official journal of the National Kidney Foundation 59(2): 177-85

Yokoyama, Keitaro, Hirakata, Hideki, Akiba, Takashi et al. (2014a) Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. Clinical journal of the American Society of Nephrology : CJASN 9(3): 543-52

1.1.12.2 Economic

Habbous S, Przech S, Martin J et al. (2018) Cost-Effectiveness of First-Line Sevelamer and Lanthanum versus Calcium-Based Binders for Hyperphosphatemia of Chronic Kidney

Disease. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 21(3): 318-325

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1.1.12.3 Other

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Use of phosphate binders for people with stage 5 CKD who are on dialysis

1.1 Review question

RQ5.2 For people with stage 5 CKD who are on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?

1.1.1 Introduction

As kidney dysfunction advances, there is a higher risk of mortality and some comorbidities become more severe. Hyperphosphataemia is one example of this and occurs because of insufficient filtering of phosphate from the blood by poorly functioning kidneys. This means that a certain amount of the phosphate does not leave the body in the urine, instead remaining in the blood at abnormally elevated levels. High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to the development of secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism increases morbidity and mortality and may lead to renal bone disease, with people experiencing bone and muscular pain, increased incidence of fracture, abnormalities of bone and joint morphology, and vascular and soft tissue calcification.

The NICE guideline on chronic kidney disease (stage 4 or 5): management of hyperphosphataemia (NICE guideline CG157) was reviewed in 2017 as part of NICE's routine surveillance programme to determine whether new evidence was available that could alter the current recommendations. The surveillance report identified that sevelamer carbonate is available at considerably reduced cost to sevelamer hydrochloride as a generic version. However, sevelamer is still significantly more expensive than the calcium products. There is therefore a potential need to revise the health economic modelling in CG157, and to consider sevelamer carbonate which was not included in the original guideline. Sucroferric oxyhydroxide (Velphoro) was not considered in NICE guideline CG157 as it was not licensed when the guideline was developed. However, it is now licensed for adult CKD patients on dialysis for the control of serum phosphorus levels. The RCT evidence has demonstrated that Velphoro may be non-inferior to sevelamer carbonate, with a similar safety profile for serious adverse effects. As a result, the decision was made to update this part of the guideline.

The aim of this review is to compare phosphate binders, calcium and non-calcium based, to determine the most effective treatments for hyperphosphataemia in people with stage 5 CKD who are on dialysis. This review identified studies that fulfilled the conditions specified in Table 10. For full details of the review protocol, see Appendix A.

1.1.2 Summary of the protocol

Table 10: PICO table for the use of phosphate binders for people with stage 5 CKD who are on dialysis

Population	**Inclusion:** Adults, children and young people with stage 5 chronic kidney disease who are on dialysis **Exclusion:** Pregnant women
Intervention	Calcium and non-calcium based phosphate binders:

	• Lanthanum carbonate • Ferric carboxymaltose • Sevelamer hydrochloride • Sevelamer carbonate • Aluminium hydroxide • Magnesium carbonate • Calcium carbonate • Calcium acetate • Sucroferric oxyhydroxide • Calcium acetate/magnesium carbonate (Osvaren)
Comparator	• Placebo • other phosphate binding treatment (or combinations) from the list above
Outcomes	Over the duration of follow up of the study: • Overall and cardiovascular related mortality and morbidity • Serum phosphate • Adverse effects (#, bone density, Ectopic calcification (inc PAD) Cardiovascular calcification scores, Parathyroidectomy) • Patient concordance (author defined) • Serum calcium QoL (validated QoL measures)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods in Appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The following methods were specific for this review:

1. The NMA models for a dichotomous outcome were based on models from the NICE DSU technical support document 2 (models 1c and 1d for probabilities of events [logit link; odds ratio scale]; 3a and 3b for rates of events over time [cloglog link; hazard ratio scale]). The NMA models for a continuous outcome were based on models from the NICE DSU technical support document 2 (models 5a and 5b). The models are shown in Appendix P.
2. Results were reported as the posterior median and 95% credible interval from the NMA models.
3. The choice of NMA model (fixed effect versus random effects) was based on models with lower values of the posterior mean residual deviance (a measure of model fit to the data) and deviance information criteria (DIC) (a measure of parsimony balancing fit and complexity by penalising models with more parameters). In most cases, we considered a difference in DIC of 3 points or more as meaningful; however, we also preferred RE models with smaller benefits according to DIC where the total residual deviance was markedly closer to the number of datapoints in the network.
4. A continuity correction was used where the data contained zero events in 1 arm of a trial, but not the other, but only if there were problems running the model. Continuity correction was used to help the models converge because there were issues with data containing 0 events. The continuity correction involved adding 0.5 to the zero event arm and its matching comparator arm and 1 to the denominator for both arms. The use of a continuity correction is noted in the model fit statistics table.
5. For the NMA of mortality, we used a shared parameter model with a cloglog link for arm-level dichotomous event data and identity link for contrast-level log(HRs). HR data was

extracted instead of event data if a trial reported both outcome measures. The model combines the cloglog model (3a and 3b from the NICE DSU technical support document 2) and the identity (model 7a and 7b), using the shared parameter approach set out in 8a and 8b of the same document. This is consistent with the approach used by Oba et al. (2018). The models are shown in Appendix P.

6. Inconsistency checking of the NMA was carried out (see Appendix P).

We would like to acknowledge the Technical Support Unit, at University of Bristol, particularly Nicky Welton, Hugo Pedder, Tony Ades, and Caitlin Daly, for providing advice, models, and quality assurance for the network meta-analyses included in this review.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A single systematic search was carried out for the 2 review questions in this evidence review to identify randomised controlled trials (RCTs) and systematic reviews of RCTs, which found 575 references (see Appendix C). Evidence included in the original guideline and evidence from systematic reviews and network meta-analyses were also reviewed to identify primary studies. In total, 632 references were identified for screening at title and abstract level. Of these, 501 were excluded based on their titles and abstracts and 131 references (20 systematic reviews and 111 RCTs) were ordered for screening based on their full texts.

Of the 131 references screened at full text, 75 RCTs published in 87 references were included for the 2 review questions based on their relevance to the review protocols (Appendix A). Of the 87 included references, 80 presented data and met the inclusion criteria for the review on the use of phosphate binders for people with stage 5 CKD who are on dialysis. Only one study presented data for children and young people.

The clinical evidence study selection is presented as a PRISMA diagram in Appendix D.

See 1.1.12 References – included studies for a list of references for included studies.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 47 references for this review question, these were screen on title and abstract. Eight references were ordered for full text screening. None of these references were included based on their relevance to the review protocol (Appendix A).

1.1.4.2 Excluded studies

See Appendix M for a list of excluded studies with reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 11: Clinical studies on children and young people with stage 5 CKD who are on dialysis

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
Salusky et al. (2005) N=29	Calcium Carbonate versus Sevelamer	USA	Peritoneal	224 days	From 1.29 to 1.94	Achieved phosphate control Serum Ca (mmol/L) Serum

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
						Phosphate (mmol/L)

Table 12: Clinical studies on adults with stage 5 CKD who are on dialysis

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
Phosphate binders compared to no treatment						
Wang et al. (2015) N=53	Lanthanum carbonate versus No treatment	China	Haemodialysis	90 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Abdominal aortic calcification
Phosphate binders compared to placebo						
Al-Baaj et al. (2005) N=36 Related articles Hutchison et al. (2013)	Lanthanum carbonate versus Placebo	UK	Either Haemodialysis or Peritoneal	56 days	From 1.3 to 1.8	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Compliance
Chen et al. (2014) N=205	Sevelamer carbonate versus Placebo	China	Haemodialysis	56 days	Up to 1.78	Serum Phosphate (mmol/L) Constipation Nausea Abdominal discomfort Abdominal distension Compliance Serum phosphate (mg/dL)
Chertow et al. (1997) N=36	Sevelamer hydrochloride versus Placebo	USA	Haemodialysis	14 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Abdominal pain upper Diarrhoea Nausea & Vomiting Compliance
Chiang et al. (2005) N=61	Lanthanum Carbonate versus Placebo	Taiwan	Haemodialysis	28 days	From 0.6 to 1.8	Achieved phosphate control Serum Phosphate (mmol/L)

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
Emmett et al. (1991) N=68	Calcium Acetate versus Placebo	USA	Haemodialysis	14 days	From 1.45 to 1.78	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Finn et al. (2004) N=257	Placebo versus Lanthanum carbonate 225 versus Lanthanum carbonate 675 versus Lanthanum carbonate 1350 versus Lanthanum carbonate 2250 versus Lanthanum carbonate All groups	USA	Haemodialysis	42 days	Up to 1.78	Achieved phosphate control Serum Phosphate (mmol/L) Abdominal pain upper Diarrhoea Nausea & Vomiting
Jalal et al. (2017) N=537 Related articles Van Buren et al. (2015) Lewis et al. (2015)	Ferric citrate versus Calcium acetate or sevelamer carbonate versus Placebo	US and Israel	Either Haemodialysis or Peritoneal	392 days	From 1.13 to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Gastrointestinal serious adverse events Gastrointestinal non-serious adverse events Infection serious adverse events Infection non-serious adverse events Cardiac serious adverse events Cardiac non-serious adverse events Compliance
Joy et al. (2003) N=93	Lanthanum carbonate versus Placebo	USA	Haemodialysis	28 days	Up to 1.91	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Diarrhoea Nausea & Vomiting

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
Koiwa et al. (2017a) N=183	Sucroferric oxyhydroxide 750 versus Sucroferric oxyhydroxide 1500 versus Sucroferric oxyhydroxide 2250 versus Sucroferric oxyhydroxide 3000 versus Placebo	Japan	Either Haemodialysis or online haemodiafiltration	42 days	Up to 1.93	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Contusion Nasopharyngitis Abdominal pain Pain in extremity Haemorrhoids Insomnia Upper respiratory tract Upper respiratory tract inflammation
Lee et al. (2015) N=183	Ferric citrate 4g/d versus Ferric citrate 6g/d versus Placebo	Taiwan	Haemodialysis	56 days	Up to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Abdominal Distension Constipation Diarrhoea Discoloured faeces Hyperphosphatemia Abdominal pain
Shigematsu et al. (2008b) N=142	Lanthanum Carbonate 750mg/d versus Lanthanum Carbonate 1500mg/d versus Lanthanum Carbonate 2250mg/d versus Lanthanum Carbonate 3000mg/d versus Placebo	Japan	Haemodialysis	42 days	From 1.78 to 1.13	Achieved phosphate control Serum Phosphate (mmol/L) Abdominal pain upper Constipation Diarrhoea Nausea & Vomiting
Xu et al. (2013) N=227	Lanthanum carbonate versus Placebo	China	Either Haemodialysis or Peritoneal	56 days	Up to 1.78	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Nausea Vomiting Anorexia

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
						Aggravated itching Compliance
Yokoyama et al. (2012) N=192	Ferric citrate 1.5 g/day versus Ferric citrate 3 g/day versus Ferric citrate 6 g/day versus Placebo	Japan	Haemodialysis	28 days	Up to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Vomiting Abdominal discomfort Abdominal distension Rash Nasopharyngitis Abdominal pain Increased blood aluminium Venipuncture site swelling Myalgia Stomach discomfort Gastrointestinal disorder Arthralgia Subcutaneous haemorrhage
Phosphate binders compared to any binder						
Finn et al. (2006) N=1,359	Lanthanum carbonate versus Standard Treatment (any binder)	USA, Puerto Rico, Poland and South Africa	Haemodialysis	728 days	Up to 1.9	Achieved phosphate control Serum Ca (mmol/L) Abdominal pain upper Diarrhoea Nausea & Vomiting
Kalil et al. (2012) N=13	Lanthanum carbonate versus Non-lanthanum carbonate binder (any binder)	US	Haemodialysis	365 days	From 1.13 to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Coronary arterial calcification
Malluche et al. (2008) N=211	Lanthanum carbonate versus Standard Therapy (any binder)	USA, Puerto Rico, Poland, South Africa	Haemodialysis	728 days	Up to 1.91	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Wilson et al. (2009)	Lanthanum carbonate	USA, Puerto	Haemodialysis	970 days	Up to 1.9	All-cause mortality

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
N=1,354	versus Any binder	Rico, Poland and South Africa				
Phosphate binders compared to calcium based binders						
Block et al. (2005) N=148 Related articles Block 2007 Galassi 2006	Calcium based binders versus Sevelamer hydrochloride	USA	Haemodialysis	504 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Coronary arterial calcification Proportion with hypercalcaemia
Chertow et al. (2002) N=200 Related articles Raggi (2005)	Sevelamer hydrochloride versus Calcium based binders	USA, Germany and Austria	Haemodialysis	364 days	From 0.97 to 1.61	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Compliance Proportion with hypercalcaemia
Ferreira et al. (2008) N=91	Sevelamer Hydrochloride versus Calcium based binders	Portugal	Haemodialysis	378 days	From 1 to 1.6	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Raggi et al. (2004) N=186	Sevelamer hydrochloride versus Calcium based binders	USA, Germany and Austria	Haemodialysis	364 days	From 0.97 to 1.61	Coronary arterial calcification
Suki et al. (2007) N=2,103	Sevelamer hydrochloride versus Calcium based binders	USA	Haemodialysis	1369 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Nausea & Vomiting All-cause mortality Cardiovascular Mortality
Phosphate binders compared to each other						
Abraham et al. (2012) N=97	Sevelamer Carbonate versus Sevelamer hydrochloride	India	Haemodialysis	42 days	Up to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Ahmed et al. (2014) N=140	Sevelamer hydrochloride versus	Pakistan	Haemodialysis	168 days	Not reported	Serum Ca (mmol/L) Serum

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
	Calcium acetate					Phosphate (mmol/L)
Asmus et al. (2005) N=72	Sevelamer Hydrochloride versus Calcium Carbonate	Germany	Haemodialysis	672 days	From 1 to 1.6	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Coronary arterial calcification Proportion with hypercalcaemia
Babarykin et al. (2004) N=53	Calcium Bread versus calcium Acetate	Latvia	Haemodialysis	56 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Barreto et al. (2008) N=101	Calcium acetate versus Sevelamer Hydrochloride	Brazil	Haemodialysis	365 days	From 1.78 to 1.13	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Coronary arterial calcification Numbers on Ca dialysate 1.25mmol/L
Braun et al. (2004) N=114	Sevelamer hydrochloride versus Calcium Carbonate	Germany	Haemodialysis	364 days	From 1 to 1.6	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Coronary arterial calcification Compliance Proportion with hypercalcaemia
Chang et al. (2017) N=25	Lanthanum carbonate versus Calcium carbonate	Taiwan	Haemodialysis	168 days	Up to 1.93	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Diarrhoea
Chertow et al. (2003) N=108	Sevelamer Hydrochloride versus Calcium acetate	USA	Haemodialysis	364 days	From 1.6 to 0.97	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Nausea & Vomiting Coronary arterial calcification

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
						Compliance Proportion with hypercalcaemia
De Santo et al. (2006) N=16	Sevelamer Hydrochloride versus Calcium Carbonate	Italy	Haemodialysis	168 days	Up to 1.78	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
de Francisco et al. (2010) N=255	Calcium Acetate/Magnesium Carbonate versus Sevelamer Hydrochloride	Germany, Poland, Portugal, Romania and Spain	Haemodialysis	175 days	Up to 1.78	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Di Iorio et al. (2013) N=466	Sevelamer hydrochloride versus Calcium carbonate	Italy	Haemodialysis	1095 days	From 0.8 to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Coronary arterial calcification All-cause mortality Cardiovascular Mortality
Evenepoel et al. (2009) N=143	Sevelamer Hydrochloride versus Calcium Acetate	Belgium, Denmark, France, Italy, Spain, The Netherlands and UK	Peritoneal	84 days	From 0.97 to 1.78	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Proportion with hypercalcaemia
Fishbane et al. (2010) N=217	Sevelamer Carbonate Powder once a day versus Sevelamer Hydrochloride tablets 3 time per day	USA	Haemodialysis	168 days	From 1.13 to 1.78	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Nausea & Vomiting Compliance
Freemont et al. (2005) N=98	Lanthanum carbonate versus Calcium carbonate	12 countries (no further details provided)	Haemodialysis	364 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
						Nausea & Vomiting Proportion with hypercalcaemia
Fujii et al. (2018) N=108	Lanthanum carbonate versus Calcium carbonate	Japan	Haemodialysis	548 days	From 1.13 to 1.93	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Infection Rash Coronary arterial calcification Cardiovascular Mortality Cardiovascular events
Hervas et al. (2003) N=51	Sevelamer hydrochloride versus Calcium Acetate	Spain	Haemodialysis	224 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Hutchison et al. (2005) N=800	Lanthanum Carbonate versus Calcium Carbonate	UK, Germany, Belgium, The Netherlands	Haemodialysis	140 days	Up to 1.8	Achieved phosphate control Serum Phosphate (mmol/L) Constipation Diarrhoea Nausea & Vomiting Proportion with hypercalcaemia
Jalal et al. (2017) N=441 Related articles Van Buren et al. (2015) Lewis et al. (2015)	Ferric citrate versus Calcium acetate or sevelamer carbonate	US and Israel	Either Haemodialysis or Peritoneal	392 days	From 1.13 to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Gastrointestinal serious adverse events Gastrointestinal non-serious adverse events Infection serious adverse events Infection non-serious adverse events Cardiac serious adverse events Cardiac non-serious adverse

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
						events Compliance
Janssen et al. (1995) N=34	Calcium Acetate versus Calcium Carbonate	Netherlands	Haemodialysis	364 days	Up to 1.6	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Janssen et al. (1996) N=38	Calcium Acetate versus Calcium Carbonate		Haemodialysis	364 days	Up to 1.6	Achieved phosphate control Serum Phosphate (mmol/L) Proportion with hypercalcaemia
Kakuta et al. (2011) N=183	Sevelamer versus Calcium Carbonate	Japan	Haemodialysis	364 days	Up to 2.1	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Coronary arterial calcification
Katopodis et al. (2006) N=30	Sevelamer Hydrochloride versus Aluminium Hydroxide	Greece	Peritoneal	56 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation
Ketteler et al. (2019) N=1,059 Related articles Floege et al. (2014) Floege et al. (2015) Floege et al. (2017)	Sucroferric oxyhydroxide versus Sevelamer carbonate	Europe, US, Russia, Ukraine, Croatia, Serbia, South Africa	Either Haemodialysis or Peritoneal	365 days	From 0.81 to 2.75	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Nausea Vomiting Discoloured faeces Hyperphosphatemia Hypertension Compliance
Koiwa et al. (2005a) N=86	Sevelamer hydrochloride versus Sevelamer hydrochloride + Calcium Carbonate versus	Japan	Haemodialysis	28 days	Up to 1.78	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Abdominal

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
	Calcium Carbonate					Distension Constipation Proportion with hypercalcaemia
Koiwa et al. (2005b) N=46	Sevelamer hydrochloride + Calcium carbonate versus Calcium Carbonate	Japan	Haemodialysis	28 days	Not reported	Serum Phosphate (mmol/L)
Koiwa et al. (2017b) N=213	Sucroferric oxyhydroxide versus Sevelamer hydrochloride	Japan	Either Haemodialysis or online haemodiafiltration	84 days	From 1.13 to 1.78	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Diarrhoea Nasopharyngitis
Lee et al. (2013) N=50	Lanthanum carbonate versus Calcium carbonate	Korea	Peritoneal	168 days	From 1.13 to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Lin et al. (2011) N=52	Sevelamer hydrochloride versus Calcium acetate	Taiwan	Haemodialysis	56 days	From 1.13 to 1.78	Abdominal pain upper Constipation Nausea & Vomiting Compliance Proportion with hypercalcaemia
Lin et al. (2016) N=50 Related articles Lin et al. (2014)	Sevelamer hydrochloride versus Calcium carbonate	Taiwan	Haemodialysis	336 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Abdominal pain upper Constipation
Liu et al. (2006) N=70	Sevelamer hydrochloride versus Calcium acetate	Taiwan	Haemodialysis		From 1.13 to 1.94	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Proportion with hypercalcaemia
Maruyama et al. (2018) N=60	Ferric citrate versus Lanthanum carbonate	Japan	Either Haemodialysis or online haemodiafiltration	84 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Diarrhoea

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
						Stools loose Compliance
Navarro-Gonzalez et al. (2011) N=65	Sevelamer Hydrochloride versus Calcium Acetate	Spain	Haemodialysis	84 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Ohtake et al. (2013) N=42	Calcium carbonate versus Lanthanum carbonate	Japan	Haemodialysis	182 days	From 1.13 to 1.93	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Constipation Nausea Abdominal discomfort Pneumonia Arrythmia Loss of appetite Headache Rhinitis Cramps Oedema Hypotension Coronary arterial calcification All-cause mortality
Otsuki et al. (2018) N=63	Sucroferric oxyhydroxide versus Lanthanum carbonate	Japan	Either Haemodialysis or online haemodiafiltration	168 days	From 1.13 to 1.93	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Qunibi et al. (2008) N=203	Calcium Acetate versus Sevelamer hydrochloride	USA	Haemodialysis	364 days	From 1.13 to 1.78	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Abdominal pain upper Constipation Diarrhoea Nausea & Vomiting Coronary arterial calcification Compliance Proportion with hypercalcaemia
Ring et al. (1993) N=15	Calcium Acetate versus Calcium Carbonate	Denmark	Haemodialysis	21 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L)

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
Shigematsu et al. (2008a) N=258	Lanthanum carbonate versus Calcium Carbonate	Japan	Haemodialysis	56 days	From 1.13 to 1.78	Serum Phosphate (mmol/L) Abdominal Distension Abdominal pain upper Constipation Nausea & Vomiting Proportion with hypercalcaemia
Spasovski et al. (2006) N=24	Lanthanum carbonate versus Calcium Carbonate	Macedonia	On dialysis but no further details	364 days	Up to 1.8	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Proportion with hypercalcaemia
Spiegel et al. (2007) N=30	Magnesium Carbonate versus Calcium acetate	USA	Haemodialysis	84 days	Up to 1.78	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Tzanakis et al. (2008) N=51	Magnesium Carbonate versus Calcium carbonate	Greece	Haemodialysis	182 days	Up to 1.78	Achieved phosphate control Serum Ca (mmol/L) Serum Phosphate (mmol/L) Proportion with hypercalcaemia
Tzanakis et al. (2014) N=59	Calcium acetate + Magnesium carbonate versus Calcium acetate	Greece	Haemodialysis	365 days	Up to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L)
Wada et al. (2015) N=41 Related articles Wada et al. (2014)	Lanthanum carbonate versus Calcium carbonate	Japan	Haemodialysis	730 days	From 1.45 to 1.77	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Bone-mass density Aortic calcification index
Wuthrich et al. (2013)	Sucroferric oxyhydroxide 1.25 g/day	Eight European countries	Haemodialysis	42 days	From 1.13 to 1.77	Serum Ca (mmol/L) Serum

Study	Comparators	Country	Dialysis	Follow-up	Phosphate target	Outcomes
N=154	versus Sucroferric oxyhydroxide 5.0 g/day versus Sucroferric oxyhydroxide 7.5 g/day versus Sucroferric oxyhydroxide 10.0 g/day versus Sucroferric oxyhydroxide 12.5 g/day versus Sevelamer hydrochloride	and the US				Phosphate (mmol/L) Constipation Diarrhoea Vomiting Discoloured faeces Hyperphosphatemia Hypertension Pain in extremity Hypophosphatemia Hypercalcemia Muscle spasms Hypotension Anaemia All-cause mortality
Yokoyama et al. (2014b) N=229	Ferric citrate versus Sevelamer hydrochloride	Japan	Haemodialysis	84 days	From 1.13 to 1.94	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Abdominal Distension Constipation Diarrhoea Abdominal discomfort Haemoglobin increased Compliance
Other comparisons						
Chow et al. (2007) N=30	Treat to Goal (sevelamer hydrochloride) versus Low dose treatment (sevelamer hydrochloride)	China	Peritoneal	182 days	Up to 1.78	Achieved phosphate control Serum Phosphate (mmol/L) Compliance
Iwasaki et al. (2005) N=51	Sevelamer hydrochloride + Calcium carbonate (low) versus Sevelamer hydrochloride + Calcium Carbonate (high)	Japan	Haemodialysis	56 days	Not reported	Serum Ca (mmol/L) Serum Phosphate (mmol/L) Abdominal Distension Constipation Diarrhoea

1 See Appendix E for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 13: Mortality in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	1.24 (0.28, 5.99)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	1.11 (0.35, 4.38)	Very low	Could not differentiate
Calcium Based Binders	Calcium Carbonate	0.29 (0.18, 0.46)	Very low	Effect
Ferric citrate	Calcium Carbonate	1.05 (0.18, 6.44)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	1.06 (0.24, 5.02)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	0.26 (0.17, 0.40)	Very low	Effect favours sevelamer hydrochloride
Calcium acetate	Any binder	0.90 (0.13, 6.83)	Very low	Could not differentiate
Calcium Based Binders	Any binder	0.23 (0.04, 1.11)	Very low	Could not differentiate
Ferric citrate	Any binder	0.83 (0.35, 2.12)	Very low	Could not differentiate
Lanthanum carbonate	Any binder	0.86 (0.68, 1.08)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	0.21 (0.04, 0.99)	Very low	Effect favours sevelamer hydrochloride
Calcium Based Binders	Calcium acetate	0.26 (0.07, 0.77)	Very low	Effect favours calcium based binders
Ferric citrate	Calcium acetate	0.93 (0.11, 8.12)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	0.97 (0.13, 6.88)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	0.23 (0.06, 0.69)	Very low	Effect favours sevelamer hydrochloride
Ferric citrate	Calcium Based Binders	3.66 (0.62, 23.77)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Based Binders	3.74 (0.79, 18.99)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Based Binders	0.90 (0.77, 1.07)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	1.03 (0.39, 2.56)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	0.25 (0.04, 1.47)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Sevelamer hydrochloride	Lanthanum carbonate	0.24 (0.05, 1.15)	Very low	Could not differentiate

(a) *No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was the line of no effect.*

Table 14: Serum phosphate levels at 3 months in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	-0.18 (-0.43, 0.05)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	-0.15 (-0.43, 0.11)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Calcium Carbonate	-0.33 (-0.72, 0.03)	Very low	Could not differentiate
Ferric citrate	Calcium Carbonate	-0.14 (-0.43, 0.13)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	-0.05 (-0.26, 0.14)	Very low	No meaningful difference
Magnesium Carbonate	Calcium Carbonate	-0.22 (-0.79, 0.33)	Very low	Could not differentiate
No treatment	Calcium Carbonate	0.01 (-0.36, 0.37)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Carbonate	-0.21 (-0.53, 0.10)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	-0.15 (-0.35, 0.04)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Carbonate	-0.20 (-0.53, 0.11)	Very low	Could not differentiate
Calcium acetate	Any binder	0.03 (-0.27, 0.30)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Any binder	-0.15 (-0.54, 0.22)	Very low	Could not differentiate
Ferric citrate	Any binder	0.04 (-0.25, 0.32)	Very low	No meaningful difference
Lanthanum carbonate	Any binder	0.14 (-0.07, 0.32)	Very low	Could not differentiate
Magnesium Carbonate	Any binder	-0.04 (-0.62, 0.51)	Very low	Could not differentiate
No treatment	Any binder	0.19 (-0.18, 0.55)	Very low	Could not differentiate
Sevelamer Carbonate	Any binder	-0.03 (-0.36, 0.30)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	0.03 (-0.19, 0.25)	Very low	No meaningful difference
Sucroferric oxyhydroxide	Any binder	-0.02 (-0.35, 0.30)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Calcium Acetate + Magnesium Carbonate	Calcium acetate	-0.18 (-0.55, 0.19)	Very low	Could not differentiate
Ferric citrate	Calcium acetate	0.01 (-0.29, 0.32)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	0.10 (-0.18, 0.39)	Very low	Could not differentiate
Magnesium Carbonate	Calcium acetate	-0.07 (-0.56, 0.41)	Very low	Could not differentiate
No treatment	Calcium acetate	0.16 (-0.25, 0.58)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium acetate	-0.06 (-0.36, 0.27)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	0.00 (-0.18, 0.20)	Very low	No meaningful difference
Sucroferric oxyhydroxide	Calcium acetate	-0.05 (-0.36, 0.27)	Very low	Could not differentiate
Ferric citrate	Calcium Acetate + Magnesium Carbonate	0.19 (-0.20, 0.59)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Acetate + Magnesium Carbonate	0.28 (-0.09, 0.67)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Acetate + Magnesium Carbonate	0.11 (-0.50, 0.72)	Very low	Could not differentiate
No treatment	Calcium Acetate + Magnesium Carbonate	0.35 (-0.15, 0.84)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Acetate + Magnesium Carbonate	0.12 (-0.27, 0.54)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Acetate + Magnesium Carbonate	0.19 (-0.13, 0.51)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Acetate + Magnesium Carbonate	0.14 (-0.27, 0.54)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.09 (-0.16, 0.34)	Very low	Could not differentiate
Magnesium Carbonate	Ferric citrate	-0.08 (-0.66, 0.49)	Very low	Could not differentiate
No treatment	Ferric citrate	0.16 (-0.24, 0.55)	Very low	Could not differentiate
Sevelamer Carbonate	Ferric citrate	-0.07 (-0.41, 0.28)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	0.00 (-0.25, 0.23)	Very low	No meaningful difference
Sucroferric oxyhydroxide	Ferric citrate	-0.05 (-0.41, 0.28)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Magnesium Carbonate	Lanthanum carbonate	-0.17 (-0.75, 0.38)	Very low	Could not differentiate
No treatment	Lanthanum carbonate	0.06 (-0.24, 0.37)	Very low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	-0.16 (-0.48, 0.18)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	-0.10 (-0.31, 0.12)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	-0.15 (-0.48, 0.18)	Very low	Could not differentiate
No treatment	Magnesium Carbonate	0.23 (-0.40, 0.87)	Very low	Could not differentiate
Sevelamer Carbonate	Magnesium Carbonate	0.01 (-0.55, 0.60)	Very low	Could not differentiate
Sevelamer hydrochloride	Magnesium Carbonate	0.07 (-0.45, 0.61)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Magnesium Carbonate	0.02 (-0.55, 0.60)	Very low	Could not differentiate
Sevelamer Carbonate	No treatment	-0.22 (-0.66, 0.23)	Very low	Could not differentiate
Sevelamer hydrochloride	No treatment	-0.16 (-0.53, 0.21)	Very low	Could not differentiate
Sucroferric oxyhydroxide	No treatment	-0.21 (-0.66, 0.23)	Very low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	0.06 (-0.19, 0.30)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	0.01 (-0.24, 0.23)	Very low	No meaningful difference
Sucroferric oxyhydroxide	Sevelamer hydrochloride	-0.05 (-0.30, 0.19)	Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was +/- 0.28.

Table 15: Serum phosphate levels at 6 months in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	-0.05 (-0.21, 0.15)	Very low	No meaningful difference
Calcium acetate	Calcium Carbonate	0.09 (-0.18, 0.30)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Calcium Carbonate	-0.12 (-0.43, 0.22)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	0.01 (-0.12, 0.15)	Very low	No meaningful difference
Magnesium Carbonate	Calcium Carbonate	-0.07 (-0.36, 0.22)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Sevelamer Carbonate	Calcium Carbonate	0.10 (-0.16, 0.37)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	-0.07 (-0.22, 0.11)	Very low	No meaningful difference
Sucroferric oxyhydroxide	Calcium Carbonate	0.08 (-0.20, 0.35)	Very low	Could not differentiate
Calcium acetate	Any binder	0.14 (-0.18, 0.36)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Any binder	-0.07 (-0.40, 0.26)	Very low	Could not differentiate
Lanthanum carbonate	Any binder	0.05 (-0.11, 0.19)	Very low	No meaningful difference
Magnesium Carbonate	Any binder	-0.03 (-0.38, 0.30)	Very low	Could not differentiate
Sevelamer Carbonate	Any binder	0.14 (-0.14, 0.41)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	-0.02 (-0.20, 0.16)	Very low	No meaningful difference
Sucroferric oxyhydroxide	Any binder	0.12 (-0.19, 0.39)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Calcium acetate	-0.21 (-0.51, 0.20)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	-0.09 (-0.30, 0.21)	Very low	Could not differentiate
Magnesium Carbonate	Calcium acetate	-0.17 (-0.50, 0.25)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium acetate	0.00 (-0.26, 0.36)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	-0.16 (-0.31, 0.10)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium acetate	-0.02 (-0.31, 0.35)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Acetate + Magnesium Carbonate	0.12 (-0.22, 0.44)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Acetate + Magnesium Carbonate	0.05 (-0.40, 0.47)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Acetate + Magnesium Carbonate	0.21 (-0.16, 0.58)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Acetate + Magnesium Carbonate	0.05 (-0.23, 0.33)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Acetate + Magnesium Carbonate	0.19 (-0.21, 0.56)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Magnesium Carbonate	Lanthanum carbonate	-0.08 (-0.40, 0.23)	Very low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	0.09 (-0.17, 0.35)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	-0.07 (-0.24, 0.11)	Very low	No meaningful difference
Sucroferric oxyhydroxide	Lanthanum carbonate	0.07 (-0.20, 0.33)	Very low	Could not differentiate
Sevelamer Carbonate	Magnesium Carbonate	0.17 (-0.22, 0.57)	Very low	Could not differentiate
Sevelamer hydrochloride	Magnesium Carbonate	0.01 (-0.31, 0.35)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Magnesium Carbonate	0.15 (-0.26, 0.54)	Very low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	-0.16 (-0.39, 0.08)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	-0.02 (-0.25, 0.19)	Very low	No meaningful difference
Sucroferric oxyhydroxide	Sevelamer hydrochloride	0.14 (-0.15, 0.39)	Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was +/- 0.27.

Table 16: Serum phosphate levels at 12 months in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	0.07 (-0.07, 0.19)	Low	No meaningful difference
Calcium acetate	Calcium Carbonate	-0.05 (-0.24, 0.11)	Low	No meaningful difference
Calcium acetate + sevelamer carbonate	Calcium Carbonate	-0.17 (-0.60, 0.24)	Low	Could not differentiate
Ferric citrate	Calcium Carbonate	-0.03 (-0.34, 0.26)	Low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	0.16 (0.04, 0.27)	Low	There is an effect favouring calcium carbonate, but it is less than the defined MID
Sevelamer Carbonate	Calcium Carbonate	-0.05 (-0.40, 0.27)	Low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	0.01 (-0.10, 0.10)	Low	No meaningful difference
Sucroferric oxyhydroxide	Calcium Carbonate	-0.12 (-0.51, 0.24)	Low	Could not differentiate
Calcium acetate	Any binder	-0.12 (-0.31, 0.05)	Low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Calcium acetate + sevelamer carbonate	Any binder	-0.24 (-0.66, 0.18)	Low	Could not differentiate
Ferric citrate	Any binder	-0.10 (-0.41, 0.20)	Low	Could not differentiate
Lanthanum carbonate	Any binder	0.09 (-0.01, 0.21)	Low	No meaningful difference
Sevelamer Carbonate	Any binder	-0.12 (-0.46, 0.21)	Low	Could not differentiate
Sevelamer hydrochloride	Any binder	-0.06 (-0.17, 0.05)	Low	No meaningful difference
Sucroferric oxyhydroxide	Any binder	-0.19 (-0.57, 0.18)	Low	Could not differentiate
Calcium acetate + sevelamer carbonate	Calcium acetate	-0.11 (-0.50, 0.26)	Low	Could not differentiate
Ferric citrate	Calcium acetate	0.02 (-0.22, 0.27)	Low	Could not differentiate
Lanthanum carbonate	Calcium acetate	0.21 (0.03, 0.42)	Low	There is an effect favouring calcium acetate, but it is less than the defined MID
Sevelamer Carbonate	Calcium acetate	0.00 (-0.29, 0.29)	Low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	0.06 (-0.08, 0.21)	Low	No meaningful difference
Sucroferric oxyhydroxide	Calcium acetate	-0.07 (-0.40, 0.26)	Low	Could not differentiate
Ferric citrate	Calcium acetate + sevelamer carbonate	0.14 (-0.20, 0.47)	Low	Could not differentiate
Lanthanum carbonate	Calcium acetate + sevelamer carbonate	0.33 (-0.09, 0.77)	Low	Could not differentiate
Sevelamer Carbonate	Calcium acetate + sevelamer carbonate	0.11 (-0.25, 0.48)	Low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate + sevelamer carbonate	0.18 (-0.22, 0.59)	Low	Could not differentiate
Sucroferric oxyhydroxide	Calcium acetate + sevelamer carbonate	0.04 (-0.35, 0.44)	Low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.19 (-0.11, 0.52)	Low	Could not differentiate
Sevelamer Carbonate	Ferric citrate	-0.02 (-0.25, 0.20)	Low	No meaningful difference
Sevelamer hydrochloride	Ferric citrate	0.04 (-0.24, 0.33)	Low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Sucroferric oxyhydroxide	Ferric citrate	-0.09 (-0.37, 0.19)	Low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	-0.21 (-0.57, 0.13)	Low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	-0.15 (-0.29, -0.03)	Low	There is an effect favouring sevelamer hydrochloride, but it is less than the defined MID
Sucroferric oxyhydroxide	Lanthanum carbonate	-0.28 (-0.67, 0.09)	Low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	0.07 (-0.25, 0.39)	Low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	-0.07 (-0.24, 0.10)	Low	No meaningful difference
Sucroferric oxyhydroxide	Sevelamer hydrochloride	-0.14 (-0.50, 0.23)	Low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was +/- 0.25.

Table 17: Proportion of adults with stage 5 CKD who are on dialysis achieving phosphate control

Treatment 1	Treatment 2	Effect size Odds ratio (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	0.99 (0.09, 10.34)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	1.01 (0.23, 4.52)	Very low	Could not differentiate
Ferric citrate	Calcium Carbonate	1.14 (0.19, 6.83)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	0.87 (0.19, 3.70)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Carbonate	1.52 (0.25, 9.28)	Very low	Could not differentiate
Placebo	Calcium Carbonate	0.07 (0.01, 0.34)	Very low	Effect favours calcium carbonate
Sevelamer Carbonate	Calcium Carbonate	0.82 (0.13, 4.92)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	0.75 (0.17, 3.07)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Calcium Carbonate	2.78 (0.38, 21.05)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Carbonate	0.95 (0.18, 4.82)	Very low	Could not differentiate
Calcium acetate	Any binder	1.02 (0.08, 13.10)	Very low	Could not differentiate
Ferric citrate	Any binder	1.15 (0.11, 12.09)	Very low	Could not differentiate
Lanthanum carbonate	Any binder	0.87 (0.14, 5.27)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Odds ratio (95% CIr)	Quality	Interpretation of effect[a]
Magnesium Carbonate	Any binder	1.53 (0.09, 28.30)	Very low	Could not differentiate
Placebo	Any binder	0.07 (0.01, 0.52)	Very low	Effect favours any binder
Sevelamer Carbonate	Any binder	0.82 (0.07, 10.36)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	0.76 (0.07, 7.77)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Any binder	2.75 (0.16, 53.59)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Any binder	0.95 (0.09, 9.62)	Very low	Could not differentiate
Ferric citrate	Calcium acetate	1.13 (0.18, 6.90)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	0.86 (0.14, 4.81)	Very low	Could not differentiate
Magnesium Carbonate	Calcium acetate	1.51 (0.22, 10.25)	Very low	Could not differentiate
Placebo	Calcium acetate	0.07 (0.01, 0.39)	Very low	Effect favours calcium acetate
Sevelamer Carbonate	Calcium acetate	0.81 (0.14, 4.41)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	0.74 (0.20, 2.61)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Calcium acetate	2.77 (0.29, 26.64)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium acetate	0.94 (0.18, 4.57)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.76 (0.17, 3.09)	Very low	Could not differentiate
Magnesium Carbonate	Ferric citrate	1.33 (0.12, 14.61)	Very low	Could not differentiate
Placebo	Ferric citrate	0.06 (0.02, 0.21)	Very low	Effect favours ferric citrate
Sevelamer Carbonate	Ferric citrate	0.72 (0.12, 4.02)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	0.66 (0.16, 2.62)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Ferric citrate	2.45 (0.22, 27.23)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Ferric citrate	0.83 (0.17, 3.67)	Very low	Could not differentiate
Magnesium Carbonate	Lanthanum carbonate	1.75 (0.20, 16.86)	Very low	Could not differentiate
Placebo	Lanthanum carbonate	0.09 (0.04, 0.19)	Very low	Effect favours lanthanum carbonate
Sevelamer Carbonate	Lanthanum carbonate	0.95 (0.16, 5.61)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	0.87 (0.20, 3.77)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Odds ratio (95% CIr)	Quality	Interpretation of effect[a]
Sevelamer hydrochloride + Calcium Carbonate	Lanthanum carbonate	3.20 (0.34, 33.01)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	1.10 (0.25, 4.67)	Very low	Could not differentiate
Placebo	Magnesium Carbonate	0.05 (0.00, 0.43)	Very low	Effect favours magnesium carbonate
Sevelamer Carbonate	Magnesium Carbonate	0.54 (0.05, 5.43)	Very low	Could not differentiate
Sevelamer hydrochloride	Magnesium Carbonate	0.49 (0.06, 3.77)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Magnesium Carbonate	1.84 (0.14, 24.34)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Magnesium Carbonate	0.62 (0.07, 5.75)	Very low	Could not differentiate
Sevelamer Carbonate	Placebo	11.06 (2.16, 60.66)	Very low	Effect favours sevelamer carbonate
Sevelamer hydrochloride	Placebo	10.21 (2.74, 40.42)	Very low	Effect favours sevelamer hydrochloride
Sevelamer hydrochloride + Calcium Carbonate	Placebo	37.84 (4.06, 385.80)	Very low	Effect favours sevelamer hydrochloride + calcium carbonate
Sucroferric oxyhydroxide	Placebo	12.84 (3.58, 47.65)	Very low	Effect favours sucroferric oxyhydroxide
Sevelamer hydrochloride	Sevelamer Carbonate	0.92 (0.29, 2.98)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Sevelamer Carbonate	3.37 (0.34, 35.59)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	1.15 (0.32, 4.20)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Sevelamer hydrochloride	3.70 (0.50, 29.31)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride	1.25 (0.45, 3.55)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride + Calcium Carbonate	0.34 (0.04, 3.11)	Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 18: Serum calcium levels at 3 months in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	-0.05 (-0.19, 0.07)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	-0.07 (-0.20, 0.05)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Calcium Carbonate	-0.06 (-0.21, 0.10)	Very low	Could not differentiate
Ferric citrate	Calcium Carbonate	-0.10 (-0.22, 0.03)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	-0.10 (-0.21, 0.02)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Carbonate	-0.08 (-0.30, 0.13)	Very low	Could not differentiate
No treatment	Calcium Carbonate	0.00 (-0.19, 0.19)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	-0.14 (-0.22, -0.05)	Very low	Effect favours sevelamer hydrochloride
Sucroferric oxyhydroxide	Calcium Carbonate	-0.10 (-0.25, 0.06)	Very low	Could not differentiate
Calcium acetate	Any binder	-0.02 (-0.16, 0.13)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Any binder	0.00 (-0.17, 0.18)	Very low	Could not differentiate
Ferric citrate	Any binder	-0.05 (-0.16, 0.09)	Very low	Could not differentiate
Lanthanum carbonate	Any binder	-0.05 (-0.12, 0.05)	Very low	Could not differentiate
Magnesium Carbonate	Any binder	-0.03 (-0.26, 0.20)	Very low	Could not differentiate
No treatment	Any binder	0.05 (-0.11, 0.23)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	-0.08 (-0.19, 0.04)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Any binder	-0.05 (-0.21, 0.14)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Calcium acetate	0.02 (-0.14, 0.19)	Very low	Could not differentiate
Ferric citrate	Calcium acetate	-0.03 (-0.16, 0.12)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	-0.03 (-0.16, 0.13)	Very low	Could not differentiate
Magnesium Carbonate	Calcium acetate	-0.01 (-0.19, 0.17)	Very low	Could not differentiate
No treatment	Calcium acetate	0.07 (-0.12, 0.29)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	-0.06 (-0.15, 0.03)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Sucroferric oxyhydroxide	Calcium acetate	-0.02 (-0.18, 0.14)	Very low	Could not differentiate
Ferric citrate	Calcium Acetate + Magnesium Carbonate	-0.04 (-0.22, 0.13)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Acetate + Magnesium Carbonate	-0.05 (-0.21, 0.13)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Acetate + Magnesium Carbonate	-0.03 (-0.27, 0.21)	Very low	Could not differentiate
No treatment	Calcium Acetate + Magnesium Carbonate	0.05 (-0.17, 0.28)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Acetate + Magnesium Carbonate	-0.08 (-0.22, 0.05)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Acetate + Magnesium Carbonate	-0.04 (-0.23, 0.14)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.00 (-0.11, 0.11)	Very low	Could not differentiate
Magnesium Carbonate	Ferric citrate	0.02 (-0.22, 0.23)	Very low	Could not differentiate
No treatment	Ferric citrate	0.10 (-0.08, 0.28)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	-0.04 (-0.15, 0.07)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Ferric citrate	0.00 (-0.17, 0.17)	Very low	Could not differentiate
Magnesium Carbonate	Lanthanum carbonate	0.02 (-0.22, 0.23)	Very low	Could not differentiate
No treatment	Lanthanum carbonate	0.10 (-0.05, 0.25)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	-0.04 (-0.15, 0.07)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	0.00 (-0.17, 0.17)	Very low	Could not differentiate
No treatment	Magnesium Carbonate	0.08 (-0.18, 0.36)	Very low	Could not differentiate
Sevelamer hydrochloride	Magnesium Carbonate	-0.05 (-0.25, 0.15)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Magnesium Carbonate	-0.01 (-0.25, 0.23)	Very low	Could not differentiate
Sevelamer hydrochloride	No treatment	-0.14 (-0.32, 0.04)	Very low	Could not differentiate
Sucroferric oxyhydroxide	No treatment	-0.10 (-0.33, 0.13)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride	0.04 (-0.09, 0.17)	Very low	Could not differentiate

(a) *No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was +/- 0.09.*

Table 19: Serum calcium levels at 6 months in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	-0.09 (-0.23, 0.05)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	-0.05 (-0.22, 0.11)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Calcium Carbonate	-0.06 (-0.30, 0.17)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	-0.11 (-0.21, 0.00)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Carbonate	-0.26 (-0.47, -0.05)	Very low	Effect favours magnesium carbonate
Sevelamer Carbonate	Calcium Carbonate	-0.13 (-0.32, 0.07)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	-0.13 (-0.24, -0.02)	Very low	Effect favours sevelamer hydrochloride
Sucroferric oxyhydroxide	Calcium Carbonate	-0.11 (-0.30, 0.09)	Very low	Could not differentiate
Calcium acetate	Any binder	0.05 (-0.16, 0.23)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Any binder	0.03 (-0.22, 0.28)	Very low	Could not differentiate
Lanthanum carbonate	Any binder	-0.02 (-0.13, 0.10)	Very low	Could not differentiate
Magnesium Carbonate	Any binder	-0.17 (-0.42, 0.09)	Very low	Could not differentiate
Sevelamer Carbonate	Any binder	-0.04 (-0.24, 0.18)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	-0.04 (-0.18, 0.11)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Any binder	-0.01 (-0.22, 0.19)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Calcium acetate	-0.02 (-0.25, 0.25)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	-0.06 (-0.24, 0.14)	Very low	Could not differentiate
Magnesium Carbonate	Calcium acetate	-0.21 (-0.47, 0.07)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium acetate	-0.08 (-0.29, 0.16)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	-0.08 (-0.22, 0.08)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Sucroferric oxyhydroxide	Calcium acetate	-0.06 (-0.29, 0.19)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Acetate + Magnesium Carbonate	-0.05 (-0.29, 0.20)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Acetate + Magnesium Carbonate	-0.20 (-0.51, 0.12)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Acetate + Magnesium Carbonate	-0.07 (-0.34, 0.20)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Acetate + Magnesium Carbonate	-0.07 (-0.28, 0.14)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Acetate + Magnesium Carbonate	-0.04 (-0.32, 0.24)	Very low	Could not differentiate
Magnesium Carbonate	Lanthanum carbonate	-0.15 (-0.39, 0.08)	Very low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	-0.02 (-0.21, 0.17)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	-0.02 (-0.15, 0.11)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	0.00 (-0.18, 0.18)	Very low	Could not differentiate
Sevelamer Carbonate	Magnesium Carbonate	0.13 (-0.15, 0.42)	Very low	Could not differentiate
Sevelamer hydrochloride	Magnesium Carbonate	0.13 (-0.11, 0.37)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Magnesium Carbonate	0.15 (-0.14, 0.44)	Very low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	0.00 (-0.18, 0.17)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	0.02 (-0.15, 0.19)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride	0.02 (-0.17, 0.22)	Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was +/- 0.10.

Table 20: Serum calcium levels at 12 months in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	-0.03 (-0.15, 0.09)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	-0.11 (-0.25, 0.01)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Calcium acetate + sevelamer carbonate	Calcium Carbonate	-0.13 (-0.40, 0.11)	Very low	Could not differentiate
Ferric citrate	Calcium Carbonate	-0.18 (-0.43, 0.04)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	-0.09 (-0.19, 0.01)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Carbonate	-0.19 (-0.45, 0.04)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	-0.13 (-0.22, -0.05)	Very low	Effect favours sevelamer hydrochloride
Sucroferric oxyhydroxide	Calcium Carbonate	-0.19 (-0.50, 0.09)	Very low	Could not differentiate
Calcium acetate	Any binder	-0.08 (-0.25, 0.06)	Very low	Could not differentiate
Calcium acetate + sevelamer carbonate	Any binder	-0.10 (-0.38, 0.15)	Very low	Could not differentiate
Ferric citrate	Any binder	-0.15 (-0.41, 0.09)	Very low	Could not differentiate
Lanthanum carbonate	Any binder	-0.06 (-0.16, 0.04)	Very low	Could not differentiate
Sevelamer Carbonate	Any binder	-0.16 (-0.43, 0.08)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	-0.10 (-0.21, 0.01)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Any binder	-0.16 (-0.49, 0.13)	Very low	Could not differentiate
Calcium acetate + sevelamer carbonate	Calcium acetate	-0.02 (-0.24, 0.20)	Very low	Could not differentiate
Ferric citrate	Calcium acetate	-0.07 (-0.27, 0.12)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	0.02 (-0.13, 0.19)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium acetate	-0.08 (-0.28, 0.12)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	-0.02 (-0.12, 0.10)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium acetate	-0.08 (-0.35, 0.18)	Very low	Could not differentiate
Ferric citrate	Calcium acetate + sevelamer carbonate	-0.05 (-0.26, 0.16)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate + sevelamer carbonate	0.04 (-0.22, 0.32)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium acetate + sevelamer carbonate	-0.06 (-0.28, 0.15)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate + sevelamer carbonate	0.01 (-0.24, 0.26)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Mean difference (95% CIr)	Quality	Interpretation of effect[a]
Sucroferric oxyhydroxide	Calcium acetate + sevelamer carbonate	-0.06 (-0.35, 0.22)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.09 (-0.15, 0.35)	Very low	Could not differentiate
Sevelamer Carbonate	Ferric citrate	-0.01 (-0.20, 0.17)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	0.05 (-0.17, 0.28)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Ferric citrate	-0.01 (-0.28, 0.24)	Very low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	-0.10 (-0.37, 0.14)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	-0.04 (-0.16, 0.07)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	-0.10 (-0.43, 0.19)	Very low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	0.06 (-0.16, 0.30)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	0.00 (-0.19, 0.18)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride	-0.06 (-0.36, 0.21)	Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was +/- 0.11.

Table 21: Risk of hypercalcaemia in adults with stage 5 CKD who are on dialysis at the end of follow-up

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Calcium acetate	Calcium Carbonate	1.16 (0.37, 3.98)	Very low	Could not differentiate
Calcium Based Binders	Calcium Carbonate	1.42 (0.25, 8.04)	Very low	Could not differentiate
Ferric citrate	Calcium Carbonate	0.01 (0.00, 0.25)	Very low	Effect favours ferric citrate
Lanthanum carbonate	Calcium Carbonate	0.06 (0.02, 0.18)	Very low	Effect favours lanthanum carbonate
Magnesium Carbonate	Calcium Carbonate	0.23 (0.03, 1.72)	Very low	Could not differentiate
Placebo	Calcium Carbonate	0.02 (0.00, 0.80)	Very low	Effect favours palcebo
Sevelamer Carbonate	Calcium Carbonate	0.03 (0.00, 0.99)	Very low	Effect favours sevelamer carbonate
Sevelamer hydrochloride	Calcium Carbonate	0.42 (0.15, 1.14)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Sevelamer hydrochloride + Calcium Carbonate	Calcium Carbonate	0.32 (0.05, 1.80)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Carbonate	0.21 (0.01, 3.12)	Very low	Could not differentiate
Calcium Based Binders	Calcium acetate	1.22 (0.22, 6.10)	Very low	Could not differentiate
Ferric citrate	Calcium acetate	0.01 (0.00, 0.17)	Very low	Effect favours ferric citrate
Lanthanum carbonate	Calcium acetate	0.05 (0.01, 0.26)	Very low	Effect favours lanthanum carbonate
Magnesium Carbonate	Calcium acetate	0.20 (0.02, 1.97)	Very low	Could not differentiate
Placebo	Calcium acetate	0.02 (0.00, 0.53)	Very low	Effect favours placebo
Sevelamer Carbonate	Calcium acetate	0.03 (0.00, 0.68)	Very low	Effect favours sevelamer carbonate
Sevelamer hydrochloride	Calcium acetate	0.36 (0.14, 0.84)	Very low	Effect favours sevelamer hydrochloride
Sevelamer hydrochloride + Calcium Carbonate	Calcium acetate	0.27 (0.04, 1.82)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium acetate	0.18 (0.01, 2.46)	Very low	Could not differentiate
Ferric citrate	Calcium Based Binders	0.00 (0.00, 0.21)	Very low	Effect favours ferric citrate
Lanthanum carbonate	Calcium Based Binders	0.04 (0.01, 0.33)	Very low	Effect favours lanthanum carbonate
Magnesium Carbonate	Calcium Based Binders	0.16 (0.01, 2.39)	Very low	Could not differentiate
Placebo	Calcium Based Binders	0.01 (0.00, 0.67)	Very low	Effect favours placebo
Sevelamer Carbonate	Calcium Based Binders	0.02 (0.00, 0.83)	Very low	Effect favours sevelamer carbonate
Sevelamer hydrochloride	Calcium Based Binders	0.30 (0.07, 1.20)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Calcium Based Binders	0.22 (0.02, 2.18)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Based Binders	0.14 (0.01, 2.50)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	8.57 (0.20, 4952.00)	Very low	Could not differentiate
Magnesium Carbonate	Ferric citrate	32.97 (0.51, 22610.00)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Placebo	Ferric citrate	2.86 (0.00, 1792.00)	Very low	Could not differentiate
Sevelamer Carbonate	Ferric citrate	4.24 (0.01, 2523.00)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	56.94 (1.89, 27870.00)	Very low	Effect favours ferric citrate
Sevelamer hydrochloride + Calcium Carbonate	Ferric citrate	44.67 (0.90, 28880.00)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Ferric citrate	30.30 (0.37, 24550.00)	Very low	Could not differentiate
Magnesium Carbonate	Lanthanum carbonate	3.69 (0.38, 39.17)	Very low	Could not differentiate
Placebo	Lanthanum carbonate	0.34 (0.00, 15.32)	Very low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	0.49 (0.00, 20.63)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	6.87 (1.54, 33.03)	Very low	Effect favours lanthanum carbonate
Sevelamer hydrochloride + Calcium Carbonate	Lanthanum carbonate	5.14 (0.62, 44.30)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	3.37 (0.18, 68.12)	Very low	Could not differentiate
Placebo	Magnesium Carbonate	0.09 (0.00, 6.31)	Very low	Could not differentiate
Sevelamer Carbonate	Magnesium Carbonate	0.13 (0.00, 7.91)	Very low	Could not differentiate
Sevelamer hydrochloride	Magnesium Carbonate	1.86 (0.19, 18.19)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Magnesium Carbonate	1.39 (0.09, 20.06)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Magnesium Carbonate	0.92 (0.03, 25.46)	Very low	Could not differentiate
Sevelamer Carbonate	Placebo	1.44 (0.00, 1248.00)	Very low	Could not differentiate
Sevelamer hydrochloride	Placebo	20.06 (0.58, 15370.00)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Placebo	15.37 (0.27, 12840.00)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Placebo	10.71 (0.12, 10990.00)	Very low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	13.70 (0.47, 6042.00)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Sevelamer Carbonate	10.57 (0.23, 5175.00)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Sucroferric oxyhydroxide	Sevelamer Carbonate	7.27 (0.10, 4083.00)	Very low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Sevelamer hydrochloride	0.74 (0.12, 4.50)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride	0.49 (0.04, 6.02)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride + Calcium Carbonate	0.66 (0.03, 14.59)	Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 22: Adverse events (constipation) in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Aluminium Hydroxide	Calcium Carbonate	0.44 (0.00, 9.46)	Low	Could not differentiate
Calcium acetate	Calcium Carbonate	3.86 (1.26, 12.81)	Low	Effect favours calcium carbonate
Calcium Based Binders	Calcium Carbonate	0.90 (0.00, 30.15)	Low	Could not differentiate
Ferric citrate	Calcium Carbonate	0.76 (0.22, 2.60)	Low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	0.70 (0.45, 1.10)	Low	Could not differentiate
Placebo	Calcium Carbonate	0.39 (0.12, 1.16)	Low	Could not differentiate
Sevelamer Carbonate	Calcium Carbonate	1.60 (0.51, 5.22)	Low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	4.46 (1.94, 11.70)	Low	Effect favours calcium carbonate
Sevelamer hydrochloride + Calcium Carbonate	Calcium Carbonate	1.44 (0.42, 4.80)	Low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Carbonate	0.85 (0.28, 2.66)	Low	Could not differentiate
Calcium acetate	Aluminium Hydroxide	8.85 (0.42, 4339.00)	Low	Could not differentiate
Calcium Based Binders	Aluminium Hydroxide	2.09 (0.00, 2016.00)	Low	Could not differentiate
Ferric citrate	Aluminium Hydroxide	1.74 (0.08, 886.30)	Low	Could not differentiate
Lanthanum carbonate	Aluminium Hydroxide	1.63 (0.07, 814.50)	Low	Could not differentiate
Placebo	Aluminium Hydroxide	0.91 (0.04, 447.70)	Low	Could not differentiate
Sevelamer Carbonate	Aluminium Hydroxide	3.70 (0.17, 1845.00)	Low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Sevelamer hydrochloride	Aluminium Hydroxide	10.22 (0.55, 4991.00)	Low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Aluminium Hydroxide	3.33 (0.14, 1627.00)	Low	Could not differentiate
Sucroferric oxyhydroxide	Aluminium Hydroxide	1.96 (0.09, 971.60)	Low	Could not differentiate
Calcium Based Binders	Calcium acetate	0.23 (0.00, 7.56)	Low	Could not differentiate
Ferric citrate	Calcium acetate	0.19 (0.06, 0.64)	Low	Effect favours ferric citrate
Lanthanum carbonate	Calcium acetate	0.18 (0.05, 0.59)	Low	Effect favours lanthanum carbonate
Placebo	Calcium acetate	0.10 (0.03, 0.34)	Low	Effect favours placebo
Sevelamer Carbonate	Calcium acetate	0.41 (0.13, 1.28)	Low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	1.16 (0.57, 2.42)	Low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Calcium acetate	0.37 (0.11, 1.22)	Low	Could not differentiate
Sucroferric oxyhydroxide	Calcium acetate	0.22 (0.07, 0.64)	Low	Effect favours sucroferric oxyhydroxide
Ferric citrate	Calcium Based Binders	0.85 (0.02, 480.60)	Low	Could not differentiate
Lanthanum carbonate	Calcium Based Binders	0.79 (0.02, 425.90)	Low	Could not differentiate
Placebo	Calcium Based Binders	0.44 (0.01, 231.20)	Low	Could not differentiate
Sevelamer Carbonate	Calcium Based Binders	1.79 (0.05, 943.20)	Low	Could not differentiate
Sevelamer hydrochloride	Calcium Based Binders	4.97 (0.16, 2647.00)	Low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Calcium Based Binders	1.61 (0.04, 894.90)	Low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Based Binders	0.95 (0.03, 499.90)	Low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.93 (0.26, 3.30)	Low	Could not differentiate
Placebo	Ferric citrate	0.52 (0.15, 1.52)	Low	Could not differentiate
Sevelamer Carbonate	Ferric citrate	2.12 (0.66, 7.11)	Low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	5.93 (2.40, 16.41)	Low	Effect favours ferric citrate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Sevelamer hydrochloride + Calcium Carbonate	Ferric citrate	1.92 (0.49, 7.45)	Low	Could not differentiate
Sucroferric oxyhydroxide	Ferric citrate	1.12 (0.36, 3.64)	Low	Could not differentiate
Placebo	Lanthanum carbonate	0.56 (0.17, 1.61)	Low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	2.28 (0.70, 7.66)	Low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	6.40 (2.54, 17.50)	Low	Effect favours lanthanum carbonate
Sevelamer hydrochloride + Calcium Carbonate	Lanthanum carbonate	2.06 (0.57, 7.20)	Low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	1.21 (0.38, 3.92)	Low	Could not differentiate
Sevelamer Carbonate	Placebo	4.07 (1.47, 12.91)	Low	Effect favours placebo
Sevelamer hydrochloride	Placebo	11.52 (4.34, 34.95)	Low	Effect favours placebo
Sevelamer hydrochloride + Calcium Carbonate	Placebo	3.73 (0.91, 14.81)	Low	Could not differentiate
Sucroferric oxyhydroxide	Placebo	2.16 (0.79, 6.73)	Low	Could not differentiate
Sevelamer hydrochloride + Calcium Carbonate	Sevelamer Carbonate	0.32 (0.11, 0.81)	Low	Effect favours sevelamer hydrochloride + calcium Carbonate
Sucroferric oxyhydroxide	Sevelamer Carbonate	0.19 (0.08, 0.40)	Low	Effect favours sucroferric oxyhydroxide
Sucroferric oxyhydroxide	Sevelamer hydrochloride + Calcium Carbonate	0.59 (0.17, 2.12)	Low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 23: Adverse events (diarrhoea) in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	1.87 (0.37, 9.92)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	1.11 (0.13, 9.36)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Ferric citrate	Calcium Carbonate	7.68 (1.40, 44.94)	Very low	Effect favours calcium carbonate
Lanthanum carbonate	Calcium Carbonate	1.33 (0.48, 3.73)	Very low	Could not differentiate
Placebo	Calcium Carbonate	3.67 (0.90, 14.94)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Carbonate	1.55 (0.20, 11.26)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	0.99 (0.15, 6.43)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Carbonate	4.40 (0.67, 23.74)	Very low	Could not differentiate
Calcium acetate	Any binder	0.59 (0.06, 5.70)	Very low	Could not differentiate
Ferric citrate	Any binder	4.18 (0.61, 27.40)	Very low	Could not differentiate
Lanthanum carbonate	Any binder	0.72 (0.19, 2.63)	Very low	Could not differentiate
Placebo	Any binder	1.99 (0.37, 9.55)	Very low	Could not differentiate
Sevelamer Carbonate	Any binder	0.84 (0.08, 6.63)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	0.53 (0.07, 3.98)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Any binder	2.38 (0.29, 14.78)	Very low	Could not differentiate
Ferric citrate	Calcium acetate	6.95 (1.22, 42.54)	Very low	Effect favours calcium acetate
Lanthanum carbonate	Calcium acetate	1.21 (0.18, 7.98)	Very low	Could not differentiate
Placebo	Calcium acetate	3.30 (0.64, 17.23)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium acetate	1.40 (0.26, 6.68)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	0.89 (0.31, 2.45)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium acetate	3.96 (0.82, 15.69)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.17 (0.04, 0.69)	Very low	Effect favours lanthanum carbonate
Placebo	Ferric citrate	0.48 (0.15, 1.36)	Very low	Could not differentiate
Sevelamer Carbonate	Ferric citrate	0.20 (0.03, 1.03)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	0.13 (0.03, 0.52)	Very low	Effect favours sevelamer hydrochloride
Sucroferric oxyhydroxide	Ferric citrate	0.56 (0.13, 2.15)	Very low	Could not differentiate
Placebo	Lanthanum carbonate	2.76 (1.01, 7.43)	Very low	Effect favours lanthanum carbonate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Sevelamer Carbonate	Lanthanum carbonate	1.17 (0.19, 6.47)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	0.74 (0.15, 3.63)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	3.27 (0.68, 13.34)	Very low	Could not differentiate
Sevelamer Carbonate	Placebo	0.42 (0.09, 1.81)	Very low	Could not differentiate
Sevelamer hydrochloride	Placebo	0.27 (0.07, 0.96)	Very low	Effect favours sevelamer hydrochloride
Sucroferric oxyhydroxide	Placebo	1.19 (0.37, 3.45)	Very low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	0.64 (0.19, 2.28)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	2.86 (0.87, 8.23)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride	4.43 (1.47, 11.89)	Very low	Effect favours sevelamer hydrochloride

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 24: Adverse events (nausea/vomiting) in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	1.55 (0.12, 16.76)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	0.27 (0.01, 7.48)	Very low	Could not differentiate
Ferric citrate	Calcium Carbonate	5.81 (0.11, 3527.00)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	2.28 (0.64, 8.69)	Very low	Could not differentiate
Placebo	Calcium Carbonate	0.94 (0.15, 5.59)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Carbonate	0.23 (0.01, 3.97)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	0.23 (0.01, 3.94)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Carbonate	0.14 (0.00, 3.55)	Very low	Could not differentiate
Calcium acetate	Any binder	0.18 (0.01, 5.05)	Very low	Could not differentiate
Ferric citrate	Calcium Carbonate	3.97 (0.06, 2986.00)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	1.47 (0.21, 13.64)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Placebo	Calcium Carbonate	0.61 (0.07, 6.64)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Carbonate	0.15 (0.01, 2.86)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	0.15 (0.01, 2.53)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Carbonate	0.09 (0.00, 2.51)	Very low	Could not differentiate
Ferric citrate	Calcium acetate	23.06 (0.23, 20840.00)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	8.54 (0.42, 197.20)	Very low	Could not differentiate
Placebo	Calcium acetate	3.51 (0.18, 67.65)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium acetate	0.86 (0.06, 9.99)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	0.85 (0.15, 4.55)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium acetate	0.52 (0.03, 7.55)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.39 (0.00, 16.20)	Very low	Could not differentiate
Placebo	Ferric citrate	0.17 (0.00, 5.11)	Very low	Could not differentiate
Sevelamer Carbonate	Ferric citrate	0.04 (0.00, 2.71)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	0.04 (0.00, 2.87)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Ferric citrate	0.02 (0.00, 2.17)	Very low	Could not differentiate
Placebo	Lanthanum carbonate	0.41 (0.11, 1.36)	Very low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	0.10 (0.01, 1.24)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	0.10 (0.01, 1.23)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	0.06 (0.00, 1.16)	Very low	Could not differentiate
Sevelamer Carbonate	Placebo	0.24 (0.02, 2.61)	Very low	Could not differentiate
Sevelamer hydrochloride	Placebo	0.24 (0.02, 2.67)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Placebo	0.15 (0.01, 2.54)	Very low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	0.99 (0.16, 7.34)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	0.60 (0.09, 4.36)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride	0.61 (0.07, 5.03)	Very low	Could not differentiate

(a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.

Table 25: Discontinuation due to adverse events in adults with stage 5 CKD who are on dialysis

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Any binder	Calcium Carbonate	0.87 (0.35, 2.37)	Very low	Could not differentiate
Calcium acetate	Calcium Carbonate	1.83 (0.56, 5.76)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Calcium Carbonate	0.46 (0.06, 3.24)	Very low	Could not differentiate
Ferric citrate	Calcium Carbonate	2.17 (0.65, 7.57)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Carbonate	2.07 (0.97, 4.50)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Carbonate	2.81 (0.38, 28.97)	Very low	Could not differentiate
Placebo / no treatment	Calcium Carbonate	1.77 (0.60, 5.21)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Carbonate	2.15 (0.68, 7.71)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Carbonate	1.51 (0.69, 3.32)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Carbonate	2.65 (0.94, 7.77)	Very low	Could not differentiate
Calcium acetate	Any binder	2.09 (0.60, 6.64)	Very low	Could not differentiate
Calcium Acetate + Magnesium Carbonate	Any binder	0.52 (0.06, 3.75)	Very low	Could not differentiate
Ferric citrate	Any binder	2.49 (0.84, 7.24)	Very low	Could not differentiate
Lanthanum carbonate	Any binder	2.36 (1.01, 5.24)	Very low	Effect favours any binder
Magnesium Carbonate	Any binder	3.22 (0.39, 35.77)	Very low	Could not differentiate
Placebo / no treatment	Any binder	2.03 (0.69, 5.69)	Very low	Could not differentiate
Sevelamer Carbonate	Any binder	2.47 (0.76, 8.47)	Very low	Could not differentiate
Sevelamer hydrochloride	Any binder	1.73 (0.73, 3.80)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Any binder	3.04 (1.02, 8.85)	Very low	Effect favours any binder
Calcium Acetate + Magnesium Carbonate	Calcium acetate	0.25 (0.03, 1.91)	Very low	Could not differentiate
Ferric citrate	Calcium acetate	1.20 (0.30, 4.92)	Very low	Could not differentiate
Lanthanum carbonate	Calcium acetate	1.13 (0.34, 3.88)	Very low	Could not differentiate
Magnesium Carbonate	Calcium acetate	1.55 (0.21, 16.12)	Very low	Could not differentiate
Placebo / no treatment	Calcium acetate	0.97 (0.26, 3.74)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium acetate	1.18 (0.34, 4.87)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium acetate	0.82 (0.35, 2.05)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Sucroferric oxyhydroxide	Calcium acetate	1.45 (0.45, 4.99)	Very low	Could not differentiate
Ferric citrate	Calcium Acetate + Magnesium Carbonate	4.77 (0.58, 44.77)	Very low	Could not differentiate
Lanthanum carbonate	Calcium Acetate + Magnesium Carbonate	4.51 (0.62, 38.81)	Very low	Could not differentiate
Magnesium Carbonate	Calcium Acetate + Magnesium Carbonate	6.31 (0.42, 128.80)	Very low	Could not differentiate
Placebo / no treatment	Calcium Acetate + Magnesium Carbonate	3.87 (0.49, 35.59)	Very low	Could not differentiate
Sevelamer Carbonate	Calcium Acetate + Magnesium Carbonate	4.75 (0.63, 44.96)	Very low	Could not differentiate
Sevelamer hydrochloride	Calcium Acetate + Magnesium Carbonate	3.29 (0.53, 23.50)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Calcium Acetate + Magnesium Carbonate	5.84 (0.80, 49.89)	Very low	Could not differentiate
Lanthanum carbonate	Ferric citrate	0.95 (0.30, 2.96)	Very low	Could not differentiate
Magnesium Carbonate	Ferric citrate	1.30 (0.14, 16.09)	Very low	Could not differentiate
Placebo / no treatment	Ferric citrate	0.81 (0.27, 2.36)	Very low	Could not differentiate
Sevelamer Carbonate	Ferric citrate	0.99 (0.26, 4.17)	Very low	Could not differentiate
Sevelamer hydrochloride	Ferric citrate	0.69 (0.23, 2.02)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Ferric citrate	1.22 (0.34, 4.28)	Very low	Could not differentiate
Magnesium Carbonate	Lanthanum carbonate	1.37 (0.17, 14.75)	Very low	Could not differentiate
Placebo / no treatment	Lanthanum carbonate	0.86 (0.34, 2.12)	Very low	Could not differentiate
Sevelamer Carbonate	Lanthanum carbonate	1.05 (0.33, 3.61)	Very low	Could not differentiate
Sevelamer hydrochloride	Lanthanum carbonate	0.73 (0.31, 1.66)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Lanthanum carbonate	1.28 (0.47, 3.59)	Very low	Could not differentiate
Placebo / no treatment	Magnesium Carbonate	0.62 (0.05, 5.54)	Very low	Could not differentiate
Sevelamer Carbonate	Magnesium Carbonate	0.76 (0.07, 7.32)	Very low	Could not differentiate
Sevelamer hydrochloride	Magnesium Carbonate	0.53 (0.05, 3.91)	Very low	Could not differentiate

Treatment 1	Treatment 2	Effect size Hazard ratio (95% CIr)	Quality	Interpretation of effect[a]
Sucroferric oxyhydroxide	Magnesium Carbonate	0.93 (0.08, 8.06)	Very low	Could not differentiate
Sevelamer Carbonate	Placebo / no treatment	1.23 (0.39, 4.34)	Very low	Could not differentiate
Sevelamer hydrochloride	Placebo / no treatment	0.85 (0.32, 2.29)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Placebo / no treatment	1.50 (0.54, 4.32)	Very low	Could not differentiate
Sevelamer hydrochloride	Sevelamer Carbonate	0.70 (0.25, 1.78)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer Carbonate	1.23 (0.43, 3.14)	Very low	Could not differentiate
Sucroferric oxyhydroxide	Sevelamer hydrochloride	1.76 (0.78, 4.08)	Very low	Could not differentiate

(a) *No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: significant and point estimate >MID; There is an effect, but it is less than the defined MID: significant and point estimate <MID. The MID for this outcome was 0.8, 1.25.*

See Appendix I for full GRADE tables.

1.1.7 Economic evidence

The search for and initial screening of economic evidence for the 2 questions in this evidence review are described in '1.1.7 Economic evidence' in 'Use of phosphate binders for people with stage 4 or 5 CKD who are not on dialysis', above.

25 of the potentially relevant CUAs related to the population with CKD 5 who are on dialysis (3 of which include both the pre-dialysis and on dialysis populations). As for the non-dialysis population, we selectively excluded a number of studies.

- For the comparison of sevelamer hydrochloride vs calcium-based binders (either combined or individually), 2 UK studies were available (Taylor et al., 2008 and Bernard et al., 2013) therefore we selectively excluded 5 from other countries (Huybrechts et al., 2005; Manns et al., 2007; Cho et al., 2018; Ruggeri et al., 2015; Yang et al., 2016)
  - The only exception to this being Habbous et al. (2018) from Canada, which was included as it was included for the pre-dialysis population.
- For the comparison of lanthanum carbonate versus calcium-based binders, 2 non-UK studies (Gros et al., 2015; Vegter et al., 2012) were selectively excluded because 2 UK studies comparing the same binders were available (Brennan et al., 2007; Vegter et al., 2011).

After exclusion based on the PICO and the selective exclusions, this left a total of 7 economic evaluations people with stage 5 CKD who are on dialysis in the synthesis.

1.1.7.1 Included studies

The included studies are summarised in evidence profiles, below; full evidence tables are provided in Appendix K.

1.1.7.2 Excluded studies

Details of excluded studies (including those that were selectively excluded as described above) are provided in Appendix M.

1.1.8 Summary of included economic evidence

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Cost (£)[a]	Effects (QALYs)	ICER (£/QALY)	
Bernard et al. (2013) A modeled economic evaluation of sevelamer for treatment of hyperphosphatemia associated with chronic kidney disease among patients on dialysis in the United Kingdom	Potentially serious [b]	Partially applicable [c]	Sevelamer hydrochloride vs calcium-based binders Modelled cost-utility analysis, UK NHS perspective Dialysis costs excluded in base case	£11,069	0.445	£24,986	Results sensitive to overall survival assumptions and inclusion of dialysis costs ICER decreases with increasing age cut offs
Brennan et al. (2007) The cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in patients with end-stage renal disease	Minor	Directly applicable	Lanthanum carbonate (second-line after therapy failure with calcium carbonate) vs calcium carbonate alone Modelled cost-utility analysis, UK NHS perspective Dialysis costs excluded in base case	£483	0.018	£26,860	Subgroup analysis suggests lanthanum carbonate not cost-effective in people with lower phosphate at baseline (ICER > £120,000/QALY for 5.6–6.5 mg/dl)
Gutzwiller et al. (2015)	Potentially serious [d]	Partially applicable [e]	Sucroferric oxyhydroxide vs	-£1,609	-0.009	£187,920 (southwest quadrant)	When dialysis costs included, ICER = £134,546

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Cost (£)[a]	Effects (QALYs)	ICER (£/QALY)	
Cost Effectiveness of Sucroferric Oxyhydroxide Compared with Sevelamer Carbonate in the Treatment of Hyperphosphataemia in Patients Receiving Dialysis, from the Perspective of the National Health Service in Scotland			sevelamer carbonate Modelled cost-utility analysis, Scottish NHS perspective Dialysis costs excluded in base case				per QALY gained (southwest quadrant)
Habbous et al. (2018) Cost-Effectiveness of First-Line Sevelamer and Lanthanum versus Calcium-Based Binders for Hyperphosphatemia of Chronic Kidney Disease	Potentially serious [f]	Partially applicable [g]	Sevelamer hydrochloride vs lanthanum carbonate vs calcium-based binders Modelled cost-utility analysis, Canadian public payer perspective Dialysis costs included in base case	Sevelamer hydrochloride vs calcium-based binders			Sevelamer hydrochloride vs calcium-based binders: when dialysis costs excluded >70% probability sevelamer has an ICER better than $50K/QALY in CAD2015 (~=£25K/QALY in GBP2018)
				£108,278	1.43	£75,719	
				Lanthanum carbonate vs calcium-based binders			
				£70,204	0.87	Extendedly dominated	
Park et al. (2011) Cost-effectiveness of lanthanum carbonate versus sevelamer hydrochloride for the treatment of hyperphosphatemia in patients	Potentially serious [h]	Partially applicable [i]	Lanthanum carbonate vs sevelamer hydrochloride	£492	0.025	£19,669	PSA illustrated a 61.9% probability of lanthanum carbonate being cost-effective at threshold of $50,000 / QALY (USD2009)

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Cost (£)[a]	Effects (QALYs)	ICER (£/QALY)	
with end-stage renal disease: a US payer perspective			Modelled cost-utility analysis, US payer perspective Dialysis costs excluded in base case				Results of the base-case most sensitive to variations in phosphate binder drug costs
Taylor et al. (2008) An economic evaluation of sevelamer in patients new to dialysis	Very serious [j]	Directly applicable	Sevelamer (first-line use) vs calcium-based binders Modelled cost-utility analysis, UK NHS perspective Dialysis costs excluded in base case	£7,829	0.24	£32,619	ICER ranges from £18,355 to £41,042 per QALY in OSA
Vegter et al. (2011) Cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in chronic kidney disease before and during dialysis	Potentially serious [k]	Partially applicable	Lanthanum carbonate (second-line after therapy failure with calcium-based binders) vs calcium-based binders alone Modelled cost-utility analysis, UK NHS perspective	£434	0.0558	£7,758	Calcium-based binders alone are favoured if dialysis costs are included

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Cost (£)[a]	Effects (QALYs)	ICER (£/QALY)	
			Dialysis costs excluded in base case				

Key: CAD, Canadian dollars; GBP, British pound sterling; ICER, incremental cost-effectiveness ratio; OSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; USD, United States Dollars.

a. Costs were uprated to 2017/18 values using the Hospital and Community Health Service (HCHS) pay and prices inflator from the Unit Costs of Health and Social Care 2018 (Curtis and Burns, 2018). Where applicable, costs were converted from other currencies to GBP using purchasing power parities from the OECD (OECD, 2019).

b. Effects of PO4 and Ca on fractures, non-fatal CV events, and hyperparathyroidism were not modelled. Also, it was based on a US trial. Did not report PSA.

c. Analysis of CKD patients in dialysis for 38 months. Lumped calcium-based binders. Also, other interventions relevant to the review were not included.

d. Effects of PO4 and Ca on fractures, non-fatal CV events, and hyperparathyroidism were not modelled.

e. Modelled cohort was assumed to be intolerant to calcium-based phosphate binders. Also, other interventions relevant to the review were not included.

f. Effects of PO4 and Ca on fractures, non-fatal CV events, and hyperparathyroidism were not modelled.

g. CKD stages undefined. Lumped calcium-based binders. It is unclear if the Canadian healthcare system was sufficiently similar to the NHS context. Other interventions not included.

h. Cardiovascular events were modelled, however, effects of PO4 and Ca on fractures, non-fatal CV events, and hyperparathyroidism were not modelled.

i. Simulated patients assumed to be previously treated with calcium-based binder therapy. Also, other interventions relevant to the review were not included. Moreover, a US study.

j. Major methodological limitations: inadequate time horizon (5 years), inappropriate model structure (2 states; alive and dead), inadequate assessment of uncertainty (PSA was not conducted). Cost estimates not from the best available source (hospitalisation costs from CIPFA and not NHS reference costs). Potential conflict of interest.

k. The effects of lowering PO4 on non-fatal cardiovascular events, fractures, hospitalisation and parathyroidectomy were not included. Also, effects of calcium were not modelled. Additionally, the majority of people treated with lanthanum were phosphate-binder naive, and so the trial was not truly reflective of lanthanum as second-line.

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1.1.9 Economic model

An original economic model was developed to answer this review question. Table 26 presents an economic evidence profile summarising the model. See Appendix A for a full model report.

Table 26: Original cost–utility model – economic evidence profile

Limitations	Applicability	Other comments	Summary of cost-effectiveness results					Uncertainty
			Scenario	Strategy	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
Minor	Directly applicable	Individual patient simulation with a lifetime horizon	First-line therapies	CC				CA has a 75% probability of being most cost effective if a QALY is valued at £20,000 (based on 1,000 PSA iterations)
				CA	£1,175	0.143	£8,226	
				FC	£1,075	-0.008	dominated	
				SC	£3,414	0.113	£30,139	
				LC	£188	-0.100	dominated	
				SO	£2,944	0.058	£51,186	
				SH	£235	-0.109	dominated	
			Sequential use	CC				CA → SC has a 32% probability of being most cost effective if a QALY is valued at £20,000 (based on 1,000 PSA iterations)
				CA	£1,175	0.143	£8,226	
				CC -> LC	£1,075	-0.008	dominated	
				CC -> SC	£1,129	0.056	ext. dom.	
				CA -> LC	£1,326	0.057	ext. dom.	
				CA -> SC	£1,415	0.096	£14,738	
				CA -> SH	£753	-0.035	dominated	
				CC -> SH	£843	-0.102	dominated	
				CA -> SO	£1,225	0.037	£33,293	
				CA -> FC	£119	-0.010	dominated	

Limitations	Applicability	Other comments	Summary of cost-effectiveness results					Uncertainty
			Scenario	Strategy	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
				CC -> FC	£313	-0.049	dominated	
				CC -> SO	£390	-0.025	dominated	
				SC	£774	-0.020	dominated	
				LC	£963	-0.120	dominated	
				SO	£3,718	0.038	£97,903	
				SH	£235	-0.109	dominated	
				FC	£344	-0.020	dominated	

CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

1.1.10 The committee's discussion and interpretation of the evidence

This section contains the joint discussion section for the use of phosphate binders for people with stage 4 or 5 CKD who are not on dialysis and stage 5 CKD who are on dialysis. the evidence review for the use of phosphate binders for people with stage 4 or 5 CKD who are not on dialysis is above.

1.1.10.1. The outcomes that matter most

The committee agreed that the key outcomes for people with hyperphosphatemia were serum phosphate and serum calcium levels, proportion of people achieving phosphate control, risk of hypercalcemia, and adverse events (constipation, diarrhoea, nausea/vomiting, and discontinuation due to adverse events). The committee agreed that other outcomes were also important such as cardiovascular morbidity and other adverse events (for example, abdominal pain/discomfort and cardiovascular calcification) but shortage of evidence on these outcomes made harder to use them for decision making. No data were found about quality of life. The committee agreed that mortality is a critical outcome to make decisions but only 4 RCTs used the appropriate method (hazard ratio) of survival analysis with high risk of bias which made harder to use them for decision making. The rest of RCTs only reported the number of deaths. Therefore, analyses based on mortality data were received with caution and not central to decision making. The committee preferred to concentrate on plausible evidence of important outcomes rather than implausible evidence of a critical outcome. The committee also agreed that adherence is a critical outcome but included studies did not define how they analysed adherence, therefore, results were difficult to interpret for decision making.

1.1.10.2 The quality of the evidence

Ferric citrate was not available in the UK when the committee discussed the evidence on phosphate binders for the management of hyperphosphatemia, but it was included in the NMAs to explore its efficacy in case it becomes available in the future. Therefore, the committee looked at the evidence on ferric citrate, but this treatment was not included in the discussion leading to recommendations.

Most of the evidence was for adults with stage 5 CKD who were on dialysis. Only 7 RCTs were on adults with stage 4 or 5 CKD who were not on dialysis. Only 1 RCT was on children and young people with stage 5 CKD who were on dialysis.

The committee discussed the results of all the network meta-analyses (NMAs). However, they made decisions based on the NMAs in adults with stage 5 CKD who were on dialysis because most of the evidence came from this group of people and longer follow-up times were reported (see below for a list of outcomes and follow-ups for each population). The committee agreed that the large body of evidence found for the use of phosphate binders in adults with stage 5 CKD (who were on dialysis) was a stronger foundation from which to make recommendations than the small, limited evidence base found for adults with stage 4 or 5 CKD who were not on dialysis. Early intervention to prevent or manage high phosphate levels was considered key to preventing downstream complications resulting from the poor management of serum calcium. The committee emphasised the importance of starting phosphate binder therapy early, and stressed that this should be in the context of concurrent dietary management of serum phosphate.

The list below has outcomes and follow-up time for each of the population groups:

- Adults with stage 4 or 5 CKD who were not on dialysis
  - Serum phosphate levels (2 to 4 months)
  - Serum calcium levels (2 to 4 months)

  - Proportion of people achieving phosphate control (end of treatment)
  - Adverse events (constipation, diarrhoea, nausea/vomiting, discontinuation due to adverse events)
- Adults with stage 5 CKD who were on dialysis
  - Mortality
  - Serum phosphate levels (3, 6 and 12 months)
  - Serum calcium levels (3, 6 and 12 months)
  - Proportion of people achieving phosphate control (end of treatment)
  - Risk of hypercalcemia
  - Adverse events (constipation, diarrhoea, nausea/vomiting, discontinuation due to adverse events)

Overall, the quality of the NMAs was from low to very low, with the main reasons for downgrading being due to imprecision of the evidence on the different outcomes and the risk of bias of the included studies. In most of the pairwise comparisons, imprecision was considered to be serious because the 95% credible interval (CrI) of at least one of the comparisons crossed a defined minimal clinically important difference (MID) and no meaningful distinct treatments were identified. Risk of bias for some of the included studies was due to lack of detailed report of the randomisation process, lack of report of type of analysis (intention-to-treat or modified intention-to-treat analyses), use of inappropriate analysis ('as treated' or 'per-protocol' analyses), lack of reporting of protocols, and participants either being aware of which intervention were assigned or poor description of the assignment of interventions. The committee discussed the quality of the evidence (being mainly low) and agreed that recommendations should be written to reflect the clinical importance of treating hyperphosphataemia as a serious condition in people with CKD.

The NMA on mortality combined contrast-level hazard ratios with arm-level event data, with the latter using a clog-log link function (see section of 1.1.3 Methods and process for a description of the clog-log models).

In most of the RCTs reporting adherence, it was measured with pill counts but there was not a definition on how the results were analysed. Percentage of adherence was reported in the results of these RCTs but it was unclear whether the percentage referred to people taking the number of prescribed pills or whether the percentage was the mean percentage of pills taken during the study. Therefore, data on adherence was not used in this review.

1.1.10.3 Benefits and harms

The committee noted that people often find it hard to take phosphate binders. Therefore, they agreed that it is particularly important to involve people with stage 4 or 5 CKD who are not on dialysis and people with stage 5 CKD who are on dialysis as well as their families or carers (as appropriate) in the decision-making process as much as possible to ensure that they understand why they need to take phosphate binders and what the consequences are of not taking them and, that if they are unable to take the phosphate binder they are prescribed, then they may be prescribed an alternative formulation. They agreed to start the section on phosphate binders with a recommendation to reflect this issue. The committee also agreed that diet and dialysis (when appropriate) should be optimised before offering phosphate treatment and they added a recommendation to reflect this. The committee mentioned that making changes to diet and dialysis might prevent the need to use a phosphate binder.

The committee highlighted that, from their experience, most people with stage 4 and 5 CKD have a high tablet burden before starting phosphate binders and that many people find phosphate binders unpalatable and difficult to swallow. These contribute to the poor adherence to phosphate binders. The committee agreed that people need education about the reason for offering phosphate binders and the risks if they are not taken. If a person is

not taking their phosphate binder as recommended, it is suggested to evaluate their understanding of the consequences of high phosphate levels and to evaluate measures to improve engagement. The committee added this to a recommendation which includes what to discuss with people when offering phosphate binders.

Regarding the treatment for children and young people, the committee agreed to keep all 3 recommendations previously published in 2013 apart from replacing sevelamer hydrochloride by sevelamer carbonate based on the evidence found from the economic analysis that sevelamer carbonate offered a similar gain in QALYs at a lower price compared with hydrochloride (see section 1.1.10.4 Cost effectiveness and resource use for more details). There was no change on the content of the recommendations previously published in 2013 (details on each recommendation is described in the following sentences). The committee agreed that a calcium-based binder would be desirable as the first-line phosphate binder used in children. This is because children require additional calcium for their growing bones, but also to avoid the effects of secondary hyperparathyroidism that can rise in young people with chronically low serum calcium levels. In children with high serum calcium or at risk from hypercalcemia, a combination of a calcium-based and a non-calcium-based binder should be used as the first-line binder regimen. In this way, serum phosphate can be controlled to the desired level without further raising the serum calcium, but also without allowing calcium to decrease to levels that lead to the adverse effects outlined above. In some children taking a calcium-based binder, serum phosphate can still remain above the recommended level and serum calcium may reach the age-adjusted upper limit of normal. In these patients it was felt that no further increase should be made to the dose of calcium-based binders. Instead, a non-calcium binder could be added to the regimen, either in substitution for some of the calcium-based binder or in replacement of it.

Adults with stage 4 or 5 CKD who are not on dialysis

The committee noted that there was a shortage of RCTs that recruited people with stage 4 or 5 CKD who are not on dialysis. Therefore, the committee decided to make recommendations for this group to follow the treatments that were effective in adults with stage 5 CKD who are on dialysis because of the clinical importance of treating hyperphosphataemia as a serious condition in people with stage 4 or 5 CKD with or without dialysis. It also made a research recommendation in the hope that this gap could be addressed in future updates of the guideline.

Adults with stage 5 CKD who are on dialysis

The committee discussed the evidence for adults with stage 5 CKD who are on dialysis based on the results of the NMAs. The committee also looked at the summary graphic in Appendix Q when discussing the best treatment option for all outcomes.

The committee agreed that it was important to have a range of options available because each phosphate binder is different and people might prefer one type over another based on its characteristics (presentation [tablets or sachets], size, or palatability) and adverse events.

The committee discussed that calcium carbonate showed a clinically significant increase in levels of serum calcium at the 3 times points (3, 6, and 12 months) compared with sevelamer hydrochloride, clinically significant increase in levels of serum calcium at 6 months compared with magnesium carbonate, and a higher risk of hypercalcemia compared with lanthanum carbonate and sevelamer carbonate (see Appendix H, tables 42 to 44). Therefore, it agreed that calcium carbonate should not be considered as a substitute for calcium acetate which is recommended as a first-line phosphate binder unless people can not tolerate calcium acetate as explain below. The committee noted that people taking calcium acetate had higher risk of hypercalcemia, but there was no clinical difference on serum calcium levels at any of the time points compared with other treatments. Therefore, the committee agreed to keep calcium acetate as a first-line phosphate binder as it showed a clinically significant effect compared with placebo increasing the proportion of adults achieving target (<1.78 mmol/l)

phosphate levels. The committee also made a recommendation to consider calcium carbonate if a calcium-based agent is required in adults who do not tolerate calcium acetate. This decision was based on the data showing that, even though it carried a risk of hypercalcaemia, calcium carbonate was effective at increasing the proportion of adults achieving phosphate control compared with placebo and at reducing the risk of constipation compared with calcium acetate and sevelamer hydrochloride (see Appendix H, tables 41 and 46).

The committee discussed that sevelamer carbonate showed a clinically significant effect increasing the proportion of adults achieving phosphate control compared with placebo and a clinically significant effect reducing the risk of hypercalcemia compared with calcium carbonate and calcium acetate (see Appendix H, tables 41 and 45). Based on this evidence and cost effectiveness evidence (see below), the committee agreed to recommend sevelamer carbonate if calcium acetate was not indicated, tolerated or palatable.

The committee discussed the evidence of a new iron-based phosphate binder (sucroferric oxyhydroxide) available in the UK. Sucroferric oxyhydroxide showed a clinical significant effect increasing the proportion of adults achieving phosphate control compared with placebo and a clinically significant effect reducing the risk of constipation compared with calcium acetate and sevelamer carbonate but there was a higher risk of diarrhoea compared with sevelamer hydrochloride (see Appendix H, tables 41, 46 - 47). Therefore, the committee recommended considering sucroferric oxyhydroxide in adults on dialysis if a non-calcium agent is required and sevelamer carbonate is not suitable.

The committee discussed that lanthanum carbonate showed a clinically significant effect increasing the proportion of adults achieving phosphate control compared with placebo, a clinically significant effect reducing serum calcium levels at 6 months compared with calcium carbonate, a clinically significant effect reducing the risk of hypercalcemia compared with calcium carbonate and calcium acetate, and a clinically significant effect decreasing the risk of constipation compared with calcium acetate and sevelamer hydrochloride (see Appendix H, tables 41, 43, 45 - 46). Based on the clinical and economic evidence that lanthanum carbonate had a high cost and relatively low efficacy versus the other non-calcium-containing binders, the committee agreed to recommend lanthanum carbonate only if other preparations were not tolerated.

The committee also discussed evidence on the combination of calcium acetate and magnesium carbonate which showed that results could not differentiate between this combination and the rest of interventions (calcium carbonate, any binder, calcium acetate, ferric citrate, lanthanum carbonate, magnesium carbonate, sevelamer carbonate, sevelamer hydrochloride or sucroferric oxyhydroxide) for serum phosphate levels at 3 months or at 6 months or for serum calcium levels at 3 months or 6 months or for discontinuation due to adverse events. Longer term outcomes and adverse events were not reported for the combination of calcium acetate and magnesium carbonate. The committee agreed to replace magnesium carbonate with calcium acetate plus magnesium carbonate in a research recommendation on its effectiveness and safety in adults with stage 5 CKD who are on dialysis (minimum 12 months follow-up).

The committee also discussed the old recommendation on combinations of phosphate binders for adults. It was agreed that if patients reached the maximum recommended (or tolerated) daily dose of calcium-based binders, no further increases in the dose of calcium-based binder should be made. Instead, a non-calcium-based binder may need to be added to the regimen, producing a combination. The aim would be for the added phosphate-binding capacity to raise phosphate control to the desired level without exceeding the recommended daily intake for elemental calcium.

The committee discussed the list of all research recommendations made in 2013. They agreed to remove the research recommendation on aluminium hydroxide because this has been withdrawn as a phosphate binder. They also agreed to remove the research

recommendation on sequencing and combining of phosphate binders in adults because this type of research might encounter feasibility limitations. The committee agreed to keep both research recommendations on phosphate binders in adults and in children and young people with CKD stage 4 or 5 who are not on dialysis because there is still a lack of research in this population. They also highlighted that there were no data for this population on the new iron-based phosphate binder (sucroferric oxyhydroxide). Finally, the committee agreed to make a new qualitative research recommendation to explore people with CKD and their carers' views and beliefs about taking oral phosphate binders. Members of the committee, including lay members with experience of taking phosphate binders agreed that compliance with phosphate binder regimens was an important factor in their effectiveness. Anecdotal evidence suggested that people were reluctant to take phosphate binders because they are large and unpleasant to take. They also require a large part of a persons restricted fluid intake. The committee agreed that understanding this problem better would enable them to improve their recommendations in future updates of this guideline. They highlighted that no data was found on quality of life.

1.1.10.4 Cost effectiveness and resource use

The committee discussed the economic evidence relating to the use of phosphate binders to control serum phosphate in children, young people and adults with CKD. This included a number of published economic evaluations of varying quality that were partially relevant to the review questions. The committee reviewed the results of these economic evaluations, but as none of them included all relevant comparators, committee discussion instead focused on the results of a *de novo* economic model that was developed to be directly applicable to the decision problem.

Because of insufficient data in children and in people with CKD stages 4 and 5 who are not on dialysis, it was not possible to conduct separate analyses for these groups. The committee took a view as to whether results could be extrapolated to people with CKD stages 4 and 5 pre-dialysis, and to children. Furthermore, there are some interventions for which there are insufficient data for inclusion in the model (for example, magnesium carbonate with or without calcium acetate); these were not considered for recommendation by the committee due to the lack of evidence.

The results of the model were presented to the committee, including probabilistic and deterministic sensitivity analyses and scenario analyses. Two separate scenarios were discussed. The first assumes people are assigned to a single binder and are not allowed to switch due to hypercalcaemia; they remain on their initial binder indefinitely (unless they need to switch due to adverse events). The second assumes people can switch from a calcium-based to non-calcium-based binder (in pre-defined sequences) in the event of hypercalcaemia.

In the first scenario, calcium acetate had the best balance of benefits, harms and costs, with an ICER of £8,226 per QALY gained versus calcium carbonate. None of the other options would be considered cost effective if a QALY is valued at £20,000; sevelamer carbonate has an ICER of £30,139 versus calcium acetate, while sucroferric oxyhydroxide has an ICER of £51,186 versus sevelamer carbonate. In the second scenario with switches allowed, a strategy in which calcium acetate is given first followed by sevelamer carbonate in the event of hypercalcaemia was most cost effective, with an ICER of £14,738 versus calcium acetate alone.

Calcium acetate was recommended by the committee as the preferred first-line agent because results show that it is most cost effective; this is true in both presented scenarios. Although calcium carbonate has the cheapest acquisition cost of all the interventions, evidence indicates that it results in elevated serum calcium levels which contribute towards adverse outcomes. As such, calcium carbonate generates the fewest QALYs overall. Despite this, the committee acknowledged that there is a population for whom calcium carbonate is

still a valid option and should be recommended, for example people who require a calcium-based binder but for whom calcium acetate is not suitable.

The committee recommended sevelamer carbonate if calcium acetate is not indicated (for example due to hypercalcaemia or low serum parathyroid hormone levels). This is in contrast with the previous iteration of the guideline in which sevelamer hydrochloride was recommended as an option following calcium-based binders. Sevelamer carbonate was not included previously due to a lack of data. Unlike sevelamer hydrochloride, it is now available in generic formulations, making it less expensive. In the updated analysis, the committee were satisfied that sevelamer carbonate offers a similar gain in QALYs at a lower price compared with hydrochloride, and therefore decided to recommend sevelamer carbonate as a cost-effective option following calcium acetate. This update to the recommendation from sevelamer hydrochloride to carbonate may result in lower overall costs to the NHS given that we estimate carbonate costs approximately £500 less per patient per quarter than hydrochloride.

The committee considered whether a 'do not offer' recommendation might be appropriate given that sevelamer hydrochloride is not cost-effective; however, they came to a consensus that this is not necessary given that the recommendation clearly specifies that sevelamer carbonate should be used. The committee highlighted that if sevelamer carbonate was not suitable for somebody due to tolerability or efficacy issues, that person would not be switched to sevelamer hydrochloride as they would likely experience the same issues; they would be switched to a different type of binder instead.

Importantly, the committee highlighted that people often struggle to find a binder that they can tolerate or find palatable and, in practice, they may be switched between binders until they find one that is suitable for them. For this reason, the committee wanted their recommendations to reflect a preferred sequence in which the evidence suggests options should be tried, rather than a rigid formula that can be followed in all cases. If a person finds a given regimen impossible to adhere to, they will not gain the level of benefit experienced by the average trial participant, so it would not be appropriate to leave them no option but to continue with it. On the other hand, there are small differences in effect and large differences in costs between some of the options, meaning it is important to give preference to strategies that are likely to control people's phosphate at reasonable cost without exposing them to unnecessary risk. Therefore, despite some strategies being dominated by others in the full incremental analysis, the committee did not want to rule these out totally; instead, they tried to strike a balance between reflecting evidence of average benefit and cost and ensuring that people have enough binder options to try.

As some people may not be able to take sevelamer carbonate, the committee considered the evidence with this option removed from the decision space. The ICER for calcium acetate followed by sucroferric oxyhydroxide decreases to £19,877 per QALY gained (versus calcium acetate alone) when all strategies that include sevelamer carbonate are removed from the decision space. The committee were satisfied that sucroferric oxyhydroxide is an effective and cost-effective next option for people in whom sevelamer carbonate is not suitable. Lanthanum carbonate has a high cost and relatively low efficacy versus the other non-calcium-containing binders. The committee felt that, although it should not be put forward as an 'offer' recommendation, it should not be removed as an option entirely, and they therefore recommend it only for people who cannot tolerate all other options.

Evidence in children and young people was extremely limited; there were no published economic evaluations in this population and only one randomised controlled trial. Given the limited new evidence since the last guideline, the committee were reluctant to change the recommendations substantially. They did, however, feel that the model results showing sevelamer carbonate to be more cost effective than sevelamer hydrochloride was generalisable from the adult population to the paediatric population. They noted that these agents were sufficiently similar that it was unlikely their comparative effectiveness would be

so different between adults and children that this conclusion would change. Furthermore, the committee advised that sevelamer carbonate is available in powder form and therefore is easier for children to take than tablets, which can be very large and hard to swallow. Because the powder sachets are more expensive than the tablets, the committee saw a one-way sensitivity analysis comparing sevelamer hydrochloride with carbonate in which it was assumed all carbonate prescriptions incurred the full cost of the powder form. Sevelamer carbonate remained the preferred option in this analysis.

As it was not possible to separately model the CKD stage 4 and 5 population who are not on dialysis, the committee made recommendations for this population based on the limited clinical evidence presented to them and by generalising the model results that relate to people who are on dialysis. The committee felt that the evidence, and therefore the recommendations, could be generalised to the non-dialysis population, with the only exception being sucroferric oxyhydroxide. There was no evidence for sucroferric oxyhydroxide in the non-dialysis population; therefore, the committee restricted its use to people on dialysis only.

1.1.10.5 Other factors the committee took into account

No other factors were discussed.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.11.5 – 1.11.16 and 1.11.8 – 1.11.17 and the research recommendations on phosphate binders (see Appendix N for further details about the research recommendation).

1.1.12 References – included studies

1.1.12.1 Effectiveness

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1.1.12.3 Other

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Appendices

Appendix A – Review protocols

Review protocol for RQ5.1: For people with stage 4 or 5 CKD who are not on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?

ID	Field	Content
0.	PROSPERO registration number	CRD42019147287
1.	Review title	Diagnosis and management of hyperphosphateamia in CKD: the use of calcium and non-calcium based phosphate binders to manage serum phosphate and its associated outcomes.
2.	Review question	RQ5.1 For people with stage 4 or 5 CKD who are not on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?
3.	Objective	To determine which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes in people with stage 4 or 5 CKD who are not on dialysis.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effect (DARE) • Embase (Ovid) • MEDLINE (Ovid)

		• MEDLINE In-Process (Ovid) • MEDLINE Epub Ahead of Print Searches will be restricted by: • English language • Human studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	As kidney dysfunction advances, there is a higher risk of mortality and some comorbidities become more severe. Hyperphosphataemia is one example of this, and occurs because of insufficient filtering of phosphate from the blood by poorly functioning kidneys. This means that a certain amount of the phosphate does not leave the body in the urine, instead remaining in the blood at abnormally elevated levels. High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to the development of secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism increases morbidity and mortality and may lead to renal bone disease, with people experiencing bone and muscular pain, increased incidence of fracture, abnormalities of bone and joint morphology, and vascular and soft tissue calcification.

6.	Population	**Inclusion**: Adults, children and young people with stage 4 or 5 chronic kidney disease who are not on dialysis **Exclusion**: Pregnant women
7.	Intervention/Exposure/Test	Calcium and non-calcium based phosphate binders: • Lanthanum carbonate • Ferric carboxymaltose • Sevelamer hydrochloride • Sevelamer carbonate • Aluminium hydroxide • Magnesium carbonate • Calcium carbonate • Calcium acetate • Sucroferric oxyhydroxide • Calcium acetate/magnesium carbonate (Osvaren)
8.	Comparator	• Placebo • other phosphate binding treatment (or combinations) from the list above.

9.	Types of study to be included	• RCTs • SRs of RCTs • NMAs of RCTs
10.	Other exclusion criteria	• People with CKD disease stages 1 to 3 • People on dialysis • Non-English language • Abstracts and conference proceedings • Theses • Non-human studies
11.	Context	NICE guideline CG157 Hyperphosphataemia in chronic kidney disease will be updated by this question. This guideline will be combined with guidelines CG182 chronic kidney disease in adults: assessment and management and NG8 chronic kidney disease: managing anaemia. The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people.

12.	Primary outcomes (critical outcomes)	Over the duration of follow up of the study: • Overall and cardiovascular related mortality and morbidity • Serum phosphate • Adverse effects (#, bone density, Ectopic calcification (inc PAD) Cardiovascular calcification scores, Parathyroidectomy) • Patient concordance (author defined) • Serum calcium • QoL (validated QoL measures)
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer 5 and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and

		control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias for RCTs will be assessed using the Cochrane RoB (2.0) checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of interventional data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3

		Hierarchical Bayesian Network Meta-Analysis (NMA) will be performed using WinBUGS version 1.4.3. The models that will be used reflect the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 will be used without substantive alteration to specify synthesis models. Results will be reported summarising 10,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values will be used. Non-informative prior distributions will used in all models. Fixed- and random-effects models will be explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC is at least 3 points lower for the random-effects model, it will be used; otherwise, the fixed effects model will be considered to provide an equivalent fit to the data in a more parsimonious analysis.
17.	Analysis of sub-groups	Where data allow, and if there is heterogeneity, the following subgroups analyses will be undertaken: • Anticoag vs no antcoag • Age band • Diabetes vs no diabetes • Gender

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]
22.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]

23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** GUTprospero@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) Guideline Updates Team		
25.	Review team members	From the Guideline Updates Team:		

		• Mr Chris Carmona • Dr Yolanda Martinez • Ms Hannah Nicholas • Ms Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team, which is part of NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10118
29.	Other registration details	None

30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	anaemia, chronic kidney disease, iron therapy, intravenous iron
33.	Details of existing review of same topic by same authors	This review is a partial update of NICE guideline CG182: Chronic kidney disease in adults: assessment and management
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Review protocol for RQ5.2: For people with stage 5 CKD who are on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?

ID	Field	Content
0.	PROSPERO registration number	CRD42019147215
1.	Review title	Diagnosis and management of hyperphosphateamia in CKD: the use of calcium and non-calcium based phosphate binders to manage serum phosphate and its associated outcomes.
2.	Review question	For people with stage 5 CKD who are on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?
3.	Objective	To determine which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes in people with stage 5 CKD who are on dialysis.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effect (DARE) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) • MEDLINE Epub Ahead of Print Searches will be restricted by:

		• English language • Human studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	As kidney dysfunction advances, there is a higher risk of mortality and some comorbidities become more severe. Hyperphosphataemia is one example of this, and occurs because of insufficient filtering of phosphate from the blood by poorly functioning kidneys. This means that a certain amount of the phosphate does not leave the body in the urine, instead remaining in the blood at abnormally elevated levels. High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to the development of secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism increases morbidity and mortality and may lead to renal bone disease, with people experiencing bone and muscular pain, increased incidence of fracture, abnormalities of bone and joint morphology, and vascular and soft tissue calcification.

6.	Population	**Inclusion**: Adults, children and young people with stage 5 chronic kidney disease who are on dialysis **Exclusion**: Pregnant women
7.	Intervention/Exposure/Test	Calcium and non-calcium based phosphate binders: • Lanthanum carbonate • Ferric carboxymaltose • Sevelamer hydrochloride • Sevelamer carbonate • Aluminium hydroxide • Magnesium carbonate • Calcium carbonate • Calcium acetate • Sucroferric oxyhydroxide • Calcium acetate/magnesium carbonate (Osvaren)
8.	Comparator	• Placebo • other phosphate binding treatment (or combinations) from the list above

9.	Types of study to be included	• RCTs • SRs of RCTs • NMAs of RCTs
10.	Other exclusion criteria	• People with CKD disease stages 1 to 4 • People not on dialysis • Non-English language • Abstracts and conference proceedings • Theses • Non-human studies
11.	Context	NICE guideline CG157 Hyperphosphataemia in chronic kidney disease will be updated by this question. This guideline will be combined with guidelines CG182 chronic kidney disease in adults: assessment and management and NG8 chronic kidney disease: managing anaemia. The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people.

12.	Primary outcomes (critical outcomes)	Over the duration of follow up of the study: • Overall and cardiovascular related mortality and morbidity • Serum phosphate • Adverse effects (#, bone density, Ectopic calcification (inc PAD) Cardiovascular calcification scores, Parathyroidectomy) • Patient concordance (author defined) • Serum calcium • QoL (validated QoL measures)
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer 5 and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and

		control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias for RCTs will be assessed using the Cochrane RoB (2.0) checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of interventional data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3

		Hierarchical Bayesian Network Meta-Analysis (NMA) will be performed using WinBUGS version 1.4.3. The models that will be used reflect the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 will be used without substantive alteration to specify synthesis models. Results will be reported summarising 10,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values will be used. Non-informative prior distributions will used in all models. Fixed- and random-effects models will be explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC is at least 3 points lower for the random-effects model, it will be used; otherwise, the fixed effects model will be considered to provide an equivalent fit to the data in a more parsimonious analysis.
17.	Analysis of sub-groups	Where data allow, and if there is heterogeneity, the following subgroups analyses will be undertaken: • Anticoag vs no antcoag • Age band • Diabetes vs no diabetes • Gender

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]
22.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]

<table>
<tr><td rowspan="8">23.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">5a. Named contact
Guidelines Update Team

5b Named contact e-mail
GUTprospero@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) Guideline Updates Team</td></tr>
</table>

25.	Review team members	From the Guideline Updates Team: • Mr Chris Carmona • Dr Yolanda Martinez • Ms Hannah Nicholas • Ms Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team, which is part of NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10118

29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	anaemia, chronic kidney disease, iron therapy, intravenous iron
33.	Details of existing review of same topic by same authors	This review is a partial update of NICE guideline CG182: Chronic kidney disease in adults: assessment and management
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None

36.	Details of final publication	www.nice.org.uk

1

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination) and was always a minimum of 250.
- A random 10% sample of the studies remaining in the database when the threshold were additionally screened, to check if a substantial number of relevant studies were not being correctly classified by the algorithm, with the full database being screened if concerns were identified.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search. If additional studies were identified that were erroneously excluded during the priority screening process, the full database was subsequently screened.

Evidence synthesis and meta-analyses of pair-wise data

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Other study were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences.

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.

- The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%.

However, in cases where the results from individual pre-specified subgroup analyses are less heterogeneous (with I2 < 50%) the results from these subgroups will be reported using fixed effects models. This may lead to situations where pooled results are reported from random-effects models and subgroup results are reported from fixed-effects models.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from studies with indirectness according to GRADE criteria (partially indirect or indirect studies), a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. For mortality, the MID was the line of no effect.

When decisions were made in situations where MIDs were not available, the ‘Evidence to Recommendations’ section of that review makes explicit the committee’s view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in ‘Developing NICE guidelines: the manual (2014)’. Data from all randomised controlled trials was initially rated as high quality and data from observations studies were originally rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 27.

Table 27: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I2 was less than 33.3%, the outcome was not downgraded. Serious: If the I2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Methods for combining direct and indirect evidence (network meta-analysis) for interventions

Conventional 'pairwise' meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from two or more separate studies (for example, where there are two or more studies comparing A vs B).

In situations where there are more than two interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis overcomes these problems by combining all evidence into a single, internally coherent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions. Network meta-analyses were undertaken in all situations where the following two criteria were met:

- At least three treatment alternatives.
- The aim of the review was to produce recommendations on the most effective option, rather than simply describe the effectiveness of treatment alternatives.

Synthesis

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 was used without substantive alteration to specify synthesis models.

Results were reported summarising at least 50,000 samples from the posterior distribution of each model, having first run and discarded at least 10,000 'burn-in' iterations. The MC error was assessed to check that it was sufficiently small (less than 5% of the standard deviation of the posterior distribution for each parameter) and additional samples were summarised if this was the case. At least two separate chains with different initial values were used.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned Normal (0, 10000) priors, and the between-trial standard deviations used in random-effects models were given Uniform (0, 5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

Fixed- and random-effects models were explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC was at least 3 points lower for the random-effects model, it was preferred; otherwise, the fixed effects model was considered to provide an equivalent fit to the data in a more parsimonious analysis, and was preferred.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from studies with indirectness according to GRADE criteria (partially indirect or indirect studies), a sensitivity analysis was conducted, excluding those studies from the analysis.

Modified GRADE for network meta-analyses

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA, which can then be combined with pairwise quality ratings for individual comparisons (if appropriate), to judge the overall strength of evidence for each comparison.

Table 28: Rationale for downgrading quality of evidence for intervention studies

GRADE tables	Reasons for downgrading quality
Risk of bias	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses conducted under a Bayesian framework, the network was downgraded one level if the DIC for a random-effects model was lower than the DIC for a fixed-effects model. For network meta-analyses conducted under a frequentist framework, the network was downgraded one level if the I2 was greater than 50%. In addition, under both frameworks, the direct and indirect treatment estimates were compared as a check on the consistency of the network.
Imprecision	The overall network was downgraded for imprecision if it was not possible to differentiate between any meaningfully distinct treatments options in the network (based on 95% confidence/credible intervals). Whether two options were meaningfully distinct was judged using the MIDs defined above for pairwise meta-analysis of the outcomes, if available; or statistical significance if MIDs were not available. **Where MIDs were used** Not serious: if any meaningfully distinct options were identified. Serious: if the 95% CI of at least 1 of the comparisons crossed an MID (and no meaningfully distinct options were identified).

GRADE tables	Reasons for downgrading quality
	Very serious: if the 95% CI of at least 1 of the comparisons crossed both MIDs (and no meaningfully distinct options or cases where only 1 MID was crossed were identified). **Where MIDs were not available** Not serious: At least 1 comparison does not cross the line of no effect. Serious: if the 95% CI of at least 1 of the comparisons crossed the line of no effect and no options were statistically different and the sample size was sufficiently large. Very serious: if the 95% CI of at least 1 of the comparisons crossed the line of no effect and no options were statistically different and the sample size was sufficiently was sufficiently small that it is not plausible any realistic effect size could have been detected.

Appendix C – Literature search strategies

RQ5.1 For people with stage 4 or 5 CKD who are not on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?

RQ5.2 For people with stage 5 CKD who are on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?

Sources searched to identify the clinical evidence – adults

Databases	Date searched	Version/files	No. retrieved	EPPI-R5 data
Cochrane Central Register of Controlled Trials (CENTRAL)	9th July 2019	Issue 7 of 12, July 2019	273	
Cochrane Database of Systematic Reviews (CDSR)	9th July 2019	Issue 7 of 12, July 2019	0	
Database of Abstracts of Reviews of Effect (DARE)	9th July 2019	Up to 2015	6	
Embase (Ovid)	9th July 2019	Embase <1974 to 2019 Week 27>	388	
MEDLINE (Ovid)	9th July 2019	Ovid MEDLINE(R) <1946 to July 08, 2019>	228	
MEDLINE In-Process (Ovid)	9th July 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 08, 2019>	45	
MEDLINE Epub Ahead of Print[a]	9th July 2019	Ovid MEDLINE(R) Epub Ahead of Print <July 08, 2019>	7	

Clinical search strategies

Databases
Database: Ovid MEDLINE(R) <1946 to July 08, 2019> ----------

[a] Please search for both development and re-run searches

1 exp Renal Insufficiency, Chronic/ (108298)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (69043)

3 ((kidney* or renal*) adj1 insufficien*).tw. (20938)

4 ckd*.tw. (20933)

5 ((kidney* or renal*) adj1 fail*).tw. (84856)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (33803)

7 (esrd* or eskd*).tw. (13475)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3391)

9 or/1-8 (205559)

10 Hyperphosphatemia/ (1161)

11 hyperphosphat*.tw. (3967)

12 or/10-11 (4340)

13 9 or 12 (207778)

14 (phosph* adj3 bind*).tw. (22695)

15 Sevelamer/ (634)

16 Lanthanum/ (4688)

17 (sevelamer or lanthanum).tw. (4205)

18 Calcium Carbonate/ (6965)

19 (calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*)).tw. (7596)

20 magnesium carbonate*.tw. (229)

21 Aluminum Hydroxide/ (3662)

22 aluminum hydroxide*.tw. (1888)

23 Sucroferri* oxyhydroxide*.tw. (38)

24 ferric citrate*.tw. (539)

25 or/14-24 (44934)

26 13 and 25 (2687)

27 (MEDLINE or pubmed).tw. (142510)

28 systematic review.tw. (101620)

29 systematic review.pt. (108891)

30 meta-analysis.pt. (102487)

31 intervention$.ti. (112989)

32 or/27-31 (337295)

33 randomized controlled trial.pt. (484751)

34 randomi?ed.mp. (748162)

35 placebo.mp. (186315)

36 or/33-35 (798233)

37 32 or 36 (1038575)

38 26 and 37 (524)

39 animals/ not humans/ (4563292)

40 38 not 39 (515)

41 limit 40 to english language (487)

42 limit 41 to ed=20111001-20190709 (228)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 08, 2019>

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (8930)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1055)

4 ckd*.tw. (4305)

5 ((kidney* or renal*) adj1 fail*).tw. (6108)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4501)

7 (esrd* or eskd*).tw. (1895)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17575)

10 Hyperphosphatemia/ (0)

11 hyperphosphat*.tw. (427)

12 or/10-11 (427)

13 9 or 12 (17790)

14 (phosph* adj3 bind*).tw. (1183)

15 Sevelamer/ (0)

16 Lanthanum/ (0)

17 (sevelamer or lanthanum).tw. (1323)

18 Calcium Carbonate/ (0)

19 (calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*)).tw. (1451)

20 magnesium carbonate*.tw. (51)

21 Aluminum Hydroxide/ (0)

22 aluminum hydroxide*.tw. (204)

23 Sucroferri* oxyhydroxide*.tw. (12)

24 ferric citrate*.tw. (67)

25 or/14-24 (4146)

26 13 and 25 (230)

27 (MEDLINE or pubmed).tw. (29927)

28 systematic review.tw. (24401)

29 systematic review.pt. (260)

30 meta-analysis.pt. (34)

31 intervention$.ti. (18615)

32 or/27-31 (58264)

33 randomized controlled trial.pt. (276)

34 randomi?ed.mp. (66285)

35 placebo.mp. (16273)

36 or/33-35 (72124)

37 32 or 36 (117385)

38 26 and 37 (46)

39 animals/ not humans/ (0)

40 38 not 39 (46)

41 limit 40 to english language (46)

42 limit 41 to dt=20110101-20190709 (45)

Database: Ovid MEDLINE(R) Epub Ahead of Print <July 08, 2019>

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1377)

3 ((kidney* or renal*) adj1 insufficien*).tw. (171)

4 ckd*.tw. (694)

5 ((kidney* or renal*) adj1 fail*).tw. (748)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (667)

7 (esrd* or eskd*).tw. (311)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2564)

10 Hyperphosphatemia/ (0)

11 hyperphosphat*.tw. (51)

12 or/10-11 (51)

13 9 or 12 (2597)

14 (phosph* adj3 bind*).tw. (197)

15 Sevelamer/ (0)

16 Lanthanum/ (0)

17 (sevelamer or lanthanum).tw. (98)

18 Calcium Carbonate/ (0)

19 (calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*)).tw. (133)

20 magnesium carbonate*.tw. (2)

21 Aluminum Hydroxide/ (0)

22 aluminum hydroxide*.tw. (13)

23 Sucroferri* oxyhydroxide*.tw. (6)

24 ferric citrate*.tw. (5)

25 or/14-24 (431)

26 13 and 25 (21)

27 (MEDLINE or pubmed).tw. (6259)

28 systematic review.tw. (5863)

29 systematic review.pt. (17)

30 meta-analysis.pt. (5)

31 intervention$.ti. (3799)

32 or/27-31 (12383)

33 randomized controlled trial.pt. (1)

34 randomi?ed.mp. (12591)

35 placebo.mp. (3031)

36 or/33-35 (13634)

37 32 or 36 (23131)

38 26 and 37 (7)

39 animals/ not humans/ (0)

40 38 not 39 (7)

41 limit 40 to english language (7)

Database: Embase <1974 to 2019 Week 27>

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1 exp kidney failure/ (332686)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (115855)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29333)

4 ckd*.tw. (45487)

5 ((kidney* or renal*) adj1 fail*).tw. (128424)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (55156)

7 (esrd* or eskd*).tw. (25737)

8 or/1-7 (422507)

9 hyperphosphatemia/ (6656)

10 hyperphosphat*.tw. (6123)

11 or/9-10 (8939)

12 8 or 11 (426798)

13 (phosph* adj3 bind*).tw. (27594)

14 sevelamer carbonate/ (329)

15 sevelamer/ (2359)

16 lanthanum carbonate/ (1051)

17 lanthanum chloride/ (851)

18 lanthanum/ (7202)

19 (sevelamer or lanthanum).tw. (5882)

20 calcium carbonate/ (17161)

21 (calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*)).tw. (11551)

22 magnesium carbonate/ (1053)

23 magnesium carbonate*.tw. (349)

24 aluminum hydroxide/ (8768)

25 aluminum hydroxide*.tw. (2350)

26 sucroferric oxyhydroxide/ (157)

27 sucroferric oxyhydroxide.tw. (102)

28 ferric citrate/ (675)

29 ferric citrate*.tw. (710)

30 or/13-29 (69456)

31 12 and 30 (6243)

32 (MEDLINE or pubmed).tw. (224800)

33 exp systematic review/ or systematic review.tw. (253559)

34 meta-analysis/ (165810)

35 intervention$.ti. (181758)

36 or/32-35 (581866)

37 random:.tw. (1427111)

38 placebo:.mp. (435468)

39 double-blind:.tw. (199431)

40 or/37-39 (1675576)

41 36 or 40 (2075256)

42 31 and 41 (999)

43 nonhuman/ not human/ (4418737)

44 42 not 43 (977)

45 limit 44 to english language (945)

46 limit 45 to dc=20110101-20190709 (545)

47 limit 46 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (157)

48 46 not 47 (388)

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees	5972
#2	(((chronic* or progressi*) near/1 (renal* or kidney*))):ti,ab,kw	9606
#3	(((kidney* or renal*) near/1 insufficien*)):ti,ab,kw	4650
#4	(ckd*):ti,ab,kw	4402
#5	(((kidney* or renal*) near/1 fail*)):ti,ab,kw	15610
#6	(((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*))):ti,ab,kw	4226
#7	((esrd* or eskd*)):ti,ab,kw	1930
#8	MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only	81
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	24397
#10	MeSH descriptor: [Hyperphosphatemia] this term only	170
#11	hyperphosphat*:ti,ab,kw	767
#12	#10 or #11	767
#13	#9 or #12	24694
#14	phosph* near/3 bind*	872
#15	MeSH descriptor: [Sevelamer] this term only	178
#16	MeSH descriptor: [Lanthanum] this term only	56
#17	(sevelamer or lanthanum):ti,ab,kw	597
#18	MeSH descriptor: [Calcium Carbonate] this term only	589
#19	(calcium near/3 (carbonate* or acetate* or alginate* or ketoglutarate*)):ti,ab,kw	1762
#20	magnesium carbonate*:ti,ab,kw	180
#21	MeSH descriptor: [Aluminum Hydroxide] this term only	519
#22	aluminum hydroxide*:ti,ab,kw	1072
#23	(Sucroferri* oxyhydroxide*):ti,ab,kw	45
#24	ferric citrate*:ti,ab,kw	120
#25	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24	3624
#26	#13 and #25 with Publication Year from 2011 to 2019, with Cochrane Library publication date Between Jan 2011 and Jul 2019, in Trials	499

#27 "conference":pt or (clinicaltrials or trialsearch):so 412446

#28 #26 not #27 273 (0 CDSR, 273 CENTRAL)

CRD databases

1 (MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES) 538 Delete

2 (((chronic* or progressi*) near1 (renal* or kidney*))) 489 Delete

3 (((kidney* or renal*) near1 insufficien*)) 320 Delete

4 (ckd*) 93 Delete

5 ((kidney* or renal*) near1 fail*) 836 Delete

6 ((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*)) 354 Delete

7 (esrd* or eskd*) 150 Delete

8 (MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder) 0 Delete

9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) 1407 Delete

10 MeSH DESCRIPTOR Hyperphosphatemia 22 Delete

11 (hyperphosphat*) 31 Delete

12 (#10 or #11) 31 Delete

13 (#9 or #12) 1413 Delete

14 (phosph* near3 bind*) 24 Delete

15 MeSH DESCRIPTOR Sevelamer 11 Delete

16 MeSH DESCRIPTOR Lanthanum 11 Delete

17 (sevelamer or lanthanum) 27 Delete

18 MeSH DESCRIPTOR Calcium Carbonate 13 Delete

19 ((calcium near3 (carbonate* or acetate* or alginate* or ketoglutarate*))) 42 Delete

20 (magnesium carbonate*) 1 Delete

21 MeSH DESCRIPTOR Aluminum Hydroxide 4 Delete

22 (aluminum hydroxide*) 4 Delete

23 (Sucroferri* oxyhydroxide*) 2 Delete

24	(ferric citrate*)	1	Delete
25	(#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)	71	Delete
26	(#13 and #25)	36	Delete
27	(#26) FROM 2011 TO 2019	16	Delete
28	(#26) IN DARE FROM 2011 TO 2019	6	Delete
29	(#26) IN NHSEED FROM 2011 TO 2019	8	Delete
30	(#26) IN HTA FROM 2011 TO 2019	2	Delete

Sources searched to identify the clinical evidence – children and young people

Databases	Date searched	Version/files	No. retrieved	EPPI-R5 data
Cochrane Central Register of Controlled Trials (CENTRAL)	12th July 2019	Issue 7 of 12, July 2019	42	
Cochrane Database of Systematic Reviews (CDSR)	12th July 2019	Issue 7 of 12, July 2019	6	
Database of Abstracts of Reviews of Effect (DARE)	12th July 2019	Up to 2015	13	
Embase (Ovid)	11th July 2019	Embase <1974 to 2019 Week 27>	82	
MEDLINE (Ovid)	11th July 2019	Ovid MEDLINE(R) <1946 to July 10, 2019>	56	
MEDLINE In-Process (Ovid)	11th July 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 10, 2019>	1	
MEDLINE Epub Ahead of Print[b]	11th July 2019	Ovid MEDLINE(R) Epub Ahead of Print <July 10, 2019>	1	

Clinical search strategies

[b] Please search for both development and re-run searches

Databases
Database: Ovid MEDLINE(R) <1946 to July 10, 2019>
1 exp Renal Insufficiency, Chronic/ (108358)
2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (69096)
3 ((kidney* or renal*) adj1 insufficien*).tw. (20945)
4 ckd*.tw. (20968)
5 ((kidney* or renal*) adj1 fail*).tw. (84881)
6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (33819)
7 (esrd* or eskd*).tw. (13486)
8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3391)
9 or/1-8 (205671)
10 Hyperphosphatemia/ (1164)
11 hyperphosphat*.tw. (3970)
12 or/10-11 (4343)
13 9 or 12 (207893)
14 (phosph* adj3 bind*).tw. (22701)
15 Sevelamer/ (634)
16 Lanthanum/ (4688)
17 (sevelamer or lanthanum).tw. (4205)
18 Calcium Carbonate/ (6973)
19 (calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*)).tw. (7602)
20 magnesium carbonate*.tw. (229)
21 Aluminum Hydroxide/ (3663)
22 aluminum hydroxide*.tw. (1888)
23 Sucroferri* oxyhydroxide*.tw. (38)
24 ferric citrate*.tw. (539)
25 or/14-24 (44952)
26 13 and 25 (2687)
27 (MEDLINE or pubmed).tw. (142680)

28 systematic review.tw. (101764)

29 systematic review.pt. (109015)

30 meta-analysis.pt. (102607)

31 intervention$.ti. (113076)

32 or/27-31 (337621)

33 randomized controlled trial.pt. (484973)

34 randomi?ed.mp. (748564)

35 placebo.mp. (186399)

36 or/33-35 (798657)

37 32 or 36 (1039230)

38 26 and 37 (524)

39 animals/ not humans/ (4564528)

40 38 not 39 (515)

41 limit 40 to english language (487)

42 exp Infant/ or Infant Health/ or Infant Welfare/ (1101320)

43 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (814318)

44 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1843938)

45 Minors/ (2509)

46 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2222589)

47 exp pediatrics/ (55507)

48 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (772523)

49 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (1943682)

50 Puberty/ (13005)

51 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (395618)

52 Schools/ (35314)

53 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (8611)

54 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (442453)

55 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (3671)

56 or/42-55 (4953659)

57 41 and 56 (56)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 10, 2019>

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (8878)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1051)

4 ckd*.tw. (4265)

5 ((kidney* or renal*) adj1 fail*).tw. (6081)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4476)

7 (esrd* or eskd*).tw. (1880)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17459)

10 Hyperphosphatemia/ (0)

11 hyperphosphat*.tw. (425)

12 or/10-11 (425)

13 9 or 12 (17672)

14 (phosph* adj3 bind*).tw. (1181)

15 Sevelamer/ (0)

16 Lanthanum/ (0)

17 (sevelamer or lanthanum).tw. (1326)

18 Calcium Carbonate/ (0)

19 (calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*)).tw. (1448)

20 magnesium carbonate*.tw. (51)

21 Aluminum Hydroxide/ (0)

22 aluminum hydroxide*.tw. (203)

23 Sucroferri* oxyhydroxide*.tw. (12)

24 ferric citrate*.tw. (67)

25 or/14-24 (4143)

26 13 and 25 (230)

27 (MEDLINE or pubmed).tw. (29801)

28 systematic review.tw. (24324)

29 systematic review.pt. (256)

30 meta-analysis.pt. (34)

31 intervention$.ti. (18566)

32 or/27-31 (58067)

33 randomized controlled trial.pt. (276)

34 randomi?ed.mp. (66138)

35 placebo.mp. (16204)

36 or/33-35 (71945)

37 32 or 36 (117058)

38 26 and 37 (46)

39 animals/ not humans/ (0)

40 38 not 39 (46)

41 limit 40 to english language (46)

42 exp Infant/ or Infant Health/ or Infant Welfare/ (0)

43 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (70860)

44 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)

45 Minors/ (0)

46 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (282090)

47 exp pediatrics/ (0)

48 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (105119)

49 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)

50 Puberty/ (0)

51 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (52629)

52 Schools/ (0)

53 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)

54 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (61252)

55 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (512)

56 or/42-55 (409232)

57 41 and 56 (1)

Database: Ovid MEDLINE(R) Epub Ahead of Print <July 10, 2019>

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1384)

3 ((kidney* or renal*) adj1 insufficien*).tw. (173)

4 ckd*.tw. (698)

5 ((kidney* or renal*) adj1 fail*).tw. (747)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (676)

7 (esrd* or eskd*).tw. (313)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2575)

10 Hyperphosphatemia/ (0)

11 hyperphosphat*.tw. (51)

12 or/10-11 (51)

13 9 or 12 (2608)

14 (phosph* adj3 bind*).tw. (189)

15 Sevelamer/ (0)

16 Lanthanum/ (0)

17 (sevelamer or lanthanum).tw. (96)

18 Calcium Carbonate/ (0)

19 (calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*)).tw. (130)

20 magnesium carbonate*.tw. (2)

21 Aluminum Hydroxide/ (0)

22 aluminum hydroxide*.tw. (13)

23 Sucroferri* oxyhydroxide*.tw. (6)

24 ferric citrate*.tw. (5)

25 or/14-24 (418)

26 13 and 25 (21)

27 (MEDLINE or pubmed).tw. (6275)

28 systematic review.tw. (5879)

29 systematic review.pt. (17)

30 meta-analysis.pt. (5)

31 intervention$.ti. (3786)

32 or/27-31 (12379)

33 randomized controlled trial.pt. (1)

34 randomi?ed.mp. (12524)

35 placebo.mp. (3012)

36 or/33-35 (13563)

37 32 or 36 (23056)

38 26 and 37 (7)

39 animals/ not humans/ (0)

40 38 not 39 (7)

41 limit 40 to english language (7)

42 exp Infant/ or Infant Health/ or Infant Welfare/ (0)

43 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (14233)

44 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)

45 Minors/ (0)

46 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (48675)

47 exp pediatrics/ (0)

48 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (19384)

49 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)

50 Puberty/ (0)

51 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (12384)

52 Schools/ (0)

53 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)

54 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (11502)

55 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (94)

56 or/42-55 (71856)

57 41 and 56 (1)

Database: Embase <1974 to 2019 Week 27>

Search Strategy:

---

1 exp kidney failure/ (332686)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (115855)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29333)

4 ckd*.tw. (45487)

5 ((kidney* or renal*) adj1 fail*).tw. (128424)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (55156)

7 (esrd* or eskd*).tw. (25737)

8 or/1-7 (422507)

9 hyperphosphatemia/ (6656)

10 hyperphosphat*.tw. (6123)

11 or/9-10 (8939)

12 8 or 11 (426798)

13 (phosph* adj3 bind*).tw. (27594)

14 sevelamer carbonate/ (329)

15 sevelamer/ (2359)

16 lanthanum carbonate/ (1051)

17 lanthanum chloride/ (851)

18 lanthanum/ (7202)

19 (sevelamer or lanthanum).tw. (5882)

20 calcium carbonate/ (17161)

21 (calcium adj3 (carbonate* or acetate* or alginate* or ketoglutarate*)).tw. (11551)

22 magnesium carbonate/ (1053)

23 magnesium carbonate*.tw. (349)

24 aluminum hydroxide/ (8768)

25 aluminum hydroxide*.tw. (2350)

26 sucroferric oxyhydroxide/ (157)

27 sucroferric oxyhydroxide.tw. (102)

28 ferric citrate/ (675)

29 ferric citrate*.tw. (710)

30 or/13-29 (69456)

31 12 and 30 (6243)

32 (MEDLINE or pubmed).tw. (224800)

33 exp systematic review/ or systematic review.tw. (253559)

34 meta-analysis/ (165810)

35 intervention$.ti. (181758)

36 or/32-35 (581866)

37 random:.tw. (1427111)

38 placebo:.mp. (435468)

39 double-blind:.tw. (199431)

40 or/37-39 (1675576)

41 36 or 40 (2075256)

42 31 and 41 (999)

43 nonhuman/ not human/ (4418737)

44 42 not 43 (977)

45 limit 44 to english language (945)

46 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3254518)

47 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,ad,jw. (1145561)

48 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,ad,jw. (3423201)

49 exp pediatrics/ (100078)

50 (pediatric* or paediatric* or peadiatric*).ti,ab,in,ad,jw. (1537929)

51 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (97709)

52 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,ad,jw. (614583)

53 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (97862)

54 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jw. (652711)

55 ("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*").ti,ab. (6744)

56 or/46-55 (6083018)

57 45 and 56 (96)

58 limit 57 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (14)

59 57 not 58 (82)

Search Name: GU - CKD - phosphate binders - Lynda

Date Run: 12/07/2019 13:48:07

Comment:

ID	Search	Hits
#1	MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees	5972
#2	(((chronic* or progressi*) near/1 (renal* or kidney*))):ti,ab,kw	9606
#3	(((kidney* or renal*) near/1 insufficien*)):ti,ab,kw	4650
#4	(ckd*):ti,ab,kw	4402
#5	(((kidney* or renal*) near/1 fail*)):ti,ab,kw	15610
#6	(((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*))):ti,ab,kw	4226
#7	((esrd* or eskd*)):ti,ab,kw	1930
#8	MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only	81
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	24397
#10	MeSH descriptor: [Hyperphosphatemia] this term only	170
#11	hyperphosphat*:ti,ab,kw	767
#12	#10 or #11	767
#13	#9 or #12	24694
#14	phosph* near/3 bind*	872
#15	MeSH descriptor: [Sevelamer] this term only	178
#16	MeSH descriptor: [Lanthanum] this term only	56

#17 (sevelamer or lanthanum):ti,ab,kw 597

#18 MeSH descriptor: [Calcium Carbonate] this term only 589

#19 (calcium near/3 (carbonate* or acetate* or alginate* or ketoglutarate*)):ti,ab,kw 1762

#20 magnesium carbonate*:ti,ab,kw180

#21 MeSH descriptor: [Aluminum Hydroxide] this term only 519

#22 aluminum hydroxide*:ti,ab,kw 1072

#23 (Sucroferri* oxyhydroxide*):ti,ab,kw 45

#24 ferric citrate*:ti,ab,kw 120

#25 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 3624

#26 #13 and #25 904

#27 "conference":pt or (clinicaltrials or trialsearch):so 412446

#28 #26 not #27 587

#29 MeSH descriptor: [Infant] explode all trees 15409

#30 MeSH descriptor: [Infant Health] this term only 38

#31 MeSH descriptor: [Infant Welfare] this term only 81

#32 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies* or toddler*)):ti,ab,kw 82882

#33 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies* or toddler*)):so 4836

#34 MeSH descriptor: [Child] explode all trees 1178

#35 MeSH descriptor: [Child Behavior] explode all trees 1906

#36 MeSH descriptor: [Child Health] this term only 81

#37 MeSH descriptor: [Child Welfare] this term only 320

#38 MeSH descriptor: [Minors] this term only 8

#39 ((child* or minor or minors or boy* or girl* or kid or kids or young*)):ti,ab,kw 247020

#40 ((child* or minor or minors or boy* or girl* or kid or kids or young*)):so 9898

#41 MeSH descriptor: [Pediatrics] explode all trees 634

#42 ((pediatric* or paediatric* or peadiatric*)):ti,ab,kw 30909

#43 ((pediatric* or paediatric* or peadiatric*)):so 31146

#44 MeSH descriptor: [Adolescent] this term only 100107

#45 MeSH descriptor: [Adolescent Behavior] this term only 1304

#46 MeSH descriptor: [Adolescent Health] this term only 22

#47 MeSH descriptor: [Puberty] this term only 298

#48 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*)):ti,ab,kw 134395

#49 ((adolescen* or pubescen* or prepubescen* or pre-pubecen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or juvenil* or youth* or under*age*)):so 3625

#50 MeSH descriptor: [Schools] this term only 1747

#51 MeSH descriptor: [Child Day Care Centers] this term only 217

#52 MeSH descriptor: [Nurseries] this term only 8

#53 MeSH descriptor: [Schools, Nursery] this term only 36

#54 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)):ti,ab,kw 90462

#55 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)):so 1114

#56 (("under 18*" or "under eighteen*" or "under 25*" or "under twenty five*")):ti,ab,kw 14096

#57 {or #29-#56} 391832

#58 #28 and #57 68 (6 CDSR, 62 Central)

CRD databases

1 (MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES) 538 Delete

2 ((((chronic* or progressi*) near1 (renal* or kidney*)))) 489 Delete

3 ((((kidney* or renal*) near1 insufficien*))) 320 Delete

4 ((ckd*)) 93 Delete

5 (((kidney* or renal*) near1 fail*)) 836 Delete

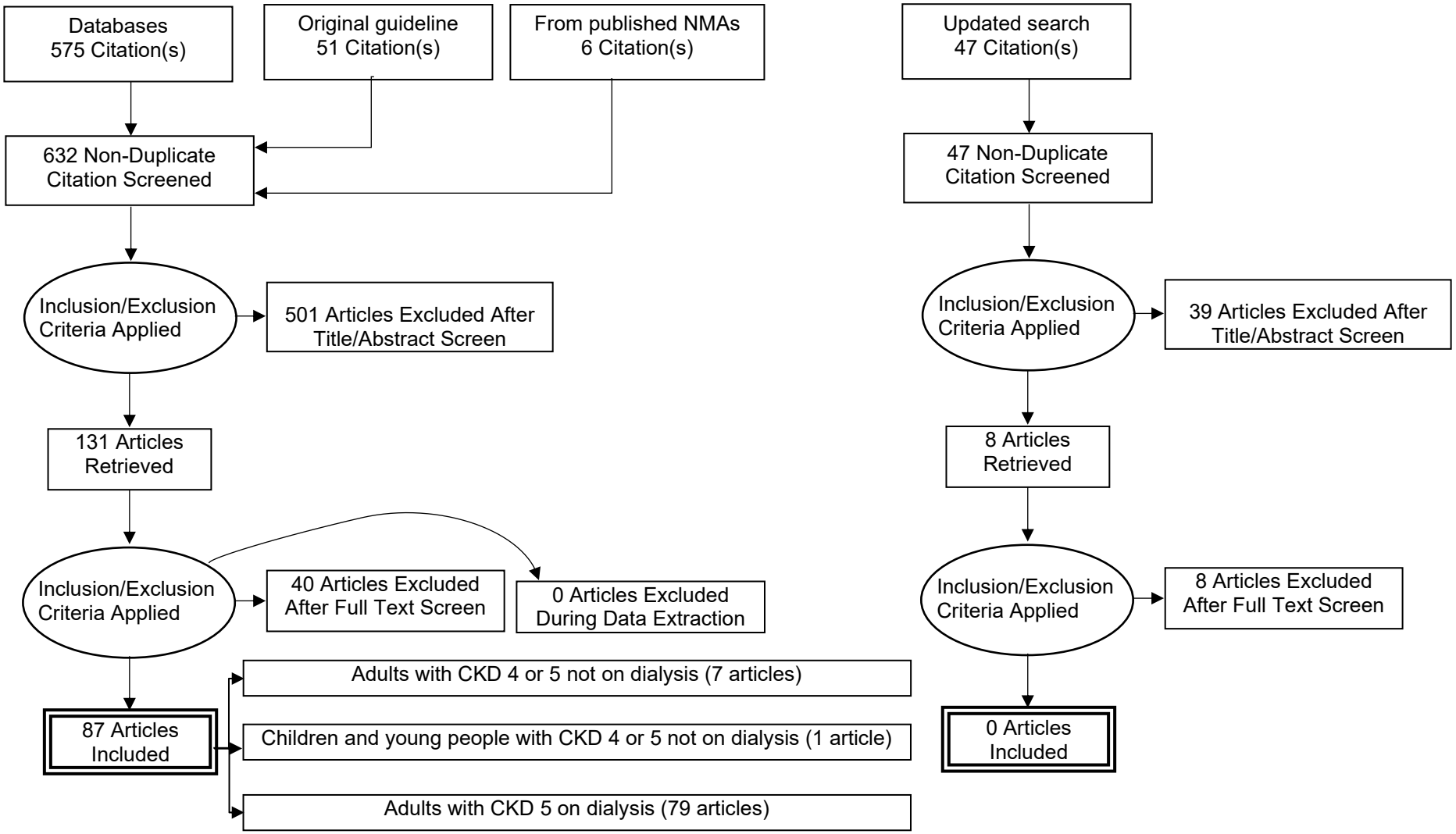
6 (((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*))) 354 Delete

7 ((esrd* or eskd*)) 150 Delete

8 (MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder) 0 Delete

9	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)	1407	Delete		
10	(MeSH DESCRIPTOR Hyperphosphatemia)	22	Delete		
11	(hyperphosphat*)	31	Delete		
12	(#10 or #11)	31	Delete		
13	(#9 or #12)	1413	Delete		
14	(phosph* near3 bind*)	24	Delete		
15	(MeSH DESCRIPTOR Sevelamer)	11	Delete		
16	(MeSH DESCRIPTOR Lanthanum)	11	Delete		
17	(sevelamer or lanthanum)	27	Delete		
18	(MeSH DESCRIPTOR Calcium Carbonate)	13	Delete		
19	(((calcium near3 (carbonate* or acetate* or alginate* or ketoglutarate*))))	42	Delete		
20	(magnesium carbonate*)	1	Delete		
21	(Aluminum Hydroxide*)	4	Delete		
22	(MeSH DESCRIPTOR Aluminum Hydroxide)	4	Delete		
23	((Sucroferri* oxyhydroxide*))	2	Delete		
24	((ferric citrate*))	1	Delete		
25	((#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24))	71	Delete		
26	(#13 and #25)	36	Delete		
27	(#26) IN DARE	13	Delete		
28	(#26) IN NHSEED	16	Delete		
29	(#26) IN HTA	7	Delete		

Appendix D – Effectiveness evidence study selection



Appendix E – Effectiveness evidence tables

Adults with stage 4 or 5 CKD who are not on dialysis

Qunibi et al. (2011) – evidence table

Bibliographic reference	Qunibi,W., Winkelmayer,W.C., Solomon,R., Moustafa,M., Kessler,P., Ho,C.H., Greenberg,J. A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease. BMC Nephrology 2011;12():9.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years of age or older **Washout phosphate level (mmol/L):** >1.45 Additional notes: An estimated GFR of under 30mL/min/1.73m **Exclusions:** Significant Unstable Medical conditions Significant GI disease History of non-adherence to medications. **Baseline characteristics:**

		Calcium Acetate			Placebo				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	37		2.27 (SD 0.17)	41		2.27 (SD 0.15)		
Serum Phosphate (mmol/L) – 0wk	Continuous	37		1.65 (SD 0.4)	41		1.65 (SD 0.36)		
Demographics: Gender-Female	Dichotomous	46	23	(50.0%)	64	29	(45.3%)		
Gender-Male	Dichotomous	46	23	(50.0%)	64	35	(54.7%)		
Age	Continuous	46		63.2 (SD 11.7)	64		62.2 (SD 14.2)		
Number Diabetic	Dichotomous	46	31	(67.4%)	64	49	(76.6%)		
GFR	Continuous	46		17.3 (SD 5.6)	64		16.4 (SD 6.2)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.45 **Lower serum PO4 limit:** 0.87 **Upper serum Ca limit:** 2.54 **Lower serum Ca limit:** 2.12
Intervention(s)	**Drug:** Calcium acetate **N:** 46 Dose varied by washout phosphate: The initial dose was varied in line with the washout phase serum phosphate level Dose varied to maintain patients within study endpoints: The dose was tirated every 2 weeks during the treatment period Notes: The average dose is not provided within the paper **Drug:** Placebo **N:** 64
Concomitant treatments	**Dialysis:** None **Vit D:** No **Rescue Binder use permitted:** No **Were other medications allowed:** **Changes to diet allowed:** No **Changes to dialysate allowed:** N/A
Length of follow up	**Washout period (d):** 42 **Follow-up (d):** 84 **Protocol-specified reasons for withdrawal:** Serum phosphate: If after 3 months the serum phsphate was >1.78mmol/L iPTH was >11.67pmol/L
Location	**Country:** USA

Outcomes measures and effect sizes

		Calcium Acetate			Placebo			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 12wk	Dichotomous	46	9	(19.6%)	64	23	(35.9%)		
Withdrawal (AEs) – 12wk	Dichotomous	46	2	(4.3%)	64	4	(6.3%)		
Biochemical Data: Achieved phosphate control – 12wk	Dichotomous	37	22	(59.5%)	41	15	(36.6%)		
Serum Ca (mmol/L) – 12wk	Continuous	37		2.37 (SD 0.2)	41		2.2 (SD 0.2)		

	Serum Phosphate (mmol/L) – 12wk	Continuous	37		1.42 (SD 0.39)	41		1.65 (SD 0.45)		
	Mortality:									
	All cause mortality – -1wk	Time-to-event	46			64				
	All cause mortality – 12wk	Dichotomous	46	1	(2.2%)	64	3	(4.7%)		
	Treatment:									
	Compliance – 12wk	Continuous	37		88.6 (SD 15)	41		89.3 (SD 14)		
	Biochemical Data:									
	Proportion with hypercalcaemia – 12wk	Dichotomous	37	5	(13.5%)	41	0[a]	(0.0%)		

[a] *approximated to nearest integer (percentages only presented in text)*

Authors' conclusion	
Source of funding	
Comments	

Russo et al. (2007) – evidence table

Bibliographic reference	Russo,D., Miranda,I., Ruocco,C., Battaglia,Y., Buonanno,E., Manzi,S., et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney International 2007;72(10):1255-61.
Study type & aim	**Blinded:** yes (single-blind) **Crossover trial:** no **Multicentre:** no Notes: The person allocating the treatments was blind to the patients characteristics.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years and older **Washout phosphate level (mmol/L):** Additional notes: No washout phase as these patients had not previously been on phosphate binders **Exclusions:** Heart Failure Diabetes or poorly controlled diabetes Stroke, arrhytmia and progressive renal disease, any previous use of phosphate binders, vitamin D sterols or statins **Baseline characteristics:**

		Sevelamer and low phosphate diet		
		N	**k**	**mean**
Biochemical Data:				
Serum Ca (mmol/L) – 0mo	Continuous	27		2.3 (SD 0.05)
Serum Ca (mmol/L) – 0mo	Continuous	27		2.3 (SD 0.05)

Serum Phosphate (mmol/L) – 0mo	Continuous	27		1.45 (SD 0.55)
Serum Phosphate (mmol/L) – 0mo	Continuous	27		1.45 (SD 0.55)
Coronary: Coronary arterial calcification – 0mo	Continuous	27		415 (SD 795.011320674115)
Coronary arterial calcification – 0mo	Continuous	27		415 (SD 795.011320674115)
Demographics: Gender-Female	Dichotomous	27	3	(11.1%)
Gender-Male	Dichotomous	27	24	(88.9%)
Age	Continuous	27		54.4 (SD 12.9)
GFR	Continuous	27		26.3 (SD 15.6)

		Control-low phosphate diet only			Calcium Carbonate and low phosphate diet			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	29		2.3 (SD 0.15)	28		2.24 (SD 0.17)		
Serum Phosphate (mmol/L) – 0mo	Continuous	29		1.26 (SD 0.22)	28		1.48 (SD 0.48)		
Coronary: Coronary arterial calcification – 0mo	Continuous	29		369 (SD 619.294)	28		340 (SD 201.077)		
Demographics: Gender-Female	Dichotomous	29	4	(13.8%)	28	5	(17.9%)		
Gender-Male	Dichotomous	29	25	(86.2%)	28	23	(82.1%)		
Age	Continuous	29		54.4 (SD 13.7)	28		55.2 (SD 12)		
GFR	Continuous	29		33.4 (SD 20.2)	28		26.2 (SD 8.3)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: -
Lower serum PO4 limit: -

	Upper serum Ca limit: - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Placebo **N:** 30 Notes: Patients were on a low phosphate diet **Drug:** Calcium Carbonate **N:** 30 Fixed daily dose (mg): 2000 Notes: Patients were also on a low phosphate diet **Drug:** Sevelamer hydrochloride **N:** 30 Fixed daily dose (mg): 1600
Concomitant treatments	**Dialysis:** None **Vit D:** No **Rescue Binder use permitted:** No details given **Were other medications allowed:** **Changes to diet allowed:** No **Changes to dialysate allowed:** N/A
Length of follow up	**Washout period (d):** - **Follow-up (d):** 728 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Italy
Outcomes measures and effect sizes	

		Sevelamer and low phosphate diet		
		N	**k**	**mean**
Biochemical Data: Serum Ca (mmol/L) – 24mo	Continuous	27		2.25 (SD 0.07)
Serum Ca (mmol/L) – 24mo	Continuous	27		2.25 (SD 0.07)
Serum Phosphate (mmol/L) – 24mo	Continuous	27		1.55 (SD 0.29)
Serum Phosphate (mmol/L) – 24mo	Continuous	27		1.55 (SD 0.29)
Coronary: Coronary arterial calcification – 12mo	Mean change	27		36 (SD 166.276877526612)
Coronary arterial calcification – 12mo	Mean change	27		36 (SD 166.276877526612)
Coronary arterial calcification – 24mo	Continuous	27		453 (SD 659.911357683742)

Coronary arterial calcification – 24mo	Continuous	27		453 (SD 659.911357683742)
Mortality:				
Cardiovascular Mortality – 24mo	Dichotomous	30	0	(0.0%)

		Control-low phosphate diet only			Calcium Carbonate and low phosphate diet			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 24mo	Continuous	29		2.3 (SD 0.12)	28		2.27 (SD 0.2)		
Serum Phosphate (mmol/L) – 24mo	Continuous	29		1.26 (SD 0.29)	28		1.52 (SD 0.48)		
Coronary:									
Coronary arterial calcification – 12mo	Mean change	29		205 (SD 441.584)	28		178 (SD 211.66)		
Coronary arterial calcification – 24mo	Continuous	29		547 (SD 942.404)	28		473 (SD 365.114)		
Mortality:									
Cardiovascular Mortality – 24mo	Dichotomous	30	1	(3.3%)	30	0	(0.0%)		

Authors' conclusion	
Source of funding	
Comments	

Soriano et al. (2013) – evidence table

Bibliographic reference	Soriano, Sagrario, Ojeda, Raquel, Rodriguez, Mencarnacion, Almaden, Yolanda, Rodriguez, Mariano, Martin-Malo, Alejandro. The effect of phosphate binders, calcium and lanthanum carbonate on FGF23 levels in chronic kidney disease patients. Clinical nephrology 2013;80(1):17-22.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Adults **Washout phosphate level (mmol/L):** >1.29

Additional notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).

Exclusions:

Liver dysfunction

Cancer

Nephrotic syndrome; systemic or autoimmune disease; those on phosphate binders; anticonvulsant therapy or vitamin D.

Baseline characteristics:

		Calcium Carbonate			Lanthanum carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 0mo	Continuous	16		2.3 (SD 0.05)	16		2.375 (SD 0.05)		
Serum Phosphate (mmol/L) – 0mo	Continuous	16		1.55 (SD 0.065)	16		1.647 (SD 0.032)		
Serum iPTH (pmmol/L) – 0mo	Continuous	16		14.104 (SD 2.651)	16		11.029 (SD 2.227)		
Demographics:									
Gender-Female	Dichotomous	16	6	(37.5%)	16	5	(31.3%)		
Gender-Male	Dichotomous	16	10	(62.5%)	16	11	(68.8%)		
Age	Continuous	16		med: 62.3 [rng 30–84]	16		med: 58.4 [rng 46–83]		
Number Diabetic	Dichotomous	16	4	(25.0%)	16	2	(12.5%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.45
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Calcium Carbonate
N: 16
Mean daily dose (mg): 1850 (SD: 600)
Dose varied by washout phosphate: <1.45 mmol/l
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Drug: Lanthanum carbonate
N: 16
Mean daily dose (mg): 1640 (SD: 780)

	Dose varied by washout phosphate: <1.45 mmol/l Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Concomitant treatments	**Dialysis:** None **Vit D:** No **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** N/A
Length of follow up	**Washout period (d):** 30 **Follow-up (d):** 120 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Spain

Outcomes measures and effect sizes

		Calcium Carbonate			Lanthanum carbonate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 4mo	Continuous	16		2.3 (SD 0.05)	16		2.35 (SD 0.05)		
Serum Phosphate (mmol/L) – 4mo	Continuous	16		1.454 (SD 0.065)	16		1.518 (SD 0.032)		
Serum iPTH (pmmol/L) – 4mo	Continuous	16		16.861 (SD 2.121)	16		13.892 (SD 2.545)		

Authors' conclusion	
Source of funding	
Comments	

Sprague et al. (2009) – evidence table

Bibliographic reference	Sprague,S.M., Abboud,H., Qiu,P., Dauphin,M., Zhang,P. Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: A randomized trial. Clinical Journal of the American Society of Nephrology 2009;4 (1) (pp 178-185)-(2009. Date of Publication: 01 Jan 2009.):n. pag..
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 to 80

Washout phosphate level (mmol/L): >1.49

Additional notes: Patients with serum Ca below 2.0mmol were withdrawn

Exclusions:

Serum Ca (Patients with serum Ca below 2.0mmol at baseline were withdrawn)

Liver dysfunction

Significant GI disease

Requirement for cinacalcet or compounds containing phosphorus, aluminum, magensium or calcium (except calcium supplements). Pregnant of breatfeeding women, or acute renal failure within 12 weeks of screening.

Baseline characteristics:

		Lanthanam			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	56		2.22 (SD 0.15)	34		2.24 (SD 0.117)		
Serum Phosphate (mmol/L) – 0wk	Continuous	56		1.71 (SD 0.224)	34		1.74 (SD 0.233)		
Demographics: Gender-Female	Dichotomous	78	38	(48.7%)	41	20	(48.8%)		
Gender-Male	Dichotomous	78	40	(51.3%)	41	21	(51.2%)		
Age	Continuous	78		61.8 (SD 12.9)	41		63 (SD 12.7)		
Number Diabetic	Dichotomous	78	21	(26.9%)	41	24	(58.5%)		
GFR[a]	Continuous	56		22.7 (SD 6.735)	34		24 (SD 11.079)		

[a] *these figures come from the modified ITT population*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.49
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 80
Mean daily dose (mg): 2645 (SD: 733)
Notes: The average dose is that given at week 8 of treatment
Drug: Placebo
N: 41

Concomitant treatments	**Dialysis:** None **Vit D:** Yes - changed during the study period (Vitamin D could be lowered if patients became hypercalcaemic. The dose could not be rasied and patients could not start vitamin D during the course of the trial) **Rescue Binder use permitted:** No **Were other medications allowed:** Yes (Calcium supplements could be continued but the dose could only be altered if the subject suffered hypercalcaemia) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** N/A
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:** Serum Ca: Patients with serum Ca below 2.0mmol at baseline were withdrawn
Location	**Country:** USA

Outcomes measures and effect sizes

		Lanthanam			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 8wk	Dichotomous	80	37	(46.3%)	41	13	(31.7%)		
Withdrawal (AEs) – 8wk	Dichotomous	80	2	(2.5%)	41	4	(9.8%)		
Biochemical Data:									
Achieved phosphate control – 8wk	Dichotomous	56	25	(44.6%)	34	9	(26.5%)		
Serum Ca (mmol/L) – 8wk	Mean change	56		0.03 (SD 0.075)	34		-0.02 (SD 0.117)		
Serum Phosphate (mmol/L) – 8wk	Mean change	56		-0.18 (SD 0.224)	34		-0.06 (SD 0.233)		
Adverse Events:									
Nausea OR vomiting – 8wk[a]	Dichotomous	78	7	(9.0%)	41	4	(9.8%)		
Nausea – 8wk	Dichotomous	78	7	(9.0%)	41	4	(9.8%)		
Vomiting – 8wk	Dichotomous	78	5	(6.4%)	41	1	(2.4%)		

[a] *approximated to nearest integer (percentages only presented in text)*

Authors' conclusion	
Source of funding	
Comments	

Takahara et al. (2014) – evidence table

Bibliographic reference	Takahara, Yuki, Matsuda, Yoshimi, Takahashi, Shunichi, Shigematsu, Takashi. Efficacy and safety of lanthanum carbonate in pre-dialysis CKD patients with hyperphosphatemia: a randomized trial. Clinical nephrology 2014;82(3):181-90.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 20 years and older **Washout phosphate level (mmol/L):** >1.8, <3.55 Additional notes: Serum phosphate was calculated from mg/dl to mmol by GUT (x0.323). **Exclusions:** Serum Ca (Hypocalcemia or hypercalcemia (corrected serum calcium level of <2.26 mmol/L or =3.55 mmol/L) at week –2. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).) Liver dysfunction Cancer HIV positive Alcohol abuse Significant GI disease significant renal disease, including rapidly progressing glomerulonephritis, hydronephrosis, transplanted kidney; acute renal failure within 3 months before the run-in period; known or suspected intolerance or hypersensitivity to the study drug(s); pregnant or lactating females; other conditions considered ineligible for the study by the investigators. **Baseline characteristics:**

		Lanthanum carbonate			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Phosphate (mmol/L) – 0wk	Continuous	86		1.993 (SD 0.42)	55		1.986 (SD 0.336)		
Serum iPTH (pmmol/L) – 0wk	Continuous	86		45.537 (SD 44.04)	55		35.594 (SD 23.432)		
Demographics: Gender-Female	Dichotomous	86	47	(54.7%)	55	27	(49.1%)		
Gender-Male	Dichotomous	86	39	(45.3%)	55	28	(50.9%)		
Age	Continuous	86		61.3 (SD 11.4)	55		62.1 (SD 12.8)		
GFR (ml/min/1.73 m2) <7.0	Dichotomous	86	52	(60.5%)	55	32	(58.2%)		
GFR (ml/min/1.73 m2) 7.0 - 10.0	Dichotomous	86	29	(33.7%)	55	17	(30.9%)		
GFR (ml/min/1.73 m2) >10.0	Dichotomous	86	5	(5.8%)	55	6	(10.9%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.48 **Lower serum PO4 limit:** 0.87 **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 86 Dose varied to maintain patients within study endpoints: Starting dose was 750 mg/day, which was up-titrated to 2,250 mg/day depending on the serum phosphate level (target level: 0.87 – 1.48 mmol/L) and tolerability. The dose was adjusted every 2 weeks by 750 mg/day at the discretion of the investigator or sub-investigator, and subjects were followed at 2-week intervals for 8 weeks. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Drug:** Placebo **N:** 55 Notes: Placebo tablets were indistinguishable from lanthanum carbonate tablets.
Concomitant treatments	**Dialysis:** None **Vit D:** Not stated **Rescue Binder use permitted:** No details given **Were other medications allowed:** No (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.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** N/A
Length of follow up	**Washout period (d):** 4 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:** null
Location	**Country:** Japan

Outcomes measures and effect sizes

		Lanthanum carbonate			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (AEs) – 8wk	Dichotomous	86	6	(7.0%)	55	7	(12.7%)		
Biochemical Data: Achieved phosphate control – 8wk	Dichotomous	86	32	(37.2%)	55	6	(10.9%)		

	Serum Phosphate (mmol/L) – 8wk[a]	Mean change	86		-0.333 (SD 0.039)	55		-0.019 (SD 0.052)		
	Serum Phosphate (mmol/L) – 8wk	Continuous	86		1.66 (SD 0.462)	55		1.97 (SD 0.339)		
	Serum iPTH (pmmol/L) – 8wk[a]	Mean change	86		0.105 (SD 0.11)	55		0.1 (SD 0.111)		
	Serum iPTH (pmmol/L) – 8wk	Continuous	86		45.115 (SD 47.105)	55		33.335 (SD 22.08)		
	Adverse Events:									
	Constipation – 8wk	Dichotomous	86	14	(16.3%)	55	3	(5.5%)		
	Nausea OR vomiting – 8wk	Dichotomous	86	11	(12.8%)	55	2	(3.6%)		
	Nausea – 8wk	Dichotomous	86	11	(12.8%)	55	1	(1.8%)		
	Vomiting – 8wk	Dichotomous	86	11	(12.8%)	55	2	(3.6%)		
	Renal failure chronic – 8wk	Dichotomous	86	14	(16.3%)	55	4	(7.3%)		
	Renal impairment – 8wk	Dichotomous	86	0	(0.0%)	55	1	(1.8%)		
	Azotemia – 8wk	Dichotomous	86	1	(1.2%)	55	0	(0.0%)		
	Hyperkalemia – 8wk	Dichotomous	86	2	(2.3%)	55	1	(1.8%)		
	[a] *change reported as least square mean and SE instead of SD*									
Authors' conclusion										
Source of funding										
Comments										

Yilmaz et al. (2012) – evidence table

Bibliographic reference	Yilmaz, Mahmut Ilker, Sonmez, Alper, Saglam, Mutlu, Yaman, Halil, Kilic, Selim, Eyileten, Tayfun, et al. Comparison of calcium acetate and sevelamer on vascular function and fibroblast growth factor 23 in CKD patients: a randomized clinical trial. American journal of kidney diseases : the official journal of the National Kidney Foundation 2012;59(2):177-85.
Study type & aim	**Blinded:** yes (single-blind) **Crossover trial:** no **Multicentre:** no Notes: Measurements were done by blinded observer/operator
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No details given **Washout phosphate level (mmol/L):** >1.77 Additional notes: Only 16 patients went through a washout period as they were already on phosphate binders. Phosphate levels were reported as one of the inclusion criteria. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:**

Serum Ca (Hypercalcemia (serum calcium >2.75 mmol/L).
Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).)
Diabetes or poorly controlled diabetes
History of coronary heart disease, smokers, and those using statins, renin-angiotensin blockers, or vitamin D because of the established effect of these factors on vascular function.

Baseline characteristics:

		Sevelamer hydrochloride			Calcium acetate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous	47		2.05	53		2.025		
Serum Phosphate (mmol/L) – 0wk	Continuous	47		2.487	53		2.487		
Serum iPTH (pmmol/L) – 0wk	Continuous	47		16.904	53		15.472		
Demographics:									
Age[a]	Continuous	47		med: 45 [rng 21–67]	53		med: 46 [rng 21–64]		
GFR	Continuous	47		24 (SD 3)	53		22 (SD 4)		

[a] *25th; 75th percentile*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.77
Lower serum PO4 limit: -
Upper serum Ca limit: 2.7
Lower serum Ca limit: -

Intervention(s)

Drug: Sevelamer hydrochloride
N: 47
Dose varied to maintain patients within study endpoints: The starting dose for sevelamer was 2 capsules (800 mg) 3 times a day given with meals and dose was titrated to bring serum phosphate levels to <1.77 mmol/L.
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Drug: Calcium acetate
N: 53
Dose varied to maintain patients within study endpoints: The starting dose for calcium acetate was 1 tablet (1,000 mg) 3 times a day given with meals and dose was titrated to bring serum phosphate levels to <1.77 mmol/L.
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).

Concomitant treatments

Dialysis: None
Vit D: Not stated
Rescue Binder use permitted: No details given

	Were other medications allowed: No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** N/A
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:** null
Location	**Country:** Turkey

Outcomes measures and effect sizes

		Sevelamer hydrochloride			Calcium acetate				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 8wk	Dichotomous	47	0	(0.0%)	53	0	(0.0%)		
Withdrawal (AEs) – 8wk	Dichotomous	47	0	(0.0%)	53	0	(0.0%)		
Biochemical Data:									
Serum Ca (mmol/L) – 8wk[a]	Percentage change from baseline	47		-0.075	53		0.725		
Serum Ca (mmol/L) – 8wk	Continuous	47		2.025	53		2.075		
Serum Phosphate (mmol/L) – 8wk[a]	Percentage change from baseline	47		-10.045	53		-4.813		
Serum Phosphate (mmol/L) – 8wk	Continuous	47		1.712	53		2.1		
Serum iPTH (pmmol/L) – 8wk[a]	Percentage change from baseline	47		0.477	53		1.241		
Serum iPTH (pmmol/L) – 8wk	Continuous	47		17.614	53		17.126		

[a] *95% CI for percentage change*

Authors' conclusion	
Source of funding	
Comments	

Yokoyama et al. (2014a) – evidence table

Bibliographic reference	Yokoyama, Keitaro, Hirakata, Hideki, Akiba, Takashi, Fukagawa, Masafumi, Nakayama, Masaaki, Sawada, Kenichi, Kumagai, Yuji. Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. Clinical journal of the American Society of Nephrology : CJASN 2014;9(3):543-52.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no

Multicentre: yes

Number and characteristics of patients

Gender: Male and Female
Age range: 20 years of age or older
Washout phosphate level (mmol/L): >1.61, <2.58
Additional notes: Washout period was not reported. Phosphate levels were reported as one of the inclusion criteria at screening (screening period was 2- to 4-week).
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Exclusions:
Serum Ca (Corrected serum calcium <2.0 or >2.75 mmol/l.
Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).)
Significant GI disease
Patients scheduled for dialysis or renal transplantation =4 months after the initial screening date; AKI =3 months before the initial screening date previous gastrectomy or duodenectomy; hemochromatosis, ferritin>500 ng/ml, or transferrin saturation>50%; and any significant comorbidity that the investigators deemed would interfere with completion of study procedures.
Baseline characteristics:

		Ferric citrate hydrate			Placebo				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	57		2.152 (SD 0.13)	29		2.142 (SD 0.11)		
Serum Phosphate (mmol/L) – 0wk	Continuous	57		1.828 (SD 0.242)	29		1.799 (SD 0.203)		
Serum iPTH (pmmol/L) – 0wk	Continuous	57		med: 26.087 [rng 13.68–38.6]	29		med: 25.027 [rng 16.543–35.101]		
Demographics: Gender-Female	Dichotomous	57	24	(42.1%)	29	12	(41.4%)		
Gender-Male	Dichotomous	57	33	(57.9%)	29	17	(58.6%)		
Age	Continuous	57		65.3 (SD 10.2)	29		64.6 (SD 13.5)		
GFR (ml/min/1.73 m2) <5	Dichotomous	57	3	(5.3%)	29	3	(10.3%)		
GFR (ml/min/1.73 m2) 5 to <10	Dichotomous	57	38	(66.7%)	29	18	(62.1%)		
GFR (ml/min/1.73 m2) 10 to <15	Dichotomous	57	12	(21.1%)	29	6	(20.7%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.45
Lower serum PO4 limit: 0.8

	Upper serum Ca limit: - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Ferric citrate **N:** 57 Dose varied to maintain patients within study endpoints: Starting dose was 1.5 g/d (6 tablets per day) administered orally 3 times daily immediately after a meal. The dose was increased to 3.0 g/d at week 2. At week 4, the dose was adjusted between 1.5 and 6.0 g/d according to the target range of serum phosphate (0.80 to 1.45 mmol/L). When serum phosphate exceeded 1.45 mmol/L, the dose was increased by 2 tablets per dose, and when serum phosphate fell below 0.80 mmol/L, the dose was reduced by 2 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. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Drug:** Placebo **N:** 29 Dose varied to maintain patients within study endpoints: Same as ferric citrate hydrate
Concomitant treatments	**Dialysis:** None **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Intravenous iron preparations as iron replacement therapy for renal anemia were permitted.) **Changes to diet allowed:** No **Changes to dialysate allowed:** N/A
Length of follow up	**Washout period (d):** - **Follow-up (d):** 84 **Protocol-specified reasons for withdrawal:** Serum phosphate: Two consecutive serum phosphates<0.80 or =2.58 mmol/l. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Serum Ca: Corrected serum calcium<1.87 mmol/l. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4). Investigator decision to introduce RRT; ferritin=800 ng/ml
Location	**Country:** Japan

Outcomes measures and effect sizes

		Ferric citrate hydrate			Placebo			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 12wk	Dichotomous	60	14	(23.3%)	30	7	(23.3%)		
Withdrawal (AEs) – 12wk	Dichotomous	60	6	(10.0%)	30	1	(3.3%)		
Biochemical Data: Achieved phosphate control – 12wk[a]	Dichotomous	57	37	(64.9%)	29	2	(6.9%)		
Serum Ca (mmol/L) – 12wk	Continuous	57		2.205 (SD 0.142)	29		2.142 (SD 0.108)		

	Serum Ca (mmol/L) – 12wk[b]	Mean change	57		0.052 (SD 0.135)	29		-0.002 (SD 0.089)		
	Serum Phosphate (mmol/L) – 12wk[b]	Mean change	57		-0.417 (SD 0.421)	29		0.019 (SD 0.232)		
	Serum Phosphate (mmol/L) – 12wk	Continuous	57		1.412 (SD 0.41)	29		1.815 (SD 0.287)		
	Serum iPTH (pmmol/L) – 12wk[c]	Mean change	57		med: -2.651 [rng -11.771–2.227]	29		med: 0.742 [rng -3.181–5.09]		
	Serum iPTH (pmmol/L) – 12wk	Continuous	57		med: 20.467 [rng 12.407–32.026]	29		med: 22.694 [rng 13.574–35.949]		
	Adverse Events:									
	Constipation – 12wk	Dichotomous	57	7	(12.3%)	29	2	(6.9%)		
	Diarrhea – 12wk	Dichotomous	57	8	(14.0%)	29	2	(6.9%)		
	Nausea OR vomiting – 12wk	Dichotomous	57	1	(1.8%)	29	2	(6.9%)		
	Nausea – 12wk	Dichotomous	57	1	(1.8%)	29	2	(6.9%)		
	Abdominal discomfort – 12wk	Dichotomous	57	3	(5.3%)	29	3	(10.3%)		
	Abdominal distension – 12wk	Dichotomous	57	3	(5.3%)	29	0	(0.0%)		
	Duodenal ulcer – 12wk	Dichotomous	57	2	(3.5%)	29	0	(0.0%)		
	Mortality:									
	All cause mortality – 12wk	Dichotomous	60	1	(1.7%)	30	0	(0.0%)		
	[a] *Approximated to nearest integer (percentages only presented in text)* [b] *95% CI for mean change* [c] *25th, 75th percentile interval for median change*									
Authors' conclusion										
Source of funding										
Comments										

Children and young people with stage 5 CKD who are on dialysis

Salusky et al. (2005) – evidence table

Bibliographic reference	Salusky,I.B., Goodman,W.G., Sahney,S., Gales,B., Perilloux,A., Wang,H.J., Elashoff,R.M. Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. Journal of the American Society of Nephrology 2005;16(8):2501-08.
Study type & aim	**Blinded:** no

Crossover trial: no
Multicentre: no

Number and characteristics of patients

Gender: Male and Female
Age range: 2 to 20 years old
Washout phosphate level (mmol/L):
Additional notes: these patients were recruited as part of a different study that contained 4 arms. 1)Calcitrol+calcium carbonate, 2)doxercalciferol+calcium carbonate, 3)calcitrol+severlamer, 4)doexrcalciferol+ severlamer. No interaction was seen between calcitrol and doxercalcciferol and comparisons only reported between the two phosphate binders.
Exclusions:
Baseline characteristics:

		Calcium Carbonate			Sevelamer			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	15		2.25 (SD 0.155)	15		2.25 (SD 0.155)		
Serum Phosphate (mmol/L) – 0mo	Continuous	15		1.91 (SD 0.503)	15		1.81 (SD 0.376)		
Demographics: History of dialysis (year)	Continuous	14		1.25 (SD 1)	15		1.08 (SD 0.92)		
Gender-Female	Dichotomous	14	4	(28.6%)	15	7	(46.7%)		
Gender-Male	Dichotomous	14	10	(71.4%)	15	8	(53.3%)		
Age	Continuous	14		11 (SD 18.708)	15		15 (SD 11.619)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.94
Lower serum PO4 limit: 1.29
Upper serum Ca limit: 2.54
Lower serum Ca limit: 2.1

Intervention(s)

Drug: Calcium Carbonate
N: 14
Mean daily dose (mg): 3000 (SD: 200)
Notes: The dose was based upon the patients previous prescriptions. The study is unclear as to whether the dose varied during the course of the study. The dose quoted was elemental calcium
Drug: Sevelamer hydrochloride
N: 15

	Mean daily dose (mg): 9700 (SD: 200) Notes: The dose was based upon the patients previous prescriptions. The study is unclear as to whether the dose varied during the course of the study
Concomitant treatments	**Dialysis:** Peritoneal **Vit D:** Yes - not changed during the study (The particpants were initially recruited as part of a trial to examine whether the use of less calcemic Vit D sterols, such as doxercalciferol and sevelamer modified the skeletal response during the treatment of seconday hyperparathyroidism) **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (In those sevelamer patients whose serum calcium levels were <2.05mmol/L 1000mg of elemental calcium was given at bedtime.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** - **Follow-up (d):** 224 **Protocol-specified reasons for withdrawal:** Serum phosphate: If serum phosphate was exceeded 2.26mmol/L for 3 months patients were withdrawn
Location	**Country:** USA

Outcomes measures and effect sizes

		Calcium Carbonate			Sevelamer			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 1mo	Continuous	14		2.31 (SD 0.224)	15		2.21 (SD 0.077)		
Serum Ca (mmol/L) – 2mo	Continuous	14		2.27 (SD 0.262)	15		2.2 (SD 0.15)		
Serum Ca (mmol/L) – 3mo	Continuous	14		2.39 (SD 0.15)	15		2.16 (SD 0.15)		
Serum Ca (mmol/L) – 4mo	Continuous	14		2.47 (SD 0.224)	15		2.22 (SD 0.349)		
Serum Ca (mmol/L) – 5mo	Continuous	14		2.41 (SD 0.22)	15		2.29 (SD 0.155)		
Serum Ca (mmol/L) – 6mo	Continuous	14		2.41 (SD 0.299)	15		2.27 (SD 0.15)		
Serum Ca (mmol/L) – 7mo	Continuous	14		2.47 (SD 0.3)	15		2.27 (SD 0.232)		
Serum Ca (mmol/L) – 8mo	Continuous	14		2.41 (SD 0.15)	15		2.2 (SD 0.15)		
Serum Phosphate (mmol/L) – 1mo	Continuous	14		1.68 (SD 0.337)	15		1.87 (SD 0.426)		
Serum Phosphate (mmol/L) – 2mo	Continuous	14		1.68 (SD 0.34)	15		1.77 (SD 0.426)		

	Serum Phosphate (mmol/L) – 3mo	Continuous	14		1.94 (SD 0.34)	15		1.83 (SD 0.503)		
	Serum Phosphate (mmol/L) – 4mo	Continuous	14		1.61 (SD 0.34)	15		1.77 (SD 0.232)		
	Serum Phosphate (mmol/L) – 5mo	Continuous	14		1.7 (SD 0.412)	15		1.77 (SD 0.387)		
	Serum Phosphate (mmol/L) – 6mo	Continuous	14		1.77 (SD 0.15)	15		1.68 (SD 0.194)		
	Serum Phosphate (mmol/L) – 7mo	Continuous	14		1.83 (SD 0.486)	15		1.7 (SD 0.503)		
	Serum Phosphate (mmol/L) – 8mo	Continuous	14		2.12 (SD 0.449)	15		1.96 (SD 0.426)		
Authors' conclusion										
Source of funding										
Comments										

Adults with stage 5 CKD who are on dialysis

Abraham et al. (2012) – evidence table

Bibliographic reference	Abraham G., Kher V., Saxena S., Jayakumar M., Chafekar D., Pargaonkar P., Shetty M. Sevelamer carbonate experience in Indian end stage renal disease patients. Indian Journal of Nephrology 2012;22(3):189-92.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Adults **Washout phosphate level (mmol/L):** >1.93 Additional notes: Phosphate levels were not reported at washout only at screening **Exclusions:** Serum Ca (Significant hypercalcemia or hypocalcemia (serum calcium >11.0 mg/dl or <7.9 mg/dl)) Significant Unstable Medical conditions Cancer Significant GI disease Medications containing aluminum, calcium, phosphorus, or magnesium, patients with clinically significant abnormal laboratory values (excluding markers of ESRD) and patients with known hypersensitivity to sevelamer; women who were pregnant or lactating or of child bearing potential and not practicing effective methods of contraception.

Baseline characteristics:

		Sevelamer Carbonate			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	44		2.22 (SD 0.198)	44		2.21 (SD 0.242)		
Serum Phosphate (mmol/L) – 0wk	Continuous	44		2.41 (SD 0.539)	44		2.348 (SD 0.323)		
Demographics: Gender-Female	Dichotomous	49	12	(24.5%)	48	17	(35.4%)		
Gender-Male	Dichotomous	49	37	(75.5%)	48	31	(64.6%)		
Age	Continuous	49		47.69 (SD 12.78)	48		49.83 (SD 11.74)		
History of dialysis (months)	Continuous	49		20.86 (SD 14.08)	48		30.07 (SD 30.94)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.77
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Sevelamer Carbonate
N: 49
Dose varied to maintain patients within study endpoints: For serum phosphorus >1.77 and <2.42 mmol/l, the dose was 2400 mg/day and for serum phosphorus =2.4 mmol/l, the dose was 4800 mg/day in divided doses. After every 2-week intervals, the dose was to be increased (if serum phosphorus >1.77 mmol/l) or decreased (if serum phosphorus <1.13 mmol/l) by one tablet per meal.
Notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Drug: Sevelamer hydrochloride
N: 48
Dose varied to maintain patients within study endpoints: For serum phosphorus >1.77 and <2.42 mmol/l, the dose was 2400 mg/day and for serum phosphorus =2.4 mmol/l, the dose was 4800 mg/day in divided doses. After every 2-week intervals, the dose was to be increased (if serum phosphorus >1.77 mmol/l) or decreased (if serum phosphorus <1.13 mmol/l) by one tablet per meal.
Notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Yes - not changed during the study

	Rescue Binder use permitted: No details given **Were other medications allowed:** Yes (Any concomitant treatment taken by the patient was recorded in the case report form.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 42 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** India

Outcomes measures and effect sizes

		Sevelamer Carbonate			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 6wk	Dichotomous	49	5	(10.2%)	48	4	(8.3%)		
Withdrawal (AEs) – 6wk	Dichotomous	49	4	(8.2%)	48	2	(4.2%)		
Biochemical Data:									
Achieved phosphate control – 6wk[a]	Dichotomous	44	33	(75.0%)	44	30	(68.2%)		
Serum Ca (mmol/L) – 6wk	Continuous	44		2.252 (SD 0.208)	44		2.21 (SD 0.228)		
Serum Ca (mmol/L) – 6wk	Mean difference over whole trial period	44		-0.032 [rng -0.084–0.019] [b]	44		0.012 [rng -0.062–0.087] [c]		
Serum Phosphate (mmol/L) – 6wk[b]	Mean difference over whole trial period	44		0.565 [rng 0.417–0.714]	44		0.536 [rng 0.407–0.665]		
Serum Phosphate (mmol/L) – 6wk	Continuous	44		1.844 (SD 0.578)	44		1.806 (SD 0.472)		

[a] *Approximated to nearest integer (percentages only presented in text)*
[b] *95% CI for mean difference*
[c] *95% CI for mean difference (mean dif doesn't match values at baseline and after 6 weeks)*

Authors' conclusion	
Source of funding	
Comments	

Ahmed et al. (2014) – evidence table

Bibliographic reference	Ahmed W., Rizwan-Ul-Haq, Akram M., Khan S., Haider S. Comparative efficacy of sevelamer hydrochloride versus calcium acetate on bone biomarkers in patients with end stage renal disease on hemodialysis. Pakistan Journal of Medical and Health Sciences 2014;8(3):769-71.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no

Number and characteristics of patients

Gender: Male and Female
Age range: 18 to 80 years
Washout phosphate level (mmol/L): >1.29
Additional notes: Phosphate levels were not reported at washout only as one of the inclusion criteria.
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Exclusions:
Serum Ca (>=2.6 mmol/l
Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).)
Cancer
Severe Hyperparathyroidism
Salt wasting nephropathy
Baseline characteristics:

		Sevelamer hydrochloride			Calcium acetate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	70		2.12 (SD 0.222)	70		1.975 (SD 0.195)		
Serum Phosphate (mmol/L) – 0wk	Continuous	70		2.174 (SD 0.436)	70		2.032 (SD 0.336)		
Serum iPTH (pmmol/L) – 0wk	Continuous	70		66.471 (SD 27.511)	70		54.709 (SD 22.822)		
Demographics: Gender-Female	Dichotomous	70	33	(47.1%)	70	29	(41.4%)		
Gender-Male	Dichotomous	70	37	(52.9%)	70	41	(58.6%)		
Age	Continuous	70		44.9	70		41.9		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: -
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Sevelamer hydrochloride
N: 70
Fixed daily dose (mg): 2400
Notes: Sevelamer hydrochloride 800mg three times a day.

	Drug: Calcium acetate **N:** 70 Fixed daily dose (mg): 2000 Notes: Calcium acetate 667mg three times a day.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Not stated **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 168 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Pakistan

Outcomes measures and effect sizes

		Sevelamer hydrochloride			Calcium acetate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 24wk	Continuous	70		2.088 (SD 0.188)	70		2.148 (SD 0.162)		
Serum Ca (mmol/L) – 24wk	Mean change	70		-0.03 (SD 0.155)	70		0.172 (SD 0.132)		
Serum Phosphate (mmol/L) – 24wk	Continuous	70		1.602 (SD 0.226)	70		1.689 (SD 0.245)		
Serum Phosphate (mmol/L) – 24wk	Mean change	70		-0.568 (SD 0.3)	70		-0.342 (SD 0.197)		
Serum iPTH (pmmol/L) – 24wk	Continuous	70		57.62 (SD 28.534)	70		41.16 (SD 16.698)		
Serum iPTH (pmmol/L) – 24wk	Mean change	70		-8.848 (SD 11.126)	70		-13.184 (SD 13.905)		

Authors' conclusion	
Source of funding	
Comments	

Al-Baaj et al. (2005) – evidence table

Bibliographic reference	Al-Baaj,F. & Speake,M. Control of serum phosphate by oral lanthanum carbonate in patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis in a short-term, placebo-controlled study. Nephrology Dialysis Transplantation 2005;20(4):775-82. Related publication Hutchison, Alastair J, Gill, Maggie, Copley, J Brian et al. (2013) Lanthanum carbonate versus placebo for management of hyperphosphatemia in patients undergoing peritoneal dialysis: a subgroup analysis of a phase 2 randomized controlled study of dialysis patients. BMC nephrology 14: 40
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** >18 years **Washout phosphate level (mmol/L):** >1.8, <3 **Exclusions:** **Baseline characteristics:**

		Lantham			Placebo				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Phosphate (mmol/L) – 0wk	Continuous	17		1.536 (SD 0.286)	19		1.68 (SD 0.267)		
Demographics: History of dialysis (year)	Continuous	17		2.62 (SD 2.23)	19		2.85 (SD 2.74)		
Gender-Female	Dichotomous	17	7	(41.2%)	19	9	(47.4%)		
Gender-Male	Dichotomous	17	10	(58.8%)	19	10	(52.6%)		
Age	Continuous	17		57 (SD 17)	19		53.3 (SD 16)		
Type of dialysis-Haemodialysis	Dichotomous	17	7	(41.2%)	19	8	(42.1%)		
Type of dialysis-CAPD	Dichotomous	17	10	(58.8%)	19	11	(57.9%)		
Peritoneal dialysis Biochemical Data: Serum Ca (mmol/L) – 4wk[a]	Continuous	10		2.34 [rng 2.18–2.49]	11		2.42 [rng 2.3–2.54]		
Serum Ca (mmol/L) – 4wk[a]	Continuous	10		2.36 [rng 2.18–2.53]	11		2.45 [rng 2.23–2.68]		
Serum Ca (mmol/L) – 4wk[a]	Continuous	10		2.36 [rng 2.18–2.53]	11		2.42 [rng 2.3–2.54]		
Serum Ca (mmol/L) – 4wk[a]	Continuous	10		2.34 [rng 2.18–2.49]	11		2.45 [rng 2.23–2.68]		
Serum Phosphate (mmol/L) – 4wk[a]	Continuous	10		1.57 [rng 1.34–1.81]	11		2.25 [rng 1.81–2.68]		

	Serum Phosphate (mmol/L) – 4wk[a]	Continuous	10		1.57 [rng 1.34–1.81]	11		1.58 [rng 1.4–1.76]		
	Serum Phosphate (mmol/L) – 4wk[a]	Continuous	10		1.56 [rng 1.33–1.79]	11		2.25 [rng 1.81–2.68]		
	Serum Phosphate (mmol/L) – 4wk[a]	Continuous	10		1.56 [rng 1.33–1.79]	11		1.58 [rng 1.4–1.76]		
	Demographics:									
	Gender-Female[b]	Dichotomous	10	4	(40.0%)	11	3	(27.3%)		
	Gender-Male[b]	Dichotomous	10	6	(60.0%)	11	8	(72.7%)		
	Age[b]	Continuous	10		51.5 (SD 17.5)	11		54.4 (SD 15.3)		
	History of dialysis (months)[c]	Continuous	10		med: 11 [rng 6–87]	11		med: 13 [rng 6–107]		
	[a] *Hutchison 2013; mean (95% CI)* [b] *Hutchison 2013* [c] *Hutchison 2013; median (minimum, maximum)*									
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.8 **Lower serum PO4 limit:** 1.3 **Upper serum Ca limit:** - **Lower serum Ca limit:** -									
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 17 Mean daily dose (mg): 1213 (SD: 657) Dose varied to maintain patients within study endpoints: during the 4 week titration phase the dose could vary between 375 to 2250mg. During the treatment phase these doses were maintained and not changed. **Drug:** Placebo **N:** 19									
Concomitant treatments	**Dialysis:** Either Haemodialysis or Peritoneal **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given									
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:**									

	Serum phosphate: >3.0mmol/L								
Location	**Country:** UK								
Outcomes measures and effect sizes			**Lantham**			**Placebo**			
			N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
	Disposition: Withdrawal (total) – 4wk	Dichotomous	17	0	(0.0%)	19	2	(10.5%)		
	Withdrawal (AEs) – 4wk	Dichotomous	17	0	(0.0%)	19	1	(5.3%)		
	Biochemical Data: Achieved phosphate control – 4wk	Dichotomous	10	6	(60.0%)	11	1	(9.1%)		
	Achieved phosphate control – 4wk	Dichotomous	10	6	(60.0%)	14	3	(21.4%)		
	Achieved phosphate control – 4wk	Dichotomous	17	11	(64.7%)	11	1	(9.1%)		
	Achieved phosphate control – 4wk	Dichotomous	17	11	(64.7%)	14	3	(21.4%)		
	Serum Phosphate (mmol/L) – 1wk	Continuous	17		1.5 (SD 0.421)	19		1.85 (SD 0.556)		
	Serum Phosphate (mmol/L) – 2wk	Continuous	17		1.6 (SD 0.21)	19		2 (SD 0.378)		
	Serum Phosphate (mmol/L) – 3wk	Continuous	17		1.525 (SD 0.305)	19		2.13 (SD 0.645)		
	Serum Phosphate (mmol/L) – 4wk	Continuous	17		1.56 (SD 0.3)	19		2.03 (SD 0.31)		
	Serum iPTH (pmmol/L) – 4wk	Continuous	17		22.906 (SD 18.982)	19		26.511 (SD 23.966)		
	Treatment: Compliance – 4wk	Dichotomous	17	16	(94.1%)	19	18[a]	(94.7%)		
	Peritoneal dialysis Disposition: Withdrawal (AEs) – 4wk	Dichotomous	10	0	(0.0%)	11	1	(9.1%)		
	Biochemical Data: Serum Ca (mmol/L) – 4wk[b]	Continuous	10		2.34 [rng 2.18–2.49]	11		2.45 [rng 2.23–2.68]		
	Serum Ca (mmol/L) – 4wk[b]	Continuous	10		2.34 [rng 2.18–2.49]	11		2.42 [rng 2.3–2.54]		
	Serum Ca (mmol/L) – 4wk[b]	Continuous	10		2.36 [rng 2.18–2.53]	11		2.45 [rng 2.23–2.68]		
	Serum Ca (mmol/L) – 4wk[b]	Continuous	10		2.36 [rng 2.18–2.53]	11		2.42 [rng 2.3–2.54]		
	Serum Phosphate (mmol/L) – 4wk[b]	Continuous	10		1.57 [rng 1.34–1.81]	11		2.25 [rng 1.81–2.68]		

	Serum Phosphate (mmol/L) – 4wk[b]	Continuous	10		1.56 [rng 1.33–1.79]	11		1.58 [rng 1.4–1.76]		
	Serum Phosphate (mmol/L) – 4wk[b]	Continuous	10		1.56 [rng 1.33–1.79]	11		2.25 [rng 1.81–2.68]		
	Serum Phosphate (mmol/L) – 4wk[b]	Continuous	10		1.57 [rng 1.34–1.81]	11		1.58 [rng 1.4–1.76]		
	Serum iPTH (pmmol/L) – 4wk[b]	Mean change	10		0.389 [rng -2.998–3.776]	11		4.572 [rng -0.715–9.858]		
	Adverse Events:									
	Constipation – 4wk[c]	Dichotomous	10	1	(10.0%)	11	1	(9.1%)		
	Diarrhea – 4wk	Dichotomous	10	0	(0.0%)	11	1	(9.1%)		
	Nausea OR vomiting – 4wk	Dichotomous	10	1	(10.0%)	11	1	(9.1%)		
	Nausea – 4wk	Dichotomous	10	0	(0.0%)	11	1	(9.1%)		
	Vomiting – 4wk	Dichotomous	10	1	(10.0%)	11	1	(9.1%)		
	Dental disorder – 4wk	Dichotomous	10	1	(10.0%)	11	0	(0.0%)		
	Flatulence – 4wk	Dichotomous	10	0	(0.0%)	11	1	(9.1%)		
	Indigestion – 4wk	Dichotomous	10	0	(0.0%)	11	1	(9.1%)		
	Treatment:									
	Compliance – 4wk[d]	Dichotomous	10	9	(90.0%)	11	10	(90.9%)		
	[a] *approximated to nearest integer (percentages only presented in text)* [b] *Hutchison 2013; mean (95% CI)* [c] *Hutchison 2013* [d] *Hutchison 2013; approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Asmus et al. (2005) – evidence table

Bibliographic reference	Asmus,H.G., Braun,J., Krause,R., Brunkhorst,R., Holzer,H., Schulz,W., et al. Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. Nephrology Dialysis Transplantation 2005;20(8):1653-61.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Aged 19 years and over

Washout phosphate level (mmol/L): >1.8
Exclusions:
Diabetes or poorly controlled diabetes
Cancer
Hypertension or poorly controlled hypertension
HIV positive
Significant GI disease
Baseline characteristics:

		Sevelamer Hydrochloride			Calcium Carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 0mo	Continuous	31		2.4 (SD 0.1)	41		2.3 (SD 0.2)		
Serum Phosphate (mmol/L) – 0mo	Continuous	31		2.4 (SD 0.6)	41		2.2 (SD 0.5)		
Serum iPTH (pmmol/L) – 0mo	Continuous	31		37.222 (SD 30.965)	41		34.359 (SD 34.359)		
Coronary:									
Coronary arterial calcification – 0mo	Continuous	31		1488 (SD 1820)	41		1259 (SD 1848)		
Demographics:									
History of dialysis (year)	Continuous	31		5.67 (SD 5.33)	41		4.58 (SD 5.33)		
Gender-Female	Dichotomous	31	6[a]	(19.4%)	41	16	(39.0%)		
Gender-Male	Dichotomous	31	25	(80.6%)	41	25	(61.0%)		
Age	Continuous	31		54 (SD 14)	41		55 (SD 64)		
Number Diabetic	Dichotomous	31	4	(12.9%)	41	7	(17.1%)		

[a] *approximated to nearest integer (percentages only presented in text)*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.6
Lower serum PO4 limit: 1
Upper serum Ca limit: 2.6
Lower serum Ca limit: -

Intervention(s)

Drug: Sevelamer hydrochloride
N: 31
Mean daily dose (mg): 6900 (SD: 2600)
Dose varied to maintain patients within study endpoints: Dose was varied to maintain study endpoints
Notes: The average dose provided was for the first year of the study
Drug: Calcium Carbonate

	N: 41 Mean daily dose (mg): 4300 (SD: 1700) Dose varied to maintain patients within study endpoints: Dose varied to maintain study endpoints Notes: The average dose provided was for the first year of the study
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (No details provided) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** No details provided (Aluminum hydroxide was provided as a resuce binder) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 672 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Germany

Outcomes measures and effect sizes

		Sevelamer Hydrochloride			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 3mo	Continuous	31		2.3 (SD 0.2)	41		2.4 (SD 0.2)		
Serum Ca (mmol/L) – 6mo	Continuous	31		2.4 (SD 0.2)	41		2.4 (SD 0.1)		
Serum Ca (mmol/L) – 9mo	Continuous	31		2.4 (SD 0.2)	41		2.5 (SD 0.2)		
Serum Ca (mmol/L) – 12mo	Continuous	31		2.4 (SD 0.2)	41		2.5 (SD 0.2)		
Serum Ca (mmol/L) – 15mo	Continuous	31		2.3 (SD 0.3)	41		2.5 (SD 0.2)		
Serum Ca (mmol/L) – 18mo	Continuous	31		2.3 (SD 0.1)	41		2.4 (SD 0.2)		
Serum Ca (mmol/L) – 21mo	Continuous	31		2.2 (SD 0.2)	41		2.4 (SD 0.2)		
Serum Ca (mmol/L) – 24mo	Continuous	31		2.2 (SD 0.1)	41		2.4 (SD 0.2)		
Serum Phosphate (mmol/L) – 3mo	Continuous	31		2 (SD 0.6)	41		1.8 (SD 0.4)		
Serum Phosphate (mmol/L) – 6mo	Continuous	31		1.9 (SD 0.5)	41		1.6 (SD 0.3)		

	Serum Phosphate (mmol/L) – 9mo	Continuous	31		1.8 (SD 0.4)	41		1.7 (SD 0.4)		
	Serum Phosphate (mmol/L) – 12mo	Continuous	31		1.8 (SD 0.5)	41		1.7 (SD 0.4)		
	Serum Phosphate (mmol/L) – 15mo	Continuous	31		2.1 (SD 0.6)	41		1.8 (SD 0.3)		
	Serum Phosphate (mmol/L) – 18mo	Continuous	31		1.9 (SD 0.5)	41		1.7 (SD 0.3)		
	Serum Phosphate (mmol/L) – 21mo	Continuous	31		2.1 (SD 0.5)	41		1.7 (SD 0.4)		
	Serum Phosphate (mmol/L) – 24mo	Continuous	31		2 (SD 0.6)	41		1.9 (SD 0.5)		
	Serum iPTH (pmmol/L) – 12mo	Continuous	31		34.465 (SD 25.981)	41		23.436 (SD 31.92)		
	Serum iPTH (pmmol/L) – 24mo	Continuous	31		52.704 (SD 44.539)	41		27.148 (SD 28.95)		
	Coronary: Coronary arterial calcification – 21mo	Mean change	31		142 (SD 829)	41		637 (SD 898)		
	Biochemical Data: Proportion with hypercalcaemia – 24mo	Dichotomous	31	8	(25.8%)	41	22[a]	(53.7%)		
	[a] *approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Babarykin et al. (2004) – evidence table

Bibliographic reference	Babarykin,D., Adamsone,I., Amerika,D., Spudass,A., Moisejev,V., Berzina,N., Michule,L. Calcium-enriched bread for treatment of uremic hyperphosphatemia. Journal of Renal Nutrition 2004;14(3):149-56.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No details of inclusion age **Washout phosphate level (mmol/L):** >2 **Exclusions:** Serum Ca (No details) Diabetes or poorly controlled diabetes **Baseline characteristics:**

		Calcium Bread			calcium Acetate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	27		2 (SD 0.25)	27		2.15 (SD 0.2)		
Serum Phosphate (mmol/L) – 0wk	Continuous	26		2.57 (SD 0.47)	27		2.1 (SD 0.18)		
Demographics: History of dialysis (year)	Continuous	27		2.26 (SD 0.8)	26		1.92 (SD 0.625)		
Gender-Female	Dichotomous	27	15	(55.6%)	26	12	(46.2%)		
Gender-Male	Dichotomous	27	12	(44.4%)	26	14	(53.8%)		
Age	Continuous	27		50.7 (SD 11.6)	26		49.2 (SD 8.3)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: -
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Calcium Carbonate (Bread)
N: 27
Dose varied to maintain patients within study endpoints: 750 to 1000mg of elemental calcium 3 times daily
Drug: Calcium acetate
N: 26
Dose varied to maintain patients within study endpoints: 3500 to 4900mg/day

Concomitant treatments

Dialysis: Haemodialysis
Vit D: No
Rescue Binder use permitted: No details given
Were other medications allowed:
Changes to diet allowed: No details given
Changes to dialysate allowed: No details given

Length of follow up

Washout period (d): 14
Follow-up (d): 56
Protocol-specified reasons for withdrawal:

	Serum phosphate: No details Serum Ca: No details
Location	**Country:** Latvia

Outcomes measures and effect sizes

		Calcium Bread			calcium Acetate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 2wk	Continuous	27		2.1 (SD 0.2)	26		2.2 (SD 0.2)		
Serum Ca (mmol/L) – 4wk	Continuous	27		2.2 (SD 0.2)	26		2.15 (SD 0.15)		
Serum Ca (mmol/L) – 6wk	Continuous	27		2.2 (SD 0.2)	26		2.1 (SD 0.2)		
Serum Ca (mmol/L) – 8wk	Continuous	27		1.5 (SD 0.15)	26		2.15 (SD 0.2)		
Serum Phosphate (mmol/L) – 2wk	Continuous	27		2.45 (SD 0.23)	26		2.16 (SD 0.23)		
Serum Phosphate (mmol/L) – 4wk	Continuous	27		2.28 (SD 0.18)	26		2.19 (SD 0.23)		
Serum Phosphate (mmol/L) – 6wk	Continuous	27		1.93 (SD 0.41)	26		2.1 (SD 0.12)		
Serum Phosphate (mmol/L) – 8wk	Continuous	27		1.75 (SD 0.06)	26		2.1 (SD 0.12)		

Baseline data taken at 2 weeks which is the end of the washout period. Data only taken up to the point that the intervention became a supplement due to the timing of administration, which changed at week 8.

Authors' conclusion	
Source of funding	
Comments	

Barreto et al. (2008) – evidence table

Bibliographic reference	Barreto,D.V., Barreto,Fde C., de Carvalho,A.B., Cuppari,L., Draibe,S.A., Dalboni,M.A., et al. Phosphate binder impact on bone remodeling and coronary calcification--results from the BRiC study. Nephron 2008;110(4):c273-83.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No restrictions given **Washout phosphate level (mmol/L):** >1.78

Exclusions:
Diabetes or poorly controlled diabetes
Use of antiarrhythmics or antiseizure medication
Cancer
Steroid use
Severe Hyperparathyroidism
HIV positive
Alcohol abuse
Significant GI disease
Body weight >100Kg
Chronic inflammatory disease

Baseline characteristics:

		Calcium acetate			Sevelamer Hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	30		1.23 (SD 0.512)	41		1.23 (SD 0.438)		
Serum Ca (mmol/L) – 0mo	Continuous	30		1.23 (SD 0.512)	41		1.23 (SD 0.08)		
Serum Ca (mmol/L) – 0mo	Continuous	30		1.23 (SD 0.08)	41		1.23 (SD 0.438)		
Serum Ca (mmol/L) – 0mo	Continuous	30		1.23 (SD 0.08)	41		1.23 (SD 0.08)		
Serum Phosphate (mmol/L) – 0mo	Continuous	30		2.3 (SD 0.45)	41		2.33 (SD 0.7)		
Coronary: Coronary arterial calcification – 0mo	Continuous	30		657 (SD 1267)	41		507 (SD 814)		
Demographics: History of dialysis (year)	Continuous	30		3.17 (SD 1.92)	41		3 (SD 2.25)		
Gender-Female	Dichotomous	30	9	(30.0%)	41	14	(34.1%)		
Gender-Male	Dichotomous	30	21[a]	(70.0%)	41	27	(65.9%)		
Age	Continuous	30		47 (SD 14)	41		47 (SD 13)		
Patients with basline CAC>30 Coronary: Coronary arterial calcification – 0mo	Continuous	16		1263 (SD 1521)	27		767 (SD 902)		

[a] *approximated to nearest integer (percentages only presented in text)*

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.13 **Lower serum PO4 limit:** 1.78 **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Calcium acetate **N:** 49 Dose varied to maintain patients within study endpoints: up to 2028mg of elemental calcium to achieve serum phosphorus 0.8 to 1.78mmol/L, ionized calcium 1.11-1.4mmol/L, iPTH 15.92 to 31,883pmol/L **Drug:** Sevelamer hydrochloride **N:** 52 Dose varied to maintain patients within study endpoints: up to 12,000mg daily to achieve serum phosphorus 0.8 to 1.78mmol/L, ionized calcium 1.11-1.4mmol/L, iPTH 15.92 to 31,883pmol/L
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Vitamin D allowed to be altered depending upon baseline bone biopsy findings) **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** Yes (Caclium dialystate allowed to be altered depending upon baseline bone biopsy findings)
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 365 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Brazil

Outcomes measures and effect sizes

		Calcium acetate			Sevelamer Hydrochloride				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 12mo	Dichotomous	49	19	(38.8%)	52	11	(21.2%)		
Biochemical Data: Serum Ca (mmol/L) – 1mo	Continuous	30		1.23 (SD 0.438)	41		1.25 (SD 0.576)		
Serum Ca (mmol/L) – 2mo	Continuous	30		1.25 (SD 0.44)	41		1.25 (SD 0.512)		
Serum Ca (mmol/L) – 3mo	Continuous	30		1.25 (SD 0.44)	41		1.27 (SD 0.51)		
Serum Ca (mmol/L) – 4mo	Continuous	30		1.26 (SD 0.493)	41		1.28 (SD 0.58)		

	Serum Ca (mmol/L) – 5mo	Continuous	30		1.27 (SD 0.49)	41		1.27 (SD 0.51)		
	Serum Ca (mmol/L) – 6mo	Continuous	30		1.26 (SD 0.548)	41		1.28 (SD 0.51)		
	Serum Ca (mmol/L) – 7mo	Continuous	30		1.27 (SD 0.49)	41		1.29 (SD 0.51)		
	Serum Ca (mmol/L) – 8mo	Continuous	30		1.28 (SD 0.438)	41		1.29 (SD 0.64)		
	Serum Ca (mmol/L) – 9mo	Continuous	30		1.28 (SD 0.44)	41		1.28 (SD 0.512)		
	Serum Ca (mmol/L) – 10mo	Continuous	30		1.28 (SD 0.55)	41		1.28 (SD 0.448)		
	Serum Ca (mmol/L) – 11mo	Continuous	30		1.28 (SD 0.44)	41		1.28 (SD 0.51)		
	Serum Ca (mmol/L) – 12mo	Continuous	30		1.28 (SD 0.44)	41		1.28 (SD 0.576)		
	Serum Phosphate (mmol/L) – 1mo	Continuous	30		1.94 (SD 0.59)	41		1.99 (SD 0.43)		
	Serum Phosphate (mmol/L) – 2mo	Continuous	30		1.67 (SD 0.43)	41		1.88 (SD 0.48)		
	Serum Phosphate (mmol/L) – 3mo	Continuous	30		1.67 (SD 0.38)	41		1.67 (SD 0.38)		
	Serum Phosphate (mmol/L) – 4mo	Continuous	30		1.88 (SD 0.59)	41		1.78 (SD 0.48)		
	Serum Phosphate (mmol/L) – 5mo	Continuous	30		1.86 (SD 0.48)	41		1.91 (SD 0.43)		
	Serum Phosphate (mmol/L) – 6mo	Continuous	30		1.94 (SD 0.54)	41		1.83 (SD 0.43)		
	Serum Phosphate (mmol/L) – 7mo	Continuous	30		1.88 (SD 0.43)	41		1.88 (SD 0.54)		
	Serum Phosphate (mmol/L) – 8mo	Continuous	30		1.94 (SD 0.43)	41		1.78 (SD 0.43)		
	Serum Phosphate (mmol/L) – 9mo	Continuous	30		1.91 (SD 0.43)	41		1.78 (SD 0.54)		
	Serum Phosphate (mmol/L) – 10mo	Continuous	30		1.88 (SD 0.38)	41		1.67 (SD 0.43)		
	Serum Phosphate (mmol/L) – 11mo	Continuous	30		1.88 (SD 0.43)	41		1.72 (SD 0.38)		
	Serum Phosphate (mmol/L) – 12mo	Continuous	30		1.78 (SD 0.38)	41		1.88 (SD 0.43)		

	Coronary: Coronary arterial calcification – 12mo	Mean change	30		182 (SD 333)	41		139 (SD 240)		
	Coronary arterial calcification – 12mo	Continuous	30		857 (SD 1559)	41	22	646 (SD 973) [a]		
	Mortality: All cause mortality – 12mo	Dichotomous	49	8	(16.3%)	52	1	(1.9%)		
	Cardiovascular Mortality – 12mo	Dichotomous	49	5	(10.2%)	52	1	(1.9%)		
	Dialystate: Numbers on Ca dialystate 1.25mmol/L – 12mo	Dichotomous	30	16[b]	(53.3%)	41	15[c]	(36.6%)		
	Patients with basline CAC>30 Coronary: Coronary arterial calcification – 12mo	Mean change	16		339 (SD 397)	27		208 (SD 272)		
	Coronary arterial calcification – 12mo	Continuous	16		1602 (SD 1851)	27		976 (SD 1062)		
	[a] *approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)* [b] *approximated to nearest integer (percentages only presented in text)* [c] *approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Block et al. (2005) – evidence table

Bibliographic reference	Block,G.A., Spiegel,D.M., Ehrlich,J., Mehta,R., Lindbergh,J., Dreisbach,A. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney International 2005;68(4):1815-24. Related publications Block GA, Raggi P, Bellasi A et al. (2007) Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney international 71(5): 438-441 Galassi, A., Spiegel, D. M., Bellasi, A. et al. (2006) Accelerated vascular calcification and relative hypoparathyroidism in incident haemodialysis diabetic patients receiving calcium binders. Nephrology Dialysis Transplantation 21(11): 3215-3222
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** >18 years **Washout phosphate level (mmol/L):** Additional notes: Only those new to haemodialysis were included. Those with a prior history of dialysis were excluded

Exclusions:
Heart Failure
A prior history of dialysis, kidney transplant, coronary bypass surgery, weight >130kg or current atrial fibrillation.
Baseline characteristics:

		Calcium			Sevelamer			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 0mo	Continuous	55		2.32 (SD 0.2)	54		2.32 (SD 0.25)		
Serum Phosphate (mmol/L) – 0mo	Continuous	55		1.74 (SD 0.45)	54		1.68 (SD 0.52)		
Coronary:									
Coronary arterial calcification – 0mo	Continuous	55		667 (SD 1248)	54		648 (SD 1499)		
Demographics:									
Gender-Female	Dichotomous	55	18[a]	(32.7%)	54	22[b]	(40.7%)		
Gender-Male[b]	Dichotomous	55	37	(67.3%)	54	32	(59.3%)		
Age	Continuous	55		59 (SD 15)	54		57 (SD 15)		
Number Diabetic	Dichotomous	55	28	(50.9%)	54	30[b]	(55.6%)		
Patients with basline CAC>30									
Coronary:									
Coronary arterial calcification – 0mo	Continuous	35		1047 (SD 1437)	29		1205 (SD 1886)		

[a] *approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)*
[b] *approximated to nearest integer (percentages only presented in text)*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: -
Lower serum PO4 limit: -
Upper serum Ca limit: 2.54
Lower serum Ca limit: -

Intervention(s)

Drug: Calcium Based Binders
N: 75
Mean daily dose (mg): 2300
Dose varied to maintain patients within study endpoints: Investigators were free to alter the dose to meet individual clinic endpoints
Notes: This average dose was elemental Ca.
Drug: Sevelamer hydrochloride
N: 73
Mean daily dose (mg): 8000

	Dose varied to maintain patients within study endpoints: Investigators were free to alter the dose to meet individual clinic endpoints
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Investigators were free to manage the patient a per their clinic protocols, no restrictions were placed on them. It is therefore likely that Vit D was altered during the study) **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (HMG Co-A reductase, ACE inhibitors, Beta blockers, Vitamin D) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** - **Follow-up (d):** 504 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** USA

Outcomes measures and effect sizes

		Calcium			Sevelamer				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 18mo	Dichotomous	67	12	(17.9%)	62	8	(12.9%)		
Withdrawal (AEs) – 18mo	Dichotomous	67	1	(1.5%)	62	1	(1.6%)		
Biochemical Data: Serum Ca (mmol/L) – 18mo	Mean value over whole trial period	55		2.4 (SD 0.12)	54		2.27 (SD 0.12)		
Serum Phosphate (mmol/L) – 1mo	Continuous	55		1.71 (SD 0.519)	54		1.84 (SD 0.441)		
Serum Phosphate (mmol/L) – 2mo	Continuous	55		1.64 (SD 0.52)	54		1.8 (SD 0.514)		
Serum Phosphate (mmol/L) – 3mo	Continuous	55		1.75 (SD 0.52)	54		1.78 (SD 0.51)		
Serum Phosphate (mmol/L) – 4mo	Continuous	55		1.68 (SD 0.371)	54		1.74 (SD 0.367)		
Serum Phosphate (mmol/L) – 5mo	Continuous	55		1.68 (SD 0.37)	54		1.71 (SD 0.37)		
Serum Phosphate (mmol/L) – 6mo	Continuous	55		1.78 (SD 0.445)	54		1.68 (SD 0.51)		
Serum Phosphate (mmol/L) – 7mo	Continuous	55		1.68 (SD 0.44)	54		1.64 (SD 0.51)		
Serum Phosphate (mmol/L) – 8mo	Continuous	55		1.61 (SD 0.44)	54		1.61 (SD 0.441)		

	Serum Phosphate (mmol/L) – 9mo	Continuous	55		1.64 (SD 0.519)	54		1.68 (SD 0.51)		
	Serum Phosphate (mmol/L) – 10mo	Continuous	55		1.63 (SD 0.371)	54		1.55 (SD 0.367)		
	Serum Phosphate (mmol/L) – 11mo	Continuous	55		1.55 (SD 0.52)	54		1.59 (SD 0.37)		
	Serum Phosphate (mmol/L) – 12mo	Continuous	55		1.59 (SD 0.37)	54		1.61 (SD 0.37)		
	Serum Phosphate (mmol/L) – 13mo	Continuous	55		1.59 (SD 0.445)	54		1.59 (SD 0.441)		
	Serum Phosphate (mmol/L) – 14mo	Continuous	55		1.61 (SD 0.593)	54		1.59 (SD 0.367)		
	Serum Phosphate (mmol/L) – 15mo	Continuous	55		1.68 (SD 0.59)	54		1.68 (SD 0.37)		
	Serum Phosphate (mmol/L) – 16mo	Continuous	55		1.75 (SD 0.519)	54		1.71 (SD 0.514)		
	Serum Phosphate (mmol/L) – 17mo	Continuous	55		1.68 (SD 0.52)	54		1.61 (SD 0.37)		
	Serum Phosphate (mmol/L) – 18mo	Continuous	55		1.68 (SD 0.59)	54		1.57 (SD 0.51)		
	Coronary:									
	Coronary arterial calcification – 6mo	Mean change	53		48 (SD 452)	51		16 (SD 286)		
	Coronary arterial calcification – 12mo	Mean change	47		169 (SD 311)	45		87 (SD 324)		
	Coronary arterial calcification – 18mo	Mean change	45		338 (SD 707)	40		138 (SD 412)		
	Mortality:									
	All cause mortality – -1mo	Time-to-event	75			73				
	All cause mortality – 66mo	Time-to-event	67			60			HR=3.100 (CI: 1.235, 7.782)	[a]
	All cause mortality – 66mo	Time-to-event				73			HR=3.100 (CI: 1.235, 7.782)	[a]
	Biochemical Data:									
	Proportion with hypercalcaemia – 18mo[b]	Dichotomous	55	30	(54.5%)	54	12	(22.2%)		
	Patients with basline CAC>30									
	Coronary:									
	Coronary arterial calcification – 6mo	Mean change	35		77 (SD 557)	26		28 (SD 404)		

	Coronary arterial calcification – 12mo	Mean change	29		271 (SD 362)	25		153 (SD 427)		
	Coronary arterial calcification – 18mo	Mean change	29		520 (SD 830)	20		260 (SD 562)		
	[a] *95% CI 1.23, 7.61; Block 2007; n=127; SE of ln(HR) estimated from CI* [b] *approximated to nearest integer (percentages only presented in text)* a significant increase in mortality was observed for calcium-treated patients									
Authors' conclusion										
Source of funding										
Comments										

Braun et al. (2004) – evidence table

Bibliographic reference	Braun,J., Asmus,H.G., Holzer,H., Brunkhorst,R., Krause,R., Schulz,W., et al. Long-term comparison of a calcium-free phosphate binder and calcium carbonate--phosphorus metabolism and cardiovascular calcification. Clinical Nephrology 2004;62(2):104-15.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 19 years and older **Washout phosphate level (mmol/L):** >1.8 **Exclusions:** Diabetes or poorly controlled diabetes Cancer Hypertension or poorly controlled hypertension Severe Hyperparathyroidism HIV positive Alcohol abuse Significant GI disease **Baseline characteristics:**

		Sevelamer			Caclium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	36	6	2.34 (SD 0.148) [a]	46		2.32 (SD 0.136)		
Serum Phosphate (mmol/L) – 0wk	Continuous	36		2.44 (SD 0.48)	46		2.29 (SD 0.475)		

	Coronary: Coronary arterial calcification – 0wk	Continuous	36		1784 (SD 2986)	46		1466 (SD 2074)		
	Demographics: History of dialysis (year)	Continuous	55		5.75 (SD 5.42)	57		4.83 (SD 5.5)		
	Gender-Female	Dichotomous	55	20[a]	(36.4%)	57	12	(21.1%)		
	Gender-Male	Dichotomous	55	35	(63.6%)	57	45	(78.9%)		
	Age	Continuous	55		55 (SD 13)	57		58 (SD 15)		
	Number Diabetic	Dichotomous	55	9[a]	(16.4%)	57	12	(21.1%)		
	[a] *approximated to nearest integer (percentages only presented in text)*									
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.6 **Lower serum PO4 limit:** 1 **Upper serum Ca limit:** 2.6 **Lower serum Ca limit:** -									
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 55 Mean daily dose (mg): 5900 (SD: 2400) Dose varied by washout phosphate: Dose was intially determined on the subjects previous dose of phosphate binders Dose varied to maintain patients within study endpoints: Dose was varied to maintain the study endpoints **Drug:** Calcium Carbonate **N:** 59 Mean daily dose (mg): 3900 (SD: 1700) Dose varied by washout phosphate: Dose was intially determined on the subjects previous dose of phosphate binders Dose varied to maintain patients within study endpoints: Dose was varied to maintain the study endpoints									
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Altered to maintain serum phosphate and serum calcium and iPTH within the target ranges.) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** Yes (Altered to maintain serum phosphate and serum calcium and iPTH within the target ranges.)									
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** none specified									
Location	**Country:** Germany									

Outcomes measures and effect sizes			Sevelamer			Caclium Carbonate			Δ	p
			N	k	mean	N	k	mean		
Disposition:										
Withdrawal (total) – 52wk		Dichotomous	55	19	(34.5%)	59	13	(22.0%)		
Withdrawal (AEs) – 52wk		Dichotomous	55	14	(25.5%)	59	6	(10.2%)		
Biochemical Data:										
Serum Ca (mmol/L) – 3wk		Continuous	36		2.33 (SD 0.12)	46		2.33 (SD 0.203)		
Serum Ca (mmol/L) – 6wk		Continuous	36		2.34 (SD 0.18)	46		2.46 (SD 0.203)		
Serum Ca (mmol/L) – 9wk		Continuous	36		2.35 (SD 0.18)	46		2.44 (SD 0.2)		
Serum Ca (mmol/L) – 12wk		Continuous	36		2.38 (SD 0.12)	46		2.48 (SD 0.2)		
Serum Ca (mmol/L) – 16wk		Continuous	36		2.35 (SD 0.12)	46		2.46 (SD 0.2)		
Serum Ca (mmol/L) – 20wk		Continuous	36		2.36 (SD 0.18)	46		2.45 (SD 0.2)		
Serum Ca (mmol/L) – 24wk		Continuous	36		2.34 (SD 0.18)	46		2.43 (SD 0.2)		
Serum Ca (mmol/L) – 28wk		Continuous	36		2.32 (SD 0.18)	46		2.46 (SD 0.2)		
Serum Ca (mmol/L) – 32wk		Continuous	36		2.37 (SD 0.12)	46		2.46 (SD 0.136)		
Serum Ca (mmol/L) – 36wk		Continuous	36		2.35 (SD 0.18)	46		2.46 (SD 0.2)		
Serum Ca (mmol/L) – 40wk		Continuous	36		2.34 (SD 0.18)	46		2.45 (SD 0.2)		
Serum Ca (mmol/L) – 44wk		Continuous	36		2.35 (SD 0.12)	46		2.48 (SD 0.2)		
Serum Ca (mmol/L) – 48wk		Continuous	36		2.35 (SD 0.12)	46		2.49 (SD 0.2)		
Serum Ca (mmol/L) – 52wk		Mean change	36		0.01 (SD 0.1)	46		0.15 (SD 0.16)		
Serum Ca (mmol/L) – 52wk		Continuous	36		2.35 (SD 0.12)	46		2.47 (SD 0.2)		
Serum Phosphate (mmol/L) – 3wk		Continuous	36		1.96 (SD 0.48)	46		1.75 (SD 0.475)		

	Serum Phosphate (mmol/L) – 6wk	Continuous	36		1.81 (SD 0.48)	46		1.68 (SD 0.339)		
	Serum Phosphate (mmol/L) – 9wk	Continuous	36		1.73 (SD 0.36)	46		1.77 (SD 0.543)		
	Serum Phosphate (mmol/L) – 12wk	Continuous	36		1.79 (SD 0.48)	46		1.77 (SD 0.271)		
	Serum Phosphate (mmol/L) – 16wk	Continuous	36		1.65 (SD 0.36)	46		1.81 (SD 0.407)		
	Serum Phosphate (mmol/L) – 20wk	Continuous	36		1.78 (SD 0.18)	46		1.81 (SD 0.543)		
	Serum Phosphate (mmol/L) – 24wk	Continuous	36		1.73 (SD 0.36)	46		1.83 (SD 0.407)		
	Serum Phosphate (mmol/L) – 28wk	Continuous	36		1.81 (SD 0.3)	46		1.89 (SD 0.475)		
	Serum Phosphate (mmol/L) – 32wk	Continuous	36		1.89 (SD 0.3)	46		1.92 (SD 0.543)		
	Serum Phosphate (mmol/L) – 36wk	Continuous	36		1.8 (SD 0.36)	46		1.84 (SD 0.61)		
	Serum Phosphate (mmol/L) – 40wk	Continuous	36		1.8 (SD 0.48)	46		1.85 (SD 0.61)		
	Serum Phosphate (mmol/L) – 44wk	Continuous	36		1.77 (SD 0.48)	46		1.69 (SD 0.543)		
	Serum Phosphate (mmol/L) – 48wk	Continuous	36		1.72 (SD 0.36)	46		1.7 (SD 0.475)		
	Serum Phosphate (mmol/L) – 52wk	Mean change	36		-0.58 (SD 0.68)	46		-0.52 (SD 0.5)		
	Serum Phosphate (mmol/L) – 52wk	Continuous	36		1.69 (SD 0.42)	46		1.69 (SD 0.475)		
	Coronary: Coronary arterial calcification – 26wk	Mean change	36		-260 (SD 782)	46		111 (SD 518)		
	Coronary arterial calcification – 52wk	Mean change	36		-130 (SD 791)	46		200 (SD 620)		
	Treatment: Compliance – 52wk[a]	Dichotomous	36	30	(83.3%)	46	39	(84.8%)		
	Biochemical Data: Proportion with hypercalcaemia – 52wk[a]	Dichotomous	55	9	(16.4%)	59	27	(45.8%)		
	Patients with basline CAC>30 Coronary: Coronary arterial calcification – 52wk	Mean change	29	5	-166 (SD 880)[a]	37		244 (SD 685)		

	[a] *approximated to nearest integer (percentages only presented in text)*
Authors' conclusion	
Source of funding	
Comments	

Chang et al. (2017) – evidence table

Bibliographic reference	Chang, Yu-Ming, Tsai, Shih-Ching, Shiao, Chih-Chung, Liou, Hung-Hsiang, Yang, Chuan-Lan, Tung, Nai-Yu, et al. Effects of lanthanum carbonate and calcium carbonate on fibroblast growth factor 23 and hepcidin levels in chronic hemodialysis patients. Clinical and experimental nephrology 2017;21(5):908-16.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** - **Age range:** >18 years **Washout phosphate level (mmol/L):** >1.93, <2.42 Additional notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:** Liver dysfunction Diabetes or poorly controlled diabetes Post parathyroidectomy, life expectancy less than 6 months, gastrectomy or enterectomy, active infection, malnutrition, intolerant to lanthanum carbonate or calcium carbonate, or inadequate dialysis. **Baseline characteristics:**

		Lanthanum carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	13		2.31	12		2.395		
Serum Phosphate (mmol/L) – 0wk	Continuous	13		2.206	12		2.119		
Serum iPTH (pmmol/L) – 0wk	Continuous	13		52.263	12		54.969		
Demographics: Age	Continuous	13		56.52 (SD 11.51)	12		61.17 (SD 7.76)		
History of dialysis (months)	Continuous	13		74.46 (SD 61.79)	12		73.75 (SD 43.76)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.93 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 13 Mean daily dose (mg): 1644 (SD: 584) Dose varied to maintain patients within study endpoints: Serum phosphate <2.09 mmol/l = lanthanum carbonate 375 mg three times a day. Serum phosphate 2.09 to 2.26 mmol/l = lanthanum carbonate 750 mg three times a day. Serum phosphate >2.26 mmol/l = lanthanum carbonate 375 mg three times a day. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Drug:** Calcium Carbonate **N:** 12 Mean daily dose (mg): 3375 (SD: 1299) Dose varied to maintain patients within study endpoints: Serum phosphate <2.09 mmol/l = calcium carbonate 500 mg three times a day. Serum phosphate 2.09 to 2.26 mmol/l = calcium carbonate 1000 mg three times a day. Serum phosphate >2.26 mmol/l = calcium carbonate 1500 mg three times a day. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Not stated **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Iron, erythropoiesis-stimulating agent, calcitriol, statin, renin-angiotensin-aldosterone system inhibitor) **Changes to diet allowed:** Yes (During the course of study, a dietitian was in charge of patient's diet education to achieve daily phosphorus intake within 600–800 mg.) **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 28 **Follow-up (d):** 168 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Taiwan

Outcomes measures and effect sizes

		Lanthanum carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 24wk	Dichotomous	13	0	(0.0%)	13	1	(7.7%)		
Biochemical Data: Serum Ca (mmol/L) – 24wk	Continuous	13		2.35	12		2.51		

	Serum Ca (mmol/L) – 24wk	Mean difference over whole trial period	13		0.04	12		0.115		
	Serum Phosphate (mmol/L) – 24wk	Continuous	13		1.534	12		1.776		
	Serum Phosphate (mmol/L) – 24wk	Mean difference over whole trial period	13		-0.669	12		0.333		
	Serum iPTH (pmmol/L) – 24wk	Continuous	13		42.429	12		52.14		
	Serum iPTH (pmmol/L) – 24wk	Mean difference over whole trial period	13		-9.834	12		-2.828		
	Adverse Events: Diarrhea – 24wk	Dichotomous	13	1	(7.7%)	12	0	(0.0%)		
Authors' conclusion										
Source of funding										
Comments										

Chen et al. (2014) – evidence table

Bibliographic reference	Chen, Nan, Wu, Xiongfei, Ding, Xiaoqiang, Mei, Changlin, Fu, Ping, Jiang, Gengru, et al. Sevelamer carbonate lowers serum phosphorus effectively in haemodialysis patients: a randomized, double-blind, placebo-controlled, dose-titration study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2014;29(1):152-60.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years and older **Washout phosphate level (mmol/L):** >1.78 **Exclusions:** Significant Unstable Medical conditions Diabetes or poorly controlled diabetes Hypertension or poorly controlled hypertension Significant GI disease **Baseline characteristics:**

			Sevelamer carbonate			Placebo				
			N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Phosphate (mmol/L) – 0wk		Continuous	135		2.568 (SD 0.627)	70		2.52 (SD 0.58)		
Demographics: History of dialysis (year)		Continuous	135		4.2 (SD 4.3)	70		4.9 (SD 4.5)		
Gender-Female		Dichotomous	135	51	(37.8%)	70	30	(42.9%)		
Gender-Male		Dichotomous	135	84	(62.2%)	70	40	(57.1%)		
Age		Continuous	135		48.1 (SD 13.1)	70		49.5 (SD 12.3)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.78 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer Carbonate **N:** 135 Mean daily dose (mg): 7.1 (SD: 2.5) Median daily dose (mg): 9.6 (Range: 7.2–9.6) Dose varied to maintain patients within study endpoints: Starting dose was 800 mg tablet three times daily with meals. If the serum phosphorus level was >1.78 mmol/L at weeks 2, 4 or 6, the patient was instructed at the next haemodialysis session to increase their study drug dose by one tablet per meal. At Week 8 or early termination (ET), study drug was stopped and patients returned to their usual phosphate binder(s). Notes: Average and median doses reported in grams. **Drug:** Placebo **N:** 70 Mean daily dose (mg): 8.8 (SD: 1.6) Median daily dose (mg): 7.2 (Range: 4.8–9.6) Notes: Placebo was also administered with meals. Average and median doses reported in grams.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Lipid medications)

	Changes to diet allowed: No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** China

Outcomes measures and effect sizes

		Sevelamer carbonate			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 8wk	Dichotomous	135	7	(5.2%)	70	2	(2.9%)		
Withdrawal (AEs) – 8wk	Dichotomous	135	4	(3.0%)	70	1	(1.4%)		
Biochemical Data: Serum Phosphate (mmol/L) – 8wk	Continuous	135		1.88 (SD 0.501)	70		2.455 (SD 0.556)		
Serum Phosphate (mmol/L) – 8wk	Mean change	135		-0.69 (SD 0.64)	70		-0.065 (SD 0.572)		
Adverse Events: Constipation – 8wk	Dichotomous	135	10	(7.4%)	70	0	(0.0%)		
Nausea OR vomiting – 8wk	Dichotomous	135	0	(0.0%)	70	4	(5.7%)		
Nausea – 8wk	Dichotomous	135	0	(0.0%)	70	4	(5.7%)		
Abdominal discomfort – 8wk	Dichotomous	135	4	(3.0%)	70	4	(5.7%)		
Abdominal distension – 8wk	Dichotomous	135	6	(4.4%)	70	1	(1.4%)		
Treatment: Compliance – 8wk	Dichotomous	135	130	(96.3%)	70	68	(97.1%)		
Biochemical Data: Serum phosphate (mg/dL) – 8wk	Continuous	135			70				

Authors' conclusion	
Source of funding	
Comments	

Chertow et al. (1997) – evidence table

Bibliographic reference	Chertow,G.M., Burke,S.K., Lazarus,J.M., Stenzel,K.H., Wombolt,D., Goldberg,D., Bonventre,J.V. Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. American Journal of Kidney Diseases 1997;29(1):66-71.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years and older **Washout phosphate level (mmol/L):** **Exclusions:** Significant Unstable Medical conditions Diabetes or poorly controlled diabetes Hypertension or poorly controlled hypertension Significant GI disease **Baseline characteristics:**

		Sevelamer			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	24		2.32 (SD 0.22)	12		2.4 (SD 0.12)		
Serum Phosphate (mmol/L) – 0wk	Continuous	24		2.13 (SD 0.68)	12		2.32 (SD 0.77)		
Demographics: Gender-Female	Dichotomous	24	13	(54.2%)	12	10	(83.3%)		
Gender-Male	Dichotomous	24	11	(45.8%)	12	2	(16.7%)		
Age	Continuous	24		58.8	12		53.7 (SD 13.9)		
Number Diabetic	Dichotomous	24	8	(33.3%)	12	4	(33.3%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride

	N: 24 Notes: The dose was selected based upon the subjects original calcium binder dose, the average number of capsules was 7.2 however there are no details on the dose contained within each capsule. **Drug:** Placebo **N:** 12
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Not stated **Rescue Binder use permitted:** No **Were other medications allowed:** No details provided **Changes to diet allowed:** No **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 14 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** USA
Outcomes measures and effect sizes	

		Sevelamer			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 2wk	Continuous	24		2.32 (SD 0.15)	12		2.35 (SD 0.15)		
Serum Phosphate (mmol/L) – 2wk	Continuous	24		1.74 (SD 0.55)	12		2.26 (SD 0.68)		
Adverse Events: Abdominal pain upper – 2wk	Dichotomous	24	0	(0.0%)	12	1	(8.3%)		
Diarrhea – 2wk	Dichotomous	24	0	(0.0%)	12	1	(8.3%)		
Nausea OR vomiting – 2wk	Dichotomous	24	1	(4.2%)	12	1	(8.3%)		
Treatment: Compliance – 2wk[a]	Continuous	24		90 (SD 12)	12		86 (SD 17)		

[a] *recorded as % pill count*

Authors' conclusion	
Source of funding	
Comments	

Chertow et al. (2002) – evidence table

Bibliographic reference

Chertow,G.M., Burke,S.K., Raggi,P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney International 2002;62(1):245-52.

Study type & aim

Blinded: no
Crossover trial: no
Multicentre: yes

Number and characteristics of patients

Gender: Male and Female
Age range: 19 years and older.
Washout phosphate level (mmol/L): >1.78
Exclusions:
Diabetes or poorly controlled diabetes
Cancer
Hypertension or poorly controlled hypertension
HIV positive
Alcohol abuse
Significant GI disease
Baseline characteristics:

		Sevelamer			Calcium based binders				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	99	5	2.35 (SD 0.17)	101		2.32 (SD 0.17)		
Serum Phosphate (mmol/L) – 0wk	Continuous	99		2.45 (SD 0.58)	101		2.39 (SD 0.61)		
Demographics: History of dialysis (year)	Continuous	99		med: 3.6	101		med: 2.9		
Gender-Female[a]	Dichotomous	99	36	(36.4%)	101	34	(33.7%)		
Gender-Male[a]	Dichotomous	99	63	(63.6%)	101	67	(66.3%)		
Age	Continuous	99		57 (SD 14)	101		56 (SD 16)		

[a] *approximated to nearest integer (percentages only presented in text)*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.61
Lower serum PO4 limit: 0.97
Upper serum Ca limit: 2.62
Lower serum Ca limit: 2.12

Intervention(s)

Drug: Sevelamer hydrochloride

	N: 99 Mean daily dose (mg): 6500 (SD: 2900) Dose varied to maintain patients within study endpoints: Dose varied to maintain serum phosphorus, calcium and intact PTH as previously stated. **Drug:** Calcium Based Binders **N:** 101 Mean daily dose (mg): 4.3 (SD: 1.9) Dose varied to maintain patients within study endpoints: Dose varied to maintain subjects within study endpoints of serum phosphate, calcium and intact PTH Notes: US subjects were given calcium acetate (mean 4600mg), while european subjects were given calcium carbonate (mean 3900mg)
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Titrated to achieve the phosphorus and calcium target levels and PTH within 15.91and 31.83 pmol/L.) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** No details provided (Aluminium binder) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** Yes (Titrated to achieve the phosphorus and calcium target levels)
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** Serum phosphate: No details provided Serum Ca: No details provided Binder use: No details provided
Location	**Country:** USA, Germany and Austria

Outcomes measures and effect sizes

		Sevelamer			Calcium based binders				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 52wk	Continuous	99		2.37 (SD 0.15)	101		2.42 (SD 0.17)		
Serum Phosphate (mmol/L) – 52wk	Continuous	99		1.65 (SD 0.39)	101		1.65 (SD 0.45)		
Mortality: All cause mortality – 52wk	Dichotomous	99	6	(6.1%)	101	5	(5.0%)		
Treatment: Compliance – 52wk[a]	Dichotomous	99	85	(85.9%)	101	81	(80.2%)		
Biochemical Data: Proportion with hypercalcaemia – 52wk	Dichotomous	99	5	(5.1%)	101	16[b]	(15.8%)		

[a] *the number of people who adhered to treatment; approximated to nearest integer (percentages only presented in text)*
[b] *approximated to nearest integer (percentages only presented in text)*

Authors' conclusion	
Source of funding	
Comments	

Chertow et al. (2003) – evidence table

Bibliographic reference	Chertow,G.M., Raggi,P., McCarthy,J.T., Schulman,G., Silberzweig,J., Kuhlik,A., et al. The effects of sevelamer and calcium acetate on proxies of atherosclerotic and arteriosclerotic vascular disease in hemodialysis patients. American Journal of Nephrology 2003;23(5):307-14.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 19 years and older **Washout phosphate level (mmol/L):** >1.78 **Exclusions:** Diabetes or poorly controlled diabetes Cancer Hypertension or poorly controlled hypertension HIV positive Alcohol abuse Significant GI disease **Baseline characteristics:**

		Sevelamer Hydrochloride			Calcium acetate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	54		2.34 (SD 0.17)	54		2.34 (SD 0.17)		
Serum Phosphate (mmol/L) – 0wk	Continuous	54		2.45 (SD 0.61)	54		2.48 (SD 0.67)		
Demographics: History of dialysis (year)	Continuous	54		med: 2.33 [rng 1.25–5.92]	54		med: 2.75 [rng 1–4.67]		
Gender-Female	Dichotomous	54	222	(411.1%)	54	16	(29.6%)		
Gender-Male	Dichotomous	54	32	(59.3%)	54	38	(70.4%)		
Age	Continuous	54		58 (SD 15)	54		54 (SD 17)		
Number Diabetic	Dichotomous	54	25	(46.3%)	54	23	(42.6%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 0.97 **Lower serum PO4 limit:** 1.6 **Upper serum Ca limit:** 2.12 **Lower serum Ca limit:** 2.62
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 54 Mean daily dose (mg): 6700 (SD: 3400) Dose varied to maintain patients within study endpoints: Stud endpoints - Calcium (2.12 to 2.62 mmol/L) and phosphorus (0.97 to 1.61mmol/L) targets **Drug:** Calcium acetate **N:** 54 Mean daily dose (mg): 4600 (SD: 2100) Dose varied to maintain patients within study endpoints: Study endpoints- calcium (2.12 to 2.62 mmol/L) and phosphorus (0.97 to 1.61mmol/L) targets
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (After 12 weeks the dose could be changed achieve calcium (2.12 to 2.62 mmol/L) and phosphorus (0.97 to 1.61mmol/L) targets.) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** No **Changes to diet allowed:** No details given **Changes to dialysate allowed:** Yes (After 12 weeks the dialystate Ca concentration could be changed achieve calcium (2.12 to 2.62 mmol/L) and phosphorus (0.97 to 1.61mmol/L) targets.)
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** Serum phosphate: No details Serum Ca: No details Binder use: No details
Location	**Country:** USA

Outcomes measures and effect sizes

		Sevelamer Hydrochloride			Calcium acetate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 52wk	Continuous	54		2.37 (SD 0.17)	54		2.4 (SD 0.15)		
Serum Phosphate (mmol/L) – 52wk	Continuous	54		1.58 (SD 0.39)	54		1.61 (SD 0.48)		

	Serum Phosphate (mmol/L) – 52wk	Mean change	54		-0.9 (SD 0.65)	54		-0.81 (SD 0.58)		
	Adverse Events:									
	Constipation – 52wk	Dichotomous	54	6	(11.1%)	54	9	(16.7%)		
	Diarrhea – 52wk	Dichotomous	54	10	(18.5%)	54	13	(24.1%)		
	Nausea OR vomiting – 52wk	Dichotomous	54	10	(18.5%)	54	14	(25.9%)		
	Nausea – 52wk	Dichotomous	54	10	(18.5%)	54	13	(24.1%)		
	Vomiting – 52wk	Dichotomous	54	9	(16.7%)	54	14	(25.9%)		
	Coronary:									
	Coronary arterial calcification – 52wk	Mean change	54		64 (SD 471)	54		182 (SD 350)		
	Treatment:									
	Compliance – 52wk	Dichotomous	54	42[a]	(77.8%)	54	39[b]	(72.2%)		
	Biochemical Data:									
	Proportion with hypercalcaemia – 52wk	Dichotomous	54	7	(13.0%)	54	19[a]	(35.2%)		
	[a] *approximated to nearest integer (percentages only presented in text)* [b] *approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Chiang et al. (2005) – evidence table

Bibliographic reference	Chiang,S.S. & Chen,J.B. Lanthanum carbonate (Fosrenol) efficacy and tolerability in the treatment of hyperphosphatemic patients with end-stage renal disease. Clinical Nephrology 2005;63(6):461-70.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 20 years and older **Washout phosphate level (mmol/L):** >1.8 **Exclusions:** Severe Hyperparathyroidism Significant GI disease **Baseline characteristics:**

			Lanthanam Carbonate			Placebo				
			N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Phosphate (mmol/L) – 0wk		Continuous	30		1.77 (SD 0.11)	31		1.83 (SD 0.16)		
Demographics: History of dialysis (year)		Continuous	30		5.7 (SD 3.4)	31		5.3 (SD 3.2)		
Gender-Female		Dichotomous	30	14	(46.7%)	31	17	(54.8%)		
Gender-Male		Dichotomous	30	16	(53.3%)	31	14	(45.2%)		
Age		Continuous	30		53.6 (SD 11.2)	31		51.7 (SD 9.4)		
Number Diabetic		Dichotomous	30	6	(20.0%)	31	6	(19.4%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.8 **Lower serum PO4 limit:** 0.6 **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 30 Dose varied by washout phosphate: Dose was titrated to maintain subjects within the study endpoints. Notes: No average dose was provided **Drug:** Placebo **N:** 31
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No **Were other medications allowed:** Yes (antihypertensive and anti-arrhythmic drugs) **Changes to diet allowed:** No **Changes to dialysate allowed:** Yes (The calcium concentration could be altered if the patient became hypocalcemic)
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 28 **Protocol-specified reasons for withdrawal:** Serum phosphate: If serum phsophate went outside the target ranges.
Location	**Country:** Taiwan

Outcomes measures and effect sizes			Lanthanam Carbonate			Placebo			Δ	p
			N	k	mean	N	k	mean		
	Disposition: Withdrawal (total) – 4wk	Dichotomous	30	2	(6.7%)	31	17	(54.8%)		
	Biochemical Data: Achieved phosphate control – 4wk	Dichotomous	30	18	(60.0%)	31	3[a]	(9.7%)		
	Serum Phosphate (mmol/L) – 1wk	Continuous	30		1.69 (SD 0.13)	31		2.31 (SD 0.23)		
	Serum Phosphate (mmol/L) – 2wk	Continuous	30		1.69 (SD 0.19)	31		2.31 (SD 0.16)		
	Serum Phosphate (mmol/L) – 3wk	Continuous	30		1.67 (SD 0.21)	31		2.36 (SD 0.27)		
	Serum Phosphate (mmol/L) – 4wk	Continuous	30		1.64 (SD 0.2)	31		2.28 (SD 0.16)		
	[a] *approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Chow et al. (2007) – evidence table

Bibliographic reference	Chow,K.M., Szeto,C.C., Kwan,B.C., Leung,C.B. Sevelamer treatment strategy in peritoneal dialysis patients: conventional dose does not make best use of resources. Journal of Nephrology 2007;20(6):674-82.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Aged over 18 years **Washout phosphate level (mmol/L):** Additional notes: Patients could not be on sevelamer prior to study entry **Exclusions:** Cancer Significant GI disease Expected survival <2years, history of non-compliance or have taken investigational drugs within the last 30 days **Baseline characteristics:**

			Treat to Goal			Low dose treatment				
			N	k	mean	N	k	mean	Δ	p
	Biochemical Data: Serum Phosphate (mmol/L) – 0mo	Continuous	9	6	2.38 (SD 0.379)	18		2.25 (SD 0.313)		
	Demographics: History of dialysis (year)	Continuous	9		med: 2.7 [rng 1.9–4.9]	18		med: 3.8 [rng 1.7–6.9]		
	Gender-Female	Dichotomous	9	5	(55.6%)	18	9	(50.0%)		
	Gender-Male	Dichotomous	9	4	(44.4%)	18	9	(50.0%)		
	Age	Continuous	9		56 (SD 12)	18		54 (SD 15)		
	Number Diabetic	Dichotomous	9	2	(22.2%)	18	8	(44.4%)		
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.78 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -									
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 10 Fixed daily dose (mg): 4000 **Drug:** Sevelamer hydrochloride **N:** 20 Fixed daily dose (mg): 1200									
Concomitant treatments	**Dialysis:** Peritoneal **Vit D:** Yes - but no further details **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** Yes **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given									
Length of follow up	**Washout period (d):** - **Follow-up (d):** 182 **Protocol-specified reasons for withdrawal:** none specified									
Location	**Country:** China									

Outcomes measures and effect sizes			Treat to Goal			Low dose treatment			Δ	p
			N	k	mean	N	k	mean		
Biochemical Data: Achieved phosphate control – 6mo[a]		Dichotomous	9	7	(77.8%)	18	6	(33.3%)		
Serum Phosphate (mmol/L) – 1mo		Continuous	9		2.04 (SD 0.822)	18		2.04 (SD 1.163)		
Serum Phosphate (mmol/L) – 2mo		Continuous	9		2.05 (SD 0.727)	18		2.05 (SD 1.029)		
Serum Phosphate (mmol/L) – 4mo		Continuous	9		1.95 (SD 0.506)	18		1.95 (SD 0.716)		
Serum Phosphate (mmol/L) – 6mo		Continuous	9		1.67 (SD 0.51)	18		2.17 (SD 0.581)		
Treatment: Compliance – 6mo		Dichotomous	9	8	(88.9%)	18	16[b]	(88.9%)		
[a] *approximated to nearest integer (percentages only presented in text)* [b] *approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)*										
Authors' conclusion										
Source of funding										
Comments										

De Santo et al. (2006) – evidence table

Bibliographic reference	De Santo,N.G., Frangiosa,A., Anastasio,P., Marino,A., Correale,G., Perna,A., et al. Sevelamer worsens metabolic acidosis in hemodialysis patients. Journal of Nephrology 2006;19():Suppl-14.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no Notes: No blinding details provided however, unlikely to be blinded as one treatment was capsules the other tablets.
Number and characteristics of patients	**Gender:** Male **Age range:** 35-50 years **Washout phosphate level (mmol/L):** >1.78 Additional notes: Text states they were only male patients, however the baseline characteristics suggest otherwise. **Exclusions:** Serum Ca (>2.74mmol/L) Cancer HIV positive Alcohol abuse Significant GI disease

iPTH>42pmol/L, non-compliant patients, those who have had a parathyroidectomy,

Baseline characteristics:

		Sevelamer Hydrochloride			Calcium Carbaonte				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous	8		2.28 (SD 0.19)	8		2.28 (SD 0.24)		
Serum Phosphate (mmol/L) – 0wk	Continuous	8		2.38 (SD 0.35)	8		2.42 (SD 0.34)		
Demographics:									
History of dialysis (year)	Continuous	8		[rng 0.5–0.83]	8		[rng 0.5–0.83]		
Gender-Male	Dichotomous	8	8	(100.0%)	8	8	(100.0%)		
Age	Continuous	8		[rng 35–50]	8		[rng 36–50]		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: -
Upper serum Ca limit: 2.62
Lower serum Ca limit: 2.12

Intervention(s)

Drug: Sevelamer hydrochloride
N: 8
Dose varied by washout phosphate: 1.94 to 2.42mmol/L - 4800mg/day, 2.42 to 2.9mmol/L - 7200mg/day, >2.9mmol/L 7200mg/day
Dose varied to maintain patients within study endpoints: The dose was then varied every two weeks to maintain people within the study endpoints, both serum PO4 and serum Ca
Notes: No average dose data was provided
Drug: Calcium Carbonate
N: 8
Dose varied by washout phosphate: It was varied by washout pahse but no details were provided
Dose varied to maintain patients within study endpoints: The dose was then varied every two weeks to maintain people within the study endpoints, both serum PO4 and serum Ca
Notes: No average dose data was provided

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Yes - changed during the study period (No details provided, however the final average values change therefore suggesting that these were altered during the study period.)
Rescue Binder use permitted: No details given

	Were other medications allowed: Yes (The only drugs detailed were hypotensive drugs) **Changes to diet allowed:** No **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 168 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Italy

Outcomes measures and effect sizes

		Sevelamer Hydrochloride			Calcium Carbaonte				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 4wk	Continuous	8		2.25 (SD 0.12)	8		2.37 (SD 0.12)		
Serum Ca (mmol/L) – 8wk	Continuous	8		2.27 (SD 0.14)	8		2.4 (SD 0.1)		
Serum Ca (mmol/L) – 12wk	Continuous	8		2.25 (SD 0.12)	8		2.37 (SD 0.12)		
Serum Ca (mmol/L) – 16wk	Continuous	8		2.25 (SD 0.12)	8		2.37 (SD 0.12)		
Serum Ca (mmol/L) – 20wk	Continuous	8		2.18 (SD 0.1)	8		2.37 (SD 0.18)		
Serum Ca (mmol/L) – 24wk	Continuous	8		2.25 (SD 0.15)	8		2.37 (SD 0.18)		
Serum Phosphate (mmol/L) – 4wk	Continuous	8		2.23 (SD 0.27)	8		2.31 (SD 0.3)		
Serum Phosphate (mmol/L) – 8wk	Continuous	8		2.1 (SD 0.32)	8		2.31 (SD 0.3)		
Serum Phosphate (mmol/L) – 12wk	Continuous	8		2.06 (SD 0.31)	8		2.29 (SD 0.38)		
Serum Phosphate (mmol/L) – 16wk	Continuous	8		2.15 (SD 0.43)	8		1.67 (SD 0.38)		
Serum Phosphate (mmol/L) – 20wk	Continuous	8		2.1 (SD 0.38)	8		1.7 (SD 0.35)		
Serum Phosphate (mmol/L) – 24wk	Continuous	8		2.13 (SD 0.22)	8		1.67 (SD 0.32)		

Authors' conclusion	
Source of funding	
Comments	

de Francisco et al. (2010) – evidence table

Bibliographic reference	de Francisco,A.L., Leidig,M., Covic,A.C., Ketteler,M., Benedyk-Lorens,E., Mircescu,G.M., et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. Nephrology Dialysis Transplantation 2010;25(11):3707-17.
Study type & aim	**Blinded:** yes () **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 to 85 years **Washout phosphate level (mmol/L):** >1.78 Additional notes: Not taking an magnesium or calcium containing supplements. **Exclusions:** Serum Ca (>2.6mmol/L after washout period) Serum Magnesium >1.5mmol/L after phosphate binder washout. **Baseline characteristics:**
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.78 **Lower serum PO4 limit:** - **Upper serum Ca limit:** 2.37 **Lower serum Ca limit:** 2.1

		Calcium Acetate/Magnesium Carbonate			Sevelamer Hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk[a]	Continuous	122		2.148 (SD 0.228)	122		2.185 (SD 0.182)		
Serum Phosphate (mmol/L) – 0wk[b]	Continuous	105		2.464 (SD 0.49)	99		2.48 (SD 0.47)		
Demographics: History of dialysis (year)	Continuous	126			129				
Gender-Female	Dichotomous	126			129				
Gender-Male	Dichotomous	126			129				
Age	Continuous	126			129				
Number Diabetic	Dichotomous	126			129				

[a] *Based on the full analysis set LOCF*
[b] *Based on the per-protocol set those that finished the study*

Intervention(s)	**Drug:** Calcium Acetate+Magnesium Carbonate **N:** 126 Mean daily dose (mg): 4891 (SD: 2030) Dose varied to maintain patients within study endpoints: Dose could be increased by one to three tablets per day to reduce serum phosphorus levels below 1.78mmol/L Notes: This is the average dose at week 25. No data available on the average dose over the course of the study. The CaMg tablet consisted of 435mg Ca acetate and 235mg MgCO3, therefore the total dose of one tablet was assumed to be 670mg. The dose is calculated on the basis of the average number of tablets. **Drug:** Sevelamer hydrochloride **N:** 129 Mean daily dose (mg): 6480 (SD: 2296) Dose varied to maintain patients within study endpoints: Dose could be increased by one to three tablets per day to reduce serum phosphorus levels below 1.78mmol/L Notes: This is the average dose at week 25. No data available on the average dose over the course of the study. The dose is calculated on the basis of the average number of tablets.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Some patients were on Calcimetics however no details on wether the dose could be varied during the study period.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** Yes (Ca Dialystate was fixed to either 1.25mmol or 1.5mmol/L. However, those on 1.25mmol were allowed to be moved upwards to 1.5mmol/L)
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 175 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Germany, Poland, Portugal, Romania and Spain

Outcomes measures and effect sizes

		Calcium Acetate/Magnesium Carbonate			Sevelamer Hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 25wk	Dichotomous	126	18	(14.3%)	129	34	(26.4%)		
Withdrawal (AEs) – 25wk	Dichotomous	126	3	(2.4%)	129	9	(7.0%)		
Biochemical Data:									
Serum Ca (mmol/L) – 1wk[a]	Continuous	122		2.17 (SD 0.221)	122		2.17 (SD 0.221)		
Serum Ca (mmol/L) – 2wk[a]	Continuous	122		2.19 (SD 0.22)	122		2.21 (SD 0.22)		
Serum Ca (mmol/L) – 3wk[a]	Continuous	122		2.22 (SD 0.22)	122		2.21 (SD 0.22)		

Serum Ca (mmol/L) – 5wk[a]	Continuous	122		2.2 (SD 0.331)	122		2.17 (SD 0.22)		
Serum Ca (mmol/L) – 7wk[a]	Continuous	122		2.24 (SD 0.22)	122		2.19 (SD 0.22)		
Serum Ca (mmol/L) – 9wk[a]	Continuous	122		2.22 (SD 0.22)	122		2.2 (SD 0.11)		
Serum Ca (mmol/L) – 13wk[a]	Continuous	122		2.236 (SD 0.22)	122		2.19 (SD 0.11)		
Serum Ca (mmol/L) – 17wk[a]	Continuous	122		2.2 (SD 0.33)	122		2.18 (SD 0.22)		
Serum Ca (mmol/L) – 21wk[a]	Continuous	122		2.25 (SD 0.22)	122		2.21 (SD 0.22)		
Serum Ca (mmol/L) – 25wk[a]	Continuous	122		2.219 (SD 0.156)	122		2.189 (SD 0.157)		
Serum Ca (mmol/L) – 25wk	Mean change	122		0.071 (SD 0.179)	122		0.004 (SD 0.152)		
Serum Phosphate (mmol/L) – 1wk[b]	Continuous	105		2.38 (SD 0.512)	99		2.42 (SD 0.83)		
Serum Phosphate (mmol/L) – 2wk[b]	Continuous	105		1.94 (SD 0.512)	99		2.15 (SD 0.5)		
Serum Phosphate (mmol/L) – 3wk[b]	Continuous	105		1.82 (SD 0.51)	99		2.03 (SD 0.5)		
Serum Phosphate (mmol/L) – 5wk[b]	Continuous	105		1.76 (SD 0.41)	99		1.93 (SD 0.5)		
Serum Phosphate (mmol/L) – 7wk[b]	Continuous	105		1.72 (SD 0.307)	99		1.88 (SD 0.41)		
Serum Phosphate (mmol/L) – 9wk[b]	Continuous	105		1.68 (SD 0.41)	99		1.81 (SD 0.5)		
Serum Phosphate (mmol/L) – 13wk[b]	Continuous	105		1.72 (SD 0.51)	99		1.92 (SD 0.5)		
Serum Phosphate (mmol/L) – 17wk[b]	Continuous	105		1.7 (SD 0.51)	99		1.9 (SD 0.58)		
Serum Phosphate (mmol/L) – 21wk[b]	Continuous	105		1.67 (SD 0.51)	99		1.83 (SD 0.58)		
Serum Phosphate (mmol/L) – 25wk	Mean change	105		-0.761 (SD 0.58)	99		-0.711 (SD 0.585)		
Serum Phosphate (mmol/L) – 25wk[b]	Continuous	105		1.704 (SD 0.48)	99		1.769 (SD 0.6)		

[a] *Based on the full analysis set LOCF*
[b] *Based on the per-protocol set those that finished the study*

Authors' conclusion	
Source of funding	
Comments	

Di Iorio et al. (2013) – evidence table

Bibliographic reference	Di Iorio, Biagio, Molony, Donald, Bell, Cynthia, Cucciniello, Emanuele, Bellizzi, Vincenzo, Russo, Domenico. Sevelamer Versus Calcium Carbonate in Incident Hemodialysis Patients: Results of an Open-Label 24-Month Randomized Clinical Trial. American Journal of Kidney Diseases 2013;62(4):771-78.
Study type & aim	**Blinded:** yes (single-blind) **Crossover trial:** no **Multicentre:** no Notes: Blind event adjudication for coronary artery calcification
Number and characteristics of patients	**Gender:** Male and Female **Age range:** >18 years **Washout phosphate level (mmol/L):** >0.8, <1.77 Additional notes: Washout was not reported. Phosphate levels were taken from target levels. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:** Liver dysfunction Age older than 75 years, history of cardiac arrhythmia (reported history of cardiac arrhythmias, evidence of arrhythmias on an electrocardiogram, 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, hypothyroidism, and use of drugs known to prolong the QT interval. **Baseline characteristics:**

		Sevelamer hydrochloride			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	232		2.225 (SD 0.2)	234		2.2 (SD 0.175)		
Serum Phosphate (mmol/L) – 0mo	Continuous	232		1.809 (SD 0.549)	234		1.55 (SD 0.452)		
Serum iPTH (pmmol/L) – 0mo	Continuous	232		med: 22.057 [rng 14.316–28.102]	234		med: 23.118 [rng 14.316–30.011]		
Coronary: Coronary arterial calcification – 0mo	Continuous	232		med: 19 [rng 0–30]	234		med: 30 [rng 7–180]		
Demographics: Gender-Male[a]	Dichotomous	232	116	(50.0%)	234	112	(47.9%)		
Age	Continuous	232		66.6 (SD 14.1)	234		64.6 (SD 15.4)		

	Number Diabetic[a]	Dichotomous	232	70	(30.2%)	234	68	(29.1%)		
	[a] *estimated from percentage*										
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.77 **Lower serum PO4 limit:** 0.8 **Upper serum Ca limit:** - **Lower serum Ca limit:** -										
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 232 Mean daily dose (mg): 4300 (SD: 1400) Median daily dose (mg): 4800 **Drug:** Calcium Carbonate **N:** 234 Mean daily dose (mg): 2200 (SD: 1000) Median daily dose (mg): 2000										
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** Yes (Aluminum hydroxide was used as rescue therapy only as per the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) recommendations. Investigators were free to adjust medication dosages to achieve therapeutic targets for blood pressure (<=130/80 mm Hg), anemia (hemoglobin >11 g/dL and transferrin saturation >20%), acidosis (bicarbonate, 20-24 mmol/L), diabetes (hemoglobin A1c <7.0%), dyslipidemia (total cholesterol <200 mg/dL, low-density lipoprotein cholesterol <100 mg/dL, and triglycerides <180 mg/dL), and the other parameters of bone mineral metabolism (i.e., calcium and intact parathyroid hormone [iPTH] at 8.0-9.9 mg/dL and 150-300 pg/mL, respectively) per NKF-KDOQI guidelines.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given										
Length of follow up	**Washout period (d):** - **Follow-up (d):** 1095 **Protocol-specified reasons for withdrawal:** none specified										
Location	**Country:** Italy										
Outcomes measures and effect sizes			**Sevelamer hydrochloride**			**Calcium carbonate**			**Δ**	**p**
			N	**k**	**mean**	**N**	**k**	**mean**		
	Biochemical Data: Serum Ca (mmol/L) – 24mo	Continuous	232		2.05 (SD 0.125)	234		2.4 (SD 0.275)		
	Serum Ca (mmol/L) – 24mo	Mean change	232		-0.175 (SD 0.228)	234		0.21 (SD 0.302)		

	Serum Phosphate (mmol/L) – 24mo	Continuous	232		1.357 (SD 0.388)	234		1.55 (SD 0.355)		
	Serum Phosphate (mmol/L) – 24mo	Mean change	232		-0.443 (SD 0.623)	234		-0.032 (SD 0.539)		
	Serum iPTH (pmmol/L) – 24mo	Mean change	232		-16.299 (SD 19.979)	234		0.223 (SD 33.245)		
	Serum iPTH (pmmol/L) – 24mo	Continuous	232		med: 12.725 [rng 8.272–14.528]	234		med: 25.451 [rng 15.058–42.206]		
	Mortality: All cause mortality – 36mo	Time-to-event	232			234			HR=0.260 (CI: 0.165, 0.410)	[a]
	Cardiovascular Mortality – 36mo	Time-to-event	232			234			HR=0.110 (CI: 0.055, 0.220)	[b]
	[a] *95% CI 0.17, 0.41; n=466; SE of ln(HR) estimated from CI* [b] *95% CI 0.05, 0.22; n=466; SE of ln(HR) estimated from CI*									
Authors' conclusion										
Source of funding										
Comments										

Emmett et al. (1991) – evidence table

Bibliographic reference	Emmett,M., Sirmon,M.D., Kirkpatrick,W.G., Nolan,C.R., Schmitt,G.W. Calcium acetate control of serum phosphorus in hemodialysis patients. American Journal of Kidney Diseases 1991;17(5):544-50.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** no details provided **Washout phosphate level (mmol/L):** >1.81 **Exclusions:** Serum Ca (Persistent hypercalcaemia >2.74mmol/L) Pregnant, mentally unstable, unable to comply with protocol **Baseline characteristics:**

		All study participants		
		N	k	mean
Demographics:				
Gender-Female	Dichotomous	69	31	(44.9%)
Gender-Male	Dichotomous	69	38	(55.1%)
Age	Continuous	69		55.5

		Calcium Acetate							
		N	k	mean	N	k	mean	Δ	p
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous	36		2.2 (SD 0.18)	32		2.25 (SD 0.226)		
Serum Phosphate (mmol/L) – 0wk	Continuous	36		2.42 (SD 0.54)	32		2.29 (SD 0.453)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: 1.45
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Calcium acetate
N: 36
Mean daily dose (mg): 2334.5 (SD: 55.41)
Dose varied to maintain patients within study endpoints: The dose was maintained from paer A which aimed to maintain the serum phosphate within the specified ranges
Notes: Dose was calculated from the average number of pills taken at the end of part A of the study, which was effectively a dose titration phase.
Drug: Placebo
N: 32

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Not stated
Rescue Binder use permitted: No details given
Were other medications allowed: No details provided
Changes to diet allowed: No details given

	Changes to dialysate allowed: Yes (Dialystate in Phase A could be between 1.5 and 1.75mmol/L. No details on whether this could chage during phase B.)
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 14 **Protocol-specified reasons for withdrawal:** Serum phosphate: no details given Serum Ca: no details given Binder use: no details given no details given
Location	**Country:** USA
Outcomes measures and effect sizes	

		Calcium Acetate							
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 2wk	Continuous	36		2.35 (SD 0.24)	32		2.2 (SD 0.17)		
Serum Phosphate (mmol/L) – 2wk	Continuous	36		1.9 (SD 0.54)	32		2.52 (SD 0.622)		

Authors' conclusion	
Source of funding	
Comments	

Evenepoel et al. (2009) – evidence table

Bibliographic reference	Evenepoel,P., Selgas,R., Caputo,F., Foggensteiner,L., Heaf,J.G., Ortiz,A., et al. Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. Nephrology Dialysis Transplantation 2009;24(1):278-85.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Aged 18 years and older **Washout phosphate level (mmol/L):** >1.78 **Exclusions:** Serum Ca (Serum calcium outside of the normal range (2.1 to 2.59mmol/L)) Significant Unstable Medical conditions Use of antiarrhythmics or antiseizure medication Alcohol abuse

Peritonitis

Baseline characteristics:

		Sevelamer Hydrochloride			Calcium Acetate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	95		2.38 (SD 0.15)	44		2.39 (SD 0.12)		
Serum Phosphate (mmol/L) – 0wk	Continuous	95		2.42 (SD 0.45)	44		2.4 (SD 0.45)		
Demographics: History of dialysis (year)	Continuous	97		med: 1.03 [rng 0.17–21.25]	46		med: 1.5 [rng 1.03–7.83]		
Gender-Female	Dichotomous	97	32	(33.0%)	46	18	(39.1%)		
Gender-Male	Dichotomous	97	65	(67.0%)	46	28	(60.9%)		
Age	Continuous	97		54.6 (SD 15.7)	46		54.1 (SD 15.8)		
Number Diabetic	Dichotomous	97	19	(19.6%)	46	12	(26.1%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: 0.97
Upper serum Ca limit: 2.59
Lower serum Ca limit: 2.1

Intervention(s)

Drug: Sevelamer hydrochloride
N: 97
Mean daily dose (mg): 5800 (SD: 2600)
Dose varied to maintain patients within study endpoints: Dose was varied to maintain study endpoints
Drug: Calcium acetate
N: 46
Mean daily dose (mg): 4500 (SD: 2200)
Dose varied to maintain patients within study endpoints: The dose varied to maintain study endpoints

Concomitant treatments

Dialysis: Peritoneal
Vit D: Yes - changed during the study period (The dose could be changed to maintain serum intact PTH levels between 150 and 300pg/dL)
Rescue Binder use permitted: No

	Were other medications allowed: Yes (Calcium supplementation was allowed in the evenings if serum Ca levels dropped outside of the target range) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 84 **Protocol-specified reasons for withdrawal:** Poor compliance
Location	**Country:** Belgium, Denmark, France, Italy, Spain, The Netherlands and UK

Outcomes measures and effect sizes

		Sevelamer Hydrochloride			Calcium Acetate				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 12wk	Dichotomous	74	23	(31.1%)	46	16	(34.8%)		
Withdrawal (AEs) – 12wk[a]	Dichotomous	97	17	(17.5%)	46	13	(28.3%)		
Biochemical Data:									
Achieved phosphate control – 12wk[a]	Dichotomous	97	45	(46.4%)	46	19	(41.3%)		
Serum Ca (mmol/L) – 12wk	Continuous	95		2.39 (SD 0.14)	44		2.5 (SD 0.25)		
Serum Ca (mmol/L) – 12wk	Mean change	95		0.01 (SD 0.14)	44		0.11 (SD 0.21)		
Serum Phosphate (mmol/L) – 12wk	Continuous	95		1.91 (SD 0.4)	44		1.86 (SD 0.52)		
Serum Phosphate (mmol/L) – 12wk	Mean change	95		-0.51 (SD 0.38)	44		-0.53 (SD 0.49)		
Proportion with hypercalcaemia – 12wk	Dichotomous	97	2	(2.1%)	46	8[a]	(17.4%)		

[a] *approximated to nearest integer (percentages only presented in text)*

Authors' conclusion	
Source of funding	
Comments	

Ferreira et al. (2008) – evidence table

Bibliographic reference	Ferreira,A., Frazao,J.M., Monier-Faugere,M.C., Gil,C., Galvao,J., Oliveira,C., et al. Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. Journal of the American Society of Nephrology 2008;19(2):405-12.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes

Number and characteristics of patients

Gender: Male and Female
Age range: -
Washout phosphate level (mmol/L):
Exclusions:
Significant Unstable Medical conditions
Steroid use
Alcohol abuse
A serum phosphorus above 2.6mmol/L as otherwise this was suggestive of non-compliance. The use of alluminium based binders in the previous year for longer than 3 months. Treatment with medications know to affect bone metabolism and tetracycline allergy.
Baseline characteristics:

		Sevelamer Hydrochloride			Calcium based binders				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	44		2.33 (SD 0.265)	47		2.38 (SD 0.274)		
Serum Phosphate (mmol/L) – 0wk	Continuous	44		1.914 (SD 0.73)	47		1.74 (SD 0.48)		
Demographics: History of dialysis (year)	Continuous	44		med: 1.92 [rng 0.3–18.5]	47		med: 2.08 [rng 0.17–15.1]		
Gender-Female	Dichotomous	44	11	(25.0%)	47	17	(36.2%)		
Gender-Male	Dichotomous	44	22	(50.0%)	47	18	(38.3%)		
Age	Continuous	44		55.5 (SD 15.4)	47		53.9 (SD 13.7)		
Number Diabetic	Dichotomous	44	2	(4.5%)	47	7	(14.9%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.6
Lower serum PO4 limit: 1
Upper serum Ca limit: 2.6
Lower serum Ca limit: -

Intervention(s)

Drug: Sevelamer hydrochloride
N: 44
Mean daily dose (mg): 5000 (SD: 2700)
Notes: Average does is that give at the end of year 1
Drug: Calcium Based Binders

	N: 47 Mean daily dose (mg): 4000 (SD: 2500) Notes: Average does is that give at the end of year 1
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Titrated to maintain iPTH at 150 to 300pg/ml) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** No (Alluminium rescue therapy was permitted for treatment resistant hyperphosphataemia) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** - **Follow-up (d):** 378 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Portugal

Outcomes measures and effect sizes

		Sevelamer Hydrochloride			Calcium based binders			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 54wk	Dichotomous	44	10	(22.7%)	47	14	(29.8%)		
Withdrawal (AEs) – 54wk	Dichotomous	44	2	(4.5%)	47	2	(4.3%)		
Biochemical Data: Serum Ca (mmol/L) – 2wk	Continuous	44		2.43 (SD 0.398)	47		2.38 (SD 0.27)		
Serum Ca (mmol/L) – 6wk	Continuous	44		2.33 (SD 0.133)	47		2.4 (SD 0.206)		
Serum Ca (mmol/L) – 10wk	Continuous	44		2.35 (SD 0.265)	47		2.41 (SD 0.137)		
Serum Ca (mmol/L) – 14wk	Continuous	44		2.31 (SD 0.27)	47		2.4 (SD 0.21)		
Serum Ca (mmol/L) – 18wk	Continuous	44		2.35 (SD 0.199)	47		2.4 (SD 0.27)		
Serum Ca (mmol/L) – 22wk	Continuous	44		2.34 (SD 0.2)	47		2.42 (SD 0.27)		
Serum Ca (mmol/L) – 26wk	Continuous	44		2.3 (SD 0.27)	47		2.31 (SD 0.27)		
Serum Ca (mmol/L) – 30wk	Continuous	44		2.33 (SD 0.2)	47		2.38 (SD 0.343)		
Serum Ca (mmol/L) – 34wk	Continuous	44		2.31 (SD 0.2)	47		2.33 (SD 0.27)		

Serum Ca (mmol/L) – 38wk	Continuous	44		2.25 (SD 0.27)	47		2.36 (SD 0.21)		
Serum Ca (mmol/L) – 42wk	Continuous	44		2.3 (SD 0.332)	47		2.41 (SD 0.21)		
Serum Ca (mmol/L) – 46wk	Continuous	44		2.31 (SD 0.2)	47		2.41 (SD 0.21)		
Serum Ca (mmol/L) – 50wk	Continuous	44		2.37 (SD 0.27)	47		2.45 (SD 0.27)		
Serum Ca (mmol/L) – 54wk	Continuous	44		2.26 (SD 0.332)	47		2.3 (SD 0.21)		
Serum Phosphate (mmol/L) – 2wk	Continuous	44		1.9 (SD 0.597)	47		1.84 (SD 0.548)		
Serum Phosphate (mmol/L) – 6wk	Continuous	44		1.82 (SD 0.464)	47		1.82 (SD 0.48)		
Serum Phosphate (mmol/L) – 10wk	Continuous	44		1.76 (SD 0.531)	47		1.72 (SD 0.343)		
Serum Phosphate (mmol/L) – 14wk	Continuous	44		1.7 (SD 0.597)	47		1.76 (SD 0.617)		
Serum Phosphate (mmol/L) – 18wk	Continuous	44		1.914 (SD 0.73)	47		1.67 (SD 0.55)		
Serum Phosphate (mmol/L) – 22wk	Continuous	44		1.82 (SD 0.597)	47		1.71 (SD 0.55)		
Serum Phosphate (mmol/L) – 26wk	Continuous	44		1.84 (SD 0.6)	47		1.71 (SD 0.55)		
Serum Phosphate (mmol/L) – 30wk	Continuous	44		1.73 (SD 0.6)	47		1.63 (SD 0.343)		
Serum Phosphate (mmol/L) – 34wk	Continuous	44		1.75 (SD 0.531)	47		1.64 (SD 0.34)		
Serum Phosphate (mmol/L) – 38wk	Continuous	44		1.78 (SD 0.332)	47		1.68 (SD 0.48)		
Serum Phosphate (mmol/L) – 42wk	Continuous	44		1.7 (SD 0.464)	47		1.72 (SD 0.617)		
Serum Phosphate (mmol/L) – 46wk	Continuous	44		1.68 (SD 0.531)	47		1.68 (SD 0.548)		
Serum Phosphate (mmol/L) – 50wk	Continuous	44		1.83 (SD 0.597)	47		1.92 (SD 0.823)		
Serum Phosphate (mmol/L) – 54wk	Continuous	44		1.9 (SD 0.531)	47		1.87 (SD 0.62)		

Authors' conclusion	
Source of funding	
Comments	

Finn et al. (2004) – evidence table

Bibliographic reference	Finn,W.F., Joy,M.S., Hladik,G. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis. Clinical Nephrology 2004;62(3):193-201.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years and older **Washout phosphate level (mmol/L):** >1.8 Additional notes: Patients also needed to be at least 80% compliant with placebo treatment during the washout phase **Exclusions:** Serum Ca (>2.8mmol/L) Severe Hyperparathyroidism Significant GI disease If they required more than 4000mg of elemental calcium to achieve phosphorus control, or if they have been precribed aluminium salts, or if they had significant abnormal laboratory results **Baseline characteristics:**

		Placebo			Lanthanam 225			Δ	p
		N	k	mean	N	k	mean		
Demographics: History of dialysis (year)	Continuous	32		2.5 (SD 1.8)	27		3.5 (SD 3.9)		
Gender-Female	Dichotomous	32	19[a]	(59.4%)	27	13	(48.1%)		
Gender-Male	Dichotomous	32	13[a]	(40.6%)	27	14	(51.9%)		
Age	Continuous	32		56.8	27		53.6		
Number Diabetic	Dichotomous	32	18	(56.3%)	27	10	(37.0%)		

[a] *approximated to nearest integer (percentages only presented in text)*

			Lanthanam 675			Lanthanam 1350				
			N	k	mean	N	k	mean	Δ	p
Demographics:										
History of dialysis (year)	Continuous	29		3.5 (SD 3)	30		3.1 (SD 1.4)		
Gender-Female	Dichotomous	29	10[a]	(34.5%)	30	13	(43.3%)		
Gender-Male	Dichotomous	29	19[a]	(65.5%)	30	17	(56.7%)		
Age	Continuous	29		57.5	30		59.4		
Number Diabetic	Dichotomous	29	15	(51.7%)	30	14	(46.7%)		

[a] *approximated to nearest integer (percentages only presented in text)*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Placebo
N: 32
Drug: Lanthanum carbonate
N: 27
Fixed daily dose (mg): 225
Drug: Lanthanum carbonate
N: 29
Fixed daily dose (mg): 675
Drug: Lanthanum carbonate
N: 30
Fixed daily dose (mg): 1350
Drug: Lanthanum carbonate
N: 26
Fixed daily dose (mg): 2250
Drug: Lanthanum carbonate
N: 113
Mean daily dose (mg): 1112.9 (SD: 748.3)
Notes: Combined Lanthanam group dose ranges from

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Not stated
Rescue Binder use permitted: No details given

	Were other medications allowed: **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 42 **Protocol-specified reasons for withdrawal:** Serum phosphate: >3.2 or <0.6mmol/L CaxP exceeded 80m2/dl2. Or if PTH levels increased by more than 500pg/ml above baseline.
Location	**Country:** USA

Outcomes measures and effect sizes

		Placebo			Lanthanam 225			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Achieved phosphate control – 6wk	Dichotomous	32	3	(9.4%)	27	6	(22.2%)		
Serum Phosphate (mmol/L) – 1wk	Mean change	32		0.07 (SD 0.339) [a]	27		0.11 (SD 0.364) [b]		
Serum Phosphate (mmol/L) – 2wk[b]	Mean change	32		0.18 (SD 0.509)	27		0.09 (SD 0.468)		
Serum Phosphate (mmol/L) – 3wk[b]	Mean change	32		0.11 (SD 0.396)	27		0.15 (SD 0.468)		
Serum Phosphate (mmol/L) – 4wk[b]	Mean change	32		0.11 (SD 0.396)	27		0.3 (SD 0.312)		
Serum Phosphate (mmol/L) – 5wk	Mean change	32		0.11 (SD 0.113) [b]	27		0.15 (SD 0.104)		
Serum Phosphate (mmol/L) – 6wk	Mean change	32		0.15 (SD 0.622) [b]	27		0.16 (SD 0.572)		

[a] *the mean change is from baseline, baseline is not provided*
[b] *the mean change is from baseline*

		Lanthanam 675			Lanthanam 1350			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Achieved phosphate control – 6wk	Dichotomous	29	2	(6.9%)	30	13	(43.3%)		
Serum Phosphate (mmol/L) – 1wk[a]	Mean change	29		-0.01 (SD 0.269)	30		-0.17 (SD 0.602)		
Serum Phosphate (mmol/L) – 2wk[a]	Mean change	29		-0.1 (SD 0.431)	30		-0.29 (SD 0.438)		
Serum Phosphate (mmol/L) – 3wk[a]	Mean change	29		-0.21 (SD 0.431)	30		-0.25 (SD 0.438)		
Serum Phosphate (mmol/L) – 4wk[a]	Mean change	29		-0.12 (SD 0.431)	30		-0.44 (SD 0.438)		

	Serum Phosphate (mmol/L) – 5wk[a]	Mean change	29		0.02 (SD 0)	30		-0.19 (SD 0.219)		
	Serum Phosphate (mmol/L) – 6wk[a]	Mean change	29		-0.06 (SD 0.485)	30		-0.34 (SD 0.274)		
	[a] *the mean change is from baseline*									
Authors' conclusion										
Source of funding										
Comments										

Finn et al. (2006) – evidence table

Bibliographic reference	Finn,W.F. Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. Clinical Nephrology 2006;65(3):191-202.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 12 years and over (no one under the age of 18 was actually recruited) **Washout phosphate level (mmol/L):** >1.9 **Exclusions:** Serum Ca (Serum Ca <2mmol/L) Liver dysfunction Cancer HIV positive Significant GI disease Exposure to experimental drug 30 days prior to the study start, pregnant or breastfeeding. **Baseline characteristics:**

		Lanthanam			Standard Treatment				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	682		2.3 (SD 0.266)	677		2.27 (SD 0.266)		
Serum Phosphate (mmol/L) – 0wk	Continuous	682		2.592 (SD 0.895)	677		2.592 (SD 0.892)		
Demographics: History of dialysis (year)	Continuous	682		3.9 (SD 3.4)	677		3.8 (SD 3.2)		

	Gender-Female	Dichotomous	682	292	(42.8%)	677	262	(38.7%)		
	Gender-Male	Dichotomous	682	390	(57.2%)	677	415	(61.3%)		
	Age	Continuous	682		53.8 (SD 14.6)	677		54.9 (SD 14.4)		
	Number Diabetic	Dichotomous	682	235	(34.5%)	677	236	(34.9%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.9 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 682 Dose varied by washout phosphate: Initial dose varied by washout phase Dose varied to maintain patients within study endpoints: Dose was varied following titration to maintain study endpoints. Notes: Average doses were not provided **Drug:** Any binder **N:** 677 Dose varied to maintain patients within study endpoints: Patients were placed onto their pre-treatment phosphate binder and this could be altered during the course of the study to maintain the study endpoints Notes: Average doses were not provided. At baseline the following binders were used calcium acetate 43%, calcium carbonate 35%, sevelamer 16%, other 4%, not reported 2%.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Not stated **Rescue Binder use permitted:** No **Were other medications allowed:** Yes (Rescue binder use was not permitted in the intervention group. However, the standard treatment group could change their binder) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 728 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** USA, Puerto Rico, Poland and South Africa

Outcomes measures and effect sizes			Lanthanam			Standard Treatment			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 24mo	Dichotomous	682	487	(71.4%)	677	357	(52.7%)		
Withdrawal (AEs) – 24mo	Dichotomous	682	98	(14.4%)	677	29	(4.3%)		
Biochemical Data:									
Achieved phosphate control – 1wk[a]	Dichotomous	682	32	(4.7%)	677	59	(8.7%)		
Achieved phosphate control – 7wk[a]	Dichotomous	682	298	(43.7%)	677	407	(60.1%)		
Achieved phosphate control – 14wk[a]	Dichotomous	682	302	(44.3%)	677	348	(51.4%)		
Achieved phosphate control – 26wk[a]	Dichotomous	682	342	(50.1%)	677	351	(51.8%)		
Achieved phosphate control – 52wk	Dichotomous	682	318[b]	(46.6%)	677	332[c]	(49.0%)		
Achieved phosphate control – 78wk	Dichotomous	682	326[a]	(47.8%)	677	348[c]	(51.4%)		
Achieved phosphate control – 104wk	Dichotomous	682	310[b]	(45.5%)	677	332	(49.0%)		
Serum Ca (mmol/L) – 2wk	Continuous	682		2.21 (SD 0.266)	677		2.3 (SD 0.266)		
Serum Ca (mmol/L) – 6wk	Continuous	682		2.22 (SD 0.266)	677		2.32 (SD 0.266)		
Serum Ca (mmol/L) – 9wk	Continuous	682		2.22 (SD 0.266)	677		2.3 (SD 0.266)		
Serum Ca (mmol/L) – 13wk	Continuous	682		2.25 (SD 0.266)	677		2.32 (SD 0.266)		
Serum Ca (mmol/L) – 17wk	Continuous	682		2.22 (SD 0.266)	677		2.32 (SD 0.266)		
Serum Ca (mmol/L) – 21wk	Continuous	682		2.25 (SD 0.266)	677		2.32 (SD 0.27)		
Serum Ca (mmol/L) – 25wk	Continuous	682		2.27 (SD 0.266)	677		2.35 (SD 0.266)		
Serum Ca (mmol/L) – 33wk	Continuous	682		2.3 (SD 0.4)	677		2.35 (SD 0.27)		
Serum Ca (mmol/L) – 42wk	Continuous	682		2.32 (SD 0.266)	677		2.37 (SD 0.266)		
Serum Ca (mmol/L) – 51wk	Continuous	682		2.32 (SD 0.266)	677		2.37 (SD 0.27)		
Serum Ca (mmol/L) – 60wk	Continuous	682		2.32 (SD 0.4)	677		2.37 (SD 0.27)		
Serum Ca (mmol/L) – 68wk	Continuous	682		2.29 (SD 0.4)	677		2.37 (SD 0.27)		

	Serum Ca (mmol/L) – 77wk	Continuous	682		2.32 (SD 0.266)	677		2.37 (SD 0.27)		
	Serum Ca (mmol/L) – 86wk	Continuous	682		2.29 (SD 0.4)	677		2.37 (SD 0.27)		
	Serum Ca (mmol/L) – 94wk	Continuous	682		2.32 (SD 0.4)	677		2.37 (SD 0.27)		
	Serum Ca (mmol/L) – 103wk	Continuous	682		2.34 (SD 0.4)	677		2.36 (SD 0.266)		
	Serum Phosphate (mmol/L) – 13wk	Continuous	682		2.1 (SD 0.538)	677		1.93 (SD 0.536)		
	Serum Phosphate (mmol/L) – 25wk	Continuous	682		2.035 (SD 0.844)	677		1.93 (SD 0.429)		
	Serum Phosphate (mmol/L) – 51wk	Continuous	682		2.003 (SD 1.184)	677		2.003 (SD 0.75)		
	Serum Phosphate (mmol/L) – 103wk	Continuous	682		1.986 (SD 1.076)	677		1.962 (SD 0.858)		
	Adverse Events:									
	Abdominal pain upper – 104wk	Dichotomous	682	119	(17.4%)	677	161	(23.8%)		
	Diarrhea – 104wk	Dichotomous	682	164	(24.0%)	677	216	(31.9%)		
	Nausea OR vomiting – 104wk	Dichotomous	682	250	(36.7%)	677	266	(39.3%)		
	Nausea – 104wk	Dichotomous	682	250	(36.7%)	677	266	(39.3%)		
	Vomiting – 104wk	Dichotomous	682	184	(27.0%)	677	204	(30.1%)		
	[a] *approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)* [b] *approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text); approximated to nearest integer (percentages only presented in text)* [c] *approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Fishbane et al. (2010) – evidence table

Bibliographic reference	Fishbane,S., Delmez,J., Suki,W.N., Hariachar,S.K., Heaton,J., Chasan-Taber,S., Plone,M.A. A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis. American Journal of Kidney Diseases 2010;55(2):307-15.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no

Number and characteristics of patients

Gender: Male and Female
Age range: Aged 18 years and over
Washout phosphate level (mmol/L): >1.78
Additional notes: iPTH <84.88pmol/L at screening
Exclusions:
Significant Unstable Medical conditions
Diabetes or poorly controlled diabetes
Hypertension or poorly controlled hypertension
Significant GI disease
Baseline characteristics:

		Sevelmaer Carbonate Powder once a day			Sevelamer Hydrochloride tablets 3 time per day			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	141		2.25 (SD 0.17)	72		2.25 (SD 0.17)		
Serum Phosphate (mmol/L) – 0wk	Continuous	141		2.36 (SD 0.41)	72		1.84 (SD 0.32)		
Demographics: History of dialysis (year)	Continuous	141		3.7 (SD 3.75)	72		4.38 (SD 3.66)		
Gender-Female	Dichotomous	141	54	(38.3%)	72	30	(41.7%)		
Gender-Male	Dichotomous	141	87	(61.7%)	72	42	(58.3%)		
Age	Continuous	141		56.7 (SD 14.2)	72		59 (SD 13.8)		
Number Diabetic	Dichotomous	141	57	(40.4%)	72	25	(34.7%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: 1.13
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Sevelamer Carbonate
N: 144
Mean daily dose (mg): 6900 (SD: 2700)
Dose varied to maintain patients within study endpoints: Dose started at 4800mg/day and was titrated to achieve phosphate control

	Notes: Powder was given once a day with the largest meal. The doses that were prescribed were larger 9200 (SD 4000) **Drug:** Sevelamer hydrochloride **N:** 73 Mean daily dose (mg): 7300 (SD: 3000) Dose varied to maintain patients within study endpoints: Dose started at 4800mg/day and was titrated to achieve phosphate control Notes: Dose was split over the 3 main meals of the day. Prescribed dose was 9200 (SD 4000)
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (cinacalcet) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 168 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** USA

Outcomes measures and effect sizes

		Sevelmaer Carbonate Powder once a day			Sevelamer Hydrochloride tablets 3 time per day				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 24wk	Dichotomous	144	51	(35.4%)	73	11	(15.1%)		
Withdrawal (AEs) – 24wk	Dichotomous	144	18	(12.5%)	73	4	(5.5%)		
Biochemical Data: Achieved phosphate control – 24wk	Dichotomous	141	76[a]	(53.9%)	72	46	(63.9%)		
Serum Ca (mmol/L) – 24wk	Mean change	141		0.05 (SD 0.17)	72		0.07 (SD 0.2)		
Serum Ca (mmol/L) – 24wk	Continuous	144		2.3 (SD 0.17)	73		2.32 (SD 0.15)		
Serum Phosphate (mmol/L) – 2wk	Continuous	144		1.84 (SD 0.38)	73		1.85 (SD 0.49)		
Serum Phosphate (mmol/L) – 4wk	Continuous	144		1.72 (SD 0.4)	73		1.72 (SD 0.43)		
Serum Phosphate (mmol/L) – 6wk	Continuous	144		1.72 (SD 0.34)	73		1.72 (SD 0.41)		
Serum Phosphate (mmol/L) – 8wk	Continuous	144		1.72 (SD 0.34)	73		1.61 (SD 0.38)		

	Serum Phosphate (mmol/L) – 12wk	Continuous	144		1.68 (SD 0.36)	73		1.65 (SD 0.32)		
	Serum Phosphate (mmol/L) – 16wk	Continuous	144		1.68 (SD 0.41)	73		1.55 (SD 0.36)		
	Serum Phosphate (mmol/L) – 20wk	Continuous	144		1.72 (SD 0.49)	73		1.61 (SD 0.34)		
	Serum Phosphate (mmol/L) – 24wk	Continuous	144		1.72 (SD 0.45)	73		1.22 (SD 0.3)		
	Serum Phosphate (mmol/L) – 24wk	Mean change	141		-0.61 (SD 0.55)	72		-0.62 (SD 0.4)		
	Adverse Events:									
	Constipation – 24wk	Dichotomous	141	1	(0.7%)	72	4	(5.6%)		
	Diarrhea – 24wk	Dichotomous	141	12	(8.5%)	72	4	(5.6%)		
	Nausea OR vomiting – 24wk	Dichotomous	141	18	(12.8%)	72	4	(5.6%)		
	Nausea – 24wk	Dichotomous	144	18	(12.5%)	73	4	(5.5%)		
	Vomiting – 24wk	Dichotomous	144	8	(5.6%)	73	1	(1.4%)		
	Treatment:									
	Compliance – 24wk	Dichotomous	141	127	(90.1%)	72	66[a]	(91.7%)		
	[a] *approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Freemont et al. (2005) – evidence table

Bibliographic reference	Freemont,A.J., Hoyland,J.A., Denton,J. The effects of lanthanum carbonate and calcium carbonate on bone abnormalities in patients with end-stage renal disease. Clinical Nephrology 2005;64(6):428-37.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes Notes: 18 centres across 12 countries. No other details provided.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No details provided **Washout phosphate level (mmol/L):** **Exclusions:** Serum Ca (Severe hyporcalcemia (no values given)) Steroid use Bone biopsy within the last 5 years, kidney transplant within the last month, pregnant or breastfeeding women, treatment with bisphosphonates, sucralfate, cyclosporine

Baseline characteristics:

		Lanthanum			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous	49		2.24 (SD 0.2)	49		2.29 (SD 0.32)		
Serum Phosphate (mmol/L) – 0wk	Continuous	49		1.72 (SD 0.4)	49		1.87 (SD 0.52)		
Demographics:									
Gender-Female	Dichotomous	49	18	(36.7%)	49	28	(57.1%)		
Gender-Male	Dichotomous	49	31	(63.3%)	49	21	(42.9%)		
Age	Continuous	49		55.9 (SD 13.5)	49		54 (SD 15.2)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: -
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 49
Dose varied to maintain patients within study endpoints: Dose was titrated to achieve phosphate control. No details were provided on what this level was. Dose could rise to 3750mg/day
Drug: Calcium Carbonate
N: 49
Dose varied by washout phosphate: Dose was titrated to achieve phosphate control. No details were provided on what this level was. Dose could rise to 9000mg/day

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Yes - changed during the study period (No further details but there were no restrictions)
Rescue Binder use permitted: No details given
Were other medications allowed: Yes (It appears Calcium was allowed but it is unclear as to whether this was given as a supplement or not.)
Changes to diet allowed: No details given
Changes to dialysate allowed: No details given

Length of follow up

Washout period (d): 28
Follow-up (d): 364

	Protocol-specified reasons for withdrawal: none specified
Location	**Country:** 12 countries (no further details provided)

Outcomes measures and effect sizes

		Lanthanum			Calcium carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 52wk	Dichotomous	49	15	(30.6%)	49	15	(30.6%)		
Withdrawal (AEs) – 52wk[a]	Dichotomous	49	12	(24.5%)	49	11	(22.4%)		
Biochemical Data:									
Serum Ca (mmol/L) – 52wk	Continuous	49		2.33 (SD 0.16)	49		2.39 (SD 0.21)		
Serum Phosphate (mmol/L) – 52wk	Continuous	49		1.79 (SD 0.47)	49		1.65 (SD 0.54)		
Adverse Events:									
Constipation – 52wk	Dichotomous	49	5	(10.2%)	49	8[a]	(16.3%)		
Diarrhea – 52wk	Dichotomous	49	4	(8.2%)	49	4	(8.2%)		
Nausea OR vomiting – 52wk[a]	Dichotomous	49	7	(14.3%)	49	5	(10.2%)		
Nausea – 52wk	Dichotomous	49	5	(10.2%)	49	2	(4.1%)		
Vomiting – 52wk	Dichotomous	49	7[a]	(14.3%)	49	5	(10.2%)		
Biochemical Data:									
Proportion with hypercalcaemia – 52wk	Dichotomous	49	3	(6.1%)	49	24[a]	(49.0%)		

[a] approximated to nearest integer (percentages only presented in text)

Authors' conclusion	
Source of funding	
Comments	

Fujii et al. (2018) – evidence table

Bibliographic reference	Fujii, Hideki, Kono, Keiji, Nakai, Kentaro, Goto, Shunsuke, Nishii, Tatsuya, Kono, Atsushi. Effects of Lanthanum Carbonate on Coronary Artery Calcification and Cardiac Abnormalities After Initiating Hemodialysis. Calcified tissue international 2018;102(3):310-20.
Study type & aim	**Blinded:** yes (single-blind) **Crossover trial:** no **Multicentre:** no Notes: CAC scoring was performed by board-certified diagnostic radiologists, who were blinded.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 20 years and older **Washout phosphate level (mmol/L):** Additional notes: Washout period not reported.

Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).

Exclusions:

Contraindications to lanthanum carbonate and calcium carbonate; history of parathyroidectomy; and patient refusal.

Baseline characteristics:

		Lanthanum carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	50		2.175 (SD 0.175)	55		2.075 (SD 0.225)		
Serum Phosphate (mmol/L) – 0mo	Continuous	53		1.841 (SD 0.485)	55		1.906 (SD 0.485)		
Coronary: Coronary arterial calcification – 0mo	Continuous	50		med: 207.5 [rng 10.3–1000.3]	55		med: 213 [rng 13.8–829.2]		
Demographics: Gender-Male	Dichotomous	53	44	(83.0%)	55	38	(69.1%)		
Age	Continuous	53		65 (SD 14)	55		63 (SD 13)		
Number Diabetic	Dichotomous	53	26	(49.1%)	55	23	(41.8%)		
GFR	Continuous	53		5.8 (SD 2.3)	55		5.2 (SD 1.3)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.93
Lower serum PO4 limit: 1.13
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 53
Median daily dose (mg): 750 (Range: 375–1500)
Dose varied to maintain patients within study endpoints: Phosphate levels between 1.13 and 1.93 mmol/l according to the Japanese Society of Dialysis Therapy guidelines.
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Drug: Calcium Carbonate
N: 55
Median daily dose (mg): 1500 (Range: 1000–3000)
Dose varied to maintain patients within study endpoints: Phosphate levels between 1.13 and 1.93 mmol/l according to the Japanese Society of Dialysis Therapy guidelines.
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).

Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; statin; warfarin; sevelamer and/or bixalomer) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** - **Follow-up (d):** 548 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Japan

Outcomes measures and effect sizes

		Lanthanum carbonate			Calcium carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 12mo	Dichotomous	50	7	(14.0%)	55	9	(16.4%)		
Withdrawal (total) – 18mo	Dichotomous	50	3	(6.0%)	55	5	(9.1%)		
Biochemical Data: Serum Ca (mmol/L) – 6mo	Continuous	50		2.2 (SD 0.125)	55		2.25 (SD 0.15)		
Serum Ca (mmol/L) – 12mo	Continuous	50		2.225 (SD 0.15)	55		2.275 (SD 0.15)		
Serum Ca (mmol/L) – 18mo	Continuous	50		2.2 (SD 0.15)	55		2.269 (SD 0.144)		
Serum Phosphate (mmol/L) – 6mo	Continuous	50		1.647 (SD 0.388)	55		1.76 (SD 0.533)		
Serum Phosphate (mmol/L) – 12mo	Continuous	50		1.744 (SD 0.549)	55		1.631 (SD 0.549)		
Serum Phosphate (mmol/L) – 18mo	Continuous	50		1.712 (SD 0.388)	55		1.68 (SD 0.485)		
Coronary: Coronary arterial calcification – 12mo	Mean difference over whole trial period	43		med: 53.3 [rng 1.2–179.4]	52		med: 64.7 [rng 0.9–269]		
Coronary arterial calcification – 12mo[a]	Percentage change from baseline	43		med: 29.4	52		med: 47.8		
Coronary arterial calcification – 12mo	Continuous	43		med: 320.6 [rng 24.4–1032.7]	52		med: 433.9 [rng 116.3–1375]		

	Coronary arterial calcification – 18mo[a]	Percentage change from baseline	41		med: 42.2	50		med: 59.1		
	Coronary arterial calcification – 18mo	Continuous	41		med: 349.9 [rng 65.1–981.7]	50		med: 500 [rng 178.1–1512.1]		
	Coronary arterial calcification – 18mo	Mean difference over whole trial period	41		med: 76 [rng 0–250.9]	50		med: 164.4 [rng 5.7–331.7]		
	Mortality:									
	Cardiovascular Mortality – 18mo	Dichotomous	53	1	(1.9%)	55	1	(1.8%)		
	Long-term morbidity:									
	Cardiovascular events – 18mo	Dichotomous	53	4	(7.5%)	55	2	(3.6%)		
	[a] *This is percentage difference rather than change difference*									
Authors' conclusion										
Source of funding										
Comments										

Galassi et al. (2006) – evidence table

Bibliographic reference	Galassi,A., Spiegel,D.M., Bellasi,A., Block,G.A. Accelerated vascular calcification and relative hypoparathyroidism in incident haemodialysis diabetic patients receiving calcium binders. Nephrology Dialysis Transplantation 2006;21(11):3215-22.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Over 18 years of age. **Washout phosphate level (mmol/L):** **Exclusions:** Previously undergone dialysis, kidney transplant, coronary artery stenting or bypass, weighed over 136kg. **Baseline characteristics:**

		Sevelamer Hydrochloride			Calcium based binders				
		N	k	mean	N	k	mean	Δ	p
Diabetes									
Biochemical Data:									
Serum Ca (mmol/L) – 0mo	Continuous	34		2.3 (SD 0.68)	30		2.3 (SD 0.15)		

	Serum Phosphate (mmol/L) – 0mo	Continuous	34		1.6 (SD 0.42)	30		1.7 (SD 0.45)		
	Coronary: Coronary arterial calcification – 0mo	Continuous	34		682 (SD 1160)	30		880 (SD 1487)		
	Demographics: Gender-Female	Dichotomous	34	15	(44.1%)	30	10	(33.3%)		
	Gender-Male	Dichotomous	34	19	(55.9%)	30	20	(66.7%)		
	Age	Continuous	34		58 (SD 14)	30		61 (SD 14)		
	No diabetes Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	20		2.3 (SD 0.15)	25		2.3 (SD 0.2)		
	Serum Phosphate (mmol/L) – 0mo	Continuous	20		1.8 (SD 0.68)	25		1.7 (SD 0.45)		
	Coronary: Coronary arterial calcification – 0mo	Continuous	20		589 (SD 1981)	25		412 (SD 842)		
	Demographics: Gender-Female	Dichotomous	20	7	(35.0%)	25	18	(72.0%)		
	Gender-Male	Dichotomous	20	13	(65.0%)	25	17	(68.0%)		
	Age	Continuous	20		54 (SD 15)	25		55 (SD 15)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 54 Mean daily dose (mg): 8000 **Drug:** Calcium Based Binders **N:** 55 Mean daily dose (mg): 2300 Notes: The average dose of CaCO3 or calcium aceteate is provided. However, the average elemental calcium was 2300/day
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Not stated **Rescue Binder use permitted:** No **Were other medications allowed:** Yes (Calcium supplements were allowed in the sevelamer group at the discretion of the investigator)

	Changes to diet allowed: No details given **Changes to dialysate allowed:** No (Calcium dialystate maintained at 1.25mmol/L)
Length of follow up	**Washout period (d):** - **Follow-up (d):** 534 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** USA

Outcomes measures and effect sizes

		Sevelamer Hydrochloride			Calcium based binders				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 18mo	Dichotomous	54	14	(25.9%)	55	10	(18.2%)		
Withdrawal (AEs) – 18mo	Dichotomous	54	1	(1.9%)	55	2	(3.6%)		
Diabetes Biochemical Data: Serum Ca (mmol/L) – 18mo	Continuous	34		2.27 (SD 0.1)	30		2.35 (SD 0.15)		
Serum Phosphate (mmol/L) – 18mo	Continuous	34		1.7 (SD 0.22)	30		1.6 (SD 0.25)		
Coronary: Coronary arterial calcification – 12mo	Mean change	34		98 (SD 389)	30		191 (SD 379)		
Coronary arterial calcification – 18mo	Mean change	34		151 (SD 475)	30		440 (SD 911)		
No diabetes Biochemical Data: Serum Ca (mmol/L) – 18mo	Continuous	20		2.3 (SD 0.15)	25		2.45 (SD 0.12)		
Serum Phosphate (mmol/L) – 18mo	Continuous	20		1.6 (SD 0.35)	25		1.6 (SD 0.35)		
Coronary: Coronary arterial calcification – 6mo	Mean change	20		-26 (SD 360)	25		48 (SD 236)		
Coronary arterial calcification – 12mo	Mean change	20		66 (SD 122)	25		145 (SD 215)		
Coronary arterial calcification – 18mo	Mean change	20		110 (SD 251)	25		210 (SD 283)		

Authors' conclusion	
Source of funding	
Comments	

Hervas et al. (2003) – evidence table

Bibliographic reference	Hervas,J.G. & Prados,D. Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: a comparison with calcium acetate. Kidney International - Supplement 2003;(85):S69-72.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years and older **Washout phosphate level (mmol/L):** >1.94 **Exclusions:** Significant Unstable Medical conditions Diabetes or poorly controlled diabetes Hypertension or poorly controlled hypertension Significant GI disease **Baseline characteristics:**

		All study participants		
		N	**k**	**mean**
Demographics:				
History of dialysis (year)	Continuous	51		4.74 (SD 4.05)
Gender-Female	Dichotomous	51	20[a]	(39.2%)
Gender-Female	Dichotomous	51	31[a]	(60.8%)
Age	Continuous	51		60.4 (SD 15.1)
Number Diabetic	Dichotomous	51	8[a]	(15.7%)

[a] *approximated to nearest integer (percentages only presented in text)*

		Sevelamer			Calcium Acetate				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous			2.46			2.46		
Serum Phosphate (mmol/L) – 0wk	Continuous			2.61 (SD 0.52)			2.42 (SD 0.48)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 0 Mean daily dose (mg): 4090 Dose varied by washout phosphate: Initial dose was determined by the washout phase serum phosphate. Sevelamer ranged from 2 to 4 capsules (403mg) three times a day Dose varied to maintain patients within study endpoints: Every 4 weeks the dose of each could be increased by one capsule per meal (three per day) Notes: No details given on the number within each arm **Drug:** Calcium acetate **N:** 0 Mean daily dose (mg): 3.9 Dose varied by washout phosphate: Initial dose was determined by the washout phase serum phosphate. Calcium acetate ranged from 1 to 4 tablets (500mg) three times a day. Dose varied to maintain patients within study endpoints: Every 4 weeks the dose of each could be increased by one capsule per meal (three per day) Notes: No details given on the number within each arm
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (No details were given.) **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** Yes (No details were given) **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 224 **Protocol-specified reasons for withdrawal:** Serum phosphate: No details given Serum Ca: No details given Binder use: No details given
Location	**Country:** Spain

Outcomes measures and effect sizes

		Sevelamer			Calcium Acetate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data:									
Serum Ca (mmol/L) – 4wk	Continuous			2.5			2.45		
Serum Ca (mmol/L) – 8wk	Continuous			2.5			2.45		

	Serum Ca (mmol/L) – 12wk	Continuous			2.46			2.46		
	Serum Ca (mmol/L) – 16wk	Continuous			2.46			2.46		
	Serum Ca (mmol/L) – 20wk	Continuous			2.54			2.48		
	Serum Ca (mmol/L) – 24wk	Continuous			2.45			2.45		
	Serum Ca (mmol/L) – 28wk	Continuous			2.5			2.45		
	Serum Ca (mmol/L) – 32wk	Continuous			2.48			2.48		
	Serum Phosphate (mmol/L) – 4wk	Continuous			2			1.91		
	Serum Phosphate (mmol/L) – 8wk	Continuous			1.98			1.86		
	Serum Phosphate (mmol/L) – 12wk	Continuous			1.76			1.66		
	Serum Phosphate (mmol/L) – 16wk	Continuous			1.81			1.74		
	Serum Phosphate (mmol/L) – 20wk	Continuous			1.86			1.76		
	Serum Phosphate (mmol/L) – 24wk	Continuous			1.88			1.76		
	Serum Phosphate (mmol/L) – 28wk	Continuous			1.98			1.93		
	Serum Phosphate (mmol/L) – 32wk	Mean change			-0.74 (SD 0.01)			-0.51 (SD 0.03)		
	Serum Phosphate (mmol/L) – 32wk	Continuous			1.94			1.91		
	Baseline data taken at 2 weeks from the paper as this was the end of the washout period. In addition no data is provided on how mnay subjects were recruited									
Authors' conclusion										
Source of funding										
Comments										

Hutchison et al. (2005) – evidence table

Bibliographic reference	Hutchison,A.J., Maes,B., Vanwalleghem,J., Asmus,G., Mohamed,E., Schmieder,R., et al. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized, comparative trial versus calcium carbonate. Nephron 2005;100(1):c8-19.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** - **Age range:** 18 years or over **Washout phosphate level (mmol/L):** **Exclusions:** Serum Ca (>2.65mmol/L) Liver dysfunction

Use of antiarrhythmics or antiseizure medication
Cancer
Severe Hyperparathyroidism
HIV positive
Alcohol abuse

Baseline characteristics:

		Lantham Carbonate			Calcium Carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	467		0.58 (SD 0.06)	213		0.63 (SD 0.08)		
Serum Phosphate (mmol/L) – 0wk	Continuous	504		2.67 (SD 0.63)	254		2.67 (SD 0.63)		
Serum Phosphate (mmol/L) – 0wk	Continuous	504		2.67 (SD 0.63)	209				
Serum Phosphate (mmol/L) – 0wk	Continuous	453			254		2.67 (SD 0.63)		
Serum Phosphate (mmol/L) – 0wk	Continuous	453			209				
Demographics: History of dialysis (year)	Continuous	510		3.58 (SD 3.25)	257		3.65 (SD 3.66)		
Gender-Female	Dichotomous	510	169	(33.1%)	257	93[a]	(36.2%)		
Gender-Male	Dichotomous	510	341	(66.9%)	257	164	(63.8%)		
Age	Continuous	510		57 (SD 14.3)	257		58.4 (SD 13.38)		

[a] *approximated to nearest integer (percentages only presented in text)*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.8
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 533
Dose varied to maintain patients within study endpoints: Initial daily dose of 375mg Lantham. If plasma phosphate reduced to <1.0mmol/L dose was reduced to provide 250mg/day. Throughout the dose titration lantham Carbonate was provided to supply elemental Lantham at375, 750, 1500. 2250 or 3000mg/day.
Drug: Calcium Carbonate
N: 267

	Dose varied to maintain patients within study endpoints: Initial dailt dose of 1500mg Calcium. If plasma phosphate reduced to <1.0mmol/L dose was reduced to provide 1000mg/day. Throughout the dose titration Calcium Carbonate was provided to supply elemental calcium at 1500, 3000, 4500. 6000 or 9000mg/day. The target enpoints were serum phosphate <1.8mmol/L.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (For the first 18 weeks patients were maintained on their initial does. After week 18 vitamin D could be used as required.) **Rescue Binder use permitted:** No **Were other medications allowed:** No **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 140 **Protocol-specified reasons for withdrawal:** Serum phosphate: Plasma phosphate >1.8mmol/L at the end of the titration phase, or >1.8mmol/L for 5 consecutive weeks during the treatment phase Serum Ca: >3mmol/L
Location	**Country:** UK, Germany, Belgium, The Netherlands

Outcomes measures and effect sizes

		Lantham Carbonate			Calcium Carbonate			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 25wk	Dichotomous	533	244	(45.8%)	267	113	(42.3%)		
Biochemical Data: Achieved phosphate control – 9wk	Dichotomous	277	188	(67.9%)	152	100	(65.8%)		
Achieved phosphate control – 13wk	Dichotomous	255	179	(70.2%)	138	104	(75.4%)		
Achieved phosphate control – 17wk	Dichotomous	242	166	(68.6%)	131	90	(68.7%)		
Achieved phosphate control – 21wk	Dichotomous	228	158	(69.3%)	117	85	(72.6%)		
Achieved phosphate control – 25wk	Dichotomous	222	146	(65.8%)	122	78	(63.9%)		
Serum Phosphate (mmol/L) – 1wk	Continuous	533			267				
Serum Phosphate (mmol/L) – 2wk	Continuous	533			267				
Serum Phosphate (mmol/L) – 3wk	Continuous	533			267				
Serum Phosphate (mmol/L) – 4wk	Continuous	533			267				
Serum Phosphate (mmol/L) – 5wk	Continuous	453		1.83 (SD 0.53)	209		1.63 (SD 0.47)		
Serum Phosphate (mmol/L) – 9wk	Continuous	277		1.67 (SD 0.48)	152		1.67 (SD 0.53)		
Serum Phosphate (mmol/L) – 13wk	Continuous	255		1.67 (SD 0.47)	138		1.6 (SD 0.47)		

	Serum Phosphate (mmol/L) – 17wk	Continuous	242		1.67 (SD 0.47)	131		1.67 (SD 0.47)		
	Serum Phosphate (mmol/L) – 21wk	Continuous	228		1.73 (SD 0.8)	117		1.67 (SD 0.43)		
	Serum Phosphate (mmol/L) – 25wk	Continuous	222		1.7 (SD 0.47)	122		1.7 (SD 0.47)		
	Adverse Events:									
	Constipation – 25wk	Dichotomous	533	32	(6.0%)	267	18	(6.7%)		
	Diarrhea – 25wk	Dichotomous	533	67	(12.6%)	267	26	(9.7%)		
	Nausea OR vomiting – 25wk	Dichotomous	533	98	(18.4%)	267	34	(12.7%)		
	Nausea – 25wk	Dichotomous	533	85	(15.9%)	267	34	(12.7%)		
	Vomiting – 25wk	Dichotomous	533	98	(18.4%)	267	30	(11.2%)		
	Biochemical Data:									
	Proportion with hypercalcaemia – 25wk	Dichotomous	533	2	(0.4%)	267	54	(20.2%)		
Authors' conclusion										
Source of funding										
Comments										

Iwasaki et al. (2005) – evidence table

Bibliographic reference	Iwasaki,Y., Takami,H., Tani,M., Yamaguchi,Y., Goto,H., Goto,Y., Goto,Y. Efficacy of combined sevelamer and calcium carbonate therapy for hyperphosphatemia in Japanese hemodialysis patients. Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2005;9(4):347-51.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no Notes: Patients initially started on different doses of callcium carboante which were reduced by 1500mg to different levels before being given different doses of sevelamer hydrochloride as well.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No details provided **Washout phosphate level (mmol/L):** >1.94 Additional notes: The washout level was not achieved during a washout pphase but was abstracted from medical records. Only patients with serum phosphate >1.94mmol/l were recruited. **Exclusions:** **Baseline characteristics:**

			Sevelamer + Calcium carbonate (low)			Sevelamer + Calcium Carbonate (high)				
			N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous		30		2.54 (SD 0.17)	21		2.47 (SD 0.15)		
Serum Phosphate (mmol/L) – 0wk	Continuous		30		2.23 (SD 0.26)	21		2.42 (SD 0.26)		
Demographics: History of dialysis (year)	Continuous		30		7 (SD 6.5)	21		5.1 (SD 3.9)		
Duration of dialysis (min)	Continuous		30		228 (SD 23.4)	21		222 (SD 22.2)		
Gender-Female	Dichotomous		30	20	(66.7%)	21	10	(47.6%)		
Gender-Male	Dichotomous		30	10	(33.3%)	21	11	(52.4%)		
Age	Continuous		30		60.1 (SD 10)	21		62.3 (SD 11.4)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride+Calcium Carbonate **N:** 30 Notes: Sevelamer 2250mg/day+1616.7mg/day **Drug:** Sevelamer hydrochloride+Calcium Carbonate **N:** 21 Notes: Sevelamer 3000mg/day+ Calcium Carbonate 2452.4mg/day
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 0

	Follow-up (d): 56 **Protocol-specified reasons for withdrawal:** Serum phosphate: No details provided Serum Ca: No details provided Binder use: No detals provided No details provided
Location	**Country:** Japan

Outcomes measures and effect sizes

		Sevelamer + Calcium carbonate (low)			Sevelamer + Calcium Carbonate (high)			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 8wk	Continuous	30		2.42 (SD 0.25)	21		2.4 (SD 0.15)		
Serum Phosphate (mmol/L) – 8wk	Continuous	30		2.23 (SD 0.45)	21		2.13 (SD 0.42)		
Adverse Events: Abdominal Distension – 8wk	Dichotomous	30	9	(30.0%)	21	8	(38.1%)		
Constipation – 8wk	Dichotomous	30	13	(43.3%)	21	10	(47.6%)		
Diarrhea – 8wk	Dichotomous	30	0	(0.0%)	21	0	(0.0%)		

Authors' conclusion	
Source of funding	
Comments	

Jalal et al. (2017) – evidence table

Bibliographic reference	Jalal, Diana, McFadden, Molly, Dwyer, Jamie P, Umanath, Kausik, Aguilar, Erwin, Yagil, Yoram, et al. Adherence rates to ferric citrate as compared to active control in patients with end stage kidney disease on dialysis. Hemodialysis international. International Symposium on Home Hemodialysis 2017;21(2):243-49. Related publications Lewis, Julia B, Sika, Mohammed, Koury, Mark J et al. (2015) Ferric citrate controls phosphorus and delivers iron in patients on dialysis. Journal of the American Society of Nephrology : JASN 26(2): 493-503 Van Buren, Peter N, Lewis, Julia B, Dwyer, Jamie P et al. (2015) The Phosphate Binder Ferric Citrate and Mineral Metabolism and Inflammatory Markers in Maintenance Dialysis Patients: Results From Prespecified Analyses of a Randomized Clinical Trial. American journal of kidney diseases : the official journal of the National Kidney Foundation 66(3): 479-88
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no

Multicentre: yes Notes: This trial had three periods. A 2-week washout period was followed by a 52-week randomized, open-label, active control period to determine the safety of ferric citrate as well as its capacity to supplement iron stores and reduce iv iron and ESA usage. This period was followed by a 4-week, randomized, open-label, placebo control period to determine the efficacy of ferric citrate to control phosphorus compared with placebo.

Subjects who were on ferric citrate after 52 weeks were rerandomized to either continue on ferric citrate or receive placebo for the 4-week placebo control period.

Number and characteristics of patients

Gender: Male and Female

Age range: Adults

Washout phosphate level (mmol/L): >1.93

Additional notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323)

Exclusions:

Parathyroidectomy within 6 months before the screening visit, an absolute requirement for oral iron or vitamin C therapy, or intolerance to calcium acetate and sevelamer; baseline ferritin>1000 ng/ml and/or TSAT>50% or inability to achieve a phosphorus>1.93 mmol/l in washout.

Baseline characteristics:

		Ferric citrate			Calcium acetate or sevelamer carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk[a]	Continuous	292		2.225 (SD 0.214)	149		2.24 (SD 0.214)		
Serum Phosphate (mmol/L) – 0wk[a]	Continuous	292		2.393 (SD 0.552)	149		2.442 (SD 0.552)		
Serum iPTH (pmmol/L) – 0wk[a]	Continuous	292		65.854 (SD 48.927)	149		61.294 (SD 49.189)		
Demographics: Gender-Male[a]	Dichotomous	292	183	(62.7%)	149	87	(58.4%)		
Age[a]	Continuous	292		med: 56 [rng 45–63]	149		med: 54 [rng 45–63]		

[a] *Lewis 2015*

		Ferric citrate			Placebo			Δ	p
		N	k	mean	N	k	mean		
Randomised withdrawal phase Biochemical Data: Serum Phosphate (mmol/L) – 0wk[a]	Continuous	96		1.654 (SD 0.38)	96		1.757 (SD 0.475)		
Demographics: Gender-Male[a]	Dichotomous	96	70	(72.9%)	96	47	(49.0%)		

	Age[a]	Continuous	96		med: 54 [rng 45–62.5]	96		med: 56 [rng 48.5–62]		
	[a] *Lewis 2015*									
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.77 **Lower serum PO4 limit:** 1.13 **Upper serum Ca limit:** - **Lower serum Ca limit:** -									
Intervention(s)	**Drug:** Ferric citrate **N:** 292 Mean daily dose (mg): 8.1 (SD: 2.4) Dose varied by washout phosphate: Phosphate <0.80 mmol/l, hold ferric citrate until serum phosphate is =1.13 mmol/l, then restart at a lower dose after consultation with Clinical Coordinating Center. Phosphate = 0.80 to 1.09 mmol/l, reduce dose by 1 tablet per day. Phosphate = 1.13 to 1.77 mmol/l, no action required (phosphate at goal). Phosphate = 1.80 to 2.22 mmol/l, increase dose by 1 tablet per day. Phosphate >2.22 mmol/l, increase dose by 3 tablets per day for a daily maximum total of 12 tablets per day. Notes: Average dose was reported as number of tablets. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Drug:** Calcium acetate or sevelamer carbonate **N:** 149 Mean daily dose (mg): 8 (SD: 2.8) Dose varied to maintain patients within study endpoints: Calcium acetate (667-mg capsules) and sevelamer carbonate (800-mg tablets) were titrated according to the FDA-approved package inserts that could be used alone or combined. Notes: Average dose was reported as number of tablets. **Drug:** Placebo **N:** 96 Notes: No further details about placebo. **Drug:** Calcium acetate **N:** 0 **Drug:** Sevelamer Carbonate **N:** 0 **Drug:** Calcium acetate+sevelamer carbonate **N:** 0									
Concomitant treatments	**Dialysis:** Either Haemodialysis or Peritoneal **Vit D:** Yes - changed during the study period (at the discretion of the treating physician) **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Vitamin D analogs, cinacalcet, fasting calcium supplements, ESAs, iv iron was permitted, at the discretion of the site, if ferritin was =1000 ng/ml and TSAT was=30%.) **Changes to diet allowed:** No details given									

	Changes to dialysate allowed: Yes (at the discretion of the treating physician)
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 392 **Protocol-specified reasons for withdrawal:** Serum phosphate: Subjects were considered treatment failures if they were =80% compliant with 12 doses/d of either ferric citrate or calcium acetatel and had two consecutive visits with a serum phosphorus>8.0 mg/dl. These subjects discontinued the study drug but completed all study visits. For the 4-week placebo control period: serum phosphorus levels were checked weekly, and any subject who developed a phosphorus level=9.0 mg/dl was considered a treatment failure. Serum Ca: Subjects assigned to calcium acetate with adjusted serum calcium>10.5 mg/dl unresponsive to conservative management were also considered treatment failures. Per the protocol, these subjects were switched to ferric citrate and allowed to enter the final 4-week placebo control period.
Location	**Country:** US and Israel
Outcomes measures and effect sizes	

		Calcium acetate		
		N	**k**	**mean**
Biochemical Data:				
Serum Ca (mmol/L) – 52wk	Mean change	39		0.1225 (SD 0.24) [a]
Serum Ca (mmol/L) – 52wk	Mean change	39		0.1225 (SD 0.24) [a]
Serum Phosphate (mmol/L) – 52wk	Mean change	39		-0.68153 (SD 0.62016) [a]
Serum Phosphate (mmol/L) – 52wk	Mean change	39		-0.68153 (SD 0.62016) [a]
Serum iPTH (pmmol/L) – 52wk	Mean change	35		-10.4878505 (SD 26.6491085) [a]
Serum iPTH (pmmol/L) – 52wk	Mean change	35		-10.4878505 (SD 26.6491085) [a]
Adverse Events:				
Hypercalcemia – 52wk	Dichotomous	35	4	(11.4%)

[a] *Van Buren 2015*

		Sevelamer carbonate		
		N	**k**	**mean**
Biochemical Data:				
Serum Ca (mmol/L) – 52wk	Mean change	78		0.0425 (SD 0.2025) [a]
Serum Ca (mmol/L) – 52wk	Mean change	78		0.0425 (SD 0.2025) [a]
Serum Phosphate (mmol/L) – 52wk	Mean change	78		-0.68153 (SD 0.74613) [a]
Serum Phosphate (mmol/L) – 52wk	Mean change	78		-0.68153 (SD 0.74613) [a]
Serum iPTH (pmmol/L) – 52wk	Mean change	72		-14.2418435 (SD 44.475273) [a]
Serum iPTH (pmmol/L) – 52wk	Mean change	72		-14.2418435 (SD 44.475273) [a]

Adverse Events: Hypercalcemia – 52wk	Dichotomous	72	0	(0.0%)

[a] *Van Buren 2015*

		Calcium acetate and sevelamer carbonate		
		N	k	mean
Biochemical Data: Serum Ca (mmol/L) – 52wk	Mean change	29		0.1025 (SD 0.31) [a]
Serum Ca (mmol/L) – 52wk	Mean change	29		0.1025 (SD 0.31) [a]
Serum Phosphate (mmol/L) – 52wk	Mean change	29		-0.79458 (SD 0.81396) [a]
Serum Phosphate (mmol/L) – 52wk	Mean change	29		-0.79458 (SD 0.81396) [a]
Serum iPTH (pmmol/L) – 52wk	Mean change	26		-25.9280025 (SD 51.198526) [a]
Serum iPTH (pmmol/L) – 52wk	Mean change	26		-25.9280025 (SD 51.198526) [a]

[a] *Van Buren 2015*

		Ferric citrate			Calcium acetate or sevelamer carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 52wk[a]	Dichotomous	293	98	(33.4%)	149	34	(22.8%)		
Withdrawal (AEs) – 52wk[a]	Dichotomous	293	35	(11.9%)	149	7	(4.7%)		
Biochemical Data: Serum Ca (mmol/L) – 52wk[b]	Continuous	292		2.28 (SD 0.214)	149		2.318 (SD 0.244)		
Serum Ca (mmol/L) – 52wk[c]	Mean change	281		0.055 (SD 0.225)	146		0.078 (SD 0.238)		
Serum Phosphate (mmol/L) – 52wk[b]	Continuous	292		1.731 (SD 0.552)	149		1.738 (SD 0.513)		
Serum Phosphate (mmol/L) – 52wk[c]	Mean change	281		-0.659 (SD 0.643)	146		-0.704 (SD 0.727)		
Serum iPTH (pmmol/L) – 52wk[b]	Continuous	292		48.038 (SD 41.678)	149		45.811 (SD 37.539)		
Serum iPTH (pmmol/L) – 52wk[c]	Mean change	247		-17.72 (SD 42.397)	133		-15.536 (SD 42.1)		

Adverse Events: Gastrointestinal serious adverse events – 52wk[a]	Dichotomous	292	24	(8.2%)	149	19	(12.8%)		
Gastrointestinal non-serious adverse events – 52wk[a]	Dichotomous	292	141	(48.3%)	149	55	(36.9%)		
Infection serious adverse events – 52wk[a]	Dichotomous	292	42	(14.4%)	149	29	(19.5%)		
Infection non-serious adverse events – 52wk[a]	Dichotomous	292	79	(27.1%)	149	36	(24.2%)		
Cadiac serious adverse events – 52wk[a]	Dichotomous	292	27	(9.2%)	149	20	(13.4%)		
Cadiac non-serious adverse events – 52wk[a]	Dichotomous	292	33	(11.3%)	149	14	(9.4%)		
Mortality: All cause mortality – 52wk	Dichotomous	292	13	(4.5%)	149	8	(5.4%)		
Treatment: Compliance – 52wk[d]	Continuous	292		81.4 [rng 78.2–84.6]	149		81.5 [rng 77.7–85.2]		
Male Treatment: Compliance – 52wk[d]	Continuous	168		80.4 [rng 76.2–84.5]	81		80.2 [rng 75–85.5]		
Female Treatment: Compliance – 52wk[d]	Continuous	101		83 [rng 78.4–87.5]	62		80.6 [rng 74.4–86.8]		
>55 Treatment: Compliance – 52wk[d]	Continuous	0		82.5 [rng 78.3–86.8]	0		81.1 [rng 75.2–87]		
<55 Treatment: Compliance – 52wk[e]	Continuous	0		80.8 [rng 76.4–85.2]	0		79.7 [rng 74.1–85.3]		

[a] *Lewis 2015*
[b] *Lewis 2015; mean and standard error of the mean*
[c] *Van Buren 2015*
[d] *Jalal 2017; adjusted mean adherence in percentage with 95% confidence interval*
[e] *Jalal 2017; number of people >55 not reported; adjusted mean adherence in percentage with 95% confidence interval*

		Ferric citrate			Placebo				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 52wk	Continuous	292		2.28 (SD 0.214)[a]	96				
Serum Phosphate (mmol/L) – 52wk	Continuous	292		1.731 (SD 0.552)[a]	96				
Serum iPTH (pmmol/L) – 52wk	Continuous	292		48.038 (SD 41.678)[a]	96				

Adverse Events: Hypercalcemia – 52wk	Dichotomous	292	0	(0.0%)	96	0	(0.0%)		
Gastrointestinal serious adverse events – 52wk	Dichotomous	292	24[b]		96				
Gastrointestinal non-serious adverse events – 52wk	Dichotomous	292	141[b]		96				
Infection serious adverse events – 52wk	Dichotomous	292	42[b]		96				
Infection non-serious adverse events – 52wk	Dichotomous	292	79[b]		96				
Cadiac serious adverse events – 52wk	Dichotomous	292	27[b]		96				
Cadiac non-serious adverse events – 52wk	Dichotomous	292	33[b]		96				
Randomised withdrawal phase Biochemical Data: Serum Phosphate (mmol/L) – 4wk[c]	Continuous	96		1.57 (SD 0.411)	96		2.329 (SD 0.601)		

[a] *Lewis 2015; mean and standard error of the mean*
[b] *Lewis 2015*
[c] *Lewis 2015; 4-week placebo control; mean and standard error of the mean*

		Calcium acetate or sevelamer carbonate			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 52wk	Continuous	149		2.318 (SD 0.244)[a]	96				
Serum Phosphate (mmol/L) – 52wk	Continuous	149		1.738 (SD 0.513)[a]	96				
Serum iPTH (pmmol/L) – 52wk	Continuous	149		45.811 (SD 37.539)[a]	96				
Adverse Events: Gastrointestinal serious adverse events – 52wk	Dichotomous	149	19[b]		96				
Gastrointestinal non-serious adverse events – 52wk	Dichotomous	149	55[b]		96				
Infection serious adverse events – 52wk	Dichotomous	149	29[b]		96				
Infection non-serious adverse events – 52wk	Dichotomous	149	36[b]		96				
Cadiac serious adverse events – 52wk	Dichotomous	149	20[b]		96				
Cadiac non-serious adverse events – 52wk	Dichotomous	149	14[b]		96				

[a] *Lewis 2015; mean and standard error of the mean*
[b] *Lewis 2015*

Adherence, as a continuous variable, was defined as percent of actual number of pills taken to total number of pills prescribed during the full duration of the study. Any adherence above 100% was treated as 100% in this analysis (Jalal 2017).

Authors' conclusion

Source of funding	
Comments	

Janssen et al. (1995) – evidence table

Bibliographic reference	Janssen,M.J., van der Kuy,A., ter Wee,P.M. Calcium acetate versus calcium carbonate and erythropoietin dosages in haemodialysis patients. Nephrology Dialysis Transplantation 1995;10(12):2321-24.
Study type & aim	**Blinded:** yes () **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No details given **Washout phosphate level (mmol/L):** **Exclusions:** **Baseline characteristics:**
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.6 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** 2.2
Intervention(s)	**Drug:** Calcium acetate **N:** 17 Dose varied to maintain patients within study endpoints: Dose varied to maintain serum phosphate below 1.6mmol/L Notes: No details were provided on the average dose or its variance. **Drug:** Calcium Carbonate **N:** 17 Dose varied to maintain patients within study endpoints: Dose varied to maintain serum phosphate below 1.6mmol/L Notes: No details were provided on the average dose or its variance.

		Calcium Acetate			Calcium Carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	11		2.3 (SD 0.199)	9		2.33 (SD 0.18)		
Serum Phosphate (mmol/L) – 0mo	Continuous	11		2.95 (SD 0.862)	9		2.45 (SD 0.54)		

Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Those with normal range phosphate and calcium above <2.20mmol/L had vitamin D3) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** Yes (Aluminum hydroxide was given if patients exceeded the target phosphate range 31 of the 34 patients were treated with erythropoietin. Only those who recieved this throughout the study were analysed. The dose was adjusted monthly according to the haemoglobin level, which had to reach a value of 6.4mmol/L) **Changes to diet allowed:** No **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** Serum phosphate: No details given Serum Ca: No details given Binder use: No details given Those who recieved blood transfusions, those whose erythropoietin dose was changed
Location	**Country:** Netherlands

Outcomes measures and effect sizes

		Calcium Acetate			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 12mo	Dichotomous	17	6	(35.3%)	17	8	(47.1%)		
Biochemical Data: Serum Ca (mmol/L) – 2mo	Continuous	11		2.51 (SD 0.2)	9		2.86 (SD 0.36)		
Serum Ca (mmol/L) – 4mo	Continuous	11		2.48 (SD 0.298)	9		2.8 (SD 0.36)		
Serum Ca (mmol/L) – 6mo	Continuous	11		2.51 (SD 0.199)	9		2.74 (SD 0.18)		
Serum Ca (mmol/L) – 8mo	Continuous	11		2.57 (SD 0.2)	9		2.68 (SD 0.18)		
Serum Ca (mmol/L) – 10mo	Continuous	11		2.63 (SD 0.3)	9		2.68 (SD 0.09)		
Serum Ca (mmol/L) – 12mo	Continuous	11		2.45 (SD 0.2)	9		2.8 (SD 0.27)		
Serum Phosphate (mmol/L) – 2mo	Continuous	11		1.87 (SD 0.597)	9		1.4 (SD 0.36)		
Serum Phosphate (mmol/L) – 4mo	Continuous	11		1.87 (SD 0.663)	9		1.4 (SD 0.36)		

	Serum Phosphate (mmol/L) – 6mo	Continuous	11		1.78 (SD 0.497)	9		1.6 (SD 0.36)		
	Serum Phosphate (mmol/L) – 8mo	Continuous	11		1.75 (SD 0.663)	9		1.63 (SD 0.36)		
	Serum Phosphate (mmol/L) – 10mo	Continuous	11		1.69 (SD 0.597)	9		1.58 (SD 0.36)		
	Serum Phosphate (mmol/L) – 12mo	Continuous	11		1.75 (SD 0.398)	9		1.52 (SD 0.54)		
Authors' conclusion										
Source of funding										
Comments										

Janssen et al. (1996) – evidence table

Bibliographic reference	Janssen,M.J., van der Kuy,A., ter Wee,P.M. Aluminum hydroxide, calcium carbonate and calcium acetate in chronic intermittent hemodialysis patients. Clinical Nephrology 1996;45(2):111-19.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Unclear **Washout phosphate level (mmol/L):** **Exclusions:** No exclusion criteria were provided **Baseline characteristics:**

		Calcium Acetate			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Phosphate (mmol/L) – 0mo	Continuous	14		3.03 (SD 0.861)	13		2.33 (SD 1.478)		
Demographics: History of dialysis (year)	Continuous	18		3.42 (SD 3.903)	20		4.5 (SD 5.232)		
Gender-Female	Dichotomous	18	7	(38.9%)	20	13	(65.0%)		
Gender-Male	Dichotomous	18	11	(61.1%)	20	7	(35.0%)		

	Age	Continuous	18		51 (SD 16.971)	20		58 (SD 17.889)		
	Number Diabetic	Dichotomous	18	2	(11.1%)	20	3	(15.0%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.6 **Lower serum PO4 limit:** - **Upper serum Ca limit:** 3 **Lower serum Ca limit:** 2.2
Intervention(s)	**Drug:** Calcium acetate **N:** 18 Mean daily dose (mg): 4900 (SD: 490) Dose varied to maintain patients within study endpoints: Dose was varied to maintain study endpoints of serum phosphate and calcium **Drug:** Calcium Carbonate **N:** 20 Mean daily dose (mg): 3460 (SD: 490) Dose varied to maintain patients within study endpoints: Dose varied to maintain seru phosphate and calcium endpoints
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Vitamin D was introduced in serum phosphate was within the target range but the serum calcium was too high.) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** -

Outcomes measures and effect sizes

		Calcium Acetate			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 12mo	Dichotomous	18	4	(22.2%)	20	7	(35.0%)		
Biochemical Data: Achieved phosphate control – 12mo[a]	Dichotomous	14	9	(64.3%)	13	8	(61.5%)		

	Serum Phosphate (mmol/L) – 1mo	Continuous	14		1.81 (SD 0.67)	13		1.81 (SD 0.649)		
	Serum Phosphate (mmol/L) – 2mo	Continuous	14		1.81 (SD 0.56)	13		1.58 (SD 0.65)		
	Serum Phosphate (mmol/L) – 3mo	Continuous	14		1.81 (SD 0.56)	13		1.69 (SD 0.433)		
	Serum Phosphate (mmol/L) – 4mo	Continuous	14		1.81 (SD 0.67)	13		1.52 (SD 0.43)		
	Serum Phosphate (mmol/L) – 5mo	Continuous	14		1.63 (SD 0.56)	13		1.72 (SD 0.43)		
	Serum Phosphate (mmol/L) – 6mo	Continuous	14		1.75 (SD 0.449)	13		1.63 (SD 0.216)		
	Serum Phosphate (mmol/L) – 7mo	Continuous	14		1.69 (SD 0.56)	13		1.52 (SD 0.43)		
	Serum Phosphate (mmol/L) – 8mo	Continuous	14		1.75 (SD 0.67)	13		1.69 (SD 0.22)		
	Serum Phosphate (mmol/L) – 9mo	Continuous	14		1.75 (SD 0.224)	13		1.78 (SD 0.22)		
	Serum Phosphate (mmol/L) – 10mo	Continuous	14		1.75 (SD 0.449)	13		1.63 (SD 0.43)		
	Serum Phosphate (mmol/L) – 11mo	Continuous	14		1.93 (SD 0.45)	13		1.63 (SD 0.43)		
	Serum Phosphate (mmol/L) – 12mo	Continuous	14		1.63 (SD 0.22)	13		1.63 (SD 0.324)		
	Proportion with hypercalcaemia – 12mo[b]	Dichotomous	14	9	(64.3%)	13	12	(92.3%)		
	[a] *calculated from the % who needed a rescue binder* [b] *Value set at 2.8mmol/L*									
Authors' conclusion										
Source of funding										
Comments										

Joy et al. (2003) – evidence table

Bibliographic reference	Joy,M.S. & Finn,W.F. Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. American Journal of Kidney Diseases 2003;42(1):96-107.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** no Notes: Following the washout phase all patients were tirated on Lanthanam for 6 weeks. Patients were then randomised to Lanthanam or placebo for a 4 week treatment phase. Only the data from the treatment phase was deemed relevant.

Number and characteristics of patients

Gender: Male and Female
Age range: Aged 18 years and older
Washout phosphate level (mmol/L): >1.91
Exclusions:
Serum Ca (Significant hypercalcemia >2.75 mmol/L or hypocalcemia <1.98mmol/L)
Significant Unstable Medical conditions
Cancer
Significant GI disease
Pregnan or lactating women or exposure to investigational drugs 30 days prior to the study were excluded.
Baseline characteristics:

		Lanthanam			Placebo				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	49		2.2 (SD 0.16)	44		2.17 (SD 0.18)		
Serum Phosphate (mmol/L) – 0wk	Continuous	49		1.76 (SD 0.47)	44		1.82 (SD 0.53)		
Demographics: History of dialysis (year)	Continuous	49		3.3 (SD 3.2)	44		3 (SD 3.4)		
Gender-Female	Dichotomous	49	17	(34.7%)	44	15	(34.1%)		
Gender-Male	Dichotomous	49	32	(65.3%)	44	29	(65.9%)		
Age	Continuous	49		60.2 (SD 13.3)	44		60.5 (SD 13.6)		
Number Diabetic	Dichotomous	49	20	(40.8%)	44	12	(27.3%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.91
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 49
Dose varied to maintain patients within study endpoints: The dose was varied during the titration phase to maintain the phosphorus target. During the treatment phase the dose did not alter.
Notes: No average dose of Lantham was provided

	Drug: Placebo **N:** 44
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details **Rescue Binder use permitted:** No **Were other medications allowed:** No **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 28 **Protocol-specified reasons for withdrawal:** Serum phosphate: Patients withdrawn during the titration phase (prior to randmisation) if serum phosphorus became >3.23mmol/L or <0.65mmol/L Serum Ca: No details Binder use: No details
Location	**Country:** USA

Outcomes measures and effect sizes

		Lanthanam			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 4wk	Dichotomous	49	4	(8.2%)	44	8	(18.2%)		
Withdrawal (AEs) – 4wk	Dichotomous	49	2	(4.1%)	44	1	(2.3%)		
Biochemical Data:									
Achieved phosphate control – 4wk[a]	Dichotomous	45	29	(64.4%)	36	14	(38.9%)		
Serum Ca (mmol/L) – 4wk	Continuous	49		2.2 (SD 0.17)	44		2.11 (SD 0.2)		
Serum Phosphate (mmol/L) – 1wk	Continuous	49		1.87 (SD 0.55)	44		2.21 (SD 0.57)		
Serum Phosphate (mmol/L) – 2wk	Continuous	49		1.87 (SD 0.45)	44		2.42 (SD 0.55)		
Serum Phosphate (mmol/L) – 3wk	Continuous	49		1.78 (SD 0.43)	44		2.48 (SD 0.66)		
Serum Phosphate (mmol/L) – 4wk	Continuous	49		1.87 (SD 0.49)	44		2.49 (SD 0.62)		
Adverse Events:									
Diarrhea – 4wk	Dichotomous	49	2	(4.1%)	44	3	(6.8%)		
Nausea OR vomiting – 4wk	Dichotomous	49	3	(6.1%)	44	2	(4.5%)		
Nausea – 4wk	Dichotomous	49	3	(6.1%)	44	2	(4.5%)		

	Vomiting – 4wk	Dichotomous	49	3	(6.1%)	44	1	(2.3%)		
	[a] *approximated to nearest integer (percentages only presented in text)*										
Authors' conclusion											
Source of funding											
Comments											

Kakuta et al. (2011) – evidence table

Bibliographic reference	Kakuta,T., Tanaka,R., Hyodo,T., Suzuki,H., Kanai,G., Nagaoka,M., et al. Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients. American Journal of Kidney Diseases 2011;57(3):422-31.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes Notes: Only investigators were blinded in terms of the multislice CT scan.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Over 20 years of age **Washout phosphate level (mmol/L):** **Exclusions:** Diabetes or poorly controlled diabetes Cancer Hypertension or poorly controlled hypertension Alcohol abuse Significant GI disease **Baseline characteristics:**

		Sevelamer			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	91		2.44 (SD 0.2)	92		2.42 (SD 0.16)		
Serum Phosphate (mmol/L) – 0wk	Continuous	91		1.82 (SD 0.18)	92		1.86 (SD 0.25)		
Coronary: Coronary arterial calcification – 0wk	Continuous	91		879 (SD 1334)	92		872 (SD 1186)		
Demographics: History of dialysis (year)	Continuous	91		8.75 (SD 7)	92		9.92 (SD 7.67)		
Gender-Female	Dichotomous	91	39	(42.9%)	92	45	(48.9%)		
Gender-Male	Dichotomous	91	52	(57.1%)	92	47	(51.1%)		

	Age	Continuous	91		59 (SD 12)	92		57 (SD 12)		
	Number Diabetic	Dichotomous	91	21	(23.1%)	92	17[a]	(18.5%)		
	[a] *approximated to nearest integer (percentages only presented in text)*									
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 2.1 **Lower serum PO4 limit:** - **Upper serum Ca limit:** 2.54 **Lower serum Ca limit:** -									
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 91 Dose varied to maintain patients within study endpoints: The dose was varied to maintain study endpoints. Calcium carboante 1500mg was given if subjects serum phosphorus could not be controlled. Notes: No average dose was provided. **Drug:** Calcium Carbonate **N:** 92 Dose varied to maintain patients within study endpoints: Dose was varied to maintain study endpoints Notes: No average dose was provided.									
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Vitamin D could be decreased or discontinued when serum Ca went above 2.62mmol/L) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** No (Cinacalcet was not allowed. For those in the sevelamer arm Calcium carbonate could be given when serum phosphorus could not be controlled below 2.1mmol/L.) **Changes to diet allowed:** No **Changes to dialysate allowed:** No details given									
Length of follow up	**Washout period (d):** - **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** none specified									
Location	**Country:** Japan									
Outcomes measures and effect sizes			**Sevelamer**			**Calcium Carbonate**			**Δ**	**p**
			N	**k**	**mean**	**N**	**k**	**mean**		
	Disposition: Withdrawal (total) – 52wk	Dichotomous	91	12	(13.2%)	92	8	(8.7%)		
	Withdrawal (AEs) – 52wk	Dichotomous	91	2	(2.2%)	92	5	(5.4%)		
	Biochemical Data: Serum Ca (mmol/L) – 52wk	Continuous	91		2.4 (SD 0.15)	92		2.45 (SD 0.2)		

	Serum Ca (mmol/L) – 52wk	Mean change	91		-0.04 (SD 0.195)	92		0.03 (SD 0.152)		
	Serum Phosphate (mmol/L) – 52wk	Continuous	91		1.66 (SD 0.27)	92		1.66 (SD 0.3)		
	Serum Phosphate (mmol/L) – 52wk	Mean change	91		-0.16 (SD 0.292)	92		-0.2 (SD 0.294)		
	Adverse Events: Constipation – 52wk	Dichotomous	91	2	(2.2%)	92	0	(0.0%)		
	Coronary: Coronary arterial calcification – 52wk	Continuous	91		961 (SD 1438)	92		1066 (SD 1380)		
	Coronary arterial calcification – 52wk	Mean change	91		81.8 (SD 189.331)	92		194 (SD 265.733)		
Authors' conclusion										
Source of funding										
Comments										

Kalil et al. (2012) – evidence table

Bibliographic reference	Kalil, Roberto S, Flanigan, Michael, Stanford, William. Dissociation between progression of coronary artery calcification and endothelial function in hemodialysis patients: a prospective pilot study. Clinical nephrology 2012;78(1):1-9.
Study type & aim	**Blinded:** yes (single-blind) **Crossover trial:** no **Multicentre:** no Notes: Radiologist and sonographer were blinded.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years or older **Washout phosphate level (mmol/L):** >1.13, <1.77 Additional notes: Washout phosphate levels were not reported, only target levels. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:** Patients treated with lanthanum carbonate, pregnant, in nursing homes, or with poor compliance to dialysis treatment. **Baseline characteristics:**

			Lanthanum carbonate			Non-lanthanum carbonate binder			Δ	p
			N	k	mean	N	k	mean		
	Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	7		2.45 (SD 0.05)	6		2.375 (SD 0.075)		
	Serum Phosphate (mmol/L) – 0mo	Continuous	7		2.261 (SD 0.162)	6		2.487 (SD 0.162)		
	Serum iPTH (pmmol/L) – 0mo	Continuous	7		34.889 (SD 9.014)	6		34.04 (SD 9.014)		
	Coronary: Coronary arterial calcification – 0mo[a]	Continuous	7		2669 (SD 2723)	6		1245 (SD 15.7)		
	Demographics: History of dialysis (year)	Continuous	7		7.5 (SD 5)	6		3.7 (SD 2)		
	Age	Continuous	7		65 (SD 9)	6		68 (SD 9)		
	Number Diabetic	Dichotomous	7	5	(71.4%)	6	3	(50.0%)		

[a] *Not stated but it seems to be range (minimum-maximum)*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.77
Lower serum PO4 limit: 1.13
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 7
Dose varied to maintain patients within study endpoints: Started at 500 mg 3 times a day with meals. To achieve target of phosphate levels (1.13 to 1.77 mmol/l), dose increments of 250 mg were used as needed. The maximum allowed daily dose was 4,500 mg.
Notes: After randomisation, the daily dose of lanthanum carbonate varied from 2,250 to 4,000 mg.
Drug: Any binder
N: 6
Dose varied by washout phosphate: Patients randomised to stay on the same binders were started on the same dose after the washout period.
Notes: Patients taking calcium-based binders were on a dose range of 2,500 to 4,002 mg daily, and patients on sevelamer were on a dose range of 1,600 to 4,800 mg.

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Not stated
Rescue Binder use permitted: No details given
Were other medications allowed: No details provided
Changes to diet allowed: No details given

	Changes to dialysate allowed: No details given								
Length of follow up	**Washout period (d):** 10 **Follow-up (d):** 365 **Protocol-specified reasons for withdrawal:** none specified								
Location	**Country:** US								
Outcomes measures and effect sizes			**Lanthanum carbonate**			**Non-lanthanum carbonate binder**				
			N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
	Disposition: Withdrawal (total) – 12mo	Dichotomous	10	3	(30.0%)	10	4	(40.0%)		
	Withdrawal (AEs) – 12mo	Dichotomous	10	1	(10.0%)	10	0	(0.0%)		
	Biochemical Data: Serum Ca (mmol/L) – 6mo	Continuous	7		2.35 (SD 0.05)	6		2.225 (SD 0.05)		
	Serum Ca (mmol/L) – 12mo	Continuous	7		2.175 (SD 0.075)	6		2.325 (SD 0.1)		
	Serum Phosphate (mmol/L) – 6mo	Continuous	7		1.744 (SD 0.162)	6		2.035 (SD 0.194)		
	Serum Phosphate (mmol/L) – 12mo	Continuous	7		1.68 (SD 0.194)	6		1.647 (SD 0.194)		
	Serum iPTH (pmmol/L) – 6mo	Continuous	7		34.677 (SD 9.014)	6		40.509 (SD 9.014)		
	Serum iPTH (pmmol/L) – 12mo	Continuous	7		44.539 (SD 9.226)	6		32.026 (SD 12.725)		
	Coronary: Coronary arterial calcification – 6mo	Percentage change from baseline	7		-10 (SD 11)	6		33 (SD 17)		
	Coronary arterial calcification – 6mo	Mean change	7		med: -202 [rng -441–38.5]	6		med: 229.9 [rng 42–859]		
	Coronary arterial calcification – 12mo	Percentage change from baseline	7		-2 (SD 11)	6		76 (SD 22)		
	Coronary arterial calcification – 12mo	Mean change	7		med: 9.2 [rng -219.7–417]	6		med: 225.8 [rng 68–1017]		

Authors' conclusion	
Source of funding	
Comments	

Katopodis et al. (2006) – evidence table

Bibliographic reference	Katopodis,K.P., Andrikos,E.K., Gouva,C.D., Bairaktari,E.T., Nikolopoulos,P.M., Takouli,L.K., et al. Sevelamer hydrochloride versus aluminum hydroxide: effect on serum phosphorus and lipids in CAPD patients. Peritoneal Dialysis International 2006;26(3):320-27.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No limits given **Washout phosphate level (mmol/L):** >1.94 **Exclusions:** Serum Ca (N/A) Significant Unstable Medical conditions Severe Anemia Heart Failure Liver dysfunction Diabetes or poorly controlled diabetes Bowel dysfunction Chronic Hepatitis Use of antiarrhythmics or antiseizure medication Cancer **Baseline characteristics:**

		Sevelamer Hydrochloride			Aluminium Hydroxide				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous	15		2.3 (SD 0.2)	15		2.27 (SD 0.2)		
Serum Phosphate (mmol/L) – 0wk	Continuous	15		2.4 (SD 0.44)	15		2.31 (SD 0.41)		
Serum Phosphate (mmol/L) – 0wk	Continuous	15		2.4 (SD 0.44)	15		2.28 (SD 0.39)		
Serum Phosphate (mmol/L) – 0wk	Continuous	15		2.38 (SD 0.43)	15		2.31 (SD 0.41)		

	Serum Phosphate (mmol/L) – 0wk	Continuous	15		2.38 (SD 0.43)	15		2.28 (SD 0.39)		
	Demographics:									
	Gender-Female	Dichotomous	15	7	(46.7%)	15	5	(33.3%)		
	Gender-Male	Dichotomous	15	8	(53.3%)	15	10	(66.7%)		
	Age	Continuous	15		59.9 (SD 14.3)	15		56.7 (SD 19.2)		
	Dialystate:									
	Ca Dialystate (mmol/L)	Continuous	15		1.75	15		1.75		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 15 Mean daily dose (mg): 2000 (SD: 1000) Dose varied by washout phosphate: 806mg - 11.93 to 2.42mmol/L; 1209mg-2.42 to 2.91mmol/L; 1612mg->2.91mmol/L **Drug:** Aluminium Hydroxide **N:** 15 Mean daily dose (mg): 1800 (SD: 1200) Dose varied by washout phosphate: 950mg-11.94 to 2.42mmol/L; 1425mg-2.42 to 2.91mmol/L; 1900mg->2.91mmol/L
Concomitant treatments	**Dialysis:** Peritoneal **Vit D:** No **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:** Serum phosphate: N/A Serum Ca: N/A
Location	**Country:** Greece

Outcomes measures and effect sizes			Sevelamer Hydrochloride			Aluminium Hydroxide			Δ	p
			N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 8wk		Continuous	15		2.34 (SD 0.15)	15		2.35 (SD 0.15)		
Serum Phosphate (mmol/L) – 8wk		Continuous	15		2.02 (SD 0.41)	15		1.9 (SD 0.35)		
Serum Phosphate (mmol/L) – 8wk		Mean change	15		-0.38 (SD 0.116)	15		-0.4 (SD 0.194)		
Adverse Events: Constipation – 8wk		Dichotomous	15	2	(13.3%)	15	0	(0.0%)		
	Mean change SD was converted from an SE which was stated within the paper to be an SD. However, the value appeared to be unrealistic.									
Authors' conclusion										
Source of funding										
Comments										

Ketteler et al. (2019) – evidence table

Bibliographic reference	Ketteler, Markus, Sprague, Stuart M, Covic, Adrian C, Rastogi, Anjay, Spinowitz, Bruce, Rakov, Viatcheslav, Walpen, Sebastian. Effects of sucroferric oxyhydroxide and sevelamer carbonate on chronic kidney disease-mineral bone disorder parameters in dialysis patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2019;34(7):1163-70. Related publications Floege, Jurgen, Covic, Adrian C, Ketteler, Markus et al. (2014) A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney international 86(3): 638-47 Floege, Jurgen, Covic, Adrian C, Ketteler, Markus et al. (2015) Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 30(6): 1037-46 Floege, Jurgen, Covic, Adrian C, Ketteler, Markus et al. (2017) One-year efficacy and safety of the iron-based phosphate binder sucroferric oxyhydroxide in patients on peritoneal dialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 32(11): 1918-1926
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes Notes: This was a two-stage, randomized, active-controlled, parallel-group, multicentre, open-label and Phase 3 study (NCT01324128) [Floege 2014] investigating the efficacy and safety of sucroferric oxyhydroxide versus sevelamer, followed by an extension study (NCT01464190) [Floege 2015].
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years or older **Washout phosphate level (mmol/L):** >1.94 **Exclusions:**

Liver dysfunction

Significant GI disease

Intact parathyroid hormone concentrations >800 ng/l (88 pmol/l) at screening, or if parathyroidectomy was planned or expected; major GI surgery or serum ferritin >4494 pmol/l (>2000 mg/l) at screening; peritoneal dialysis with a history of peritonitis in the past 3 months or >=3 episodes in the past 12 months; receiving non-calcium-based phosphate binders with hypercalcemia (total serum calcium >2.60 mmol/l), or with hypocalcemia (total serum calcium <1.9 mmol/l) at screening.

Baseline characteristics:

		Sucroferric oxyhydroxide			Sevelamer carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Phosphate (mmol/L) – 0wk[a]	Continuous	694		2.5 (SD 0.588)	347		2.4 (SD 0.569)		
Serum iPTH (pmmol/L) – 0wk[b]	Continuous	707		med: 39.78 [rng 22.48–61.49]	348		med: 35.87 [rng 22.25–59.29]		
Demographics:									
Gender-Male[c]	Dichotomous	694	383	(55.2%)	347	219	(63.1%)		
Age[d]	Continuous	694		56 (SD 13)	347		56 (SD 15)		
Type of dialysis-Haemodialysis[c]	Dichotomous	694	638	(91.9%)	347	318	(91.6%)		
Type of dialysis-CAPD[c]	Dichotomous	694	56	(8.1%)	347	29	(8.4%)		
History of dialysis (months)[d]	Continuous	694		51 (SD 49)	347		54 (SD 55)		
Peritoneal dialysis									
Biochemical Data:									
Serum Ca (mmol/L) – 0wk[e]	Continuous	56		1.12 (SD 0.09)	28		1.16 (SD 0.11)		
Serum iPTH (pmmol/L) – 0wk[e]	Continuous	56		48.23 (SD 30.17)	28		42.15 (SD 26.29)		
Completers set									
Biochemical Data:									
Serum Ca (mmol/L) – 0wk[f]	Continuous	322		2.21 (SD 0.17)	227		2.21 (SD 0.19)		
Serum Phosphate (mmol/L) – 0wk[f]	Continuous	322		2.4 (SD 0.5)	227		2.4 (SD 0.6)		
Serum iPTH (pmmol/L) – 0wk[f]	Continuous	322		45.8 (SD 30.9)	227		42.8 (SD 28)		

[a] *Floege 2014 (full analysis set, n=1041); data extracted from graph*
[b] *Floege 2014 (safety set, n=1055)*
[c] *Floege 2014 (full analysis set, n=1041); approximated to nearest integer (percentages only presented in text)*
[d] *Floege 2014 (full analysis set, n=1041)*
[e] *Floege 2017 (subgroup with peritoneal dialysis, n=84)*
[f] *Ketteler 2019 (completers set, n=549)*

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.78 **Lower serum PO4 limit:** 1.13 **Upper serum Ca limit:** 2.75 **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sucroferric oxyhydroxide **N:** 710 Dose varied to maintain patients within study endpoints: Patients receiving sucroferric oxyhydroxide began stage 1 with a dose of 1.0 g per day. The study comprised an 8-week dose titration, during which doses could be titrated for efficacy or tolerability, followed by 4 weeks during which dose changes were only permitted for tolerability. A 12-week maintenance period followed, during which dose titration was permitted for efficacy and tolerability. The permitted dose titration was 500 mg per day every 2 weeks (minimum dose, 1.0 g per day; maximum dose, 3.0 g per day). Patients participating in stage 2 were randomized to receive either the same dose that they had been receiving at the end of stage 1 (week 24) or low-dose (250 mg per day) for 3 weeks, with no dose adjustments permitted. Notes: After 24 weeks, 99 hemodialysis patients in the sucroferric oxyhydroxide group were re-randomized (1:1) to continue receiving their maintenance dose (n=50, median dose 1.5 g/day) or receive low-dose sucroferric oxyhydroxide [n=49; 250 mg/day (ineffective control)] for 3 weeks (Stage 2). **Drug:** Sevelamer Carbonate **N:** 349 Dose varied to maintain patients within study endpoints: Patients receiving sevelamer carbonate began stage 1 with a dose of 4.8 g per day. The study comprised an 8-week dose titration, during which doses could be titrated for efficacy or tolerability, followed by 4 weeks during which dose changes were only permitted for tolerability. A 12-week maintenance period followed, during which dose titration was permitted for efficacy and tolerability. The permitted dose titration was 2.4 g per day every 2 weeks (minimum dose, 2.4 g per day; maximum dose, 14.4 g per day).
Concomitant treatments	**Dialysis:** Either Haemodialysis or Peritoneal **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** **Changes to diet allowed:** No **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 28 **Follow-up (d):** 365 **Protocol-specified reasons for withdrawal:** Serum phosphate: exceeding the upper safety limit of 2.75 mmol/l or decreased below the lower safety limit of 0.81 mmol/l Serum Ca: exceeding 2.75 mmol/l
Location	**Country:** Europe, US, Russia, Ukraine, Croatia, Serbia, South Africa

Outcomes measures and effect sizes

		Sucroferric oxyhydroxide			Sevelamer carbonate			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 24wk	Dichotomous	710	195	(27.5%)	349	56	(16.0%)		
Withdrawal (AEs) – 24wk	Dichotomous	710	94	(13.2%)	349	21	(6.0%)		

Biochemical Data: Achieved phosphate control – 52wk[a]	Dichotomous	322	167	(51.9%)	227	125	(55.1%)		
Serum Ca (mmol/L) – 24wk[b]	Continuous	391		med: 2.2 [rng 0.2–]	267		med: 2.2 [rng 0.2–]		
Serum Ca (mmol/L) – 52wk[c]	Mean change	368		med: 0 [rng 0.2–]	258		med: 0 [rng 0.2–]		
Serum Ca (mmol/L) – 52wk[c]	Continuous	368		med: 2.3 [rng 0.2–]	258		med: 2.3 [rng 0.2–]		
Serum Phosphate (mmol/L) – 12wk[d]	Continuous	694		1.8 (SD 0.469)	347		1.7 (SD 0.425)		
Serum Phosphate (mmol/L) – 12wk[e]	Mean change	694		-0.66 (SD 0.79)	347		-0.76 (SD 0.559)		
Serum Phosphate (mmol/L) – 24wk[d]	Mean change	694		-0.7 (SD 0.656)	347		-0.7 (SD 0.631)		
Serum Phosphate (mmol/L) – 24wk[d]	Continuous	694		1.8 (SD 0.5)	347		1.7 (SD 0.45)		
Serum Phosphate (mmol/L) – 24wk	Continuous	694		1.8 (SD 0.5)[d]	260		1.68 (SD 0.46)[b]		
Serum Phosphate (mmol/L) – 24wk	Continuous	384		1.75 (SD 0.48)[b]	347		1.7 (SD 0.45)[d]		
Serum Phosphate (mmol/L) – 24wk[b]	Continuous	384		1.75 (SD 0.48)	260		1.68 (SD 0.46)		
Serum Phosphate (mmol/L) – 52wk[c]	Mean change	384		0.02 (SD 0.52)	260		0.09 (SD 0.58)		
Serum Phosphate (mmol/L) – 52wk[c]	Continuous	384		1.77 (SD 0.54)	260		1.77 (SD 0.52)		
Serum iPTH (pmmol/L) – 24wk[b]	Continuous	391		med: 30 (SD 40)	267		med: 28.4 (SD 39.3)		
Serum iPTH (pmmol/L) – 24wk	Continuous	391		med: 30 (SD 40)[b]	348		med: 32.47 [rng 18.28–54.02][f]		
Serum iPTH (pmmol/L) – 24wk	Continuous	707		med: 31.75 [rng 18.74–53.39][f]	267		med: 28.4 (SD 39.3)[b]		
Serum iPTH (pmmol/L) – 24wk[f]	Mean change	707		med: -4.49 [rng -18.3–6.29]	348		med: -1.59 [rng -14.54–8.5]		
Serum iPTH (pmmol/L) – 24wk[f]	Continuous	707		med: 31.75 [rng 18.74–53.39]	348		med: 32.47 [rng 18.28–54.02]		
Serum iPTH (pmmol/L) – 52wk[c]	Continuous	383		med: 40.8 (SD 46.1)	260		med: 34.9 (SD 46)		
Serum iPTH (pmmol/L) – 52wk[c]	Mean change	383		med: 29.3 (SD 6.1)	260		med: 28.8 (SD 7.4)		

Adverse Events:										
Constipation – 24wk[g]	Dichotomous	707	27	(3.8%)	348	25	(7.2%)			
Diarrhea – 24wk[g]	Dichotomous	707	142	(20.1%)	348	26	(7.5%)			
Nausea OR vomiting – 24wk[g]	Dichotomous	707	51	(7.2%)	348	39	(11.2%)			
Nausea – 24wk[g]	Dichotomous	707	51	(7.2%)	348	39	(11.2%)			
Vomiting – 24wk[g]	Dichotomous	707	31	(4.4%)	348	19	(5.5%)			
Feces discolored – 24wk[g]	Dichotomous	707	109	(15.4%)	348	1	(0.3%)			
Hyperphosphatemia – 24wk[g]	Dichotomous	707	79	(11.2%)	348	27	(7.8%)			
Hypertension – 24wk[g]	Dichotomous	707	45	(6.4%)	348	26	(7.5%)			
Mortality:										
All cause mortality – -1wk	Time-to-event	710			349					
All cause mortality – 24wk[g]	Dichotomous	707	13	(1.8%)	348	7	(2.0%)			
Treatment:										
Compliance – 24wk	Dichotomous	384	331[h]	(86.2%)	348	269[g]	(77.3%)			
Compliance – 24wk[h]	Dichotomous	384	331	(86.2%)	260	200	(76.9%)			
Compliance – 24wk[g]	Dichotomous	707	584	(82.6%)	348	269	(77.3%)			
Compliance – 24wk	Dichotomous	707	584[g]	(82.6%)	260	200[h]	(76.9%)			
Compliance – 52wk[i]	Dichotomous	694	576	(83.0%)	347	276	(79.5%)			
Peritoneal dialysis										
Biochemical Data:										
Achieved phosphate control – 24wk[j]	Dichotomous	56	32	(57.1%)	28	17	(60.7%)			
Achieved phosphate control – 52wk[j]	Dichotomous	56	35	(62.5%)	28	18	(64.3%)			
Serum Ca (mmol/L) – 24wk[k]	Mean change	56		0.06 (SD 0.08)	28		0.03 (SD 0.08)			
Serum Ca (mmol/L) – 52wk[k]	Mean change	56		0.04 (SD 0.11)	28		0.02 (SD 0.1)			
Serum iPTH (pmmol/L) – 24wk[k]	Mean change	56		-0.4 (SD 27.21)	28		-4.74 (SD 20.94)			
Serum iPTH (pmmol/L) – 52wk[k]	Mean change	56		0.83 (SD 29.1)	28		0.05 (SD 28.61)			
Completers set										
Biochemical Data:										
Serum Ca (mmol/L) – 24wk[l]	Continuous	301		2.23 (SD 0.16)	218		2.24 (SD 0.17)			
Serum Ca (mmol/L) – 24wk[l]	Mean change	301		0.03 (SD 0.17)	218		0.03 (SD 0.19)			
Serum Ca (mmol/L) – 52wk[l]	Continuous	322		2.26 (SD 0.19)	227		2.25 (SD 0.2)			
Serum Ca (mmol/L) – 52wk[l]	Mean change	322		0.05 (SD 0.2)	227		0.05 (SD 0.23)			

	Serum Phosphate (mmol/L) – 24wk[l]	Mean change	301		-0.7 (SD 0.6)	218		-0.7 (SD 0.6)		
	Serum Phosphate (mmol/L) – 24wk[l]	Continuous	301		1.7 (SD 0.4)	218		1.7 (SD 0.4)		
	Serum Phosphate (mmol/L) – 52wk[l]	Mean change	322		-0.7 (SD 0.7)	227		-0.7 (SD 0.7)		
	Serum Phosphate (mmol/L) – 52wk[l]	Continuous	322		1.7 (SD 0.5)	227		1.7 (SD 0.5)		
	Serum iPTH (pmmol/L) – 24wk[l]	Mean change	310		-5 (SD 26)	219		-4.1 (SD 25.3)		
	Serum iPTH (pmmol/L) – 24wk[l]	Continuous	310		40.9 (SD 31.4)	219		38.5 (SD 27)		
	Serum iPTH (pmmol/L) – 52wk[l]	Continuous	322		46.8 (SD 42.4)	227		46 (SD 34.2)		
	Serum iPTH (pmmol/L) – 52wk[l]	Mean change	322		1 (SD 37.6)	227		3.2 (SD 30.7)		
	[a] Floege 2015 (completers set, n=549); approximated to nearest integer (percentages only presented in text) *[b] Floege 2015 (full analysis set extension study, n=644); baseline of extension study was week 24 of the phase III study* *[c] Floege 2015 (full analysis set extension study, n=644)* *[d] Floege 2014 (full analysis set, n=1041); data extracted from graph* *[e] Floege 2014 (full analysis set, n=1041); least square mean* *[f] Floege 2014 (safety set, n=1055)* *[g] Floege 2014 (safety set, n=1055); approximated to nearest integer (percentages only presented in text)* *[h] Floege 2015 (full analysis set extension study, n=644); approximated to nearest integer (percentages only presented in text)* *[i] Floege 2015 (full analysis set, n=1041); approximated to nearest integer (percentages only presented in text)* *[j] Floege 2017 (subgroup with peritoneal dialysis, n=84); serum phosphate <=1.78 mmol/l* *[k] Floege 2017 (subgroup with peritoneal dialysis, n=84)* *[l] Ketteler 2019 (completers set, n=549)* Mean change of serum phosphate was also reported for the per-protocol set but number of participants per arm was not reported. Full analysis set: defined as patients randomised to treatment who received at least one dose of study medication and had at least one post-baseline evaluable efficacy assessment (Floege 2014). Safety set: defined as patients randomised to treatment who received at least one dose of study medication (Floege 2014). Full analysis set extensio study: patients who received =1 dose of extension study medication and had =1 evaluable efficacy assessment during the extension study (Floege 2015). Completers set: all patients who completed at least 52 weeks of continuous treatment in the initial Phase 3 study and its extension study (Ketteler 2019).									
Authors' conclusion										
Source of funding										
Comments										

Koiwa (2017a) – evidence table

Bibliographic reference	Koiwa, Fumihiko. Dose-response efficacy and safety of PA21 in Japanese hemodialysis patients with hyperphosphatemia: a randomized, placebo-controlled, double-blind, Phase II study. Clinical and experimental nephrology 2017;21(3):513-22.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** >=20 years **Washout phosphate level (mmol/L):** >1.93, <3.23 Additional notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:** Serum Ca (<=1.87 or >2.75 mmol/l. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).) Liver dysfunction Significant GI disease iPTH >800 pg/mL or >500 pg/mL if determined to have poor control; history of hemochromatosis, any other iron overload disorder, serum ferritin >800 ng/mL, or transferrin saturation >50%; subjects planning to undergo parathyroidectomy or percutaneous ethanol injection therapy (PEIT) during the study period, or who underwent parathyroidectomy or PEIT <=24 weeks before their wash-out period; or history of a clinically significant digestive tract procedure according to the investigator's diagnosis; and history of brain/cardiovascular disorder (e.g., myocardial infarct, unstable angina, cerebral infarct, cerebral hemorrhage). Other phosphate binders, agents with a phosphorus adsorption effect, agents that affect serum phosphorus levels, and intravenous and oral iron therapies were not permitted. **Baseline characteristics:**

		Sucroferric oxyhydroxide 750			Placebo				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	39		med: 0.115 (SD 2.122)	37		med: 0.152 (SD 2.145)		
Serum Phosphate (mmol/L) – 0wk	Continuous	39		med: 0.381 (SD 2.377)	37		med: 0.436 (SD 2.345)		
Serum iPTH (pmmol/L) – 0wk	Continuous	39		med: 15.79 (SD 29.47)	37		med: 14.899 (SD 29.947)		
Demographics: Gender-Female	Dichotomous	39	12	(30.8%)	37	14	(37.8%)		
Gender-Male	Dichotomous	39	27	(69.2%)	37	23	(62.2%)		
Age	Continuous	39		59.4 (SD 10.4)	37		60.8 (SD 10.2)		
History of dialysis (months)	Continuous	39		77.6 (SD 67.5)	37		71 (SD 45)		

		Sucroferric oxyhydroxide 1500			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	35		med: 0.13 (SD 2.162)	37		med: 0.152 (SD 2.145)		
Serum Phosphate (mmol/L) – 0wk	Continuous	35		med: 0.426 (SD 2.484)	37		med: 0.436 (SD 2.345)		
Serum iPTH (pmmol/L) – 0wk	Continuous	35		med: 14.814 (SD 27.794)	37		med: 14.899 (SD 29.947)		
Demographics: Gender-Female	Dichotomous	35	12	(34.3%)	37	14	(37.8%)		
Gender-Male	Dichotomous	35	23	(65.7%)	37	23	(62.2%)		
Age	Continuous	35		63.8 (SD 12)	37		60.8 (SD 10.2)		
History of dialysis (months)	Continuous	35		85.1 (SD 60.7)	37		71 (SD 45)		

		Sucroferric oxyhydroxide 2250			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	33		med: 0.165 (SD 2.148)	37		med: 0.152 (SD 2.145)		
Serum Phosphate (mmol/L) – 0wk	Continuous	33		med: 0.281 (SD 2.397)	37		med: 0.436 (SD 2.345)		
Serum iPTH (pmmol/L) – 0wk	Continuous	33		med: 18.675 (SD 36.586)	37		med: 14.899 (SD 29.947)		
Demographics: Gender-Female	Dichotomous	33	10	(30.3%)	37	14	(37.8%)		
Gender-Male	Dichotomous	33	23	(69.7%)	37	23	(62.2%)		
Age	Continuous	33		61.9 (SD 10.5)	37		60.8 (SD 10.2)		

History of dialysis (months)	Continuous	33		95.8 (SD 81.9)	37		71 (SD 45)		

		Sucroferric oxyhydroxide 3000			Placebo				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous	34		med: 0.13 (SD 2.172)	37		med: 0.152 (SD 2.145)		
Serum Phosphate (mmol/L) – 0wk	Continuous	34		med: 0.43 (SD 2.445)	37		med: 0.436 (SD 2.345)		
Serum iPTH (pmmol/L) – 0wk	Continuous	34		med: 15.196 (SD 27.869)	37		med: 14.899 (SD 29.947)		
Demographics:									
Gender-Female	Dichotomous	34	15	(44.1%)	37	14	(37.8%)		
Gender-Male	Dichotomous	34	19	(55.9%)	37	23	(62.2%)		
Age	Continuous	34		61.4 (SD 11.2)	37		60.8 (SD 10.2)		
History of dialysis (months)	Continuous	34		91.5 (SD 58.6)	37		71 (SD 45)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.93
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Sucroferric oxyhydroxide
N: 39
Fixed daily dose (mg): 750
Drug: Sucroferric oxyhydroxide
N: 36
Fixed daily dose (mg): 1500
Drug: Sucroferric oxyhydroxide
N: 35
Fixed daily dose (mg): 2250

	Drug: Sucroferric oxyhydroxide **N:** 36 Fixed daily dose (mg): 3000 **Drug:** Placebo **N:** 37 Notes: The placebo tablet did not contain active moiety.
Concomitant treatments	**Dialysis:** Either Haemodialysis or online haemodiafiltration **Vit D:** Yes - but no further details **Rescue Binder use permitted:** No details given **Were other medications allowed:** No **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 42 **Protocol-specified reasons for withdrawal:** Serum phosphate: >3.23 mmol/l or <0.96 mmol/l during 2 consecutive evaluations. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Serum Ca: >1.87 mmol/l. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).
Location	**Country:** Japan

Outcomes measures and effect sizes

		Sucroferric oxyhydroxide 750			Placebo				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Disposition: Withdrawal (total) – 6wk	Dichotomous	39	2	(5.1%)	37	7	(18.9%)		
Withdrawal (AEs) – 6wk	Dichotomous	39	1	(2.6%)	37	2	(5.4%)		
Biochemical Data: Achieved phosphate control – 6wk[a]	Dichotomous	39	29	(74.4%)	37	11	(29.7%)		
Serum Ca (mmol/L) – 6wk	Mean change	39		med: 0.085 (SD 0.05)	37		med: 0.078 (SD -0.022)		
Serum Ca (mmol/L) – 6wk	Continuous	39		med: 0.122 (SD 2.172)	37		med: 0.158 (SD 2.122)		
Serum Phosphate (mmol/L) – 6wk	Mean change	39		med: 0.452 (SD -0.578)	37		med: 0.394 (SD 0.078)		
Serum Phosphate (mmol/L) – 6wk	Continuous	39		med: 0.51 (SD 1.799)	37		med: 0.556 (SD 2.422)		

Serum iPTH (pmmol/L) – 6wk	Continuous	39		med: 16.861 (SD 25.737)	37		med: 18.038 (SD 32.227)		
Serum iPTH (pmmol/L) – 6wk	Mean change	39		med: 9.523 (SD -3.733)	37		med: 8.749 (SD 2.28)		
Adverse Events:									
Constipation – 6wk	Dichotomous	39	0	(0.0%)	37	1	(2.7%)		
Diarrhea – 6wk	Dichotomous	39	6	(15.4%)	37	7	(18.9%)		
Contusion – 6wk	Dichotomous	39	0	(0.0%)	37	0	(0.0%)		
Nasopharyngitis – 6wk	Dichotomous	39	5	(12.8%)	37	4	(10.8%)		
Abdominal pain – 6wk	Dichotomous	39	0	(0.0%)	37	0	(0.0%)		
Pain in extremity – 6wk	Dichotomous	39	0	(0.0%)	37	0	(0.0%)		
Hemorrhoids – 6wk	Dichotomous	39	0	(0.0%)	37	0	(0.0%)		
Insomnia – 6wk	Dichotomous	39	2	(5.1%)	37	0	(0.0%)		
Upper respiratory tract Upperrespiratory tract inflammation – 6wk	Dichotomous	39	2	(5.1%)	37	0	(0.0%)		

[a] *Approximated to nearest integer (percentages only presented in text)*

		Sucroferric oxyhydroxide 1500			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 6wk	Dichotomous	36	5	(13.9%)	37	7	(18.9%)		
Withdrawal (AEs) – 6wk	Dichotomous	36	2	(5.6%)	37	2	(5.4%)		
Biochemical Data:									
Achieved phosphate control – 6wk[a]	Dichotomous	36	30	(83.3%)	37	11	(29.7%)		
Serum Ca (mmol/L) – 6wk	Mean change	35		med: 0.082 (SD 0.04)	37		med: 0.078 (SD -0.022)		
Serum Ca (mmol/L) – 6wk	Continuous	35		med: 0.122 (SD 2.202)	37		med: 0.158 (SD 2.122)		
Serum Phosphate (mmol/L) – 6wk	Mean change	35		med: 0.42 (SD -0.872)	37		med: 0.394 (SD 0.078)		
Serum Phosphate (mmol/L) – 6wk	Continuous	35		med: 0.384 (SD 1.612)	37		med: 0.556 (SD 2.422)		
Serum iPTH (pmmol/L) – 6wk	Continuous	34		med: 14.984 (SD 23.457)	37		med: 18.038 (SD 32.227)		
Serum iPTH (pmmol/L) – 6wk	Mean change	34		med: 8.399 (SD -4.836)	37		med: 8.749 (SD 2.28)		

Adverse Events:									
Constipation – 6wk	Dichotomous	36	1	(2.8%)	37	1	(2.7%)		
Diarrhea – 6wk	Dichotomous	36	6	(16.7%)	37	7	(18.9%)		
Contusion – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		
Nasopharyngitis – 6wk	Dichotomous	36	5	(13.9%)	37	4	(10.8%)		
Abdominal pain – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		
Pain in extremity – 6wk	Dichotomous	36	1	(2.8%)	37	0	(0.0%)		
Hemorrhoids – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		
Insomnia – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		
Upper respiratory tract Upperrespiratory tract inflammation – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		

[a] *Approximated to nearest integer (percentages only presented in text)*

		Sucroferric oxyhydroxide 2250			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 6wk	Dichotomous	35	12	(34.3%)	37	7	(18.9%)		
Withdrawal (AEs) – 6wk	Dichotomous	35	9	(25.7%)	37	2	(5.4%)		
Biochemical Data:									
Achieved phosphate control – 6wk[a]	Dichotomous	35	31	(88.6%)	37	11	(29.7%)		
Serum Ca (mmol/L) – 6wk	Mean change	33		med: 0.11 (SD 0.095)	37		med: 0.078 (SD -0.022)		
Serum Ca (mmol/L) – 6wk	Continuous	33		med: 0.145 (SD 2.242)	37		med: 0.158 (SD 2.122)		
Serum Phosphate (mmol/L) – 6wk	Mean change	33		med: 0.439 (SD -1.017)	37		med: 0.394 (SD 0.078)		
Serum Phosphate (mmol/L) – 6wk	Continuous	33		med: 0.368 (SD 1.379)	37		med: 0.556 (SD 2.422)		
Serum iPTH (pmmol/L) – 6wk	Continuous	31		med: 17.826 (SD 27.752)	37		med: 18.038 (SD 32.227)		
Serum iPTH (pmmol/L) – 6wk	Mean change	31		med: 9.83 (SD -10.286)	37		med: 8.749 (SD 2.28)		
Adverse Events:									
Constipation – 6wk	Dichotomous	35	2	(5.7%)	37	1	(2.7%)		
Diarrhea – 6wk	Dichotomous	35	13	(37.1%)	37	7	(18.9%)		

Contusion – 6wk	Dichotomous	35	0	(0.0%)	37	0	(0.0%)		
Nasopharyngitis – 6wk	Dichotomous	35	3	(8.6%)	37	4	(10.8%)		
Abdominal pain – 6wk	Dichotomous	35	0	(0.0%)	37	0	(0.0%)		
Pain in extremity – 6wk	Dichotomous	35	2	(5.7%)	37	0	(0.0%)		
Hemorrhoids – 6wk	Dichotomous	35	2	(5.7%)	37	0	(0.0%)		
Insomnia – 6wk	Dichotomous	35	0	(0.0%)	37	0	(0.0%)		
Upper respiratory tract Upperrespiratory tract inflammation – 6wk	Dichotomous	35	0	(0.0%)	37	0	(0.0%)		

[a] *Approximated to nearest integer (percentages only presented in text)*

		Sucroferric oxyhydroxide 3000			Placebo			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 6wk	Dichotomous	36	21	(58.3%)	37	7	(18.9%)		
Withdrawal (AEs) – 6wk	Dichotomous	36	6	(16.7%)	37	2	(5.4%)		
Biochemical Data: Achieved phosphate control – 6wk[a]	Dichotomous	36	29	(80.6%)	37	11	(29.7%)		
Serum Ca (mmol/L) – 6wk	Mean change	34		med: 0.098 (SD 0.095)	37		med: 0.078 (SD -0.022)		
Serum Ca (mmol/L) – 6wk	Continuous	34		med: 0.162 (SD 2.268)	37		med: 0.158 (SD 2.122)		
Serum Phosphate (mmol/L) – 6wk	Mean change	34		med: 0.514 (SD -1.24)	37		med: 0.394 (SD 0.078)		
Serum Phosphate (mmol/L) – 6wk	Continuous	34		med: 0.378 (SD 1.208)	37		med: 0.556 (SD 2.422)		
Serum iPTH (pmmol/L) – 6wk	Continuous	31		med: 10.244 (SD 18.388)	37		med: 18.038 (SD 32.227)		
Serum iPTH (pmmol/L) – 6wk	Mean change	31		med: 11.029 (SD -9.173)	37		med: 8.749 (SD 2.28)		
Adverse Events: Constipation – 6wk	Dichotomous	36	2	(5.6%)	37	1	(2.7%)		
Diarrhea – 6wk	Dichotomous	36	15	(41.7%)	37	7	(18.9%)		
Contusion – 6wk	Dichotomous	36	4	(11.1%)	37	0	(0.0%)		
Nasopharyngitis – 6wk	Dichotomous	36	3	(8.3%)	37	4	(10.8%)		
Abdominal pain – 6wk	Dichotomous	36	2	(5.6%)	37	0	(0.0%)		

	Pain in extremity – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		
	Hemorrhoids – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		
	Insomnia – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		
	Upper respiratory tract Upperrespiratory tract inflammation – 6wk	Dichotomous	36	0	(0.0%)	37	0	(0.0%)		
	[a] *Approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Koiwa et al. (2005a) – evidence table

Bibliographic reference	Koiwa,F., Onoda,N., Kato,H., Tokumoto,A., Okada,T., Fukagawa,M., Shigematsu,T. Prospective randomized multicenter trial of sevelamer hydrochloride and calcium carbonate for the treatment of hyperphosphatemia in hemodialysis patients in Japan. Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2005;9(4):340-46.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no Notes: Subjects were placed on calcium carbonate for 4 weeks then sevelamer hydrochloride for 4 weeks before being randomised into the three arms.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No details given **Washout phosphate level (mmol/L):** **Exclusions:** **Baseline characteristics:**

		All study participants		
		N	**k**	**mean**
Demographics:				
Gender-Female	Dichotomous	62	23	(37.1%)
Gender-Male	Dichotomous	62	39	(62.9%)
Age	Continuous	62		57.1 (SD 10.6)

		Calcium Carbonate		
		N	k	mean
Biochemical Data:				
Serum Ca (mmol/L) – 0wk	Continuous	20		2.28 (SD 0.17)
Serum Ca (mmol/L) – 0wk	Continuous	20		2.28 (SD 0.17)
Serum Phosphate (mmol/L) – 0wk	Continuous	20		2.2 (SD 0.39)
Serum Phosphate (mmol/L) – 0wk	Continuous	20		2.2 (SD 0.39)

		Sevelamer			Sevelamer + Calcium Carboonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous	16		2.15 (SD 0.22)	26		2.28 (SD 0.17)		
Serum Phosphate (mmol/L) – 0wk	Continuous	16		2.09 (SD 0.28)	26		1.92 (SD 0.54)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: -
Upper serum Ca limit: 2.37
Lower serum Ca limit: 2.1

Intervention(s)

Drug: Sevelamer hydrochloride
N: 29
Fixed daily dose (mg): 6000
Drug: Sevelamer hydrochloride+Calcium Carbonate
N: 30
Notes: The drug dose consisted of 3000mg of sevelamer and 3000mg of calcium carbonate
Drug: Calcium Carbonate
N: 27
Fixed daily dose (mg): 3000

Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No **Were other medications allowed:** **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** - **Follow-up (d):** 28 **Protocol-specified reasons for withdrawal:** Serum phosphate: >1.94mmol/L Serum Ca: >2.74 mmol/L or <2.12mmol/L Any changes in intervention dosing or Ca concentration of the dialystate or Vit D resulted in withdrawal from the study.
Location	**Country:** Japan

Outcomes measures and effect sizes

		Calcium Carbonate		
		N	**k**	**mean**
Biochemical Data: Achieved phosphate control – 4wk	Dichotomous	20	9	(45.0%)
Serum Ca (mmol/L) – 4wk	Continuous	20		2.42 (SD 0.22)
Serum Ca (mmol/L) – 4wk	Continuous	20		2.42 (SD 0.22)
Serum Phosphate (mmol/L) – 4wk	Continuous	20		1.92 (SD 0.5)
Serum Phosphate (mmol/L) – 4wk	Continuous	20		1.92 (SD 0.5)
Adverse Events: Abdominal Distension – 4wk	Dichotomous	27	2	(7.4%)
Constipation – 4wk	Dichotomous	27	4	(14.8%)
Biochemical Data: Proportion with hypercalcaemia – 4wk	Dichotomous	20	11	(55.0%)

		Sevelamer			Sevelamer + Calcium Carboonate				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Biochemical Data: Achieved phosphate control – 4wk	Dichotomous	16	5	(31.3%)	26	17	(65.4%)		

	Serum Ca (mmol/L) – 4wk	Continuous	16		2.18 (SD 0.17)	26		2.4 (SD 0.28)		
	Serum Phosphate (mmol/L) – 4wk	Continuous	16		1.96 (SD 0.22)	26		1.61 (SD 0.37)		
	Adverse Events:									
	Abdominal Distension – 4wk	Dichotomous	29	5	(17.2%)	30	1	(3.3%)		
	Constipation – 4wk	Dichotomous	29	14	(48.3%)	30	6	(20.0%)		
	Biochemical Data:									
	Proportion with hypercalcaemia – 4wk	Dichotomous	16	13	(81.3%)	26	11	(42.3%)		
Authors' conclusion										
Source of funding										
Comments										

Koiwa et al. (2005b) – evidence table

Bibliographic reference	Koiwa,F., Kazama,J.J., Tokumoto,A., Onoda,N., Kato,H., Okada,T., et al. Sevelamer hydrochloride and calcium bicarbonate reduce serum fibroblast growth factor 23 levels in dialysis patients. Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2005;9(4):336-39.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no Notes: There was no washout period instead all patients were placed on 3000mg of sevelamer for 4 weeks prior to randomisation.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** No details provided **Washout phosphate level (mmol/L):** **Exclusions:** **Baseline characteristics:**

		Sevelamer+Calcium carboante			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data:									
Serum Phosphate (mmol/L) – 0wk	Continuous	26		1.91 (SD 0.39)	20		2 (SD 0.29)		
Demographics:									
History of dialysis (year)	Continuous	26		9.5 (SD 6.9)	20		6.4 (SD 4.4)		
Gender-Female	Dichotomous	26	12	(46.2%)	20	8	(40.0%)		

	Gender-Male	Dichotomous	26	14	(53.8%)	20	12	(60.0%)		
	Age	Continuous	26		57.1 (SD 9.5)	20		61.5 (SD 9.4)		
	Number Diabetic	Dichotomous	26	7	(26.9%)	20	4	(20.0%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: -
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Sevelamer hydrochloride+Calcium Carbonate
N: 26
Notes: 3000mg of sevelamer + 3000mg of calcium carbonate
Drug: Calcium Carbonate
N: 20
Fixed daily dose (mg): 3000

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Not stated
Rescue Binder use permitted: No
Were other medications allowed: No details provided
Changes to diet allowed: No details given
Changes to dialysate allowed: No details given

Length of follow up

Washout period (d): 0
Follow-up (d): 28
Protocol-specified reasons for withdrawal: none specified

Location

Country: Japan

Outcomes measures and effect sizes

		Sevelamer+Calcium carboante			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Phosphate (mmol/L) – 4wk	Continuous	26		1.61 (SD 0.39)	20		1.93 (SD 0.52)		

Authors' conclusion

Source of funding

Comments	

Koiwa et al. (2017b) – evidence table

Bibliographic reference	Koiwa, Fumihiko, Yokoyama, Keitaro, Fukagawa, Masafumi, Terao, Akira. Efficacy and safety of sucroferric oxyhydroxide compared with sevelamer hydrochloride in Japanese haemodialysis patients with hyperphosphataemia: A randomized, open-label, multicentre, 12-week phase III study. Nephrology (Carlton, Vic.) 2017;22(4):293-300.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 20 years or older **Washout phosphate level (mmol/L):** >1.94, <3.23 **Exclusions:** Serum Ca (=1.88mmol/L or >2.75mmol/L, atWeek 1;) Significant GI disease iPTH concentration was >800 ng/L at the beginning of the washout period; history of haemochromatosis, or any other iron accumulation disorder, or serum ferritin was >1797.60 pmol/L or transferrin saturation >50% at the beginning of the washout period, or history of a severe digestive tract procedure based on the investigator's diagnosis. **Baseline characteristics:**

		Sucroferric oxyhydroxide			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	100		2.24 (SD 0.15)	92		2.22 (SD 0.14)		
Serum Phosphate (mmol/L) – 0wk	Continuous	100		2.51 (SD 0.45)	92		2.45 (SD 0.39)		
Serum iPTH (pmmol/L) – 0wk	Continuous	100		med: 24.921 [rng 18.664–35.949]	92		med: 29.905 [rng 18.452–40.933]		
Demographics: Gender-Female	Dichotomous	108			105				
Gender-Male	Dichotomous	108			105				
Age	Continuous	108			105				
History of dialysis (months)	Continuous	108			105				

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.78 **Lower serum PO4 limit:** 1.13 **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sucroferric oxyhydroxide **N:** 108 Dose varied to maintain patients within study endpoints: Initiation dosage was 250mg 3 times per day (750mg/day). If phosphate at the beginning of the previous week was >1.94mmol/L, the dose was increased by 750mg/day ; if it was 1.13–1.94mmol/L, dose was maintained; and if it was <1.13mmol/L, the dose was reduced by 750mg/day. The maximum allowed dose was 1000mg 3 times per day (3000mg/day). The dose was maintained from Week 8 to Week 12. **Drug:** Sevelamer hydrochloride **N:** 105 Dose varied to maintain patients within study endpoints: Initiation dosage was 1000mg or 2000mg if phosphate before dialysis at Week -1 was <2.58mmol/L or =2.58mmol/L, respectively. If phosphate at the beginning of the previous week was >1.94mmol/L, the dose was increased by 1500mg/day; if it was 1.13–1.94mmol/L, dose was maintained; and if it was <1.13mmol/L, the dose was reduced by 750 or 1500mg/day. The maximum allowed dose was 3000mg 3 times per day (9000mg/day). The dose was maintained from Week 8 to Week 12.
Concomitant treatments	**Dialysis:** Either Haemodialysis or online haemodiafiltration **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (The use of intravenous iron was permitted if the investigator considered it necessary. The use of calcimimetics was allowed as long as the subjects were receiving it for 4 weeks or more before the start of the observation period, and the dose was not to be changed during 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.) **Changes to diet allowed:** No **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 84 **Protocol-specified reasons for withdrawal:** Serum phosphate: <0.97mmol/L or >3.23mmol/L, twice consecutively Serum Ca: =1.88mmol/L Development of any adverse event that would make study continuation difficult; serum ferritin >1797.60 pmol/L.
Location	**Country:** Japan

Outcomes measures and effect sizes

		Sucroferric oxyhydroxide			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 12wk	Dichotomous	108	14	(13.0%)	105	18	(17.1%)		
Withdrawal (AEs) – 12wk	Dichotomous	108	7	(6.5%)	105	10	(9.5%)		

	Biochemical Data:									
	Achieved phosphate control – 12wk[a]	Dichotomous	100	82	(82.0%)	92	62	(67.4%)		
	Serum Ca (mmol/L) – 12wk	Continuous	100		2.29 (SD 0.17)	92		2.23 (SD 0.18)		
	Serum Ca (mmol/L) – 12wk	Mean change	100		0.05 (SD 0.13)	92		0.01 (SD 0.15)		
	Serum Phosphate (mmol/L) – 12wk	Continuous	100		1.62 (SD 0.33)	92		1.72 (SD 0.33)		
	Serum Phosphate (mmol/L) – 12wk	Mean change	100		-0.9 (SD 0.53)	92		-0.73 (SD 0.45)		
	Serum iPTH (pmmol/L) – 12wk	Continuous	100		med: 20.149 [rng 13.044–27.466]	92		med: 24.178 [rng 13.044–36.904]		
	Serum iPTH (pmmol/L) – 12wk	Mean change	100		med: -5.514 [rng -12.513–-0.848]	92		med: -5.196 [rng -9.226–-0.53]		
	Adverse Events:									
	Constipation – 12wk	Dichotomous	100	2	(2.0%)	92	19	(20.7%)		
	Diarrhea – 12wk	Dichotomous	100	27	(27.0%)	92	3	(3.3%)		
	Nasopharyngitis – 12wk	Dichotomous	100	24	(24.0%)	92	24	(26.1%)		
	[a] *Approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Lee et al. (2013) – evidence table

Bibliographic reference	Lee, Yong Kyu, Choi, Hoon Young, Shin, Sug Kyun. Effect of lanthanum carbonate on phosphate control in continuous ambulatory peritoneal dialysis patients in Korea: a randomized prospective study. Clinical nephrology 2013;79(2):136-42.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** >18 years **Washout phosphate level (mmol/L):** >1.8 Additional notes: There was no washout period. Phosphate level at enrolment. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:**

Serum Ca (Severe hypocalcemia: serum calcium <1.87 mmol/l
Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).)
Liver dysfunction
Diabetes or poorly controlled diabetes
Cancer
Severe Hyperparathyroidism
Serum iPTH level = 1,000 pg/ml; sepsis; oral immunosuppressant use; cardiac failure (= NYHA III); and non-compliance.
Baseline characteristics:

		Lanthanum carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	20		2.222 (SD 0.245)	30		2.3 (SD 0.202)		
Serum Phosphate (mmol/L) – 0wk	Continuous	20		2.193 (SD 0.339)	30		1.812 (SD 0.352)		
Serum iPTH (pmmol/L) – 0wk	Continuous	20		0.406 (SD 0.298)	30		0.301 (SD 0.347)		
Demographics: Gender-Female	Dichotomous	20	9	(45.0%)	30	19	(63.3%)		
Gender-Male	Dichotomous	20	11	(55.0%)	30	11	(36.7%)		
Age	Continuous	20		48.25 (SD 11.06)	30		51.8 (SD 11.62)		
History of dialysis (months)	Continuous	20		55.73 (SD 48.09)	30		69.67 (SD 53.89)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.77
Lower serum PO4 limit: 1.13
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 20
Dose varied to maintain patients within study endpoints: Initial dose was 1,500 mg/day. Dose was adjusted to maintain a serum phosphate level between 1.13 to 1.77 mmol/l.
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Drug: Calcium Carbonate
N: 30

	Dose varied to maintain patients within study endpoints: Initial dose was 3 g/d. Dose was adjusted to maintain a serum phosphate level between 1.13 to 1.77 mmol/l. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Concomitant treatments	**Dialysis:** Peritoneal **Vit D:** Not stated **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** - **Follow-up (d):** 168 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Korea

Outcomes measures and effect sizes

		Lanthanum carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 24wk	Dichotomous	35	15	(42.9%)	37	7	(18.9%)		
Withdrawal (AEs) – 24wk	Dichotomous	35	10	(28.6%)	37	0	(0.0%)		
Biochemical Data: Serum Ca (mmol/L) – 4wk	Continuous	20		2.21 (SD 0.17)	30		2.32 (SD 0.212)		
Serum Ca (mmol/L) – 8wk	Continuous	20		2.24 (SD 0.21)	30		2.36 (SD 0.225)		
Serum Ca (mmol/L) – 12wk	Continuous	20		2.25 (SD 0.225)	30		2.38 (SD 0.25)		
Serum Ca (mmol/L) – 16wk	Continuous	20		2.27 (SD 0.185)	30		2.34 (SD 0.172)		
Serum Ca (mmol/L) – 20wk	Continuous	20		2.26 (SD 0.158)	30		2.36 (SD 0.182)		
Serum Ca (mmol/L) – 24wk	Continuous	20		2.28 (SD 0.172)	30		2.35 (SD 0.245)		
Serum Phosphate (mmol/L) – 4wk	Continuous	20		1.93 (SD 0.491)	30		1.81 (SD 0.313)		
Serum Phosphate (mmol/L) – 8wk	Continuous	20		1.66 (SD 0.465)	30		1.67 (SD 0.352)		
Serum Phosphate (mmol/L) – 12wk	Continuous	20		1.7 (SD 0.397)	30		1.64 (SD 0.365)		

	Serum Phosphate (mmol/L) – 16wk	Continuous	20		1.7 (SD 0.433)	30		1.62 (SD 0.381)		
	Serum Phosphate (mmol/L) – 20wk	Continuous	20		1.72 (SD 0.452)	30		1.6 (SD 0.439)		
	Serum Phosphate (mmol/L) – 24wk	Continuous	20		1.76 (SD 0.465)	30		1.53 (SD 0.252)		
	Serum iPTH (pmmol/L) – 24wk	Continuous	20		0.354 (SD 0.283)	30		0.187 (SD 0.256)		

Authors' conclusion	
Source of funding	
Comments	

Lee et al. (2015) – evidence table

Bibliographic reference	Lee, Chien-Te, Wu, I-Wen, Chiang, Shou-Shan, Peng, Yu-Sen, Shu, Kuo-Hsiung, Wu, Ming-Ju. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. Journal of nephrology 2015;28(1):105-13.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** >=18 years **Washout phosphate level (mmol/L):** >1.77, <3.23 Additional notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:** Significant Unstable Medical conditions Heart Failure Diabetes or poorly controlled diabetes Cancer Severe Hyperparathyroidism Significant GI disease Pregnancy, lactating, unstable psychiatric condition, clinically significant abnormality on screening ECG, other than basal cell or squamous cell carcinoma, serum ferritin >800 ng/ml, history of iron allergy or hemochromatosis, or treatment with an investigational agent within 30 days of enrollment. **Baseline characteristics:**

		Ferric citrate 4g/d			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	72		2.215 (SD 0.178)	28		2.252 (SD 0.195)		
Serum Phosphate (mmol/L) – 0wk	Continuous	72		2.248 (SD 0.349)	28		2.381 (SD 0.407)		
Demographics: Gender-Female	Dichotomous	75	28	(37.3%)	36	11	(30.6%)		
Gender-Male	Dichotomous	75	47	(62.7%)	36	25	(69.4%)		
Age	Continuous	75		53.4 (SD 11.7)	36		53 (SD 11.8)		

		Ferric citrate 6g/d			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	66		2.268 (SD 0.19)	28		2.252 (SD 0.195)		
Serum Phosphate (mmol/L) – 0wk	Continuous	66		2.245 (SD 0.371)	28		2.381 (SD 0.407)		
Demographics: Gender-Female	Dichotomous	72	31	(43.1%)	36	11	(30.6%)		
Gender-Male	Dichotomous	72	41	(56.9%)	36	25	(69.4%)		
Age	Continuous	72		56.4 (SD 10.5)	36		53 (SD 11.8)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.77
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Ferric citrate
N: 75

	Fixed daily dose (mg): 4000 **Drug:** Ferric citrate **N:** 72 Fixed daily dose (mg): 6000 **Drug:** Placebo **N:** 36
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** **Were other medications allowed:** Yes (Medications containing minimal amounts of aluminum, calcium, phosphorus, or magnesium, or used at a dose that would not interfere with phosphorus or calcium absorption.) **Changes to diet allowed:** No **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:** Serum phosphate: >=2.90 mmol/l at 2 consecutive measurements after randomisation. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Transferrin saturation levels of >=55%.
Location	**Country:** Taiwan

Outcomes measures and effect sizes

		Ferric citrate 4g/d			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 8wk	Dichotomous	75	9	(12.0%)	36	24	(66.7%)		
Withdrawal (AEs) – 8wk	Dichotomous	75	2	(2.7%)	36	3	(8.3%)		
Biochemical Data: Achieved phosphate control – 8wk[a]	Dichotomous	75	43	(57.3%)	36	6	(16.7%)		
Serum Ca (mmol/L) – 4wk	Continuous	69		2.258 (SD 0.18)	13		2.255 (SD 0.222)		
Serum Ca (mmol/L) – 8wk	Continuous	66		2.26 (SD 0.165)	12		2.27 (SD 0.195)		
Serum Ca (mmol/L) – 8wk	Mean change	66		0.038 (SD 0.128)	12		0.042 (SD 0.095)		
Serum Phosphate (mmol/L) – 1wk	Continuous	72		1.802 (SD 0.556)	28		2.432 (SD 0.517)		

Serum Phosphate (mmol/L) – 4wk	Continuous	69		1.809 (SD 0.526)	13		2.471 (SD 0.31)		
Serum Phosphate (mmol/L) – 8wk	Mean change	66		-0.517 (SD 0.446)	12		0.026 (SD 0.488)		
Serum Phosphate (mmol/L) – 8wk	Continuous	66		1.738 (SD 0.468)	12		2.397 (SD 0.61)		
Adverse Events:									
Abdominal Distension – 8wk	Dichotomous	75	2	(2.7%)	36	0	(0.0%)		
Constipation – 8wk	Dichotomous	75	2	(2.7%)	36	0	(0.0%)		
Diarrhea – 8wk	Dichotomous	75	5	(6.7%)	36	2	(5.6%)		
Feces discolored – 8wk	Dichotomous	75	28	(37.3%)	36	2	(5.6%)		
Hyperphosphatemia – 8wk	Dichotomous	75	0	(0.0%)	36	0	(0.0%)		
Abdominal pain – 8wk	Dichotomous	75	0	(0.0%)	36	1	(2.8%)		

[a] *Approximated to nearest integer (percentages only presented in text)*

		Ferric citrate 6g/d			Placebo			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 8wk	Dichotomous	72	18	(25.0%)	36	24	(66.7%)		
Withdrawal (AEs) – 8wk	Dichotomous	72	7	(9.7%)	36	3	(8.3%)		
Biochemical Data:									
Achieved phosphate control – 8wk[a]	Dichotomous	72	53	(73.6%)	36	6	(16.7%)		
Serum Ca (mmol/L) – 4wk	Continuous	59		2.315 (SD 0.2)	13		2.255 (SD 0.222)		
Serum Ca (mmol/L) – 8wk	Continuous	54		2.298 (SD 0.16)	12		2.27 (SD 0.195)		
Serum Ca (mmol/L) – 8wk	Mean change	54		0.045 (SD 0.132)	12		0.042 (SD 0.095)		
Serum Phosphate (mmol/L) – 1wk	Continuous	65		1.596 (SD 0.497)	28		2.432 (SD 0.517)		
Serum Phosphate (mmol/L) – 4wk	Continuous	59		1.567 (SD 0.552)	13		2.471 (SD 0.31)		
Serum Phosphate (mmol/L) – 8wk	Mean change	54		-0.733 (SD 0.417)	12		0.026 (SD 0.488)		
Serum Phosphate (mmol/L) – 8wk	Continuous	54		1.515 (SD 0.404)	12		2.397 (SD 0.61)		

	Adverse Events:									
	Abdominal Distension – 8wk	Dichotomous	72	1	(1.4%)	36	0	(0.0%)		
	Constipation – 8wk	Dichotomous	72	1	(1.4%)	36	0	(0.0%)		
	Diarrhea – 8wk	Dichotomous	72	3	(4.2%)	36	2	(5.6%)		
	Feces discolored – 8wk	Dichotomous	72	27	(37.5%)	36	2	(5.6%)		
	Hyperphosphatemia – 8wk	Dichotomous	72	2	(2.8%)	36	0	(0.0%)		
	Abdominal pain – 8wk	Dichotomous	72	1	(1.4%)	36	1	(2.8%)		

[a] *Approximated to nearest integer (percentages only presented in text)*

Compliance was measured but no specific results were reported for each arm.

Authors' conclusion	
Source of funding	
Comments	

Lin et al. (2011) – evidence table

Bibliographic reference	Lin,Y.F., Chien,C.T., Kan,W.C., Chen,Y.M., Chu,T.S., Hung,K.Y., et al. Pleiotropic effects of sevelamer beyond phosphate binding in end-stage renal disease patients: a randomized, open-label, parallel-group study. Clinical Drug Investigation 2011;31(4):257-67.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Aged over 18 years **Washout phosphate level (mmol/L):** **Exclusions:** Serum Ca (>2.74mmol/L during the washout period) Heart Failure Liver dysfunction Cancer Hypertension or poorly controlled hypertension Significant GI disease **Baseline characteristics:**

		Sevelamer			Calcium acetate				
		N	k	mean	N	k	mean	Δ	p
Demographics:									
History of dialysis (year)	Continuous	26		4.6 (SD 5.2)	26		2.6 (SD 2.6)		

	Gender-Female	Dichotomous	26	14	(53.8%)	26	8	(30.8%)		
	Gender-Male	Dichotomous	26	12	(46.2%)	26	18	(69.2%)		
	Age	Continuous	26		58.5 (SD 10.3)	26		56 (SD 13.6)		
	Number Diabetic	Dichotomous	26	11	(42.3%)	26	7	(26.9%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.78 **Lower serum PO4 limit:** 1.13 **Upper serum Ca limit:** 2.74 **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 26 Dose varied by washout phosphate: The dose varied by the serum phosphate obtained during the washout phase; 1.78 to 2.10mmol/L 2400mg/day; 2.10 to 2.42mmol/L 4800mg/day; >2.42mmol/L 7200mg/day Dose varied to maintain patients within study endpoints: Following the initial washout phase the dose was titrated to maintain the serum phosphate levels within the study endpoints. Notes: The average doses were not provided **Drug:** Calcium acetate **N:** 26 Dose varied by washout phosphate: The dose varied by the serum phosphate obtained during the washout phase; 1.78 to 2.10mmol/L 2001mg/day; 2.10 to 2.42mmol/L 4002mg/day; >2.42mmol/L 6003mg/day Dose varied to maintain patients within study endpoints: Following the initial washout phase the dose was titrated to maintain the serum phosphate levels within the study endpoints. Notes: The average doses were not provided
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details (Patients needed to be stablefor one month prior to entry into the stdy. However, there are no details on what happened during the treatment phase) **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Taiwan

Outcomes measures and effect sizes			Sevelamer			Calcium acetate			Δ	p
			N	k	mean	N	k	mean		
Disposition:										
Withdrawal (total) – 8wk		Dichotomous	26	3	(11.5%)	26	6	(23.1%)		
Withdrawal (AEs) – 8wk		Dichotomous	26	3	(11.5%)	26	6	(23.1%)		
Treatment:										
Compliance – 56d[a]		Dichotomous	26	23	(88.5%)	26	23	(88.5%)		
Biochemical Data:										
Proportion with hypercalcaemia – 8wk		Dichotomous	26	1	(3.8%)	26	3[a]	(11.5%)		
[a] *approximated to nearest integer (percentages only presented in text)*										
Authors' conclusion										
Source of funding										
Comments										

Lin et al. (2016) – evidence table

Bibliographic reference	Lin, Hsin-Hung, Liou, Hung-Hsiang, Wu, Ming-Shiou. Factors associated with serum fetuin-A concentrations after long-term use of different phosphate binders in hemodialysis patients. BMC nephrology 2016;17():33. Related publications Lin, Hsin-Hung, Liou, Hung-Hsiang, Wu, Ming-Shiou et al. (2014) Long-term sevelamer treatment lowers serum fibroblast growth factor 23 accompanied with increasing serum Klotho levels in chronic haemodialysis patients. Nephrology 19(11): 672-678
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** =45 years **Washout phosphate level (mmol/L):** >1.77, <2.74 Additional notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:** Serum Ca (Hypercalcemia (corrected serum total calcium >2.62 mmol/l) during the 2 weeks of washout period. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).) Chronic inflammatory disease ALT or AST >3 times upper normal limit or iPTH > 1000 pg/mL before screening; infectious diseases, gastrointestinal bleeding or any other cause of hospital admission within 3 months before enrollment; thyroid disease, parathyroidectomy, swallowing disorders, gastrectomy or intestinal resection; osteoporosis and concurrently receiving related medications (including bisphosphonates, calcitonin or hormone replacement therapy) and known hypersensitivity to any components of the formulation of the study medications. **Baseline characteristics:**

		Sevelamer			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk[a]	Continuous	23		2.342 (SD 0.165)	27		2.342 (SD 0.182)		
Serum Phosphate (mmol/L) – 0wk[a]	Continuous	23		2.112 (SD 0.294)	27		2.332 (SD 0.317)		
Serum iPTH (pmmol/L) – 0wk[a]	Continuous	23		37.614 (SD 35.281)	27		34.03 (SD 39.428)		
Demographics: History of dialysis (year)[b]	Continuous	23		7.48 (SD 3.45)	27		7.33 (SD 5.21)		
Gender-Male[b]	Dichotomous	23	11	(47.8%)	27	18	(66.7%)		
Age[b]	Continuous	23		59.61 (SD 8.16)	27		56.96 (SD 7.72)		
Number Diabetic[b]	Dichotomous	23	9	(39.1%)	27	8	(29.6%)		

[a] *Lin 2016*
[b] *Lin 2014*

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: -
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Sevelamer hydrochloride
N: 23
Mean daily dose (mg): 6248 (SD: 2576)
Dose varied to maintain patients within study endpoints: Sevelamer (800 mg per tablet) three times per day with 1 tablet (1.78 - 2.10 mmol/L), 2 tablets (phosphate 2.10 - 2.42 mmol/L), or
3 tablets (phosphate >=2.42 mmol/L). Doses were titrated according to a fixed algorithm: increase 1 tablet per meal (phosphate >1.78 mmol/L), no change (phosphate 1.13 - 1.78 mmol/L), or decrease one tablet per meal (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.
Drug: Calcium Carbonate
N: 27
Mean daily dose (mg): 3260 (SD: 1305)
Dose varied to maintain patients within study endpoints: Calcium carbonate (500 mg per tablet) 3 times per day with 1 tablet (1.78 - 2.10 mmol/L), 2 tablets (phosphate 2.10 - 2.42 mmol/L), or

	3 tablets (phosphate >=2.42 mmol/L). Doses were titrated according to a fixed algorithm: increase 1 tablet per meal (phosphate >1.78 mmol/L), no change (phosphate 1.13 - 1.78 mmol/L), or decrease one tablet per meal (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.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No **Were other medications allowed:** Yes (Prescribed medication for diabetes mellitus (insulin or oral anti-diabetic drugs, except for metformin and glitazones), dyslipidemia (statin), and hypertension (anti-hypertension drugs) throughout the study period by the physicians in the three centers.) **Changes to diet allowed:** No **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 336 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Taiwan
Outcomes measures and effect sizes	

		Sevelamer			Calcium carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 48wk	Dichotomous	36	13	(36.1%)	39	12	(30.8%)		
Withdrawal (AEs) – 48wk	Dichotomous	36	11	(30.6%)	39	8	(20.5%)		
Biochemical Data:									
Serum Ca (mmol/L) – 48wk[a]	Continuous	23		2.408 (SD 0.2)	27		2.542 (SD 0.225)		
Serum Ca (mmol/L) – 48wk[a]	Mean change	23		0.065 (SD 0.138)	27		0.2 (SD 0.232)		
Serum Phosphate (mmol/L) – 48wk[a]	Continuous	23		1.638 (SD 0.275)	27		1.841 (SD 0.326)		
Serum iPTH (pmmol/L) – 48wk[a]	Continuous	23		34.952 (SD 33.913)	27		17.519 (SD 43.012)		
Adverse Events:									
Abdominal pain upper – 48wk[b]	Dichotomous	23	2	(8.7%)	27	0	(0.0%)		
Constipation – 48wk[b]	Dichotomous	23	1	(4.3%)	27	2	(7.4%)		

[a] *Lin 2016*
[b] *Lin 2016; Approximated to nearest integer (percentages only presented in text)*

Authors' conclusion	
Source of funding	
Comments	

Liu et al. (2006) – evidence table

Bibliographic reference	Liu,Y.L., Lin,H.H., Yu,C.C., Kuo,H.L., Yang,Y.F., Chou,C.Y., et al. A comparison of sevelamer hydrochloride with calcium acetate on biomarkers of bone turnover in hemodialysis patients. Renal Failure 2006;28(8):701-07.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 20 years or older **Washout phosphate level (mmol/L):** >1.94 **Exclusions:** Serum Ca (>2.74mmol/L) **Baseline characteristics:**
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.94 **Lower serum PO4 limit:** 1.13 **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 37 Mean daily dose (mg): 4500 (SD: 1300)

		Sevelamer			Calcium acetate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	37		2.26 (SD 0.304)	37		2.25 (SD 0.365)		
Serum Phosphate (mmol/L) – 0wk	Continuous	37		2.62 (SD 0.791)	33		2.62 (SD 0.747)		
Demographics: History of dialysis (year)	Continuous	37		7.3 (SD 6.1)	33		7.4 (SD 4.8)		
Gender-Female	Dichotomous	37	16	(43.2%)	33	16	(48.5%)		
Gender-Male	Dichotomous	37	21	(56.8%)	33	17	(51.5%)		
Age	Continuous	37		47.6 (SD 11.9)	33		50.4 (SD 10.9)		
Number Diabetic	Dichotomous	37	3	(8.1%)	33	5	(15.2%)		

	Dose varied by washout phosphate: >1.94 to <2.42 mmol/L 800mg; >2.42 to <2.9 mmol/L 1200mg; >2.9mmol/L 1600mg. Three times daily. Dose varied to maintain patients within study endpoints: Dose was titrated every two weeks to maintain serum phosphorus between 1.13 and 1.94mmol/L **Drug:** Calcium acetate **N:** 33 Mean daily dose (mg): 3800 (SD: 1600) Dose varied by washout phosphate: >1.94 to <2.42 mmol/L 667mg; >2.42 to <2.9 mmol/L 1334mg; >2.9mmol/L 2001mg. Three times daily. Dose varied to maintain patients within study endpoints: Dose was titrated every two weeks to maintain serum phosphorus between 1.13 and 1.94mmol/L. In addition if serum Ca rose above 2.75mmol/L the dose of calcium acetate was reduced by one to three tablets per meal.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (For four participants this was varied due to significant hypercalcaemia. Otherwise the original dose was maintained) **Rescue Binder use permitted:** No **Were other medications allowed:** No **Changes to diet allowed:** No **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** - **Follow-up (d):** - **Protocol-specified reasons for withdrawal:** Serum phosphate: No details given Serum Ca: No details given Binder use: No details given
Location	**Country:** Taiwan

Outcomes measures and effect sizes

		Sevelamer			Calcium acetate				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 8wk	Dichotomous	37	4	(10.8%)	36	6	(16.7%)		
Biochemical Data: Achieved phosphate control – 8wk	Dichotomous	21	12	(57.1%)	25	19	(76.0%)		
Serum Ca (mmol/L) – 2wk	Continuous	37		2.32 (SD 0.304)	33		2.48 (SD 0.287)		
Serum Ca (mmol/L) – 4wk	Continuous	37		2.26 (SD 0.365)	33		2.45 (SD 0.345)		
Serum Ca (mmol/L) – 6wk	Continuous	37		2.37 (SD 0.304)	33		2.5 (SD 0.345)		
Serum Ca (mmol/L) – 8wk	Continuous	37		2.28 (SD 0.304)	33		2.43 (SD 0.345)		

	Serum Ca (mmol/L) – 8wk	Mean change	37		0.03 (SD 0.217)	33		0.2 (SD 0.234)		
	Serum Phosphate (mmol/L) – 2wk	Continuous	37		2.16 (SD 0.608)	33		1.78 (SD 0.345)		
	Serum Phosphate (mmol/L) – 4wk	Continuous	37		1.94 (SD 0.365)	33		1.65 (SD 0.574)		
	Serum Phosphate (mmol/L) – 6wk	Continuous	37		1.97 (SD 0.365)	33		1.61 (SD 0.574)		
	Serum Phosphate (mmol/L) – 8wk	Continuous	37		1.94 (SD 0.365)	33		1.71 (SD 0.919)		
	Serum Phosphate (mmol/L) – 8wk	Mean change	37		-0.62 (SD 0.497)	33		-0.8 (SD 0.498)		
	Proportion with hypercalcaemia – 8wk	Dichotomous	37	5	(13.5%)	33	15	(45.5%)		
Authors' conclusion										
Source of funding										
Comments										

Malluche et al. (2008) – evidence table

Bibliographic reference	Malluche,H.H., Siami,G.A., Swanepoel,C., Wang,G.H., Mawad,H., Confer,S., et al. Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. Clinical Nephrology 2008;70(4):284-95.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Aged 18 years and older **Washout phosphate level (mmol/L):** >1.91 **Exclusions:** Serum Ca (Screening Calcium level <1.97mmol/L) Cancer Steroid use HIV positive Significant GI disease Pregnancy or lactation, exposure to an experimental drug within the last 30 days, medications know to affect bone metabolism (except vit D) **Baseline characteristics:**

			Lanthanam			Standard Therapy				
			N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk		Continuous	51		2.2 (SD 0.24)	48		2.3 (SD 0.28)		
Serum Phosphate (mmol/L) – 0wk		Continuous	51		2.45 (SD 0.48)	48		2.62 (SD 0.65)		
Demographics: History of dialysis (year)		Continuous	51		3.5 (SD 3.1)	48		5.1 (SD 4.1)		
Gender-Female		Dichotomous	51	14	(27.5%)	48	11	(22.9%)		
Gender-Male		Dichotomous	51	37	(72.5%)	48	37	(77.1%)		
Age		Continuous	51		48.5 (SD 13.4)	48		50.6 (SD 13.9)		
Number Diabetic		Dichotomous	51	14	(27.5%)	48	8	(16.7%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.91 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 108 Dose varied to maintain patients within study endpoints: Dose was varied to maintain the serum phospphate within the study endpoints. Notes: No details provided on the average dose. **Drug:** Any binder **N:** 103 Dose varied by washout phosphate: Dose was varied to maintain study endpoints Notes: Patients were on a variety of drugs including caclium acetate, calcium carbonate, sevelamer hydrochloride and others.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (The dose could be changed and patients could initiated onto Vitamin D also) **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** No (Binders within the comparison group could be changed and added to.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 21

	Follow-up (d): 728 **Protocol-specified reasons for withdrawal:** none specified								
Location	**Country:** USA, Puerto Rico, Poland, South Africa								
Outcomes measures and effect sizes			**Lanthanam**			**Standard Therapy**			**Δ**	**p**
			N	**k**	**mean**	**N**	**k**	**mean**		
	Disposition: Withdrawal (total) – 105wk	Dichotomous	108	39	(36.1%)	103	39	(37.9%)		
	Withdrawal (AEs) – 105wk	Dichotomous	108	3	(2.8%)	103	3	(2.9%)		
	Biochemical Data: Serum Ca (mmol/L) – 7wk	Continuous	51		2.23 (SD 0.214)	48		2.42 (SD 0.208)		
	Serum Ca (mmol/L) – 10wk	Continuous	51		2.27 (SD 0.286)	48		2.45 (SD 0.277)		
	Serum Ca (mmol/L) – 14wk	Continuous	51		2.28 (SD 0.21)	48		2.36 (SD 0.21)		
	Serum Ca (mmol/L) – 18wk	Continuous	51		2.26 (SD 0.29)	48		2.4 (SD 0.28)		
	Serum Ca (mmol/L) – 22wk	Continuous	51		2.31 (SD 0.21)	48		2.38 (SD 0.28)		
	Serum Ca (mmol/L) – 26wk	Continuous	51		2.26 (SD 0.21)	48		2.4 (SD 0.21)		
	Serum Ca (mmol/L) – 34wk	Continuous	51		2.28 (SD 0.29)	48		2.38 (SD 0.139)		
	Serum Ca (mmol/L) – 43wk	Continuous	51		2.35 (SD 0.29)	48		2.38 (SD 0.28)		
	Serum Ca (mmol/L) – 52wk	Continuous	51		2.29 (SD 0.143)	48		2.38 (SD 0.21)		
	Serum Ca (mmol/L) – 61wk	Continuous	51		2.31 (SD 0.29)	48		2.36 (SD 0.28)		
	Serum Ca (mmol/L) – 69wk	Continuous	51		2.25 (SD 0.29)	48		2.36 (SD 0.21)		
	Serum Ca (mmol/L) – 78wk	Continuous	51		2.34 (SD 0.29)	48		2.38 (SD 0.21)		
	Serum Ca (mmol/L) – 87wk	Continuous	51		2.26 (SD 0.357)	48		2.38 (SD 0.14)		
	Serum Ca (mmol/L) – 95wk	Continuous	51		2.34 (SD 0.214)	48		2.41 (SD 0.21)		
	Serum Ca (mmol/L) – 105wk	Continuous	51		2.36 (SD 0.21)	48		2.38 (SD 0.28)		

	Serum Phosphate (mmol/L) – 7wk	Continuous	51		1.74 (SD 0.428)	48		1.98 (SD 0.416)		
	Serum Phosphate (mmol/L) – 10wk	Continuous	51		1.81 (SD 0.643)	48		1.87 (SD 0.624)		
	Serum Phosphate (mmol/L) – 14wk	Continuous	51		1.98 (SD 0.43)	48		1.96 (SD 0.42)		
	Serum Phosphate (mmol/L) – 18wk	Continuous	51		1.89 (SD 0.64)	48		1.89 (SD 0.62)		
	Serum Phosphate (mmol/L) – 22wk	Continuous	51		1.87 (SD 0.64)	48		2.02 (SD 0.346)		
	Serum Phosphate (mmol/L) – 26wk	Continuous	51		1.81 (SD 0.43)	48		1.89 (SD 0.62)		
	Serum Phosphate (mmol/L) – 34wk	Continuous	51		1.77 (SD 0.64)	48		1.83 (SD 0.62)		
	Serum Phosphate (mmol/L) – 43wk	Continuous	51		1.87 (SD 0.43)	48		1.98 (SD 0.762)		
	Serum Phosphate (mmol/L) – 52wk	Continuous	51		1.97 (SD 0.357)	48		2.14 (SD 0.831)		
	Serum Phosphate (mmol/L) – 61wk	Continuous	51		1.92 (SD 0.64)	48		1.925 (SD 0.624)		
	Serum Phosphate (mmol/L) – 69wk	Continuous	51		1.97 (SD 0.64)	48		1.86 (SD 0.62)		
	Serum Phosphate (mmol/L) – 78wk	Continuous	51		1.94 (SD 0.64)	48		1.82 (SD 0.62)		
	Serum Phosphate (mmol/L) – 87wk	Continuous	51		1.89 (SD 0.64)	48		1.99 (SD 0.62)		
	Serum Phosphate (mmol/L) – 95wk	Continuous	51		1.94 (SD 0.43)	48		1.81 (SD 0.762)		
	Serum Phosphate (mmol/L) – 105wk	Continuous	51		1.85 (SD 0.36)	48		1.98 (SD 0.346)		
Authors' conclusion										
Source of funding										
Comments										

Maruyama et al. (2018) – evidence table

Bibliographic reference	Maruyama N., Otsuki T., Yoshida Y., Nagura C., Kitai M., Shibahara N., et al. Ferric Citrate Decreases Fibroblast Growth Factor 23 and Improves Erythropoietin Responsiveness in Hemodialysis Patients. American Journal of Nephrology 2018;47(6):406-14.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** =20 and =85 years **Washout phosphate level (mmol/L):** Additional notes: Washout was not reported. Target phosphate or calcium levels were not reported. **Exclusions:** Heart Failure Cancer Angina, myocardial infarction, or stroke within the past 6 months; infectious disease, or treatment with steroids or immunosuppressants; current hospitalisation; treatment with ferric citrate hydrate or sucroferric oxyhydroxide within the past 6 months. **Baseline characteristics:**

		Ferric citrate			Lanthanum carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 0wk	Continuous	30		2.25 (SD 0.1)	30		2.275 (SD 0.125)		
Serum Phosphate (mmol/L) – 0wk	Continuous	30		1.841 (SD 0.323)	30		1.841 (SD 0.291)		
Serum iPTH (pmmol/L) – 0wk	Continuous	30		13.362 (SD 6.999)	30		12.195 (SD 9.12)		
Demographics:									
Gender-Female[a]	Dichotomous	30	9	(30.0%)	30	10	(33.3%)		
Gender-Male[a]	Dichotomous	30	21	(70.0%)	30	20	(66.7%)		
Age	Continuous	30		62.7 (SD 13)	30		63.6 (SD 11.8)		
Number Diabetic	Dichotomous	30	15	(50.0%)	30	14	(46.7%)		
History of dialysis (months)	Continuous	30		med: 50 [rng 25–100]	30		med: 51 [rng 26–97]		

[a] *Approximated to nearest integer (percentages only presented in text)*

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Ferric citrate **N:** 30 Median daily dose (mg): 1500 (Range: 750–1500) Dose varied to maintain patients within study endpoints: Initial dose was 1,500 mg/day. If phosphate levels remained =1.93 mmol/l after 2 weeks of treatment, the dose would be increased. If phosphate levels remained <1.13 mmol/l, the dose would be decreased. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Drug:** Lanthanum carbonate **N:** 30 Median daily dose (mg): 1500 (Range: 750–1812) Dose varied to maintain patients within study endpoints: If phosphate levels remained =1.93 mmol/l after 2 weeks of treatment, the dose would be increased. If phosphate levels remained <1.13 mmol/l, the dose would be decreased. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Concomitant treatments	**Dialysis:** Either Haemodialysis or online haemodiafiltration **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Other phosphate binders, such as calcium carbonate and sevelamer, cinacalcet, anti-hypertensive drugs, anti-diabetic agents, and lipid-lowering agents.) **Changes to diet allowed:** Yes (Patients were regularly given dietary guidance by a dietician, especially those with dietary restrictions such as those on salt or protein restriction.) **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** - **Follow-up (d):** 84 **Protocol-specified reasons for withdrawal:** If the investigator believed that ferric citrate presented a safety problem, administration was to be interrupted.
Location	**Country:** Japan

Outcomes measures and effect sizes

		Ferric citrate			Lanthanum carbonate			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 12wk	Dichotomous	30	0	(0.0%)	30	0	(0.0%)		
Withdrawal (AEs) – 12wk	Dichotomous	30	0	(0.0%)	30	0	(0.0%)		

	Biochemical Data: Serum Ca (mmol/L) – 12wk	Continuous	30		2.25 (SD 0.1)	30		2.275 (SD 0.1)		
	Serum Phosphate (mmol/L) – 12wk	Continuous	30		1.809 (SD 0.291)	30		1.841 (SD 0.258)		
	Serum iPTH (pmmol/L) – 12wk	Continuous	30		13.256 (SD 6.575)	30		11.665 (SD 8.484)		
	Adverse Events: Diarrhea – 12wk	Dichotomous	30	2	(6.7%)	30	0	(0.0%)		
	Treatment: Compliance – 12wk[a]	Dichotomous	30	29	(96.7%)	30	29	(96.7%)		
	[a] *Approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Navarro-Gonzalez et al. (2011) – evidence table

Bibliographic reference	Navarro-Gonzalez,J.F., Mora-Fernandez,C., Muros de,Fuentes M., Donate-Correa,J., Cazana-Perez,V. Effect of phosphate binders on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients. Clinical Journal of The American Society of Nephrology: CJASN 2011;6(9):2272-79.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no Notes: The investigator lab was blinded to the treatment allocation.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Aged over 18 years **Washout phosphate level (mmol/L):** **Exclusions:** Cancer HIV positive Alcohol abuse Significant GI disease Smokers, drug dependence, immunicological disease, acute inflammatory episode or infection in the last month, prior transplantation, those immunotherapy **Baseline characteristics:**

			Sevelamer Hydrochloride			Calcium Acetate				
			N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous		30		2.25 (SD 0.17)	29		2.25 (SD 0.12)		
Serum Phosphate (mmol/L) – 0wk	Continuous		30		1.74 (SD 0.32)	29		1.65 (SD 0.19)		
Demographics: History of dialysis (year)	Continuous		30		2.5 (SD 0.83)	29		2.33 (SD 0.92)		
Gender-Female	Dichotomous		30	15	(50.0%)	29	15	(51.7%)		
Gender-Male	Dichotomous		30	15	(50.0%)	29	14	(48.3%)		
Age	Continuous		30		59.6 (SD 16.9)	29		62.8 (SD 14.1)		
Number Diabetic	Dichotomous		30	13	(43.3%)	29	12[a]	(41.4%)		

[a] *approximated to nearest integer (percentages only presented in text)*

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 33 Fixed daily dose (mg): 4800 **Drug:** Calcium acetate **N:** 32 Fixed daily dose (mg): 1500
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** No **Rescue Binder use permitted:** **Were other medications allowed:** Yes (Antihypertensive treatments) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 84 **Protocol-specified reasons for withdrawal:** Renal transplantation.

Location	**Country:** Spain
Outcomes measures and effect sizes	

		Sevelamer Hydrochloride			Calcium Acetate			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 12wk	Dichotomous	33	2	(6.1%)	32	3	(9.4%)		
Withdrawal (AEs) – 12wk	Dichotomous	33	1	(3.0%)	32	0	(0.0%)		
Biochemical Data:									
Serum Ca (mmol/L) – 12wk	Continuous	30		2.27 (SD 0.12)	29		2.32 (SD 0.12)		
Serum Phosphate (mmol/L) – 12wk	Continuous	30		1.58 (SD 0.32)	29		1.52 (SD 0.23)		

Authors' conclusion	
Source of funding	
Comments	

Ohtake et al. (2013) – evidence table

Bibliographic reference	Ohtake, Takayasu, Kobayashi, Shuzo, Oka, Machiko, Furuya, Rei, Iwagami, Masao, Tsutsumi, Daimu, et al. Lanthanum Carbonate Delays Progression of Coronary Artery Calcification Compared With Calcium-Based Phosphate Binders in Patients on Hemodialysis: A Pilot Study. Journal of Cardiovascular Pharmacology and Therapeutics 2013;18(5):439-46.
Study type & aim	**Blinded:** yes (single-blind) **Crossover trial:** no **Multicentre:** no Notes: The CAC score was calculated by a radiologist who was completely blinded to patient information, including group allocation.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Adults **Washout phosphate level (mmol/L):** Additional notes: Washout was not reported. **Exclusions:** Liver dysfunction Cancer Significant GI disease Pregnancy, endocrine disease, and arrhytmia. **Baseline characteristics:**

		All study participants		
		N	k	mean
Demographics:				
Gender-Male	Dichotomous	42	25	(59.5%)
Age	Continuous	42		67.8 (SD 6.3)
Number Diabetic	Dichotomous	42	18	(42.9%)
History of dialysis (months)	Continuous	42		124.4 (SD 47.5)

		Calcium carbonate			Lanthanum carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L) – 0mo	Continuous	23		2.175 (SD 0.2)	19		2.225 (SD 0.2)		
Serum Phosphate (mmol/L) – 0mo	Continuous	23		1.776 (SD 0.388)	19		1.873 (SD 0.258)		
Serum iPTH (pmmol/L) – 0mo	Continuous	23		5.09 (SD 1.124)	19		5.43 (SD 0.711)		
Coronary:									
Coronary arterial calcification – 0mo	Continuous	23		1588.9 (SD 1980.5)	19		1928.4 (SD 2383.8)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.93
Lower serum PO4 limit: 1.13
Upper serum Ca limit: 2.5
Lower serum Ca limit: 2.1

Intervention(s)

Drug: Calcium Carbonate
N: 23
Mean daily dose (mg): 3000 (SD: 1700)
Drug: Lanthanum carbonate
N: 19
Mean daily dose (mg): 1430.6 (SD: 652)

Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (If serum calcium <2.1 mmol/l (lower normal limit), vitamin D was newly added or increased to increase calcium absorption from the gastrointestinal tract. If serum calcium was >2.6 mmol/l (upper normal limit), vitamin D dosage was decreased. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).) **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Cinacalcet was added or increased as needed to maintain the levels of i-PTH within their target range.) **Changes to diet allowed:** Yes (Patients were guided by a specialised dietician, using a diet report to restrict dietary phosphate intake to 700 mg/d or less.) **Changes to dialysate allowed:** No (null)
Length of follow up	**Washout period (d):** - **Follow-up (d):** 182 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Japan

Outcomes measures and effect sizes

		Calcium carbonate			Lanthanum carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 6mo	Dichotomous	26	3	(11.5%)	26	7	(26.9%)		
Withdrawal (AEs) – 6mo	Dichotomous	26	2	(7.7%)	26	7	(26.9%)		
Biochemical Data:									
Serum Ca (mmol/L) – 6mo	Mean change	23		0.1 (SD 0.2)	19		-0.1 (SD 0.275)		
Serum Ca (mmol/L) – 6mo	Continuous	23		2.275 (SD 0.25)	19		2.125 (SD 0.175)		
Serum Phosphate (mmol/L) – 6mo	Mean change	23		-0.162 (SD 0.452)	19		-0.162 (SD 0.485)		
Serum Phosphate (mmol/L) – 6mo	Continuous	23		1.615 (SD 0.42)	19		1.712 (SD 0.42)		
Serum iPTH (pmmol/L) – 6mo	Mean change	23		-0.233 (SD 1.4)	19		-0.647 (SD 1.262)		
Serum iPTH (pmmol/L) – 6mo	Continuous	23		4.857 (SD 1.654)	19		4.793 (SD 1.166)		
Adverse Events:									
Constipation – 6mo	Dichotomous	23	3	(13.0%)	19	2	(10.5%)		
Nausea OR vomiting – 6mo	Dichotomous	23	1	(4.3%)	19	3	(15.8%)		
Nausea – 6mo	Dichotomous	23	1	(4.3%)	19	3	(15.8%)		
Abdominal discomfort – 6mo	Dichotomous	23	0	(0.0%)	19	2	(10.5%)		
Pneumonia – 6mo	Dichotomous	23	1	(4.3%)	19	0	(0.0%)		
Arrythmia – 6mo	Dichotomous	23	2	(8.7%)	19	0	(0.0%)		

	Loss of appetite – 6mo	Dichotomous	23	1	(4.3%)	19	2	(10.5%)		
	Headache – 6mo	Dichotomous	23	3	(13.0%)	19	1	(5.3%)		
	Rhinitis – 6mo	Dichotomous	23	4	(17.4%)	19	2	(10.5%)		
	Cramps – 6mo	Dichotomous	23	1	(4.3%)	19	2	(10.5%)		
	Edema – 6mo	Dichotomous	23	1	(4.3%)	19	0	(0.0%)		
	Hypotension – 6mo	Dichotomous	23	1	(4.3%)	19	0	(0.0%)		
	Coronary: Coronary arterial calcification – 6mo	Continuous	23		1696 (SD 1890.3)	19		1639.5 (SD 2189.5)		
	Mortality: All cause mortality – -1mo	Time-to-event	23			19				
	All cause mortality – 6mo	Dichotomous	23	1	(4.3%)	19	0	(0.0%)		
	Mean and SD of the log-transformed were also reported for coronary artery calcification.									
Authors' conclusion										
Source of funding										
Comments										

Otsuki et al. (2018) – evidence table

Bibliographic reference	Otsuki T., Utsunomiya K., Moriuchi M., Horikoshi S., Suzuki H., Okamura M., et al. Effect of sucroferric oxyhydroxide on fibroblast growth factor 23 levels in hemodialysis patients. Nephron 2018;140(3):161-68.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** =20 and =85 years **Washout phosphate level (mmol/L):** Additional notes: Washout was not reported. **Exclusions:** Heart Failure Liver dysfunction Cancer Angina, myocardial infarction, or stroke within the previous 6 months; concomitant hemorrhagic disease, infectious disease, thyroid disease, or treatment with steroids or immunosuppressants; current hospitalisation; and treatment with sucroferric oxyhydroxide or ferric citrate hydrate within the previous 6 months. **Baseline characteristics:**

			Sucroferric oxyhydroxide			Lanthanum carbonate			Δ	p
			N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk		Continuous	31		2.25 (SD 0.1)	32		2.25 (SD 0.15)		
Serum Phosphate (mmol/L) – 0wk		Continuous	31		1.873 (SD 0.42)	32		1.841 (SD 0.517)		
Serum iPTH (pmmol/L) – 0wk		Continuous	31		med: 17.497 [rng 9.332–23.648]	32		med: 16.013 [rng 11.135–20.255]		
Demographics: Gender-Male		Dichotomous	31	20	(64.5%)	32	20	(62.5%)		
Age		Continuous	31		63.2 (SD 12.8)	32		64.3 (SD 10.8)		
Number Diabetic		Dichotomous	31	13	(41.9%)	32	14	(43.8%)		
History of dialysis (months)		Continuous	31		med: 49 [rng 19–88]	32		med: 49 [rng 14–83]		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.93
Lower serum PO4 limit: 1.13
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Sucroferric oxyhydroxide
N: 31
Dose varied to maintain patients within study endpoints: If the serum phosphate levels were not within the target range of 1.13 - 1.93 mmol/l, the dose was adjusted every 2 weeks as usual, up to a maximum of 3,000 mg.
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).
Drug: Lanthanum carbonate
N: 32
Dose varied to maintain patients within study endpoints: If the serum phosphate levels were not within the target range of 1.13 - 1.93 mmol/l, the dose was adjusted every 2 weeks as usual, up to a maximum of 2,250 mg.
Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).

Concomitant treatments

Dialysis: Either Haemodialysis or online haemodiafiltration
Vit D: Yes - not changed during the study
Rescue Binder use permitted: No details given

	Were other medications allowed: Yes (Calcium carbonate, sevelamer, and cinacalcet.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** - **Follow-up (d):** 168 **Protocol-specified reasons for withdrawal:** Patients could be withdrawn if ferritin levels increased to >300 ng/mL, if an adverse event that might pose a risk to the patient occurred, if the patient requested withdrawal, or if the patient was hospitalised or transferred to another dialysis center.
Location	**Country:** Japan

Outcomes measures and effect sizes

		Sucroferric oxyhydroxide			Lanthanum carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 24wk	Dichotomous	34	3	(8.8%)	34	2	(5.9%)		
Withdrawal (AEs) – 24wk	Dichotomous	34	3	(8.8%)	34	1	(2.9%)		
Biochemical Data:									
Serum Ca (mmol/L) – 24wk	Continuous	31		2.25 (SD 0.175)	32		2.225 (SD 0.15)		
Serum Phosphate (mmol/L) – 24wk	Continuous	31		1.906 (SD 0.517)	32		1.873 (SD 0.388)		
Serum iPTH (pmmol/L) – 24wk	Continuous	31		med: 12.937 [rng 8.484–18.028]	32		med: 13.044 [rng 10.604–19.618]		

Authors' conclusion	
Source of funding	
Comments	

Qunibi et al. (2008) – evidence table

Bibliographic reference	Qunibi,W., Moustafa,M., Muenz,L.R., He,D.Y., Kessler,P.D., Diaz-Buxo,J.A., Budoff,M. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. American Journal of Kidney Diseases 2008;51(6):952-65.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no

Number and characteristics of patients

Gender: Male and Female
Age range: 18 years and older
Washout phosphate level (mmol/L): >1.78
Exclusions:
Serum Ca (>2.87mmol/L)
Significant Unstable Medical conditions
Severe Hyperparathyroidism
Baseline characteristics:

		Calcium Acetate			Sevelamer			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	103		2.2 (SD 0.2)	100		2.2 (SD 0.17)		
Serum Phosphate (mmol/L) – 0wk	Continuous	103		2.1 (SD 0.61)	100		2.13 (SD 0.48)		
Coronary: Coronary arterial calcification – 0mo	Continuous	103		1098 (SD 1440)	100		969 (SD 1386)		
Demographics: History of dialysis (year)	Continuous	103		1.9 (SD 1.1)	100		1.8 (SD 1.1)		
Gender-Female	Dichotomous	103	44	(42.7%)	100	54	(54.0%)		
Gender-Male	Dichotomous	103	59	(57.3%)	100	46	(46.0%)		
Age	Continuous	103		58.5 (SD 12.8)	100		60.3 (SD 12.1)		
Number Diabetic	Dichotomous	103	59	(57.3%)	100	57	(57.0%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: 1.13
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Calcium acetate
N: 103
Mean daily dose (mg): 5500
Dose varied by washout phosphate: Yes- no further details provided.
Notes: The mean dose is only representative of the last week of treatment

	Drug: Sevelamer hydrochloride **N:** 100 Mean daily dose (mg): 7300 Dose varied by washout phosphate: Yes- no further details provided. Notes: The mean dose is only representative of the last week of treatment
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (If serum Ca exceeded 2.54mmol/L vit D therapy was discontinued for 1 week. If hypercalcemia persisted calcium acetate dose was decreased by 1 gel cap per meal.) **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Lipitor was given to lower LDL-cholesterol. Ca acetate patients were given this at randomisation, however this was not given to the sevelamer group until week 8.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No (Dialystate was maintained at 1.25mmol/L)
Length of follow up	**Washout period (d):** 42 **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** USA

Outcomes measures and effect sizes

		Calcium Acetate			Sevelamer				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 52wk	Dichotomous	103	44	(42.7%)	100	30	(30.0%)		
Withdrawal (AEs) – 52wk	Dichotomous	103	6	(5.8%)	100	8	(8.0%)		
Biochemical Data: Serum Ca (mmol/L) – 52wk	Continuous	59		2.35 (SD 0.17)	70		2.25 (SD 0.17)		
Serum Phosphate (mmol/L) – 52wk	Continuous	59		1.61 (SD 0.52)	70		1.74 (SD 0.58)		
Adverse Events: Abdominal pain upper – 52wk	Dichotomous	103	4	(3.9%)	100	8	(8.0%)		
Constipation – 52wk	Dichotomous	103	5	(4.9%)	100	10	(10.0%)		
Diarrhea – 52wk	Dichotomous	103	16	(15.5%)	100	16	(16.0%)		
Nausea OR vomiting – 52wk	Dichotomous	103	18	(17.5%)	100	18	(18.0%)		
Nausea – 52wk	Dichotomous	103	18	(17.5%)	100	17	(17.0%)		
Vomiting – 52wk	Dichotomous	103	18	(17.5%)	100	18	(18.0%)		
Coronary: Coronary arterial calcification – 6mo	Continuous	71		1197 (SD 1413)	68		996 (SD 1386)		

	Coronary arterial calcification – 6mo	Mean change	71		109 (SD 374)	68		97 (SD 211)		
	Coronary arterial calcification – 12mo	Continuous	58		1297 (SD 1487)	68		1116 (SD 1569)		
	Coronary arterial calcification – 12mo	Mean change	58		228 (SD 355)	68		227 (SD 485)		
	Mortality:									
	All cause mortality – -1wk	Time-to-event	103			100				
	All cause mortality – 52wk	Dichotomous	103	7	(6.8%)	100	3	(3.0%)		
	Treatment:									
	Compliance – 52wk	Dichotomous	103			100				
	Biochemical Data:									
	Proportion with hypercalcaemia – 52wk	Dichotomous	103	32	(31.1%)	100	19	(19.0%)		
Authors' conclusion										
Source of funding										
Comments										

Raggi et al. (2004) – evidence table

Bibliographic reference	Raggi,P. & Bommer,J. Valvular calcification in hemodialysis patients randomized to calcium-based phosphorus binders or sevelamer. Journal of Heart Valve Disease 2004;13(1):134-41.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** aged 19 years and over **Washout phosphate level (mmol/L):** >1.78 **Exclusions:** Diabetes or poorly controlled diabetes Bowel dysfunction Cancer Hypertension or poorly controlled hypertension HIV positive Alcohol abuse **Baseline characteristics:**

		All study participants		
		N	k	mean
Demographics: Gender-Female	Dichotomous	186	40	(21.5%)
Gender-Male	Dichotomous	186	146	(78.5%)
Age	Continuous	186		56.5 (SD 14.9)
Number Diabetic	Dichotomous	186	65	(34.9%)

		Sevelamer			Calcium Binders				
		N	k	mean	N	k	mean	Δ	p
Coronary: Coronary arterial calcification – 0wk	Continuous	92		med: 683 [rng 0–4167]	94		med: 600 [rng 0–2788]		
Demographics: History of dialysis (year)	Continuous	92		med: 3.58	94		med: 2.92		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.61
Lower serum PO4 limit: 0.97
Upper serum Ca limit: 2.62
Lower serum Ca limit: 2.12

Intervention(s)

Drug: Sevelamer hydrochloride
N: 92
Dose varied to maintain patients within study endpoints: Yes- no other details given
Drug: Calcium Based Binders
N: 94
Dose varied to maintain patients within study endpoints: Yes - no further details provided
Notes: American participants recieved calcium acetate, the european participants recieved calcium carbonate

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Yes - changed during the study period (The dose could be changed to achieve serum phosphorus and serum calcium levels)
Rescue Binder use permitted: Yes - different to allocation

	Were other medications allowed: No details provided (Resuce biner was aluminum hydroxide) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** Yes (The dose could be changed to achieve serum phosphorus and serum calcium levels)
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** Serum phosphate: no details provided Serum Ca: no details provided Binder use: no details provided
Location	**Country:** USA, Germany and Austria

Outcomes measures and effect sizes

		Sevelamer			Calcium Binders				
		N	k	mean	N	k	mean	Δ	p
Coronary: Coronary arterial calcification – 52wk	Mean change	62		-46 (SD 692)	70		151 (SD 471)		

Authors' conclusion	
Source of funding	
Comments	

Ring et al. (1993) – evidence table

Bibliographic reference	Ring,T., Nielsen,C., Andersen,S.P., Behrens,J.K., Sodemann,B. Calcium acetate versus calcium carbonate as phosphorus binders in patients on chronic haemodialysis: a controlled study. Nephrology Dialysis Transplantation 1993;8(4):341-46.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** no Notes: no real washout there was a 1 week control period where patients were maintained on Calcium Carbonate
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 19 to 75 years **Washout phosphate level (mmol/L):** **Exclusions:** No details provided **Baseline characteristics:**

		All study participants		
		N	k	mean
Dialystate: Ca Dialystate (mmol/L)	Continuous	15		1.74

		Calcium Acetate			Calcium Carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	7		2.48 (SD 0.16)	8		2.4 (SD 0.31)		
Serum Phosphate (mmol/L) – 0wk	Continuous	7		2.09 (SD 0.24)	8		2.3 (SD 0.59)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Calcium acetate **N:** 7 Median daily dose (mg): 1440 (Range: 540–2700) Notes: No details provided on how the variable dose was determined for the patients. The dose was however maintained throughout the study period, the media dose provided is the daily dose of binder calcium. **Drug:** Calcium Carbonate **N:** 8 Median daily dose (mg): 1440 (Range: 570–2700) Notes: No details provided on how the variable dose was determined for the patients. The dose was however maintained throughout the study period, the media dose provided is the daily dose of binder calcium.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** No **Rescue Binder use permitted:** No details given **Were other medications allowed:** No

	Changes to diet allowed: No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** - **Follow-up (d):** 21 **Protocol-specified reasons for withdrawal:** Serum phosphate: No details given Serum Ca: No details given Binder use: No details given No details given
Location	**Country:** Denmark

Outcomes measures and effect sizes

		Calcium Acetate			Calcium Carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 3wk	Continuous	7		2.51 (SD 0.14)	8		2.42 (SD 0.28)		
Serum Ca (mmol/L) – 3wk	Mean change	7		0.02 (SD 0.08)	8		0.01 (SD 0.08)		
Serum Phosphate (mmol/L) – 3wk	Continuous	7		1.95 (SD 0.25)	8		2.04 (SD 0.44)		
Serum Phosphate (mmol/L) – 3wk	Mean change	7		-0.14 (SD 0.16)	8		-0.26 (SD 0.44)		

Authors' conclusion	
Source of funding	
Comments	

Shigematsu et al. (2008a) – evidence table

Bibliographic reference	Shigematsu,T. Multicenter prospective randomized, double-blind comparative study between lanthanum carbonate and calcium carbonate as phosphate binders in Japanese hemodialysis patients with hyperphosphatemia. Clinical Nephrology 2008;70(5):404-10.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** - **Age range:** Aged 20 years and older **Washout phosphate level (mmol/L):** >1.8, <3.55

Exclusions:
Serum Ca (Serum Calcium <1.75 or >2.74mmol/L at the start of the washout period and/or during the washout period)
Serum iPTH >106pmol/L
Baseline characteristics:

		Lanthanam			Calcium Carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Phosphate (mmol/L) – 0wk	Continuous	126		2.7 (SD 0.45)	132		2.71 (SD 0.46)		
Demographics: History of dialysis (year)	Continuous	126		9.8 (SD 7.3)	132		9.7 (SD 7.2)		
Gender-Female	Dichotomous	126	39	(31.0%)	132	45	(34.1%)		
Gender-Male	Dichotomous	126	87	(69.0%)	132	87	(65.9%)		
Age	Continuous	126		58.8 (SD 10.5)	132		56.1 (SD 11.5)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: 1.13
Upper serum Ca limit: 2.59
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 126
Dose varied to maintain patients within study endpoints: Doses were titrated to maintaiin the study endpoints. Doses ranged from 750mg/day to 2250mg/day
Notes: Average doses not provided. Daily doses at the last visit were provided.
Drug: Calcium Carbonate
N: 132
Dose varied to maintain patients within study endpoints: Doses were titrated to maintaiin the study endpoints. Doses ranged from 1500mg/day to 4500mg/day
Notes: Average doses not provided. Daily doses at the last visit were provided.

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Yes - changed during the study period (The vitamin d was only changed in instances where it was ethical to do so. For example hyperparathyroidism)
Rescue Binder use permitted: No details given
Were other medications allowed: No details provided
Changes to diet allowed: No details given

	Changes to dialysate allowed: No details given (Almost all patients were on a dialystate of 1.75mmol/L)
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 56 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Japan

Outcomes measures and effect sizes

		Lanthanam			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (AEs) – 8wk	Dichotomous	126	4	(3.2%)	132	6	(4.5%)		
Biochemical Data: Serum Phosphate (mmol/L) – 8wk	Mean change	126		-0.83 (SD 0.438)	132		-0.91 (SD 0.448)		
Adverse Events: Abdominal Distension – 8wk[a]	Dichotomous	126	3	(2.4%)	132	5	(3.8%)		
Abdominal pain upper – 8wk[a]	Dichotomous	126	4	(3.2%)	132	7	(5.3%)		
Constipation – 8wk[a]	Dichotomous	126	3	(2.4%)	132	7	(5.3%)		
Nausea OR vomiting – 8wk[a]	Dichotomous	126	14	(11.1%)	132	4	(3.0%)		
Nausea – 8wk	Dichotomous	126	13[a]	(10.3%)	132	4	(3.0%)		
Vomiting – 8wk[a]	Dichotomous	126	14	(11.1%)	132	1	(0.8%)		
Biochemical Data: Proportion with hypercalcaemia – 8wk	Dichotomous	123	7	(5.7%)	130	39	(30.0%)		

[a] *approximated to nearest integer (percentages only presented in text)*

Authors' conclusion	
Source of funding	
Comments	

Shigematsu et al. (2008b) – evidence table

Bibliographic reference	Shigematsu,T. Lanthanum carbonate effectively controls serum phosphate without affecting serum calcium levels in patients undergoing hemodialysis. Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2008;12(1):55-61.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 20-75 years

Washout phosphate level (mmol/L): >1.8, <3.23
Exclusions:
Serum Ca (<2mmol/L or >2.74mmol/L)
Baseline characteristics:

		Placebo		
		N	k	mean
Biochemical Data:				
Serum Ca (mmol/L)	Continuous	31		2.34 (SD 0.14)
Serum Phosphate (mmol/L) – 0wk	Continuous	31		2.62 (SD 0.59)
Serum Phosphate (mmol/L) – 0wk	Continuous	31		2.62 (SD 0.59)
Demographics:				
History of dialysis (year)	Continuous	31		99.3 (SD 5.9)
Duration of dialysis (min)	Continuous	31		239 (SD 14)
Gender-Female	Dichotomous	31	13	(41.9%)
Gender-Male	Dichotomous	31	18	(58.1%)
Age	Continuous	31		58.9 (SD 9.9)

		Lantham Carbonate 750mg/d			Lantham Carbonate 1500mg/d			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Serum Ca (mmol/L)	Continuous	30		2.34 (SD 0.15)	28		2.34 (SD 0.16)		
Serum Phosphate (mmol/L) – 0wk	Continuous	30		2.56 (SD 0.39)	28		2.67 (SD 0.51)		
Demographics:									
History of dialysis (year)	Continuous	30		9.8 (SD 6.6)	28		9.8 (SD 5.3)		
Duration of dialysis (min)	Continuous	30		237.1 (SD 18.3)	28		246.4 (SD 14.2)		
Gender-Female	Dichotomous	30	17	(56.7%)	28	7	(25.0%)		
Gender-Male	Dichotomous	30	13	(43.3%)	28	21	(75.0%)		
Age	Continuous	30		54.2 (SD 9.6)	28		58.6 (SD 10.3)		

		Lantham Carbonate 2250mg/d			Lantham Carbonate 3000mg/d				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L)	Continuous	31		2.3 (SD 0.13)	22		2.333 (SD 0.13)		
Serum Phosphate (mmol/L) – 0wk	Continuous	31		2.53 (SD 0.37)	22		2.46 (SD 0.37)		
Demographics: History of dialysis (year)	Continuous	31		8.8 (SD 7.3)	22		8.1 (SD 4.6)		
Duration of dialysis (min)	Continuous	31		236.3 (SD 20.4)	22		242.6 (SD 22.5)		
Gender-Female	Dichotomous	31	13	(41.9%)	22	5	(22.7%)		
Gender-Male	Dichotomous	31	18	(58.1%)	22	17	(77.3%)		
Age	Continuous	31		59.5 (SD 8.6)	22		60 (SD 10.3)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.13
Lower serum PO4 limit: 1.78
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Lanthanum carbonate
N: 30
Fixed daily dose (mg): 750
Drug: Lanthanum carbonate
N: 28
Fixed daily dose (mg): 1500
Drug: Lanthanum carbonate
N: 31
Fixed daily dose (mg): 2250
Drug: Lanthanum carbonate
N: 22
Fixed daily dose (mg): 3000
Drug: Placebo

	N: 31
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No **Were other medications allowed:** No **Changes to diet allowed:** No **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 42 **Protocol-specified reasons for withdrawal:** Serum phosphate: pre-dialysis <0.97mmol/L or >2.23mmol/L at two consecutive sessions Serum Ca: pre-dialysis <2mmol/L at two consecutive sessions
Location	**Country:** Japan

Outcomes measures and effect sizes

		Placebo		
		N	**k**	**mean**
Biochemical Data:				
Achieved phosphate control – 6wk	Dichotomous	31	0	(0.0%)
Serum Phosphate (mmol/L) – 1wk	Continuous	31		2.62 (SD 0.43)
Serum Phosphate (mmol/L) – 1wk	Continuous	31		2.62 (SD 0.43)
Serum Phosphate (mmol/L) – 2wk	Continuous	31		2.62 (SD 0.48)
Serum Phosphate (mmol/L) – 2wk	Continuous	31		2.62 (SD 0.48)
Serum Phosphate (mmol/L) – 3wk	Continuous	31		2.62 (SD 0.56)
Serum Phosphate (mmol/L) – 3wk	Continuous	31		2.62 (SD 0.56)
Serum Phosphate (mmol/L) – 4wk	Continuous	31		2.47 (SD 0.48)
Serum Phosphate (mmol/L) – 4wk	Continuous	31		2.47 (SD 0.48)
Serum Phosphate (mmol/L) – 5wk	Continuous	31		2.47 (SD 0.32)
Serum Phosphate (mmol/L) – 5wk	Continuous	31		2.47 (SD 0.32)
Serum Phosphate (mmol/L) – 6wk	Continuous	31		2.62 (SD 0.48)
Serum Phosphate (mmol/L) – 6wk	Continuous	31		2.62 (SD 0.48)
Adverse Events:				
Abdominal pain upper – 6wk	Dichotomous	31	1	(3.2%)
Constipation – 6wk	Dichotomous	31	1	(3.2%)
Diarrhea – 6wk	Dichotomous	31	1	(3.2%)
Nausea OR vomiting – 6wk	Dichotomous	31	0	(0.0%)

Nausea – 6wk	Dichotomous	33	0	(0.0%)
Vomiting – 6wk	Dichotomous	33	0	(0.0%)

		Lantham Carbonate 750mg/d			Lantham Carbonate 1500mg/d			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data:									
Achieved phosphate control – 6wk	Dichotomous	30	15	(50.0%)	28	19	(67.9%)		
Serum Phosphate (mmol/L) – 1wk	Continuous	30		2.13 (SD 0.58)	28		1.84 (SD 0.58)		
Serum Phosphate (mmol/L) – 2wk	Continuous	30		2.13 (SD 0.48)	28		1.89 (SD 0.63)		
Serum Phosphate (mmol/L) – 3wk	Continuous	30		2.08 (SD 0.44)	28		1.78 (SD 0.53)		
Serum Phosphate (mmol/L) – 4wk	Continuous	30		1.99 (SD 0.48)	28		1.74 (SD 0.48)		
Serum Phosphate (mmol/L) – 5wk	Continuous	30		2.03 (SD 0.53)	28		1.69 (SD 0.48)		
Serum Phosphate (mmol/L) – 6wk	Continuous	30		2.08 (SD 0.53)	28		1.74 (SD 0.58)		
Adverse Events:									
Abdominal pain upper – 6wk	Dichotomous	30	1	(3.3%)	28	0	(0.0%)		
Constipation – 6wk	Dichotomous	30	0	(0.0%)	28	2	(7.1%)		
Diarrhea – 6wk	Dichotomous	30	0	(0.0%)	28	2	(7.1%)		
Nausea OR vomiting – 6wk	Dichotomous	30	1	(3.3%)	28	2	(7.1%)		
Nausea – 6wk	Dichotomous	31	1	(3.2%)	28	2	(7.1%)		
Vomiting – 6wk	Dichotomous	31	1	(3.2%)	28	2	(7.1%)		
LOCF									
Biochemical Data:									
Serum Phosphate (mmol/L) – 6wk	Mean change	28		-0.43 (SD 0.09)	31		-0.82 (SD 0.09)		

			Lantham Carbonate 2250mg/d			Lantham Carbonate 3000mg/d			Δ	p
			N	k	mean	N	k	mean		
	Biochemical Data:									
	Achieved phosphate control – 6wk[a]	Dichotomous	31	25	(80.6%)	22	15	(68.2%)		
	Serum Phosphate (mmol/L) – 1wk	Continuous	31		1.6 (SD 0.63)	22		1.4 (SD 0.44)		
	Serum Phosphate (mmol/L) – 2wk	Continuous	31		1.6 (SD 0.68)	22		1.35 (SD 0.44)		
	Serum Phosphate (mmol/L) – 3wk	Continuous	31		1.54 (SD 0.48)	22		1.6 (SD 0.39)		
	Serum Phosphate (mmol/L) – 4wk	Continuous	31		1.48 (SD 0.39)	22		1.54 (SD 0.44)		
	Serum Phosphate (mmol/L) – 5wk	Continuous	31		1.63 (SD 0.48)	22		1.69 (SD 0.53)		
	Serum Phosphate (mmol/L) – 6wk	Continuous	31		1.5 (SD 0.58)	22		1.5 (SD 0.48)		
	Adverse Events:									
	Abdominal pain upper – 6wk	Dichotomous	31	2	(6.5%)	22	0	(0.0%)		
	Constipation – 6wk	Dichotomous	31	1	(3.2%)	22	1	(4.5%)		
	Diarrhea – 6wk	Dichotomous	31	0	(0.0%)	22	0	(0.0%)		
	Nausea OR vomiting – 6wk	Dichotomous	31	7	(22.6%)	22	12	(54.5%)		
	Nausea – 6wk	Dichotomous	33	7	(21.2%)	31	8	(25.8%)		
	Vomiting – 6wk	Dichotomous	33	6	(18.2%)	31	12	(38.7%)		
	LOCF									
	Biochemical Data:									
	Serum Phosphate (mmol/L) – 6wk	Mean change	22		-0.98 (SD 0.08)	31		-1.01 (SD 0.1)		
	[a] *approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Spasovski et al. (2006) – evidence table

Bibliographic reference	Spasovski,G.B., Sikole,A., Gelev,S., Masin-Spasovska,J., Freemont,T., Webster,I., et al. Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. Nephrology Dialysis Transplantation 2006;21(8):2217-24.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no

	Multicentre: yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Over 18 years of age **Washout phosphate level (mmol/L):** **Exclusions:** Steroid use Significant GI disease Treatment with bisphosphonates **Baseline characteristics:**

		Lanthanam			Calcium Carbonate				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0yr	Continuous	10		2.13 (SD 0.2)	10		2.27 (SD 0.23)		
Serum Phosphate (mmol/L) – 0yr	Continuous	10		1.58 (SD 0.24)	10		1.76 (SD 0.39)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.8 **Lower serum PO4 limit:** - **Upper serum Ca limit:** 2.6 **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 12 Dose varied to maintain patients within study endpoints: Dose was titrated to maintain serum phosphate within the study endpoints **Drug:** Calcium Carbonate **N:** 12 Dose varied to maintain patients within study endpoints: Dose was titrated to maintain serum phosphate within the study endpoints
Concomitant treatments	**Dialysis:** On dialysis but no further details **Vit D:** Yes - but no further details **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given

Length of follow up	**Washout period (d):** 0 **Follow-up (d):** 364 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Macedonia

Outcomes measures and effect sizes

		Lanthanam			Calcium Carbonate			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (AEs) – 1yr	Dichotomous	12	0	(0.0%)	12	0	(0.0%)		
Biochemical Data: Serum Ca (mmol/L) – 1yr	Continuous	10		2.18 (SD 0.9)	10		2.33 (SD 0.23)		
Serum Phosphate (mmol/L) – 1yr	Continuous	10		1.55 (SD 0.25)	10		1.59 (SD 0.38)		
Mortality: All cause mortality – 1yr	Dichotomous	12	0	(0.0%)	12	1	(8.3%)		
Biochemical Data: Proportion with hypercalcaemia – 1yr	Dichotomous	10	0	(0.0%)	10	5	(50.0%)		

Authors' conclusion	
Source of funding	
Comments	

Spiegel et al. (2007) – evidence table

Bibliographic reference	Spiegel,D.M. & Farmer,B. Magnesium carbonate is an effective phosphate binder for chronic hemodialysis patients: a pilot study. Journal of Renal Nutrition 2007;17(6):416-22.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years and older **Washout phosphate level (mmol/L):** >1.61 Additional notes: Patients had to have been receiving a phosphate binder before entry into the study and the average of the last three monthly lab data had to have a serum Ca 2-2.54mmol/L and a serum phosphate 0.97-2.23mmol/L **Exclusions:** Those with frequent diarrhea >1 episode per week during the last 3 months

Baseline characteristics:

		Magnesium Carbonate			Calcium acetate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	20		2.06 (SD 0.134)	10		2.1 (SD 0.19)		
Serum Phosphate (mmol/L) – 0wk	Continuous	20		2.1 (SD 0.268)	10		2.13 (SD 0.19)		
Demographics: History of dialysis (year)	Continuous	20		3.08 (SD 3.58)	10		3.25 (SD 2.67)		
Gender-Female	Dichotomous	20	8	(40.0%)	10	6	(60.0%)		
Gender-Male	Dichotomous	20	12	(60.0%)	10	4	(40.0%)		
Age	Continuous	20		55.5 (SD 12.6)	10		55.9 (SD 12)		
Number Diabetic	Dichotomous	20	12	(60.0%)	10	7	(70.0%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.78
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Magnesium Carbonate
N: 20
Dose varied to maintain patients within study endpoints: Dose was varied to maintain the serum phosphate limit
Notes: Average dosages not provided
Drug: Calcium acetate
N: 10
Dose varied to maintain patients within study endpoints: Dose was varied to maintain the serum phosphate limit
Notes: Average doses not provided

Concomitant treatments

Dialysis: Haemodialysis
Vit D: Yes - changed during the study period (Dose reductions were allowed if the serum Ca was >2.62mmol/L or if the iPTH decreased to <100ng/L.)
Rescue Binder use permitted: No
Were other medications allowed: Yes (Cinacalcet could be reduced if the iPTH decreased to <100ng/L)
Changes to diet allowed: No details given

	Changes to dialysate allowed: No
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 84 **Protocol-specified reasons for withdrawal:** Serum phosphate: No details Serum Ca: no details Binder use: no details
Location	**Country:** USA

Outcomes measures and effect sizes

		Magnesium Carbonate			Calcium acetate			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 12wk	Dichotomous	20	3	(15.0%)	10	2	(20.0%)		
Withdrawal (AEs) – 12wk	Dichotomous	20	3	(15.0%)	10	1	(10.0%)		
Biochemical Data: Achieved phosphate control – 12wk	Dichotomous	17	12	(70.6%)	8	5	(62.5%)		
Serum Ca (mmol/L) – 2wk	Continuous	20		2.12 (SD 0.089)	10		2.22 (SD 0.095)		
Serum Ca (mmol/L) – 4wk	Continuous	17		2.15 (SD 0.124)	8		2.26 (SD 0.085)		
Serum Ca (mmol/L) – 6wk	Continuous	17		2.16 (SD 0.12)	8		2.26 (SD 0.198)		
Serum Ca (mmol/L) – 8wk	Continuous	17		2.15 (SD 0.165)	8		2.26 (SD 0.17)		
Serum Ca (mmol/L) – 10wk	Continuous	17		2.12 (SD 0.206)	8		2.2 (SD 0.198)		
Serum Ca (mmol/L) – 12wk	Continuous	17		2.15 (SD 0.124)	8		2.2 (SD 0.17)		
Serum Phosphate (mmol/L) – 2wk	Continuous	20		2.03 (SD 0.268)	10		1.73 (SD 0.348)		
Serum Phosphate (mmol/L) – 4wk	Continuous	17		1.74 (SD 0.33)	8		1.94 (SD 0.17)		
Serum Phosphate (mmol/L) – 6wk	Continuous	17		1.81 (SD 0.412)	8		1.71 (SD 0.368)		
Serum Phosphate (mmol/L) – 8wk	Continuous	17		1.61 (SD 0.41)	8		1.49 (SD 0.283)		
Serum Phosphate (mmol/L) – 10wk	Continuous	17		1.74 (SD 0.41)	8		1.7 (SD 0.368)		

	Serum Phosphate (mmol/L) – 12wk	Continuous	17		1.71 (SD 0.33)	8		1.81 (SD 0.509)		
Authors' conclusion										
Source of funding										
Comments										

Suki et al. (2007) – evidence table

Bibliographic reference	Suki,W.N., Zabaneh,R., Cangiano,J.L., Reed,J., Fischer,D., Garrett,L., et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney International 2007;72(9):1130-37.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years and over **Washout phosphate level (mmol/L):** **Exclusions:** Bowel dysfunction Significant GI disease **Baseline characteristics:**

		Sevelamer			Calcium Based Biinders				
		N	k	mean	N	k	mean	Δ	p
Demographics: History of dialysis (year)	Continuous	1053		3.18 (SD 3.3)	1050		3.13 (SD 3.3)		
Gender-Female	Dichotomous	1053	479	(45.5%)	1050	481	(45.8%)		
Gender-Male	Dichotomous	1053	574	(54.5%)	1050	569	(54.2%)		
Age	Continuous	1053		60 (SD 14.7)	1050		60.1 (SD 15.2)		
Number Diabetic	Dichotomous	1053	532	(50.5%)	1050	524	(49.9%)		
>65 years Demographics: History of dialysis (year)	Continuous	598		30.8 (SD 31)	578		28.9 (SD 29.2)		
Gender-Female	Dichotomous	598	235	(39.3%)	578	233	(40.3%)		

	Gender-Male	Dichotomous	598	220	(36.8%)	578	239	(41.3%)		
	Age	Continuous	598		73.1 (SD 5.7)	578		73.7 (SD 6.2)		
	Number Diabetic	Dichotomous	598	251	(42.0%)	578	255	(44.1%)		
	<65 years Demographics: History of dialysis (year)	Continuous	455		45 (SD 44.1)	472		44.7 (SD 45.3)		
	Gender-Female	Dichotomous	455	244	(53.6%)	472	248	(52.5%)		
	Gender-Male	Dichotomous	455	354	(77.8%)	472	330	(69.9%)		
	Age	Continuous	455		49.8 (SD 10.1)	472		49 (SD 10.5)		
	Number Diabetic	Dichotomous	455	281	(61.8%)	472	269	(57.0%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Sevelamer hydrochloride **N:** 1053 Mean daily dose (mg): 6900 **Drug:** Calcium Based Binders **N:** 1050 Notes: Calcium Acetate - n=735, average dose 5300mg Calcium Carbonate - n= 315, average dose 4900mg
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Not stated **Rescue Binder use permitted:** No details given **Were other medications allowed:** **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** - **Follow-up (d):** 1369 **Protocol-specified reasons for withdrawal:** Binder use: Failure to use allocated binder for 5 consecutive weeks or 20 weeks in total
Location	**Country:** USA

Outcomes measures and effect sizes			Sevelamer			Calcium Based Biinders				
			N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 44mo		Dichotomous	1053	502	(47.7%)	1050	533	(50.8%)		
Withdrawal (AEs) – 44mo		Dichotomous	1053	81	(7.7%)	1050	50	(4.8%)		
Biochemical Data: Serum Ca (mmol/L) – 44mo		Mean value over whole trial period	843		2.3 (SD 0.18)	835		2.38 (SD 0.18)		
Serum Phosphate (mmol/L) – 44mo		Mean value over whole trial period	843		1.87 (SD 0.42)	835		1.84 (SD 0.42)		
Adverse Events: Constipation – 44mo		Dichotomous	1053	1	(0.1%)	1050	0	(0.0%)		
Nausea & Vomiting – 44mo		Dichotomous	1053	1	(0.1%)	1050	1	(0.1%)		
Nausea OR vomiting – 44mo		Dichotomous	1053	1	(0.1%)	1050	1	(0.1%)		
Mortality: All cause mortality – 44mo		Time-to-event	1053			1050			HR=0.930 (CI: 0.790, 1.095)	
Cardiovascular Mortality – 44mo		Time-to-event	1053			1050			HR=0.930 (CI: 0.740, 1.169)	
>65 years Mortality: All cause mortality – 44mo		Time-to-event	1053			1050			HR=0.770 (CI: 0.610, 0.972)	
Cardiovascular Mortality – 44mo		Time-to-event	1053			1050			HR=1.180 (CI: 0.910, 1.530)	
<65 years Mortality: All cause mortality – 44mo		Time-to-event	1053			1050			HR=0.780 (CI: 0.580, 1.049)	
Cardiovascular Mortality – 44mo		Time-to-event	1053			1050			HR=1.190 (CI: 0.820, 1.727)	
Authors' conclusion										
Source of funding										
Comments										

Tzanakis et al. (2008) – evidence table

Bibliographic reference	Tzanakis,I.P., Papadaki,A.N., Wei,M., Kagia,S., Spadidakis,V.V., Kallivretakis,N.E. Magnesium carbonate for phosphate control in patients on hemodialysis. A randomized controlled trial. International Urology & Nephrology 2008;40(1):193-201.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** no Notes: 4 of the participants refused to take Magnesium Carbonate and were therefore kept on their original treatment of Calcium Carbonate
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Over 18 years of age **Washout phosphate level (mmol/L):** >1.87 **Exclusions:** Significant Unstable Medical conditions Severe Hyperparathyroidism Previous parthyroidectomy, diseases resulting diarrhea **Baseline characteristics:**
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.78 **Lower serum PO4 limit:** - **Upper serum Ca limit:** 2.62 **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Magnesium Carbonate **N:** 26 Mean daily dose (mg): 1690 Dose varied to maintain patients within study endpoints: The dose was varied to maintain the serum phosphorus within the study endpoint **Drug:** Calcium Carbonate **N:** 25

		Magnesium Carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	25		2.35 (SD 0.13)	21		2.28 (SD 0.11)		
Serum Phosphate (mmol/L) – 0mo	Continuous	25		2.14 (SD 0.28)	21		2.12 (SD 0.28)		
Demographics: Age	Continuous	26		63.23 (SD 12.19)	25		65.32 (SD 11.68)		

	Mean daily dose (mg): 2608 Dose varied to maintain patients within study endpoints: The dose was varied to maintain the serum phosphorus within the study endpoint
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** No **Rescue Binder use permitted:** No **Were other medications allowed:** No details provided **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No (Dialystate was maintained at 1.5mmol/L)
Length of follow up	**Washout period (d):** 28 **Follow-up (d):** 182 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Greece

Outcomes measures and effect sizes

		Magnesium Carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 6mo	Dichotomous	26	3	(11.5%)	25	5	(20.0%)		
Withdrawal (AEs) – 6mo	Dichotomous	26	2	(7.7%)	25	1	(4.0%)		
Biochemical Data:									
Achieved phosphate control – 6mo	Dichotomous	23	17	(73.9%)	20	13	(65.0%)		
Serum Ca (mmol/L) – 6mo	Continuous	25		2.23 (SD 0.14)	21		2.42 (SD 0.1)		
Serum Phosphate (mmol/L) – 6mo	Continuous	25		1.65 (SD 0.23)	21		1.7 (SD 0.24)		
Proportion with hypercalcaemia – 6mo	Dichotomous	23	6	(26.1%)	21	15	(71.4%)		

Authors' conclusion	
Source of funding	
Comments	

Tzanakis et al. (2014) – evidence table

Bibliographic reference	Tzanakis, Ioannis P, Stamataki, Elisavet E, Papadaki, Antonia N, Giannakis, Nektarios, Damianakis, Nikolaos E. Magnesium retards the progress of the arterial calcifications in hemodialysis patients: a pilot study. International urology and nephrology 2014;46(11):2199-05.
Study type & aim	**Blinded:** yes (double-blind)

	Crossover trial: no **Multicentre:** no
Number and characteristics of patients	**Gender:** Male and Female **Age range:** >18 years **Washout phosphate level (mmol/L):** Additional notes: Phosphate level was not reported at washout. **Exclusions:** Bowel dysfunction Cancer Severe Hyperparathyroidism parathyroidectomy **Baseline characteristics:**
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.77 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Calcium Acetate+Magnesium Carbonate **N:** 32 Mean daily dose (mg): 715 (SD: 240) Dose varied to maintain patients within study endpoints: The starting dose was three tablets daily; the dose was adjusted thereafter according to serum phosphate values, weekly for the first month and then monthly. The dosage of the drugs was increased by one or two tablets per meal as required to achieve the of serum phosphate target level of <=1.77 mmol/l. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Notes: The average dose refers to the daily ingested elemental calcium. **Drug:** Calcium acetate

		Calcium acetate+Magnesium carbonate			Calcium acetate				
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**	**p**
Demographics: Gender-Male	Dichotomous	32	20	(62.5%)	27	17	(63.0%)		
Age	Continuous	32		66.71 (SD 12.03)	27		68.56 (SD 11.58)		
History of dialysis (months)	Continuous	32		40 (SD 49)	27		37 (SD 56)		

	N: 27 Mean daily dose (mg): 866 (SD: 250) Dose varied to maintain patients within study endpoints: The starting dose was three tablets daily; the dose was adjusted thereafter according to serum phosphate values, weekly for the first month and then monthly. The dosage of the drugs was increased by one or two tablets per meal as required to achieve the of serum phosphate target level of <=1.77 mmol/l. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Notes: The average dose refers to the daily ingested elemental calcium.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details **Rescue Binder use permitted:** Yes - different to allocation **Were other medications allowed:** No details provided **Changes to diet allowed:** No **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 365 **Protocol-specified reasons for withdrawal:** If severe hypermagnesemia persisted for more than 3 weeks, the administration of calcium acetate/magnesium carbonate was stopped, and the patient dropped out from the study. The same approach was used if persisted or recurrent diarrhea occurred.
Location	**Country:** Greece
Outcomes measures and effect sizes	
Authors' conclusion	
Source of funding	
Comments	

Wada et al. (2015) – evidence table

Bibliographic reference	Wada K., Wada Y., Uchida H.A. Effects of lanthanum carbonate versus calcium carbonate on vascular stiffness and bone mineral metabolism in hemodialysis patients with type 2 diabetes mellitus: A randomized controlled trial. International Journal of Nephrology and Renovascular Disease 2015;8():111-18. Related publications Wada, Kentaro and Wada, Yuko (2014) Evaluation of aortic calcification with lanthanum carbonate vs. calcium-based phosphate binders in maintenance hemodialysis patients with type 2 diabetes mellitus: an open-label randomized controlled trial. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 18(4): 353-60
Study type & aim	**Blinded:** yes (single-blind) **Crossover trial:** no **Multicentre:** no Notes: Outcome assessors were blinded to treatment allocation and patient demographics.

Number and characteristics of patients

Gender: Male and Female

Age range: >20 years

Washout phosphate level (mmol/L):

Additional notes: Phosphate levels were not reported at washout.

Exclusions:

Serum Ca (Hypocalcemia (adjusted serum calcium level <1.87 mmol/l).)

Diabetes or poorly controlled diabetes

Hypertension or poorly controlled hypertension

Significant GI disease

High risk of bleeding, elevated serum transaminase levels (>3 times the normal upper limits for aspartate aminotransferase or alanine aminotransferase), severe cardiovascular complications, contraindications for intervention therapy, extended duration or nighttime haemodialysis, scheduled for parathyroidectomy, having undergone renal transplant within 6 months of enrollment, or having a life expectancy of <3 months.

Baseline characteristics:

		Lanthanum carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo[a]	Continuous	19		2.132 (SD 0.178)	22		2.212 (SD 0.212)		
Serum Phosphate (mmol/L) – 0mo[a]	Continuous	19		1.641 (SD 0.433)	22		1.657 (SD 0.472)		
Serum iPTH (pmmol/L) – 0mo[a]	Continuous	19		med: 18.749 [rng 8.081–27.651]	22		med: 19.385 [rng 5.207–31.729]		
Adverse Events: Bone-mass density – 0mo[b]	Continuous	19		med: 1.02 [rng 0.93–1.1]	22		med: 0.98 [rng 0.88–1.06]		
Coronary: Aortic calcification index – 0mo[c]	Continuous	19		med: 0.48 [rng 0.16–0.78]	22		med: 0.55 [rng 0.2–0.72]		
Demographics: History of dialysis (year)	Continuous	21		5.13 (SD 4.28)	22		5.26 (SD 3.72)		
Gender-Female	Dichotomous	21	5	(23.8%)	22	3	(13.6%)		
Gender-Male	Dichotomous	21	16	(76.2%)	22	19	(86.4%)		
Age	Continuous	21		65.57 (SD 10.24)	22		65.77 (SD 8.47)		

[a] *Wada 2015*
[b] *Wada 2015; g/cm2*
[c] *Wada 2014*

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.77 **Lower serum PO4 limit:** 1.45 **Upper serum Ca limit:** 2.62 **Lower serum Ca limit:** 2.12
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 19 Mean daily dose (mg): 2060 (SD: 280) Dose varied to maintain patients within study endpoints: Dose titrations every 2 weeks for the first 6 weeks to achieve normalization of serum phosphate (1.45 - 1.77 mmol/l) and corrected calcium levels (2.12 - 2.62 mmol/l). Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Serum calcium was calculated from mg/dl to mmol/l by GUT (/4). **Drug:** Calcium Carbonate **N:** 22 Mean daily dose (mg): 2640 (SD: 530) Dose varied to maintain patients within study endpoints: Dose titrations every 2 weeks for the first 6 weeks to achieve normalization of serum phosphate (1.45 - 1.77 mmol/l) and corrected calcium levels (2.12 - 2.62 mmol/l). Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (Administered per usual care and optimal management of chronic kidney disease - mineral bone disorder.) **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Agiotensin receptor blocker, calcium channel blocker, statin.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 730 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** Japan

Outcomes measures and effect sizes

		Lanthanum carbonate			Calcium carbonate			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 24mo	Dichotomous	21	2	(9.5%)	22	0	(0.0%)		
Withdrawal (AEs) – 24mo	Dichotomous	21	0	(0.0%)	22	0	(0.0%)		
Biochemical Data: Serum Ca (mmol/L) – 6mo[a]	Continuous	19		2.058 (SD 0.17)	22		2.118 (SD 0.21)		

Serum Ca (mmol/L) – 12mo[a]	Continuous	19		2.115 (SD 0.152)	22		2.165 (SD 0.23)		
Serum Ca (mmol/L) – 24mo[b]	Continuous	19		2.11 (SD 0.1)	22		2.202 (SD 0.208)		
Serum Phosphate (mmol/L) – 6mo[a]	Continuous	19		1.919 (SD 0.543)	22		1.66 (SD 0.601)		
Serum Phosphate (mmol/L) – 12mo[a]	Continuous	19		1.718 (SD 0.443)	22		1.628 (SD 0.517)		
Serum Phosphate (mmol/L) – 24mo[b]	Continuous	19		1.466 (SD 0.262)	22		1.586 (SD 0.375)		
Serum iPTH (pmmol/L) – 6mo[a]	Continuous	19		med: 20.53 [rng 9.417–32.747]	22		med: 24.974 [rng 10.021–35.408]		
Serum iPTH (pmmol/L) – 12mo[a]	Continuous	19		med: 21.707 [rng 9.502–40.88]	22		med: 26.458 [rng 5.143–45.843]		
Serum iPTH (pmmol/L) – 24mo[b]	Continuous	19		med: 22.948 [rng 16.31–33.128]	22		med: 29.29 [rng 12.333–40.711]		
Adverse Events:									
Bone-mass density – 24mo[c]	Continuous	19		med: 0.95 [rng 0.93–1.06]	22		med: 0.99 [rng 0.9–1.04]		
Bone-mass density – 24mo[b]	Percentage change from baseline	19		med: -2	22		med: -1		
Coronary:									
Aortic calcification index – 12mo[a]	Continuous	19		med: 0.59 [rng 0.23–0.87]	22		med: 0.61 [rng 0.23–0.78]		
Aortic calcification index – 12mo[a]	Percentage change from baseline	19		med: 12.96	22		med: 15.72		
Mortality:									
All cause mortality – 12mo[a]	Dichotomous	21	2	(9.5%)	22	0	(0.0%)		
Treatment:									
Compliance – 0mo	Dichotomous	19			22				
Compliance – 24mo[b]	Continuous	21		91.8 (SD 8.8)	22		70.3 (SD 19.6)		

[a] *Wada 2014*
[b] *Wada 2015*
[c] *Wada 2015; g/cm2*
Aortic calcification index (ACI) results were also reported by baseline ACI <=0.48 and >0.48.

	For estimation of treatment adherence, the self-reported adherence score and the visual analog score were used to evaluate the subjects' compliant behaviors in the last 4 weeks.
Authors' conclusion	
Source of funding	
Comments	

Wang et al. (2015) – evidence table

Bibliographic reference	Wang XH, Zhang X, Mu CJ, He Y, Peng QP, Yang GS, et al. Effects of lanthanum carbonate on vascular calcification in elderly maintenance hemodialysis patients. Journal of Huazhong University of Science and Technology. Medical sciences = Hua zhong ke ji da xue xue bao. Yi xue Ying De wen ban = Huazhong keji daxue xuebao. Yixue Yingdewen ban 2015;35(4):508-13.
Study type & aim	**Blinded:** yes () **Crossover trial:** no **Multicentre:** no Notes: Radiologists were blinded.
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Age =60 years **Washout phosphate level (mmol/L):** >1.78 **Exclusions:** Serum Ca (>2.60 or <2.10 mmol/L) Heart Failure Bowel dysfunction Cancer Severe Hyperparathyroidism HIV positive Previous history of gastrointestinal surgery, active peptic ulcer, or gastrointestinal bleeding within 6 months; serum transaminases or bilirubin levels >2.5-fold the upper normal limit; known allergy to lanthanum, or exposure to other experimental drugs within 30 days before screening or who were pregnant or lactating were excluded from the study. **Baseline characteristics:**

		Lanthanum carbonate			No treatment			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0mo	Continuous	27		2.37 (SD 0.21)	26		2.25 (SD 0.12)		
Serum Phosphate (mmol/L) – 0mo	Continuous	27		2.35 (SD 0.29)	26		2.52 (SD 0.25)		
Serum iPTH (pmmol/L) – 0mo	Continuous	27		0.517 (SD 0.173)	26		0.5 (SD 0.184)		

	Coronary: Abdominal aortic calcification – 0mo	Continuous	27		15.12 (SD 5.15)	26		15.75 (SD 5.74)		
	Demographics: History of dialysis (year)	Continuous	27		2.8 (SD 1.2)	26		3.2 (SD 1.3)		
	Gender-Female	Dichotomous	27	12	(44.4%)	26	11	(42.3%)		
	Gender-Male	Dichotomous	27	16	(59.3%)	26	15	(57.7%)		
	Age	Continuous	27		68.87 (SD 9.62)	26		69.93 (SD 10.86)		
	Number Diabetic	Dichotomous	27	5	(18.5%)	26	5	(19.2%)		
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** - **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -									
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 27 Fixed daily dose (mg): 1500 Notes: 500 mg taken three times per day **Drug:** No treatment **N:** 26 Notes: 'No treatment' arm received a control diet (phosphorus intake 800–1000 mg/day).									
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Conventional antihypertensive drugs, iron, and erythropoietin injection.) **Changes to diet allowed:** No details given **Changes to dialysate allowed:** No details given									
Length of follow up	**Washout period (d):** - **Follow-up (d):** 90 **Protocol-specified reasons for withdrawal:** none specified									
Location	**Country:** China									

Outcomes measures and effect sizes			Lanthanum carbonate			No treatment			Δ	p
			N	k	mean	N	k	mean		
	Disposition: Withdrawal (AEs) – 3mo	Dichotomous	28	1	(3.6%)	26	0	(0.0%)		
	Biochemical Data: Serum Ca (mmol/L) – 3mo	Continuous	27		2.35 (SD 0.15)	26		2.33 (SD 0.17)		
	Serum Phosphate (mmol/L) – 3mo	Continuous	27		1.7 (SD 0.17)	26		1.93 (SD 0.05)		
	Serum iPTH (pmmol/L) – 3mo	Continuous	27		0.29 (SD 0.179)	26		0.629 (SD 0.196)		
	Coronary: Abdominal aortic calcification – 3mo	Continuous	27		14.44 (SD 4.84)	26		14.81 (SD 4.05)		
Authors' conclusion										
Source of funding										
Comments										

Wilson et al. (2009) – evidence table

Bibliographic reference	Wilson,R., Zhang,P., Smyth,M. Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. Current Medical Research & Opinion 2009;25(12):3021-28.
Study type & aim	**Blinded:** no **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18 years and older **Washout phosphate level (mmol/L):** >1.9 **Exclusions:** Serum Ca (<1.98mmol/L at screening) **Baseline characteristics:**

			Lanthanam			any binder				
			N	k	mean	N	k	mean	Δ	p
Demographics:										
History of dialysis (year)	Continuous	680		3.4 (SD 3.4)	674		3.3 (SD 3.2)		
Gender-Female	Dichotomous	680	291	(42.8%)	674	260	(38.6%)		
Gender-Male	Dichotomous	680	389	(57.2%)	674	414	(61.4%)		
Age	Continuous	680		53.8 (SD 14.5)	674		54.9 (SD 14.4)		
Number Diabetic	Dichotomous	680	234	(34.4%)	674	233	(34.6%)		
>65 years Demographics:										
History of dialysis (year)	Continuous	163		3.2 (SD 22.7)	173		2.9 (SD 2.7)		
Gender-Female	Dichotomous	163	77	(47.2%)	173	67	(38.7%)		
Gender-Male	Dichotomous	163	86	(52.8%)	173	106	(61.3%)		
Age	Continuous	163		72.6 (SD 5)	173		73.1 (SD 5.5)		
Number Diabetic	Dichotomous	163	63	(38.7%)	173	66	(38.2%)		

Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.9 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 680 Dose varied to maintain patients within study endpoints: Yes- no further details provided **Drug:** Any binder **N:** 674 Dose varied to maintain patients within study endpoints: No details provided
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - but no further details **Rescue Binder use permitted:** No **Were other medications allowed:** Yes (Calcium supplements allowed at night time in the Lanthanam group) **Changes to diet allowed:** No details given

	Changes to dialysate allowed: No details given
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 970 **Protocol-specified reasons for withdrawal:** none specified
Location	**Country:** USA, Puerto Rico, Poland and South Africa

Outcomes measures and effect sizes

		Lanthanam			any binder				
		N	k	mean	N	k	mean	Δ	p
Mortality: All cause mortality – 40mo	Time-to-event	680			674			HR=0.860 (CI: 0.684, 1.081)	
All cause mortality – 40mo	Time-to-event							HR=0.860 (CI: 0.684, 1.081)	
>65 years Mortality: All cause mortality – 40mo	Time-to-event	163			173			HR=0.680 (CI: 0.460, 1.005)	
All cause mortality – 40mo	Time-to-event							HR=0.680 (CI: 0.460, 1.005)	
<65 years Mortality: All cause mortality – 40mo	Time-to-event	517			501			HR=1.000 (CI: 0.750, 1.333)	
All cause mortality – 40mo	Time-to-event							HR=1.000 (CI: 0.750, 1.333)	

Authors' conclusion	
Source of funding	
Comments	

Wuthrich et al. (2013) – evidence table

Bibliographic reference	Wuthrich, Rudolf P, Chonchol, Michel, Covic, Adrian, Gaillard, Sylvain, Chong, Edward. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. Clinical journal of the American Society of Nephrology : CJASN 2013;8(2):280-9.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no

Multicentre: yes

Number and characteristics of patients

Gender: Male and Female

Age range: >=18 years

Washout phosphate level (mmol/L): >1.77

Additional notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323).

Exclusions:

Serum Ca (hypercalcemia (serum calcium >2.5 mmol/l) or hypocalcemia (serum calcium <1.9 mmol/l) at screening or during washout.

Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).)

Uncontrolled hyperphosphatemia (serum phosphorus >2.48 mmol/l) at screening, iPTH >600 ng/L at screening, iron deficiency anemia (hemoglobin <10 g/dl) in combination with either serum ferritin <100 ng/ml or transferrin saturation <20% at screening, a history of hemochromatosis or other iron storage disorders, use of oral iron preparations within 1 month before screening, and a history of nonresponse to phosphate binders.

Baseline characteristics:

		Sucroferric oxyhydroxide 1.25 g/day			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	26		2.132 (SD 0.17)	26		2.142 (SD 0.142)		
Serum Phosphate (mmol/L) – 0wk	Continuous	26		2.203 (SD 0.53)	26		2.242 (SD 0.52)		
Serum iPTH (pmmol/L) – 0wk	Continuous	26		25.239 (SD 20.043)	26		27.784 (SD 15.27)		
Demographics: Gender-Male	Dichotomous	26	17	(65.4%)	26	14	(53.8%)		
Age	Continuous	26		60.1 (SD 12.3)	26		61.6 (SD 11.2)		
Number Diabetic	Dichotomous	26	8	(30.8%)	26	9	(34.6%)		

		Sucroferric oxyhydroxide 5.0 g/day			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	26		2.138 (SD 0.178)	26		2.142 (SD 0.142)		

Serum Phosphate (mmol/L) – 0wk	Continuous	26		2.135 (SD 0.349)	26		2.242 (SD 0.52)		
Serum iPTH (pmmol/L) – 0wk	Continuous	26		24.178 (SD 18.134)	26		27.784 (SD 15.27)		
Demographics: Gender-Male	Dichotomous	26	19	(73.1%)	26	14	(53.8%)		
Age	Continuous	26		59.7 (SD 13.8)	26		61.6 (SD 11.2)		
Number Diabetic	Dichotomous	26	7	(26.9%)	26	9	(34.6%)		

		Sucroferric oxyhydroxide 7.5 g/day			Sevelamer hydrochloride				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	25		2.158 (SD 0.108)	26		2.142 (SD 0.142)		
Serum Phosphate (mmol/L) – 0wk	Continuous	25		2.213 (SD 0.371)	26		2.242 (SD 0.52)		
Serum iPTH (pmmol/L) – 0wk	Continuous	25		28.844 (SD 15.695)	26		27.784 (SD 15.27)		
Demographics: Gender-Male	Dichotomous	25	16	(64.0%)	26	14	(53.8%)		
Age	Continuous	25		61.9 (SD 13.7)	26		61.6 (SD 11.2)		
Number Diabetic	Dichotomous	25	9	(36.0%)	26	9	(34.6%)		

		Sucroferric oxyhydroxide 10.0 g/day			Sevelamer hydrochloride				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	27		2.098 (SD 0.21)	26		2.142 (SD 0.142)		
Serum Phosphate (mmol/L) – 0wk	Continuous	27		2.187 (SD 0.565)	26		2.242 (SD 0.52)		

Serum iPTH (pmmol/L) – 0wk	Continuous	27		25.981 (SD 14.74)	26		27.784 (SD 15.27)		
Demographics: Gender-Male	Dichotomous	27	15	(55.6%)	26	14	(53.8%)		
Age	Continuous	27		60.8 (SD 13.2)	26		61.6 (SD 11.2)		
Number Diabetic	Dichotomous	27	7	(25.9%)	26	9	(34.6%)		

		Sucroferric oxyhydroxide 12.5 g/day			Sevelamer hydrochloride				
		N	k	mean	N	k	mean	Δ	p
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	24		2.135 (SD 0.14)	26		2.142 (SD 0.142)		
Serum Phosphate (mmol/L) – 0wk	Continuous	24		2.09 (SD 0.384)	26		2.242 (SD 0.52)		
Serum iPTH (pmmol/L) – 0wk	Continuous	24		23.542 (SD 16.119)	26		27.784 (SD 15.27)		
Demographics: Gender-Male	Dichotomous	24	13	(54.2%)	26	14	(53.8%)		
Age	Continuous	24		59.3 (SD 12.3)	26		61.6 (SD 11.2)		
Number Diabetic	Dichotomous	24	9	(37.5%)	26	9	(34.6%)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.77
Lower serum PO4 limit: 1.13
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Sucroferric oxyhydroxide
N: 26
Fixed daily dose (mg): 1.25
Drug: Sucroferric oxyhydroxide
N: 26

	Fixed daily dose (mg): 5 **Drug:** Sucroferric oxyhydroxide **N:** 25 Fixed daily dose (mg): 7.5 **Drug:** Sucroferric oxyhydroxide **N:** 27 Fixed daily dose (mg): 10 **Drug:** Sucroferric oxyhydroxide **N:** 24 Fixed daily dose (mg): 12.5 **Drug:** Sevelamer hydrochloride **N:** 26 Fixed daily dose (mg): 4.8
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (calcimimetics, erythropoiesis stimulating agent) **Changes to diet allowed:** No **Changes to dialysate allowed:** No details given
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 42 **Protocol-specified reasons for withdrawal:** Serum phosphate: Hyperphosphatemia (serum phosphate >2.74 mmol/l) at any time after 2 weeks of treatment, hypophosphatemia (serum phosphate <1.13 mmol/l) at any time after start of treatment. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Serum Ca: Hypercalcemia (serum calcium >2.5 mmol/l) at any time after the washout period. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).
Location	**Country:** Eight European countries and the US

Outcomes measures and effect sizes

		Sucroferric oxyhydroxide 1.25 g/day			Sevelamer hydrochloride				
		N	k	mean	N	k	mean	Δ	p
Disposition: Withdrawal (total) – 6wk	Dichotomous	26	8	(30.8%)	26	8	(30.8%)		
Withdrawal (AEs) – 6wk	Dichotomous	26	5	(19.2%)	26	6	(23.1%)		
Biochemical Data: Achieved phosphate control – 6wk	Dichotomous	19	4	(21.1%)	19	8	(42.1%)		

Serum Ca (mmol/L) – 6wk	Mean change	26		-0.058 (SD 0.305)	24		0.062 (SD 0.142)		
Serum Ca (mmol/L) – 6wk	Continuous	26		2.075 (SD 0.305)	26		2.212 (SD 0.142)		
Serum Phosphate (mmol/L) – 6wk	Mean change	26		-0.042 (SD 0.649)	24		-0.342 (SD 0.436)		
Serum Phosphate (mmol/L) – 6wk	Continuous	26		2.161 (SD 0.662)	26		1.899 (SD 0.475)		
Serum iPTH (pmmol/L) – 6wk	Mean change	26		0.742 (SD 7.317)	24		-4.136 (SD 8.484)		
Serum iPTH (pmmol/L) – 6wk	Continuous	26		26.087 (SD 20.255)	26		23.86 (SD 14.528)		
Adverse Events:									
Constipation – 6wk	Dichotomous	26	0	(0.0%)	26	0	(0.0%)		
Diarrhea – 6wk	Dichotomous	26	1	(3.8%)	26	3	(11.5%)		
Nausea OR vomiting – 6wk	Dichotomous	26	0	(0.0%)	26	1	(3.8%)		
Vomiting – 6wk	Dichotomous	26	0	(0.0%)	26	1	(3.8%)		
Feces discolored – 6wk	Dichotomous	26	2	(7.7%)	26	0	(0.0%)		
Hyperphosphatemia – 6wk	Dichotomous	26	5	(19.2%)	26	2	(7.7%)		
Hypertension – 6wk	Dichotomous	26	1	(3.8%)	26	1	(3.8%)		
Pain in extremity – 6wk	Dichotomous	26	1	(3.8%)	26	1	(3.8%)		
Hypophosphatemia – 6wk	Dichotomous	26	2	(7.7%)	26	3	(11.5%)		
Hypercalcemia – 6wk	Dichotomous	26	2	(7.7%)	26	2	(7.7%)		
Muscle spasms – 6wk	Dichotomous	26	1	(3.8%)	26	0	(0.0%)		
Hypotension – 6wk	Dichotomous	26	0	(0.0%)	26	3	(11.5%)		
Anemia – 6wk	Dichotomous	26	0	(0.0%)	26	0	(0.0%)		
Mortality:									
All cause mortality – 6wk	Dichotomous	26	0	(0.0%)	26	0	(0.0%)		

		Sucroferric oxyhydroxide 5.0 g/day			Sevelamer hydrochloride				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 6wk	Dichotomous	26	9	(34.6%)	26	8	(30.8%)		

Withdrawal (AEs) – 6wk	Dichotomous	26	5	(19.2%)	26	6	(23.1%)		
Biochemical Data:									
Achieved phosphate control – 6wk	Dichotomous	17	7	(41.2%)	19	8	(42.1%)		
Serum Ca (mmol/L) – 6wk	Mean change	26		0.03 (SD 0.2)	24		0.062 (SD 0.142)		
Serum Ca (mmol/L) – 6wk	Continuous	26		2.168 (SD 0.23)	26		2.212 (SD 0.142)		
Serum Phosphate (mmol/L) – 6wk	Mean change	26		-0.349 (SD 0.685)	24		-0.342 (SD 0.436)		
Serum Phosphate (mmol/L) – 6wk	Continuous	26		1.786 (SD 0.627)	26		1.899 (SD 0.475)		
Serum iPTH (pmmol/L) – 6wk	Mean change	26		-1.166 (SD 13.574)	24		-4.136 (SD 8.484)		
Serum iPTH (pmmol/L) – 6wk	Continuous	26		23.012 (SD 17.497)	26		23.86 (SD 14.528)		
Adverse Events:									
Constipation – 6wk	Dichotomous	26	1	(3.8%)	26	0	(0.0%)		
Diarrhea – 6wk	Dichotomous	26	2	(7.7%)	26	3	(11.5%)		
Nausea OR vomiting – 6wk	Dichotomous	26	2	(7.7%)	26	1	(3.8%)		
Vomiting – 6wk	Dichotomous	26	2	(7.7%)	26	1	(3.8%)		
Feces discolored – 6wk	Dichotomous	26	3	(11.5%)	26	0	(0.0%)		
Hyperphosphatemia – 6wk	Dichotomous	26	3	(11.5%)	26	2	(7.7%)		
Hypertension – 6wk	Dichotomous	26	0	(0.0%)	26	1	(3.8%)		
Pain in extremity – 6wk	Dichotomous	26	1	(3.8%)	26	1	(3.8%)		
Hypophosphatemia – 6wk	Dichotomous	26	4	(15.4%)	26	3	(11.5%)		
Hypercalcemia – 6wk	Dichotomous	26	2	(7.7%)	26	2	(7.7%)		
Muscle spasms – 6wk	Dichotomous	26	1	(3.8%)	26	0	(0.0%)		
Hypotension – 6wk	Dichotomous	26	1	(3.8%)	26	3	(11.5%)		
Anemia – 6wk	Dichotomous	26	0	(0.0%)	26	0	(0.0%)		
Mortality:									
All cause mortality – 6wk	Dichotomous	26	1	(3.8%)	26	0	(0.0%)		

		Sucroferric oxyhydroxide 7.5 g/day			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 6wk	Dichotomous	25	5	(20.0%)	26	8	(30.8%)		
Withdrawal (AEs) – 6wk	Dichotomous	25	4	(16.0%)	26	6	(23.1%)		
Biochemical Data:									
Achieved phosphate control – 6wk	Dichotomous	20	7	(35.0%)	19	8	(42.1%)		
Serum Ca (mmol/L) – 6wk	Mean change	25		0.04 (SD 0.15)	24		0.062 (SD 0.142)		
Serum Ca (mmol/L) – 6wk	Continuous	25		2.198 (SD 0.148)	26		2.212 (SD 0.142)		
Serum Phosphate (mmol/L) – 6wk	Mean change	25		-0.404 (SD 0.391)	24		-0.342 (SD 0.436)		
Serum Phosphate (mmol/L) – 6wk	Continuous	25		1.809 (SD 0.381)	26		1.899 (SD 0.475)		
Serum iPTH (pmmol/L) – 6wk	Mean change	25		0 (SD 15.058)	24		-4.136 (SD 8.484)		
Serum iPTH (pmmol/L) – 6wk	Continuous	25		28.844 (SD 20.891)	26		23.86 (SD 14.528)		
Adverse Events:									
Constipation – 6wk	Dichotomous	25	1	(4.0%)	26	0	(0.0%)		
Diarrhea – 6wk	Dichotomous	25	2	(8.0%)	26	3	(11.5%)		
Nausea OR vomiting – 6wk	Dichotomous	25	0	(0.0%)	26	1	(3.8%)		
Vomiting – 6wk	Dichotomous	25	0	(0.0%)	26	1	(3.8%)		
Feces discolored – 6wk	Dichotomous	25	3	(12.0%)	26	0	(0.0%)		
Hyperphosphatemia – 6wk	Dichotomous	25	1	(4.0%)	26	2	(7.7%)		
Hypertension – 6wk	Dichotomous	25	2	(8.0%)	26	1	(3.8%)		
Pain in extremity – 6wk	Dichotomous	25	1	(4.0%)	26	1	(3.8%)		
Hypophosphatemia – 6wk	Dichotomous	25	2	(8.0%)	26	3	(11.5%)		
Hypercalcemia – 6wk	Dichotomous	25	1	(4.0%)	26	2	(7.7%)		
Muscle spasms – 6wk	Dichotomous	25	2	(8.0%)	26	0	(0.0%)		
Hypotension – 6wk	Dichotomous	25	0	(0.0%)	26	3	(11.5%)		
Anemia – 6wk	Dichotomous	25	3	(12.0%)	26	0	(0.0%)		
Mortality:									
All cause mortality – 6wk	Dichotomous	25	0	(0.0%)	26	0	(0.0%)		

		Sucroferric oxyhydroxide 10.0 g/day			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 6wk	Dichotomous	27	12	(44.4%)	26	8	(30.8%)		
Withdrawal (AEs) – 6wk	Dichotomous	27	8	(29.6%)	26	6	(23.1%)		
Biochemical Data:									
Achieved phosphate control – 6wk	Dichotomous	14	6	(42.9%)	19	8	(42.1%)		
Serum Ca (mmol/L) – 6wk	Mean change	25		0.025 (SD 0.24)	24		0.062 (SD 0.142)		
Serum Ca (mmol/L) – 6wk	Continuous	27		2.122 (SD 0.308)	26		2.212 (SD 0.142)		
Serum Phosphate (mmol/L) – 6wk	Mean change	25		-0.646 (SD 0.552)	24		-0.342 (SD 0.436)		
Serum Phosphate (mmol/L) – 6wk	Continuous	27		1.541 (SD 0.62)	26		1.899 (SD 0.475)		
Serum iPTH (pmmol/L) – 6wk	Mean change	25		-2.121 (SD 9.014)	24		-4.136 (SD 8.484)		
Serum iPTH (pmmol/L) – 6wk	Continuous	27		23.86 (SD 16.543)	26		23.86 (SD 14.528)		
Adverse Events:									
Constipation – 6wk	Dichotomous	27	2	(7.4%)	26	0	(0.0%)		
Diarrhea – 6wk	Dichotomous	27	1	(3.7%)	26	3	(11.5%)		
Nausea OR vomiting – 6wk	Dichotomous	27	1	(3.7%)	26	1	(3.8%)		
Vomiting – 6wk	Dichotomous	27	1	(3.7%)	26	1	(3.8%)		
Feces discolored – 6wk	Dichotomous	27	4	(14.8%)	26	0	(0.0%)		
Hyperphosphatemia – 6wk	Dichotomous	27	1	(3.7%)	26	2	(7.7%)		
Hypertension – 6wk	Dichotomous	27	0	(0.0%)	26	1	(3.8%)		
Pain in extremity – 6wk	Dichotomous	27	0	(0.0%)	26	1	(3.8%)		
Hypophosphatemia – 6wk	Dichotomous	27	8	(29.6%)	26	3	(11.5%)		
Hypercalcemia – 6wk	Dichotomous	27	1	(3.7%)	26	2	(7.7%)		
Muscle spasms – 6wk	Dichotomous	27	1	(3.7%)	26	0	(0.0%)		
Hypotension – 6wk	Dichotomous	27	0	(0.0%)	26	3	(11.5%)		

Anemia – 6wk	Dichotomous	27	0	(0.0%)	26	0	(0.0%)		
Mortality: All cause mortality – 6wk	Dichotomous	27	0	(0.0%)	26	0	(0.0%)		

		Sucroferric oxyhydroxide 12.5 g/day			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Disposition: Withdrawal (total) – 6wk	Dichotomous	24	9	(37.5%)	26	8	(30.8%)		
Withdrawal (AEs) – 6wk	Dichotomous	24	5	(20.8%)	26	6	(23.1%)		
Biochemical Data: Achieved phosphate control – 6wk	Dichotomous	15	9	(60.0%)	19	8	(42.1%)		
Serum Ca (mmol/L) – 6wk	Mean change	24		-0.038 (SD 0.22)	24		0.062 (SD 0.142)		
Serum Ca (mmol/L) – 6wk	Continuous	24		2.098 (SD 0.27)	26		2.212 (SD 0.142)		
Serum Phosphate (mmol/L) – 6wk	Mean change	24		-0.546 (SD 0.585)	24		-0.342 (SD 0.436)		
Serum Phosphate (mmol/L) – 6wk	Continuous	24		1.544 (SD 0.539)	26		1.899 (SD 0.475)		
Serum iPTH (pmmol/L) – 6wk	Mean change	24		-6.469 (SD 11.241)	24		-4.136 (SD 8.484)		
Serum iPTH (pmmol/L) – 6wk	Continuous	24		17.179 (SD 9.862)	26		23.86 (SD 14.528)		
Adverse Events: Constipation – 6wk	Dichotomous	24	0	(0.0%)	26	0	(0.0%)		
Diarrhea – 6wk	Dichotomous	24	1	(4.2%)	26	3	(11.5%)		
Nausea OR vomiting – 6wk	Dichotomous	24	0	(0.0%)	26	1	(3.8%)		
Vomiting – 6wk	Dichotomous	24	0	(0.0%)	26	1	(3.8%)		
Feces discolored – 6wk	Dichotomous	24	3	(12.5%)	26	0	(0.0%)		
Hyperphosphatemia – 6wk	Dichotomous	24	0	(0.0%)	26	2	(7.7%)		
Hypertension – 6wk	Dichotomous	24	2	(8.3%)	26	1	(3.8%)		
Pain in extremity – 6wk	Dichotomous	24	0	(0.0%)	26	1	(3.8%)		
Hypophosphatemia – 6wk	Dichotomous	24	7	(29.2%)	26	3	(11.5%)		

	Hypercalcemia – 6wk	Dichotomous	24	1	(4.2%)	26	2	(7.7%)		
	Muscle spasms – 6wk	Dichotomous	24	3	(12.5%)	26	0	(0.0%)		
	Hypotension – 6wk	Dichotomous	24	0	(0.0%)	26	3	(11.5%)		
	Anemia – 6wk	Dichotomous	24	0	(0.0%)	26	0	(0.0%)		
	Mortality: All cause mortality – 6wk	Dichotomous	24	0	(0.0%)	26	0	(0.0%)		
	Compliance was reported for the whole sample receiving sucroferric oxyhydroxide (98%, IQR 95% to 100%); sevelamer (96%, IQR 90% to 99%).									
Authors' conclusion										
Source of funding										
Comments										

Xu et al. (2013) – evidence table

Bibliographic reference	Xu, Jing, Zhang, Yi-Xiang, Yu, Xue-Qing, Liu, Zhi-Hong, Wang, Li-Ning, Chen, Jiang-Hua, et al. Lanthanum carbonate for the treatment of hyperphosphatemia in CKD 5D: multicenter, double blind, randomized, controlled trial in mainland China. BMC nephrology 2013;14():29.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** 18–70 years **Washout phosphate level (mmol/L):** >1.78 **Exclusions:** Serum Ca (hypercalcemia (serum calcium >2.60 mmol/L) or hypocalcemia (serum calcium <2.10 mmol/L).) Heart Failure Cancer Severe Hyperparathyroidism HIV positive Significant GI disease Previous gastrointestinal surgery; serum transaminases or bilirubin >2.5 times the upper limit of normal; known allergy to lanthanum; pregnant or lactating women; exposure to other experimental drugs within 30 days before screening. **Baseline characteristics:**

			Lanthanum carbonate			Placebo				
			N	k	mean	N	k	mean	Δ	p
	Biochemical Data: Serum Phosphate (mmol/L) – 0d	Continuous	114		2.41 (SD 0.5)	113		2.41 (SD 0.5)		
	Demographics: Gender-Female	Dichotomous	114	54	(47.4%)	113	41	(36.3%)		
	Gender-Male	Dichotomous	114	60	(52.6%)	113	72	(63.7%)		
	Age	Continuous	114		47.6 (SD 13)	113		48.4 (SD 11.7)		
	Type of dialysis-Haemodialysis	Dichotomous	114	82	(71.9%)	113	82	(72.6%)		
	Type of dialysis-CAPD	Dichotomous	114	32	(28.1%)	113	31	(27.4%)		
Monitoring information and definitions	**Target ranges:** **Upper serum PO4 limit:** 1.78 **Lower serum PO4 limit:** - **Upper serum Ca limit:** - **Lower serum Ca limit:** -									
Intervention(s)	**Drug:** Lanthanum carbonate **N:** 114 (Range: 1500–3000) Dose varied to maintain patients within study endpoints: Starting daily dose was 1500 mg and could be uptitrated to =3000 mg/d as necessary to achieve and maintain serum phosphate =1.78 mmol/L. The dose was uptitrated one level (500 mg) in hemodialysis or two levels (1000 mg) in continuous ambulatory peritoneal dialys patients at each visit, if the serum phospahte target level had not been achieved. **Drug:** Placebo **N:** 113 Notes: No further details about the placebo arm.									
Concomitant treatments	**Dialysis:** Either Haemodialysis or Peritoneal **Vit D:** Not stated **Rescue Binder use permitted:** No details given **Were other medications allowed:** No details provided **Changes to diet allowed:** Yes (Patients were put on a low-phosphorus diet (800–1000 mg/d) in the study.) **Changes to dialysate allowed:** No details given									
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 56									

	Protocol-specified reasons for withdrawal: Serum phosphate: Phosphate =1.78 mmol/L at the end of week 3 of the washout period were withdrawn from the study. Patients with poor compliance or who failed to take medicine according to the protocol were also excluded.
Location	**Country:** China

Outcomes measures and effect sizes

		Lanthanum carbonate			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 56d	Dichotomous	115	1	(0.9%)	115	2	(1.7%)		
Withdrawal (AEs) – 56d	Dichotomous	115	1	(0.9%)	115	1	(0.9%)		
Biochemical Data:									
Achieved phosphate control – 56d[a]	Dichotomous	114	66	(57.9%)	113	15	(13.3%)		
Serum Ca (mmol/L) – 56d	Mean change	108		0.02 (SD 0.32)	110		-0.02 (SD 0.19)		
Serum Phosphate (mmol/L) – 28d	Continuous	114		1.64 (SD 0.46)	113		1.71 (SD 0.49)		
Serum Phosphate (mmol/L) – 42d	Mean change	113		0.04 (SD 0.52)	113		0.55 (SD 0.63)		
Serum Phosphate (mmol/L) – 42d	Continuous	114		1.67 (SD 0.51)	113		2.26 (SD 0.61)		
Serum Phosphate (mmol/L) – 56d	Mean change	113		0.15 (SD 0.52)	113		0.63 (SD 0.62)		
Serum Phosphate (mmol/L) – 56d	Continuous	114		1.79 (SD 0.63)	113		2.34 (SD 0.56)		
Serum iPTH (pmmol/L) – 56d	Mean change	109		2.078 (SD 19.386)	110		6.005 (SD 14.515)		
Adverse Events:									
Constipation – 4wk	Dichotomous	115	0	(0.0%)	115	1	(0.9%)		
Nausea OR vomiting – 4wk	Dichotomous	115	8	(7.0%)	115	0	(0.0%)		
Nausea – 4wk	Dichotomous	115	8	(7.0%)	115	0	(0.0%)		
Vomiting – 4wk	Dichotomous	115	7	(6.1%)	115	0	(0.0%)		
Anorexia – 4wk	Dichotomous	115	1	(0.9%)	115	0	(0.0%)		
Aggravated itching – 4wk	Dichotomous	115	0	(0.0%)	115	1	(0.9%)		
Treatment:									
Compliance – 4wk[b]	Dichotomous	115	107	(93.0%)	115	109	(94.8%)		

	Peritoneal dialysis Biochemical Data: Serum Phosphate (mmol/L) – 42d	Mean change	32		-0.06 (SD 0.24)	31		0.61 (SD 0.33)		
	Serum Phosphate (mmol/L) – 56d	Mean change	32		0.01 (SD 0.32)	31		0.65 (SD 0.42)		
	Hemodialysis Biochemical Data: Serum Phosphate (mmol/L) – 42d	Mean change	81		0.07 (SD 0.59)	82		0.53 (SD 0.71)		
	Serum Phosphate (mmol/L) – 56d	Mean change	81		0.2 (SD 0.57)	82		0.62 (SD 0.68)		
	[a] *Approximated to nearest integer (percentages only presented in text)* [b] *Approximated to nearest integer (percentages only presented in text; n=115)*									
Authors' conclusion										
Source of funding										
Comments										

Yokoyama et al. (2012) – evidence table

Bibliographic reference	Yokoyama, Keitaro, Hirakata, Hideki, Akiba, Takashi, Sawada, Kenichi. Effect of oral JTT-751 (ferric citrate) on hyperphosphatemia in hemodialysis patients: results of a randomized, double-blind, placebo-controlled trial. American journal of nephrology 2012;36(5):478-87.
Study type & aim	**Blinded:** yes (double-blind) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** Adults **Washout phosphate level (mmol/L):** >1.97, <3.23 Additional notes: Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). **Exclusions:** Serum Ca (Corrected serum calcium level >2.75 mmol/l at week-1. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4).) Liver dysfunction Any complications of gastrointestinal diseases including peptic ulcer, ulcerative colitis and regional enteritis, patients with a history of gastrectomy or duodenectomy, hemochromatosis or a ferritin level >300 ng/ml, patients requiring or undergoing a parathyroidectomy or percutaneous ethanol injection therapy within 24 weeks before week 0 and patients with any complications of advanced heart disease. **Baseline characteristics:**

		Ferric citrate 1.5 g/day			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	49		2.232 (SD 0.155)	48		2.198 (SD 0.18)		
Serum Phosphate (mmol/L) – 0wk	Continuous	49		2.484 (SD 0.413)	48		2.532 (SD 0.388)		
Serum iPTH (pmmol/L) – 0wk	Continuous	49		25.557 (SD 16.649)	48		27.731 (SD 16.225)		
Demographics: History of dialysis (year)	Continuous	49		med: 5 [rng 4–9]	48		med: 6 [rng 4–9]		
Duration of dialysis (min)	Continuous	49		244 (SD 23.5)	48		240.4 (SD 26)		
Gender-Female	Dichotomous	49	19	(38.8%)	48	21	(43.8%)		
Gender-Male	Dichotomous	49	30	(61.2%)	48	27	(56.3%)		
Age	Continuous	49		60.9 (SD 8.9)	48		62.7 (SD 11)		

		Ferric citrate 3 g/day			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	50		2.215 (SD 0.185)	48		2.198 (SD 0.18)		
Serum Phosphate (mmol/L) – 0wk	Continuous	50		2.532 (SD 0.417)	48		2.532 (SD 0.388)		
Serum iPTH (pmmol/L) – 0wk	Continuous	50		27.201 (SD 16.967)	48		27.731 (SD 16.225)		
Demographics: History of dialysis (year)	Continuous	50		med: 5 [rng 3–8]	48		med: 6 [rng 4–9]		
Duration of dialysis (min)	Continuous	50		241.6 (SD 18.7)	48		240.4 (SD 26)		
Gender-Female	Dichotomous	50	18	(36.0%)	48	21	(43.8%)		
Gender-Male	Dichotomous	50	32	(64.0%)	48	27	(56.3%)		
Age	Continuous	50		58.6 (SD 12.3)	48		62.7 (SD 11)		

		Ferric citrate 6 g/day			Placebo			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	45		2.225 (SD 0.162)	48		2.198 (SD 0.18)		
Serum Phosphate (mmol/L) – 0wk	Continuous	45		2.561 (SD 0.452)	48		2.532 (SD 0.388)		
Serum iPTH (pmmol/L) – 0wk	Continuous	45		34.253 (SD 20.891)	48		27.731 (SD 16.225)		
Demographics: History of dialysis (year)	Continuous	45		med: 5 [rng 3–7]	48		med: 6 [rng 4–9]		
Duration of dialysis (min)	Continuous	45		246.7 (SD 27.8)	48		240.4 (SD 26)		
Gender-Female	Dichotomous	45	14	(31.1%)	48	21	(43.8%)		
Gender-Male	Dichotomous	45	31	(68.9%)	48	27	(56.3%)		
Age	Continuous	45		58.1 (SD 10.6)	48		62.7 (SD 11)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.77
Lower serum PO4 limit: -
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Ferric citrate
N: 49
Fixed daily dose (mg): 1.5
Drug: Ferric citrate
N: 50
Fixed daily dose (mg): 3
Drug: Ferric citrate
N: 45
Fixed daily dose (mg): 6
Drug: Placebo

	N: 48 Notes: No further details given for the placebo arm.
Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - not changed during the study **Rescue Binder use permitted:** No details given **Were other medications allowed:** No **Changes to diet allowed:** No **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 21 **Follow-up (d):** 28 **Protocol-specified reasons for withdrawal:** Serum phosphate: <0.96 mmol/l and >3.23 mmol/l for 2 consecutive observation days. Serum phosphate was calculated from mg/dl to mmol/l by GUT (x0.323). Serum Ca: Corrected serum calcium <2.0 mmol/l for 2 consecutive observation days. Serum calcium was calculated from mg/dl to mmol/l by GUT (/4). Serum ferritin of >=800 ng/ml or 50% for each observation day.
Location	**Country:** Japan

Outcomes measures and effect sizes

		Ferric citrate 1.5 g/day			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 4wk	Dichotomous	49	10	(20.4%)	48	13	(27.1%)		
Withdrawal (AEs) – 4wk	Dichotomous	49	0	(0.0%)	48	1	(2.1%)		
Biochemical Data:									
Achieved phosphate control – 4wk[a]	Dichotomous	42	7	(16.7%)	40	1	(2.5%)		
Serum Ca (mmol/L) – 4wk	Mean change	49		0.028	48		0.008		
Serum Phosphate (mmol/L) – 4wk	Mean change	42		-0.413 (SD 0.371)	40		0.013 (SD 0.352)		
Serum Phosphate (mmol/L) – 4wk	Continuous	42		2.109 (SD 0.339)	40		2.506 (SD 0.397)		
Serum iPTH (pmmol/L) – 4wk	Mean change	42		-0.636 (SD -7.317)	40		-0.318 (SD -3.128)		
Serum iPTH (pmmol/L) – 4wk	Continuous	42		23.012 (SD 14.952)	40		26.299 (SD 18.293)		
Adverse Events:									
Constipation – 4wk	Dichotomous	49	3	(6.1%)	48	0	(0.0%)		
Diarrhea – 4wk	Dichotomous	49	5	(10.2%)	48	3	(6.3%)		

Nausea OR vomiting – 4wk	Dichotomous	49	1	(2.0%)	48	0	(0.0%)		
Vomiting – 4wk	Dichotomous	49	1	(2.0%)	48	0	(0.0%)		
Abdominal discomfort – 4wk	Dichotomous	49	0	(0.0%)	48	2	(4.2%)		
Abdominal distension – 4wk	Dichotomous	49	0	(0.0%)	48	0	(0.0%)		
Rash – 4wk	Dichotomous	49	1	(2.0%)	48	1	(2.1%)		
Nasopharyngitis – 4wk	Dichotomous	49	5	(10.2%)	48	3	(6.3%)		
Abdominal pain – 4wk	Dichotomous	49	1	(2.0%)	48	0	(0.0%)		
Increased blood aluminium – 4wk	Dichotomous	49	1	(2.0%)	48	0	(0.0%)		
Venipuncture site swelling – 4wk	Dichotomous	49	1	(2.0%)	48	0	(0.0%)		
Myalgia – 4wk	Dichotomous	49	0	(0.0%)	48	1	(2.1%)		
Stomach discomfort – 4wk	Dichotomous	49	0	(0.0%)	48	2	(4.2%)		
Gastrointestinal disorder – 4wk	Dichotomous	49	2	(4.1%)	48	0	(0.0%)		
Arthralgia – 4wk	Dichotomous	49	0	(0.0%)	48	1	(2.1%)		
Subcutaneous hemorrhage – 4wk	Dichotomous	49	1	(2.0%)	48	1	(2.1%)		

[a] *Approximated to nearest integer (percentages only presented in text)*

		Ferric citrate 3 g/day			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 4wk	Dichotomous	50	15	(30.0%)	48	13	(27.1%)		
Withdrawal (AEs) – 4wk	Dichotomous	50	2	(4.0%)	48	1	(2.1%)		
Biochemical Data:									
Achieved phosphate control – 4wk[a]	Dichotomous	40	20	(50.0%)	40	1	(2.5%)		
Serum Ca (mmol/L) – 4wk	Mean change	50		0.03	48		0.008		
Serum Phosphate (mmol/L) – 4wk	Mean change	40		-0.698 (SD 0.426)	40		0.013 (SD 0.352)		
Serum Phosphate (mmol/L) – 4wk	Continuous	40		1.873 (SD 0.488)	40		2.506 (SD 0.397)		
Serum iPTH (pmmol/L) – 4wk	Mean change	40		-3.393 (SD -7.688)	40		-0.318 (SD -3.128)		
Serum iPTH (pmmol/L) – 4wk	Continuous	40		21.474 (SD 15.483)	40		26.299 (SD 18.293)		
Adverse Events:									
Constipation – 4wk	Dichotomous	50	0	(0.0%)	48	0	(0.0%)		

Diarrhea – 4wk	Dichotomous	50	3	(6.0%)	48	3	(6.3%)		
Nausea OR vomiting – 4wk	Dichotomous	50	1	(2.0%)	48	0	(0.0%)		
Vomiting – 4wk	Dichotomous	50	1	(2.0%)	48	0	(0.0%)		
Abdominal discomfort – 4wk	Dichotomous	50	2	(4.0%)	48	2	(4.2%)		
Abdominal distension – 4wk	Dichotomous	50	2	(4.0%)	48	0	(0.0%)		
Rash – 4wk	Dichotomous	50	1	(2.0%)	48	1	(2.1%)		
Nasopharyngitis – 4wk	Dichotomous	50	6	(12.0%)	48	3	(6.3%)		
Abdominal pain – 4wk	Dichotomous	50	0	(0.0%)	48	0	(0.0%)		
Increased blood aluminium – 4wk	Dichotomous	50	0	(0.0%)	48	0	(0.0%)		
Venipuncture site swelling – 4wk	Dichotomous	50	1	(2.0%)	48	0	(0.0%)		
Myalgia – 4wk	Dichotomous	50	1	(2.0%)	48	1	(2.1%)		
Stomach discomfort – 4wk	Dichotomous	50	1	(2.0%)	48	2	(4.2%)		
Gastrointestinal disorder – 4wk	Dichotomous	50	0	(0.0%)	48	0	(0.0%)		
Arthralgia – 4wk	Dichotomous	50	2	(4.0%)	48	1	(2.1%)		
Subcutaneous hemorrhage – 4wk	Dichotomous	50	1	(2.0%)	48	1	(2.1%)		

[a] *Approximated to nearest integer (percentages only presented in text)*

		Ferric citrate 6 g/day			Placebo				
		N	k	mean	N	k	mean	Δ	p
Disposition:									
Withdrawal (total) – 4wk	Dichotomous	45	25	(55.6%)	48	13	(27.1%)		
Withdrawal (AEs) – 4wk	Dichotomous	45	0	(0.0%)	48	1	(2.1%)		
Biochemical Data:									
Achieved phosphate control – 4wk[a]	Dichotomous	27	25	(92.6%)	40	1	(2.5%)		
Serum Ca (mmol/L) – 4wk	Mean change	45		0.085	48		0.008		
Serum Phosphate (mmol/L) – 4wk	Mean change	27		-1.324 (SD 0.352)	40		0.013 (SD 0.352)		
Serum Phosphate (mmol/L) – 4wk	Continuous	27		1.244 (SD 0.397)	40		2.506 (SD 0.397)		
Serum iPTH (pmmol/L) – 4wk	Mean change	27		-7.317 (SD -18.452)	40		-0.318 (SD -3.128)		
Serum iPTH (pmmol/L) – 4wk	Continuous	27		21.633 (SD 12.619)	40		26.299 (SD 18.293)		

	Adverse Events:									
	Constipation – 4wk	Dichotomous	45	4	(8.9%)	48	0	(0.0%)		
	Diarrhea – 4wk	Dichotomous	45	11	(24.4%)	48	3	(6.3%)		
	Nausea OR vomiting – 4wk	Dichotomous	45	1	(2.2%)	48	0	(0.0%)		
	Vomiting – 4wk	Dichotomous	45	1	(2.2%)	48	0	(0.0%)		
	Abdominal discomfort – 4wk	Dichotomous	45	1	(2.2%)	48	2	(4.2%)		
	Abdominal distension – 4wk	Dichotomous	45	1	(2.2%)	48	0	(0.0%)		
	Rash – 4wk	Dichotomous	45	0	(0.0%)	48	1	(2.1%)		
	Nasopharyngitis – 4wk	Dichotomous	45	4	(8.9%)	48	3	(6.3%)		
	Abdominal pain – 4wk	Dichotomous	45	4	(8.9%)	48	0	(0.0%)		
	Increased blood aluminium – 4wk	Dichotomous	45	2	(4.4%)	48	0	(0.0%)		
	Venipuncture site swelling – 4wk	Dichotomous	45	1	(2.2%)	48	0	(0.0%)		
	Myalgia – 4wk	Dichotomous	45	1	(2.2%)	48	1	(2.1%)		
	Stomach discomfort – 4wk	Dichotomous	45	1	(2.2%)	48	2	(4.2%)		
	Gastrointestinal disorder – 4wk	Dichotomous	45	0	(0.0%)	48	0	(0.0%)		
	Arthralgia – 4wk	Dichotomous	45	0	(0.0%)	48	1	(2.1%)		
	Subcutaneous hemorrhage – 4wk	Dichotomous	45	0	(0.0%)	48	1	(2.1%)		
	[a] *Approximated to nearest integer (percentages only presented in text)*									
Authors' conclusion										
Source of funding										
Comments										

Yokoyama et al. (2014b) – evidence table

Bibliographic reference	Yokoyama, Keitaro, Akiba, Takashi, Fukagawa, Masafumi, Nakayama, Masaaki, Sawada, Kenichi, Kumagai, Yuji, Chertow, Glenn M. A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2014;29(5):1053-60.
Study type & aim	**Blinded:** yes (details not given) **Crossover trial:** no **Multicentre:** yes
Number and characteristics of patients	**Gender:** Male and Female **Age range:** =20 years **Washout phosphate level (mmol/L):** >1.97, <3.23 **Exclusions:** Serum Ca (Corrected serum calcium concentrations <2.00 mmol/L or >2.75 mmol/L at 1 week after the initial screening date.) Liver dysfunction

Significant GI disease

History of gastrectomy or enterectomy; hemochromatosis or serum ferritin concentrations >500 ng/mL or transferrin saturation >50% on the initial screening date; parathyroidectomy or percutaneous ethanol injection therapy within 24 weeks prior to the initial screening date; any history of severe heart disease.

Baseline characteristics:

		Ferric citrate			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Biochemical Data: Serum Ca (mmol/L) – 0wk	Continuous	115		2.21 (SD 0.13)	110		2.22 (SD 0.15)		
Serum Phosphate (mmol/L) – 0wk	Continuous	115		2.53 (SD 0.39)	110		2.52 (SD 0.44)		
Serum iPTH (pmmol/L) – 0wk	Continuous	115		med: 24.39 [rng 15.907–35.101]	110		med: 26.405 [rng 16.861–36.267]		
Demographics: History of dialysis (year)	Continuous	115		8.74 (SD 6.1)	110		8.56 (SD 7.02)		
Gender-Female	Dichotomous	115	42	(36.5%)	110	38	(34.5%)		
Gender-Male	Dichotomous	115	73	(63.5%)	110	72	(65.5%)		
Age	Continuous	115		60.2 (SD 10.7)	110		61.4 (SD 9.5)		

Monitoring information and definitions

Target ranges:
Upper serum PO4 limit: 1.94
Lower serum PO4 limit: 1.13
Upper serum Ca limit: -
Lower serum Ca limit: -

Intervention(s)

Drug: Ferric citrate
N: 116 (Range: 1.5–6)
Dose varied to maintain patients within study endpoints: Dose was increased by 2 tablets/dose if serum phosphate was =1.97 mmol/L and decreased by 2 tablets/dose if serum phosphate was <1.13 mmol/L.
Drug: Sevelamer hydrochloride
N: 113 (Range: 3–6)
Dose varied to maintain patients within study endpoints: Dose was increased by 1 or 2 tablets/dose if serum phosphate was =1.97 mmol/L and decreased by 1 or 2 tablets/dose if serum phosphate was <1.13 mmol/L.

Concomitant treatments	**Dialysis:** Haemodialysis **Vit D:** Yes - changed during the study period (kept constant, except when they were changed to correct or prevent adverse events.) **Rescue Binder use permitted:** No details given **Were other medications allowed:** Yes (Calcitonin preparations, cinacalcet. Concurrent use of intravenous iron preparations was permitted when the investigator considered that iron-replacement therapy was necessary to treat ESRD-associated anemia.) **Changes to diet allowed:** No **Changes to dialysate allowed:** No
Length of follow up	**Washout period (d):** 14 **Follow-up (d):** 84 **Protocol-specified reasons for withdrawal:** Serum phosphate: Two consecutive serum phosphate concentrations <0.97 mmol/L or =3.23 mmol/L. Serum Ca: Two consecutive corrected serum calcium concentrations <1.88 mmol/L. Ferritin =800 ng/mL.
Location	**Country:** Japan

Outcomes measures and effect sizes

		Ferric citrate			Sevelamer hydrochloride			Δ	p
		N	k	mean	N	k	mean		
Disposition:									
Withdrawal (total) – 12wk	Dichotomous	116	14	(12.1%)	113	16	(14.2%)		
Withdrawal (AEs) – 12wk	Dichotomous	116	6	(5.2%)	113	2	(1.8%)		
Biochemical Data:									
Achieved phosphate control – 12wk[a]	Dichotomous	115	71	(61.7%)	110	66	(60.0%)		
Serum Ca (mmol/L) – 12wk[b]	Mean change	115		0.08 (SD 0.164)	110		0.04 (SD 0.107)		
Serum Ca (mmol/L) – 12wk	Continuous	115		2.29 (SD 0.16)	110		2.26 (SD 0.16)		
Serum Phosphate (mmol/L) – 12wk[b]	Mean change	115		-0.82 (SD 0.547)	110		-0.78 (SD 0.482)		
Serum Phosphate (mmol/L) – 12wk	Continuous	115		1.72 (SD 0.4)	110		1.74 (SD 0.34)		
Serum iPTH (pmmol/L) – 12wk[c]	Mean change	115		0.078 (SD 0.035)	110		0.077 (SD 0.028)		
Serum iPTH (pmmol/L) – 12wk	Continuous	115		med: 18.77 [rng 11.453–28.738]	110		med: 18.558 [rng 11.771–28.95]		
Adverse Events:									
Abdominal Distension – 12wk	Dichotomous	116	2	(1.7%)	113	4	(3.5%)		
Constipation – 12wk	Dichotomous	116	3	(2.6%)	113	21	(18.6%)		

	Diarrhea – 12wk	Dichotomous	116	12	(10.3%)	113	1	(0.9%)		
	Abdominal discomfort – 12wk	Dichotomous	116	4	(3.4%)	113	4	(3.5%)		
	Hemoglobin increased – 12wk	Dichotomous	116	4	(3.4%)	113	0	(0.0%)		
	Treatment: Compliance – 12wk[d]	Dichotomous	115	112	(97.4%)	110	106	(96.4%)		
	[a] *Approximated to nearest integer (percentages only presented in text)* [b] *95% CI for mean change* [c] *ratio of geometric mean (95% confidence interval)* [d] *Approximated to nearest integer (percentages only presented in text; full analysis set)*									
Authors' conclusion										
Source of funding										
Comments										

Appendix F – Risk of bias assessment for included studies

Adults with stage 4 or 5 CKD who are not on dialysis

Qunibi, 2011

Bibliographic Reference	Qunibi W.; Winkelmayer W.C.; Solomon R.; Moustafa M.; Kessler P.; Ho C.-H.; Greenberg J.; Diaz-Buxo J.A. ; A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease; BMC Nephrology; 2011; vol. 12 (no. 1); 9

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(80.4% (calcium acetate) and 64.0% (placebo) of available data.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
Some concerns
Overall Directness
Directly applicable

Russo, 2007

Bibliographic Reference	Russo, D.; Miranda, I.; Ruocco, C.; Battaglia, Y.; Buonanno, E.; Manzi, S.; Russo, L.; Scafarto, A.; Andreucci, V. E.; The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer; Kidney International; 2007; vol. 72 (no. 10); 1255-1261

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Some concerns
(Protocol was not reported.)
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Soriano, 2013

Bibliographic Reference	Soriano, Sagrario; Ojeda, Raquel; Rodriguez, Mencarnacion; Almaden, Yolanda; Rodriguez, Mariano; Martin-Malo, Alejandro; Aljama, Pedro; The effect of phosphate binders, calcium and lanthanum carbonate on FGF23 levels in chronic kidney disease patients.; Clinical nephrology; 2013; vol. 80 (no. 1); 17-22

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(No information about missing data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Sprague, 2009

Bibliographic Reference	Sprague, S. M.; Abboud, H.; Qiu, P.; Dauphin, M.; Zhang, P.; Finn, W.; Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial; Clinical Journal of The American Society of Nephrology: CJASN; 2009; vol. 4 (no. 1); 178-185

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(53.7% (lanthanum carbonate) and 68.2% (placebo) completed study.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Takahara, 2014

Bibliographic Reference	Takahara, Yuki; Matsuda, Yoshimi; Takahashi, Shunichi; Shigematsu, Takashi; Lanthanum Carbonate Study Group; Efficacy and safety of lanthanum carbonate in pre-dialysis CKD patients with hyperphosphatemia: a randomized trial.; Clinical nephrology; 2014; vol. 82 (no. 3); 181-90

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(No information about participants' adherence to interventions.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
Some concerns
Overall Directness
Directly applicable

Yilmaz, 2012

Bibliographic Reference	Yilmaz, Mahmut Ilker; Sonmez, Alper; Saglam, Mutlu; Yaman, Halil; Kilic, Selim; Eyileten, Tayfun; Caglar, Kayser; Oguz, Yusuf; Vural, Abdulgaffar; Yenicesu, Mujdat; Mallamaci, Francesca; Zoccali, Carmine; Comparison of calcium acetate and sevelamer on vascular function and fibroblast growth factor 23 in CKD patients: a randomized clinical trial.; American journal of kidney diseases : the official journal of the National Kidney Foundation; 2012; vol. 59 (no. 2); 177-85

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Yokoyama, 2014a

Bibliographic Reference	Yokoyama, Keitaro; Hirakata, Hideki; Akiba, Takashi; Fukagawa, Masafumi; Nakayama, Masaaki; Sawada, Kenichi; Kumagai, Yuji; Block, Geoffrey A; Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD.; Clinical journal of the American Society of Nephrology : CJASN; 2014; vol. 9 (no. 3); 543-52

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Children and young people with stage 5 CKD who are on dialysis

Salusky, 2005

Bibliographic Reference	Salusky, I. B.; Goodman, W. G.; Sahney, S.; Gales, B.; Perilloux, A.; Wang, H. J.; Elashoff, R. M.; Juppner, H.; Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols; Journal of the American Society of Nephrology; 2005; vol. 16 (no. 8); 2501-2508

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Adults with stage 5 CKD who are on dialysis

Abraham, 2012

Bibliographic Reference	Abraham G.; Kher V.; Saxena S.; Jayakumar M.; Chafekar D.; Pargaonkar P.; Shetty M.; Reddy Y.N.V. ; Sevelamer carbonate experience in Indian end stage renal disease patients; Indian Journal of Nephrology; 2012; vol. 22 (no. 3); 189-192

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(From consort diagram, it seems the authors did a 'per-protocol' analysis)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(There was no analysis to estimate the effect of co-interventions or adhering to interventions)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Some concerns
(Pre-specified analysis plan not reported)
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Ahmed, 2014

Bibliographic Reference	Ahmed W.; Rizwan-Ul-Haq; Akram M.; Khan S.; Haider S.; Abad-Ur-Rehman ; Comparative efficacy of sevelamer hydrochloride versus calcium acetate on bone biomarkers in patients with end stage renal disease on hemodialysis; Pakistan Journal of Medical and Health Sciences; 2014; vol. 8 (no. 3); 769-771

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information about blinding, deviations from protocol or whether the analysis was intention-to-treat.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information about blinding, adherence or analysis to estimate adherence.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(No information about missing data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Al-Baaj, 2005

Bibliographic Reference	Al-Baaj, F.; Speake, M.; Hutchison, A. J.; Control of serum phosphate by oral lanthanum carbonate in patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis in a short-term, placebo-controlled study; Nephrology Dialysis Transplantation; 2005; vol. 20 (no. 4); 775-782

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Some concerns
(Protocol was not reported.)
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Asmus, 2005

Bibliographic Reference	Asmus, H. G.; Braun, J.; Krause, R.; Brunkhorst, R.; Holzer, H.; Schulz, W.; Neumayer, H. H.; Raggi, P.; Bommer, J.; Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density; Nephrology Dialysis Transplantation; 2005; vol. 20 (no. 8); 1653-1661

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(No information about correction of bias from missing data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Babarykin, 2004

Bibliographic Reference	Babarykin, D.; Adamsone, I.; Amerika, D.; Spudass, A.; Moisejev, V.; Berzina, N.; Michule, L.; Rozental, R.; Calcium-enriched bread for treatment of uremic hyperphosphatemia; Journal of Renal Nutrition; 2004; vol. 14 (no. 3); 149-156

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(Baseline data not reported for each arm.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Barreto, 2008

Bibliographic Reference	Barreto, D. V.; Barreto, Fde C.; de Carvalho, A. B.; Cuppari, L.; Draibe, S. A.; Dalboni, M. A.; Moyses, R. M.; Neves, K. R.; Jorgetti, V.; Miname, M.; Santos, R. D.; Canziani, M. E.; Phosphate binder impact on bone remodeling and coronary calcification--results from the BRiC study; Nephron; 2008; vol. 110 (no. 4); c273-c283

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(There were more deaths in people receiving calcium acetate compared to people receiving sevelamer.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Block, 2005

Bibliographic Reference	Block, G. A.; Spiegel, D. M.; Ehrlich, J.; Mehta, R.; Lindbergh, J.; Dreisbach, A.; Raggi, P.; Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis; Kidney International; 2005; vol. 68 (no. 4); 1815-1824

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(73% (calcium) and 74% (sevelamer) of available data.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Braun, 2004

Bibliographic Reference	Braun, J.; Asmus, H. G.; Holzer, H.; Brunkhorst, R.; Krause, R.; Schulz, W.; Neumayer, H. H.; Raggi, P.; Bommer, J.; Long-term comparison of a calcium-free phosphate binder and calcium carbonate--phosphorus metabolism and cardiovascular calcification; Clinical Nephrology; 2004; vol. 62 (no. 2); 104-115

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(78% (calcium carbonate) and 65% (sevelamer) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Chang, 2017

Bibliographic Reference	Chang, Yu-Ming; Tsai, Shih-Ching; Shiao, Chih-Chung; Liou, Hung-Hsiang; Yang, Chuan-Lan; Tung, Nai-Yu; Hsu, Kua-Sui; Chen, I-Ling; Liu, Mei-Chyn; Kao, Jsun-Liang; Jhen, Rong-Na; Huang, Ya-Ting; Effects of lanthanum carbonate and calcium carbonate on fibroblast growth factor 23 and hepcidin levels in chronic hemodialysis patients.; Clinical and experimental nephrology; 2017; vol. 21 (no. 5); 908-916

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information about blinding, deviations from protocol or whether the analysis was intention-to-treat or not.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information about blinding, adherence or analysis to estimate adherence.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Chen, 2014

Bibliographic Reference	Chen, Nan; Wu, Xiongfei; Ding, Xiaoqiang; Mei, Changlin; Fu, Ping; Jiang, Gengru; Li, Xuemei; Chen, Jianghua; Liu, Bicheng; La, Yan; Hou, Fanfan; Ni, Zhaohui; Fu, Junzhou; Xing, Changying; Yu, Xuequing; Huang, Chaoxing; Zuo, Li; Wang, Li; Hunter, John; Dillon, Maureen; Plone, Melissa; Neylan, John; Sevelamer carbonate lowers serum phosphorus effectively in haemodialysis patients: a randomized, double-blind, placebo-controlled, dose-titration study.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2014; vol. 29 (no. 1); 152-60

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Chertow, 1997

Bibliographic Reference	Chertow, G. M.; Burke, S. K.; Lazarus, J. M.; Stenzel, K. H.; Wombolt, D.; Goldberg, D.; Bonventre, J. V.; Slatopolsky, E.; Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure; American Journal of Kidney Diseases; 1997; vol. 29 (no. 1); 66-71

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Chertow, 2002

Bibliographic Reference	Chertow, G. M.; Burke, S. K.; Raggi, P.; Group, Treat to Goal Working; Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients; Kidney International; 2002; vol. 62 (no. 1); 245-252

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(63% (sevelamer) and 69% (calcium) of available data.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Chertow, 2003

Bibliographic Reference	Chertow, G. M.; Raggi, P.; McCarthy, J. T.; Schulman, G.; Silberzweig, J.; Kuhlik, A.; Goodman, W. G.; Boulay, A.; Burke, S. K.; Toto, R. D.; The effects of sevelamer and calcium acetate on proxies of atherosclerotic and arteriosclerotic vascular disease in hemodialysis patients; American Journal of Nephrology; 2003; vol. 23 (no. 5); 307-314

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(No information about missing data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

High

(No information about blinding of assessor for measuring coronary artery calcification.)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Chiang, 2005

Bibliographic Reference	Chiang, S. S.; Chen, J. B.; Yang, W. C.; Lanthanum carbonate (Fosrenol) efficacy and tolerability in the treatment of hyperphosphatemic patients with end-stage renal disease; Clinical Nephrology; 2005; vol. 63 (no. 6); 461-470

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(Discontinuation was higher in the placebo arm (55%) compared to the lanthanum arm (7%).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(93% (lanthanum carbonate) and 45% (placebo) of available data. The primary efficacy parameter was the last-observation-carried-forward serum phosphorus levels at the end of the study.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Chow, 2007

Bibliographic Reference	Chow, K. M.; Szeto, C. C.; Kwan, B. C.; Leung, C. B.; Li, P. K.; Sevelamer treatment strategy in peritoneal dialysis patients: conventional dose does not make best use of resources; Journal of Nephrology; 2007; vol. 20 (no. 6); 674-682

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(No information about missing data.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

de, 2010

Bibliographic Reference	de Francisco, Angel L M; Leidig, Michael; Covic, Adrian C; Ketteler, Markus; Benedyk-Lorens, Ewa; Mircescu, Gabriel M; Scholz, Caecilia; Ponce, Pedro; Passlick-Deetjen, Jutta; Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2010; vol. 25 (no. 11); 3707-17

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(Per protocol analysis)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(Per protocol analysis)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(83% (calcium acetate/magnesium carbonate) and 77% (sevelamer hydrochloride) of available data.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

De Santo, 2006

Bibliographic Reference	De Santo, N. G.; Frangiosa, A.; Anastasio, P.; Marino, A.; Correale, G.; Perna, A.; Di, Stazio E.; Stellato, D.; Santoro, D.; Di, Meglio E.; Iacono, G.; Ciacci, C.; Savica, V.; Cirillo, M.; Sevelamer worsens metabolic acidosis in hemodialysis patients; Journal of Nephrology; 2006; vol. 19; Suppl-14

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(No information about missing data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Di, 2013

Bibliographic Reference	Di Iorio, Biagio; Molony, Donald; Bell, Cynthia; Cucciniello, Emanuele; Bellizzi, Vincenzo; Russo, Domenico; Bellasi, Antonio; Sevelamer Versus Calcium Carbonate in Incident Hemodialysis Patients: Results of an Open-Label 24-Month Randomized Clinical Trial; American Journal of Kidney Diseases; 2013; vol. 62 (no. 4); 771-778

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(Serum phosphate and serum calcium were significantly different at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Low
Overall bias and Directness
Risk of bias judgement
Some concerns
Overall Directness
Directly applicable

Emmett, 1991

Bibliographic Reference	Emmett, M.; Sirmon, M. D.; Kirkpatrick, W. G.; Nolan, C. R.; Schmitt, G. W.; Cleveland, M. B.; Calcium acetate control of serum phosphorus in hemodialysis patients; American Journal of Kidney Diseases; 1991; vol. 17 (no. 5); 544-550

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment; baseline data not reported for each arm.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(Per protocol analysis.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(Per protocol analysis.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Evenepoel, 2009

Bibliographic Reference	Evenepoel, P.; Selgas, R.; Caputo, F.; Foggensteiner, L.; Heaf, J. G.; Ortiz, A.; Kelly, A.; Chasan-Taber, S.; Duggal, A.; Fan, S.; Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis; Nephrology Dialysis Transplantation; 2009; vol. 24 (no. 1); 278-285

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(Trial was not blinded and there was no information on whether there were deviations from intended interventions because of the experimental context.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(Failures in implementing the intervention could have affected the outcome.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(76% (sevelamer hydrochloride) and 65% (calcium acetate) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Ferreira, 2008

Bibliographic Reference	Ferreira, A.; Frazao, J. M.; Monier-Faugere, M. C.; Gil, C.; Galvao, J.; Oliveira, C.; Baldaia, J.; Rodrigues, I.; Santos, C.; Ribeiro, S.; Hoenger, R. M.; Duggal, A.; Malluche, H. H.; Group, Sevelamer Study; Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients; Journal of the American Society of Nephrology; 2008; vol. 19 (no. 2); 405-412

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)
Some concerns
(Trial was not blinded and there was no information on whether there were deviations from intended interventions because of the experimental context.)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)
Some concerns
(Failures in implementing the intervention could have affected the outcome.)
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data
Some concerns
(75% (sevelamer) and 74% (calcium) of available data.)
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement Some concerns *Overall Directness* Directly applicable

Finn, 2006

Bibliographic Reference	Finn W.F. ; Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: Safety and efficacy in chronic maintenance hemodialysis patients; Clinical Nephrology; 2006; vol. 65 (no. 3); 191-202

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(Trial was not blinded and there was no information on whether there were deviations from intended interventions because of the experimental context.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(Failures in implementing the intervention could have affected the outcome.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(29% (lanthanum carbonate) and 47% (standard therapy) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Finn, 2004

Bibliographic Reference	Finn, W. F.; Joy, M. S.; Hladik, G.; Group, Lanthanum Study; Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis; Clinical Nephrology; 2004; vol. 62 (no. 3); 193-201

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(Failures in implementing the intervention could have affected the outcome.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(47% placebo-treated patients completed the trial as did 46%, 69%, 70%, and 85% in the lanthanum 225, 675, 1,350 and 2,250 mg/day groups, respectively.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Fishbane, 2010

Bibliographic Reference	Fishbane, S; Delmez, J; Suki, WN; Hariachar, SK; Heaton, J; Chasan-Taber, S; Plone, MA; Moe, S; A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis; American journal of kidney diseases; 2010; vol. 55 (no. 2); 307-315

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(Trial was not blinded and there was no information on whether there were deviations from intended interventions because of the experimental context.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(Failures in implementing the intervention could have affected the outcome.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(65% (sevelamer carbonate) and 85% (sevelamer hydrochloride) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
Some concerns
Overall Directness
Directly applicable

Freemont, 2005

Bibliographic Reference	Freemont, A. J.; Hoyland, J. A.; Denton, J.; Lanthanum Carbonate, S. P. D.; The effects of lanthanum carbonate and calcium carbonate on bone abnormalities in patients with end-stage renal disease; Clinical Nephrology; 2005; vol. 64 (no. 6); 428-437

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(Trial was not blinded and there was no information on whether there were deviations from intended interventions because of the experimental context.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(Trial was not blinded and there was no information on whether important co-interventions were balanced across intervention groups.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(67% (lanthanum carbonate) and 61% (calcium carbonate) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Fujii, 2018

Bibliographic Reference	Fujii, Hideki; Kono, Keiji; Nakai, Kentaro; Goto, Shunsuke; Nishii, Tatsuya; Kono, Atsushi; Nishi, Shinichi; Effects of Lanthanum Carbonate on Coronary Artery Calcification and Cardiac Abnormalities After Initiating Hemodialysis.; Calcified tissue international; 2018; vol. 102 (no. 3); 310-320

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(Participants and researchers were not blinded and there was no information about deviations from intended interventions.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(Participants and researchers were not blinded and failures in implementing the intervention could have affected the outcome.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
Some concerns
Overall Directness
Directly applicable

Hervas, 2003

Bibliographic Reference	Hervas, J. G.; Prados, D.; Cerezo, S.; Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: a comparison with calcium acetate; Kidney International - Supplement; 2003; (no. 85); S69-S72

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment; baseline data not reported for each arm.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(Missing data was not reported by arm.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Hutchison, 2005

Bibliographic Reference	Hutchison, A. J.; Maes, B.; Vanwalleghem, J.; Asmus, G.; Mohamed, E.; Schmieder, R.; Backs, W.; Jamar, R.; Vosskuhler, A.; Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized, comparative trial versus calcium carbonate; Nephron; 2005; vol. 100 (no. 1); c8-19

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(No information about deviations because of the experimental context.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(No information about participants' adherence to interventions.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(54.2% (lanthanum carbonate) and 57.7% (calcium carbonate) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Iwasaki, 2005

Bibliographic Reference	Iwasaki, Y.; Takami, H.; Tani, M.; Yamaguchi, Y.; Goto, H.; Goto, Y.; Goto, Y.; Shigematsu, T.; Efficacy of combined sevelamer and calcium carbonate therapy for hyperphosphatemia in Japanese hemodialysis patients; Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy; 2005; vol. 9 (no. 4); 347-351

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(Participants (21.5%) were excluded because they had adverse events with sevelamer.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Jalal, 2017

Bibliographic Reference	Jalal, Diana; McFadden, Molly; Dwyer, Jamie P; Umanath, Kausik; Aguilar, Erwin; Yagil, Yoram; Greco, Barbara; Sika, Mohammed; Lewis, Julia B; Greene, Tom; Goral, Simin; Adherence rates to ferric citrate as compared to active control in patients with end stage kidney disease on dialysis.; Hemodialysis international. International Symposium on Home Hemodialysis; 2017; vol. 21 (no. 2); 243-249

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(Last observation carried forward was used.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Some concerns

(Unlikely to affect the actual measurement of serum phosphate but likely to affect the reporting of adverse events.)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Janssen, 1995

Bibliographic Reference	Janssen, M. J.; van der Kuy, A.; ter Wee, P. M.; van Boven, W. P.; Calcium acetate versus calcium carbonate and erythropoietin dosages in haemodialysis patients; Nephrology Dialysis Transplantation; 1995; vol. 10 (no. 12); 2321-2324

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(Dropped outs were not reported by arm.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Janssen, 1996

Bibliographic Reference	Janssen, M. J.; van der Kuy, A.; ter Wee, P. M.; van Boven, W. P.; Aluminum hydroxide, calcium carbonate and calcium acetate in chronic intermittent hemodialysis patients; Clinical Nephrology; 1996; vol. 45 (no. 2); 111-119

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(66.6% (aluminum hydroxide), 77.7% (calcium acetate), and 65.0% (calcium carbonate) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Joy, 2003

Bibliographic Reference	Joy, M. S.; Finn, W. F.; Group, Study; Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia; American Journal of Kidney Diseases; 2003; vol. 42 (no. 1); 96-107

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Kakuta, 2011

Bibliographic Reference	Kakuta, T; Tanaka, R; Hyodo, T; Suzuki, H; Kanai, G; Nagaoka, M; Takahashi, H; Hirawa, N; Oogushi, Y; Miyata, T; et, al.; Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients; American journal of kidney diseases; 2011; vol. 57 (no. 3); 422-431

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)
Some concerns *(No information about deviations because of the experimental context.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)
Some concerns *(No information about participants' adherence to interventions.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data
Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome
Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
Some concerns
Overall Directness
Directly applicable

Kalil, 2012

Bibliographic Reference	Kalil, Roberto S; Flanigan, Michael; Stanford, William; Haynes, William G; Dissociation between progression of coronary artery calcification and endothelial function in hemodialysis patients: a prospective pilot study.; Clinical nephrology; 2012; vol. 78 (no. 1); 1-9

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process High *(Significant difference in during of dialysis between the groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(70% (intervention) and 60% (control) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Katopodis, 2006

Bibliographic Reference	Katopodis, K. P.; Andrikos, E. K.; Gouva, C. D.; Bairaktari, E. T.; Nikolopoulos, P. M.; Takouli, L. K.; Tzallas, C. S.; Elisaf, M. S.; Pappas, M. V.; Siamopoulos, K. C.; Sevelamer hydrochloride versus aluminum hydroxide: effect on serum phosphorus and lipids in CAPD patients; Peritoneal Dialysis International; 2006; vol. 26 (no. 3); 320-327

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Ketteler, 2019

Bibliographic Reference	Ketteler, Markus; Sprague, Stuart M; Covic, Adrian C; Rastogi, Anjay; Spinowitz, Bruce; Rakov, Viatcheslav; Walpen, Sebastian; Floege, Jurgen; Effects of sucroferric oxyhydroxide and sevelamer carbonate on chronic kidney disease-mineral bone disorder parameters in dialysis patients.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2019; vol. 34 (no. 7); 1163-1170

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(Per-protocol analysis.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(Per-protocol analysis.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(Withdrawn: 27.5% ferric citrate and 16.0% sevelamer carbonate; last observation carried forward approach of missing data imputation.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

(Outcome assessors were not blinded but this was unlikely to affect outcomes.)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Koiwa, 2005b

Bibliographic Reference	Koiwa, F.; Kazama, J. J.; Tokumoto, A.; Onoda, N.; Kato, H.; Okada, T.; Nii-Kono, T.; Fukagawa, M.; Shigematsu, T.; Group, Clinical Research; Sevelamer hydrochloride and calcium bicarbonate reduce serum fibroblast growth factor 23 levels in dialysis patients; Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy; 2005; vol. 9 (no. 4); 336-339

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(No information about missing data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Koiwa, 2005a

Bibliographic Reference	Koiwa, F.; Onoda, N.; Kato, H.; Tokumoto, A.; Okada, T.; Fukagawa, M.; Shigematsu, T.; Group, Clinical Research; Prospective randomized multicenter trial of sevelamer hydrochloride and calcium carbonate for the treatment of hyperphosphatemia in hemodialysis patients in Japan; Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy; 2005; vol. 9 (no. 4); 340-346

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process High *(No information about randomisation method and allocation concealment; baseline data not reported for each arm.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(55.2% (sevelamer), 86.7% (sevelamer + calcium carbonate), and 74.1% (calcium carbonate) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Koiwa, 2017a

Bibliographic Reference	Koiwa, Fumihiko; Terao, Akira; Dose-response efficacy and safety of PA21 in Japanese hemodialysis patients with hyperphosphatemia: a randomized, placebo-controlled, double-blind, Phase II study.; Clinical and experimental nephrology; 2017; vol. 21 (no. 3); 513-522

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Koiwa, 2017b

Bibliographic Reference	Koiwa, Fumihiko; Yokoyama, Keitaro; Fukagawa, Masafumi; Terao, Akira; Akizawa, Tadao; Efficacy and safety of sucroferric oxyhydroxide compared with sevelamer hydrochloride in Japanese haemodialysis patients with hyperphosphataemia: A randomized, open-label, multicentre, 12-week phase III study.; Nephrology (Carlton, Vic.); 2017; vol. 22 (no. 4); 293-300

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(Per-protocol analysis.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(Per-protocol analysis.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Lee, 2015

Bibliographic Reference	Lee, Chien-Te; Wu, I-Wen; Chiang, Shou-Shan; Peng, Yu-Sen; Shu, Kuo-Hsiung; Wu, Ming-Ju; Wu, Mai-Szu; Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study.; Journal of nephrology; 2015; vol. 28 (no. 1); 105-13

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(Less than 50% available data for placebo arm (92% for ferric citrate 4 g/d and 82% for ferric citrate 6 g/d).)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

(Outcome assessors were not blinded but this was unlikely to affect outcomes.)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Lee, 2013

Bibliographic Reference	Lee, Yong Kyu; Choi, Hoon Young; Shin, Sug Kyun; Lee, Ho Yung; Effect of lanthanum carbonate on phosphate control in continuous ambulatory peritoneal dialysis patients in Korea: a randomized prospective study.; Clinical nephrology; 2013; vol. 79 (no. 2); 136-42

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(No information about randomisation method and allocation concealment; height, weight and body mass index were significantly different between arms.)

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

High

(No information on the type of analysis (intention-to-treat or per-protocol analyses); 57% (lanthanum carbonate) and 81% (calcium carbonate) of available data.)

Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)

High

(No information on the type of analysis (intention-to-treat or per-protocol analyses).)

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

Some concerns

(No information about sensitivity analysis or methods to correct for bias.)

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low *(Outcome assessors were not blinded but this was unlikely to affect outcomes.)*
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Lin, 2011

Bibliographic Reference	Lin Y.-F.; Chien C.-T.; Kan W.-C.; Chen Y.-M.; Chu T.-S.; Hung K.-Y.; Tsai T.-J.; Wu K.-D.; Wu M.-S. ; Pleiotropic effects of sevelamer beyond phosphate binding in end-stage renal disease patients: A randomized, open-label, parallel-group study; Clinical Drug Investigation; 2011; vol. 31 (no. 4); 257-267

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(88.4% (sevelamer) and 76.9% (calcium acetate) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Lin, 2016

Bibliographic Reference	Lin, Hsin-Hung; Liou, Hung-Hsiang; Wu, Ming-Shiou; Huang, Chiu-Ching; Factors associated with serum fetuin-A concentrations after long-term use of different phosphate binders in hemodialysis patients.; BMC nephrology; 2016; vol. 17; 33

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Some concerns *(Most participants did not complete follow-up for gastrointestinal problems.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Liu, 2006

Bibliographic Reference	Liu, Y. L.; Lin, H. H.; Yu, C. C.; Kuo, H. L.; Yang, Y. F.; Chou, C. Y.; Lin, P. W.; Liu, J. H.; Liao, P. Y.; Huang, C. C.; A comparison of sevelamer hydrochloride with calcium acetate on biomarkers of bone turnover in hemodialysis patients; Renal Failure; 2006; vol. 28 (no. 8); 701-707

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(No information about deviations because of the experimental context.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(No information about participants' adherence to interventions.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement Some concerns *Overall Directness* Directly applicable

Malluche, 2008

Bibliographic Reference	Malluche, H. H.; Siami, G. A.; Swanepoel, C.; Wang, G. H.; Mawad, H.; Confer, S.; Smith, M.; Pratt, R. D.; Monier-Faugere, M. C.; Group, Lanthanum Carbonate Study; Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years; Clinical Nephrology; 2008; vol. 70 (no. 4); 284-295

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(47.2% (lanthanum carbonate) and 46.6% (standard therapy) of available data at baseline. Unclear number of participants with data on phosphate, calcium and PTH levels.)*
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Maruyama, 2018

Bibliographic Reference	Maruyama N.; Otsuki T.; Yoshida Y.; Nagura C.; Kitai M.; Shibahara N.; Tomita H.; Maruyama T.; Abe M. ; Ferric Citrate Decreases Fibroblast Growth Factor 23 and Improves Erythropoietin Responsiveness in Hemodialysis Patients; American Journal of Nephrology; 2018; vol. 47 (no. 6); 406-414

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Navarro-Gonzalez, 2011

Bibliographic Reference	Navarro-Gonzalez, Juan F; Mora-Fernandez, Carmen; Muros de Fuentes, Mercedes; Donate-Correa, Javier; Cazana-Perez, Violeta; Garcia-Perez, Javier; Effect of phosphate binders on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients.; Clinical journal of the American Society of Nephrology : CJASN; 2011; vol. 6 (no. 9); 2272-9

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Ohtake, 2013

Bibliographic Reference	Ohtake, Takayasu; Kobayashi, Shuzo; Oka, Machiko; Furuya, Rei; Iwagami, Masao; Tsutsumi, Daimu; Mochida, Yasuhiro; Maesato, Kyoko; Ishioka, Kunihiro; Moriya, Hidekazu; Hidaka, Sumi; Lanthanum Carbonate Delays Progression of Coronary Artery Calcification Compared With Calcium-Based Phosphate Binders in Patients on Hemodialysis: A Pilot Study; Journal of Cardiovascular Pharmacology and Therapeutics; 2013; vol. 18 (no. 5); 439-446

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process High *(Allocation sequence was not concealed; baseline data not reported for each arm.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(27% of participants from the lanthanum carbonate were excluded from analysis because they developed gastrointestinal symptoms that prevented them to continue taking the medication.)*

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Some concerns
(Protocol was not reported.)
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Otsuki, 2018

Bibliographic Reference	Otsuki T.; Utsunomiya K.; Moriuchi M.; Horikoshi S.; Suzuki H.; Okamura M.; Maruyama N.; Shibahara N.; Abe M. ; Effect of sucroferric oxyhydroxide on fibroblast growth factor 23 levels in hemodialysis patients; Nephron; 2018; vol. 140 (no. 3); 161-168

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Qunibi, 2008

Bibliographic Reference	Qunibi, W.; Moustafa, M.; Muenz, L. R.; He, D. Y.; Kessler, P. D.; Diaz-Buxo, J. A.; Budoff, M.; Investigators, Care; A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study; American Journal of Kidney Diseases; 2008; vol. 51 (no. 6); 952-965

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process High *(Treatment assignment was not blinded.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(No information about blinding or whether there were deviations from protocol.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(No information about participants' adherence to interventions.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Raggi, 2004

Bibliographic Reference	Raggi P.; Bommer J.; Chertow G.M. ; Valvular calcification in hemodialysis patients randomized to calcium-based phosphorus binders or sevelamer; Journal of Heart Valve Disease; 2004; vol. 13 (no. 1); 134-141

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(67.3% (sevelamer) and 74.4% (calcium) of available data.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Ring, 1993

Bibliographic Reference	Ring, T.; Nielsen, C.; Andersen, S. P.; Behrens, J. K.; Sodemann, B.; Kornerup, H. J.; Calcium acetate versus calcium carbonate as phosphorus binders in patients on chronic haemodialysis: a controlled study; Nephrology Dialysis Transplantation; 1993; vol. 8 (no. 4); 341-346

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment; baseline data not reported for each arm.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Some concerns
(Protocol was not reported.)
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Shigematsu, 2008a

Bibliographic Reference	Shigematsu, T.; Group, Lanthanum Carbonate; Multicenter prospective randomized, double-blind comparative study between lanthanum carbonate and calcium carbonate as phosphate binders in Japanese hemodialysis patients with hyperphosphatemia; Clinical Nephrology; 2008; vol. 70 (no. 5); 404-410

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

Some concerns

Overall Directness

Directly applicable

Shigematsu, 2008b

Bibliographic Reference	Shigematsu, T.; Group, Lanthanum Carbonate Research; Lanthanum carbonate effectively controls serum phosphate without affecting serum calcium levels in patients undergoing hemodialysis; Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy; 2008; vol. 12 (no. 1); 55-61

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(Per protocol analysis.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(Per protocol analysis.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(Proportions of missing outcome data differed between intervention groups: 3.3% lanthanum 750, 0% lanthanum 1500, 6.1% lanthanum 2250, 29.1% lanthanum 3000, and 6.1% placebo.)*

Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Some concerns
(Protocol was not reported.)
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Spasovski, 2006

Bibliographic Reference	Spasovski, G. B.; Sikole, A.; Gelev, S.; Masin-Spasovska, J.; Freemont, T.; Webster, I.; Gill, M.; Jones, C.; De Broe, M. E.; D'Haese, P. C.; Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up; Nephrology Dialysis Transplantation; 2006; vol. 21 (no. 8); 2217-2224

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Spiegel, 2007

Bibliographic Reference	Spiegel, D. M.; Farmer, B.; Smits, G.; Chonchol, M.; Magnesium carbonate is an effective phosphate binder for chronic hemodialysis patients: a pilot study; Journal of Renal Nutrition; 2007; vol. 17 (no. 6); 416-422

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Suki, 2007

Bibliographic Reference	Suki, W. N.; Zabaneh, R.; Cangiano, J. L.; Reed, J.; Fischer, D.; Garrett, L.; Ling, B. N.; Chasan-Taber, S.; Dillon, M. A.; Blair, A. T.; Burke, S. K.; Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients; Kidney International; 2007; vol. 72 (no. 9); 1130-1137

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Some concerns *(Unclear if intention-to-treat was used.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) Some concerns *(Unclear if intention-to-treat was used.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(52.3% (sevelamer) and 49.2% (calcium) completed study.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Tzanakis, 2008

Bibliographic Reference	Tzanakis, I. P.; Papadaki, A. N.; Wei, M.; Kagia, S.; Spadidakis, V. V.; Kallivretakis, N. E.; Oreopoulos, D. G.; Magnesium carbonate for phosphate control in patients on hemodialysis. A randomized controlled trial; International Urology & Nephrology; 2008; vol. 40 (no. 1); 193-201

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Tzanakis, 2014

Bibliographic Reference	Tzanakis, Ioannis P; Stamataki, Elisavet E; Papadaki, Antonia N; Giannakis, Nektarios; Damianakis, Nikolaos E; Oreopoulos, Dimitrios G; Magnesium retards the progress of the arterial calcifications in hemodialysis patients: a pilot study.; International urology and nephrology; 2014; vol. 46 (no. 11); 2199-205

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Wada, 2015

Bibliographic Reference	Wada K.; Wada Y.; Uchida H.A.; Tsuruoka S. ; Effects of lanthanum carbonate versus calcium carbonate on vascular stiffness and bone mineral metabolism in hemodialysis patients with type 2 diabetes mellitus: A randomized controlled trial; International Journal of Nephrology and Renovascular Disease; 2015; vol. 8; 111-118

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Wang, 2015

Bibliographic Reference	Wang XH; Zhang X; Mu CJ; He Y; Peng QP; Yang GS; Li MM; Liu D; Li J; Ding GH; Effects of lanthanum carbonate on vascular calcification in elderly maintenance hemodialysis patients.; Journal of Huazhong University of Science and Technology. Medical sciences = Hua zhong ke ji da xue xue bao. Yi xue Ying De wen ban = Huazhong keji daxue xuebao. Yixue Yingdewen ban; 2015; vol. 35 (no. 4)

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result Some concerns *(Protocol was not reported.)*
Overall bias and Directness
Risk of bias judgement High *Overall Directness* Directly applicable

Wilson, 2009

Bibliographic Reference	Wilson, R., Zhang, P., Smyth, M. et al. (2009) Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. Current Medical Research & Opinion 25(12): 3021-3028

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(No information about randomisation method and allocation concealment.)

Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)

Some concerns

(Trial was not blinded and there was no information on whether there were deviations from intended interventions because of the experimental context.)

Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)

Some concerns

(Failures in implementing the intervention could have affected the outcome.)

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for missing outcome data

High

(29% (lanthanum carbonate) and 47% (standard therapy) of available data.)

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement for selection of the reported result

Some concerns

(Protocol was not reported.)

Overall bias and Directness

Risk of bias judgement

High

Overall Directness

Directly applicable

Wuthrich, 2013

Bibliographic Reference	Wuthrich, Rudolf P; Chonchol, Michel; Covic, Adrian; Gaillard, Sylvain; Chong, Edward; Tumlin, James A; Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients.; Clinical journal of the American Society of Nephrology : CJASN; 2013; vol. 8 (no. 2); 280-9

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data High *(Hypophosphatemia, hyperphosphatemia, and hypercalcemia were more frequent reasons for withdrawal in the sucroferric oxyhydroxide arm.)*
Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Xu, 2013

Bibliographic Reference	Xu, Jing; Zhang, Yi-Xiang; Yu, Xue-Qing; Liu, Zhi-Hong; Wang, Li-Ning; Chen, Jiang-Hua; Fan, Ya-Ping; Ni, Zhao-Hui; Wang, Mei; Yuan, Fa-Huan; Ding, Guo-Hua; Chen, Xiang-Mei; Zhang, Ai-Ping; Mei, Chang-Lin; Lanthanum carbonate for the treatment of hyperphosphatemia in CKD 5D: multicenter, double blind, randomized, controlled trial in mainland China.; BMC nephrology; 2013; vol. 14; 29

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)
Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)
Low
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data
Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low

Overall bias and Directness
Risk of bias judgement
Low
Overall Directness
Directly applicable

Yokoyama, 2014b

Bibliographic Reference	Yokoyama, Keitaro; Akiba, Takashi; Fukagawa, Masafumi; Nakayama, Masaaki; Sawada, Kenichi; Kumagai, Yuji; Chertow, Glenn M; Hirakata, Hideki; A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2014; vol. 29 (no. 5); 1053-60

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about randomisation method and allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(No information on the type of analysis (intention-to-treat or per-protocol analyses).)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome

Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Yokoyama, 2012

Bibliographic Reference	Yokoyama, Keitaro; Hirakata, Hideki; Akiba, Takashi; Sawada, Kenichi; Kumagai, Yuji; Effect of oral JTT-751 (ferric citrate) on hyperphosphatemia in hemodialysis patients: results of a randomized, double-blind, placebo-controlled trial.; American journal of nephrology; 2012; vol. 36 (no. 5); 478-87

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process Some concerns *(No information about allocation concealment.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for deviations from the intended interventions (effect of assignment to intervention) Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) High *(Analysis used to estimate the effect of assignment to intervention was not reported.)*
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for missing outcome data Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for measurement of the outcome Low

Domain 5. Bias in selection of the reported result
Risk-of-bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High
Overall Directness
Directly applicable

Appendix G – Forest plots

Forest plots were not prioritised for this review question.

Appendix H – Network meta-analysis results

Table 29 and table 37 show which models were selected for each outcome (fixed or random effect models).

Adults with stage 4 or 5 CKD who are not on dialysis

Model fit statistics

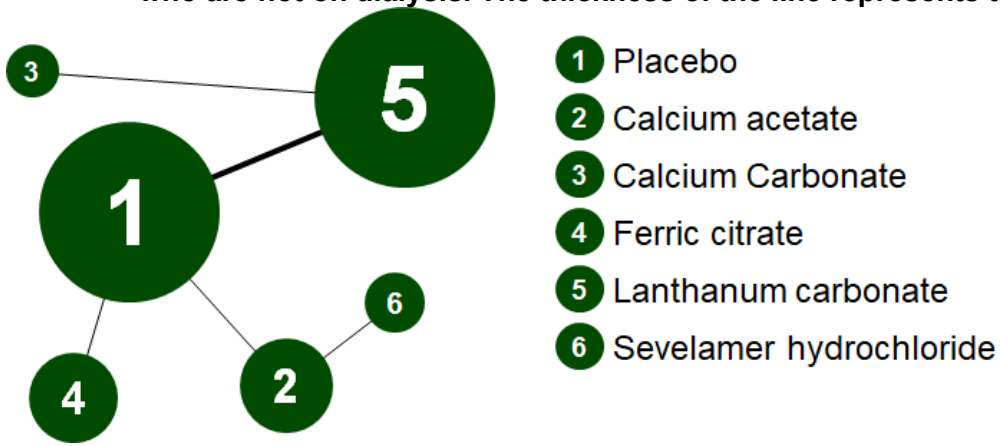
Table 29: Model fit statistics

No. of studies	Outcome	Likelihood	Link function	Model	Total model DIC	Total residual deviance	No. of datapoints	Between-study SD (95% CrI)
6	Serum phosphate at 2 to 4 months	Normal	Identity	FE	-23.955	16.61	12	---
4	Proportion of participants achieving phosphate control	Binomial	Logit	FE	47.335	8.538	8	---
5	Serum calcium at 2 to 4 months	Normal	Identity	FE	-34.841	10.06	10	---
2	Adverse events: constipation	Binomial	Cloglog	FE	21.475	4.147	4	---
1	Adverse events: diarrhoea	Binomial	Cloglog	FE	10.397	2.122	2	---
3	Adverse events: nausea/vomiting	Binomial	Cloglog	FE	30.184	7.346	6	---
5	Adverse events: discontinuation	Binomial	Cloglog	FE	45.703	10.43	10	---

Serum phosphate at 2 to 4 months

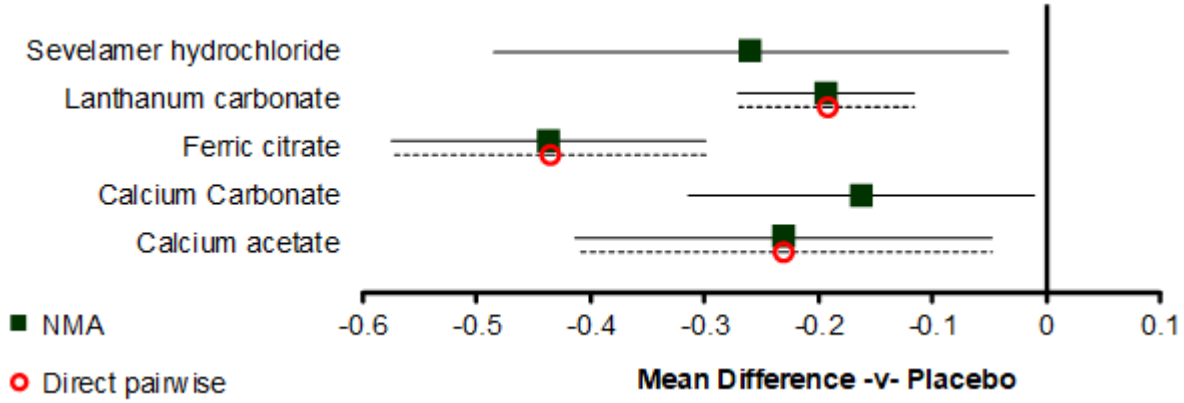
Network diagram

Figure 1: Diagram of the network of studies underlying the NMA for serum phosphate at 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis. The thickness of the line represents the number of studies.



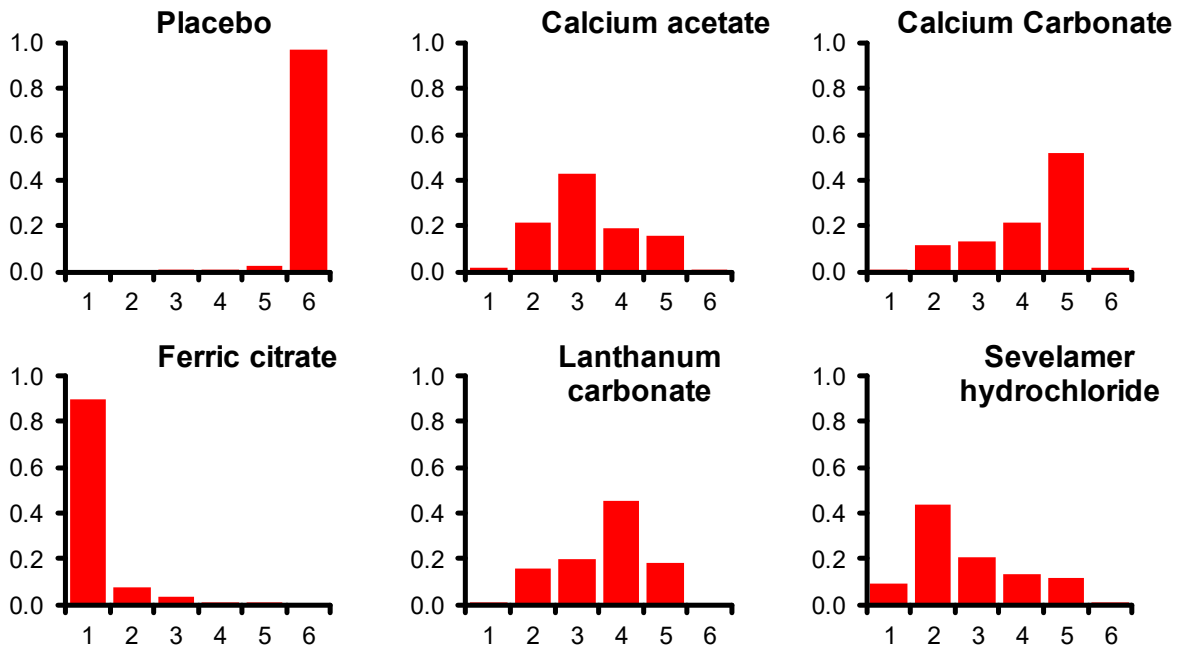
Caterpillar plot

Figure 2: Relative effectiveness of all options versus placebo for serum phosphate at 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis. (Mean differences with 95% credible intervals; values higher than 0 favour placebo; values lower than 0 favour the other treatments).



Rank probability histograms

Figure 3: Serum phosphate at 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).


Placebo
Calcium acetate
Calcium Carbonate
Ferric citrate
Lanthanum carbonate
Sevelamer hydrochloride
1.0
0.8
0.6
0.4
0.2
0.0
1 2 3 4 5 6

Relative effectiveness

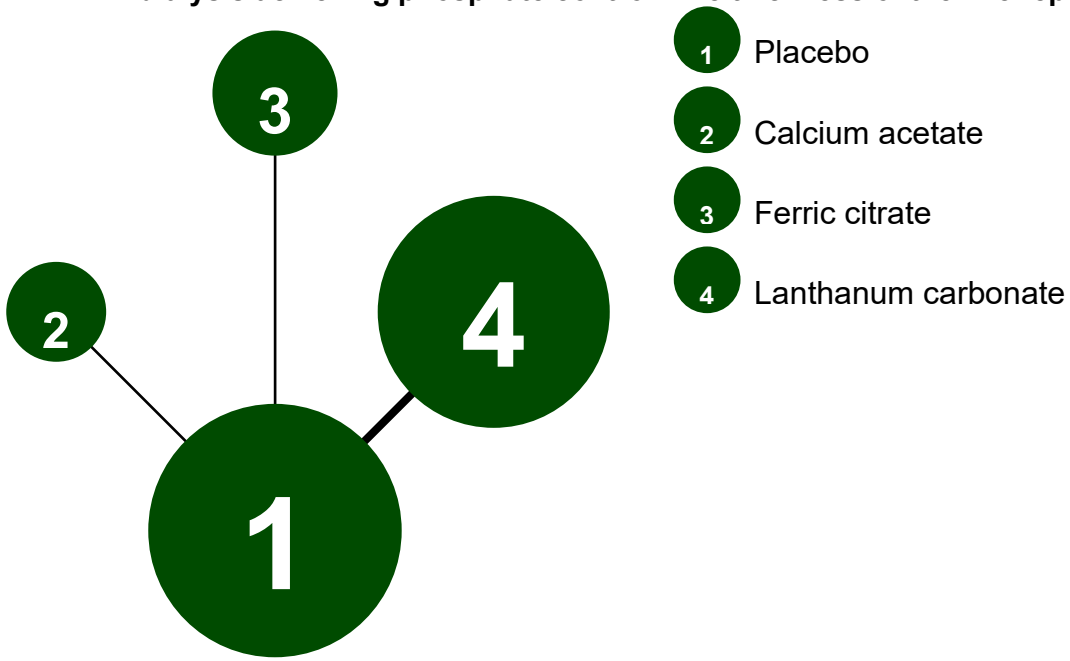
Table 30: Relative effectiveness of all pairwise combinations for serum phosphate at 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis. (Upper diagonal: mean difference (MD) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment, MDs greater than 0 favour the row defining treatment. Lower diagonal: posterior median MD with 95% credible intervals from NMA results, MDs less than 0 favour the row defining treatment. MDs greater than 0 favour the column defining treatment).

	Placebo	Calcium acetate	Calcium Carbonate	Ferric citrate	Lanthanum carbonate	Sevelamer hydrochloride
Placebo		-0.23 (-0.41, -0.05)	-	-0.44 (-0.57, -0.30)	-0.19 (-0.27, -0.11)	-
Calcium acetate	-0.23 (-0.41, -0.05)		-	-	-	-0.03 (-0.17, 0.11)
Calcium Carbonate	-0.16 (-0.31, -0.01)	0.07 (-0.17, 0.31)		-	-0.03 (-0.16, 0.10)	-
Ferric citrate	-0.44 (-0.58, -0.30)	-0.21 (-0.43, 0.02)	-0.27 (-0.48, -0.07)		-	-
Lanthanum carbonate	-0.19 (-0.27, -0.12)	0.04 (-0.16, 0.24)	-0.03 (-0.16, 0.10)	0.24 (0.08, 0.40)		-
Sevelamer hydrochloride	-0.26 (-0.49, -0.03)	-0.03 (-0.17, 0.11)	-0.10 (-0.37, 0.17)	0.18 (-0.09, 0.44)	-0.07 (-0.30, 0.18)	

Proportion of participants achieving phosphate control

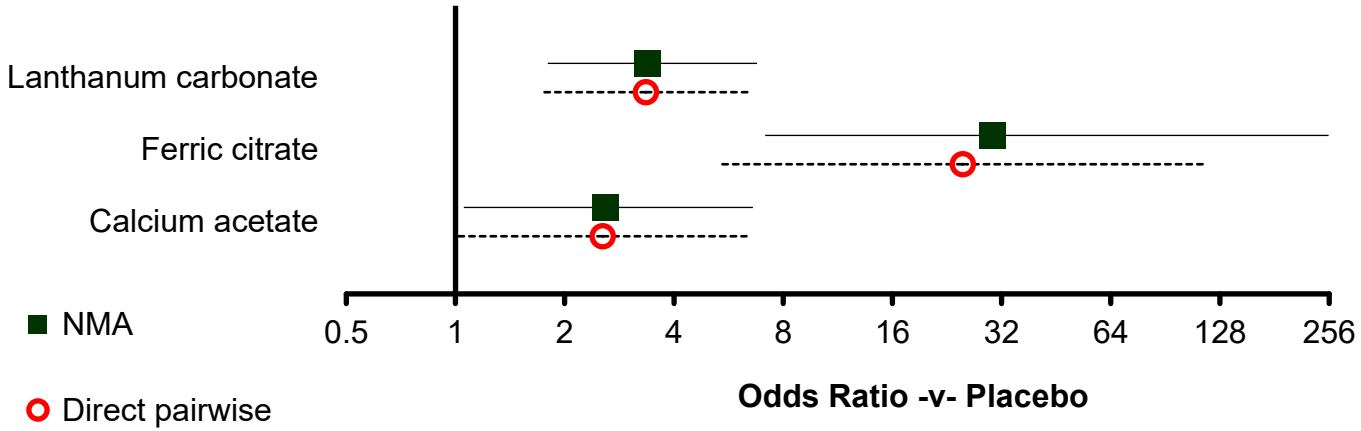
Network diagram

Figure 4: Diagram of the network of studies underlying the NMA for the proportion of adults with stage 4 or 5 CKD who are not on dialysis achieving phosphate control. The thickness of the line represents the number of studies.



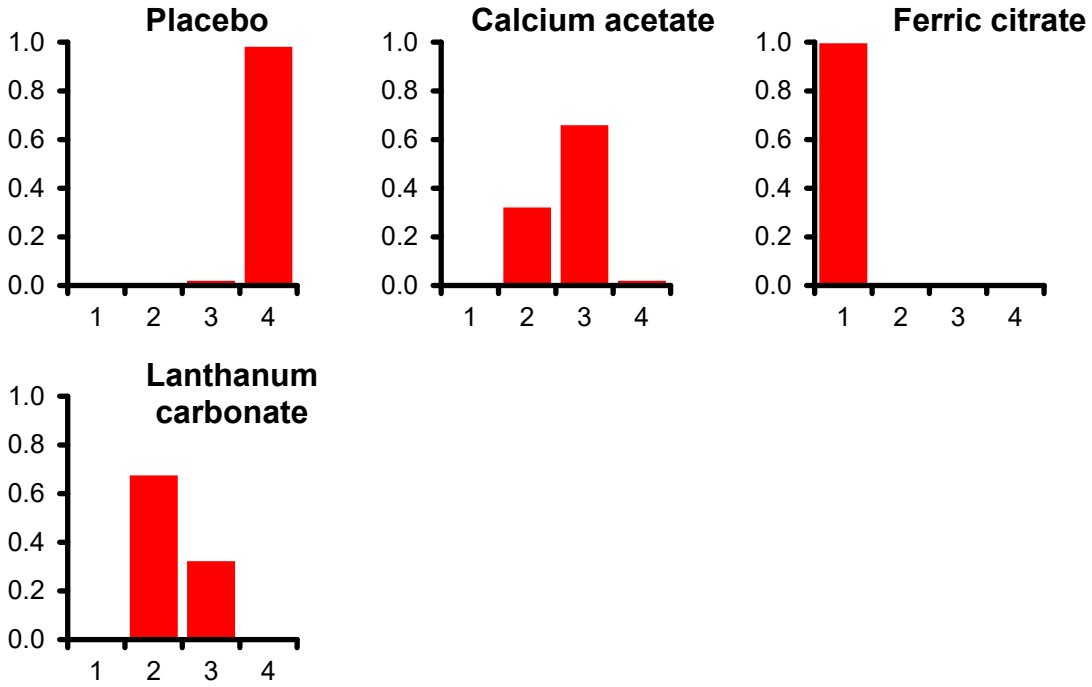
Caterpillar plot

Figure 5: Relative effectiveness of all options versus placebo for the proportion of adults with stage 4 or 5 CKD who are not on dialysis achieving phosphate control. (Odds ratios with 95% credible intervals; values lower than 1.0 favour placebo; values higher than 1.0 favour the other treatments).



Rank probability histograms

Figure 6: Proportion of adults with stage 4 or 5 CKD who are not on dialysis achieving phosphate control. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

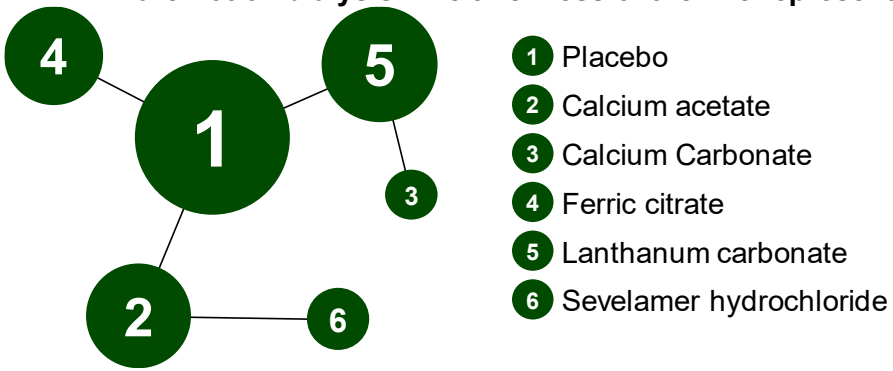
Table 31: Relative effectiveness of all pairwise combinations for the proportion of adults with stage 4 or 5 CKD who are not on dialysis achieving phosphate control. (Upper diagonal: odds ratios (OR) with 95% confidence intervals from the pair-wise meta-analysis. ORs higher than 1 favour the column defining treatment, ORs lower than 1 favour the row defining treatment. Lower diagonal: posterior median ORs with 95% credible intervals from NMA results, OR higher than 1 favour the row defining treatment. ORs lower than 1 favour the column defining treatment).

	Placebo	Calcium acetate	Ferric citrate	Lanthanum carbonate
Placebo		2.54 (1.02, 6.34)	24.98 (5.38, 116.02)	3.35 (1.74, 6.45)
Calcium acetate	2.59 (1.05, 6.60)		-	-
Ferric citrate	30.30 (7.13, 255.00)	11.88 (2.07, 114.20)		-
Lanthanum carbonate	3.38 (1.80, 6.78)	1.31 (0.43, 4.03)	0.11 (0.01, 0.56)	

Serum calcium at 2 to 4 months

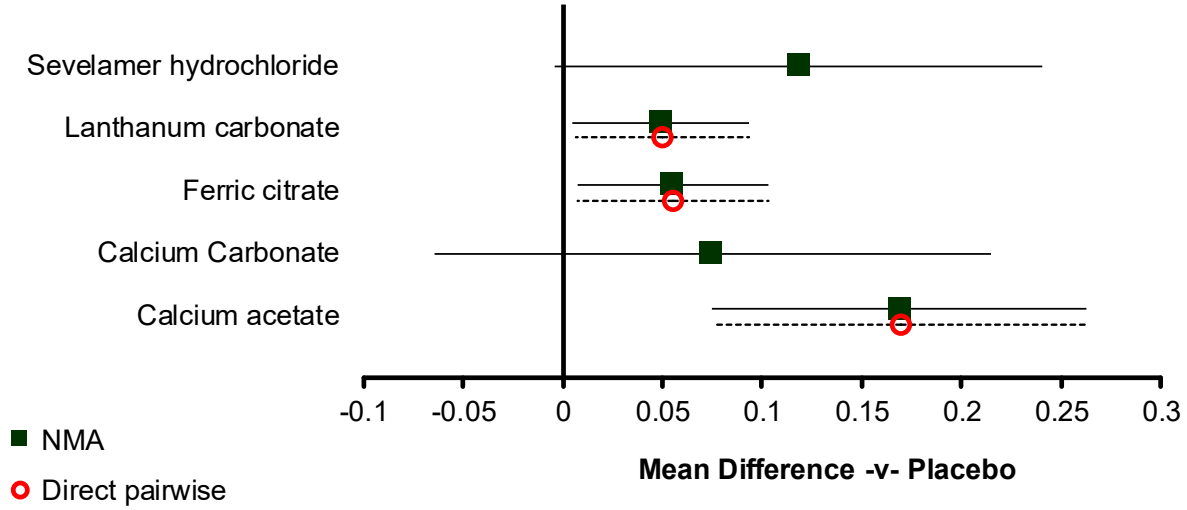
Network diagram

Figure 7: Diagram of the network of studies underlying the NMA for serum calcium at 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis. The thickness of the line represents the number of studies.



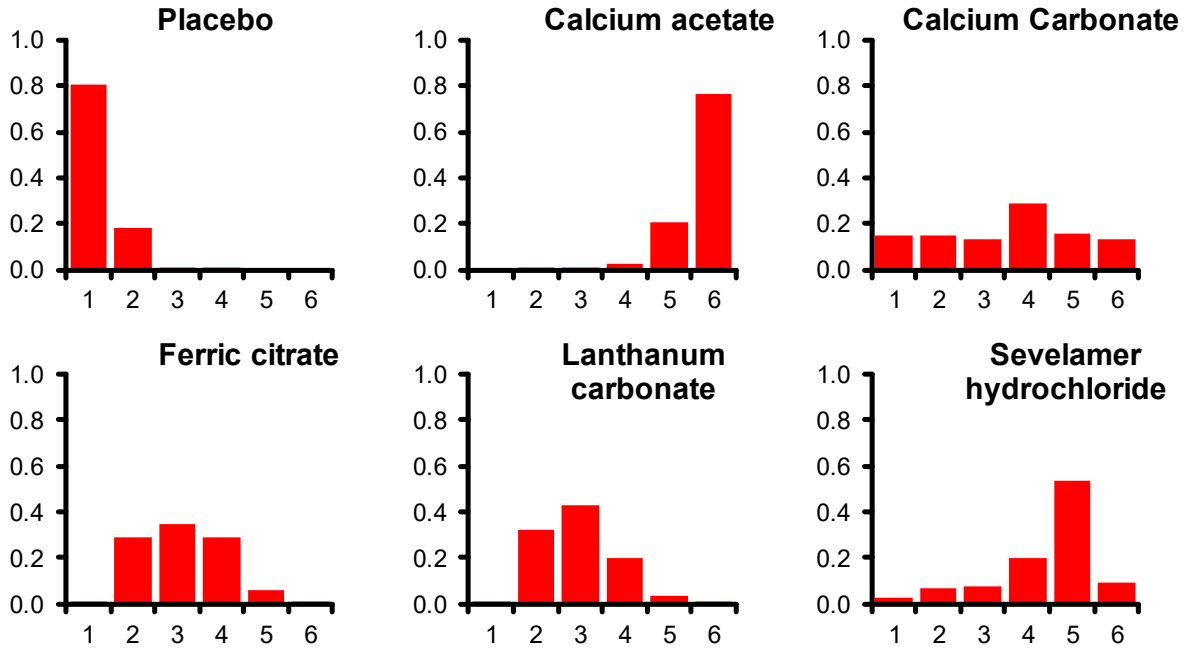
Caterpillar plot

Figure 8: Relative effectiveness of all options versus placebo for serum calcium at 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis. (Mean differences with 95% credible intervals; values higher than 0 favour placebo; values lower than 0 favour the other treatments).



Rank probability histograms

Figure 9: Serum calcium at 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

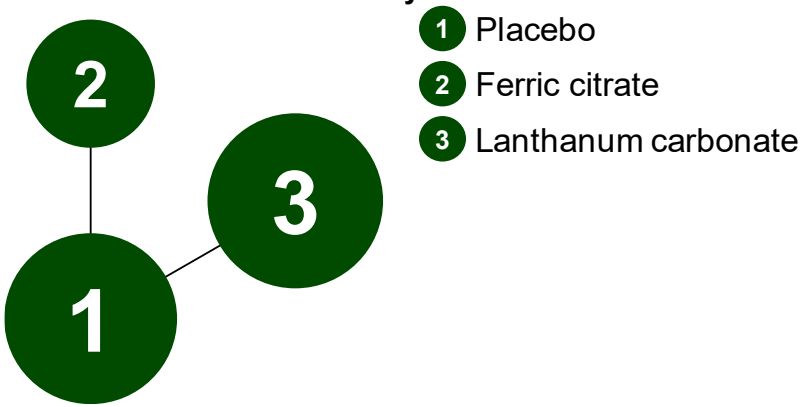
Table 32: Relative effectiveness of all pairwise combinations for serum calcium at 2 to 4 months in adults with stage 4 or 5 CKD who are not on dialysis. (Upper diagonal: mean difference (MD) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment, MDs greater than 0 favour the row defining treatment. Lower diagonal: posterior median MD with 95% credible intervals from NMA results, MDs less than 0 favour the row defining treatment. MDs greater than 0 favour the column defining treatment).

	Placebo	Calcium acetate	Calcium Carbonate	Ferric citrate	Lanthanum carbonate	Sevelamer hydrochloride
Placebo		0.17 (0.08, 0.26)	-	0.06 (0.01, 0.10)	0.05 (0.01, 0.09)	-
Calcium acetate	0.17 (0.07, 0.26)		-	-	-	-0.05 (-0.13, 0.03)
Calcium Carbonate	0.07 (-0.06, 0.21)	-0.10 (-0.26, 0.08)		-	-0.02 (-0.16, 0.11)	-
Ferric citrate	0.06 (0.01, 0.10)	-0.11 (-0.22, -0.01)	-0.02 (-0.17, 0.13)		-	-
Lanthanum carbonate	0.05 (0.00, 0.09)	-0.12 (-0.22, -0.01)	-0.02 (-0.16, 0.11)	-0.01 (-0.07, 0.06)		-
Sevelamer hydrochloride	0.12 (0.00, 0.24)	-0.05 (-0.13, 0.03)	0.04 (-0.14, 0.23)	0.06 (-0.07, 0.19)	0.07 (-0.06, 0.20)	

Adverse events: constipation

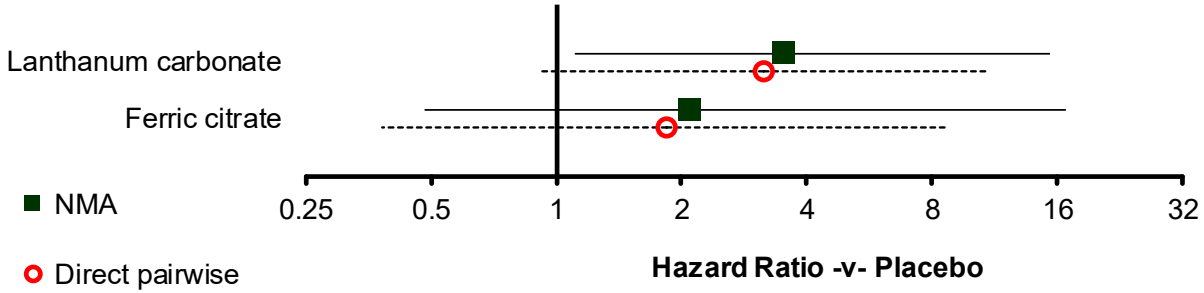
Network diagram

Figure 10: Diagram of the network of studies underlying the NMA for adverse events (constipation) in adults with stage 4 or 5 CKD who are not on dialysis. The thickness of the line represents the number of studies.



Caterpillar plot

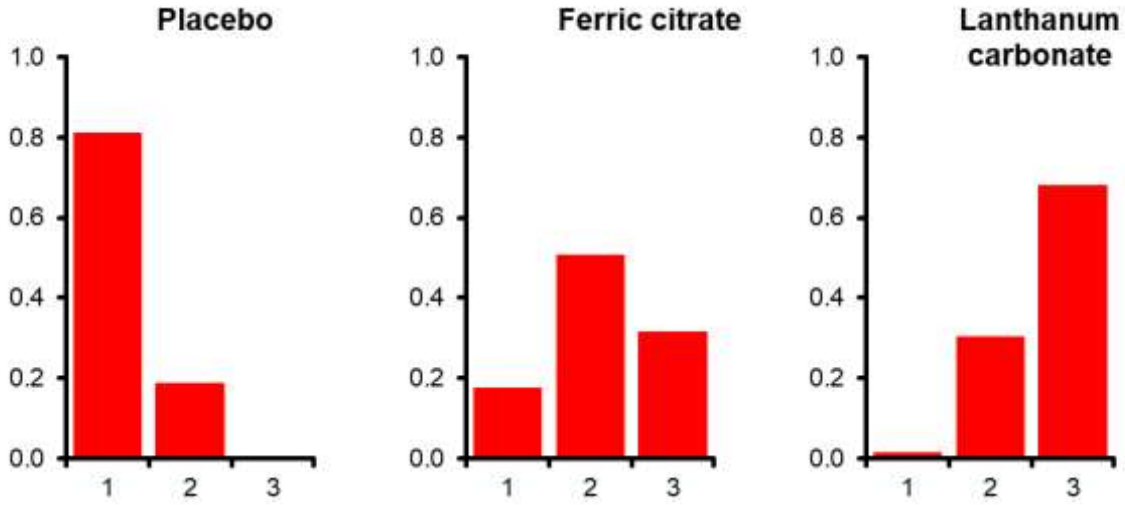
Figure 11: Relative effectiveness of all options versus placebo for adverse events (constipation) in adults with stage 4 or 5 CKD who are not on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour placebo; values lower than 1.0 favour the other treatments).



Direct pairwise and NMA estimates are not exactly the same because pairwise estimates use approximated HRs; whereas NMA estimates do not rely on this estimation.

Rank probability histograms

Figure 12: Adverse events (constipation) in adults with stage 4 or 5 CKD who are not on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

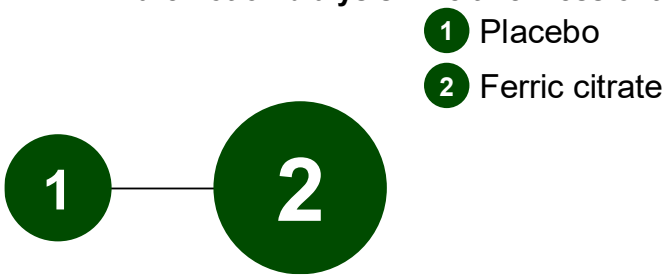
Table 33: Relative effectiveness of all pairwise combinations for adverse events (constipation) in adults with stage 4 or 5 CKD who are not on dialysis. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs less than 1 favour the column defining treatment, HRs greater than 1 favour the row defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

	Placebo	Ferric citrate	Lanthanum carbonate
Placebo		1.83 (0.38, 8.83)	3.17 (0.91, 11.03)
Ferric citrate	2.11 (0.48, 16.78)		-
Lanthanum carbonate	3.53 (1.11, 15.38)	1.68 (0.16, 13.60)	

Adverse events: diarrhoea

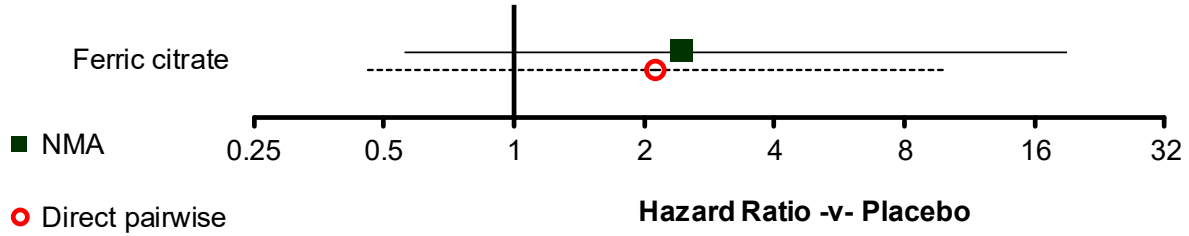
Network diagram

Figure 13: Diagram of the network of studies underlying the NMA for adverse events (diarrhoea) in adults with stage 4 or 5 CKD who are not on dialysis. The thickness of the line represents the number of studies.



Caterpillar plot

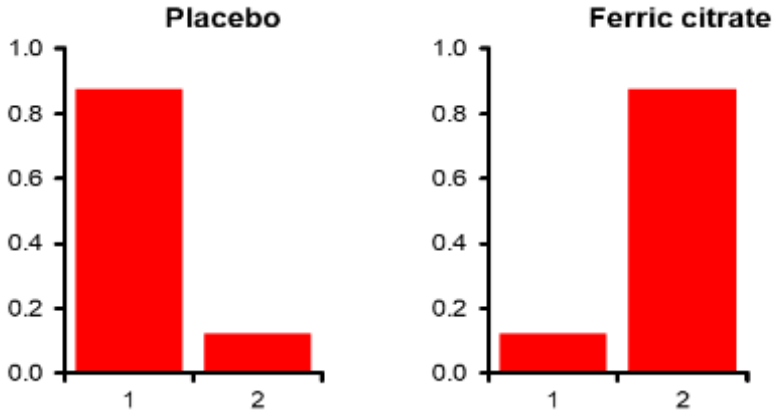
Figure 14: Relative effectiveness of ferric citrate versus placebo for adverse events (diarrhoea) in adults with stage 4 or 5 CKD who are not on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour placebo; values lower than 1.0 favour ferric citrate).



Direct pairwise and NMA estimates are not exactly the same because pairwise estimates use approximated HRs; whereas NMA estimates do not rely on this estimation.

Rank probability histograms

Figure 15: Adverse events (diarrhoea) in adults with stage 4 or 5 CKD who are not on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 34: Relative effectiveness of all pairwise combinations for adverse events (diarrhoea) in adults with stage 4 or 5 CKD who are not on dialysis. (Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

	Placebo	Ferric citrate
Placebo		2.12 (0.45, 9.97)
Ferric citrate	2.46 (0.56, 19.03)	

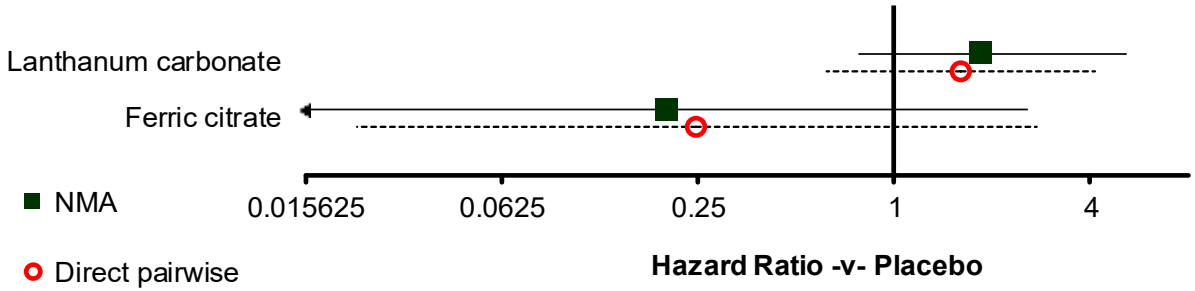
Adverse events: nausea and/or vomiting

Network diagram

Figure 16: Diagram of the network of studies underlying the NMA for adverse events (nausea and/or vomiting) in adults with stage 4 or 5 CKD who are not on dialysis. The thickness of the line represents the number of studies.

Caterpillar plot

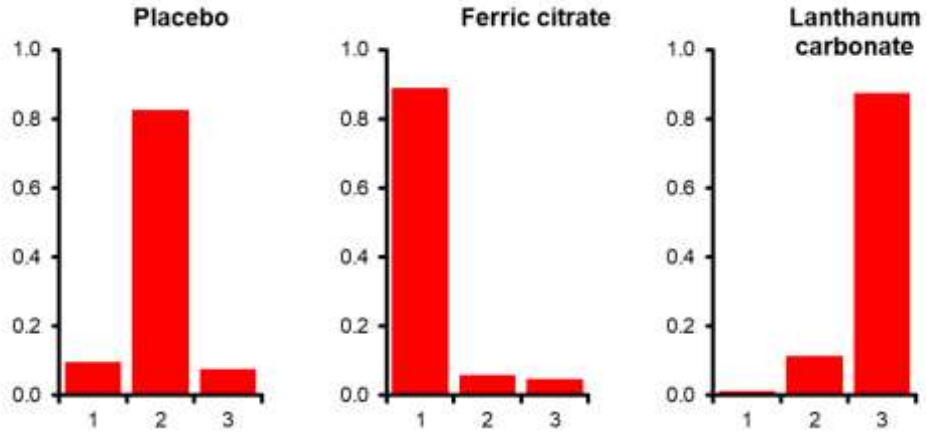
Figure 17: Relative effectiveness of all options versus placebo for adverse events (nausea and/or vomiting) in adults with stage 4 or 5 CKD who are not on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour placebo; values lower than 1.0 favour the other treatments).



Direct pairwise and NMA estimates are not exactly the same because pairwise estimates use approximated HRs; whereas NMA estimates do not rely on this estimation.

Rank probability histograms

Figure 18: Adverse events (nausea and/or vomiting) in adults with stage 4 or 5 CKD who are not on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

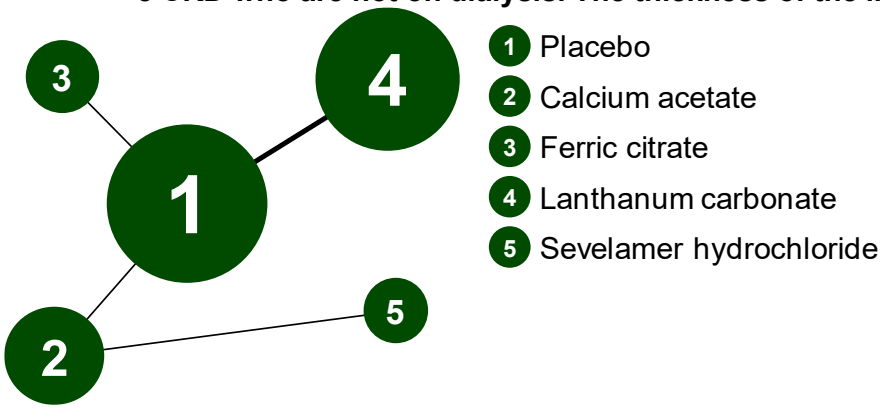
Table 35: Relative effectiveness of all pairwise combinations for adverse events (nausea and/or vomiting) in adults with stage 4 or 5 CKD who are not on dialysis. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs less than 1 favour the column defining treatment, HRs greater than 1 favour the row defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

	Placebo	Ferric citrate	Lanthanum carbonate
Placebo		0.25 (0.02, 2.73)	1.60 (0.62, 4.14)
Ferric citrate	0.20 (0.01, 2.56)		-
Lanthanum carbonate	1.85 (0.78, 5.17)	9.54 (0.62, 336.20)	

Discontinuation due to adverse events

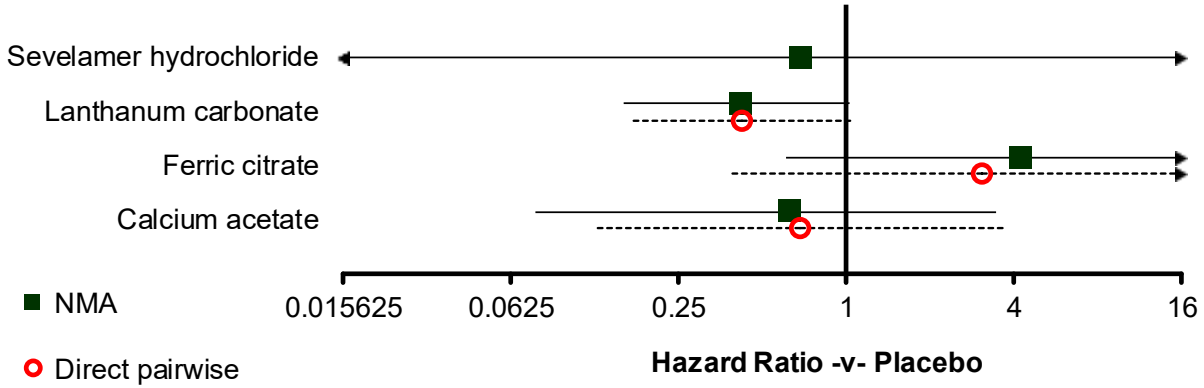
Network diagram

Figure 19: Diagram of the network of studies underlying the NMA for discontinuation due to adverse events in adults with stage 4 or 5 CKD who are not on dialysis. The thickness of the line represents the number of studies.



Caterpillar plot

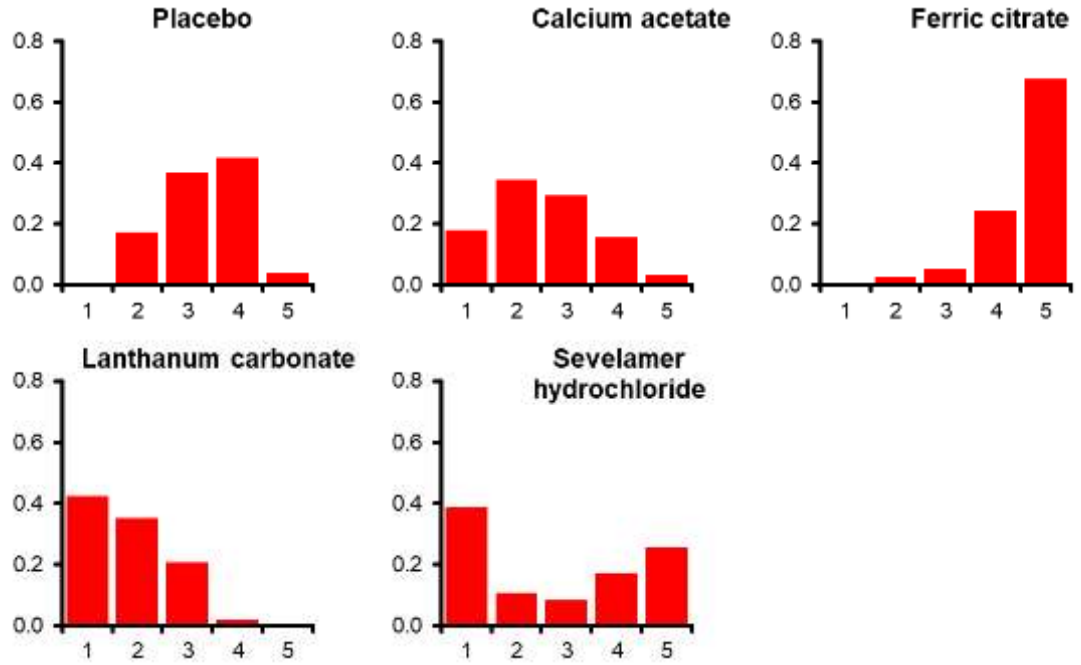
Figure 20: Relative effectiveness of all options versus placebo for discontinuation due to adverse events in adults with stage 4 or 5 CKD who are not on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour placebo; values lower than 1.0 favour the other treatments).



Direct pairwise and NMA estimates are not exactly the same because pairwise estimates use approximated HRs; whereas NMA estimates do not rely on this estimation.

Rank probability histograms

Figure 21: Discontinuation due to adverse events in adults with stage 4 or 5 CKD who are not on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 36: Relative effectiveness of all pairwise combinations for discontinuation due to adverse events in adults with stage 4 or 5 CKD who are not on dialysis. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs less than 1 favour the column defining treatment, HRs greater than 1 favour the row defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

	Placebo	Calcium acetate	Ferric citrate	Lanthanum carbonate	Sevelamer hydrochloride
Placebo		0.69 (0.13, 3.76)	3.11 (0.37, 25.82)	0.42 (0.17, 1.06)	-
Calcium acetate	0.64 (0.08, 3.46)		-	-	1.13 (0.02, 56.73)
Ferric citrate	4.29 (0.61, 103.20)	7.38 (0.49, 292.00)		-	-
Lanthanum carbonate	0.42 (0.16, 1.03)	0.66 (0.09, 6.37)	0.10 (0.00, 0.84)		-
Sevelamer hydrochloride	0.69 (0.00, 587.00)	1.14 (0.00, 828.70)	0.14 (0.00, 166.40)	1.67 (0.00, 1569.00)	

Adults with stage 5 CKD who are on dialysis

Model fit statistics

Table 37: Model fit statistics

No. of studies	Outcome	Likelihood	Link function	Model	Total model DIC	Total residual deviance	No. of datapoints	Between-study SD (95% CrI)	Preferred model
21	Serum phosphate at 3 months	Normal	Identity	FE	-55.072	51.61	42	---	RE
				RE	-59.539	41.6		0.111 (0.024, 0.252)	
21	Serum phosphate at 3 months[a]	Normal	Identity	RE	-59.5	41.62	42	0.110 (0.027, 0.251)	RE
22	Serum phosphate at 6 months	Normal	Identity	FE	-55.79	54.67	44	---	RE
				RE	-56.074	49.0		0.087 (0.004, 0.240)	
22	Serum phosphate at 6 months[b]	Normal	Identity	RE	-55.88	49.11	44	0.087 (0.004, 0.242)	RE
21	Serum phosphate at 12 months	Normal	Identity	FE	-68.696	45.08	44	---	RE
				RE	-67.747	42.37		0.051 (0.003, 0.144)	
21	Serum phosphate at 12 months[b]	Normal	Identity	RE	-67.69	42.49	44	0.050 (0.003, 0.143)	RE
23	Proportion of participants achieving phosphate control	Binomial	Logit	FE	388.507	122.9	59	---	RE
				RE	345.779	61.42		0.869 (0.545, 1.341)	
23	Proportion of participants achieving phosphate control[c]	Binomial	Logit	RE	345.7	61.35	59	0.871 (0.551, 1.348)	RE
16	Serum calcium at 3 months	Normal	Identity	FE	-110.677	39.55	32	---	RE
				RE	-114.369	31.56		0.048 (0.010, 0.127)	
16	Serum calcium at 3 months[a]	Normal	Identity	RE	-114.3	31.61	32	0.048 (0.009, 0.128)	RE
19	Serum calcium at 6 months	Normal	Identity	FE	-93.218	78.9	38	---	RE
				RE	-125.625	38.1		0.091 (0.049, 0.172)	
19	Serum calcium at 6 months[b]	Normal	Identity	RE	-125.8	38	38	0.091 (0.049, 0.170)	RE
19	Serum calcium at 12 months	Normal	Identity	FE	-108.757	67.99	40	---	RE
				RE	-126.389	41.04		0.079 (0.036, 0.151)	
19	Serum calcium at 12 months[b]	Normal	Identity	RE	-126.4	41	40	0.080 (0.037, 0.151)	RE
18		Binomial	Logit	FE	220.306	58.16	41	---	RE

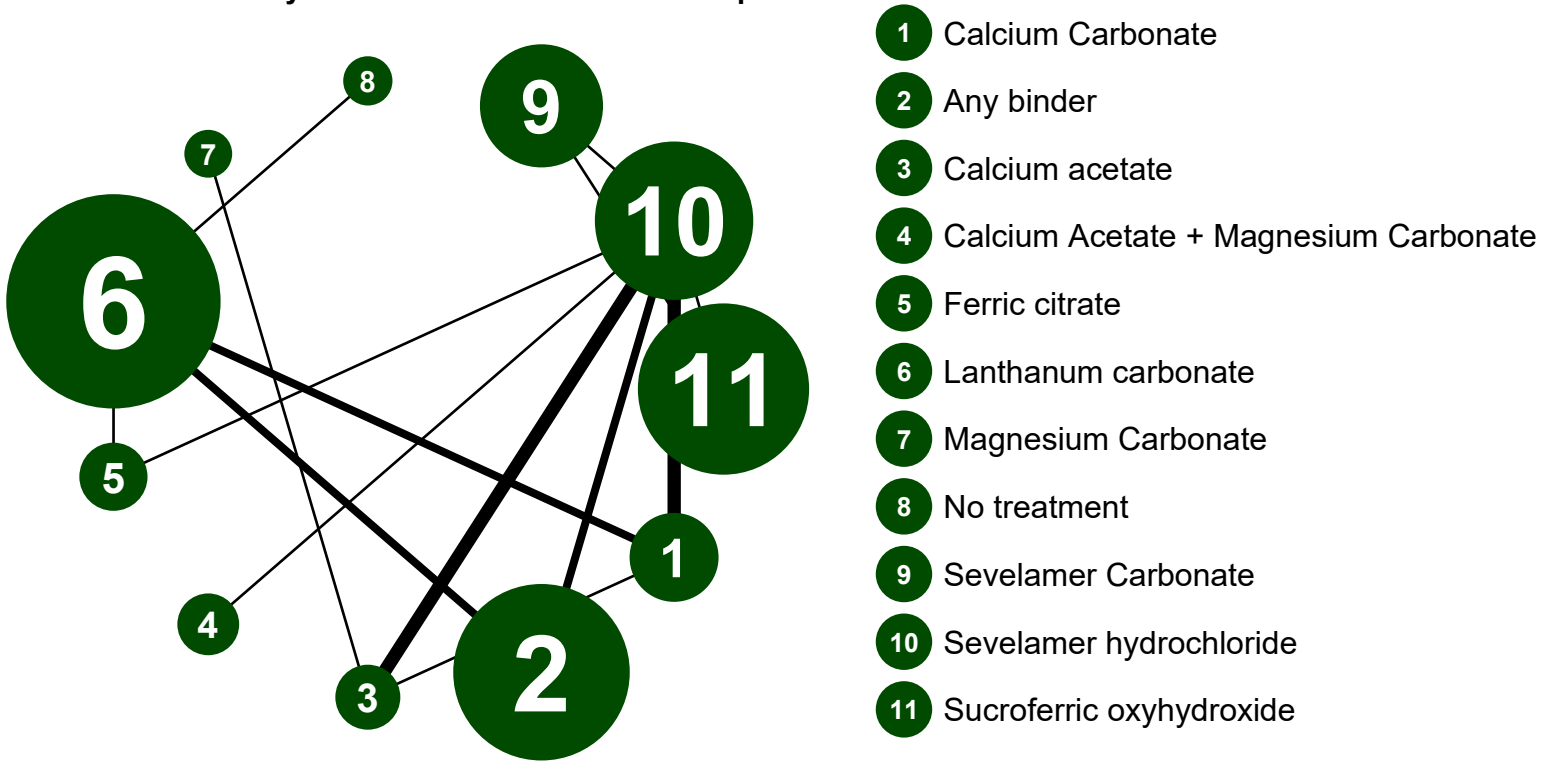
No. of studies	Outcome	Likelihood	Link function	Model	Total model DIC	Total residual deviance	No. of datapoints	Between-study SD (95% CrI)	Preferred model
	Proportion of participants experiencing hypercalcaemia*			RE	212.037	41.95		0.880 (0.281, 1.648)	
18	Proportion of participants experiencing hypercalcaemia[d]	Binomial	Logit	RE	211.9	41.92	41	0.849 (0.290, 1.704)	RE
23	Adverse events: constipation	Binomial	Cloglog	FE	256.001	63.82	58	---	FE
				RE	256.498	58.83		0.436 (0.031, 1.118)	
23	Adverse events: constipation[d]	Binomial	Cloglog	FE	256	63.8	58	---	FE
20	Adverse events: diarrhoea	Binomial	Cloglog	FE	258.48	62.66	51	---	RE
				RE	254.357	50.46		0.549 (0.076, 1.112)	
20	Adverse events: diarrhoea[c]	Binomial	Cloglog	RE	254.3	50.36	51	0.555 (0.097, 1.112)	RE
19	Adverse events: nausea and/or vomiting	Binomial	Cloglog	FE	245.292	73.69	45	---	RE
				RE	225.483	43.95		1.055 (0.553, 1.773)	
19	Adverse events: nausea and/or vomiting[c]	Binomial	Cloglog	RE	225.4	43.84	45	1.065 (0.564, 1.888)	RE
37	Adverse events: discontinuation*	Binomial	Cloglog	FE	409.407	106.3	82	---	RE
				RE	397.46	80.5		0.607 (0.275, 1.018)	
37	Adverse events: discontinuation[e]	Binomial	Cloglog	RE	397.3	80.57	82	0.604 (0.264, 1.015)	RE
11	All-cause mortality*	Normal/ Binomial	Identity/ Cloglog	FE	67.974	22.59	22	---	FE
11	All-cause mortality[f]	Normal/ Binomial	Identity/ Cloglog	FE	63.377	22.63	22	---	FE

(b) Network without 'any binder' and 'no treatment' nodes.
(c) Network without 'any binder' node.
(d) Network without 'any binder' and 'placebo' nodes.
(e) Network without 'calcium based binders' and 'placebo' nodes.
(f) Network without 'any binder' and 'placebo/no treatment' nodes.
(g) Network without 'any binder' and 'calcium based binders' nodes.
** Continuity correction used (0.5 was added to both arms of studies with zero events in one arm, and 1 was added to the denominator for both groups for these models).*

Serum phosphate at 3 months

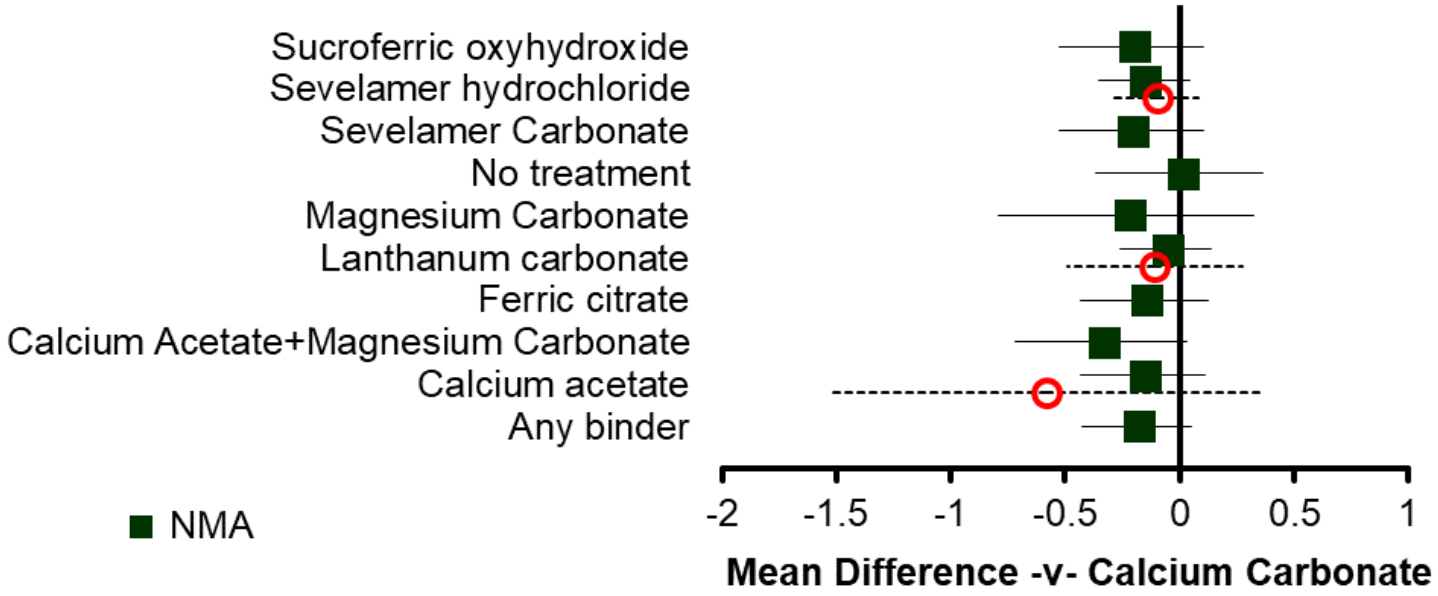
Network diagram

Figure 22: Diagram of the network of studies underlying the NMA for serum phosphate at 3 months in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



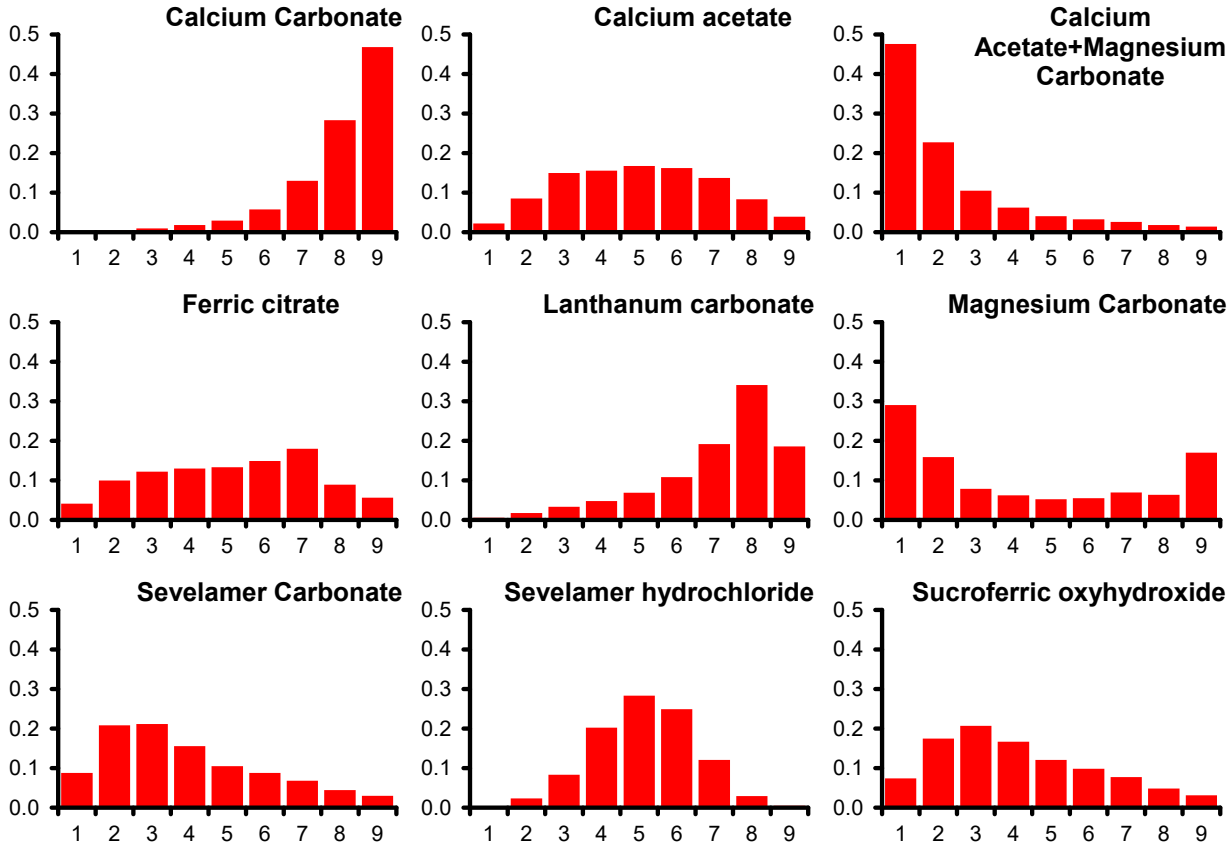
Caterpillar plot

Figure 23: Relative effectiveness of all options versus calcium carbonate for serum phosphate at 3 months in adults with stage 5 CKD who are on dialysis. (Mean differences with 95% credible intervals; values higher than 0 favour calcium carbonate; values lower than 0 favour the other treatments).



Rank probability histograms

Figure 24: Serum phosphate at 3 months in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 38: Relative effectiveness of all pairwise combinations for serum phosphate at 3 months in adults with stage 5 CKD who are on dialysis. (Upper diagonal: mean difference (MD) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment, MDs greater than 0 favour the row defining treatment. Lower diagonal: posterior median MD with 95% credible intervals from NMA results, MDs less than 0 favour the row defining treatment. MDs greater than 0 favour the column defining treatment).

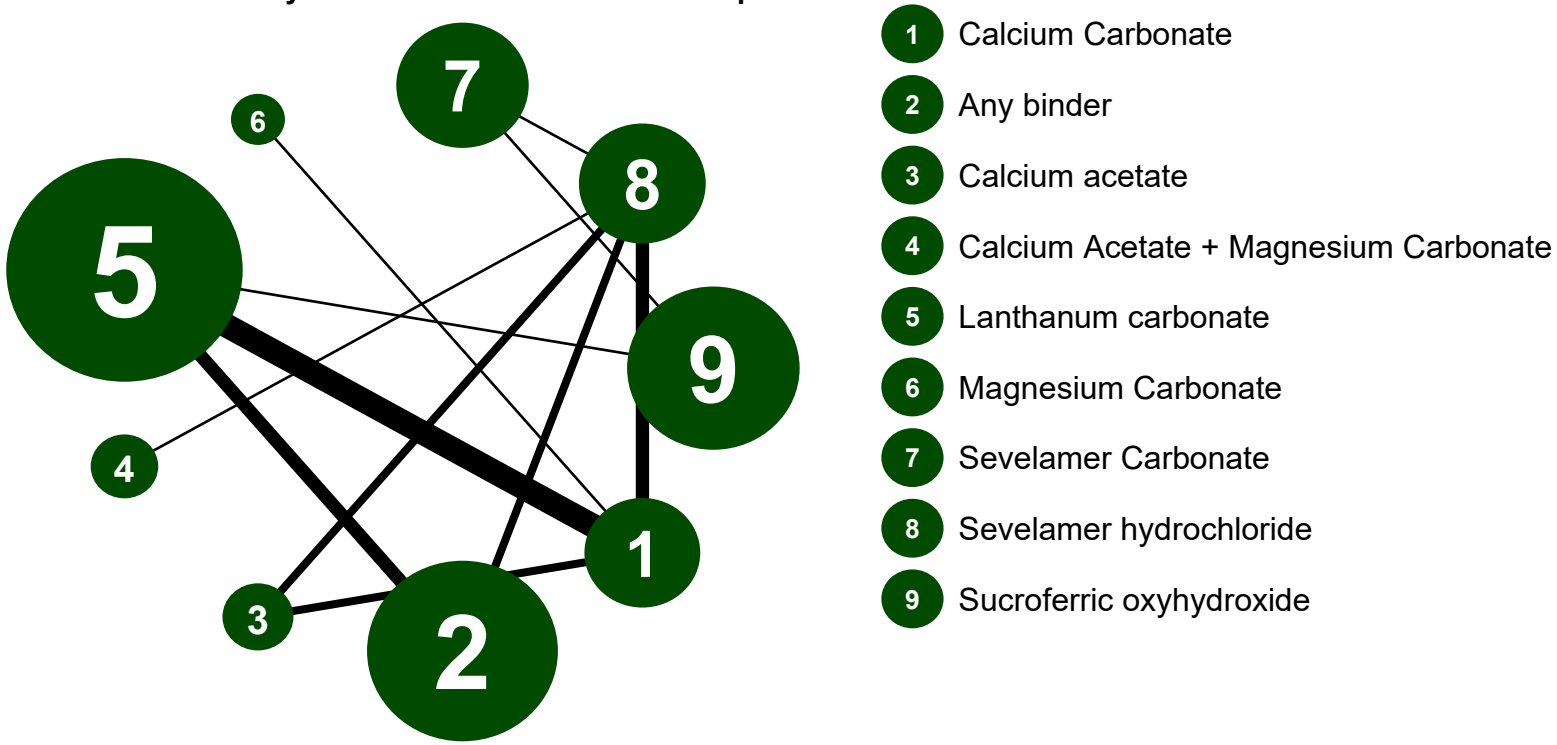
	Calcium Carbonate	Any binder	Calcium acetate	Calcium Acetate + Magnesium Carbonate	Ferric citrate	Lanthanum carbonate	Magnesium Carbonate	No treatment	Sevelamer Carbonate	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-0.58 (-1.53, 0.37)	-	-	-0.11 (-0.49, 0.27)	-	-	-	-0.10 (-0.28, 0.08)	-
Any binder	-0.18 (-0.43, 0.05)		-	-	-	0.17 (0.08, 0.27)	-	-	-	-0.05 (-0.37, 0.26)	-
Calcium acetate	-0.15 (-0.43, 0.11)	0.03 (-0.27, 0.30)		-	-	-	-0.07 (-0.48, 0.34)	-	-	-0.01 (-0.12, 0.11)	-
Calcium Acetate + Magnesium Carbonate	-0.33 (-0.72, 0.03)	-0.15 (-0.54, 0.22)	-0.18 (-0.55, 0.19)		-	-	-	-	-	0.18 (0.01, 0.36)	-
Ferric citrate	-0.14 (-0.43, 0.13)	0.04 (-0.25, 0.32)	0.01 (-0.29, 0.32)	0.19 (-0.20, 0.59)		0.03 (-0.16, 0.23)	-	-	-	0.04 (-0.09, 0.17)	-
Lanthanum carbonate	-0.05 (-0.26, 0.14)	0.14 (-0.07, 0.32)	0.10 (-0.18, 0.39)	0.28 (-0.09, 0.67)	0.09 (-0.16, 0.34)		-	0.06 (-0.09, 0.21)	-	-	-
Magnesium Carbonate	-0.22 (-0.79, 0.33)	-0.04 (-0.62, 0.51)	-0.07 (-0.56, 0.41)	0.11 (-0.50, 0.72)	-0.08 (-0.66, 0.49)	-0.17 (-0.75, 0.38)		-	-	-	-
No treatment	0.01 (-0.36, 0.37)	0.19 (-0.18, 0.55)	0.16 (-0.25, 0.58)	0.35 (-0.15, 0.84)	0.16 (-0.24, 0.55)	0.06 (-0.24, 0.37)	0.23 (-0.40, 0.87)		-	-	-
Sevelamer Carbonate	-0.21 (-0.53, 0.10)	-0.03 (-0.36, 0.30)	-0.06 (-0.36, 0.27)	0.12 (-0.27, 0.54)	-0.07 (-0.41, 0.28)	-0.16 (-0.48, 0.18)	0.01 (-0.55, 0.60)	-0.22 (-0.66, 0.23)		-0.06 (-0.21, 0.08)	0.10 (0.02, 0.18)
Sevelamer hydrochloride	-0.15 (-0.35, 0.04)	0.03 (-0.19, 0.25)	0.00 (-0.18, 0.20)	0.19 (-0.13, 0.51)	0.00 (-0.25, 0.23)	-0.10 (-0.31, 0.12)	0.07 (-0.45, 0.61)	-0.16 (-0.53, 0.21)	0.06 (-0.19, 0.30)		-0.17 (-0.31, -0.03)

Sucroferric oxyhydroxide	-0.20 (-0.53, 0.11)	-0.02 (-0.35, 0.30)	-0.05 (-0.36, 0.27)	0.14 (-0.27, 0.54)	-0.05 (-0.41, 0.28)	-0.15 (-0.48, 0.18)	0.02 (-0.55, 0.60)	-0.21 (-0.66, 0.23)	0.01 (-0.24, 0.23)	-0.05 (-0.30, 0.19)	

Serum phosphate at 6 months

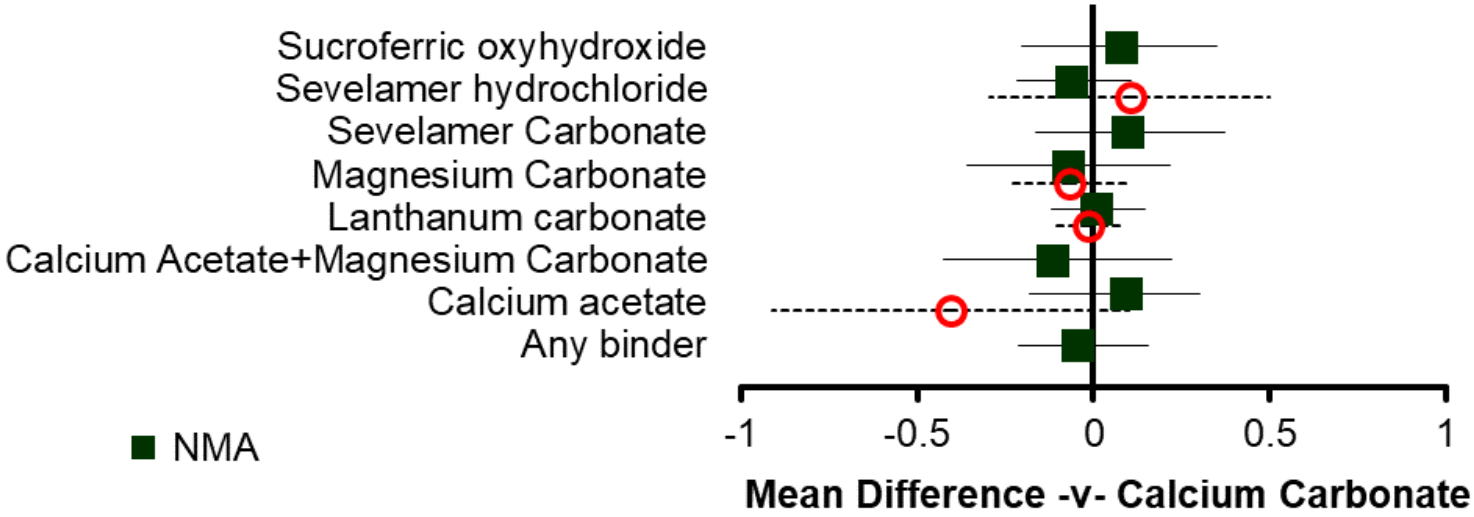
Network diagram

Figure 25: Diagram of the network of studies underlying the NMA for serum phosphate at 6 months in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



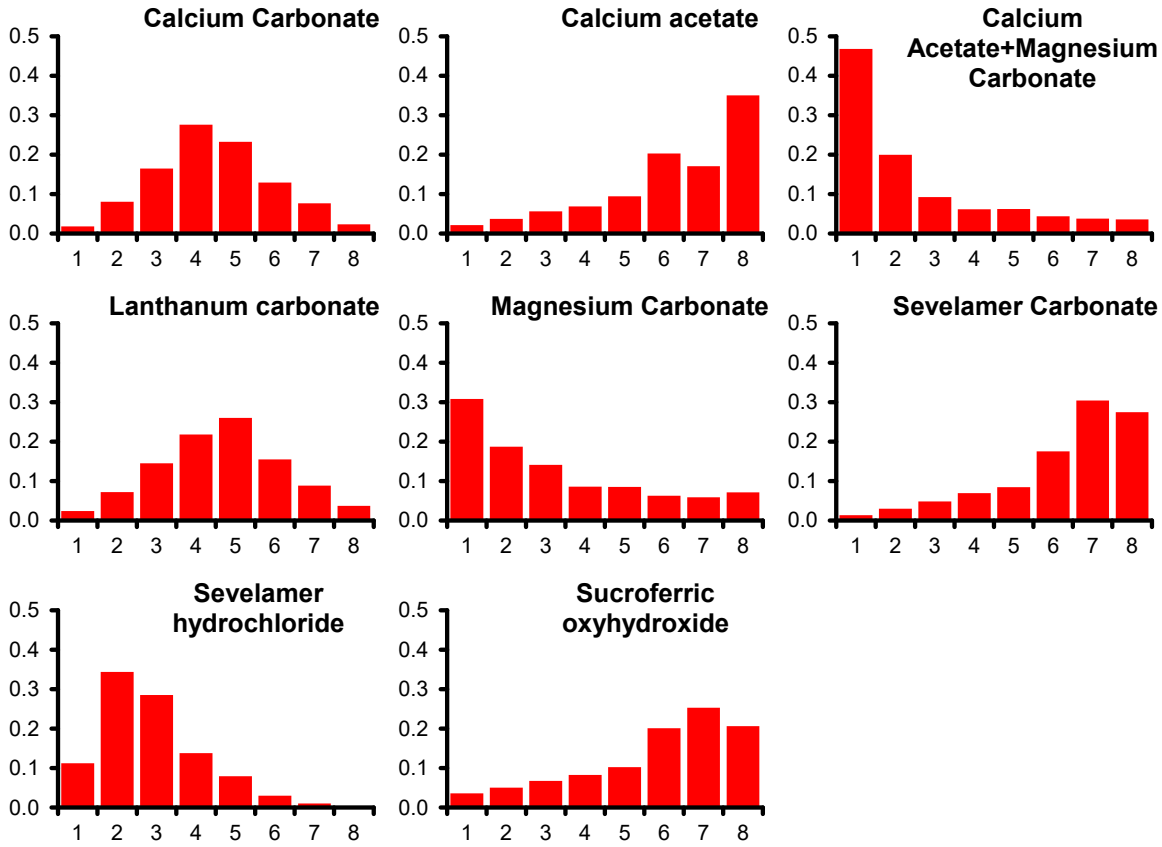
Caterpillar plot

Figure 26: Relative effectiveness of all options versus calcium carbonate for serum phosphate at 6 months in adults with stage 5 CKD who are on dialysis. (Mean differences with 95% credible intervals; values higher than 0 favour calcium carbonate; values lower than 0 favour the other treatments).



Rank probability histograms

Figure 27: Serum phosphate at 6 months in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

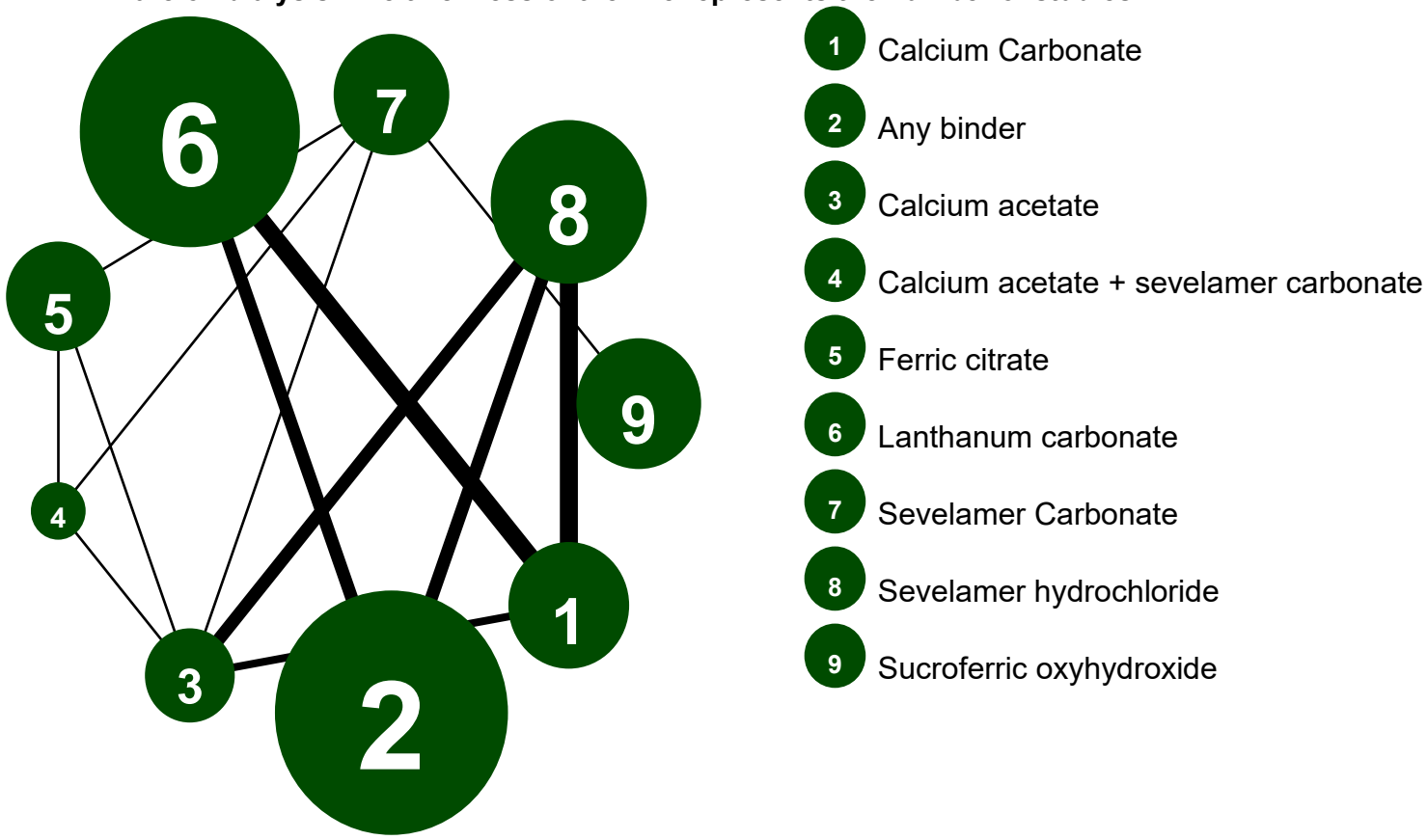
Table 39: Relative effectiveness of all pairwise combinations for serum phosphate at 6 months in adults with stage 5 CKD who are on dialysis. (Upper diagonal: mean difference (MD) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment, MDs greater than 0 favour the row defining treatment. Lower diagonal: posterior median MD with 95% credible intervals from NMA results, MDs less than 0 favour the row defining treatment. MDs greater than 0 favour the column defining treatment).

	Calcium Carbonate	Any binder	Calcium acetate	Calcium Acetate + Magnesium Carbonate	Lanthanum carbonate	Magnesium Carbonate	Sevelamer Carbonate	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-0.40 (-0.91, 0.10)	-	-0.01 (-0.11, 0.08)	-0.07 (-0.25, 0.11)	-	0.10 (-0.29, 0.50)	-
Any binder	-0.05 (-0.21, 0.15)		-	-	0.08 (-0.01, 0.16)	-	-	-0.04 (-0.21, 0.13)	-
Calcium acetate	0.09 (-0.18, 0.30)	0.14 (-0.18, 0.36)		-	-	-	-	-0.22 (-0.30, -0.14)	-
Calcium Acetate + Magnesium Carbonate	-0.12 (-0.43, 0.22)	-0.07 (-0.40, 0.26)	-0.21 (-0.51, 0.20)		-	-	-	0.05 (-0.11, 0.21)	-
Lanthanum carbonate	0.01 (-0.12, 0.15)	0.05 (-0.11, 0.19)	-0.09 (-0.30, 0.21)	0.12 (-0.22, 0.44)		-	-	-	0.00 (-0.27, 0.27)
Magnesium Carbonate	-0.07 (-0.36, 0.22)	-0.03 (-0.38, 0.30)	-0.17 (-0.50, 0.25)	0.05 (-0.40, 0.47)	-0.08 (-0.40, 0.23)		-	-	-
Sevelamer Carbonate	0.10 (-0.16, 0.37)	0.14 (-0.14, 0.41)	0.00 (-0.26, 0.36)	0.21 (-0.16, 0.58)	0.09 (-0.17, 0.35)	0.17 (-0.22, 0.57)		-0.19 (-0.34, -0.04)	0.00 (-0.08, 0.08)
Sevelamer hydrochloride	-0.07 (-0.22, 0.11)	-0.02 (-0.20, 0.16)	-0.16 (-0.31, 0.10)	0.05 (-0.23, 0.33)	-0.07 (-0.24, 0.11)	0.01 (-0.31, 0.35)	-0.16 (-0.39, 0.08)		-
Sucroferric oxyhydroxide	0.08 (-0.20, 0.35)	0.12 (-0.19, 0.39)	-0.02 (-0.31, 0.35)	0.19 (-0.21, 0.56)	0.07 (-0.20, 0.33)	0.15 (-0.26, 0.54)	-0.02 (-0.25, 0.19)	0.14 (-0.15, 0.39)	

Serum phosphate at 12 months

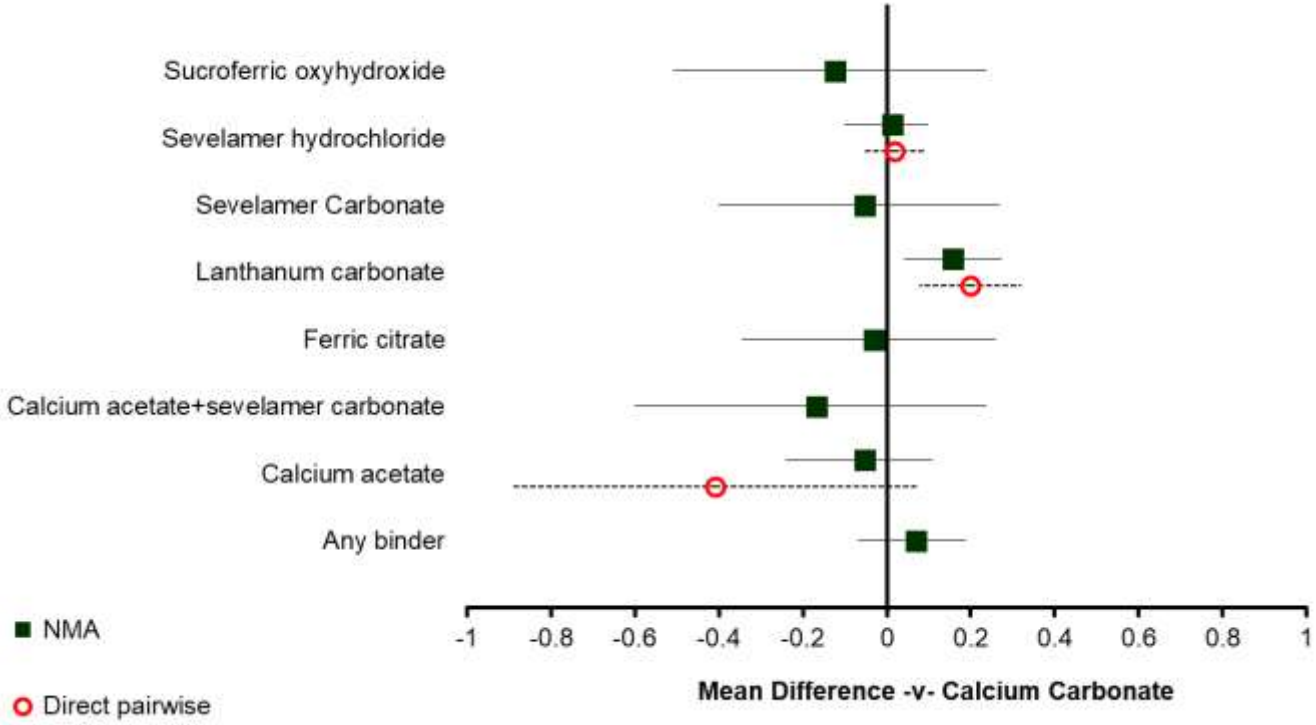
Network diagram

Figure 28: Diagram of the network of studies underlying the NMA for serum phosphate at 12 months in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



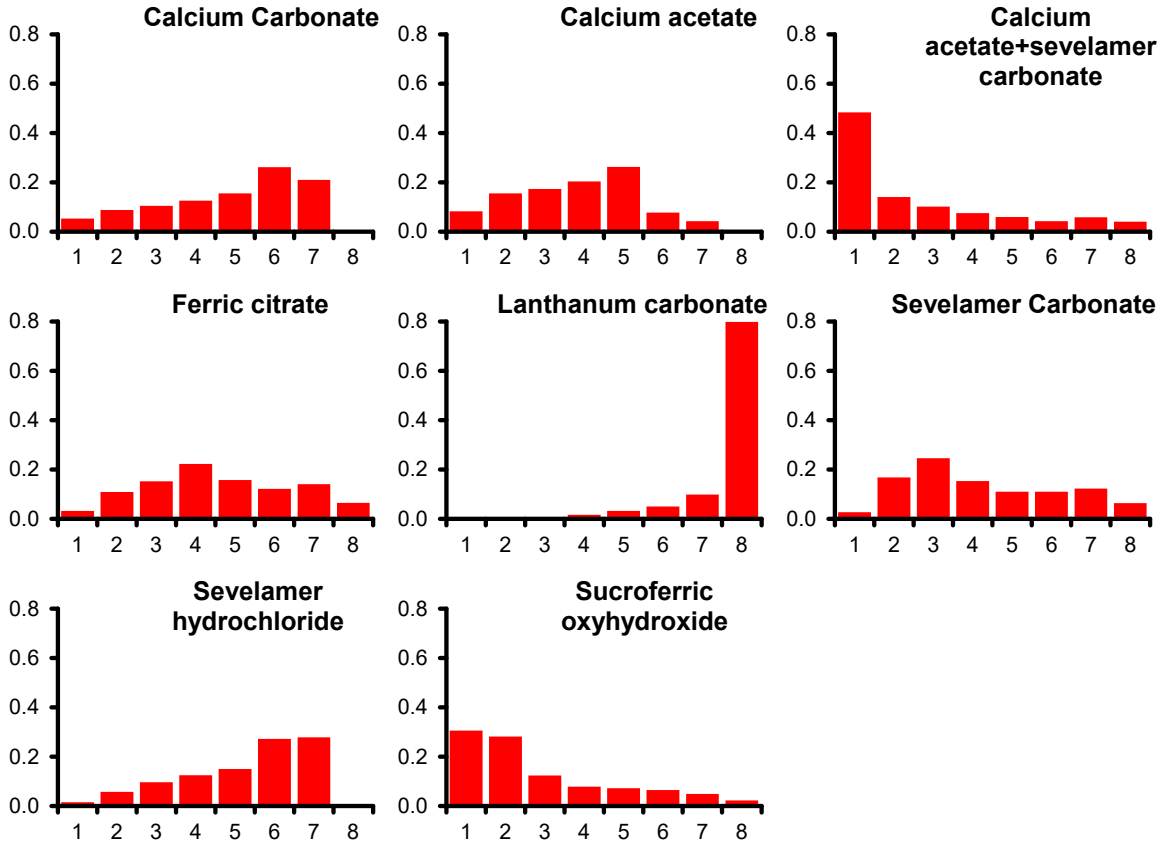
Caterpillar plot

Figure 29: Relative effectiveness of all options versus calcium carbonate for serum phosphate at 12 months in adults with stage 5 CKD who are on dialysis. (Mean differences with 95% credible intervals; values higher than 0 favour calcium carbonate; values lower than 0 favour the other treatments).



Rank probability histograms

Figure 30: . Serum phosphate at 12 months in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

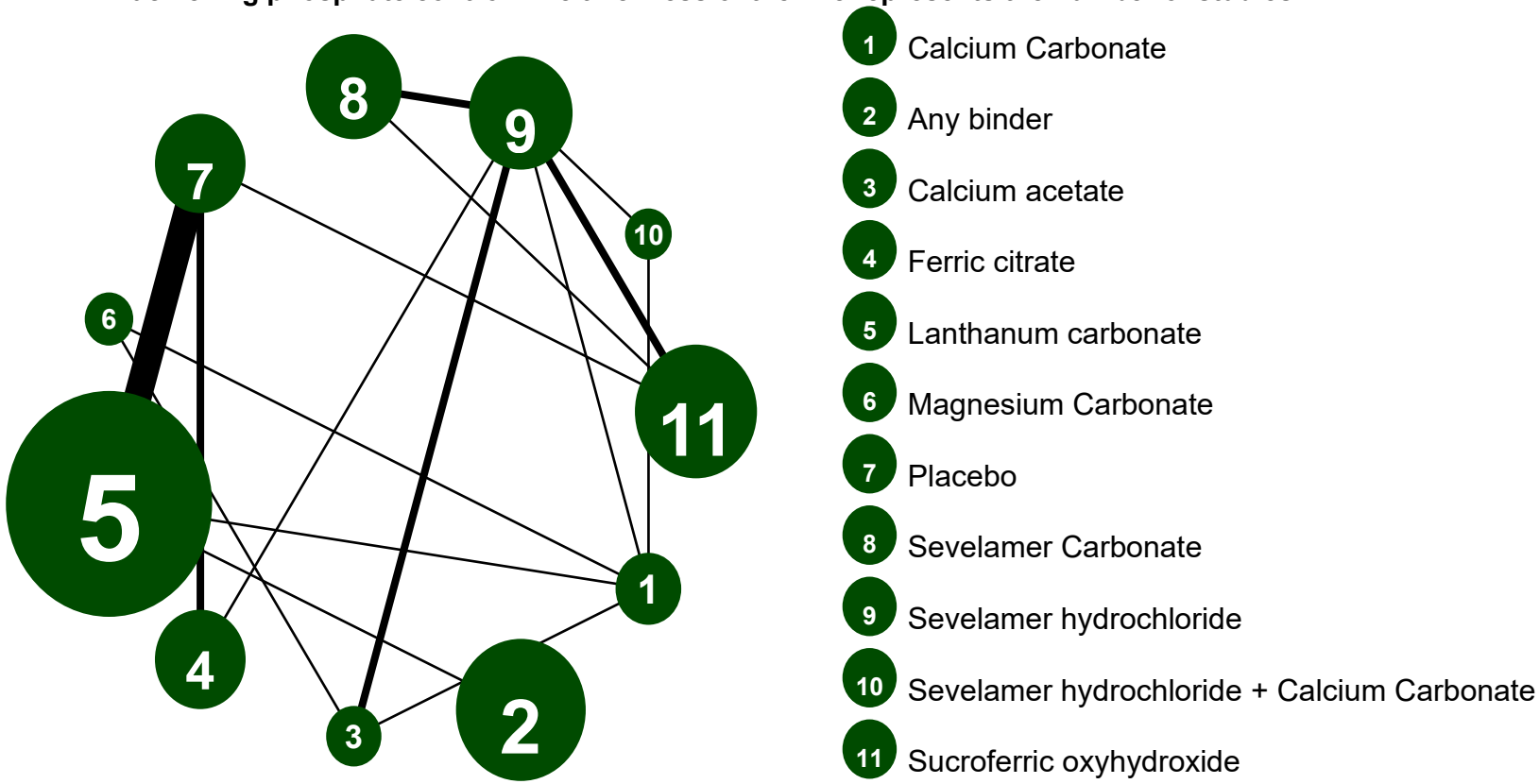
Table 40: Relative effectiveness of all pairwise combinations for serum phosphate at 12 months in adults with stage 5 CKD who are on dialysis. (Upper diagonal: mean difference (MD) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment, MDs greater than 0 favour the row defining treatment. Lower diagonal: posterior median MD with 95% credible intervals from NMA results, MDs less than 0 favour the row defining treatment. MDs greater than 0 favour the column defining treatment).

	Calcium Carbonate	Any binder	Calcium acetate	Calcium acetate + sevelamer carbonate	Ferric citrate	Lanthanum carbonate	Sevelamer Carbonate	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-0.41 (-0.89, 0.07)	-	-	0.20 (0.08, 0.32)	-	0.02 (-0.05, 0.09)	-
Any binder	0.07 (-0.07, 0.19)		-	-	-	0.08 (-0.09, 0.24)	-	-0.02 (-0.14, 0.09)	-
Calcium acetate	-0.05 (-0.24, 0.11)	-0.12 (-0.31, 0.05)		-0.11 (-0.47, 0.24)	0.02 (-0.19, 0.23)	-	0.00 (-0.26, 0.26)	0.03 (-0.10, 0.16)	-
Calcium acetate + sevelamer carbonate	-0.17 (-0.60, 0.24)	-0.24 (-0.66, 0.18)	-0.11 (-0.50, 0.26)		0.14 (-0.17, 0.44)	-	0.11 (-0.23, 0.45)	-	-
Ferric citrate	-0.03 (-0.34, 0.26)	-0.10 (-0.41, 0.20)	0.02 (-0.22, 0.27)	0.14 (-0.20, 0.47)		-	-0.02 (-0.20, 0.16)	-	-
Lanthanum carbonate	0.16 (0.04, 0.27)	0.09 (-0.01, 0.21)	0.21 (0.03, 0.42)	0.33 (-0.09, 0.77)	0.19 (-0.11, 0.52)		-	-	-
Sevelamer Carbonate	-0.05 (-0.40, 0.27)	-0.12 (-0.46, 0.21)	0.00 (-0.29, 0.29)	0.11 (-0.25, 0.48)	-0.02 (-0.25, 0.20)	-0.21 (-0.57, 0.13)		-	-0.07 (-0.16, 0.02)
Sevelamer hydrochloride	0.01 (-0.10, 0.10)	-0.06 (-0.17, 0.05)	0.06 (-0.08, 0.21)	0.18 (-0.22, 0.59)	0.04 (-0.24, 0.33)	-0.15 (-0.29, -0.03)	0.07 (-0.25, 0.39)		-
Sucroferric oxyhydroxide	-0.12 (-0.51, 0.24)	-0.19 (-0.57, 0.18)	-0.07 (-0.40, 0.26)	0.04 (-0.35, 0.44)	-0.09 (-0.37, 0.19)	-0.28 (-0.67, 0.09)	-0.07 (-0.24, 0.10)	-0.14 (-0.50, 0.23)	

Proportion of participants achieving phosphate control

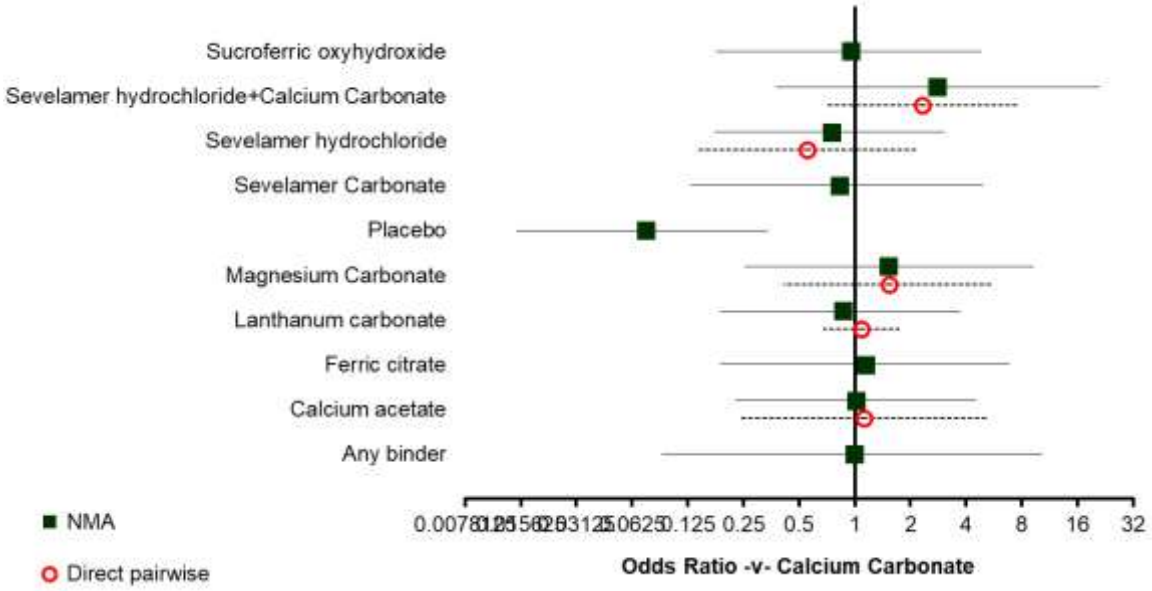
Network diagram

Figure 31: Diagram of the network of studies underlying the NMA for the proportion of adults with stage 5 CKD who are on dialysis achieving phosphate control. The thickness of the line represents the number of studies.



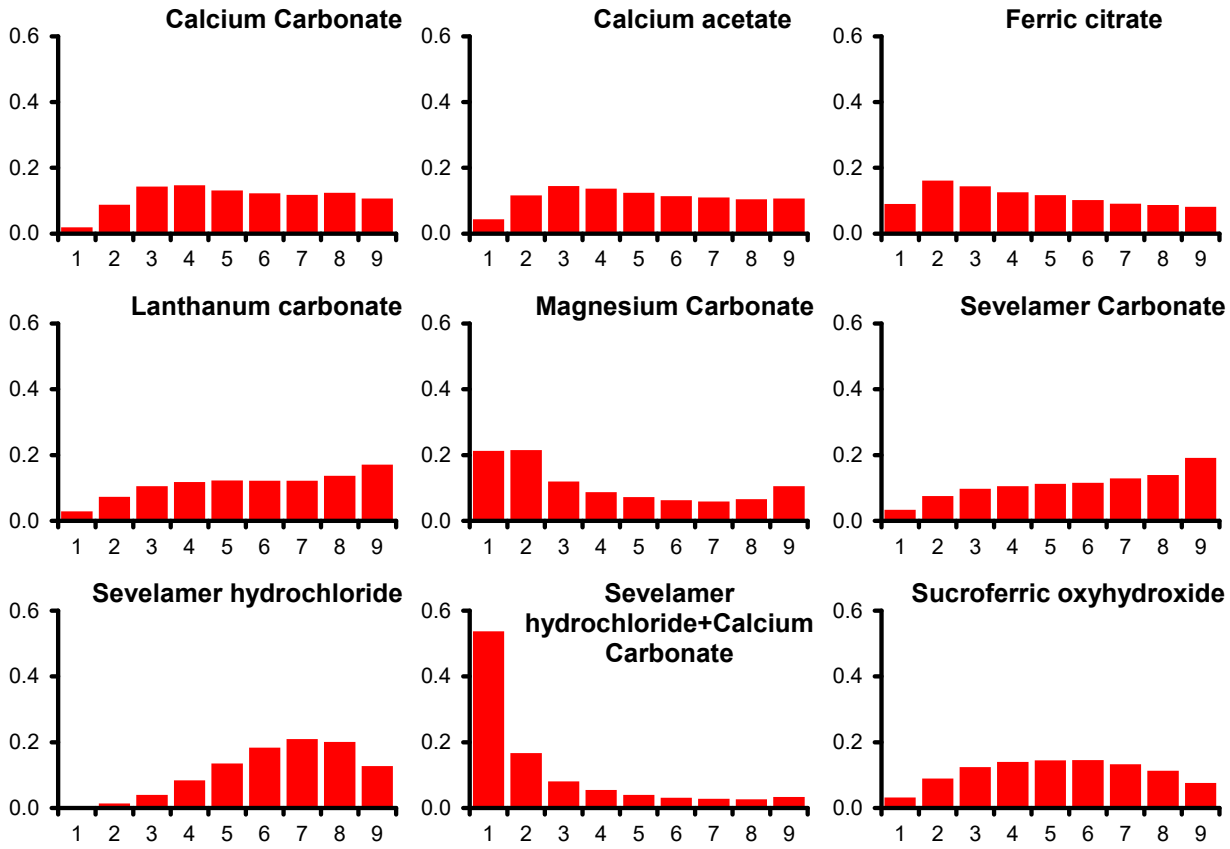
Caterpillar plot

Figure 32: Relative effectiveness of all options versus calcium carbonate for the proportion of adults with stage 5 CKD who are on dialysis achieving phosphate control. (Odds ratios with 95% credible intervals; values lower than 1.0 favour calcium carbonate; values higher than 1.0 favour the other treatments).



Rank probability histograms

Figure 33: Proportion of adults with stage 5 CKD who are on dialysis achieving phosphate control. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 41: Relative effectiveness of all pairwise combinations for the proportion of adults with stage 5 CKD who are on dialysis achieving phosphate control. (Upper diagonal: odds ratios (OR) with 95% confidence intervals from the pair-wise meta-analysis. ORs higher than 1 favour the column defining treatment, ORs lower than 1 favour the row defining treatment. Lower diagonal: posterior median ORs with 95% credible intervals from NMA results, OR higher than 1 favour the row defining treatment. ORs lower than 1 favour the column defining treatment).

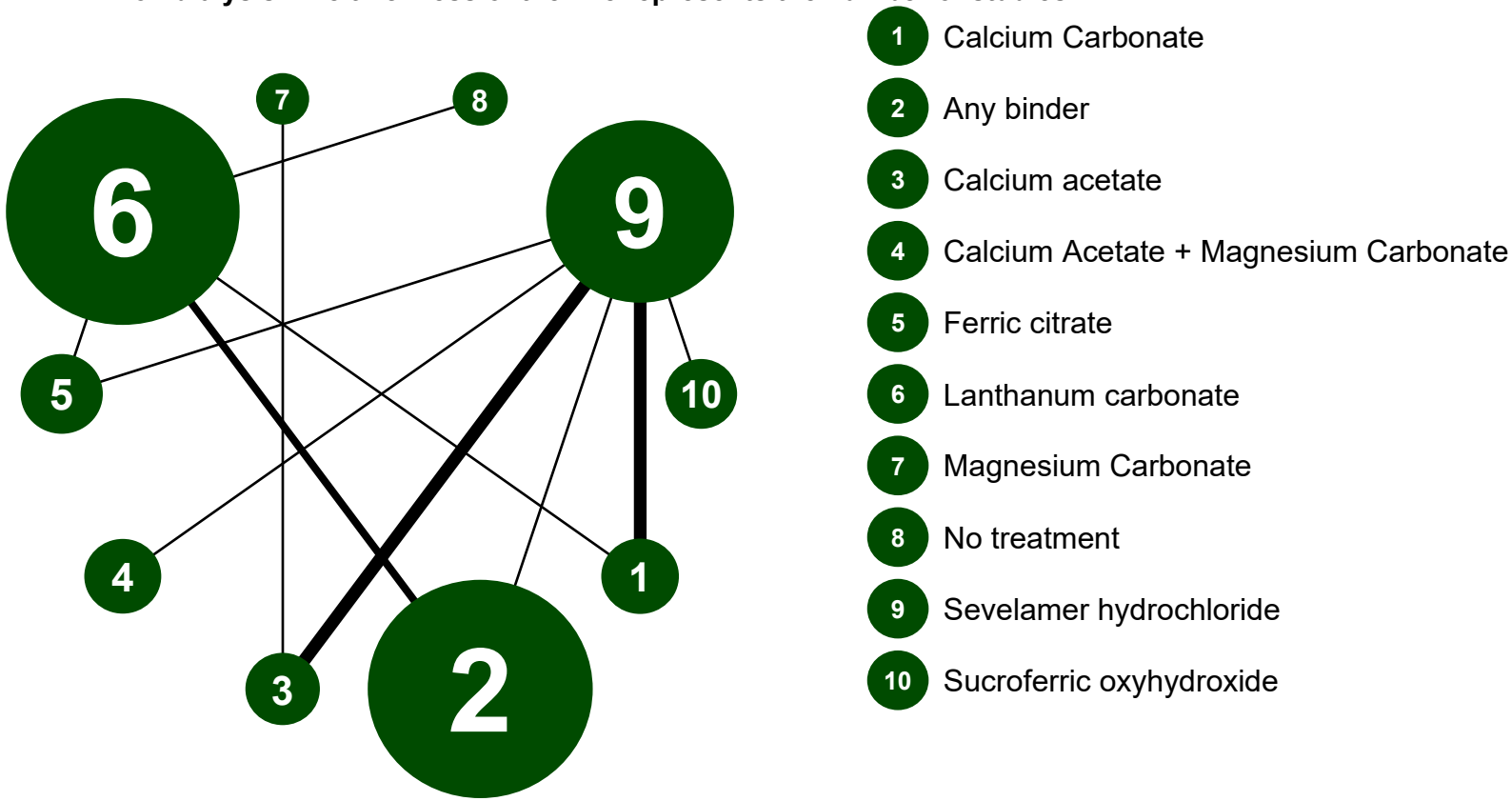
	Calcium Carbonate	Any binder	Calcium acetate	Ferric citrate	Lanthanum carbonate	Magnesium Carbonate	Placebo	Sevelamer Carbonate	Sevelamer hydrochloride	Sevelamer hydrochloride + Calcium Carbonate	Sucroferric oxyhydroxide
Calcium Carbonate		-	1.13 (0.24, 5.37)	-	1.08 (0.68, 1.72)	1.53 (0.41, 5.64)	-	-	0.56 (0.14, 2.20)	2.31 (0.70, 7.63)	-
Any binder	0.99 (0.09, 10.34)		-	-	0.87 (0.70, 1.07)	-	-	-	-	-	-
Calcium acetate	1.01 (0.23, 4.52)	1.02 (0.08, 13.10)		-	-	1.44 (0.24, 8.46)	-	-	0.82 (0.30, 2.27)	-	-
Ferric citrate	1.14 (0.19, 6.83)	1.15 (0.11, 12.09)	1.13 (0.18, 6.90)		-	-	0.07 (0.02, 0.24)	-	0.93 (0.54, 1.59)	-	-
Lanthanum carbonate	0.87 (0.19, 3.70)	0.87 (0.14, 5.27)	0.86 (0.14, 4.81)	0.76 (0.17, 3.09)		-	0.13 (0.06, 0.25)	-	-	-	-
Magnesium Carbonate	1.52 (0.25, 9.28)	1.53 (0.09, 28.30)	1.51 (0.22, 10.25)	1.33 (0.12, 14.61)	1.75 (0.20, 16.86)		-	-	-	-	-
Placebo	0.07 (0.01, 0.34)	0.07 (0.01, 0.52)	0.07 (0.01, 0.39)	0.06 (0.02, 0.21)	0.09 (0.04, 0.19)	0.05 (0.00, 0.43)		-	-	-	10.42 (4.59, 23.64)

Sevelamer Carbonate	0.82 (0.13, 4.92)	0.82 (0.07, 10.36)	0.81 (0.14, 4.41)	0.72 (0.12, 4.02)	0.95 (0.16, 5.61)	0.54 (0.05, 5.43)	11.06 (2.16, 60.66)		1.14 (0.56, 2.33)	-	0.88 (0.63, 1.24)
Sevelamer hydrochloride	0.75 (0.17, 3.07)	0.76 (0.07, 7.77)	0.74 (0.20, 2.61)	0.66 (0.16, 2.62)	0.87 (0.20, 3.77)	0.49 (0.06, 3.77)	10.21 (2.74, 40.42)	0.92 (0.29, 2.98)		4.16 (1.10, 15.72)	1.80 (0.98, 3.30)
Sevelamer hydrochloride + Calcium Carbonate	2.78 (0.38, 21.05)	2.75 (0.16, 53.59)	2.77 (0.29, 26.64)	2.45 (0.22, 27.23)	3.20 (0.34, 33.01)	1.84 (0.14, 24.34)	37.84 (4.06, 385.80)	3.37 (0.34, 35.59)	3.70 (0.50, 29.31)		-
Sucroferric oxyhydroxide	0.95 (0.18, 4.82)	0.95 (0.09, 9.62)	0.94 (0.18, 4.57)	0.83 (0.17, 3.67)	1.10 (0.25, 4.67)	0.62 (0.07, 5.75)	12.84 (3.58, 47.65)	1.15 (0.32, 4.20)	1.25 (0.45, 3.55)	0.34 (0.04, 3.11)	

Serum calcium at 3 months

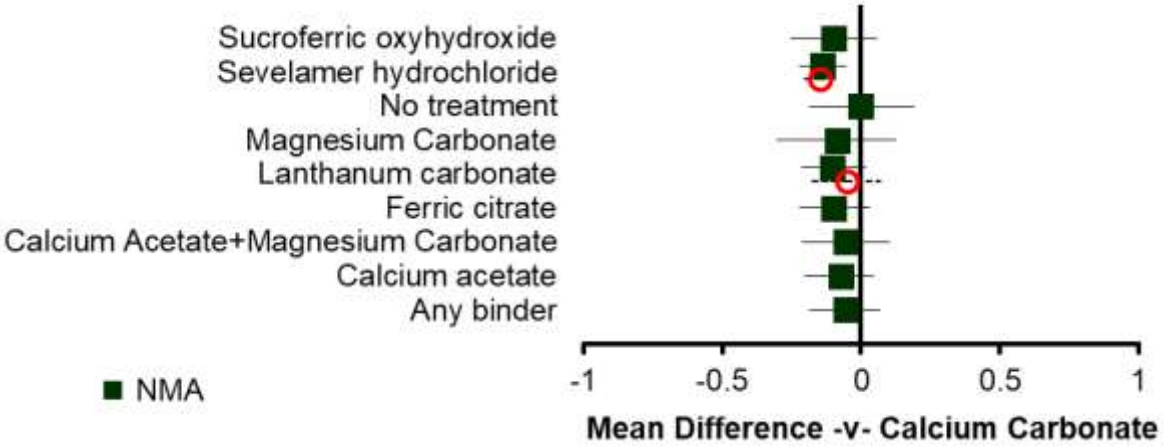
Network diagram

Figure 34: Diagram of the network of studies underlying the NMA for serum calcium at 3 months in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



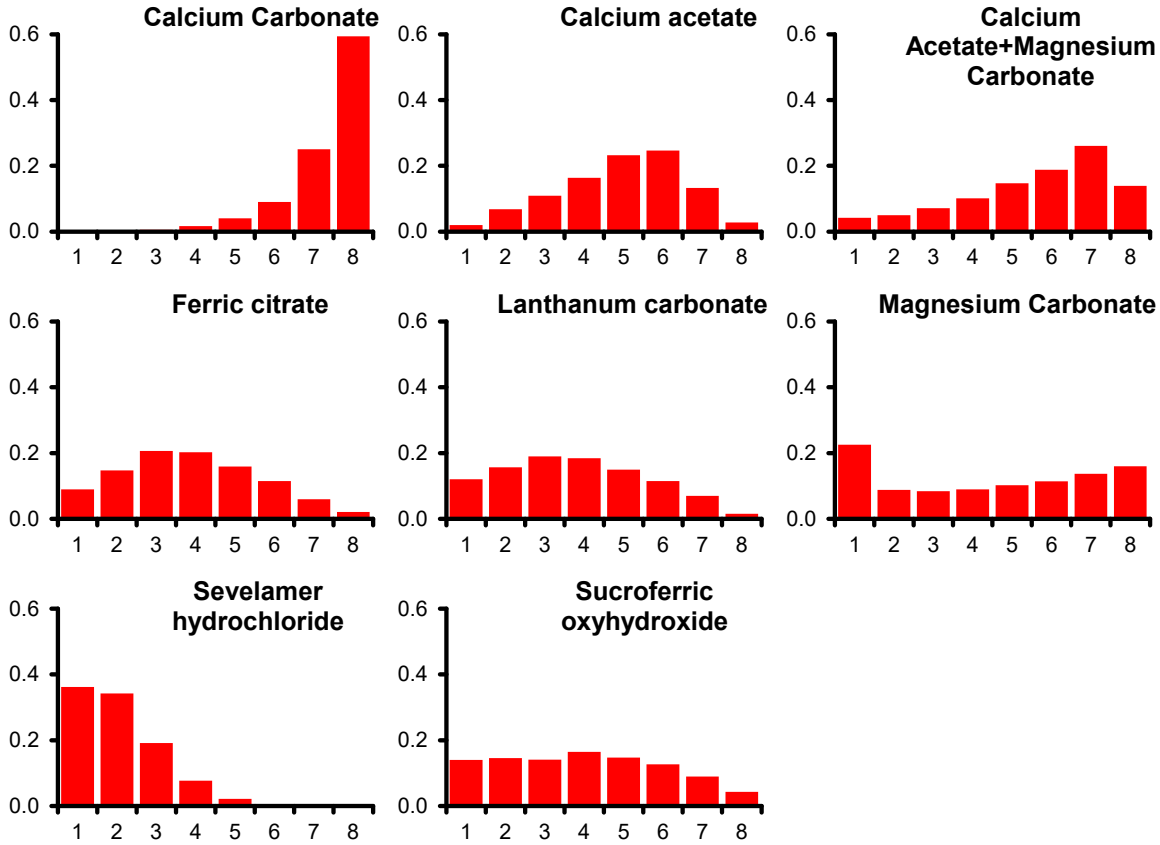
Caterpillar plot

Figure 35: Relative effectiveness of all options versus calcium carbonate for serum calcium at 3 months in adults with stage 5 CKD who are on dialysis. (Mean differences with 95% credible intervals; values higher than 0 favour calcium carbonate; values lower than 0 favour the other treatments).



Rank probability histograms

Figure 36: Serum calcium at 3 months in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 42: Relative effectiveness of all pairwise combinations for serum calcium at 3 months in adults with stage 5 CKD who are on dialysis. (Upper diagonal: mean difference (MD) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment, MDs greater than 0 favour the row defining treatment. Lower diagonal: posterior median MD with 95% credible intervals from NMA results, MDs less than 0 favour the row defining treatment. MDs greater than 0 favour the column defining treatment).

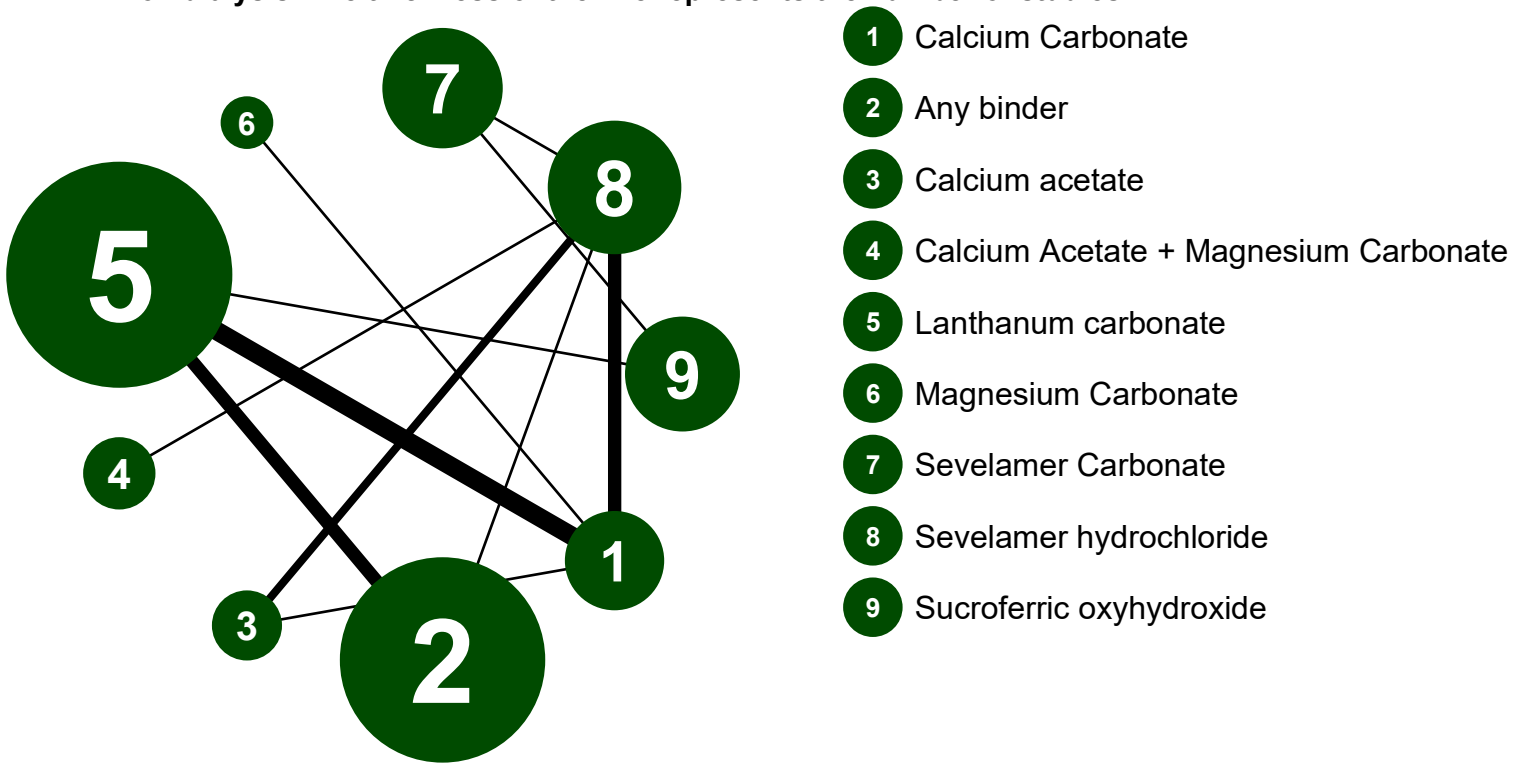
	Calcium Carbonate	Any binder	Calcium acetate	Calcium Acetate + Magnesium Carbonate	Ferric citrate	Lanthanum carbonate	Magnesium Carbonate	No treatment	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-	-	-	-0.05 (-0.17, 0.07)	-	-	-0.15 (-0.21, -0.09)	-
Any binder	-0.05 (-0.19, 0.07)		-	-	-	-0.05 (-0.16, 0.07)	-	-	-0.04 (-0.14, 0.06)	-
Calcium acetate	-0.07 (-0.20, 0.05)	-0.02 (-0.16, 0.13)		-	-	-	-0.01 (-0.14, 0.12)	-	-0.07 (-0.11, -0.02)	-
Calcium Acetate + Magnesium Carbonate	-0.06 (-0.21, 0.10)	0.00 (-0.17, 0.18)	0.02 (-0.14, 0.19)		-	-	-	-	-0.08 (-0.13, -0.04)	-
Ferric citrate	-0.10 (-0.22, 0.03)	-0.05 (-0.16, 0.09)	-0.03 (-0.16, 0.12)	-0.04 (-0.22, 0.13)		0.00 (-0.05, 0.05)	-	-	-0.04 (-0.08, 0.00)	-
Lanthanum carbonate	-0.10 (-0.21, 0.02)	-0.05 (-0.12, 0.05)	-0.03 (-0.16, 0.13)	-0.05 (-0.21, 0.13)	0.00 (-0.11, 0.11)		-	0.10 (0.02, 0.18)	-	-
Magnesium Carbonate	-0.08 (-0.30, 0.13)	-0.03 (-0.26, 0.20)	-0.01 (-0.19, 0.17)	-0.03 (-0.27, 0.21)	0.02 (-0.22, 0.23)	0.02 (-0.22, 0.23)		-	-	-
No treatment	0.00 (-0.19, 0.19)	0.05 (-0.11, 0.23)	0.07 (-0.12, 0.29)	0.05 (-0.17, 0.28)	0.10 (-0.08, 0.28)	0.10 (-0.05, 0.25)	0.08 (-0.18, 0.36)		-	-

Sevelamer hydrochloride	-0.14 (-0.22, -0.05)	-0.08 (-0.19, 0.04)	-0.06 (-0.15, 0.03)	-0.08 (-0.22, 0.05)	-0.04 (-0.15, 0.07)	-0.04 (-0.15, 0.07)	-0.05 (-0.25, 0.15)	-0.14 (-0.32, 0.04)		0.04 (0.00, 0.08)
Sucroferric oxyhydroxide	-0.10 (-0.25, 0.06)	-0.05 (-0.21, 0.14)	-0.02 (-0.18, 0.14)	-0.04 (-0.23, 0.14)	0.00 (-0.17, 0.17)	0.00 (-0.17, 0.17)	-0.01 (-0.25, 0.23)	-0.10 (-0.33, 0.13)	0.04 (-0.09, 0.17)	

Serum calcium at 6 months

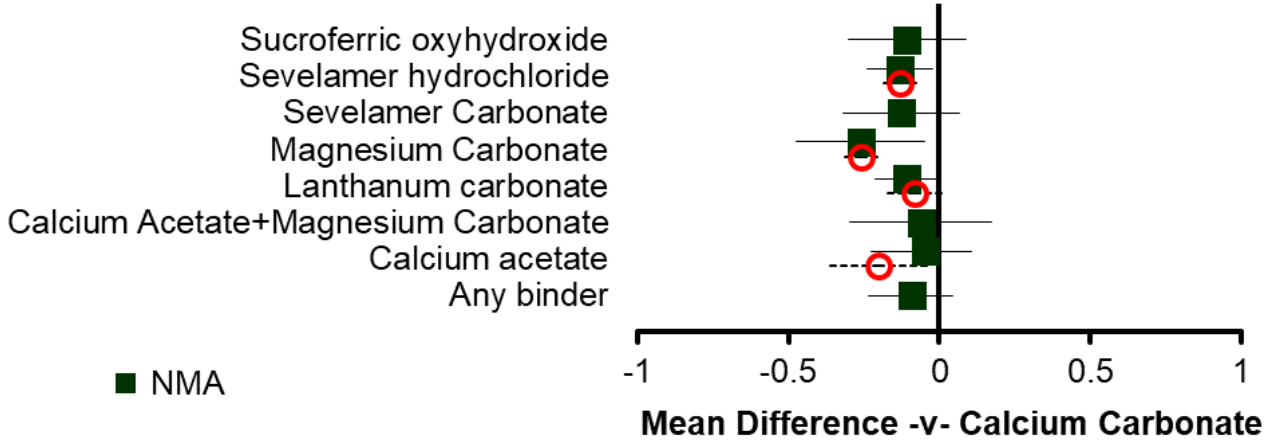
Network diagram

Figure 37: Diagram of the network of studies underlying the NMA for serum calcium at 6 months in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



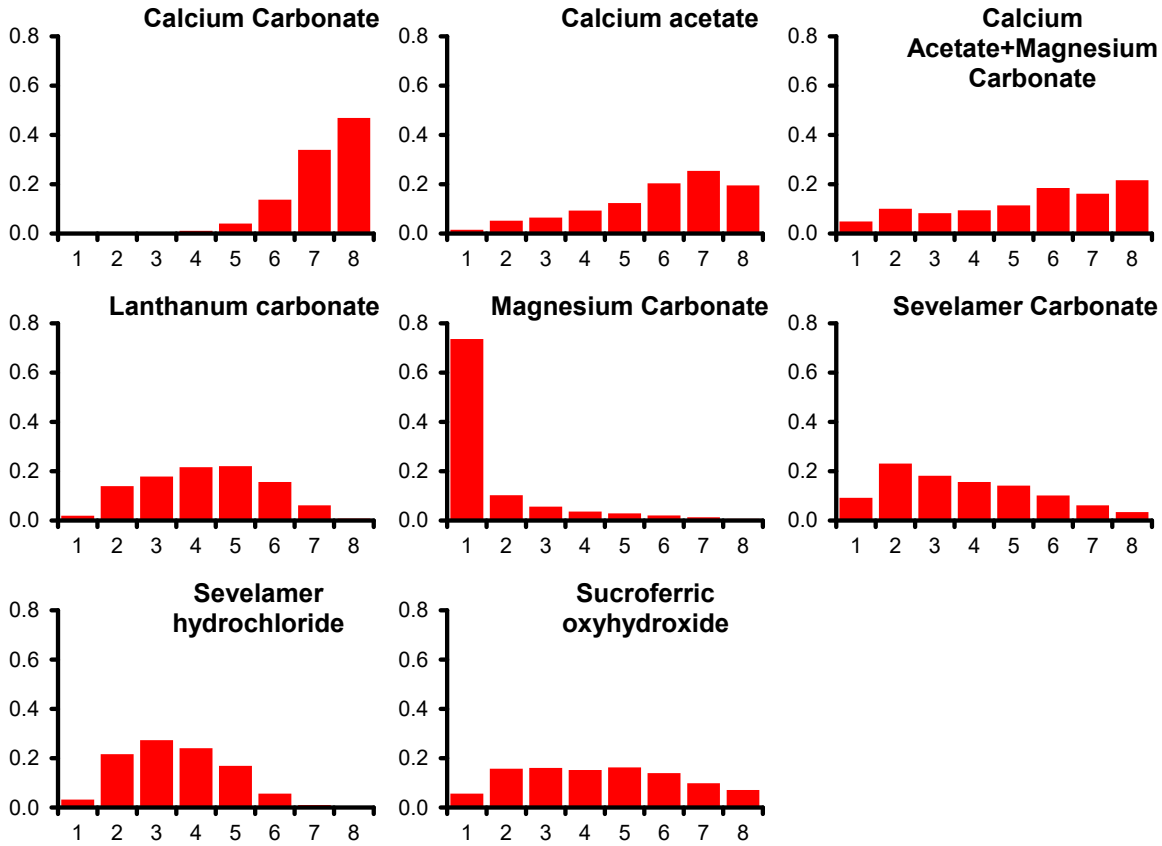
Caterpillar plot

Figure 38: Relative effectiveness of all options versus calcium carbonate for serum calcium at 6 months in adults with stage 5 CKD who are on dialysis. (Mean differences with 95% credible intervals; values higher than 0 favour calcium carbonate; values lower than 0 favour the other treatments).



Rank probability histograms

Figure 39: Serum calcium at 6 months in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

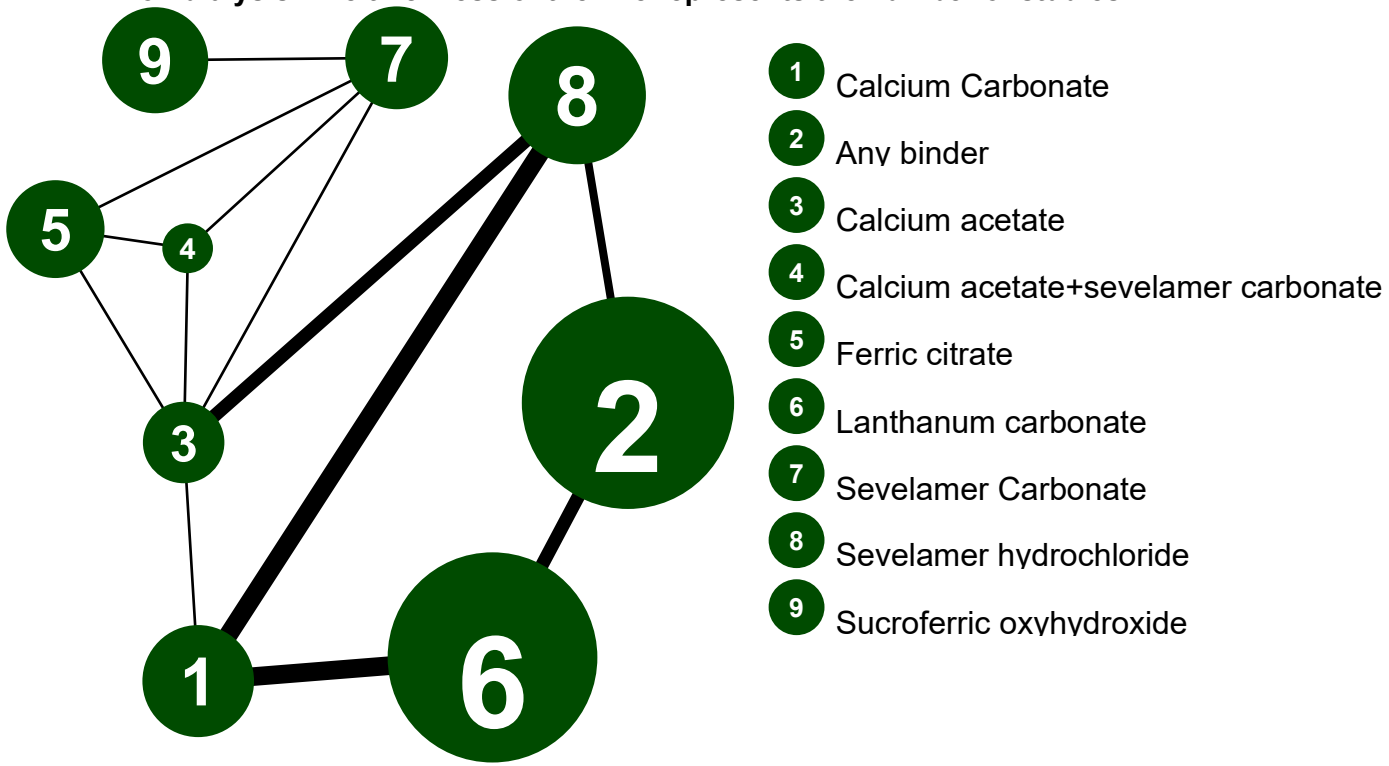
Table 43: Relative effectiveness of all pairwise combinations for serum calcium at 6 months in adults with stage 5 CKD who are on dialysis. (Upper diagonal: mean difference (MD) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment, MDs greater than 0 favour the row defining treatment. Lower diagonal: posterior median MD with 95% credible intervals from NMA results, MDs less than 0 favour the row defining treatment. MDs greater than 0 favour the column defining treatment).

	Calcium Carbonate	Any binder	Calcium acetate	Calcium Acetate + Magnesium Carbonate	Lanthanum carbonate	Magnesium Carbonate	Sevelamer Carbonate	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-0.20 (-0.36, -0.04)	-	-0.08 (-0.19, 0.02)	-0.26 (-0.33, -0.19)	-	-0.13 (-0.18, -0.08)	-
Any binder	-0.09 (-0.23, 0.05)		-	-	-0.04 (-0.15, 0.07)	-	-	0.04 (-0.07, 0.15)	-
Calcium acetate	-0.05 (-0.22, 0.11)	0.05 (-0.16, 0.23)		-	-	-	-	-0.12 (-0.33, 0.09)	-
Calcium Acetate + Magnesium Carbonate	-0.06 (-0.30, 0.17)	0.03 (-0.22, 0.28)	-0.02 (-0.25, 0.25)		-	-	-	-0.07 (-0.11, -0.03)	-
Lanthanum carbonate	-0.11 (-0.21, 0.00)	-0.02 (-0.13, 0.10)	-0.06 (-0.24, 0.14)	-0.05 (-0.29, 0.20)		-	-	-	0.02 (-0.05, 0.10)
Magnesium Carbonate	-0.26 (-0.47, -0.05)	-0.17 (-0.42, 0.09)	-0.21 (-0.47, 0.07)	-0.20 (-0.51, 0.12)	-0.15 (-0.39, 0.08)		-	-	-
Sevelamer Carbonate	-0.13 (-0.32, 0.07)	-0.04 (-0.24, 0.18)	-0.08 (-0.29, 0.16)	-0.07 (-0.34, 0.20)	-0.02 (-0.21, 0.17)	0.13 (-0.15, 0.42)		0.02 (-0.03, 0.07)	0.00 (-0.03, 0.03)
Sevelamer hydrochloride	-0.13 (-0.24, -0.02)	-0.04 (-0.18, 0.11)	-0.08 (-0.22, 0.08)	-0.07 (-0.28, 0.14)	-0.02 (-0.15, 0.11)	0.13 (-0.11, 0.37)	0.00 (-0.18, 0.17)		-
Sucroferric oxyhydroxide	-0.11 (-0.30, 0.09)	-0.01 (-0.22, 0.19)	-0.06 (-0.29, 0.19)	-0.04 (-0.32, 0.24)	0.00 (-0.18, 0.18)	0.15 (-0.14, 0.44)	0.02 (-0.15, 0.19)	0.02 (-0.17, 0.22)	

Serum calcium at 12 months

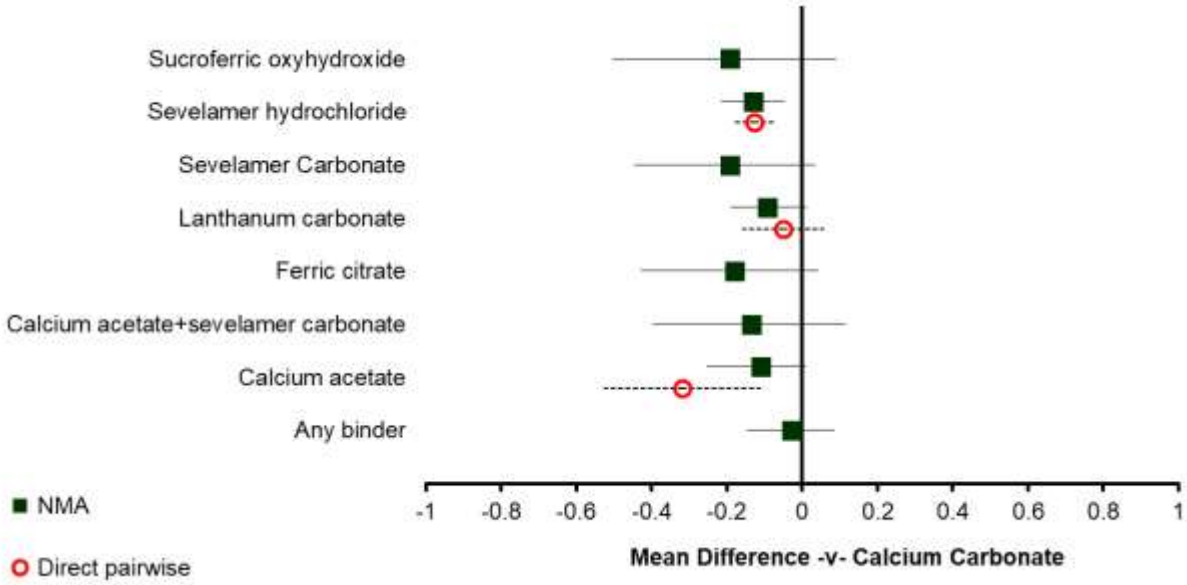
Network diagram

Figure 40: Diagram of the network of studies underlying the NMA for serum calcium at 12 months in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



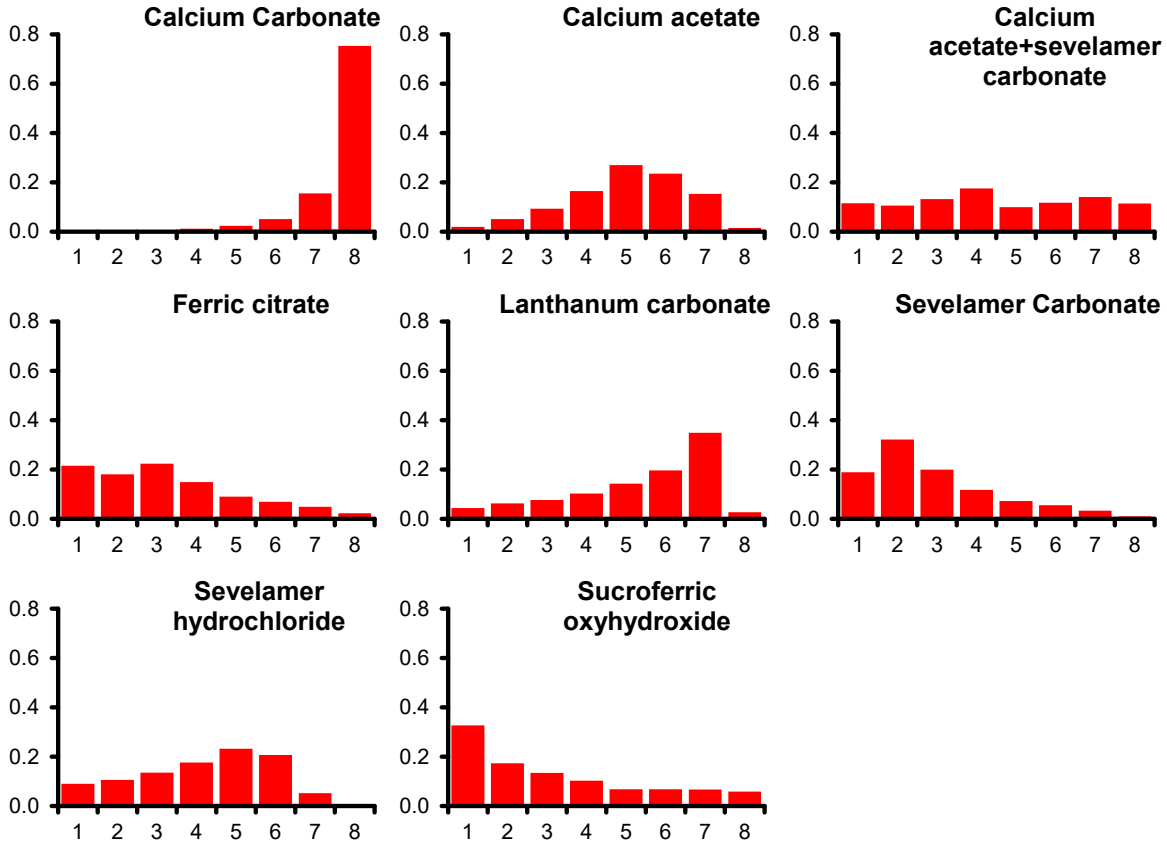
Caterpillar plot

Figure 41: Relative effectiveness of all options versus calcium carbonate for serum calcium at 12 months in adults with stage 5 CKD who are on dialysis. (Mean differences with 95% credible intervals; values higher than 0 favour calcium carbonate; values lower than 0 favour the other treatments).



Rank probability histograms

Figure 42: Serum calcium at 12 months in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

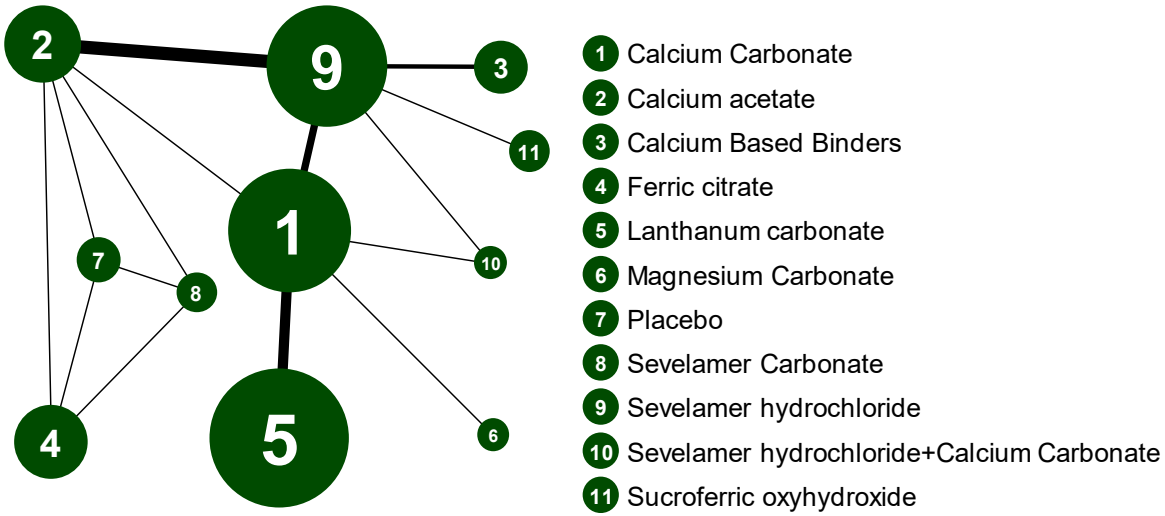
Table 44: Relative effectiveness of all pairwise combinations for serum calcium at 12 months in adults with stage 5 CKD who are on dialysis. (Upper diagonal: mean difference (MD) with 95% confidence intervals from direct pair-wise meta-analysis. MDs less than 0 favour the column defining treatment, MDs greater than 0 favour the row defining treatment. Lower diagonal: posterior median MD with 95% credible intervals from NMA results, MDs less than 0 favour the row defining treatment. MDs greater than 0 favour the column defining treatment).

	Calcium Carbonate	Any binder	Calcium acetate	Calcium acetate + sevelamer carbonate	Ferric citrate	Lanthanum carbonate	Sevelamer Carbonate	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-0.32 (-0.53, -0.11)	-	-	-0.05 (-0.16, 0.06)	-	-0.13 (-0.18, -0.07)	-
Any binder	-0.03 (-0.15, 0.09)		-	-	-	-0.10 (-0.20, 0.01)	-	-0.05 (-0.13, 0.03)	-
Calcium acetate	-0.11 (-0.25, 0.01)	-0.08 (-0.25, 0.06)		-0.02 (-0.16, 0.12)	-0.07 (-0.15, 0.01)	-	-0.08 (-0.17, 0.01)	-0.06 (-0.12, -0.01)	-
Calcium acetate + sevelamer carbonate	-0.13 (-0.40, 0.11)	-0.10 (-0.38, 0.15)	-0.02 (-0.24, 0.20)		-0.05 (-0.16, 0.07)	-	-0.06 (-0.18, 0.06)	-	-
Ferric citrate	-0.18 (-0.43, 0.04)	-0.15 (-0.41, 0.09)	-0.07 (-0.27, 0.12)	-0.05 (-0.26, 0.16)		-	-0.01 (-0.06, 0.04)	-	-
Lanthanum carbonate	-0.09 (-0.19, 0.01)	-0.06 (-0.16, 0.04)	0.02 (-0.13, 0.19)	0.04 (-0.22, 0.32)	0.09 (-0.15, 0.35)		-	-	-
Sevelamer Carbonate	-0.19 (-0.45, 0.04)	-0.16 (-0.43, 0.08)	-0.08 (-0.28, 0.12)	-0.06 (-0.28, 0.15)	-0.01 (-0.20, 0.17)	-0.10 (-0.37, 0.14)		-	0.00 (-0.04, 0.04)
Sevelamer hydrochloride	-0.13 (-0.22, -0.05)	-0.10 (-0.21, 0.01)	-0.02 (-0.12, 0.10)	0.01 (-0.24, 0.26)	0.05 (-0.17, 0.28)	-0.04 (-0.16, 0.07)	0.06 (-0.16, 0.30)		-
Sucroferric oxyhydroxide	-0.19 (-0.50, 0.09)	-0.16 (-0.49, 0.13)	-0.08 (-0.35, 0.18)	-0.06 (-0.35, 0.22)	-0.01 (-0.28, 0.24)	-0.10 (-0.43, 0.19)	0.00 (-0.19, 0.18)	-0.06 (-0.36, 0.21)	

Risk of hypercalcaemia

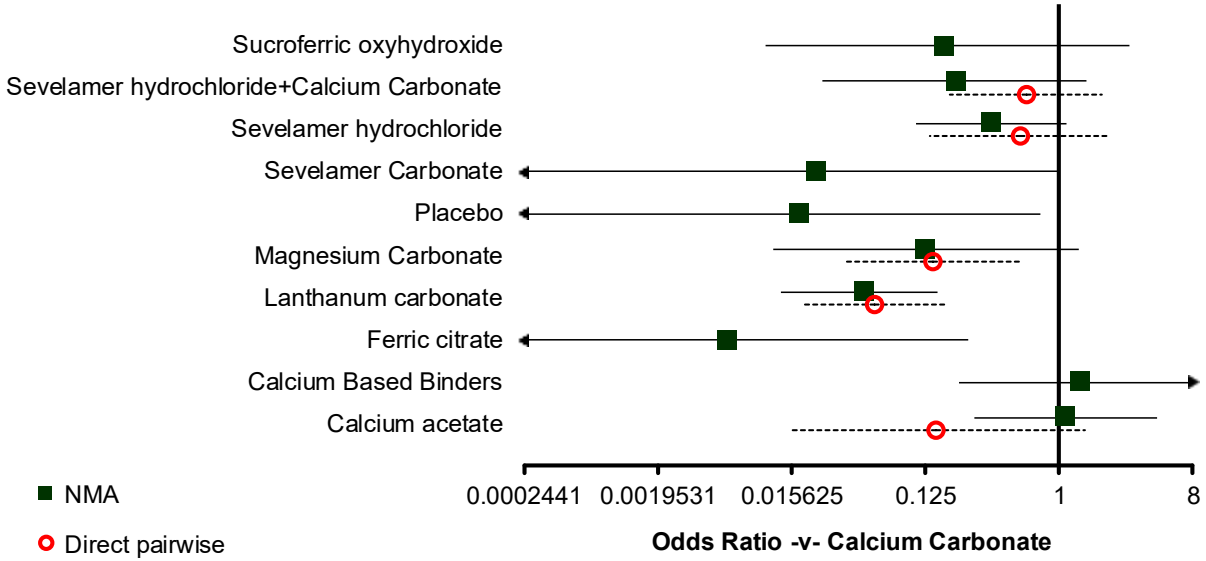
Network diagram

Figure 43: Diagram of the network of studies underlying the NMA for risk of hypercalcaemia in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



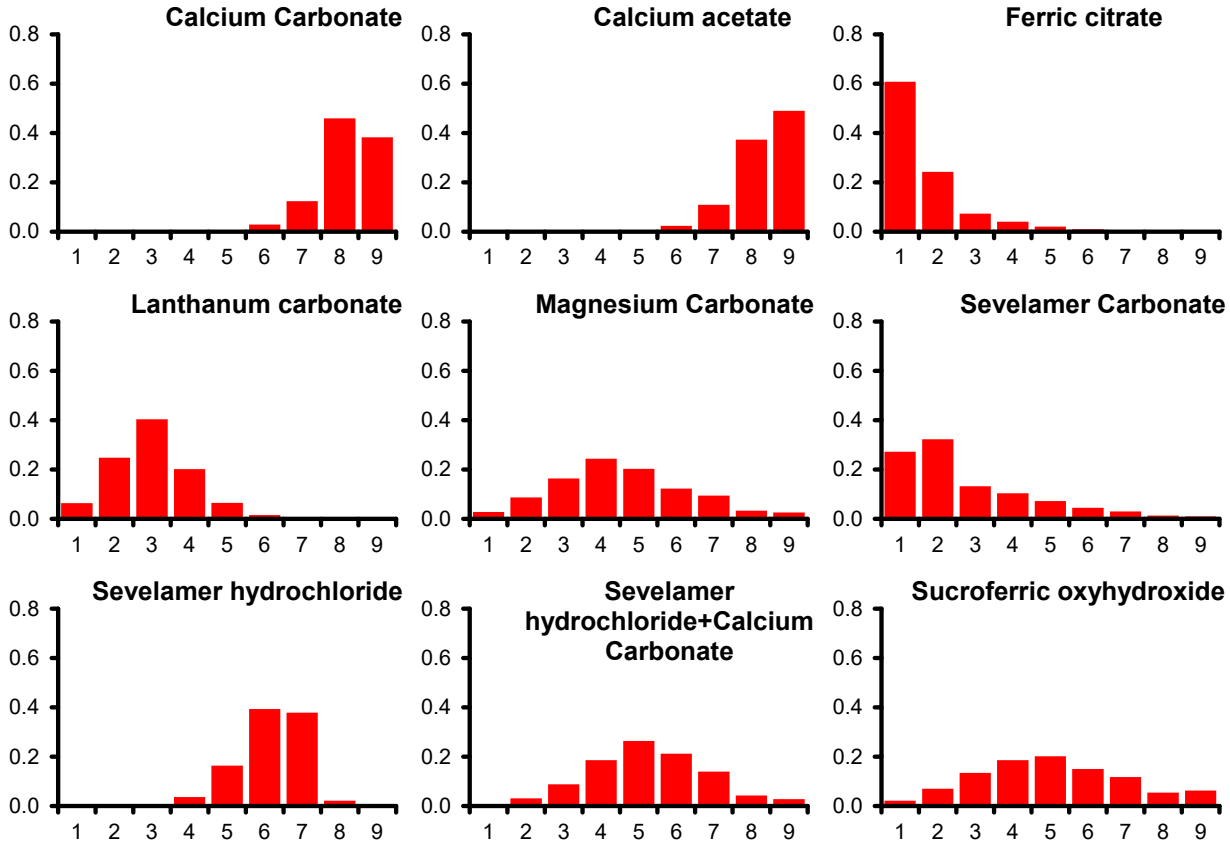
Caterpillar plot

Figure 44: Relative effectiveness of all options versus calcium carbonate for risk of hypercalcaemia in adults with stage 5 CKD who are on dialysis. (Odds ratios with 95% credible intervals; values higher than 1.0 favour calcium carbonate; values lower than 1.0 favour the other treatments).



Rank probability histograms

Figure 45: Risk of hypercalcaemia in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 45: Relative effectiveness of all pairwise combinations for risk of hypercalcaemia in adults with stage 5 CKD who are on dialysis. (Upper diagonal: odds ratios (OR) with 95% confidence intervals from the pair-wise meta-analysis. ORs less than 1 favour the column defining treatment, ORs greater than 1 favour the row defining treatment. Lower diagonal: posterior median ORs with 95% credible intervals from NMA results, OR less than 1 favour the row defining treatment. ORs greater than 1 favour the column defining treatment).

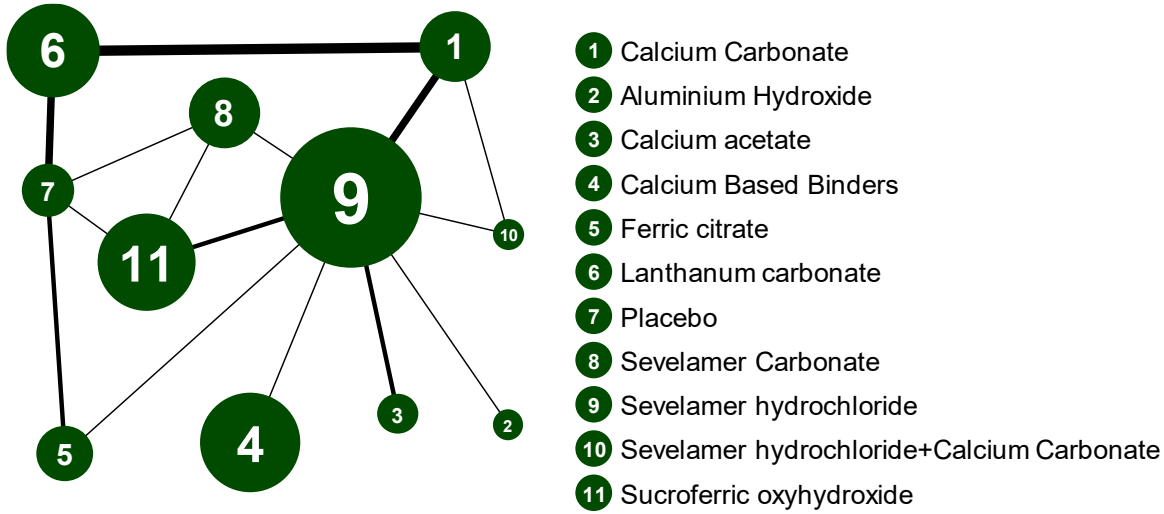
	Calcium Carbonate	Calcium acetate	Calcium Based Binders	Ferric citrate	Lanthanum carbonate	Magnesium Carbonate	Placebo	Sevelamer Carbonate	Sevelamer hydrochloride	Sevelamer hydrochloride +Calcium Carbonate	Sucroferric oxyhydroxide
Calcium Carbonate		0.15 (0.01, 1.52)	-	-	0.06 (0.02, 0.17)	0.14 (0.04, 0.53)	-	-	0.55 (0.14, 2.23)	0.60 (0.19, 1.94)	-
Calcium acetate	1.11 (0.27, 4.58)		-	0.01 (0.00, 0.23)	-	-	0.04 (0.00, 0.69)	0.05 (0.00, 0.92)	0.30 (0.17, 0.52)	-	-
Calcium Based Binders	1.40 (0.21, 9.63)	1.28 (0.20, 7.81)		-	-	-	-	-	0.25 (0.13, 0.49)	-	-
Ferric citrate	0.01 (0.00, 0.25)	0.01 (0.00, 0.16)	0.00 (0.00, 0.20)		-	-	3.03 (0.06, 153.79)	4.03 (0.08, 205.05)	-	-	-
Lanthanum carbonate	0.05 (0.01, 0.15)	0.04 (0.01, 0.26)	0.03 (0.00, 0.32)	8.30 (0.16, 5844.00)		-	-	-	-	-	-
Magnesium Carbonate	0.13 (0.01, 1.36)	0.12 (0.01, 1.76)	0.09 (0.00, 1.87)	22.60 (0.27, 19300.00)	2.62 (0.19, 39.48)		-	-	-	-	-

Placebo	0.02 (0.00, 0.74)	0.02 (0.00, 0.49)	0.01 (0.00, 0.62)	3.03 (0.00, 2365.00)	0.37 (0.00, 18.87)	0.13 (0.00, 11.52)		1.33 (0.03, 67.88)	-	-	-
Sevelamer Carbonate	0.02 (0.00, 0.99)	0.02 (0.00, 0.66)	0.02 (0.00, 0.85)	3.97 (0.01, 3231.00)	0.47 (0.00, 25.52)	0.18 (0.00, 15.27)	1.33 (0.00, 1224.00)		-	-	-
Sevelamer hydrochloride	0.35 (0.11, 1.14)	0.32 (0.12, 0.84)	0.25 (0.05, 1.14)	58.32 (1.74, 35180.00)	7.14 (1.42, 41.74)	2.72 (0.20, 38.64)	19.65 (0.55, 13250.00)	14.71 (0.40, 8280.00)		0.17 (0.04, 0.74)	0.49 (0.08, 3.13)
Sevelamer hydrochloride +Calcium Carbonate	0.20 (0.03, 1.53)	0.18 (0.02, 1.67)	0.14 (0.01, 1.75)	35.23 (0.55, 27410.00)	4.17 (0.40, 45.72)	1.61 (0.07, 33.94)	11.72 (0.18, 10060.00)	8.98 (0.13, 6292.00)	0.58 (0.07, 4.40)		-
Sucroferric oxyhydroxide	0.17 (0.01, 2.99)	0.15 (0.01, 2.52)	0.12 (0.01, 2.44)	30.46 (0.36, 28830.00)	3.45 (0.17, 79.11)	1.32 (0.04, 52.13)	10.23 (0.12, 10030.00)	7.92 (0.08, 6060.00)	0.48 (0.04, 6.64)	0.83 (0.03, 23.25)	

Adverse events: constipation

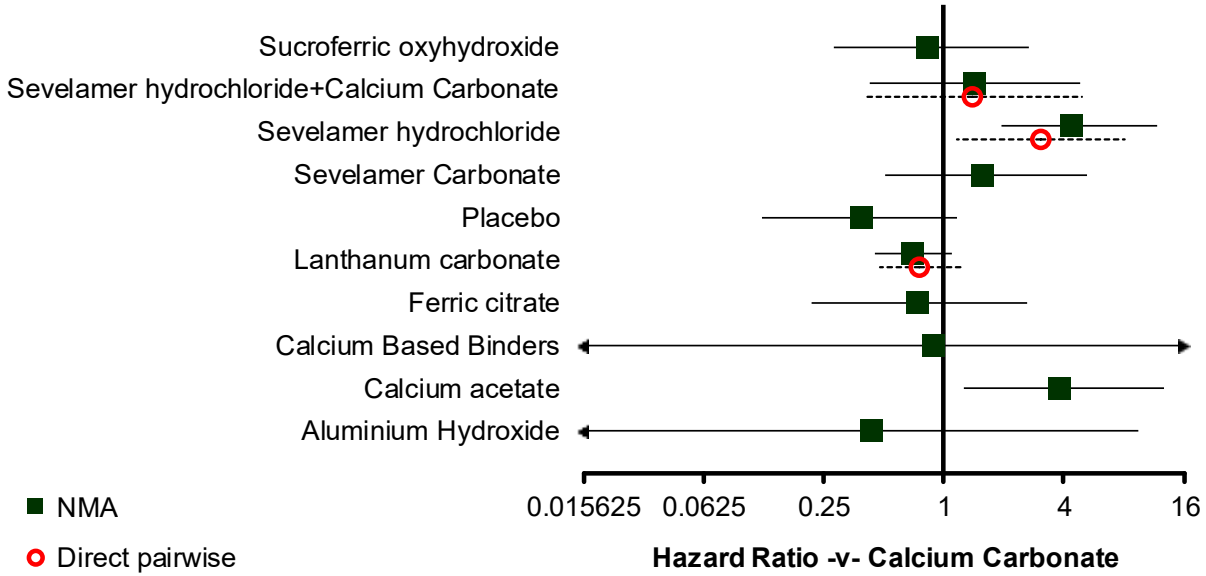
Network diagram

Figure 46: Diagram of the network of studies underlying the NMA for adverse events (constipation) in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



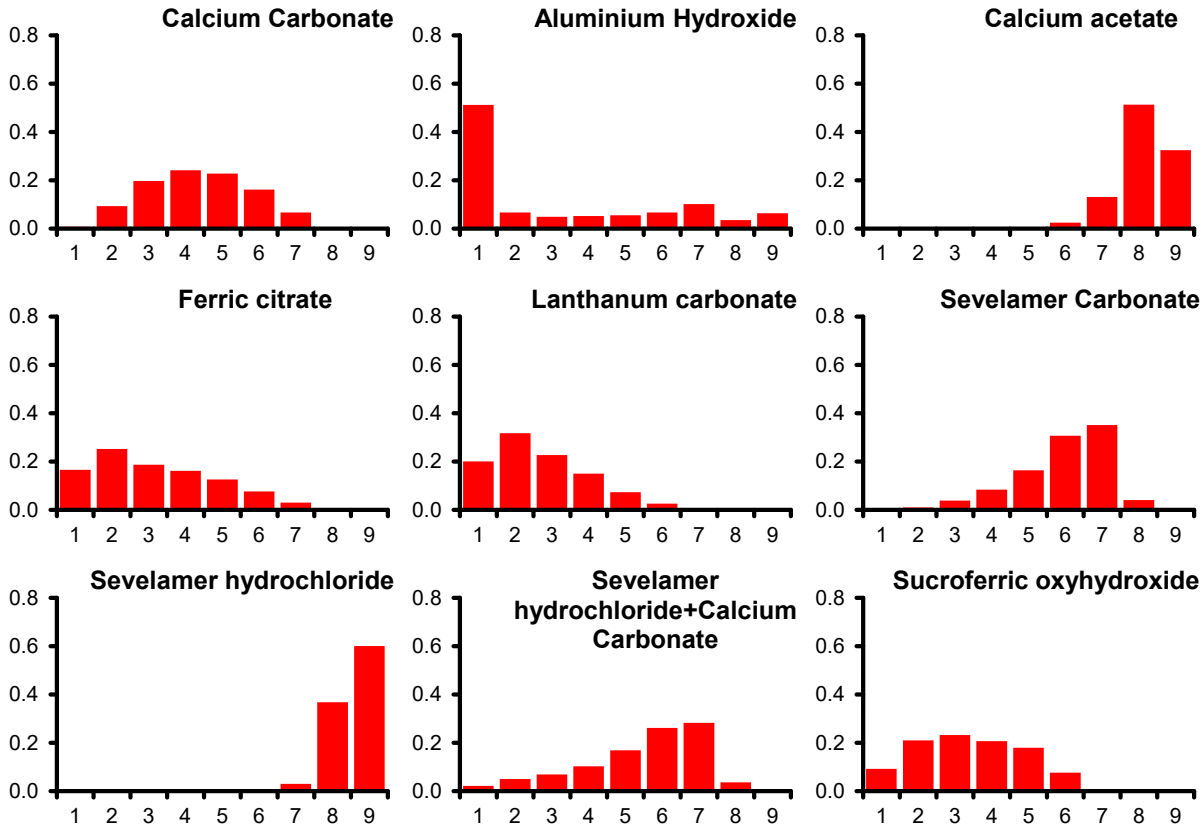
Caterpillar plot

Figure 47: Relative effectiveness of all options versus calcium carbonate for adverse events (constipation) in adults with stage 5 CKD who are on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour calcium carbonate; values lower than 1.0 favour the other treatments).



Rank probability histograms

Figure 48: Adverse events (constipation) in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 46: Relative effectiveness of all pairwise combinations for adverse events (constipation) in adults with stage 5 CKD who are on dialysis. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs less than 1 favour the column defining treatment, HRs greater than 1 favour the row defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

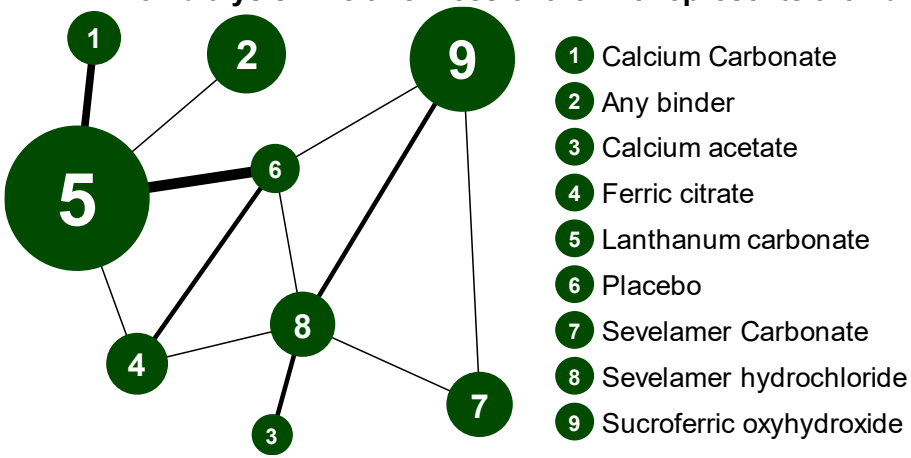
	Calcium Carbonate	Aluminium Hydroxide	Calcium acetate	Calcium Based Binders	Ferric citrate	Lanthanum carbonate	Placebo	Sevelamer Carbonate	Sevelamer hydrochloride	Sevelamer hydrochloride +Calcium	Sucroferric oxyhydroxide
Calcium Carbonate		-	-	-	-	0.76 (0.48, 1.21)	-	-	3.07 (1.17, 8.02)	1.39 (0.39, 4.94)	-
Aluminium Hydroxide	0.44 (0.00, 9.46)		-	-	-	-	-	-	5.35 (0.26, 111.55)	-	-
Calcium acetate	3.86 (1.26, 12.81)	8.85 (0.42, 4339.00)		-	-	-	-	-	1.14 (0.54, 2.41)	-	-
Calcium Based Binders	0.90 (0.00, 30.15)	2.09 (0.00, 2016.00)	0.23 (0.00, 7.56)		-	-	-	-	2.99 (0.12, 73.47)	-	-
Ferric citrate	0.76 (0.22, 2.60)	1.74 (0.08, 886.30)	0.19 (0.06, 0.64)	0.85 (0.02, 480.60)		-	0.33 (0.04, 2.55)	-	7.85 (2.34, 26.31)	-	-
Lanthanum carbonate	0.70 (0.45, 1.10)	1.63 (0.07, 814.50)	0.18 (0.05, 0.59)	0.79 (0.02, 425.90)	0.93 (0.26, 3.30)		1.18 (0.26, 5.35)	-	-	-	-
Placebo	0.39 (0.12, 1.16)	0.91 (0.04, 447.70)	0.10 (0.03, 0.34)	0.44 (0.01, 231.20)	0.52 (0.15, 1.52)	0.56 (0.17, 1.61)		11.37 (0.67, 194.03)	-	-	1.27 (0.15, 10.89)

Sevelamer Carbonate	1.60 (0.51, 5.22)	3.70 (0.17, 1845.00)	0.41 (0.13, 1.28)	1.79 (0.05, 943.20)	2.12 (0.66, 7.11)	2.28 (0.70, 7.66)	4.07 (1.47, 12.91)		8.03 (0.90, 71.85)	-	0.52 (0.30, 0.90)
Sevelamer hydrochloride	4.46 (1.94, 11.70)	10.22 (0.55, 4991.00)	1.16 (0.57, 2.42)	4.97 (0.16, 2647.00)	5.93 (2.40, 16.41)	6.40 (2.54, 17.50)	11.52 (4.34, 34.95)	2.81 (1.23, 6.72)		0.34 (0.13, 0.89)	0.17 (0.05, 0.62)
Sevelamer hydrochloride +Calcium Carbonate	1.44 (0.42, 4.80)	3.33 (0.14, 1627.00)	0.37 (0.11, 1.22)	1.61 (0.04, 894.90)	1.92 (0.49, 7.45)	2.06 (0.57, 7.20)	3.73 (0.91, 14.81)	0.90 (0.24, 3.24)	0.32 (0.11, 0.81)		-
Sucroferric oxyhydroxide	0.85 (0.28, 2.66)	1.96 (0.09, 971.60)	0.22 (0.07, 0.64)	0.95 (0.03, 499.90)	1.12 (0.36, 3.64)	1.21 (0.38, 3.92)	2.16 (0.79, 6.73)	0.53 (0.32, 0.89)	0.19 (0.08, 0.40)	0.59 (0.17, 2.12)	

Adverse events: diarrhoea

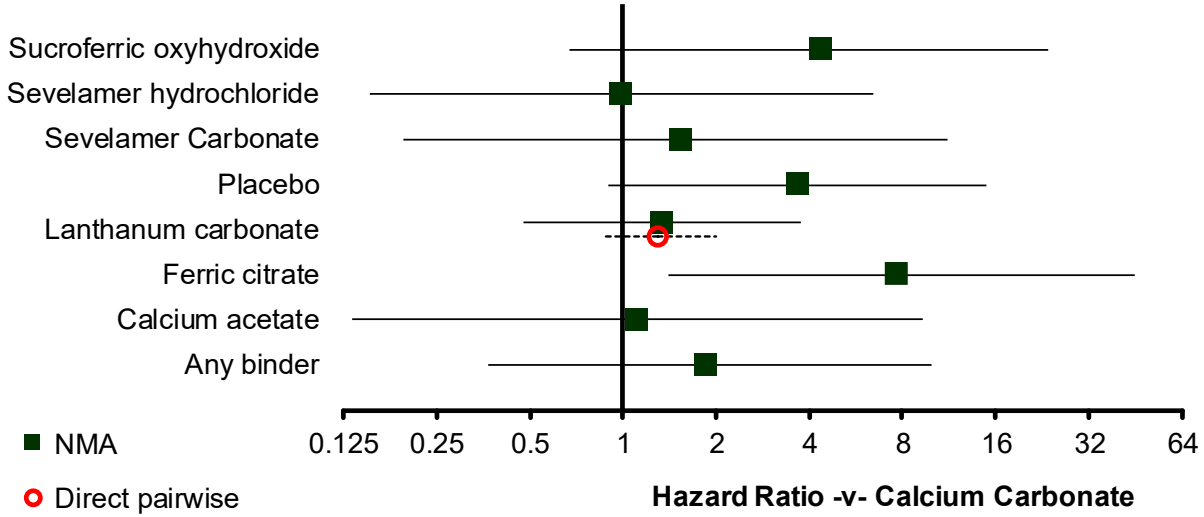
Network diagram

Figure 49: Diagram of the network of studies underlying the NMA for adverse events (diarrhoea) in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



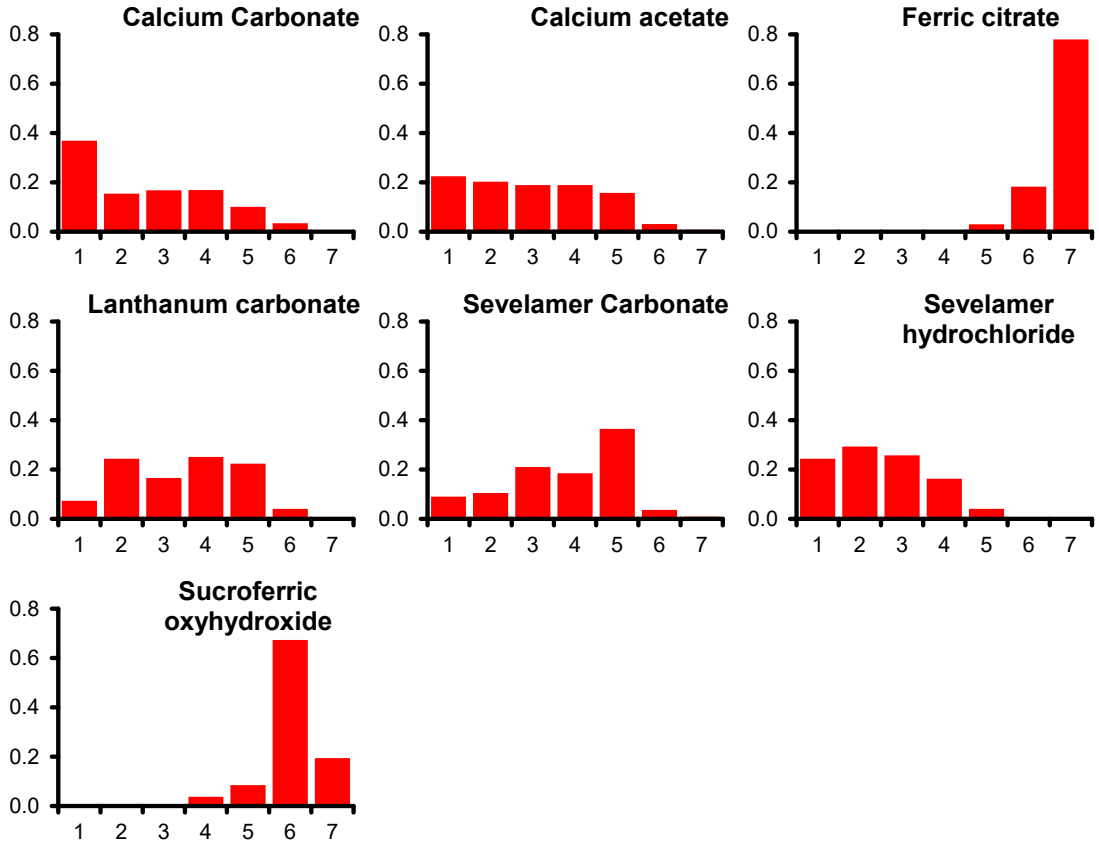
Caterpillar plot

Figure 50: Relative effectiveness of all options versus calcium carbonate for adverse events (diarrhoea) in adults with stage 5 CKD who are on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour calcium carbonate; values lower than 1.0 favour the other treatments).



Rank probability histograms

Figure 51: Adverse events (diarrhoea) in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

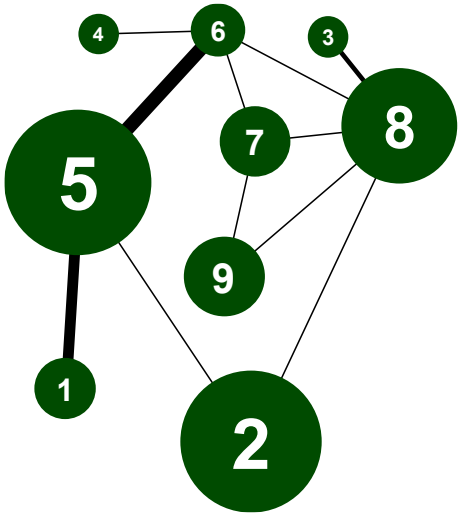
Table 47: Relative effectiveness of all pairwise combinations for adverse events (diarrhoea) in adults with stage 5 CKD who are on dialysis. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs less than 1 favour the column defining treatment, HRs greater than 1 favour the row defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

	Calcium Carbonate	Any binder	Calcium acetate	Ferric citrate	Lanthanum carbonate	Placebo	Sevelamer Carbonate	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-	-	1.30 (0.85, 1.99)	-	-	-	-
Any binder	1.87 (0.37, 9.92)		-	-	0.72 (0.58, 0.88)	-	-	-	-
Calcium acetate	1.11 (0.13, 9.36)	0.59 (0.06, 5.70)		-	-	-	-	0.90 (0.53, 1.53)	-
Ferric citrate	7.68 (1.40, 44.94)	4.18 (0.61, 27.40)	6.95 (1.22, 42.54)		0.19 (0.01, 4.03)	0.62 (0.24, 1.62)	-	0.08 (0.01, 0.63)	-
Lanthanum carbonate	1.33 (0.48, 3.73)	0.72 (0.19, 2.63)	1.21 (0.18, 7.98)	0.17 (0.04, 0.69)		3.33 (1.54, 7.19)	-	-	-
Placebo	3.67 (0.90, 14.94)	1.99 (0.37, 9.55)	3.30 (0.64, 17.23)	0.48 (0.15, 1.36)	2.76 (1.01, 7.43)		-	0.16 (0.01, 4.05)	1.53 (0.68, 3.41)
Sevelamer Carbonate	1.55 (0.20, 11.26)	0.84 (0.08, 6.63)	1.40 (0.26, 6.68)	0.20 (0.03, 1.03)	1.17 (0.19, 6.47)	0.42 (0.09, 1.81)		0.64 (0.21, 1.99)	2.89 (1.90, 4.39)
Sevelamer hydrochloride	0.99 (0.15, 6.43)	0.53 (0.07, 3.98)	0.89 (0.31, 2.45)	0.13 (0.03, 0.52)	0.74 (0.15, 3.63)	0.27 (0.07, 0.96)	0.64 (0.19, 2.28)		2.12 (0.10, 42.85)
Sucroferric oxyhydroxide	4.40 (0.67, 23.74)	2.38 (0.29, 14.78)	3.96 (0.82, 15.69)	0.56 (0.13, 2.15)	3.27 (0.68, 13.34)	1.19 (0.37, 3.45)	2.86 (0.87, 8.23)	4.43 (1.47, 11.89)	

Adverse events: nausea and/or vomiting

Network diagram

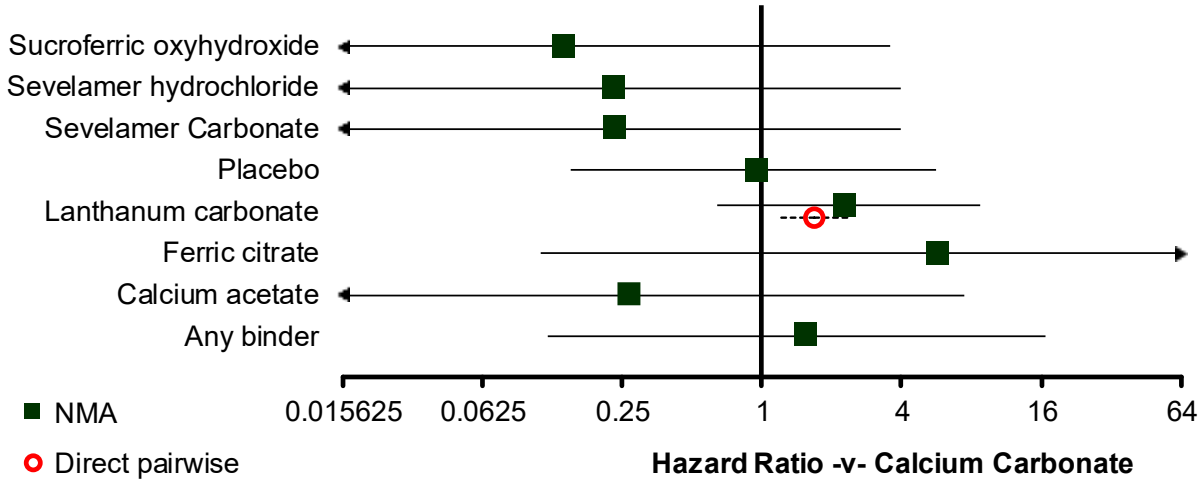
Figure 52: Diagram of the network of studies underlying the NMA for adverse events (nausea and/or vomiting) in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



1. Calcium Carbonate
2. Any binder
3. Calcium acetate
4. Ferric citrate
5. Lanthanum carbonate
6. Placebo
7. Sevelamer Carbonate
8. Sevelamer hydrochloride
9. Sucroferric oxyhydroxide

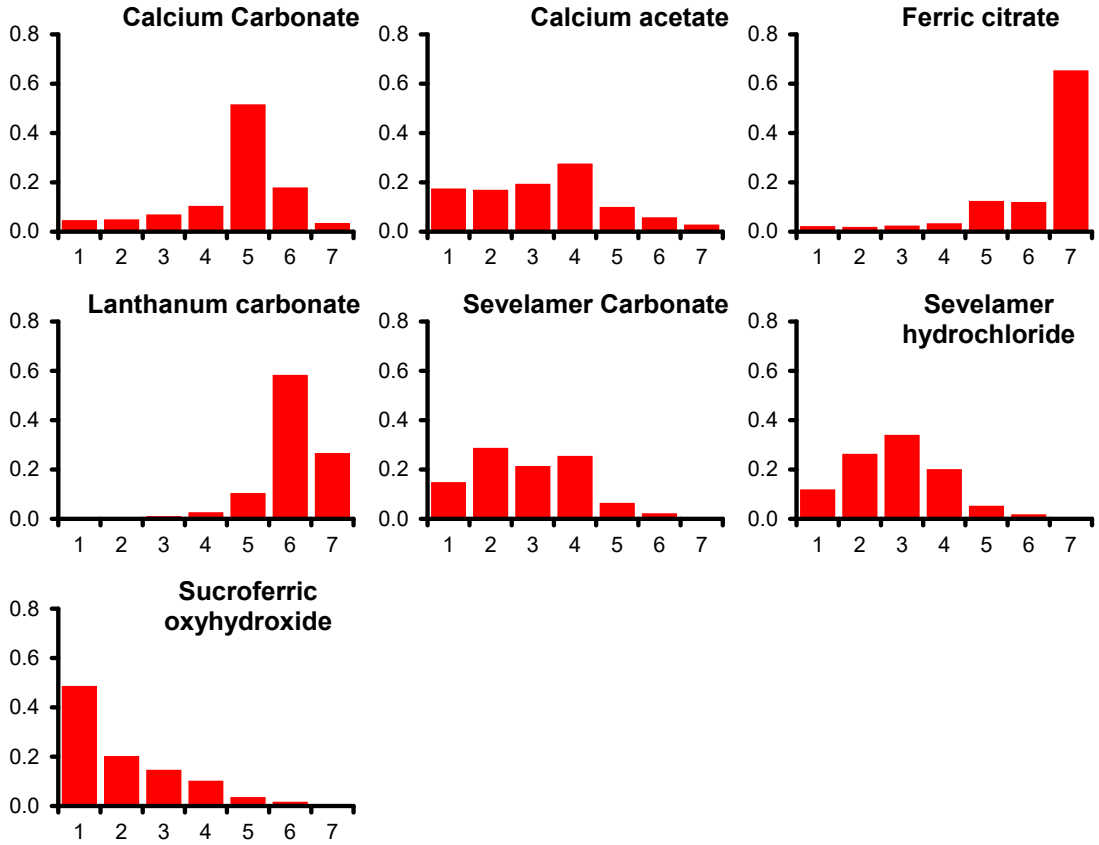
Caterpillar plot

Figure 53: Relative effectiveness of all options versus calcium carbonate for adverse events (nausea and/or vomiting) in adults with stage 5 CKD who are on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour calcium carbonate; values lower than 1.0 favour the other treatments).



Rank probability histograms

Figure 54: Adverse events (nausea and/or vomiting) in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

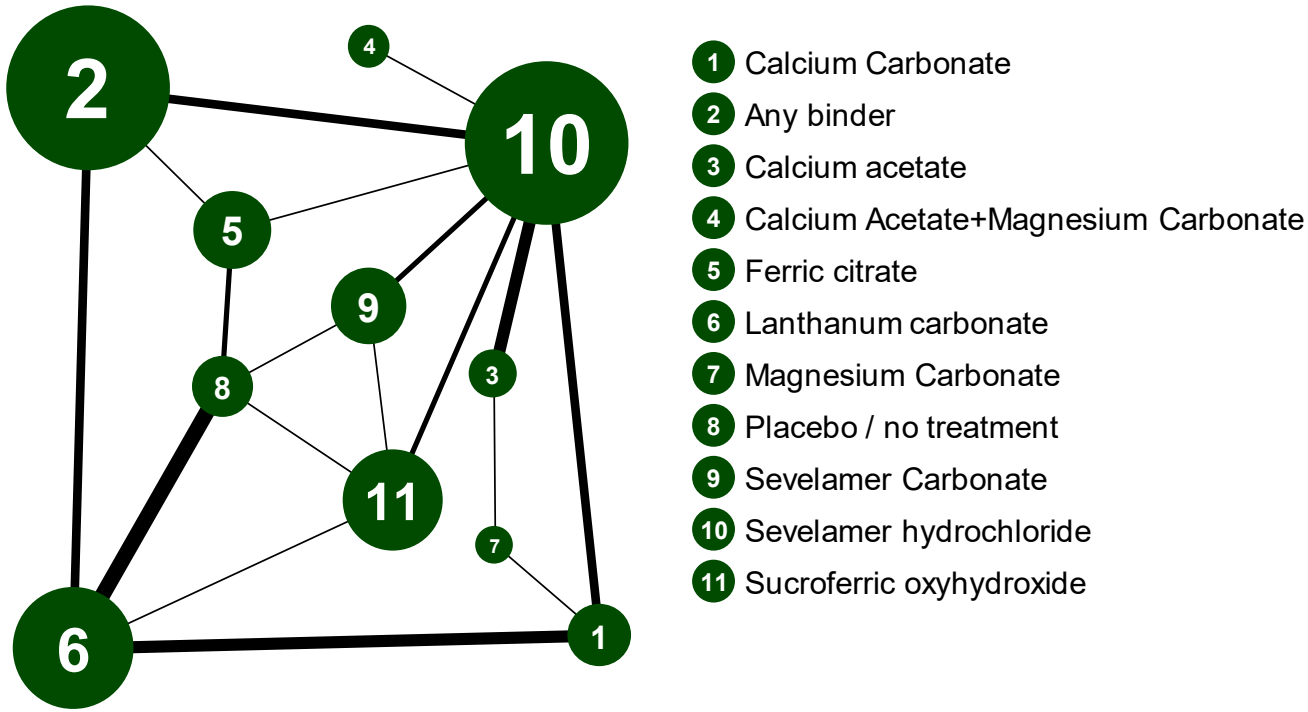
Table 48: Relative effectiveness of all pairwise combinations for adverse events (nausea and/or vomiting) in adults with stage 5 CKD who are on dialysis. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs less than 1 favour the column defining treatment, HRs greater than 1 favour the row defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

	Calcium Carbonate	Any binder	Calcium acetate	Ferric citrate	Lanthanum carbonate	Placebo	Sevelamer Carbonate	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-	-	1.68 (1.17, 2.42)	-	-	-	-
Any binder	1.55 (0.12, 16.76)		-	-	0.91 (0.77, 1.09)	-	-	1.00 (0.06, 15.94)	-
Calcium acetate	0.27 (0.01, 7.48)	0.18 (0.01, 5.05)		-	-	-	-	0.88 (0.53, 1.46)	-
Ferric citrate	5.81 (0.11, 3527.00)	3.97 (0.06, 2986.00)	23.06 (0.23, 20840.00)		-	0.42 (0.02, 8.13)	-	-	-
Lanthanum carbonate	2.28 (0.64, 8.69)	1.47 (0.21, 13.64)	8.54 (0.42, 197.20)	0.39 (0.00, 16.20)		0.49 (0.14, 1.80)	-	-	-
Placebo	0.94 (0.15, 5.59)	0.61 (0.07, 6.64)	3.51 (0.18, 67.65)	0.17 (0.00, 5.11)	0.41 (0.11, 1.36)		0.06 (0.00, 1.04)	0.49 (0.03, 7.82)	-
Sevelamer Carbonate	0.23 (0.01, 3.97)	0.15 (0.01, 2.86)	0.86 (0.06, 9.99)	0.04 (0.00, 2.71)	0.10 (0.01, 1.24)	0.24 (0.02, 2.61)		0.42 (0.14, 1.24)	0.63 (0.42, 0.96)
Sevelamer hydrochloride	0.23 (0.01, 3.94)	0.15 (0.01, 2.53)	0.85 (0.15, 4.55)	0.04 (0.00, 2.87)	0.10 (0.01, 1.23)	0.24 (0.02, 2.67)	0.99 (0.16, 7.34)		0.34 (0.02, 5.40)
Sucroferric oxyhydroxide	0.14 (0.00, 3.55)	0.09 (0.00, 2.51)	0.52 (0.03, 7.55)	0.02 (0.00, 2.17)	0.06 (0.00, 1.16)	0.15 (0.01, 2.54)	0.60 (0.09, 4.36)	0.61 (0.07, 5.03)	

Discontinuation due to adverse events

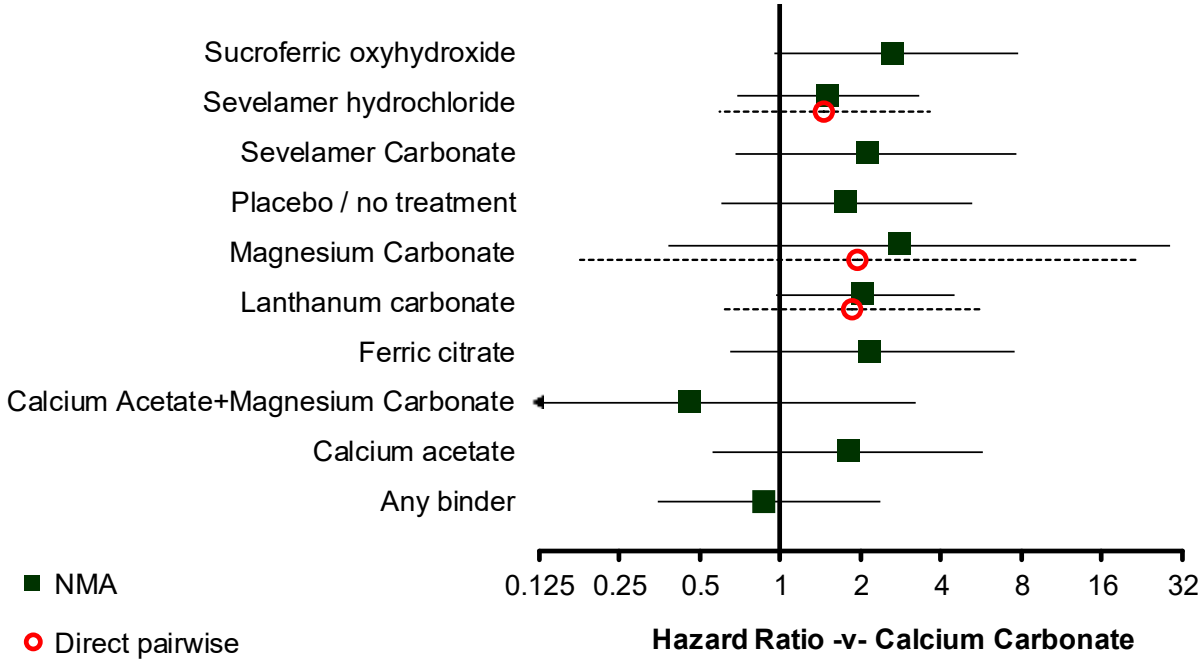
Network diagram

Figure 55: Diagram of the network of studies underlying the NMA for discontinuation due to adverse events in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies.



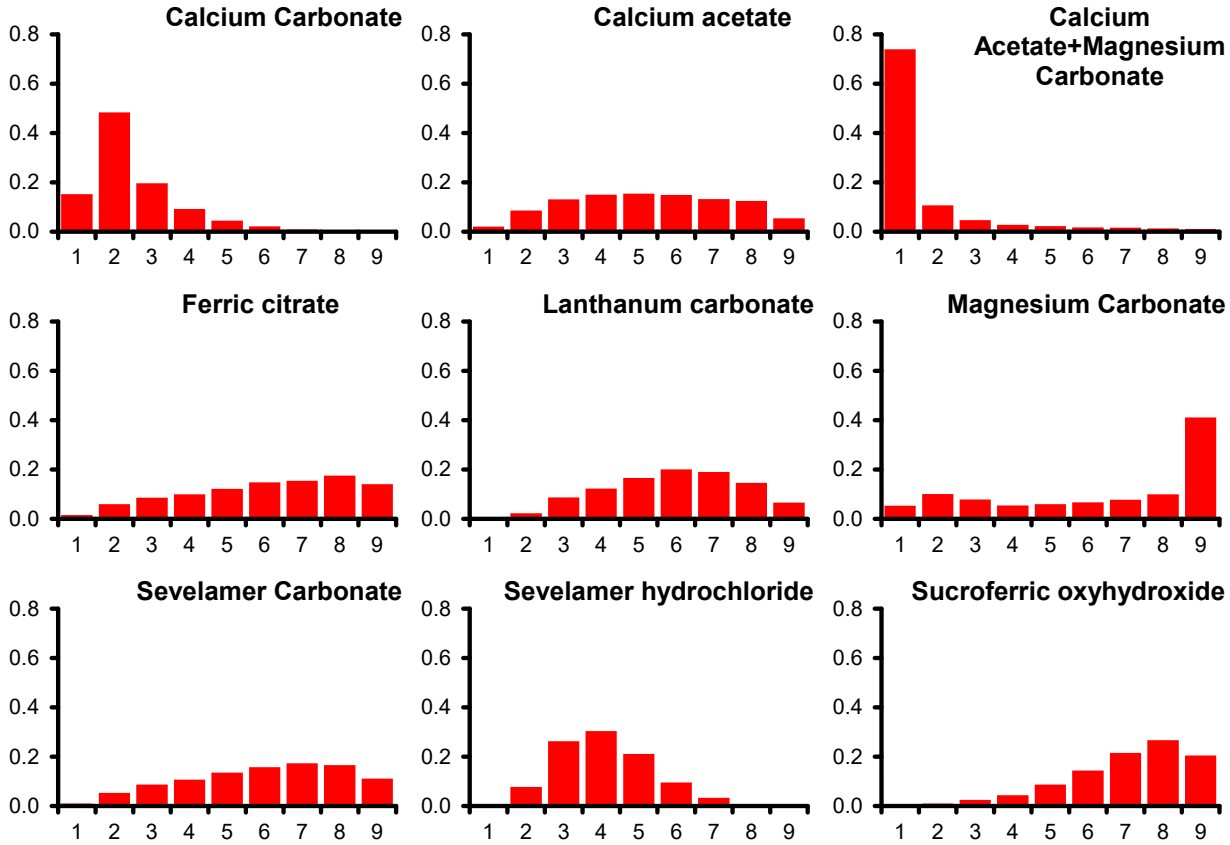
Caterpillar plot

Figure 56: Relative effectiveness of all options versus calcium carbonate for discontinuation due to adverse events in adults with stage 5 CKD who are on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour calcium carbonate; values lower than 1.0 favour the other treatments).



Rank probability histograms

Figure 57: Discontinuation due to adverse events in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 49: Relative effectiveness of all pairwise combinations for discontinuation due to adverse events in adults with stage 5 CKD who are on dialysis. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs less than 1 favour the column defining treatment, HRs greater than 1 favour the row defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

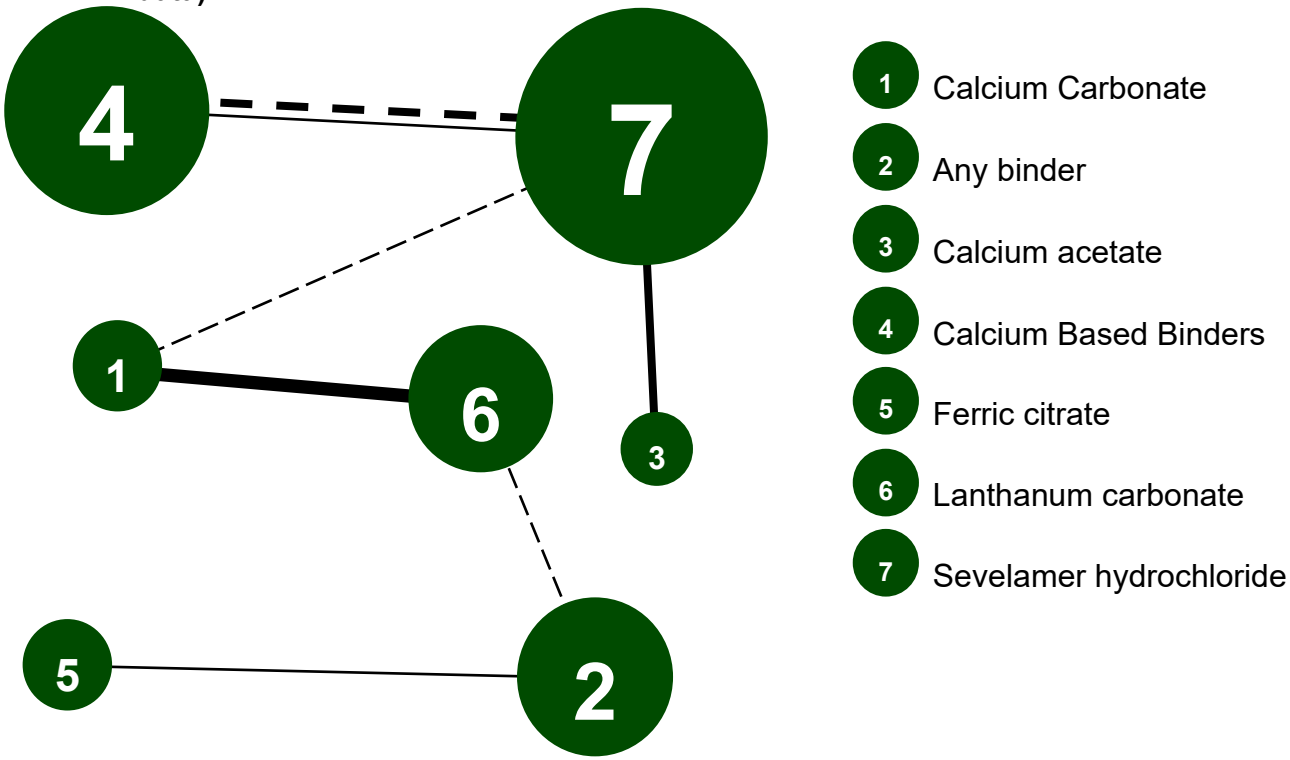
	Calcium Carbonate	Any binder	Calcium acetate	Calcium Acetate +Magnesium Carbonate	Ferric citrate	Lanthanum carbonate	Magnesium Carbonate	Placebo / no treatment	Sevelamer Carbonate	Sevelamer hydrochloride	Sucroferric oxyhydroxide
Calcium Carbonate		-	-	-	-	1.87 (0.62, 5.63)	1.96 (0.18, 21.63)	-	-	1.46 (0.59, 3.63)	-
Any binder	0.87 (0.35, 2.37)		-	-	2.64 (1.17, 5.95)	2.83 (1.40, 5.76)	-	-	-	1.61 (1.14, 2.27)	-
Calcium acetate	1.83 (0.56, 5.76)	2.09 (0.60, 6.64)		-	-	-	1.54 (0.16, 14.85)	-	-	0.74 (0.43, 1.27)	-
Calcium Acetate +Magnesium Carbonate	0.46 (0.06, 3.24)	0.52 (0.06, 3.75)	0.25 (0.03, 1.91)		-	-	-	-	-	3.00 (0.81, 11.09)	-
Ferric citrate	2.17 (0.65, 7.57)	2.49 (0.84, 7.24)	1.20 (0.30, 4.92)	4.77 (0.58, 44.77)		-	-	1.41 (0.45, 4.43)	-	0.34 (0.07, 1.67)	-
Lanthanum carbonate	2.07 (0.97, 4.50)	2.36 (1.01, 5.24)	1.13 (0.34, 3.88)	4.51 (0.62, 38.81)	0.95 (0.30, 2.96)		-	0.94 (0.36, 2.44)	-	-	3.09 (0.32, 29.75)

Magnesium Carbonate	2.81 (0.38, 28.97)	3.22 (0.39, 35.77)	1.55 (0.21, 16.12)	6.31 (0.42, 128.80)	1.30 (0.14, 16.09)	1.37 (0.17, 14.75)		-	-	-	-
Placebo / no treatment	1.77 (0.60, 5.21)	2.03 (0.69, 5.69)	0.97 (0.26, 3.74)	3.87 (0.49, 35.59)	0.81 (0.27, 2.36)	0.86 (0.34, 2.12)	0.62 (0.05, 5.54)		2.09 (0.23, 18.70)	-	2.37 (0.55, 10.21)
Sevelamer Carbonate	2.15 (0.68, 7.71)	2.47 (0.76, 8.47)	1.18 (0.34, 4.87)	4.75 (0.63, 44.96)	0.99 (0.26, 4.17)	1.05 (0.33, 3.61)	0.76 (0.07, 7.32)	1.23 (0.39, 4.34)		0.44 (0.18, 1.10)	2.29 (1.43, 3.67)
Sevelamer hydrochloride	1.51 (0.69, 3.32)	1.73 (0.73, 3.80)	0.82 (0.35, 2.05)	3.29 (0.53, 23.50)	0.69 (0.23, 2.02)	0.73 (0.31, 1.66)	0.53 (0.05, 3.91)	0.85 (0.32, 2.29)	0.70 (0.25, 1.78)		0.81 (0.41, 1.58)
Sucroferric oxyhydroxide	2.65 (0.94, 7.77)	3.04 (1.02, 8.85)	1.45 (0.45, 4.99)	5.84 (0.80, 49.89)	1.22 (0.34, 4.28)	1.28 (0.47, 3.59)	0.93 (0.08, 8.06)	1.50 (0.54, 4.32)	1.23 (0.43, 3.14)	1.76 (0.78, 4.08)	

All-cause mortality

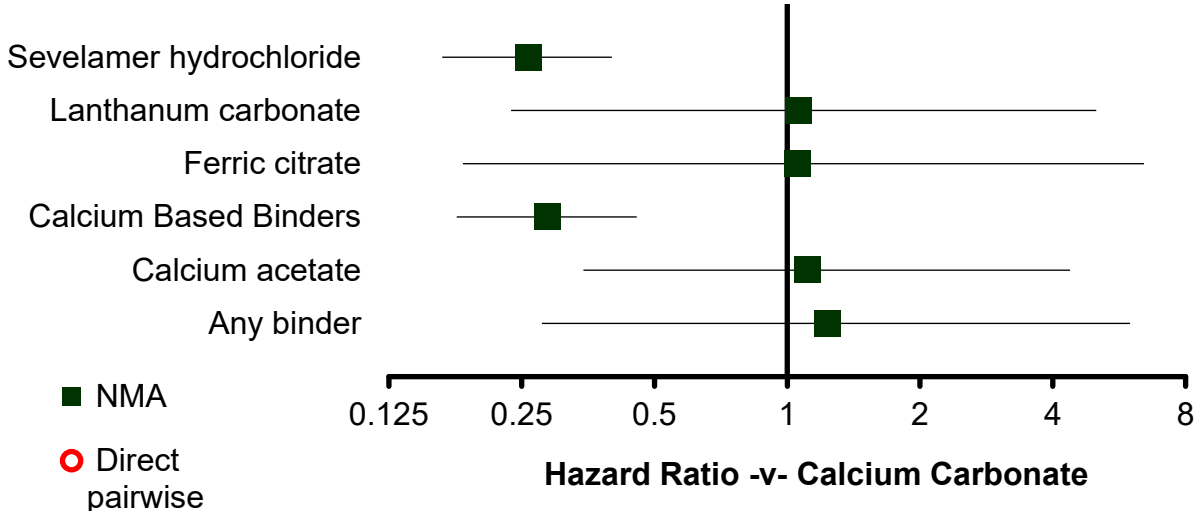
Network diagram

Figure 58: Diagram of the network of studies underlying the NMA for mortality in adults with stage 5 CKD who are on dialysis. The thickness of the line represents the number of studies (dashed lines represent HR data; continuous lines represent event data).



Caterpillar plot

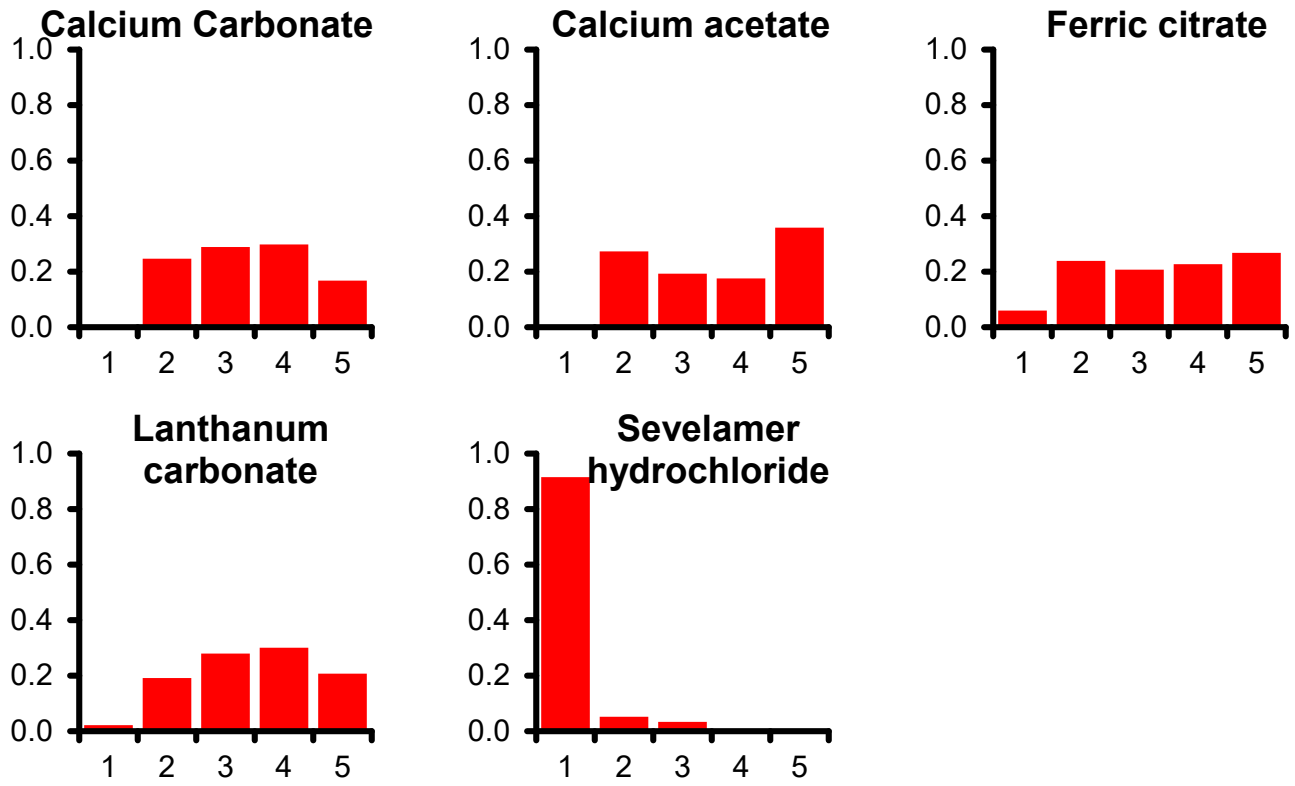
Figure 59: Relative effectiveness of all options versus calcium carbonate for mortality in adults with stage 5 CKD who are on dialysis. (Hazard ratios with 95% credible intervals; values higher than 1.0 favour calcium carbonate; values lower than 1.0 favour the other treatments).



Direct pairwise data could not be estimated. For NMA, a shared parameter model was used.

Rank probability histograms

Figure 60: Mortality in adults with stage 5 CKD who are on dialysis. Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).



Relative effectiveness

Table 50: Relative effectiveness of NMA results for mortality in adults with stage 5 CKD who are on dialysis. (Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment).

	Calcium Carbonate	Any binder	Calcium acetate	Calcium Based Binders	Ferric citrate	Lanthanum carbonate	Sevelamer hydrochloride
Calcium Carbonate		N/A	N/A	N/A	N/A	N/A	N/A
Any binder	1.24 (0.28, 5.99)		N/A	N/A	N/A	N/A	N/A
Calcium acetate	1.11 (0.35, 4.38)	0.90 (0.13, 6.83)		N/A	N/A	N/A	N/A
Calcium Based Binders	0.29 (0.18, 0.46)	0.23 (0.04, 1.11)	0.26 (0.07, 0.77)		N/A	N/A	N/A
Ferric citrate	1.05 (0.18, 6.44)	0.83 (0.35, 2.12)	0.93 (0.11, 8.12)	3.66 (0.62, 23.77)		N/A	N/A
Lanthanum carbonate	1.06 (0.24, 5.02)	0.86 (0.68, 1.08)	0.97 (0.13, 6.88)	3.74 (0.79, 18.99)	1.03 (0.39, 2.56)		N/A
Sevelamer hydrochloride	0.26 (0.17, 0.40)	0.21 (0.04, 0.99)	0.23 (0.06, 0.69)	0.90 (0.77, 1.07)	0.25 (0.04, 1.47)	0.24 (0.05, 1.15)	

Direct pairwise data could not be estimated. For NMA, a shared parameter model was used.

Appendix I – GRADE tables

Pairwise analysis

Adults with stage 4 or 5 CKD who are not on dialysis

Calcium acetate vs Placebo

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium acetate	Placebo	Relative (95% CI)	Absolute	
Serum Phosphate (mmol/L) at 3 months (Better indicated by lower values) [MID +/- 0.22]											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	37	41	-	MD 0.23 lower (0.42 to 0.04 lower)	LOW
Proportion achieving phosphate control											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	22/37 (59.5%)	36.6%	RR 1.63 (1 to 2.63)	23 more per 100 (from 0 more to 60 more)	LOW
Serum Calcium (mmol/L) at 3 months (Better indicated by lower values) [MID +/- 0.10]											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	37	41	-	MD 0.17 higher (0.08 to 0.26 higher)	LOW
Risk of hypercalcaemia											

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/37 (13.5%)	0%	RR 12.16 (0.7 to 212.64)	-	VERY LOW
All-cause mortality											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	Serious[5]	none	1/46 (2.2%)	4.7%	RR 0.46 (0.05 to 4.32)	3 fewer per 100 (from 4 fewer to 16 more)	VERY LOW
Discontinuation due to adverse events											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/46 (4.3%)	6.3%	RR 0.7 (0.13 to 3.64)	2 fewer per 100 (from 5 fewer to 17 more)	VERY LOW
Adherence (Better indicated by higher values) [MID +/- 7]											
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	37	41	-	MD 0.7 lower (7.16 lower to 5.76 higher)	LOW

[1] Qunibi 2011
[2] Study at moderate or high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses both ends of a defined MID interval
[5] 95% confidence interval crosses line of no effect

Calcium carbonate vs Lanthanum carbonate

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium carbonate**	**Lanthanum carbonate**	**Relative (95% CI)**	**Absolute**	

Serum Phosphate (mmol/L) at 4 months (Better indicated by lower values) [MID +/- 0.06]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	16	16	-	MD 0.06 lower (0.13 lower to 0.01 higher)	VERY LOW
Serum Calcium (mmol/L) at 4 months (Better indicated by lower values) [MID +/- 0.02]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	16	16	-	MD 0.05 lower (0.15 lower to 0.05 higher)	VERY LOW

[1] Soriano 2013
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses both ends of a defined MID interval

Lanthanum carbonate vs Placebo

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lanthanum carbonate**	**Placebo**	**Relative (95% CI)**	**Absolute**	
Serum Phosphate (mmol/L) - Less than 3 months (Better indicated by lower values) [MID +/- 0.15]											
2[1]	randomised trials	very serious[2]	very serious[3]	no serious indirectness	serious[4]	none	142	89	-	MD 0.22 lower (0.41 to 0.02 lower)	VERY LOW
Proportion achieving phosphate control											
2[1]	randomised trials	very serious[2]	serious[5]	no serious indirectness	no serious imprecision	none	57/142 (40.1%)	18.7%	RR 2.37 (1.44 to 3.9)	26 more per 100 (from 8 more to 54 more)	VERY LOW

Serum Calcium (mmol/L) - Less than 3 months (Better indicated by lower values) [MID +/- 0.05]											
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[4]	none	56	34	-	MD 0.05 higher (0.01 to 0.09 higher)	VERY LOW
Adverse events: constipation											
1[8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious	none	14/86 (16.3%)	5.5%	RR 2.98 (0.9 to 9.91)	11 more per 100 (from 1 fewer to 49 more)	LOW
Adverse events: nausea and/or vomiting											
2[1]	randomised trials	very serious[2]	serious[5]	no serious indirectness	very serious[10]	none	18/164 (11%)	6.7%	RR 1.74 (0.72 to 4.2)	5 more per 100 (from 2 fewer to 21 more)	VERY LOW
Discontinuation due to adverse events											
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	8/166 (4.8%)	11.2%	RR 0.44 (0.18 to 1.04)	6 fewer per 100 (from 9 fewer to 0 more)	VERY LOW

[1] Sprague 2009; Takahara 2014
[2] >33.3% of weighted data from studies at high risk of bias
[3] i-squared >66.7%
[4] 95% confidence interval crosses one end of a defined MID interval
[5] i-squared >33.3%
[6] Sprague 2009
[7] Study at high risk of bias
[8] Takahara 2014
[9] Study at moderate risk of bias
[10] 95% confidence interval crosses both ends of a defined MID interval

Sevelamer hydrochloride vs Calcium acetate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sevelamer hydrochloride	Calcium acetate	Relative (95% CI)	Absolute	
Serum Phosphate (mmol/L) - Less than 3 months (Better indicated by lower values) [MID +/- 0.11]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	25	25	-	MD 0.03 lower (0.18 lower to 0.12 higher)	VERY LOW
Serum Calcium (mmol/L) - Less than 3 months (Better indicated by lower values) [MID +/- 0.03]											
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	25	25	-	MD 0.07 lower (0.12 to 0.02 lower)	VERY LOW

[1] Yilmaz 2012
[2] Study at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] 95% confidence interval crosses one end of a defined MID interval

Ferric citrate vs Placebo

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ferric citrate	Placebo	Relative (95% CI)	Absolute	
Serum Phosphate (mmol/L) at 3 months (Better indicated by lower values) [MID +/- 0.14]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	29	-	MD 0.41 lower (0.56 to 0.26 lower)	LOW

Proportion achieving phosphate control											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/57 (64.9%)	6.9%	RR 9.41 (2.44 to 36.34)	58 more per 100 (from 10 more to 100 more)	LOW
Serum Calcium (mmol/L) at 3 months (Better indicated by lower values) [MID +/- 0.05]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	57	29	-	MD 0.06 higher (0.01 to 0.11 higher)	VERY LOW
All-cause mortality											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	1/60 (1.7%)	0%	RR 1.52 (0.06 to 36.34)	-	VERY LOW
Adverse events: constipation											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	7/57 (12.3%)	6.9%	RR 1.78 (0.39 to 8.03)	5 more per 100 (from 4 fewer to 49 more)	VERY LOW
Adverse events: diarrhoea											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	8/57 (14%)	6.9%	RR 2.04 (0.46 to 8.97)	7 more per 100 (from 4 fewer to 55 more)	VERY LOW
Adverse events: nausea and/or vomiting											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/57 (1.8%)	6.9%	RR 0.25 (0.02 to 2.69)	5 fewer per 100 (from 7 fewer to 12 more)	VERY LOW
Discontinuation due to adverse events											

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/60 (10%)	3.3%	RR 3 (0.38 to 23.8)	7 more per 100 (from 2 fewer to 75 more)	VERY LOW

[1] Yokoyama 2014a
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses line of no effect
[5] 95% confidence interval crosses both ends of a defined MID interval

Calcium carbonate + low phosphate diet vs Low phosphate diet

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium carbonate + low phosphate diet**	**Low phosphate diet**	**Relative (95% CI)**	**Absolute**	
Serum Phosphate (mmol/L) at 24 months (Better indicated by lower values) [MID +/- 0.14]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	28	15	-	MD 0.26 higher (0.03 to 0.49 higher)	VERY LOW
Serum Calcium (mmol/L) at 24 months (Better indicated by lower values) [MID +/- 0.06]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	28	15	-	MD 0.03 lower (0.13 lower to 0.07 higher)	VERY LOW
Cardiovascular mortality											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	Serious[5]	none	0/30 (0%)	3.3%	RR 0.17 (0.01 to 3.99)	3 fewer per 100 (from 3 fewer to 10 more)	VERY LOW

Coronary artery calcification (Better indicated by lower values)) [MID +/- 182.5]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	29	14	-	MD 74 higher (318.71 lower to 466.71 higher)	VERY LOW

[1] Russo 2007
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses both ends of a defined MID interval
[5] 95% confidence interval crosses line of no effect

Sevelamer hydrochloride + low phosphate diet vs Low phosphate diet

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sevelamer hydrochloride + low phosphate diet**	**Low phosphate diet**	**Relative (95% CI)**	**Absolute**	
Serum Phosphate (mmol/L) at 24 months (Better indicated by lower values) [MID +/- 0.14]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	27	14	-	MD 0.29 higher (0.10 to 0.48 higher)	VERY LOW
Serum Calcium (mmol/L) at 24 months (Better indicated by lower values) [MID +/- 0.06]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	27	14	-	MD 0.05 lower (0.12 lower to 0.02 higher)	VERY LOW
Cardiovascular mortality											

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	0/30 (0%)	3.3%	RR 0.17 (0.01 to 3.99)	3 fewer per 100 (from 3 fewer to 10 more)	VERY LOW
Coronary artery calcification (Better indicated by lower values) [MID +/- 471.2]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	27	29	-	MD 94 lower (646.86 lower to 458.86 higher)	VERY LOW

[1] Russo 2007
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses line of no effect

Children and young people with stage 5 CKD who are on dialysis

Calcium carbonate vs Sevelamer hydrochloride

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium carbonate**	**Sevelamer hydrochloride**	**Relative (95% CI)**	**Absolute**	
Serum Phosphate (mmol/L) - 3 months (Better indicated by lower values) [MID +/- 0.25]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	14	15	-	MD 0.11 higher (0.2 lower to 0.42 higher)	VERY LOW
Serum Phosphate (mmol/L) - 6 months (Better indicated by lower values) [MID +/- 0.09]											

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	14	15	-	MD 0.09 higher (0.03 lower to 0.21 higher)	VERY LOW
Serum Calcium (mmol/L) - 3 months (Better indicated by lower values) [MID +/- 0.07]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	15	-	MD 0.23 higher (0.12 to 0.34 higher)	LOW
Serum Calcium (mmol/L) - 6 months (Better indicated by lower values) [MID +/- 0.07]											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	14	15	-	MD 0.14 higher (0.03 lower to 0.31 higher)	VERY LOW

[1] Salusky 2005
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

Network meta-analysis

Adults with stage 4 or 5 CKD who are not on dialysis

Serum phosphate at 2 to 4 months

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum phosphate at 2 to 4 months								
6[1]	RCT	477	See Appendix H	Very serious[2]	No serious	Not applicable	No serious	Low

1. Qunibi et al. (2011); Soriano et al. (2013); Sprague et al. (2009); Takahara et al. (2014); Yilmaz et al. (2012); Yokoyama et al. (2014)
2. >33.3% of studies in the NMA at high risk of bias

Proportion of participants achieving phosphate control

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Proportion of participants achieving phosphate control								

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
4[1]	RCT	395	See Appendix H	Very serious[2]	No serious	Not applicable	No serious	Low

1. Qunibi et al. (2011); Sprague et al. (2009); Takahara et al. (2014); Yokoyama et al. (2014)
2. >33.3% of studies in the NMA at high risk of bias

Serum calcium at 2 to 4 months

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum calcium at 2 to 4 months								
5[1]	RCT	336	See Appendix H	Very serious[2]	No serious	Not applicable	No serious	Low

1. Qunibi et al. (2011); Soriano et al. (2013); Sprague et al. (2009); Yilmaz et al. (2012); Yokoyama et al. (2014)
2. >33.3% of studies in the NMA at high risk of bias

Adverse events: constipation

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adverse events: constipation								
2[1]	RCT	227	See Appendix H	Very serious[2]	No serious	Not applicable	No serious	Low

1. Takahara et al. (2014); Yokoyama et al. (2014)
2. >33.3% of studies in the NMA at high risk of bias

Adverse events: diarrhoea

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adverse events: diarrhoea								
1[1]	RCT	86	See Appendix H	Very serious[2]	No serious	Not applicable	Serious[3]	Very low

1. Yokoyama et al. (2014)
2. >33.3% of studies in the NMA at high risk of bias
3. 95% CI of at least 1 of the comparisons crossed an MID (and no meaningfully distinct options were identified)

Adverse events: nausea/vomiting

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adverse events: nausea/vomiting								
3[1]	RCT	346	See Appendix H	Very serious[2]	No serious	Not applicable	Serious[3]	Very low

1. Sprague et al. (2009); Takahara et al. (2014); Yokoyama et al. (2014)

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2. >33.3% of studies in the NMA at high risk of bias 3. 95% CI of at least 1 of the comparisons crossed an MID (and no meaningfully distinct options were identified)								

Discontinuation due to adverse events

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Discontinuation due to adverse events								
5[1]	RCT	562	See Appendix H	Very serious[2]	No serious	Not applicable	No serious	Low
1. Qunibi et al. (2011); Sprague et al. (2009); Takahara et al. (2014); Yilmaz et al. (2012); Yokoyama et al. (2014) 2. >33.3% of studies in the NMA at high risk of bias 3. 95% CI of at least 1 of the comparisons crossed an MID (and no meaningfully distinct options were identified)								

Adults with stage 5 CKD who are on dialysis

All-cause mortality

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
All-cause mortality								
11[1]	RCT	5104	See Appendix H	Very serious[2]	No serious	Serious[3]	No serious	Very low
1. Barreto et al. (2008); Block 2005; Chertow et al. (2002); Di Iorio et al. (2013); Jalal et al. (2017); Ohtake et al. (2013); Qunibi et al. (2008); Spasovski et al. (2006); Suki 2007; Wada et al. (2015); Wilson 2009 2. >33.3% of studies in the NMA at high risk of bias 3. DIC for a random-effects model lower than the DIC for a fixed-effects model								

Serum phosphate at 3 months

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum phosphate at 3 months								
21[1]	RCT	4584	See Appendix H	Very serious[2]	No serious	Serious[3]	Serious[4]	Very low
3. Asmus et al. (2005); Barreto et al. (2008); Block et al. (2005); Braun et al. (2004); De Santo et al. (2006); de Francisco et al. (2010); Evenepoel et al. (2009); Ferreira et al. (2008); Finn et al. (2006); Fishbane et al. (2010); Hutchison et al. (2005); Janssen et al. (1996); Ketteler et al. (2019); Koiwa et al. (2017); Lee et al. (2013); Malluche et al. (2008); Maruyama et al. (2018); Navarro-Gonzalez et al. (2011); Spiegel et al. (2007); Wang et al. (2015); Yokoyama et al. (2014) 4. >33.3% of studies in the NMA at high risk of bias								

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

5. DIC for a random-effects model lower than the DIC for a fixed-effects model
6. 95% CI of at least 1 of the comparisons crossed an MID (and no meaningfully distinct options were identified)

Serum phosphate at 6 months

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum phosphate at 6 months								
22[1]	RCT	4248	See Appendix H	Very serious[2]	No serious	Serious[3]	Serious[4]	Very low

1. Ahmed et al. (2014); Asmus et al. (2005); Barreto et al. (2008); Block et al. (2005); Braun et al. (2004); De Santo et al. (2006); de Francisco et al. (2010); Ferreira et al. (2008); Finn et al. (2006); Fishbane et al. (2010); Fujii et al. (2018); Hutchison et al. (2005); Janssen et al. (1995); Janssen et al. (1996); Kalil et al. (2012); Ketteler et al. (2019); Lee et al. (2013); Malluche et al. (2008); Ohtake et al. (2013); Otsuki et al. (2018); Tzanakis et al. (2008); Wada et al. (2015)
2. >33.3% of studies in the NMA at high risk of bias
3. DIC for a random-effects model lower than the DIC for a fixed-effects model
4. 95% CI of at least 1 of the comparisons crossed an MID (and no meaningfully distinct options were identified)

Serum phosphate at 12 months

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum phosphate at 12 months								
21[1]	RCT	3948	See Appendix H	Very serious[2]	No serious	No serious	No serious	Low

1. Asmus et al. (2005); Barreto et al. (2008); Block et al. (2005); Braun et al. (2004); Chertow et al. (2002); Chertow et al. (2003); Ferreira et al. (2008); Finn et al. (2006); Freemont et al. (2005); Fujii et al. (2018); Jalal et al. (2017); Janssen et al. (1995); Janssen et al. (1996); Kakuta et al. (2011); Kalil et al. (2012); Ketteler et al. (2019); Lin et al. (2016); Malluche et al. (2008); Qunibi et al. (2008); Spasovski et al. (2006); Wada et al. (2015)
2. >33.3% of studies in the NMA at high risk of bias

Proportion of participants achieving phosphate control

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Proportion of participants achieving phosphate control								
23[1]	RCT	4259	See Appendix H	Very serious[2]	No serious	Serious[3]	No serious	Very low

1. Abraham et al. (2012); Al-Baaj et al. (2005); Chiang et al. (2005); Evenepoel et al. (2009); Finn et al. (2006); Finn et al. (2004); Fishbane et al. (2010); Hutchison et al. (2005); Janssen et al. (1996); Joy et al. (2003); Ketteler et al. (2019); Koiwa et al. (2017a); Koiwa et al. (2017b); Koiwa et

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
al. (2005); Lee et al. (2015); Liu et al. (2006); Shigematsu et al. (2008); Spiegel et al. (2007); Tzanakis et al. (2008); Wuthrich et al. (2013); Xu et al. (2013); Yokoyama et al. (2012); Yokoyama et al. (2014) 2. >33.3% of studies in the NMA at high risk of bias 3. DIC for a random-effects model lower than the DIC for a fixed-effects model								

Serum calcium at 3 months

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum calcium at 3 months								
16[1]	RCT	2837	See Appendix H	Very serious[2]	No serious	Serious[3]	No serious	Very low
1. Asmus et al. (2005); Barreto et al. (2008); Braun et al. (2004); De Santo et al. (2006); de Francisco et al. (2010); Evenepoel et al. (2009); Ferreira et al. (2008); Finn et al. (2006); Koiwa et al. (2017); Lee et al. (2013); Malluche et al. (2008); Maruyama et al. (2018); Navarro-Gonzalez et al. (2011); Spiegel et al. (2007); Wang et al. (2015); Yokoyama et al. (2014) 2. >33.3% of studies in the NMA at high risk of bias 3. DIC for a random-effects model lower than the DIC for a fixed-effects model								

Serum calcium at 6 months

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum calcium at 6 months								
19[1]	RCT	3286	See Appendix H	Very serious[2]	No serious	Serious[3]	No serious	Very low
1. Ahmed et al. (2014); Asmus et al. (2005); Barreto et al. (2008); Braun et al. (2004); De Santo et al. (2006); de Francisco et al. (2010); Ferreira et al. (2008); Finn et al. (2006); Fishbane et al. (2010); Fujii et al. (2018); Janssen et al. (1995); Kalil et al. (2012); Ketteler et al. (2019); Lee et al. (2013); Malluche et al. (2008); Ohtake et al. (2013); Otsuki et al. (2018); Tzanakis et al. (2008); Wada et al. (2015) 2. >33.3% of studies in the NMA at high risk of bias 3. DIC for a random-effects model lower than the DIC for a fixed-effects model								

Serum calcium at 12 months

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Serum calcium at 12 months								
19[1]	RCT	3717	See Appendix H	Very serious[2]	No serious	Serious[3]	Serious[4]	Very low

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Asmus et al. (2005); Barreto et al. (2008); Braun et al. (2004); Chertow et al. (2002); Chertow et al. (2003); Ferreira et al. (2008); Finn et al. (2006); Freemont et al. (2005); Fujii et al. (2018); Jalal et al. (2017); Janssen et al. (1995); Kakuta et al. (2011); Kalil et al. (2012); Ketteler et al. (2019); Lin et al. (2016); Malluche et al. (2008); Qunibi et al. (2008); Spasovski et al. (2006); Wada et al. (2015)
2. >33.3% of studies in the NMA at high risk of bias
3. DIC for a random-effects model lower than the DIC for a fixed-effects model
4. 95% CI of at least 1 of the comparisons crossed an MID (and no meaningfully distinct options were identified)

Risk of hypercalcaemia

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Risk of hypercalcaemia								
18[1]	RCT	2972	See Appendix H	Very serious[2]	No serious	Serious[3]	No serious	Very low

1. Asmus et al. (2005); Block et al. (2005); Braun et al. (2004); Chertow et al. (2002); Chertow et al. (2003); Evenepoel et al. (2009); Freemont et al. (2005); Hutchison et al. (2005); Jalal et al. (2017); Janssen et al. (1996); Koiwa et al. (2005); Lin et al. (2011); Liu et al. (2006); Qunibi et al. (2008); Shigematsu et al. (2008); Spasovski et al. (2006); Tzanakis et al. (2008); Wuthrich et al. (2013)
2. >33.3% of studies in the NMA at high risk of bias
3. DIC for a random-effects model lower than the DIC for a fixed-effects model

Adverse events: constipation

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adverse events: constipation								
23[1]	RCT	6908	See Appendix H	Very serious[2]	No serious	No serious	No serious	Low

1. Al-Baaj et al. (2005); Chen et al. (2014); Chertow et al. (2003); Fishbane et al. (2010); Freemont et al. (2005); Hutchison et al. (2005); Kakuta et al. (2011); Katopodis et al. (2006); Ketteler et al. (2019); Koiwa et al. (2005); Koiwa et al. (2017a); Koiwa et al. (2017b); Lee et al. (2015); Lin et al. (2016); Ohtake et al. (2013); Qunibi et al. (2008); Shigematsu et al. (2008a); Shigematsu et al. (2008b); Suki et al. (2007); Wuthrich et al. (2013); Xu et al. (2013); Yokoyama et al. (2012); Yokoyama et al. (2014)
2. >33.3% of studies in the NMA at high risk of bias

Adverse events: diarrhoea

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adverse events: diarrhoea								

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
20[1]	RCT	5439	See Appendix H	Very serious[2]	No serious	Serious[3]	No serious	Very low

1. Al-Baaj et al. (2005); Chang et al. (2017); Chertow et al. (1997); Chertow et al. (2003); Finn et al. (2004); Finn et al. (2006); Fishbane et al. (2010); Freemont et al. (2005); Hutchison et al. (2005); Joy et al. (2003); Ketteler et al. (2019); Koiwa et al. (2017a); Koiwa et al. (2017b); Lee et al. (2015); Maruyama et al. (2018); Qunibi et al. (2008); Shigematsu et al. (2008b); Wuthrich et al. (2013); Yokoyama et al. (2012); Yokoyama et al. (2014)
2. >33.3% of studies in the NMA at high risk of bias
3. DIC for a random-effects model lower than the DIC for a fixed-effects model

Adverse events: nausea and/or vomiting

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Adverse events: nausea and/or vomiting								
19[1]	RCT	7405	See Appendix H	Very serious[2]	No serious	Serious[3]	Serious[4]	Very low

1. Al-Baaj et al. (2005); Chen et al. (2014); Chertow et al. (1997); Chertow et al. (2003); Finn et al. (2004); Finn et al. (2006); Fishbane et al. (2010); Freemont et al. (2005); Hutchison et al. (2005); Joy et al. (2003); Ketteler et al. (2019); Ohtake et al. (2013); Qunibi et al. (2008); Shigematsu et al. (2008a); Shigematsu et al. (2008b); Suki et al. (2007); Wuthrich et al. (2013); Xu et al. (2013); Yokoyama et al. (2012)
2. >33.3% of studies in the NMA at high risk of bias
3. DIC for a random-effects model lower than the DIC for a fixed-effects model
4. 95% CI of at least 1 of the comparisons crossed an MID (and no meaningfully distinct options were identified)

Discontinuation due to adverse events

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Discontinuation due to adverse events								
37[1]	RCT	9312	See Appendix H	Very serious[2]	No serious	Serious[3]	No serious	Very low

1. Abraham et al. (2012); Al-Baaj et al. (2005); Block et al. (2005); Braun et al. (2004); Chen et al. (2014); de Francisco et al. (2010); Evenepoel et al. (2009); Ferreira et al. (2008); Finn et al. (2006); Finn et al. (2004); Fishbane et al. (2010); Freemont et al. (2005); Jalal et al. (2017); Joy et al. (2003); Kakuta et al. (2011); Kalil et al. (2012); Ketteler et al. (2019); Koiwa et al. (2017a); Koiwa et al. (2017b); Lee et al. (2013); Lee et al. (2015); Lin et al. (2011); Lin et al. (2016); Malluche et al. (2008); Navarro-Gonzalez et al. (2011); Ohtake et al. (2013); Otsuki et al. (2018); Qunibi et al. (2008); Shigematsu et al. (2008); Spiegel et al. (2007); Suki et al. (2007); Tzanakis et al. (2008); Wang et al. (2015); Wuthrich et al. (2013); Xu et al. (2013); Yokoyama et al. (2012); Yokoyama et al. (2014)
2. >33.3% of studies in the NMA at high risk of bias

No. of studies	Study design	Sample size	Effect estimate	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
3. DIC for a random-effects model lower than the DIC for a fixed-effects model								

Appendix J – Economic evidence study selection

Appendix K – Economic evidence tables

Bibliographic reference	Study type	Study quality	Setting	Intervention	Comparator	Number of participants	Participant characteristics	Methods of analysis	Results[a]	Limitations	Additional comments
Pre-dialysis											
Thompson M, Bartko-Winters S, Bernard L et al. (2013) Economic evaluation of sevelamer for the treatment of hyperphosphatemia in chronic kidney disease patients not on dialysis in the United Kingdom. Journal of medical economics 16(6): 744-55	Cost-utility analysis, Markov decision analytic model	Partially applicable Potentially serious limitations	UK	Sevelamer (hydrochloride or carbonate not specified)	Calcium carbonate	Simulated cohort of 1,000 patients	Taken from the INDEPENDENT-CKD study: 239 adult patients with CKD stage 3–4 in 12 nephrology clinics across South Italy randomised to sevelamer or calcium carbonate; average age 57.9 years; 61% male	Markov decision-model with a lifetime horizon and a monthly cycle Costs and outcomes discounted at 3.5% Mortality, initiation of dialysis, intervention doses from INDEPENDENT-CKD study Costs from NHS reference costs Dialysis costs: included in base case, excluded as sensitivity analysis Uncertainty explored in OSA and PSA	Sevelamer vs calcium carbonate: Costs: £89,154 vs £49,299 (difference £39,854) QALYs: 4.88 vs 3.32 (difference 1.56) ICER: £25,526 per QALY gained PSA: sevelamer cost-effective in 93% of simulations (at a threshold of £30,000/QALY) Excluding dialysis costs led to a decreased cost per QALY	Important outcomes excluded (e.g. non-fatal cardiovascular events, fractures, hospitalisation) Overly simple model structure Clinical trial data from Italy rather than UK	Funded by manufacturer of sevelamer hydrochloride
Pre- and on dialysis											
Habbous S, Przech S, Martin J et al. (2018) Cost-Effectiveness of First-Line Sevelamer and Lanthanum versus Calcium-Based Binders for Hyperphosphatemia of Chronic Kidney Disease. Value in health: the journal of	Cost-utility analysis, Markov decision analytic model	Partially applicable Potentially serious limitations	Canada	Sevelamer hydrochloride, lanthanum carbonate	Calcium-based binders	Model cohort size not specified	Two cohorts: non-dialysis dependent and dialysis-dependent Patient age at cohort entry modelled using mean age of combined trial populations (58.5 ± 14.3 years)	Markov decision-model with a lifetime horizon and a yearly cycle Public payer perspective in Canada Costs and effects discounted at 1.5% Effects from meta-analysis of	Sevelamer hydrochloride vs calcium-based binders: **Pre-dialysis** Incremental costs: £96,039 Incremental QALYs: 1.59	Important outcomes excluded (e.g. non-fatal cardiovascular events, fractures, hospitalisation) CKD stages undefined	Independently funded

Bibliographic reference	Study type	Study quality	Setting	Intervention	Comparator	Number of participants	Participant characteristics	Methods of analysis	Results[a]	Limitations	Additional comments
the International Society for Pharmacoeconomics and Outcomes Research 21(3): 318-325								randomised controlled trials Dialysis costs from the literature, hospitalisation costs from Canadian national sources Utilities derived from published literature Dialysis costs: included in base case, excluded as sensitivity analysis Uncertainty explored in OSA and PSA	ICER: £60,402 per QALY gained **Dialysis** Incremental costs: £108,278 Incremental QALYs: 1.43 ICER: £75,719 per QALY gained **Uncertainty** In both populations, when dialysis costs excluded >70% probability sevelamer has an ICER better than $50K/QALY in CAD2015 (~=£25K/QALY in GBP2018) Lanthanum carbonate vs calcium-based binders: **Pre-dialysis** Incremental costs: £65,765 Incremental QALYs: 0.98 ICER: Extendedly dominated **Dialysis**	Grouped analysis of calcium-based binders	

Bibliographic reference	Study type	Study quality	Setting	Intervention	Comparator	Number of participants	Participant characteristics	Methods of analysis	Results[a]	Limitations	Additional comments
									Incremental costs: £70,204 Incremental QALYs: 0.87 ICER: Extendedly dominated **Uncertainty** Dominated by sevelamer when dialysis costs excluded		
Vegter S, Tolley K, Keith MS et al. (2011) Cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in chronic kidney disease before and during dialysis. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 14(6): 852-8	Cost-utility analysis, Markov decision analytic model	Partially applicable Potentially serious limitations	UK	Lanthanum carbonate (second-line after therapy failure with calcium-based binders)	Calcium-based binders alone	Two simulated cohorts of 1,000 patients (dialysis and pre-dialysis)	Two cohorts: pre-dialysis CKD patients and incident dialysis patients Patient-level data obtained from clinical trials in pre-dialysis and dialysis (characteristics not reported)	Markov decision-model with a lifetime horizon and a yearly cycle UK NHS perspective Costs and effects discounted at 3.5% Drug efficacy from RCTs (pre-dialysis: US 8-week RCT; dialysis: European 6-month RCT) Mortality from epidemiological studies Drug doses from efficacy trials, costs from British National Formulary Quality of life estimates from systematic review Dialysis costs: excluded in base case, included as sensitivity analysis	Lanthanum carbonate versus calcium-based binders: **Pre-dialysis** Incremental costs: -£381 Incremental QALYs: 0.0441 ICER: Lanthanum carbonate dominates **Dialysis** Incremental costs: £434 Incremental QALYs: 0.0558 ICER: £7,758 per QALY gained **Uncertainty** Calcium-based binders alone are favoured if dialysis costs are included	Important outcomes excluded (e.g. non-fatal cardiovascular events, fractures, hospitalisation, parathyroidectomy) Effects of calcium not modelled In pre-dialysis population, most lanthanum carbonate-treated patients were phosphate binder naive, thereby not accurately modelling second-line treatment	Base-case drug efficacy for pre-dialysis patients was based on pooled data of pre-dialysis and dialysis patients Funded by manufacturer of lanthanum carbonate

Bibliographic reference	Study type	Study quality	Setting	Intervention	Comparator	Number of participants	Participant characteristics	Methods of analysis	Results[a]	Limitations	Additional comments
								Uncertainty explored in scenario analysis and PSA			
On dialysis											
Bernard L, Mendelssohn D, Dunn E et al. (2013) A modeled economic evaluation of sevelamer for treatment of hyperphosphatemia associated with chronic kidney disease among patients on dialysis in the United Kingdom. Journal of medical economics 16(1): 1-9	Cost-utility analysis, Markov decision analytic model	Partially applicable Potentially serious limitations	UK	Sevelamer hydrochloride	Calcium-based binders	Model cohort size not specified	Cohort reflected patients in the DCOR study (US patients on dialysis) Mean age 60 years	Markov decision-model with a lifetime horizon and a monthly cycle UK NHS perspective Costs and outcomes discounted at 3.5% Treatment-specific overall survival up to 44 months and hospitalizations derived from the US DCOR study Resource utilisation from US DCOR study, unit costs from UK sources Utilities: weighted average from several non-UK studies Dialysis costs: excluded in base case, included as sensitivity analysis	Sevelamer hydrochloride versus calcium-based binders: Costs: £44,637 vs £33,568 (difference £11,069) QALYs: 3.261 vs 2.816 (difference 0.445) ICER: £24,986 per QALY gained Results were sensitive to overall survival assumptions and inclusion of dialysis costs ICER decreases with increasing age cut offs	Effects of phosphate and/or Ca on non-fatal cardiovascular events, fractures, hospitalisation and parathyroidectomy not modelled Based on US trial Did not do PSA Overly-simplified model structure with only two health states (alive on phosphate binder, dead) Unclear whether sevelamer carbonate or hydrochloride (hospitalisation rates and doses use carbonate, cost uses hydrochloride)	Funded by manufacturer of sevelamer hydrochloride
Brennan A, Akehurst R, Davis S, Sakai H, Abbott V (2007) The cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in patients with end-stage renal disease.	Cost-utility analysis, Markov decision analytic model	Directly applicable Minor limitations	UK	Lanthanum carbonate (second-line after therapy failure with calcium carbonate)	Calcium carbonate alone	Simulated cohort of 1,000 patients	People with ESRD (on dialysis) who have hyperphosphataemia and are not adequately maintained on calcium carbonate Three subgroup analyses according	Markov decision-model with a lifetime horizon and a yearly cycle UK NHS perspective Costs and effects discounted at 3.5%	Lanthanum carbonate versus calcium carbonate: Incremental costs: £483 Incremental QALYs: 0.018 ICER: £26,860	Long-term survival data from the US renal database was used in preference to the UK renal registry database PSA not conducted	Funded by manufacturer of lanthanum carbonate No costs accounted for other than drug costs

Bibliographic reference	Study type	Study quality	Setting	Intervention	Comparator	Number of participants	Participant characteristics	Methods of analysis	Results[a]	Limitations	Additional comments
Value in Health 10(1): 32-41							to baseline phosphorus (5.6 to 6.5 mg/dl, 6.6 to 7.8 mg/dl, >7.9 mg/dl)	Efficacy from 6-month European RCT Calcium carbonate costs from RCT (BNF for unit costs); lanthanum carbonate cost from the US as no UK price available Utility data from review of QoL literature and the Harvard Catalog of Preference Scores Dialysis costs: excluded Uncertainty explored in OSA	Subgroup analysis suggests lanthanum carbonate not cost-effective in people with lower phosphate at baseline (ICER > £120,000/QALY for 5.6–6.5 mg/dl)		
Gutzwiller FS, Pfeil AM, Ademi Z et al. (2015) Cost Effectiveness of Sucroferric Oxyhydroxide Compared with Sevelamer Carbonate in the Treatment of Hyperphosphataemia in Patients Receiving Dialysis, from the Perspective of the National Health Service in Scotland. PharmacoEconomics 33(12): 1311-24	Cost-utility analysis, Markov decision analytic model	Partially applicable Potentially serious limitations	Scotland	Sucroferric oxyhydroxide	Sevelamer carbonate	Model cohort size not specified	People in Scotland on dialysis who are intolerant to phosphate binders Mean age 56 years	Markov decision-model with a lifetime horizon and a monthly cycle Scottish NHS perspective Costs and effects discounted at 3.5% Effects from European 6-month RCT Drug costs from BNF, RRT costs from NHS reference costs; inflated to 2012; AEs from CG157; no other costs Utilities from published systematic review,	Sucroferric oxyhydroxide versus sevelamer carbonate: Costs: £13,119 vs £14,728 (difference -£1,609) QALYs: 2.826 vs 2.835 (difference -0.009) ICER: £187,920 per QALY gained (southwest quadrant) When dialysis costs included, ICER = £134,546 per	Effects of phosphate and/or Ca on non-fatal cardiovascular events, fractures, hospitalisation and parathyroidectomy were not modelled	Funded by manufacturer of sucroferric oxyhydroxide Modelled cohort was assumed to be intolerant to calcium-based phosphate binders

Bibliographic reference	Study type	Study quality	Setting	Intervention	Comparator	Number of participants	Participant characteristics	Methods of analysis	Results[a]	Limitations	Additional comments
								as reanalysed in CG157 Dialysis costs: excluded in base case, included as sensitivity analysis	QALY gained (southwest quadrant)		
Park H, Rascati KL, Keith MS et al. (2011) Cost-effectiveness of lanthanum carbonate versus sevelamer hydrochloride for the treatment of hyperphosphatemia in patients with end-stage renal disease: a US payer perspective. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 14(8): 1002-9	Cost-utility analysis, Markov decision analytic model	Partially applicable Potentially serious limitations	US	Lanthanum carbonate	Sevelamer hydrochloride	Model cohort size not specified	People with ESRD and hyperphosphatemia who were previously treated with calcium-based binder therapy	Markov decision-model with a 10-year horizon and a yearly cycle US payer perspective Costs and effects discounted at 5% Treatment effects from US-based head-to-head crossover study. Other risks (e.g. mortality, CVD) from large US database Drug doses from same study as effects Drug costs from US average wholesale prices Utilities from multiple published sources Dialysis costs: excluded	Lanthanum carbonate versus sevelamer hydrochloride: Costs: £38,776 vs £38,284 (difference £492) QALYs: 3.078 vs 3.053 (difference 0.025) ICER: £19,669 per QALY gained PSA illustrated a 61.9% probability of lanthanum carbonate being cost-effective at threshold of $50,000 / QALY (USD2009) Results of the base-case most sensitive to variations in phosphate binder drug costs	Effects of phosphate and/or Ca on non-fatal cardiovascular events, fractures, hospitalisation and parathyroidectomy were not modelled Other interventions relevant for the review not included	Funded by manufacturer of lanthanum carbonate
Taylor MJ, Elgazzar HA, Chaplin S, Goldsmith D, Molony	Cost-utility analysis,	Directly applicable	UK	Sevelamer (first-line use)	Calcium-based binders	Model cohort size not specified	People new to dialysis	Markov decision-model with a 5-year	Sevelamer (first-line use)	Major methodological limitations:	Funded by manufacturer

Bibliographic reference	Study type	Study quality	Setting	Intervention	Comparator	Number of participants	Participant characteristics	Methods of analysis	Results[a]	Limitations	Additional comments
DA (2008) An economic evaluation of sevelamer in patients new to dialysis. Current Medical Research & Opinion 24(2): 601-08	Markov decision analytic model	Very serious limitations			(acetate and carbonate)		Other characteristics not specified	time horizon and a monthly cycle UK NHS perspective Costs and outcomes discounted at 3.5% Effectiveness based on US trial by Block et al. (2007) Data on hospitalisation were obtained from the UK-based DOPPS study (Rayner et al. 2004) Costs from UK published sources Average utility value for dialysis taken from published literature Dialysis costs: excluded	versus calcium-based binders: Incremental costs: £7,829 Incremental QALYs: 0.24 ICER: £32,619 ICER ranges from £18,355 to £41,042 per QALY in OSA	inadequate time horizon (5 years), inappropriate model structure (2 states; alive and dead), inadequate assessment of uncertainty (PSA was not conducted) Cost estimates not from the best available source (hospitalisation costs from CIPFA and not NHS reference costs) Potential conflict of interest	of sevelamer hydrochloride

Key: AEs, adverse events; BNF, British National Formulary; Ca, calcium; CAD, Canadian dollars; CIPFA, Chartered Institute of Public Finance; CVD, cardiovascular disease; DCOR, Dialysis Clinical Outcomes Revisited; DOPPS, Dialysis Outcomes and Practice Patterns Study; ESRD, end-stage renal disease; GBP, British pound sterling; ICER, incremental cost-effectiveness ratio; OECD, Organisation for Economic Co-operation and Development; OSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; QoL, quality of life; RCT, randomised controlled trial; USD, United States Dollars.

a. Costs were uprated to 2017/18 values using the Hospital and Community Health Service (HCHS) pay and prices inflator from the Unit Costs of Health and Social Care 2018 (Curtis and Burns, 2018). Where applicable, costs were converted from other currencies to GBP using purchasing power parities from the OECD.

Appendix L – Health economic model

Introduction

We developed a de novo economic model to address the review questions relating to hyperphosphataemia in chronic kidney disease (CKD) outlined in Table 51. Although we found published economic evaluations that partially address these questions, they generally focus on 2 specific comparators rather than evaluating the entire decision space. Furthermore, published economic evaluations tend to use data from a limited number of trials in order to inform the relative effects of treatments, whereas the network meta-analyses (NMAs) conducted for the clinical evidence review (see Appendix H) allow the relative effects of treatments to be modelled using all available evidence.

Table 51: Research questions addressed by economic model

RQ 5.1	For people with stage 4 or 5 CKD who are not on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?
RQ 5.2	For people with stage 5 CKD who are on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?

Methods

Model overview

We adapted an existing model developed for the previous iteration of the guideline (CG157; NICE, 2013), as the committee agreed it was suitable for decision-making.

Modelled population(s), intervention(s), comparator(s) and outcome(s)

The population in this analysis is adults, children and young people with CKD stages 4 and 5 (both off and on dialysis). However, because of insufficient data in children and people with CKD 4 and 5 pre-dialysis, it was not possible to conduct separate analyses for these groups.

We analysed the interventions according to 2 approaches:

1. First-line phosphate binder use: each individual phosphate binder compared with each other, with no option to switch other than following adverse events
2. Sequential phosphate binder use: switching from a calcium-based to a non-calcium-based binder versus remaining on a calcium-based binder – for people who develop hypercalcaemia.

The model predicts costs and QALYs using surrogate relationship between biochemical treatment effects (serum phosphate and calcium) and the clinical outcomes of interest (cardiovascular events, fractures, parathyroidectomy, mortality). The population, interventions, comparators and outcomes are presented in Table 52.

Table 52: Economic Model PICO

Population	Adults, children and young people with: [a] • Stage 4 or 5 CKD who are not on dialysis • Stage 5 chronic kidney disease who are on dialysis

Interventions	First-line use • Calcium carbonate • Calcium acetate • Ferric citrate • Lanthanum carbonate • Sevelamer carbonate • Sevelamer hydrochloride • Sucroferric oxyhydroxide Sequential use • Calcium carbonate → ferric citrate • Calcium carbonate → lanthanum carbonate • Calcium carbonate → sevelamer carbonate • Calcium carbonate → sevelamer hydrochloride • Calcium carbonate → sucroferric oxyhydroxide • Calcium acetate → ferric citrate • Calcium acetate → lanthanum carbonate • Calcium acetate → sevelamer carbonate • Calcium acetate → sevelamer hydrochloride • Calcium acetate → sucroferric oxyhydroxide
Comparator	Each other
Outcomes	• Serum phosphate and calcium levels • Mortality • Cardiovascular events • Fractures • Transplantation • Parathyroidectomy • Adverse events (constipation, diarrhoea, nausea / vomiting) • Costs • QALYs

[a] *Because of insufficient data for children and people with CKD 4 and 5 pre-dialysis, it was not possible to conduct separate analyses for these groups.*

Type of evaluation, time horizon, perspective, discount rate

As per the NICE Reference Case, this evaluation is a cost–utility analysis (reporting health benefits in terms of QALYs), conducted from the perspective of the NHS/PSS, which assesses costs and health benefits using a lifetime horizon, and uses a discount rate of 3.5% per annum for both costs and health benefits.

Model structure

We chose an individual patient simulation approach, capturing costs and effects associated with events in a cohort of simulated individual patients. We considered this to be the most appropriate method for the analysis because of the complex relationships between the biochemical outcomes typically reported in the effectiveness evidence (serum phosphate and serum calcium concentrations) and long-term, patient-relevant outcomes such as cardiovascular risk, fractures and death. Figure 61 presents a schematic representation of the model structure, which was based on the natural history of CKD stage 5. The committee agreed that this structure remained appropriate for the current update.

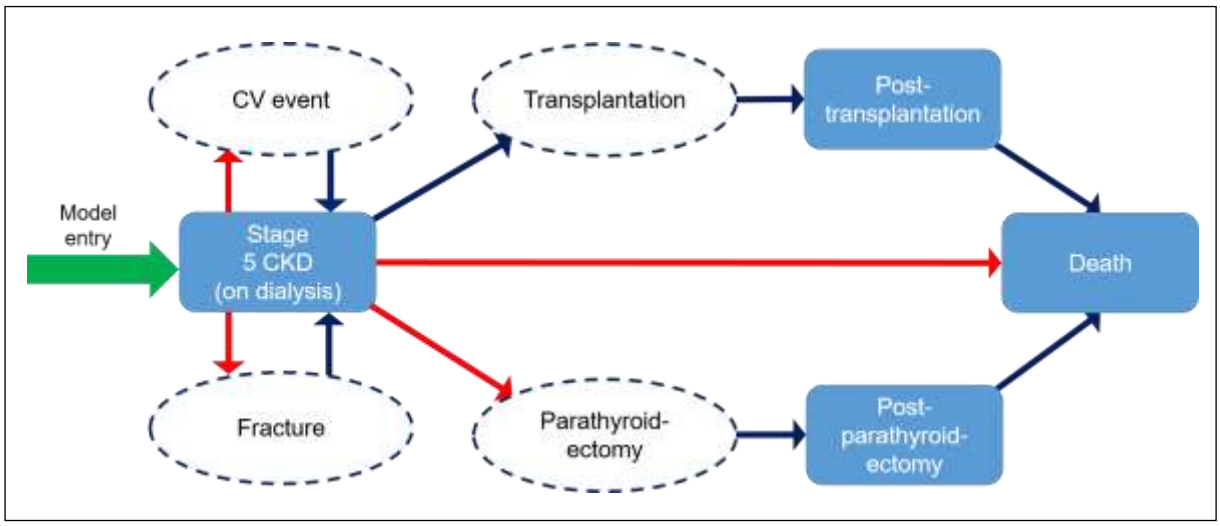


Figure 61: Model structure

In simulating the course of an individual patient, we firstly create a virtual patient with several characteristics, including age, sex, baseline serum phosphate level and baseline serum calcium level, with these data drawn from distributions reflecting patients in the UK Renal Registry (UK Renal Registry, 2019). Based on these baseline characteristics, the model estimates the phosphate and calcium profiles of the simulated individual receiving 1 year's treatment with calcium carbonate, which is used as a common baseline upon which the relative effects of all other treatments are applied. The model then simulates relevant events using serum phosphate and serum calcium levels as surrogate predictors to calculate event probabilities (given the two main mechanisms by which these treatments affect outcomes are via changes in calcium and phosphate levels, these were agreed to be the most appropriate surrogate variables to use, and are commonly used for modelling in this area). Costs and quality-of-life values are attached to the events and underlying states and aggregated for each individual. In this analysis, we created a cohort of 100,000 virtual patients for each treatment arm, average age 63.8 years, 64.2% males and CKD stage 5. Finally, we calculated the average cost and quality-of-life values for each cohort.

The relationships identified by the red outlined arrows in Figure 61 indicate transitions that were estimated using a surrogate relationship via the effect of treatment on biochemical measures (serum phosphate and serum calcium). We parameterised the relationships between biochemical parameters and long-term consequences using a formal systematic literature review (for details, see 'Systematic review of prognostic studies'). The post-parathyroidectomy, transplant and death states are effectively absorbing states.

We simulated various combinations of treatment with phosphate binders over the lifetime of patients, and corresponding costs were attached to treatments and outcomes using an NHS and PSS perspective. We were able to find substantial effectiveness evidence for calcium acetate, calcium carbonate, ferric citrate, lanthanum carbonate, sevelamer carbonate, sevelamer hydrochloride and sucroferric oxyhydroxide, so these were included in the model. Note that although we include ferric citrate in the base case, the committee did not deem it to be a feasible option for recommendation, as it is not currently available in the UK. Insufficient data were available to derive conclusions on the use of aluminium hydroxide and magnesium carbonate. The model was implemented in Visual Basic for Applications, using Excel as a 'front-end' in which parameters are specified and results collected and analysed.

Treatments simulated

First-line binders

To provide a cost–utility estimate for different phosphate binders used as first-line agents, we assumed a simplified scenario in which patient cohorts were assigned to a single binder. Apart from dropout due to adverse events, no switching or addition of different binders was simulated, and the model allowed serum phosphate and calcium levels to change based on the observed effect in the evidence base without additional intervention. Importantly, this means that the model allowed the calcium level of simulated patients receiving calcium-based binders to rise indefinitely. This approach is likely to be at odds with current practice as it is likely additional interventions would occur should levels continue to rise; however, it is useful to simplify the clinical problem to examine the differences that could be expected between binder if there were no constraint on their use (to estimate the comparative effectiveness of different binders, in the absence of additional interventions).

Sequential use of binders

As well as estimating the costs and effects of first-line treatment with various phosphate binders, we configured the model to simulate cohorts receiving predetermined sequences of binders, with patients switching between them as time progresses. We carried forward the advice from the CG157 committee that the main reason for switching in practice is hypercalcaemia associated with the use of calcium-based binders. As such, the scenario of greatest interest is one in which people switch from a calcium-based to a non-calcium binder when simulated serum calcium levels exceed 2.6 mmol/l (National Kidney Foundation, 2003). The sequences modelled are outlined in the 'Interventions' section of Table 52. We also include the 7 first-line binders in the decision space to estimate the potential opportunity costs of switching treatment. Sequences were modelled on basis of generic evidence (based on the NMAs) because of a lack of primary evidence on the sequential use of binders.

Key assumptions

All assumptions were agreed with the committee before being included in the model, and in particular they were asked to validate all the assumptions carried forward from the previous version of the model used in the 2014 NICE CKD guideline.

- Levels of blood calcium and blood phosphate determine the probability of:
  - fractures
  - cardiovascular events
  - need for parathyroidectomy (or commencement of cinacalcet therapy for people who are unsuitable for parathyroidectomy; see NICE, 2007 [TA117])
  - death.
- The probabilities of joining the waiting list for renal transplantation and receiving a transplant are independent of blood calcium and blood phosphate.
- The clinical effect achieved by phosphate binders in the evidence base at reported doses approximates clinical effect across a dose range.
- Owing to an absence of evidence on combination therapy, there is no mixing of different phosphate binding agents for a single patient. When a prescriber wishes to change the phosphate binding agent they will switch entirely to the new agent.
- The utility associated with congestive heart failure as reported in the evidence base is an acceptable proxy for all cardiovascular events that occur in people with CKD stage 5 on dialysis.

- Patients who receive parathyroidectomy are no longer subject to differences in the relative effectiveness of phosphate binders. Although patients are likely to restart phosphate binders following parathyroidectomy (Stracke et al., 1999), there is no evidence on the relative effectiveness of various binders in this population. Therefore, although the model reflects some costs (explicitly) and effects (implicitly) of the continued prescription of phosphate binders, these values do not vary between different modelled cohorts. The CG157 committee felt that this simplifying assumption was acceptable, and therefore it was carried forward for our model update.
- The costs associated with the following procedures can be approximated by using weighted averages of corresponding heterogeneous values from NHS reference costs (NHS Improvement, 2018):
  - fracture
  - parathyroidectomy
  - transplantation
  - biochemistry blood tests
  - dialysis.
- The prices of phosphate binders as listed in the NHS Drug Tariff (NHS Business Services Authority, 2019a) and British National Formulary (BNF; Joint Formulary Committee, 2019) can be used to approximate the average cost to the NHS.

Model parameterisation

Identifying sources of parameters

With the exception of treatment effects, which were comprehensively updated (see below), we used the parameters from the previous iteration of the model unless we could find anything more appropriate or recent from informal searches. These informal searches aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed) and GoogleScholar. We validated any parameters that were different to the previous iteration of the model with the committee.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should be drawn from the UK population).
- All other things being equal, we prefer more powerful studies (based on sample size and/or number of events).
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

Parameters

Key calculations and parameters are summarised here. Please see the full table of parameters (Table 81) for a complete summary of all parameters used in the model, including their distributions and sources.

Clinical parameters and variables

Cohort demographics

The base-case cohort has stage 5 CKD and is receiving dialysis. Based on the latest UK Renal Registry data available to us (UK Renal Registry, 2019), we estimated that this population is 64.2% male and has a median age of 63.8 years.

Biochemical profiles over time with calcium carbonate (reference treatment)

We based the parameters used to estimate the serum phosphate and serum calcium profiles over time for a person receiving calcium carbonate on the German randomised controlled trial reported by Braun et al. (2004). This data source was chosen as, from the assembled evidence on the effectiveness of calcium carbonate, the Braun et al. trial was the largest with at least 1 year's follow-up of haemodialysis patients in a European population, with mean age of 56.5 and 29% female. Serum phosphate and serum calcium levels of the participants were recorded weekly over a period of 52 weeks, and presented in a graph. We extracted data for baseline, 3 months' follow-up (12-week datapoints), 6 month's follow-up (mean of 24- and 28-week datapoints) and 1 year (52-week datapoints).

Table 53: Baseline profile for serum phosphate and serum calcium (calcium carbonate; Braun et al. 2004)

	Baseline	3 months	6 months	12 months
Serum phosphate	2.290 (SD: 0.509)	1.770 (SD: 0.407)	1.865 (SD: 0.509)	1.700 (SD: 0.475)
Serum calcium	2.320 (SD: 0.136)	2.480 (SD: 0.203)	2.445 (SD: 0.203)	2.470 (SD: 0.203)

SD, standard deviation.

To reflect interpatient variability in biochemistry, we used a multivariate normal distribution to sample each simulated patient's profile, parameterised using the reported mean and standard deviation (SD) for the measure in the Braun et al. cohort at each of the 4 junctures (Table 53). To complete this calculation, it is necessary to specify the correlation between measurements at each juncture. Where available, these were estimated from studies in the effectiveness evidence base. Where a study reports SD at baseline (σb), SD at follow-up (σf) and the SD of changes between baseline and follow-up (σc), the correlation (C) between baseline and follow-up may be estimated by:

$$C = \frac{\sigma_b^2 + \sigma_f^2 - \sigma_c^2}{2 \times \sigma_b \times \sigma_f}.$$

We calculated C for each arm (regardless of treatment assignment) in each study reporting the necessary information for the juncture in question. These values were combined by a

weighted average according to the number of people in the arm. Where no evidence was available, we assumed a correlation of 0.5. The values used are shown in Table 54 and Table 55.

Table 54: Correlation matrix – serum phosphate

	Baseline	3 months	6 months	12 months
Baseline	1			
3 months	0.129[a]	1		
6 months	0.311[a]	0.5[b]	1	
12 months	0.295[a]	0.5[b]	0.5[b]	1

(a) Weighted average of calculated correlations from studies reporting baseline, follow-up and mean change.
(b) Assumed in absence of evidence.

Table 55: Correlation matrix – serum calcium

	Baseline	3 months	6 months	12 months
Baseline	1			
3 months	0.582[a]	1		
6 months	0.511[a]	0.5[b]	1	
12 months	0.436[a]	0.5[b]	0.5[b]	1

(a) Weighted average of calculated correlations from studies reporting baseline, follow-up and mean change.
(b) Assumed in absence of evidence.

Relative treatment effects

We generated effect measures from a synthesis of direct and indirect evidence comparing each drug with calcium carbonate (see Appendix H for full NMA results). A total of 6 NMAs are used – phosphate and calcium each analysed at 3 months, 6 months and 1 year. We combined the mean difference in the relevant measure for each treatment compared with calcium carbonate with each virtual patient's simulated baseline profile to provide an estimate of their profile with the treatment in question over the first year (see Table 82 and Table 83 for mean differences, standard deviations and correlations between treatment effects for different interventions).

Extrapolation beyond 1 year

Because it was only possible to synthesise evidence on the treatments of interest over the first year of treatment, we had to rely on assumptions to project the future biochemical profile of simulated patients. Different approaches were adopted for the 2 measures:

- For **serum phosphate**, we did not simulate any further changes in level beyond year 1 in the base case. This means that each simulated individual's serum phosphate level remains constant at the level reached after 12 months of treatment. The committee agreed this was appropriate as it was the simplest approach in the absence of meaningful evidence, and was also a reflection of the relatively laminar trends in serum phosphate seen in the latter phase of follow-up in studies of a year's duration.
- For **serum calcium**, it would not be appropriate to assume no further changes, as the continued use of calcium-based phosphate binders in particular will clearly have implications for a patient's calcium levels. For this reason, the committee agreed to extrapolate the linear trend observed across the empirical 12 months' treatment into the future. The average increase or reduction over the period (sampled baseline profile plus treatment effect) was extended indefinitely. With more data, we may have been able to

project a more realistic trend than a simple linear one; however, inspection of the available evidence did not provide an unambiguous indication of the likely trajectory.

Treatment switching

Similarly, in the analysis of sequences of phosphate binders, we had no direct evidence with which to estimate the biochemical profile of people switching from one phosphate binder to another. This necessitated reliance on the same evidence used to parameterise first-line treatment effect, coupled with some additional assumptions. Again, our approach differed between measures:

- For **serum calcium**, first-line treatment evidence was applied in a 3-stage process:
  - Firstly, we combined the baseline (calcium carbonate) profile of the simulated patient over the first year of treatment with effectiveness evidence relating to the new treatment.
  - Secondly, we calculated and averaged the change in serum calcium over the theoretical year's treatment.
  - Lastly, we applied this average rate of change in calcium to the patient's calcium levels going forward (starting from the level reached at the end of treatment with the previous binder). For the same reasons considered above, this trajectory continued indefinitely beyond the year's treatment with the new binder.
- For **serum phosphate**, we could not apply the first-line treatment evidence in a similar way, because the trials in the effectiveness evidence-base comprise participants with established hyperphosphataemia, invariably demonstrated via a pre-randomisation washout phase, with the result that the initial phase of treatment features an exaggerated drop in serum phosphate. It would be misleading to apply such a dramatic effect in a second-line context, and would result in artificially low phosphate levels. Therefore, we adopted a modified version of the approach used for calcium in the base case:
  - We estimated a theoretical profile in the same way by combining the baseline (calcium carbonate) profile with effectiveness evidence.
  - We calculated and averaged the change in serum phosphate from 6 months to 12 months.
  - We applied this average change in phosphate to the patient's phosphate level across the whole first year of treatment with the binder they had switched to. As in the first-line context, an effect on phosphate was not projected beyond a year's treatment.

Hypocalcaemia and hypophosphataemia

As a simplifying measure, we assumed hypocalcaemia and hypophosphataemia are trivially controlled in this model, with calcium levels constrained to be 2 mmol/l or greater and phosphate limited to at least 1 mmol/l. This assumption reflects the fact that a variety of strategies can be used to manage hypocalcaemia and hypophosphataemia, including manipulation of binder regimen, diet, dialysate and, where necessary, prescription of minimally expensive supplements. Therefore, whenever either measure is projected to fall below the relevant minimum level, it is assumed to reach a floor at that lower bound. We assume no additional costs, benefits or disutilities are incurred.

Simulating events based on serum phosphate and calcium

The events that were deemed relevant for this analysis are:

- all-cause mortality

- cardiovascular events
- need for a parathyroidectomy (or cinacalcet therapy, for those unable to undergo surgery) – for people on dialysis
- fractures.

We obtained the estimates used to calculate the event probabilities from a systematic review of prognostic evidence (for full details see 'Systematic review of prognostic studies'). This review was originally conducted for CG157 (NICE, 2013) and then updated for the current guideline. In brief: we identified 45 studies in adults and children with CKD (stage 4 or 5) relating serum phosphate and serum calcium in a single multivariate model to the relevant events. The studies were all observational in design, with very limited evidence in children. The studies adjusted the measures of effect for a variety of variables and reported in various formats, either as continuous data (for example an increase in risk per 1 mmol/l increase in serum phosphate), or as categorical – binary or ordered – data with a variety of cut-offs (for example, a relative risk for phosphate levels ≥2 mmol/l when compared with the risk for levels <2 mmol/l). We could not perform a meta-analysis of the various measures of effect because it would be inappropriate to pool estimates that come from a heterogeneous collection of multivariable models. Instead, we systematically appraised the evidence and the most appropriate individual study(s) were selected. Overriding selection criteria were as follows:

- The selected study should report outcomes that correspond as closely as possible to the events simulated in the model.
- The selected study should report a population that closely matches the UK population (ideally, it should be drawn from the UK population).
- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.

All-cause mortality

In order to model mortality in people with CKD stages 4 and 5, we obtained hazard ratios of death from the UK Renal Registry (stratified according to age) for people with end-stage renal disease (ESRD) compared with the general population, and applied these ratios to general population mortality estimates from UK life tables (UK Renal Registry, 2019; Office for National Statistics, 2019). As people get older, the hazard ratios of death decrease; this is because the hazard of death increases with age in the general population. For example, a 22-year old with ESRD faces an instantaneous risk of death 26 times greater than a 22 year-old without ESRD, whereas a 90 year-old with ESRD has only 2.7 times more hazard if death than a person of the same age without ESRD.

We did not find any evidence on the interaction between the type of renal replacement therapy (that is, either dialysis or renal transplantation) and age, which we would have ideally used to analyse how the relative likelihood of death changes with age. To approximate this, we assumed a linear relationship over time, and split the hazard ratio of death between the hazard in people who have undergone transplantation and those who are on dialysis (HR=0.2; Jain et al., 2009), assuming this hazard ratio remains constant over time. This implies that, in the model, people who are on dialysis are 5 times more likely to die at any given time than those who have received a renal transplant. We applied this to the various populations up until the age of 80, beyond which we assumed that there is no difference in mortality between people on dialysis and people who have received renal transplantation. This assumption was necessary to prevent people on renal transplants being less likely to die than the general population (thus conferring an unrealistic survival advantage to people

on renal transplants). This is because age has a confounding effect on the hazard ratio of death between renal transplantation and dialysis which, because of data constraints, we are unable to account for empirically. Accordingly, beyond the age of 80, all simulated patients are subject to the hazard ratio for people with ESRD, regardless of the type of renal replacement therapy they have received.

Excess mortality

We obtained estimates used in the model for predicting the additional hazard of death faced by people with CKD stage 5 on dialysis (using serum phosphate and serum calcium levels) from a retrospective cohort study of 7,076 patients from the UK renal registry reported by Tangri et al. (2011). The study reports hazard ratios for mortality – from multivariable Cox regression analysis – which suggest that high phosphate and calcium levels are independently associated with an increased risk of death (Table 56).

Table 56: Relationship between serum phosphate, serum calcium and mortality (Tangri et al., 2011)

Serum phosphate		Serum calcium	
mg/dl	HR (95% CI)	mg/dl	HR (95% CI)
<3.5	0.74 (0.53–1.03)	<8.4	1.35 (0.24–7.56)
3.5–5.5	1 (Ref)	8.4–9.5	1 (Ref)
5.5–6.5	1.17 (0.94–1.46)	9.5–10.4	1.13 (0.83–1.53)
6.5–7.5	1.42 (1.06–1.90)	>10.4	1.35 (0.93–1.65)
>7.5	1.64 (1.02–2.63)		

CI, confidence interval.

In order to extrapolate results beyond the reported range, our base-case model relied on a function fitted to these data, as illustrated in Figure 62. We fitted a quadratic function to the log hazard ratios, and this provided an acceptable fit to the data (r2>0.87, in each case). An alternative mode of calculation, in which the reported hazard ratios were applied to simulated patients in each category (as a step function) was tested in sensitivity analysis.

Cardiovascular events

The estimates used in the model for predicting cardiovascular events from phosphate and calcium levels were based on a retrospective cohort study of 14,829 USA patients receiving haemodialysis by Slinin et al. (2005). Although many other studies report the association between biochemical parameters and cardiovascular mortality, this was the only study we identified that assessed the relationship between both phosphate and calcium and all fatal and non-fatal cardiovascular events. A cardiovascular event was defined as hospitalisation with ischaemic heart disease, congestive heart failure, stroke, transient ischaemic attack, or peripheral vascular disease. The results suggest that high levels of phosphate and calcium are independently associated with increased risk of a cardiovascular event.

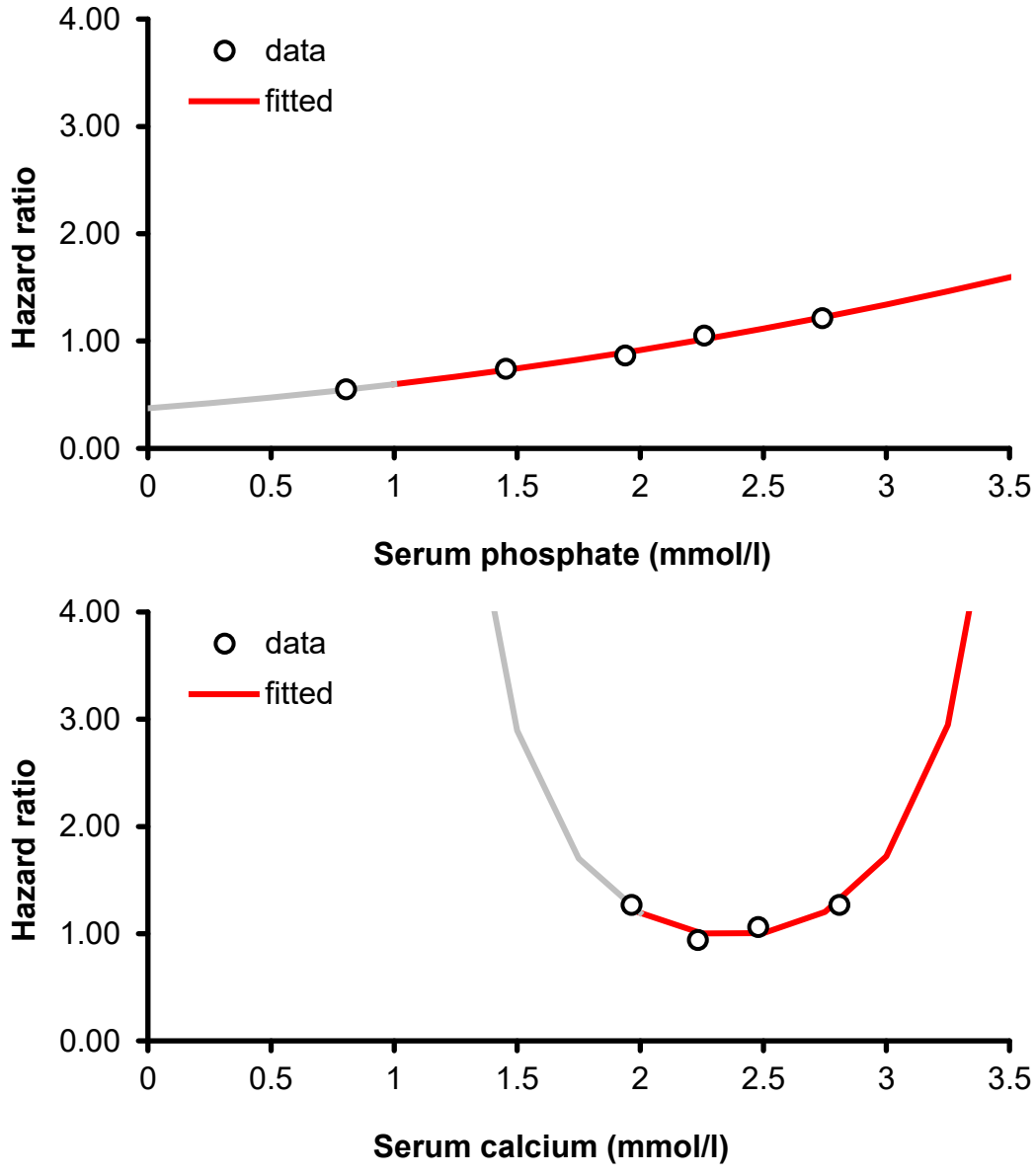
Table 57: Relationship between serum phosphate, serum calcium and cardiovascular events (Slinin et al., 2005)

Serum phosphate		Serum calcium	
mg/dl	HR (95% CI)	mg/dl	HR (95% CI)
≤4.4	1 (Ref)	<8.7	1 (Ref)

Serum phosphate		Serum calcium	
4.5–5.3	1.06 (1.00–1.13)	8.8–9.2	1.03 (0.97–1.09)
5.4–6.3	1.13 (1.06–1.19)	9.3–9.6	1.04 (0.97–1.10)
6.4–7.5	1.14 (1.07–1.22)	9.7–10.2	1.03 (0.97–1.10)
>7.5	1.25 (1.17–1.33)	>10.2	1.08 (1.01–1.15)

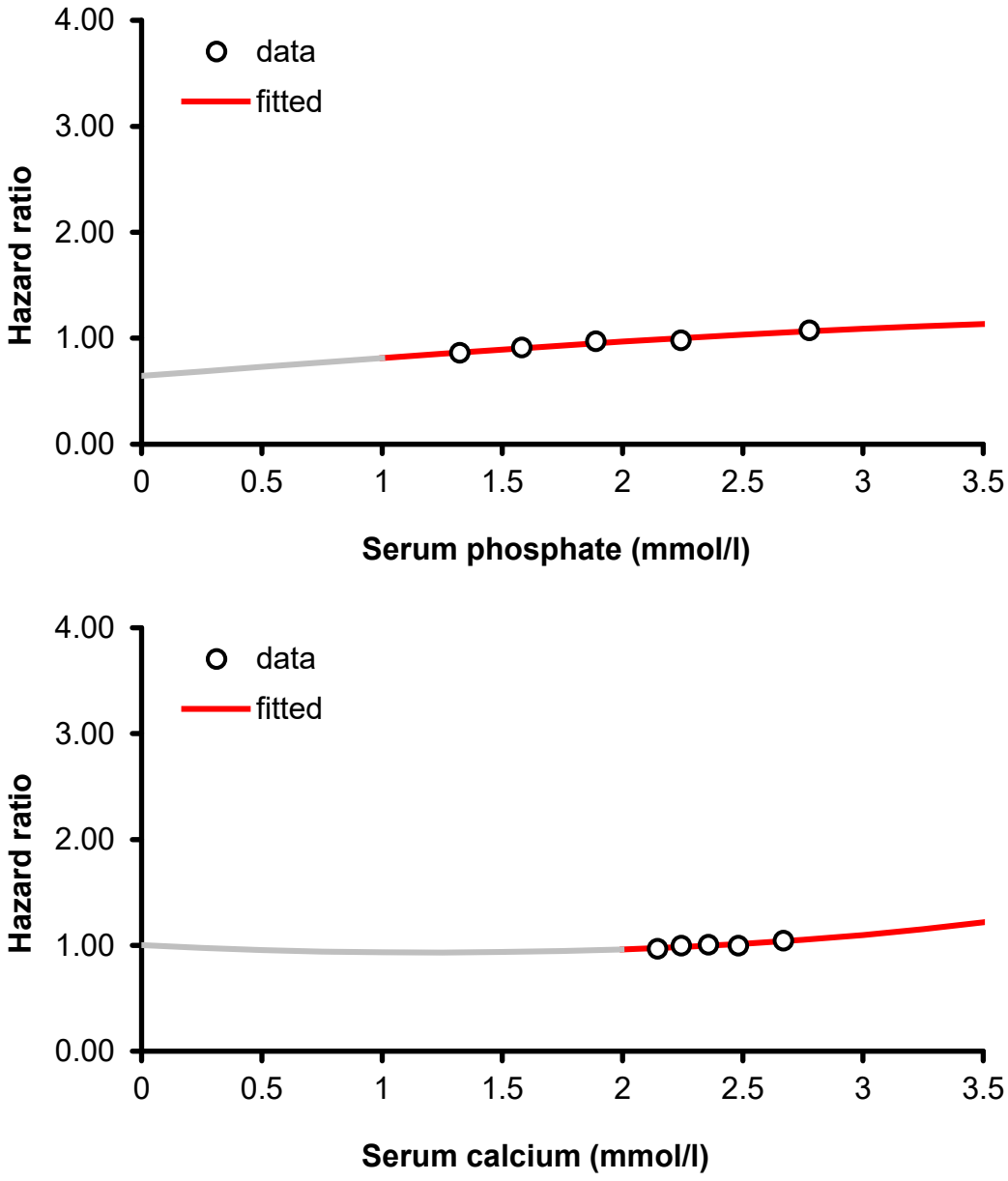
CI, confidence interval.

As for mortality, the base-case model relied on a function fitted to these data, as illustrated in Figure 63, and we tested the alternative, categorical approach in sensitivity analysis.



Red segment shows range used in model (floors of 1 mmol/l for phosphate and 2 mmol/l for calcium applied; see above)

Figure 62: Relationship between serum phosphate, serum calcium and mortality – raw data and fitted functions



Red segment shows range used in model (floors of 1 mmol/l for phosphate and 2 mmol/l for calcium applied; see above)

Figure 63: Relationship between serum phosphate, serum calcium and cardiovascular events – raw data and fitted functions

We obtained the baseline risk of cardiovascular events upon which to apply the HRs in Table 57 from the Study of Heart and Renal Protection (SHARP; Schlackow et al., 2017).

Fractures

We obtained the estimates for predicting bone fractures from phosphate levels from a retrospective cohort study of 40,538 USA patients receiving haemodialysis by Block et al.

(2004). The results suggest that serum phosphate is a significant predictor of fracture events (HR=1.12 per mg/dl [95% CI 1.03–1.22]). However, calcium was not shown to have an effect.

Parathyroidectomy

We based the estimates used in the model to predict parathyroidectomy from phosphate and calcium levels on a prospective cohort study of 17,236 dialysis patients randomly sampled from the UK, France, Germany, Italy, Spain, USA and Japan by Young et al. (2005). The results showed that high levels of phosphate and calcium were independently associated with an increased risk of parathyroidectomy (phosphate HR=1.17 per mg/dl [95% CI 1.09–1.25]; calcium HR=1.58 per mg/dl [95% CI 1.35–1.85]).

We accounted for both surgical and medical parathyroidectomy (cinacalcet for people in whom surgery is contraindicated).

Estimated costs and effects for people needing a parathyroidectomy were derived from the cinacalcet model published by the Peninsula Technology Assessment Group (PenTAG; Garside et al., 2007). We updated the drug and event cost parameters in this model to match those used in our model and configured it to simulate 2 arms: 1 comprising people undergoing surgical parathyroidectomy, and 1 for people taking cinacalcet. We then ran the model for every age from 18 years to 120 years (that is, changing only the starting age of the cohort for each iteration), capturing the resultant costs and QALYs for each arm. From these data, we were able to create a meta-model for each treatment path with the starting age of the cohort as a covariate of expected costs and QALYs. We found that quartic functions gave excellent fits to the data (all r^2 values >0.9999).

Table 58: Meta-model of PenTAG model for people needing parathyroidectomy – parameter coefficients

	Age	Age^2	Age^3	Age^4	Intercept
Surgery					
Undiscounted costs, excluding dialysis (£)	-1576.7	22.69	-0.154	0.00040	49744.0
Undiscounted costs, excluding dialysis (£)	-22858.7	319.3	-2.117	0.00544	692686.9
Undiscounted costs, excluding dialysis (£)	-679.2	7.345	-0.0370	0.00007	29466.5
Undiscounted costs, excluding dialysis (£)	-9668.9	96.78	-0.431	0.00066	389521.2
Life-years	-1.361	0.0190	-0.0001	0.0000003	41.35
Undiscounted QALYs	-0.851	0.0118	-0.00008	0.0000002	26.09
Discounted QALYs	-0.356	0.00348	-0.00001	0.00000002	14.60
Cinacalcet					
Undiscounted costs, excluding dialysis (£)	-6462.9	88.21	-0.574	0.00145	202643.3
Undiscounted costs, excluding dialysis (£)	-27590.7	382.3	-2.518	0.00644	846514.8
Undiscounted costs, excluding dialysis (£)	-2702.3	25.61	-0.104	0.00013	114531.1
Undiscounted costs, excluding dialysis (£)	-11566.0	113.9	-0.494	0.00072	473975.8

	Age	Age^2	Age^3	Age^4	Intercept
Surgery					
Life-years	-1.351	0.0188	-0.0001	0.0000003	41.41
Undiscounted QALYs	-0.848	0.0117	-0.0001	0.0000002	26.17
Discounted QALYs	-0.352	0.00347	-0.00002	0.00000002	14.59

QALY, quality-adjusted life-year.

When a simulated patient in our model needs a parathyroidectomy, we assign them the discounted costs and QALYs pertaining to their age in the meta-model. The default treatment option is surgery; however, a proportion of patients are assumed to be unsuitable for surgery and receive cinacalcet instead (in line with the recommendations of NICE TA117; NICE, 2007). As in the original PenTAG model, the proportion of people who are assumed to be unsuitable for surgery is 15% until the age of 55, with a subsequent increase of 0.5% for each year above that age.

Renal transplantation

Transplantation is an absorbing state in the model. We acknowledge that many people who have received a transplant experience recurrent kidney failure and will require further treatment with phosphate binders; however, we did not identify evidence that looked at the use of different binders in this population specifically. Therefore, we inferred that conclusions from a pre-transplant population could be generalised to this setting, so it was not necessary to investigate a separate decision-point. For this reason, we handled all simulated patients identically, regardless of treatment assignment, when they reach the transplantation event.

We model the path to transplantation as a two-stage event – entering the waiting list and, once on the list, receiving a transplant. Neither event is dependent on the simulated patient's serum phosphate or serum calcium level; this dictates that, in the model, the choice of binder has no direct influence on the likelihood of receiving a transplant.

We based the rates of renal transplantation on estimates from the UK Renal Registry database (UK Renal Registry, 2019). The registry provides ORs (from logistic regression) for getting on the waiting list, stratified according to age and gender. We applied these ORs to baseline rate of people joining the waiting list (56.5% over 2 years, also reported in the Renal Registry). The same process was used for the likelihood of having a transplant – using ORs from the Renal Registry for receiving a transplant given that an individual is on the waiting list. Separate odds ratios were provided in the registry for receiving transplants from brain-stem-dead donors and from cardiac-dead/living donors.

Adverse events

Based on advice from the committee and the adverse events (AEs) that were commonly reported in the trials, 3 AEs were considered important: diarrhoea, constipation and nausea/vomiting. We estimated the log hazard ratios (lnHRs) for experiencing each of the 3 AEs versus calcium carbonate using an NMA. We applied these lnHRs to the baseline annual log rates of each AE with calcium carbonate. We derived these from meta-analyses using the same models used for the relative effect NMAs (binomial likelihood; cloglog link), as suggested in NICE DSU TSD5 (Dias et al. 2011). As these events are unlikely to be materially influenced by geographical or other setting, we included all calcium carbonate arms in the included RCTs. We combined the relative and absolute data to provide the overall per- three-month cycle rates (Table 59).

Table 59: Per three month cycle adverse event rates

	Diarrhoea	Constipation	Nausea/vomiting
Calcium carbonate	0.042	0.034	0.055
Calcium acetate	0.046	0.132	0.015
Ferric citrate	0.324	0.025	0.440
Lanthanum carbonate	0.056	0.024	0.126
Sevelamer carbonate	0.064	0.054	0.012
Sevelamer hydrochloride	0.041	0.153	0.012
Sucroferric oxyhydroxide	0.178	0.029	0.008

Discontinuation due to adverse events

We only used data reflecting discontinuations due to adverse events; although several studies reported withdrawal for any reason, it was important not to double-count the likelihood of switching treatment because of hypercalcaemia (which is modelled separately, as described above). Similarly to the AEs, we obtained lnHRs for the dropout rates for each binder, then applied them to the baseline dropout rate (synthesised from all calcium carbonate trial-arms) to obtain the per three month cycle dropout rates for each binder (Table 60).

Table 60: Per three month cycle rates of discontinuation due to adverse events

	Discontinuation rate
Calcium carbonate	0.032
Calcium acetate	0.058
Ferric citrate	0.071
Lanthanum carbonate	0.067
Sevelamer carbonate	0.071
Sevelamer hydrochloride	0.048
Sucroferric oxyhydroxide	0.086

Resource use and costs

Phosphate binder doses and costs

We used the average dose at which each binder was delivered to achieve the clinical effect observed in the clinical trial evidence base. This allows the cost needed to achieve a particular dose to directly link to the clinical effect observed. We excluded any doses that were outside of the licensed range and calculated a weighted average from trial-arms reporting fixed or mean doses (weighted according to the number of participants in each arm). Table 61 shows the resulting average daily doses of each binder.

We obtained the drug prices using the approach outlined in the NICE guideline development manual (NICE, 2018a). We firstly looked for nationally available price reductions in the NHS Commercial Medicines Unit Electronic Market Information Tool (eMIT; Commercial Medicines Unit, 2019). If not available, we then searched for the tariff price either in the online Drug Tariff (NHS Business Services Authority, 2019a) or in the BNF (Joint Formulary Committee, 2019). When multiple formulations were available for the same drug (for example tablets in different doses with different costs), we obtained the weightings from the NHS prescription cost analysis (PCA; NHS Business Services Authority, 2019b). We used the

listed costs and the average doses to obtain the per-cycle costs for each intervention. We were unable to obtain a cost for ferric citrate as it is not currently available in the UK; therefore we assumed the same cost as sevelamer hydrochloride.

Table 61: Summary of drug doses and costs

	Unit cost (per gram)	Average dose (grams per day [SE])	Cost per day	Cost per quarter
Calcium carbonate	£0.07 [a]	2.64 (0.03)	£0.18	£16.02
Calcium acetate	£0.11 [a]	3.40 (0.01)	£0.37	£32.58
Ferric citrate	£1.16 [b]	5.93 (0.14)	£6.88	£628.21
Lanthanum carbonate	£2.50 [a]	1.47 (0.04)	£3.68	£336.30
Sevelamer carbonate	£0.24 [c]	7.00 (0.16)	£1.68	£154.92
Sevelamer hydrochloride	£1.16 [a]	6.17 (0.04)	£7.16	£653.30
Sucroferric oxyhydroxide	£3.98 [a]	1.90 (NR) [d]	£7.56	£689.61

NR, not reported; SE, standard error.

(a) Cost from NHS drug tariff (NHS Business Services Authority, 2019a); quantity for weighting from PCA (NHS Business Services Authority, 2019b).

(b) No cost listed as drug not currently available in the UK. Assumes the same cost as sevelamer hydrochloride.

(c) Cost and quantity from NHS Commercial Medicines Unit Electronic Market Information Tool (Commercial Medicines Unit, 2019).

(d) It was not possible to obtain an estimate of the standard error from the studies.

Event costs

We used the National Schedule of Reference Costs (2017–18; NHS Improvement, 2018) to estimate the costs of cardiovascular events. We generated a weighted average of the total costs of arrhythmia or conduction disorders (EB07), cardiac conditions (EB14), cardiac arrest (EB05), cardiac valve disorders (EB06), myocardial infarction (EB01), heart failure (EB03), stroke (AA22), pulmonary oedema (DZ20) and peripheral vascular disease (YQ50). The estimated cost of a cardiovascular event was £1,569. We also used the reference costs to estimate the cost of a fracture to be £2,429. This involved calculating a weighted average of the costs of hip (HE11), knee (HE21), foot (HE31), hand (HE41), arm (HE51) and rib or chest (HE71) fractures. The cost of parathyroidectomy was accounted for in the PenTAG cinacalcet model of which we made a meta-model (see above).

We assumed that people who receive a transplant incur the cost of the initial operation plus some additional immunosuppressant costs over and above those that they would incur as part of the state costs. The approach to costing the transplantation procedure was adapted from the previous iteration of the hyperphosphataemia guideline (CG157) and the NICE guideline for renal replacement therapy and conservative management (NICE, 2018). We calculated a weighted average of the costs of the work-up (£1,869) and the procedure itself (£14,794) using NHS reference cost activity data to give a total cost of £16,663 for a kidney transplant. The maintenance doses of immunosuppressants were included as part of the state costs; however, we also included additional costs of induction immunosuppression as part of the initial event cost.

Adverse events were assumed to cost £28, which is the cost of one general practitioner appointment (Curtis & Burns, 2018), as the CG157 committee advised that the events in question (constipation, diarrhoea, nausea/vomiting) were usually relatively minor and easily managed. No additional costs were associated with treatment discontinuation or death. A detailed breakdown of these costs is provided in the full table of parameters (Table 81).

State costs

People in the CKD Stage 5 (on dialysis) state are assumed to require vitamin D plus 1 parathyroid hormone test, 1 calcium test and 1 phosphorus test per cycle. Calcium and phosphorus test costs were £1.11 each, while the cost of a PTH test was £10 (NHS Improvement, 2018). The per-cycle cost of vitamin D was £13, which was obtained from TA117 (NICE, 2007).

The costs associated with dialysis are substantial and are not significantly affected by the choice of phosphate binder. In order to isolate the relative impact of different phosphate binders, we excluded dialysis costs from the model in its base case. This decision is consistent with the approach taken in CG157 and has other precedents in NICE decision-making (for example, see TA117; NICE, 2007). We assessed the impact of inclusion and exclusion of dialysis costs in a sensitivity analysis. To estimate the cost of dialysis for the sensitivity analysis, we obtained the average cost of each type of dialysis session from the NHS Reference costs, the number of sessions per cycle from TA117 and the proportions of people receiving each of the types of dialysis from the UK Renal Registry (NHS Improvement, 2018; NICE, 2007; UK Renal Registry, 2019; Table 62). We added an additional 15% for travel, access and maintenance costs in line with the NICE guideline on RRT and conservative management (NICE, 2018b), which gave a total cost per cycle of £7,363 for dialysis.

Table 62: Dialysis costs

	Cost per session (£) [a]	Proportion [b]	Sessions per cycle [c]	Weighted cost per cycle (£)
Home HD	£229.42	4.9%	52.0	£582.75
Hospital HD	£157.92	32.3%	39.0	£1,991.41
Satellite HD	£145.11	50.4%	39.0	£2,850.12
Continuous ambulatory PD	£67.54	5.0%	91.3	£311.18
Automated PD	£77.77	7.4%	91.3	£522.92

HD, haemodialysis; PD, peritoneal dialysis.
(a) Source: NHS Reference costs 2017-18.
(b) Source: UK Renal Registry, 2019.
(c) Source: TA117.

People in the post-transplantation state incur the cost of ongoing immunosuppression. As per the previous iteration of the guideline, we assumed that 25% of people were on ciclosporin and 75% were on tacrolimus. Everybody was also assumed to receive azathioprine. We calculated the average cost per mg of drug using costs listed in the NHS Drug Tariff, with weightings from the PCA. Average doses were 0.2 mg/kg/day for tacrolimus, 4 mg/kg/day for ciclosporin and 1.75 mg/kg/day for azathioprine (Jones-Hughes et al., 2016). The average cost of ongoing immunosuppression for a person assumed to weigh 70 kg was £1,644 per cycle. The cost of parathyroidectomy according to patient age was included in the meta-model as described previously.

Quality of life

The unit of measure for quality of life used in the health economic analysis was the QALY, in line with 'Developing NICE guidelines: the manual' (NICE, 2018a).

Stage 5 kidney disease (on dialysis) state utility

To obtain a utility value for CKD stage 5 on dialysis, we relied on a meta-analysis conducted by Liem et al. (2008). This study provides separate pooled health state valuations for people undergoing haemodialysis and peritoneal dialysis. We reanalysed these data to give a single summary estimate. Values included were restricted to those obtained using the EQ-5D index measure. Eight studies were included, giving a utility value of 0.565 (95% CI 0.514, 0.616) for people in the CKD stage 5 on dialysis health state (Table 63). We adjusted this absolute value according to the mean age (61.4 years) and proportion of men (61%) in the source cohort to generate a relative utility of 71.3% compared with the general population.

Table 63: Utility values for CKD stage 5 on dialysis

	Reference	Publication year	n	EQ-5D index mean valuation	SD
Haemodialysis	Lee et al.	2005	99	0.44	0.32
	Manns et al.	2003	151	0.62	0.26[a]
	Roderick et al.	2005	269	0.60	0.28
	Roderick et al.	2005	314	0.60	0.31
	Sennfalt et al.	2002	27	0.44	0.08
	Wasserfallen et al.	2004	455	0.62	0.30
Peritoneal dialysis	Lee et al.	2005	74	0.53	0.34
	Manns et al.	2003	41	0.56	0.27[a]
	Sennfalt et al.	2002	27	0.65	0.15
	Wasserfallen et al.	2004	50	0.58	0.32
				0.565 (SE 0.026)	

(a) Standard deviation not reported. To enable inclusion in the meta-analysis, an estimate of the SD was obtained from the mean SD of other valuations in the dialysis type.

Transplantation state utility

An estimate of utility for patients who were post-kidney transplantation was also obtained from Liem et al. (2008) and was estimated to be 0.809. Once we had adjusted this for age and sex, the estimated relative utility was 95.7% of that of the general population.

Event utilities

The principal complications associated with hyperphosphataemia we model are cardiovascular events and fracture. The utility estimate for cardiovascular events was informed by Block et al. (2004), who found that congestive heart failure was the most common reason for cardiovascular-related admissions among people with ESRD. In a study investigating the impact of pharmacist interventions, Holland (2007) obtained health utility values for UK patients with congestive heart failure receiving standard medical management. The trial population utility was calculated to be 78% of that expected of the general UK population adjusted for age and sex. Once incurred, we applied this disutility indefinitely.

We used a review by Peasgood et al. (2009) on utility values for people who experience fractures to estimate the percentage reduction in utility that would be expected to occur in the year following a fracture compared with the general population of the same age and sex. A single average disutility value of 0.928 was used for all fractures, accounting for the wide

range of disutility associated with different types of fracture. This disutility was applied for 1 year, as this was the length of time examined in the source data.

Utility decrements associated with adverse events of phosphate binder treatment – constipation, diarrhoea and nausea/vomiting – are shown in Table 64 below.

Table 64: Utility decrements for events

	Utility decrement	Duration	Source
Cardiovascular event	78.2%	Indefinite	Holland et al., 2007
Fracture	92.8%	1 year	Peasgood et al., 2009
Transplant	79.3%	1 month	Hamidi et al., 2009
Adverse events:			
Diarrhoea	91.7% [a]	5 days	Beusterien et al., 2009
Constipation	85.4%	5 days	Belsey et al., 2010
Nausea / vomiting	90.3% [b]	5 days	Beusterien et al., 2009

(a) Based on an absolute decrement of -0.06.
(b) Based on an absolute decrement of -0.07.

All utility decrements were applied multiplicatively, as per the recommendation of Ara and Wailoo (2011).

Sensitivity analyses

In order to explore uncertainty in model results, we conducted both deterministic and probabilistic sensitivity analyses.

Deterministic sensitivity analysis

Deterministic analyses either use alternative point estimates for model parameters or test different structural assumptions, in order to investigate the impact on results. The parameters of interest for deterministic sensitivity analysis in the current analysis included:

- Inclusion or exclusion of dialysis costs
- Formulation of sevelamer carbonate (powder or tablets)
- Gender bias in the odds of being added to the transplant wait list

Further to this, we conducted a one-way sensitivity in which parameters were varied between plausible bounds to determine which have the potential to affect cost-effectiveness results. Usually we would include all parameters within the one-way sensitivity analysis; however due to the long model running times we prioritised 81 parameters based on the previous CG157 analysis (NICE, 2013) and committee advice.

Probabilistic sensitivity analyses

We configured the model to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters. We assigned probability distributions reflecting uncertainty surrounding point estimates to model input parameters. These were defined by standard error/confidence intervals and type of parameter. We sourced distribution parameters from the study in which the value was obtained, where possible, or estimated them based on the usual properties of data of that type. The model draws a random value from each of these distributions for 1,000 iterations and, for each of these iterations, records costs and QALYs for each strategy. This process allows uncertainty around model results to be characterised in terms of the proportion of iterations in which each comparator provides

the optimal balance of costs and QALYs at a particular threshold. We can then construct cost-effectiveness acceptability curves (CEACs) to represent these results visually.

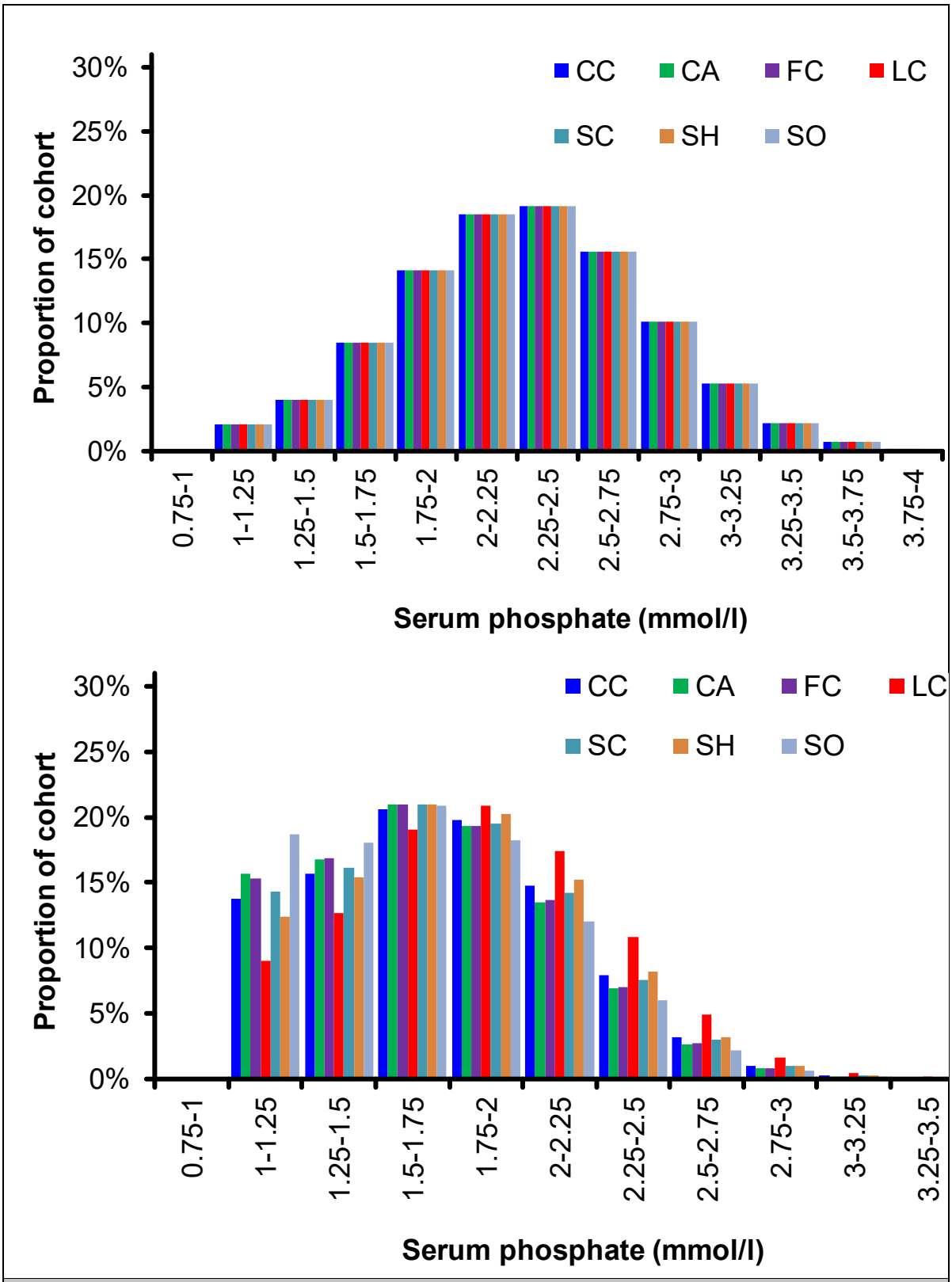
The distribution assigned to each type of model parameter reflects the nature of the data. As a rule, we use beta distributions to parameterise probabilities, to reflect the fact that these values must lie between 0 and 1. Although the majority of costs within the current model were fixed, some are given a gamma distribution, as these values are bound at 0 but theoretically have no upper limit. We assign a lognormal distribution to relative risks, ORs and hazard ratios, in order to reflect the fact that these parameters are asymmetrically distributed (i.e. values between 0 and 1 favour one comparator, whereas values between 1 and infinity favour the other). As with probabilities, we assign utilities a beta distribution, as they are bounded at 1. For the treatment effects drawn from the NMAs, we parameterised multivariate normal distributions from the WinBUGS output (the posterior estimates of mean differences or log-hazard ratios) to preserve correlation between treatment effects for different interventions (see Table 82, Table 83 and Table 84).

Original cost–utility model – results

Modelled phosphate and calcium levels

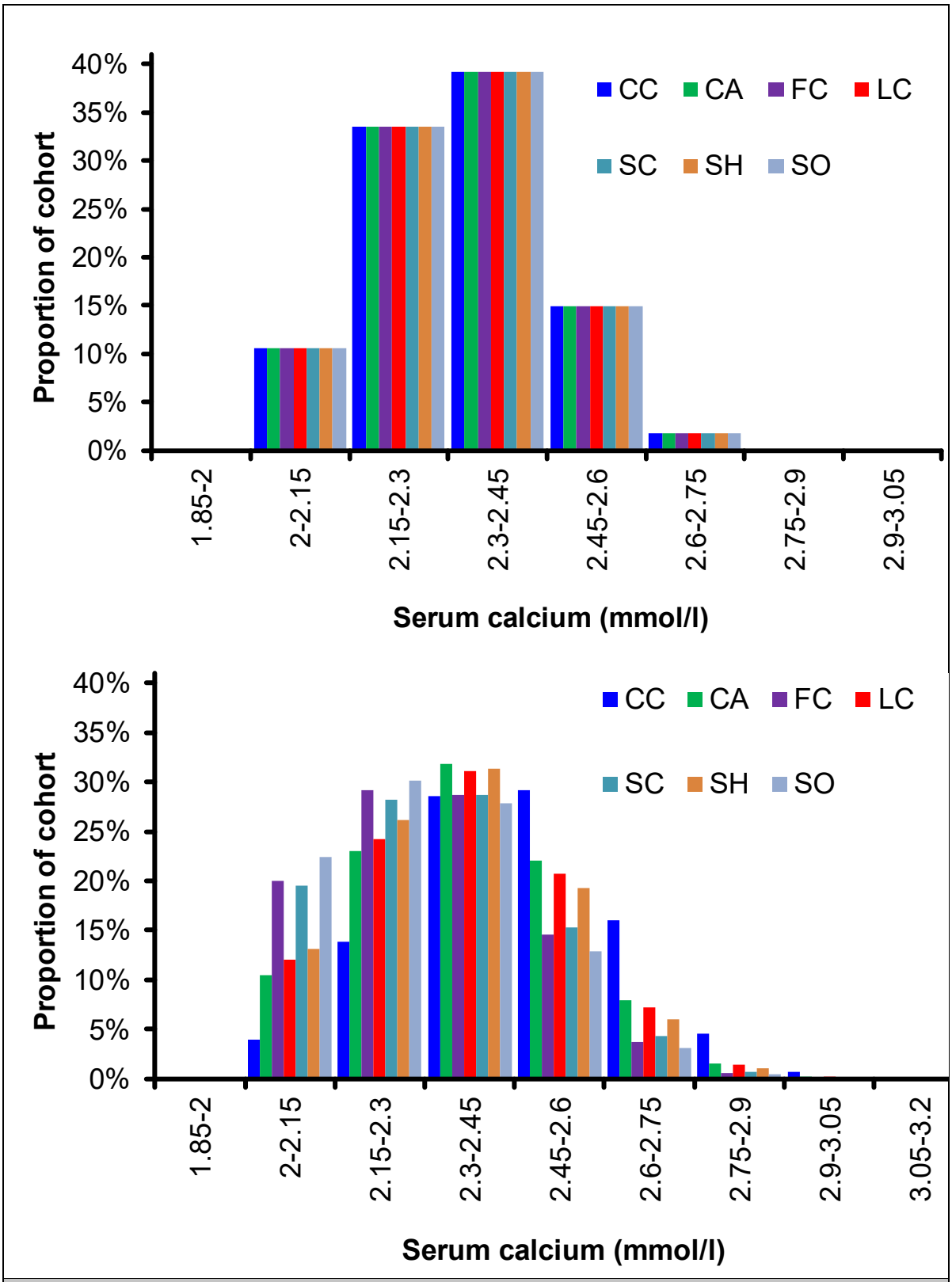
Figure 64 shows the modelled distribution of phosphate levels at baseline (top) and at 1 year (bottom) of 100,000 simulated patients for each phosphate binder used first-line, assuming no switching due to hypercalcaemia. As expected, the phosphate levels at baseline are the same for all binders. At 1 year, the distribution has shifted towards lower phosphate levels for all binders, indicating that they are all efficacious in lowering serum phosphate levels. The binders with the greatest phosphate-lowering effect based on the 1-year model outputs are sucroferric oxyhydroxide, calcium acetate and ferric citrate, while lanthanum carbonate and sevelamer hydrochloride perform the worst. These results directly reflect the NMA outputs (see Appendix H).

In Figure 65, we report calcium levels at baseline (top) and at 1 year (bottom). The model predicts that serum calcium levels of cohorts receiving non-calcium-based binders are generally lower than those of groups receiving calcium-based binders. Calcium carbonate is the only binder that leads to an overall increase in calcium levels, while calcium acetate results in a negligible decrease (also see Table 65). Ferric citrate, sevelamer carbonate and sucroferric oxyhydroxide have the most favourable calcium distributions, again directly reflecting the NMA of calcium levels at 12 months (see Appendix H).



CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 64: Simulated serum phosphate distribution at baseline (top) and at 1 year (bottom)



CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 65: Simulated serum calcium distribution at baseline (top) and at 1 year (bottom)

Based on the simulated distributions, the model estimated the proportions of people in each cohort whose phosphate levels were 1.78 mmol/L or higher (that is, outside the target range) at 1 year (Table 65). Sucroferric oxhydroxide appears to be better at controlling serum phosphate when compared with the other alternatives, followed closely by calcium acetate. As expected, the simulated proportions of people with calcium levels of 2.6 mmol/l or higher favours the non-calcium binders (sucroferric oxyhydroxide in particular, as shown in Table 65); however, calcium acetate is not much worse than the non-calcium binders.

Table 65: Modelled serum phosphate and serum calcium levels

	Serum phosphate (mmol/l)			Serum calcium (mmol/l)		
	Baseline	1 year	≥1.78 at 1 year	Baseline	1 year	≥2.6 at 1 year
Calcium carbonate	2.291	1.692	44.4%	2.320	2.387	21.1%
Calcium acetate	2.291	1.655	40.9%	2.320	2.300	9.7%
Ferric citrate	2.291	1.659	41.2%	2.320	2.229	4.3%
Lanthanum carbonate	2.291	1.791	53.6%	2.320	2.287	8.9%
Sevelamer carbonate	2.291	1.679	43.1%	2.320	2.237	5.0%
Sevelamer hydrochloride	2.291	1.707	45.6%	2.320	2.274	7.1%
Sucroferric oxyhydroxide	2.291	1.611	36.9%	2.320	2.214	3.5%

Clinical outcomes

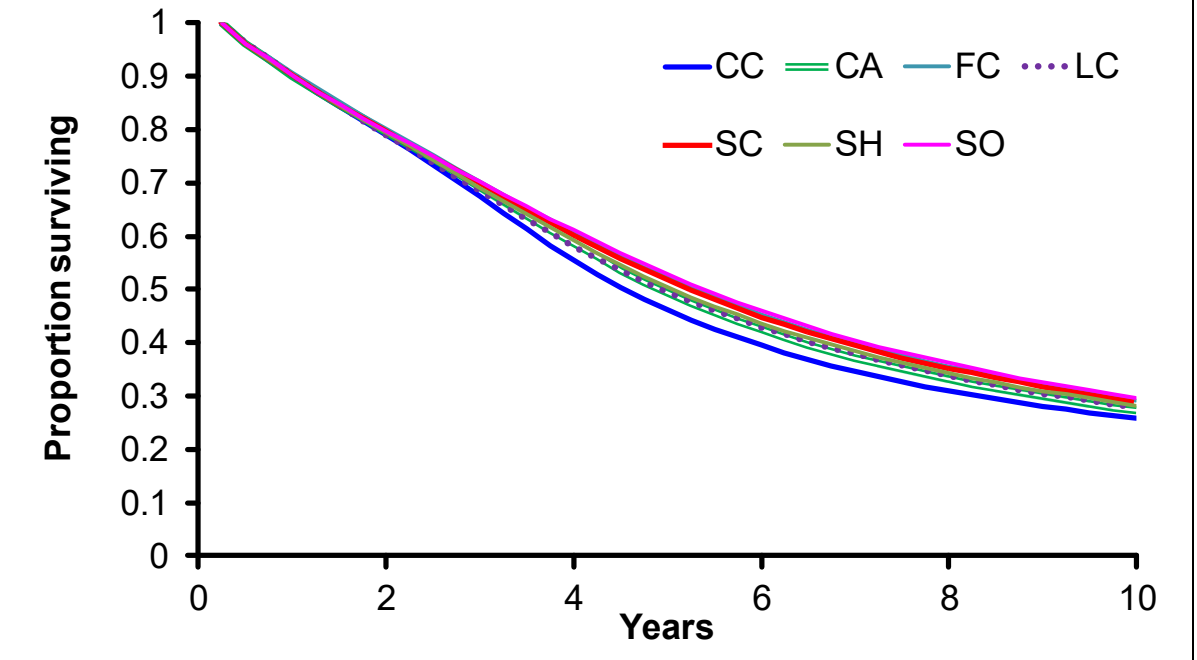
Modelled survival, average per-person incidence of fractures and cardiovascular events and probability of progression to renal transplantation and parathyroidectomy for the 7 phosphate binders are shown in Table 66. Calcium carbonate has the shortest overall survival, followed by calcium acetate then the non-calcium-based binders. The incidence of other events (fractures, cardiovascular events, transplant, parathyroidectomy) is predominantly associated with expected survival – the longer individual patients live, the greater the probability of experiencing such events.

Table 66: Predicted outcomes by phosphate-binding agent over lifetime

	Overall survival		Lifetime fractures	Lifetime CV events	% receiving Tx	% receiving PTx
	Mean	Median				
Calcium carbonate	8.546	4.286	0.0172	0.211	29.5%	5.0%
Calcium acetate	8.868	4.677	0.0174	0.218	31.0%	5.0%
Ferric citrate	9.210	5.061	0.0175	0.224	32.6%	5.2%
Lanthanum carbonate	8.920	4.700	0.0179	0.223	31.3%	5.3%
Sevelamer carbonate	9.134	4.982	0.0175	0.222	32.4%	5.3%
Sevelamer hydrochloride	9.026	4.821	0.0177	0.219	31.7%	5.2%
Sucroferric oxyhydroxide	9.274	5.141	0.0178	0.223	32.9%	5.2%

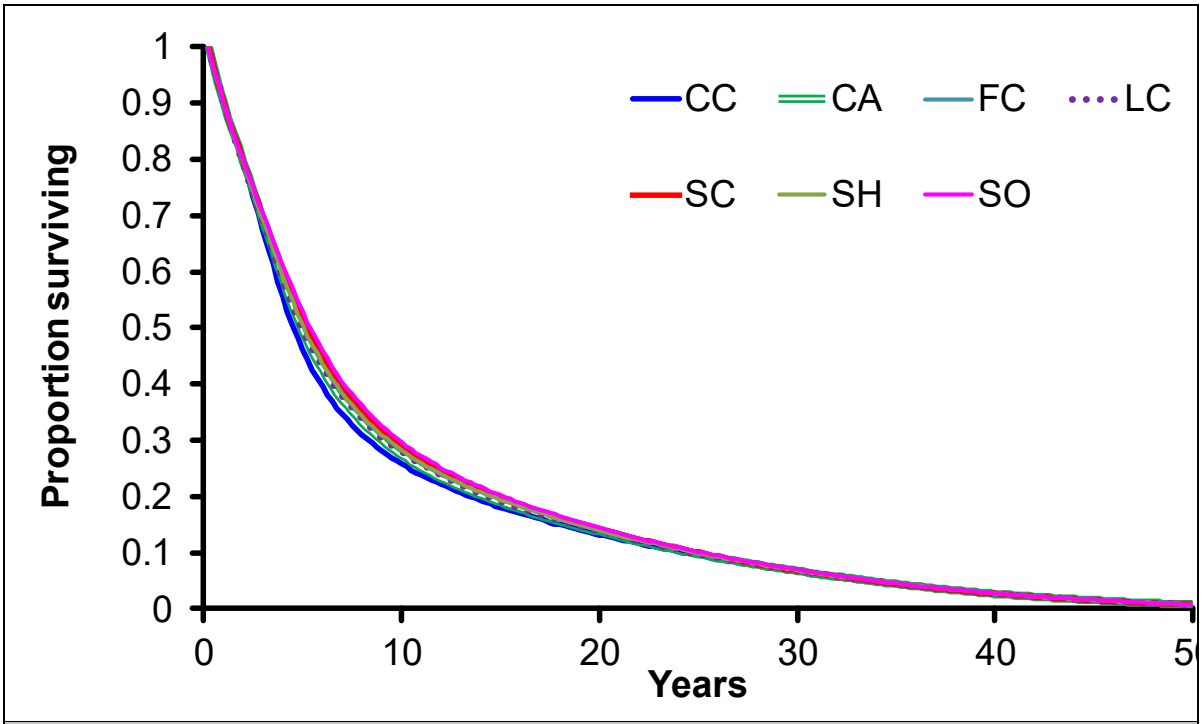
CV, cardiovascular; PTx, parathyroidectomy; Tx, transplant.

Modelled survival curves over the first 10 years (Figure 66) show that there are small differences between the binders. Calcium carbonate is associated with the shortest overall survival, and sucroferric oxyhydroxide the longest, with the other binders sharing a similar pattern between the 2. In extended follow-up over 50 years (Figure 67) all treatments appear to result in prolonged survival for a proportion of patients. This reflects the part of the cohort that receives transplantation, which is associated with substantially greater survival than remaining on dialysis.



CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 66: Modelled survival curves – 10-year follow-up



CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 67: Modelled survival curves – 50-year follow-up

We compared modelled survival with observed survival in head-to-head trials to explore model validity. Very few trials report mortality data; the best source is the long-term follow-up reported by Suki et al. (2007) of a trial comparing sevelamer hydrochloride with calcium-based binders. We found agreement between modelled survival and the empirical data in relative terms (Figure 68). In absolute terms, there is greater disparity between modelled and observed survival in our current update compared with the original analysis for CG157 (Figure 69), with people living longer in the update evidenced by a downwards shift in the modelled curves in Figure 68 compared with Figure 69. However, we know that survival has improved since the CG157 analysis due to increased life expectancy for the general population and better treatment options for people with CKD and common comorbidities (e.g. the widespread use of statins for people with cardiovascular disease); this explains why there are differences in absolute, but not relative, survival.

A survival advantage for people treated with sevelamer hydrochloride becomes apparent at around 2 years' follow-up and widens somewhat thereafter. The comparator arm of the RCT comprised participants taking a mixture of calcium-based phosphate binders; however, their relative survival experience is most comparable with the calcium carbonate arm of the model – those taking calcium acetate are simulated to experience superior survival which is closer to that of sevelamer.

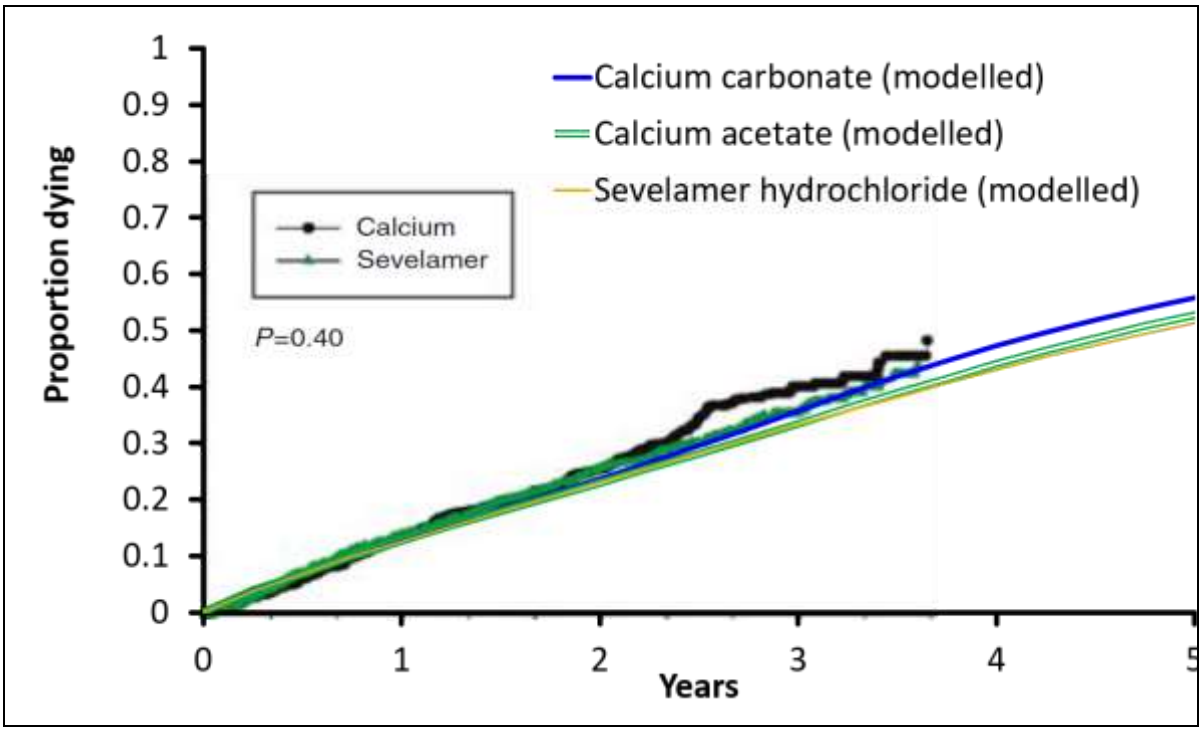


Figure 68: Modelled survival curves – observed survival data from Suki et al. (2007) overlaid: current update

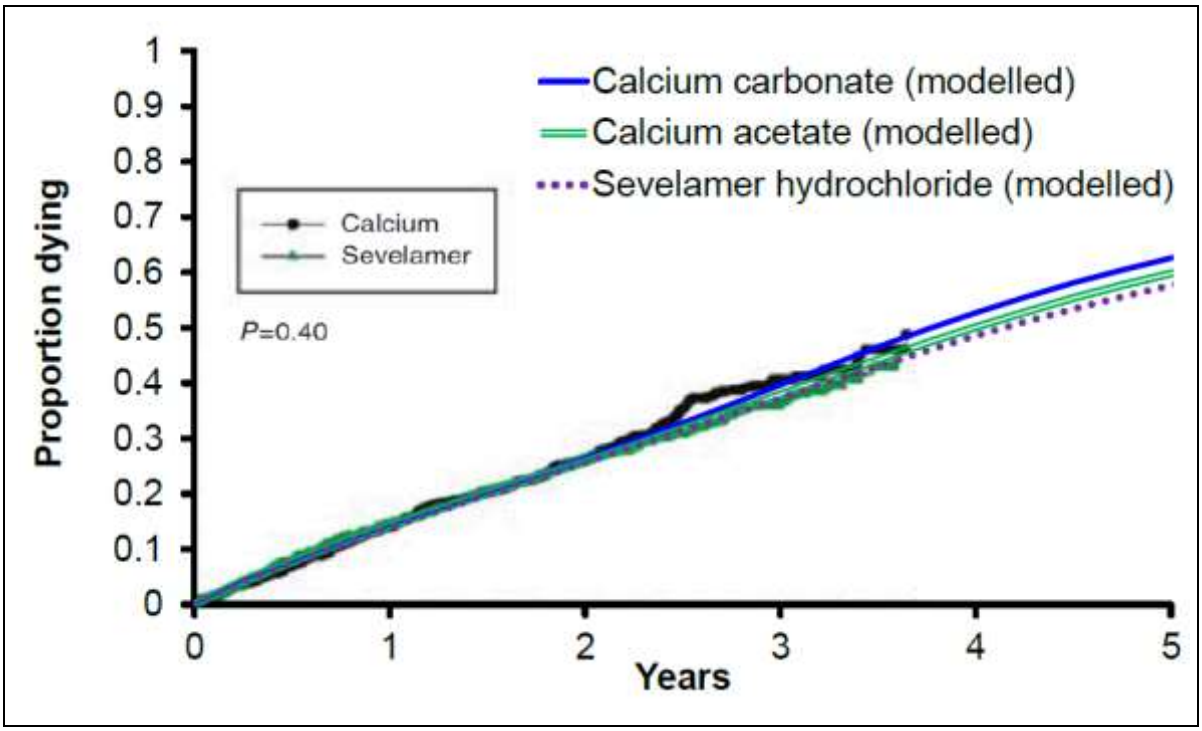


Figure 69: Modelled survival curves – observed survival data from Suki et al. (2007) overlaid: CG157

Table 67 shows the predicted lifetime incidence of adverse events associated with the different binders. These are reflective of the NMA inputs for each adverse event. Ferric citrate has particularly high rates of diarrhoea and nausea/vomiting, while calcium acetate and sevelamer hydrochloride have the highest rates of constipation.

Table 67: Average lifetime episodes of adverse events

	Diarrhoea	Constipation	Nausea / vomiting
Calcium carbonate	0.599	0.515	0.691
Calcium acetate	0.674	1.521	0.234
Ferric citrate	3.092	0.403	3.621
Lanthanum carbonate	0.881	0.372	1.327
Sevelamer carbonate	0.960	0.727	0.224
Sevelamer hydrochloride	0.638	1.748	0.207
Sucroferric oxyhydroxide	1.997	0.469	0.136

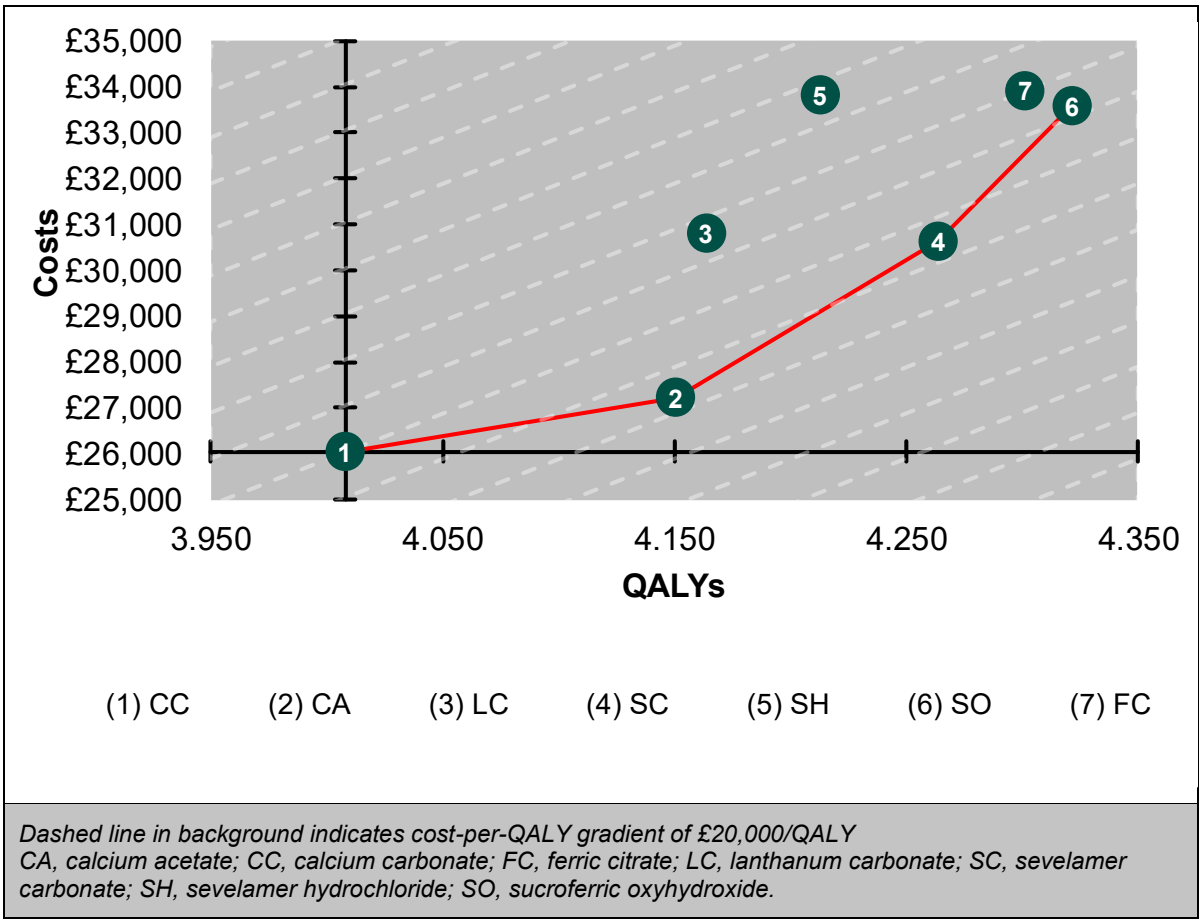
First-line use

Base-case cost–utility results

In our base case for the 7 binders used first-line, calcium acetate provides good value for money compared with calcium carbonate with an ICER of £8,226. Sevelamer carbonate has an ICER of £30,139 per QALY compared with calcium acetate, which is above a threshold of £20,000 per QALY. Sucroferric oxyhydroxide was found to be the most effective treatment in terms of QALYs; however, the additional health gains predicted versus sevelamer carbonate are not value for money if a QALY is valued at £20,000. Lanthanum carbonate, sevelamer hydrochloride and ferric citrate are dominated. Figure 70 illustrates these results on the cost–utility plane.

Table 68: Base-case deterministic cost–utility results: first-line use

Strategy	Absolute		Incremental			Absolute net health benefit @£20K/QALY
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
Calcium carbonate	£26,046	4.008				2.706
Calcium acetate	£27,221	4.151	£1,175	0.143	£8,226	2.790
Sevelamer carbonate	£30,635	4.264	£3,414	0.113	£30,139	2.732
Lanthanum carbonate	£30,823	4.164	£188	-0.100	dominated	2.623
Sucroferric oxyhydroxide	£33,578	4.322	£2,944	0.058	£51,186	2.643
Sevelamer hydrochloride	£33,813	4.213	£235	-0.109	dominated	2.522
Ferric citrate	£33,922	4.301	£344	-0.020	dominated	2.605



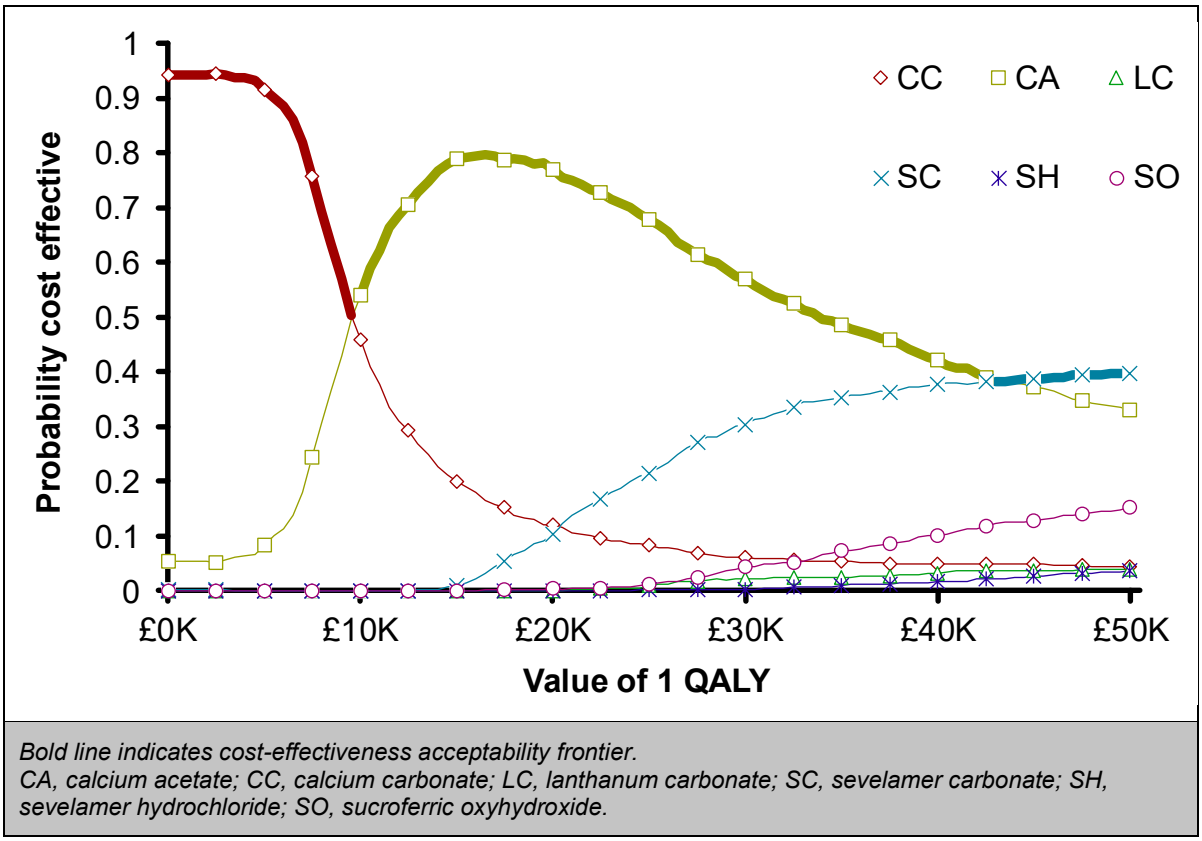
Dashed line in background indicates cost-per-QALY gradient of £20,000/QALY
CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 70: Base-case deterministic cost–utility plane: first-line use

Probabilistic sensitivity analysis

The cost-effectiveness acceptability curve (CEAC) in Figure 71 shows that at low QALY values (below approximately £10,000), calcium carbonate has the highest probability of being cost effective. At all values above this, calcium acetate has the highest probability of being cost effective. As indicated by the cost-effectiveness acceptability frontier (the bold line), sevelamer carbonate has the highest expected net benefit only at the top range of QALY values analysed (approximately £44,000 and above).

Note that we have excluded ferric citrate from all sensitivity analyses as the committee did not deem it to be a feasible option for recommendation, as it is not currently available in the UK.



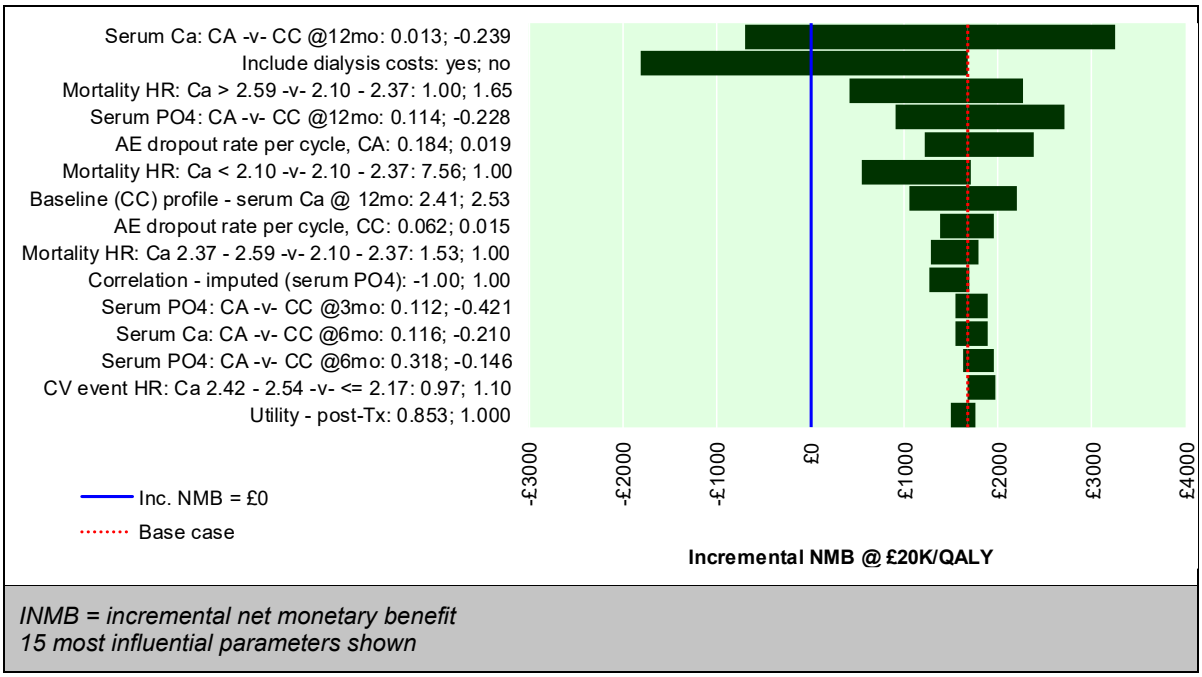
Bold line indicates cost-effectiveness acceptability frontier.
CA, calcium acetate; CC, calcium carbonate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 71: Probabilistic sensitivity analysis: first-line use

One-way sensitivity analysis

One-way sensitivity analyses were conducted to explore the impact on the results of changing the value of 1 parameter while keeping the value of all other parameters unchanged. It also highlights areas where further exploration of uncertainty may be useful. We show the 15 most influential parameters for each comparison.

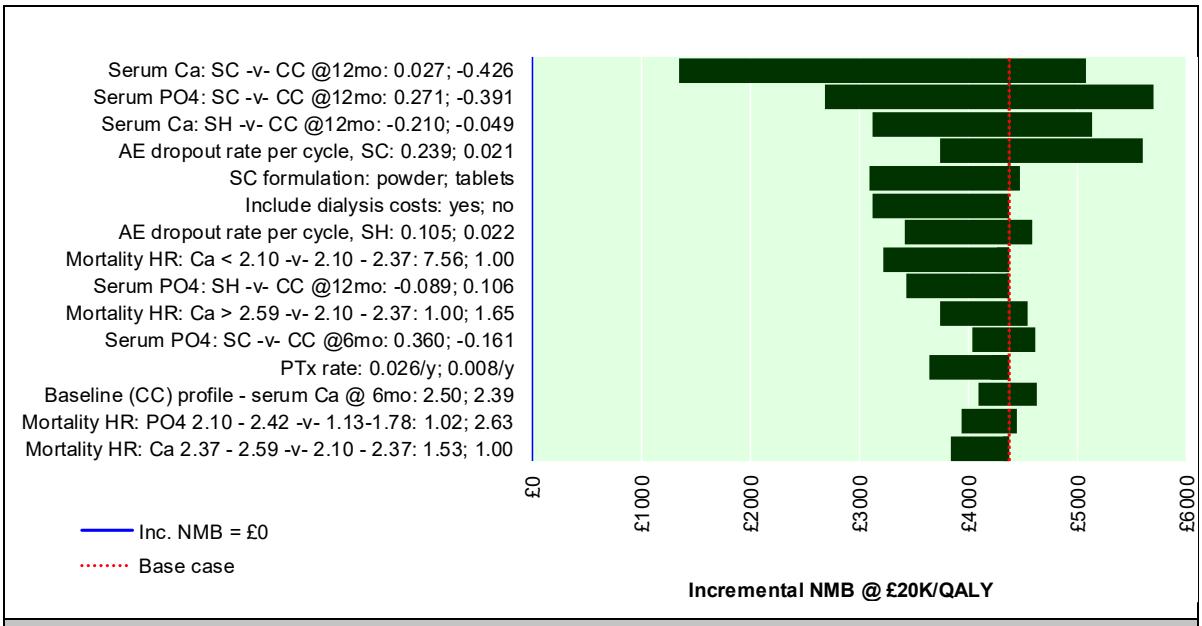
As illustrated in Figure 72, calcium acetate remained good value for money compared with calcium carbonate, except when the difference in serum calcium at 12 months was varied so that calcium acetate was associated with higher levels than calcium carbonate (mean difference +0.013 mmol/l, compared with a base-case point estimate of −0.113 mmol/l). Including dialysis costs in calculations also had an important impact on findings; however, this is the case because time on dialysis is minimised by the inferior survival profile of calcium carbonate (in other words, calcium carbonate looks more cost effective because people are dying earlier). Independently varying all other parameters within plausible ranges had no effect on the implied decision.



INMB = incremental net monetary benefit
15 most influential parameters shown

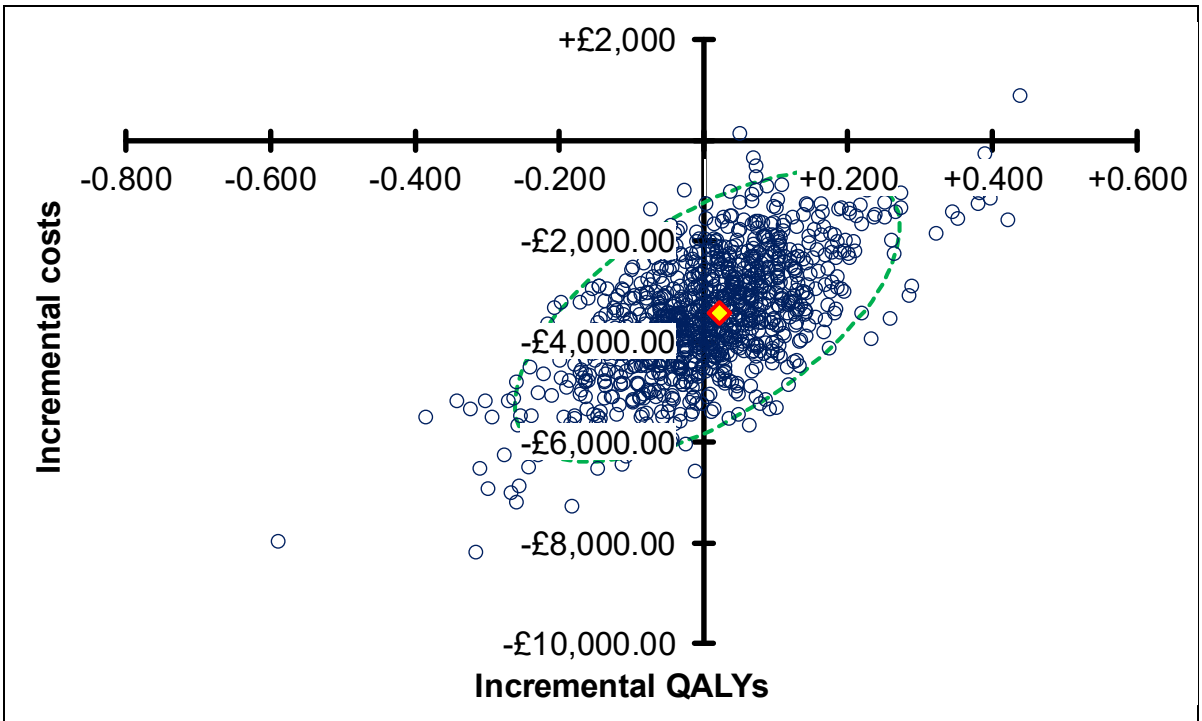
Figure 72: One-way sensitivity analysis – calcium acetate versus calcium carbonate

Figure 73 shows the comparison between sevelamer carbonate and sevelamer hydrochloride. Sevelamer hydrochloride is (very marginally) less effective and (substantially) more expensive than sevelamer carbonate; as such, varying parameters within plausible ranges does not result in a positive net monetary benefit for sevelamer hydrochloride. This can be seen clearly in pairwise PSA outputs (Figure 74), where our confidence that sevelamer carbonate is cheaper than sevelamer hydrochloride is almost total, but the spread of incremental QALYs is very even between the 2 options.



INMB = incremental net monetary benefit
15 most influential parameters shown

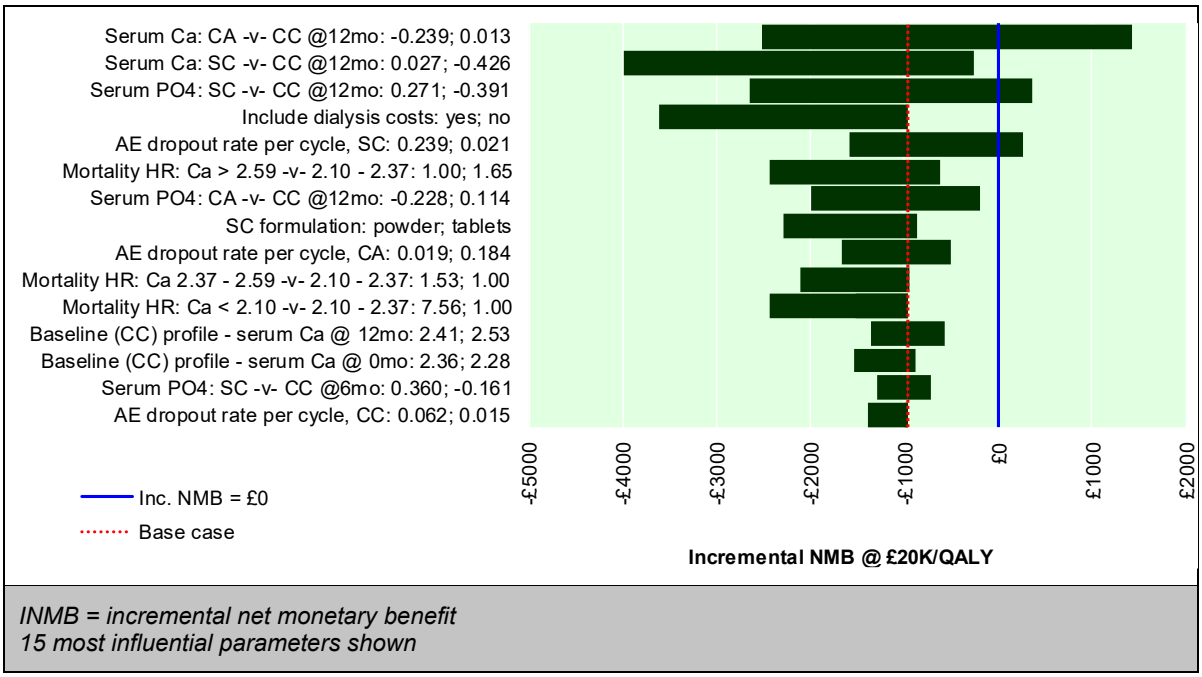
Figure 73: One-way sensitivity analysis – sevelamer carbonate versus sevelamer hydrochloride



INMB = incremental net monetary benefit
15 most influential parameters shown

Figure 74: Pairwise probabilistic sensitivity analysis – sevelamer carbonate versus sevelamer hydrochloride

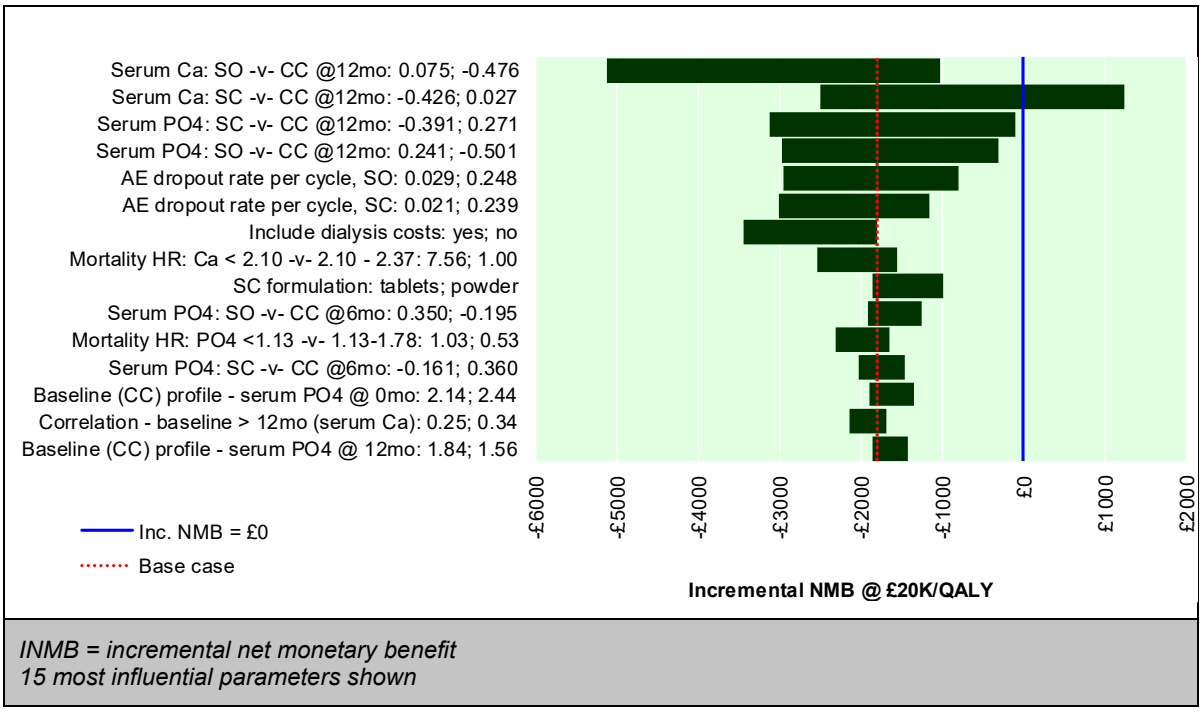
Although calcium acetate would be preferred based on a QALY value of £20,000, both calcium acetate and sevelamer carbonate have ICERs that are within, or approaching, the range of the usually accepted cost-effectiveness threshold. When certain parameters are varied to make calcium acetate less effective (calcium at 12 months) or sevelamer carbonate more effective (phosphate at 12 months), sevelamer carbonate would be associated with an ICER better than £20,000 / QALY. Decreasing the AE dropout rate with sevelamer carbonate also has this effect.



INMB = incremental net monetary benefit
15 most influential parameters shown

Figure 75: One-way sensitivity analysis – sevelamer carbonate versus calcium acetate

In the base case, sucroferric oxyhydroxide has an ICER of approximately £50,000 versus sevelamer carbonate. There is only 1 parameter which, when varied, results in sucroferric oxyhydroxide becoming the better choice when QALYs are valued at £20,000 each – this is if sevelamer carbonate is at the higher bound of its 95% confidence interval for effect on serum calcium (Figure 76).



INMB = incremental net monetary benefit
15 most influential parameters shown

Figure 76: One-way sensitivity analysis – sucroferric oxyhydroxide versus sevelamer carbonate

We also compared both lanthanum carbonate and sevelamer hydrochloride to calcium acetate (the most cost effective first-line agent based on a threshold of £20,000) in one-way sensitivity analyses (not shown). No variation in any parameter led to a positive incremental net monetary benefit for either.

Sequential use

Base-case cost–utility results

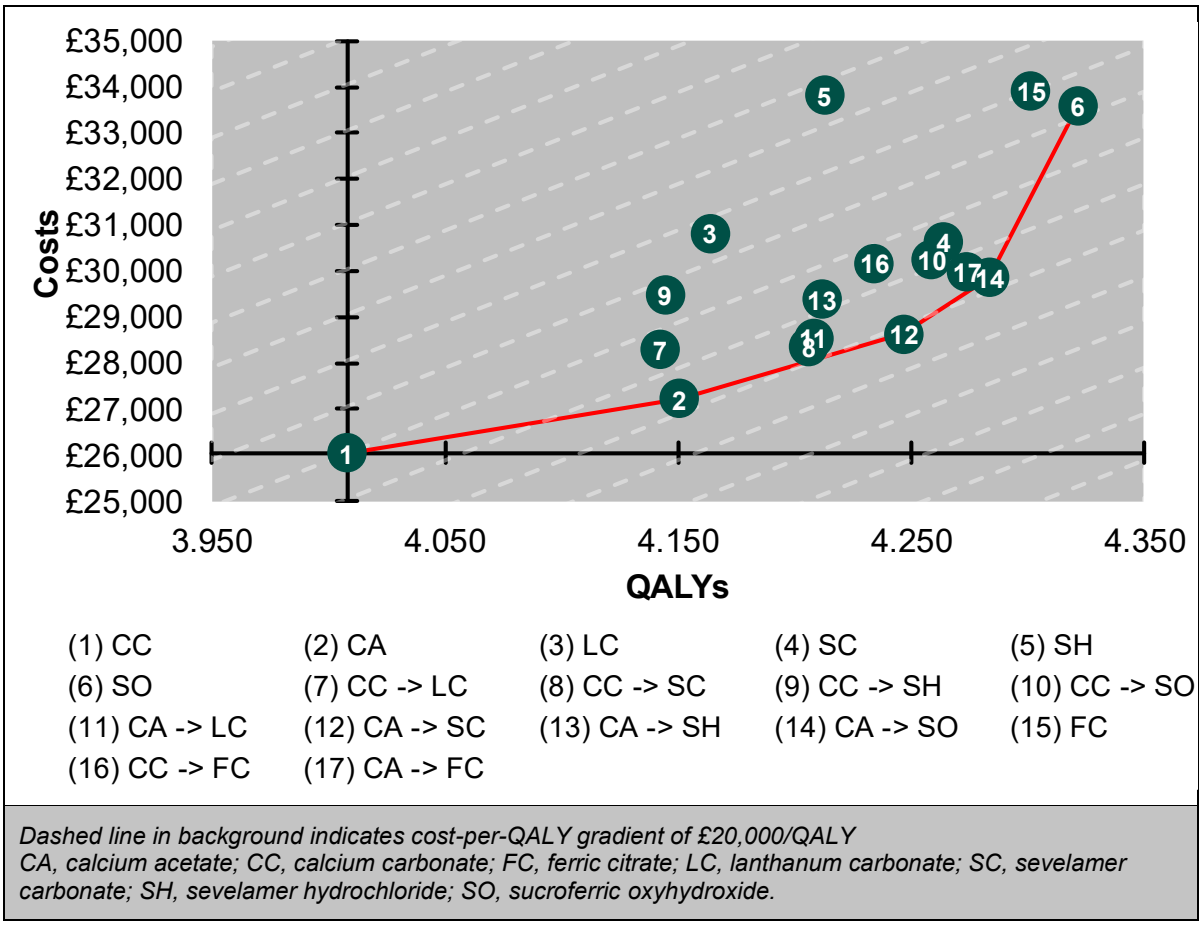
Base-case cost–utility results for the sequential treatment scenarios are presented in Table 69. Figure 77 illustrates these results on the cost–utility plane.

Table 69: Base-case deterministic cost–utility results: sequential use

Name	Absolute		Incremental			Absolute net health benefit @£20K/QALY
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
CC	£26,046	4.008				2.706
CA	£27,221	4.151	£1,175	0.143	£8,226	2.790
CC -> LC	£28,296	4.142	£1,075	-0.008	dominated	2.728
CC -> SC	£28,350	4.206	£1,129	0.056	ext. dom.	2.789
CA -> LC	£28,547	4.208	£1,326	0.057	ext. dom.	2.781
CA -> SC	£28,636	4.247	£1,415	0.096	£14,738	2.815
CA -> SH	£29,389	4.212	£753	-0.035	dominated	2.742
CC -> SH	£29,479	4.144	£843	-0.102	dominated	2.670
CA -> SO	£29,861	4.284	£1,225	0.037	£33,293	2.790
CA -> FC	£29,980	4.274	£119	-0.010	dominated	2.775
CC -> FC	£30,174	4.234	£313	-0.049	dominated	2.725
CC -> SO	£30,251	4.259	£390	-0.025	dominated	2.746
SC	£30,635	4.264	£774	-0.020	dominated	2.732
LC	£30,823	4.164	£963	-0.120	dominated	2.623
SO	£33,578	4.322	£3,718	0.038	£97,903	2.643
SH	£33,813	4.213	£235	-0.109	dominated	2.522
FC	£33,922	4.301	£344	-0.020	dominated	2.605

Calcium acetate followed by sevelamer carbonate (if a switch due to hypercalcaemia is required) provides the best value for money if a QALY is valued at £20,000, with an ICER of £14,738 per QALY gained. The option to switch to sucroferric oxyhydroxide rather than sevelamer carbonate generates more QALYs, but the ICER is £33,293 versus the sevelamer carbonate option, which is above the usual threshold of £20,000 per QALY. However, if somebody is unable to take sevelamer carbonate, thereby removing it from the decision space, sucroferric oxyhydroxide (after calcium acetate) becomes cost effective with an ICER of £19,877 per QALY gained versus calcium acetate (incremental costs: £2,640 and incremental QALYs: 0.133).

The option to use sevelamer carbonate first-line is dominated and first-line sucroferric oxyhydroxide is associated with an extremely high ICER. This indicates that they only represent good value for money if they are reserved for people with hypercalcaemia who have already received calcium acetate.



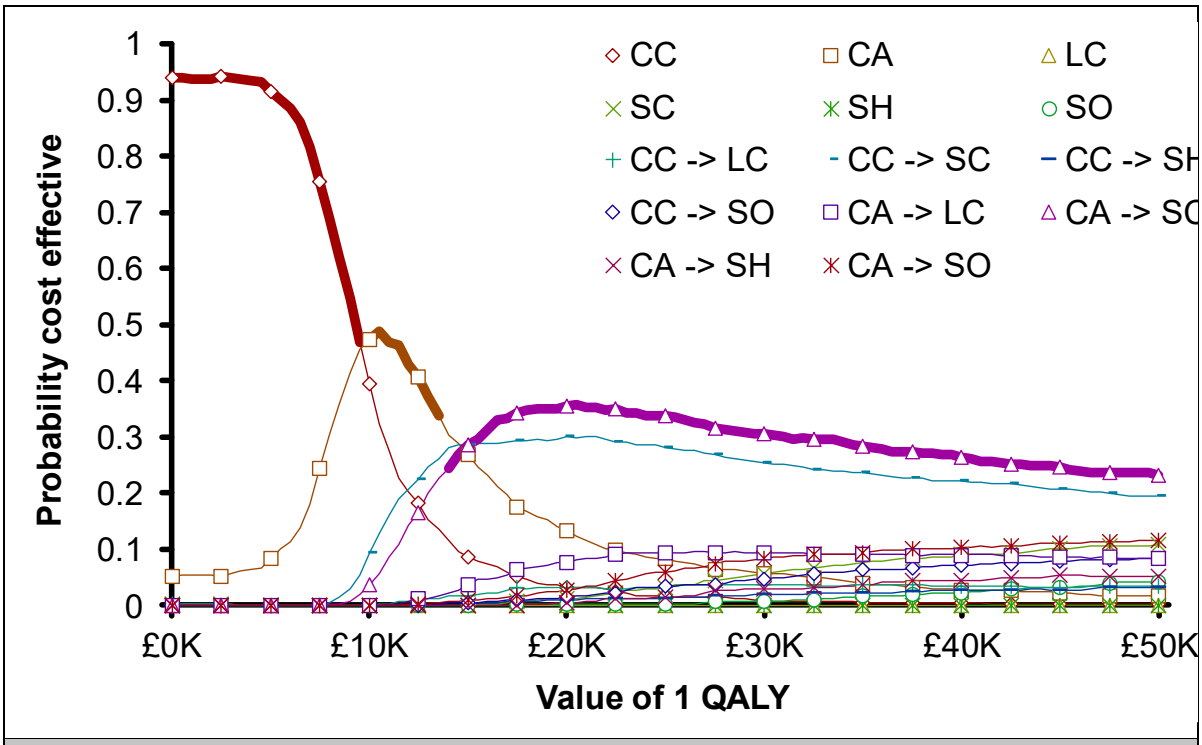
Dashed line in background indicates cost-per-QALY gradient of £20,000/QALY
CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 77: Base-case deterministic cost–utility plane: sequential use

Probabilistic sensitivity analysis

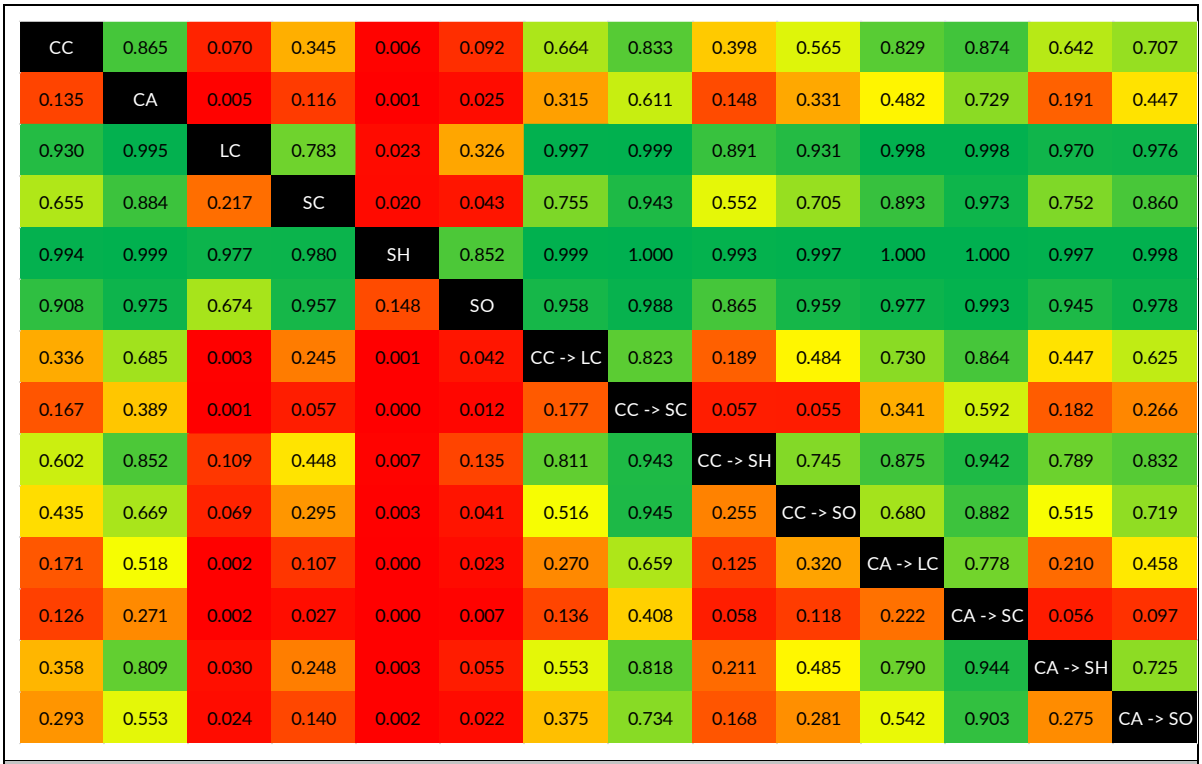
Figure 78 shows results of the probabilistic sensitivity analysis for sequential use. Similarly to the first-line use analysis, calcium carbonate monotherapy has the highest probability of being cost-effective and highest expected net benefit if a QALY is valued at £10,000 and under. There is a small range of QALY values (approximately £10,000 to £13,000) for which calcium acetate monotherapy is the preferred option, above which the sequential use of calcium acetate followed by sevelamer carbonate has the highest expected net benefit and highest probability of being cost-effective.

As shown in Figure 79, our confidence that the sequential use of calcium acetate followed by sevelamer carbonate delivers greater net benefit than any other option is high; there is little probability that any strategies including lanthanum carbonate or sevelamer hydrochloride could provide best value, unless all other options are ruled out.



Bold line indicates cost-effectiveness acceptability frontier.
CA, calcium acetate; CC, calcium carbonate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 78: Probabilistic sensitivity analysis: sequential use



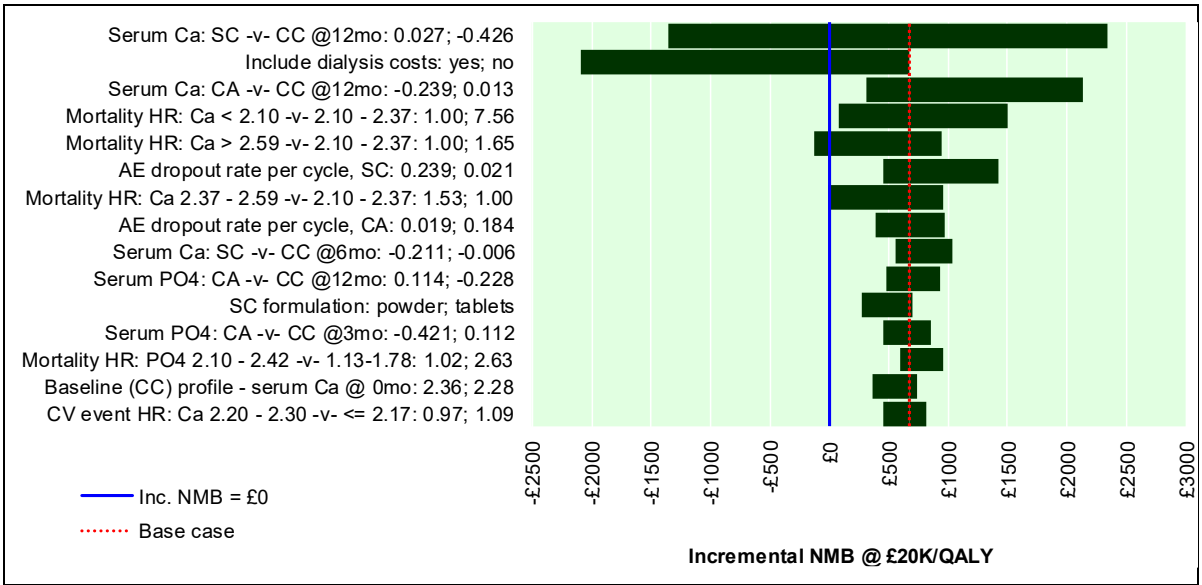
Values are the probability that the option in the column provides better value for money than the option in the row (when QALYs are valued at £20,000 each).
CA, calcium acetate; CC, calcium carbonate; LC, lanthanum carbonate; SC, sevelamer carbonate; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Figure 79: Probabilistic sensitivity analysis: pairwise probabilities of greater net benefit (when QALYs are valued at £20,000 each)

One-way sensitivity analysis

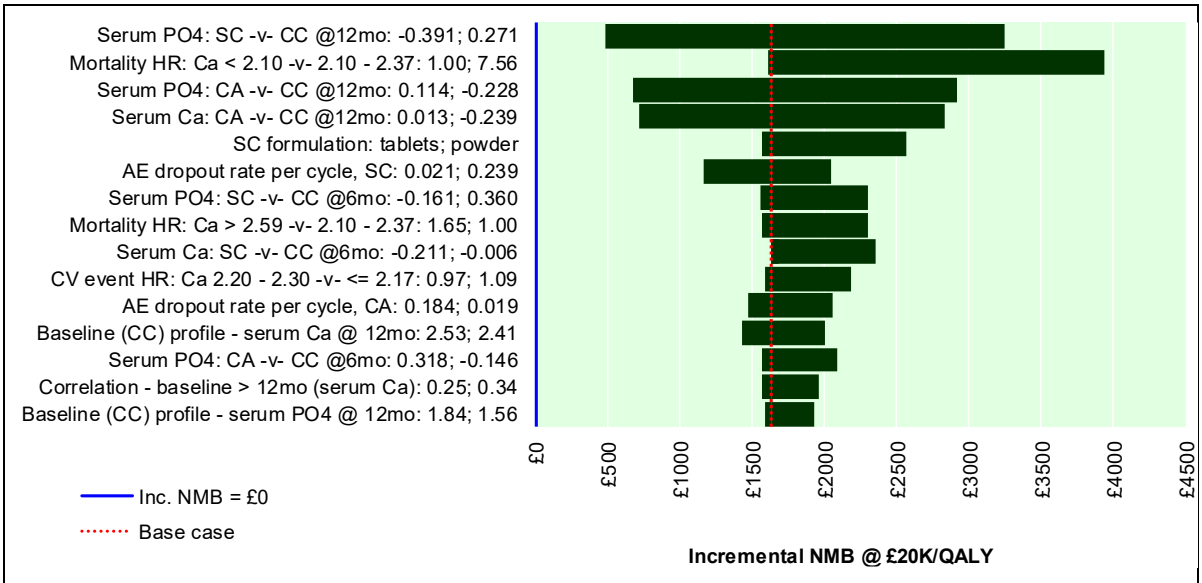
We conduced one-way sensitivity analyses to determine the impact of individually varying parameters between their plausible bounds. As displayed in Figure 80, varying some parameters can lead to first-line calcium acetate becoming the preferred option over sequential use of calcium acetate followed by sevelamer carbonate. Namely, decreasing the effectiveness of sevelamer carbonate versus calcium carbonate, including dialysis costs, and increasing the hazard of death with increasing serum calcium levels. Independently varying all other parameters within plausible ranges had no effect on the implied decision.

When we change the comparator from first-line calcium acetate to first-line sevelamer carbonate (Figure 81), there are no variations in parameters that led to sevelamer carbonate becoming the cost-effective option.



INMB = incremental net monetary benefit
15 most influential parameters shown

Figure 80: One-way sensitivity analysis – calcium acetate → sevelamer carbonate versus calcium acetate

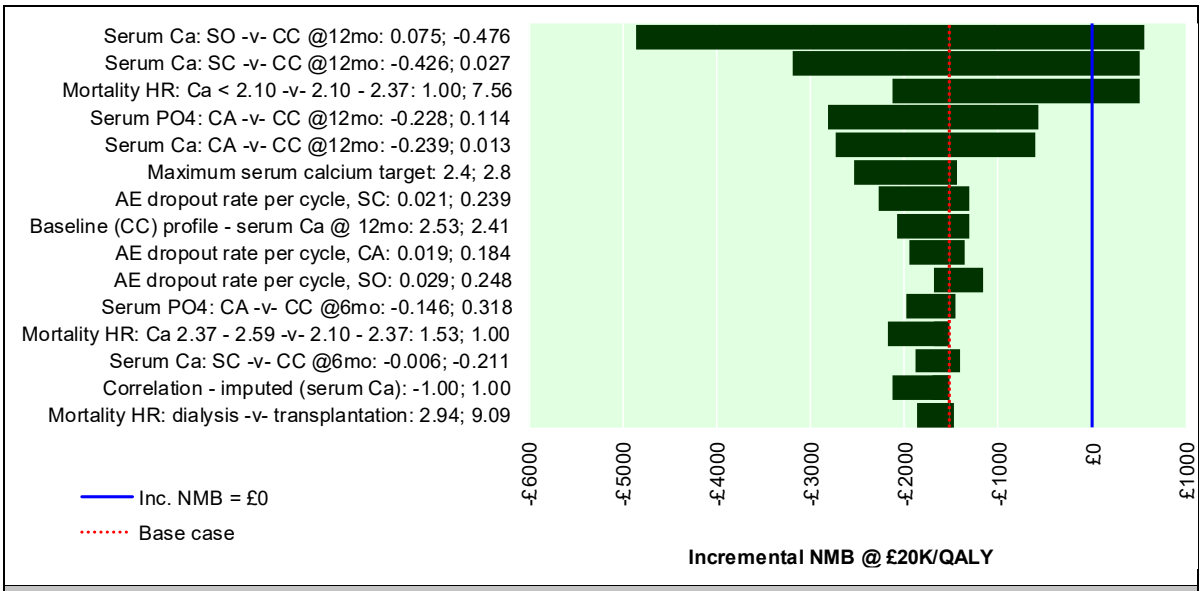


INMB = incremental net monetary benefit
15 most influential parameters shown

Figure 81: One-way sensitivity analysis – calcium acetate → sevelamer carbonate versus sevelamer carbonate

Figure 82 shows the comparison between switching to sucroferric oxyhydroxide versus switching to sevelamer carbonate following initial treatment with calcium acetate. There are three parameter alterations that have the potential to lead to a positive net monetary benefit when switching to sucroferric oxyhydroxide: increasing the effectiveness of sucroferric oxyhydroxide versus calcium carbonate, decreasing the effectiveness of sevelamer

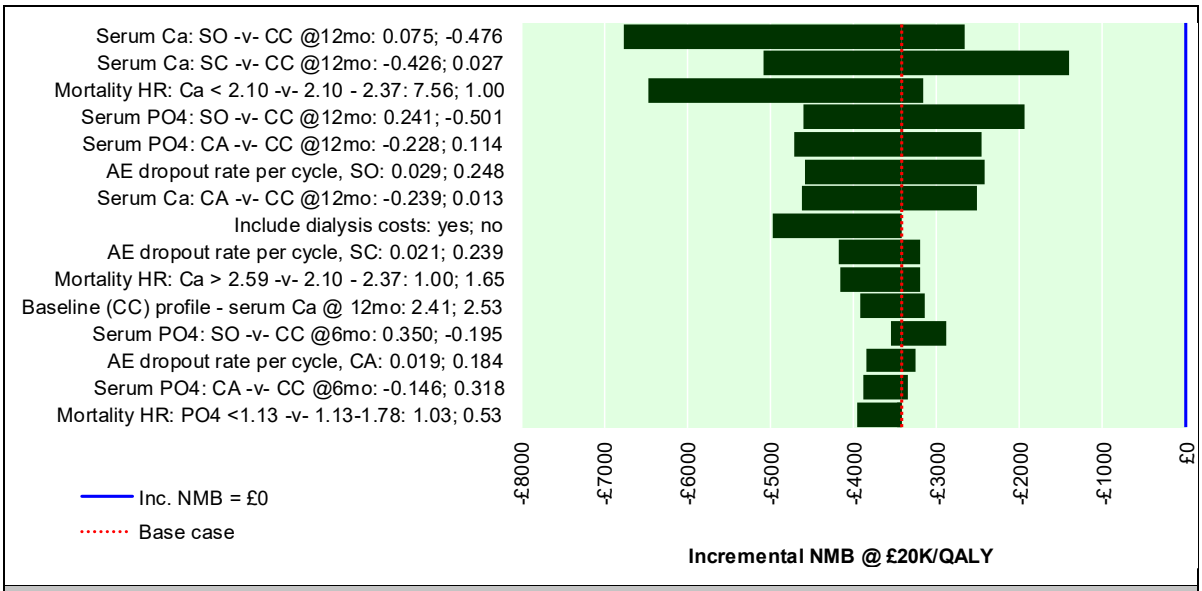
carbonate versus calcium carbonate, and increasing the hazard of death with increasing serum calcium levels.



INMB = incremental net monetary benefit
15 most influential parameters shown

Figure 82: One-way sensitivity analysis – calcium acetate → sucroferric oxyhydroxide versus calcium acetate → sevelamer carbonate

When sucroferric oxyhydroxide as a first-line option is compared against the sequential use of calcium acetate followed by sucroferric oxyhydroxide (Figure 83), independently varying parameters within plausible ranges had no effect on the implied decision.



INMB = incremental net monetary benefit
15 most influential parameters shown

Figure 83: One-way sensitivity analysis – sucroferric oxyhydroxide versus calcium acetate → sucroferric oxyhydroxide

Discussion

Principal findings

We created an individual patient simulation model which aimed to help answer the research questions:

- For people with stage 4 or 5 CKD who are not on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?
- For people with stage 5 CKD who are on dialysis, which phosphate binder, calcium and non-calcium based, is most effective in managing serum phosphate and its associated outcomes?

The base-case economic model suggests that calcium acetate is likely to be the preferred first-line phosphate binder for the management of hyperphosphataemia in people with CKD stage 5 who are on dialysis. When second-line treatment options are taken into account, the most effective strategy is to start with calcium acetate but switch to sevelamer carbonate if hypercalcaemia develops. These results are robust to probabilistic and deterministic sensitivity analyses.

Although our model suggests that other non-calcium-based binders may generate very slightly more QALYs than sevelamer carbonate (e.g. sucroferric oxyhydroxide and ferric citrate), we are much less uncertain about the additional cost with which they are associated, with the result that, if a QALY is valued at £20,000, they have a lower overall net benefit both as individual first-line therapies or following hypercalcaemia on calcium-based binders. However, due to committee advice that people often struggle to find a binder they can tolerate, we also present results in which people are unable to tolerate sevelamer carbonate (by removing it from the decision space). For these people, a strategy in which people move from calcium acetate to sucroferric oxyhydroxide if they develop hypercalcaemia becomes the preferred option.

Although we included it in the base case cost–utility results, ferric citrate is not currently available in the UK. Because of this, we were unable to obtain an estimate for how much it costs, and therefore the cost-effectiveness results are subject to a large degree of uncertainty. As it is not currently a viable option for recommendation, we removed ferric citrate from all sensitivity analyses.

Strengths of the analysis

The model takes an individual patient simulation approach, which allows us to capture the complex relationships between serum phosphate and serum calcium concentrations and long-term, patient-relevant outcomes such as cardiovascular risk, fractures and death. To date, we have not found any long-term data on the effects of phosphate binders on the patient outcomes included within the model. Therefore, we think our approach of using serum phosphate and serum calcium as surrogates for long-term, patient-relevant outcomes is more appropriate than if we were to attempt to extrapolate based on very limited data. An individual patient simulation approach is the best way of achieving this, while also allowing us to easily incorporate switching between treatments.

A key strength of the analysis is that it relies on a series of NMAs for estimates of the relative treatment effects. To our knowledge, this is the most up-to-date estimate of the treatment effects for the included interventions. Furthermore, as well as the randomised controlled trial data within the NMA, we synthesised a wealth of additional types of data from various sources. We benefitted from the availability of UK Renal Registry data to inform epidemiological parameters within the model. The UK Renal Registry population is directly applicable to our modelled population (people in the UK who have stage 5 CKD and are receiving renal replacement therapy); therefore we expect patient trajectories to have a high degree of external validity.

The analyses presented here benefit from deterministic and probabilistic sensitivity analyses. Most parameters were included in univariable analyses, and we explored certain scenarios in more detail, for example the inclusion or exclusion of dialysis costs. Finally, the model was updated in close collaboration with the expert guideline committee. As part of this, the committee had several opportunities to review and discuss the model structure and inputs. This ensured the model had a high degree of external validity and was an appropriate representation of the clinical pathway in hyperphosphataemia.

Limitations of the analysis

The model has good validity over its first year, accurately reflecting biochemical measures reported in the trials. It also makes a relatively good prediction of observed survival with the treatments of interest over the first 3 years of treatment. However, beyond the first year of the model, we estimate biochemical profiles based on extrapolation and simplification and it is impossible to tell how well the model represents reality. It is possible that, as they extend into the future, the biochemical profiles of a small number of simulated patients become implausible (especially modelled serum calcium, which may rise very high in a few instances).

We acknowledge that the use of serum phosphate and serum calcium alone as determinants of treatment effect is a simplification of a highly complex biological interaction. Moreover, it is well known that serum calcium is a suboptimal index of calcium balance in humans, perhaps especially in those with advanced kidney disease (Houillier et al., 2006). If people who are exposed to excess calcium intake in their phosphate binding regimen are subject to greater risks than can be inferred from their serum calcium levels, the model will underestimate the benefit of switching these people to calcium-free binders.

When simulating second-line treatment for people experiencing hypercalcaemia, the model is necessarily reliant on evidence of the effectiveness of treatments in a broader population, many of whom are likely not prone to hypercalcaemia. If people with hypercalcaemia respond differently to treatment than people without, it is possible that different cost–utility conclusions would be reached if more specific evidence were available.

There were some parameters for which suitable data could not be found or did not exactly match our needs or our population of interest. In such cases we carried forward assumptions from the CG157 analysis or used data sources that were not directly applicable to the population of interest. For example, we were unable to find appropriate UK studies that report utility values associated with the relevant adverse events in people with CKD taking phosphate binders; therefore, we used data in patients experiencing unintended toxicities associated with treatment for melanoma (Beusterien et al., 2009). In addition, there were some sources that did not report the data with the appropriate uncertainty estimates for the PSA. An example of this is the version of the NHS reference costs used within the model (2017–18) does not report the lower and upper quartiles for the cost estimates. We therefore assumed costs were fixed, which means uncertainty surrounding the reference costs is not

accounted for within the model. Arguably, however, there is no parameter uncertainty attached to NHS reference costs, as they represent all NHS activity, and are, therefore, not subject to sampling error.

Unfortunately, there was insufficient evidence to develop a separate model for people in CKD stages 4 and 5 who are not on dialysis, and for children at any stage of disease. There was also insufficient evidence to perform any meaningful modelling to support a recommendation on some of the other available binders, for example magnesium carbonate.

A key strength of the analysis is the incorporation of one-way sensitivity analysis; however, due to the extremely long running times we were forced to prioritise which parameters to include in this based on the previous CG157 analysis (NICE, 2013) and committee advice. Although we suspect we have captured all parameters that are likely to have any meaningful effect on results when varied, we cannot be certain that any of those that we decided to exclude are not important.

Comparison with other CUAs

None of the analyses included within our systematic review of published economic evaluations of phosphate binders compared all our comparators of interest. As a result, it is not possible to make direct comparisons between the present model and other published analyses. However, we can compare the pairwise models with the relevant pairwise comparisons from our model, focusing on UK studies in the dialysis population.

In our systematic review, only 1 analysis was judged to be both directly applicable to the setting of present interest and subject to only minor internal limitations – Brennan's 2007 pairwise comparison of lanthanum carbonate with calcium carbonate in a second-line setting (Brennan et al., 2007). This model produced results that are somewhat different to ours: they estimate an ICER of £26,860 per QALY gained for switching to lanthanum carbonate compared with remaining on calcium carbonate, whereas our model suggests an ICER of £16,725 for the same comparison. The CG157 analysis estimated an ICER of £29,619, which is more aligned with the Brennan (2007) study. We suspect that the lower ICER in our current analysis could be due to a lower cost for lanthanum carbonate (£3.68 per day in the current analysis versus £4.36 per day in CG157). The cost of calcium carbonate has also decreased; however, due to its low absolute cost this is likely to have less of an impact on results. The other UK study comparing lanthanum carbonate (second-line after therapy failure with calcium-based binders) with calcium carbonate alone estimates an ICER of £7,758 per QALY gained for switching to lanthanum carbonate compared with remaining on calcium-based binders (Vegter et al., 2011). Our estimate of £16,725 per QALY sits between the estimates from the 2 published studies.

We found 2 UK studies comparing first-line sevelamer with calcium-based binders in people receiving dialysis; one reported an ICER of £32,619 per QALY for sevelamer versus calcium-based binders (Taylor et al., 2008), while the other reported an ICER of £24,986 per QALY (Bernard et al., 2013). Notably, it is not entirely clear which sevelamer salt is included in these two evaluations (e.g. Bernard et al. use the cost of hydrochloride, but the drug dose and hospitalisation days associated with carbonate). Our cost-effectiveness results differ greatly between sevelamer hydrochloride and sevelamer carbonate, predominantly due to the higher cost of patented sevelamer hydrochloride versus generic carbonate. If we assume calcium carbonate as the comparator, sevelamer carbonate has an ICER of £17,919 per QALY gained while sevelamer hydrochloride has an ICER of £37,919 – carbonate would be considered cost effective while hydrochloride would not. It is worth noting that sevelamer carbonate was still under patent when the two published analyses were undertaken, and would therefore have been associated with a greater cost.

We only found one economic evaluation that included sucroferric oxyhydroxide; it compared sucroferric oxyhydroxide versus sevelamer carbonate in people assumed to be intolerant to calcium-based phosphate binders in a Scottish setting (Gutzwiller et al., 2015). The investigators found sevelamer carbonate to be more effective and more costly than sucroferric oxyhydroxide, with sucroferric oxyhydroxide falling into the southwest quadrant of the cost-effectiveness plane (ICER £187,920 per QALY gained). This is in contrast to our results, in which we find sucroferric oxyhydroxide to be more effective but more expensive than sevelamer carbonate. If we assume the initial binder is calcium carbonate, the ICER for sucroferric oxyhydroxide followed versus sevelamer carbonate is £36,171 per QALY gained, while if we assume the initial binder is calcium acetate, the analogous ICER is £33,293 per QALY gained. The discrepancy in cost can be explained by the recent emergence of generic sevelamer carbonate.

Conclusions

When first- and second-line binder options are taken into account, the base-case economic model results suggest that calcium acetate is likely to be the preferred first-line phosphate binder for the management of hyperphosphataemia in people with CKD stage 5 who are on dialysis. If people experience hypercalcaemia, the most cost-effective strategy is to switch them to sevelamer carbonate. If sevelamer carbonate is not an option, sucroferric oxyhydroxide may provide a cost-effective alternative.

Systematic review of prognostic studies

Methods

We performed a systematic review of prognostic studies assessing the relationship between serum phosphate and serum calcium and the following: death, cardiovascular events, fractures, kidney failure and parathyroidectomy in people with CKD. This systematic review is an update of a review performed previously for CG157 (NICE, 2013). Here we report the 2 reviews together, noting any variations in methods. The review adheres to the methods stipulated in the NICE guideline development manual (NICE, 2018a).

Inclusion and exclusion criteria

Studies were included or excluded from the reviews according to the criteria listed in Table 70.

Table 70: Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	• CKD 4 pre-dialysis • CKD 5 pre-dialysis • CKD 5 on dialysis	• CKD stage 1–3 • CKD-free • Kidney transplant recipient
Prognostic factor	• Serum phosphate • Serum calcium	• Surrogate of a surrogate • Not serum phosphate and serum calcium
Outcome	• All-cause mortality • Cardiovascular events • Kidney failure • Secondary hyperthyroidism • Fractures	• Not all-cause mortality, hyperthyroidism, kidney failure, cardiovascular events, or fractures
Study design	• Retrospective cohort • Prospective cohort	• Case-report and case-series • Case-control • RCTs • Review articles • Commentaries and editorials
Analysis	• Multivariable time-to-event analysis • Control for phosphate in calcium models, and vice versa.	• Multivariate regression analysis • Univariate analysis • Did not control for phosphate in calcium models, and vice versa.
Measure of effect	• Hazard Ratios	• Relative risks • Odds ratios
Others	• Written or published in English	• Not written or published in English

CKD: Chronic kidney disease; RCT: Randomised controlled trial.

Search strategy

We used the same search strategy as the original review (see Table 80 for an example search strategy). Electronic databases were searched by an information specialist. Bibliographies of articles were also searched.

Identification of studies

Abstracts returned by the search strategy were examined by a single researcher and screened for inclusion or exclusion using 'EPPI-reviewer 5'. Full texts were obtained and

assessed for inclusion or exclusion. Articles that did not clearly meet the inclusion and exclusion criteria were included or excluded after discussion with a senior researcher.

Quality appraisal

To be consistent with the work undertaken for CG157, we used the Quality in Prognosis Studies (QUIPS) tool methodology checklist for prognostic studies. The most recent version of the manual recommends the use of the Prediction model Risk Of Bias Assessment Tool (PROBAST); however, to employ this tool, studies included in the CG157 prognostic review had to be reassessed, which was not possible within the timeframe of the project.

Data extraction

We extracted information on the type of study design, participants, prognostic factor (exposure), measure of effect, type of analysis, and covariates, together with the outcomes of mortality, cardiovascular events, kidney failure, and parathyroidectomy. We extracted the sample size, and the adjusted hazard ratio or relative risk per unit baseline serum levels of phosphate and calcium (1 mg/dL) where both biochemical markers were reported and analysed in the same multivariable model. In instances where the hazard ratios were reported for ranges (categories with upper and lower bounds) of serum phosphate and serum calcium exposure, we assigned the midpoint of each range, as the exposure (level of serum phosphorous) that corresponds to the reported relative risk as described in the study by Palmer et al. (2011).

We did not conduct a meta-analysis because it would be inappropriate to pool estimates from various multivariable models which have adjusted for different variables. Instead, we appraised the evidence systematically and, with input from the committee, selected the most appropriate study(s): ones with a population that most closely matches that of the UK, that report data in the most useful way, or that are the most powerful (based on sample size and number of events).

Results

The searches for CG157 conducted in 2012 returned 1699 separate references. From the screening of abstracts, 1554 were excluded, leaving 145 potentially relevant studies to be reviewed in full. After examining the full texts, 109 papers were excluded, and a total of 36 studies were included for the review (Figure 84).

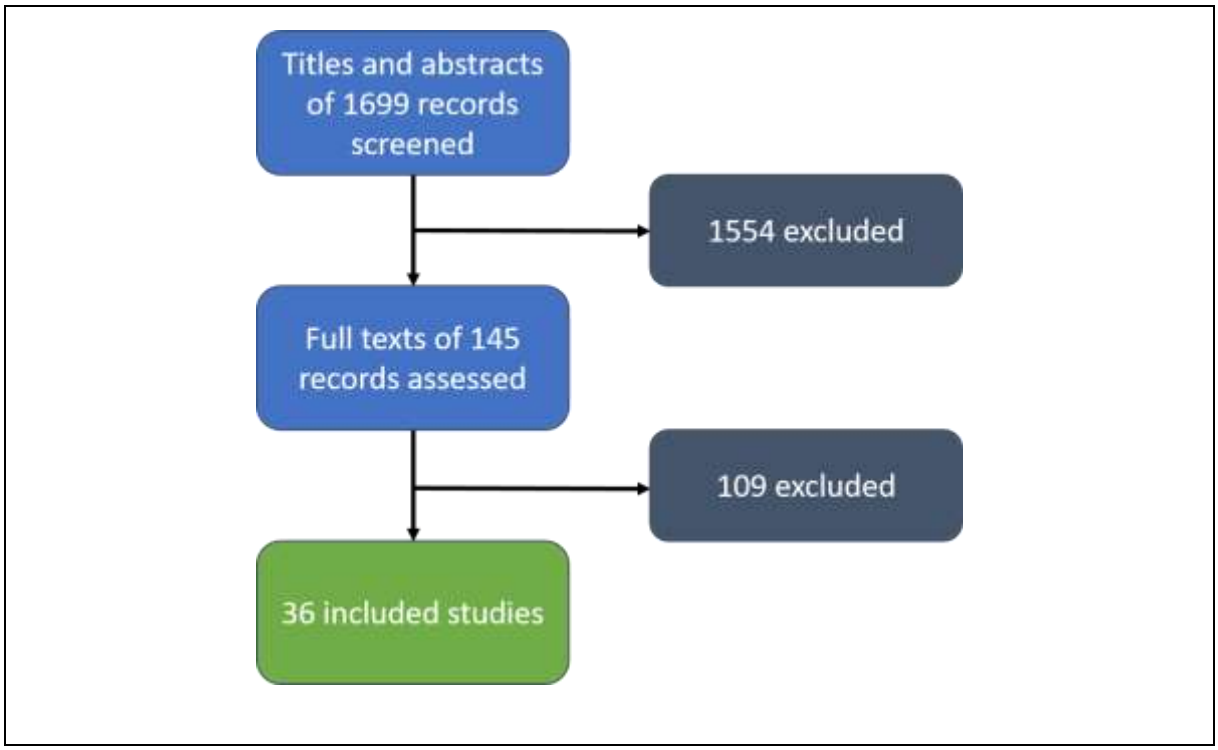


Figure 84: PRISMA diaram for CG157

The searches for the current update conducted in 2019 identified 2420 citations (2414 from the electronic searches); of these 625 duplicates were excluded. From title and abstract screening, 1756 citations were excluded, leaving 39 studies to be retrieved for full-text review. After examining the full texts, 9 studies were included (Figure 85).

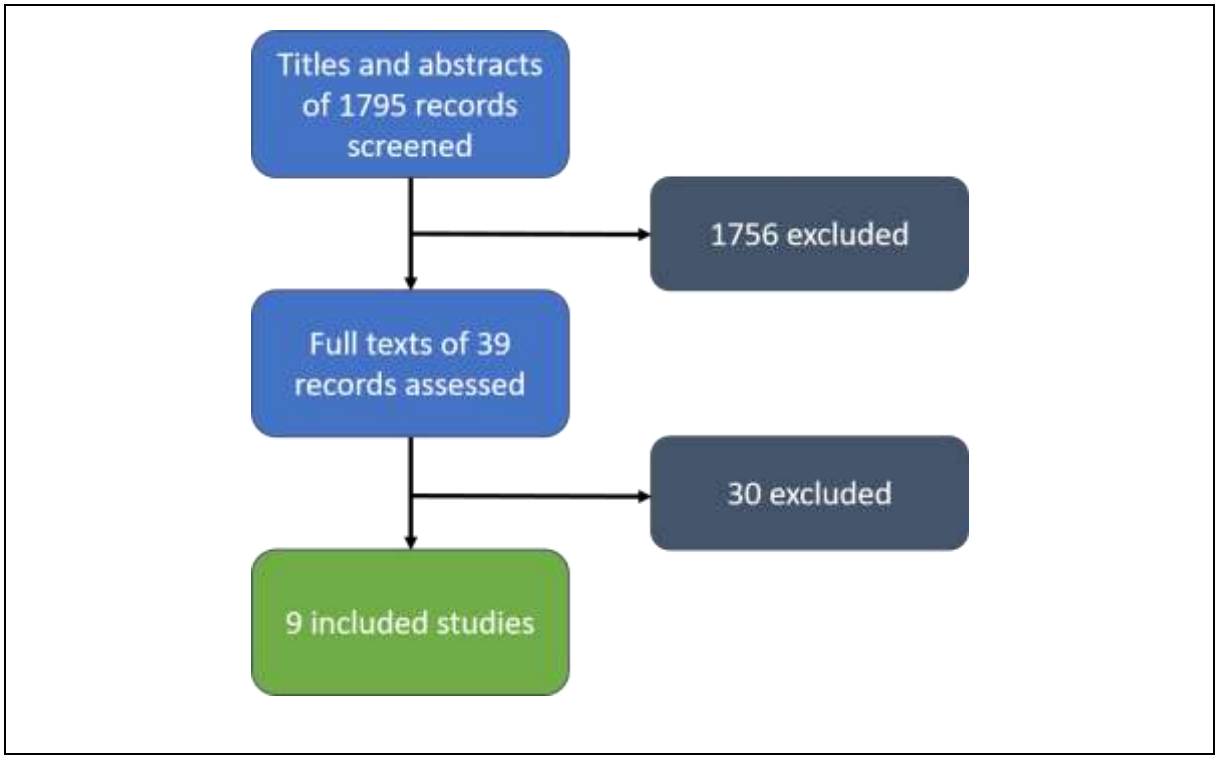


Figure 85: PRISMA diaram for updated review

Results and characteristics of the included studies from both the CG157 review and the update are summarised in Table 71 to Table 79 below.

Table 71: Relative risk of death (all cause) predicted by PO4– and Ca2+ in CKD stage 5 on dialysis

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Abe M (2019)	8954	1.23 (1.05–1.45)			1.15 (0.88–1.49)		
Block GA (1998)	6407	1.06 (1.06–1.06)	1.1–4.5 4.4–5.5 5.6–6.5 6.6–7.8 7.9–16.9	1.0 (0.87–1.13) 1. (Ref) 1.02 (0.88–1.18) 1.18 (1.02–1.38) 1.39 (1.20–1.61)		3.7–8.6 8.7–9.1 9.2–9.5 9.6–10.1 10.2–17.5	0.96 (0.75–1.18) 1.05 (0.87–1.23) 1 (Ref) 0.95 (0.75–1.10) 0.91 (0.71–1.10)
Block GA (2004)	40538		<3 3–4 4–5 5–6 6–7 7–8 8–9 >9	1.10 (0.98–1.24) 1.00 (0.93–1.08) 1.00 (ref) 1.07 (1.01–1.14) 1.26 (1.18–1.33) 1.43 (1.32–1.54) 1.68 (1.52–1.86) 2.02 (1.79–2.27)		<8 8.0–8.5 8.5–9.0 9.0–9.5 9.5–10.0 10.0–10.5 10.5–11.0 >11	0.72 (0.66–0.78) 0.80 (0.75–0.86) 0.89 (0.84–0.94) 1.00 (ref) 1.06 (0.99–1.13) 1.15 (1.06–1.24) 1.27 (1.13–1.42) 1.41 (1.17–1.70)
Block GA (2004)	19186		<3 3–5 5–6 6–7 7–8 >8	1.06 (0.85–1.33) 1 (Ref) 1.07 (0.98–1.16) 1.15 (1.04–1.27) 1.23 (1.07–1.41) 1.44 (1.25–1.66)		<9.0 9.0–10.2 >10.2	0.94 (0.80–1.10) 1 (Ref) 1.14 (1.04–1.24)
Bradbury BD (2007)	4802	0.99 (0.95–1.04)	<3.5 3.5–5.5 >5.5	1.34 (1.05–1.70) 1 (Ref) 1.15 (0.96–1.36)	1.16 (1.07–1.26)	<8.4 8.4–9.5 >9.5	0.85 (0.66–1.09) 1 (Ref) 1.18 (1.05–1.57)
Danese MD (2008)	22937		3.5–5.5 >5.5	1 (Ref)[a] 1.20 (1.10–1.30)[b]		8.4–9.5 >9.5	1 (Ref)[c] 1.21 (1.13–34)[d]

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Fernandez-Martin JL (2015)	6307		<3.6 3.6–5.2 >5.2	1.34 (1.13–1.59) 1 (Ref) 1.34 (1.18–1.53)		<7.9 7.9–9.5 >9.5	1.13 (0.87–1.46) 1 (Ref) 1.32 (1.14–1.52)
Floege J (2011)	7970		<3.5 3.5–5.5 5.5	1.18 (1.01–1.37) 1.0 (Ref) 1.32 (1.13–1.55)		<8.4 8.4–9.5 9.5–11.0 >11.0	0.98 (0.83–1.16) 1.00 (Ref) 1.05 (0.90–1.22) 1.70 (1.19–2.42)
Foley RN (1996)	433		<6.0 >6.0	1 (Ref) 0.96		<8 >8	1.74 1 (Ref)
Iseki K (1996)	1982	0.97				1.068	
Jadoul M (2007)	538		≤4.5 >4.5	1.00 (Ref) 1.11		≤9.5 >9.5	1.00 (Ref) 1.16
Kalantar-Zadeh K (2006)	58058		<3 3.0–3.99 4.0–4.99 5.0–5.99 6.0–6.99 7.0–7.99 8.0–8.99 >9	1.3 (1.2–1.6) 0.90 (0.70–1.10) 0.95 (0.8–1.20) 1 (Ref) 1.25 (1.15–1.35) 1.35 (1.25–1.45) 1.5 (1.1.3–1.7) 1.9 (1.55–2.25)		<8 8.0–8.49 8.5–8.99 9.0–9.49 9.5–9.99 10.0–10.49 10.5–10.99 >11.0	0.99 (0.85–1.13) 0.90 (0.84–0.96) 0.92 (0.88–0.96) 1 (Ref) 1.04 (0.99–1.09) 1.10 (1.05–1.15) 1.30 (1.20–1.40) 1.38 (1.22–1.54)
Kim Y (2018)	21433		≤ 3.59 3.60–4.39 4.40–5.10 5.11–6.10 ≥ 6.11	1.239 (1.077–1.43) 1.073 (0.927–1.24) 1 (Ref) 1.01 (0.87–1.18) 1.04 (0.88–1.24)		≤ 8.40 8.41–8.80 8.81–9.14 9.15–9.60 ≥ 9.61	0.84 (0.71–0.99) 0.89 (0.76–1.03) 1 (Ref) 1.04 (0.89–1.20) 1.39 (1.20–1.61)
Kimata N (2007)	5041	1.00 (0.94–1.07)	<3.5 3.5–4.5	1.61 1.21	1.22 (1.09–1.36)	<8.4 8.4–9.0	0.90 1.00 (Ref)

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
			4.5–5.5	1.0 (Ref)		9.0–9.5	0.98
			5.5–6.5	1.05		9.5–10.4	1.12
			>6.5	1.33		>10.4	1.53
Lacson E Jr (2009)	78420	1.18 (1.13–1.23)	≤3.5	0.80	1.14 (1.11–1.18)	≤8.0	0.80
			3.51–4.0	0.75		8.01–8.5	0.85
			4.01–4.5	0.74		8.51–9.0	1.0
			4.51–5.0	0.80		9.01–9.5	1.0 (Ref)
			5.01–5.5	1 (Ref)		9.51–10.0	1.10
			5.51–6.0	1.10		10.01–10.5	1.25
			6.01–6.5	1.30		10.51–11	1.30
			6.51–7.0	1.40		>11	1.40
			7.01–7.5	1.50			
			7.51–8.0	1.50			
			8.01–8.5	2.00			
			8.51–9.5	2.00			
			>9.5	2.70			
Li D (2017) [e]	8530		<1.13	1.18 (0.98–1.41)		<2.1	1.51 (1.34–1.70)
			1.13–1.45	1 (Ref)		2.1–2.5	1 (Ref)
			1.45–1.78	0.86 (0.72–1.02)		2.5–2.75	0.65 (0.53–0.81)
			>1.78	0.69 (0.76–1.03)		>2.75	0.65 (0.46–0.92)
Liu CT (2017)	12116		<3.5	1.21 (1.09–1.35)		<8.5	1.06 (0.95–1.18)
			3.5–5.5	1 (Ref)		8.5–9.5	1 (Ref)
			5.5–6.5	0.98 (0.87–1.09)		9.5–10.5	1.11 (1.01–1.22)
			6.5–7.5	1.19 (1.04–1.37)		≥ 10.5	1.36 (1.18–1.56)
			7.5–8.5	1.47 (1.22–1.77)			
			≥ 8.5	1.43 (1.10–1.86)			
Lowrie EG (1992)	13535		<2	2.40		<6	0.45

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
			2–3 3–5 5–7 7–9 9–11 >11	1.60 0.80 1 (Ref) 1.50 2.40 3.70		6–7 7–8 8–9 9–10 10–12 >12	0.60 0.80 0.75 1 (Ref) 1.3 3.25
Maeno Y (2009)	635	1.43 (0.88–2.33)			1.07 (0.32–3.58)		
Matos JP (2011)	3082	1.06 (1.00–1.12)			1.03 (0.97–1.10)		
Melamed ML (2006)	1007		<4.3 4.3–5.1 5.1–6.0 >6.0	1.04 (0.70–1.53) 1.0 (Ref) 1.01 (0.69–1.47) 1.54 (1.01–2.53)		<8.97 8.97–9.33 9.33–9.73 >9.73	0.92 (0.60–1.39) 1.0 (Ref) 1.13 (0.78–1.64) 1.05 (0.69–1.62)
Nakai S (2008)	27404	1.08 (1.06–1.10)	<3 3.0–3.9 4.0–4.9 5.0–5.9 6.0–6.9 7.0–7.9 8.0–8.9 >9	1.142 (0.990–1.316) 1.102 (0.999–1.215) 1.000 (Ref) 1.105 (1.017–1.202) 1.172 (1.065–1.289) 1.425 (1.265–1.605) 1.893 (1.620–2.213) 1.985 (1.621–2.432)	1.05 (1.02–1.08)	<7 7.0–7.9 8.0–8.9 9.0–9.9 10.0–10.9 >10	1.008 (0.835–1.217) 1.067 (0.879–1.296) 0.992 (0.916–1.074) 1.000 (Ref) 1.098 (1.020–1.182) 1.243 (1.113–1.388)
Naves-Diaz M (2011)	16173		<3 3.0–4.0 4.0–5.0 5.0–5.5 5.5–6.5 6.5–7.5 >7.5	1.70 (0.90–2.50) 1.25 (0.95–1.25) 1.15 (0.95–1.35) 1 (Ref) 1.30 (1.09–1.51) 1.04 (1.05–1.75) 2.30 (1.30–3.30)		<8.0 8.5–9.0 9.0–9.5 9.5–10.5 10.5–11 >11	3.9 (2.06–5.20) 1.6 (1.40–1.80) 1.30 (1.10–1.50) 1 (Ref) 1.35 (1.10–1.60) 1.75 (1.25–2.25)

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Noordzij M (2005)	1629		HD			HD	
			<3.5	0.7 (0.5–1.1)		<8.4	1.3 (0.7–2.4)
			3.5–5.5	1.0 (Ref)		8.4–9.5	1.0 (Ref)
			>5.5	1.4 (1.1–1.7)		>9.5	1.0 (0.8–1.4)
			PD			PD	
			<3.5	0.8 (0.4–1.7)		<8.4	1.4 (0.5–4.2)
			3.5–5.5	1.0 (Ref)		8.4–9.5	1.0 (Ref)
			>5.5	1.6 (1.1–2.4)		>9.5	0.9 (0.6–1.4)
Ossareh S (2016)	560		<3.5	3.16 (2.06–4.85)		<8.4	1.53 (1.10–2.13)
			3.5–5.5	1 (Ref)		8.4–9.5	1 (Ref)
			>5.5	1.38 (1.02–1.86)		>9.5	1.35 (0.95–1.92)
Rodriguez-Benot A (2005)	385	1.26 (1.08–1.46)	<3	0.41 (0.05–3.17)	0.96 (0.93–0.99)		
			3–5	1 (Ref)			
			5.01–6.5	1.94 (1.17–3.19)			
			>6.5	2.02 (1.10–3.73)			
Slinin Y (2005)	14829		≤4.4	1 (Ref)		≤8.7	1 (Ref)
			4.5–5.3	1.02 (0.96–1.09)		8.8–9.2	1.07 (1.01–1.14)
			5.4–6.3	1.02 (0.96–1.08)		9.3–9.6	1.05 (0.99–1.12)
			6.4–7.5	1.10 (1.04–1.17)		9.7–10.2	1.11 (1.04–1.18)
			>7.5	1.19 (1.12–1.27)		>10.2	1.14 (1.07–1.21)
Soleymanian T (2017)	532	0.95 (0.83–1.08)			0.94 (0.76–1.16)		
Stevens LA (2004)	515	1.56 (1.15–2.12)	<5.5	1 (Ref)	1.35 (0.61–2.98)	<10	1 (Ref)
			5.5–6.0	1.32 (0.79–2.22)		10.0–10.2	1.15 (0.62–2.13)
			6.0–7.0	1.53 (1.02–2.30)		10.2–10.6	0.98 (0.52–1.82)
			>7.0	1.82 (1.16–2.84)		>10.6	1.33 (0.79–2.25)
Tangri N (2011)	7076		<3.5	0.74 (0.53–1.03)		<8.4	1.35 (0.24–7.56)
			3.5–5.5	1 (Ref)		8.4–9.5	1 (Ref)

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
			5.5–6.5 6.5–7.5 >7.5	1.17 (0.94–1.46) 1.42 (1.06–1.90) 1.64 (1.02–2.63)		9.5–10.4 >10.4	1.13 (0.83–1.53) 1.35 (0.93–1.65)
Tentori F (2008)	25588		<3.6 3.6–5.0 5.1–6.0 6.1–7.0 >7.0	1.06 (0.94–1.10) 1 (Ref) 1.02 (0.94–1.01) 1.18 (1.08–1.28) 1.43 (1.32–1.56)		<8.6 8.6–10.0 >10.0	1.02 (0.94–1.10) 1 (Ref) 1.16 (1.08–1.25
Wald R (2008)	1846		≤3 3.1–4.0 4.1–5.0 5.1–6.0 >6	0.98 (0.71–1.36) 1.07 (0.84–1.35) 1 (Ref) 1.04 (0.84–1.28) 1.24 (1.03–1.51)		≤8 8.1–9.0 9.1–10.0 10.1–11.0 >11	1.09 (0.83–1.44) 1.04 (0.88–1.23) 1 (Ref) 0.96 (0.79–1.16) 1.15 (0.84–1.56)
Wu M (2019)[e]	1662	1.20 (1.12–1.29)	<1.13 1.13–1.78 >1.78	0.83 (0.62–1.12) 1 (Ref) 1.818 (1.38–2.40)	0.86 (0.75–0.98)	<2.10 2.10–2.37 >2.37	1.13 (0.85–1.51) 1 (Ref) 0.76 (0.530–1.095)
Young EW (2005)	17236	1.04 (1.02–1.06)	<2.5 2.5–3.0 3.0–3.5 3.5–4.0 4.0–4.5 4.5–5.0 5.0–5.5 5.5–6.0 6.0–6.5 6.5–7.0 >7.0	1.6 1.2 1.23 1.08 1.01 1 (Ref) 1.12 1.06 1.15 1.28 1.35	1.10 (1.06–1.15)	<7.8 7.8–8.4 8.4–9.0 9.0–9.5 9.5–9.9 9.9–10.4 10.4–10.9 10.9–11.4 >11.4	0.66 1.04 0.98 1 (Ref) 1.03 1.11 1.14 1.18 1.22

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Zhu JG (2018)	1126		<2.0	1.99 (0.86–4.61)		<7.0	1.45 (0.19–11.0)
			2.0–2.5	1.38 (0.64–2.99)		7.0–7.9	1.27 (0.71–2.27)
			2.5–4.5	1 (Ref)		7.9–9.9	1 (Ref)
			4.5–5.0	1.03 (0.63–1.68)		9.9–10.9	1.07 (0.72–1.58)
			5.0–6.0	1.24 (0.85–1.82)		10.9–11.9	1.41 (0.65–3.03)
			6.0–7.0	0.75 (0.45–1.27)		>11.9	15.8 (1.79–138)
			7.0–8.0	1.02 (0.52–2.02)			
			8.0–9.0	1.4 (0.49–3.97)			
			>9.0	1.07 (0.14–8.33)			

a. KDOQI recommended target for serum phosphate.
b. Hazard ratio for serum phosphate outside KDOQI target.
c. KDOQI recommended target for serum calcium.
d. Hazard ratio for serum calcium outside KDOQI target.
e. Serum calcium and serum phosphate hazard ratios are per 1 mmol/L.

Table 72: Relative risk of death (all cause) predicted by PO4– and Ca2+ in CKD stages 4 and 5 pre-dialysis

Study (year)	n	Phosphate			Calcium	
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical
Bellasi A (2011)	1716		<3.3 3.3–3.7 3.8–4.2 >4.2	0.47 (0.43–1.28) 1 (Ref) 0.64 (0.36–1.14) 2.49 (1.44–4.32)	1.01 (0.78–1.31)	
Kestenbaum B (2006)	6730	1.23 (1.12–1.36)	<2.5 2.5–2.999 3.0–3.499 3.5–3.999 4.0–4.499 4.5–4.999 >5.0	0.95 (0.69–1.32) 1 (Ref) 1.15 (0.95–1.39) 1.32 (1.09–1.61) 1.34 (1.05–1.71) 1.83 (1.33–2.51) 1.90 (1.30–2.79)	1.02 (0.90–1.16)	
Kovesdy CP (2008)	515	1.65 (1.30–2.09) per standard deviation			1.10 (0.89–1.35) per standard deviation	
Levin A (2008)	4231	1.02 (1.01–1.04)			NS; variable eliminated from final model	
Voormolen N (2007)	448	1.62 (1.02–2.58)			1.32 (0.69–2.52)	

Table 73: Relative risk of Parathyroidectomy predicted by PO4– and Ca2+ in CKD–5D

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Jorna FH (2004)	202	1.107[a] (1.035–1.184)	≤5.73[b] >5.73[b]	1 (Ref) 2.63 (1.22–5.26)		≤9.86[c] >9.86[c]	1 (Ref) 3.23 (1.19–8.23)
Slinin Y (2007)	10588		≤4.4 4.5–5.3 5.4–6.3 6.4–7.5 >7.5	1 (Ref) 1.34 (0.89–2.01) 2.07 (1.43–2.98) 2.17 (1.52–3.11) 2.92 (2.06–4.15)		≤8.7 8.8–9.2 9.3–9.6 9.7–10.3 >10.3	1 (Ref) 1.73 (1.20–2.49) 2.60 (1.84–3.66) 3.38 (2.41–4.73) 5.09 (3.64–7.10)
Young EW (2005)	17236	1.17 (1.09–1.25)			1.58 (1.35–1.85)		

[a] *Hazard ratio per 0.1 mmol/L increase.*
[b] *converted from mmol/L to mg/dl using conversion factor of (*3.0974).*
[c] *converted from mmol/L to mg/dl using conversion factor of (*4.008).*

Table 74: Relative risk of end-stage renal failure predicted by PO4– and Ca2+ in CKD stages 4 and 5 pre-dialysis

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Levin A (2008)	4231	1.019[a] (1.010–1.029)			NS; excluded from final model		
Schwarz S (2006)	985	1.29 (1.12–1.48)	<3.3 3.3–3.8 3.81–4.3 >4.3	1 (Ref) 0.83 (0.54–1.27) 1.24 (0.82–1.88) 1.60 (1.06–2.41)	0.80 (0.63–1.02)	<9.1 9.1–9.4 9.41–9.7 >9.7	1 (Ref) 0.88 (0.61–1.25) 0.89 (0.62–1.68) 0.80 (0.63–1.02)
Staples AO (2010)	4166		Normal[b] High[b]	1 (Ref) 1.41 (1.25–1.59)		<8.5 ≥8.5	1.29 (1.06–1.58) 1 (Ref)
Tangri N (2011)	8391	1.34 (CI not provided)			0.82 (CI not provided)		
Bellasi A (2011)	1716		<3.3 3.3–3.7	0.61 (0.30–1.24) 1 (Ref)	0.75 (0.61–0.92)		

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
			3.8–4.2 1.36 (0.84–2.18) >4.2 2.88 (1.77–4.67)		

[a] *per 0.1mg/dl increase.*
[b] *the definition of hyperphosphataemia was adjusted for age as follows: ≥6.5mg/dl for 2 to 5 years; ≥5.8 for 6 to 12 years; ≥4.5 for 13 to 20 years.*

Table 75: Relative risk of fractures predicted by PO4– and Ca2+ (both CKD populations)

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Block GA (2004)	40538	1.12 (1.03–1.22)			

Table 76: Relative risk of a cardiac event predicted by PO4– and Ca2+ (CKD stage 5 on dialysis)

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Block GA (2004)	40538		4–5 1 (Ref) 5–6 1.10 6–7 1.15 7–8 1.29 8–9 1.28 >9 1.38		
Foley RN (1996)	433				New IHD[a] 4.33[b] Recurrent IHD[a] 7.05[b] New CF[c] 2.43[b] Recurrent CF[c] 2.66[b]

Study (year)	n	Phosphate			Calcium		
		Continuous (per mg/dl)	Categorical		Continuous (per mg/dl)	Categorical	
Wald R (2008)	1846		Reported composite endpoint of all-cause death and first cardiac hospitalisation				
Slinin Y (2005)	14829		≤4.4	1 (Ref)		≤8.7	1 (Ref)
			4.5–5.3	1.06 (1.00–1.13)		8.8–9.2	1.03 (0.97–1.09)
			5.4–6.3	1.13 (1.06–1.19)		9.3–9.6	1.04 (0.97–1.10)
			6.4–7.7	1.14 (1.07–1.22)		9.7–10.2	1.03 (0.97–1.10)
			>7.5	1.25 (1.17–1.33)		>10.2	1.08 (1.01–1.15)

[a] *Ischemic Heart Disease.*
[b] *Relative risk of death associated with calcium ≤8.8mg/dl compared with calcium >8.8.*
[c] *cardiac failure.*

Table 77: Relative risk of a cardiac event predicted by PO4– and Ca2+ (CKD stages 4 and 5 pre-dialysis)

Study (year)	n	Phosphate		Calcium	
		Continuous (per mg/dl)	Categorical	Continuous (per mg/dl)	Categorical
Kestenbaum B (2006)	6730	1.35 (1.09–1.67)			

Table 78: Prognostic studies CKD stage 5 on dialysis

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Abe M (2019)	Japan	8954	Retrospective Cohort	2	Cox proportional hazards regression analysis	Nationwide surveys, conducted by the Japanese Society for Dialysis Therapy (JSDT), of patients on dialysis.	Y	Y[a]	?	Y	Y	Y
Block GA (1998)	USA	6407	Retrospective cohort	2	Cox proportional hazards model	Data was obtained from 2 USRDS (US Renal Data System) special studies; the CMAS (Case mix Adequacy Studies) and the DMMS (Dialysis Morbidity and Mortality Study) wave 1. Both studies represent a random national sample of prevalent HD patients in the US	Y	N	Y	Y	Y	Y
Block GA (2004)	USA	40538	Retrospective cohort	2	Cox proportional hazards model	Sample taken from the Fresenius Medical Care North America Patient Statistical Profile system	Y	?	Y	Y	Y	Y
Block GA (2004)	USA	19186	Retrospective cohort	2	Time dependent cox proportional hazards	Data from DaVita (a large dialysis provider) were merged with data from the USRDS	Y	?	Y	Y	Y	Y
Bradbury BD (2007)	USA	4802	Retrospective cohort using incident cases	not stated (study lasted for 8 years)	Cox proportional hazards	Data from DOPPS phase 1 and 2	?	Y	N	Y	Y	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Danese MD (2008)	USA	22937	Retrospective cohort using incident cases	2	Time dependent cox proportional hazards	Fresenius Medicare database Lexington MA	Y	?	Y	Y	Y	Y
Fernandez-Martin JL (2015)	Europe	6,307	Prospective Cohort	3	Time dependent cox proportional hazards model	Patients enrolled from 227 dialysis centres from 20 European countries.	?	Y	?	Y	Y	Y
Floege J (2011)	12 European countries including UK	7970	Retrospective cohort	2	Baseline and time dependent cox proportional hazards	Data obtained from participating European Fresenius medical care (EU-FME) dialysis facilities from 11 countries including the UK	Y	?	?	Y	Y	Y
Foley RN (1996)	Canada	433	Prospective cohort	3.5	Cox proportional hazards model	Patients enrolled from 2 hospitals in Canada	Y	?	?	Y	Y	Y
Iseki K (1996)	Japan	1982	Retrospective cohort	not stated (data collected over a period of 20 years)	Cox proportional hazards model	Data obtained from OKIDS registry in japan	Y	?	?	Y	N	Y
Jadoul M (2007)	Belgium	538	Retrospective analysis of DOPPS phase 2 data	2	Cox proportional hazards model	Data obtained from DOPPS 2 study	Y	?	?	?	N	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Jorna FH (2004)	Netherlands	202	Retrospective cohort	3.5	Cox proportional hazards model	Data obtained from a dialysis centre in the Netherlands	Y	?	?	Y	Y	Y
Kalantar-Zadeh K (2006)	USA	58058	Retrospective cohort	2	Time dependent and fixed covariate cox regression models	Obtained historical data on all HD patients from all DaVita dialysis facilities in the US	Y	?	Y	Y	Y	Y
Kim Y (2018)	Korea	21,433	Retrospective Cohort	5.25	Cox proportional hazards model	The nationwide Korean Society of Nephrology (KSN) ESRD Registry.	Y	Y[a]	?	Y	Y	Y
Kimata N (2007)	Japan	5041	Prospective cohort	5	Cox proportional hazards model	Data derived from 2 studies; the phase 1 and phase 2 DOPPS	Y	?	?	Y	Y	Y
Lacson E Jr (2009)	USA	78420	Retrospective cohort	1	Cox proportional hazards model	Data obtained from the knowledge centre (Fresenius medical care)	Y	?	Y	Y	Y	Y
Li D (2017)	China	8,530	Retrospective Cohort	5.8	Kaplan–Meir, Cox proportional and competing risk regression analysis	The Beijing Hemodialysis Quality Control and Improvement Center (BJHDQCIC)	Y	Y[a]	?	Y	N	Y
Liu CT (2017)	Taiwan	12,116	Retrospective Cohort	8	Kaplan–Meir and Cox proportional regression model	The Taiwan Renal Registry Data System (TWRDS)	Y	Y[a]	?	Y	Y	Y
Lowrie EG (1992)	USA	13535	Retrospective analysis of previously published data	1	Logistic regression models	Sample consisted of patients on HD from National medical care affiliated dialysis facilities in 1989	Y	?	?	Y	N	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Maeno Y (2009)	Japan	635	Prospective cohort	4.5	Kaplan–Meir and cox proportional hazard models	Participants sampled from a hospital kidney centre in Japan	Y	Y	Y	Y	Y	Y
Matos JP (2011)	Brazil	3082	Retrospective cohort	5	Kaplan–Meir and cox proportional hazard models	All incident patients on HD at all centres franchised by Fresenius medical care in Brazil	Y	?	?	Y	Y	Y
Melamed ML (2006)	USA	1007	Prospective cohort	2.5	Cox proportional hazards model	HD and PD patients from the CHOICE (choices for healthy outcomes in caring for ESRD)	Y	?	?	Y	Y	Y
Nakai S (2008)	Japan	27404	Retrospective cohort	3	Cox proportional hazards model	Data obtained from the Japanese society for dialysis therapy registry	Y	?	?	Y	Y	Y
Naves-Diaz M (2011)	Argentina, Brazil, Colombia, Argentina, Chile, Mexico and Venezuela	16173	Retrospective cohort	1.3	Cox proportional hazards model	Data from 6 Latin American countries in 183 different dialysis facilities associated with or operated by Fresenius medical care in the CORES study	Y	?	?	Y	Y	Y
Noordzij M (2005)	Netherlands	1629	Prospective multicentre cohort	7	Multivariate cox regression models	All incident patients in 38 dialysis units in the NECOSAD (Netherlands cooperative study on the adequacy of dialysis) study, Netherlands	Y	?	Y	Y	Y	Y
Ossareh S (2016)	Iran	560	Retrospective Cohort	9	TD Cox proportional hazards	Hasheminejad Kidney Centre.	Y	?	Y	Y	Y	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Rodriguez-Benot A (2005)	Spain	385	Prospective cohort	11	Cox proportional hazards model	Patients were recruited from HD centres participating in a dialysis program (specific details not provided) over 11 years. Mean FU and number of centres not provided	Y	?	Y	Y	Y	Y
Slinin Y (2005)	USA	14829	Retrospective cohort	3.9	Cox regression	Data was obtained from the USRDS waves 1, 2, 3 and 4 studies (Dialysis morbidity and mortality study) a historical cohort study of dialysis patients from over 1300 randomly sampled dialysis units in the US	Y	?	?	Y	Y	Y
Slinin Y (2007)	USA	10588	Retrospective cohort	3.6	Cox regression	Data was obtained from the USRDS waves 1, 2, 3 and 4 above was linked to Medicare claims data to identify associations of parathyroidectomy. Patients without a unique USRDS ID number or DOB, or who died before the study start date or were not covered by Medicare insurance were further excluded from the initial sample of 16,733	Y	Y	N	Y	Y	Y
Soleymanian T (2017)	Iran	532	Prospective Cohort	2.5	Cox proportional hazards model	HD patients enrolled from 9 haemodialysis facilities.	Y	Y	Y	Y	Y	Y
Stevens LA (2004)	Canada	515	Retrospective cohort	2.6	Cox proportional hazards model	Data obtained from the British Columbia renal agency provincial database – PROMIS (patient registration, outcome and management information system) –	Y	Y	Y	Y	Y	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
						which is routinely collected for administration purposes						
Tangri N (2011)	UK	7076	Retrospective cohort	2	cox proportional hazards model	UK renal registry	Y	?	Y	Y	Y	Y
Tentori F (2008)	UK, France, Germany, Japan, USA, Spain, Italy, Australia, Canada, New Zealand, Belgium, Sweden	25588	Prospective cohort	1.4	Cox proportional hazards model	Used data from DOPPS 1, 2 and 3 from a total of 12 countries	Y	?	Y	Y	Y	Y
Wald R (2008)	USA	1846	Retrospective cohort	4.48	Cox proportional hazard model exploring baseline–time dependent and cumulative time dependent associations of biochemical markers	Used data from the HEMO study (RCT)	Y	?	?	Y	Y	Y
Wu M (2019)	China	1,662	Retrospective Cohort	7	Cox proportional hazards model	Records of PD patients at The First Affiliated Hospital, Sun Yat-sen University	Y	Y	Y	Y	Y	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Young EW (2005)	UK, France, Germany, Italy, Spain, USA and Japan	17236	Prospective cohort	variable	Cox proportional hazards model	Study conducted as part of DOPPS 1 which comprised of participants from randomly selected representative samples of haemodialysis facilities across 7 countries: UK, USA, Japan, France, Germany, Italy and Spain	Y	?	Y	Y	Y	Y
Zhu JG (2018)	Taiwan	1,126	Retrospective Cohort	5	Cox proportional hazards models (TA and TD).	Records of outpatient HD patients at Kaohsiung Chang Gung Memorial Hospital	Y	Y[a]	Y	Y	Y	Y

Y = Yes (low risk of bias); N = No (high risk of bias); ? = Unclear (uncertain risk).
FU, follow-up period; N, sample size; TA, Time Average; TD, Time-Dependent; HD, Haemodialysis; PD, Peritoneal dialysis; ESRD, End-stage Renal Disease.
[a] Assessment of 'low risk of bias' based on QUIPS tool seems inappropriate; risk of bias may be higher.

Table 79: Prognostic studies CKD stages 4 and 5 pre-dialysis

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Bellasi A (2011)	Italy	1716	Retrospective cohort	3	Cox proportional hazards model	Data was obtained from the patient records of a large renal database (PIRP) sponsored by the Emilia-Romagna Health Institute, Italy	Y	?	?	Y	?	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
Kestenbaum B (2006)	USA	6730	Retrospective cohort	2.1	Cox proportional hazards model	Data was obtained from 8 veteran affairs medical centres	Y	?	N	Y	Y	Y
Kovesdy CP (2008)	USA	515	Retrospective cohort	2.3	Cox proportional hazards model	Data was obtained from Salem veteran affairs medical centre CA	N	?	?	Y	Y	Y
Levin A (2008)	Canada	4231	Retrospective cohort	4	Cox proportional hazards model	Data was obtained from the patients' registration and outcomes management information system (PROMIS) database, which captures all nephrology referrals	Y	Y	?	Y	Y	Y
Schwarz S (2006)	USA	985	Retrospective cohort	2.1	Cox proportional hazards model	Data was obtained from Salem veteran affairs medical centre CA	Y	?	Y	Y	N	Y
Staples AO (2010)	USA	4166	Retrospective cohort	not stated	Kaplan–Meier analysis and Cox proportional hazards model. In addition, the definition of hyperphosphataemia was adjusted for age as follows: ≥6.5mg/dl for 2 to 5 years; ≥5.8 for 6 to 12 years; ≥4.5 for 13 to 20 years	Data was obtained from the NAPRTCS database; details not provided	Y	?	?	Y	?	Y
Tangri N (2011)	Canada	8391	Prospective cohort	2	Series of 7 Cox proportional hazards models analysed	The 'development' cohort derived from the nephrology clinic electronic health record at Sunnybrook hospital (a part of	Y	?	Y	Y	N	Y

Study (year)	Location	n	Study design	FU (years)	Analysis	Data source	Critical appraisal					
							Participation	Attrition	Factor measurement	Outcome measurement	Confounding	Analysis
					using metrics of discrimination (c-statistic) and goodness of fit (Akaike information criteria – AIC)	the university of Toronto health network). The 'validation' cohort was derived from the British Columbia renal registry (patient registration and outcome management information services)						
Voormolen N (2007)	Netherlands	448	Retrospective cohort	1	Linear regression and Cox proportional hazards regression	Data was obtained from CKD stage 4 and 5 patients attending outpatient clinics of 8 hospitals.	Y	Y	?	Y	N	Y

Y = Yes (low risk of bias); N = No (high risk of bias); ? = Unclear (uncertain risk).
FU, follow-up period; N, sample size; TA, Time Average; TD, Time-Dependent; HD, Haemodialysis; PD, Peritoneal dialysis; ESRD, End-stage Renal Disease.

Table 80: Example of prognostic review strategy

Database: Ovid MEDLINE(R) <1946 to June 27, 2019>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (108155)
2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (68923)
3 ((kidney* or renal*) adj1 insufficien*).tw. (20930)
4 ckd*.tw. (20868)
5 ((kidney* or renal*) adj1 fail*).tw. (84815)
6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (33756)
7 (esrd* or eskd*).tw. (13458)
8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3385)
9 or/1-8 (205327)
10 exp Renal Replacement Therapy/ (197327)
11 (haemodialys* or hemodialys* or dialys* or predialys* or pre-dialys*).tw. (138915)
12 ((kidney* or renal*) adj1 replac*).tw. (10638)
13 or/10-12 (245160)
14 9 or 13 (361468)
15 Hyperphosphatemia/ (1157)
16 hyperphosphat*.tw. (3963)
17 Phosphates/ (61572)
18 (phosphate* or phosphorus).tw. (261105)
19 or/15-18 (288746)
20 exp Risk/ (1134045)
21 exp Regression Analysis/ (403802)
22 hazard ratio*.tw. (84740)
23 (proportional adj3 hazard*).tw. (50212)
24 (relative adj3 risk).tw. (59594)
25 (cox adj3 model*).tw. (42708)
26 (regression or survival).tw. (1279643)
27 exp survival analysis/ (275392)
28 Prognosis/ (475145)
29 prognos*.tw. (479054)
30 or/20-29 (2771233)
31 exp Mortality/ (360954)
32 mortality.tw. (601700)
33 exp Cardiovascular Diseases/mo [Mortality] (129733)
34 exp Death, Sudden, Cardiac/ (14611)
35 Coronary Artery Disease/ (57517)
36 ((Cardiovascular or cv* or cardiac or heart or valvular or coronary) adj3 (disease* or event* or death*)).tw. (421903)
37 (myocardial infarction* or MI or heart attack*).tw. (175711)
38 exp Vascular Calcification/ (3681)
39 (vascular adj3 calcificat*).tw. (3893)
40 exp Fractures, Bone/ (176263)
41 fracture*.tw. (205566)
42 ((time or need or progress* or requir*) adj3 (rrt or renal replacement or dialys* or transplant* or kidney failure* or renal failure*)).tw. (31343)

Database: Ovid MEDLINE(R) <1946 to June 27, 2019>	
43	exp disease progression/ (166207)
44	or/31-43 (1725246)
45	14 and 19 and 30 and 44 (1806)
46	Animals/ not Humans/ (4560694)
47	45 not 46 (1758)
48	limit 47 to english language (1596)
49	limit 48 to ed=20120101-20190701 (784)

Table of parameters

Table 81: Table of parameters

Parameter name	Value (95% CI)	Distribution and parameters	Source
Model settings			
Cycles per year	4		
Discount rate (costs)	3.5%	Not varied in PSA	
Discount rate (benefits)	3.5%	Not varied in PSA	
Maximum serum phosphate target (mmol/l)	1.78	Not varied in PSA	National Kidney Foundation, 2003
Maximum serum calcium target (mmol/l)	2.60	Not varied in PSA	NICE, 2019
Cohort demographics at baseline			
Age	63.8 (63.4, 64.2)	Normal: μ=63.8; σ=0.2	UK Renal Registry, 2019
Sex (% male)	64.2% (63.1%, 65.3%)	Beta: α=4347; β=2424	UK Renal Registry, 2019
Serum phosphate (mmol/l)	2.290	Not varied in PSA	
SD serum phosphate (mmol/l)	0.509	Not varied in PSA	
Serum calcium (mmol/l)	2.320	Not varied in PSA	
SD serum calcium (mmol/l)	0.136	Not varied in PSA	
Baseline model			
Biochemical progression with calcium carbonate:			
Serum phosphate at baseline (mmol/l)	2.290 (2.147, 2.440)	Lognormal: μ=0.828; σ=0.033	Braun et al. 2004
Serum phosphate at 3 months (mmol/l)	1.770 (1.655, 1.890)	Lognormal: μ=0.570; σ=0.034	Braun et al. 2004
Serum phosphate at 6 months (mmol/l)	1.865 (1.722, 2.016)	Lognormal: μ=0.622; σ=0.040	Braun et al. 2004
Serum phosphate at 12 months (mmol/l)	1.700 (1.567, 1.841)	Lognormal: μ=0.530; σ=0.041	Braun et al. 2004
Serum calcium at baseline (mmol/l)	2.320 (2.281, 2.359)	Lognormal: μ=0.842; σ=0.009	Braun et al. 2004
Serum calcium at 3 months (mmol/l)	2.480 (2.422, 2.539)	Lognormal: μ=0.908; σ=0.012	Braun et al. 2004
Serum calcium at 6 months (mmol/l)	2.445 (2.387, 2.504)	Lognormal: μ=0.894; σ=0.012	Braun et al. 2004

Parameter name	Value (95% CI)	Distribution and parameters	Source
Serum calcium at 12 months (mmol/l)	2.470 (2.412, 2.529)	Lognormal: μ=0.904; σ=0.012	Braun et al. 2004
Correlation between baseline and follow-up:			
Serum phosphate at 3 months (mmol/l)	0.129 (0.08, 0.18)	Fisher Normal	Clinical review
Serum phosphate at 6 months (mmol/l)	0.321 (0.27, 0.37)	Fisher Normal	Clinical review
Serum phosphate at 12 months (mmol/l)	0.295 (0.24, 0.35)	Fisher Normal	Clinical review
Serum calcium at 3 months (mmol/l)	0.582 (0.50, 0.67)	Fisher Normal	Clinical review
Serum calcium at 6 months (mmol/l)	0.511 (0.45, 0.57)	Fisher Normal	Clinical review
Serum calcium at 12 months (mmol/l)	0.436 (0.38, 0.49)	Fisher Normal	Clinical review
Imputed correlation when data are absent (e.g. 3mo to 6mo follow-up)			
Serum phosphate (mmol/l)	0.5 (-0.48, 1.48)	Fisher Normal	Assumption
Serum calcium (mmol/l)	0.5 (-0.48, 1.48)	Fisher Normal	Assumption
Treatment effects			
Phosphate: mean change -v- calcium carbonate			
Calcium acetate - 3mo	-0.154 (-0.42, 0.11)	Multivariate Normal	Clinical review
Calcium acetate + Mg carbonate - 3mo	-0.334 (-0.70, 0.04)	Multivariate Normal	Clinical review
Ferric citrate - 3mo	-0.143 (-0.41, 0.13)	Multivariate Normal	Clinical review
Lanthanum carbonate - 3mo	-0.050 (-0.25, 0.15)	Multivariate Normal	Clinical review
Sevelamer carbonate - 3mo	-0.207 (-0.51, 0.10)	Multivariate Normal	Clinical review
Sevelamer hydrochloride - 3mo	-0.149 (-0.35, 0.05)	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide - 3mo	-0.200 (-0.51, 0.11)	Multivariate Normal	Clinical review
Calcium acetate - 6mo	0.086 (-0.15, 0.32)	Multivariate Normal	Clinical review
Calcium acetate + Mg carbonate - 6mo	-0.111 (-0.42, 0.20)	Multivariate Normal	Clinical review

Parameter name	Value (95% CI)	Distribution and parameters	Source
Ferric citrate - 6mo	NR [a]	Multivariate Normal	Clinical review
Lanthanum carbonate - 6mo	0.008 (-0.12, 0.14)	Multivariate Normal	Clinical review
Sevelamer carbonate - 6mo	0.100 (-0.16, 0.36)	Multivariate Normal	Clinical review
Sevelamer hydrochloride - 6mo	-0.063 (-0.22, 0.10)	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide - 6mo	0.077 (-0.20, 0.35)	Multivariate Normal	Clinical review
Calcium acetate - 12mo	-0.057 (-0.23, 0.11)	Multivariate Normal	Clinical review
Calcium acetate + Mg carbonate - 12mo	NR [b]	Multivariate Normal	Clinical review
Ferric citrate - 12mo	-0.037 (-0.33, 0.26)	Multivariate Normal	Clinical review
Lanthanum carbonate - 12mo	0.159 (0.04, 0.27)	Multivariate Normal	Clinical review
Sevelamer carbonate - 12mo	-0.060 (-0.39, 0.27)	Multivariate Normal	Clinical review
Sevelamer hydrochloride - 12mo	0.009 (-0.09, 0.11)	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide - 12mo	-0.130 (-0.50, 0.24)	Multivariate Normal	Clinical review
Calcium: mean change -v- calcium carbonate			
Calcium acetate - 3mo	-0.075 (-0.20, 0.05)	Multivariate Normal	Clinical review
Calcium acetate + Mg carbonate - 3mo	-0.055 (-0.21, 0.10)	Multivariate Normal	Clinical review
Ferric citrate - 3mo	-0.099 (-0.22, 0.02)	Multivariate Normal	Clinical review
Lanthanum carbonate - 3mo	-0.102 (-0.22, 0.01)	Multivariate Normal	Clinical review
Sevelamer carbonate - 3mo	NR [c]	Multivariate Normal	Clinical review
Sevelamer hydrochloride - 3mo	-0.138 (-0.22, -0.06)	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide - 3mo	-0.099 (-0.25, 0.05)	Multivariate Normal	Clinical review
Calcium acetate - 6mo	-0.047 (-0.21, 0.12)	Multivariate Normal	Clinical review

Parameter name	Value (95% CI)	Distribution and parameters	Source
Calcium acetate + Mg carbonate - 6mo	-0.061 (-0.29, 0.17)	Multivariate Normal	Clinical review
Ferric citrate - 6mo	NR	Multivariate Normal	Clinical review
Lanthanum carbonate - 6mo	-0.108 (-0.21, -0.01)	Multivariate Normal	Clinical review
Sevelamer carbonate - 6mo	-0.108 (-0.21, -0.01)	Multivariate Normal	Clinical review
Sevelamer hydrochloride - 6mo	-0.126 (-0.31, 0.06)	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide - 6mo	-0.129 (-0.24, -0.02)	Multivariate Normal	Clinical review
Calcium acetate - 12mo	-0.113 (-0.24, 0.01)	Multivariate Normal	Clinical review
Calcium acetate + Mg carbonate - 12mo	NR	Multivariate Normal	Clinical review
Ferric citrate - 12mo	-0.186 (-0.41, 0.04)	Multivariate Normal	Clinical review
Lanthanum carbonate - 12mo	-0.092 (-0.19, 0.00)	Multivariate Normal	Clinical review
Sevelamer carbonate - 12mo	-0.199 (-0.43, 0.03)	Multivariate Normal	Clinical review
Sevelamer hydrochloride - 12mo	-0.130 (-0.21, -0.05)	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide - 12mo	-0.200 (-0.48, 0.08)	Multivariate Normal	Clinical review
Hazard ratios for all-cause mortality			
Phosphate (mmol/l)			
< 1.13	0.740 (0.463, 1.124)	Lognormal: μ=-0.327; σ=0.226	Tangri et al., 2011
1.13 - 1.78	1.000	Not varied in PSA	
1.78 - 2.10	1.170 (0.965, 1.405)	Lognormal: μ=0.152; σ=0.096	Tangri et al., 2011
2.10 - 2.42	1.420 (1.151, 1.733)	Lognormal: μ=0.345; σ=0.105	Tangri et al., 2011
> 2.42	1.640 (1.217, 2.162)	Lognormal: μ=0.484; σ=0.147	Tangri et al., 2011
Phosphate (mmol/l) in UK Renal Registry (assuming lognormal)			
< 1.13	0.001		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
1.13 - 1.78	0.149		Calculated
1.78 - 2.10	0.238		Calculated
2.10 - 2.42	0.253		Calculated
> 2.42	0.359		Calculated
HR for average UK Renal Registry patient	1.355		Calculated
HRs normalised to UK Renal Registry population:			
< 1.13	0.546		Calculated
1.13 - 1.78	0.738		Calculated
1.78 - 2.10	0.864		Calculated
2.10 - 2.42	1.048		Calculated
> 2.42	1.211		Calculated
Calcium (mmol/l)			
< 2.10	1.350 (0.352, 3.631)	Lognormal: μ=0.123; σ=0.595	Tangri et al., 2011
2.10 - 2.37	1.000	Not varied in PSA	
2.37 - 2.59	1.130 (0.855, 1.465)	Lognormal: μ=0.113; σ=0.137	Tangri et al., 2011
> 2.59	1.350 (1.086, 1.659)	Lognormal: μ=0.294; σ=0.108	Tangri et al., 2011
Calcium (mmol/l) in UK Renal Registry (assuming lognormal)			
< 2.10	0.047		Calculated
2.10 - 2.37	0.606		Calculated
2.37 - 2.59	0.319		Calculated
> 2.59	0.028		Calculated
HR for average UK Renal Registry patient	1.063		Calculated
HRs normalised to UK Renal Registry population:			
< 2.10	1.270		Calculated
2.10 - 2.37	0.940		Calculated
2.37 - 2.59	1.063		Calculated
> 2.59	1.270		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
ln(HRs) estimated via regression: phosphate			
Intercept	-0.989		Calculated
Serum phosphate (mmol/l)	0.497		Calculated
Serum phosphate (mmol/l) ^ 2	-0.023		Calculated
ln(HRs) estimated via regression: calcium:			
Intercept	7.993		Calculated
Serum calcium (mmol/l)	-6.757		Calculated
Serum calcium (mmol/l) ^ 2	1.425		Calculated
Other mortality parameters:			
Mortality HR for dialysis -v- transplantation	5.0 (4.5, 5.6)	Lognormal: μ=1.608; σ=0.058	Jain et al., 2009
Age at which dialysis and transplantation assumed equivalent	70.0 (54.5, 85.5)	Triangular: min=50.0; mode=70.0; max=90.0	
Hazard ratios for CV events			
Phosphate (mmol/l)			
<= 1.42	1.000	Not varied in PSA	
1.45 - 1.71	1.060 (1.000, 1.122)	Lognormal: μ=0.058; σ=0.029	Slinin et al., 2005
1.74 - 2.03	1.130 (1.073, 1.189)	Lognormal: μ=0.122; σ=0.026	Slinin et al., 2005
2.07 - 2.42	1.140 (1.076, 1.207)	Lognormal: μ=0.131; σ=0.029	Slinin et al., 2005
> 2.42	1.250 (1.187, 1.315)	Lognormal: μ=0.223; σ=0.026	Slinin et al., 2005
Phosphate (mmol/l) in UK Renal Registry (assuming lognormal)			
<= 1.42	0.019		Calculated
1.45 - 1.71	0.092		Calculated
1.74 - 2.03	0.219		Calculated
2.07 - 2.42	0.311		Calculated
> 2.42	0.359		Calculated
HR for average UK Renal Registry patient	1.165		Calculated
HRs normalised to UK Renal Registry population:			

Parameter name	Value (95% CI)	Distribution and parameters	Source
<= 1.42	0.858		Calculated
1.45 - 1.71	0.910		Calculated
1.74 - 2.03	0.970		Calculated
2.07 - 2.42	0.978		Calculated
> 2.42	1.073		Calculated
Calcium (mmol/l)			
<= 2.17	1.000	Not varied in PSA	
2.20 - 2.30	1.030 (0.973, 1.090)	Lognormal: μ=0.029; σ=0.029	Slinin et al., 2005
2.32 - 2.40	1.040 (0.979, 1.104)	Lognormal: μ=0.039; σ=0.031	Slinin et al., 2005
2.42 - 2.54	1.030 (0.969, 1.094)	Lognormal: μ=0.029; σ=0.031	Slinin et al., 2005
> 2.54	1.080 (1.017, 1.146)	Lognormal: μ=0.076; σ=0.031	Slinin et al., 2005
Calcium (mmol/l) in UK Renal Registry (assuming lognormal)			
<= 2.17	0.132		Calculated
2.20 - 2.30	0.320		Calculated
2.32 - 2.40	0.276		Calculated
2.42 - 2.54	0.169		Calculated
> 2.54	0.102		Calculated
HR for average UK Renal Registry patient	1.034		Calculated
HRs normalised to UK Renal Registry population:			
<= 2.17	0.967		Calculated
2.20 - 2.30	0.996		Calculated
2.32 - 2.40	1.006		Calculated
2.42 - 2.54	0.996		Calculated
> 2.54	1.045		Calculated
Rate of CV events per cycle	0.066 (0.021, 0.156)	Lognormal: μ=-2.852; σ=0.509	Schlackow et al., 2017 (Supplementary)
ln(HRs) estimated via regression: phosphate			
Intercept	-0.439		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Serum phosphate (mmol/l)	0.258		Calculated
Serum phosphate (mmol/l) ^ 2	-0.028		Calculated
ln(HRs) estimated via regression: calcium			
Intercept	0.003		Calculated
Serum calcium (mmol/l)	-0.121		Calculated
Serum calcium (mmol/l) ^ 2	0.050		Calculated
Predicting fracture events			
HR per mg/dl serum phosphate	1.120 (1.038, 1.207)	Lognormal: μ=0.113; σ=0.039	Block et al., 2004
HR per mmol/l serum phosphate	1.420		Calculated
Phosphate levels of participants in regression cohort:			
2.0mg/dl (<3mg/dl)	0.022	Not varied in PSA	Block et al., 2004
3.5mg/dl (3-4mg/dl)	0.095	Not varied in PSA	Block et al., 2004
4.5mg/dl (4-5mg/dl)	0.215	Not varied in PSA	Block et al., 2004
5.5mg/dl (5-6mg/dl)	0.257	Not varied in PSA	Block et al., 2004
6.5mg/dl (6-7mg/dl)	0.206	Not varied in PSA	Block et al., 2004
7.5mg/dl (7-8mg/dl)	0.112	Not varied in PSA	Block et al., 2004
8.5mg/dl (8-9mg/dl)	0.055	Not varied in PSA	Block et al., 2004
10.0mg/dl (>9mg/dl)	0.037	Not varied in PSA	Block et al., 2004
Mean serum phosphate in regression cohort (mmol/L)	1.866 (1.861, 1.871)	Lognormal: μ=0.624; σ=0.001	Calculated
Rate of fractures per cycle in regression cohort	0.005 (0.000, 0.033)	Lognormal: μ=-7.824; σ=2.248	Block et al., 2004
Parathyroidectomy			
Predicting the need for surgery:			
HR for phosphate (per 1 mg/dl)	1.170 (1.103, 1.240)	Lognormal: μ=0.157; σ=0.030	Young et al., 2005
HR for phosphate (per 0.1 mmol/l)	1.626		Calculated
Mean serum phosphate in regression cohort (mmol/l)	1.873 (1.860, 1.885)	Lognormal: μ=0.627; σ=0.003	Young et al., 2005
Rate of PTx in regression cohort (UK sample)	0.015 (0.000, 0.092)	Lognormal: μ=-7.158; σ=2.433	Young et al., 2005

Parameter name	Value (95% CI)	Distribution and parameters	Source
Suitability for surgery:			
Proportion suitable for surgery	0.850 (0.734, 0.966)	Triangular: min=0.700; mode=0.850; max=1.000	
Age at which proportion begins to decrease	55.0 (26.3, 83.7)	Triangular: min=18.0; mode=55.0; max=92.0	
Decrease in suitability for surgery per year of age above threshold	0.5% (0.1%, 0.9%)	Triangular: min=0.0%; mode=0.5%; max=1.0%	
Probability of transplantation			
Getting on the waiting list:			
Probability of joining waiting list within 2 years of dialysis	0.565 (0.555, 0.574)	Beta: α=5741.151; β=4428.849	UK Renal Registry, 2019
Per-cycle probability of joining waiting list	0.099		Calculated
Per-cycle odds of joining waiting list	0.110		Calculated
% men in regression cohort	0.615 (0.606, 0.625)	Beta: α=6257.0; β=3913.0	UK Renal Registry, 2019
OR: women -v- men	0.870 (0.740, 1.022)	Lognormal: μ=-0.139; σ=0.082	UK Renal Registry, 2019
Odds in men			
Odds in women			
Proportion aged 18-29	0.076	Dirichlet	UK Renal Registry, 2019
Proportion aged 30-39	0.123	Dirichlet	UK Renal Registry, 2019
Proportion aged 40-49	0.241	Dirichlet	UK Renal Registry, 2019
Proportion aged 50-59	0.345	Dirichlet	UK Renal Registry, 2019
Proportion aged 60-64	0.214	Dirichlet	UK Renal Registry, 2019
Men			
OR: 18-29	1.000		UK Renal Registry, 2019

Parameter name	Value (95% CI)	Distribution and parameters	Source
OR: 30-39	0.660 (0.413, 1.053)	Lognormal: μ=-0.416; σ=0.239	UK Renal Registry, 2019
OR: 40-49	0.400 (0.261, 0.613)	Lognormal: μ=-0.916; σ=0.217	UK Renal Registry, 2019
OR: 50-59	0.230 (0.151, 0.351)	Lognormal: μ=-1.470; σ=0.216	UK Renal Registry, 2019
OR: 60-64	0.130 (0.081, 0.208)	Lognormal: μ=-2.040; σ=0.240	UK Renal Registry, 2019
Odds in 18-29	0.319		Calculated
Odds in 30-39	0.211		Calculated
Odds in 40-49	0.128		Calculated
Odds in 50-59	0.073		Calculated
Odds in 60-64	0.041		Calculated
Probability in 18-29	0.242		Calculated
Probability in 30-39	0.174		Calculated
Probability in 40-49	0.113		Calculated
Probability in 50-59	0.068		Calculated
Probability in 60-64	0.040		Calculated
Women			
OR: 18-29	0.870		Calculated
OR: 30-39	0.574		Calculated
OR: 40-49	0.348		Calculated
OR: 50-59	0.200		Calculated
OR: 60-64	0.113		Calculated
Odds in 18-29	0.309		Calculated
Odds in 30-39	0.178		Calculated
Odds in 40-49	0.108		Calculated
Odds in 50-59	0.062		Calculated
Odds in 60-64	0.035		Calculated
Probability in 18-29	0.236		Calculated
Probability in 30-39	0.151		Calculated
Probability in 40-49	0.097		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Probability in 50-59	0.058		Calculated
Probability in 60-64	0.034		Calculated
Median time waiting time to transplant (days)	706 (689, 723)	Normal: μ=706; σ=17.347	NHS Blood and Transplant, 2019
Per-cycle probability of receiving transplant from waiting list	0.086		Calculated
Brainstem-dead donors:			
Proportion of Tx	0.533 (0.511, 0.556)	Beta: α=1015.0; β=888.0	UK Renal Registry, 2019
Per-cycle prob. of Tx from waiting list	0.046		Calculated
Per-cycle odds of Tx from waiting list	0.048		Calculated
% men in regression cohort	0.625 (0.613, 0.637)	Beta: α=3668.0; β=2201.0	UK Renal Registry, 2019
OR: women -v- men	0.940 (0.707, 1.250)	Lognormal: μ=-0.062; σ=0.145	UK Renal Registry, 2019
Odds in men	0.049		Calculated
Odds in women	0.046		Calculated
Proportion aged 18-29	0.112	Dirichlet	UK Renal Registry, 2019
Proportion aged 30-39	0.165	Dirichlet	UK Renal Registry, 2019
Proportion aged 40-49	0.277	Dirichlet	UK Renal Registry, 2019
Proportion aged 50-59	0.312	Dirichlet	UK Renal Registry, 2019
Proportion aged 60-64	0.135	Dirichlet	UK Renal Registry, 2019
Men			
OR: 18-29	1.000		UK Renal Registry, 2019
OR: 30-39	1.090 (0.679, 1.749)	Lognormal: μ=0.086; σ=0.241	UK Renal Registry, 2019
OR: 40-49	0.730 (0.460, 1.158)	Lognormal: μ=-0.315; σ=0.235	UK Renal Registry, 2019
OR: 50-59	0.450 (0.284, 0.713)	Lognormal: μ=-0.799; σ=0.234	UK Renal Registry, 2019

Parameter name	Value (95% CI)	Distribution and parameters	Source
OR: 60-64	0.330 (0.180, 0.605)	Lognormal: μ=-1.109; σ=0.309	UK Renal Registry, 2019
Odds in 18-29	0.072		Calculated
Odds in 30-39	0.079		Calculated
Odds in 40-49	0.053		Calculated
Odds in 50-59	0.032		Calculated
Odds in 60-64	0.024		Calculated
Probability in 18-29	0.067		Calculated
Probability in 30-39	0.073		Calculated
Probability in 40-49	0.050		Calculated
Probability in 50-59	0.031		Calculated
Probability in 60-64	0.023		Calculated
Women			
OR: 18-29	0.940		Calculated
OR: 30-39	1.025		Calculated
OR: 40-49	0.686		Calculated
OR: 50-59	0.423		Calculated
OR: 60-64	0.310		Calculated
Odds in 18-29	0.071		Calculated
Odds in 30-39	0.073		Calculated
Odds in 40-49	0.049		Calculated
Odds in 50-59	0.030		Calculated
Odds in 60-64	0.022		Calculated
Probability in 18-29	0.067		Calculated
Probability in 30-39	0.068		Calculated
Probability in 40-49	0.047		Calculated
Probability in 50-59	0.029		Calculated
Probability in 60-64	0.022		Calculated
Cardiac-dead or living donors:			
Proportion of Tx	0.467		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Per-cycle prob. of Tx from waiting list	0.040		Calculated
Per-cycle odds of Tx from waiting list	0.042		Calculated
OR: women -v- men	0.750 (0.554, 1.015)	Lognormal: μ=-0.288; σ=0.155	UK Renal Registry, 2019
Odds in men	0.046		Calculated
Odds in women	0.034		Calculated
Men:			
OR: 18-29	1.000		Calculated
OR: 30-39	1.150		Calculated
OR: 40-49	1.160		Calculated
OR: 50-59	1.340		Calculated
OR: 60-64	1.390		Calculated
Odds in 18-29	0.037		Calculated
Odds in 30-39	0.043		Calculated
Odds in 40-49	0.043		Calculated
Odds in 50-59	0.050		Calculated
Odds in 60-64	0.052		Calculated
Probability in 18-29	0.036		Calculated
Probability in 30-39	0.041		Calculated
Probability in 40-49	0.042		Calculated
Probability in 50-59	0.048		Calculated
Probability in 60-64	0.049		Calculated
Women:			
OR: 18-29	0.750		Calculated
OR: 30-39	0.863		Calculated
OR: 40-49	0.870		Calculated
OR: 50-59	1.005		Calculated
OR: 60-64	1.043		Calculated
Odds in 18-29	0.036		Calculated
Odds in 30-39	0.031		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Odds in 40-49	0.032		Calculated
Odds in 50-59	0.036		Calculated
Odds in 60-64	0.038		Calculated
Probability in 18-29	0.035		Calculated
Probability in 30-39	0.030		Calculated
Probability in 40-49	0.031		Calculated
Probability in 50-59	0.035		Calculated
Probability in 60-64	0.036		Calculated
Maximum age for transplantation	80.00 (64.47, 95.53)	Triangular: min=60; mode=80; max=100	
Adverse events and discontinuation			
Baseline ln(rates) from NMAs (Ca Carbonate)			
Constipation	-2.003 (-4.018, 0.012)	Normal: μ=-2.003; σ=1.028	Clinical review
Diarrhoea	-1.775 (-2.138, -1.413)	Normal: μ=-1.775; σ=0.185	Clinical review
Nausea and vomiting	-1.513 (-1.814, -1.213)	Normal: μ=-1.513; σ=0.153	Clinical review
Discontinuation	-2.048 (-2.768, -1.328)	Normal: μ=-2.048; σ=0.367	Clinical review
ln(HR) -v- calcium carbonate			
Calcium acetate – Constipation	1.361	Multivariate Normal	Clinical review
Calcium acetate + Magnesium – Constipation	NR	Multivariate Normal	Clinical review
Ferric citrate – Constipation	-0.287	Multivariate Normal	Clinical review
Lanthanum carbonate – Constipation	-0.355	Multivariate Normal	Clinical review
Sevelamer Carbonate – Constipation	0.475	Multivariate Normal	Clinical review
Sevelamer hydrochloride – Constipation	1.511	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide – Constipation	-0.158	Multivariate Normal	Clinical review
Calcium acetate – Diarrhoea	0.084	Multivariate Normal	Clinical review

Parameter name	Value (95% CI)	Distribution and parameters	Source
Calcium acetate + Magnesium – Diarrhoea	NR	Multivariate Normal	Clinical review
Ferric citrate – Diarrhoea	2.035	Multivariate Normal	Clinical review
Lanthanum carbonate – Diarrhoea	0.285	Multivariate Normal	Clinical review
Sevelamer Carbonate – Diarrhoea	0.408	Multivariate Normal	Clinical review
Sevelamer hydrochloride – Diarrhoea	-0.036	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide – Diarrhoea	1.435	Multivariate Normal	Clinical review
Calcium acetate – NausVom	-1.333	Multivariate Normal	Clinical review
Calcium acetate + Magnesium – NausVom	NR	Multivariate Normal	Clinical review
Ferric citrate – NausVom	2.079	Multivariate Normal	Clinical review
Lanthanum carbonate – NausVom	0.827	Multivariate Normal	Clinical review
Sevelamer Carbonate – NausVom	-1.502	Multivariate Normal	Clinical review
Sevelamer hydrochloride – NausVom	-1.497	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide – NausVom	-1.990	Multivariate Normal	Clinical review
Calcium acetate – Discontinuation	0.592	Multivariate Normal	Clinical review
Calcium acetate + Magnesium – Discontinuation	-0.808	Multivariate Normal	Clinical review
Ferric citrate – Discontinuation	0.789	Multivariate Normal	Clinical review
Lanthanum carbonate – Discontinuation	0.729	Multivariate Normal	Clinical review
Sevelamer Carbonate – Discontinuation	0.786	Multivariate Normal	Clinical review
Sevelamer hydrochloride – Discontinuation	0.406	Multivariate Normal	Clinical review
Sucroferric oxyhydroxide – Discontinuation	0.976	Multivariate Normal	Clinical review
Probability AE leads to dropout [d]			
Calcium carbonate	0.258		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Calcium acetate	0.324		Calculated
Ferric citrate	0.125		Calculated
Lanthanum carbonate	0.348		Calculated
Sevelamer carbonate	0.560		Calculated
Sevelamer hydrochloride	0.254		Calculated
Sucroferric oxyhydroxide	0.425		Calculated
Health state utilities			
Decrements:			
CKD-5D	0.713		Calculated
Transplanted	0.957		Calculated
PostPTx	N/A [e]		N/A
Dead	0.000		Calculated
Derivation: CKD5D			
Absolute utility	0.565 (0.514, 0.615)	Beta: α=204.385; β=157.466	Liem et al., 2008
Mean age of source cohorts	61.45 (55.43, 67.47)	Normal: μ=61.45; σ=3.07	Liem et al., 2008
Proportion of men in source cohorts	0.607 (0.582, 0.631)	Beta: α=914.000; β=593.000	Liem et al., 2008
General population utility matched for age and sex	0.792 (0.767, 0.816)	Beta: α=852.307; β=224.103	Kind et al., 1999
Relative utility decrement	0.713		Calculated
Derivation: transplantation (maintenance state)			
Absolute utility	0.809 (0.691, 0.903)	Beta: α=41.302; β=9.762	Liem et al., 2008
Mean age of source cohorts	52.67 (47.51, 57.83)	Normal: μ=52.67; σ=2.63	Liem et al., 2008
Proportion of men in source cohorts	0.493 (0.436, 0.550)	Beta: α=145.000; β=149.000	Liem et al., 2008
General population utility matched for age and sex	0.845 (0.822, 0.867)	Beta: α=864.940; β=158.575	Kind et al., 1999
Event utilities			
Relative utility decrement associated with events			
Initialise	1.000	Not varied in PSA	

Parameter name	Value (95% CI)	Distribution and parameters	Source
EndOfEvidence	1.000	Not varied in PSA	
KidneyFailure	1.000	Not varied in PSA	
CVEvent	0.782		Calculated
Fracture	0.928		Calculated
Parathyroidectomy	1.000	Not varied in PSA	
TxWaitListed	1.000	Not varied in PSA	
HaveTransplant	0.793		Calculated
AEDiarrhoea	0.917		Calculated
AEConstipation	0.854		Calculated
AENauseaVom	0.903		Calculated
AEUpperAbdoPain	0.730 (0.619, 0.828)	Beta: α=49.403; β=18.272	Latimer et al., 2009
EndUtilityDecrement	1.000	Not varied in PSA	
Dropout	1.000	Not varied in PSA	
DeathPostPTx	1.000	Not varied in PSA	
Death	1.000	Not varied in PSA	
AE Diarrhoea (absolute decrement)	-0.06 (-0.08, -0.04)	Beta: α=38.220; β=-675.220	Beusterien et al., 2009
AE Nausea and Vomiting (absolute decrement)	-0.07 (-0.09, -0.05)	Beta: α=52.500; β=-802.500	Beusterien et al., 2009
Assumed baseline utility for absolute -> relative decrements	0.725 (0.628, 0.822)	Triangular: min=0.600; mode=0.725; max=0.850	
Duration of disutility (cycles)			
Initialise	0.000	Not varied in PSA	
EndOfEvidence	0.000	Not varied in PSA	
KidneyFailure	0.000	Not varied in PSA	
CVEvent	9999	Not varied in PSA	
Fracture	4.000	Not varied in PSA	
Parathyroidectomy	0.000	Not varied in PSA	
TxWaitListed	0.000	Not varied in PSA	
HaveTransplant	0.333	Not varied in PSA	

Parameter name	Value (95% CI)	Distribution and parameters	Source
AEDiarrhoea	0.055	Not varied in PSA	
AEConstipation	0.055	Not varied in PSA	
AENauseaVom	0.055	Not varied in PSA	
AEUpperAbdoPain	0.055	Not varied in PSA	
EndUtilityDecrement	0.000	Not varied in PSA	
Dropout	0.000	Not varied in PSA	
DeathPostPTx	0.000	Not varied in PSA	
Death	0.000	Not varied in PSA	
Transplantation (perioperative disutility)			
Mean utility preoperatively	0.825 (0.805, 0.845)	Beta: α=1141.343; β=241.375	Hamidi et al., 2009
Mean utility 1mo postoperatively	0.654 (0.633, 0.676)	Beta: α=1238.594; β=654.214	Hamidi et al., 2009
Congestive heart failure			
EQ-5D (Group1)	0.580	Not varied in PSA	Holland et al., 2007
EQ-5D (Group2)	0.570	Not varied in PSA	Holland et al., 2007
EQ-5D (Average)	0.575 (0.521, 0.628)	Beta: α=187.006; β=138.193	
Age (Group1)	77.60	Not varied in PSA	Holland et al., 2007
Age (Group2)	76.40	Not varied in PSA	Holland et al., 2007
Age (Average)	77.01 (75.51, 78.51)	Normal: μ=77.01; σ=0.76	
Sex (% male) (Average)	0.635 (0.579, 0.689)	Beta: α=186.000; β=107.000	Holland et al., 2007
General population utility matched for age and sex	0.735 (0.704, 0.765)	Beta: α=587.644; β=211.445	Kind et al., 1999
Fractures			
Serious fracture (proxy: hip)			
Relative utility decrement (Yr1)	0.700 (0.633, 0.763)	Beta: α=132.955; β=56.981	Peasgood et al., 2009
Minor fracture (proxy: wrist)			
Relative utility decrement (Yr1)	0.956 (0.864, 0.997)	Beta: α=30.570; β=1.407	Peasgood et al., 2009
Proportion of fractures that are serious	0.111 (0.028, 0.241)	Beta: α=3.444; β=27.556	NICE, 2007 (TA117)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Adverse events:			
Constipation			
Absolute utility with constipation	0.522	Not varied in PSA	Belsey et al., 2010
Absolute utility (controls)	0.611	Not varied in PSA	Belsey et al., 2010
Relative utility decrement	0.854 (0.651, 0.976)	Beta: α=13.712; β=2.338	
Intervention costs			
Cost per cycle			
calcium carbonate	£16.02		Calculated
calcium acetate	£32.58		Calculated
ferric citrate	£628.21		Calculated
lanthanum carbonate	£336.30		Calculated
sevelamer carbonate	£154.92		Calculated
sevelamer hydrochloride	£653.30		Calculated
sucroferric oxyhydroxide	£689.61		Calculated
no binder	£0.00		Calculated
Unit cost (per g)			
Calcium carbonate			
Calcium carbonate 1.25g chewable tablet sugar free	£0.09	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Calcium carbonate 1.5g chewable tablet sugar free	£0.09	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Calcium carbonate 2.5g chewable tablet sugar free	£0.22	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Calcium carbonate 500mg chewable tablet	£0.06	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Weighted average cost per mg	£0.07		Calculated
Calcium acetate			

Parameter name	Value (95% CI)	Distribution and parameters	Source
Calcium acetate 1g tablet	£0.11	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Calcium acetate 475mg tablet	£0.05	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Calcium acetate 950mg tablet	£0.09	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Weighted average cost per mg	£0.11		Calculated
Ferric citrate	£1.16	Not varied in PSA	
Lanthanum carbonate			
Lanthanum carbonate 1g chewable tablet	£2.15	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Lanthanum carbonate 1g oral powder sachet	£2.15	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Lanthanum carbonate 500mg chewable tablet	£1.38	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Lanthanum carbonate 750mg chewable tablet	£2.03	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Lanthanum carbonate 750mg oral powder sachet	£2.03	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Weighted average cost per mg	£2.50		Calculated
Sevelamer carbonate			
Sevelamer 2.4g oral powder sachets sugar free / Packsize 60	£1.37	Not varied in PSA	CMU, eMIT database (April 2019)
Sevelamer Carbonate 800mg tablets (Renvela or eqv) / Packsize 180	£0.17	Not varied in PSA	CMU, eMIT database (April 2019)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Weighted average cost per mg	£0.24		Calculated
Sevelamer hydrochloride			
Renagel 800mg tablets (Sanofi)	£0.93	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Cost per mg	£1.16		Calculated
Sucroferric oxyhydroxide			
Iron (as Sucroferric oxyhydroxide) 500 mg	£1.99	Not varied in PSA	Cost from NHS drug tariff (Sep 2019); quantity for weighting from PCA (Mar 2019)
Cost per mg	£3.98		Calculated
Assumed dose (g/d)			
calcium carbonate	£2.64 (£2.47, £2.82)	Lognormal: μ=0.97; σ=0.03	Included studies - pooled
calcium acetate	£3.40 (£3.34, £3.46)	Lognormal: μ=1.22; σ=0.01	Included studies - pooled
ferric citrate	£5.93 (£4.50, £7.81)	Lognormal: μ=1.78; σ=0.14	Included studies - pooled
lanthanum carbonate	£1.47 (£1.37, £1.58)	Lognormal: μ=0.39; σ=0.04	Included studies - pooled
sevelamer carbonate	£7.00 (£5.16, £9.49)	Lognormal: μ=1.95; σ=0.16	Included studies - pooled
sevelamer hydrochloride	£6.17 (£5.70, £6.67)	Lognormal: μ=1.82; σ=0.04	Included studies - pooled
sucroferric oxyhydroxide	£1.90 (£1.62, £2.80)	Triangular: min=£1.50; mode=£1.90; max=£3.00	Sucroferric oxyhydroxide SmPC
Event costs			
Initialise	£0.00	Not varied in PSA	
EndOfEvidence	£0.00	Not varied in PSA	
KidneyFailure	£0.00	Not varied in PSA	
CVEvent	£1569.20		Calculated
Fracture	£2428.76		Calculated
Parathyroidectomy	£0.00	Not varied in PSA	

Parameter name	Value (95% CI)	Distribution and parameters	Source
TxWaitListed	£0.00	Not varied in PSA	
HaveTransplant	£19200.67		Calculated
AEDiarrhoea	£28.00		Calculated
AEConstipation	£28.00		Calculated
AENauseaVom	£28.00		Calculated
AEUpperAbdoPain	£28.00		Calculated
EndUtilityDecrement	£0.00	Not varied in PSA	
Dropout	£0.00	Not varied in PSA	
DeathPostPTx	£0.00	Not varied in PSA	
Death	£0.00	Not varied in PSA	
Adverse events			
Unit costs:			
GP appointment	£28.00	Not varied in PSA	Curtis & Burns, 2018
Resource use:			
GP appointments:			
Diarrhoea	1.00 (0.22, 1.78)	Triangular: min=0.00; mode=1.00; max=2.00	
Constipation	1.00 (0.22, 1.78)	Triangular: min=0.00; mode=1.00; max=2.00	
NauseaVom	1.00 (0.22, 1.78)	Triangular: min=0.00; mode=1.00; max=2.00	
UpperAbdoPain	1.00 (0.22, 1.78)	Triangular: min=0.00; mode=1.00; max=2.00	
Unit costs: dialysis initial procedures			
Haemodialysis - initial access procedure			
YR41A Insertion of Tunnelled Central Venous Catheter, 19 years and over	£848.38	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
YQ42Z Open Arteriovenous Fistula, Graft or Shunt Procedures	£2345.06	Not varied in PSA	NHS Reference costs 2017-18
Average weighted by haemodialysis access type	£2490.10		Calculated
Peritoneal dialysis - associated procedures			
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£1694.60	Not varied in PSA	NHS Reference costs 2017-18
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£1818.23	Not varied in PSA	NHS Reference costs 2017-18
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£1029.78	Not varied in PSA	NHS Reference costs 2017-18
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£908.02	Not varied in PSA	NHS Reference costs 2017-18
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£167.84	Not varied in PSA	NHS Reference costs 2017-18
LA05Z Renal Replacement Peritoneal Dialysis Associated Procedures	£158.92	Not varied in PSA	NHS Reference costs 2017-18
Pooled average peritoneal dialysis associated procedures	£860.00		Calculated
Unit costs: transplantation			
Work-up			
LA11Z Kidney Pre-Transplantation Workup of Live Donor	£254.68	Not varied in PSA	NHS Reference costs 2017-18
LA12A Kidney Pre-Transplantation Workup of Recipient, 19 years and over	£277.77	Not varied in PSA	NHS Reference costs 2017-18
Average work-up per transplant	£1868.98		Calculated
Procedure			
LB46Z Live Donation of Kidney	£7027.00	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
LA01A Kidney Transplant, 19 years and over, from Cadaver Non-Heart-Beating Donor	£13165.83	Not varied in PSA	NHS Reference costs 2017-18
LA02A Kidney Transplant, 19 years and over, from Cadaver Heart-Beating Donor	£12555.28	Not varied in PSA	NHS Reference costs 2017-18
LA03A Kidney Transplant, 19 years and over, from Live Donor	£13058.95	Not varied in PSA	NHS Reference costs 2017-18
Pooled average kidney transplant procedure	£14793.66		Calculated
Pooled average kidney transplant procedure	£16662.64		Calculated
Basiliximab induction therapy			
20mg vial (adult dose)	£842.38	Not varied in PSA	Cost from BNF (accessed Oct 2019); quantity for weighting from PCA (Mar 2019)
Number of doses	1.96 (1.93, 2.00)	Normal: μ=1.96; σ=0.02	Brennan et al., (2006)
First infusion (SB12Z)	£228.99	Not varied in PSA	NHS Reference costs 2017-18
Subsequent infusion (SB15Z)	£289.33	Not varied in PSA	NHS Reference costs 2017-18
Cost per person	£2162.33		Calculated
Tacrolimus, additional perioperative cost			
Daily dose per kg (mg, initial month)	0.25 (0.21, 0.29)	Triangular: min=0.20; mode=0.25; max=0.30	BNF (accessed Oct 2019)
Weight (kg)	70.00	Not varied in PSA	Assumption
Total	£164.46		Calculated
Ciclosporin, additional perioperative cost			
Daily dose per kg (mg, initial 15d)	12.50 (10.56, 14.44)	Triangular: min=10.00; mode=12.50; max=15.00	BNF (accessed Oct 2019)
Weight (kg)	70.00	Not varied in PSA	Assumption
Total	£211.24		Calculated

Parameter name	Value (95% CI)	Distribution and parameters	Source
Total cost of transplant (procedure + induction therapy)	£19200.67		Calculated
Unit costs: fracture			
HE11A Hip Fracture with Multiple Interventions, with CC Score 8+	£9894.67	Not varied in PSA	NHS Reference costs 2017-18
HE11B Hip Fracture with Multiple Interventions, with CC Score 0-7	£6028.60	Not varied in PSA	NHS Reference costs 2017-18
HE11C Hip Fracture with Single Intervention, with CC Score 8+	£6665.70	Not varied in PSA	NHS Reference costs 2017-18
HE11D Hip Fracture with Single Intervention, with CC Score 0-7	£5075.13	Not varied in PSA	NHS Reference costs 2017-18
HE11E Hip Fracture without Interventions, with CC Score 12+	£5623.63	Not varied in PSA	NHS Reference costs 2017-18
HE11F Hip Fracture without Interventions, with CC Score 8-11	£4153.91	Not varied in PSA	NHS Reference costs 2017-18
HE11G Hip Fracture without Interventions, with CC Score 4-7	£2993.81	Not varied in PSA	NHS Reference costs 2017-18
HE11H Hip Fracture without Interventions, with CC Score 0-3	£2186.52	Not varied in PSA	NHS Reference costs 2017-18
HE21A Knee Fracture with Multiple Interventions	£8166.23	Not varied in PSA	NHS Reference costs 2017-18
HE21B Knee Fracture with Single Intervention, with CC Score 5+	£7322.03	Not varied in PSA	NHS Reference costs 2017-18
HE21C Knee Fracture with Single Intervention, with CC Score 2-4	£4130.43	Not varied in PSA	NHS Reference costs 2017-18
HE21D Knee Fracture with Single Intervention, with CC Score 0-1	£3070.38	Not varied in PSA	NHS Reference costs 2017-18
HE21E Knee Fracture without Interventions, with CC Score 5+	£4539.56	Not varied in PSA	NHS Reference costs 2017-18
HE21F Knee Fracture without Interventions, with CC Score 2-4	£2772.43	Not varied in PSA	NHS Reference costs 2017-18
HE21G Knee Fracture without Interventions, with CC Score 0-1	£1717.84	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
HE31A Foot Fracture with Multiple Interventions	£5303.94	Not varied in PSA	NHS Reference costs 2017-18
HE31B Foot Fracture with Single Intervention, with CC Score 2+	£4252.23	Not varied in PSA	NHS Reference costs 2017-18
HE31C Foot Fracture with Single Intervention, with CC Score 0-1	£1902.67	Not varied in PSA	NHS Reference costs 2017-18
HE31D Foot Fracture without Interventions, with CC Score 8+	£3746.76	Not varied in PSA	NHS Reference costs 2017-18
HE31E Foot Fracture without Interventions, with CC Score 4-7	£2376.34	Not varied in PSA	NHS Reference costs 2017-18
HE31F Foot Fracture without Interventions, with CC Score 2-3	£1901.77	Not varied in PSA	NHS Reference costs 2017-18
HE31G Foot Fracture without Interventions, with CC Score 0-1	£1181.61	Not varied in PSA	NHS Reference costs 2017-18
HE41A Hand Fracture with Interventions	£1856.92	Not varied in PSA	NHS Reference costs 2017-18
HE41B Hand Fracture without Interventions, with CC Score 3+	£1299.57	Not varied in PSA	NHS Reference costs 2017-18
HE41C Hand Fracture without Interventions, with CC Score 1-2	£676.23	Not varied in PSA	NHS Reference costs 2017-18
HE41D Hand Fracture without Interventions, with CC Score 0	£437.91	Not varied in PSA	NHS Reference costs 2017-18
HE51A Arm Fracture with Interventions, with CC Score 6+	£5171.92	Not varied in PSA	NHS Reference costs 2017-18
HE51B Arm Fracture with Interventions, with CC Score 3-5	£2953.62	Not varied in PSA	NHS Reference costs 2017-18
HE51C Arm Fracture with Interventions, with CC Score 0-2	£2179.66	Not varied in PSA	NHS Reference costs 2017-18
HE51D Arm Fracture without Interventions, with CC Score 9+	£3063.34	Not varied in PSA	NHS Reference costs 2017-18
HE51E Arm Fracture without Interventions, with CC Score 6-8	£2467.52	Not varied in PSA	NHS Reference costs 2017-18
HE51F Arm Fracture without Interventions, with CC Score 4-5	£1814.36	Not varied in PSA	NHS Reference costs 2017-18
HE51G Arm Fracture without Interventions, with CC Score 2-3	£1443.84	Not varied in PSA	NHS Reference costs 2017-18
HE51H Arm Fracture without Interventions, with CC Score 0-1	£993.22	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
HE71A Rib or Chest Fracture, with Interventions	£4174.99	Not varied in PSA	NHS Reference costs 2017-18
HE71B Rib or Chest Fracture, without Interventions, with CC Score 6+	£2274.80	Not varied in PSA	NHS Reference costs 2017-18
HE71C Rib or Chest Fracture, without Interventions, with CC Score 3-5	£1519.14	Not varied in PSA	NHS Reference costs 2017-18
HE71D Rib or Chest Fracture, without Interventions, with CC Score 0-2	£1079.52	Not varied in PSA	NHS Reference costs 2017-18
Pooled average fracture	£2428.76		Calculated
Unit costs: CV event			
Arrhythmia or conduction disorders			
EB07A: Arrhythmia or Conduction Disorders, with CC Score 13+	£2446.70	Not varied in PSA	NHS Reference costs 2017-18
EB07B: Arrhythmia or Conduction Disorders, with CC Score 10-12	£1673.78	Not varied in PSA	NHS Reference costs 2017-18
EB07C: Arrhythmia or Conduction Disorders, with CC Score 7-9	£1195.31	Not varied in PSA	NHS Reference costs 2017-18
EB07D: Arrhythmia or Conduction Disorders, with CC Score 4-6	£866.17	Not varied in PSA	NHS Reference costs 2017-18
EB07E: Arrhythmia or Conduction Disorders, with CC Score 0-3	£599.68	Not varied in PSA	NHS Reference costs 2017-18
Pooled average arrhythmia or conduction disorders	£952.89		Calculated
Cardiac conditions			
EB14A: Other Acquired Cardiac Conditions with CC Score 13+	£3500.75	Not varied in PSA	NHS Reference costs 2017-18
EB14B: Other Acquired Cardiac Conditions with CC Score 9-12	£2341.61	Not varied in PSA	NHS Reference costs 2017-18
EB14C: Other Acquired Cardiac Conditions with CC Score 6-8	£1717.31	Not varied in PSA	NHS Reference costs 2017-18
EB14D: Other Acquired Cardiac Conditions with CC Score 3-5	£1247.63	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
EB14E: Other Acquired Cardiac Conditions with CC Score 0-2	£813.63	Not varied in PSA	NHS Reference costs 2017-18
Pooled average cardiac conditions	£1727.01		Calculated
Cardiac arrest			
EB05A: Cardiac Arrest with CC Score 9+	£2169.31	Not varied in PSA	NHS Reference costs 2017-18
EB05B: Cardiac Arrest with CC Score 5-8	£1268.73	Not varied in PSA	NHS Reference costs 2017-18
EB05C: Cardiac Arrest with CC Score 0-4	£1014.60	Not varied in PSA	NHS Reference costs 2017-18
Pooled average cardiac arrest	£1620.21		Calculated
Cardiac valve disorders			
EB06A: Cardiac Valve Disorders with CC Score 13+	£3522.55	Not varied in PSA	NHS Reference costs 2017-18
EB06B: Cardiac Valve Disorders with CC Score 9-12	£2675.67	Not varied in PSA	NHS Reference costs 2017-18
EB06C: Cardiac Valve Disorders with CC Score 5-8	£1958.99	Not varied in PSA	NHS Reference costs 2017-18
EB06D: Cardiac Valve Disorders with CC Score 0-4	£1468.12	Not varied in PSA	NHS Reference costs 2017-18
Pooled average cardiac valve disorders	£2259.43		Calculated
Myocardial infarction			
EB10A: Actual or Suspected Myocardial Infarction, with CC Score 13+	£2734.94	Not varied in PSA	NHS Reference costs 2017-18
EB10B: Actual or Suspected Myocardial Infarction, with CC Score 10-12	£1926.74	Not varied in PSA	NHS Reference costs 2017-18
EB10C: Actual or Suspected Myocardial Infarction, with CC Score 7-9	£1460.52	Not varied in PSA	NHS Reference costs 2017-18
EB10D: Actual or Suspected Myocardial Infarction, with CC Score 4-6	£1214.16	Not varied in PSA	NHS Reference costs 2017-18
EB10E: Actual or Suspected Myocardial Infarction, with CC Score 0-3	£986.95	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
Pooled average myocardial infarction	£1514.86		Calculated
Heart failure			
EB03A: Heart Failure or Shock, with CC Score 14+	£3295.44	Not varied in PSA	NHS Reference costs 2017-18
EB03B: Heart Failure or Shock, with CC Score 11-13	£2455.03	Not varied in PSA	NHS Reference costs 2017-18
EB03C: Heart Failure or Shock, with CC Score 8-10	£1790.58	Not varied in PSA	NHS Reference costs 2017-18
EB03D: Heart Failure or Shock, with CC Score 4-7	£1317.89	Not varied in PSA	NHS Reference costs 2017-18
EB03E: Heart Failure or Shock, with CC Score 0-3	£939.78	Not varied in PSA	NHS Reference costs 2017-18
Pooled average heart failure	£1979.71		Calculated
Stroke			
AA22C: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 14+	£5755.32	Not varied in PSA	NHS Reference costs 2017-18
AA22D: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 11-13	£3652.73	Not varied in PSA	NHS Reference costs 2017-18
AA22E: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 8-10	£2906.35	Not varied in PSA	NHS Reference costs 2017-18
AA22F: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 5-7	£2228.40	Not varied in PSA	NHS Reference costs 2017-18
AA22G: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 0-4	£1483.55	Not varied in PSA	NHS Reference costs 2017-18
Pooled average stroke	£2541.97		Calculated
Pulmonary oedema			
DZ20D: Pulmonary Oedema with Interventions	£3588.34	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
DZ20E: Pulmonary Oedema without Interventions, with CC Score 6+	£1544.19	Not varied in PSA	NHS Reference costs 2017-18
DZ20F: Pulmonary Oedema without Interventions, with CC Score 0-5	£895.36	Not varied in PSA	NHS Reference costs 2017-18
Pooled average pulmonary oedema	£1470.21		Calculated
Peripheral vascular disease			
YQ50A: Peripheral Vascular Disorders with CC Score 15+	£4662.26	Not varied in PSA	NHS Reference costs 2017-18
YQ50B: Peripheral Vascular Disorders with CC Score 11-14	£3315.48	Not varied in PSA	NHS Reference costs 2017-18
YQ50C: Peripheral Vascular Disorders with CC Score 8-10	£2401.36	Not varied in PSA	NHS Reference costs 2017-18
YQ50D: Peripheral Vascular Disorders with CC Score 5-7	£1705.57	Not varied in PSA	NHS Reference costs 2017-18
YQ50E: Peripheral Vascular Disorders with CC Score 2-4	£1111.58	Not varied in PSA	NHS Reference costs 2017-18
YQ50F: Peripheral Vascular Disorders with CC Score 0-1	£636.76	Not varied in PSA	NHS Reference costs 2017-18
Pooled average vascular disease	£1665.98		Calculated
Total pooled average: CV events	£1569.20		Calculated
State costs per cycle			
CKD-4&5	£25.22		Calculated
CKD-5D	£25.22		Calculated
Transplanted	£1644.09		Calculated
PostPTx	£0.00	Not varied in PSA	
Dead	£0.00	Not varied in PSA	
Tests			
PTH test	1.0 (0.3, 2.6)	Triangular: min=0.0; mode=1.0; max=3.0	
Calcium test	1.0 (0.3, 2.6)	Triangular: min=0.0;	

Parameter name	Value (95% CI)	Distribution and parameters	Source
		mode=1.0; max=3.0	
Phosphorus test	1.0 (0.3, 2.6)	Triangular: min=0.0; mode=1.0; max=3.0	
PTH test	£10.00 (£6.37, £18.06)	Triangular: min=£5.00; mode=£10.00; max=£20.00	NHS Reference costs 2017-18
Calcium test	£1.11 (£0.65, £1.82)	Triangular: min=£0.50; mode=£1.11; max=£2.00	NHS Reference costs 2017-18
Phosphorus test	£1.11 (£0.65, £1.82)	Triangular: min=£0.50; mode=£1.11; max=£2.00	NHS Reference costs 2017-18
Dialysis			
Unit costs			
Haemodialysis: adults			
LD10A Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	£201.33	Not varied in PSA	NHS Reference costs 2017-18
LD10A Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over, away from base	£115.17	Not varied in PSA	NHS Reference costs 2017-18
LD09A Home Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	£302.85	Not varied in PSA	NHS Reference costs 2017-18
LD01A Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	£151.44	Not varied in PSA	NHS Reference costs 2017-18
LD01A Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over, away from base	£147.39	Not varied in PSA	NHS Reference costs 2017-18
LD03A Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with	£159.05	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
Blood-Borne Virus, 19 years and over			
LD02A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	£161.05	Not varied in PSA	NHS Reference costs 2017-18
LD02A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over, away from base	£171.65	Not varied in PSA	NHS Reference costs 2017-18
LD04A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	£180.91	Not varied in PSA	NHS Reference costs 2017-18
LD05A Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	£138.12	Not varied in PSA	NHS Reference costs 2017-18
LD05A Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over, awawy from base	£227.65	Not varied in PSA	NHS Reference costs 2017-18
LD07A Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	£130.64	Not varied in PSA	NHS Reference costs 2017-18
LD06A Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	£148.21	Not varied in PSA	NHS Reference costs 2017-18
LD06A Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over, away from base	£245.15	Not varied in PSA	NHS Reference costs 2017-18
LD08A Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	£151.97	Not varied in PSA	NHS Reference costs 2017-18
Pooled average per session (haemodialysis: adults)	£153.36		Calculated
Haemodialysis: children			

Parameter name	Value (95% CI)	Distribution and parameters	Source
LD09B Home Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 18 years and under	£531.19	Not varied in PSA	NHS Reference costs 2017-18
LD10B Home Haemodialysis or Filtration, with Access via Arteriovenous FistulB or Graft, 18 years and under	£473.94	Not varied in PSA	NHS Reference costs 2017-18
LD01B Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 18 years and under	£497.30	Not varied in PSA	NHS Reference costs 2017-18
LD02B Hospital Haemodialysis or Filtration, with Access via Arteriovenous FistulB or Graft, 18 years and under	£617.54	Not varied in PSA	NHS Reference costs 2017-18
LD04B Hospital Haemodialysis or Filtration, with Access via Arteriovenous FistulB or Graft, with Blood-Borne Virus, 18 years and under	£760.28	Not varied in PSA	NHS Reference costs 2017-18
LD05B Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 18 years and under	£254.91	Not varied in PSA	NHS Reference costs 2017-18
LD06B Satellite Haemodialysis or Filtration, with Access via Arteriovenous FistulB or Graft, 18 years and under	£242.60	Not varied in PSA	NHS Reference costs 2017-18
LD08B Satellite Haemodialysis or Filtration, with Access via Arteriovenous FistulB or Graft, with Blood-Borne Virus, 18 years and under	£243.85	Not varied in PSA	NHS Reference costs 2017-18
Pooled average per session (haemodialysis: children)	£490.39		Calculated
Peritoneal dialysis: adults			
LD11A Continuous Ambulatory Peritoneal Dialysis, 19 years and over	£67.60	Not varied in PSA	NHS Reference costs 2017-18
LD11A Continuous Ambulatory Peritoneal Dialysis, 19 years and over, away from base	£62.45	Not varied in PSA	NHS Reference costs 2017-18
LD12A Automated Peritoneal Dialysis, 19 years and over	£76.61	Not varied in PSA	NHS Reference costs 2017-18

Parameter name	Value (95% CI)	Distribution and parameters	Source
LD12A Automated Peritoneal Dialysis, 19 years and over, away from base	£69.74	Not varied in PSA	NHS Reference costs 2017-18
LD13A Assisted Automated Peritoneal Dialysis, 19 years and over	£84.44	Not varied in PSA	NHS Reference costs 2017-18
LD13A Assisted Automated Peritoneal Dialysis, 19 years and over, away from base	£78.08	Not varied in PSA	NHS Reference costs 2017-18
Pooled average (peritoneal dialysis)	£74.37		Calculated
Peritoneal dialysis: children			
LD11B Continuous Ambulatory Peritoneal Dialysis, 18 years and under	£144.23	Not varied in PSA	NHS Reference costs 2017-18
LD12B Automated Peritoneal Dialysis, 18 years and under	£123.52	Not varied in PSA	NHS Reference costs 2017-18
LD13B Assisted Automated Peritoneal Dialysis, 18 years and under	£84.10	Not varied in PSA	NHS Reference costs 2017-18
Pooled average (peritoneal dialysis)	£133.65		Calculated
Dialysis cost per session:			
Adults:			
Home haemodialysis	£229.42		Calculated
Hospital haemodialysis	£157.92		Calculated
Satellite haemodialysis	£145.11		Calculated
Continuous ambulatory PD	£67.54		Calculated
Automated PD	£77.77		Calculated
Children:			
Home haemodialysis	£529.30		Calculated
Hospital haemodialysis	£514.85		Calculated
Satellite haemodialysis	£246.22		Calculated
Continuous ambulatory PD	£144.23		Calculated
Automated PD	£118.79		Calculated
Resource use			

Parameter name	Value (95% CI)	Distribution and parameters	Source
Proportion of adults receiving home HD	0.049	Dirichlet	UK Renal Registry, 2019
Proportion of adults receiving hospital HD	0.323	Dirichlet	UK Renal Registry, 2019
Proportion of adults receiving satellite HD	0.504	Dirichlet	UK Renal Registry, 2019
Proportion of adults receiving continuous ambulatory PD	0.050	Dirichlet	UK Renal Registry, 2019
Proportion of adults receiving automated PD	0.074	Dirichlet	UK Renal Registry, 2019
Proportion of paediatric sessions home HD	0.035	Dirichlet	NHS Reference costs 2017-18
Proportion of paediatric sessions hospital HD	0.437	Dirichlet	NHS Reference costs 2017-18
Proportion of paediatric sessions satellite HD	0.049	Dirichlet	NHS Reference costs 2017-18
Proportion of paediatric sessions continuous ambulatory PD	0.279	Dirichlet	NHS Reference costs 2017-18
Proportion of paediatric sessions automated PD	0.199	Dirichlet	NHS Reference costs 2017-18
Number of sessions per year			
home HD	208 (168, 248)	Triangular: min=156; mode=208; max=260	NICE, 2007 (TA117)
hospital HD	156 (116, 196)	Triangular: min=104; mode=156; max=208	NICE, 2007 (TA117)
satellite HD	156 (116, 196)	Triangular: min=104; mode=156; max=208	NICE, 2007 (TA117)
continuous ambulatory PD	365	Not varied in PSA	NICE, 2007 (TA117)
automated PD	365	Not varied in PSA	NICE, 2007 (TA117)
Proportion of total dialysis costs for travel, access maintenance, etc.	0.150 (0.034, 0.266)	Triangular: min=0.000; mode=0.150; max=0.300	NICE, 2018b (NG107)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Post-transplantation maintenance immunosuppression			
Tacrolimus			
Prograf 500 microgram capsules	£61.88	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Prograf 1mg capsules	£80.28	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Prograf 5mg capsules	£296.58	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Adoport 500 microgram capsules	£42.92	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Adoport 1mg capsules	£55.69	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Adoport 5mg capsules	£205.74	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Weighted average cost per mg	£1.54		Calculated
Dose (mg/kg/day)	0.20	Not varied in PSA	Jones-Hughes et al., 2016
Weight (kg)	70.00	Not varied in PSA	Assumption
Cost per cycle	£1973.55		Calculated
Ciclosporin			
Ciclosporin 10mg capsules	£18.25	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Ciclosporin 25mg capsules	£18.37	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Ciclosporin 50mg capsules	£35.97	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Ciclosporin 100mg capsules	£68.28	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Sandimmun_Cap 25mg	£29.58	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Sandimmun_Cap 100mg	£109.93	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Sandimmun_Cap 50mg	£57.92	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Deximune_Cap 25mg	£13.06	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Deximune_Cap 50mg	£25.60	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Deximune_Cap 100mg	£48.90	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Capimune_Cap 25mg	£13.05	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Capimune_Cap 50mg	£25.50	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Capimune_Cap 100mg	£48.50	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Capsorin_Cap 100mg	£41.59	Not varied in PSA	Cost from NHS drug tariff (Oct 2019);

Parameter name	Value (95% CI)	Distribution and parameters	Source
			quantity for weighting from PCA (Mar 2019)
Capsorin_Cap 50mg	£21.80	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Capsorin_Cap 25mg	£11.14	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Vanquoral_Cap 10mg	£12.75	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Vanquoral_Cap 25mg	£13.05	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Vanquoral_Cap 50mg	£25.59	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Vanquoral_Cap 100mg	£48.89	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Weighted average cost per mg	£0.02		Calculated
Dose (mg/kg/day)	4.00	Not varied in PSA	Jones-Hughes et al., (2016)
Weight (kg)	70.00	Not varied in PSA	Assumption
Cost per cycle	£605.11		Calculated
Azathioprine			
Azathioprine 25mg tablets	£1.71	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Azathioprine 50mg tablets	£2.47	Not varied in PSA	Cost from NHS drug tariff (Oct 2019); quantity for weighting from PCA (Mar 2019)
Weighted average cost per mg	£0.001		Calculated
Dose (mg/kg/day)	1.75	Not varied in PSA	Jones-Hughes et al., (2016)

Parameter name	Value (95% CI)	Distribution and parameters	Source
Weight (kg)	70.00	Not varied in PSA	Assumption
Cost per cycle	£12.65		Calculated
Total costs per cycle			
Proportion of people on tacrolimus -v- ciclosporin	75.0% (55.6%, 94.4%)	Triangular: min=50.0%; mode=75.0%; max=100.0%	Assumption
Maintenance	£1644.09		Calculated
Per-cycle costs			
PTH test	£10.00		Calculated
Calcium test	£1.11		Calculated
Phosphorus test	£1.11		Calculated
Vitamin D (per year)	£52.00 (£11.63, £92.37)	Triangular: min=£0.00; mode=£52.00; max=£104.00	NICE, 2007 (TA117)
Dialysis	£7362.80		Calculated

a. Estimated by interpolation between 3 and 12 months.
b. Not evaluated in the model.
c. 6-12 month gradient extended back to 3 months.
d. Probabilities calculated by dividing the probability of dropout but the sum of the probabilities of experiencing each event.
e. Obtained from post-parathyroidectomy meta-model

Correlation matrices

Table 82: Correlations between treatment effects at 3, 6, and 12 months – phosphate

		3 months							6 months							9 months						
		CA	CA+MC	FC	LC	SC	SH	SO	CA	CA+MC	FC[a]	LC	SC	SH	SO	CA	CA+MC[a]	FC	LC	SC	SH	SO
Mean		-0.154	-0.334	-0.143	-0.050	-0.207	-0.149	-0.200	0.086	-0.111	N/A	0.008	0.100	-0.063	0.077	-0.057	N/A	-0.037	0.159	-0.060	0.009	-0.130
SD		0.136	0.189	0.138	0.100	0.155	0.101	0.157	0.118	0.159	1.000	0.066	0.133	0.081	0.139	0.087	1.000	0.150	0.059	0.169	0.050	0.189
Correlation matrix																						
3 months	CA	1.000	0.385	0.382	0.304	0.443	0.710	0.458	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	CA+MC	0.385	1.000	0.291	0.246	0.338	0.540	0.350	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	FC	0.382	0.291	1.000	0.479	0.346	0.534	0.350	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	LC	0.304	0.246	0.479	1.000	0.267	0.422	0.275	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SC	0.443	0.338	0.346	0.267	1.000	0.639	0.723	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SH	0.710	0.540	0.534	0.422	0.639	1.000	0.644	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SO	0.458	0.350	0.350	0.275	0.723	0.644	1.000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6 months	CA	0	0	0	0	0	0	0	1.000	0.246	0	0.134	0.264	0.533	0.195	0	0	0	0	0	0	0
	CA+MC	0	0	0	0	0	0	0	0.246	1.000	0	0.146	0.245	0.499	0.180	0	0	0	0	0	0	0
	FC[a]	0	0	0	0	0	0	0	0	0	1.000	0	0	0	0	0	0	0	0	0	0	0
	LC	0	0	0	0	0	0	0	0.134	0.146	0	1.000	0.286	0.306	0.326	0	0	0	0	0	0	0
	SC	0	0	0	0	0	0	0	0.264	0.245	0	0.286	1.000	0.484	0.709	0	0	0	0	0	0	0
	SH	0	0	0	0	0	0	0	0.533	0.499	0	0.306	0.484	1.000	0.352	0	0	0	0	0	0	0
	SO	0	0	0	0	0	0	0	0.195	0.180	0	0.326	0.709	0.352	1.000	0	0	0	0	0	0	0
12	CA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.000	0	0.553	0.141	0.495	0.543	0.441
	CA+MC[a]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.000	0	0	0	0	0
	FC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.553	0	1.000	0.077	0.748	0.292	0.674
	LC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.141	0	0.077	1.000	0.075	0.300	0.062

		3 months							6 months							9 months						
		CA	CA+MC	FC	LC	SC	SH	SO	CA	CA+MC	FC[a]	LC	SC	SH	SO	CA	CA+MC[a]	FC	LC	SC	SH	SO
	SC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.495	0	0.748	0.075	1.000	0.275	0.900
	SH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.543	0	0.292	0.300	0.275	1.000	0.239
	SO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.441	0	0.674	0.062	0.900	0.239	1.000

(a) No data available at this timepoint.
CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; MC, magnesium carbonate; SC, sevelamer carbonate; SD, standard deviation; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Table 83: Correlations between treatment effects at 3, 6, and 12 months – calcium

		3 months							6 months							9 months						
		CA	CA+MC	FC	LC	SC[a]	SH	SO	CA	CA+MC	FC[a]	LC	SC	SH	SO	CA	CA+MC[a]	FC	LC	SC	SH	SO
Mean		-0.075	-0.055	-0.099	-0.102	N/A	-0.138	-0.099	-0.047	-0.061	N/A	-0.108	-0.108	-0.126	-0.129	-0.113	N/A	-0.186	-0.092	-0.199	-0.130	-0.200
SD		0.062	0.078	0.062	0.058	1.000	0.042	0.077	0.083	0.116	1.000	0.052	0.052	0.095	0.055	0.064	1.000	0.114	0.049	0.116	0.041	0.141
Correlation matrix																						
3 months	**CA**	1.000	0.359	0.373	0.313	0	0.671	0.354	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	CA+MC	0.359	1.000	0.294	0.242	0	0.532	0.285	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	FC	0.373	0.294	1.000	0.585	0	0.548	0.274	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	LC	0.313	0.242	0.585	1.000	0	0.454	0.204	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SC[a]	0	0	0	0	1.000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SH	0.671	0.532	0.548	0.454	0	1.000	0.535	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SO	0.354	0.285	0.274	0.204	0	0.535	1.000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6 months	**CA**	0	0	0	0	0	0	0	1.000	0.223	0	0.099	0.189	0.468	0.133	0	0	0	0	0	0	0
	CA+MC	0	0	0	0	0	0	0	0.223	1.000	0	0.122	0.194	0.481	0.126	0	0	0	0	0	0	0
	FC[a]	0	0	0	0	0	0	0	0	0	1.000	0	0	0	0	0	0	0	0	0	0	0
	LC	0	0	0	0	0	0	0	0.099	0.122	0	1.000	0.282	0.243	0.410	0	0	0	0	0	0	0
	SC	0	0	0	0	0	0	0	0.189	0.194	0	0.282	1.000	0.436	0.589	0	0	0	0	0	0	0
	SH	0	0	0	0	0	0	0	0.468	0.481	0	0.243	0.436	1.000	0.280	0	0	0	0	0	0	0

		3 months							6 months							9 months						
		CA	CA+MC	FC	LC	SC[a]	SH	SO	CA	CA+MC	FC[a]	LC	SC	SH	SO	CA	CA+MC[a]	FC	LC	SC	SH	SO
	SO	0	0	0	0	0	0	0	0.133	0.126	0	0.410	0.589	0.280	1.000	0	0	0	0	0	0	0
12 months	CA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.000	0	0.569	0.119	0.558	0.543	0.440
	CA+MC[a]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.000	0	0	0	0	0
	FC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.569	0	1.000	0.058	0.708	0.312	0.562
	LC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.119	0	0.058	1.000	0.066	0.234	0.064
	SC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.558	0	0.708	0.066	1.000	0.305	0.791
	SH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.543	0	0.312	0.234	0.305	1.000	0.238
	SO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.440	0	0.562	0.064	0.791	0.238	1.000

(a) No data available at this timepoint.
CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; MC, magnesium carbonate; SC, sevelamer carbonate; SD, standard deviation; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

Table 84: Correlations between rates of adverse events and discontinuations

		Constipation							Dirrhoea							Nausea and vomiting							Discontinuations						
		CA	CA+MC[a]	FC	LC	SC	SH	SO	CA	CA+MC[a]	FC	LC	SC	SH	SO	CA	CA+MC[a]	FC	LC	SC	SH	SO	CA	CA+MC	FC	LC	SC[a]	SH	SO
Mean		1.36	N/A	-0.29	-0.36	0.47	1.51	-0.16	0.08	N/A	2.04	0.28	0.41	-0.04	1.43	-1.33	N/A	2.08	0.83	-1.50	-1.50	-1.99	0.59	-0.81	0.79	0.73	0.79	0.41	0.98
SD		0.59	1.00	0.64	0.23	0.60	0.47	0.58	1.07	1.00	0.86	0.50	1.01	0.93	0.89	1.65	1.00	2.62	0.65	1.48	1.45	1.65	0.59	1.03	0.63	0.39	0.62	0.40	0.54
Correlation matrix																														
Constipation	CA	1.00	0	0.50	0.08	0.53	0.78	0.57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	CA+MC[a]	0	1.00	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	FC	0.50	0	1.00	0.12	0.51	0.64	0.53	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	LC	0.08	0	0.12	1.00	0.12	0.11	0.12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SC	0.53	0	0.51	0.12	1.00	0.68	0.90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SH	0.78	0	0.64	0.11	0.68	1.00	0.72	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SO	0.57	0	0.53	0.12	0.90	0.72	1.00	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Diarrhoea	**CA**	0	0	0	0	0	0	0	1.00	0	0.59	0.45	0.70	0.87	0.73	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	CA+MC[a]	0	0	0	0	0	0	0	0	1.00	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	FC	0	0	0	0	0	0	0	0.59	0	1.00	0.56	0.59	0.67	0.66	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	LC	0	0	0	0	0	0	0	0.45	0	0.56	1.00	0.47	0.51	0.53	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SC	0	0	0	0	0	0	0	0.70	0	0.59	0.47	1.00	0.80	0.84	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SH	0	0	0	0	0	0	0	0.87	0	0.67	0.51	0.80	1.00	0.83	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	SO	0	0	0	0	0	0	0	0.73	0	0.66	0.53	0.84	0.83	1.00	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nausea + vomiting	**CA**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.00	0	0.15	0.38	0.68	0.86	0.67	0	0	0	0	0	0	0
	CA+MC[a]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.00	0	0	0	0	0	0	0	0	0	0	0	0
	FC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.15	0	1.00	0.24	0.18	0.18	0.15	0	0	0	0	0	0	0
	LC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.38	0	0.24	1.00	0.42	0.44	0.38	0	0	0	0	0	0	0
	SC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.68	0	0.18	0.42	1.00	0.79	0.82	0	0	0	0	0	0	0
	SH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.86	0	0.18	0.44	0.79	1.00	0.77	0	0	0	0	0	0	0
	SO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.67	0	0.15	0.38	0.82	0.77	1.00	0	0	0	0	0	0	0
Discontinuations	**CA**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.00	0.24	0.32	0.28	0.37	0.64	0.40
	CA+MC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.24	1.00	0.19	0.17	0.21	0.38	0.25
	FC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.32	0.19	1.00	0.41	0.37	0.49	0.41
	LC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.28	0.17	0.41	1.00	0.34	0.43	0.42
	SC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.37	0.21	0.37	0.34	1.00	0.59	0.62
	SH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.64	0.38	0.49	0.43	0.59	1.00	0.64
	SO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.40	0.25	0.41	0.42	0.62	0.64	1.00

(a) No data available at this timepoint.
CA, calcium acetate; CC, calcium carbonate; FC, ferric citrate; LC, lanthanum carbonate; MC, magnesium carbonate; SC, sevelamer carbonate; SD, standard deviation; SH, sevelamer hydrochloride; SO, sucroferric oxyhydroxide.

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Appendix M– Excluded studies

Effectiveness studies

Study	Reason
Bhargava R., Kalra P.A., Hann M. et al. (2019) A randomized controlled trial of different serum phosphate ranges in subjects on hemodialysis. BMC Nephrology 20(1): 37	- Study does not contain a relevant intervention
Block, Geoffrey A, Block, Martha S, Smits, Gerard et al. (2019) A Pilot Randomized Trial of Ferric Citrate Coordination Complex for the Treatment of Advanced CKD. Journal of the American Society of Nephrology : JASN	- Data not reported in an extractable format [Only baseline data was reported for CKD stages and for people who were or not on dialysis]
Caglar, K., Yilmaz, M. I., Saglam, M. et al. (2008) Short-term treatment with sevelamer increases serum fetuin-a concentration and improves endothelial dysfunction in chronic kidney disease stage 4 patients. Clinical Journal of The American Society of Nephrology: CJASN 3(1): 61-68	- Secondary publication of an included study that does not provide any additional relevant information
Chennasamudram, Sudha P; Noor, Tanjila; Vasylyeva, Tetyana L (2013) Comparison of sevelamer and calcium carbonate on endothelial function and inflammation in patients on peritoneal dialysis. Journal of renal care 39(2): 82-9	- Data not reported in an extractable format [crossover trials without parallel data]
Chertow, Glenn M, Block, Geoffrey A, Neylan, John F et al. (2017) Safety and efficacy of ferric citrate in patients with nondialysis-dependent chronic kidney disease. PloS one 12(11): e0188712	- Does not contain a population of people with stage 4 or 5 CKD who are not on dialysis [CKD stages 3 to 5]
Choi, Y.J.; Noh, Y.; Shin, S. (2020) Ferric citrate in the management of hyperphosphataemia and iron deficiency anaemia: A meta-analysis in patients with chronic kidney disease. British Journal of Clinical Pharmacology	- Systematic review used as source of primary studies
Chonchol, M, Wuthrich, RP, Rakov, V et al. (2012) Iron-based phosphate binder PA21: effective and well tolerated in CKD hemodialysis patients. American journal of kidney diseases 59(4): a27	- Conference abstract
Di Iorio, Biagio, Bellasi, Antonio, Russo, Domenico et al. (2012) Mortality in kidney disease patients treated with phosphate binders: a randomized study. Clinical journal of the American Society of Nephrology : CJASN 7(3): 487-93	- Does not contain a population of people with stage 4 or 5 CKD who are not on dialysis [stage 3 to 4 CKD]
Evsanaa, Baigalmaa, Liu, Irene, Aliazardeh, Babak et al. (2015) MgCaCO3 versus CaCO3 in peritoneal dialysis patients--a cross-over pilot trial. Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis 35(1): 31-4	- Data not reported in an extractable format [crossover trials without parallel data]
Gasu V., Ashong M., Seferi A. et al. (2019) Effectiveness of phosphate binders in adult	- Systematic review used as source of primary studies

Study	Reason
patients with end stage renal disease receiving hemodialysis: a systematic review. JBI database of systematic reviews and implementation reports 17(1): 49-73	
Ginsberg, C., Zelnick, L.R., Block, G.A. et al. (2020) Differential effects of phosphate binders on vitamin D metabolism in chronic kidney disease. Nephrology Dialysis Transplantation 35(4): 616-623	- Does not contain a population of people with stage 4 or 5 CKD who are not on dialysis
Goto, Kimihiko, Goto, Shunsuke, Fujii, Hideki et al. (2019) Effects of lanthanum carbonate on bone markers and bone mineral density in incident hemodialysis patients. Journal of bone and mineral metabolism 37(6): 1075-1082	- Secondary publication of an included study that does not provide any additional relevant information [Related to Fujii 2018]
Guo, Hua, Zhang, Xiaojuan, Tang, Shaowen et al. (2013) Effects and safety of lanthanum carbonate in end stage renal disease patients with hyperphosphatemia: a meta-analysis--system review of lanthanum carbonate. Renal failure 35(10): 1455-64	- Systematic review used as source of primary studies
Habbous, Steven, Przech, Sebastian, Acedillo, Rey et al. (2017) The efficacy and safety of sevelamer and lanthanum versus calcium-containing and iron-based binders in treating hyperphosphatemia in patients with chronic kidney disease: a systematic review and meta-analysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 32(1): 111-125	- Systematic review or NMA included participants with stages 3 to 5 CKD - Systematic review used as source of primary studies [Primary studies already screened/included in 2013]
Hahn, Deirdre; Hodson, Elisabeth M; Craig, Jonathan C (2015) Interventions for metabolic bone disease in children with chronic kidney disease. The Cochrane database of systematic reviews: cd008327	- Study does not contain a relevant intervention
Huang, Wenhui, Liu, Jing, Tang, Yu et al. (2014) Efficacy and tolerability of lanthanum carbonate in treatment of hyperphosphatemia patients receiving dialysis--a systematic review and meta-analysis of randomized controlled trials. Current medical research and opinion 30(1): 99-108	- Systematic review used as source of primary studies
Jiang, M., Zheng, H., Xu, C. et al. (2020) Meta-Analysis Treatment Hyperphosphatemia Chronic Renal Failure Based on Nano Lanthanum Hydroxide. Journal of nanoscience and nanotechnology 20(10): 6555-6560	- Full text paper not available
Kasai, Satoshi, Sato, Kazuto, Murata, Yaeko et al. (2012) Randomized crossover study of the efficacy and safety of sevelamer hydrochloride and lanthanum carbonate in Japanese patients undergoing hemodialysis. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 16(4): 341-9	- Data not reported in an extractable format [crossover trials without parallel data]

Study	Reason
Lioufas, N.M., Pedagogos, E., Hawley, C.M. et al. (2020) Aortic Calcification and Arterial Stiffness Burden in a Chronic Kidney Disease Cohort with High Cardiovascular Risk: Baseline Characteristics of the Impact of Phosphate Reduction On Vascular End-Points in Chronic Kidney Disease Trial. American Journal of Nephrology 51(3): 201-215	- Does not contain a population of people with stage 4 or 5 CKD who are not on dialysis
Liu L, Wang Y, Chen H, Zhu X, Zhou L, Yang Y (2014) The effects of non-calcium-based phosphate binders versus calcium-based phosphate binders on cardiovascular calcification and bone remodeling among dialysis patients: a meta-analysis of randomized trials. Renal Failure 36(8): 1244-1252	- Systematic review used as source of primary studies
Matsushima, H, Yasuda, T, Oyama, A et al. (2017) Efficacy and safety of iron-based phosphate binders, ferric citrate hydrate versus sucroferric oxyhydroxide, on hyperphosphatemia in chronic hemodialysis patients. Nephrology dialysis transplantation 32(suppl3): iii679	- Conference abstract
McCullough P.A., Uhlig K., Neylan J.F. et al. (2018) Usefulness of Oral Ferric Citrate in Patients With Iron-Deficiency Anemia and Chronic Kidney Disease With or Without Heart Failure. American Journal of Cardiology 122(4): 683-688	- Does not contain a population of people with stage 4 or 5 CKD who are not on dialysis [stage 3 to 5 non-dialysis-dependent CKD]
Murali, Karumathil M, Mullan, Judy, Chen, Jenny H C et al. (2017) Medication adherence in randomized controlled trials evaluating cardiovascular or mortality outcomes in dialysis patients: A systematic review. BMC nephrology 18(1): 42	- Systematic review used as source of primary studies
Ogata, Hiroaki, Fukagawa, Masafumi, Hirakata, Hideki et al. (2017) Design and baseline characteristics of the LANDMARK study. Clinical and experimental nephrology 21(3): 531-537	- Protocol
Palmer, Suetonia C, Gardner, Sharon, Tonelli, Marcello et al. (2016) Phosphate-Binding Agents in Adults With CKD: A Network Meta-analysis of Randomized Trials. American journal of kidney diseases : the official journal of the National Kidney Foundation 68(5): 691-702	- Systematic review used as source of primary studies
Palmer, Suetonia C, Teixeira-Pinto, Armando, Saglimbene, Valeria et al. (2015) Association of Drug Effects on Serum Parathyroid Hormone, Phosphorus, and Calcium Levels With Mortality in CKD: A Meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation 66(6): 962-71	- Systematic review used as source of primary studies
Pan, F.F., Smith, E.R., Hewitson, T.D. et al. (2020) SUN-094 A RANDOMISED CROSS-OVER TRIAL OF THE EFFECTS OF CALCIUM CARBONATE AND SEVELAMER PHOSPHATE BINDERS ON CALCIPROTEIN PARTICLES IN PREVALENT HAEMODIALYSIS PATIENTS.	- Conference abstract

Study	Reason
Kidney International Reports 5(3supplement): 240	
Pasch, A, de Francisco, ALM, Covic, A et al. (2014) Serum calcification propensity of HD patients is therapeutically improved by acalcium acetate/ magnesiumcarbonate containing phosphate binder. Nephrology dialysis transplantation 29(suppl3): iii40	- Conference abstract
Quinones H., Hamdi T., Sakhaee K. et al. (2019) Control of metabolic predisposition to cardiovascular complications of chronic kidney disease by effervescent calcium magnesium citrate: a feasibility study. Journal of Nephrology 32(1): 93-100	- Study does not contain a relevant intervention [Intervention specific for study: effervescent calcium magnesium citrate]
Rosen, M., Ficociello, L.H., Mullon, C. et al. (2020) PUK11 COST EFFECTIVENESS OF PHARMACEUTICAL TREATMENT OF HYPERPHOSPHATEMIA WITH PHOSPHATE BINDERS: A SYSTEMATIC REVIEW. Value in Health 23(supplement1): 378-s379	- Conference abstract
Rosenbaum, D. and Yang, Y. (2020) EFFICACY OF TENAPANOR FOR THE CONTROL OF SERUM PHOSPHORUS IN PATIENTS WITH CKD ON DIALYSIS: NOVEL MECHANISM OF ACTION ALLOWS FOR BOTH MONOTHERAPY AND DUAL MECHANISM APPROACH. American Journal of Kidney Diseases 75(4): 627	- Conference abstract
Ruggiero B., Trillini M., Tartaglione L. et al. (2019) Effects of Sevelamer Carbonate in Patients With CKD and Proteinuria: The ANSWER Randomized Trial. American Journal of Kidney Diseases	- Comparator in study does not match that specified in protocol
Ruospo, Marinella, Palmer, Suetonia C, Natale, Patrizia et al. (2018) Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). The Cochrane database of systematic reviews 8: cd006023	- Systematic review used as source of primary studies
Sekercioglu, Nigar, Angeliki Veroniki, Argie, Thabane, Lehana et al. (2017) Effects of different phosphate lowering strategies in patients with CKD on laboratory outcomes: A systematic review and NMA. PloS one 12(3): e0171028	- Systematic review used as source of primary studies
Sekercioglu, Nigar, Thabane, Lehana, Diaz Martinez, Juan Pablo et al. (2016) Comparative Effectiveness of Phosphate Binders in Patients with Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis. PloS one 11(6): e0156891	- Systematic review used as source of primary studies
Song, F-R, Cheng, H, Zhao, D-M et al. (2014) Effects of lanthanum carbonate on serum calcium and phosphorus of CAPD patients with chronic renal failure receiving calcitriol pulse therapy due to secondary hyperparathyroidism.	- Study not reported in English

Study	Reason
Chinese journal of evidence-based medicine 14(6): 651-654	
Sprague, Stuart M, Ketteler, Markus, Covic, Adrian C et al. (2018) Long-term efficacy and safety of sucroferric oxyhydroxide in African American dialysis patients. Hemodialysis international. International Symposium on Home Hemodialysis 22(4): 480-491	- Secondary publication of an included study that does not provide any additional relevant information
Toida, Tatsunori, Fukudome, Keiichi, Fujimoto, Shouichi et al. (2012) Effect of lanthanum carbonate vs. calcium carbonate on serum calcium in hemodialysis patients: a crossover study. Clinical nephrology 78(3): 216-23	- Data not reported in an extractable format [crossover trials without parallel data]
Umanath, Kausik, Sika, Mohammed, Niecestro, Robert et al. (2013) Rationale and study design of a three-period, 58-week trial of ferric citrate as a phosphate binder in patients with ESRD on dialysis. Hemodialysis international. International Symposium on Home Hemodialysis 17(1): 67-74	- Protocol
Wang, Fang, Lu, Xiangxue, Zhang, Jingli et al. (2018) Effect of Lanthanum Carbonate on All-Cause Mortality in Patients Receiving Maintenance Hemodialysis: a Meta-Analysis of Randomized Controlled Trials. Kidney & blood pressure research 43(2): 536-544	- Systematic review used as source of primary studies
Wang, Yong, Xie, Guoqiang, Huang, Yuanhang et al. (2015) Calcium acetate or calcium carbonate for hyperphosphatemia of hemodialysis patients: a meta-analysis. PloS one 10(3): e0121376	- Systematic review used as source of primary studies
Wei, Yong, Kong, Xiang Lei, Li, Wen Bin et al. (2014) Effect of calcium carbonate combined with calcitonin on hypercalcemia in hemodialysis patients. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 18(6): 618-22	- Study does not contain a relevant intervention [Calcitonin]
Wilson R.J.; Jones B.; Marelli C. (2018) Iron parameters in patients with end-stage renal disease receiving lanthanum carbonate or other non-iron-based phosphate binders: Results from a phase 3, randomized open-label study. SAGE Open Medicine 6	- Study does not contain a relevant outcome [iron parameters and haemoglobin levels]
Wilson, RJ and Copley, JB (2017) Elemental calcium intake associated with calcium acetate/calcium carbonate in the treatment of hyperphosphatemia. Drugs in context 6(nopagination)	- Not a relevant study design [Not an RCT]
Xie, Dengpiao; Ye, Naijing; Li, Mingquan (2018) A systematic review on the efficacy and safety of PA21 versus sevelamer in dialysis patients. International urology and nephrology 50(5): 905-909	- Systematic review used as source of primary studies

Study	Reason
Yang X., Bai Q., Li Y. et al. (2018) Comparative Efficacy and Safety of Phosphate Binders in Hyperphosphatemia Patients With Chronic Kidney Disease. Journal of Parenteral and Enteral Nutrition 42(4): 766-777	- Systematic review used as source of primary studies
Zhai, Chun-Juan, Yang, Xiao-Wei, Sun, Jing et al. (2015) Efficacy and safety of lanthanum carbonate versus calcium-based phosphate binders in patients with chronic kidney disease: a systematic review and meta-analysis. International urology and nephrology 47(3): 527-35	- Systematic review used as source of primary studies
Zhai, Chun-Juan, Yu, Xin-Shuang, Yang, Xiao-Wei et al. (2015) Effects and safety of iron-based phosphate binders in dialysis patients: a systematic review and meta-analysis. Renal failure 37(1): 7-15	- Systematic review used as source of primary studies
Zhang, Chenglong, Wen, Ji, Li, Zi et al. (2013) Efficacy and safety of lanthanum carbonate on chronic kidney disease-mineral and bone disorder in dialysis patients: a systematic review. BMC nephrology 14: 226	- Systematic review used as source of primary studies
Zhao, H, Wang, J-D, Zhao, D-M et al. (2014) Efficacy of sevelamer carbonate for hyperphosphatemia in patients with end-stage renal disease: a randomized controlled trial. Chinese journal of evidence-based medicine 14(11): 1293-1298	- Study not reported in English
Zhou, Tianbiao, Li, Hongyan, Xie, Weiji et al. (2018) A meta-analysis of phosphate binders lanthanum carbonate versus sevelamer hydrochloride in patients with end-stage renal disease undergoing hemodialysis. African health sciences 18(3): 689-696	- Systematic review used as source of primary studies
Zwiech, R, Dryja, P, Łacina, D et al. (2011) The influence of short-term magnesium carbonate treatment on calcium-phosphorus balance in dialysis patients. Wiadomosci lekarskie (Warsaw, Poland 64(1): 9-14	- Study not reported in English

Cost-effectiveness studies

Study	Reason
All Wales Medicines Strategy Group (AWMSG) (2015) Sucroferric oxyhydroxide (Velphoro). Penarth: All Wales Therapeutics and Toxicology Centre (AWTTC), secretariat of the All Wales Medicines Strategy Group (AWMSG)	Non-peer-reviewed evidence (grey literature).
Canadian Agency for Drugs and Technologies in Health (CADTH). Pharmacoeconomic Review Report: Sucroferric Oxyhydroxide (Velphoro): (Vifor Fresenius Medical Care Renal Pharma Ltd.): Indication: For the control of serum phosphorus levels in adult patients with end-stage renal disease on dialysis [Internet]. Ottawa	Non-peer-reviewed evidence (grey literature).

Study	Reason
(ON); 2019 [cited 2019 Sep 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542813/	
Cho, Jang-Hee, Jang, Hye Min, Jung, Hee-Yeon et al. (2018) A Real-world Cost-effectiveness Analysis of Sevelamer Versus Calcium Acetate in Korean Dialysis Patients. Clinical therapeutics 40(1): 123-134	Non-European (Korean) population. Selectively excluded: studies from the UK included looking at same intervention/comparator.
del Pino M.D., Pons R., Rodriguez-Carmona A. et al. (2016) Cost-effectiveness of sevelamer versus calcium carbonate in non-dialysis dependent chronic kidney disease patients in Spain. Pharmacoeconomics - Spanish Research Articles 13(2): 49-56	Article in Spanish.
Giotta, N and Marino, A M (2015) Pharmacoeconomic Analysis: Analysis Of Cost-Effectiveness Of Lanthanum-Carbonate (Lc) In Uncontrolled Hyperphosphatemia In Dialysis. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 18(7): a511	Abstract only.
Goh, B L, Soraya, A, Goh, A et al. (2018) Cost-Effectiveness Analysis for the Treatment of Hyperphosphatemia in Predialysis Patients: Calcium-Based versus Noncalcium-Based Phosphate Binders. International journal of nephrology 2018: 2138528	Selectively excluded: Non-OECD country (Malaysia).
Gonzalez-Parra E., Gros B., Galan A. et al. (2014) Cost-effectiveness analysis of lanthanum carbonate versus sevelamer hydrochloride in the treatment of hyperphosphatemia in patients with end-stage renal disease in Spain. Pharmacoeconomics - Spanish Research Articles 12(1): 11-22	Article in Spanish.
Goto, Shunsuke, Komaba, Hirotaka, Moriwaki, Kensuke et al. (2011) Clinical efficacy and cost-effectiveness of lanthanum carbonate as second-line therapy in hemodialysis patients in Japan. Clinical journal of the American Society of Nephrology: CJASN 6(6): 1375-84	Selectively excluded: non-European (Japanese) population.
Gros B., Galan A., Gonzalez-Parra E. et al. (2015) Cost effectiveness of lanthanum carbonate in chronic kidney disease patients in Spain before and during dialysis. Health Economics Review 5(1): 14	Selectively excluded: studies from the UK included looking at same intervention/comparator.
Keith, Michael S, Wilson, Rosamund J, Preston, Peter et al. (2014) Cost-minimization analysis of lanthanum carbonate versus sevelamer hydrochloride in US patients with end-stage renal disease. Clinical therapeutics 36(9): 1276-86	Does not include quality of life data.
Koulouridis E., Kostimpa I., Klonou E. et al. (2011) Magnesium levels and magnesium containing phosphate binders in haemodialysis patients. Hippokratia 15(suppl2): 21-26	Does not include quality of life data.

Study	Reason
Nguyen, Hai V; Bose, Saideep; Finkelstein, Eric (2016) Incremental cost-utility of sevelamer relative to calcium carbonate for treatment of hyperphosphatemia among pre-dialysis chronic kidney disease patients. BMC nephrology 17(1): 45	Non-European (Singaporean) population. Selectively excluded: studies from the UK included looking at same intervention/comparator.
Ossareh S. (2014) Clinical and economic aspects of sevelamer therapy in end-stage renal disease patients. International Journal of Nephrology and Renovascular Disease 7: 161-168	Review article.
Panichi, Vincenzo, Rosati, Alberto, Di Giorgio, Adriana et al. (2015) A pharmacoeconomic analysis of phosphate binders cost-effectiveness in the RISCAVID study. Blood purification 39(13): 174-80	Does not include quality of life data.
Petrou, Panagiotis (2019) A systematic review of the economic evaluations of non-calcium-containing phosphate binders, sevelamer and Lanthanum, in end-stage renal disease patients with hyperphosphatemia. Expert review of pharmacoeconomics & outcomes research 19(3): 287-298	Review article.
Petrov, M K; Dimitrova, M; Petrova, G I (2014) Cost-minimization analysis of the direct costs of sevelamer carbonate and lanthanum carbonate in the treatment of CKD-ND patients. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(7): a470	Abstract only.
Rizk, Rana (2016) Cost-effectiveness of phosphate binders among patients with chronic kidney disease not yet on dialysis: a long way to go. BMC nephrology 17(1): 75	Review article.
Rizk, Rana, Hiligsmann, Mickael, Karavetian, Mirey et al. (2016) Economic evaluations of interventions to manage hyperphosphataemia in adult haemodialysis patients: A systematic review. Nephrology (Carlton, Vic.) 21(3): 178-87	Review article.
Ruggeri, Matteo, Bellasi, Antonio, Cipriani, Filippo et al. (2015) Sevelamer is cost effective versus calcium carbonate for the first-line treatment of hyperphosphatemia in new patients to hemodialysis: a patient-level economic evaluation of the INDEPENDENT-HD study. Journal of nephrology 28(5): 593-602	Does not include quality of life data (uses life-years as outcome rather than quality-adjusted life-years).
Ruggeri, Matteo, Cipriani, Filippo, Bellasi, Antonio et al. (2014) Sevelamer is cost-saving vs. calcium carbonate in non-dialysis-dependent CKD patients in italy: a patient-level cost-effectiveness analysis of the INDEPENDENT study. Blood purification 37(4): 316-24	Does not include quality of life data.
Subira, R, Rubio, M, Rodriguez-Carmona, A et al. (2014) A Spanish Cost-Effectiveness Analysis Of Sevelamer Versus Calcium	Abstract only.

Study	Reason
Carbonate In Nondialysis-Dependent Chronic Kidney Disease (Ckd) Patients. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(7): a470	
Vegter, Stefan, Tolley, Keith, Keith, Michael S et al. (2012) Cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in dialysis patients: a Canadian payer perspective. Clinical therapeutics 34(7): 1531-43	Non-European (Canadian) population. Selectively excluded: studies from the UK included looking at same intervention/comparator.
Yang, Li, Chuen Tan, Seng, Chen, Can et al. (2016) Economic Evaluation of Sevelamer versus Calcium-based Binders in Treating Hyperphosphatemia among Patients with End-stage Renal Disease in China. Clinical therapeutics 38(11): 2459-2467e1	Selectively excluded: non-OECD country (China).

Appendix N – Research recommendations – full details

N.1.1 Research recommendation

Which binders are most effective in controlling serum phosphate in adults with stage 4 or 5 CKD who are not on dialysis?

Why this is important

Limited evidence was found on the use of phosphate binders in adults with stage 4 or 5 CKD who are not on dialysis (7 RCTs). While it is possible in some instances to extrapolate from the evidence on people with stage 5 CKD who are on dialysis, it is not ideal. Therefore, a series of RCTs should be conducted to examine the comparative effectiveness of various phosphate binders against each other for the management of serum phosphate in adults with stage 4 or 5 CKD. These trials should examine the long-term (ideally 12-month) effects of the various binders on outcomes such as serum phosphate, serum calcium, adverse events and the ability of the binders to control serum phosphate and calcium within the given ranges.

None of these seven RCTs reported on sucroferric oxyhydroxide which is now available for adults with CKD to control serum phosphate levels. The committee noted that further research is needed to inform future updates of this guidance. New evidence could lead to specific recommendations for adults with stage 4 or 5 CKD who are not on dialysis.

Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the use of phosphate binders in adults with stage 4 or 5 CKD who are not on dialysis. There might be a benefit for patients in the management of their hyperphosphataemia if further evidence shows that some phosphate binders are better than others.
Relevance to NICE guidance	The use of phosphate binders in adults with stage 4 or 5 CKD who are not on dialysis has been considered in this guideline and there was a lack of data on this population. Further evidence might fill in the gap in this area during future updates of the guideline.
Relevance to the NHS	The outcome could affect the type of treatment to lower hyperphosphataemia in adults with stage 4 or 5 CKD who are not on dialysis. If new recommendations are made in future, this may change the cost of phosphate binders provided by the NHS.
National priorities	High
Current evidence base	7 RCTs reporting on calcium acetate, calcium carbonate, sevelamer hydrochloride, lanthanum carbonate, and ferric citrate
Equality considerations	None known

Modified PICO table

Population	Adults with stage 4 or 5 CKD who are not on dialysis
Intervention	Phosphate binders
Comparator	Other phosphate binders
Outcome	• Serum phosphate • Serum calcium • Adverse events
Study design	Randomised controlled trial
Timeframe	Long term follow-up at least 12 months
Additional information	Adequately powered

N.1.2 Research recommendation

In adults with stage 4 or 5 CKD, including those on dialysis, what is the long-term effectiveness and safety of calcium acetate combined with magnesium carbonate in controlling serum phosphate?

Why this is important

Limited evidence was found on the use of calcium acetate combined with magnesium carbonate to control serum phosphate (2 RCTs). However, the evidence that was assessed suggested that magnesium carbonate could be effective in controlling serum phosphate. A series of RCTs should be conducted separately in adults with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis. These trials should be run for a minimum of 12 months and should examine the effect of calcium acetate combined with magnesium carbonate on outcomes such as serum phosphate, serum calcium, adverse events and the ability of the binders to control serum phosphate and calcium within the given ranges. In addition, specific data should be collected on aspects relating to magnesium toxicity.

Research in this area is essential to inform future updates of this guidance and could lead to recommendations for the use of calcium acetate combined with magnesium carbonate in adults with stage 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis.

Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the use of calcium acetate combined with magnesium carbonate to control serum phosphate. There might be a benefit for patients in the management of their hyperphosphataemia if further evidence confirms that magnesium carbonate is effective in controlling serum phosphate.
Relevance to NICE guidance	The use of calcium acetate combined with magnesium carbonate to control serum phosphate has been considered in this guideline and there was a lack of data for this intervention.

	Further evidence might fill in the gap in this area during future updates of the guideline.
Relevance to the NHS	The outcome could affect the type of treatment to lower hyperphosphataemia in adults with stage 4 or 5 CKD who are not on dialysis or those who are on dialysis. If new recommendations are made in future, this may change the cost of phosphate binders provided by the NHS.
National priorities	High
Current evidence base	2 RCTs reporting on calcium acetate combined with magnesium carbonate compared to calcium acetate or sevelamer hydrochloride
Equality considerations	None known

Modified PICO table

Population	Adults with stage 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis
Intervention	Calcium acetate combined with magnesium carbonate
Comparator	Other phosphate binders
Outcome	• Serum phosphate • Serum calcium • Adverse events
Study design	Randomised controlled trial
Timeframe	Long term follow-up at least 12 months
Additional information	Adequately powered

N.1.3 Research recommendation

Which binders are most effective in controlling serum phosphate in children and young people with stage 4 or 5 CKD, including those who are on dialysis?

Why this is important

Limited evidence was found on the use of phosphate binders in children with stage 5 CKD who are on dialysis (1 RCT), and none was found for those with stage 4 or 5 CKD who are not on dialysis. Therefore, a series of RCTs should be conducted that examine the comparative effectiveness of various phosphate binders against each other for the management of serum phosphate. These RCTs should be conducted separately in those with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis. These trials should examine the long-term (ideally 12-month) effects of the various binders on outcomes such as serum phosphate, serum calcium, adverse events and the ability of the binders to control serum phosphate and calcium within the given ranges, as well as the most appropriate sequencing of binders.

Research in this area is essential to inform future updates of this guidance and could lead to specific recommendations for children and young people with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis.

Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the use of phosphate binders in children and young people with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis. There might be a benefit for patients in the management of their hyperphosphataemia if further evidence shows that some phosphate binders are better than others.
Relevance to NICE guidance	The use of phosphate binders in children and young people with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis has been considered in this guideline and there was a lack of data on this population. Further evidence might fill in the gap in this area during future updates of the guideline.
Relevance to the NHS	The outcome could affect the type of treatment to lower hyperphosphataemia in children and young people with stages 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis. If new recommendations are made in future, this may change the cost of phosphate binders provided by the NHS.
National priorities	High
Current evidence base	1 RCT reporting on calcium carbonate compared to calcium acetate or sevelamer hydrochloride
Equality considerations	None known

Modified PICO table

Population	Children and young people with stage 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis
Intervention	Phosphate binders
Comparator	Other phosphate binders
Outcome	• Serum phosphate • Serum calcium • Adverse events
Study design	Randomised controlled trial
Timeframe	Long term follow-up at least 12 months
Additional information	Adequately powered

N.1.4 Research recommendation

What are people with CKD and their parents/carers views and beliefs about taking oral phosphate binders?

Why this is important

Members of the committee, including lay members with experience of taking phosphate binders agreed that compliance with phosphate binder regimens was an important factor in their effectiveness. Anecdotal evidence suggested that people were reluctant to take phosphate binders because they are large and unpleasant to take. They also require a large part of a persons restricted fluid intake. The committee agreed that understanding this problem better would enable them to improve their recommendations in future updates of this guideline.

Rationale for research recommendation

Importance to 'patients' or the population	Little is known about people's views and beliefs of taking oral phosphate binders as part of the treatment for CKD. The committed discussed that in their personal and clinical experience, people with CKD find difficult to take oral phosphate binders and that there was a need to increase the evidence on this topic.
Relevance to NICE guidance	The committee discussed the importance about people's views and beliefs of taking oral phosphate binders as part of the treatment for CKD. Further evidence might fill in the gap in this area during future updates of the guideline.
Relevance to the NHS	The outcome could affect the type of phosphate binder prescribed to lower hyperphosphataemia in adults, children and young people with CKD G4 or G5. If new recommendations are made in future, this may change the treatment provided by the NHS.
National priorities	High
Current evidence base	No evidence was found
Equality considerations	None known

Modified PICO table

Sample	Adults, children and young people with stage 4 or 5 CKD who are not on dialysis and those with stage 5 who are on dialysis
Phenomenon of Interest	Oral phosphate binders including adherence to treatment.
Design	Any suitable qualitative design that collects and analyses interview, focus group or other means to collect rich data – thematic analysis, phenomenological analysis, ethnography, grounded theory
Evaluation	Patient, parent/carer, professional views, beliefs and experiences
Study design	Qualitative study
Timeframe	
Additional information	None

Appendix O – NMA models

Fixed-effect model for mean differences

```
# Normal likelihood, identity link
# Fixed-effect model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                                # indexes studies
  mu[i] ~ dnorm(0, .0001)                               # vague priors for all trial
baselines
  for (j in 1:NumArms[i]) {                             # indexes arms
    se[i,j]    <- SD[i,j] / sqrt(N[i,j])
    var[i,j]   <- pow(se[i,j],2)                        # calculate variances
    prec[i,j]  <- 1/var[i,j]                            # set precisions
    MC[i,j]    ~  dnorm(theta[i,j],prec[i,j])           # normal likelihood
    theta[i,j] <- mu[i] + d[Rx[i,j]] - d[Rx[i,1]]       # model for linear predictor
    dev[i,j]   <- (MC[i,j] - theta[i,j]) * (MC[i,j]
                  - theta[i,j]) * prec[i,j]             # deviance contribution
    }                                                   # close arm loop
  resdev[i]    <- sum(dev[i,1:NumArms[i]])              # summed deviance contribution
  }                                                     # close study loop
totresdev      <- sum(resdev[])                         # total residual deviance

d[1]<-0                                                 # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                    # indexes treatments
  d[j] ~ dnorm(0, .0001)                                # vague priors for treatment effects
  }                                                     # close treatment loop

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  Tmean[j] <- AMean + d[j]
  Tpred[j] <- APred + d[j]
  }

# pairwise MDs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    MD[c,j] <- (d[j] - d[c])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                        # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                        # probability that treat j is hth
best
    }
  }
}
```

Random effects model for mean differences

```
# Normal likelihood, identity link
# Fixed effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                                # indexes studies
  w[i,1]       <- 0                                     # multi-arm adjustment = 0 for
control
  delta[i,1]   <- 0                                     # treatment effect is 0 for control
  mu[i]        ~  dnorm(0, .0001)                       # vague priors for all trial
baselines
  for (j in 1:NumArms[i]) {                             # indexes arms
    se[i,j]    <- SD[i,j] / sqrt(N[i,j])
    var[i,j]   <- pow(se[i,j],2)                        # calculate variances
    prec[i,j]  <- 1/var[i,j]                            # set precisions
    MC[i,j]    ~  dnorm(theta[i,j], prec[i,j])          # normal likelihood
    theta[i,j] <- mu[i] + delta[i,j]                    # model for linear predictor
    dev[i,j]   <- (MC[i,j] - theta[i,j]) * (MC[i,j]
                  - theta[i,j]) * prec[i,j]             # deviance contribution
    dummy[i,j] <- ArmNo[i,j]                            # data not used in this model
    }                                                   # close arm loop
  for (j in 2:NumArms[i]) {                             # indexes arms
    delta[i,j] ~  dnorm(md[i,j],taud[i,j])              # trial-specific MD distributions
    md[i,j]    <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j]     # mean of MD dists, with multiarm
    taud[i,j]  <- tau *2*(j-1)/j                        # precision of MD dists, with
multiarm
    w[i,j]     <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]]) # adjustment, multi-arm RCTs
    sw[i,j]    <- sum(w[i,1:j-1])/(j-1)                 # cumulative adjustment for multi-
arm
    }
  resdev[i]    <- sum(dev[i,1:NumArms[i]])              # summed deviance contribution
  dummy2[i]    <- Yrs[i] * RefID[i]                     # data not used in this model
  }                                                     # close study loop
totresdev      <- sum(resdev[])                         # total residual deviance

d[1]<-0                                                 # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                    # indexes treatments
  d[j] ~  dnorm(0, .0001)                               # vague priors for treatment effects
  }                                                     # close treatment loop
sdu ~  dunif(RFXpriorParam1, RFXpriorParam2)            # uniform between-trial prior
sdn ~  dnorm(RFXpriorParam1, RFXpriorParam2)            # normal between-trial prior
sdl ~  dlnorm(RFXpriorParam1, RFXpriorParam2)           # lognormal between-trial prior
sd  <- sdu * equals(RFXpriorD,1) + sdn * equals(RFXpriorD,2) + sdl * equals(RFXpriorD,3)
tau  <- pow(sd,-2)                                      # between-trial precision

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  Tmean[j] <- AMean + d[j]
  Tpred[j] <- APred + d[j]
  }
dummy3         <- YrsA                                  # data not used in this model

# pairwise MDs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    MD[c,j] <- (d[j] - d[c])
```

```
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                    # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth
best
    }
  }
}
```

Fixed-effect model for binomial data (logit link) – for odds ratios

```
# Binomial likelihood, logit link
# Fixed-effect model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                            # indexes studies
  mu[i] ~ dnorm(0, .0001)                           # vague priors for all trial
baselines
  for (j in 1:NumArms[i]) {                         # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])            # binomial likelihood
    logit(p[i,j]) <- mu[i] + d[Rx[i,j]] - d[Rx[i,1]] # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                    # deviance contribution
    }                                               # close arm loop
  resdev[i]     <- sum(dev[i,1:NumArms[i]])         # summed deviance contribution
  }                                                 # close study loop
totresdev     <- sum(resdev[])                      # total residual deviance

d[1]<-0                                             # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                # indexes treatments
  d[j] ~ dnorm(0, .0001)                            # vague priors for treatment effects
  }                                                 # close treatment loop

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  logit(Tmean[j]) <- AMean + d[j]
  logit(Tpred[j]) <- APred + d[j]
  }

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lOR[c,j] <- (d[j]-d[c])
    OR[c,j]  <- exp(lOR[c,j])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
```

```
  best[j]     <- equals(rk[j],1)                    # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth
best
    }
  }
}
```

Random effects model for binomial data (logit link) – for odds ratios

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                            # indexes studies
  mu[i] ~ dnorm(0, .0001)                           # vague priors for all trial
baselines
  delta[i,1] <- 0                                   # effect is zero for control arm
  w[i,1] <- 0                                       # multi-arm adjustment = zero for
ctrl
  for (j in 1:NumArms[i]) {                         # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])            # binomial likelihood
    logit(p[i,j]) <- mu[i] + delta[i,j]             # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                    # deviance contribution
    }                                               # close arm loop
  for (j in 2:NumArms[i]) {                         # indexes arms
    delta[i,j]  ~  dnorm(md[i,j],taud[i,j])         # trial-specific LOR distributions
    md[i,j]     <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j] # mean of LOR distributions (with
multi-arm trial correction)
    taud[i,j]   <- tau *2*(j-1)/j                   # precision of LOR distributions
(with                                                      multi-arm trial correction)
    w[i,j]      <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]])
                                                    # adjustment for multi-arm RCTs
    sw[i,j]     <- sum(w[i,1:j-1])/(j-1)            # cumulative adjustment for multi-
arm                                                       trials
    }
  resdev[i]     <- sum(dev[i,1:NumArms[i]])         # summed deviance contribution
  }                                                 # close study loop
totresdev     <- sum(resdev[])                      # total residual deviance

d[1]<-0                                             # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                # indexes treatments
  d[j] ~ dnorm(0, .0001)                            # vague priors for treatment effects
  }                                                 # close treatment loop
sdu ~  dunif(RFXpriorParam1, RFXpriorParam2)        # uniform between-trial prior
sdn ~  dnorm(RFXpriorParam1, RFXpriorParam2)        # normal between-trial prior
sdl ~  dlnorm(RFXpriorParam1, RFXpriorParam2)       # lognormal between-trial prior
sd  <- sdu * equals(RFXpriorD,1) + sdn * equals(RFXpriorD,2) + sdl * equals(RFXpriorD,3)
                                                    # select correct between-trial prior
tau <- pow(sd,-2)                                   # between-trial precision

# Provide estimates of treatment effects T[k] on the natural (probability) scale
AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  logit(Tmean[j]) <- AMean + d[j]
  logit(Tpred[j]) <- APred + d[j]
  }
```

```
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lOR[c,j] <- (d[j]-d[c])
    OR[c,j]  <- exp(d[j]-d[c])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                    # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth
best
    }
  }
}
```

Fixed-effect model for binomial data (cloglog link) – for hazard ratios

```
# Binomial likelihood, cloglog link
# Fixed-effect model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                            # indexes studies
  mu[i] ~ dnorm(0, .0001)                           # vague priors for all trial
baselines
  for (j in 1:NumArms[i]) {                         # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])            # binomial likelihood
    cloglog(p[i,j]) <- log(Yrs[i]/1) + mu[i] + d[Rx[i,j]] - d[Rx[i,1]]
                                                    # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                    # deviance contribution
    }                                               # close arm loop
  resdev[i]     <- sum(dev[i,1:NumArms[i]])         # summed deviance contribution
  }                                                 # close study loop
totresdev     <- sum(resdev[])                      # total residual deviance

d[1]<-0                                             # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                # indexes treatments
  d[j] ~ dnorm(0, .0001)                            # vague priors for treatment effects
  }                                                 # close treatment loop

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA, over a time period timeA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  cloglog(Tmean[j]) <- log(YrsA) + AMean + d[j]
  cloglog(Tpred[j]) <- log(YrsA) + APred + d[j]
  }

# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
```

```
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                    # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth
best
    }
  }
}
```

Random effects model for binomial data (cloglog link) – for hazard ratios

```
# Binomial likelihood, cloglog link
# Random effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                            # indexes studies
  mu[i] ~ dnorm(0, .0001)                           # vague priors for all trial
baselines
  delta[i,1] <- 0                                   # effect is zero for control arm
  w[i,1] <- 0                                       # multi-arm adjustment = zero for
ctrl
  for (j in 1:NumArms[i]) {                         # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])            # binomial likelihood
    cloglog(p[i,j]) <- log(Yrs[i] / 1) + mu[i] + delta[i,j] # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                    # deviance contribution
    dummy[i,j]    <- ArmNo[i,j]                     # data not used in this model
    }                                               # close arm loop
  for (j in 2:NumArms[i]) {                         # indexes arms
    delta[i,j]  ~  dnorm(md[i,j],taud[i,j])         # trial-specific LOR distributions
    md[i,j]     <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j] # mean of LOR distributions (with
                                                    # multi-arm trial correction)
    taud[i,j]   <- tau *2*(j-1)/j                   # precision of LOR distributions
(with
                                                    # multi-arm trial correction)
    w[i,j]      <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]]) # adjustment for multi-arm RCTs
    sw[i,j]     <- sum(w[i,1:j-1])/(j-1)            # cumulative adjustment for multi-
arm
                                                    # trials
    }
  resdev[i]   <- sum(dev[i,1:NumArms[i]])           # summed deviance contribution
  dummy2[i]   <- RefID[i]                           # data not used in this model
  }                                                 # close study loop
totresdev   <- sum(resdev[])                        # total residual deviance

d[1]<-0                                             # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                # indexes treatments
  d[j] ~ dnorm(0, .0001)                            # vague priors for treatment effects
  }                                                 # close treatment loop
sdu ~  dunif(RFXpriorParam1, RFXpriorParam2)        # uniform between-trial prior
sdn ~  dnorm(RFXpriorParam1, RFXpriorParam2)        # normal between-trial prior
sdl ~  dlnorm(RFXpriorParam1, RFXpriorParam2)       # lognormal between-trial prior
sd  <- sdu * equals(RFXpriorD,1) + sdn * equals(RFXpriorD,2) + sdl * equals(RFXpriorD,3)
                                                    # select correct between-trial prior
tau <- pow(sd,-2)                                   # between-trial precision
```

```
# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA, over a time period timeA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  cloglog(Tmean[j]) <- log(YrsA) + AMean + d[j]
  cloglog(Tpred[j]) <- log(YrsA) + APred + d[j]
  }

# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                    # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                    # probability that treat j is hth
best
    }
  }
}
```

Fixed effect model for mortality data – shared parameter model for arm-level and contrast-level data

This code is appropriate for the case where all studies have 2 arms only

```
# Effectiveness model for mixed arm-level event and contrast-level HR data
# Binomial likelihood, cloglog link / normal likelihood, identity link
# Fixed effects
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudiesD) {                           # indexes studies with dichotomous
data
  mu[i] ~ dnorm(0, .0001)                           # vague priors for all trial
baselines
  for (j in 1:NumArms[i]) {                         # indexes arms
    k[i,j]          ~  dbin(p[i,j],N[i,j])          # binomial likelihood
    cloglog(p[i,j]) <- log(Yrs[i]/1) + mu[i] + d[Rx[i,j]] - d[Rx[i,1]]
                                                    # model for linear predictor
    rhat[i,j]       <- p[i,j] * N[i,j]              # expected value of the numerators
    dev[i,j]        <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                       + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j])
                       - log(N[i,j]-rhat[i,j])))    # deviance contribution
    }                                               # close arm loop
  resdev[i] <- sum(dev[i,1:NumArms[i]])             # summed deviance contribution
  }                                                 # close study loop

for(i in 1:NumStudiesC) {                           # indexes studies with contrast data
    prec[i] <- pow(SElnHR[i],-2) # set precisions
    lnHR[i] ~  dnorm(theta[i+NumStudiesD,2], prec[i]) # normal likelihood
    theta[i+NumStudiesD, 2] <- d[RxC[i,1]] - d[RxC[i,2]] # model for linear predictor
    resdev[i+NumStudiesD] <- (lnHR[i]-theta[i+NumStudiesD,2])*(lnHR[i]-
theta[i+NumStudiesD,2])* prec[i]
```

```
                                                        # summed deviance contribution
  }                                                     # close study loop

totresdev     <- sum(resdev[])                          # total residual deviance

d[1]<-0                                                 # effect is 0 for reference
treatment
for (j in 2:NumRx) {                                    # indexes treatments
  d[j] ~ dnorm(0, .0001)                                # vague priors for treatment effects
  }                                                     # close treatment loop

# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                        # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                        # probability that treat j is hth
best
    }
  }
}
```

Appendix P – Checking for inconsistency in the NMA results

Introduction

The purpose of this analysis was to assess the consistency assumption in the network meta-analysis (NMA) model used to estimate the comparative effectiveness of different phosphate binders for treating hyperphosphatemia in adults with stage 5 chronic kidney disease (CKD) who are on dialysis. Checking for inconsistency was only possible for NMAs in adults with stage 5 CKD who are on dialysis. Therefore, all results in this appendix relate to this population.

Methods

An important assumption made in NMA concerns the consistency of the direct and indirect evidence informing the treatment contrasts [1,2]. There should be no meaningful differences between these two sources of evidence.

To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects, model [1,2]. The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that the consistency assumption can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 independent sources of evidence [3].

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model [4]. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point) [4].

In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters, and thus penalizes model fit with model complexity [4]. Lower values are preferred and typically differences of 3-5 points are considered meaningful [4].

The posterior mean between-study standard deviation, which measures the heterogeneity of treatment effects estimated by trials within contrasts, was also used to compare models. When comparing consistency and inconsistency models, if the inconsistency model has the smallest heterogeneity, then this indicates potential inconsistency in the data.

Results

Outcome: Serum phosphate at 3 months in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 85).

Table 85: Model fit statistics for serum phosphate at 3 months in adults with stage 5 CKD who are on dialysis

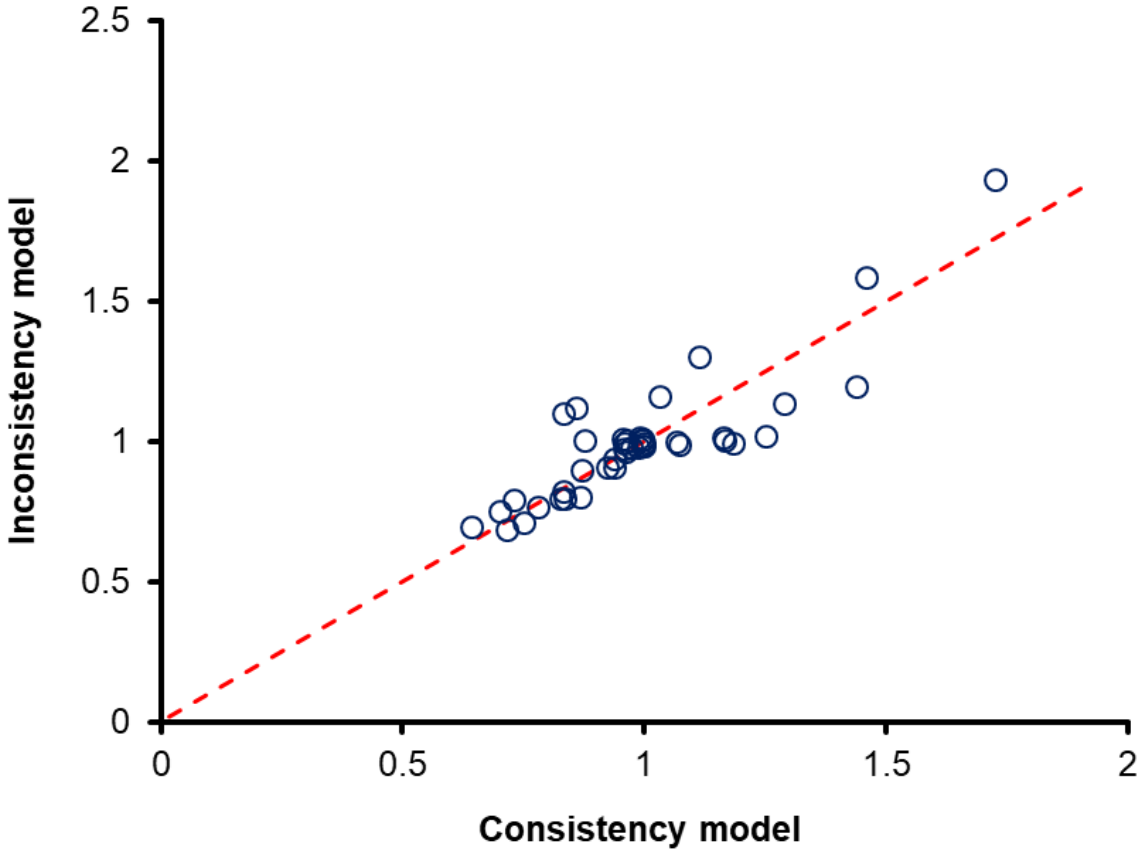
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	51.61	-55.072
Random effects - consistency	0.111 (0.024, 0.252)	41.6	-59.539
Random effects - inconsistency	0.106 (0.005, 0.302)	41.73	-57.794

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 42 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 85). The area below the line of equality in Figure 86 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 85).

Figure 86: Deviance contributions for the random effects consistency and inconsistency models for serum phosphate at 3 months in adults with stage 5 CKD who are on dialysis



Outcome: Serum phosphate at 6 months in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 86).

Table 86: Model fit statistics for serum phosphate at 6 months in adults with stage 5 CKD who are on dialysis

Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	54.67	-55.79
Random effects - consistency	0.087 (0.004, 0.240)	49.0	-56.074
Random effects - inconsistency	0.109 (0.008, 0.273)	45.86	-56.824

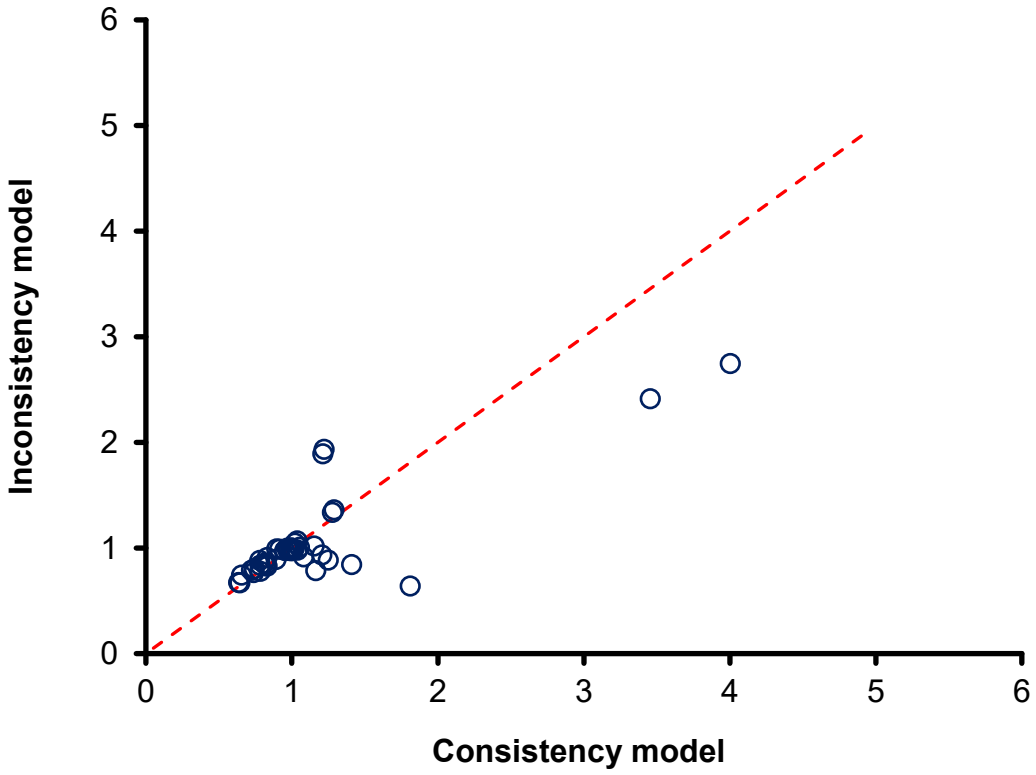
(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 44 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after

50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 86). The area below the line of equality in Figure 87 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in De (2006) for calcium carbonate and sevelamer hydrochloride. There were no errors in data extraction for De (2006). The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 86).

Figure 87: Deviance contributions for the random effects consistency and inconsistency models for serum phosphate at 6 months in adults with stage 5 CKD who are on dialysis



Outcome: Serum phosphate at 12 months in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 87).

Table 87: Model fit statistics for serum phosphate at 12 months in adults with stage 5 CKD who are on dialysis

Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	45.08	-68.696
Random effects - consistency	0.051 (0.003, 0.144)	42.37	-67.747

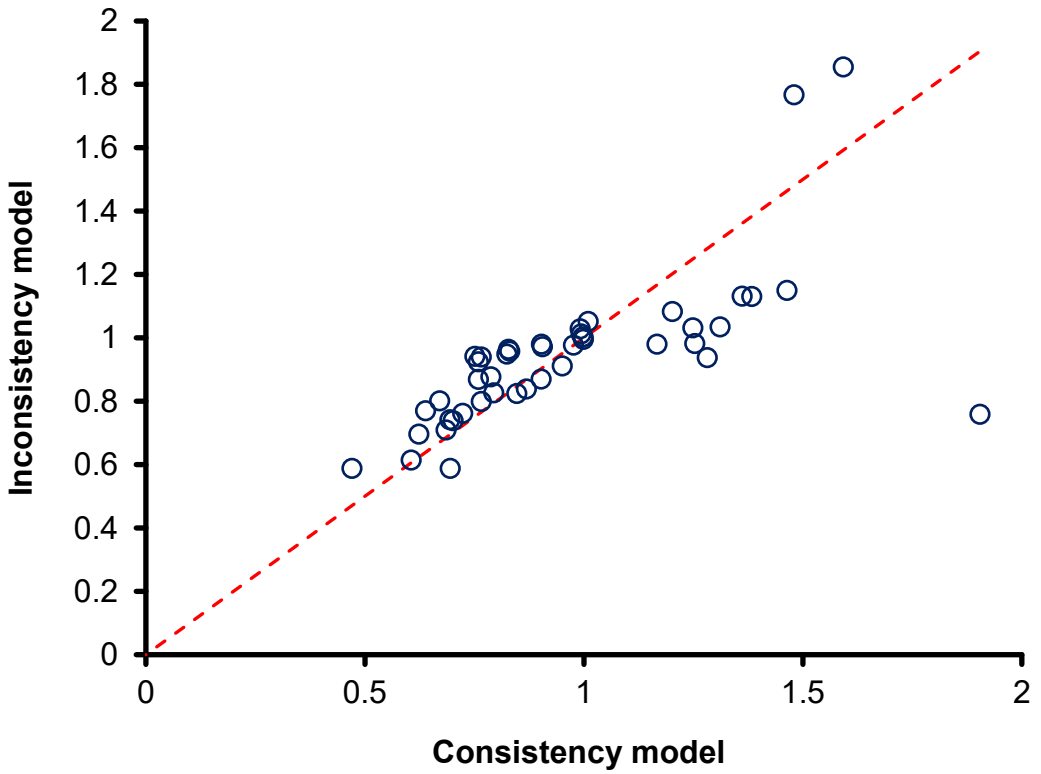
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Random effects - inconsistency	0.058 (0.004, 0.146)	41.35	-67.102

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 44 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 87). The area below the line of equality in Figure 88 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Janssen (1996) for calcium carbonate. There were no errors in data extraction for Janssen (1996). The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 87).

Figure 88: Deviance contributions for the random effects consistency and inconsistency models for serum phosphate at 12 months in adults with stage 5 CKD who are on dialysis



Outcome: Proportion of participants achieving phosphate control in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 88).

Table 88: Model fit statistics for proportion of participants achieving phosphate control in adults with stage 5 CKD who are on dialysis

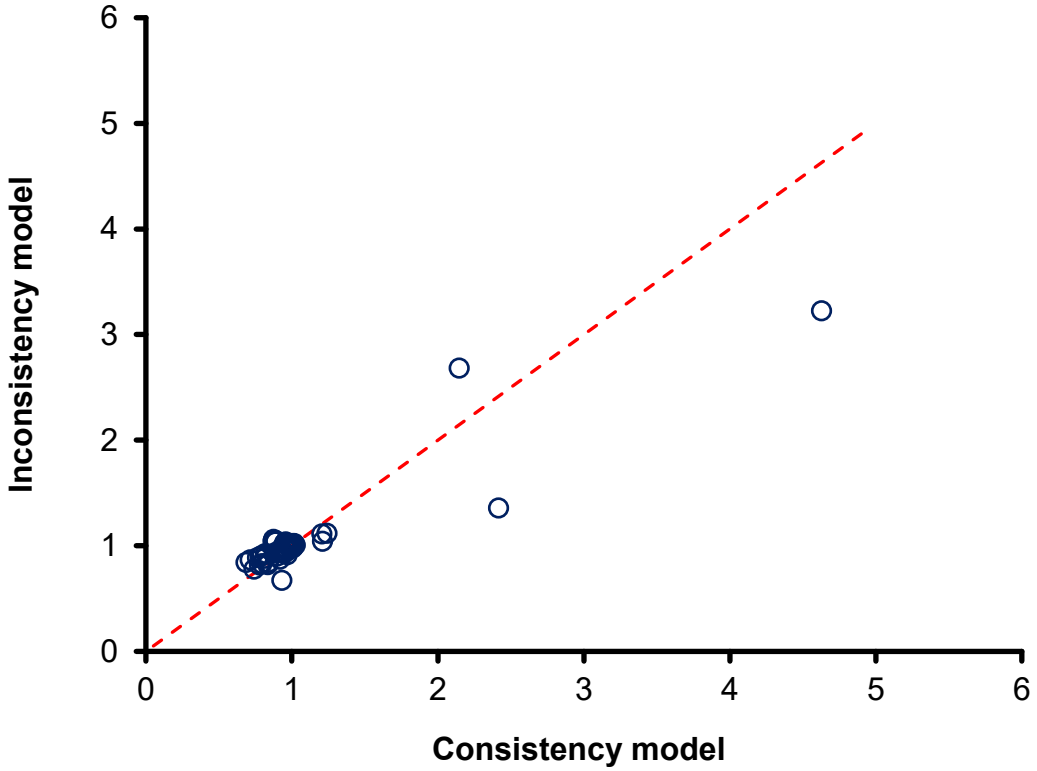
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	122.9	388.507
Random effects - consistency	0.869 (0.545, 1.341)	61.42	345.779
Random effects - inconsistency	0.999 (0.596, 1.547)	61.17	348.668

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 59 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 88). The area below the line of equality in Figure 89 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Shigematsu (2008) for placebo and in Yokoyama (2012) for ferric citrate 6 g/day. There were no errors in data extraction for Shigematsu (2008) and for Yokoyama (2012). The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 88).

Figure 89: Deviance contributions for the random effects consistency and inconsistency models for proportion of participants achieving phosphate control in adults with stage 5 CKD who are on dialysis



Outcome: Serum calcium at 3 months in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 89).

Table 89: Model fit statistics for serum calcium at 3 months in adults with stage 5 CKD who are on dialysis

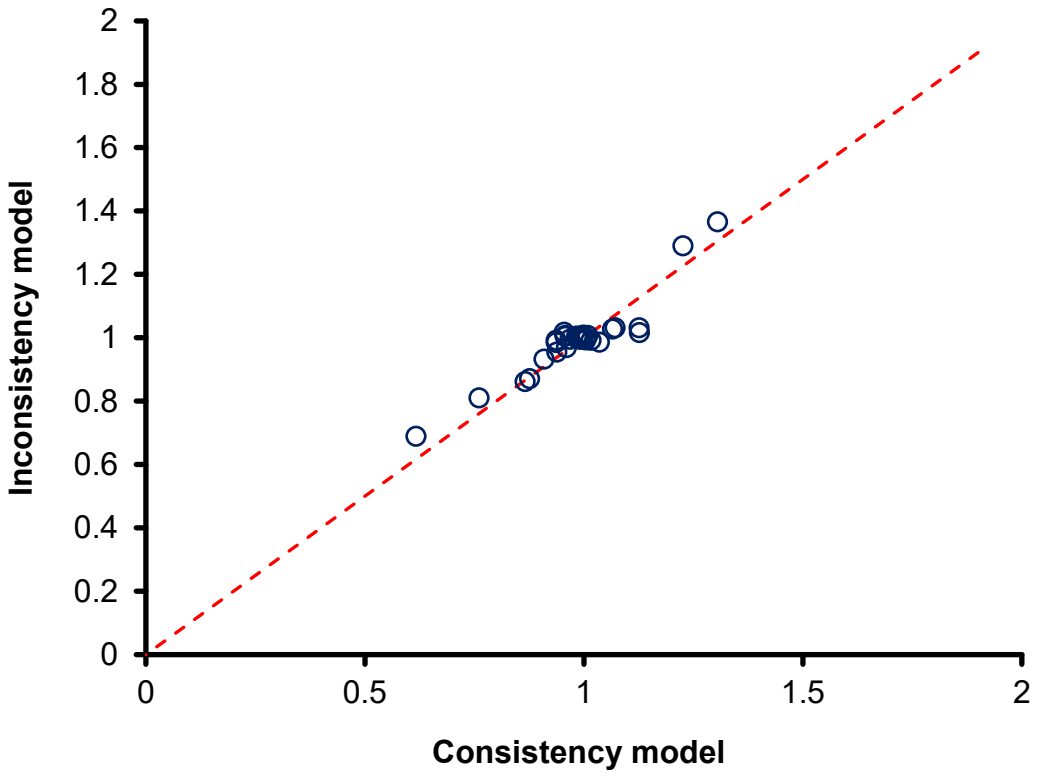
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	39.55	-110.677
Random effects - consistency	0.048 (0.010, 0.127)	31.56	-114.369
Random effects - inconsistency	0.059 (0.008, 0.193)	31.83	-112.951

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 32 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 89). The area below the line of equality in Figure 90 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 89).

Figure 90: Deviance contributions for the random effects consistency and inconsistency models for serum calcium at 3 months in adults with stage 5 CKD who are on dialysis



Outcome: Serum calcium at 6 months in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 90).

Table 90: Model fit statistics for serum calcium at 6 months in adults with stage 5 CKD who are on dialysis

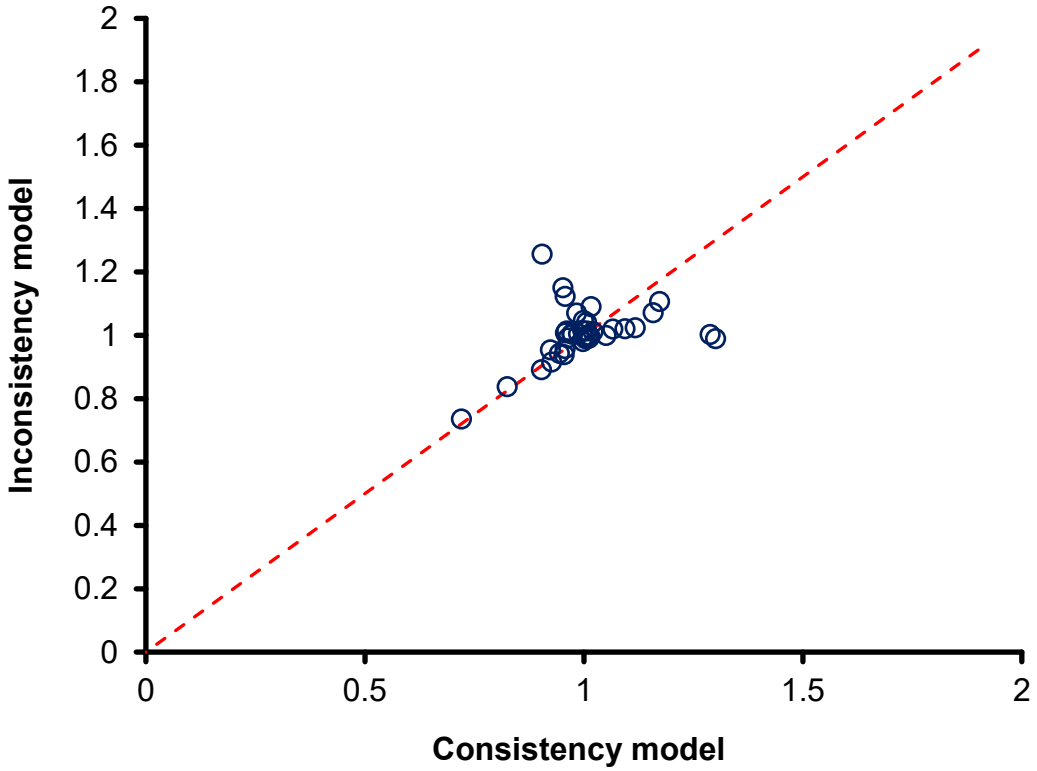
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	78.9	-93.218
Random effects - consistency	0.091 (0.049, 0.172)	38.1	-125.625
Random effects - inconsistency	0.087 (0.041, 0.194)	38.21	-124.923

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 38 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 90). The area below the line of equality in Figure 91 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 90).

Figure 91: Deviance contributions for the random effects consistency and inconsistency models for serum calcium at 6 months in adults with stage 5 CKD who are on dialysis



Outcome: Serum calcium at 12 months in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 91).

Table 91: Model fit statistics for serum calcium at 12 months in adults with stage 5 CKD who are on dialysis

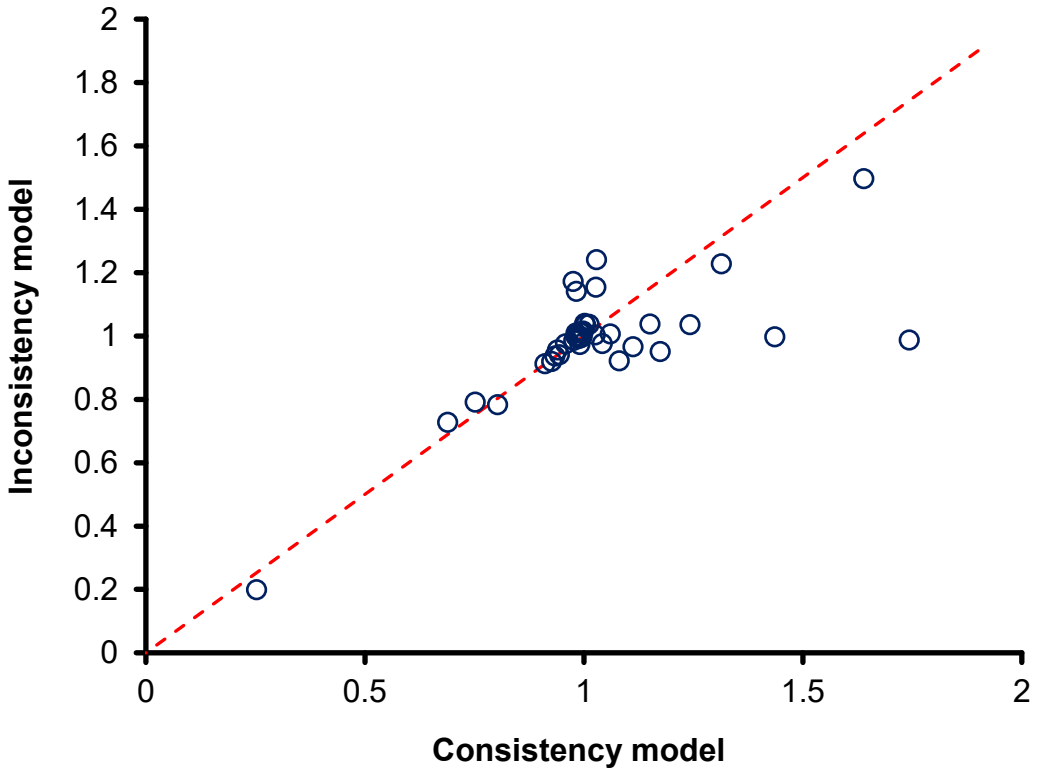
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	67.99	-108.757
Random effects - consistency	0.079 (0.036, 0.151)	41.04	-126.389
Random effects - inconsistency	0.071 (0.033, 0.142)	39.58	-127.548

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 40 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 91). The area below the line of equality in Figure 92 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 91).

Figure 92: Deviance contributions for the random effects consistency and inconsistency models for serum calcium at 12 months in adults with stage 5 CKD who are on dialysis



Outcome: Risk of hypercalcaemia in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 92).

Table 92: Model fit statistics for risk of hypercalcaemia in adults with stage 5 CKD who are on dialysis

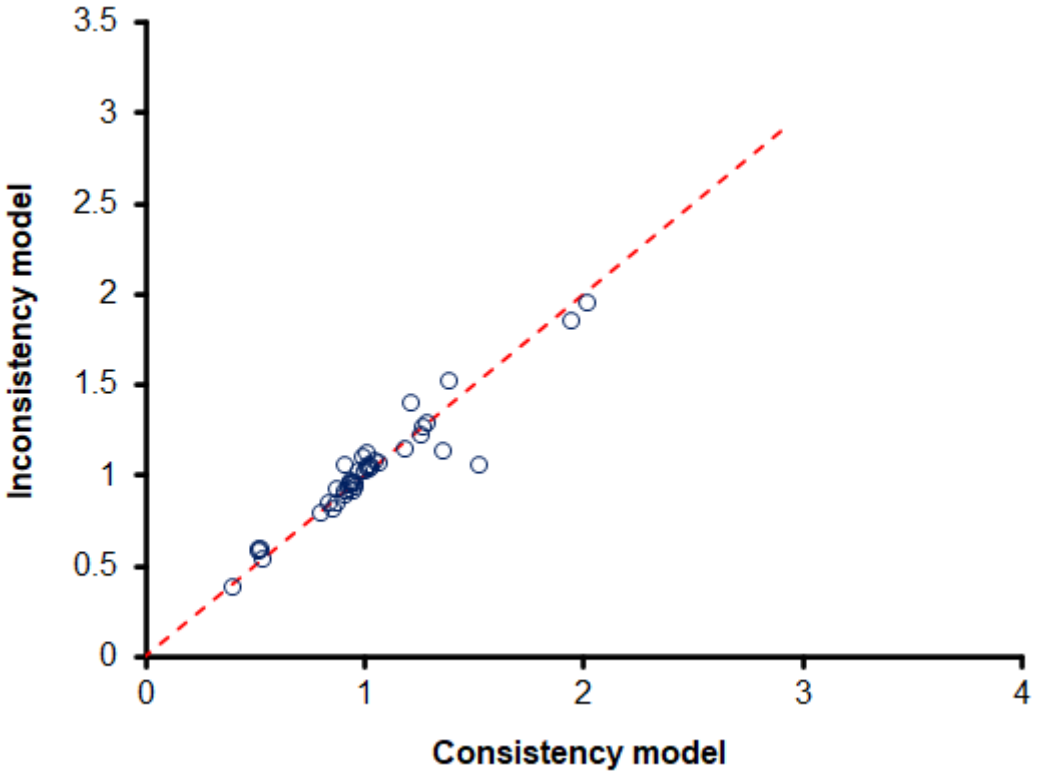
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	58.16	220.306
Random effects - consistency	0.847 (0.281, 1.648)	41.95	212.037
Random effects - inconsistency	0.746 (0.180, 1.516)	41.45	211.397

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 41 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 92). The area below the line of equality in Figure 93 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 92).

Figure 93: Deviance contributions for the random effects consistency and inconsistency models for risk of hypercalcaemia in adults with stage 5 CKD who are on dialysis



Outcome: Adverse events: constipation in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the fixed effects model, as there were no meaningful differences in the DIC. Nevertheless, the model fit was poor, since the posterior total residual deviance is notably larger than the number of data points (Table 93).

Table 93: Model fit statistics for adverse events (constipation) in adults with stage 5 CKD who are on dialysis

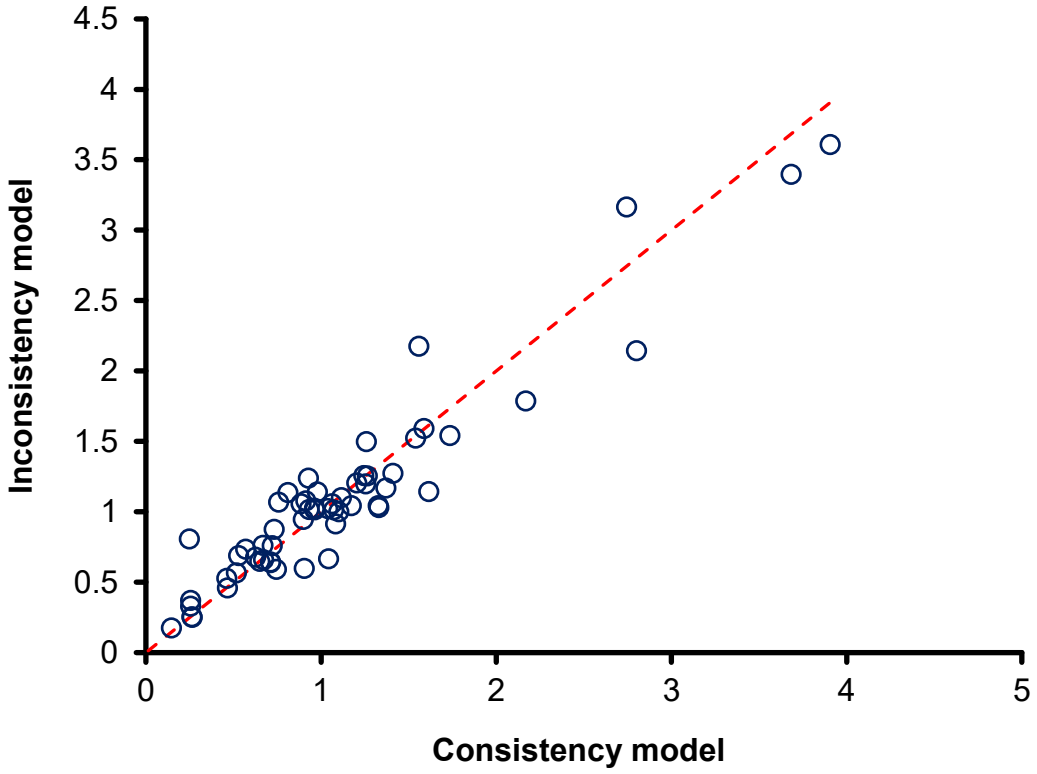
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	63.82	256.001
Fixed effect - inconsistency	---	63.57	259.111

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 58 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency fixed effects models, as little difference was observed between the fit of the models (Table 93). The area below the line of equality in Figure 94 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 93).

Figure 94: Deviance contributions for the random effects consistency and inconsistency models for adverse events (constipation) in adults with stage 5 CKD who are on dialysis



Outcome: Adverse events: diarrhoea in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 94).

Table 94: Model fit statistics for adverse events (diarrhoea) in adults with stage 5 CKD who are on dialysis

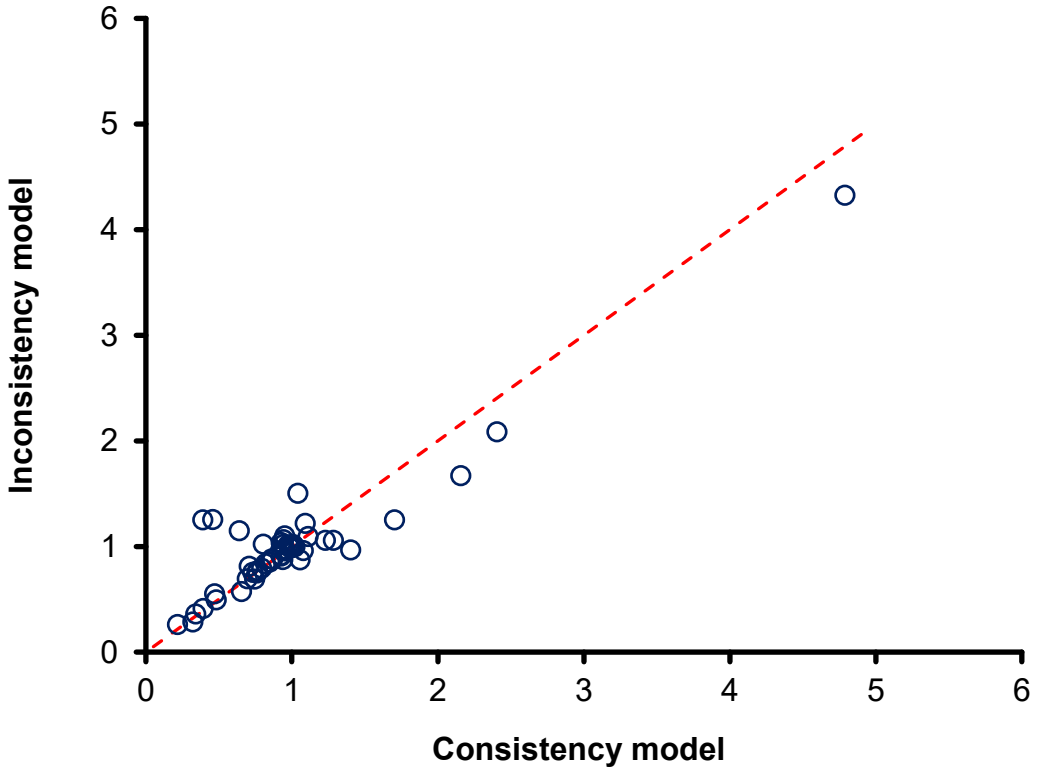
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	62.66	258.48
Random effects - consistency	0.549 (0.076, 1.112)	50.46	254.357
Random effects - inconsistency	0.554 (0.168, 1.121)	51.29	258.393

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 51 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 94). The area below the line of equality in Figure 95 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 94).

Figure 95: Deviance contributions for the random effects consistency and inconsistency models for adverse events (diarrhoea) in adults with stage 5 CKD who are on dialysis



Outcome: Adverse events: nausea and/or vomiting in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 95).

Table 95: Model fit statistics for adverse events (nausea and/or vomiting) in adults with stage 5 CKD who are on dialysis

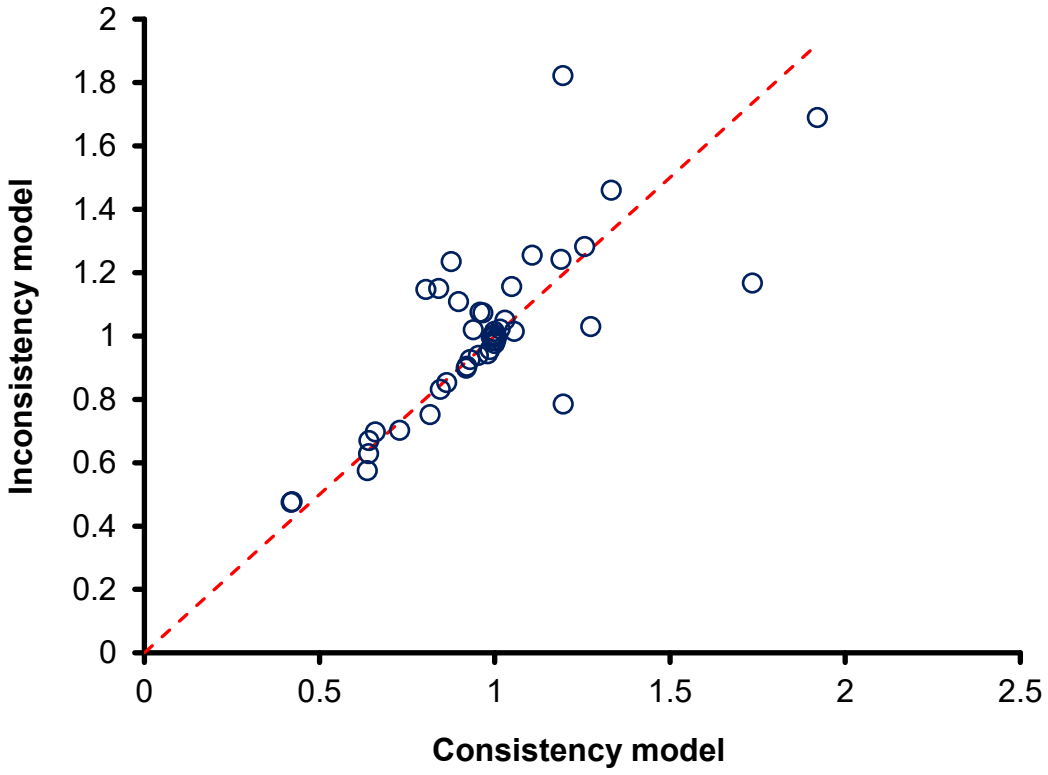
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	73.69	245.292
Random effects - consistency	1.055 (0.553, 1.773)	43.95	225.483
Random effects - inconsistency	0.934 (0.473, 1.683)	44.97	227.321

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 45 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 95). The area below the line of equality in Figure 96 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 95).

Figure 96: Deviance contributions for the random effects consistency and inconsistency models for adverse events (nausea and/or vomiting) in adults with stage 5 CKD who are on dialysis



Outcome: Discontinuation due to adverse events in adults with stage 5 CKD who are on dialysis

Inconsistency checks were performed using the random effects model, as lower posterior mean residual deviance and DIC models compared to the fixed effect model suggest the random effects model provided a better fit for the data (Table 96).

Table 96: Model fit statistics for discontinuation due to adverse events in adults with stage 5 CKD who are on dialysis

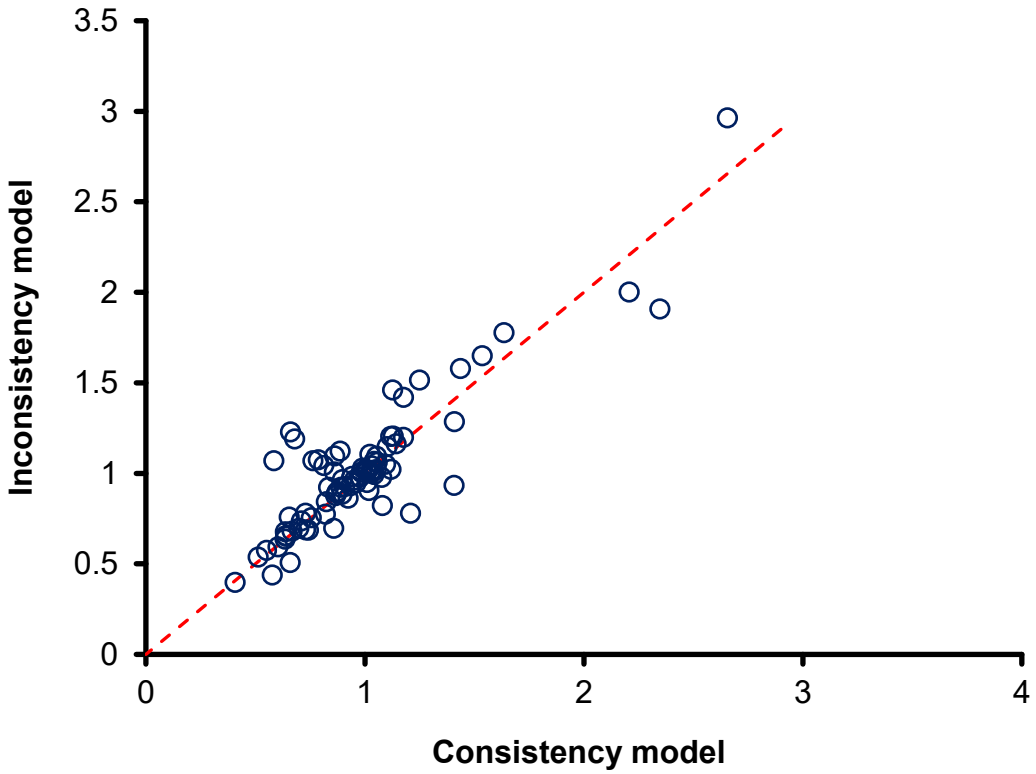
Model	Between Study Heterogeneity - Standard Deviation (95% CrI[a])	Residual deviance[b]	DIC[c]
Fixed effect - consistency	---	106.3	409.407
Random effects - consistency	0.607 (0.275, 1.018)	80.5	397.46
Random effects - inconsistency	0.562 (0.007, 1.037)	82.7	403.747

(a) Credible Interval (CrI)
(b) Posterior mean residual deviance compared to 82 total data points
(c) Deviance information criteria (DIC) – lower values preferred

Since there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 10,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix P.1.

No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as little difference was observed between the fit of the models (Table 96). The area below the line of equality in Figure 97 highlights where the inconsistency model better predicted data points, and the improvements were minimal. The additional parameters in the inconsistency model, which eliminates variation between treatment contrasts, did not result in a decrease in the between-study heterogeneity (Table 96).

Figure 97: Deviance contributions for the random effects consistency and inconsistency models discontinuation due to adverse events in adults with stage 5 CKD who are on dialysis



Conclusions

The inconsistency checks did not identify any evidence of inconsistency between the direct and indirect evidence included in the network meta-analysis.

Appendix P.1

WinBUGS code for inconsistency model used in this report

The examples given here are for binomial data with a logit link; other likelihoods and link functions were the same as those given in Appendix O.

Fixed-effect

```
model {
for(i in 1:NumStudies) {
  mu[i] ~ dnorm(0, .0001)                          # vague priors for trial baselines
  for (j in 1:NumArms[i]) {                        # indexes arms
    k[i,j]        ~  dbin(p[i,j], N[i,j])          # binomial likelihood
    logit(p[i,j]) <- mu[i] + d[Rx[i,1],Rx[i,j]]    # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]               # expected value of numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                   # deviance contribution
    }                                              # close arm loop
  resdev[i]     <- sum(dev[i,1:NumArms[i]])        # summed deviance contribution
  }
totresdev <- sum(resdev[])                         # total residual deviance
for (j in 1:NumRx) {
  d[j,j] <- 0                                      # effect=0 for j vs j
  }
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    d[c,j]  ~  dnorm(0, .0001)
             OR[c,j] <- exp(d[c,j])
    }
  }
dummy3 <- meanA + precA + predA + predPrecA + YrsA + blnHiGood # not used in this model
}
```

Random effects

```
model {
for(i in 1:NumStudies) {
  mu[i]      ~  dnorm(0, .0001)                    # vague priors for trial baselines
  delta[i,1] <- 0                                  # treatment effect is zero in control
arm
  for (j in 2:NumArms[i]) {
    delta[i,j] ~  dnorm(d[Rx[i,1],Rx[i,j]], tau)  # trial-specific LOR distributions
  }
  for (j in 1:NumArms[i]) {
    k[i,j]        ~  dbin(p[i,j], N[i,j])         # binomial likelihood
    logit(p[i,j]) <- mu[i] + delta[i,j]           # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]              # expected value of numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                  # deviance contribution
    }
  resdev[i]     <- sum(dev[i,1:NumArms[i]])       # summed residual deviance contribution
  }
totresdev <- sum(resdev[])                        # total residual deviance
for (j in 1:NumRx) {
  d[j,j] <- 0                                     # effect=0 for j vs j
  }
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    d[c,j]  ~  dnorm(0, .0001)
             OR[c,j] <- exp(d[c,j])
    }
  }
```

```
sdu ~  dunif(RFXpriorParam1, RFXpriorParam2)      # uniform between-trial prior
sdn ~  dnorm(RFXpriorParam1, RFXpriorParam2)      # normal between-trial prior
sdl ~  dlnorm(RFXpriorParam1, RFXpriorParam2)     # lognormal between-trial prior
sd  <- sdu * equals(RFXpriorD,1) + sdn * equals(RFXpriorD,2) + sdl * equals(RFXpriorD,3)
                                                  # select correct between-trial prior
tau <- pow(sd,-2)                                 # between-trial precision
dummy3 <- meanA + precA + predA + predPrecA + YrsA + blnHiGood
                                                  # not used in this model
}
```

References

1. Dias, S., Welton, N. J., Sutton, A. J., Caldwell, D. M., Lu, G., Ades, A. E., Evidence Synthesis for Decision Making 4: Inconsistency in Networks of Evidence Based on Randomized Controlled Trials, Medical Decision Making, 33, 641-656, 2013.

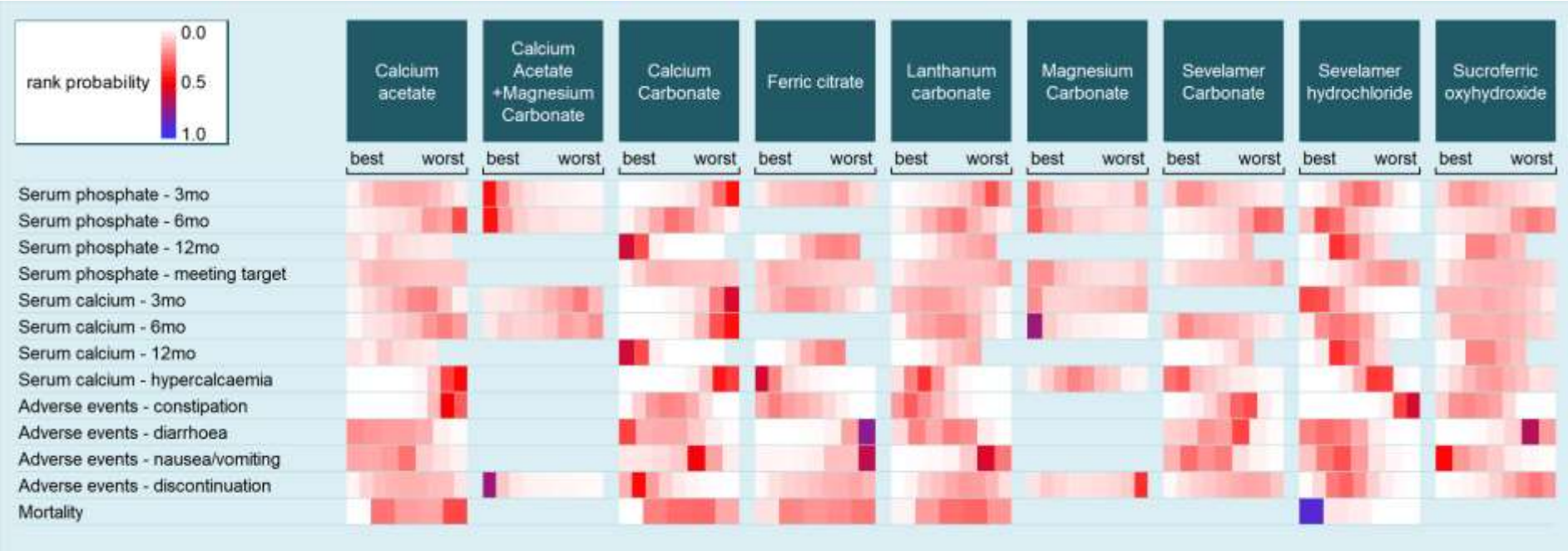
2. Dias, S., Welton, N. J., Sutton, A. J., Caldwell, D. M., Guobing, L., Ades, A. E., NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials, 2011, last updated April 2014, available from http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/

3. van Valkenhoef, G., Dias, S., Ades, A. E., Welton, N. J., Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis, Research Synthesis Methods, 7, 80-93, 2016

4. Spiegelhalter, D. J., Best, N. G., Carlin, B. P., van der Linde, A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B, 64, 583-616, 2002

Appendix Q – Summary graphic

Figure 98: CKD 5D NMAs – Summary of rank probabilities for all outcomes



This graphic contains exactly the same information as the rank probability histograms that appear in the detailed outputs of each individual analysis, but collects the data in a single figure. For each outcome, it indicates the probability that each treatment is the best option for which evidence is available, the worst available option, or any point in between. In this instance, the probabilities are indicated by intensity of colour (see key), rather than height of column, as in the histograms. All outcome rankings are presented on a standardised scale, from best (left) to worst (right). 'Best' always reflects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes). Bars presenting a relatively pale colour across a broad spread of the scale are indicative of results that are subject to substantial uncertainty – that is, there is a

probability that the treatment could be ranked anywhere along the continuum. In contrast, bars in which all colour is intensely concentrated at one point on the scale reflect unambiguous results: we are relatively certain that the treatment is ranked at that point.

3 options that only provide data for 1 or 2 NMAs – aluminium hydroxide, sevelamer carbonate + calcium acetate, and sevelamer hydrochloride + calcium carbonate – are omitted for clarity.