Therapeutic Class Overview
Phosphorus Depleters

Therapeutic Class

- **Overview/Summary:** Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (CaxP) product, is associated with an increased risk of vascular, valvular and other soft-tissue calcification in patients with CKD. The two principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and the administration of phosphorus binders (or phosphorus depleters). When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphorus binders is recommended. There are several different phosphorus binders that are currently available; however, the class can be divided into two subcategories: calcium- and non-calcium-containing products.[1-4] In general, calcium-containing phosphorus binders (Eliphos®, PhosLo®, Phoslyra®) are associated with higher serum calcium and lower serum parathyroid hormone levels compared to the non-calcium-containing products.[5-7] Increased serum calcium levels leads to hypercalcemia and also increases the risk of vascular calcification and arterial disease in CKD patients.[4] As a result, these products are typically avoided in CKD patients with hypercalcemia or severe vascular calcification.[2-4] The available non-calcium-containing phosphorus binders include sevelamer, available in two salt forms (hydrochloride [Renagel®] and carbonate [Renvela®]), lanthanum carbonate (Fosrenol®), ferric citrate (Auryxia®) and sucroferric oxyhydroxide (Velphoro®).[8-10] These products are typically reserved for use in CKD patients with hypercalcemia, or as adjunct to a regimen supplying the maximum allotted dose of elemental calcium from calcium-containing phosphorus binders.[1-4] The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a new, buffered formulation was created. The newer, sevelamer carbonate formulation will most likely be thought of as the preferred formulation of sevelamer because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products.[4]

Table 1. Current Medications Available in the Class[5-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Calcium acetate (Eliphos®*, PhosLo®*, Phoslyra®)	Control hyperphosphatemia in end stage renal failure. Reduce Phosphate with End Stage renal disease (Phoslyra®).	Capsule: 667 mg Oral solution: 667 mg/5 mL Tablet: 667 mg	✔
Ferric citrate (Auryxia®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet: 1 gram	
Lanthanum carbonate (Fosrenol®)	Reduce phosphate with end stage renal disease.	Tablet, chewable: 250 mg 500 mg 750 mg 1,000 mg	-
Sevelamer carbonate (Renvela®*)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Powder for oral suspension: 0.8 g 2.4 g	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Tablet: 800 mg	
Sevelamer hydrochloride (Renagel®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.†	Tablet: 400 mg 800 mg	-
Sucroferric oxyhydroxide (Velphoro®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet, chewable: 500 mg	

*Generic available in at least one dosage form or strength.
† The safety and efficacy of sevelamer hydrochloride in chronic kidney disease patients who are not on dialysis have not been studied.

Evidence-based Medicine

- The available evidence supports the hypothesis that all of the phosphorus binders (or phosphorus depleters) are efficacious in controlling serum phosphorus levels.[13-54] In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials evaluate surrogate endpoints. In addition, due to ethical concerns regarding a prolonged lack of appropriate treatment, most trials evaluating the newer phosphorus binders against placebo have been short term, with longer trials using calcium-containing binders as the comparator.[1]
- No prospective trials have specifically examined the benefits of targeting different phosphorus levels to determine the effect on patient-level endpoints. Epidemiological data suggests that phosphorus levels above the normal range are associated with increased morbidity and mortality.[1]
- The results of a recent Cochrane Systematic Review by Navaneethan and colleagues demonstrated that there was no statistically significant reduction in all-cause mortality when patients received sevelamer hydrochloride compared to those receiving calcium-based phosphate binders (relative risk, 0.73; 95% confidence interval, 0.46 to 1.16). No comparison of lanthanum carbonate to calcium-containing salts was made.[47]
- Two meta-analysis have been published reviewing the clinical trials of the phosphate binders.[48,49] Tonelli et al compared sevelamer products to any other therapy or placebo in patients with ESRD, on dialysis or who had had a kidney transplant. The pooled analysis showed that phosphate levels with sevelamer was similar or slightly higher than with calcium-based phosphate binders by 0.12 mmol/L (95% CI, 0.05 to 0.19). However, the overall weighted mean difference in serum calcium was significantly lower with sevelamer therapy (0.10 mmol/L; 95% CI, −0.12 to −0.07).[48] Jamal et al evaluated all-cause mortality and compared calcium-based phosphate binders to non-calcium phosphate binders in patients with chronic kidney disease. The results of this meta-analysis showed that patients randomly assigned to non-calcium-based phosphate binders had a statistically significant 22% reduction in all-cause mortality compared with those randomly assigned to calcium-based phosphate binders (RR,0.78; 95% CI, 0.61 to 0.98). When non-randomized trials were added to the pooled analysis, the reduction in all-cause mortality was 13% (RR,0.87; 0.77 to 0.97) in favor of non-calcium-based phosphate binders.[49]
- The safety and efficacy of ferric citrate was established in two clinical trials.[50,51]
    - The demonstrated reductions from baseline to week four in mean serum phosphorus were significantly greater with 6 and 8 grams/day than with 1 gram/day dose (-1.3 mg/dL and -1.5 mg/dL placebo-corrected differences, respectively; P<0.0001).[50]
    - Patients were eligible to enter a four-week, placebo-controlled withdrawal phase if they had been receiving ferric citrate during the 52-week study. During the placebo-controlled period, the serum phosphorus concentration rose by 2.2 mg/dL in patients receiving placebo compared to patients who remained on ferric citrate (-0.24 mg/dL vs 1.79 mg/dL; P<0.001).[51]

- The safety and efficacy of sucroferric oxyhydroxide was demonstrated in two randomized clinical trials, one six-week, open label, active controlled dose-finding study and one 55-week, active controlled, parallel group, dose-titration and extension study.[12,52-54]
    - In the phase II, dose-finding study, at six weeks, sucroferric oxyhydroxide decreased serum phosphorus compared to baseline in the 5.0, 7.5, 10.0 and 12.5 grams/day arms but not the 1.25 grams/day arm (P≤0.016). A similar decrease to sevelamer hydrochloride was seen in the 5.0 and 7.5 grams/day arms.[1,52]
    - In the after the dose-titration study, serum phosphorus control was maintained with both sucroferric oxyhydroxide and sevelamer throughout the extension study and the difference between groups was not statistically significant (P=0.14).[53,54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Currently available evidence supports the hypothesis that all of the phosphorus binders are efficacious in controlling serum phosphorus levels. Furthermore, it is generally accepted that no one product is effective and acceptable to every patient.[2,3]
    - Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on chronic kidney disease [CKD] Stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD.
    - It is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.[1]
    - Combination therapy, with multiple binders, may also be an option in order to control serum phosphorus levels while minimizing the side effects associated with any specific binder.[2,3]
    - Phosphorus binders should be utilized in patients with CKD Stages 3 to 5D who cannot adequately maintain serum phosphorus levels within the normal range with dietary phosphorus restriction.[1-3]
    - Choice of product should take into account the Stage of CKD, the presence of other components of CKD-Mineral and Bone Disorder, concomitant therapies and adverse event profiles.[1]
- Other Key Facts:
    - Currently, the calcium-containing products (Eliphos®, PhosLo®) are available generically in tablet and capsule formulations along with sevelamer carbonate tablets.
    - Calcium acetate (Phoslyra®) is available as an oral solution, and sevelamer carbonate (Renvela®) is available as oral powder for suspension.[7,10]
    - Lanthanum, and sevelamer carbonate/hydrochloride are contraindicated in patients with bowel obstruction, while calcium acetate is contraindicated in hypercalcemia[9-11]
    - Ferric citrate is contraindicated in iron overload syndromes.[8]

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Therapeutic Class Review
Phosphorus Depleters

Overview/Summary

Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (Ca x P) product, is associated with an increased risk of vascular, valvular and other soft-tissue calcification in patients with CKD. Elevated phosphorus levels may also directly influence several components of CKD-Mineral and Bone Disorder. Specifically, secondary hyperparathyroidism, bone abnormalities, calcitriol deficiency and extraskeletal calcification. In addition, there is evidence consistently demonstrating that hyperphosphatemia is a predictor of mortality in CKD Stage 5 patients who are receiving dialysis. It is because of these reasons that control of serum phosphorus levels in patients with CKD is an important component of care.[1-4]

The two principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and the administration of phosphorus binders (or phosphorus depleters). When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphorus binders is recommended. There are several different phosphorus binders that are currently available; however, the class can be divided into two subcategories: calcium- and non-calcium-containing products.[1-4] In general, calcium-containing phosphorus binders (Eliphos®, PhosLo®, Phoslyra®) are associated with higher serum calcium and lower serum parathyroid hormone levels compared to the non-calcium-containing products.[5-7] Increased serum calcium levels leads to hypercalcemia and also increases the risk of vascular calcification and arterial disease in CKD patients.[4] As a result, these products are typically avoided in CKD patients with hypercalcemia or severe vascular calcification.[2-4] The available non-calcium-containing phosphorus binders include sevelamer, available in two salt forms (hydrochloride [Renagel®] and carbonate [Renvela®]), lanthanum carbonate (Fosrenol®), ferric citrate (Auryxia®) and sucroferric oxyhydroxide (Velphoro®).[8-12] These products are typically reserved for use in CKD patients with hypercalcemia, or as adjunct to a regimen supplying the maximum allotted dose of elemental calcium from calcium-containing phosphorus binders.[1-4] The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a new, buffered formulation was created. The newer, sevelamer carbonate formulation will most likely be thought of as the preferred formulation of sevelamer because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products.[4] Currently, sevelamer carbonate and calcium acetate tablets and capsules are available generically.

Available evidence supports the hypothesis that all of the phosphorus binders are efficacious in controlling serum phosphorus levels. It is generally accepted that no one product is effective and acceptable to every patient.[2] Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on CKD Stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD. Despite this lack of evidence, it is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.[1] Combination therapy, with multiple binders, may also be an option in order to control serum phosphorus levels while minimizing the side effects associated with any specific binder.[2,3] According to the current clinical guidelines, phosphorus binders are to be utilized in patients with CKD Stages 3 to 5D who cannot adequately maintain serum phosphorus levels within the normal range with dietary phosphorus restriction.[1-3] Choice of product should take into account the Stage of CKD, the presence of other components of CKD-Mineral and Bone Disorder, concomitant therapies and side effects.[1]

Medications

Table 1. Medications Included Within Class Review[5-12]

Generic Name (Trade name)	Medication Class	Generic Availability
Calcium acetate (Eliphos®*, PhosLo®*, Phoslyra®)	Phosphorus depleters	✔
Ferric citrate (Auryxia®)	Phosphorus depleters	-
Lanthanum carbonate (Fosrenol®)	Phosphorus depleters	-
Sevelamer carbonate (Renvela®*)	Phosphorus depleters	✔
Sevelamer hydrochloride (Renagel®)	Phosphorus depleters	-
Sucroferric oxyhydroxide (Velphoro®)	Phosphorus depleters	-

*Generic available in at least one dosage form or strength.

Indications

In general, phosphorus binders (or phosphorus depleters) are used to control hyperphosphatemia in patients with chronic kidney disease.[5-12] Specific Food and Drug Administration approved indications are outlined in Table 2.

Table 2. Food and Drug Administration Approved Indications[5-12]

Generic Name	Control Hyperphosphatemia in End Stage Renal Failure	Reduce Phosphate with End Stage Renal Disease	Control Serum Phosphorus in Patients with Chronic Kidney Disease on Dialysis
Calcium acetate	✔ *	✔ (Phoslyra®)	
Ferric citrate			✔
Lanthanum carbonate		✔	
Sevelamer carbonate			✔
Sevelamer hydrochloride			✔ †
Sucroferric oxyhydroxide			✔

*Does not promote aluminum absorption.
†The safety and efficacy of sevelamer hydrochloride in chronic kidney disease patients who are not on dialysis have not been studied.

Pharmacokinetics

Table 3. Pharmacokinetics[5-12]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Calcium acetate	30 to 40†	Not reported	Not reported	Not reported
Lanthanum carbonate	<0.002	<2	Not metabolized	53
Ferric citrate	0*	0	Not reported	Not reported
Sevelamer carbonate	0*	0	Not reported	Not reported
Sevelamer hydrochloride	0*	0	Not reported	Not reported
Sucroferric oxyhydroxide	0*	0	Not metabolized	Not reported

*Not systemically absorbed.
†Bioavailability of Phoslyra® not reported, but is expected to be the same as other oral dosage forms.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the phosphorus binders in their respective Food and Drug Administration-approved indications are outlined in Table 4.[13-54]

The available evidence supports the hypothesis that all of the phosphorus binders (or phosphorus depleters) are efficacious in controlling serum phosphorus levels.[2,3] In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been well established, and most clinical trials evaluate surrogate end points. In addition, due to ethical concerns regarding a prolonged lack of appropriate treatment, most trials evaluating the newer phosphorus binders against placebo have been short term, with longer trials using calcium-containing binders as the comparator.[1] In addition, no prospective trials have specifically examined the benefits of targeting different phosphorus levels to determine the effect on patient-level end points. Epidemiological data suggests that phosphorus levels above the normal range are associated with increased morbidity and mortality.[1] The results of a Cochrane Systematic Review by Navaneethan and colleagues demonstrated that there was no statistically significant reduction in all-cause mortality when patients received sevelamer hydrochloride compared to those receiving calcium-based phosphate binders (relative risk [RR], 0.73; 95% confidence interval [CI], 0.46 to 1.16).[47] Two meta-analysis have been published reviewing the clinical trials of the phosphate binders.[48,49] Tonelli et al compared sevelamer products to any other therapy or placebo in patients with end-stage kidney disease (ESRD), on dialysis or who had had a kidney transplant. The pooled analysis showed that phosphate levels with sevelamer was similar or slightly higher than with calcium-based phosphate binders by 0.12 mmol/L (95% CI, 0.05 to 0.19). However, the overall weighted mean difference in serum calcium was significantly lower with sevelamer therapy (0.10 mmol/L; 95% CI, −0.12 to −0.07).[48] Jamal et al evaluated all-cause mortality and compared calcium-based phosphate binders to non-calcium phosphate binders in patients with chronic kidney disease. The results of this meta-analysis showed that patients randomly assigned to non-calcium-based phosphate binders had a statistically significant 22% reduction in all-cause mortality compared with those randomly assigned to calcium-based phosphate binders (RR=0.78; 95% CI, 0.61 to 0.98). When non-randomized trials were added to the pooled analysis, the reduction in all-cause mortality was 13% (RR=0.87; 0.77 to 0.97) in favor of non-calcium-based phosphate binders.[49]

The safety and efficacy of ferric citrate was established in two clinical trials.[50,51] In one four-week, open-label trial, 154 patients were randomized to receive 1, 6, or 8 grams/day. Dose-dependent decreases in serum phosphorus were observed by day seven and remained relatively stable for the duration of treatment. The demonstrated reductions from baseline to week four in mean serum phosphorus were significantly greater with 6 and 8 grams/day than with 1 gram/day (-1.3 mg/dL and -1.5 mg/dL placebo-corrected differences, respectively; P<0.0001). Mean reduction in serum phosphorus at week four was 0.1 mg/dL, 1.9 mg/dL and 2.1 mg/dL, respectively.[50] The second study was a 56-week, placebo-controlled, randomized trial. The study concluded that serum phosphorus levels declined following initiation of therapy and the phosphorus lowering effect was maintained over 52 weeks of treatment. Patients were eligible to enter a four-week, placebo-controlled withdrawal phase if they had been receiving ferric citrate during the 52-week study. During the placebo-controlled period, the serum phosphorus concentration rose by 2.2 mg/dL in patients receiving placebo compared to patients who remained on ferric citrate (-0.24 mg/dL vs 1.79 mg/dL; P<0.001). Compared to active control (calcium acetate or sevelamer carbonate), subjects on ferric citrate received less intravenous elemental iron (median, 12.95 mg/week ferric citrate; 26.88 mg/week active control; P<0.001) and less erythropoietin-stimulating agent (median epoetin-equivalent units per week, 5,306 units/week ferric citrate; 6,951 units/week active control; P=0.04).[51]

The safety and efficacy of sucroferric oxyhydroxide was demonstrated in two randomized clinical trials, one six-week, open label, active controlled dose-finding study and one 55-week, active controlled, parallel group, dose-titration and extension study. The decrease in serum phosphorus levels appeared to be broadly dose-dependent with the largest decreases being shown in the two highest dose groups.[12,52-54] In the phase II, dose-finding study, 154 patients on hemodialysis who were hyperphosphatemic were randomized to receive one dose of sucroferric oxyhydroxide (1.25, 5.0, 7.5, 10.0 or 12.5 grams/day) or sevelamer hydrochloride 4.8 grams/day with no dose titration allowed for any patient in any group. At six weeks, sucroferric oxyhydroxide decreased serum phosphorus compared to baseline in all treatment arms except the 1.25 grams/day arm (P≤0.016). A similar decrease to sevelamer hydrochloride was seen in the 5.0 and 7.5 grams/day arms.[1,52] In the dose-titration study, 1,054 patients on hemodialysis or peritoneal dialysis were randomized and treated with sucroferric oxyhydroxide, 1 to 3 grams/day, or active-control for 24 weeks. At the end of week 24, 93 patients on hemodialysis whose serum phosphorus levels were controlled (<5.5 mg/dL) with sucroferric oxyhydroxide, were re-randomized to continue treatment with either their week 24 maintenance dose or a non-effective low dose sucroferric oxyhydroxide control (250 mg/day) for an additional three weeks. There was a significant difference in serum phosphorus concentrations at week 27 in favor of the sucroferric oxyhydroxide maintenance group compared to the non-effective low dose control (P<0.001). Patients who completed the study that did not receive the low dose control were eligible to enter a 28-week extension study. During the extension study, 658 patients were treated with either sucroferric oxyhydroxide or sevelamer carbonate according to their original randomization. Serum phosphorus control was maintained with both sucroferric oxyhydroxide and sevelamer throughout the extension study and the difference between groups was not statistically significant (P=0.14).[53,54]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Shigematsu et al[13] Lanthanum carbonate 750 mg/day, titrated up by 750 mg/day, depending on serum phosphate	MC, OL Patients 20 to 75 years of age with CKD on dialysis TIW for ≥3 months, on a stable dose of vitamin D for ≥1 month and pre-dialysis serum phosphate ≥5.6 and <10.0 mg/dL during a 3 week wash out period	N=145 12 months	Primary: Efficacy based on target serum phosphate control (≥3.5 and ≤5.5 mg/dL) and safety Secondary: Not reported	Primary: Mean serum phosphate decreased from 8.03±1.51 mg/dL at baseline to 5.33±1.33 mg/dL at week 10 and the decreased level was maintained afterward (5.33±1.27 mg/dL at one year). The mean reductions in serum phosphate from baseline to each time point were within the range of -1.51±1.48 (week one, 95% CI, -3.36 to -1.27) to -2.98±2.00 mg/dL (week 32, 95% CI, -3.36 to -2.59), and at all time points the reductions were significant (P<0.05). The target achievement rate at week one was 33.8%, but it increased gradually and reached 67.2% at week 16, and was maintained at 56.4 to 70.1% thereafter. Almost all patients (99%) experienced at least one adverse event, and 57% had an adverse event related to the study drug. Thirty-two (22%) patients experienced at least one serious adverse event and four (3%) patients had serious drug-related adverse events. Thirty-six (25%) patients were discontinued from the study because of adverse events and one death (acute MI deemed unrelated to study drug) occurred. Secondary: Not reported
Vemuri et al[14] Lanthanum carbonate 1,500 mg/day titrated up by 750 mg/day to achieve serum phosphorus levels between 3.5 and 5.5 mg/dL Patients could be titrated up to a maximum dose of 3,750 mg/day.	MC, OL Adult patients ≥18 years of age with ESRD requiring treatment for hyperphos-phatemia	N=2,763 16 weeks (12 week titration and 4 week maintenance)	Primary: Efficacy (phosphorus levels) and patient and physician satisfaction and preference Secondary: Tablet burden and daily dose of medication, PTH, corrected serum calcium, CAxP levels and safety	Primary: After conversion to lanthanum carbonate, mean serum phosphorus levels throughout the study were similar to those achieved with the patient's previous phosphate binder. The mean change from baseline was -0.06±0.05 mg/dL at week 12 and 0.02±0.05 mg/dL at week 16. Similar results were observed regardless of prior phosphate binder treatment. Patients who were treatment naïve to phosphate-binders experienced a statistically significant reduction in phosphorus levels at week 12 (-0.41±0.19 mg/dL) and week 16 (-0.62±0.19 mg/dL; P values not reported). Similar proportions of patients achieved target serum phosphorus levels (≤5.5 mg/dL) at baseline (41.8%) and throughout treatment with lanthanum carbonate (44.9% at week 12 and 41.6% at week 16).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In the treatment-naïve group, the percentage with phosphorous control increased from 36.5% at baseline to 58.7% at week 12 and 50.6% at week 16 (P values not reported). Significant increases from baseline in physician satisfaction was occurred in domains for overall satisfaction, patient compliance, control of hyperphosphatemia, and ease of medication use ($P<0.0001$ for all). Patient satisfaction was significantly greater after lanthanum treatment on each satisfaction domain with the exception of stomach sickness and other side effects (P value not reported). Satisfaction with current lanthanum treatment was similar for patients who previously received sevelamer or calcium-based phosphate binders. Significantly more patients (73 vs 27%; $P<0.0001$) and physicians (83 vs 17%; $P<0.0001$) preferred lanthanum carbonate therapy to previous treatment. Secondary: There were significant reductions in pill burden with lanthanum carbonate compared to previous phosphate-binder treatments at weeks 12 and 16 ($P<0.001$ and $P<0.0001$, respectively). For patients previously treated with calcium acetate, sevelamer, or 'other,' there were significant ($P<0.0001$) reductions in the dose of phosphate binder required to maintain serum phosphorus control when patients were converted to treatment with lanthanum carbonate. At both weeks 12 and 16 of lanthanum carbonate treatment, there were statistically significant improvements in the serum calcium levels and the changes in Ca×P product. There was a statistically significant increase in PTH after following the initiation of lanthanum carbonate ($P<0.0001$ for all). Adverse events were reported by 36.0% of patients, and 12.4% of patients discontinued treatment. Most adverse events were mild or moderate, with severe events reported by 12.1% of all patients. The most common adverse events included nausea (7.9%), diarrhea (5.4%) and vomiting (5.0%). No statistically significant changes in liver enzymes were reported with the exception of alkaline

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				phosphatase. The mean±SD alkaline phosphatase levels increases from screening by 5.3±70.6 and 6.8±74.8 U/L at weeks 12 and 16, respectively.
Almirall et al[15] Lanthanum carbonate 1,000 mg/day titrated to target serum phosphate levels Lanthanum carbonate was initially added to the patients' background phosphate binder therapy, while simultaneously reducing the doses of other phosphate binders as tolerated.	OS, PRO Patients ≥18 years of age on a stable hemodialysis regimen TIW for ≥6 months and uncontrolled serum phosphate (average level during the last 6 months >5.5 mg/dL) despite adequate dialysis treatment, regular use of sevelamer or calcium-based phosphate binders during the last 6 months with dose-limiting side-effects	N=34 6 months	Primary: Serum phosphate and calcium levels, the Kt/V, intact PTH, alkaline phosphatase Secondary: Safety and patient preference	Primary: Mean phosphate levels during the six months before the study and at baseline were 5.45±0.97 and 5.74±1.45 mg/dL, respectively, and decreased to 4.48±1.1 mg/dL after six months (P<0.001 for both comparisons), resulting in a mean decrease of 18 and 22%, respectively. There was no statistically significant change from baseline in serum calcium levels six months after initiating lanthanum carbonate treatment (9.37±0.56 vs 9.52± 0.63; P=NS) The average hemodialysis dose (Kt/V) did not significantly change from baseline following lanthanum carbonate treatment (P=NS). Intact PTH levels increased to 247±167 pg/mL from 189±120 pg/mL at baseline (P=NS). No statistically significant change in alkaline phosphatase was reported over six months (P=NS). The percentage of patients with serum phosphate within the target range (3.5 to 5.5 mg/dL) was 52% at baseline and 91% at six months. Similarly, CaxP product<55 was reported in 55% of patients at baseline and increased to 95% of patients at six months (P<0.00). The addition of lanthanum carbonate reduced serum phosphate while also allowing for a dose reduction by 75% in calcium carbonate, 61% in calcium acetate, 66% in sevelamer and 100% in aluminum hydroxide. Secondary: Compared to baseline individual symptoms scores for nausea and vomiting significantly improved (P≤0.02 for both) following the addition of lanthanum carbonate therapy for six months; however no changes occurred with regard to bloating, heart burn or abdominal pain.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				On a 10-point scale, the average rating of treatment satisfaction increased from 6.6±2 at baseline to 8.1±1.4 after six months of lanthanum carbonate treatment (P=0.001).
Finn et al[16] Lanthanum carbonate, dosage could be titrated to maintain a serum phosphate ≤5.9 mg/dL Patients had received treatment in one of two previous trials.[12,13]	ES, OL Patients with serum phosphate 2 and 10 mg/dL	N=154 12 months	Primary: Safety Secondary: Not reported	Primary: The most common body system categories of adverse events were gastrointestinal (55.8%), respiratory (55.8%), general disorders (49.4%), cardiovascular (36.4%), dialysis graft complications (36.4%) and musculoskeletal (36.4%). The most commonly reported adverse events were nausea (26.0%), peripheral edema (23.4%) and myalgia (20.8%). Eight patients withdrew from the study due to adverse events, which included nausea, diarrhea, vomiting, MI, elevated PTH, constipation, tongue irritation and inflammation, noncompliance, serum phosphate >10 mg/dL and, in one case, long-term rehabilitation, which led the investigator to terminate the patient from the study. Thirty-seven patients experienced a serious adverse event, the most frequently reported being dialysis graft complications (7.8%), sepsis (6.5%) and hospitalization for a renal transplant (6.5%). The only other serious adverse events with an incidence >5% were dialysis graft occlusion, osteomyelitis and MI (all 5.2%). None of these serious adverse events were unexpected and reflects the ESRD in the study population and no event was considered treatment-related. Secondary: Not reported
Hutchison et al[17] Lanthanum carbonate 375 to 9,000 mg/day	ES, OL Patients ≥18 years of age who participated in four previous studies who continued to require treatment for hyper-	N=93 2 years (efficacy and safety data reported in conjunction with that from the previous	Primary: Pre-dialysis serum phosphate and CaxP product levels Secondary: Safety	Primary: Although no target was specified for this trial, reductions of serum phosphate and CaxP product levels were successfully maintained for up to six years of treatment. Serum phosphate levels were 7.80±2.10 mg/dL at baseline, reducing to 5.50±1.70 mg/dL after six months, 5.74±1.53 mg/dL after three years and 5.23±1.19 mg/dL after five years (month 60). The range of values at six years (month 72, 4.5 to 6.5 mg/dL) was within the range seen at earlier time points.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	phosphatemia[11,12,15,16]	studies giving a total treatment duration of up to 6 years)		Overall Ca x P product levels were 70.2±19.0 mg^2/dL^2 at baseline, reducing to 50.4±15.2 mg^2/dL^2 after six months, 53.75±14.51 mg^2/dL^2 after three years and 50.05±11.30 mg^2/dL^2 after five years (month 60). The range of values at six years (month 72, 46.4 to 68.2 mg^2/dL^2) was within the range seen at earlier time points. Secondary: There were no new or unexpected adverse events, or any increase in the incidences of adverse events with increasing exposure to lanthanum carbonate over long-term treatment. The most common adverse events occurring at any time during treatment were episodes of myalgia (n=48, 51.6%), nausea (n=46, 49.5%), hypotension (n=39, 41.9%) and influenza like symptoms (n=38, 40.9%). There was a low incidence of hypercalcemia in five (5.4%) patients and hypocalcemia in 10 (10.8%) patients. During the total treatment period, adverse events that were considered to be related to lanthanum carbonate occurred in 24 (25.8%) patients, with the most being gastrointestinal in nature (mainly nausea, diarrhea and flatulence).
Hutchison et al[18] Lanthanum carbonate 375 to 3,000 mg/day	ES, OL Patients who participated in a 6 month RCT comparing lanthanum carbonate with calcium carbonate[15]	N=161 2 years	Primary: Serum phosphate, CaxP product, calcium and PTH levels Secondary: Safety	Primary: One hundred and sixteen patients were re-titrated between weeks 49 and 58 in order to re-establish optimal control of serum phosphate. At week 58, all patients had been re-titrated, and the various doses were administered at a frequency of: 11 (750 mg), 27 (1,500 mg), 30 (2,250 mg) and 32% (3,000 mg). At the start of the two year extension, the mean serum phosphate level was 6.29 mg/dL. After two months, and re-titration of patients, mean serum phosphate had decreased to 5.67 mg/dL. Patients in the long term-exposure group (those completing all phases of the trial) had a mean serum phosphate level that was consistently lower than that of the safety population (all patients receiving at least one dose of study medication). A greater proportion of patients from this group had serum phosphate levels at each time point that met the criteria defined for control in the earlier phases of the trial. By the end of the study, serum phosphate levels were ≤5.6 mg/dL in 69% of the long term-exposure group and in 54% of the overall safety population. Throughout the two year extension, the mean CaxP product level decreased substantially from 62.9 mg^2/dL^2 at week 49 to 48.6 mg^2/dL^2 at week 75.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Mean serum calcium levels remained within values considered to be representative of a normal range (8.2 to 10.6 mg/dL) during the two-year extension, although the level was marginally higher than this at the beginning of this phase (week 49). Sixty three percent of patients had no hypercalcemic episodes, and 17% of patients had just a single hypercalcemic episode. PTH levels remained broadly unchanged in a high proportion of patients (43%). In the long term-exposure group, a greater proportion of patients moved from low or high PTH levels toward levels deemed in this trial to represent normal bone turnover. Secondary: A total of 1,810 adverse events were reported by 92% of patients during this phase; with 50 (2.8%) being considered likely to be related to treatment. Of all adverse events reported during this time, only 44 (2.4%) led to treatment discontinuation.
Finn et al (abstract)[19] Lanthanum carbonate 225 to 2,250 mg/day vs placebo	DB, PC, RCT Patients ≥18 years of age receiving hemodialysis for ≥6 months	N=196 9 weeks (Phase 1, 1 to 3 week SB, PC run-in phase; Phase 2, 6 week DB, PC, randomized maintenance phase)	Primary: Serum phosphate levels Secondary: Adverse events	Primary: The ITT analysis (n=144) showed significant dose-related reductions in serum phosphate at lanthanum doses of 675, 1,350 and 2,250 mg. After six weeks of treatment phosphate levels were significantly lower in the lanthanum carbonate groups receiving 1,350 and 2,250 mg/day, compared to placebo (respective changes from randomization, -0.95±1.39, -1.13±2.01 and 0.75±1.47 mg/dL; P<0.001). Significant reductions in serum phosphate, compared to placebo, occurred by the second (1,350 mg/day) and first (2,250 mg/day) weeks of treatment. Secondary: Adverse events were mainly gastrointestinal. Treatment-related adverse events occurred in 39% of patients treated with lanthanum carbonate and 44% of the patients treated with placebo.
Joy et al[20] Lanthanum carbonate up to 3,000 mg/day administered in divided	DB, PC, PG, RCT Patients ≥18 years of age with ESRD who received	N=163 13 weeks (Phase 1, 1 to 3 week	Primary: Serum phosphate, calcium, CaxP product and iPTH levels	Primary: Serum phosphate concentrations decreased during dose titration with lanthanum carbonate. Following randomization, mean serum phosphate remained <6.0 mg/dL in the lanthanum carbonate group but was substantially raised in the placebo group. At the end of randomization treatment, there was a highly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
doses after meals vs placebo	dialysis TIW for ≥2 months and who were medically stable	washout period; Phase 2, 6 week OL, dose titration phase; Phase 3, 4 week DB, PC, randomized maintenance phase vs placebo)	 Secondary: Adverse events	significant difference in mean phosphate concentrations between the lanthanum carbonate- and placebo-treated patients (5.94±1.62 vs 7.85±1.96 mg/dL; 95% CI, -2.60 to -1.23 mg/dL; P<0.0001). At study endpoint, the difference between mean serum calcium levels between the two groups (0.35 mg/dL) was not statistically significant (P value not reported). Mean levels were statistically significant different compared with the end of dose titration in placebo-treated patients (P<0.05), but not in the lanthanum carbonate-treated patients (P value not reported). At study endpoint, there was a highly statistically significant mean difference (-14.22 mg^2/dL^2) in CaxP product between the two groups (P<0.001). There was also a significant increase in CaxP product between the end of dose titration and study endpoint in placebo-treated patients (P<0.0001) but not in the lanthanum carbonate-treated patients. At study endpoint, iPTH levels were substantially and significantly higher in the placebo group than in the lanthanum carbonate group (mean treatment difference, -83 pg/mL; P<0.01). Mean iPTH levels were statistically significantly higher (P<0.0001) at study endpoint compared with the end of dose titration in placebo-treated patients, but not in lanthanum carbonate-treated patients. Secondary: Adverse events were reported by 82.2% (n=134) of all patients enrolled in the study. The adverse events reported with the highest incidence (>10%) were nausea (18.4%), vomiting (13.5%) and rhinitis (12.3%). During titration, 346 adverse events were reported by 62.6% (n=102). Of these, 15.6% (54) were considered to be related to treatment.
Sprague et al[21] Lanthanum carbonate 750 mg TID with meals, titrated up to a maximum of 3,000 mg/day to achieve target serum	DB, PC, RCT Patients ≥18 years of age with an eGFR 15 to 59 mL/min/1.73 m^2 at screening, undergoing	N=121 8 weeks	Primary: Percentage of patients with serum phosphate <4.6 mg/dL at eight weeks Secondary:	Primary: At the end of treatment, 44.6% of lanthanum carbonate-treated patients and 26.5% of placebo-treated patients had serum phosphate levels ≤4.6 mg/dL; the difference between groups (18.1%) was not significantly different (P=0.12). Secondary: At the end of treatment, mean serum phosphate concentrations had decreased from baseline by 0.55±0.10 and 0.18±0.13 mg/dL in the lanthanum carbonate and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
phosphate level <4 mg/dL vs placebo All patients went through a 2 to 3 week run in period where their previous phosphorus binder medications were discontinued and dietary phosphorus counseling was reinforced. Patients with a serum phosphate level >4.6 mg/dL after 2 weeks were randomized to treatment.	physician care for CKD for >2 months and not expected to begin dialysis for ≥4 months		Changes in serum phosphate, iPTH and CaxP product levels from baseline, and safety	placebo groups, respectively (P=0.02). At the end of treatment, mean serum iPTH levels had decreased by 23.8±8.6 pg/mL in the lanthanum carbonate group and had increased by 8.8±11.0 pg/mL in the placebo group (P=0.02). Mean CaxP product levels decreased slightly from baseline in both groups, however; at the end of treatment, the difference in reduction from baseline was not significantly different between them (P value not reported). Adverse events were experienced by 47.4 and 61.0% in the lanthanum carbonate and placebo groups. Adverse events were mainly gastrointestinal in nature with nausea (9.0 vs 9.8%) and vomiting (6.4 and 2.4%) being the most commonly reported.
Shigematsu et al[22] Lanthanum carbonate 250, 500, 750 or 1,000 mg TID with meals vs placebo	DB, DR, MC, PC, PG, RCT Patients 20 to 75 years of age with CKD on dialysis TIW for ≥3 months, on a stable dose of vitamin D for ≥1 month and pre-dialysis serum phosphate ≥5.6 and <10.0 mg/dL	N=156 6 weeks	Primary: Change from baseline in phosphate levels at six weeks Secondary: Achievement rate of the target pre-dialysis serum phosphate level (≥3.5 and ≤5.5 mg/dL), corrected	Primary: The reductions in baseline serum phosphate levels were significantly greater in all lanthanum carbonate groups compared to the placebo group (P values not reported). The changes at the end of treatment in the lanthanum carbonate groups were -1.35±0.27, -2.55±0.28, -3.03±0.26 and -3.12±0.32 mg/dL for the 750, 1,500, 2,250 and 3,000 mg/day groups, respectively. Secondary: There was a significant difference in the proportion of patients reaching target pre-dialysis serum phosphate levels between the lanthanum carbonate and placebo groups (P values not reported). The cumulative proportions of patients who reached target levels in the 750, 1,500, 2,250 and 3,000 mg/day lanthanum carbonate groups at week six were 50, 68, 82 and 69%, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	during a 3 week wash out period		serum calcium; CaxP product and serum PTH levels	Corrected serum calcium levels remained unchanged throughout the treatment period. The changes in serum CaxP product levels observed were consistent with those observed with serum phosphate levels. Serum PTH levels remained elevated during the treatment period in the placebo group but decreased in the lanthanum carbonate groups.
Al-Baaj et al[23] Lanthanum carbonate 375 to 2,250 mg/day administered in 3 equally divided doses with meals vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age, receiving hemodialysis or CAPD for ≥6 months, including patients who had undergone renal transplantation	N=56 10 weeks (Phase 1, 2 week washout period; Phase 2, 4 week OL, dose-titration phase; Phase 3, 4 week DB, PC phase)	Primary: Reduction of serum phosphate levels to 4.03 to 5.58 mg/dL Secondary: Changes over time in pre-dialysis serum calcium and PTH levels and adverse events	Primary: By the end of the dose-titration phase, 60% (30/50) of patients on hemodialysis had controlled phosphate levels (4.03 to 5.58 mg/dL) and 70% (35/50) had serum phosphate levels ≤5.58 mg/dL During the DB phase, lanthanum carbonate continued to maintain the reduction in serum phosphate levels, whereas levels increased with placebo. Treatment groups differed significantly with regard to the mean serum phosphate level at 10 weeks (4.84±0.93 vs 6.29±0.96 mg/dL; P<0.001). Similar results were observed in patients receiving CAPD. Secondary: There was no difference in mean serum calcium levels between the two groups at the end of the study (P value not reported). Mean PTH levels increased more in placebo-treated patients; however, there was no significant difference in PTH levels between the lanthanum carbonate (216±179 ng/L) and placebo (250±226 ng/L) groups at week 10 (P=0.41). The occurrence of adverse events was similar in both groups. The most common adverse events and treatment-related events throughout the study were gastrointestinal in nature, with nausea (19%) and vomiting (17%) being most common.
Mehrotra et al[24] Lanthanum carbonate	RCT Patients ≥18 years	N=513 8 weeks	Primary: Control rate for pre-dialysis serum	Primary: One hundred and forty two patients entered Cohort B. Twenty five percent of these patients who were randomly assigned to receive lanthanum carbonate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
up to 3,000 mg/day vs placebo All patients went through a 3 week run in period where their previous phosphorus binder medications were discontinued. Followed by Part 1; an OL, titration phase with only patients achieving doses ≥1,500 mg/day moving to Part 2. Patients in Part 2 were assigned to two separate cohorts. Patients with target serum phosphate levels at the end of Part 1 entered a 4 week OL phase in which they continued on the same final daily dosage from Part 1 (Cohort A). Patients with non-target serum phosphate levels, therefore not controlled with 3,000	of age with CKD Stage 5 who required treatment for hyper-phosphatemia (>5.5 mg/dL after washout) and on a stable hemodialysis regimen TIW for ≥2 months before screening	(with an additional 4 month OL, ES)	phosphate levels at eight weeks among Cohort B Secondary: Weekly levels and control rates for serum phosphate, calcium, CaxP product and iPTH; satisfaction, pill count, and adherence	3,000 mg/day and had not achieved target serum phosphate levels at week four with an identical dosage did so by treatment week eight. Among patients who were randomly assigned to 3,750 or 4,500 mg/day, 38 and 32% of patients achieved target levels. The difference between groups for rate of controlled levels suggests a benefit of titrating to higher doses, but statistical significant was not reached. Secondary: After the initial four weeks of treatment with lanthanum carbonate doses ≤3,000 mg/day (n=383), serum phosphate decreased to 5.6±1.6 from 7.0±1.8 mg/dL at baseline, with reductions from baseline being significant at all visits through the end of the study (P<0.0001). Increased serum calcium levels were observed at several assessments throughout the full 24 weeks of treatment (baseline [n=431], 9.38±0.73 mg/dL vs end of study [n=404], 9.53±0.79 mg/dL; P≤0.0001). CaxP product levels were significantly reduced compared with baseline at all visits (baseline [n=352], 66.0±17.5 mg^2/dL^2 vs end of study [n=336], 56.8±16.8 mg^2/dL^2; P≤0.0001). Measurements of iPTH showed slight reductions during the initial four weeks of treatment and slight increases at subsequent visits (baseline [n=422], 266±192 pg/mL vs end of study [n=410], 287±239 pg/mL; P=0.0042). Preference for lanthanum carbonate over previous phosphorus binder was expressed by both patients and physicians after four weeks of treatment. Overall, 64% of patients preferred lanthanum carbonate, 21% had equal preference and 15% preferred their previous medication (P<0.001). “Number of tablets” was the domain in which patients indicated the strongest preference for the study drug. Overall, 81 and 76% of Cohort A and B were adherent to study drug (consumption >80% of prescribed study dose).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day at the end of Part 1, entered a DD, DB, forced-dosage titration phase in which they received a final daily dosage of 3,000, 3,750 or 4,500 mg/day (Cohort B).				
Ketteler et al[25] Sevelamer carbonate 4.8 g/day administered as two 800 mg tablets TID Doses were titrated as necessary to a maximum of 12 g/day. Patients were also supplemented with a 400 IU/day dose of the native form of vitamin D at bedtime.	DR, MC, OL Patients ≥18 years of age with CKD and hyper-phosphatemia not on dialysis with serum phosphate ≥5.5 mg/dL at screening or after a wash out period, 25-hydroxy vitamin D ≥10 ng/mL and iPTH ≤800 pg/mL	N=49 8 weeks	Primary: Change from baseline in serum phosphate Secondary: Percentage of serum phosphate responders, changes in serum lipids, CaxP product and bicarbonate levels, and safety	Primary: Mean serum phosphate was 6.2±0.8 mg/dL at treatment initiation and decreased to 4.8±1.0 mg/dL after eight weeks of treatment. Treatment with sevelamer carbonate resulted in a significant mean decrease of 1.4±1.0 mg/dL in mean serum phosphate levels from baseline (P<0.001). Secondary: By the end of eight weeks of treatment, 75% of patients with CKD Stage 4 had reached the titration target level of serum phosphate ≥2.7 and ≤4.6 mg/dL, and 70% of patients with CKD Stage 5 had achieved a serum phosphate level ≤5.5 mg/dL. There were statistically significant decreases in serum CaxP product, total cholesterol and LDL-cholesterol levels, and an increase in serum calcium from baseline to the end of treatment (P<0.001 for all). No clinically meaningful changes in HDL-cholesterol were observed. There was a significant increase in mean serum bicarbonate (1.3 mEq/L; range, -4.0 to 8.0 mEq/L; P=0.005), with 28 (61%) patients experiencing an increase. Overall treatment was well tolerated with the highest frequency of adverse events being mild to moderate gastrointestinal disorders. No serious adverse events or deaths that occurred during the study were considered to be related to treatment. Two patients withdrew from the study to begin dialysis treatment.
Fischer et al[26] Sevelamer, salt not specified, QD	OL, RCT, XO Patients ≥18 years of age receiving maintenance	N=21 8 weeks	Primary: Evaluate the equivalence of QD and TID dosing on control of serum	Primary: QD dosing was equivalent to TID dosing for controlling serum phosphate levels (5.0±0.3 vs 4.6±0.3 mg/dL; LSMR, 0.92; 90% CI, 0.83 to 1.01). The majority of patients maintained similar phosphate levels regardless of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sevelamer, salt not specified, TID Patients were randomized to receive sevelamer QD with the largest meal for 4 weeks followed by sevelamer TID with meals for 4 weeks or vice versa. All patients went through a 2 week run in period, during which the investigator maintained a stable dose of sevelamer and vitamin D.	hemodialysis with a life expectancy ≥12 months, receiving hemodialysis TIW for ≥3 months, maintained on sevelamer ≤9,600 mg/day as their only phosphorus binder and serum phosphate concentrations at the last 2 measurements between 3.0 and 6.5 mg/dL		phosphate levels and safety Secondary: Evaluate the equivalence of QD and TID dosing on serum corrected calcium, CaxP product, albumin, iPTH and serum lipids	treatment regimen, however; one patient's level increased substantially during QD treatment. During the XO phase, nine (42.9%) and 12 (57.1%) patients reported an adverse event during the TID and QD regimen. The majority of reported treatment-emergent adverse events were mild to moderate in intensity and gastrointestinal symptoms were the most frequently reported. None of them led to discontinuation of treatment. Seven (33.3%) patients experienced a total of 15 serious adverse events; all were deemed not to be related to the study drug. Secondary: QD dosing was equivalent to TID dosing with respect to values for corrected calcium (9.4±0.2 vs 9.5±9.4 mg/dL; LSMR, 1.01; 90% CI, 0.99 to 1.03), CaxP product (47.3±2.7 vs 44.0±2.8 mg^2/dL^2; LSMR, 0.93; 90% CI, 0.84 to 1.03), albumin (3.8±0.1 vs 3.8±0.1 g/dL; LSMR, 1.00; 90% CI, 0.99 to 1.01), total cholesterol (135.0±7.8 vs 132.5±7.7 mg/dL; LSMR, 0.98; 90% CI, 0.95 to 1.01), LDL-cholesterol (60.5±5.4 vs 58.1±6.0 mg/dL; LSMR, 0.96; 90% CI, 0.89 to 1.04), HDL-cholesterol (39.8±2.4 vs 39.2±2.4 mg/dL; LSMR, 0.98; 90% CI, 0.95 to 1.03), non-HDL-cholesterol (92.5±7.8 vs 90.4±7.8 mg/dL; LSMR, 0.98; 90% CI, 0.91 to 1.04) and TG (144.3±24.0 vs 148.4±22.1 mg/dL; LSMR, 1.03; 90% CI, 0.94 to 1.12). Equivalence between the two dosing regimens was not observed with regard to iPTH levels (247.0±40.8 vs 216.8±38.2 pg/mL; LSMR, 0.88; 90% CI, 0.75 to 1.02), likely because of high variability.
Ouellet et al[27] Sevelamer, salt not specified, plus calcium carbonate administered simultaneously with meals (concomitant) vs sevelamer, salt not	RCT, XO Patients already requiring both sevelamer and calcium carbonate for serum phosphate control and receiving hemodialysis TIW	N=14 8 weeks	Primary: Change from baseline in serum phosphate Secondary: Changes in serum calcium, CaxP product and bicarbonate	Primary: Mean serum phosphate levels were similar at week four in both periods (1.50±0.46 vs 1.51±0.31 mmol/L; mean difference, -0.01 mmol/L; 95% CI, -0.26 to 0.24; P=0.97). Three patients still had serum phosphate levels above the target range (1.78 mmol/L) at the end of both periods. Secondary: Serum calcium (2.26±0.19 vs 2.27±0.15 mmol/L; mean difference, -0.02 mmol/L; 95% CI, -0.14 to 0.10; P=0.64), CaxP product (3.36±0.94 vs 3.41±0.71 $mmol^2/L^2$; mean difference, -0.05 $mmol^2/L^2$; 95% CI, -0.60 to 0.50; P=0.84) and bicarbonate levels (21.5±3.3 vs 21.6±3.1 mmol/L; mean difference, -0.1 mmol/L; 95% CI, -1.3

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
specified, plus calcium carbonate administered separately with meals (only one agent administered at meal time; alternating medications) (separate) Patients were randomized to administer sevelamer plus calcium carbonate simultaneously with meals for 4 weeks followed by administration of either sevelamer or calcium carbonate, alternatively, with meals for 4 weeks or vice versa. The dose of phosphate binders were determined for each patient based on their pre-study dose.				to 1.0; P=0.81) were similar at the end of the two study periods.
Iwasaki et al[28] Sevelamer hydrochloride 2,250 mg/day plus calcium carbonate 1,500 mg/day (Group A) vs	PRO, RCT Patients receiving haemodialysis, with hyper-phosphatemia and without hypocalcemia	N=65 8 weeks	Primary: Efficacy Secondary: Not reported	Primary: Serum phosphate levels, initially non-significantly higher in Group B, were decreased significantly in Group B and unchanged in Group A after eight weeks. Mean serum calcium levels decreased in both groups from 10.1±0.7 to 9.7±0.9 mg/dL (P<0.001). In all patients, the mean reduction in serum calcium levels was 0.35 mg/dL. The CaxP product was not significantly changed in Group A (P value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sevelamer hydrochloride 3,000 mg/day plus calcium carbonate 1,500 mg/day (Group B)				reported), but was significantly decreased in Group B (P value not reported). iPTH was slightly increased from 292±882 to 340±222 ng/L without any significance in Group A, but was significantly increased from 226.3±223.4 to 358.5±399.3 ng/L (P<0.01) in Group B. Alkaline phosphatase increased significantly in both groups (Group A, 175.2±75.3 to 257.0±94.1 U/L; P<0.001; Group B, 178.1±78.3 to 253.7±127.7 U/L; P<0.001). Secondary: Not reported
Qunibi et al[29] Calcium acetate vs sevelamer hydrochloride Initial doses were based on package insert recommendations indexed to serum phosphate at the end of a washout period: ≥6.0 and <7.5 mg/dL, 2 capsules TID; ≥7.5 and <9.0 mg/dL, 3 capsules TID and ≥9.0 mg/dL, 4 capsules TID. All study medications were administered with meals and doses were	DB, MC, PRO, RCT Adult patients with ESRD receiving haemodialysis for ≥3 months, receiving a stable dose of phosphate binder and intravenous vitamin D for ≥1 month	N=98 8 weeks	Primary: Change from baseline in serum phosphate, calcium and CaxP product levels Secondary: Hypercalcemia and hypocalcemia, binder dosage, adherence, iPTH and sodium bicarbonate levels, and safety	Primary: Covariate-adjusted comparisons of C_{avg} between treatment groups show that, during weeks one to eight, in calcium acetate treated patients, mean serum phosphate was lower (1.08 mg/dL difference; P=0.0006), mean serum calcium was higher (0.63 mg/dL difference; P<0.0001) and mean CaxP product level was lower (6.1 mg^2/dL^2 difference; P=0.022). During weeks five to eight, treatment effects on C_{avg} for phosphate and calcium were significant and similar to the effects for weeks one to eight, but there were no significant treatment effects on CaxP product. Beginning one week after the start of treatment, in each week's observation, calcium acetate-treated patients were 20 to 24% more likely to attain the serum phosphate goals (weeks one to eight: OR, 2.37; 95% CI, 1.28 to 1.37; P=0.0058 and weeks five to eight: P=0.016). Calcium acetate-treated patients were 15 to 20% more likely to attain the CaxP product goal in each week (weeks one to eight: OR, 2.16; 95% CI, 1.20 to 3.86; P=0.0097 and weeks five to eight: P=0.054). Main effects of treatment were not significant for the serum calcium goal, but proportions attaining the serum calcium goal were higher in weeks one to five for calcium acetate treated patients, and higher in weeks six to eight for sevelamer hydrochloride treated patients (weeks one to eight; P=0.16, weeks five to eight; P=0.79).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
titrated as necessary to achieve a goal phosphorus level ≤5.5 mg/dL.				Secondary: Calcium acetate-treated patients generally had a higher probability of post-baseline hypercalcemia and a lower probability of hypocalcemia than sevelamer hydrochloride-treated patients. The average daily dose was 10.7±7.5 capsules (7.1±5.0 g/day) in the calcium acetate treated patients compared with 17.2±9.0 capsules (6.9±3.6 g/day) in the sevelamer hydrochloride treated patients. Calcium acetate treated patients received significantly fewer pills each day (P=0.0017) with the difference increasing over time (P<0.0001). Individual patient compliance varied substantially, with patients' average compliance over the eight weeks (mean±SD) 69±22% in calcium acetate treated patients, and 71±19% in sevelamer hydrochloride treated patients. In calcium acetate treated patients, iPTH declined 37% from baseline to week four, but only an additional 6% in weeks four to eight. In sevelamer hydrochloride treated patients, iPTH declined 6% from baseline to week four, and 11% in weeks four to eight. There was no significant difference in iPTH levels between the two groups at week eight (P value not reported). Relatively few patients reached the lowest threshold of 17 mEq/L for serum bicarbonate, but this was more likely in sevelamer hydrochloride treated patients. There were no significant differences between the two groups in the overall incidence of adverse events or serious adverse events. None of the serious adverse events were related to treatment. There was no significant difference between the groups in the overall incidence of subjective symptom scores for gastrointestinal side effects.
Finn et al (abstract)[30] Lanthanum carbonate, up to 3,000 mg/day vs	AC, MC, OL, PG, RCT Patients ≥18 years of age who had received hemodialysis TIW	N=1,359 2 years	Primary: Serum phosphate, calcium, CaxP product and PTH levels Secondary:	Primary: Over two years, phosphate control was similar in both groups. In the lanthanum carbonate group, serum calcium and PTH levels were maintained in the range recommended by the K/DOQI. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
standard therapy (any approved phosphate binder)	for ≥2 months prior to enrollment		Adverse events	The most common adverse events were gastrointestinal-related. The incidence of adverse events in the treatment groups were nausea, 37 vs 29%; vomiting, 27 vs 22% and diarrhea, 24 vs 24%. In addition, hypercalcemia (that was reported as an adverse event) occurred in 4.3 and 8.4% of patients, respectively. There was no indication of liver toxicity, suppression of erythropoiesis or changes in the mini-mental state exam.
Wilson et al[31] Lanthanum carbonate, up to 3,000 mg/day vs standard therapy (any approved phosphate binder)	AC, MC, OL, PG, RCT Patients enrolled in Finn et al[27]	N=1,354 2 years (Patients were followed for up to 40 months)	Primary: Mortality Secondary: Not reported	Primary: There was no significant difference in overall mortality with lanthanum carbonate compared to standard therapy (19.0 vs 23.3%; HR, 0.86; 95% CI, 0.68 to 1.08; P=0.18). Increasing age (HR, 1.041; 95% CI, 1.031 to 1.050), the presence of diabetes (HR, 1.603; 95% CI, 1.272 to 2.021) and vitamin D use (HR, 0.597; 95% CI, 0.460 to 0.774) were predictors of mortality. In a subgroup analysis, mortality was significantly lower in patients >65 years of age treated with lanthanum carbonate compared to standard therapy (27.0 vs 39.3%, HR, 0.68; 95% CI, 0.46 to 0.99; P=0.04). Secondary: Not reported
Hutchison et al[32] Lanthanum carbonate 375 to 3,000 mg/day vs calcium acetate 1,500 to 9,000 mg/day	AC, MC, OL, PG, RCT Patients ≥18 years of age receiving hemodialysis TIW for ≥3 months and serum phosphate >5.58 mg/dL after screening and a washout period	N=800 6 months	Primary: Percentage of patients achieving phosphate control (≤5.58 mg/dL) Secondary: Maintenance of serum phosphate ≤5.58 mg/dL, CaxP product levels, and tolerability	Primary: At the end of five weeks of dose titration, the percentages of phosphate-controlled patients were 57.8 and 70.3%, respectively, in the lanthanum carbonate and calcium acetate groups (P=0.002). Secondary: The reductions in mean serum phosphate levels to <5.58 mg/dL achieved within the dose titration phase were maintained throughout the six months of therapy. Generally, the proportions of patients in whom control was achieved were similar between the two treatment groups during the maintenance phase (P>0.05 at all time points). At 25 weeks, 65.8 and 63.9% of the lanthanum carbonate and calcium acetate groups were controlled (P>0.05). Reductions in CaxP product levels were generally greater with the lanthanum carbonate maintenance treatment group (week 17, -1.80±1.65 vs -1.34±1.51

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mg^2/mL^2; P=0.009 and week 25, -1.59±1.70 vs -1.26±1.25 mg^2/mL^2; P=0.061). The most noticeable difference between the tolerability and safety profiles of the two treatments was the frequency of clinically significant hypercalcemia with calcium acetate (20.2 vs 0.4%; P value not reported). Mean serum calcium levels remained unchanged or marginally decreased with lanthanum carbonate. Gastrointestinal adverse events were reported most frequently and occurred with similar frequency in the two treatment groups.
Kasai et al[33] Sevelamer hydrochloride titrated every 2 weeks to a dose of 750 mg to 9,000 mg/day to maintain serum phosphorus levels within the target range vs lanthanum carbonate, titrated every 2 weeks to 375 mg to 2,250 mg to maintain serum phosphorus levels within the target range There was a four-week initial screening period and a four-week washout period between treatments. The doses of vitamin D, calcium-containing	PRO, RCT, XO Patients ≥18 years of age who been on hemodialysis for ≥3 months	N=42 26 weeks (13 for each treatment then XO)	Primary: Drug dose, serum calcium, and serum phosphate Secondary: Biochemical markers of bone metabolism and adverse events	Primary: After 13 weeks of treatment, the average daily doses of sevelamer hydrochloride and lanthanum carbonate were 2,971±1,464 mg and 945±449 mg, respectively. Although the daily doses typically increased during the treatment periods, the rate of increase for both drugs was similar (P value not reported). The serum calcium levels were similar between patients receiving sevelamer hydrochloride and lanthanum carbonate (P value not reported). The serum phosphate levels were slightly lower with lanthanum carbonate treatment compared to sevelamer; however, the difference was not statistically significant (P value not reported). Approximately 90% of patients achieved targeted serum calcium levels in both treatment groups. The proportion of patients with a controlled serum phosphate level was slightly higher with lanthanum carbonate treatment (93%) compared to sevelamer hydrochloride treatment (78%); however, the difference was not statistically significant. Secondary: There were no statistically significant differences between sevelamer hydrochloride and lanthanum carbonate with regard to biochemical markers of bone metabolism (CaxP, intact PTH, and bone alkaline phosphatase) levels between the two treatment groups. No fractures or bone-related musculoskeletal disorders were reported during either of the treatment periods. Treatment-related adverse events occurred in 56% of patients during treatment with sevelamer hydrochloride and 39% with lanthanum carbonate. The most common adverse events were gastrointestinal-related. Constipation occurred in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
phosphate binders, cinacalcet hydrochloride, and other drugs depended on the individual patient's condition and were maintained throughout the study.				significantly more patients during treatment with sevelamer hydrochloride compared to lanthanum carbonate (27 vs 5%; P=0.007). Flatulence was more common during sevelamer hydrochloride while diarrhea and anorexia were more common during lanthanum carbonate treatment; however, these differences were not statistically significant.
Delmez et al (abstract)[34] Sevelamer carbonate, dosing and frequency not specified vs sevelamer hydrochloride, dosing and frequency not specified	DB, RCT, XO Hemodialysis patients	N=76 16 weeks	Primary: Serum phosphate, lipids and bicarbonate levels Secondary: Not reported	Primary: Mean serum phosphate was 4.6±0.9 and 4.7±0.9 mg/dL during sevelamer carbonate and hydrochloride treatment, respectively. The treatments were equivalent in controlling serum phosphate; the geometric LSMR was 0.99 (90% CI, 0.95 to 1.03). Mean total cholesterol and LDL-cholesterol were 144.0±33.9 and 59.9±24.9 mg/dL, respectively during sevelamer carbonate treatment and 139.0±33.6 and 56.0±23.3 mg/dL, respectively during sevelamer hydrochloride treatment. Serum bicarbonate levels increased by 1.3±4.1 mEq/L during sevelamer carbonate treatment. There were fewer gastrointestinal adverse events with sevelamer carbonate. Secondary: Not reported
Fan et al[35] Sevelamer carbonate TID with meals vs sevelamer hydrochloride TID with meals	MC, OL, RCT, XO Patients ≥18 years of age receiving maintenance hemodialysis for ≥3 months, maintained on sevelamer hydrochloride alone or in combination with other	N=31 8 weeks	Primary: Evaluate the equivalence of sevelamer carbonate and sevelamer hydrochloride on serum phosphate control Secondary:	Primary: The mean time-weighted average serum phosphate was 5.0±1.5 mg/dL during sevelamer carbonate treatment and 5.2±1.1 mg/dL during sevelamer hydrochloride treatment. The LSMR was 0.95 (90% CI, 0.87 to 1.03), indicating that the two treatments are equivalent in controlling serum phosphate. Secondary: No statistically significant or clinically meaningful differences were observed in CaxP product (P=0.749) and lipid levels (total cholesterol; P=0.218, LDL-cholesterol; P=0.109, HDL-cholesterol; P=0.537 and TG; P=0.992) between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were randomized to receive sevelamer carbonate for 4 weeks followed by sevelamer hydrochloride for 4 weeks or vice versa. All patients went through a 2 week run-in period with their previous dose of sevelamer hydrochloride before being randomized to treatment.	phosphorus binders, serum phosphate ≥5.5 mg/dL after a washout period, iPTH ≤800 pg/mL and serum calcium within normal range (8.5 to 10.3 mg/dL)		CaxP product, serum lipids, and safety	Both treatments were well tolerated. A total of nine events in seven (22.6%) of the 31 randomized patients were considered to be treatment related during the sevelamer hydrochloride run-in period including dyspepsia, abdominal distension, abdominal pain, diarrhea, gastritis, nausea and stomach discomfort.
Fishbane et al[36] Sevelamer carbonate 4.8 g QD with the largest meal vs sevelamer hydrochloride 4.8 g/day administered TID in equal doses with meals Doses were titrated as necessary to achieve a target serum phosphate level 3.5 to 5.5 mg/dL.	OL, PG, RCT Patients ≥18 years of age receiving maintenance hemodialysis for ≥3 months, with a serum phosphate >5.5 mg/dL after a washout period and iPTH ≤800 ng/mL	N=217 24 weeks	Primary: Noninferiority with respect to change from baseline in serum phosphate levels at 24 weeks or early termination Secondary: Percentage of patients meeting target phosphate levels at 24 weeks or early termination, changes in CaxP product and serum lipids, and safety	Primary: Mean serum phosphate levels decreased significantly for both sevelamer carbonate (-2.0±1.8 mg/dL; P<0.001) and sevelamer hydrochloride (-2.9±1.3 mg/dL; P<0.001) after 24 weeks or early termination. The upper confidence bound of the difference in change from baseline to week 24 or early termination was 1.50 mg/dL; therefore, noninferiority of sevelamer carbonate QD compared to sevelamer hydrochloride TID based on prespecified noninferiority margin of 1 mg/dL was not shown. Secondary: Percentages of patients achieving target phosphate levels at week 24 or early termination were 54 and 64% in the sevelamer carbonate and hydrochloride groups (P value not reported). Both treatments resulted in significant decreases in CaxP product (P values not reported), with sevelamer hydrochloride producing significantly greater reductions compared to sevelamer carbonate (P=0.01). Both treatments resulted in significant decreases in total cholesterol and LDL-cholesterol (sevelamer carbonate, P<0.001 for both; sevelamer hydrochloride,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.001 for both), with sevelamer hydrochloride producing significantly greater reductions compared to sevelamer carbonate (P<0.001 for both). The overall percentages of patients who reported at least one adverse event were similar between the two groups. A larger percentage of treatment-related upper-gastrointestinal events, including nausea and vomiting, were noted with sevelamer carbonate. Four (3%) sevelamer carbonate-treated patients experienced stimulation of the gag reflex and two (1%) experienced dislike of the taste with the powder formulation.
Suki et al[37] Sevelamer hydrochloride, dosing and frequency not specified vs calcium-based phosphorus binder (acetate or carbonate), dosing and frequency not specified Calcium acetate was encouraged, but patients who did not tolerate calcium acetate could choose calcium carbonate.	MC, OL, PG, RCT Patients ≥18 years of age receiving hemodialysis for ≥3 months, required phosphate binder therapy and had Medicare as their primary insurance	N=2,103 <12 to >36 months	Primary: All-cause mortality Secondary: Cause-specific mortality, all-cause and specific-cause mortality by age, hospitalizations, lab values and safety	Primary: There was no difference between treatment groups with respect to all-cause mortality. There were 267 and 275 deaths in the sevelamer hydrochloride and calcium-based groups. The sevelamer hydrochloride mortality rate was 15.0/100 patient-years and the calcium-based mortality rate was 16.1/100 patient-years (HR, 0.93; 95% CI, 0.79 to 1.10; P=0.40). There was no difference observed in mortality risk for the patients in the study for less than two years; however, for those patients remaining in the study for over two years (43% of the study population), a difference between groups, favoring sevelamer hydrochloride, appears to emerge (P=0.02). Secondary: Among sevelamer hydrochloride- and calcium-based-treated patients, the cardiovascular mortality rate was 8.0 and 8.6/100 patient-years, respectively (HR, 0.93; 95% CI, 0.74 to 1.17; P=0.53). There were 47 deaths due to infection in the sevelamer hydrochloride group with a rate of 2.6/100 patient-years and 41 deaths due to infection in the calcium-based group with a rate of 2.4/100 patient-years (P=0.68). There were 78 deaths due to other causes in the sevelamer hydrochloride group, with a rate of 4.4/100 patient-years, and 87 deaths due to other causes in the calcium-based group, with a rate of 5.1/100 patient-years (P=0.33). A significant interaction between treatment and age (<65 years and ≥65 years) was observed for all-cause mortality (P=0.02). In subjects ≥65 years of age (44% of the study population), the all-cause mortality rate was 18.2/100 patient-years

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				for the sevelamer hydrochloride group and 23.4/100 patient-years for the calcium-based group (HR, 0.77; 95% CI, 0.61 to 0.96). In subjects <65 years of age, the all-cause mortality rate was 12.5/100 patient-years for the sevelamer hydrochloride group and 10.6/100 patient-years for the calcium-based group; there was no difference between groups (HR, 1.18; 95% CI, 0.91 to 1.53). No treatment-by age interaction was observed for cardiovascular mortality. The mean number of hospitalizations/patient-year was 2.1 for the sevelamer hydrochloride-treated patients and 2.3 for the calcium-based-treated patients (P=0.0738). The mean hospital days per patient-year was 14.8 and 17.4 for sevelamer hydrochloride- and calcium-based-treated patients (P=0.0897). Lab values were consistent with what is typically seen in U.S. hemodialysis patients. The data demonstrate a higher serum calcium and lower iPTH level in the calcium-based-treated patients, and a lower total and LDL-cholesterol in the sevelamer hydrochloride treated patients. There were eight subjects with 11 possibly drug-related serious adverse events in the study. Eight related serious adverse events occurred in five patients in the calcium-based group and three in three patients in the sevelamer hydrochloride group.
St. Peter et al[38] Sevelamer hydrochloride, dosing and frequency not specified vs calcium-based binder (acetate or carbonate), dosing and frequency not specified A preplanned	RETRO Patients ≥18 years of age receiving hemodialysis for ≥3 months, required phosphorus binder therapy and had Medicare as their primary insurance	N=2,103 <12 to >36 months	Primary: Mortality, morbidity and hospitalization Secondary: Not reported	Primary: Subjects randomly assigned to either sevelamer hydrochloride or calcium-based were followed for an average of 2.3 years. During this follow-up time, 431 and 426 deaths were recorded in the sevelamer hydrochloride and calcium-based groups. The all-cause mortality rate was not significantly different between the sevelamer hydrochloride and calcium-based groups (17.7 vs 17.4 deaths/100 patient-years; adjusted RR, 1.01; 95% CI, 0.89 to 1.16; P=0.9). Cardiovascular mortality was not significantly different between the sevelamer hydrochloride and calcium-based groups (9.0 vs 8.2 deaths/100 patient-years; adjusted RR, 1.09; 95% CI, 0.90 to 1.33; P=0.4). Differences in infection (adjusted RR, 1.38; 95% CI, 0.94 to 2.04; P=0.1) and other causes (adjusted RR, 0.83; 95% CI, 0.67 to 1.04; P=0.1) of mortality lacked statistical significance.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
secondary analysis using CMS data of Suki et al.[32]				Cause-specific inpatient events combined with similar cause-specific outpatient events (e.g., outpatient and inpatient vascular access was grouped together) was used to evaluate morbidity. Sevelamer hydrochloride-treated patients consistently showed lower risks of multiple morbidities (cardiovascular, vascular access, fracture and infection); however, none of the differences were statistically significant. During an average of 2.1 years of follow-up for both groups, 3,439 and 3,782 all-cause hospitalizations were identified for the sevelamer hydrochloride and calcium-based groups (P value not reported). All-cause (adjusted RR, 0.89; 95% CI, 0.82 to 0.98; P=0.03) and other-cause (adjusted RR, 0.87; 95% CI, 0.77 to 0.98; P=0.02) multiple hospitalizations were significantly less for the sevelamer hydrochloride group. Number of hospital days was also less in the sevelamer hydrochloride group (12.3 vs 13.9 days/patient-year; adjusted RR, 0.88; 95% CI, 0.78 to 0.99; P=0.03). Sevelamer hydrochloride did not have a significant effect on first hospitalization or cause-specific (except other-cause) multiple hospitalizations and hospital days. Secondary: Not reported
Pieper et al[39] Sevelamer, salt not specified, initiated at the dose administered before inclusion in the study vs calcium acetate initiated at the dose administered before inclusion in the study	MC, OL, RCT, XO Children <18 years of age receiving hemodialysis or peritoneal dialysis or with CKD and a GFR ≥20 and ≤60 mL/min/1.73m^2, on constant doses of phosphorus binders and vitamin D and serum phosphate ≥6.2 (≥2 years of age) or	N=40 16 weeks	Primary: Change in serum phosphate levels after eight weeks Secondary: Changes in serum CaxP product, phosphate-binder consumption, adverse events, number of hypercalcemic episodes and effects on hyper-	Primary: A total of 18 patients were available for safety and efficacy analysis. Serum phosphate levels decreased significantly with both treatments (-1.5±1.6 vs -1.7±1.7 mg/dL). The 95% confidence limits of the treatment difference in phosphate level control were entirely within the prespecified equivalence boundaries (-1.1±1.1 mg/dL), therefore; equivalence of sevelamer and calcium acetate in decreasing serum phosphate was demonstrated. Secondary: CaxP product levels decreased significantly with both treatments (-1.37±1.41 vs -1.12±1.25 mmol^2/L^2; P values not reported). For sevelamer, mean dose administration was 5.38±3.24 g/day and for calcium acetate it was 4.28±1.97 g/day at the end of the treatment phase (P value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were randomized to receive sevelamer for 8 weeks followed by calcium acetate for 8 weeks or vice versa.	≥7.0 mg/dL (<2 years of age) after a washout period		parathyroidism, and uremic dyslipidemia	significant). The number of patients experiencing at least one drug-related adverse event was slightly lower with calcium acetate compared to sevelamer (33.3 vs 43.8%; P value not significant). Serious adverse events occurred in 25.0% of sevelamer- and 33.3% of calcium acetate-treated patients, and adverse events with intensity considered to be severe occurred in 9.4 and 6.7% of patients (P value not significant). Serum calcium levels did not change significantly with both treatments and the difference between them was not significant (P value not reported). iPTH levels and cyclase-activating PTH/cyclase-inhibitory PTH ratio showed no significant change during each treatment period (P values not significant for all), but there was a significant increase in alkaline phosphatase levels with sevelamer treatment (P<0.05).
Evenepoel et al[40] Sevelamer hydrochloride administered as two 800 mg tablets TID vs calcium acetate administered as three 538 mg tablets TID Doses were titrated as necessary to achieve a target serum phosphate level 3.0 to 5.5 mg/dL.	MC, OL, PG, RCT Patients ≥18 years of age on stable peritoneal dialysis for ≥8 weeks, serum phosphate >5.5 mg/dL and serum calcium within the normal range (8.4 to 10.4 mg/dL) following a 2 week phosphorus binder washout period	N=143 12 weeks	Primary: Change in serum phosphate levels at 12 weeks Secondary: Change in CaxP product, serum lipids, and pre-specified plasma biomarkers and safety	Primary: Serum phosphate levels were significantly reduced after 12 weeks with both treatments. In the PP population, mean serum phosphate decreased from 7.48±1.43 to 5.86±1.57 mg/dL with sevelamer hydrochloride (-1.61±1.16 mg/dL; P<0.001) and from 7.29±1.39 to 5.48±1.40 mg/dL with calcium acetate (-1.81±1.52 mg/dL; P<0.001). The difference in the mean change between the groups was 0.197 mg/dL with an upper 97.5% confidence limit of 0.741 mg/dL establishing non-inferiority of sevelamer hydrochloride compared to calcium carbonate. Comparable results were observed in the ITT population thus confirming non-inferiority. Similar proportions of patients in both groups achieved the serum phosphate target of <5.5 mg/dL after 12 weeks of treatment (49 vs 48% in the PP population and 46 vs 41% in the ITT population; P values not reported). Secondary: Ca x P product was significantly reduced (P<0.001), with mean decreases at 12 weeks of 15.0±12.1 and 15.3±15.1 mg^2/dL^2 in the sevelamer hydrochloride and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				calcium acetate groups (PP population). No difference between the groups was observed (P value not reported). Significant decreases in total-, LDL- and non-HDL-cholesterol (P<0.001 for all) were observed for sevelamer hydrochloride but not with calcium acetate. These changes were significantly different between groups (P<0.001). HDL-cholesterol did not change from baseline for either group. Mean percentage increase in TG was significant in both groups (P=0.006 and P=0.041). Treatment with sevelamer hydrochloride resulted in a significant decrease in uric acid (-0.53±0.79; P<0.001) and a significant increase in BSAP (4.2±12.3; P<0.001). Changes in both of these parameters were significantly different between groups (P=0.010 and P<0.001). There were no significant within or between group differences in changes in random blood glucose, HbA_{1c} or CRP. Overall, both treatments were well tolerated. The percentage of patients experiencing adverse events considered to be related to study medication were similar in both groups (36 vs 35%; P=1.0). More patients treated with sevelamer hydrochloride experienced gastrointestinal adverse events (27 vs 13%).
Hervas et al[41] Sevelamer hydrochloride 2 to 4 capsules TID with meals vs calcium acetate 1 to 4 tablets TID with meals Initial doses were determined by the initial phosphate level.	RCT Patients ≥18 years of age receiving hemodialysis TIW for ≥3 months, on stable doses of calcium-based phosphorus binders and vitamin D therapy for ≥1 month and serum phosphate >6.0 mg/dL after a washout period	N=51 34 weeks	Primary: Changes in serum phosphate, calcium, alkaline phosphatase,iPTH and serum lipids Secondary: Not reported	Primary: There was a significant decrease in serum phosphate levels with both treatments that ranged from 8.09±1.60 to 5.80±1.01 mg/dL (P=0.001) for sevelamer hydrochloride, and from 7.5±1.6 to 5.9±1.5 mg/dL (P=0.005) for calcium acetate. The mean change from baseline to end of treatment was similar between treatments (-2.29±0.05 [28.3%] vs -1.6±0.1 mg/dL [21.3%]; P value not reported). There were no significant increases in serum calcium levels in either group. Mean change from baseline to the end of treatment for CaxP product were similar between treatments (-20.3 vs -15.4 mg^2/dL^2; P value not reported). Serum alkaline phosphatase did not increase significantly with either treatment (P=0.3 and P=0.9). iPTH levels decreased with both treatments, from 479±288 to 330±205 pg/mL (P=0.04) for sevelamer hydrochloride, and from 501±303 to 346±250 pg/mL

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P=0.02) for calcium carbonate. For sevelamer hydrochloride, decreases in total and LDL-cholesterol, and increases in HDL-cholesterol from baseline were significant (P<0.05 for all). For the calcium acetate group mean changes in these values were not significant (P values not reported).
Bleyer et al[42] Sevelamer hydrochloride 2 to 4 capsules TID with meals vs calcium acetate 1 to 3 tablets TID with meals Patients were randomized to receive sevelamer hydrochloride for 8 weeks followed by calcium acetate for 8 weeks or vice versa. Initial doses were determined by the initial degree of hyperphosphatemia. Doses were titrated as necessary to achieve a target serum phosphate level 2.5 to 5.5 mg/dL.	OL, RCT, XO Patients ≥18 years of age receiving hemodialysis, on stable doses of calcium- or aluminum-based phosphorus binders, on stable doses or no calcitriol for 1 month and serum phosphate >6 mg/dL after a washout period	N=83 16 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: Although mean baseline serum phosphate levels were higher before treatment with sevelamer hydrochloride (8.4±2.3 vs 8.0±2.0 mg/dL; P=0.09), the mean change in serum phosphate from baseline to the end of treatment was similar between treatments (-2.0±2.3 vs -2.1±1.9 mg/dL; P value not reported). There was a significant increase in serum calcium during treatment with both treatments, but much less so with sevelamer hydrochloride (0.2 vs 0.7 mg/dL; P values not reported). iPTH levels decreased significantly with both treatments, but more so with calcium acetate (P values not reported). Serum alkaline phosphatase increased significantly with sevelamer hydrochloride treatment (86±56 to 114±73 U/L; P<0.0001) and did not change significantly with calcium acetate (P=0.85). Sevelamer hydrochloride-treated patients sustained a reduction in total cholesterol, resulting from a decrease in LDL-cholesterol while HDL-cholesterol remained stable. The occurrence of adverse events was similar between groups. Gastrointestinal adverse events occurred during sevelamer hydrochloride treatment in 34% of patients compared to 28% during calcium acetate treatment (P=0.26). The incidence of nausea, vomiting, diarrhea and constipation was not statistically different between groups. No serious adverse events related to study medication occurred during either treatment. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Xu et al[43] Phase 1 – OL dose titration: All patients received lanthanum carbonate dose titrated to achieve and maintain serum phosphorus ≤5.5 mg/dL Phase 2 – randomization and maintenance phase: Lanthanum carbonate dose titrated vs placebo Patients were on a low-phosphorus diet (800 to 1000 mg/day).	DB, MC, PC, RCT (OL dose titration) Patients 18 to 70 years of age with stage 5 CKD who had been receiving hemodialysis or continuous ambulatory peritoneal dialysis for at least three months	N=227 8 weeks	Primary: Serum phosphorus level at the end of the maintenance phase compared with baseline (time of randomization) Secondary: Serum phosphorus levels at each visit, proportion of patients with controlled serum phosphorous levels or response to the experimental drugs at the end of the maintenance phase, and iPTH level at the end of the titration and maintenance stage	Primary: During dose titration with lanthanum carbonate, serum phosphorus concentration decreased; for patients assigned to lanthanum carbonate and placebo treatment groups this parameter was 1.64 and 1.71 mmol/L, respectively, at randomization (P=0.24). During the maintenance phase, the mean serum phosphorus remained low for the lanthanum carbonate group, but was substantially increased in the placebo group. Compared with baseline, phosphorus levels at the end of the maintenance phase were significantly lower in patients treated with lanthanum carbonate than in those on placebo (0.15 mmol/L vs. 0.63 mmol/L; mean difference between groups, −0.48; 95% CI, -0.63 to -0.33; P<0.001). Secondary: Mean differences between the two groups were significant throughout randomized treatment (P<0.001 at all time-points). After four weeks titration, 61.6% of patients had controlled serum phosphorus levels. At the end of the maintenance phase,13.3% patients in the placebo group and 57.9% patients in the lanthanum carbonate group had serum phosphorus <1.78 mmol/L (P=0.0001). In patients receiving lanthanum carbonate 1500 (40.3%, 46/114), 2000 (20.2%, 23/114), 2500 (26.3%, 30/114), or 3000 (13.2%, 15/114) mg and those on placebo, the proportion achieving the target serum phosphorus level (≤1.78 mmol/L) was 76.1%, 56.5%, 50.0%, 20.0%, and 13.3%, respectively. At randomization, the difference in the mean iPTH level between the lanthanum carbonate and placebo-treated group was not significant (286.4 vs. 315.6 pg/mL; P=0.48). Although the difference in the mean iPTH levels between the two groups remained not significant at the end of the maintenance phase, a significant difference in variation of the iPTH level from baseline was observed between the two groups (19.60 mmol/L vs. 53.63 mmol/L; mean difference between groups, −34.03; 95%CI, -77.02 to 8.96; P = 0.017).
Ando et al[44] Lanthanum carbonate	MC, PRO, OL Patients on chronic	N=101 2 years	Primary: Dosage, serum phosphorus,	Primary: Almost all of the subjects started from a dosage of 750 mg/day (average dosage: 744 mg/day). After two years of administration, 47% of the subjects were taking

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dose adjusted Patients may take lanthanum in combination with other phosphorus binders (calcium carbonate or calcium acetate), cinacalcet, or vitamin D receptor activators.	maintenance hemodialysis who presented with hyper-phosphatemia		calcium and IPTH levels at each measurement time point Secondary: Not reported	750 mg/day, 24% were taking from 1000 mg/day or more to less than 1500 mg/day, and 26% were taking 1500 mg/day or more. The average dosage after one year and two years had increased to 1266 mg and 1246 mg, respectively. After six months the percentage of subjects taking lanthanum carbonate by itself increased to 40%, but after that it stabilized and remained at around 30%. A significant reduction in phosphorus levels was observed after three months from the start of lanthanum carbonate administration. After that, reduction continued, and it fell to 5.5 mg/dL or below (P<0.01 or P<0.001 or P<0.0001 at every three month time point starting at month three). A significant reduction in corrected calcium was observed after one year from the start of administration, but after that it returned to the values at the start of administration. No changes were observed in PTH. Secondary: Not reported
Gotoh et al[45] Lanthanum carbonate dose adjusted Concomitant use of phosphorus absorbents (calcium carbonate or calcium acetate), cinacalcet and active vitamin D3 agents were permitted.	PRO, OL Patients on dialysis who could not maintain a serum phosphorus level at 6.0 mg/dL or lower	N=53 36 months	Primary: Dose, serum phosphorus, calcium, and iPTH, and adverse effects Secondary: Not reported	Primary: The lanthanum carbonate dosages were 1528.3 ± 549.6 mg/day five months after the initiation of administration and 1447.9 ± 423.4 mg/day 36 months after the initiation of treatment. Before the initiation of lanthanum carbonate administration, the dosages of calcium carbonate and sevelamer hydrochloride were 1301.9 ± 1381.0 and 2462.3 ± 1833.4 mg/day, respectively. However, those dosages were decreased to 562.5 ± 1154.5 and 1052.1 ± 1518.0 mg/day after 36 months as a result of the administration of lanthanum carbonate. Phosphorus levels significantly decreased to 7.0 mg/dL a month after, and to 6.3 mg/dL three months after, the initiation of administration. It eventually reached 5.3 mg/dL, within the range of management goals for phosphorus concentration (3.5 to 6.0 mg/dL; P≤0.001). The range of average phosphorus concentration decreased to a level within the range of management goals 36 months after the initiation of treatment for both the subgroup of patients for with baseline levels

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				≥8.0 and <8.0 mg/dL (P≤0.01). The Calcium and iPTH levels showed a nearly constant value within a range of 8 to 10 mg/dL and 200 to 300 pg/mL respectively. Adverse events were observed in six out of 53 cases during the study period: two cases of nausea (4%); one case of constipation (2%); three cases where the serum phosphorus concentration decreased to lower than 4 mg/dL (6%). However, no serious side effects of lanthanum carbonate administration were observed. Secondary: Not reported
Takeuchi et al[46] Lanthanum carbonate dose adjusted Concomitant use of phosphorus absorbents (calcium carbonate or calcium acetate) and active vitamin D3 agents were permitted.	PRO, OL Patients on chronic maintenance dialysis who presented with hyper-phosphatemia	N=53 36 months	Primary: Dose, serum phosphorus, calcium, and wPTH Secondary: Not reported	Primary: The average daily dosage of lanthanum carbonate was 0.74 g at the time of the start of administration, 0.85 g after one year, 0.82 g after two years later, and 0.87 g after three years. The average phosphorus level was 6.29 mg/dL before lanthanum administration, and after administration was started it fell to below 6 mg/dL. Over the 36 months it continued to be lower than before lanthanum administration. Significant reduction to 5.70 mg/dL was observed, and mean values of below 6 mg/dL were maintained after 3 month until 36 month (P<0.01). We observed a reduction in the average serum calcium value from the 9.82 mg/dL before the start of lanthanum carbonate administration, and LOCF showed a significant reduction at 9.58 mg/dL (P<0.01). Secondary: Not reported
Navaneethan et al[47] Aluminum hydroxide	SR of 60 RCT RCT of patients	N=7,631 ≥8 weeks	Primary: All-cause mortality,	Primary: There was no statistically significant reduction in all-cause mortality for patients treated with sevelamer hydrochloride compared to those receiving calcium-based

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs calcium acetate vs calcium carbonate vs calcium ketoglutarate vs sevelamer hydrochloride vs sevelamer carbonate vs lanthanum carbonate vs magnesium carbonate vs placebo	>18 years of age with CKD in stage 3, 4, 5 and 5D as defined by the K/DOQI guidelines (stage 3: GFR 30 to 59 mL/minute; stage 4: GFR 15 to 29 mL/minute; stage 5: GFR <15 mL/minute; stage 5D: on dialysis)		cardiovascular mortality, cardiovascular events, hospitalization, fracture, hypercalcemia, hyper-phosphatemia, serum phosphorus and calcium, calcium-phosphate product, intact PTH or PTH, alkaline phosphatase, serum bicarbonate, total serum cholesterol, vascular calcification, bone mineral density, bone turnover and adverse events Secondary: Not reported	phosphate binders (RR, 0.73; 95%CI, 0.46 to 1.16). No deaths were reported in two studies comparing lanthanum carbonate to calcium carbonate. No statistically significant difference in hospitalizations, or days hospitalized/ patient-year for those receiving sevelamer compared to calcium salts; however, this outcome was only evaluated in two studies. Data on hospitalizations were not reported with lanthanum carbonate compared to calcium carbonate. The serum calcium by phosphorus product was not significantly different between sevelamer hydrochloride and calcium based phosphate binders (mean difference, 0.86 mg^2/dL^2; 95% CI, -0.69 to 2.40). The calcium by phosphorus product was significantly lower with lanthanum carbonate treatment compared to calcium carbonate (mean difference, -6.01 mg^2/dL^2; 95% CI -9.66 to -2.36). There was a significant reduction in serum phosphorus (mean difference, 0.23 mg/dL; 95% CI, 0.04 to 0.42), PTH (mean difference, 59.74 pg/mL; 95% CI, 26 to 84) but a significant increase the risk of hypercalcemia (RR, 0.45; 95% CI, 0.35 to 0.59) with calcium-based agents compared to sevelamer hydrochloride. A statistically significant reduction in hypercalcemic events was reported with lanthanum carbonate compared to calcium carbonate (RR, 0.17; 95% CI; 0.09 to 0.31). No difference was reported between lanthanum carbonate and calcium carbonate with regard to serum phosphorus levels (mean difference, 0.22 mg/dL; 95% CI, -0.32 to 0.75); however, serum calcium levels were significantly lower with lanthanum carbonate (mean difference, -0.30 mg/dL; 95% CI, -0.57 to -0.03). No statistically significant differences in PTH levels were reported between lanthanum carbonate and calcium carbonate (mean difference, 100.91 pg/mL; 95% CI -75.30 to 277.12). There were significantly lower calcium levels with sevelamer hydrochloride in comparison to calcium salts (mean difference, -0.34 mg/dL; 95% CI, -0.45 to -0.24). There were significantly lower serum bicarbonate levels with sevelamer hydrochloride in comparison to calcium salts (mean difference, -1.43 mEq/L; 95% CI, -2.07 to -0.79).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Sevelamer was associated with a significant increase in gastrointestinal-related adverse events compared to calcium salts (RR, 1.58; 95% CI, 1.11 to 2.25). There was no statistically significant difference in gastrointestinal adverse events with lanthanum carbonate compared to patients treated with calcium carbonate (RR, 1.04; 95% CI, 0.70 to 1.55); however, this outcome was only reported in one study. There was no statistically significant change in serum alkaline phosphatase levels between treatment with sevelamer hydrochloride compared to calcium salts (mean difference, 10.13 IU/L; 95% CI,-11.28 to 31.53). Sevelamer hydrochloride was associated with a significant reduction in total cholesterol levels compared to calcium salts (mean difference, -19.16 mg/dL; 95% CI, -27.42 to -10.90). Secondary: Not reported
Tonelli et al[48] Sevelamer vs any other therapy or placebo Included therapies were either calcium acetate, calcium carbonate, or aluminum hydroxide.	MA of 14 RCTs using PG or XO design Adult patients with ESRD, on dialysis, or kidney transplant recipients.	N= Duration varied (2 to 45 months)	Primary: Effects on serum measures, hypercalcemia, mortality, hospitalizations, health-related quality of life, and adverse events Secondary: Not reported	Primary: Ten RCTs with 2501 participants reported serum phosphate, serum calcium and intact parathyroid hormone (iPTH). In pooled analyses, serum phosphate was significantly lower with calcium-based phosphate binders by 0.12 mmol/L (95% CI, 0.05 to 0.19); and the between-study heterogeneity was large (I^2=64%). All RCTs favored calcium-based phosphate binders. Removing the unpublished studies, increased the overall effect (0.17 mmol/L; 95% CI, 0.07 to 0.27). The overall weighted mean difference in serum calcium was significantly lower with sevelamer therapy (0.10 mmol/L; 95% CI, −0.12 to −0.07). Between-study variance was also large (I^2=53%). The data for iPTH was skewed so that results could not be combined. Mean (or median) differences of iPTH ranged from 0.7 to 9.5 pmol/L. All RCTs demonstrated numerically lower mean on-treatment iPTH (or in some cases, a smaller increase in PTH) in calcium recipients, although only two were statistically significant. Nine RCTs with 2271 participants reported serum calcium–phosphate product. On-treatment calcium–phosphate product was non-significantly lower in patients receiving calcium-based phosphate binders (weighted mean difference,0.12

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				$mmol^2/l^2$; 95% CI, −0.05 to 0.29) and the between-study heterogeneity was large (I^2=57%). Four RCTs with 338 participants reported serum bicarbonate. The overall weighted mean difference was significant and was lower with sevelamer therapy (2.8 mmol/l; 95% CI, −3.5 to −2.2; I^2=0%). The rate of hypercalcemia (13 trials, 634 participants) was a median of 7% and ranged from 0 to 36. Eight RCTs (570 participants) reported the number of patients who became hypercalcemic during the course of follow-up. The absolute risk of hypercalcemia was 21% lower in sevelamer recipients (95% CI, 13 to 29; I^2=36%). The number needed to harm was five. The median duration of hypercalcemia or its clinical consequences were not reported for any trial. Five RCTs with 2429 participants reported all-cause mortality. The duration of follow-up varied from two to 45 months. Only one RCT specified all-cause mortality as the primary outcome. The overall risk difference was non-significant (−2%; 95% CI, −6 to 2). The point estimate for three RCTs favored sevelamer over calcium-based phosphate binders, and the percent of variance due to between-study variance was modest (I^2 = 22%). Two of the RCTs with 89% of the weight did not follow all participants until the end of the study or death. Both of these RCTs had losses to follow-up which considerably exceeded 10% (range 15 to 48%). The most recent trial had median follow-up of 44 months, and found significantly reduced mortality among sevelamer recipients in both adjusted and unadjusted analyses. Results were similar when the unpublished study, was excluded (−5%; 95% CI, −15 to 5). Three RCTs with 2102 participants reported cardiovascular mortality and the overall risk difference was non-significant (−1%; 95% CI, −4 to 2). Two studies showed non-significant differences in hospitalizations, but favored sevelamer therapy (P value not reported). No RCTs reported a measure of health-related quality of life. No RCTs reported CVD events, or the frequency of symptomatic bone disease such as fractures or bone pain.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Seventeen sevelamer trials with 1834 participants reported serious adverse events. Frequencies of serious adverse effects ranged from 2 to 33% for an approximate median duration of follow-up of <2 years. The median frequency of serious adverse effects was 15%. The frequency of serious adverse gastrointestinal events ranged from 0% to 40% (median 24 weeks duration of follow-up). Three trials with 260 participants reported chest pain; one trial (N=34; median follow-up six months) reported one incident as serious, while the other two trials reported frequencies of 7% and 8% (median follow-up eight weeks) but did not distinguish between serious and non-serious events. Secondary: Not Reported
Jamal et al[49] Calcium-based phospate binders vs non-calcium based phosphate binders	MA of 11 RCTs (12 to 14 clinical trials for secondary outcomes) Patients with CKD taking either calcium- or non-calcium based phosphate binders	N= 4,622 Duration varied (9 to 36 months)	Primary: All-cause mortality (from randomized trials) Secondary: All-cause mortality (from non-randomized trails), all-cause mortality (from all trials), differences in mortality by type of non-calcium-based binder, duration of follow-up, dialysis status, cardiovascular events, and coronary artery calcification	Primary: patients randomly assigned to non-calcium-based phosphate binders had a statistically significant 22% reduction in all-cause mortality compared with those randomly assigned to calcium-based phosphate binders (RR,0.78; 95% CI, 0.61 to 0.98). Secondary: In the three non-randomized trials (2813 patients with 791 events), the reduction in all-cause mortality was 11% (RR,0·89; 0.78 to 1.00) in those taking non-calcium-based phosphate binders. When evaluating randomized and non-randomized trials together, the reduction in all-cause mortality was 13% (RR,0.87; 0.77 to 0.97) in favor of non-calcium-based phosphate binders. There was a non-statistically significant decrease in mortality in patients randomly assigned to sevelamer (RR,0.89; 95% CI, 0.78 to 1.01) and lanthanum (RR,0·74; 0.49 to 1.13), compared with those randomly assigned to calcium-based phosphate binders. There was only a statistically significant difference in mortality between patients assigned to non-calcium-based binders and those assigned to calcium-based binders in the five trials that reported outcomes at 24 months; these trials had the largest number of patients and events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Differences in mortality by dialysis status (i.e., predialysis and dialysis) and noted that both in patients on dialysis and those not, mortality was reduced in patients assigned to non-calcium-based phosphate binders compared with those assigned to calcium-based binders (P=0.03 and P=0.02 for dialysis and predialysis respectively). Regarding cardiovascular events, there was a non-significant reduction in mortality of 15% (RR,0.85; 95% CI, 0.35 to 2.03). The reduction in vascular calcification was greater in patients assigned to non-calcium- based phosphate binders than in those assigned to calcium binders at all time points; this finding was statistically significant when the data was analyzed from the longest follow-up point for each study (mean difference in Agatston score=−95.26; 95% CI, −146.68 to −43.84).
Dwyer et al[50] Ferric citrate 1 gram daily vs ferric citrate 6 grams daily vs ferric citrate 8 grams daily The local investigator determined the distribution of caplets throughout the day. Vitamin D, its	MC, OL, RCT Patients with ESRD currently managed on three-times-weekly dialysis for at least three months who were prescribed 3 to 15 doses of doses of commercially available phosphate binder and had serum ferritin <1,000 µg/L, TSAT <50%, and serum phosphorus ≥3.5 to ≤8.0 mg/dL	N=154 28 days	Primary: Change in serum phosphorus level at end of treatment period Secondary: Change in serum phosphorus level at end point	Primary: Mean serum phosphorus levels of approximately 5.5 mg/dL at screening increased throughout the washout period. By the baseline visit (end of the washout period), there was no significant difference between treatment groups, with baseline phosphorus levels of 7.3 mg/dL in the 1-gram/day group, 7.6 mg/dL in the 6-gram/day group, and 7.5 mg/dL in the 8-gram/day group (P>0.05). Following the initiation of treatment, serum phosphorus levels decreased in a dose-dependent manner, with mean changes of −0.1 mg/dL in the 1-gram/day, −1.9 mg/dL in the 6-gram/day, and −2.1 mg/dL in 8-gram/day groups at the end of treatment. Mean differences in change from baseline values between the 1-gram/day and the 6- and 8-gram/day groups were significant (P<0.001), whereas the difference between the 6- and 8-gram/day groups was not (P=0.5). Secondary: A total of 22 patients (15.1%) were considered treatment failures by the end of treatment. Seven (4.8%) patients had serum phosphorus levels ≤2.5 mg/dL, and 15 (10.3%) had serum phosphorus levels ≥9 mg/dL. No patient randomly assigned to 1 gram/day had a serum phosphorus level ≤2.5 mg/dL, whereas 22% had serum phosphorus levels ≥9 mg/dL. Four patients (7.8%) in the 6-gram/day group and three (6.7%) in the 8-gram/day group had a serum phosphorus level ≤2.5 mg/dL, whereas three (5.9%) in the 6-gram/day and one (2.2%) in the 8-

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analogues, and cinacalcet were permitted during the study and dose must remain stable.				gram/day groups had a serum phosphorus level ≥9 mg/dL.
Lewis et al[51] Ferric citrate 1 gram TID vs calcium acetate or sevelamer carbonate alone or in combination at a starting dose that the patient was stabilized on prior to washout Study drugs were titrated to achieve serum phosphorus control. Following 52 weeks of therapy, patients receiving active control were re-randomized to ferric citrate or placebo.	AC, MC, OL, PC Patients with ESRD currently managed on three-times-weekly dialysis for at least three months who were prescribed 3 to 18 doses of commercially available phosphate binder and had serum ferritin,1,000 ng/ml, serum TSAT, 50%, and serum phosphorus ≥2.5 and ≤8.0 mg/dL	N=441 56 weeks	Primary: Serum phosphorus control Secondary: Iron parameters, ESA use, IV iron use and safety endpoints	Primary: Serum phosphorus levels declined following initiation of therapy. The phosphorus lowering effect was maintained over 52 weeks of treatment. During the placebo-controlled period, the serum phosphorus concentration rose by 2.2 mg/dL on placebo relative to patients who remained on ferric citrate (-0.24 mg/dL vs. 1.79 mg/dL; P<0.001). Secondary: Compared to active control, subjects on ferric citrate achieved higher mean iron parameters (ferritin,=899 ±488 ng/mL; transferrin saturation,=39 ±17%) vs 30±12%; subjects on active control (ferritin=628 +/-367 ng/mL; transferrin saturation=30% +/- 12%; P<0.001 for both). Compared to active control, subjects on ferric citrate received less intravenous elemental iron (median,=12.95 mg/week ferric citrate; 26.88 mg/week active control; P<0.001) and less ESA (median epoetin-equivalent units/week, : 5,306 units/week ferric citrate; 6,951 units/week active control; P=0.04). Ferric citrate had a similar adverse event profile compared to active control.
Floege et al[53] Sucroferric oxyhydroxide 1 to 3 g/day (divided BID) vs	AC, MC, OL, PRO, PG, RCT Patients ≥18 years of age with CKD on hemodialysis or peritoneal dialysis	N=1,054 Phase I, 24 weeks Phase II, 3 weeks	Primary: Change in serum phosphorus from weeks 24 to 27 for sucroferric oxyhydroxide maintenance dose	Primary: At week 27, there was no change in mean serum phosphorus concentrations from week 24. However, in the low-dose control group serum phosphorus levels increased 0.6 mmol/L (P<0.001). Secondary: Serum phosphorus reductions at week 12 were -0.71 mmol/L and -0.79 mmol/L,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sevelamer carbonate 4.8 to 14.4 g/day (divided TID) (phase I) and sucroferric oxyhydroxide 250 mg/day (phase II) Following a 2 to 4 week phosphate binder washout period, dose titration for efficacy and safety occurred over the first eight weeks of the study. Following 24 weeks of therapy, a subset of patients, were re- randomized to continue treatment with either their week 24 maintenance dose (N=44) or a non-effective low dose control 250 mg/day (N=49) for an additional 3 weeks. Concomitant medications that have a direct influence on serum phosphorus concentrations (e.g., vitamin D, vitamin D	and serum phosphorus concentrations ≥1.94 mmol/L who were treated with stable doses of phosphate binders ≥1 month before screening	(27 weeks total)	compared to low dose sucroferric oxyhydroxide control Secondary: Change in serum phosphorus at week 12 for sucroferric oxyhydroxide compared to sevelamer carbonate, pillburden, serum parathyroid hormone at week 24, 25(OH) D at week 24, 1,25$(OH)_2$D at week 24 and safety evaluations	respectively, demonstrating non-inferiority of, on average, three tablets of sucroferric oxyhydroxide compared to eight of sevelamer carbonate. This reduction in serum phosphorus was maintained through week 24. For the first 12 weeks, mean pill burden in the sucroferric oxyhydroxide and sevelamer carbonate treatment groups was 2.8 and 7.6 tablets per day, respectively. In addition, the mean pill burden in the maintenance phase was 3.6 and 8.7 tablets per day, respectively. Median serum intact parathyroid hormone concentrations decreased significantly from baseline to week 24 in both treatment groups; however, the decrease was greater in the sucroferric oxyhydroxide group (P=0.04). Median serum concentrations of 25(OH)D also decreased from baseline to week 24 in both treatment groups . This change was statistically significant in both treatment groups, with the decrease being greater with sevelamer carbonate (P=0.019) Median serum concentrations of 1,25(OH)2D remained unchanged from baseline to week 24 in the sucroferric oxyhydroxide group, but decreased significantly in the sevelamer carbonate group (P=0.0316). The percentage of patients that reported at least one treatment-emergent adverse event was 83.2% with sucroferric oxyhydroxide and 76.1% with sevelamer carbonate. Mild, transient diarrhea, discolored feces and hyperphosphatemia were more frequent with sucroferric oxyhydroxide; nausea and constipation were more frequent with sevelamer carbonate.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
analogs, and calcimimetics) remained unchanged as far as possible, in accordance with local clinical practice.				
Floege et al[54] Sucroferric oxyhydroxide 1 g to 3 g/day (divided BID) vs. sevelamer carbonate 4.8 to 14.4 g/day (divided TID)	ES of Floege et al[53] (AC, MC, OL, PG, RCT) Patients who completed phase I or those who received the maintenance dose of the study drug during phase II	N=644 28 weeks (52 to 55 weeks total)	Primary: Change in serum phosphorus concentration from baseline (last measurement before entry into extension study), safety (treatment-emergent adverse events, iron-related parameters, bone markers and hematology and biochemical laboratory parameters), pill burden Secondary: Not reported	Primary: Serum phosphorus control was maintained with sucroferric oxyhydroxide and sevelamer throughout the extension study. The sucroferric oxyhydroxide group baseline mean (SD) serum phosphorus was 1.75 (0.48) mmol/L at extension study baseline and 1.77 (0.54) mmol/L at week 52, representing a change from baseline of 0.02 (0.52)(P=0.42). The sevelamer carbonate group had a mean (SD) extension study baseline serum phosphorus of 1.68 (0.48) mmol/L and a level of 1.77 (0.52) at week 52, representing a change from baseline of 0.09 (0.58) (P=0.02). The difference was not statistically significant between groups (P=0.14). Over one year, from the start of the initial phase III study, mean (SD) serum phosphorus concentrations among completers in the sucroferric oxyhydroxide group decreased by 0.70 (0.66) mmol/L for sucroferric oxyhydroxide from a baseline value of 2.45 (0.55) mmol/L to a value of 1.74 (0.50) mmol/L at week 52. For sevelamer carbonate completers, the serum phosphorus decreased by 0.66 (0.68) mmol/L from a baseline of 2.38 (0.57) mmol/L to 1.72 (0.45) mmol/L at week 52. Changes in serum phosphorus concentrations were not significantly different between treatment groups (P=0.45). At each time-point throughout the extension study, mean serum phosphorus concentrations for both treatment groups remained within the KDOQI target range of 1.13 to 1.78 mmol/L. Of 549 patients who completed ≥1 year of continuous treatment, the proportion within the KDOQI target range was 52% for sucroferric oxyhydroxide and 55% for sevelamer at week 52. Of the patients who completed ≥1 year of continuous treatment, the proportion below the KDOQI upper limit (≤1.78 mmol/L) was 60% for sucroferric oxyhydroxide and 62% for sevelamer at week 52. Control of serum phosphorus concentrations throughout the extension study was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				achieved with an overall lower mean (SD) pill burden of 4.0 (1.5) tablets/day for sucroferric oxyhydroxide, compared with 10.1 (6.6) tablets/day for sevelamer. Over one year, the overall mean (SD) number of tablets taken per day was 3.3 (1.3) for sucroferric oxyhydroxide and 8.7 (3.6) for sevelamer. Mean serum intact PTH concentrations increased slightly during the extension study in both sucroferric oxyhydroxide and sevelamer treatment groups, with no difference between treatment groups (P=0.60). Mean bone-specific alkaline phosphatase concentrations decreased in both treatment groups during the extension study, with a more pronounced decrease in the sucroferric oxyhydroxide group. However, there was no significant difference between treatment groups in change from extension study baseline to week 52 end point (P=0.40). Total serum calcium concentrations were generally stable during the extension study. No significant change in concentrations was observed in either sucroferric oxyhydroxide or sevelamer treatment groups, and no significant differences between treatment groups were observed (P=0.77). There was no significant difference between treatment groups in change in mean serum ferritin concentrations, TSAT, iron or hemoglobin from extension study baseline to week 52 end point (P=0.42, P=0.93, P=0.56 and P=0.51, respectively). Secondary: Not Reported

Drug regimen abbreviations: TID=three times daily, TIW=three times weekly, QD=once daily
Study abbreviations: AC=active-control, CI=confidence interval, DB=double-blind, DD=double-dummy, DR=dose-ranging, ES=extension study, HR=hazard ratio, ITT=intention to treat, LSMR=least squares mean ratio, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single-blind, SD=standard deviation, SR=systematic review, XO=crossover
Miscellaneous abbreviations: BSAP=bone specific alkaline phosphatase, CaxP=calcium x phosphorus, CAPD=continuous ambulatory peritoneal dialysis, CKD=chronic kidney disease, CMS=Centers for Medicare & Medicaid Services, CRP=C reactive protein, CVD=cardiovascular disease, eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease, GFR=glomerular filtration rate, HbA_{1c}=glycosylated hemoglobin, HDL=high-density lipoprotein, iPTH=intact parathyroid hormone, IU=international units, K/DOQI=Kidney Disease Outcomes Quality Initiative, LDL=low-density lipoprotein, LOCF=last observation carried forward,MI=myocardial infarction, PTH=parathyroid hormone, TG=triglycerides, U.S.=United States, wPTH=whole parathyroid hormone

Special Populations

Table 5. Special Populations[5-12]

Generic Name	Population and Precaution				
	Elderly/ Children	**Renal Dysfunction**	**Hepatic Dysfunction**	**Pregnancy Category**	**Excreted in Breast Milk**
Calcium acetate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. The safety and efficacy in children have not been established.	Indicated for use in patients with end stage renal disease.	Not reported	C	Excreted in milk; not expected to harm an infant, provided maternal serum calcium levels are appropriately monitored.
Ferric citrate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. The safety and efficacy in children have not been established.	Indicated for use in patients with chronic kidney disease on dialysis.	Not reported	B	Unknown; use with caution.
Lanthanum carbonate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Use is not recommended in children.	Indicated for use in patients with end stage renal disease.	Not reported	C	Unknown; use with caution.
Sevelamer carbonate	Use with caution in the elderly; start at the low end of the dosing range. The safety and efficacy in children have not been established.	Indicated for use in patients with chronic kidney disease on dialysis.	Not reported	C	Not reported
Sevelamer hydro-chloride	Use with caution in the elderly; start at the low end of the dosing range. The safety and efficacy in children have not been established.	Indicated for use in patients with chronic kidney disease.	Not reported	C	Not reported
Sucroferric oxy-hdroxide	No evidence of overall differences in safety or efficacy observed between elderly and	Indicated for use in patients with chronic	Not reported	B	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	younger adult patients. The safety and efficacy in children have not been established.	kidney disease on dialysis.			

Adverse Drug Events

Table 6. Adverse Drug Events (%)[5-12]

Adverse Event	Calcium acetate	Lanthanum carbonate	Ferric citrate	Sevelamer	Sucroferric oxyhydroxide
Abdominal pain	-	5 to 17	-	9	-
Bronchitis	-	5	-	-	-
Constipation	-	6 to 14	8	8	-
Cough	-	-	6	-	-
Dialysis graft complication	-	3 to 26	-	-	-
Dialysis graft occlusion	-	4 to 21	-	-	-
Diarrhea	-	13 to 23	21	19	6 to 24
Dyspepsia	-	-	-	16	-
Fecal discoloration	-	-	✔	-	12 to 16
Fecal impaction	-	-	-	✔ *	-
Flatulence	-	-	-	8	-
Headache	-	5 to 21	-	-	-
Hypercalcemia	✔	0 to 4	-	-	-
Hypotension	-	8 to 16	-	-	-
Ileus	-	-	-	✔ *	-
Intestinal obstruction	-	-	-	✔ *	-
Intestinal perforation	-	-	-	✔ *	-
Nausea	✔	11 to 36	11	20	10
Pruritus	✔	-	-	✔ *	-
Rash	-	-	-	✔ *	-
Rhinitis	-	5 to 7	-	-	-
Vomiting	✔	9 to 26	7	22	-

✔ Percent not specified.
- Event not reported.
*Post marketing experience.

Contraindications

Table 7. Contraindications[5-12]

Contraindications	Calcium acetate	Lanthanum carbonate	Ferric citrate	Sevelamer	Sucroferric oxyhydroxide
Bowel Obstruction		✔		✔	
Hypercalcemia	✔				
Iron overload syndromes			✔		

Warnings and Precautions:

Table 8. Warnings and Precautions[5-12]

Warnings and precautions	Calcium acetate	Lanthanum carbonate	Ferric citrate	Sevelamer	Sucroferric oxyhydroxide
Dysphagia and esophageal tablet retention have been reported.		✔		✔	
Hypercalcemia; avoid use of other calcium supplements.	✔ *†				
Iron overdose may occur, keep out of reach of children and call a poison control center if accidental overdose occurs			✔		
Iron overload may occur, monitor iron while on therapy			✔		
Laboratory monitoring throughout therapy for bicarbonate, chlorine, vitamin D, E, K and folic acid.				✔	
Laboratory monitoring in patients with gastrointestinal disorders or iron accumulation disorders					✔
Safety and efficacy not established in gastrointestinal bleeding or inflammation			✔		
Use with caution in patients with peptic ulcer, ulcerative colitis, bowel obstruction or Crohn's disease.		✔			
Use with cation in patients with dysphagia, swallowing disorders, severe GI motility disorders, including severe constipation or major GI tract surgery.				✔	

*Maintain serum Ca x P product below 55 mg^2/dL^2 (PhosLo® and Phoslyra®)
†Maintain serum Ca x P product below 66 mg^2/dL^2 (Eliphos®)

Drug Interactions

Table 9. Drug Interactions[5-12]

Generic Name	Interacting Medication or Disease	Potential Result
Calcium acetate	Bisphosphonates	Concurrent use may decrease bisphosphonate absorption, resulting in reduced pharmacologic effect.
Calcium acetate	Tetracyclines	Concurrent use may result in reduced tetracycline pharmacologic effect.
Calcium acetate	Digitalis	Hypercalcemia may aggravate digitalis toxicity, use caution in patients on digoxin.
Calcium acetate (Phoslyra®)	Maltitol (and other laxatives)	Phoslyra contains maltitol (1 g/5 mL) and may induce a laxative effect, especially if taken with other products.
Calcium acetate	Quinolones	Concurrent use may result in reduced quinolone pharmacologic effect.
Ferric citrate	Doxycycline	Administer doxycycline at least one hour before tetraferric tricitrate decahydrate.
Lanthanum carbonate	Compounds which bind to cationic antacids (e.g. quinolones, levothyroxine, tetracyclines)	Concurrent use may result in reduced pharmacologic effect of interacting medication. Separate administration by at least two hours.
Sevelamer	Ciprofloxacin	Decreased bioavailability of ciprofloxacin by

Generic Name	Interacting Medication or Disease	Potential Result
carbonate		approximately 50% (2.8 g dose).
Sevelamer hydrochloride	Ciprofloxacin	Decreased bioavailability of ciprofloxacin by approximately 50% (2.8 g dose).
Sucroferric oxyhydroxide	Doxycycline	Administer doxycycline at least one hour before ferric oxyhydroxide.
Sucroferric oxyhydroxide	Levothyroxine	Decreased absorption, it is recommended that these agents not be prescribed together for the same patient.

Dosage and Administration

Table 10. Dosing and Administration[5-12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Calcium acetate	Control hyperphosphatemia in end stage renal failure: Capsule, tablet: initial, 1334 mg three times a day with each meal; maintenance, increase dose gradually to bring the serum phosphate level <6 mg/dL (usually 2001 to 2668 mg three times a day) Reduce phosphate with end stage renal disease: Oral solution: initial, 1334 mg (10 mL) three times a day with each meal; maintenance, increase dose gradually to lower serum phosphorus levels to the target range (usually 2001 to 2668 mg [15 to 20 ml] three times a day)	The safety and efficacy in children have not been established.	Capsule: 667 mg Oral solution: 667 mg/5 mL Tablet: 667 mg
Ferric citrate	Control Serum Phosphorus in Patients with Chronic Kidney Disease on Dialysis: Tablet: initial, 2 grams TID with meals; maintenance, the dose should be titrated every week or longer in increments of 1 to 2 grams/day as needed to maintain target phosphorus levels; maximum 12 tablets per day (4 grams TID)	The safety and efficacy in children have not been established.	Tablet: 1 gram
Lanthanum carbonate	Reduce phosphate with end stage renal disease: Chewable tablet: initial, 1,500 mg/day divided and taken with meals; maintenance, the dose should be titrated every two to three weeks until an acceptable serum phosphate level is reached (usually 1,500 to 3,000 mg/day)	Use is not recommended in children.	Tablet, chewable: 500 mg 750 mg 1,000 mg
Sevelamer carbonate	Control serum phosphorus in patients with chronic kidney disease on dialysis: Powder for oral suspension: initial, 800 to 1,600 mg TID with meals; maintenance, titrate by 800 mg TID with meals at two week intervals as necessary with the goal of controlling serum phosphorus within the target range	The safety and efficacy in children have not been established.	Powder for oral suspension: 0.8 g 2.4 g Tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Tablet: initial, 800 to 1,600 mg TID; maintenance, titrate by 800 mg TID with meals at two week intervals as necessary with the goal of controlling serum phosphorus within the target range		800 mg
Sevelamer hydrochloride	Control serum phosphorus in patients with chronic kidney disease on dialysis: Tablet: initial, 800 to 1,600 mg TID with meals; maintenance, dosage should be adjusted based on the serum phosphorus concentration with a goal of lowering serum phosphorus to ≤5.5 mg/dL	The safety and efficacy in children have not been established.	Capsule: 400 mg 800 mg
Sucroferric oxyhydroxide	Control Serum Phosphorus in Patients with Chronic Kidney Disease on Dialysis: Tablet: initial, 500 mg TID; maintenance, the dose should be titrated every week or longer in increments of 500 mg per day as needed to maintain target phosphorus levels; maximum 6 tablets per day (3,000 mg TID)	The safety and efficacy in children have not been established.	Tablet, chewable: 500 mg

TID=three times daily

Clinical Guidelines

Current guidelines are summarized in Table 11. Please note, associated clinical guideline summaries focus only on phosphorus levels and the role of phosphorus depleters in disease management of chronic kidney disease.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations

Kidney Disease: Improving Global Outcomes: **Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (2009)**[1]	Treatment of Chronic Kidney Disease (CKD)-Mineral and Bone Disorder (MBD) targeted at lowering high serum phosphorus and maintaining serum calcium
	• CKD stages 3 to 5: maintain normal range of serum calcium and phosphorus.
	  o In CKD stage 5D, maintain phosphorus levels within the normal range and calcium levels between 1.25 and 1.50 mmol/L.
	• If hyperphosphatemia is present in CKD stage 3 to 5D:
	  o Limit dietary phosphates and combine with other treatments if needed (phosphorus binding agents are suggested to be used to treat hyperphosphatemia in CKD Stages 3 to 5 and 5D).
	• Choice of phosphorus binder takes into account:
	  o CKD Stage,
	  o Presence of other components of CKD-MBD,
	  o Concomitant therapies, and
	  o Side effect profile.
	• The dose of calcium-based phosphate binders and/or calcitriol and vitamin D analogs should be restricted in the following situations:
	  o Persistent or recurrent hypercalcemia,
	  o Arterial calcification and/or adynamic bone disease,
	  o Hyperphosphatemia, and
	  o Persistently low PTH levels.
	• Long-term use of aluminum-containing phosphate binders in patients with CKD Stages 3 to 5D should be avoided to prevent aluminum intoxication.

Clinical Guideline	Recommendations
	• Dialytic phosphorus removal is suggested to be increased in CKD Stage 5D in the treatment of persistent hyperphosphatemia.
Kidney Disease Outcomes Quality Initiative: **Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (2003)**[2]	Evaluation of serum phosphorus levels • Serum phosphorus levels in CKD Stages 3 and 4 are suggested to be maintained at or above 2.7 mg/dL and no higher than 4.6 mg/dL. • Serum phosphorus levels in CKD Stage 5 with kidney failure and those treated with hemodialysis or peritoneal dialysis should be maintained between 3.5 and 5.5 mg/dL. Restriction of dietary phosphorus in patient with CKD • Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted for dietary protein needs) when serum phosphorus levels are elevated (CKD Stages 3 and 4, >4.6 mg/dL and CKD Stage 5, >5.5 mg/dL). • Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted to dietary protein needs) when the plasma levels of intact parathyroid hormone (iPTH) are elevated above target range of the CKD Stage. • The serum phosphorus levels are suggested to be monitored every month following the initiation of dietary phosphorus restrictions. Use of phosphate binders in CKD • If phosphorus or iPTH levels cannot be controlled within target range, despite dietary restriction, in CKD Stages 3 and 4, phosphate binders are suggested to be prescribed. • Calcium-based binders are effective in lowering serum phosphorus levels in CKD Stages 3 and 4, and are suggested for use as initial therapy. • Both calcium- and noncalcium-, nonaluminum- and nonmagnesium-based binders are effective in lowering serum phosphorus levels in CKD Stage 5 with kidney failure, and either is suggested as initial therapy. • In dialysis patients who remain hyperphosphatemic (>5.5 mg/dL) despite the use of either calcium- or other noncalcium-, nonaluminum-and nonmagnesium-based binders, combination of both is suggested. • The total dose of elemental calcium provided by the calcium-based binder is suggested not to exceed 1,500 mg/day and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day in CKD Stage 5 with kidney failure. • Calcium-based phosphorus binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium >10.2 mg/dL) or whose plasma PTH levels are <150 pg/mL on two consecutive measurements. • Noncalcium-based binders are suggested to be preferred in dialysis patients with severe vascular and/or other soft tissue calcifications. • In patients with serum phosphorus levels >7.0 mg/dL, aluminum-based binders are suggested to be used as short term therapy (four weeks), and for one course only, to be replaced thereafter by other phosphorus binders in CKD Stage 5 with renal failure. In these patients, it is recommended that more frequency dialysis should also be considered. Serum calcium and calcium times phosphorus (CaxP) product • In CKD Stages 3 and 4, the serum levels of corrected total calcium should be maintained within the “normal” range for the laboratory used. • In CKD patients with kidney failure (Stage 5): o Serum levels of corrected total calcium should be maintained within

Clinical Guideline	Recommendations
	the normal range for the laboratory used, preferably toward the lower end (8.4 to 9.5 mg/dL). o In the event corrected total serum calcium level exceeds 10.2 mg/dL, therapies that cause serum calcium to rise should be adjusted as follows: ▪ The dose of calcium-based phosphorus binders should be reduced or therapy switched to a noncalcium-, nonaluminum- or nonmagnesium-containing phosphorus binder. ▪ The dose of active vitamin D sterols should be reduced or therapy discontinued until the serum levels of corrected total calcium return to the target range. ▪ If hypercalcemia (>10.2 mg/dL) persists despite modification of therapy, dialysis using a low dialysate calcium may be used for three to four weeks. • In CKD Stages 3 to 5 o Total elemental calcium intake should not exceed 2,000 mg/day. o The serum CaxP product should be maintained at <55 mg^2/dL^2. This is best achieved by controlling serum levels of phosphorus within the target range. o Patients whose serum levels of corrected total calcium are below the lower limit of the laboratory used should receive therapy to increase serum calcium levels if: ▪ There are clinical symptoms of hypocalcemia. ▪ The plasma iPTH level is above the target range for the CKD Stage. o Therapy for hypocalcemia should include calcium salts such as calcium carbonate and/or oral vitamin D sterols.
National Institute for Health and Clinical Excellence: **Hyperphosphataemia in Chronic Kidney Disease: Management of Hyperphosphataemia in Patients with Stage 4 or 5 Chronic Kidney Disease. (2014)**[3]	<u>Dietary Management: Children, Young People and Adults</u>: • A specialist renal dietitian should carry out a dietary assessment and give individualized advice on dietary phosphate management. • Advice on dietary phosphate management should be tailored to individual learning needs and preferences • Give information about controlling intake of phosphate-rich foods (in particular, foods with a high phosphate content per gram of protein, as well as food and drinks with high levels of phosphate additives) to control serum phosphate, while avoiding malnutrition by maintaining a protein intake at or above the minimum recommended level. For people on dialysis, take into account possible dialysate protein losses. • If a nutritional supplement is needed to maintain protein intake in children and young people with hyperphosphatemia, offer a supplement with lower phosphate content, taking into account patient preference and other nutritional requirements. <u>Phosphate Binders: Children and Young People*</u>: • For children and young people, offer a calcium-based phosphate binder as the first-line phosphate binder to control serum phosphate in addition to dietary management. • For children and young people, if a series of serum calcium measurements shows a trend towards the age-adjusted upper limit of normal, consider a calcium-based binder in combination with sevelamer hydrochloride, having taken into account other causes of rising calcium levels.

Clinical Guideline	Recommendations
	• For children and young people who remain hyperphosphatemic despite adherence to a calcium-based phosphate binder, and whose serum calcium goes above the age-adjusted upper limit of normal, consider either combining with, or switching to, sevelamer hydrochloride ,having taken into account other causes of raised calcium. Phosphate Binders: Adults: • For adults, offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management. • For adults, consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable. • For adults with stage 4 or 5 chronic kidney disease (CKD) who are not on dialysis and who are taking a calcium-based binder consider switching to a non-calcium-based binder if calcium-based phosphate binders are not tolerated. • For adults with stage 4 or 5 chronic kidney disease (CKD) who are not on dialysis and who are taking a calcium-based binder consider either combining with, or switching to, a non-calcium based binder if hypercalcemia develops (having taken into account other causes of raised calcium), or if serum parathyroid hormone levels are low. • For adults with stage 5 CKD who are on dialysis and remain hyperphosphatemic despite adherence to the maximum recommended or tolerated dose of calcium-based phosphate binder, consider either combining with, or switching to, a non-calcium-based binder. • For adults with stage 5 CKD who are on dialysis and who are taking a calcium based binder, if serum phosphate is controlled by the current diet and phosphate binder regimen but serum calcium goes above the upper limit of normal, or serum parathyroid hormone levels are low, consider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having taken into account other causes of raised calcium. Phosphate Binders: Children, Young People, and Adults*: • If a combination of phosphate binders is used, titrate the dosage to achieve control of serum phosphate while taking into account the effect of any calcium-based binders used on serum calcium levels. • Take into account patient preference and the ease of administration, as well as the clinical circumstances, when offering a phosphate binder in line with recommendations. • Advise patients (or, as appropriate, their parents and/or carers) that it is necessary to take phosphate binders with food to control serum phosphate. • At every routine clinical review, assess the patient's serum phosphate control, taking into account dietary phosphate management, phosphate binder regimen, adherence to diet and medication, and other factors that influence phosphate control, such as vitamin D or dialysis.

*Certain phosphate binders are approved in the UK for pediatric use; none are approved by the FDA in the United States.

Conclusions

The use of phosphorus binders (or phosphorus depleters) is an important aspect of the medical management of patients with chronic kidney disease (CKD); these agents are used to lower a patient's phosphorus level. If phosphorus levels remain elevated in this population, the patient is at a greater risk for the development of secondary hyperparathyroidism or cardiovascular disease. In addition, there is available evidence to demonstrate that hyperphosphatemia is a predictor of mortality in CKD Stage 5 patients who are receiving dialysis. When dietary restriction is inadequate for the control of phosphorus levels, the administration of phosphorus binders is appropriate.[1-4]

The two subgroups of phosphorus binders currently available include the calcium- and non-calcium-containing products. Available evidence supports the hypothesis that all of the phosphorus binders are efficacious in controlling serum phosphorus levels.[13-54] It is important to note that although the true benefits of these agents, with respect to hard clinical outcomes, have not been established, it is still reasonable to prescribe these products in patients with CKD who have elevated phosphorus levels to prevent the development of secondary hyperparathyroidism and cardiovascular disease. Of note, a meta-analysis published in 2013 suggests a statistically significant 22% reduction in relative risk reduction for patients taking non-calcium-based phosphate binders compared with calcium-based phosphate binders.[49] Currently, the calcium-containing capsules and tablets (Eliphos®, PhosLo®) are available generically and are generally administered first line; however, these products should be avoided in CKD patients who have hypercalcemia or severe vascular calcification.[5-12] Calcium acetate is also formulated as a brand-name oral solution (Phoslyra®)[7].The non-calcium containing products are typically reserved for use in those specific patient populations, but can also be used in combination with a calcium-containing product when the regimen is supplying the maximum allotted dose of elemental calcium/day. Ferric citrate (Auryxia®) and sucroferric oxyhydroxide (Velphoro®) are newer non-calcium agents along with lanthanum carbonate (Fosrenol®), sevelamer hydrochloride (Renagel®) and sevelamer carbonate (Renvela®).[8-12] The hydrochloride formulation of sevelamer was developed first, but due to the incidence of metabolic acidosis associated with its use, a buffered sevelamer formulation was later developed. The newer, sevelamer carbonate product will most likely be preferred in this patient population due to a decrease in the incidence of metabolic acidosis associated with its use. Sevelamer carbonate tablets are available generically, but the powder currently only available as the brand name.

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