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REVIEW ARTICLE

A Review of Phosphate Binders in Chronic Kidney Disease: Incremental Progress or Just Higher Costs?

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Abstract As kidney disease progresses, phosphorus retention also increases, and phosphate binders are used to treat hyperphosphatemia. Clinicians prescribe phosphate binders thinking that reducing total body burden of phosphorus may decrease risks of mineral and bone disorder, fractures, cardiovascular disease, progression of kidney disease, and mortality. Recent meta-analyses suggest that sevelamer use results in lower mortality than use of calcium-containing phosphate binders. However, studies included in meta-analyses show significant heterogeneity, and exclusion or inclusion of specific studies alters results. Since no long-term studies have been conducted to determine whether treatment with any phosphate binder is better than placebo on any hard clinical endpoint (including mortality), it is unclear whether possible benefit with sevelamer represents net benefit of sevelamer, net harm with calcium-containing phosphate binders, or both. Although one meta-analysis suggested that calcium acetate may be more efficacious gram for gram than calcium carbonate as a binder, calcium acetate did not reduce hypercalcemia, and gastrointestinal intolerance was higher. Data are insufficient to determine whether calcium acetate provides lower risk of vascular calcification than calcium carbonate. Fears of lanthanum accumulation in the central nervous system or bone with long-term treatment do not appear to be warranted. Newer iron-containing phosphate binders have potential benefits, such as lower pill burden (sucroferric oxyhydroxide) and improved iron parameters (ferric citrate). The biggest challenge to phosphate binder efficacy is non-adherence. This article reviews the current knowledge regarding safety, effectiveness, and adherence with currently marketed phosphate binders and those in development.

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Key Points

Phosphate binders have been approved in many countries specifically for treatment of hyperphosphatemia. They are commonly used in dialysis patients and late-stage non-dialysis-dependent chronic kidney disease patients with the hope of positive effects on important clinical outcomes, despite lack of solid evidence from placebo-controlled trials.

Since some evidence suggests that sevelamer products may have survival benefits over calcium-containing phosphate binders, many clinicians prescribe sevelamer products versus calcium-containing phosphate binders, in the absence of conclusive evidence of harms versus benefits of these agents compared with placebo or with each other.

Phosphate binders, especially newer ones, represent a significant cost burden on national health care budgets. In the US alone, for example, phosphate binders contribute almost 1 billion dollars per year to Medicare Part D expenditures for dialysis patients.

It is imperative that well-designed, long-term, placebo-controlled, randomized comparative trials evaluating hard clinical endpoints be conducted with commonly used phosphate binders.

1 Introduction

Phosphorus balance is a key component of mineral and bone homeostasis and is altered in patients with chronic kidney disease (CKD). Phosphorus is essential for metabolic and enzymatic functions throughout the body, including adenosine triphosphate generation. Excess phosphorus is associated with increased vascular calcification and poor cardiovascular (CV) outcomes [1]. Hyperphosphatemia is a common complication of CKD and progressively worsens as kidney function declines [2]. Among patients with end-stage renal disease (ESRD), 37 and 42% of hemodialysis and peritoneal dialysis patients, respectively, had serum phosphorus concentrations above 5.5 mg/dL based on US data from December 2014 [3].

In the general population, elevated serum phosphorus concentration has been correlated with atherosclerosis, vascular calcification, CV events, and increased mortality [4–8]. The putative relationship between CV events and elevated serum phosphorus concentrations serves as a basis for treating hyperphosphatemia in CKD, where phosphorus accumulation is substantial. Observational or cohort studies in non-dialysis-dependent (NDD)-CKD, kidney transplant, or dialysis patients demonstrate that hyperphosphatemia is a risk factor for CV disease/events [1, 9–12]; however, recent evidence suggests gender differences with regard to risk [13]. Several studies in the general population have shown differences in risk associated with hyperphosphatemia by gender; the relationship between phosphorus and CV risk factors, morbidity, and mortality appears to be consistent in studies of men but not women in the general population [14–16]. Additional research on the gender differences in clinical outcomes associated with hyperphosphatemia in CKD is warranted.

Most [1, 10, 12, 17–21], but not all [22], observational or cohort studies also show that increased levels of phosphorus in CKD patients (NDD-CKD, dialysis, transplant) are associated with increased all-cause mortality or a composite endpoint of all-cause mortality and ESRD. In the dialysis or NDD-CKD populations, no prospective randomized trial evaluating effects of varying phosphorus concentration targets on clinical outcomes has been conducted. Prospective comparative trials of phosphate binders in dialysis patients have been conducted for various clinical outcomes, but results from single studies have been conflicting and have not clearly identified superior agents. Results from these trials have been combined in several recent systematic reviews and meta-analyses and will be evaluated in this review.

Results from a randomized placebo controlled trial (RCT) in stage 3b–4 NDD-CKD normophosphatemic patients showed that treatment with three phosphate binders (lanthanum carbonate, sevelamer carbonate, or calcium acetate) reduced serum phosphorus and urinary phosphate excretion compared with placebo, but coronary and aortic calcification increased in the active treatment group with no progression in the placebo group [23]. A subgroup analysis showed that calcification was associated with calcium acetate treatment, but neither lanthanum nor sevelamer was superior to placebo for this endpoint. A randomized placebo cross-over study in eight stage 3–4 NDD-CKD normophosphatemic patients on a controlled phosphorus diet with or without calcium carbonate supplementation showed that calcium carbonate produced a positive calcium balance while not affecting phosphorus balance or serum phosphorus concentrations. In addition, calcium kinetic data suggested soft-tissue deposition of calcium [24]. This study supported data from an earlier study [25]. Thus, available evidence from single studies is not definitive regarding whether any phosphate binder positively affects any hard clinical outcome aside from lowering phosphorus concentrations, and there is some evidence of harm with calcium-containing phosphate binder (CCPB) treatment in NDD-CKD patients.

The current standard of care is to treat hyperphosphatemia in dialysis patients and later stages of NDD-CKD

using a combination of non-pharmacologic, dialytic, and pharmacologic interventions [2].

1.1 Non-pharmacologic and Dialytic Approaches

Non-pharmacologic approaches to managing hyperphosphatemia are often the first-line interventions for patients with CKD. Identifying and limiting exogenous sources of phosphorus may be effective in controlling hyperphosphatemia in some patients and enhance phosphorus control among patients requiring phosphate-binding medications. Phosphorus is found in high concentrations in certain foods or beverages (e.g., colas, dairy products, meats, etc.); intake of these foods should be generally limited in patients with hyperphosphatemia. "Hidden" phosphate may make limiting phosphorus intake difficult for some patients, as phosphorus is a common additive in processed foods and may also be found in medication excipients [26]. While food additives can substantially increase phosphorus content, medication additives containing phosphorus are generally not considered of great importance to overall phosphorus intake [26, 27]. However, this warrants further study as few data describe the clinical impact of phosphorus content in medication products [26, 28].

Phosphorus is removed during dialysis, which contributes to overall phosphorus balance among ESRD patients. During hemodialysis, the serum phosphorus concentration drops within the first 1–2 h, then remains nearly constant throughout the remainder of the session. Phosphorus continues to be removed throughout treatment, but also continues to move from the intracellular compartment into the vascular compartment [29]. Phosphorus removal during hemodialysis averages 800–1000 mg per treatment, but significant interpatient variation may occur even with patients of similar weights or dialysis prescriptions [30]. This variability may reflect differences in rates of phosphorus moving from the intracellular to the vascular space, where it can be removed by dialysis. Differences in pre-dialysis serum phosphorus concentrations may also affect total dialytic removal; the higher the concentration in the serum, the more is available for removal during hemodialysis. Therefore, for patients who maintain lower serum phosphorus, much less than 800 mg of phosphate may be removed during hemodialysis. Finally, the hemodialysis prescription affects phosphorus removal. For example, increasing dialysis membrane surface area and frequency of hemodialysis sessions may lead to larger total phosphorus removal than increasing treatment duration. Peritoneal dialysis also contributes to phosphorus removal. However, prediction of phosphorus transport is difficult. A recent study of 87 patients on peritoneal dialysis showed that peritoneal creatinine transporter status and creatinine clearance were poor predictors of peritoneal phosphorus transport. Investigators also found that patients using continuous ambulatory peritoneal dialysis, compared with automated intermittent peritoneal dialysis, had greater peritoneal phosphate clearance [31].

1.2 Phosphate Binders

Phosphate binders have remained the predominant pharmacologic intervention for phosphorus control since the 1970s, when aluminum-based phosphate binders were used [32]. Currently, a range of phosphate-binding medications are available in a variety of dosage forms, including aluminum salts, CCPBs, sevelamer hydrochloride (Renagel®, Sanofi; available in generic form in some countries), sevelamer carbonate (Renvela®, Sanofi; available in generic form in some countries), lanthanum carbonate (Fosrenol®, Shire) and new iron-containing phosphate binders (ICPBs). All are effective at lowering serum phosphorus in ESRD patients, but key clinical outcomes including CV mortality, CV events, and/or hospitalizations may differ. Although phosphate binders are used in patients with high CV risk, the effect of phosphate binders on CV events has not been a primary endpoint in clinical trials. In the USA, phosphate binders are approved following phase III trials focusing on phosphate lowering, with no information on hard clinical outcomes in CKD. This is in contrast to medications to treat diabetes, for example, for which the Food and Drug Administration (FDA) has required large clinical trials to assess major adverse cardiac event risk for all new diabetes medications approved since 2008 [33]. This requirement was in response to data suggesting increased risk of CV events with rosiglitazone, despite its efficacy in glucose lowering. Such studies are not required for phosphate-binding medications, despite the high CV risk of the patient population in which these drugs are used.

Phosphate binders are recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines to treat hyperphosphatemia in patients with NDD-CKD stages 3 through 5 and stage 5 on dialysis [2]. While these medications are approved for use in patients with ESRD, not all are approved for use in NDD-CKD patients. In the USA, no phosphate binder is FDA-approved for use in NDD-CKD patients. However, based on increasing surrogate outcomes data suggesting the possibility of harm with calcium-based binders, draft KDIGO CKD mineral and bone disorder (MBD) guidelines suggest restricting CCPB doses [34].

2 Phosphate Binder Safety

2.1 Timeline of Phosphate Binder Safety Concerns Driving New Therapies

A relative timeline of safety concerns from marketed phosphate binders is depicted in Fig. 1. Safety evidence

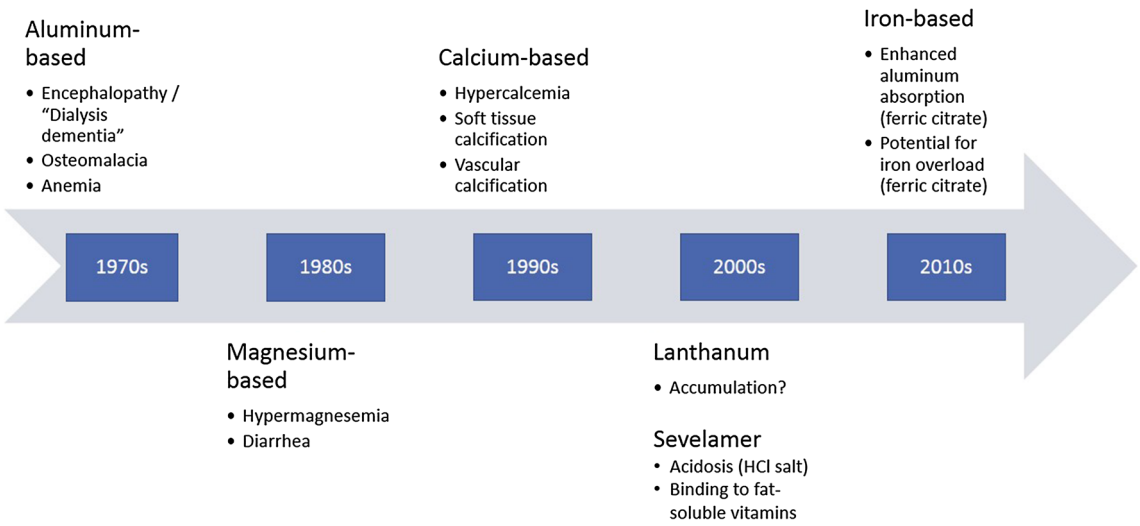

Fig. 1 Timeline for entry of various phosphate binders into US market and safety issues. The dates reflect when each phosphate binder started being used in practice—e.g., aluminum in use in the 1970s and reports of toxicities starting in the early 1980s

with phosphate binders is covered in current KDIGO CKD-MBD clinical practice guidelines [35] and new draft guidelines to be released in 2017 [34]. The main issues and findings from these guidelines are summarized here. Although aluminum-containing phosphate binders are highly effective at binding phosphorus, aluminum exposure has been linked to central nervous system toxicity, microcytic anemia, and osteomalcia in dialysis patients. Use should be restricted to the short term (days) and to situations in which high phosphorus levels must be reduced quickly. Magnesium-containing phosphate binders have dose-limiting adverse effects (diarrhea and hypermagnesemia), and are little used. The main concern with CCPBs is increased body load of calcium, increasing risks of hypercalcemia and vascular, aortic, and soft tissue calcification. Sevelamer hydrochloride has been shown to increase risk of metabolic acidosis, but availability of sevelamer carbonate, which has similar efficacy, has alleviated this problem. Accumulation of lanthanum in bones and the central nervous system has been a primary reason clinicians have been more reluctant to prescribe it, but a study evaluating cognitive function showed similar decline in lanthanum users compared to standard of care recipients [36]. Several lines of evidence suggest that long-term lanthanum use does not result in aluminum-like bone disease. There is little information on long-term adverse effects of new ICPBs. One concern with ferric citrate is that the citrate can increase gastrointestinal aluminum absorption; this may be moot if use of aluminum-based phosphate binders is restricted.

Evidence regarding safety effects has been generated from RCTs comparing placebo with active drug, and randomized comparative studies between two phosphate binders or classes. Several recent systematic reviews and meta-analyses, including network meta-analyses, give new insight into comparative safety across phosphate binder classes or specific agents.

2.2 Comparative Safety (Systematic Reviews and Meta-analysis)

Four separate groups published systematic reviews with meta-analyses in 2015 and 2016 comparing the safety of various phosphate binders in dialysis and NDD-CKD patients [37–40]. Importantly, side effects may be under-reported in clinical trials (and thus in meta-analyses combining results from clinical trials) because most trials employ exclusions that result in select populations. For more information, see Sect. 5.1. In addition, some information in this section and in Sect. 3.3 comes from two network meta-analyses by two research groups [37, 41]. Network meta-analysis differs from conventional pair-wise meta-analysis in which two or more RCTs comparing the same two interventions are grouped together for analysis. Network meta-analysis compares multiple treatments (three or more) using direct comparisons of interventions within RCTs and indirect comparisons across RCTs based on a common comparator. The risk of bias from poor design and execution of clinical trials can be magnified through network meta-analysis, as bias in the effect estimate from any single RCT may affect several pooled effect estimates within a network, in contrast to affecting a single effect estimate, as in conventional meta-analyses [42]. These caveats must be considered when interpreting the results below.

2.2.1 Hypercalcemia

Increased hypercalcemic risk occurred with CCPBs compared with sevelamer products [38, 39] and lanthanum

Table 1 Summary of more recent systematic reviews and meta-analyses comparing various phosphate binders on effectiveness and safety outcomes: study designs, general results, strengths and limitations

Author, year	Comparator	Number of included trials and patients and methods	Outcomes evaluated	General results	Strengths	Limitations
Palmer [37], 2016	CC or CA, SH or SC, LC, MgC, ICPB (iron-mag-hydrox, FC, SBR759, or SFO), colestilan, bixalomer, nicotinic acid	Systematic review, conventional and network meta-analysis used; 77 RCTs, 12,562 subjects (62 of the trials, 11,009 subjects were conducted in D patients) on studies published up to May 18, 2016. Included parallel-group RCTs with follow-up of 4 or more week in patients with CKD randomized to PB, placebo or standard care	Primary outcome: all-cause mortality. Additional outcomes: CV mortality, MI, stroke, adverse events (nausea, abdominal pain, constipation, diarrhea, hypercalcemia), CAC, achievement of sPhos target	77 Studies included. Median study duration 3 months, median age 56.7 years, median sPhos 6.5 mg/dL, median follow-up ranged from 1.8 months for placebo and ICPB to 6 months with CCPB	Evaluation performed by seasoned investigators well versed with meta-analyses techniques. Thorough description of methodology	Majority of trials were of short duration (median 6 months) and had high risk of bias. Median follow-up for studies including placebo or control patients was only 1.8 months. Substantial heterogeneity seen for studies evaluating CV mortality; less for other outcomes. There was evidence of global network inconsistency for diarrhea outcome. PC trials were of short duration (4 weeks to 3 months), thus may have not been sufficient to evaluate all-cause mortality. Data for CV mortality, MI and stroke were sparse. Evaluations between SH and SC or CC and CA limited because many studies had few observations leading to low-powered analyses
Sekercioglu [41], 2016	CCPB (CC, CA or calc citr), NCCPB (SH, SC, LC, SFO and FC), phos-restricted diet, placebo or no treatment	Systematic review, conventional and network meta-analysis; included 28 RCTs ($n = 8335$) from 1996 to 2015, with follow-up of $\geq$4 weeks. Performed network meta-analyses for individual agents and conventional meta-analysis of calc vs. NCCPB. Included adults with stage 3–5 CKD and 5D. Used GRADE criteria for quality of evidence (high, moderate, low or very low)	All-cause mortality for individual agents; all-cause mortality, CV mortality and hospitalization for CCPB vs. NCCPB	25 Studies included. Most were multi-national and all were MC. Mean age 47–69	Low risk of bias for missing data	Blinding of participants and personnel adequate in about 25% trials. Blinding of outcome assessment (detection bias) adequate in about 30% of trials. Selective reporting seen in 25% of studies. Included one non-randomized trial evaluating vasc calc with sevelamer [134]

Table 1 continued

Author, year	Comparator	Number of included trials and patients and methods	Outcomes evaluated	General results	Strengths	Limitations
Patel [38], 2016	Sevel vs. CCPB	Systematic review, conventional and network meta-analysis; included 25 RCTs and quasi-RCTs[a] ($n = 4770$), >8-week follow-up, stage 3–5 CKD and 5D, excluded post-transplant patients. Used studies from Navaneethan et al. meta-analyses [135] and added studies published from Mar 2009 to Mar 2015; 88% on HD	Primary outcomes: all-cause mortality as well as CV events and mortality, hospitalization, and adverse events. Secondary outcomes: vasc calc, bone changes, sPhos, sCa, hypercalcemia, PTH and lipids	Analyzed 25 RCTs ($n = 4770$); 22 studies in D; 3 in CKD stages 3–5 ND. All but 4 studies enrolled patients with hyperphosphatemia. 14 studies enrolled <100 patients. Study duration ranged from 2 to 26 months, with 80% (20/25) <18 months. Most studies allowed concurrent calcitriol. Hypercalcemia definitions varied	Thorough description of methodology. Funnel plots of all-cause mortality and serum phos were symmetrical; Egger linear regression test for publication bias was not significant for these events, indicating that outcomes for mortality or phos were not likely to be affected by publication bias. Did not do sensitivity analyses for all-cause mortality where 1 study at a time was removed like was done by Palmer et al. [37], but did numerous subgroup analyses that showed results were sensitive to sub-populations (e.g., NDD-CKD vs. dialysis)	Risk of allocation bias high in 1, low in 9, unclear in 15 studies. 23 studies open-label; only 2 studies masked treatments in subjects and investigators. Outcome assessors masked in 6. 8 studies were intent-to-treat. There was significant heterogeneity across studies in several evaluations. Authors compared and contrasted patient characteristics and loss-to-follow-up rates of DCOR [53] and INDEPENDENT trial [54]. However, authors did not evaluate DCOR secondary analysis [58], which had much higher follow-up because Medicare records could be used to find deaths and hospitalizations. Noted a remarkable nine-fold reduction in all-cause CV mortality in INDEPENDENT study [54]. They noted that there were some similarities among these two trials, notably, DCOR found that mortality was lower in 65+ years old, and patients in INDEPENDENT study were older. DCOR also showed reductions in mortality for those receiving sevelamer for ≥24 months (similar to INDEPENDENT study). There was either little or inconsistent data reporting for CV mortality, vasc calc, hospitalization, bone outcomes or HQOL

Table 1 continued

Author, year	Comparator	Number of included trials and patients and methods	Outcomes evaluated	General results	Strengths	Limitations
Habbous [39], 2017	Sevel and LC vs. CCPB, sevel vs. LC, sevel vs. ICPB	Systematic review and conventional meta-analysis; included 51 RCTs ($n = 8829$ patients). Study characteristics: $n = 42$, 91% OL; $n = 28$, 55% MC; $n = 12$, 24% CO; $n = 43$, 84% D ($n = 36$ chronic HD, $n = 3$ incident HD, $n = 3$ chronic PD, $n = 1$ HD/PD), $n = 17$ (53%) industry-sponsored. Studies through Feb 2016 were included. Used digitation of graphical results if numerical data were not available	Primary outcome: all-cause mortality. Secondary outcomes: MACE, bone-related events (fractures, osteoporosis), calciphylaxis and biochemical events (hypercalcemia, hyperchloremic acidosis); other secondary events included loss to follow-up and hospitalization rates as well as biochemical parameters at study end (sPhos, corrected sCa, LDL-C, iPTH and CAC)	Follow-up ranged from 2 weeks to 3 years	Low risk of selection bias and bias due to outcome ascertainment, but moderate risk of bias due to incomplete outcome data and selective reporting	Screening was conducted by only one investigator. 91% OL studies, 84% were D (only 3 studies in incident HD patients and 3 in PD, 1 HD/PD). DCOR study was not included in hospitalization analyses as results could not be pooled with data available; authors did not include results from a secondary analysis of DCOR data that included more data on hospitalizations and showed reduced hospitalizations [58]
Wang [40], 2015	CC vs. CA	Meta-analysis; included RCTs and quasi-RCTs[a] in adult HD patients. 10 studies ($n = 625$) were included through Mar 2014	All-cause mortality, CV events, fracture incidence, sPhos, sCa, Ca x Phos and iPTH	10 Studies included. Follow-up ranged from 4–24 weeks		Elemental Ca dose for CA and CC groups not similar in some studies. SS heterogeneity observed for some analyses. Authors explored sources of heterogeneity with subgroup analyses, but data were insufficient to allow definitive conclusions. For sPhos and iPTH analyses, they did further analyses by excluding one study where sPhos did not change in CC group and in another where iPTH values at baseline were much lower than other studies. Overall meta-analysis estimates did not change. Other study limitations included short study durations (4 weeks to 1 year), only 2 trials were blinded, small sample size ($n = 625$), insufficient data for all-cause mortality or CV events

Table 1 continued

Author, year	Comparator	Number of included trials and patients and methods	Outcomes evaluated	General results	Strengths	Limitations
Jamal [136], 2013	CC or CA, NCCPB (SH or SC or LC)	Systematic review and meta-analysis ($n = 4622$); included 8 (5 RCT) studies from Aug 1, 2008 to Oct 22, 2012; added these studies to previous 10 (9 RCTs) studies from previous meta-analysis by same group [137]; quasi-RCTs[a] were not included. DerSimonian and Laird random effects model used to combine studies. Included CKD patients (irrespective of stage or dialysis type). Evaluated outcomes by various follow-up times (6, 12, 18, 24, 24+ months)	All-cause mortality and CV events (fatal and non-fatal MI, fatal and non-fatal stroke and sudden death), vasc calc, fractures and vascular compliance for CCPB vs. NCCPB	Analysis of 11 RCTs; 9 were HD; 2 were stage 3–4 CKD	Used standard Cochrane protocols; large sample size for mortality outcome. Included studies were reasonable quality; no evidence of differential drop-out by treatment assignment	For mortality assessment, only 1 RCT was blinded, 10 were OL. Risk of bias was high in 2 RCTs (large loss to follow-up or shortage of documentation). Funnel plot to assess publication bias was somewhat asymmetric and was confirmed by Egger's regression. Thus, findings might be slightly overestimating the true effect size if they missed NS studies. Assumed that CC equivalent to CA and SC equivalent to SH (only one study reported specifically on SC; others did not specify sevel product used, thus cannot determine whether outcomes varied by product). Follow-up time was relatively short for most studies. Only 1/3 of studies were judged to have a low risk of bias
Zhang [43], 2013	LC vs. controls (placebo, CCPB, SH, NCCPB), plus some head-to-head analyses with specific agents	Systematic review and meta-analysis; included 14 RCTs and 2 quasi-RCTs[a] ($n = 3789$ total; $n = 2100$ LC vs. 1689 controls including: $n = 534$ CCPB, $n = 205$ SH, $n = 708$ NCCPB, $n = 241$ placebo. HD patients (11 studies), HD and PD (3 studies)	Primary outcomes: all-cause mortality and CV events. Secondary outcomes: CAC, sPhos, sCa, Ca x Phos, iPTH, 1,25 (OH)D3, 25 (OH)2D3, total and BAP, lipids, bone changes, LC tissue content, CRP, side-effects	Follow-up ranged from 4 weeks to 3 years	Used check list designed by Cochrane Renal Group to assess study quality	Follow-up <24 weeks in 9 of 16 studies. 4 studies used calcitriol, 1 study used calcimimetics in routine treatment; baseline use of these agents was parallel between LC and controls in all studies. Only 2 studies described randomization process. Most studies were not blinded (8 reported blinding of patients and physicians, 1 reported blinding of outcome assessors). Unclear what techniques were used to test study heterogeneity, no information on type of meta-analyses performed

Table 1 continued

Author, year	Comparator	Number of included trials and patients and methods	Outcomes evaluated	General results	Strengths	Limitations
Navaneethan [135], 2011	CC or CA, SH or SC, LC, placebo; not enough information to assess ICPB or magnesium-based PB	Systematic review and meta-analysis; 60 RCTs or quasi-RCT[a], $n = 7631$; included stage 3–5 CKD and 5D. Kidney transplant patients excluded. This study supersedes a previous study by same authors [138]. Essentially same authors as Palmer et al. 2016 article [37]; most of these study results superseded by Palmer 2016	All-cause mortality, sPhos, sCa, PTH, Ca x Phos			Allocation concealment adequate in only 18% of studies, unclear in others. Blinded investigation in only 17%. Only 22% of studies analyzed using intent-to-treat design. PTH assays varied. Hypercalcemia was defined differently in various studies

CA calcium acetate, *CAC* coronary artery calcification, *CC* calcium carbonate, *calc citr* calcium citrate, *Ca x Phos* serum calcium x serum phosphorus product, *CCPB* calcium-containing phosphate binder, *CKD* chronic kidney disease, *CO* cross-over trial, *CRP* c-reactive protein, *CV* cardiovascular, *D* dialysis, *DCOR* Dialysis Clinical Outcomes Revisited trial, *FC* ferric citrate, *HD* hemodialysis, *HQOL* health-related quality of life, *ICPB* Iron-containing phosphate binder, *INDEPENDENT* Reduce Cardiovascular Calcifications to Reduce QT Interval in Dialysis Study, *iPTH* intact parathyroid hormone, *iron-mag-hydrox* iron magnesium hydroxycarbonate, *LC* lanthanum carbonate, *LDL-C* low-density lipoprotein cholesterol, *MACE* major adverse cardiovascular events, *MgC* magnesium carbonate, *MC* multi-center trial, *MI* myocardial infarction, *NCCPB* non-calcium-containing phosphate binders, *ND* no difference, *NDD-CKD* non-dialysis-dependent chronic kidney disease, *NS* statistically non-significant, *OL* open-label trial, *PB* phosphate binder, *PC* placebo-controlled trial, *PD* peritoneal dialysis, *phos* phosphorus, *PTH* parathyroid hormone, *RCT* randomized controlled trial, *SS* statistically significant, *sCa* serum calcium levels, *sPhos* serum phosphorus levels, *sevel* sevelamer hydrochloride or sevelamer carbonate, *SH* sevelamer hydrochloride, *SC* sevelamer carbonate, *SFO* sucroferric oxyhydroxide, *vasc calc* vascular calcification

[a] Quasi-RCT: quasi-randomized controlled trial; these are RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable method

carbonate [39]. Despite a finding that phosphorus reduction was greater with calcium acetate than with carbonate, there was no difference between the two CCPBs in calcium levels or hypercalcemia episodes at 4 or 8 weeks [40].

2.2.2 *Gastrointestinal Events*

In a comparison of multiple phosphate binder classes in a network meta-analysis, sevelamer ranked highest for constipation, lanthanum increased nausea compared with ICPBs or CCPBs, and ICPBs increased diarrhea compared with CCPBs [37]. In two conventional meta-analyses comparing sevelamer with CCPBs, combined gastrointestinal adverse events (nausea, vomiting, diarrhea, abdominal bloating) trended higher with sevelamer, but results were not statistically significant [38, 39]. In other conventional meta-analyses, combined gastrointestinal adverse events [39] and vomiting [43] were higher with lanthanum versus CCPBs [39]. A meta-analysis comparing calcium carbonate with calcium acetate showed a higher risk of intolerance with calcium acetate (more patients dropped out of the calcium acetate groups) and a trend toward more gastrointestinal effects with calcium acetate [40].

3 Incremental Progress in Effectiveness

3.1 Should We Expect More than Phosphorus-Lowering Effect?

In retrospective studies, higher serum phosphorus levels in people with normal or near normal kidney function have been associated with CV events [8], and with increased mortality and higher likelihood of ESRD or CKD progression in CKD patients [12, 44, 45]. Nephrology practitioners prescribe phosphate binders primarily in dialysis patients to lower phosphorus, thinking that positive benefits will result. Various phosphate binders have been approved by regulatory bodies in the USA, Europe, Canada, and other countries for the indication of hyperphosphatemia. A recent network meta-analysis showed that all phosphate binders but colestilan significantly lowered serum phosphorus levels compared with placebo [37]. Results also showed that ICPBs (iron magnesium hydroxycarbonate, ferric citrate, SBR759, sucroferric oxyhydroxide) increased the odds of attaining phosphorus targets compared with CCPBs, sevelamer, and lanthanum [37]. In contrast, Habbous et al. showed similar phosphorus levels with ICPBs and other phosphate binder groups [39]. Phosphate-lowering abilities between agents are difficult to evaluate using meta-analyses since target phosphate levels, dosing, and adherence may vary between studies. However, Wang et al. found that phosphorus lowering was greater with calcium acetate than with calcium carbonate, despite the elemental calcium dose being equal or higher in the calcium carbonate group [40]. See Sect. 5.3 for information on phosphate binder equivalency compiled from single studies.

The questions are whether lowering phosphorus with phosphate binders in CKD patients (dialysis and NDD-CKD) prevents adverse outcomes such as fractures, death, or CV events, and if so, are specific phosphate binders more effective than others. These are important questions, as about $1 billion was spent on prescription phosphate binders in Medicare-covered dialysis patients in the USA in 2014 [3, 46]. Sevelamer carbonate (Renvela®, Sanofi) was listed as one of the top 10 drugs in the US contributing to explosive growth in Medicare Part D expenditures in 2010–2015 during the catastrophic coverage phase [47] of that program.

3.2 Phosphate Binder Effects in Chronic Kidney Disease (CKD) Compared with Standard Care, No Treatment, or Placebo (Meta-Analyses and Observational Studies)

Two comprehensive network meta-analyses compared effects on mortality with standard care (phosphate-lowering diet), no treatment, or placebo versus CCPBs [calcium acetate, carbonate, citrate (Sekercioglu et al. only)], sevelamer (hydrochloride, carbonate), ICPBs [ferric citrate, sucroferric oxyhyrdroxide, iron magnesium hydroxycarbonate (Palmer et al. only), SBR759 (Palmer et al. only)], colestilan (Palmer et al. only), and some combinations [37, 41]. Data were insufficient to evaluate magnesium carbonate, bixalomer, or nicotinic acid. Findings showed no evidence that any drug class lowered all-cause mortality compared with placebo or standard care; however, the quality of evidence was judged to be low [41]. In addition, these trials were of short duration (1–3 months), so were likely insufficient to evaluate mortality effect. These results are supported by results from a large observational study of the Cleveland Clinic CKD registry, which showed that any phosphate binder use in NDD-CKD stage 3–4 patients was not significantly associated with mortality in adjusted analyses or in a propensity-score matched cohort of patients treated for longer than 6 months [48], and results from a smaller study of incident dialysis patients that evaluated only CCPBs versus no treatment [49]. However, other observational studies have shown increased survival of incident hemodialysis patients [50] and male NDD-CKD veterans who received any phosphate binder versus those who did not [51]. The short-term nature of clinical trials and conflicting results from observational studies demonstrate the need for a well-designed, adequately powered, longer-term RCT to evaluate whether commonly used

Table 2 Summary of more recent systematic reviews and meta-analyses comparing various phosphate binders on effectiveness and safety outcomes: clinical and laboratory results and comments

Author, year	All-cause mortality	Cardiovascular mortality or morbidity effects	Hospitalization	Serum phos, calcium or PTH	Other outcomes	Adverse drug reactions and safety effects
Palmer [37], 2016	Assessed in 20 studies; 86,744 patient-mo of follow-up. No drug class lowered all-cause mortality as compared to placebo. Sevel reduced all-cause mortality (OR, 0.39; 95% CI 0.21–0.74) vs. CCPB; effects of LC, ICPB and colestilan were not significant. No evidence of treatment differences between SH or SC, or CC or CA. Median follow-up for pair-wise analyses was 15 months for sevel vs. CCPB, 12 months for LC vs. CCPB, 3 months for sevel vs. ICPB. Moderate-high heterogeneity between studies	No drug class lowered CV mortality vs. placebo. Substantial heterogeneity between studies	Not evaluated	Phos: all PB lowered sPhos compared to placebo; ICPB had greatest effect on lowering sPhos vs. other PBs. Low-moderate heterogeneity between studies	Not evaluated	GI events: LC more likely to cause nausea, sevel constipation, ICPB diarrhea. CCPB more likely to cause hypercalcemia vs. either sevel or LC (moderate-high heterogeneity between studies). CCPB increased CAC scores as compared to sevel. There was low-moderate heterogeneity between studies for CAC, nausea, abdominal pain and constipation; moderate-high for diarrhea and hypercalcemia
Sekercioglu [41], 2016	Higher mortality with CCPB vs. sevel (10 studies, RR 1.89, 95% CI 1.02–3.50, moderate quality evidence) or NCCPB (15 studies, RR 1.76, 95% CI 1.21–2.56, moderate quality evidence). Effects of NCCPB vs. CCPB driven by sevel results	ND in CV mortality with sevel vs. NCCPB (5 studies, RR 2.54, 95% CI 0.67–9.62). Low-quality evidence	Higher hospitalization with CCPB vs. NCCPB (3 studies, RR 1.29, 95% CI 0.94–1.74, NS, moderate quality evidence)	Not evaluated	Not evaluated	Not evaluated

Table 2 continued

Author, year	All-cause mortality	Cardiovascular mortality or morbidity effects	Hospitalization	Serum phos, calcium or PTH	Other outcomes	Adverse drug reactions and safety effects
Patel [38], 2016	Sevel vs. CCPB had lower all-cause mortality (13 studies, $n = 3799$, RR 0.54; 95% CI 0.32–0.93). Heterogeneity was significant. All-cause mortality lower in sevel vs. CC (5 studies, $n = 847$, RR 0.35, 95% CI 0.22–0.56), but not with sevel vs. CA (5 studies, $n = 522$, RR 0.43; 95% CI 0.13–1.38) or sevel vs. calcium salts–CCPB combinations (3 studies, 2430 patients, RR 0.85, 95% CI 0.57–1.27). There was not significant heterogeneity in these 3 subgroup analyses. In sensitivity analyses, mortality was shown to be SS lower in studies ≥1 year duration, in patients new to dialysis, with baseline iPTH ≥ 150 pg/mL and with baseline vasc calc. ND seen when only studies with low risk of bias because of intent-to-treat analysis were included	ND in CV mortality between sevel and CCPB (4 studies, $n = 2712$, RR 0.33, 95% CI 0.07–1.64). Heterogeneity of studies highly significant	ND seen in 2 studies evaluated. Meta-analysis was not possible due to differing measurements. But they did not include DCOR secondary analysis results [58], which showed an SS reduction in multiple hospitalizations and hospital days with sevel vs. CCPB	End of treatment lab values: sPhos: ND between sevel and CCPB (23 studies, $n = 4010$, MD 0.1 mg/dL, 95% CI −0.1 to 0.2); significant heterogeneity between studies. NS difference in subgroups of studies evaluating sevel vs. CA, sevel vs. CC or sevel vs. calcium salts (CCPB combinations). sCa: SS lower with sevel vs. CCPB, (22 studies, $n = 3933$, MD 20.4 mg/dL, 95% CI 20.6–20.2) with SS heterogeneity between studies. CCPB-specific analyses showed similar results, but not significant heterogeneity. Hypercalcemia: Risk SS lower with sevel vs. CCPB (15 studies, $n = 1537$, RR 0.30, 95% CI 0.19–0.48) with SS heterogeneity. CCPB-specific analyses results similar without SS heterogeneity. Ca X Phos: ND between sevel and CCPB (16 studies, $n = 2971$, MD 1.0 mg^2/dL^2, 95% CI −0.5 to 2.6); heterogeneity was significant. iPTH: SS higher with sevel vs. CCPB (18 studies, $n = 1835$, MD 32.9 pg/mL, 95% CI 0.1–65.7); heterogeneity was SS	End of treatment lab values: sBicarb: SS lower sBicarb with sevel vs. CCPB (7 studies, $n = 457$, MD −1.5 mEq/L, 95% CI −2.3 to −0.7 mEq/L; heterogeneity was SS. 6/7 studies used SH; 1/7 SC. sAlk Phos: ND between sevel and CCPB (7 studies, $n = 352$, MD −8.4 U/L, 95% CI −34.0 to 17.2); heterogeneity was borderline significance ($p = 0.05$). T Chol: SS lower for sevel vs. CCPB (14 studies, $n = 2039$, MD −20.2 mg/dL; 95% CI −25.9 to −14.5); heterogeneity was SS. LDL-C: SS lower with sevel vs. CCPB (12 studies, $n = 1171$, MD −21.6 mg/dL, 95% CI −27.9 to −15.4); heterogeneity was SS. Individual CCPB results similar to overall comparison. HDL-C: ND between sevel and CCPB (9 studies, $n = 847$, MD 1.5 mg/dL, 95%, CI −0.4 to 3.5); heterogeneity was NS ($p = 0.06$). Bone outcomes: 4 studies reported BMD change by dual–energy x-ray absorptiometry or quantitative computerized tomography and/or histomorphometry. Measures were inconsistent, precluding meta-analysis	GI events: ND in sevel vs. CCPB in nausea and/or vomiting (2 studies; $n = 255$, RR 0.64, 95% CI 0.12–3.45), constipation (5 studies; $n = 554$, RR 1.70, 95% CI 0.69–4.15), diarrhea (2 studies, $n = 255$, RR 1.03, 95% CI 0.55 to 1.91), or abdominal bloating (1 study, $n = 56$, RR 2.33, 95% CI 0.49–11.01). Combined GI adverse events trended higher with sevel (4 studies, $n = 384$, RR 1.42, 95% CI 0.97–2.08, NS). Vasc calc: scoring differences precluded meta-analysis. Systematic review showed 9 studies comparing sevel and CCPB. 6 studies (9 publications), CCPB showed more severe and/or more rapid increases in CAC vs. sevel. In 3 studies, calcification progression was NS

Table 2 continued

Author, year	All-cause mortality	Cardiovascular mortality or morbidity effects	Hospitalization	Serum phos, calcium or PTH	Other outcomes	Adverse drug reactions and safety effects
Habbous [39], 2017	Trend towards lower mortality in sevel vs. CCPB; ($n = 12$ studies, RR 0.62, 95% CI 0.35–1.08); after excluding DCOR trial [53], which had substantial risk of attrition, RR was strengthened ($n = 11$, RR 0.51, 95% CI 0.32–0.83) and heterogeneity between CCPB subgroups was reduced. Mortality rarely observed in studies having <1 year follow-up; removing these studies resulted in similar effect size (RR 0.58, 95% CI 0.31–1.11). Authors conducted an NNT analysis. On average, 16 patients needed to be treated with sevel vs. CCPB for up to 3 years to prevent 1 death. In substudies, sevel decreased mortality vs. CC ($n = 6$ studies, RR 0.44, 95% CI 0.25–0.76), but not vs. CA ($n = 3$ studies, RR 0.43, 95% CI 0.13–1.38). ND in LC vs. CCPB ($n = 4$ studies, RR 0.73, 95% CI 0.18–3.00); 2 included studies had high bias risk due to selective reporting. ND in sevel vs. ICPB on mortality (3 studies, $n = 1492$, RR 1.03, 95% CI 0.38–2.99)	ND sevel vs. CCPB for CV mortality and other CV events ($n = 9$, RR 0.29, 95% CI 0.05–1.82); SS heterogeneity. Less power for LC trials; RR not reported.	Sevel had SS lower risk of hospitalization vs. CCPB (4 studies, RR 0.50, 95% CI 0.31–0.81). NNT analysis showed that 4 patients would need to be treated to prevent 1 additional hospitalization. ND in LC vs. CCPB in hospitalizations (2 studies, RR 0.80, 95% CI 0.34–1.93); analysis was underpowered	sPhos: ND in sPhos reduction in sevel vs. CCPB (MD −0.01, 95% CI −0.16 to 0.14) irrespective of CCPB type; in subgroup analysis, sevel less effective vs. CCPB in chronic HD. LC provided slightly less sPhos reduction vs. CCPB (MD 0.18, 95% CI 0.10–0.25). Similar sPhos with sevel vs. LC (3 trials). Similar sPhos with sevel vs. ICPB ($n = 1206$, MD 0.07, 95% CI −0.42 to 0.56). sCa: Lower with sevel vs. CCPB (MD −0.35, 95% CI −0.50 to −0.21) and LC vs. CCPB (MD −0.26, 95% CI −0.46 to −0.07). Similar sCa with sevel vs. ICPB ($n = 398$, MD −0.03, 95% CI −0.12 to 0.05) and with sevel vs. LC. Hypercalcemic events less with sevel vs. CCPB (RR 0.27, 95% CI 0.05–0.32) and with LC vs. CCPB (RR 0.12, 95% CI 0.05–0.32); publication bias with these analyses trended towards significance. iPTH: SS higher with sevel vs. CCPB (MD 43.5, 95% CI 11.1–75.9) and LC vs. CCPB (MD 63.3 pg/mL, 95% CI 1.5–115). Similar iPTH levels with sevel vs. ICPB based on median values from 3 studies (no meta-analysis possible)	LDL-C: Sevel (MD 20.9 mg/dL, 95% CI 18.6–23.3), but not LC (only 2 studies available) vs. CCPB had lower LDL-C. Sevel had lower LDL vs. LC (MD −20.9 mg/dL, 95% CI −29.9 to −11.9) Bone-related outcomes too sparse for meta-analyses	GI events (vomiting, diarrhea, constipation, abdominal pain, flatulence): ND in GI events sevel vs. CCPB (RR 1.27, 95% CI 0.97–1.66). GI events SS higher for LC vs. CCPB (RR 1.74, 95% CI 1.16–2.63); publication bias was SS ($p = 0.03$). GI events similar with sevel vs. ICPB (RR 1.30, 95% CI 0.61–2.78, $I^2 = 96\%$). Pruritis: Trend for higher risk with sevel vs. CCPB (RR 1.89, 95% CI 0.93–3.77). CAC: SS lower in sevel vs. CCPB (MD −101, 95% CI −160 to −41.7)

Table 2 continued

Author, year	All-cause mortality	Cardiovascular mortality or morbidity effects	Hospitalization	Serum phos, calcium or PTH	Other outcomes	Adverse drug reactions and safety effects
Wang [40], 2015	Insufficient data for meta-analysis	Insufficient data for meta-analysis	N/A	sPhos: SS lower in CA vs. CC at 4 weeks (MD −0.15 mmol/L, 95% CI −0.28 to −0.01) and 8 weeks (MD −0.25 mmol/L, 95% CI −0.40 to −0.11), even though elemental Ca dose was equal or higher in CC group. sCa: ND with CA or CC at 4 weeks (5 studies, $n = 319$, MD 0.03 mmol/L, 95% CI −0.01 to 0.07) or 8 weeks (8 studies, $n = 523$; MD 0.00 mmol/L, 95% CI −0.09 to 0.08). Hypercalcemia: ND at 4 or 8 weeks (6 studies, $n = 530$, RR 0.77, 95% CI 0.46–1.29). Ca x Phos: No difference (4 studies, $n = 290$: MD −7.58 $mmol^2/L^2$, 95% CI −17.65 to 2.49). iPTH: ND between CA vs. CC (6 studies, $n = 403$, MD −5.00 pg/mL, 95% CI −53.78 to 43.78)		SS higher risk of intolerance with CA vs. CC; i.e., more CA patients dropped out of studies vs. CC (RR 3.46, 95% CI 1.48–8.26). GI effects: NS trend towards more epigastric pain, bloating, nausea and anorexia in CA (11.9%) vs. CC (5.7%) (4 studies, $n = 351$, RR 1.96, 95% CI 0.91–4.19)

Table 2 continued

Author, year	All-cause mortality	Cardiovascular mortality or morbidity effects	Hospitalization	Serum phos, calcium or PTH	Other outcomes	Adverse drug reactions and safety effects
Jamal [136], 2013	NCCPB reduced all-cause mortality vs. CCPB (11 studies, $n = 4622$, RR 0.78; 95% CI 0.61–0.98). Results from 3 other non-RCTs consistent (RR 0.89, 95% CI 0.78–1900*), as were results from all 14 studies combined (RR 0.87, 95% CI 0.77–0.97). Results driven mainly by 1 study using LC not sevel. When individual PBs were considered, there was NS decrease in mortality with sevel (RR 0.89, 0.78–1.01) or LC (RR 0.74, 0.49–1.13) vs. CCPB; both RCT and non-RCT combined for these analyses. SS mortality differences for NCCPB vs. CCPB seen only in 5 trials reporting 24-mo outcomes. When results were evaluated by 5D vs. NDD-CKD, there was decreased mortality in both D (RR 0.88, 95% CI 0.79–0.99, SS) and NDD-CKD (RR 0.55, 95% CI 0.28–1.03, NS)	No added studies evaluated CV events. Effect estimate same as in previous paper (NS, RR 0.85, 95% CI 0.35–2.03)	Not evaluated	ND in sPhos change by treatment assignment	Not enough data for assessment of fracture incidence	CAC: NS decrease in NCCPB vs. CCPB using all time points (7 studies, $n = 704$); only SS when data from longest follow-up point for each study used. (MD in Agatson score −95.26, 95% CI −146.58 to −43.84). All trials used Agaston score to rate CAC; all but 2 studies' scans were read by assessor masked to treatment assignment

Table 2 continued

Author, year	All-cause mortality	Cardiovascular mortality or morbidity effects	Hospitalization	Serum phos, calcium or PTH	Other outcomes	Adverse drug reactions and safety effects
Zhang [43], 2013	Only 2 studies ($n = 1404$) reported all-cause mortality with LC vs. other binders. ND between LC vs. controls	Meta-analysis not possible. Only 1 study (45 patients) reported CV events; ND between LC and CCPB	Not evaluated	sPhos: LC lowered vs. placebo (5 studies, $n = 562$, MD −0.64, 95% CI −0.78 to −0.5). ND LC vs. CC (4 studies, $n = 377$, MD 0.09, 95% CI 0.00–0.19). ND LC vs. SH (1 study, $n = 84$, MD −0.09, 95% CI −0.19 to 0.01). **sCa:** ND LC vs. placebo (2 studies, $n = 235$, MD 0.05, 95% CI –0.02 to 0.12). ND LC vs. SH (1 study, $n = 84$, MD 0.02, 95% CI −0.03 to 0.07). SS higher sCa with CCPB vs. LC (4 studies, $n = 1099$, MD –0.12, 95% CI –0.15 to −0.09). Ca x Phos: SS lower in LC vs. placebo (3 studies, $n = 271$, MD –1.43, 95% CI –2.04 to −0.81). ND between LC and CC (3 studies, $n = 862$, MD –0.14, 95% CI –0.30 to 0.03). ND LC vs. SH (1 study, $n = 84$, MD –0.16, 95% CI −0.39 to 0.07). iPTH: LC lower vs. placebo (2 studies, $n = 235$, MD –95.04, 95% CI –151.10 to −38.98). ND between LC and CC (2 studies, $n = 282$, MD 112.12, 95% CI –23.43 to 247.66). ND LC vs. SH (1 study, $n = 84$, MD 14.30, 95% CI –27.83 to 56.43)	Meta-analysis not possible with 1,25-(OH)D3, 25-(OH)2D3 levels, total or BAP and cholesterol. Bone biopsy studies were not combinable as different bone parameters were evaluated	GI events: LC had less diarrhea vs. placebo (4 studies, $n = 395$, RR 0.31, 95% CI 0.15–0.65). LC had higher rate of vomiting vs. CCPB (2 studies, $n = 1058$ patients, RR 1.51, 95% CI 1.08–2.12). Hypercalcemia: LC lower vs. CCPB (5 studies, $n = 1220$, RR 0.12, 95% CI 0.04–0.38). ND found in the incidence of nausea, constipation, bronchitis, dyspepsia, rhinitis, pruritus, and dialysis complications. Meta-analysis not possible with cardiac or aortic vasc calc, CAC, bone LC concentrations (units different between studies) or CRP

Table 2 continued

Author, year	All-cause mortality	Cardiovascular mortality or morbidity effects	Hospitalization	Serum phos, calcium or PTH	Other outcomes	Adverse drug reactions and safety effects
Navaneethan [135], 2011	ND in mortality with SH vs. CCPB (10 studies, $n = 3079$, RR 0.73, 95% CI 0.45–1.16)	Not evaluated	Not evaluated	Phos: All studied PB lowered sPhos vs. placebo. SS higher sPhos with SH vs. CCPB (16 studies, $n = 3126$, MD 0.23 mg/dL, 95% CI 0.04–0.42) and higher PTH (12 studies, $n = 2551$, MD 56 pg/mL, 95% CI 26–84). Calcium: SS increase in hypercalcemia with CCPB vs. SH (12 studies, $n = 1144$, RR 0.45, 95% CI 0.35–0.59). SS lower sCa with LC vs. CCPB (2 studies, $n = 122$, MD −0.30 mg/dL, 95% CI −0.64 to −0.25) and decreased risk of hypercalcemic events (RR 0.17, 95% CI 0.09–0.31). Ca x Phos: ND in Ca x Phos in SH vs. CCPB. ND in sPhos or PTH with LC vs. CCPB, but LC SS reduced Ca x Phos vs. CCPB	sBicarb: SS lower with SH vs. CCPB (5 studies, $n = 381$; MD −1.43 mEq/L, 95% CI −2.07 to 0.79). T Chol: SS lower with SH vs. CCPB (10 studies, $n = 1705$, MD −19.16 mg/dL, 95% CI −27.42 to −10.90). Unable to assess vasc calc as included studies used different scoring systems to assess. Not enough information to compare fracture incidence, all-cause mortality for CC vs. CA, calcium load differences between CC vs. CA, all-cause mortality between LC and CCPB	GI events: SS increase with SH vs. CCPB (5 studies, $n = 498$, RR 1.58, 95% CI 1.11–2.25). SS higher constipation with SH vs. CCPB (2 studies, $n = 259$, RR 2.63, 95 CI 1.29–5.35). ND between CC or CA in gastritis, diarrhea or constipation

BAP bone-specific alkaline phosphatase, *BMD* bone mineral density, *CA* calcium acetate, *CAC* coronary artery calcification, *CC* calcium carbonate, *calc citr* calcium citrate, *Ca x Phos* serum calcium x serum phosphorus product, *CCPB* calcium-containing phosphate binder, *CI* confidence interval, *CKD* chronic kidney disease, *CRP* c-reactive protein, *CV* cardiovascular, *D* dialysis, *DCOR* Dialysis Clinical Outcomes Revisited trial, *GI* gastrointestinal, *HD* hemodialysis, *HDL-C* high-density lipoprotein cholesterol, *ICPB* Iron-containing phosphate binder, *iPTH* intact parathyroid hormone, *LC* lanthanum carbonate, *LDL-C* low-density lipoprotein cholesterol, *MD* mean difference, *N/A* Not applicable, *NCCPB* non-calcium-containing phosphate binders, *ND* no difference, *NDD-CKD* non-dialysis-dependent chronic kidney disease, *NNT* numbers needed to treat, *NS* statistically non-significant, *OR* odds ratio, *PB* phosphate binder, *phos* phosphorus, *PTH* parathyroid hormone, *RCT* randomized controlled trial, *RR* relative risk, *SS* Statistically significant, *sAlk Phos* serum alkaline phosphatase levels, *sBicarb* serum bicarbonate levels, *sCa* serum calcium levels, *sPhos* serum phosphorus levels, *sevel* sevelamer hydrochloride or sevelamer carbonate, *SH* sevelamer hydrochloride, *SC* sevelamer carbonate, *T Chol* total cholesterol, *vasc calc* vascular calcification

*1900 was reported in the article as the upper limit of 95% CI

phosphate binders versus placebo in NDD-CKD and dialysis patients reduces hard outcomes such as fractures, CV events, mortality, or hospitalizations.

3.3 Comparative Effectiveness of Phosphate Binders (Meta-Analyses)

Five separate research groups published systematic reviews with meta-analyses in 2015 and 2016 comparing the effectiveness of various phosphate binders in dialysis and NDD-CKD patients and evaluating numerous outcomes [37–41]. All included RCTs and some included quasi-RCTs. Tables 1 and 2 provide a description and key results from these meta-analyses and selected others published before 2015. Results from the most recent studies (2015/2016) are reviewed below as earlier meta-analyses did not include recent RCTs. Results from recent meta-analyses were not always congruent and potential explanations are provided below along with key results for selected outcomes.

3.3.1 Mortality

Several recent meta-analyses have compared various phosphate binders and effect on all-cause mortality. Three meta-analyses showed lower mortality rates in patients receiving sevelamer than in those receiving CCPBs [37, 38, 41]. Habbous et al. found a nonsignificant trend toward lower mortality with sevelamer [39]. The meta-analyses included different numbers of trials (8–29). Habbous et al. included the most trials, as they had no explicit criteria regarding study duration and used imputation and digitalization of graphs when numerical data were unavailable. Due to the former approach, they included several very short-duration trials with few or no events (i.e., no deaths in either study group), with the justification that exclusion of such studies may overestimate treatment effects. Simulation studies support this approach only when treatment effects are judged a priori to be unlikely [52]. There was moderate to high heterogeneity between the studies evaluated for the mortality endpoint when calcium products (carbonate, acetate) were grouped together [37–39, 41], but low heterogeneity when calcium carbonate or calcium acetate were separately compared with sevelamer [38, 39]. When calcium carbonate trials were separated from calcium acetate trials, sevelamer showed a mortality benefit compared with calcium carbonate, but not with calcium acetate [38, 39]. In sensitivity analyses with studies comparing sevelamer with CCPBs, Habbous et al. removed the Dialysis Clinical Outcomes Revisited (DCOR) trial [53] because patient attrition in that large study was high; they then observed a significant mortality benefit with sevelamer versus all CCPBs [39]. Importantly, a significant number of patients crossed over to the alternative treatment in this open-label trial, attenuating differences between sevelamer and calcium groups. In contrast, in another sensitivity analysis, Palmer et al. removed the INDEPENDENT study [54], which showed a much larger benefit of sevelamer versus CCPBs than other studies. Once this study was excluded, study heterogeneity changed from moderate–high to low, and sevelamer no longer showed a significant positive mortality effect compared with CCPBs. Overall, data from these meta-analyses suggest that sevelamer products reduce mortality in CKD patients compared with CCPBs, but statistical significance lost or gained by removing a single clinical trial is concerning. Mortality benefits of one phosphate binder versus another would be expected to appear only longer term. All of these meta-analyses included short- and longer-duration trials; the Habbous et al. meta-analysis [39] in particular included many more short-term trials with low or no events, likely explaining a non-significant trend toward fewer deaths with sevelamer versus CCPBs.

Results from three of four meta-analyses [37, 38, 41] are supported by a comparative effectiveness observational study, which showed that treatment with sevelamer was associated with a 6% lower risk of death compared with calcium acetate in 35,251 incident US hemodialysis patients, using propensity-score matched cohorts [55]. They used linked data from the United States Renal Data System (USRDS) and Medicare Part D; the main limitation was that laboratory data were not included, so it is unclear whether baseline phosphorus and calcium levels were similar in both cohorts. Strengths are the large numbers and data representing real-world use rather than RCT conditions where medication adherence may be better. The effect size in this study was modest and translated to approximately 44 patients needed to treat at 2 years [56] to prevent one death. However, since no phosphate binder type has been demonstrated to reduce mortality compared with no treatment/standard care/placebo in clinical trials, none of these studies can determine whether the lower mortality rate with sevelamer compared with CCPBs represents a superior sevelamer effect or harm from CCPBs or both.

No other phosphate binder types were shown to be superior with regard to mortality endpoints in these meta-analyses. Figure 2 shows results of a pair-wise comparison from Palmer et al.'s network meta-analysis [37]. However, fewer trials compared lanthanum-, iron-, and magnesium-based binders to CCPB or sevelamer products.

3.3.2 Cardiovascular Mortality and Vascular Calcification

The main hypothesized putative mechanisms for improved survival with sevelamer versus calcium are reduced

Sevelamer					
0.50 (0.09, 2.65)	Lanthanum				
0.39 (0.21, 0.74)	0.78 (0.16, 3.72)	Calcium			
1.04 (0.27, 3.97)	2.08 (0.26, 16.5)	2.67 (0.63, 11.4)	Iron		
0.71 (0.09, 5.46)	1.42 (0.12, 17.4)	1.82 (0.23, 14.7)	0.68 (0.07, 6.40)	Colestilan	
0.47 (0.08, 2.59)	0.93 (0.11, 8.05)	1.20 (0.21, 6.77)	0.45 (0.08, 2.66)	0.66 (0.10, 4.29)	Placebo

Fig. 2 Network estimated odds (ORs) of phosphate binders on all-cause mortality. Values are given as OR (95% CI). The table should be read from *left* to *right*. Risk estimate is for the column-defining treatment compared to the row-defining treatment. An OR of <1 indicates the column treatment is associated with a lower odds of mortality than the row treatment. For example, sevelamer treatment lowers the odds of all-cause mortality compared to calcium treatment (OR 0.39, 95% CI 0.21–0.74). *Bolded* numerals indicate statistically significant results. The heterogeneity tau (τ) for the network analysis was 0.74 (indicative of moderate-high heterogeneity). There were 20 studies involving 6376 participants included in the network. *OR* odds ratio, *CI* confidence interval. Reprinted with permission under the terms of the Creative Commons Attribution-Non-Commercial-No Derivatives License (CC By ND ND); http://creativecommons.org/licenses/by-nc-nd/4.0. Figure citation is Palmer et al. [37]

progressive vascular and coronary artery calcification (CAC). Six of nine studies found that CCPBs produced more severe and/or rapid CAC increases than sevelamer [38]. Although two meta-analyses also showed a significant CAC reduction with sevelamer versus CCPBs [37, 39], no meta-analysis has shown that CV mortality is significantly reduced [37–39]. This is unsurprising given the heterogeneity between studies. In addition, the power to detect differences is less for CV mortality than for all-cause mortality.

A large open-label Japanese RCT is in progress comparing lanthanum carbonate and calcium carbonate regarding survival time free of CV events, which may clarify the relative CV effects of this non-CCPB [57].

3.3.3 Hospitalization

In meta-analyses evaluating hospitalization, calcium was significantly associated with increased hospitalizations versus sevelamer [39], but not versus non-CCPBs [41]. St. Peter et al. conducted a secondary analysis of DCOR trial data, the largest long-term RCT to date comparing sevelamer with CCPBs. They linked DCOR clinical data with USRDS registry data to obtain more hospitalization data than were collected through case report forms, as many patients terminated the study early and were lost to follow-up [58, 59]. In an intent-to-treat analysis, they found that sevelamer versus CCPBs was associated with an 11% reduction in multiple hospitalizations ($p = 0.02$) and a 12% reduction in hospital days ($p = 0.03$) in a mean of 2.1 years of follow-up.

3.3.4 Interpretation of Comparative Effectiveness Literature

Interpretation of findings from meta-analyses must be tempered by the limitations of the underlying studies. Many studies providing data for meta-analyses had several limitations (Table 1), including inadequate blinding and duration too short to allow assessment of several outcomes. These meta-analyses included short- and longer-duration trials, and they had different criteria for including trials. For instance, the Habbous et al. meta-analysis [39] included many more short-term trials with low or no events, likely explaining a non-significant trend toward fewer deaths with sevelamer versus CCPBs. There was often significant heterogeneity between studies, particularly for meta-analyses evaluating mortality as an outcome. Sensitivity analyses from two meta-analyses showed that statistical significance for mortality effects could be lost or gained by removing a single clinical trial. Results from meta-analyses are only as good as the clinical trials that underlie them, and the overall quality of clinical trials in the phosphate binder space is not great. Meta-analysis cannot make up for poorly designed trials or trials carried out with inadequate study duration or power to assess hard clinical endpoints.

4 Potential Value-Added Therapy: Iron-Containing Phosphate Binders

As ICPBs are relatively new to the market, too few data are available to evaluate them in meta-analyses for hard clinical endpoints. Anemia is a ubiquitous complication of

CKD, and it affects most patients with ESRD requiring dialysis. Treatment includes both erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron. While ESAs have led to decreased need for blood transfusions in CKD patients, multiple RCTs have demonstrated that ESA treatment targeted to normal hemoglobin levels (13–15 g/dL) increases risks of death, CV complications, and stroke in CKD [60–62]. Additional concerns relate to increased use of IV iron, including the potential risk of infection and limited information regarding long-term safety. Novel strategies to reduce ESA and IV iron use may therefore improve clinical outcomes in dialysis patients. Recently, two iron-based phosphate binders, sucroferric oxyhydroxide and ferric citrate, became available in clinical practice and may provide an approach that simultaneously addresses hyperphosphatemia and anemia.

4.1 Sucroferric Oxyhydroxide

Sucroferric oxyhydroxide (Velphoro®, Vifor Fresenius Medical Care Renal Pharma) was approved by the US FDA in November 2013 and by the European Medicines Agency (EMA) in August 2014, with indications only in dialysis patients. In a phase III trial including 1059 hemodialysis patients randomly assigned to sucroferric oxyhydroxide or sevelamer carbonate, effects on serum phosphate were similar [63]. There was no significant difference between treatment groups in serum ferritin (a measure of storage iron) at 24 weeks, but there was a modest, significant effect of sucroferric oxyhydroxide on transferrin saturation (+4.0% points) [64]. This effect was concentrated in patients with low serum ferritin (<310 ng/mL) at baseline. There were also modest reductions with sucroferric oxyhydroxide in percentages of patients receiving IV iron and ESAs. Results from the extension study (28 additional weeks) indicated no differential effects on serum phosphate, intact parathyroid hormone, or calcium [65]. Effects of sucroferric oxyhydroxide on serum ferritin, transferrin saturation, and hemoglobin were also non-significant. This study demonstrated that iron absorption is not significant with this product.

Phase II and III studies in Japanese hemodialysis patients have shown that sucroferric oxyhydroxide reduced serum phosphate in a dose-dependent manner, with decreases of 1.8, 2.7, 3.2, and 3.8 mg/dL with dosages of 750, 1500, 2250, and 3000 mg/day, respectively [66]. Relative to dosages of 750 or 1500 mg/day, dosages of 2250 or 3000 mg/day more strongly increased calcium and decreased intact parathyroid hormone. However, no dose-dependent effects of sucroferric oxyhydroxide on anemia parameters have been observed. Relative to sevelamer hydrochloride, sucroferric oxyhydroxide significantly increased the percentage of patients with serum phosphate in the target range (82.0 vs. 67.4%) with decreased pill burden (5.6 vs. 18.7 tablets/day) [67].

4.2 Ferric Citrate

Ferric citrate (Auryxia®, Keryx Biopharmaceuticals) was approved by the US FDA in September 2014 and by the EMA in September 2015. Indications in the USA are only for dialysis patients, whereas indications in Europe are for dialysis and NDD-CKD patients. Among 151 hemodialysis patients in a phase II study, ferric citrate reduced serum phosphate in a dose-dependent manner, with little reduction at one tablet/day and significantly larger reductions at six to eight tablets/day [68]. In a phase III trial of 441 hemodialysis patients randomly assigned to ferric citrate or placebo control for 4 weeks and active control with calcium acetate and/or sevelamer carbonate for 52 weeks, ferric citrate versus placebo control significantly reduced serum phosphate, but ferric citrate versus active control had no effect on serum phosphate [69]. Relative to active control, ferric citrate significantly increased transferrin saturation (+9.5%), serum ferritin concentration (+282 ng/mL), and hemoglobin (+0.33 g/dL). Moreover, ferric citrate decreased IV iron use by 12.5 mg/week and ESA use by 1191 IU/week [70]. At the end of the trial, 3.9% of patients with ferric citrate and 14.1% with active control were receiving more than 70 mg/week of IV iron.

Interestingly, during the active control phase, 34.6% of ferric citrate users were hospitalized at least once, whereas 45.6% of active control users were hospitalized at least once (risk reduction, 24.2%) [71]. Hospitalization rates were 0.63 admissions per patient-year with ferric citrate and 0.83 admissions per patient-year with active control, although this difference was nominally non-significant ($p = 0.08$).

In Asia, ferric citrate hydrate (Riona®, Torii Pharmaceutical Company) has been compared with sevelamer hydrochloride in several studies. In a trial of 230 Japanese hemodialysis patients, ferric citrate hydrate versus sevelamer hydrochloride had no significant effect on serum phosphorus, a small positive effect on calcium, and no effect on intact parathyroid hormone. However, ferric citrate hydrate significantly increased serum ferritin, transferrin saturation, and hemoglobin [72]. Conversion of 27 Taiwanese hemodialysis patients from sevelamer hydrochloride to ferric citrate hydrate significantly decreased serum intact FGF23 and increased serum intact parathyroid hormone after 12 weeks [73]. Finally, ferric citrate hydrate also appeared to effectively lower serum phosphorus in peritoneal dialysis patients [74].

Both ferric citrate and ferric citrate hydrate have been studied in NDD-CKD patients. In an RCT including 149 NDD-CKD patients [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2], ferric citrate decreased serum

phosphorus, increased transferrin saturation, and increased hemoglobin [75]. In a more recent and larger trial, significantly more NDD-CKD patients on ferric citrate (52%) than on placebo (19%) achieved a 1.0 g/dL or more hemoglobin increase at any time during 16 weeks of follow-up [76]. In a phase III trial of 90 NDD-CKD patients (mean eGFR 9.2 mL/min/1.73 m^2) in Japan, ferric citrate hydrate versus placebo reduced serum phosphorus by 1.3 mg/dL [77]. Both ferritin and transferrin saturation increased with ferric citrate hydrate versus placebo, but the effect of ferric citrate hydrate on hemoglobin was not significant.

One potential safety concern with ferric citrate is iron overload. In the phase III trial of ferric citrate in hemodialysis patients, 10.4% of patients on ferric citrate achieved serum ferritin >1500 ng/mL more than once during the trial, compared with 1.3% of patients on active control [78]. One case of hemochromatosis was confirmed by liver biopsy among patients on ferric citrate; this patient did not undergo genetic testing for hereditary hemochromatosis [70]. Furthermore, transferrin saturation of >80% was observed only in patients on ferric citrate, although occurrences were rare [70]. Because of the potential for iron accumulation, the US FDA suggests that ferritin and transferrin saturation levels should be monitored regularly in ferric citrate users.

Another potential safety concern with ferric citrate is citrate itself. Citrate is known to increase absorption of dietary aluminum, possibly leading to tissue accumulation of aluminum in CKD patients, especially those who are anuric [79]. In the phase III trial of ferric citrate in dialysis patients, median serum aluminum increased from 6.0 mcg/L at baseline to 7.0 mcg/L after 52 weeks of ferric citrate, while median serum aluminum was unchanged with active control; the difference was nominally non-significant ($p = 0.1$), but power was limited by sample size ($n = 185$) [80].

In summary, sucroferric oxyhydroxide and ferric citrate represent potentially useful ICPBs. Sucroferric oxyhydroxide has limited effects on anemia parameters or IV iron use. Alternatively, ferric citrate appears to exert positive effects on anemia parameters, while lowering concomitant use of IV iron and ESAs. Results regarding ICPBs are limited by a dearth of data in clinical applications outside of protocol-driven trials. Post-market studies of both agents are needed to better understand real-world health and economic effects.

5 Incremental Improvements in Adherence

5.1 Key Reasons for Non-adherence with Phosphate Binders

A recent systematic review noted that non-adherence to phosphate binders ranged from 13.9 to 98.6% with an average of 52.5% [81]. Medication factors significantly associated with non-adherence include total pill burden, knowledge about phosphate binder medicines, total number of phosphate binders prescribed, medication regimen complexity (frequency and dosage schedule), and medication cost. Beliefs about the necessity of phosphate binders, poor tolerance or side effects, and large tablet size were the most common reasons given by patients to explain non-adherence [81].

A large US hemodialysis organization reviewed 30,933 patient records that gave a reason for phosphate binder discontinuation. The most common reasons related to hypophosphatemia and hypercalcemia. The second most common reason was patient inability to tolerate the medication. Lanthanum accounted for 14% of total discontinuations and 40% of discontinuations due to inability to tolerate. Lanthanum was also associated with a higher proportion of discontinuations due to difficulty chewing/swallowing pills (49% lanthanum; 36% sevelamer; 14% calcium acetate) and patients "refusing" (47% lanthanum; 36% sevelamer; 16% calcium acetate) [82]. These results are consistent with a small comparative study of patients switching from sevelamer to lanthanum carbonate, which noted that 31% of patients returned to sevelamer because of dislike of the chewable tablet formulation, despite lanthanum's significantly lower pill burden (13.9 tablets vs. 7.7 tablets) [83]. A study of 7299 US Medicare hemodialysis patients found that sevelamer patients were significantly more adherent by prescription refills and had fewer gaps in medication possession than calcium acetate patients. Comparison with lanthanum was not performed [84]. The phase III trial of ferric citrate noted more discontinuations in ferric citrate versus active control arm (33 vs. 23%), largely due to gastrointestinal side effects (diarrhea, bloating). In this trial, patients with a previous intolerance to calcium acetate or sevelamer carbonate were excluded, so the discontinuation rate may be higher in real-world use [69]. These studies indicate that adverse effects and insurance coverage should be considered and followed up to aid adherence.

5.2 Patient Preference in Phosphate Binder Selection

Patient phosphate binder preferences were examined in a study of patients currently receiving a combination of two or three phosphate binders or who had been recently switched from high-dose sevelamer to lanthanum carbonate; 54.5% did not like their prescribed phosphate binder. These patients had a significantly greater risk of high phosphate levels, which was linked to non-adherence by a validated patient questionnaire. Calcium acetate was the preferred phosphate binder for 47.1%, lanthanum carbonate for 40%, sevelamer for 20.6%, and aluminum hydroxide

for 19.4%. Lanthanum received negative ratings because patients did not like the chewable tablets (17.7%), sevelamer because the tablets were too large (13.2%) and many tablets were required daily (27.2%), and aluminum hydroxide because of gastric intolerance (19.4%) and bad taste (22.2%). Calcium acetate received little patient complaint (<5%). Interestingly, non-adherent patients demonstrated significantly greater knowledge of the use and importance of their phosphate binders, likely because they had received more education on phosphorus from their hemodialysis health care team [85].

5.3 Phosphate Binder Dose Equivalency and Pill Burden

Pill burden differs between phosphate binders depending on phosphate binding efficacy. Table 3 outlines the equivalent doses of each phosphate binder relative to the phosphorus binding capacity of 1 g calcium carbonate. The only agents with a higher binding capacity and, hence, lower pill burden than calcium carbonate are lanthanum and sucroferric oxyhydroxide. However, as noted, lanthanum was associated with a high proportion of discontinuations due to intolerance. Thus, pill burden alone is not enough to ensure adherence; the drug must also be well tolerated with few side effects. Tablet for tablet, sucroferric oxyhydroxide has the highest phosphate binding capacity and the lowest phosphate binder equivalent dose among several phosphate binders, thereby reducing pill burden and increasing the likelihood of achieving target serum phosphorus [86, 87]. However, gastrointestinal side effects, including diarrhea and fecal discoloration, were much more common with sucroferric oxyhydroxide than with sevelamer carbonate in a phase III trial. Importantly, more treatment-emergent adverse events leading to discontinuation occurred with sucroferric oxyhydroxide (15.7%) than with sevelamer carbonate (6.6%). Unfortunately, this significantly lower pill burden (five tablets/day less with sucroferric oxyhydroxide) produced an absolute adherence improvement of only 5.4% compared with sevelamer carbonate over 24 weeks [63].

The binding efficacies in Table 3 should be considered only a general guide, as phosphate removal can vary widely among individual patients [30]. For example, high-dose (4.3-g) calcium acetate was given before a test meal containing 345 mg of phosphate. The observed reduction in phosphate absorption ranged from 97.5 to 234 mg per dose, a 2.4-fold difference between patients [30, 88]. Another little-recognized issue is the possible nonlinear relationship between phosphate binder dose and efficacy [30]. This has been demonstrated for sevelamer; doses exceeding nine tablets per day are associated with significantly decreased phosphate binding per tablet compared with fewer tablets per day. A study of 24 healthy individuals under controlled conditions found that phosphate binding assessed by urinary phosphate excretion was 246 mg with 7.5 g (approximately nine tablets) of sevelamer and 341 mg with 15 g (approximately 18 tablets). Doubling the dose led to only an additional 95 mg of phosphate binding [30, 89]. Thus, even if patients are adherent to very high prescribed doses of phosphate binders, the benefit may be minimal.

5.4 Patient Empowerment in Determining Daily Phosphate Binder Dose

A unique approach to phosphate binder prescription allows for patient empowerment with self-adjustment of phosphate binders based on the phosphorus content of each meal, similar to patients with diabetes adjusting insulin dosing based on carbohydrates. The Phosphate Education Program provides phosphorus units (PU), 1 PU per 100 mg phosphorus, for food groups (e.g., meat, cheese, vegetables, dairy). After estimating the meal PU content (e.g., any meat, 150 g = 3 PU), patients self-adjust their phosphate binder doses according to a prescribed phosphate binder-to-PU ratio. This ratio is adjusted by measuring serum phosphate levels and correcting until phosphate targets are obtained [90]. In a small prospective study of 16 children with NDD-CKD stage 4–5 or receiving hemodialysis or peritoneal dialysis, serum phosphate levels above 1.78 mmol/L (>5.5 mg/dL) decreased from 63 to 31% and the mean daily intake of phosphate binders increased from 6.3 to 8.2 tablets per day with no reduction in dietary phosphate intake. The children were able to give up significantly fewer favorite foods high in phosphate such as meat, fast food, and chocolate [91]. Studies examining the effects of the Phosphate Education Program on adherence in more patients are needed. This approach would not be effective for uncooperative or unmotivated patients.

5.5 Association of Phosphate Binder Adherence with Mortality

Adherence and mortality were examined in a large observational cohort study of elderly incident hemodialysis patients in the USA who were started on calcium acetate or sevelamer hydrochloride or carbonate [55]. Adherence was determined based on prescription record refill records. All-cause mortality rates were significantly lower for adherent calcium acetate and adherent sevelamer patients than for non-adherent patients. These results are unsurprising; many observational studies have shown that outcomes are better for medication-adherent than for non-adherent patients, but some of this has been attributed to a healthy user effect [92]. Despite patients being well-matched for known

Table 3 Dosages of selected phosphate binders required to reach a phosphorus binder equivalent dose (PBED). Table is reprinted with permission from Coyne [139]

Phosphate binder	Tablet strength (mg)	Phosphate binder equivalent dose (to 1 gram $CaCO_3$) per tablet	Dose of binder needed to reach a PBED of 6 g/day[a]	Approximate number of tablets to reach PBED of 6 g/day	Grams of calcium in 6 g PBED dose
Calcium carbonate	750	0.75	6	8	2.4
Calcium acetate	667	0.67	6	9	1.5
Osvaren (Mg carbonate + Ca acetate)	435/235	0.75	–	8	0.5
Lanthanum	500[b]	1.0	3	6	0
Sevelamer carbonate	800	0.60	8	10	0
Sucroferric oxyhydroxide	500	1.6[c]	1.5	3.75	0
Ferric citrate	210	0.64[c]	2	9	0

[a] In US dialysis patients, PBED averages around 6 g/day. This means that patients require 6 g/day of calcium carbonate to control their serum phosphorus

[b] Tablets are sold by weight of lanthanum and not of lanthanum carbonate

[c] The equivalent doses of sucroferric oxyhydroxide and ferric citrate are based on single randomized controlled trials versus sevelamer (Floege et al. [63]) or vs. sevelamer and calcium acetate (Lewis et al. [69]), respectively. Thus, the equivalent dose is not as precise as for other binders where multiple studies were considered

characteristics, unmeasured characteristics that differ for adherent and non-adherent patients confound the relationship between medication adherence and clinical outcomes. Of more interest was the finding of no survival advantage for adherent sevelamer versus adherent calcium acetate users [55]. If the putative mechanism underlying the advantage of sevelamer over CCPBs is lower vascular and coronary calcification over time, then adherent CCPB users should be increasingly disadvantaged over time with increased cumulative calcium body burden. The limitation of this study was that laboratory values were not available, so patients could not be matched on baseline calcium, phosphorus, or intact parathyroid hormone concentrations, which may have affected findings.

The important relationship between medication non-adherence and CV or mortality outcomes is difficult to determine because most RCTs in dialysis patients do not adequately or consistently report medication adherence. A recent systematic review noted that only five of 21 RCTs examining CV or mortality endpoints in dialysis patients reported medication adherence [93].

6 Incremental Cost-Effectiveness of Phosphate Binders

6.1 Hemodialysis

A recent systematic review examined the cost-effectiveness of phosphate binders in adult hemodialysis patients and concluded that a CCPB, calcium acetate, appeared to be the most cost-effective therapy for first-line use in prevalent patients [incremental cost-effectiveness ratio (ICER) £8197 (US$11,818)/quality-adjusted life year (QALY) gained] [94]. Sevelamer hydrochloride and carbonate and lanthanum carbonate were the only non-CCPBs included. In prevalent patients, their cost-effectiveness was inconsistent between studies, with ICERs from US$26,835 to over US$100,000/QALY gained. In incident patients, CCPBs were cost-effective first line, but second-line lanthanum carbonate offered good value for money in two studies, with ICERs ranging from US$11,461 to US$11,525/QALY gained [94]. The major limitation of these lanthanum studies was that lanthanum effectiveness was based on changes in a surrogate marker, serum phosphorus [95]. The cost-effectiveness of lanthanum needs confirmation by a model based on clinical trials with mortality or other hard clinical endpoints as the primary outcome [95]. Systematic review authors noted that the overall quality of included studies was suboptimal, especially studies funded by pharmaceutical companies, which were the majority (67%). These studies were also significantly more likely to report ICERs favoring the sponsor's product [94]. Firm conclusions were not possible in the systematic review due to study quality heterogeneity.

The National Institute for Health and Care Excellence (NICE) hyperphosphatemia in CKD cost-effectiveness analysis received a perfect quality assessment score in the aforementioned systematic review [94, 96, 97]. This analysis favored first- and second-line calcium acetate use in

prevalent dialysis patients [96]. This cost-effectiveness model found that sevelamer resulted in an ICER of £87,916 (US$107,139)/QALY gained. Lanthanum carbonate accrued marginally greater health gains but at a much higher cost. Lanthanum was "extendedly dominated" so that regardless of the maximum acceptable ICER, better value was achieved by using calcium acetate or sevelamer hydrochloride. The authors also noted that if receiving calcium acetate indefinitely was a clinically appropriate option, switching to a non-CCPB would be hard to justify, as the ICERs for a switch are £38,078 (US$46,403)/QALY gained and £42,683 (US$52,246)/QALY gained for sevelamer hydrochloride and lanthanum carbonate, respectively. Even when a total serum calcium level of 3 mmol/L (12 mg/dL) was used as a switching point, the ICER for sevelamer hydrochloride remained above £30,000 (US$36,721)/QALY gained. The authors noted that it was unlikely that health gains provided by non-CCPBs were sufficient to counterbalance the extra expense unless society's maximum acceptable ICER threshold is £40,000 (US$48,962)/QALY gained [96].

A cost-effectiveness study of sucroferric oxyhydroxide versus sevelamer carbonate in hemodialysis patients showed that quality-adjusted survival was less with sucroferric oxyhydroxide; the ICER was £22,621 (US$27,689)/QALY gained compared with sevelamer. Future studies are needed, as assumptions regarding mortality and discontinuations due to adverse events were made [98]. Only cost-savings, not cost-effectiveness, models of ferric citrate have been published [71, 99–101]. In the context of 2013 Medicare reimbursement rates for phosphate binders, a reduction in hospitalization rates using ferric citrate could save approximately $3000 per patient per year [71]. Based on data from a phase III trial, conversion from active control to ferric citrate reduced annual ESA use by roughly 130,000 IU per patient and annual IV iron use by roughly 2000 mg per patient. Again, in the context of 2013 Medicare reimbursement rates, these reductions could save approximately $2100 per patient per year [100]. A Monte Carlo analysis suggested that total conversion of the US dialysis population from prevailing phosphate binders to ferric citrate could save between $3 and $4 billion per year [99]. However, these models are limited in that no large-scale phase III or IV studies confirm the cost-savings associated with ESAs, IV iron, and reduced hospitalization costs associated with the ferric citrate use [69]. Studies are also needed to confirm the efficacy of ferric citrate in improving anemia in patients with significant or long-standing iron deficiency [69]. The economic consequences of lower utilization with ferric citrate may be substantial, although ferric citrate may be a double-edged sword, as low adherence may result in inadequate control of both hyperphosphatemia and anemia.

In summary, the inconsistent results from these cost-effectiveness studies are due to different patient populations (e.g., prevalent vs. incident), study designs (e.g., Markov model vs. trial-based), source of efficacy (e.g., phosphorus control vs. survival), costs included (e.g., dialysis), different drugs compared, survival assumptions and studies conducted in several countries with different health care system costs [94].

6.2 Non-dialysis-Dependent CKD

Cost-effectiveness studies in NDD-CKD patients have been published [102–105]. They have numerous limitations including limited efficacy data for this population. Patient-level data in these studies was derived from 107 patients treated with sevelamer [103, 105], 14 [104] to 105 treated with calcium carbonate [103, 105], 14 treated with calcium acetate [104], and 56 treated with lanthanum [102–104]. As noted in the NICE hyperphosphatemia guideline update, the evidence for phosphate binders in NDD-CKD patients is insufficient to provide a worthwhile cost-effectiveness model [106]. Current clinical guidelines for NDD-CKD patients no longer recommend specific phosphate targets, as definitive evidence of the benefits of reducing phosphate levels is lacking [34]. However, specific phosphate targets of less than 4.6 mg/dL or less than 5.5 mg/dL were included in these models. Of note, the cost-effectiveness of non-CCPBs in NDD-CKD patients is mainly driven by the assumption that improved phosphate control has a direct effect on delaying the start of dialysis. However, evidence is needed to confirm this assumption [106]. For example, in a study that concluded that first-line sevelamer was cost effective versus calcium carbonate, the results were most sensitive to assumptions regarding the impact of sevelamer on dialysis initiation [103, 107]. Another study concluded that lanthanum carbonate was cost effective as a second-line agent again due to delayed CKD progression and dialysis initiation [102]. However, in this study, CCPBs were less costly and more effective at lowering serum phosphorus even as second-line therapy [107], as only 18.8% of patients with elevated serum phosphorus levels responded to lanthanum and the remaining 81.2% were switched back to CCPBs [102]. All NDD-CKD studies have been funded by pharmaceutical companies, and it has been noted that cost-effectiveness studies sponsored by industry significantly favor the sponsor's product [94, 108–110]. The lack of country-specific data for cost-effectiveness modeling inputs is another limitation. Country-specific practice pattern data and drug cost data are needed as race, health care system, and other patient characteristics vary the results [95, 111].

6.3 Summary for Cost-Effectiveness of Phosphate Binders

Future high-quality, cost-effectiveness evaluations are needed to confirm the findings noted for hemodialysis and NDD-CKD patients. The basis of excellent cost-effectiveness analyses is results from well-designed, high-quality, placebo-controlled, comparative clinical trials evaluating important clinical outcomes; these are sadly lacking for phosphate binders. Thus results of these cost-effectiveness studies cannot be considered definitive due to the limitations mentioned and should be interpreted with caution [95, 104, 107]. Medication adherence and influence of pill burden on quality of life were not included in any of the models due to lack of information. Sevelamer hydrochloride and carbonate are off patent in many countries, and generic formulations may significantly reduce the acquisition cost and thus cost-effectiveness calculations [112].

7 Potential Incremental Effectiveness or Safety of Phosphate-Binding Agents in Development

Newer agents to reduce phosphorus have been evaluated in CKD patients and include resin-based binders, salivary phosphorus-binding agents, and agents that target intestinal phosphate transporters. While consideration of new agents is encouraging, comparative effectiveness data are sparse. Overall, these agents have thus far not offered advantages over sevelamer, the binder that has been evaluated in some smaller comparative studies to date.

7.1 Targeting Intestinal Phosphate Transport

7.1.1 Nicotinamide

Nicotinamide is an amide derivative of niacin (nicotinic acid) that inhibits sodium-dependent phosphate co-transport in the renal proximal tubule (Na/Pi2a) and in the intestine (Na/Pi2b) to decrease phosphorus uptake. Nicotinamide has less risk of causing a flushing reaction, making it a more viable option for long-term administration. Trials to date in relatively small numbers of ESRD patients have shown that nicotinamide when added to other phosphate-binding agents lowers phosphate in dialysis patients while also increasing high-density lipoprotein cholesterol, although flushing reactions were reported [113–115]. Doses ranged from 100 to 750 mg (200–1500 mg per day).

Limited data are available on the effect of nicotinamide as a single agent. Recent results from the NICOREN study showed similar phosphate-lowering effects of nicotinamide compared with sevelamer in 100 hemodialysis patients after 24 weeks of treatment in this open-labeled study; however, adverse effects increased in the nicotinamide group, leading to greater treatment discontinuation [116]. One concern with nicotinamide is accumulation of the metabolite *N*-methyl-2-pyridone-5-carboxamide (2PY), a potential uremic toxin with effects including thrombocytopenia [117]. This metabolite was increased during the treatment period in the NICOREN study. Potential adverse effects reported with nicotinamide include flushing, diarrhea, nausea, and thrombocytopenia [118].

Nicotinamide effectiveness for phosphate lowering in the NDD-CKD population has not been extensively explored. Currently, the CKD Optimal Management with Binders and Nicotinamide (COMBINE) trial is underway. It will compare nicotinamide 1500 mg daily, lanthanum carbonate 1000 mg three times daily, combined therapy, and double placebo in approximately 200 individuals with eGFR 20–45 mL/min/1.73 m^2 [118]. The primary outcomes are changes in serum phosphate and FGF23 over the 12-month treatment period. Secondary outcomes include changes in bone and mineral metabolism markers (i.e., parathyroid hormone, calcitriol, klotho), surrogate CV disease markers (left ventricular mass index), and surrogate measures of CKD progression and inflammation. Results are expected in 2018.

7.1.2 Tenapanor

Tenapanor inhibits the gastrointestinal sodium/hydrogen exchanger isoform 3 (NHE23) to reduce sodium and phosphate absorption; they are not appreciably absorbed. These attributes have led to investigation of this agent for treatment of hyperphosphatemia and for constipation-predominant irritable bowel syndrome in human trials [119, 120]. Dose-dependent reductions in serum phosphate were observed in a placebo-controlled trial of tenapanor in 162 hemodialysis patients with hyperphosphatemia using six different regimens: 3 or 30 mg administered once daily or 1, 3, 10, or 30 mg administered twice daily (range 2–60 mg daily), taken before meals [119]. There was significant reduction in serum phosphate compared with placebo; after 4 weeks of treatment, the largest reduction in phosphate was with 10 and 30 mg twice daily dosing. The main adverse effect of tenapanor was diarrhea. Completion rates were lower for tenapanor (50–83%) compared with placebo (85%), with adverse effects accounting for study discontinuation in 27% of tenapanor patients. Tenapanor's phosphate-binding effect has been shown to be similar whether it is administered before or after meals. Drug interactions with drugs metabolized by the CYP450 3A4 pathway are not expected with tenapanor based on drug interaction studies with midazolam [121]. Future studies providing more information on dosing and adverse effects

are needed before this agent can be approved for use in CKD patients with hyperphosphatemia.

7.2 Resin-Based Binders (Colestilan, Bixalomer)

Colestilan (BindRen®, Mitsubishi Tanabe Pharma Corporation) is a non-absorbable, non-ionic, ion-exchange resin that binds phosphorus and bile acids in the gastrointestinal tract [122]. It is marketed for hypercholesterolemia in Japan and for hyperphosphatemia in Austria, Germany, Portugal, and the UK. Reduction in blood glucose and hemoglobin A1c levels has also been reported. The recommended starting dosage for hyperphosphatemia is 6–9 g daily with a maximum dosage of 15 g per day. Studies have shown colestilan to be effective in lowering phosphorus as well as low-density lipoprotein cholesterol, effects that were sustained over longer-term (52-week) treatment [122, 123]. In general, colestilan is well tolerated, with gastrointestinal effects including nausea, vomiting, and diarrhea the most common adverse events reported [123]. Potential advantages may include the pleiotropic effects from observed low-density lipoprotein cholesterol reductions in addition to uric acid level reductions; however, direct comparison studies with CCPBs and sevelamer have not been conducted to date and further development of this agent for hyperphosphatemia is not being pursued by the company. It is currently no longer available in Europe.

Bixalomer (Kiklin®, Astellas Pharma Inc.) is an amine-functional polymer available in Japan since 2012. It is effective in lowering phosphorus and may have fewer gastrointestinal adverse effects, including less diarrhea, reflux, constipation, and abdominal pain, a finding observed in hemodialysis patients switched from sevelamer hydrochloride to bixalomer [124]. However, the improvement in gastrointestinal symptoms is not a consistent finding among trials [125]. The potential differences in gastrointestinal side effects may be due, in part, to less expansion of bixalomer in the gastrointestinal tract, compared with sevelamer, from lower water adsorption. Bixalomer is currently available only in Japan.

7.3 Salivary Phosphorus-Binding Agents (Chitosan)

Agents that bind salivary phosphorus were investigated based on the fact that salivary phosphorus levels are higher than serum levels, particularly in patients with advanced NDD-CKD and ESRD [126]. Chitosan is a polymer of glucosamine and is derived from chitin, a natural fiber from crustacean shells. The polymer and amino residue of chitosan binds with phosphorus, which was the basis for developing a chewing gum (HS219) containing 40 mg of chitosan. Earlier studies showed that a gum containing 20 mg of chitosan when chewed for 1 h twice daily for 2 weeks was effective in lowering phosphorus in dialysis patients (31% reduction in serum phosphorus). Unfortunately, these results have not been duplicated in subsequent studies [127, 128]. The phosphate binding capacity of this agent is relatively low (estimated as 0.87 mg of phosphate bound with a 20-mg dose of chitosan gum) [129]. Chitosan is not being pursued as a viable phosphate-binding agent.

7.4 Other Phosphate-Binding Agents in Development

TRK-390 [copoly(allylamine/N^1,N^3-diallylpropane-1,3-diamine) acetate] is a polymer with higher selectivity for phosphate than sevelamer, with phosphate binding less affected by fat compared with sevelamer [130]. Another polymer under development is Genz-6444470, a non-absorbed polymer that has been studied in hemodialysis patients. It was effective in lowering phosphorus with a dose-dependent effect, but did not offer any advantage regarding phosphate lowering or tolerability compared with sevelamer [131].

SBR759 is a polymeric complex composed of iron (III) and starch that has been studied in phase I clinical trial in 44 hemodialysis patients [132]. In this open-label study, patients previously on a stable dose of sevelamer hydrochloride or a CCPB were given SBR759 in dosage levels ranging from 3.75 to 22.5 g/day for 4 weeks. Doses were titrated based on safety and tolerability up to 15 g/day. The highest dosage, 22.5 g/day, was used to test tolerability at supratherapeutic doses. More adverse reactions were experienced at this dose. Serum phosphorus decreased significantly across the dose range evaluated, and this drug was well tolerated. This agent has shown comparable phosphate-lowering effects with lower pill burden and adverse events than sevelamer hydrochloride in a 12-week study in Japanese and Taiwanese hemodialysis patients [133].

8 Overall Summary

All currently marketed phosphate binders have been shown to reduce serum phosphorus compared with placebo, which is the indication for which phosphate binders are marketed worldwide. Phosphate binders are routinely prescribed to dialysis patients to reduce serum phosphorus based on the hope of limiting progression of CKD-MBD and potentially reducing bone fractures, mortality and CV outcomes, and progression of kidney disease. Many, but not all, observational studies in the general population and in CKD patients associate higher serum phosphorus levels with higher mortality and CV events. Data are scarce for other important outcomes. No adequately powered, long-term, placebo-controlled comparative trials have been performed

to demonstrate that any phosphate binder or class in dialysis patients reduces fractures or progression of CKD, improves survival, or reduces CV events.

Recent meta-analyses based on RCTs have generally found that sevelamer use results in higher survival compared with CCPBs. However, included studies have shown significant heterogeneity and exclusion of single trials have changed results from significant to nonsignificant (or vice versa), which is concerning. Since no evidence from placebo-controlled trials shows that sevelamer reduces mortality in dialysis or in NDD-CKD patients, it is unclear whether lower mortality with sevelamer versus CCPBs represents a net benefit of sevelamer, net harm with CCPBs, or both (or neither). Studies have been insufficiently powered to evaluate differences in CV events and most trials have not evaluated fracture events, despite reduction in progression of CKD-MBD being the main rationale for using phosphate binders. There has been much less evaluation of phosphate binder use and outcomes in NDD-CKD patients. However, evidence from some small trials suggests that phosphate binders may not be efficacious and CCPBs may even be harmful in this population.

The main challenge in long-term lowering of serum phosphorus with phosphate binders is medication non-adherence. Pill burden and medication intolerance are two main identified factors that influence phosphate binder adherence. Lanthanum carbonate and sucroferric oxyhydroxide have lower pill burden than other phosphate binders, but have higher discontinuation rates than some due to patient intolerance. The lack of adherence data from most clinical trials makes it more difficult to interpret conflicting outcome results. Although newer phosphate binders are expensive, in the USA, cost is not a main driver of non-adherence for most dialysis patients, since most are covered by Medicare and most Medicare-covered dialysis patients are enrolled in Medicare Part D, which provides coverage for phosphate binders. Low-income patients receive highly subsidized medications through Part D, so out-of-pocket costs are relatively low to many patients. However, costs to the US Medicare program are substantial, reaching almost a billion dollars per year. Results from cost-effectiveness analyses must be viewed with caution, since most relied on effectiveness assumptions that may not be valid. New phosphate binders in clinical testing or under development do not appear to offer any significant advantages over currently available phosphate binders.

9 Conclusion

Phosphate binders may be valuable, particularly in treatment of hyperphosphatemia in dialysis patients, but their value should be derived not just from lowering phosphorus, but from improving hard clinical outcomes such as fractures, CKD progression, CV events, or mortality, similar to FDA guidance for evaluating CV outcomes—not just hemoglobin A1c in trials of new diabetes agents. Phosphate binders may also be useful in NDD-CKD patients, but more data are needed. Given the cost burden of newer phosphate binders on national health care budgets and out-of-pocket costs to patients, it is imperative that well-designed, randomized, blinded, adequately powered, long-term, placebo-controlled trials be conducted evaluating hard clinical endpoints. The same holds true for head-to-head comparative trials with phosphate binders. Based on the available evidence, the first priority should be a three-arm clinical trial evaluating placebo versus calcium acetate and sevelamer carbonate in dialysis patients. It is essential that these trials be blinded (a major limitation to most available evidence) and that adherence is accurately measured. Agencies that provide regulatory approval for drugs should consider providing guidance to industry to evaluate at a minimum the risk of fractures and CV events for any new phosphate binder in clinical development.

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Compliance with Ethical Standards

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Conflict of interest Katie E. Cardone declares she has served on an advisory panel for AstraZeneca and her spouse is employed by Fresenius Medical Care. Eric Weinhandl is also employed by NxStage Medical, but there are no conflicts of interest with the content of this article. Wendy L. St. Peter, Joanna Q. Hudson and Lori D. Wazny declare that they have no conflict of interest.

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