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Original Investigation

Phosphate-Binding Agents in Adults With CKD: A Network Meta-analysis of Randomized Trials

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Background: Guidelines preferentially recommend noncalcium phosphate binders in adults with chronic kidney disease (CKD). We compare and rank phosphate-binder strategies for CKD.

Study Design: Network meta-analysis.

Setting & Population: Adults with CKD.

Selection Criteria for Studies: Randomized trials with allocation to phosphate binders.

Interventions: Sevelamer, lanthanum, iron, calcium, colestilan, bixalomer, nicotinic acid, and magnesium.

Outcomes: The primary outcome was all-cause mortality. Additional outcomes were cardiovascular mortality, myocardial infarction, stroke, adverse events, serum phosphorus and calcium levels, and coronary artery calcification.

Results: 77 trials (12,562 participants) were included. Most (62 trials in 11,009 patients) studies were performed in a dialysis population. Trials were generally of short duration (median, 6 months) and had high risks of bias. All-cause mortality was ascertained in 20 studies during 86,744 patient-months of follow-up. There was no evidence that any drug class lowered mortality or cardiovascular events when compared to placebo. Compared to calcium, sevelamer reduced all-cause mortality (OR, 0.39; 95% CI, 0.21-0.74), whereas treatment effects of lanthanum, iron, and colestilan were not significant (ORs of 0.78 [95% CI, 0.16-3.72], 0.37 [95% CI, 0.09-1.60], and 0.55 [95% CI, 0.07-4.43], respectively). Lanthanum caused nausea, whereas sevelamer posed the highest risk for constipation and iron caused diarrhea. All phosphate binders lowered serum phosphorus levels to a greater extent than placebo, with iron ranked as the best treatment. Sevelamer and lanthanum posed substantially lower risks for hypercalcemia than calcium.

Limitations: Limited testing of consistency; short follow-up.

Conclusions: There is currently no evidence that phosphate-binder treatment reduces mortality compared to placebo in adults with CKD. It is not clear whether the higher mortality with calcium versus sevelamer reflects whether there is net harm associated with calcium, net benefit with sevelamer, both, or neither. Iron-based binders show evidence of greater phosphate lowering that warrants further examination in randomized trials.

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INDEX WORDS: Phosphate-binding agents; phosphate binder; sevelamer; lanthanum; calcium; iron; chronic kidney disease (CKD); mortality; meta-analysis.

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Chronic kidney disease (CKD) caused 20 million years of life to be affected by premature mortality or meaningful disability in 2010.[1] The disease is characterized by premature vascular disease,[2] in part due to accelerated vascular calcification. Phosphorus accumulation, due to impaired kidney excretion, drives transformation of vascular smooth muscle cells toward a phenotype similar to bone-forming osteoblasts.[3] Accordingly, oral phosphate binders are prescribed

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to reduce intestinal phosphorus uptake and lower serum levels. Guidelines recommend serum phosphorus levels within or toward the normal range.[4] In the United States, phosphate binders contribute $0.5 billion in health spending annually.[5]

Many different classes of phosphate binders are available. Although drugs have been compared head to head in randomized trials and meta-analyses,[6,7] uncertainty remains about which treatment option is the most effective at lowering mortality and cardiovascular complications and whether drugs are better than placebo. A previous meta-analysis concluded that noncalcium binders reduced mortality compared with calcium-based treatments, but comparative effects of specific phosphate-binder classes against each other or placebo could not be discerned due to a lack of head-to-head trials.[7] Current evidence has resulted in weak guideline recommendations[4] and considerable uncertainty about the efficacy and harms of specific phosphate binders.

Network meta-analysis can evaluate all available phosphate binders within a coherent framework and rank treatments even when drugs have not been compared in head-to-head trials.[8] In this study, the effects of all phosphate binders were compared using network meta-analysis.

METHODS

Study Design

This systematic review with network meta-analysis was conducted according to a prespecified protocol and was reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9]

Search Strategy and Selection Criteria

Cochrane, MEDLINE, and Embase databases were searched on May 18, 2016, without language restriction. Randomized trials from a previous Cochrane review were also included.[6] We included parallel-group randomized clinical trials with follow-up of 4 or more weeks allocating adults with CKD to a phosphate binder, placebo, or standard care.

Study Selection and Data Extraction

Two reviewers (S.C.P. and S.G.) independently screened titles and abstracts of the retrieved citations and reviewed the full text of all citations considered potentially eligible. Reviewers resolved any disagreements through discussion. Two reviewers (S.C.P. and S.G.) extracted and double-checked data extraction.

Risk-of-Bias Assessment

Two reviewers (S.C.P. and S.G.) critically appraised risks of bias using the Cochrane tool.[10]

Statistical Analysis

The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, nausea, abdominal pain, constipation, diarrhea, achievement of a serum phosphorus target, serum phosphorus levels, hypercalcemia, and coronary artery calcification.

First, random-effects pairwise meta-analysis was used to assess treatment effects.[11] Then random-effects network meta-analysis in a frequentist environment was conducted. The following were evaluated when considering the appropriateness of combining studies for network meta-analysis: clinical setting, age, stage of kidney disease, follow-up duration, and serum phosphorus level. A fixed-effect model was used to check for the robustness of the results for all-cause mortality. Binary outcomes were expressed as odds ratios (ORs) and continuous outcomes were calculated as standardized mean differences, together with their 95% confidence intervals (CIs). A standardized mean difference of 0.2 is considered small; 0.5, moderate; and 0.8, large.[12]

The extent of network heterogeneity was estimated by comparing a common heterogeneity variance (tau [τ]) within each network with an empirical distribution of heterogeneity variances.[13] A loop-specific approach was then used to compare the difference between direct and indirect estimates for a treatment effect (inconsistency factor) within triangular or quadrilateral loops within a network.[14] The design-by-treatment interaction model was also used to draw a single inference about the plausibility of assuming consistency within a network.[15,16]

Prespecified sensitivity analyses were restricted to studies in dialysis, younger patients (aged $<$ 60 years), follow-up of 12 or more months, and baseline serum phosphorus levels $\leq$ 1.8 mmol/L. Additional analyses were done removing one study at a time from the network for all-cause mortality and restricted to studies at low risk of bias for allocation concealment. Post hoc analysis of the comparative effectiveness between sevelamer and calcium for all-cause mortality was done that included published longer term follow-up of the Dialysis Clinical Outcomes Revisited (DCOR) Study.[17]

All analyses were generated in Stata 13 (StataCorp LP) using the network command[18] and previously reported routines.[19] To rank treatments according to their probability of being the best treatment for a specific outcome, the surface under the cumulative ranking curve was estimated using the network rank command. We assumed that the relative effects of each intervention compared to placebo followed a multivariate normal distribution.[20] We generated 1,000 relative effects and in each replicate, the treatment effects were ranked. Finally, the percentages of assuming any of the possible ranks for all interventions was computed. Statistical testing was 2 tailed. $P < 0.05$ was taken to indicate statistical significance.

RESULTS

Study Characteristics

There were 77 studies involving 12,562 adults that were eligible (Fig 1; Table S1, available as online supplementary material). There were 62 trials involving 11,009 dialysis patients. Eight phosphate-binder classes were evaluated: sevelamer (hydrochloride or carbonate), lanthanum carbonate, calcium (carbonate or acetate), iron (iron magnesium hydroxycarbonate, ferric citrate, SBR759, or sucroferric oxyhydroxide), colestilan, bixalomer, nicotinic acid, and magnesium carbonate. Median duration was 3 (interquartile range [IQR], 1.8-6) months, with a median age of 56.7 (IQR, 53.5-60.3) years and median serum phosphorus level of 6.5 (IQR, 5.3-7.7) mg/dL. Median follow-up for each drug was as follows: placebo, 1.8 (IQR, 1-3) months; sevelamer, 3 (IQR, 2-11) months; lanthanum, 3 (IQR, 1.5-9) months; calcium, 6 (IQR, 3-12) months; iron, 1.8 (IQR, 1-3) months; colestilan, 3

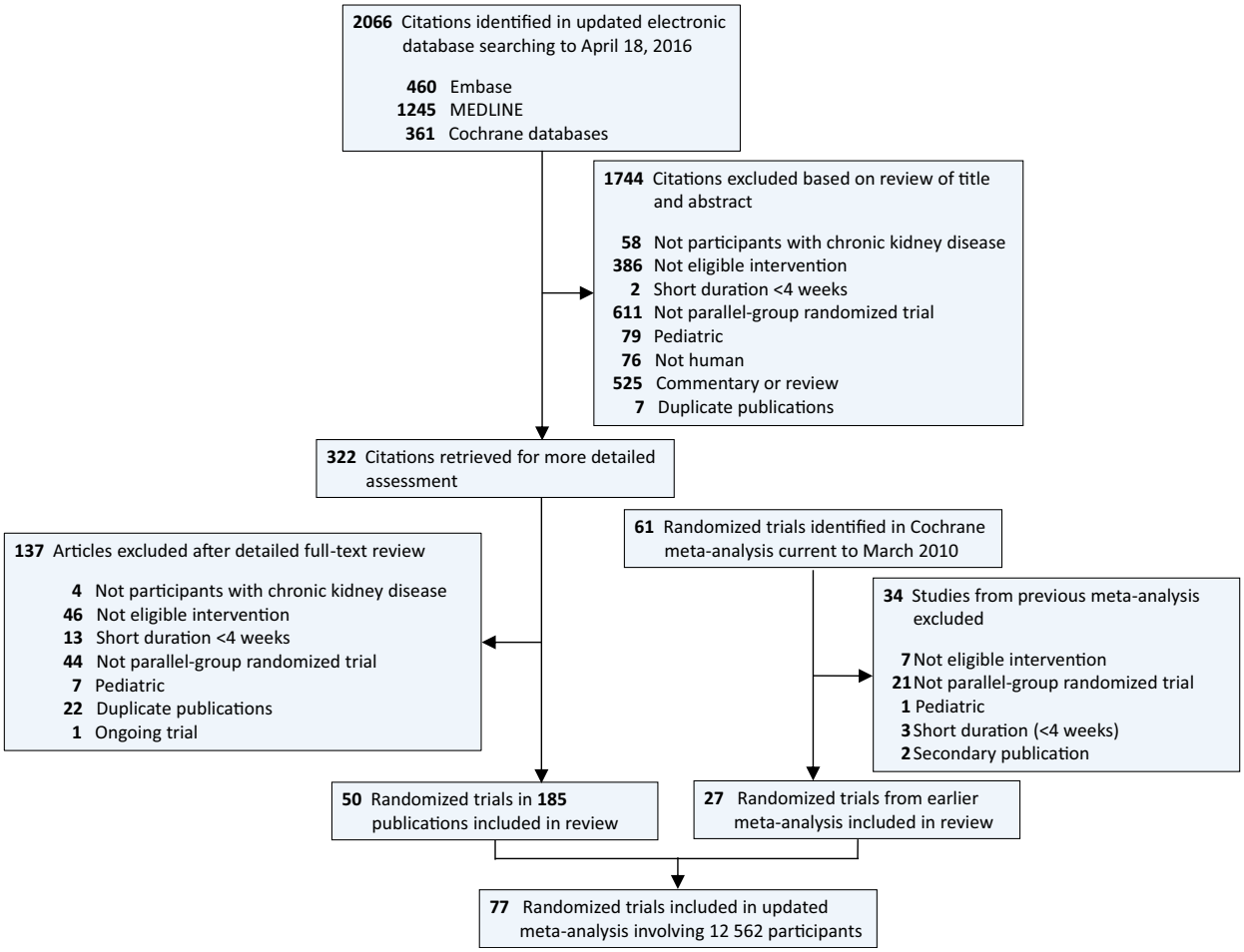

Figure 1. Flow diagram of search results and selection of included studies.

(IQR, 1-3) months; bixalomer, 2 (IQR, 1-3) months; and nicotinic acid, 1.9 (IQR, 1.4-2.4) months. Twenty studies involving 6,376 patients reported 770 deaths during 86,744 patient-months (Table 1).[21-39]

Risks of Bias

Risks of bias were frequently high (Figs S1 and S2). There were 16 (21%) studies that reported low-risk methods for random sequence generation and 8 (10%) that adequately concealed allocation. There were 24 (31%) studies that masked participants and investigators and 2 (3%) that masked outcome assessment. In 18 (23%) studies, ≥90% of participants were included in analyses according to their randomized treatment allocation. In 26 (34%) studies, all clinically relevant outcomes (mortality and/or cardiovascular events and adverse events) were reported. Analyses were reported as intention to treat in 12 (16%) studies and adverse events were systematically captured in 14 (18%) studies. Published studies tended to favor newer drug classes (sevelamer, lanthanum, and iron) for all-cause mortality (Fig S3).

Study Consistency and Heterogeneity

When considering potential effect modifiers in assessing consistency, nearly all studies (88%) included patients with end-stage kidney disease. In 51 (76%) studies, patients with a mean age of 50 to 70 years were enrolled. Baseline serum phosphorus levels were variable (3.1-9.0 mg/dL) but less diverse in studies included in the network analysis for all-cause mortality (5.0-7.8 mg/dL). Dosing regimens for phosphate binders were similar among trials (Table S1). For studies reporting all-cause mortality, more than half included follow-up of 12 months or longer (Table 1). Studies were deemed sufficiently comparable for key effect modifiers to justify the consistency assumption that meta-analysis was reasonable.

The network for cardiovascular mortality indicated the presence of substantial heterogeneity ($\tau = 1.20$), whereas networks for all-cause mortality ($\tau = 0.74$), hypercalcemia ($\tau = 0.94$), and diarrhea ($\tau = 0.81$) showed moderate-high heterogeneity and networks for nausea ($\tau = 0.55$), abdominal pain ($\tau = 0.41$), constipation ($\tau = 0.34$), serum phosphorus target

Table 1. Trials Ascertaining Treatment Effects on All-Cause Mortality

Study	Intervention Drug (dose/d)	Comparator Drug(s) (dose/d)	N	Location	BL CKD Stage	Age, y	BL Serum Phosphorus, mmol/L	Treatment Duration, mo	F/U for Mortality, patient-mo[a]
Chertow[41] (2002)	Sevelamer hydrochloride (mean, 6,500 mg)	Calcium carbonate (mean, 3,900 mg) or calcium acetate (4,600 mg)	200	US, DE, AT	5D	57 ± 14	2.5 ± 0.6	12	2,400
Sadek[33] (2003)	Sevelamer hydrochloride (1,200-4,400 mg)	Calcium carbonate (4,800 mg)	42	FR	5D	NR	1.8 ± 0.2	5	210
Block[22] (2005)	Sevelamer hydrochloride (8,000 mg)	Calcium carbonate and/or calcium acetate (2,300 mg)	148	US	5D	57 ± 15	1.7 ± 0.5	18	2,286
DCOR Study[35] (2007)	Sevelamer hydrochloride (mean, 6,900 mg)	Calcium carbonate (mean, 4,900) or calcium acetate (mean, 5,300 mg)	2103	US	5D	60 ± 14.7	NR	Sevelamer: 20.3; calcium, 19.6	42,690
BRiC Study[21] (2008)	Sevelamer hydrochloride (800-12,000 mg)	Calcium acetate (667-2,028 mg)	101	BR	5D	47 ± 13	2.2 ± 0.7	12	1,212
CARE-2 Study[31] (2008)	Sevelamer hydrochloride (mean, 7,300 mg)	Calcium acetate (mean, 5,500 mg)	203	US	5D	60.3 ± 12.1	2.1 ± 0.5	12	2,436
INDEPENDENT Study[26] (2009)	Sevelamer hydrochloride (mean, 4,300 mg)	Calcium carbonate (mean, 2,200 mg)	466	IT	5D	65.6 ± 14.8	1.7 ± 0.5	36	16,776
INDEPENDENT Study[25] (2012)	Sevelamer hydrochloride (mean, 2,184 mg)	Calcium carbonate (2,950 mg)	212	IT	3-4	57.9 ± 12.2	1.6 ± 0.4	24	5,736
Chen[24] (2011)	Sevelamer hydrochloride (mean, 4,800 mg)	SBR759 (mean, 6,200 mg)	201	JP, TW	5D	59.6 ± 11.3	NR	3	603
Wuthrich[38] (2013)	Sevelamer hydrochloride (4,800 mg)	PA21 (1.25, 5, 7.5, 10, 12.5 mg)	154	US, Europe	5D	61.6 ± 11.2	2.2 ± 0.5	1.5	231
Floege[27] (2014)	Sevelamer carbonate (4,800-14,400 mg)	Sucroferric oxyhydroxide (1,000-3,000 mg)	1,055	Europe, US, RU, UA, ZA	5D	56 ± 15	2.5 ± NR	6	654
Locatelli[29] (2014)	Sevelamer (2,400-12,000 mg)	Colestilan (3,000-15,000 mg)	336	AU, AT, CZ, FR, DE, HU, IT, PL, ZA, ES, UK	5D	59.5 ± 13.8	NR	3	108
Spasovoski[34] (2006)	Lanthanum carbonate (maximum, 3,000 mg)	Calcium carbonate (maximum, 4,000 mg)	20	MK	5D	55 ± 10	1.6 ± 0.2	12	288
Touissant[36] (2009)	Lanthanum carbonate (minimum, 750 mg)	Calcium carbonate (minimum, 1,800 mg)	45	AU	5D	56	1.9 ± 0.1	18	810
Ohtake[30] (2013)	Lanthanum carbonate (mean, 14,30.6 mg)	Calcium carbonate (mean, 3,000 mg)	42	JP	5D	67.8 ± 6.3	1.7 ± 0.5	6	252

(Continued)

Table 1 (Cont'd). Trials Ascertaining Treatment Effects on All-Cause Mortality

Study	Intervention Drug (dose/d)	Comparator Drug(s) (dose/d)	N	Location	BL CKD Stage	Age, y	BL Serum Phosphorus, mmol/L	Treatment Duration, mo	F/U for Mortality, patient-mo[a]
Wada[37] (2014)	Lanthanum carbonate (mean, 2,130 mg)	Calcium carbonate (mean, 2,730 mg)	43	JP	5D	65.57 ± 10.2	1.6 ± 0.4	12	516
Yokoyama[39] (2014)	Ferric citrate (1,500-6,000 mg)	Placebo	90	JP	3-5	65.3 ± 10.2	1.8 ± 0.2	3	270
Locatelli[28] (2013)	Colestilan (3,000-15,000 mg)	Placebo	642	HU, IT, PL, RS, MK, UA, RU, MY	5D	49.1 ± 12.7	2.4 ± NR	3	1,926
Block[23] (2015)	Ferric citrate (mean, 5,100 mg)	Placebo	149	US	3-5	66 ± 12	1.5 ± 0.2	2.75	409
Qunibi[32] (2011)	Calcium carbonate (NI)	Placebo	110	US	4-5	63.2 ± 11.7	1.6 ± 0.4	3	330

Note: Unless otherwise indicated, values are given as mean ± standard deviation.

Abbreviations: 5D, chronic kidney disease treated with dialysis; AT, Austria; AU, Australia; BL, baseline; BR, Brazil; CA, Canada; CKD, chronic kidney disease; CZ, Czech Republic; DE, Germany; ES, Spain; Fr, France; F/U, follow-up; HU, Hungary; IT, Italy; JP, Japan; MK, Macedonia; MY, Malaysia; NR, not reported; PL, Poland; RS, Serbia; RU, Russian Federation; TW, Taiwan; UA, Ukraine; UK, United Kingdom; US, United States; ZA, South Africa.

[a]Patient-months of follow-up was estimated as number of patients allocated with treatment multiplied by duration of follow-up in months.

($\tau = 0.44$), serum phosphorus values ($\tau = 0.51$), and coronary artery calcification ($\tau < 0.001$) showed low-moderate heterogeneity. Treatment estimates from direct and indirect evidence did not show loop-specific inconsistency except for serum phosphorus values. However, results of testing were very imprecise in some cases and so inconsistency could not be excluded (Table S2). There was no evidence of global network inconsistency except for the outcome of diarrhea (Table S3).

Treatment Outcomes

Overall results of pairwise meta-analyses for binary outcomes are given in Table S4. Definitions of biochemical outcomes are described in Table S5.

All-Cause Mortality, Cardiovascular Mortality, Stroke, and Myocardial Infarction

The network for all-cause mortality is shown in Fig S4. Median follow-up was 15 months for trials comparing sevelamer versus calcium, 3 months for sevelamer versus iron, and 12 months for lanthanum versus calcium.

There was no evidence of different odds of all-cause mortality between any phosphate binder and placebo (ORs of 0.45 [95% CI, 0.08-2.66], 0.47 [95% CI, 0.08-2.56], 0.66 [95% CI, 0.10-4.31], 0.93 [95% CI, 0.11-8.00], and 1.20 [95% CI, 0.21-6.75] for iron, sevelamer, colestilan, lanthanum, and calcium, respectively), although placebo-controlled trials were of short duration (4 weeks to 3 months; Fig 2).

Sevelamer appeared to reduce all-cause mortality compared to calcium (OR, 0.39; 95% CI, 0.21-0.74) and was ranked best for this outcome, whereas the effects of lanthanum, iron, and colestilan (ORs of 0.78 [95% CI, 0.16-3.72], 0.37 [95% CI, 0.09-1.60], and 0.55 [95% CI, 0.07-4.43], respectively) compared to calcium were not significant (Fig 2). When a fixed-effect model was used to estimate odds of all-cause mortality, the ORs for therapies when compared to calcium were 0.74 (95% CI, 0.62-0.89), 0.67 (95% CI, 0.26-1.72), and 0.87 (95% CI, 0.16-4.76) for sevelamer, iron, and colestilan, respectively. The noncalcium binders did not differ statistically from each other for all-cause mortality.

Data for cardiovascular mortality, myocardial infarction, and stroke were sparse due to few studies reporting these outcomes (Table S6; Fig S5).

Adverse Effects: Nausea, Constipation, Diarrhea, Abdominal Pain

The networks for adverse events are shown in Fig S6. Lanthanum ranked as the treatment with the highest probability of causing nausea (Fig 3). Lanthanum increased nausea compared with calcium (OR, 2.18; 95% CI, 1.00-4.74) and iron (OR, 4.07;

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

Figure 2. Network estimated odds ratios (ORs) of phosphate binders on all-cause mortality. Values are given as OR (95% confidence interval [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 < 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 6,376 participants included in the network.

95% CI, 1.15-14.3; Fig 4). Sevelamer increased constipation compared with calcium, lanthanum, and iron (ORs of 2.12 [95% CI, 1.01-4.45], 3.03 [95% CI, 1.31-7.02], and 3.15 [95% CI, 1.73-7.53]) and was ranked worst for this adverse effect (Fig 5). Iron increased diarrhea compared to calcium (OR, 3.30; 95% CI, 1.02-10.8), but differences between all other phosphate binders were not significant (Fig 5). No drug increased abdominal pain (Fig 4).

Serum Calcium and Phosphorus

Networks for serum phosphorus and calcium are shown in Fig S7. Iron increased odds of achieving serum phosphorus targets compared with sevelamer, lanthanum, calcium, and placebo (Fig 6; Table S7). All phosphate binders except colestilan significantly lowered serum phosphorus levels compared to placebo (Fig 6). Iron lowered serum phosphorus levels to a greater extent than lanthanum, sevelamer, and calcium and was ranked as the best treatment (Fig 3). Sevelamer (OR, 0.14; 95% CI, 0.07-0.29) and lanthanum (OR, 0.09; 95% CI, 0.03-0.25) were associated with significantly lower odds of hypercalcemia compared to calcium.

Coronary Artery Calcification

Sevelamer reduced coronary artery calcification scores compared to calcium (standardized mean difference, −0.20; 95% CI, −0.40 to −0.01; Table S8; Fig S8).

Sensitivity Analyses

Treatment estimates were similar when restricted to studies reporting low-risk methods of allocation concealment, involving dialysis patients, with longer follow-up, or with lower baseline serum phosphorus levels (Table S9). When removing 1 study at a time,

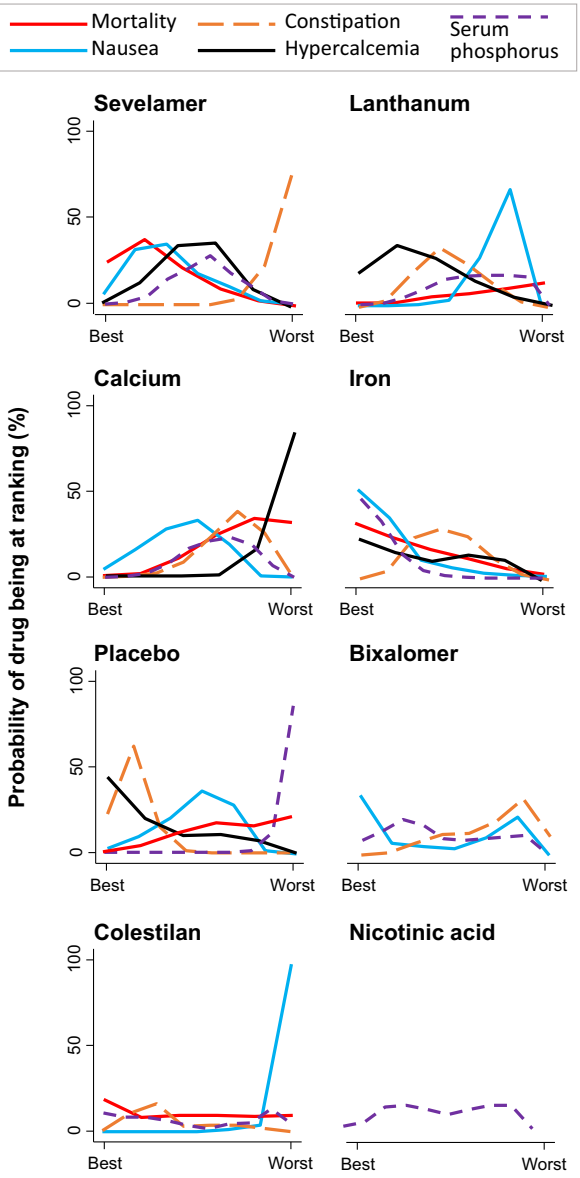

Figure 3. Rankings for efficacy and toxicity of phosphate binders. The graph shows distribution of probabilities for efficacy (all-cause mortality and serum phosphorus levels) and safety (nausea, constipation, and hypercalcemia). Ranking indicates probability that drug class is first "best," second "best," etc. For example, sevelamer showed a 25.8% probability of ranking the best treatment for all-cause mortality, whereas calcium showed a 0.0% probability of ranking the best treatment for all-cause mortality.

the estimated odds of mortality with sevelamer compared to calcium was no longer significant when the INDEPENDENT (Reduce Cardiovascular Calcifications to Reduce QT Interval in Dialysis) Study[26] was excluded (OR, 0.61; 95% CI, 0.37-1.01; Table S10) and the heterogeneity τ in the mortality network with this study removed was reduced from 0.73 (moderate-high heterogeneity) to 0.35 (low heterogeneity). There was no evidence of treatment differences based on the individual phosphate-binder

		Abdominal pain					
Nausea	**Sevelamer**	0.93 (0.23, 3.74)	1.25 (0.46, 3.42)	0.52 (0.16, 1.69)	0.37 (0.05, 2.70)	1.00 (0.05, 18.4)	0.64 (0.23, 1.74)
	0.39 (0.13, 1.16)	**Lanthanum**	1.35 (0.42, 4.36)	0.56 (0.11, 2.83)	0.40 (0.05, 3.34)	1.07 (0.04, 27.1)	0.68 (0.19, 2.42)
	0.84 (0.34, 2.08)	**2.18 (1.00, 4.74)**	**Calcium**	0.41 (0.10, 1.70)	0.30 (0.04, 2.27)	0.80 (0.04, 17.4)	0.51 (0.17, 1.53)
	1.58 (0.61, 4.06)	**4.07 (1.16, 14.3)**	1.87 (0.59,5.93)	**Iron**	0.72 (0.09, 5.69)	1.93 (0.08, 44.9)	1.23 (0.38, 3.95)
	0.02 (0.00, 0.45)	0.05 (0.00, 1.05)	**0.02 (0.00, 0.50)**	**0.01 (0.00, 0.29)**	**Colestilan**	2.68 (0.08, 90.9)	1.71 (0.31, 9.42)
	1.00 (0.05, 20.0)	2.58 (0.11, 62.7)	1.19 (0.05, 27.1)	0.63 (0.03, 14.7)	52.6 (0.68, 4097)	**Bixalomer**	0.64 (0.03, 13.9)
	0.75 (0.27, 2.08)	1.92 (0.97, 3.81)	0.88 (0.38, 2.03)	0.47 (0.15, 1.46)	**39.2 (1.98, 779)**	0.75 (0.03, 17.69)	**Placebo**

Figure 4. Network estimated odds ratios (ORs) of phosphate binders on nausea and abdominal pain. Values are given as OR (95% confidence interval [CI]). The grid should be read from left to right. The lower part of the grid reports treatment estimates for nausea. Risk estimate is for the column-defining treatment compared to the row-defining treatment. An OR < 1 indicates the column treatment is associated with a lower odds of nausea than the row treatment. For example, lanthanum-based treatment is associated with increased odds of nausea compared to calcium-based treatment (OR, 2.18; 95% CI, 1.00-4.74). The upper part of the grid reports estimates for abdominal pain. The risk estimate was for the row-defining treatment compared to the column-defining treatment. An OR < 1 indicates the row treatment is associated with a lower odds of abdominal pain than the column treatment. For example, the OR of abdominal pain with sevelamer is 1.25 (95% CI, 0.46-3.42) compared to calcium treatment. Bolded numerals indicate statistically significant results.The heterogeneity tau (τ) for each network analysis was: nausea, $\tau = 0.55$ (indicative of moderate heterogeneity); and abdominal pain, $\tau = 0.41$ (indicative of low-moderate heterogeneity). There were 26 trials involving 7,265 patients in the network for nausea and 18 trials involving 3,235 patients in the network for abdominal pain.

formulation (sevelamer [hydrochloride or carbonate] or calcium [acetate or carbonate]), although there were frequently few observations leading to low power in the analyses (Table S11). The treatment estimates for all-cause mortality repeated including extended follow-up for the DCOR Study[17] were similar (OR for sevelamer vs calcium, 0.39 [95% CI, 0.20-0.76]).

DISCUSSION

This systematic review included 77 studies involving 12,562 adults with CKD, predominantly in dialysis populations. There was no evidence that any phosphate binder lowered mortality compared to placebo. Sevelamer was associated with lower all-cause mortality in comparison to calcium-based binders. Estimated effects of other non−calcium-binding agents compared to calcium-based treatment were nonsignificant, and there were no statistical differences in mortality risk between different non–calcium-containing binders (sevelamer, lanthanum, and iron). Overall, these data cannot establish whether there is net harm associated with calcium-based phosphate binders, net benefit associated with sevelamer, both, or neither. Existing trials of phosphate binders on all-cause mortality were short, with those evaluating iron-based treatment lasting generally 3 months or less. Coronary artery calcification (a putative mechanism for death related to high serum calcium and phosphorus levels) is not clinically apparent for most patients until at least 10 years of dialysis therapy,[40] indicating that currently available phosphate-binder therapy trials may be of insufficient duration to provide definitive information about treatment effects on mortality, cardiovascular events, or vascular calcification, although sevelamer appeared to prevent coronary artery calcification compared with calcium binders in the short term.

Lanthanum and colestilan had the highest probability of nausea, sevelamer ranked worst for constipation, and iron-based binders conferred greatest odds of diarrhea. Iron lowered serum phosphorus levels compared with other binders, including sevelamer and lanthanum. All phosphate binders except colestilan lowered serum phosphorus levels compared to placebo. As expected, calcium was ranked as most likely to cause hypercalcemia.

These findings extend those of a previous pairwise meta-analysis,[7] which concluded that sevelamer or lanthanum should be first-line therapy in the management of phosphorus in CKD, in 3 ways. First, by integrating direct and indirect evidence, the benefits of noncalcium binders in the previous review might have been principally attributable to sevelamer, whereas comparative effects of other non–calcium-based agents including lanthanum were not significant compared to calcium or placebo for mortality. In the previous pairwise meta-analysis, evidence for non−calcium-based agents (sevelamer and lanthanum) was combined to identify a risk reduction in mortality with noncalcium binders of 22%, but study data were insufficient to evaluate treatment effects for individual drug classes. Importantly, due to a lack of

	Diarrhea								
Constipation	**Sevelamer**	0.93 (0.26, 3.30)	1.18 (0.38, 3.66)	**0.36 (0.15, 0.84)**	0.82 (0.11, 6.23)	3.06 (0.09, 106)	0.31 (0.01, 11.3)	0.20 (0.00, 9.06)	0.76 (0.26, 2.22)
	3.04 (1.31, 7.02)	**Lanthanum**	1.28 (0.42, 3.89)	0.39 (0.12, 1.28)	0.89 (0.12, 6.35)	3.30 (0.08, 143)	0.34 (0.01, 12.1)	0.22 (0.00, 9.50)	0.82 (0.32, 2.15)
	2.12 (1.01, 4.45)	0.70 (0.37, 1.30)	**Calcium**	**0.30 (0.09, 0.99)**	0.70 (0.09, 5.33)	2.58 (0.06, 107)	0.26 (0.01, 7.94)	0.17 (0.00, 7.71)	0.65 (0.22, 1.92)
	3.15 (1.73, 5.75)	1.04 (0.42, 2.57)	1.49 (0.62, 3.58)	**Iron**	2.30 (0.34, 15.7)	8.53 (0.22, 328)	0.87 (0.02, 32.0)	0.56 (0.01, 24.0)	2.13 (0.91, 5.03)
	3.73(0.61, 22.9)	1.23 (0.20, 7.62)	1.76 (0.28, 11.1)	1.18 (0.19, 7.20)	**Colestilan**	3.70 0.06, 220)	0.38 (0.01, 20.0)	0.24 (0.00, 13.8)	0.93 (0.17, 5.16)
	1.84 (0.64, 5.30)	0.61 (0.16, 2.27)	0.87 (0.24, 3.10)	0.59 (0.18, 1.93)	0.49 (0.06, 3.90)	**Bixalomer**	0.10 (0.00, 15.9)	0.07 (0.00, 12.0)	0.25 (0.01, 10.2)
	15.3 (0.49, 481)	5.04 (0.16, 155)	7.24 (0.25, 210)	4.86 (0.15, 158)	4.11 (0.09, 190)	8.30 (0.23, 303)	**Calcium + magnesium**	0.65 (0.00, 107)	2.45 (0.07, 87.8)
	--	--	--	--	--	**--**	--	**Nicotinamide**	3.80 (0.10, 147)
	7.39 (3.33, 16.4)	**2.43 (1.07, 5.51)**	**3.49 (1.49, 8.16)**	**2.34 (1.08, 5.08)**	1.98 (0.38, 10.1)	**4.01 (1.13, 14.2)**	0.48 (0.01, 15.5)	--	**Placebo**

Figure 5. Network estimated odds ratios (ORs) of phosphate-binding agents on constipation and diarrhea. Values are given as OR (95% confidence interval [CI]). The grid should be read from left to right. The lower part of the grid reports treatment estimates for constipation. The risk estimate is for the column-defining treatment compared to the row-defining treatment. An OR < 1 indicates the column treatment is associated with a lower odds of constipation than the row treatment. For example, sevelamer-based treatment is associated with increased odds of constipation compared to calcium-based treatment (OR, 2.12; 95% CI, 1.01-4.45). The upper part of the grid reports estimates for diarrhea. The risk estimate is for the row-defining treatment compared to the column-defining treatment. An OR < 1 indicates the row treatment is associated with a lower odds of diarrhea than the column treatment. For example, sevelamer is associated with a lower odds of diarrhea than iron treatment (OR, 0.30; 95% CI, 0.09-0.99). Bolded numerals indicate statistically significant results. The heterogeneity tau (τ) for each network analysis was: constipation, $\tau = 0.34$ (indicative of low heterogeneity); and diarrhea, $\tau = 0.81$ (indicative of moderate-high heterogeneity). There were 27 trials involving 7,862 patients in the network for constipation and 23 trials involving 4,894 patients in the network for diarrhea.

placebo-controlled trials, comparisons of phosphate binders to placebo have not been previously possible. This network meta-analysis indicates that there is no evidence that any phosphate binder improves life expectancy when compared to placebo in trials of short duration. Second, this review identifies adverse events attributable to phosphate-binder classes that can facilitate decision making aligned with patient preferences. Third, iron-based binders lowered serum phosphorus levels to a greater extent than other phosphate-binder classes, indicating that these are an important candidate intervention for larger studies against sevelamer and/or calcium, to evaluate impact on mortality and cardiovascular end points.

Proponents of noncalcium binders might argue that these findings indicating an association of sevelamer with lower all-cause mortality support the need to update existing guidelines, which cited insufficient comparative efficacy data for clinical outcomes rather than recommending a specific phosphate binder for patients with CKD.[4] However, there are several issues that preclude a preferential recommendation for sevelamer compared with other binders based on the current evidence. First, the available studies have important methodological limitations, meaning that bias could have affected the results. Smaller studies may have influenced the estimated benefit of sevelamer over calcium-based binders, indicated by the smaller benefit of treatment observed using a fixed-effect model and the absence of smaller trials with more favorable effects for calcium-based treatment. Second, after exclusion of a single study (the INDEPENDENT trial[26]), the reduction in all-cause mortality with sevelamer compared to calcium was no longer significant. Removing the INDEPENDENT Study involving 466 incident dialysis patients substantially reduced heterogeneity between studies. It is not clear why the results of the INDEPENDENT Study differed so markedly in favoring sevelamer more than other trials in this meta-analysis. Third, due to imprecision, it is possible that noncalcium binders other than sevelamer are also associated with better (or worse) associations with clinical outcomes compared to calcium. Finally, it is important to note that none of the available calcium or noncalcium agents lowered mortality compared to placebo; in other words, whether calcium-based agents are harmful or non–calcium-based agents are beneficial. Placebo-controlled trials lasted 3 months on average, precluding robust inferences about treatment effects.

Given the widespread use of phosphate binders in clinical practice, randomized trials are an urgent priority to support and inform the extensive prescribing of these medications. Such trials should include comparisons of phosphate binders with placebo (perhaps with rescue treatment for severe hyperphosphatemia and/or

	Achieving serum phosphorus target								
Hypercalcemia	**Sevelamer**	1.43 (0.56, 3.61)	1.64 (0.70, 3.89)	**0.55 (0.30, 0.99)**	0.82 (0.28, 2.39)	1.57 (0.31, 7.86)	1.14 (0.13, 9.79)	0.97 (0.11, 8.69)	6.92 (0.00, 15.9)
	1.61 (0.46, 5.61)	**Lanthanum**	1.15 (0.56, 2.36)	**0.38 (0.16, 0.94)**	0.57 (0.15, 2.12)	1.09 (0.17, 7.02)	0.80 (0.10, 6.48)	0.67 (0.06, 7.30)	**4.82 (2.79, 8.34)**
	0.14 (0.07, 0.29)	**0.09 (0.03, 0.25)**	**Calcium**	**0.33 (0.14, 0.82)**	0.50 (0.14, 1.82)	0.96 (0.15, 5.93)	0.69 (0.10, 4.97)	0.59 (0.06, 6.22)	**4.20 (2.02, 8.74)**
	1.44 (0.12, 16.8)	0.90 (0.06, 14.1)	9.96 (0.77, 128)	**Iron**	1.48 (0.45, 4.85)	2.85 (0.51, 15.9)	2.08 (0.24, 18.1)	1.76 (0.18, 17.1)	**12.6 (5.79, 27.2)**
	--	--	--	--	**Bixalomer**	1.92 (0.28, 13.3)	1.39 (0.13, 14.8)	1.18 (0.10, 13.6)	**8.47 2.45, 29.2**
	--	--	--	--	--	**Nicotinic acid**	0.73 (0.05, 10.7)	0.62 (0.04, 9.38)	4.40 (0.72, 27.0)
	--	--	--	--	--	--	**Calcium + magnesium**	0.85 (0.04, 18.3)	6.05 (0.74, 49.4)
	0.52 (0.06, 4.33)	0.33 (0.03, 3.80)	3.62 (0.39, 33.6)	0.36 (0.01, 9.30)	--	--	--	**Sevelamer + calcium**	7.10 (0.68, 74.3)
	2.39 (0.20, 28.5)	1.48 (0.11, 19.7)	**16.4 (1.49, 181)**	1.66 (0.05, 54.5)	--	--	--	4.52 (0.18, 118)	**Placebo**

Figure 6. Summary network treatment estimates of the comparative efficacy and safety of phosphate-binding agents on serum phosphorus targets and hypercalcemia. Values are given as odds ratio (OR) (95% confidence interval [CI]). The grid should be read from left to right. The lower part of the grid reports treatment estimates for hypercalcemia. The risk estimate is for the column-defining treatment compared to the row-defining treatment. An OR < 1 indicates the column treatment is associated with a lower odds of hypercalcemia than the row treatment. For example, sevelamer-based treatment is associated with lower odds of hypercalcemia compared to calcium-based treatment (OR, 0.14; 95% CI, 0.07-0.29). The upper part of the grid reports estimates for achieving a serum phosphorus target. The risk estimate is for the row-defining treatment compared to the column-defining treatment. An OR < 1 indicates the row treatment is associated with lower odds of achieving a serum phosphorus target than the column treatment. For example, sevelamer is associated with lower odds of achieving a serum phosphorus target than iron treatment (OR, 0.55; 95% CI, 0.30-0.99). Bolded numerals indicate statistically significant results. The heterogeneity tau (τ) for each network analysis was: hypercalcemia, $\tau = 0.94$ (indicative of high heterogeneity); and achieving serum phosphorus target, $\tau = 0.44$ (indicative of low-moderate heterogeneity). There were 21 trials involving 5,159 patients in the network for hypercalcemia and 21 trials involving 2,382 patients in the network for achieving target serum phosphorus levels.

hyperparathyroidism) and head-to-head comparisons between available agents, focusing on clinically relevant outcomes such as mortality and cardiovascular events. Given the significantly lower phosphorus levels associated with iron and the potential association of sevelamer with lower mortality, future trials should focus on these 2 classes of agent compared with placebo, calcium, or each other. Finally, the high absolute risk for adverse events with all binders suggests that there is value to considering patient preferences when selecting an approach to phosphorus control in kidney patients, especially those who are concerned about treatment harms. Further, the failure of any agent to reduce mortality versus placebo suggests that a less aggressive approach to phosphate-lowering treatment may be entirely appropriate in all patients pending the availability of new evidence.

Results of this network meta-analysis contrast with those of the largest randomized study to compare sevelamer with calcium (the DCOR trial), which found no effect of sevelamer compared to calcium on total death in hemodialysis patients treated for approximately 20 months.[35] First, it is possible that DCOR had insufficient statistical power to identify treatment benefit, particularly because about half the 2,103 randomly assigned participants left the study early. The current meta-analysis potentially had greater power to discern a significant association for mortality between treatments due to a larger sample size, as well as draw inferences from both direct and indirect treatment comparisons. A second interpretation is that benefits of sevelamer might be limited to older participants, as was identified in the DCOR Study in participants who were 65 years or older in prespecified subgroup analyses. However, it was unlikely that the reduction in mortality with sevelamer that was found in this meta-analysis was because of a preponderance of older participants because the mean age for participants in most included studies was 60 years or younger. Alternatively, it is possible that this meta-analysis found treatment benefits for sevelamer due to the inclusion of smaller studies at higher risk of bias for important methodological features within network meta-analyses, which may have resulted in overestimated effects on mortality that are discordant with the largest existing randomized trial. When the INDEPENDENT Study was removed from analyses, the beneficial effect of sevelamer on all-cause mortality compared with calcium was not significant, indicating that evidence of efficacy for sevelamer in this analysis may be reliant on the results of this single study.[26]

The strengths of this meta-analysis include the use of network meta-analyses to draw inferences about the comparative effects of phosphate binders with clinical outcomes that have not been directly compared in existing randomized trials including against placebo and permit greater precision for treatment effects on mortality and adverse events than has previously been possible. The analyses are drawn from a highly sensitive literature search and included assessments of study risks of bias.

The study has limitations that reduce the applicability of the findings to clinical practice, related principally to the extent and quality of information in individual trials. First, reporting risks of bias were often high or not reported sufficiently to make a judgment, lowering confidence in the results of contemporary trials of phosphate binders. Lack of reporting of many outcomes in many studies was a potential limitation. Second, most contributing trials were of short duration. This was particularly the case for trials of iron-based binders, which were commonly continued for 3 months or less. Given the natural history of vascular calcification as clinically evident after many years of end-stage kidney disease,[40] it is likely that existing trials do not have sufficient longevity to identify definitive treatment effects, and trials of iron-based binders will need to be longer to identify treatment effects on hypercalcemia, adverse events (especially iron overload), and patient-level outcomes including mortality. Such trials may benefit from efficient trial design, such as follow-up embedded within a data registry, to enable long-term follow-up for sufficient numbers of participants. Trials of placebo were often of short duration ($\leq$3 months). The longer term benefits of treatment against placebo remain uncertain for many outcomes. Third, while meta-analysis assumes that contributing studies were sufficiently similar in most respects other than the treatments under study, statistical assessment of this assumption was limited by low power, although little evidence of network inconsistency was found. There was also no evidence of different treatment associations for individual drugs within binder classes, but few data reduced confidence in these assumptions. Fourth, data for cardiovascular events were rarely reported. Because the assumed mechanism of benefit for these drugs is by reducing vascular calcification to prevent vascular injury, these outcomes must be considered as core outcomes in future trials and systematically captured in ongoing studies and prescribing surveillance. Finally, most studies involved participants with end-stage kidney disease. The findings of this review may not be generalizable across the full range of kidney function.

In conclusion, there is no evidence that phosphate-binder treatment reduces mortality compared to placebo in adults with CKD. It is not clear whether the higher mortality with calcium versus sevelamer reflects whether there is net harm associated with calcium, net benefit with sevelamer, both, or neither. Iron lowered serum phosphate levels to the greatest extent, indicating that future studies might prioritize evaluation of this treatment class. All available phosphate binders display distinct adverse-event profiles that can inform treatment decisions for individual patients.

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Contributions: Study idea and design: SCP, GFMS; identification and acquisition of reports of trials: SCP, SG; data extraction: SCP, SG; statistical oversight: DM; data analyses/interpretation and statistical inconsistency review: SCP; additional data interpretation: SG, JCC, MT, DM, DWJ, RF, MR, GFMS; funding obtainment: SCP; supervision: GFMS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. GFMS takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY MATERIAL

Table S1: Description of included studies.

Table S2: Evaluation of loop-specific consistency in triangular and quadrilateral treatment loops for each network.

Table S3: Assessment of global consistency in networks using the "design-by-treatment" interaction model.

Table S4: Pairwise meta-analysis of head-to-head drug comparisons for binary outcomes.

Table S5: Definition of biochemical outcomes in studies included in network analyses.

Table S6: Network estimated ORs of phosphate binders on cardiovascular mortality.

Table S7: Network estimated standardized mean differences of phosphate binders on end-of-treatment serum phosphorus levels.

Table S8: Network estimated standardized mean differences of phosphate binders on change in coronary artery calcification.

Table S9: Sensitivity analyses for network meta-analysis ORs of all-cause mortality with phosphate binding agents in specific study populations.

Table S10: Sensitivity analysis sequentially removing studies from network meta-analysis to assess influence of single studies on treatment estimates for all-cause mortality.

Table S11: Metaregression analyses for clinical outcomes based on type of individual drug types within phosphate binder classes.

Figure S1: Risk-of-bias summary: judgments about each bias item for each study.

Figure S2: Risk-of-bias summary graph: review authors' judgments for each risk-of-bias item shown as percentages across all included studies.

Figure S3: Comparison-specific funnel plot to assess small-study effects in network for all-cause mortality.

Figure S4: Network of treatment comparisons for cardiovascular mortality.

Figure S5: Network of treatment comparisons for cardiovascular mortality.

Figure S6: Network of treatment comparisons for toxicity outcomes.

Figure S7: Network of treatment comparisons for biochemical outcomes.

Figure S8: Network of treatment comparisons for change in coronary artery calcification.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.05.015) is available at www.ajkd.org

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