Benefits and Harms of Phosphate Binders in CKD: A Systematic Review of Randomized Controlled Trials

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Background: Phosphate binders are widely used to control serum phosphorus levels in patients with chronic kidney disease (CKD). We analyzed the effects of phosphate binders on biochemical and patient-level end points in patients with CKD.

Study Design: Systematic review and meta-analysis by searching MEDLINE (1966 to April 2009), EMBASE (1980 to April 2009), and the Cochrane Renal Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL).

Setting & Population: Patients with CKD.

Selection Criteria for Studies: Randomized controlled trials.

Intervention: Phosphate binders.

Outcomes: Serum phosphorus, calcium, and parathyroid hormone levels; incidence of hypercalcemia; all-cause mortality; adverse effects.

Results: 40 trials (6,406 patients) were included. There was no significant decrease in all-cause mortality (10 randomized controlled trials; 3,079 patients; relative risk [RR], 0.73; 95% confidence interval [CI], 0.46 to 1.16), hospitalization, or end-of-treatment serum calcium-phosphorus product levels with sevelamer compared with calcium-based agents. There was a significant decrease in end-of-treatment phosphorus and parathyroid hormone levels with calcium salts compared with sevelamer and a significant decrease in risk of hypercalcemia (RR, 0.47; 95% CI, 0.36 to 0.62) with sevelamer compared with calcium-based agents. There was a significant increase in risk of gastrointestinal adverse events with sevelamer in comparison to calcium salts (RR, 1.39; 95% CI, 1.04 to 1.87). Compared with calcium-based agents, lanthanum significantly decreased end-of-treatment serum calcium and calcium-phosphorus product levels, but with similar end-of-treatment phosphorus levels. Effects of calcium acetate on biochemical end points were similar to those of calcium carbonate. Existing data are insufficient to conclude for a differential impact of any phosphate binder on cardiovascular mortality or other patient-level outcome.

Limitations: Few long-term studies of the efficacy of phosphate binders on mortality and musculoskeletal morbidity, significant heterogeneity for many surrogate outcomes, and suboptimal reporting of study methods to determine trial quality.

Conclusion: Currently, there are insufficient data to establish the comparative superiority of non–calcium-binding agents over calcium-containing phosphate binders for such important patient-level outcomes as all-cause mortality and cardiovascular end points. Additional trials are still required to examine the differential effects of phosphate-binding agents on these end points and the mineral homeostasis pathway.

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INDEX WORDS: Phosphate binders; hyperphosphatemia; bone disease; calcification; chronic kidney disease.

The incidence of chronic kidney disease (CKD) is increasing worldwide, with about $23 billion (6.6% of the Medicare budget) spent on the care of patients with end-stage renal disease in 2006 in the United States alone.[1] Worsening kidney function results in impaired clearance of the dietary phosphorus load,[2] which directly and indirectly increases parathyroid hormone (PTH) secretion.[2-4] Secondary hyperparathyroidism is characterized by high bone turn-

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over, exaggerated marrow fibrosis, and increased musculoskeletal morbidity. Recently, epidemiological data have shifted the focus of altered mineral metabolism in CKD from renal bone disease to a broader recognition that hyperphosphatemia is associated with increased morbidity, mortality, and hospitalization; reduced quality of life; and increased costs of care.[5-7]

Cardiovascular disease accounts for more than half the deaths in dialysis patients,[1] and the development of vascular calcification of the arterial media has been advocated as a major contributing factor.[8,9] Because abnormalities in mineral metabolism involve a paradigm incorporating bone disease and vascular and soft-tissue calcification that have potential effects on fracture, cardiovascular outcomes, and mortality, the concept of CKD-mineral and bone disorder has been introduced. This condition is the target of several interventions, including phosphate binders, vitamin D analogues, and calcimimetics, all of which may suppress the development or progression of CKD-mineral and bone disorder.[10,11]

Phosphate binders containing aluminum and calcium have been used widely since 1970, and the non–calcium- or aluminum-based agents, sevelamer hydrochloride and lanthanum carbonate, more recently have become available. Their use is increasing in current practice, and although they are more expensive, the potential decrease in risk of vascular calcification and toxicity advocates for broader adoption. For control of hyperphosphatemia, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) recommends the use of calcium-based binders in patients with CKD stages 3 and 4 (glomerular filtration rate, 30 to 59 and 15 to 29 mL/min/1.73 m^2, respectively) and both calcium-based and calcium- and aluminum-free binders in patients with CKD stages 5 and 5D (glomerular filtration rate $<$ 15 mL/min/1.73 m^2 and dialysis).[12] The relative merits of available phosphate-binding agents are controversial.[13,14] We have conducted a systematic review of the benefits and harms of phosphate binders compared with calcium salts or placebo to determine whether newer agents deliver improved biochemical and patient-level outcomes, with particular reference to musculoskeletal and cardiovascular morbidity, hospitalization, and mortality.

METHODS

Inclusion Criteria

Randomized controlled trials (RCTs) and quasi-RCTs (trials that use a method of allocating participants to different forms of care that are not truly random, such as allocation by date of birth, alternate medical records, day of the week, or other forms of alternation) of phosphate binders in people with CKD, alone or in combination with other nonrandomized cointerventions (eg, vitamin D compounds), were included. Studies enrolling adult patients (age $>$ 18 years) with CKD stages 3 to 5 and 5D (dialysis) were included.

Search Strategy

RCTs of phosphate binders in patients with CKD were searched in MEDLINE (1966 to April 2009), EMBASE (1980 to April 2009), and the Cochrane Renal Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) with optimally sensitive search strategies developed by the Cochrane Collaboration[15] and using relevant medical subject terms (Item S1, provided as online supplementary material with this article at www.ajkd.org). Trials were considered without language restriction. Titles and abstracts of search results were screened according to inclusion criteria. Studies that did not meet inclusion criteria (ie, animal studies, non-RCTs, and RCTs of interventions that were not relevant to the review) were excluded.

Data Extraction, Quality Assessment, and Statistical Analysis

We followed Cochrane methods and Quality of Reporting of Meta-analyses (QUOROM) guidelines for conduct and reporting of this systematic review.[16] Two authors independently assessed each trial, and data were extracted for characteristics of participants, interventions, comparisons, and the following outcomes when reported in trials: all-cause mortality, cardiovascular mortality, nonfatal cardiovascular events, vascular calcification by any imaging modality, end-of-treatment PTH concentration (intact PTH and PTH 1-84 as reported in the studies), serum calcium (milligrams per deciliter), serum phosphorus (milligrams per deciliter), serum calcium-phosphorus product (Ca $\times$ P; milligrams squared per deciliter squared), alkaline phosphatase (international units per liter), serum bicarbonate (milliequivalents per liter), total cholesterol (milligrams per deciliter), bone mineral density, bone mineral content, bone histomorphometry, occurrence of hypercalcemia (defined as serum calcium level $>$ 10.2 mg/dL or as defined by the study investigators), and treatment-related toxicity (gastrointestinal side effects). Investigators were contacted if data related to mortality and levels of phosphorus, calcium, PTH, or Ca $\times$ P were not available or not reported in the published reports.

The quality of RCTs was assessed by using a checklist that included allocation concealment; blinding of partici-

pants, investigators, outcome assessors, and data analysts; use of intention-to-treat analyses; and completeness of follow-up.[17] Discrepancies between the 2 data extractors (S.D.N. and S.C.P.) were resolved by discussion with an arbitrator (G.F.M.S.). Dichotomous data were analyzed by using the relative risk (RR) measure and its 95% confidence intervals (CIs). Risk estimates from individual trials were pooled by using the Der Simonian-Laird random-effects model.[18] When continuous measurements of outcomes were used, the weighted mean difference (WMD) and its CI were computed by using end-of-treatment values. Heterogeneity across included trials was analyzed by means of visual analysis of the forest plot and formally using the heterogeneity χ^2 (Cochran Q) statistic and the I^2 statistic. Subgroup analyses were performed as applicable based on a predefined study protocol and were reported when significant.[19] Sources of heterogeneity to be explored in subgroup analyses were the following: older versus newer phosphate-binding agents; baseline PTH levels; baseline phosphorus levels; type of calcium assay used in the study; use of washout of phosphate binder; study duration; quality items, including allocation concealment, blinding, and use of intention-to-treat analysis; number of patients lost to follow-up; and number of trial participants. Analyses were performed using Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), and Comprehensive Meta-analysis version 2 (Biostat, NJ, USA).

RESULTS

Search Results

The combined search of MEDLINE, EMBASE, and the Cochrane Library identified 2,381 citations, of which 2,298 were excluded after title and abstract review (Fig 1). Full-text assessment of 83 potentially relevant articles identified 40 eligible trials reported in 46 publications and enrolling 6,406 patients (Fig 1).[20-65] Investigators of 19 trials were contacted for additional information and clarification relating to study methods and additional unreported data, with 8 responding.

Trial Characteristics

Characteristics of participants and interventions of the included trials are listed in Table 1. Three different groups of trials were identified. The first group of trials compared any calcium salt with another calcium salt or placebo.[20-31] Seven trials (307 patients) compared calcium acetate with calcium carbonate,[20,23-26,28,29] and

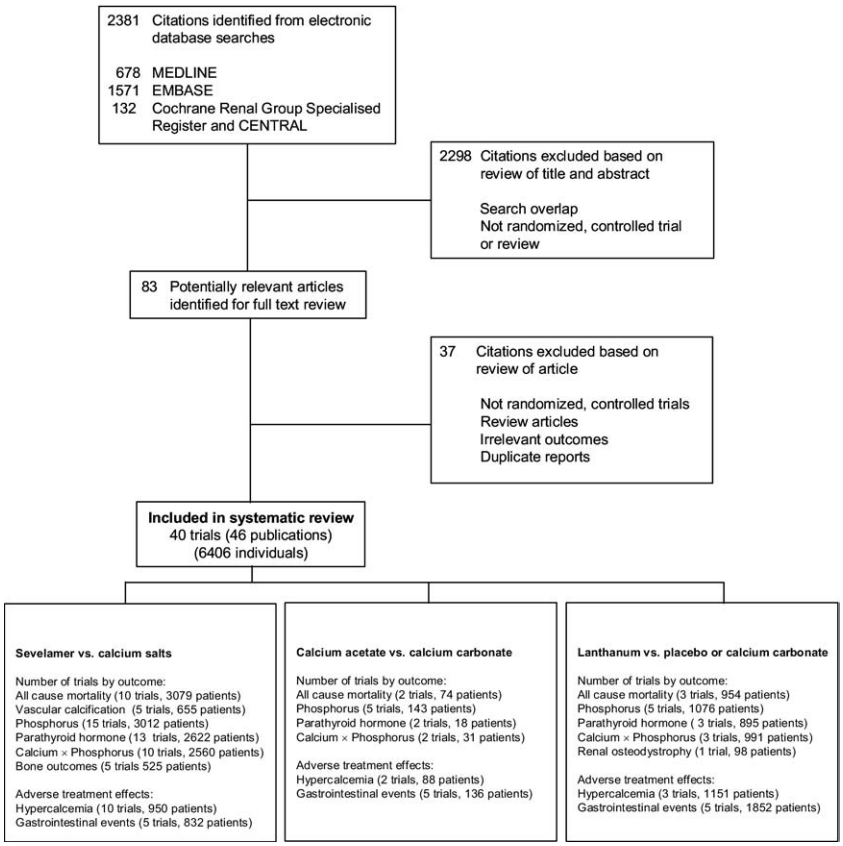

Figure 1. Literature search flow diagram. Reasons for exclusions and number of trials reporting each outcome are shown.

Table 1. Participant Characteristics and Interventions in Randomized Controlled Trials of Phosphate Binders in CKD

Study Type/Reference	Kidney Disease Stage	Intervention	Cointervention	Dialysate Calcium (mEq/L)/% Patients	No. of Patients	Follow-up (wk)
Calcium salt *v* other calcium salt/placebo						
Almirall et al,[20] 1994	HD	Calcium acetate, 3.8 g/d, *v* calcium carbonate, 4 g/d	Oral calcitriol	NA	10	24
Bro et al,[21] 1998	HD	Calcium ketoglutarate *v* calcium carbonate to achieve serum phosphorus < 5.3 mg/dL	Oral alfacalcidol	3.5/100	19	12
Birck et al,[22] 1999	HD	Calcium ketoglutarate *v* calcium carbonate to achieve serum phosphorus < 5.3 mg/dL	NA	2.5/100	28	12
Borrego et al,[23] 2000	Predialysis	Calcium acetate, 1.0 g/d, *v* calcium carbonate, 2.5 g/d	NA	2.5-3.5/100	28	6
Caravaca et al,[24] 1992	HD	Calcium acetate, 6.5 g/d, *v* calcium carbonate, 3.75 g/d	None	NA	80	16
Emmett et al,[25] 1991	HD	Calcium acetate *v* calcium carbonate to achieve serum phosphorus of 4.5-5.5 g/dL	Oral or IV vitamin D	3.25/100	91	2
d'Almeida Filho et al,[26] 2000	HD	Calcium acetate, 5.6 g/d, *v* calcium carbonate, 6.2 g/d	None	3.0-3.5/100	52	4
Phelps et al,[27] 2002	Predialysis	Calcium acetate, 2.0 g/d, *v* calcium acetate, 6.0 g/d	NA	3.5/100	18	8
Pflanz et al,[28] 1994	HD	Calcium acetate, 6.0 g/d, *v* calcium carbonate, 3.75 g/d	None	NA	31	6
Ring et al,[29] 1993	HD	Calcium acetate, 3.8 g/d, *v* calcium carbonate, 4 g/d	None	2.5/100	15	3
Rudnicki et al,[30] 1994*	HD	Calcium, 2.0 g/d, *v* placebo	Oral vitamin D	3.5/100	18	24
Schaeffer et al,[31] 1991	HD	Calcium acetate (6 g/d) *v* calcium acetate + calcitriol (4 μg, 2×/wk) *v* calcium acetate + calcitriol (0.5 μg, 2×/wk) *v* aluminum hydroxide + calcitriol (4 μg, 2×/wk)	Oral calcitriol	NA	47	7
Sevelamer *v* calcium salts						
Barreto et al,[32] 2008	HD	Sevelamer *v* calcium acetate or achieve serum phosphorus of 3.5-5.5 mg/dL	IV vitamin D	NA	101	52
Bleyer et al,[33] 1999	HD	Sevelamer *v* calcium acetate to achieve serum phosphorus of 2.5-5.5 mg/dL	Oral calcitriol	2.26-2.5/65 2.5-3.0/1.2 3.0-3.5/22.9	83	16
Block et al,[34] 2005	HD	Sevelamer *v* calcium acetate or calcium carbonate to achieve serum phosphorus < 6.5 mg/dL and serum calcium < 10.2 mg/dL	Oral or IV vitamin	2.5/100	129	72
Qunibi et al (CARE-2),[35] 2008	HD	Sevelamer + atorvastatin *v* calcium acetate + atorvastatin to achieve serum phosphorus of 3.5-5.5 mg/dL and LDL cholesterol < 70 mg/dL	NA	2.5/10	203	52
Chertow et al,[36] 1999	HD	Sevelamer *v* sevelamer + calcium carbonate to achieve serum phosphorus of 2.5-5.5 mg/dL	Oral or IV vitamin D		71	12
Chertow et al,[37] 2002	HD	Sevelamer *v* calcium acetate or calcium carbonate to achieve serum phosphorus of 3.0-5.0 mg/dL and calcium of 8.5-10.5 mg/dL	Oral or IV vitamin D	NA	200	52
Suki et al (DCOR),[38] 2007	HD	Sevelamer *v* calcium acetate or calcium carbonate	NA	NA	2,103	156
DeSanto et al,[39] 2006	HD	Sevelamer *v* calcium carbonate	NA	NA	16	24

(*Continued*)

Table 1 (Cont'd). Participant Characteristics and Interventions in Randomized Controlled Trials of Phosphate Binders in CKD

Study Type/Reference	Kidney Disease Stage	Intervention	Cointervention	Dialysate Calcium (mEq/L)/% Patients	No. of Patients	Follow-up (wk)
Evenepoel et al,[40] 2009	PD	Sevelamer *v* calcium acetate to achieve serum phosphorus of 3.0-5.5 mg/dL	IV vitamin D	NA	143	12
Ferreira et al,[41] 2008	HD	Sevelamer *v* calcium carbonate to achieve serum phosphorus of 3.2-5.0 mg/dL	IV vitamin D	NA	91	52
Kingusa et al,[42] 2001	HD	Sevelamer *v* calcium carbonate	NA	NA	230	8
Hervas et al,[43] 2003	HD	Sevelamer *v* calcium acetate	Oral or IV vitamin D	2.5/79 3.0/21	51	34
Koiwa et al,[44] 2005	HD	Sevelamer, 6 g/d, *v* sevelamer, 3 g/d, + calcium carbonate, 3 g/d, *v* calcium carbonate, 3 g/d	IV or oral calcitriol	3.0/100	86	8
Qunibi et al,[45] 2004	HD	Sevelamer *v* calcium acetate to achieve serum phosphorus < 5.5 mg/dL	IV vitamin D	2.5/100	98	8
Russo et al,[46] 2007	Predialysis	Sevelamer, 1,600 mg/d, *v* calcium carbonate, 2 g/d, *v* low-phosphate diet alone	NA	NA	90	104
Sadek et al,[47] 2003	HD	Sevelamer, 4.4 g/d, *v* calcium carbonate, 4.8 g/d	IV vitamin D	Varied	42	20
Shaheen et al,[48] 2004	HD	Sevelamer *v* calcium carbonate to achieve serum phosphorus, 2.5-5.5 mg/dL	Oral or IV vitamin D	3.5/100	20	8
Sevelamer *v* placebo						
Chertow et al,[49] 1997	HD	Sevelamer *v* placebo	Oral or IV vitamin D	NA	36	8
Lanthanum carbonate *v* calcium salts						
D'haese et al,[50] 2003	HD	Lanthanum carbonate up to 3,750 mg/d *v* calcium carbonate up to 9,000 mg/d	Oral or IV vitamin D	NA	98	52
Hutchison et al,[51] 2003	HD	Lanthanum carbonate *v* calcium carbonate to achieve serum phosphorus < 5.58 mg/dL	Oral or IV vitamin D	NA	800	20
Shigmetsu et al,[52] 2008	HD	Lanthanum carbonate *v* calcium carbonate	Oral or IV vitamin D	3.0/100	259	8
Spasovski et al,[53] 2006	HD	Lanthanum carbonate *v* calcium carbonate	Oral or IV vitamin D	NA	24	104
Lanthanum carbonate *v* placebo						
Al-Baaj et al,[54] 2003	HD	Lanthanum carbonate *v* placebo in patients with serum phosphorus of 4.03-5.58 mg/dL	Oral or IV vitamin D	NA	36	4
Chiang et al,[55] 2005	HD	Lanthanum carbonate, 375 mg-3.0 g/d, *v* placebo to achieve serum phosphorus < 5.6 mg/dL	Oral or IV vitamin D	NA	61	4
Finn et al,[56] 2004†	HD	Lanthanum carbonate *v* placebo to achieve serum phosphorus < 5.9 mg/dL	NA	NA	144	4
Joy et al,[57] 2003	HD	Lanthanum carbonate *v* placebo to achieve serum phosphorus < 5.9 mg/dL	Oral or IV vitamin D	NA	93	4
Lanthanum carbonate *v* others						
Malluche et al,[58] 2008	HD	Lanthanum carbonate *v* standard phosphate binder (sevelamer or calcium salts) to achieve serum phosphorus < 5.9 mg/dL	Oral or IV vitamin D	2.5/100	211	104
Mehrotra et al,[59] 2008‡	HD	Lanthanum carbonate, 3,000 *v* 3,750 *v* 4,500 mg/d	NA	NA	513	8

Abbreviations: CARE-2, Calcium Acetate Renagel Evaluation-2; DCOR, Dialysis Clinical Outcomes Revisited; IV, intravenous; NA, not available or not applicable or no data available; HD, hemodialysis; LDL, low-density lipoprotein; PD, peritoneal dialysis.

*All patients were continued on aluminum-containing phosphate binders.

†This study analyzed the efficacy of various doses of lanthanum carbonate.

‡This study had a 4-month open-label extension.

2 trials (47 patients) compared calcium ketoglutarate with calcium carbonate.[21,22] One trial (18 patients) compared calcium acetate with placebo,[30] and 2 trials (65 patients) compared different doses of calcium acetate.[27,31] Two studies included patients with CKD stages 3 and 4,[23,27] and the rest enrolled hemodialysis patients. Concomitant vitamin D analogues (intravenous or oral) were administered in most of these studies.

The second group compared the efficacy of sevelamer hydrochloride against calcium salts or placebo.[32-49] Five trials (476 patients) compared sevelamer with calcium acetate,[32,33,40,43,45] 6 trials (489 patients) compared sevelamer with calcium carbonate,[39,41,42,46-48] 2 trials (157 patients) compared sevelamer directly with sevelamer and calcium carbonate,[36,44] 3 trials (2,369 patients) compared sevelamer with calcium acetate and calcium carbonate,[34,37,38] 1 trial compared sevelamer plus atorvastatin with calcium acetate plus atorvastatin,[35] and 1 trial (36 patients) compared sevelamer with placebo.[49] All these trials were performed in patients on hemodialysis therapy, and oral or intravenous vitamin D compounds were used as cointervention in most patients.

The third group of trials (10 trials; 2,239 patients) compared lanthanum carbonate with calcium carbonate (4 studies; 1,181 patients),[50-53] lanthanum carbonate with placebo (4 studies; 334 patients),[54-57] different doses of lanthanum carbonate, and lanthanum carbonate with standard phosphate binders (sevelamer and calcium salts) in dialysis patients.[58,59]

The majority of trials included in this review were of short duration (1 to 18 months of treatment administration), except for the Dialysis Clinical Outcomes Revisited (DCOR) trial,[38] which analyzed the efficacy of phosphate binders to decrease serum phosphorus levels, in which 42% of patients had follow-up longer than 24 months. The number of participants ranged from 10 to 2,103, with 27 of 40 (67%) trials enrolling fewer than 100 participants. Coadministration of vitamin D analogues and route of administration of these agents varied among studies. Assays used to measure PTH also differed in the included studies. Most studies defined hypercalcemia as serum calcium level greater than 10.2 mg/dL, whereas some used greater than 10.5 mg/dL and some used greater than 11.0 mg/dL as a cutoff value to define hypercalcemia.

Trial Quality

According to current method standards for reporting, trial quality was variable. Allocation concealment was adequate in 10 of 40 (25%) trials and unclear in others. Participants and investigators were blinded in 8 of 40 (20%) trials, and outcome assessors were blinded in no trial. Only 13 of the 40 (33%) trials were analyzed on an intention-to-treat basis. Patients lost to follow-up ranged from 0% to 31%, but did not differ between the treatment and control groups of the trials.

Trial Results

Patient-Level Outcomes

All-cause Mortality. There was no significant reduction in risk of all-cause mortality with calcium acetate in comparison to calcium carbonate. Similarly, there was no significant reduction in risk of all-cause mortality with sevelamer in comparison to calcium salts (10 trials; 3,079 patients; RR, 0.73; 95% CI, 0.46 to 1.16; Fig 2); data for mortality primarily derive from 1 large trial (DCOR).[36] No deaths were reported in the included studies that compared lanthanum carbonate with placebo or calcium carbonate; thus, mortality could not be ascertained for this comparison.

Hospitalization. Two trials reported hospitalization details. However, these reports could not be pooled because of differences in reporting methods. In 1 trial, the number of patients hospitalized within 52 weeks was reported, with no significant difference in risk of hospitalization between sevelamer and calcium salts ($P = 0.15$).[37] In another trial, the number of days hospitalized per patient-year was reported, with no difference between sevelamer and calcium salts for this outcome ($P = 0.09$).[38]

Hypercalcemia. There was no significant difference in risk of hypercalcemia with calcium acetate in comparison to calcium carbonate (Table 2). However, there was a significant decrease in risk of hypercalcemia with sevelamer in comparison to calcium salts (RR, 0.47; 95% CI, 0.36 to 0.62) and with lanthanum carbonate in comparison to calcium carbonate (RR, 0.08; 95% CI, 0.02 to 0.32; Table 2).

Gastrointestinal Events. There was no significant difference in risk of adverse gastrointestinal

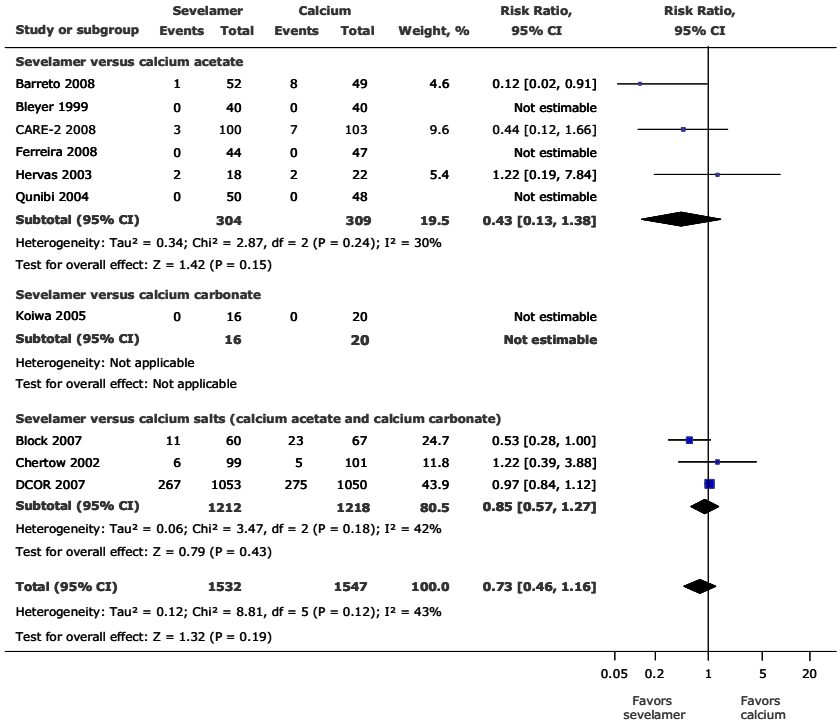

Figure 2. Effect of sevelamer compared with calcium salts on all-cause mortality in people with chronic kidney disease. Abbreviation: CI, confidence interval.

events with calcium acetate in comparison to calcium carbonate or with lanthanum carbonate in comparison to placebo or calcium carbonate (Table 2). However, there was a significant increase in risk of gastrointestinal events with sevelamer in comparison to calcium salts (RR, 1.39; 95% CI, 1.04 to 1.87; Table 2). Gastrointestinal side effects reported with sevelamer included abdominal bloating, diarrhea, and constipation.

Biochemical and Other Surrogate End Points

Serum Phosphorus. There was no significant difference in end-of-treatment serum phosphorus levels with calcium acetate in comparison to calcium carbonate or with lanthanum carbonate in comparison to calcium carbonate (Fig 3). There was a significantly greater end-of-treatment serum phosphorus level with sevelamer in comparison to calcium salts (WMD, 0.21 mg/dL; 95% CI, 0.01 to 0.41; Fig 3). There was a significant decrease in end-of-treatment phosphorus level with calcium in comparison to placebo (2 trials; 90 patients; WMD, −1.41 mg/dL; 95% CI, −2.52 to −0.29). Similarly, there was a significant decrease in end-of-treatment phosphorus level with sevelamer in comparison to placebo (1 trial; 36 patients; WMD, −1.80 mg/dL; 95% CI, −3.32 to −0.28). Combination treatment with sevelamer and calcium carbonate had no synergistic effect on serum phosphorus level compared with sevelamer alone (1 trial; 71 patients; WMD, −0.20 mg/dL; 95% CI, −1.14 to 0.74).

Serum Calcium. There was no significant difference in end-of-treatment calcium level with calcium acetate in comparison to calcium carbonate (Table 3). End-of-treatment calcium levels were significantly lower with sevelamer compared with calcium salts (WMD, −0.35 mg/dL; 95% CI, −0.46 to −0.24). Similarly, there was a significantly lower end-of-treatment calcium level with lanthanum carbonate in comparison to calcium carbonate (WMD, −0.45 mg/dL; 95% CI, −0.64 to −0.25).

Serum PTH. There was no significant difference in end-of-treatment PTH level with calcium acetate in comparison to calcium carbonate or with lanthanum carbonate compared with calcium carbonate (Fig 4). There was a significantly greater end-of-treatment PTH level with sevelamer compared with calcium salts (WMD, 55.57 pg/mL; 95% CI, 26.69 to 84.45) and a decrease in end-of-treatment PTH level with lanthanum

Table 2. Effect of Phosphate Binders on Patient-Level End Points in Patients With CKD

Outcome Analyzed	No. of Studies Reporting Outcome	Treatment n/N *v* Control n/N	Relative Risk	95% Confidence Interval	Overall *P*	χ^2	*P* for Heterogeneity	I^2 (%)
Calcium acetate *v* calcium carbonate								
Mortality	2	1/35 *v* 1/39	1.13	0.07-17.30	0.9	—	—	—
Hypercalcemia	2	6/41 *v* 10/47	1.08	0.11-10.99	0.9	2.46	0.1	59
Gastrointestinal toxicity	3	12/67 *v* 9/69	1.26	0.61-2.60	0.5	0.92	0.9	0
Calcium salts *v* placebo								
Mortality	—	—	—	—	—	—	—	—
Hypercalcemia	—	—	—	—	—	—	—	—
Gastrointestinal toxicity	—	—	—	—	—	—	—	—
Sevelamer hydrochloride *v* calcium salts								
Mortality	10	290/1,532 *v* 320/1,547	0.73	0.46-1.16	0.2	8.81	0.14	43
Hypercalcemia	10	54/503 *v* 120/457	0.47	0.36-0.62	<0.001	8.10	0.4	1
Gastrointestinal toxicity	5	104/310 *v* 64/263	1.39	1.04-1.87	0.03	6.95	0.4	0
Sevelamer hydrochloride *v* placebo								
Mortality	1	0/24 *v* 0/12	—	—	—	—	—	—
Hypercalcemia	—	—	—	—	—	—	—	—
Gastrointestinal toxicity	2	2/48 *v* 2/24	0.54	0.08-3.45	0.5	0.79	0.4	0
Lanthanum carbonate *v* calcium carbonate								
Mortality	1	0/533 *v* 0/267	—	—	—	—	—	—
Hypercalcemia	3	12/705 *v* 116/446	0.08	0.02-0.32	<0.001	8.92	0.01	78
Gastrointestinal toxicity	3	124/1,115 *v* 68/583	1.09	0.84-1.41	—	1.16	0.6	0
Lanthanum carbonate *v* placebo								
Mortality	2	0/79 *v* 0/75	—	—	—	—	—	—
Hypercalcemia	—	—	—	—	—	—	—	—
Gastrointestinal toxicity	2	10/79 *v* 9/75	1.05	0.45-2.45	0.9	0.30	0.6	0

Note: Gastrointestinal toxicity includes gastritis, diarrhea, and gastrointestinal upset. Relative risk less than 1 favors the experimental intervention, and relative risk of 1 or higher favors the control intervention.

carbonate in comparison to placebo (WMD, −83.00 pg/mL; 95% CI, −154.63 to −11.37).

Ca × P. There was no significant difference in end-of-treatment Ca × P level with calcium acetate in comparison to calcium carbonate and sevelamer in comparison to calcium salts (Table 3). There was a significantly lower end-of-treatment Ca × P level with lanthanum carbonate in comparison to placebo (WMD, −14.20 mg^2/dL^2; 95% CI, −21.03 to −7.37) and with lanthanum carbonate in comparison to calcium carbonate (WMD, −3.82 mg^2/dL^2; 95% CI, −7.47 to −0.16).

Serum Bicarbonate. There was no significant difference in end-of-treatment serum bicarbonate level between calcium acetate and calcium carbonate. There was a significantly lower end-of-treatment serum bicarbonate level with sevelamer in comparison to calcium salts (WMD, −1.43 mEq/L; 95% CI, −2.07 to −0.79; Table 3).

Other Biochemical End Points. There was no significant difference in end-of-treatment alkaline phosphatase level with sevelamer in comparison to calcium salts (Table 3). There was a significant difference in end-of-treatment total cholesterol level with sevelamer in comparison to calcium salts (WMD, −20.55 mg/dL; 95% CI, −29.15 to −11.96; Table 3).

Vascular Calcification. Five studies reported the effects of sevelamer and calcium salts on vascular calcification[32,34,35,37,41] (Table 4). One study reported slower progression of coronary, aortic, and heart valve calcification (measured by using electron beam computed tomography) with use

Figure 3. Effect of phosphate binders on end-of-treatment serum phosphorus concentration in people with chronic kidney disease. Conversion factor for phosphorus in mg/dL to mmol/L, ×0.3229. Abbreviation: CI, confidence interval.

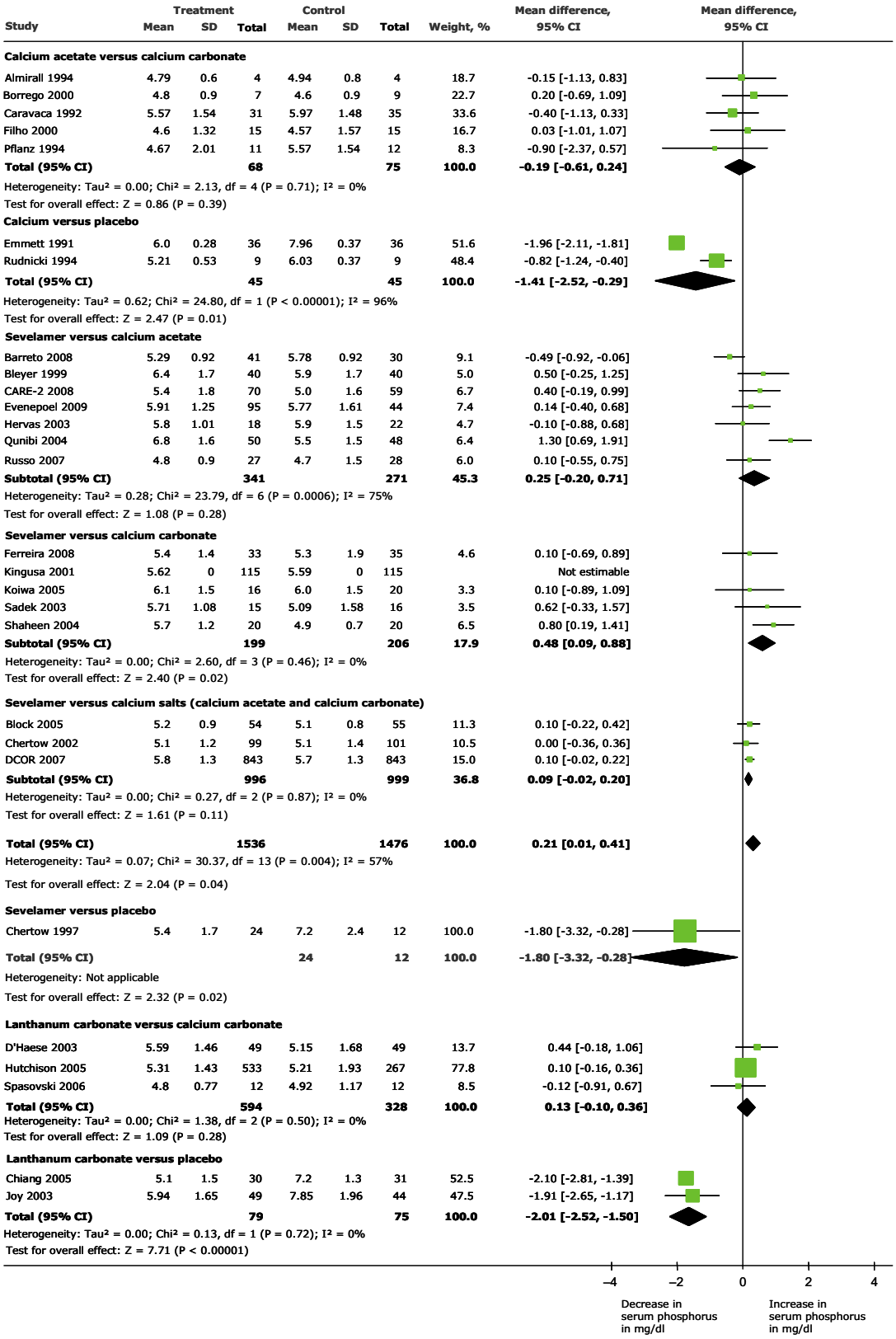
Treatment
Control
Mean difference, 95% CI
Mean difference, 95% CI
Study
Mean SD Total Mean SD Total Weight, % 95% CI
Calcium acetate versus calcium carbonate
Almirall 1994 4.79 0.6 4 4.94 0.8 4 18.7 -0.15 [-1.13, 0.83]
Borrego 2000 4.8 0.9 7 4.6 0.9 9 22.7 0.20 [-0.69, 1.09]
Caravaca 1992 5.57 1.54 31 5.97 1.48 35 33.6 -0.40 [-1.13, 0.33]
Filho 2000 4.6 1.32 15 4.57 1.57 15 16.7 0.03 [-1.01, 1.07]
Pflanz 1994 4.67 2.01 11 5.57 1.54 12 8.3 -0.90 [-2.37, 0.57]
Total (95% CI) 68 75 100.0 -0.19 [-0.61, 0.24]
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)
Calcium versus placebo
Emmett 1991 6.0 0.28 36 7.96 0.37 36 51.6 -1.96 [-2.11, -1.81]
Rudnicki 1994 5.21 0.53 9 6.03 0.37 9 48.4 -0.82 [-1.24, -0.40]
Total (95% CI) 45 45 100.0 -1.41 [-2.52, -0.29]
Heterogeneity: Tau² = 0.62; Chi² = 24.80, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.47 (P = 0.01)
Sevelamer versus calcium acetate
Barreto 2008 5.29 0.92 41 5.78 0.92 30 9.1 -0.49 [-0.92, -0.06]
Bleyer 1999 6.4 1.7 40 5.9 1.7 40 5.0 0.50 [-0.25, 1.25]
CARE-2 2008 5.4 1.8 70 5.0 1.6 59 6.7 0.40 [-0.19, 0.99]
Evenepoel 2009 5.91 1.25 95 5.77 1.61 44 7.4 0.14 [-0.40, 0.68]
Hervas 2003 5.8 1.01 18 5.9 1.5 22 4.7 -0.10 [-0.88, 0.68]
Qunibi 2004 6.8 1.6 50 5.5 1.5 48 6.4 1.30 [0.69, 1.91]
Russo 2007 4.8 0.9 27 4.7 1.5 28 6.0 0.10 [-0.55, 0.75]
Subtotal (95% CI) 341 271 45.3 0.25 [-0.20, 0.71]
Heterogeneity: Tau² = 0.28; Chi² = 23.79, df = 6 (P = 0.0006); I² = 75%
Test for overall effect: Z = 1.08 (P = 0.28)
Sevelamer versus calcium carbonate
Ferreira 2008 5.4 1.4 33 5.3 1.9 35 4.6 0.10 [-0.69, 0.89]
Kingusa 2001 5.62 0 115 5.59 0 115 Not estimable
Koiwa 2005 6.1 1.5 16 6.0 1.5 20 3.3 0.10 [-0.89, 1.09]
Sadek 2003 5.71 1.08 15 5.09 1.58 16 3.5 0.62 [-0.33, 1.57]
Shaheen 2004 5.7 1.2 20 4.9 0.7 20 6.5 0.80 [0.19, 1.41]
Subtotal (95% CI) 199 206 17.9 0.48 [0.09, 0.88]
Heterogeneity: Tau² = 0.00; Chi² = 2.60, df = 3 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.40 (P = 0.02)
Sevelamer versus calcium salts (calcium acetate and calcium carbonate)
Block 2005 5.2 0.9 54 5.1 0.8 55 11.3 0.10 [-0.22, 0.42]
Chertow 2002 5.1 1.2 99 5.1 1.4 101 10.5 0.00 [-0.36, 0.36]
DCOR 2007 5.8 1.3 843 5.7 1.3 843 15.0 0.10 [-0.02, 0.22]
Subtotal (95% CI) 996 999 36.8 0.09 [-0.02, 0.20]
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.61 (P = 0.11)
Total (95% CI) 1536 1476 100.0 0.21 [0.01, 0.41]
Heterogeneity: Tau² = 0.07; Chi² = 30.37, df = 13 (P = 0.004); I² = 57%
Test for overall effect: Z = 2.04 (P = 0.04)
Sevelamer versus placebo
Chertow 1997 5.4 1.7 24 7.2 2.4 12 100.0 -1.80 [-3.32, -0.28]
Total (95% CI) 24 12 100.0 -1.80 [-3.32, -0.28]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.32 (P = 0.02)
Lanthanum carbonate versus calcium carbonate
D'Haese 2003 5.59 1.46 49 5.15 1.68 49 13.7 0.44 [-0.18, 1.06]
Hutchison 2005 5.31 1.43 533 5.21 1.93 267 77.8 0.10 [-0.16, 0.36]
Spasovski 2006 4.8 0.77 12 4.92 1.17 12 8.5 -0.12 [-0.91, 0.67]
Total (95% CI) 594 328 100.0 0.13 [-0.10, 0.36]
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)
Lanthanum carbonate versus placebo
Chiang 2005 5.1 1.5 30 7.2 1.3 31 52.5 -2.10 [-2.81, -1.39]
Joy 2003 5.94 1.65 49 7.85 1.96 44 47.5 -1.91 [-2.65, -1.17]
Total (95% CI) 79 75 100.0 -2.01 [-2.52, -1.50]
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 7.71 (P < 0.00001)
−4 −2 0 2 4
Decrease in serum phosphorus in mg/dl
Increase in serum phosphorus in mg/dl

Table 3. Effect of Phosphate Binders on Biochemical End Points in Patients With CKD

Outcome Analyzed	No. of Studies Reporting Outcome	No. of Patients	Weighted Mean Difference	95% Confidence Interval	Overall *P*	χ^2	*P* for Heterogeneity	I^2 (%)
Calcium acetate *v* calcium carbonate								
Calcium (mg/dL)	5	143	−0.09	−0.35 to 0.17	0.5	5.0	0.3	19.9
Calcium-phosphorus product (mg^2/dL^2)	2	31	−4.92	−10.03 to 0.19	0.06	3.26	0.07	69.7
Alkaline phosphatase (IU/L)	4	74	1.42	−8.99 to 11.82	0.8	0.37	0.9	0
Total cholesterol (mg/dL)	—	—	—	—	—	—	—	—
Bicarbonate (mEq/L)	2	53	0.21	−1.32 to 1.74	0.8	1.24	0.3	19.3
Calcium acetate *v* placebo								
Calcium (mg/dL)	—	—	—	—	—	—	—	—
Calcium-phosphorus product (mg^2/dL^2)	—	—	—	—	—	—	—	—
Alkaline phosphatase (IU/L)	1	18	−1.0	−22.33 to 20.33	—	—	—	—
Total cholesterol (mg/dl)	—	—	—	—	—	—	—	—
Bicarbonate (mEq/L)	—	—	—	—	—	—	—	—
Sevelamer *v* calcium salts								
Calcium (mg/dL)	14	2,925	−0.35	−0.46 to −0.24	<0.001	28.72	0.004	58.0
Calcium-phosphorus product (mg^2/dL^2)	10	2,560	0.61	−1.02 to 2.24	0.5	13.24	0.2	32.0
Alkaline phosphatase (IU/L)	3	156	12.36	−10.79 to 35.51	0.3	1.35	0.5	0
Total cholesterol (mg/dL)	9	1,674	−20.55	−29.15 to −11.96	<0.001	22.89	0.004	65
Bicarbonate (mEq/L)	5	381	−1.43	−2.07 to −0.79	<0.001	1.75	0.8	0
Sevelamer acetate *v* placebo								
Calcium (mg/dL)	1	36	−0.10	−0.52 to 0.32	0.6	—	—	—
Calcium-phosphorus product (mg^2/dL^2)	—	—	—	—	—	—	—	—
Alkaline phosphatase (IU/L)	—	—	—	—	—	—	—	—
Total cholesterol (mg/dL)	—	—	—	—	—	—	—	—
Bicarbonate (mEq/L)	1	36	−0.50	−2.53 to 1.53	0.6	—	—	—
Lanthanum carbonate *v* calcium carbonate								
Calcium (mg/dL)	3	922	−0.45	−0.64 to −0.25	<0.001	3.05	0.2	34.4
Calcium-phosphorus product (mg^2/dL^2)	2	898	−3.82	−7.47 to −0.16	0.04	3.07	0.08	67.4
Alkaline phosphatase (IU/L)	2	824	29.01	2.28 to 55.74	0.03	2.04	0.2	51
Total cholesterol (mg/dL)	—	—	—	—	—	—	—	—
Bicarbonate (mEq/L)	—	—	—	—	—	—	—	—
Lanthanum carbonate *v* placebo								
Calcium (mg/dL)	1	93	0.35	0.04 to 0.66	0.02	—	—	—
Calcium-phosphorus product (mg^2/dL^2)	1	93	−14.20	−21.03 to −7.37	<0.001	—	—	—
Alkaline phosphatase (IU/L)	—	—	—	—	—	—	—	—
Total cholesterol (mg/dL)	—	—	—	—	—	—	—	—
Bicarbonate (mEq/L)	—	—	—	—	—	—	—	—

Note: Conversion factors for units: Calcium in mg/dL to mmol/L, ×0.2495; total cholesterol in mg/dL to mmol/L, ×0.02586. Bicarbonate in mEq/L and mmol/L requires no conversion.

of sevelamer in comparison to calcium acetate[37] by using the Agatston scoring system. Similarly, another study showed decreased progression of coronary artery calcification with sevelamer compared with calcium salts in incident hemodialysis patients[34] (Table 4). In contrast, a third study compared sevelamer plus atorvastatin with calcium acetate plus atorvastatin and reported similar coronary artery calcification progression in both groups.[35] There also was a study that reported coronary artery calcium scores in 101 dialysis patients (using a modified Agatston scoring system) and reported no difference in coronary artery calcification progression between the sevelamer and calcium groups ($P = 0.59$).[32] Included studies used different scoring systems to assess vascular calcification and thus could not be pooled.

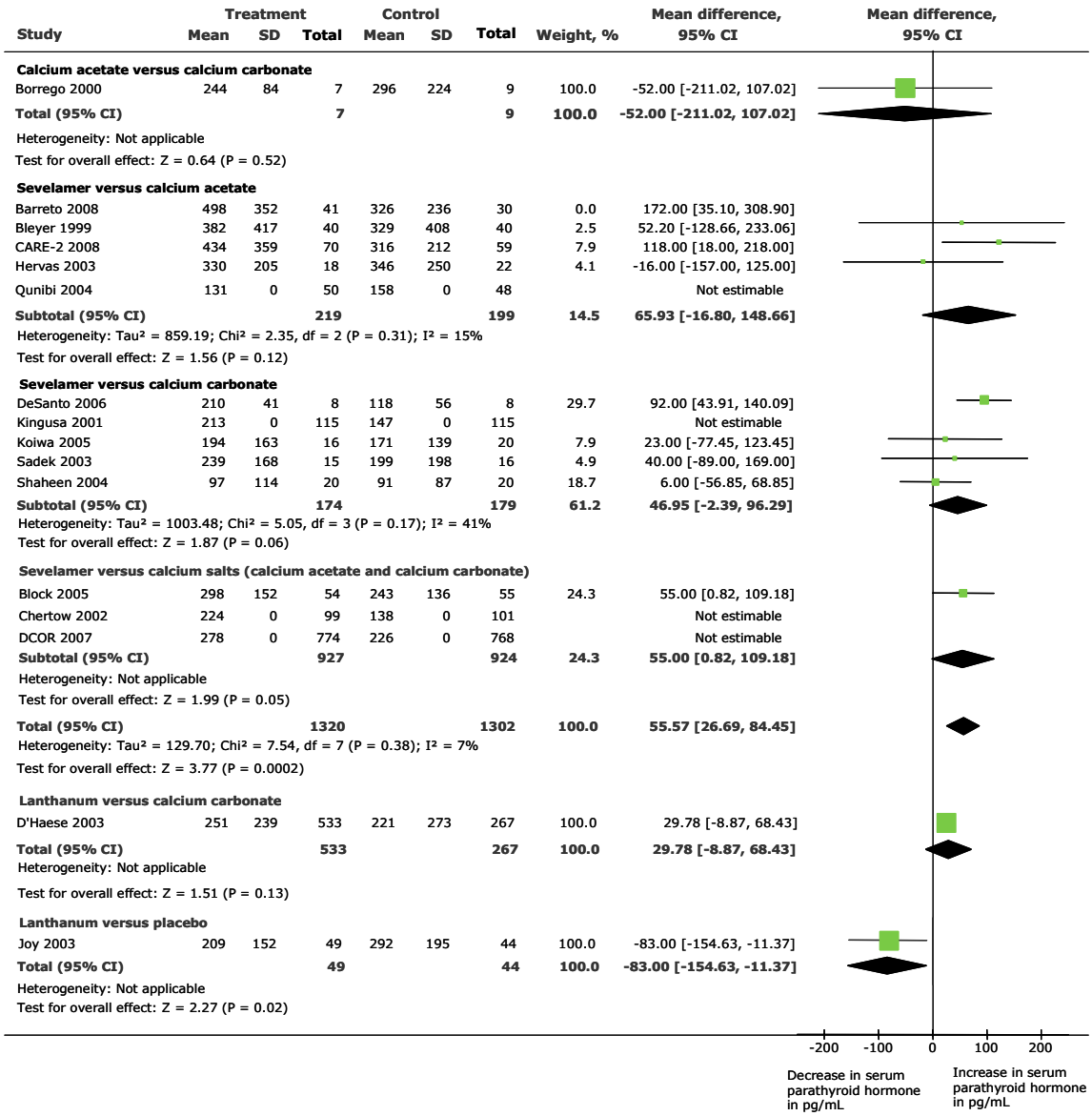

Figure 4. Effect of phosphate binders on end-of-treatment parathyroid hormone concentration (pg/mL) in people with chronic kidney disease. Parathyroid hormone in pg/mL and ng/L requires no conversion. Abbreviation: CI, confidence interval.

Bone Outcomes. Lanthanum carbonate decreased the number of patients developing low-turnover bone disease in comparison to calcium carbonate[53] and resulted in improvement in bone volume in comparison to standard phosphate-binder therapy[58] (Table 4). Aluminum-like effects on bone were not noted in follow-up studies that assessed the safety of lanthanum carbonate.[53] Based on electron beam computed tomographic results, 1 study reported a significant decrease in trabecular bone attenuation and a trend toward a decrease in cortical bone attenuation ($P = 0.05$) in thoracic vertebrae with sevelamer compared with calcium salts.[62] In another study enrolling 101 dialysis patients, there was no difference in bone remodeling between the sevelamer and calcium groups at the end of 1 year of follow-up.[31] Another study reported increased bone formation and improved trabecular architecture, but no significant change in bone

Table 4. Characteristics and Key Results of Studies Analyzing Effects of Various Phosphate Binders on Bone Densitometry, Bone Histomorphometry, and Vascular Calcification

Reference	Comparisons	Study Duration (mo)	No. of Participants	Outcomes Analyzed	Key Findings
Barreto et al,[32] 2008	Sevelamer *v* calcium acetate	12	101	(1) CAC scores using electron beam computed tomography, (2) bone histomorphometry	CAC progression and bone remodeling did not differ between the 2 groups
Block et al,[34] 2005	Sevelamer *v* calcium carbonate + calcium acetate	18	129	CAC scores by using electron beam computed tomography	Calcium-containing phosphate binders increased CAC scores compared with sevelamer ($P = 0.01$)
Chertow et al,[37] 2002	Sevelamer *v* calcium acetate	12	132	Vascular calcification scores* (Agatston scores) using electron beam computed tomography	Coronary, aortic, and valvular calcification progressed in calcium-treated patients, but no significant progression was noted in the sevelamer-treated group
Qunibi et al (CARE-2),[35] 2008	Sevelamer + atorvastatin *v* calcium acetate + atorvastatin	12	203	Vascular calcification scores (Agatston scores) using electron beam computed tomography	Coronary calcification scores were similar in both groups
Raggi et al,[62] 2005†	Sevelamer *v* calcium acetate	12	111	Thoracic vertebral bone attenuation using electron beam computed tomography	Trabecular bone attenuation decreased significantly in sevelamer-treated patients ($P < 0.05$) Cortical bone attenuation did not decrease significantly with sevelamer ($P = 0.05$)
Russo et al,[46] 2007	Sevelamer *v* calcium carbonate *v* low-phosphorus diet	24	90	CAC scores using electron beam computed tomography	Sevelamer reduced the progression of CAC, whereas calcium carbonate did not increase or decrease CAC progression
D'Haese et al,[50] 2003	Lanthanum carbonate *v* placebo	12	98	Bone histomorphometry analyzing: (1) Development or improvement in various types of renal osteodystrophy (adynamic bone disease, osteomalacia, mixed renal osteodystrophy, hyperparathyroidism) (2) Lanthanum content in bone	(1) Prevalence of renal osteodystrophy decreased from 36% to 18% in the lanthanum carbonate group and increased from 43% to 53% in calcium carbonate patients (2) Bone lanthanum levels were higher in lanthanum carbonate than calcium carbonate patients
Phelps et al,[27] 2002	Calcium acetate, 2 g/d, *v* calcium acetate, 6 g/d	18	24	BMD at lumbar spine, femoral neck, and greater trochanter by using DEXA	No significant difference between treatment groups
Ferreira et al,[41] 2008	Sevelamer *v* calcium carbonate	12	91	Mineralization lag time, changes in bone turnover, development of osteomalacia, adynamic bone disease	Bone formation and trabecular architecture increased with sevelamer, with no changes in bone turnover or mineralization
Malluche et al,[58] 2008	Lanthanum carbonate *v* standard phosphate-binder therapy	24	211	Bone histomorphometry analyzing changes in bone turnover, mineralization, bone volume, and lanthanum content in bone	Patients administered lanthanum carbonate had improvement in bone turnover and bone volume

Abbreviations: BMD, bone mineral density; CAC, coronary artery calcification; CARE-2, Calcium Acetate Renagel Evaluation-2; DEXA, dual-energy X-ray absorptiometry.

*Agatston score was obtained by multiplying the area of calcified focus by a weighted density coefficient based on the peak density of the calcification noted on electron beam computed tomography.

†Substudy of Chertow 2002.[37]

turnover or mineralization, with sevelamer in comparison to calcium salts.[41] A formal meta-analysis could not be performed for the incidence of fracture because of insufficient data.

Investigation for Sources of Heterogeneity by Subgroup Analysis

Because heterogeneity was observed in many analyses, we explored the potential sources of heterogeneity by using subgroup analysis (Table 5). This was possible for trials comparing either sevelamer hydrochloride or lanthanum carbonate with calcium salts, whereas other treatment comparisons contained too few trials. Some covariates, including measures of trial quality (blinding and intention-to-treat analysis), patient characteristics (baseline PTH concentration), and study characteristics (study duration), were significant effect modifiers on some outcomes. However, data often were insufficient to allow definitive conclusions to be drawn.

DISCUSSION

Our systematic review has identified a large number of RCTs that examine phosphate binders in people with CKD. These trials have not shown that phosphate binders compared with placebo or calcium salts compared with non–calcium- or aluminum-containing agents decrease all-cause or cardiovascular mortality. As expected, all phosphate binders decreased serum phosphorus levels compared with placebo; however, newer agents (lanthanum carbonate and sevelamer) did not result in consistently superior biochemical outcomes compared with calcium-based therapies. Rather, in direct comparisons (head-to-head studies), calcium salts were superior to sevelamer for reduction of serum phosphorus levels. Compared with calcium salts, sevelamer and lanthanum carbonate were associated with significantly lower rates of treatment-related hypercalcemia, which may result in decreased vascular calcification. The differential effect on serum calcium and phosphorus levels resulted in increased PTH suppression by treatment with calcium compared with sevelamer. The efficacy of available phosphate-binding agents on the surrogate outcomes of bone mineral density or histomorphometry and vascular calcification have been reported heterogeneously in few studies, and reliable conclusions could not be drawn through meta-analysis.

Sevelamer was associated with lower serum calcium, higher phosphorus, and higher PTH levels at the end-of-treatment period compared with calcium salts. This may be caused by noncompliance, resulting in less phosphorus reduction with sevelamer, or because it is less effective at the relative doses used. Various gastrointestinal adverse effects, such as constipation, abdominal bloating, dyspepsia, nausea, and vomiting, were reported with sevelamer and calcium salts in clinical trials. Although most individual studies reported no significant difference in gastrointestinal side effects between sevelamer and calcium salts, there was significantly greater occurrence with sevelamer when studies were pooled. This also might have contributed to lower compliance and higher pill burdens reported for sevelamer. Sevelamer resulted in lower end-of-treatment serum calcium levels, which might have contributed to the greater PTH levels noted.

The DCOR Study, the largest trial (n = 2,103) conducted to date, reported no difference in risk of all-cause mortality between sevelamer and calcium salts,[38] except for a subgroup analysis in patients older than 65 years who completed a 2-year follow-up. Because of the size of this study, DCOR was very influential and contributed 46% of the weight in our all-cause mortality analysis. Exclusion of this study resulted in a similar, but smaller, risk of all-cause mortality (RR, 0.59 [95% CI, 0.35 to 1.01] versus RR, 0.75 [95% CI, 0.48 to 1.16]). Given the limitations of the analysis by Suki et al,[38] we also conducted a sensitivity analysis using data from St Peters et al,[66] who used Centers for Medicare & Medicaid Services claims data to reassess the DCOR trial results. The risk of all-cause mortality was unchanged (RR, 0.75; 95% CI, 0.56 to 1.33) by using these data.

The occurrence, progression, and prognostic importance of vascular calcification are important questions in CKD, and the influence of calcium-based binders on progression of vascular calcification is a matter of intense debate.[67-70] Two studies in the present analysis reported a greater rate of progression of vascular calcification with calcium salts compared with sevelamer,[34,37] whereas 1 study showed no difference in calcium scores between sevelamer and cal-

Table 5. Subgroup Analyses to Explore Reasons for Heterogeneity in Trials Comparing Newer Agents With Older Phosphate-Binding Agents

Variables	All-Cause Mortality		Treatment-Related Hypercalcemia		End-of-Treatment PTH (pg/mL)		End-of-Treatment Serum Phosphorus (mg/dL)	
	Relative Risk (95% CI)/ No. of Trials	*P*	Relative Risk (95% CI)/ No. of Trials	*P*	Weighted Mean Difference (95% CI)/No. of Trials	*P*	Weighted Mean Difference (95% CI)/No. of Trials	*P*
Older *v* newer agents		0.8		0.1		0.8		0.2
Sevelamer & lanthanum *v* calcium carbonate	0.75 (0.39 to 1.44)/4		0.45 (0.28 to 0.73)/5		51.72 (17.66 to 85.78)/5		0.09 (−0.06 to 0.25)/10	
Sevelamer & lanthanum *v* calcium acetate	0.64 (0.21 to 1.94)/2		0.20 (0.07 to 0.50)/6		62.02 (−21.97 to 146.03)/3		0.41 (0.00 to 0.82)/6	
Baseline PTH (pg/mL)		0.6		**<0.001**		0.2		0.5
<150	—		0.02 (0.00 to 0.08)/1		—		0.10 (−0.13 to 0.33)/1	
150-300	0.44 (0.04 to 4.3)/2		0.30 (0.16 to 0.56)/5		42.53 (8.26 to 76.81)/8		0.11 (−0.19 to 0.43)/7	
>300	0.81 (0.48 to 1.37)/4		0.42 (0.16 to 0.54)/5		118.00 (8.18 to 218.0)/1		0.31 (0.02 to 0.60)/8	
Type of calcium assay		**0.04**		0.7		0.4		0.4
Corrected calcium	0.56 (0.29 to 1.07)/4		0.25 (0.11 to 0.55)/7		57.89 (24.55 to 91.24)/8		0.13 (−0.11 to 0.37)/9	
Absolute calcium	1.12 (0.96 to 1.29)/2		0.31 (0.14 to 0.68)/4		26.58 (−10.70 to 63.86)/3		0.28 (0.01 to 0.54)/7	
Ionized calcium	—		—		—		—	
Washout of phosphate binder		NA		0.8		0.2		0.8
Yes	0.75 (0.44 to 1.27)/5		0.27 (0.15 to 0.48)/10		58.16 (27.43 to 88.89)/9		0.18 (0.01 to 0.36)/14	
No	—		0.36 (0.04 to 3.05)/1		29.42 (−49.84 to 108.7)/2		0.36 (−0.32 to 1.05)/2	
Study duration (mo)		0.2		**0.01**		0.6		**0.008**
<6	—		0.24 (0.13 to 0.46)/5		17.61 (−29.91 to 65.12)/6		0.48 (0.11 to 0.85)/7	
6-12	0.43 (0.14 to 1.27)/3		0.62 (0.42 to 0.89)/2		59.17 (−38.19 to 156.54)/2		−0.30 (−0.65 to 0.03)/3	
>12	0.90 (0.53 to 1.53)/3		0.16 (0.04 to 0.62)/4		49.95 (11.66 to 88.25)/4		0.11 (0.01 to 0.21)/6	
Allocation concealment		0.5		0.3		0.3		0.9
Adequate	0.57 (0.31 to 1.03)/2		0.41 (0.24 to 0.68)/5		49.95 (11.66 to 88.25)/4		0.19 (−0.02 to 0.40)/7	
Unclear	0.79 (0.39 to 1.62)/4		0.21 (0.07 to 0.60)/6		67.29 (28.73 to 105.86)/6		0.19 (−0.03 to 0.43)/9	
Blinding		NA		0.7		NA		**<0.001**
Yes	—		0.36 (0.10 to 1.28)/1		—		1.30 (0.68 to 1.91)/1	
No	0.88 (0.58 to 1.35)/5		0.27 (0.15 to 0.47)/10		47.95 (23.78 to 72.13)/11		0.11 (−0.01 to 0.23)/15	
Intention-to-treat analysis		0.4		**0.03**		NA		0.7
Yes	0.67 (0.35 to 1.26)/5		0.49 (0.37 to 0.66)/6		—		0.22 (0.01 to 0.45)/7	
No	1.22 (0.38 to 1.34)/1		0.15 (0.04 to 0.44)/5		54.78 (25.90 to 83.66)/8		0.16 (−0.13 to 0.46)/9	
Lost to follow-up (%)		0.4		0.07		0.5		0.3
0	—		—		—		—	
1-10	—		0.21 (0.10 to 0.43)/3		30.76 (−7.04 to 68.56)/3		0.49 (−0.01 to 0.99)/5	
10-20	1.22 (0.38 to 3.88)/1		0.15 (0.02 to 1.26)/3		6.00 (−56.85 to 68.85)/2		0.18 (−0.10 to 0.47)/4	
>20	0.67 (0.35 to 1.26)/5		0.49 (0.33 to 0.72)/5		58.32 (15.72 to 100.92)/4		0.05 (−0.13 to 0.25)/7	
No. of trial participants		0.7		0.9		0.7		**0.05**
1-20	—		0.27 (0.08 to 0.83)/1		51.48 (−32.66 to 135.6)/2		0.80 (0.19 to 1.41)/1	
20-50	—		0.35 (0.04 to 0.62)/1		40.00 (89.00 to 169.0)/1		0.20 (−0.52 to 0.92)/2	
50-100	1.00 (0.15 to 6.42)/1		0.31 (0.14 to 0.68)/4		27.08 (−7.23 to 61.40)/5		0.44 (0.00 to 0.88)/6	
>100	0.72 (0.40 to 1.30)/5		0.24 (0.09 to 0.62)/5		71.91 (17.19 to 126.62)/4		0.06 (−0.01 to 0.19)/7	
Baseline phosphorus (mg/dL)		0.6		0.1		0.2		0.5
<5.5	0.53 (0.28 to 1.00)/1		0.41 (0.23 to 0.70)/1		55.00 (0.82 to 109.18)/1		0.10 (−0.22 to 0.42)/1	
5.5-7.0	0.57 (0.18 to 1.79)/2		0.61 (0.38 to 1.00)/2		88.72 (9.69 to 167.25)/1		0.30 (−0.13 to 0.72)/6	
7.0-8.0	1.22 (0.38 to 3.88)/1		0.31 (0.12 to 0.76)/5		92.00 (43.91 to 140.90)/4		0.63 (-0.65 to 1.90)/5	
>8.0	1.00 (0.15 to 6.42)/1		0.42 (0.22 to 0.79)/3		6.92 (−47.80 to 61.63/3		0.52 (−0.09 to 1.14)/4	

Note: P for interaction was calculated by analyzing each category compared with the first (referent) category for categorical variables. Baseline PTH level, baseline phosphorus level, duration of intervention, loss to follow-up, and number of trial participants were analyzed as continuous variables. Bold type indicates $P < 0.05$, which is considered statistically significant. Conversion factors for units: phosphorus in mg/dL to mmol/L, ×0.3229. PTH in pg/mL and ng/L requires no conversion.

Abbreviations: CI, confidence interval; NA, not applicable; PTH, parathyroid hormone.

cium salts.[32] The possibility that the cholesterol-lowering effect of sevelamer may contribute to this effect (rather than hypercalcemia from calcium salts) cannot be excluded based on the recently published CARE-2 (The Calcium Acetate Renagel Evaluation-2) study.[35] Although vascular calcification is associated with increased risk of mortality in hemodialysis patients, the impact of decreasing vascular calcification on survival outcomes has not been shown in randomized intervention trials.[69] As shown by the recent negative results of the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) study (analyzing the beneficial effects of statins in dialysis patients), even such a universally accepted surrogate end point as low-density lipoprotein cholesterol level may not predict such patient-centered end points as mortality in a different setting, such as dialysis, in which the causal pathway to cardiovascular end points and death may be different.[71,72] A surrogate end point must be validated and tested in specific settings before validating assumptions that modifying the surrogate marker will reduce clinical outcomes.

Sevelamer has not been well studied in patients with CKD stages 3 to 5 (not requiring dialysis), except for a single study.[46] Therefore, this systematic review can only inform the therapeutic use of sevelamer and calcium salts in dialysis patients and for only surrogate biochemical end points; it is still uncertain whether sevelamer reduces hypercalcemia and cardiovascular disease in patients with stages 3 to 5 CKD compared with calcium-based agents. Calcium salts are recommended in predialysis patients by various international guideline agencies for the control of hyperphosphatemia.[12,73] Our review confirms that calcium carbonate and calcium acetate are equally effective in decreasing phosphorus and PTH levels with a similar incidence of hypercalcemia and gastrointestinal adverse events; we identified only 2 studies conducted in predialysis patients.[23,27] Because few studies are available, there currently is no strong RCT evidence (for the outcomes of mortality and morbidity) for the use of calcium-based phosphate binders in patients with earlier stages of CKD.

Few studies have analyzed the use of lanthanum carbonate alone or in conjunction with calcium salts for phosphate binding in patients with CKD. Lanthanum carbonate has been compared with placebo and calcium carbonate in dialysis patients, and available data confirm their efficacy in decreasing phosphorus levels, similar to calcium carbonate, with a decreased incidence of hypercalcemia. Accumulation of lanthanum in bone has been assessed in 1 study by means of bone biopsy at the end of 2 years of treatment, and no evidence of aluminum-like toxicity was observed.[53]

To the best of our knowledge, this is the first comprehensive systematic review of RCTs that has assessed the benefits and harms of all phosphate-binding agents in patients with CKD. A previous meta-analysis (including 17 prospective and retrospective studies comparing sevelamer hydrochloride with placebo) showed that sevelamer compared with placebo or no treatment improved biochemical end points (serum phosphorus, Ca $\times$ P, PTH, and lipid levels) without increased serum calcium levels. However, data for survival, hospitalization, and vascular calcification were not included.[74] The inclusion of both observational studies and RCTs in that review decreased the strengths of its conclusions through potential for bias and unknown confounding. A second systematic review of 7 RCTs (746 patients) concluded that sevelamer had similar effects on phosphorus and Ca $\times$ P levels, with a lower incidence of hypercalcemia.[75] Similar to the previous analysis, that review focused on only the effects of sevelamer and included some, but not all, available trials. A more recent analysis by Tonelli et al[76] (an update of their previous review) analyzed the benefits of sevelamer in comparison to calcium alone and included 10 trials.[75] This review did not assess the role of other phosphate binders and did not explore the risk of vascular calcification.[77]

Our systematic review has a number of strengths and some weaknesses. It is based on prior publication of a prospectively designed peer-reviewed protocol[78] and a systematic search of medical databases, data extraction, analysis, and trial quality assessment by 2 independent reviewers with supervision by a third experienced investigator. The key findings are limited by the lack of long-term studies analyzing the efficacy of phosphate binders on mortality and musculoskeletal morbidity. Most included stud-

ies enrolled few patients (except for the large DCOR trial), and all were powered to observe differences in surrogate end points, rather than patient-focused outcomes. This attention to surrogate rather than patient-level end points in patients with CKD is not new and should be superseded by focus on major patient-level end points in future trials.[79,80,81] The strength of conclusions drawn from this review also is limited by suboptimal reporting of study methods to determine trial quality and significant heterogeneity observed for many outcomes.

The primary advantage for more recently developed phosphate binders (lanthanum carbonate and sevelamer) is a decrease in hypercalcemia in dialysis patients. Existing trials using patient-focused end points in predialysis patients are inadequate to inform clinical recommendations for any phosphate binder and are required before advocating that newer agents are superior to existing lower cost interventions. Full adoption of sevelamer and lanthanum by government drug reimbursement agencies in place of calcium salts would lead to a large increase in health care expenditure.[82,83] This can be justified only by presenting evidence for improved clinical outcomes of these agents compared with calcium salts. Additionally, it should be remembered that to date, no clinical trial has shown a survival advantage for calcium salts (compared with placebo or other agents).

Further research using an RCT design is required to assess the effect of surrogate biochemical end points (phosphorus, calcium, and PTH levels) on mortality and morbidity in patients with CKD. These might include trials of: (1) direct comparisons between sevelamer, calcium salts, and lanthanum carbonate in patients with CKD with primary outcomes of all-cause and cardiovascular mortality, fractures, hospitalization, and parathyroidectomy; (2) any phosphate binder to control hyperphosphatemia in patients with CKD stages 3 and 4; or (3) the efficacy of combination therapy (such as sevelamer with or without calcium salts) on both surrogate and patient-level end points.

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SUPPLEMENTARY MATERIAL

Item S1. Description of search strategy.

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REFERENCES

1. US Renal Data System: USRDS 2008 Annual Data Report. Chapter 11: Costs of End-Stage Renal Disease. Available at: http://www.usrds.org/2008/pdf/V2_11_2008.pdf. Accessed April 16, 2009

2. Hruska KA, Mathew S, Lund R, Qiu P, Pratt R: Hyperphosphatemia of chronic kidney disease. Kidney Int 74:148-157, 2008

3. Cozzolino M, Brancaccio D, Gallieni M, Galassi A, Slatopolsky E, Dusso A: Pathogenesis of parathyroid hyperplasia in renal failure. J Nephrol 18:5-8, 2005

4. Silver J, Levi R: Cellular and molecular mechanisms of secondary hyperparathyroidism. Clin Nephrol 63:119-126, 2005

5. Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: A national study. Am J Kidney Dis 31:607-617, 1998

6. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J: Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 52:519-530, 2008

7. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15:2208-2218, 2004

8. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 103:987-992, 2001

9. Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A: Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: Evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol 15:770-779, 2004

10. Coladonato JA: Control of hyperphosphatemia among patients with ESRD. J Am Soc Nephrol 16:107-114, 2005 (suppl 2)

11. Fadem SZ, Moe SM: Management of chronic kidney disease mineral-bone disorder. Adv Chronic Kidney Dis 14:44-43, 2007

12. National Kidney Foundation: Guideline 5: Use of phosphate binders in CKD, in K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease Patients. Am J Kidney Dis 42:S70-S77, 2003 (suppl 3)

13. Salusky IB: A new era in phosphate binder therapy: What are the options? Kidney Int Suppl 105:S10-S15, 2006

14. Sprague SM: A comparative review of the efficacy and safety of established phosphate binders: Calcium, sevelamer, and lanthanum carbonate. Curr Med Res Opin 23:3167-3175, 2007

15. Dickersin K, Scherer R, Lefebvre C: Identifying relevant studies for systematic reviews. BMJ 309:1286-1291, 1994

16. Moher D, Cook DJ, Eastwood S, et al: Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 354:1896-1900, 1999

17. Schulz KF, Chalmers I, Hayes RJ, Altman DG: Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 273:408-412, 1995

18. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 7:177-188, 1986

19. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 327:557-560, 2003

20. Almirall J, Veciana L, Llibre J: Calcium acetate versus calcium carbonate for the control of serum phosphorus in hemodialysis patients. Am J Nephrol 14:192-196, 1994

21. Bro S, Rasmussen RA, Handberg J, Olgaard K, Feldt-Rasmussen B: Randomized crossover study comparing the phosphate-binding efficacy of calcium ketoglutarate versus calcium carbonate in patients on chronic hemodialysis. Am J Kidney Dis 31:257-262, 1998

22. Birck R, Zimmermann E, Wassmer S, Nowack R, van der Woude FJ: Calcium ketoglutarate versus calcium acetate for treatment of hyperphosphataemia in patients on maintenance haemodialysis: A cross-over study. Nephrol Dial Transplant 14:1475-1479, 1999

23. Borrego J, Perez del Barrio P, Serrano P, et al: A comparison of phosphorus-chelating effect of calcium carbonate versus calcium acetate before dialysis. Nefrologia 20:348-354, 2000

24. Caravaca F, Santos I, Cubero JJ, et al: Calcium acetate versus calcium carbonate as phosphate binders in hemodialysis patients. Nephron 60:423-427, 1992

25. Emmett M, Sirmon MD, Kirkpatrick WG, Nolan CR, Schmitt GW, Cleveland MB: Calcium acetate control of serum phosphorus in hemodialysis patients. Am J Kidney Dis 17:544-550, 1991

26. d'Almeida Filho EJ, da Cruz EA, Hoette M, Ruzany F, Keen LN, Lugon JR: Calcium acetate versus calcium carbonate in the control of hyperphosphatemia in hemodialysis patients. Sao Paulo Med J 118:179-184, 2000

27. Phelps KR, Stern M, Slingerland A, Heravi M, Strogatz DS, Haqqie SS: Metabolic and skeletal effects of low and high doses of calcium acetate in patients with preterminal chronic renal failure. Am J Nephrol 22:445-454, 2002

28. Pflanz S, Henderson IS, McElduff N, Jones MC: Calcium acetate versus calcium carbonate as phosphate-binding agents in chronic haemodialysis. Nephrol Dial Transplant 9:1121-1124, 1994

29. Ring T, Nielsen C, Andersen SP, Behrens JK, Sodemann B, Kornerup HJ: Calcium acetate versus calcium carbonate as phosphorus binders in patients on chronic haemodialysis: A controlled study. Nephrol Dial Transplant 8:341-346, 1993

30. Rudnicki M, Hyldstrup L, Petersen LJ, Hojsted J, Transbol I: Effect of oral calcium on noninvasive indices of bone formation and bone mass in hemodialysis patients: A randomized double-blind placebo-controlled study. Miner Electrolyte Metab 20:130-134, 1994

31. Schaefer K, Scheer J, Asmus G, Umlauf E, Hagemann J, von Herrath D: The treatment of uraemic hyperphosphataemia with calcium acetate and calcium carbonate: A comparative study. Nephrol Dial Transplant 6:170-175, 1991

32. Barreto DV, Barreto Fde C, de Carvalho AB, et al: Phosphate binder impact on bone remodeling and coronary calcification—Results from the BRiC Study. Nephron Clin Pract 110:c273-c283, 2008

33. Bleyer AJ, Burke SK, Dillon M, et al: A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. Am J Kidney Dis 33:694-701, 1999

34. Block GA, Spiegel DM, Ehrlich J, et al: Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 68:1815-1824, 2005

35. Qunibi W, Moustafa M, Muenz LR, et al: A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: The Calcium Acetate Renagel Evaluation-2 (CARE-2) study. Am J Kidney Dis 51:952-965, 2008

36. Chertow GM, Dillon M, Burke SK, et al: A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. Clin Nephrol 51:18-26, 1999

37. Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 62:245-252, 2002

38. Suki W, Zabaneh R, Cngiano J, et al: Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int 72:1130-1137, 2007

39. DeSanto NG, Frangiosa A, Anastasio P, et al: Sevelamer worsens metabolic acidosis in hemodialysis patients. J Nephrol 199:S108-S114, 2006 (suppl 9)

40. Evenepoel P, Selgas R, Caputo F, et al: Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. Nephrol Dial Transplant 24:278-285, 2009

41. Ferreira A, Frazão JM, Monier-Faugere MC, et al: Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. J Am Soc Nephrol 19:405-412, 2008

42. Kingusa E, Koshikawa S: Effects of PB-94 (sevelamer hydrochloride), a phosphate binder, on the treatment of hyperphosphatemia in hemodialysis patients—A randomized, open label, dose titration study of PB-94 versus Caltan tablet 500 (calcium carbonate). J Am Soc Nephrol 12:755A, 2001 (abstr)

43. Hervas JG, Prados D, Cerezo S: Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: A comparison with calcium acetate. Kidney Int Suppl 85:S69-S72, 2003

44. Koiwa F, Onoda N, Kato H, et al: Prospective randomized multicenter trial of sevelamer hydrochloride and calcium carbonate for the treatment of hyperphosphatemia in hemodialysis patients in Japan. Ther Apher Dial 9:340-346, 2005

45. Qunibi WY, Hootkins RE, McDowell LL, et al: Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study). Kidney Int 65:1914-1926, 2004

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

47. Sadek T, Mazouz H, Bahlou H, et al: Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: An open-label, randomized study. Nephrol Dial Transplant 18: 582-589, 2003

48. Shaheen FA, Akeel NM, Badawi LS, Souqiyyeh MZ: Efficacy and safety of sevelamer. Comparison with calcium carbonate in the treatment of hyperphosphatemia in hemodialysis patients. Saudi Med J 25:785-791, 2004

49. Chertow GM, Burke SK, Lazarus JM, et al: Poly[allylamine hydrochloride](RenaGel): A noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. Am J Kidney Dis 29:66-71, 1997

50. D'Haese PC, Spasovski GB, Sikole A, et al: A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int Suppl 85:S73-S78, 2003

51. Hutchison AJ, Maes B, Vanwalleghem J, et al: Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: A 6-month, randomized, comparative trial versus calcium carbonate. Nephron Clin Pract 100:c8-c19, 2005

52. Shigematsu T, for the Lanthanum Carbonate Group: Multicenter prospective randomized, double-blind comparative study between lanthanum carbonate and calcium carbonate as phosphate binders in Japanese hemodialysis patients with hyperphosphatemia. Clin Nephrol 70:404-410, 2008

53. Spasovski GB, Sikole A, Gelev S, et al: Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow up. Nephrol Dial Transplant 21:2217-2224, 2006

54. Al-Baaj F, Speake M, Hutchison AJ: Control of serum phosphate by oral lanthanum carbonate in patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis in a short-term, placebo-controlled study. Nephrol Dial Transplant 20:775-782, 2005

55. Chiang SS, Chen JB, Yang WC: Lanthanum carbonate (Fosrenol) efficacy and tolerability in the treatment of hyperphosphatemic patients with end-stage renal disease. Clin Nephrol 63:461-470, 2005

56. Finn WF, Joy MS, Hladik G, for the Lanthanum Study Group: Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis. Clin Nephrol 62:193-201, 2004

57. Joy MS, Finn WF, for the LAM-302 Study Group: Randomized, double-blind, placebo-controlled, dose-titration, phase III study assessing the efficacy and tolerability of lanthanum carbonate: A new phosphate binder for the treatment of hyperphosphatemia. Am J Kidney Dis 42:96-107, 2003

58. Malluche HH, Siami GA, Swanepoel C, et al: Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. Clin Nephrol 70:284-295, 2008

59. Mehrotra R, Martin KJ, Fishbane S, et al: Higher strength lanthanum carbonate provides serum phosphorus control with a low tablet burden and is preferred by patients and physicians: A multicenter study. Clin J Am Soc Nephrol 3:1437-1445, 2008

60. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM: Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 71:438-441, 2007

61. Asmus HG, Braun J, Krause R, et al: Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. Nephrol Dial Transplant 20:1653-1661, 2005

62. Raggi P, James G, Burke SK, et al: Decrease in thoracic vertebral bone attenuation with calcium-based phosphate binders in hemodialysis. J Bone Miner Res 20:764-772, 2005

63. Hutchison AJ, Maes B, Vanwalleghem J, et al: Long-term efficacy and tolerability of lanthanum carbonate: Results from a 3-year study. Nephron Clin Pract 102:c61-c71, 2006

64. Altmann P, Barnett ME, Finn WF, for the SPD405-307 Lanthanum Carbonate Study Group: Cognitive function in stage 5 chronic kidney disease patients on hemodialysis: No adverse effects of lanthanum carbonate compared with standard phosphate-binder therapy. Kidney Int 71:252-259, 2007

65. Ferramosca E, Burke S, Chasan-Taber S, Ratti C, Chertow GM, Raggi P: Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients. Am Heart J 149:820-825, 2005

66. St Peter WL, Liu J, Weinhandl E, Fan Q: A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: A secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. Am J Kidney Dis 51:445-454, 2008

67. Moe SM, Chertown G: The case against calcium-based phosphate binders. Clin J Am Soc Nephrol 1:697-703, 2006

68. Friedman EA: Calcium-based phosphate binders are appropriate in chronic renal failure. Clin J Am Soc Nephrol 1:704-709, 2006

69. Bushinsky DA: Phosphate binders: Hold the calcium? Clin J Am Soc Nephrol 1:695-696, 2006

70. Silver J: The details bedevil DCOR. Kidney Int 72:1041-1043, 2007

71. Strippoli GF, Craig JC: Sunset for statins after AURORA? N Engl J Med 360:1455-1457, 2009

72. Fellström BC, Jardine AG, Schmieder RE, et al: Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 360:1395-1407, 2009

73. Elder G, Faull R, Branley P, Hawley C: Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. Nephrology (Carlton) 11: S230-S261, 2006 (suppl 1)

74. Burke SK, Dillon MA, Hemken DE, Rezabek MS, Balwit JM: Meta-analysis of the effect of sevelamer on phosphorus, calcium, PTH, and serum lipids in dialysis patients. Adv Ren Replace Ther 10:133-145, 2003

75. Manns B, Stevens L, Miskulin D, Owen WF Jr, Winkelmayer WC, Tonelli M: A systematic review of sevelamer in ESRD and an analysis of its potential economic impact in Canada and the United States. Kidney Int 66:1239-1247, 2004

76. Tonelli M, Wiebe N, Culleton B, et al: Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. Nephrol Dial Transplant 22:2856-2866, 2007

77. Palmer SC, Craig JC, Strippoli GF: Sevelamer: A promising but unproven drug. Nephrol Dial Transplant 22: 2742-2745, 2007

78. Navaneethan SD, Chaukiyal P, Strippoli GF, Palmer S, Craig J, Elder G: Phosphate binders for preventing and treating bone and cardiovascular disease in chronic kidney disease patients (protocol). Cochrane Database Syst Rev 2:CD006023, 2006

79. Strippoli GF, Tognoni G, Navaneethan SD, Nicolucci A, Craig JC: Haemoglobin targets: We were wrong, time to move on. Lancet 369:346-350, 2007

80. Strippoli GF, Craig JC: Hypothesis versus association: The optimal hemoglobin target debate. Am J Kidney Dis 46:970-973, 2005

81. Hutchinson AJ: Oral phosphate binders. Kidney Int 75:906-914, 2009

82. Taylor MJ, Elgazzar HA, Chaplin S, Goldsmith D, Molony DA: An economic evaluation of sevelamer in patients new to dialysis. Curr Med Res Opin 24:601-608, 2008

83. Manns B, Klarenbach S, Lee H, Culleton B, Shrive F, Tonelli M: Economic evaluation of sevelamer in patients with end-stage renal disease. Nephrol Dial Transplant 22: 2867-2878, 2007