

RESEARCH ARTICLE

New Conclusions Regarding Comparison of Sevelamer and Calcium-Based Phosphate Binders in Coronary-Artery Calcification for Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials

Caixia Wang¹*, Xun Liu¹*, Yongming Zhou²*, Shaomin Li¹, Yanbing Chen³, Yanni Wang¹, Tanqi Lou¹*

1 Department of Nephrology, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, **2** Department of Nephrology, The Affiliated Tianyou Hospital, Wuhan University of Science and Technology, Wuhan, China, **3** Medical Genetics Center, Guangdong Women and Children Hospital, Guangzhou, China

* These authors contributed equally to this work.

* naturestyle@163.com (XL); lou.tq@163.com (TQL)



OPEN ACCESS

Citation: Wang C, Liu X, Zhou Y, Li S, Chen Y, Wang Y, et al. (2015) New Conclusions Regarding Comparison of Sevelamer and Calcium-Based Phosphate Binders in Coronary-Artery Calcification for Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials. *PLoS ONE* 10(7): e0133938. doi:10.1371/journal.pone.0133938

Editor: Carmine Pizzi, University of Bologna, ITALY

Received: April 18, 2015

Accepted: July 2, 2015

Published: July 31, 2015

Copyright: © 2015 Wang et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was supported by the National Natural Science Foundation of China (Grant No. 813770866 and 81070612), the China Postdoctoral Science Foundation (Grant No. 201104335 and 20090460774), Guangdong Science and Technology Plan (Grant No. 2011B031800084 and 2013B021800190), the Fundamental Research Funds for the Central Universities (Grant No. 11ykpy38), and the National Project of Scientific and Technical Supporting Programs Funded by Ministry of

Abstract

Background

Sevelamer hydrochloride is used widely, but its impact upon cardiovascular calcification, cardiovascular mortality, all-cause mortality and hospitalization is not known.

Outcomes

Primary outcome was cardiovascular calcification (coronary artery calcification scores (CACS) and aortic calcification scores (ACS)). Secondary outcomes were serum characteristics, hospitalization, cardiovascular mortality and all-cause mortality. Risk ratio (RR), mean differences and standard mean difference with 95% confidence intervals (CIs) were pooled using random- or fixed-effects models.

Results

We identified 31 studies (on 23 randomized controlled trials with 4395 participants). An analysis pooling showed a significant decrease in serum levels of phosphate with calcium-based phosphate binders (CBPBs) by 0.17 mg/dL [mean difference (MD), 95% CI, 0.03, 0.31] than sevelamer. A significant difference in the change of CACS by -102.66 [MD: 95% CI, -159.51, -45.80] and ACS by -1008.73 [MD, 95% CI, -1664.75, -352.72] between sevelamer and CBPBs was observed. Prevalence of hypercalcemia (serum levels of calcium >10.2–10.5 mg/dL and >11.0 mg/dL) was significantly smaller for sevelamer (RR = 0.44, 95% CI, 0.33, 0.58; RR = 0.24, 95% CI, 0.14, 0.40). No significant difference was found in hospitalization, all-cause mortality or cardiovascular mortality.

Science & Technology of China (Grant No. 2011BAI10B00).

Competing Interests: The authors have declared that no competing interests exist.

Conclusions

This meta-analysis suggests that sevelamer benefits dialysis patients in terms of CACS, ACS and hypercalcemia.

Introduction

Chronic kidney disease (CKD) is a major public-health problem [1]. As a major therapy for patients with end-stage renal disease (ESRD), renal replacement therapy is used widely all over the world. However, dialysis patients can suffer from mineral metabolism. Also, cardiovascular disease is the most common cause of death, accounting for more than one-half of cases [2–4].

Higher levels of phosphate in serum are associated with worse outcomes in dialysis patients, so different types of therapies have been employed to deal with this problem. Phosphate binders taken with meals, which bind dietary phosphate, play an important part in the treatment of hyperphosphatemia [5]. Dietary phosphate binders are used widely. Calcium-based agents were traditionally employed as first-line therapy [6] but their use can result in hypercalcemia and high levels of calcium-phosphate products, which are associated with cardiovascular mortality and mortality in ESRD. Hence, magnesium- and aluminum-based agents have started to be used.

New non-calcium, non-magnesium, and aluminum-free phosphate-binding means agents such as sevelamer have been reported to reduce the Medicare costs of inpatients compared with calcium binders [7] without alerting serum levels of calcium. As a type of calcium-free agent, sevelamer may have less influence upon serum levels of calcium [8]. However, its impact upon cardiovascular calcification, cardiovascular mortality, all-cause mortality and hospitalization is not known.

Several reviews [9–13] have focused on sevelamer, one of which was conducted in 2010 involving 14 trials and 3271 patients [9]. In that meta-analysis, the authors included predialysis patients and evaluated the level of cardiovascular calcification using coronary artery calcification scores (CACS), graded by computed tomography (CT) and representing the progression or regression of coronary artery disease, [14, 15] in four randomized controlled trials (RCTs) in hemodialysis patients. Jamal et al. (2009) [10] also analyzed cardiovascular calcification by CACS, but found no significant differences in CACS between patient groups and controls. Three of those reviews [11–13] considered biochemical outcomes, and one review also evaluated the effect of sevelamer upon all-cause mortality, cardiovascular events, and other adverse events [11]. Since then, several trials related to this issue have been published. It seems that an updated review of the evidence would be of great use to clinicians and decision-makers. Hence, we conducted a meta-analysis of published RCTs on the effectiveness and safety of sevelamer in dialysis patients.

Materials and Methods

Data Sources and Literature Searches

We undertook a systematic meta-analysis of RCTs according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (S1 Fig) [16]. We conducted a MEDLINE literature search to identify all relevant studies using the search terms ‘sevelamer hydrochloride’, ‘sevelamer’, or ‘RenaGel’ from January 1998 to November 2013 and searched PUBMED, EMBASE (‘sevelamer hydrochloride’/exp OR ‘sevelamer hydrochloride’ OR

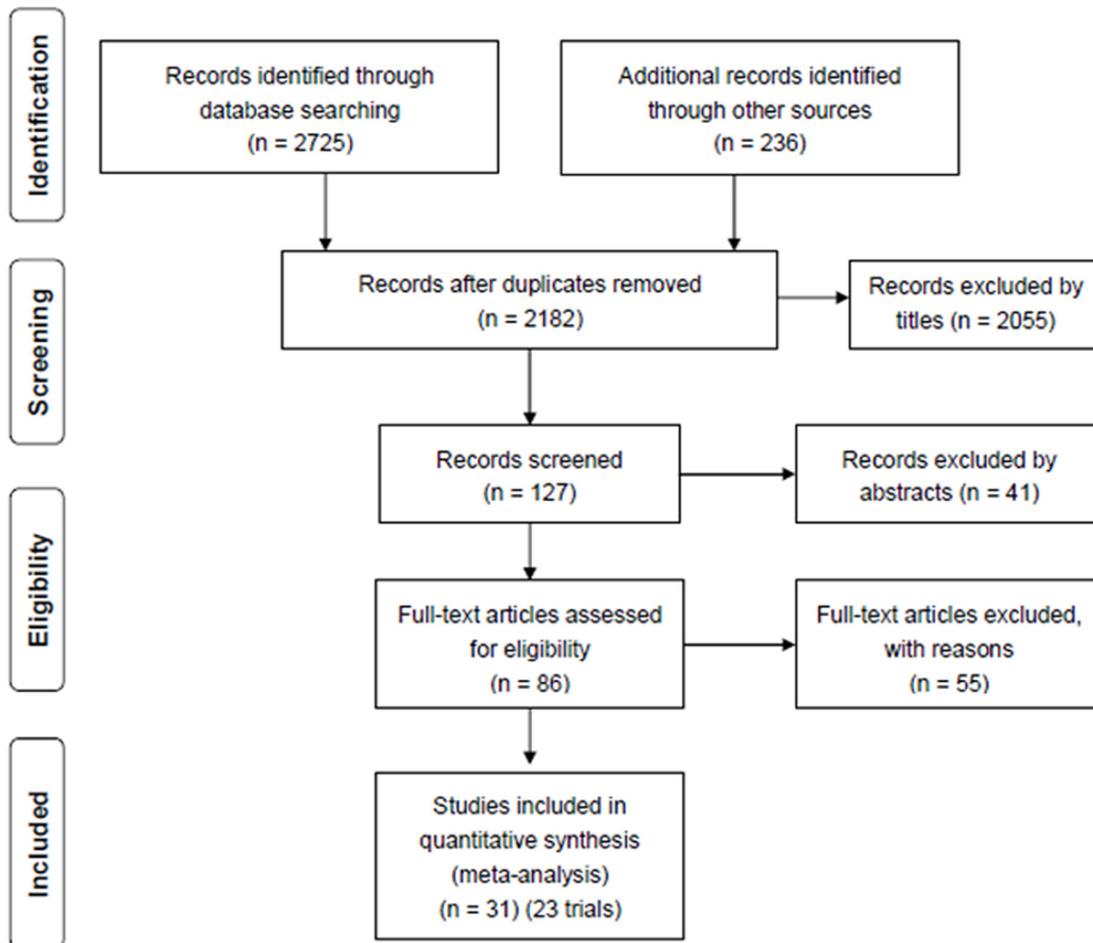


Fig 1. Flow diagram of studies considered for inclusion.

doi:10.1371/journal.pone.0133938.g001

‘sevelamer’/exp OR sevelamer AND (‘renagel’/exp OR renagel) 1811), the specialized register of the Cochrane Renal Group, and the Cochrane Central Register of Controlled Trials to identify all RCTs studying the effects of sevelamer hydrochloride using similar search terms.

We also searched (manually) the abstracts of conference proceedings of the American Society of Nephrology from 1998 to 2013. However, we did not have access to RCTs that were not reported.

Restrictions on language or dates were not imposed in our searches. Finally, we found 2961 studies for the analysis. After screening, 31 studies (on 23 trials) were included (Fig 1) in the analysis.

Study Selection

All RCTs that studied dialysis ESRD adults (age ≥ 18 years) and compared sevelamer to any calcium-based phosphate binder (CBPB) were included. Included studies are assumed to have analyzed the effect of phosphate binders on serum levels of phosphate or calcification of coronary arteries. Studies comparing sevelamer to any other types of phosphate binders or no phosphate binders were excluded. Titles and abstracts were reviewed by two reviewers independently, as well as the full-text articles.

Data Extraction and Quality Assessment

Data were extracted by two authors. A third reviewer checked the extracted data for accuracy. The following data were extracted: country of origin; year of publication; sample size; study design; mean age; percentage of men; mean duration of dialysis; prevalence of diabetes. The quality of trials was assessed by Review Manager 5.2 (Oxford, UK) according to the *Cochrane Handbook for Systematic Reviews of Interventions* (S2 Fig and S3 Fig) [17]. Levels of evidence were evaluated by the GRADE profiler (S4 Fig) [17]. A third person was available if there was disagreement concerning extraction and/or assessment of the quality of data.

Synthesis and Analysis of Data

We undertook meta-analyses using Review Manager 5.2 and meta-regression by comprehensive meta-analysis (CMA). Mean difference (MD) and standard mean difference (SMD) were used to pool results for continuous outcomes (e.g. serum levels of phosphate and calcium), and we also computed pooled risk ratios (RRs) for dichotomous outcomes (e.g. cardiovascular mortality, all-cause mortality). We used change-from-baseline results rather than final values in the analysis of CACS and aortic calcification scores (ACS) to evaluate the effect of phosphate binders upon vascular calcification. Pooling methods that account for the within-patient-correlation from crossover trials were used to combine data from crossover and parallel continuous trials [18]. A fixed- (used if $I^2 \leq 25\%$) and a random-effects model (used if $I^2 \geq 50\%$) was used to analyze data.

Ninety-five percent confidence intervals (95% CIs) were provided for all pooled estimates. Heterogeneity was assessed using the Cochrane Q test, I^2 index (which describes the percentage of total variation across studies due to true heterogeneity rather than chance) and P values were also used. Publication bias was assessed using Funnel plots.

Results

Selection and Characteristics of Studies

A total of 2961 potentially relevant citations were identified and screened. Eighty-six articles were retrieved for detailed evaluation, of which 31 (23 trials were analyzed in total) fulfilled the eligibility criteria (Fig 1). Detailed characteristics and a summary of all 31 studies (23 trials) are displayed in Tables 1 and 2. Multiple publications with no unique result were excluded from screened studies. However, unique results were extracted and studies (as well as abstracts) containing unique results were also displayed. Block 2007 [19], was a follow-up analysis of earlier studies [20–21] that compared sevelamer with CBPBs. The study of Barreto 2005 [22] was a published abstract of the study of Barreto 2008 [23], and contained some data that the full report did not mention or did not describe in detail. Chertow 2003 [24] is a short term follow-up trial which evaluated the same patients investigated in Asmus 2005 [25] which was a long term follow-up trial for them. Chertow 2002 [26], Raggi 2004 [27] and Ferramosca 2005 [28] et. al also shared data from the same patients. However, all of them (containing the same cohort of participants) were extracted only once. Sample size of studies varied from 13 patients to 2103 patients (a total of 4395 participants). Mean age was 57.9 years. Duration of dialysis was from 3 months to 18 years. Prevalence of diabetes ranged from 0% to 60%.

A total of 31 studies, including an abstract [29] and five posters [22, 30–32], were eligible for the analysis. Those studies compared sevelamer with calcium acetate, calcium carbonate, or both. One study had no baseline washout period. One study included only patients who initiated dialysis recently, and another study included only those on incident hemodialysis. All of

Table 1. Detailed characteristics of the studies.

Study	Country	Modality ^a	Duration ^b (yr)	Follow-up ^c (wk)	S dose ^d (g/d)	CBPB dose (g/d)	Sample size
Asmus 2005	USA	HD	5.1	104	6.9	4.3	72
Barreto 2005	Brazil	HD	NR	52	NR	NR	101
Barreto 2008	Brazil	HD	3.1	52	12	2.028	101
Bleyer 1999	USA	HD	NR	10	NR	NR	84
Block 2005	US	HD	0.25	78	8	2.3	129
Block 2007	USA	HD	NR	189	NR	NR	127
Braun 2004	Europe	HD	5.3	52	5.9	3.9	114
Cancela 2011	Brazil	HD	3.1	52	NR	NR	72
Chertow 1999	USA	HD	NR	16	NR	0.9	71
Chertow 2002	US, Ger, Au ^e	HD	3.3	52	6.5	4.6	200
Chertow 2003	USA	HD	2.5	52	2.4	2	108
Evenepoel 2009	NR	PD	1.2	12	4.8	4.8	143
Ferreira 2008	USA	HD	> 3.5	55	5.0	4.0	119
Francisco 2010	Europe	HD	5.0	26	3.2	1.74	255
Ferramosca 2005	USA	HD	4.8	53	6.5	4.3	108
Gallieni 2005	NR	HD	NR	12	0.403	0.403	114
Garg 2005	US, Ger, Au ^e	HD	3.3	52	NR	6.5	200
Herva's 2003	Spain	HD	4.7	34	4.09	3.9	51
Kakuta 2011	USA	HD	9.33	52	9	10.5	183
Lin 2010	Taiwan	HD	3.6	10	2.4	2.0	52
Liu 2006	USA	HD	7.3	8	0.4	0.667	70
Oliveira 2007	Brazil	HD	NR	54	NR	NR	19
Peter 2008	NR	HD	NR	104	NR	NR	2103
Qunibi 2004	USA	HD	4.3	8	6.9	7.1	100
Qunibi 2008	USA	HD	1.9	52	7.3	5.5	203
Raggi 2004	US, Ger, Au ^e	HD	3.3	52	NR	NR	200
Raggi 2005	US, Ger, Au ^e	HD	3.3	52	NR	NR	111
Sadek 2003	Europe	HD	NR	21	NR	4.85	42
Shaheen 2004	SA ^f	HD	3.4	20	2.4	1.8	20
Suki 2008	US	HD	3.2	193	6.9	5.3	2103
Takei 2008	Japan	HD	12	28	NR	NR	42

Chertow et al. 2003 and Ferramosca et al. 2005 shared the same patients, and Asmus et al. 2005 had a longer follow-up of the two studies. Block et al. 2007 had a longer follow-up than Block et al. 2007. Suki et al. 2008 and Peter et al. 2008 analyzed the same trial. Chertow et al. 2002, Raggi et al. 2004, Raggi et al. 2005 and Garge et al. 2005 analyzed the same trial. Barreto et al. 2005 is an abstract of Barreto et al. 2008, but with different types of data. Abbreviations: HD, hemodialysis; NR, not reported.

^aDialysis.

^bMean duration of dialysis

^cFollow-up of trials

^dMean dose of sevelamer

^eUSA, German, Austria

^fSaudi Arabia

doi:10.1371/journal.pone.0133938.t001

the trials were accrued on hemodialysis patients except one, which focused on patients undergoing peritoneal dialysis [33].

Table 2. Summary of the studies analyzed.

No. of studies ^a	31
No. of trials ^b	23
Sample size of the trials ^b	4395
Percentage of female participants ^b	41
Age of participants (yr) ^b	57.9
Percentage of participants with diabetes ^b	45
Body mass index (kg/m ²) ^b	26.8
Percent of current smoking (%) ^b	15.6
Cause of ESRD^b:	
Hypertension (%)	26.5
Diabetes mellitus (%)	41.6
Glomerulonephritis (%)	14.1
Polycystic kidney (%)	4.0
Other (%)	13.8

^a All studies having been analyzed are included

^b The same data were extracted for only once

doi:10.1371/journal.pone.0133938.t002

Effect of Sevelamer vs. CBPBs on Serum Measurements

In an analysis of 18 studies with 3327 participants reporting on serum levels of phosphate (duration of follow-up ranged from 8 weeks to 45 months), a significant decrease in serum levels of phosphate with CBPBs by 0.17 mg/dL (MD, 95% CI, 0.03, 0.31) was observed (Fig 2). All RCTs showed that CBPBs were better than sevelamer for the control of serum levels of phosphate.

Compared with CBPBs, the MD in serum levels of calcium (18 studies; 3425 participants; duration, 8 weeks to 45 months) and in calcium-phosphate product (14 RCTs; 3050 participants; duration, 8 weeks to 45 months) were significantly lower in patients administered sevelamer by -0.24 (95% CI, -0.34, -0.14) and by -0.14 (95% CI, -1.38, 1.10) separately.

Effect of Sevelamer vs. CBPBs upon Hypercalcemia

Level of hypercalcemia (defined in all trials as serum levels of calcium >10.2–10.5 mg/dL) reported in ten trials with 957 participants was smaller for sevelamer (RR, 0.43; 95% CI, 0.32, 0.56) compared with CBPBs (Fig 3). When hypercalcemia was defined as serum levels of calcium >11.0 mg/dL (which is viewed as “severe hypercalcemia”), the RR reported by eight trials with 605 patients was 0.22 (95% CI, 0.13, 0.37) (Fig 4). However, no trial reported on the clinical consequences or median duration of hypercalcemia.

Effect of Sevelamer vs. CBPBs on CACS and ACS

Seven studies with 731 participants, one of which had a sample size of only 52 participants, reported on the change of CACS. Considering the quality of the RCTs, we only included the six trials with 679 patients. The duration of follow-up varied from 26 weeks to 104 weeks. MD was significant, and was lower with sevelamer therapy by -102.66 (MD: 95% CI, -159.51, -45.80) (Fig 5). All RCTs analyzed showed that sevelamer was better for preventing calcification of coronary arteries than CBPB. The change in ACS was also extracted from three studies with 266 patients. Similar to the analysis of CACS, the analysis of ACS showed a significant decrease by -1008.26 (SMD: 95% CI, -1664.75, -352.72) (Fig 6).

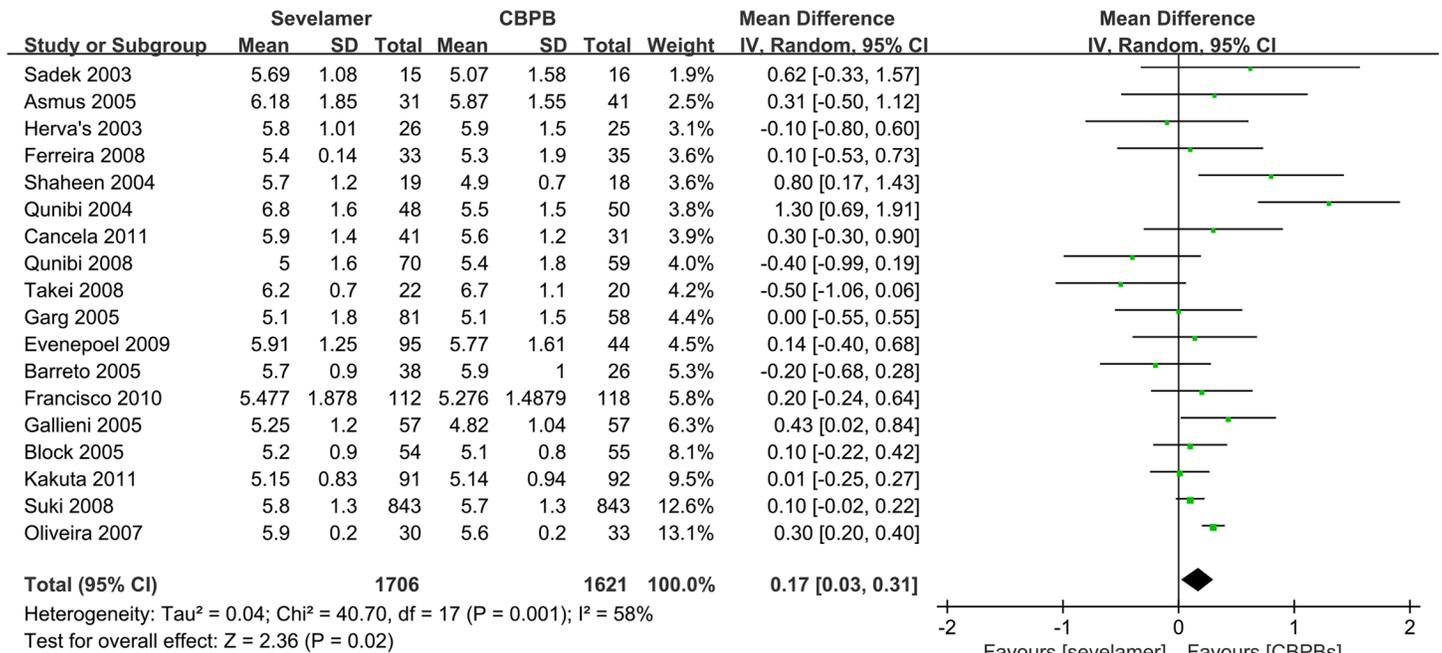


Fig 2. Forest plot of the values of phosphorus.

doi:10.1371/journal.pone.0133938.g002

Considering that the use of statins (detailed in Table 3) may have an impact on the change of CACS, we performed a linear regression on the change of CACS and the levels of low density lipoprotein (LDL) regulated mostly by statins. We found no significant relationship between CACS and LDL (Beta = -0.013; P = 0.971) (S5 Fig), which indicates that the use of statins has no significant impact on the change of CACS.

Effect of Sevelamer vs. CBPBs on Hospitalizations

Three RCTs with 2348 participants reported on the number of patients hospitalized during the study. The RR was smaller by 0.78 (95% CI, 0.61, 0.99), showing that sevelamer benefited

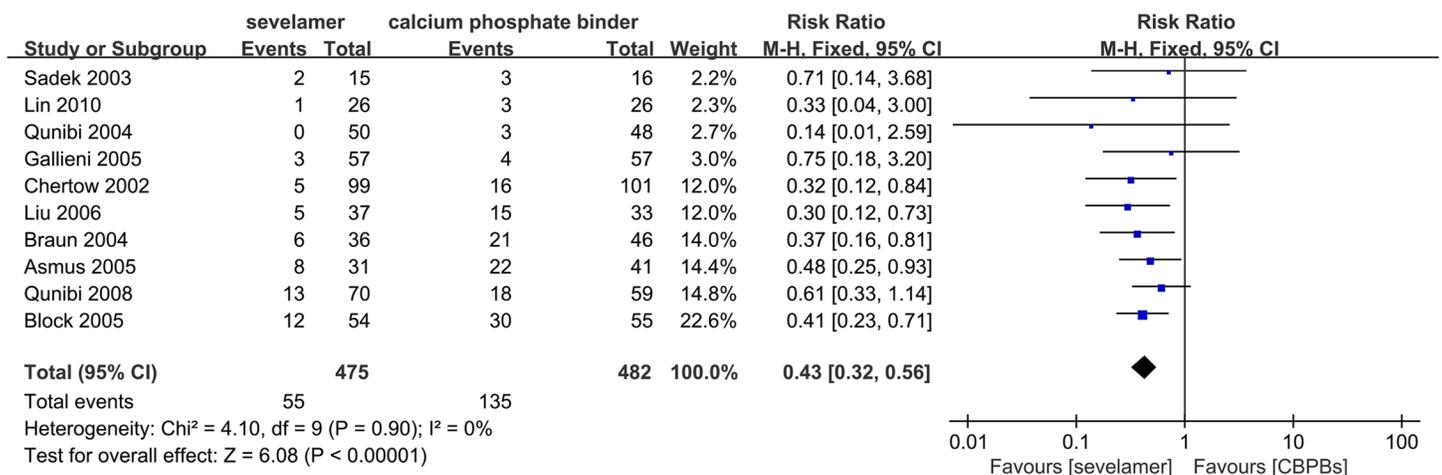


Fig 3. Forest plot of the values of hypercalcemia (above 10.2 mg/dL).

doi:10.1371/journal.pone.0133938.g003

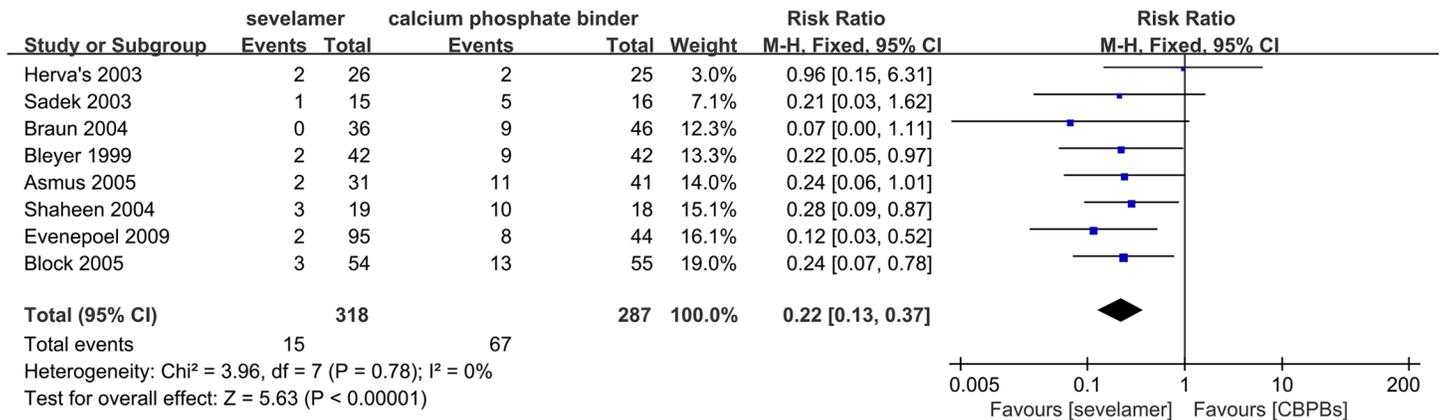


Fig 4. Forest plot of the values of heparcalcemia (above 11.0 mg-dL).

doi:10.1371/journal.pone.0133938.g004

patients with regard to hospitalization. Only one trial [34] reported on the number of days of hospitalization. Sevelamer-treated patients were hospitalized for fewer days (sevelamer (mean), 14.8 ± 27.9 ; median, 5.0 hospital days/patient-year; calcium (mean), 17.4 ± 32.0 ; median, 5.8 hospital days/patient-year; $P = 0.09$) in the trial of Suki et al. 2008 [34] but the difference was not significant.

Effect of Sevelamer vs. CBPBs on Mortality

Nine trials with 3000 participants reported all-cause mortality, and the duration of follow-up ranged from 20 weeks to 45 months. Three RCTs analyzed all-cause mortality as the primary outcome. The RR was 0.91 (95% CI, 0.79, 1.04) between sevelamer and CBPBs. Three RCTs with 2102 participants reported on cardiovascular mortality, and the RR was also non-significant by 0.94 (95% CI, 0.76, 1.16). As a result, no significant difference was found in all-cause mortality and cardiovascular mortality.

Heterogeneity and Publication Bias

All data (detailed in Table 4) were analyzed by fixed-effects ($I^2 \leq 50\%$) and random-effects ($I^2 > 50\%$) models. Between-study heterogeneity ranged from 0% to 75%. Among all the data analyzed, no between-study heterogeneity (0%) was observed in the analysis of cardiovascular mortality, all-cause mortality, change in ACS, hospitalization, and hypercalcemia. Between-study heterogeneity was low ($I^2 \leq 25\%$) in the analysis of change in CACS, and was moderate

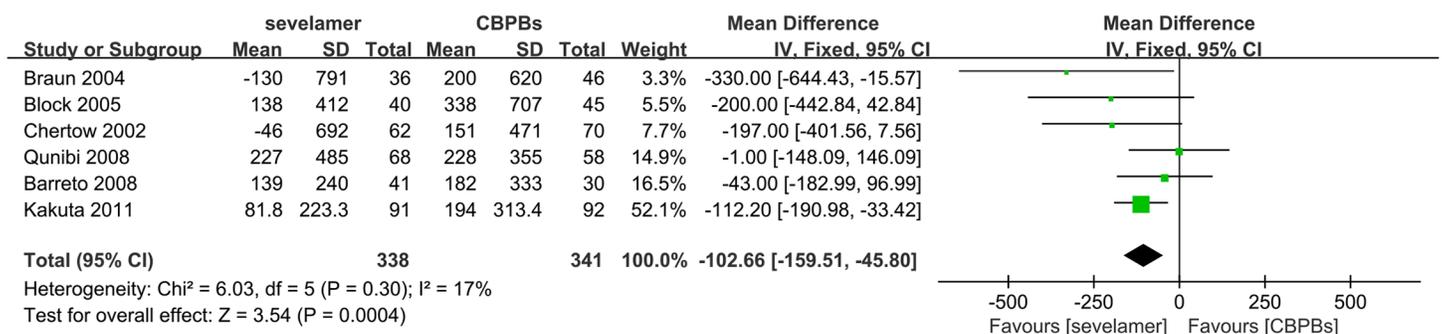


Fig 5. Forest plot of sevelamer vs. calcium phosphate binders on CACS change.

doi:10.1371/journal.pone.0133938.g005

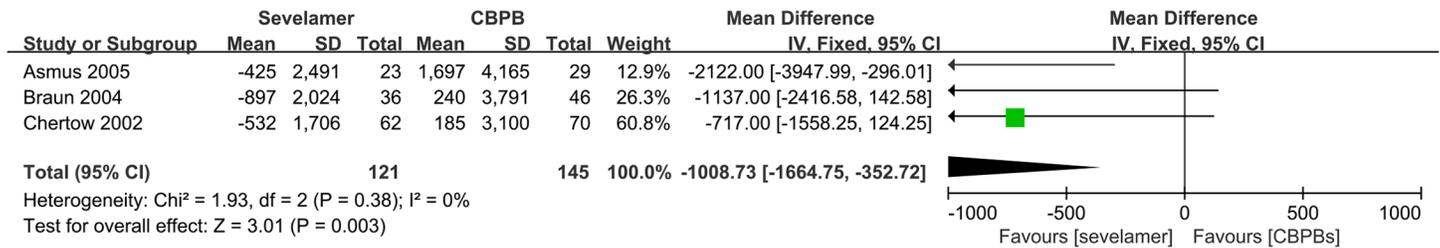


Fig 6. Forest plot of sevelamer vs. calcium phosphate binders on ACS change.

doi:10.1371/journal.pone.0133938.g006

(25% < I² ≤ 50%) in the analysis of serum calcium-phosphate product. Between-study heterogeneity of the data analyzed was high (>50%) for serum levels of phosphate and calcium. We could not undertake a subgroup analysis, so we used the random-effect model to analyze the data: serum levels of phosphorus had an I² = 58% and serum levels of calcium had an I² = 75%.

Funnel plots revealed an approximately symmetrical distribution (Fig 7). Hence, publication bias was present

Meta-Regression for Baseline Variables

As a result of high heterogeneity (I² = 58%) in the analysis of phosphorous, we undertook a meta-regression using CMA and analyzed three factors: mean duration of dialysis; designed duration of the trial; and sample size of the trial. However, we did not find a significant factor (P>0.1) that contributed to heterogeneity (S6 Fig). Hence, an appropriate subgroup analysis was not carried out.

A meta-regression on CACS was performed using baseline variables: mean duration of dialysis; designed duration of the trial; and sample size of the trial. Partially because of the low heterogeneity (17%), we did not find a significant factor that contributed to the heterogeneity (S7 Fig and S8 Fig).

Discussion

We carried out a meta-analysis to estimate the impact of sevelamer upon cardiovascular calcification, cardiovascular mortality, all-cause mortality, and hospitalization in patients on dialysis,

Table 3. Details of the use of statins.

Study	Statins	Kinds	Details	Evaluation on statins
Qunibi 2008	Yes	Atorvastatin	Different statins given time ^b	No definitive conclusions ^e
Kakuta 2011	Yes	NR ^a	Different proportion of patients given statins ^c	No significant difference
Block 2005	NR ^a	NR ^a	NR ^a	NR ^a
Barreto 2008	NR ^a	NR ^a	NR ^a	NR ^a
Chertow 2002	NR ^a	NR ^a	NR ^a	NR ^a
Braun 2004	Yes	NR ^a	Different proportion of patients given statins ^d	No significant difference ^f

^aNot reported

^bStatins were given to calcium group at start, to sevelamer group at week 8 only if their LDL-C levels were not less than 70 mg/dL

^c8% patients were given statins in sevelamer group, while 11% in calcium group

^d26% patients were given statins in sevelamer group, while 33% in calcium group

^eDefinitive conclusions about the role of LDL-C lowering in the progression of CAC was unavailable

^fStatin use was not associated with less progression of coronary artery or aortic calcification in sevelamer or calcium carbonate patients

doi:10.1371/journal.pone.0133938.t003

Table 4. Overall outcome summaries.

Outcomes	Studies	Quality ^a	Patients	Overall summary	I ² & p	F ^e (wk)	Reference
Sevelamer vs. calcium							
Serum phosphate (mg/dL)	18	High	3327	MD R ^b 0.17 [0.03, 0.31]	58%; 0.001	49	[20, 22, 24–26, 31–46]
Serum calcium (mg/dL)	18	Moderate	3425	MD R -0.24 [-0.34, -0.14]	77%; 0.001	52	[20, 22, 24–26, 31–38, 40–46]
Serum c _{xp} product ^d (mg ² /dL ²)	14	Moderate	3050	MD R -0.14 [-1.38, 1.10]	30%; 0.14	50	[20, 24–26, 31, 33, 34, 39–45]
Change in CACS	6	High	679	MD F ^c -102.66 [-159.51, -45.80]	17%; 0.3	62	[20, 23, 25, 26, 28, 40, 41, 47]
Change in ACS	4	High	453	MD R -1008.73 [-1664.75, -352.72]	0%; 0.80	65	[24–26, 47]
Hospitalization	3	Moderate	2348	RR F 0.78 [0.61, 0.99]	0%; 0.99	100	[24, 26, 34]
All-cause mortality	9	Moderate	3000	RR F 0.91 [0.79, 1.04]	0%; 0.44	81	[20, 23, 26, 34, 40, 41, 44, 45, 47]
Cardiovascular mortality	3	Moderate	2102	RR F 0.94 [0.76, 1.16]	0%; 0.80	84.5	[34, 44, 45]
Hypercalcemia (>10.2 mg/dL)	10	Moderate	957	RR F 0.43 [0.32, 0.56]	0%; 0.90	38	[20, 25, 26, 31, 41, 42, 44, 47–49]
Hypercalcemia (>11.0 mg/dL)	8	Moderate	605	RR F 0.22 [0.13, 0.37]	0%; 0.78	40	[20, 25, 30, 33, 39, 44, 45, 47]

Abbreviations: CACS, coronary artery calcification scores; ACS, aortic calcification scores

^aGraduated by GRADE profiler

^bRandom-effects model

^cFixed-effects model

^dSerum calcium-phosphate product

^eFollow-up period (wk)

doi:10.1371/journal.pone.0133938.t004

and identified 31 studies (covering 23 trials with 4395 participants). Compared with CBPBs, sevelamer therapy resulted in smaller decreases in serum levels of phosphorus and a lower prevalence of hypercalcemia. A significant difference in the CACS and ACS was observed between sevelamer and CBPBs. Evidence that sevelamer reduced all-cause mortality or cardiovascular mortality was lacking. Also, there was a slight reduction in the duration of hospitalization with sevelamer therapy according to three RCTs.

Our review updates and complements the findings of earlier systematic reviews. It also includes >3000 additional participants, including a Dialysis Clinical Outcomes Revisited (DCOR) study [21] with 2103 participants—the largest randomized trial of sevelamer conducted.

Different to former meta-analyses, this meta-analysis found a significant difference in CACS and ACS. This phenomenon may be due to a better search strategy, as well as the inclusion of more trials and different types of patients. In the analysis of CACS, compared with eight RCTs on dialysis patients, a meta-analysis by Zhang 2010 [9] included four articles, and Jamal 2009 [10] included six trials in which a trial on predialysis patients was also evaluated. Similar to other reviews, CBPBs showed slightly better results for controlling serum levels of phosphate. In the analysis of serum levels of phosphate, we also undertook a meta-regression on serum levels of phosphate, and analyzed six factors but, unfortunately, factors that influenced the heterogeneity in serum levels of phosphate were found. We did not analyze the changes in sevelamer dose or CBPB dose in different treatment phases.

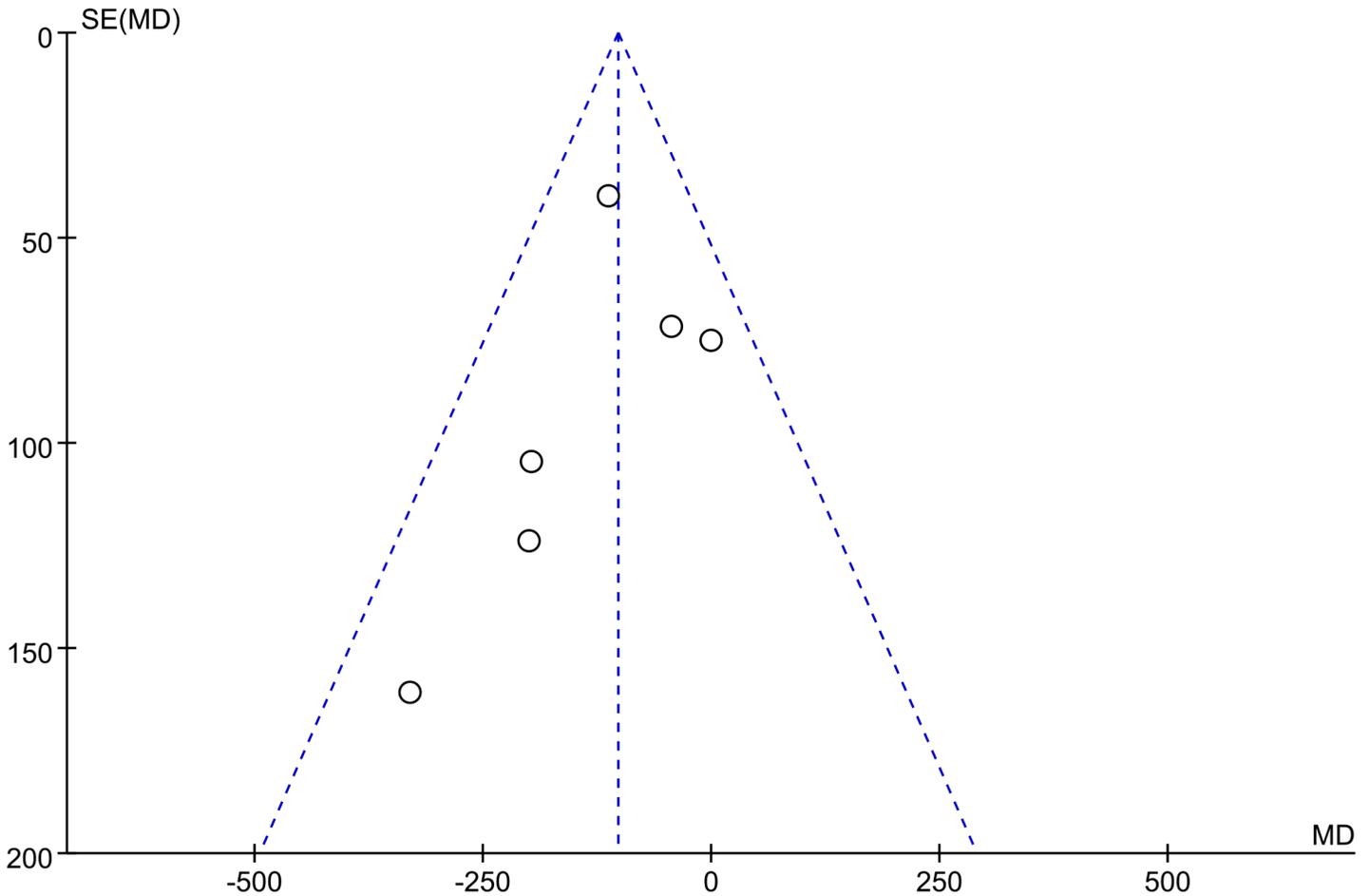


Fig 7. Funnel plot of the value of change of CACS.

doi:10.1371/journal.pone.0133938.g007

In this meta-analysis, we found a significant difference in CACS. Compared with CBPBs, sevelamer does not contain calcium, and is a type of non-calcium, non-magnesium, aluminum-free agent. As a result, sevelamer therapy can result in a smaller increase in serum levels of calcium and calcium-phosphate product. Also, the prevalence of hypercalcemia (defined as serum levels of calcium >10.2–10.5 mg/dL and serum levels of calcium >11.0 mg/dL) was also smaller. Serum levels of calcium are independent risk factors for vascular calcification, so less calcium in blood leads to a smaller increase in CACS for sevelamer therapy. However, our analysis showed no significant differences between sevelamer therapy and CBPB therapy in terms of cardiovascular mortality. A long time is required from vascular calcification to a cardiovascular event. Hence, sevelamer may reduce cardiovascular mortality in the long-term, and the fact that no significant evidence was observed for cardiovascular mortality may be due to short-term follow up.

Though sevelamer has less impact in controlling hyperphosphatemia, its use can result in a significant reduction in hospitalization. Moreover, a study showed that sevelamer-treated patients over 65 years old had a significant reduction hospitalization ($P = 0.03$) with a trend toward fewer hospital days ($P = 0.08$). In this respect, sevelamer can enhance the quality of life of patients.

Previous reviews showed no evidence to recommend use of sevelamer because there was no evidence to show that sevelamer has clinically meaningful benefits. However, our meta-analysis showed favorable use of sevelamer, especially for patients with hypercalcemia or high CACS. Also, compared with calcium-phosphate binders, the available trials mostly showed a clinically relevant beneficial effect of sevelamer.

The strengths of this meta-analysis were the number of participants and studies that we evaluated. Indeed, this is the largest systematic review of RCTs on dialysis patients to examine the effect of sevelamer compared with CBPB therapy on kidney-related serum measurements, CACS, ACS, hospitalization, and other endpoints of clinical safety.

However, several limitations must be considered. Unpublished reports could not be identified, which might have biased our results. Also, we could not assess the dosing schedules of sevelamer therapy and CBPB therapy (including dosing escalations and maximal dosing schemes), which may have contributed to the heterogeneity of our analysis (especially for the analysis of serum levels of phosphate). Patients undergoing hemodialysis or peritoneal dialysis were studied in the populations. With only four studies focusing on adequate allocation concealment, the quality of trials was not very high. Also, the duration of follow-up was short except for four Dialysis Clinical Outcomes Revisited trials. Intention-to-treat analysis was not used in some trials. In addition, some trials did not describe the number of dropouts.

In summary, compared with CBPBs, sevelamer has virtually no advantage in terms of the control of serum levels of phosphate, but it can decrease in the prevalence of hypercalcemia, and benefits vascular calcification in the long-term. We can conclude that sevelamer improves clinically relevant outcomes in ESRD patients on dialysis. Therefore, routine use of sevelamer in dialysis patients is recommended in patients that already have control of serum levels of phosphate, and if patients may suffer, or already are suffering, from hypercalcemia or cardiovascular disease. Those with severe hyperphosphatemia are recommended to choose CBPB therapy (at least in the short-term).

Supporting Information

S1 Fig. PRISMA 2009 Checklist.
(PDF)

S2 Fig. Risk of bias graph.
(TIF)

S3 Fig. Summary of risk of bias.
(TIF)

S4 Fig. Summary of findings tables.
(TIF)

S5 Fig. Linear regression of CACS and LDL.
(TIF)

S6 Fig. Meta-regression for baseline variables on serum phosphate.
(TIF)

S7 Fig. Meta-regression for baseline variables on the change of CACS.
(TIF)

S8 Fig. Regression graph of the change of CACS on total sample.
(TIF)

Author Contributions

Conceived and designed the experiments: CXW XL YMZ TQL. Performed the experiments: CXW SML YNW. Analyzed the data: CXW YBC SML. Contributed reagents/materials/analysis tools: YNW YBC CXW. Wrote the paper: CXW XL.

References

1. Levey AS, Coresh J. Chronic kidney disease. *Lancet*. [Journal Article; Review]. 2012 2012-01-14; 379 (9811):165–80. doi: [10.1016/S0140-6736\(11\)60178-5](https://doi.org/10.1016/S0140-6736(11)60178-5) PMID: [21840587](https://pubmed.ncbi.nlm.nih.gov/21840587/)
2. Chantrel F, Enache I, Bouiller M, Kolb I, Kunz K, Petitjean P, et al. Abysmal prognosis of patients with type 2 diabetes entering dialysis. *Nephrol Dial Transplant*. [Journal Article]. 1999 1999-01-01; 14 (1):129–36. PMID: [10052492](https://pubmed.ncbi.nlm.nih.gov/10052492/)
3. Tzamaloukas AH, Yuan ZY, Balaskas E, Oreopoulos DG. CAPD in end stage patients with renal disease due to diabetes mellitus—an update. *Adv Perit Dial*. [Comparative Study; Journal Article]. 1992 1992-01-19; 8:185–91. PMID: [1361783](https://pubmed.ncbi.nlm.nih.gov/1361783/)
4. Brunner FP, Selwood NH. Profile of patients on RRT in Europe and death rates due to major causes of death groups. The EDTA Registration Committee. *Kidney Int Suppl*. [Journal Article; Research Support, Non-U.S. Gov't]. 1992 1992-10-01; 38:S4–15. PMID: [1405380](https://pubmed.ncbi.nlm.nih.gov/1405380/)
5. Malberti F. Hyperphosphataemia: Treatment Options. *Drugs*. 2013; 73(7):673–88. doi: [10.1007/s40265-013-0054-y](https://doi.org/10.1007/s40265-013-0054-y) PMID: [23625273](https://pubmed.ncbi.nlm.nih.gov/23625273/)
6. Alonso A, Lau J, Jaber BL, Weintraub A, Sarnak MJ. Prevention of radiocontrast nephropathy with N-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized, controlled trials. *Am J Kidney Dis*. 2004; 43(1):1–9. PMID: [14712421](https://pubmed.ncbi.nlm.nih.gov/14712421/)
7. Wendy L. St. Peter QFEW. Economic Evaluation of Sevelamer versus Calcium-Based Phosphate Binders in Hemodialysis Patients: A Secondary Analysis using Centers for Medicare & Medicaid Services Data. *Clin J Am Soc Nephrol*. 2009(4):1954–61.
8. Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL. Timing of Renal Replacement Therapy Initiation in Acute Renal Failure: A Meta-analysis. *Am J Kidney Dis*. 2008; 52(2):272–84. doi: [10.1053/j.ajkd.2008.02.371](https://doi.org/10.1053/j.ajkd.2008.02.371) PMID: [18562058](https://pubmed.ncbi.nlm.nih.gov/18562058/)
9. QZAM A, Chuanming Hao DJC A. Meta-Analysis Comparing Sevelamer and Calcium-Based Phosphate Binders on Cardiovascular Calcification in Hemodialysis Patients. *nephron clinical practice*. 2010 (115):259–67.
10. Sophie A. Jamal DFCE. The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis. *Nephrol Dial Transplant*. 2009 (24):3168–74.
11. Marcello Tonelli NWBC, Network FSAB. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant*. 2007(22):2856–66.
12. Manns B SLMD, Owen WF JWWT. A systematic review of sevelamer in ESRD and an analysis of its potential economic impact in Canada and the United States. *Kidney Int*. 2004(66):1239–47.
13. Burke SK DMHD. Meta-analysis of the effect of sevelamer on phosphorus, calcium, PTH, and serum lipids in dialysis patients. *Adv Ren Replace Ther*. 2003; 2(10):133–45.
14. O'Rourke RA, Brundage BH, Froelicher VF, Greenland P, Grundy SM, Hachamovitch R, et al. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol*. [Consensus Development Conference; Journal Article; Review]. 2000 2000-07-01; 36(1):326–40. PMID: [10898458](https://pubmed.ncbi.nlm.nih.gov/10898458/)
15. Achenbach S, Ulzheimer S, Baum U, Kachelriess M, Ropers D, Giesler T, et al. Noninvasive coronary angiography by retrospectively ECG-gated multislice spiral CT. *Circulation*. [Journal Article]. 2000 2000-12-05; 102(23):2823–8. PMID: [11104739](https://pubmed.ncbi.nlm.nih.gov/11104739/)
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009; 62(10):e1–34. doi: [10.1016/j.jclinepi.2009.06.006](https://doi.org/10.1016/j.jclinepi.2009.06.006) PMID: [19631507](https://pubmed.ncbi.nlm.nih.gov/19631507/)
17. Green JPHA, editor *Cochrane Handbook for Systematic Reviews of Interventions*. England: John Wiley & Sons Ltd; 2008.
18. Curtin F ADED. Meta-analysis combining parallel and cross-over clinical trials. I: Continuous outcomes. *Stat Med*. 2002; 21(15):2131–44. PMID: [12210629](https://pubmed.ncbi.nlm.nih.gov/12210629/)

19. GA Block PRAB. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *International Society of Nephrology*. 2007; 71:438–41.
20. GEOFFREY A. BLOCK DMSJ, ALBERT DREISBACH APR. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *International Society of Nephrology*. 2005; 68:1815–24.
21. 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*. 2008; 51(3):445–54. doi: [10.1053/j.ajkd.2007.12.002](https://doi.org/10.1053/j.ajkd.2007.12.002) PMID: [18295060](https://pubmed.ncbi.nlm.nih.gov/18295060/)
22. Fellype C. Barreto DVBR. Sevelamer and Calcium Acetate Effects on Bone Histology in Hemodialysis Patients One-Year Follow-Up. *J Am Soc Nephrol*. 2005 2014-11-12.
23. Barreto DV, Barreto FDC, de Carvalho AI, Barbosa Z, Cuppari L, Draibe SE, et al. Phosphate Binder Impact on Bone Remodeling and Coronary Calcification – Results from the BRiC Study. *Nephron Clinical Practice*. 2008; 110(4):c273–83. doi: [10.1159/000170783](https://doi.org/10.1159/000170783) PMID: [19001830](https://pubmed.ncbi.nlm.nih.gov/19001830/)
24. Chertow GM, Raggi P, McCarthy JT, Schulman G, Silberzweig J, Kuhlik A, et al. The Effects of Sevelamer and Calcium Acetate on Proxies of Atherosclerotic and Arteriosclerotic Vascular Disease in Hemodialysis Patients. *Am J Nephrol*. 2003; 23(5):307–14. PMID: [12915774](https://pubmed.ncbi.nlm.nih.gov/12915774/)
25. Asmus HG, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, et al. Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. *Nephrol Dial Transpl*. 2005 2005-08-01; 20(8):1653–61.
26. GLENN M. CHERTOW SKBP, GROUP FTTT. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*. 2002; 62:245–52. PMID: [12081584](https://pubmed.ncbi.nlm.nih.gov/12081584/)
27. Paolo Raggi JBG. Valvular calcification in hemodialysis patients randomized to calcium-based phosphorus binders or sevelamer. *The Journal of Heart Valve Disease*. 2004; 13:134–41. PMID: [14765851](https://pubmed.ncbi.nlm.nih.gov/14765851/)
28. 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*. 2005; 149(5):820–5. PMID: [15894962](https://pubmed.ncbi.nlm.nih.gov/15894962/)
29. Chertow GM DMBS, Steg M BAGB, Domoto DT WB, Wombolt DG SE, QZAM A. A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients.; 1999. p. 18–26.
30. Bleyer ADOM, Burke SM, Garrett B, Kant K, Lynch D, Rahman S, 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*. 1999 2014-02-13; 33(4):694–701. PMID: [10196011](https://pubmed.ncbi.nlm.nih.gov/10196011/)
31. Gallieni TCMS M.. Comparison of Sevelamer HCl and Calcium Carbonate in the Treatment of Hyperphosphatemia in Dialysis Patients A Randomized Clinical Trial—Calcium Carbonate Sevelamer Evaluation Study. *J Am Soc Nephrol*. 2005 2014-04-24.
32. Rodrigo B. Oliveira FBDV, LCVJ L. E. Cancela, Eugênia Canziani RMAM. Sevelamer (SEV), but Not Calcium Acetate (CA), Decreases Serum Fibroblast Growth Factor 23 (FGF23) in Hemodialysis Patients. *J Am Soc Nephrol*. 2007 2014-02-22.
33. Evenepoel P, Selgas R, Caputo F, Foggensteiner L, Heaf JG, Ortiz A, et al. Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. *Nephrol Dial Transpl*. 2008 2008-08-06; 24(1):278–85.
34. Suki WN. Effects of Sevelamer and Calcium-Based Phosphate Binders on Mortality in Hemodialysis Patients: Results of a Randomized Clinical Trial. *Journal of Renal Nutrition*. 2008; 18(1):91–8. PMID: [18089452](https://pubmed.ncbi.nlm.nih.gov/18089452/)
35. Cancela ALE, Oliveira RB, Graciolli FG, Dos Reis LM, Barreto F, Barreto DV, et al. Fibroblast Growth Factor 23 in Hemodialysis Patients: Effects of Phosphate Binder, Calcitriol and Calcium Concentration in the Dialysate. *Nephron Clinical Practice*. 2011; 117(1):c74–82. doi: [10.1159/000319650](https://doi.org/10.1159/000319650) PMID: [20689328](https://pubmed.ncbi.nlm.nih.gov/20689328/)
36. Anı Bal Ferreira JOMF, Jose Galvao COJB, Silvia Ribeiro RMHA. Effects of Sevelamer Hydrochloride and Calcium Carbonate on Renal Osteodystrophy in Hemodialysis Patients. *J Am Soc Nephrol*. 2008; 19:405–12. doi: [10.1681/ASN.2006101089](https://doi.org/10.1681/ASN.2006101089) PMID: [18199805](https://pubmed.ncbi.nlm.nih.gov/18199805/)
37. de Francisco ALM, Leidig M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. *Nephrol Dial Transpl*. 2010 2010-11-01; 25(11):3707–17.
38. Garg JP, Chasan-Taber S, Blair A, Plone M, Bommer J, Raggi P, et al. Effects of sevelamer and calcium-based phosphate binders on uric acid concentrations in patients undergoing hemodialysis: A randomized clinical trial. *Arthritis & Rheumatism*. 2005; 52(1):290–5.

39. JOSE G. HERVA S DPAS. Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: A comparison with calcium acetate. *Kidney Int.* 2003; 63:69–72.
40. Kakuta T, Tanaka R, Hyodo T, Suzuki H, Kanai G, Nagaoka M, et al. Effect of Sevelamer and Calcium-Based Phosphate Binders on Coronary Artery Calcification and Accumulation of Circulating Advanced Glycation End Products in Hemodialysis Patients. *Am J Kidney Dis.* 2011; 57(3):422–31. doi: [10.1053/j.ajkd.2010.10.055](https://doi.org/10.1053/j.ajkd.2010.10.055) PMID: [21239096](https://pubmed.ncbi.nlm.nih.gov/21239096/)
41. Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, 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.* 2008; 51(6):952–65. doi: [10.1053/j.ajkd.2008.02.298](https://doi.org/10.1053/j.ajkd.2008.02.298) PMID: [18423809](https://pubmed.ncbi.nlm.nih.gov/18423809/)
42. WAJEH Y. QUNIBI REHL, MATTHIAS SIMON ROGR, LARRY R. MUENZ DYHA. Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study. *Kidney Int.* 2004:1914–26. PMID: [15086935](https://pubmed.ncbi.nlm.nih.gov/15086935/)
43. Paolo Raggi SKBS. Sevelamer Preserves and Calcium Reduces Trabecular Bone Mineral Density. *J Am Soc Nephrol.* 2005 2014-02-23.
44. Tarek Sadek HMHB, Isabelle El Esper FBMB. Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: an open-label, randomized study. *Nephrol Dial Transplant.* 2003; 18:582–9. PMID: [12584283](https://pubmed.ncbi.nlm.nih.gov/12584283/)
45. Faisal A. Shaheen MNMA. Efficacy and safety of sevelamer. Comparison with calcium carbonate in the treatment of hyperphosphatemia in hemodialysis patients. *Saudi Med J.* 2004; 25(6):785–91. PMID: [15195212](https://pubmed.ncbi.nlm.nih.gov/15195212/)
46. Takei T, Otsubo S, Uchida K, Matsugami K, Mimuro T, Kabaya T, et al. Effects of Sevelamer on the Progression of Vascular Calcification in Patients on Chronic Haemodialysis. *Nephron Clinical Practice.* 2008; 108(4):c278–83. doi: [10.1159/000127361](https://doi.org/10.1159/000127361) PMID: [18434749](https://pubmed.ncbi.nlm.nih.gov/18434749/)
47. Braun HGAH J., Holzer RBRK, W. Schulz HHN, Bommer PRAJ. Long-term comparison of a calcium-free phosphate binder and calcium carbonate–phosphorus metabolism and cardiovascular calcification. *Clinical Nephrology.* 2004(62):104–15.
48. Yu-Feng Lin YCKH. Benefits of Sevelamer on Markers of Bone Turnover in Taiwanese Hemodialysis Patients. *J Formos Med Assoc.* 2010; 109(9):663–72. doi: [10.1016/S0929-6646\(10\)60107-6](https://doi.org/10.1016/S0929-6646(10)60107-6) PMID: [20863994](https://pubmed.ncbi.nlm.nih.gov/20863994/)
49. Liu Y, Lin H, Yu C, Kuo H, Yang Y, Chou C, et al. A Comparison of Sevelamer Hydrochloride with Calcium Acetate on Biomarkers of Bone Turnover in Hemodialysis Patients. *Renal Failure.* 2006; 28(8):701–7. PMID: [17162430](https://pubmed.ncbi.nlm.nih.gov/17162430/)