Nephrol Dial Transplant (2017) 32: 111–125
doi: 10.1093/ndt/gfw312
Advance Access publication 20 September 2016

The efficacy and safety of sevelamer and lanthanum versus calcium-containing and iron-based binders in treating hyperphosphatemia in patients with chronic kidney disease: a systematic review and meta-analysis

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ORIGINAL ARTICLE

ABSTRACT

Background. It remains unclear which phosphate binders should be preferred for hyperphosphatemia management in chronic kidney disease (CKD).

Methods. We performed a systematic review and meta-analysis of randomized trials comparing sevelamer or lanthanum with other phosphate binders in CKD.

Results. Fifty-one trials (8829 patients) were reviewed. Compared with calcium-based binders, all-cause mortality was nonsignificantly lower with sevelamer {risk ratio [RR] 0.62 [95% confidence interval (CI) 0.35–1.08]} and lanthanum [RR 0.73 (95% CI 0.18–3.00)], but risk of bias was concerning. Compared with calcium-based binders, sevelamer reduced the risk of hypercalcemia [RR 0.27 (95% CI 0.17–0.42)], as did lanthanum [RR 0.12 (95% CI 0.05–0.32)]. Sevelamer reduced hospitalizations [RR 0.50 (95% CI 0.31–0.81)], but not lanthanum [RR 0.80 (95% CI 0.34–1.93)]. The presence/absence of other clinically relevant outcomes was infrequently reported. Compared with calcium-based binders, sevelamer reduced serum calcium, low-density lipoprotein and coronary artery calcification, but increased intact parathyroid hormone. The clinical relevance of these changes is unknown since corresponding clinical outcomes were not reported. Lanthanum had less favorable impact on biochemical parameters. Sevelamer hydrochloride and sevelamer carbonate were similar in three studies. Sevelamer was similar to lanthanum (three studies) and iron-based binders (three studies).

Conclusion. Sevelamer was associated with a nonsignificant reduction in mortality and significantly lower hospitalization rates and hypercalcemia compared with calcium-based binders. However, differences in important outcomes, such as cardiac events, fractures, calciphylaxis, hyperchloremic acidosis and health-related quality of life remain understudied. Lanthanum and iron-based binders did not show superiority for any clinically relevant outcomes. Future studies that fail to measure clinically important outcomes (the reason why phosphate binders are prescribed in the first place) will be wasteful.

Keywords: chronic kidney disease, hyperphosphatemia, lanthanum, sevelamer, systematic review

INTRODUCTION

Chronic kidney disease (CKD) affects 5% of adults, is very costly and is associated with a high risk of mortality and hospitalization [1–3]. Some of the poor outcomes for patients with CKD have been attributed to the inability of diseased kidneys to excrete dietary phosphate, leading to complex mineral and bone disorders and arterial calcification, which is thought to lead to increased risk of adverse cardiac events and premature mortality [4–7]. Phosphate binders have become the mainstay of prevention and management of hyperphosphatemia among patients with CKD, particularly the calcium-based phosphate binders (CBPBs) calcium carbonate and calcium acetate [8, 9]. Although inexpensive and highly effective in reducing serum phosphorus levels, CBPBs may result in elevated serum calcium and adverse clinical events related to hypercalcemia, potentially increasing the risk of vascular calcification and arterial stiffening. This prompted the development of calcium-free phosphate binders, including sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate and iron-based binders [10, 11].

Whether calcium-free binders improve clinically important outcomes compared with CBPBs still remains a matter of debate [12]. Recent systematic reviews failed to adequately address all clinically important outcomes (cardiac events, bone fractures, hypercalcemia, hospitalization, all-cause mortality) and failed to adequately address missing data and losses to

follow-up [13–15, 13, 16, 17]. Moreover, clinical relevance of comparisons among the non-calcium-containing binders also need to be determined [11, 18]. The purpose of this systematic review and meta-analysis is to reevaluate the evidence reporting the safety and efficacy of calcium-free phosphate binders in CKD patients and to make recommendations for future research in this area.

METHODS

Search strategy and inclusion criteria

PubMed, Embase and Cochrane Central were searched on 19 January 2015 using the search terms 'sevelamer' OR 'renagel' OR 'renvela', supplemented with 'lanthanum carbonate' on 9 February 2016; 'phosphate binder' AND 'iron' was added as an addendum to our original protocol (PROSPERO CRD42 015024667). Reference lists from publications were also reviewed for additional citations. Screening was performed by a single author (S.H.) and data extraction was performed independently by S.H. and S.P. Eligible studies were randomized trials on adults (>18 years of age) published in peer-reviewed journals (i.e. not abstracts) that compared sevelamer, lanthanum or iron-based binders with any other phosphate binder (excluding studies where only a nonactive placebo control was used or where a combination of active controls was used). Studies were not restricted by language, year of publication or study size.

Data collection

Studies were classified by dialysis modality as chronic (>2 months) hemodialysis (HD), incident HD, chronic peritoneal dialysis (PD) and non-dialysis-dependent (NDD)-CKD. Information collected included ethnicity (by patient country of origin), follow-up time, study size, age at randomization, untreated serum phosphorus levels for patient inclusion (i.e. after washout), and study design (crossover versus parallel-arm trial; single versus multicentered; double-blind versus open-label; fixed dosing versus treat to target). Results from crossover trials were combined with noncrossover trials. If numeric data were unavailable, graphical representations were digitized (http://arohatgi.info/WebPlotDigitizer/).

Risk of bias assessment

Study bias was assessed using the Cochrane Risk of Bias tool by considering the possibility of selection bias, measurement bias (blinding of subjects and study personnel ascertaining subjective outcomes such as like coronary artery calcification), number and reason for participant withdrawal, method of randomization and clear reporting of outcomes [19]. Other bias was considered 'unclear' if sample size was small (<100 patients, or <50 if crossover), or if the sample size was <200 (100 if crossover) and the trial was not registered. Double-blind studies were not considered to have a low risk of bias if the method of blinding was not described.

Study outcomes

The primary outcome was all-cause mortality. Secondary analyses included major adverse cardiovascular events, bone-related events (i.e. fractures, osteoporosis), calciphylaxis and biochemical events (hypercalcemia, hyperchloremic acidosis). Other secondary outcomes included loss to follow-up (as this may be a source of undocumented adverse events attributable to treatment) and hospitalization rates. Although they are of uncertain clinical relevance, we also extracted biochemical parameters at the end of the study, including serum phosphorus, corrected serum calcium, low-density lipoprotein (LDL), intact parathyroid hormone (iPTH) and coronary artery calcification (CAC).

Statistical methods and subgroup analyses

Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for discrete outcomes. Mean differences (MDs) were used to compare continuous outcomes (biochemical values). The number needed to treat (NNT) was calculated by pooling studies with similar follow-up time [20, 21]. The random effects model was used for all analyses. Review Manager 5.3 was used to prepare meta-analyses, present risk of bias tables, generate forest plots and calculate pooled estimates. Review Manager applies a continuity correction of 0.5 to all cells of binary outcomes for studies with single zeros (double-zero studies are omitted) [22]. The methodology for incorporating double-zero studies has been provided without the need for continuity correction [23]. Thus, we supplemented the pooled estimates generated by Review Manager with these beta-binomial regression methods using the macro provided by Kuss in SAS version 9.4 [23]. Trials that reported the absence of events were included, while those that failed to report whether or not events occurred were omitted.

A priori–defined subgroup analyses were conducted if substantive (significant and important) heterogeneity was present. Mortality was also evaluated in subgroups by the length of follow-up (*post hoc* comparison). Subgroups included CBPBs ($CaCO_3$, calcium acetate), ethnicity (White, Asian, other), dialysis status (chronic HD, incident HD, NDD-CKD, PD) and nature of dosing (treat to target/variable, fixed). Heterogeneity across studies and between subgroups was assessed using Cochrane's Q (P-values) and Higgin's I^2, together with visual inspection of forest plots [24]. When necessary, standard deviations (SDs) were calculated by multiplying standard errors by the square root of the sample size or estimated by single imputation using values from a similar study [19]. Publication bias was assessed using funnel plots and Egger's regression using Stata version 13.0. Meta-regression was conducted with Stata version 13.0 using log RR as the outcome. Regression coefficients were exponentiated for interpretability.

RESULTS

The search strategy yielded 3002 citations, of which 164 remained after screening (Figure 1). After further excluding duplicate study populations and abstracts, 51 unique

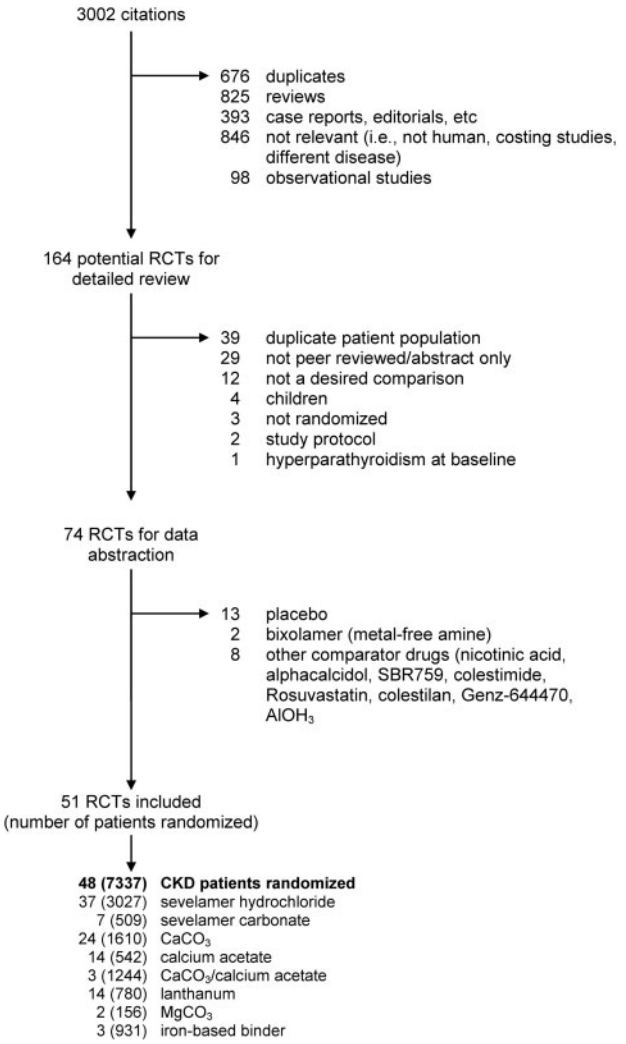

FIGURE 1: Search strategy for inclusion and exclusion of studies.

randomized trial populations met the inclusion criteria [25–75] randomizing 8829 CKD patients (Figure 1, Table 1). Additional data were extracted from four *post hoc* analyses [76–79]. Because of differences in the size and taste of the tablets, 91% (n = 42) of studies were open label. Twenty-eight (55%) trials were multicenter, 12 (24%) were crossover and 43 (84%) randomized dialysis-dependent CKD patients (36 chronic HD, 3 incident HD, 3 chronic PD and 1 HD/PD). When funding sources were provided, 17/32 (53%) were industry-sponsored trials. Trial follow-up ranged from 2 weeks to 3 years. Overall, there was a low risk of selection bias and bias due to outcome ascertainment, but there was moderate risk of bias due to incomplete outcome data and selective reporting (Supplementary data, Figure S1).

Mortality

Sevelamer versus CBPBs: While most studies individually lacked sufficient sample size to reliably detect mortality differences between groups, combination through meta-analysis suggested a trend toward lower risk of death among patients receiving sevelamer (325/1870 deaths) compared with CBPBs (426/1899 deaths) in 12 studies [RR 0.62 (95% CI 0.35–1.08)] (Figure 2, Table 2). After excluding the study with substantial risk of attrition bias (the largest study [53]), the risk reduction in mortality was strengthened [RR 0.51 (95% CI 0.32–0.83)] and the observed heterogeneity across CBPB subgroups diminished (reduced from I^2= 79% to 30%). Mortality was rarely observed in studies that had <1 year of follow-up (Table 3), and omission of these short-term studies resulted in a similar effect size for sevelamer on mortality [RR 0.58 (95% CI 0.31–1.11)]. Only two sevelamer trials reported deaths in incident HD patients, one in NDD-CKD patients, and none in PD patients (Table 3).

Lanthanum versus CBPBs: Lanthanum versus CBPBs did not significantly reduce the risk of all-cause mortality [RR 0.73 (95% CI 0.18–3.00)] based on 3/81 deaths (lanthanum) and 4/83 deaths (calcium binders) in four studies. However, two of the larger studies were considered to have a high risk of bias due to selective reporting. Hutchison *et al.* [67] randomized 800 patients who were followed for 5 weeks and 138 participants (17%) were lost during this period. Participants were selected to remain in the study for another 20 weeks (if their serum phosphorus was well controlled). While there were no deaths reported in this study, there remains concern that deaths may have been missed in the patients lost to follow-up. In the trial of D'Haese *et al.* [60], 11/98 participants died, but the number of deaths in each arm was not stated, and hence could not be included in the meta-analysis for death. Subgroup analysis by type of CBPB did not change the results.

Evidence of publication bias was not found [P = 0.51 for Egger's test (Supplementary data, Figure S2A)]. The risk of death using the beta-binomial method was RR = 0.83 (95% CI 0.38–1.82) for sevelamer, RR = 0.68 (95% CI 0.12–3.98) for lanthanum and RR = 0.81 (95% CI 0.39–1.66) combined.

Other clinically relevant outcomes (cardiac events, bone-related events)

Reporting on other important clinical outcomes was sparse (Table 2) and no significant differences were reported; however, the number of studies reporting outcomes provided insufficient power to yield definitive conclusions. Cardiovascular events were reported in six sevelamer trials: three reported cardiovascular mortality [RR 0.29 (95% CI 0.05–1.82); 152/1337 sevelamer, 232/1351 CBPBs] [29, 41, 53], two were unspecified [25, 32] and one was only qualitative [50] (an additional study reported a sudden death in a patient with a dilated cardiomyopathy [33]). Four lanthanum trials reported cardiovascular events, but these were also heterogeneous: one specified angina [67], two were unspecified [63, 66] and one reported any event inclusive of angina, heart failure, myocardial infarction, stroke or peripheral artery disease [65].

Bone-related adverse events were rarely documented (osteoporosis reported in one sevelamer patient [53], absence of fractures reported in one lanthanum trial [66]). This sparse reporting did not support meta-analysis (Table 2).

Hospitalization

Hospitalization was reported in five sevelamer trials, four of which provided data amenable to meta-analysis (Figure 5B) [25, 52, 53, 80, 81]. Sevelamer was associated with a significantly lower risk of hospitalization (113/493 events) compared with

Table 1. Characteristics of included studies

Reference	Washout[a]	Follow-up time	Crossover	Centres	Blinding	Ethnicity	Random (n)	Baseline (n)	End-of-study (n)	Age, years (SD)	Percent diabetic	Dialysis vintage	Inclusion (phosphorus mg/dL)
Sevelamer versus $CaCO_3$													
Braun (2004) [25]	2 weeks	2 years	No	M	OL	Europe	114	55/59	42/40	56.5 (14.1)	13/17	Stable HD	≥5.5
Caravaca (2007) [37]	2 weeks	3 weeks	Yes	S	OL	Spain	20	20	17	54 (17)	NR	CKD stages 3–4	None
Chennasamudram (2013) [26][b]	2 weeks	8 weeks	Yes	S	OL	USA	15	7/8	7/8	54 (9)	100	Chronic PD	≥5.5
De Santo (2006) [27]	2 weeks	24 weeks	Yes	S	OL	Italian	16	8/8	8/8	35–50 years	0	HD 6–10 months	≥5.5
Di Iorio (2012) [28]	None	24 months	No	M	OL	Italian	239	121/118	107/105	57.9 (12.2)	27/29	CKD stage 3–4	None
Di Iorio (2013) [29]	None	36 months	No	M	OL	Italian	466	232/234	199/198	65.6 (14.8)	30/29	New to HD	None
Ferreira (2008) [30]	0 weeks	12 months	No	M	OL	Portugal	91	44/47	33/35	54.7 (14.5)	6/23	HD >3 months	<8.1
Kakuta (2011) [31]	0 weeks	12 months	No	M	OL	Japan	183	91/92	79/84	58.0 (12.0)	23/19	Stable HD	None
Koiwa (2005) [38]	0 weeks	4 weeks	No	M	OL	Japan	56	29/27	16/20	57.1 (10.6)	23	HD >12 months	None
Lin (2014) [32]	2 weeks	48 weeks	No	M	OL	Taiwan	75	36/39	23/27	58.2 (8.0)	NR	HD >3 months	≥5.5
Russo (2007) [36]	0 weeks	24 months	No	M	OL	Italy	60	30/30	27/28	54.7 (12.7)	0	CKD stages 3–5	None
Sadek (2003) [33]	0 weeks	5 months	No	S	OL	France	42	21/21	15/16	NR	NR	Chronic HD	NR
Shaheen (2004) [34]	2 weeks	8 weeks	Yes	S	OL	Saudi Arabia	20	10/10	19/18	42.7 (9.9)	20	HD >3 months	≥5.5
Vlassara (2012) [35][b]	0 weeks	8 weeks	Yes	S	OL	USA	20	10/10	10/10	61.1 (11.5)	100	CKD stage 2–4	NR
Sevelamer versus Ca-acetate													
Barreto (2008) [41]	2 weeks	12 months	No	M	OL	Brazil	101	52/49	41/30	47 (13.3)	15/13	HD >3 months	≥5.5
Bleyer (1999) [39]	2 weeks	8 weeks	Yes	M	OL	USA	83	83	80	54.5 (15)	29	Stable HD	≥6
Block (2012) [49][b]	0 weeks	9 months	No	S	DB[c]	USA	90	30/30	30/30	68 (11)	53/57	CKD < stage 5D	10.8–18.6
Caglar (2008) [40]	2 weeks	8 weeks	No	S	NR	Turkey	50	25/25	25/25	40.4 (13.0)	0	CKD stage 4	≥5.5
Evenepoel (2009) [42]	2 weeks	12 weeks	No	M	OL	Europe	143	97/46	74/30	54.4 (15.7)	20/26	PD >6 months	≥5.5
Hervas (2003) [43]	2 weeks	34 weeks	No	NR	NR	Spain	51	18/22	18/22	60.4 (15.1)	15	HD >3 months	≥6
Lin (2010) [44]	2 weeks	8 weeks	No	S	OL	Taiwan	52	26/26	23/20	57.3 (12.0)	42/27	HD >3 months	≥5.5
Liu (2006) [71]	2 weeks	8 weeks	No	S	OL	Asian	73	37/36	33/30	48.9 (11.5)	8/15	HD >3 months	≥6
Navarro-González (2011) [72]	2–3 weeks	12 weeks	No	S	OL	Spain	65	33/32	30/29	61.2 (15.5)	43/41	HD >3 months	NR
Oliveira (2010) [45]	0 weeks	6 weeks	No	S	OL	Brazil	40	21/19	21/17	50.38 (11.4)	0	CKD stage 3–4	None
Qunibi (2008) [46]	6 weeks	12 months	No	M	OL	USA	203	100/103	70/59	59.4 (12.5)	57/57	HD >3 months	≥5.5
Qunibi (2004) [47]	1–3 weeks	8 weeks	No	M	DB	USA	100	50/48	45/46	53.1 (14.0)	NR	HD > 3 months	≥6
Yilmaz (2012) [48]	2 weeks	8 weeks	No	S	OL	Turkey	100	47/53	47/53	46 (median)	0	CKD stage 4	≥6
Sevelamer versus unspecified calcium-based binder													
Block (2005) [51]	0 weeks	18 months	No	M	OL	USA	148	73/75	54/55	58.0 (15.0)	63/56	New to HD	None
Chertow (2002) [52]	2 weeks	12 months	No	M	OL	USA/Europe	200	99/101	81/88	56.5 (15.0)	32/33	Stable HD	≥5.5
Suki (2007) [53]	0 weeks	36 months	No	M	OL	USA	2013	1053/1068	551/517	60.0 (14.7)	51/50	HD >3 months	None
Sevelamer versus lanthanum													
Block (2012) [49][b]	0 weeks	9 months	No	S	DB[c]	USA	90	30/30	30/28	68 (11)	53/57	CKD < stage 5D	10.8–18.6
Kasai (2012) [54]	9 weeks	13 weeks	Yes	S	OL	Japan	42	42	41	60.9 (11.9)	31	HD >3 months	NR
Sprague (2009) [55]	3 weeks	4 weeks	Yes	M	OL	Intl	182	86/95	60/59	55.5 (13.1)		HD >2 months	≥6
Sevelamer versus magnesium carbonate													
de Francisco (2010) [50][d]	2–3 weeks	24 weeks	No	M	OL	Europe	255	129/126	99/105	57.6 (12.9)	20/25	HD/HDF >3 months	≥5.5
Zwiech (2011) [56]	2 weeks	12 weeks	No	S	OL	Poland	40	10/30	10/28	57.8 (13.6)	NR	HD >6 months	≥5.5

Sevalamer hydrochloride versus sevelamer carbonate													
Abraham (2012) [57]	2 weeks	6 weeks	No	M	OL	Indian	97	48/49	44/44	47.7 (12.6)	29/20	Stable HD	≥6
Delmez (2007) [58]	0 weeks	8 weeks	Yes	M	DB	USA	79	40/39	19/21	58.1 (12.3)		Chronic HD	None
Fan (2009) [59]	2 weeks	4 weeks	Yes	M	OL	UK (London)	31	14/17	24	59.2 (13.2)	13	HD >3 months	≥5.5
Sevalamer versus iron-based binder													
Chen (2011) [73]	1–2 weeks	12 weeks	No	M	OL	Japan/Taiwan	203	68/135	54/119	58.6 (11.2)	29	HD >3 months	≥6.0
Floege (2014) [74][b]	2–4 weeks	12 weeks	No	M	OL	Intl	1059	349/710	293/515	56 (14)	28	HD/PD	≥6.0
Yokoyama (2014) [75]	2 weeks	12 weeks	No	M	OL	Japan	230	114/116	97/102	60.8 (10.1)	26	HD >3 months	≥6.1
Lanthanum versus calcium-based binder													
D'Haese (2003) [60]	8–12 d	12 months	No	M	OL	Europe	98	49/49	34/34	55 (14.3)	26	HD >3 months	None
Hutchison (2005) [67]	1–3 weeks	5 weeks	No	M	OL	Europe	800	533/267	453/209	57.5 (14.0)	NR	HD > 3 months	>5.6
Lee (2013) [68]	0 weeks	24 weeks	No	M	NR	S Korea	72	35/35	20/30	50.4 (11.4)		PD >6 months	>5.6
Ohtake (2013) [64]	0 weeks	6 months	No	S	OL	Japan	52	26/26	19/23	67.8 (6.3)	43	Stable HD	None
Scaria (2009) [70][e]	4 weeks	4 weeks	Yes	S	OL	India	26	13/13	10/10	49.9	NR	CKD stage 4	>5.5
Shigematsu (2008) [62]	2 weeks	8 weeks	No	M	DB	Japan	259	126/132	122/126	57.4 (11.1)	20	Stable HD	5.6–11.0
Soriano (2013) [65]	0 weeks	4 months	No	S	NR	Spain	32	16/16	16/16	∼60	25/12.5	CKD stages 3–5	>4
Spasovski (2006) [61]	0 weeks	12 months	No	S	NR	Macedonia	24	12/12	10/10	56 (9.8)	20	New to HD	None
Toussaint (2011) [66]	1 week	6 months	No	S	OL	Australia	45	22/23	17/13	57.4 (14.9)	36/39	HD > 3 months	>5
Toida (2012) [69]	2 weeks	3 months	Yes	S	OL	Japan	50	25/25	18/24	65.6 (11.5)		Stable HD	None
Wada (2014) [63]	2 weeks	12 months	No	S	OL	Japan	43	21/22	19/22	65.7 (9.26)	100	HD >6 months	None

Sevelamer refers to sevelamer hydrochloride, unless otherwise specified. OL, open-label; DB, double-blind; SD, standard deviation; HD, hemodialysis; PD, peritoneal dialysis; HDF, hemodiafiltration; NDD-CKD, non-dialysis-dependent chronic kidney disease; NR, not reported.

[a]Length of time (weeks) prior to randomization that current phosphate binders were removed.

[b]Intervention is sevelamer carbonate.

[c]No explanation of how this was successfully undertaken due to differences in taste and size as reported by others.

[d]Comparator also includes calcium acetate.

[e]Comparator is calcium acetate.

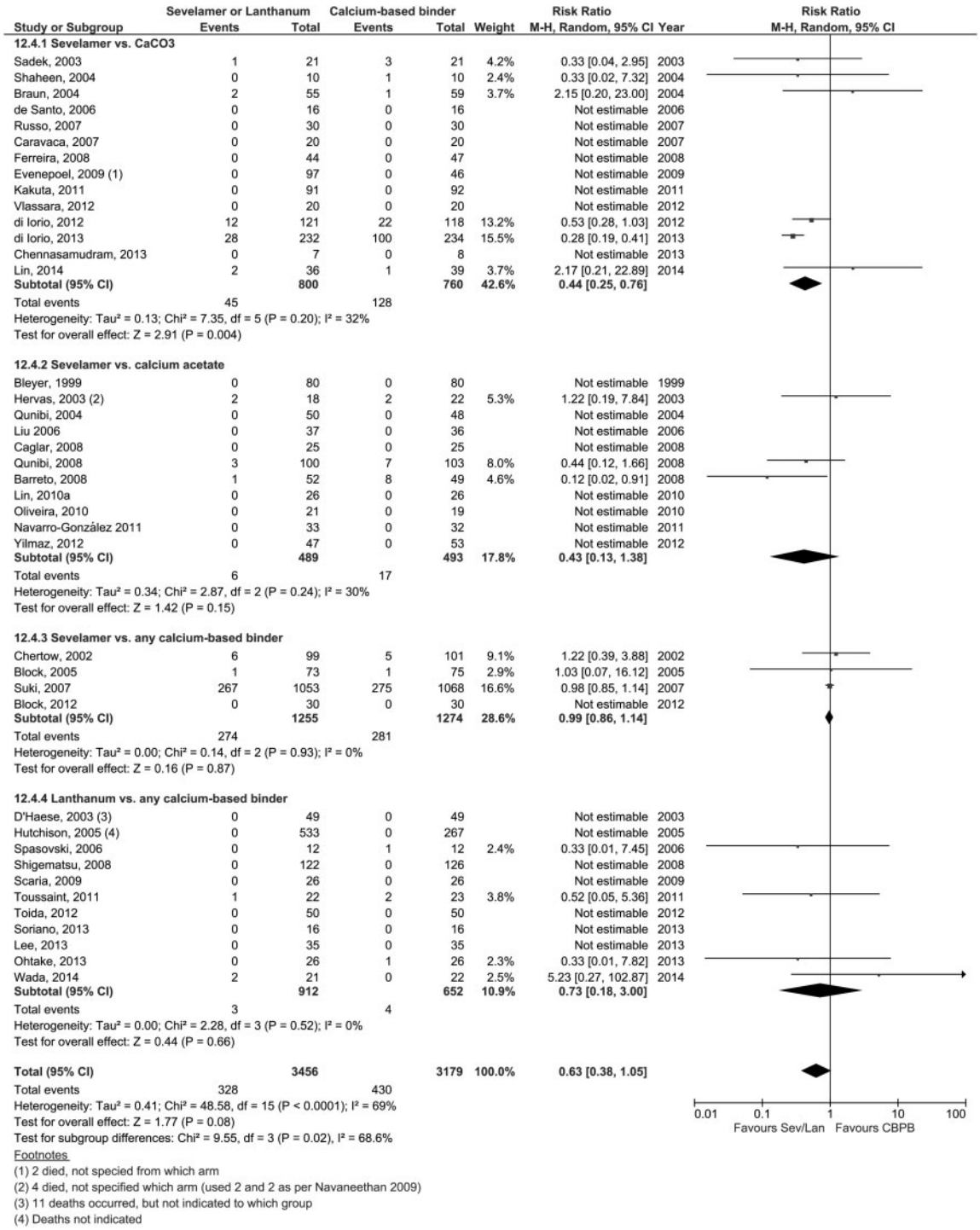

FIGURE 2: Forest plot comparing all-cause mortality over study duration between patients treated with sevelamer or lanthanum and CBPBs. (1) Two deaths were not specified to which arm, but pooled estimate was not sensitive to whether both deaths were assigned to either sevelamer [RR 0.64 (95% CI 0.37–1.11)] or CBPBs [RR 0.59 (95% CI 0.34–1.02)]. (2) Abstracted from Navaneethan *et al.* [16]. (3) Eleven deaths occurred, but not specified to which arm. (4) Deaths not reported.

CPBPs (245/499 events) [RR 0.50 (95% CI 0.31–0.81)]. The study that could not be pooled reported a hospitalization rate of 2.1 (SD 4.4) and 2.3 (SD 4.9) hospitalizations/patient-year among sevelamer and CBPBs, respectively (P = 0.06) [53]. The NNT to prevent hospitalization was 4 (95% CI 2–50) for 2 years and 4 (95% CI 3–5) for 3 years, suggesting that four patients would need to be treated with sevelamer instead of CBPBs to prevent one additional hospitalization. Two studies reported longer length of stay among patients treated with CBPBs [52, 53]. Only two trials reported hospitalization rates for lanthanum (7/43 events) compared with CBPBs (9/45 events); a significant difference was not found [RR 0.80 (95% CI 0.34–1.93)] (Table 2).

Table 2. Summary of clinical and biochemical outcomes by phosphate binder

Discrete outcomes	Sevelamer versus CBPBs					Lanthanum versus CBPBs					P-value[a]	Figure
	N	n_{sev}	n_{Ca}	RR (95% CI)	P-value	*N*	n_{lan}	n_{Ca}	RR (95% CI)	P-value		
All-cause mortality	12	325/1870	426/1899	0.62 (0.35–1.08)	0.09	4[b]	3/81	4/83	0.73 (0.18–3.00)	0.66	0.86	Figure 2
Cardiovascular deaths	3	152/1337	232/1351	0.29 (0.05–1.82)	0.19	0	–	–	–	–	–	–
Cardiovascular events[c]	2	7/91	8/98	–	–	4	11/592	8/328	–	–	–	–
Bone-related events	1	1/1053	0/1068	–	–	1	0/22	0/23	–	–	–	–
Hospitalization rates	4	113/493	245/499	0.50 (0.31–0.81)	0.005	2	7/43	9/45	0.80 (0.34–1.93)	0.62	0.36	Figure 5B
Gastrointestinal events	18	274/1406	215/1330	1.27 (0.97–1.66)	0.08	8	381/834	155/575	1.74 (1.16–2.63)	0.008	0.20	Figure 3
Hypercalcemia	18	73/1562	282/1493	0.27 (0.17–0.42)	<0.0001	7	13/797	126/38	0.12 (0.05–0.32)	<0.0001	0.15	Figure 4
Pruritis	4	21/226	11/227	1.87 (0.93–3.77)	0.08	0	–	–	–	–	–	Figure 5A
Calciphylaxis	1	0/1053	3/1068	–	–	0	–	–	–	–	–	–
Hyperchloremic acidosis	1	0/30	1/30			1	1/28	1/30	–	–	–	–
Participant attrition	23	736/2594	804/2572	0.91 (0.85–0.99)	0.02	11	142/892	103/634	1.19 (0.75–1.88)	0.46	0.27	Supplement
Continuous outcomes	***N***	n_{sev}	n_{Ca}	**MD (95% CI)**	**P-value**	***N***	n_{lan}	n_{Ca}	**MD (95% CI)**	**P-value**	**P-value[a]**	**Figure**
Phosphorus (mg/dL)	30	2178	2133	−0.01 (−0.16–0.14)	0.92	12	581	500	0.18 (0.10–0.27)	<0.0001	0.03	Supplement
Calcium (mg/dL)	28	2078	2055	−0.35 (−0.49 to −0.22)	<0.0001	12	579	499	−0.26 (−0.46 to −0.07)	0.009	0.47	Supplement
LDL (mg/dL)	18	974	979	−20.9 (−23.3 to −18.6)	<0.0001	2	47	53	−2.20 (−11.19–6.79)	0.63	<0.0001	Supplement
iPTH (pg/mL)	17	634	634	39.0 (7.74–70.3)	0.01	8	276	294	63.3 (11.5–115)	0.02	0.43	Supplement
CAC score	8	412	383	−101 (−160 to −41.7)	0.0008	1	19	23	−56.5 (−1308–1195)	0.93	–	Supplement

CBPB, calcium-based phosphate binder; RR, risk ratio; MD, mean difference; CI, confidence interval; LDL, low-density lipoprotein; iPTH, intact parathyroid hormone; CAC, coronary artery calcification; *n*, number of events/total number for dichotomous outcomes and number of measurements for continuous outcomes among participants treated with sevelamer (n_{sev}), CBPB (n_{Ca}) and lanthanum carbonate (n_{lan}); *N*, number of studies.

[a]P-value for heterogeneity for subgroups of sevelamer and lanthanum trials.

[b]One study reported 11 deaths out of 98 randomized patients but did not specify which arm.

[c]Nature of event not specified or differed between studies.

Table 3. Selected subgroup analyses for end-of-study serum phosphorus and intact parathyroid hormone

Subset (sevelamer only)	Number ofstudies	Number of patients		Heterogeneity (I^2, P-value)	RR or MD (95% CI)	P-value	Test for interaction[a] (I^2, P-value)
		Sevelamer	Calcium-based binder				
All-cause mortality							
All studies	12	325/1870	426/1899	75%, <0.0001	0.62 (0.35–1.08)	0.09	–
Comparator							79%, 0.009
$CaCO_3$	6	45/475	128/481	32%, 0.20	0.44 (0.25–0.76)	0.004	
Calcium acetate	3	6/170	17/174	30%, 0.24	0.43 (0.13–1.38)	0.15	
Any CBPB	3	274/1225	281/1244	0%, 0.93	0.99 (0.86–1.14)	0.87	
Dialysis status							94%, <0.0001
Chronic HD	9	284/1444	303/1472	0%, 0.43	0.96 (0.82–1.13)	0.66	
Incident HD	2	29/305	101/309	0%, 0.36	0.29 (0.20–0.42)	<0.0001	
Chronic PD	0	–	–	–	–	–	
NDD-CKD	1	12/314	22/315	–	0.53 (0.28–1.03)	0.06	
Study follow-up							0%, 0.67
<6 months	2	1/71	3/69	0%, 1.00	0.33 (0.06–1.98)	0.23	
6 to <12 months	2	4/54	3/61	0%, 0.71	1.52 (0.35–6.55)	0.57	
12 to <24 months	4	11/324	21/328	32%, 0.22	0.56 (0.21–1.52)	0.26	
≥24 months	4	309/1461	398/1479	92%, <0.0001	0.61 (0.26–1.43)	0.25	
Phosphorus, mg/dL							
Dialysis status							83%, 0.0005
Chronic HD	2618	20 141 517	19 271 523	3145%, 0.02	0.21 (−0.60–0.84)	0.01	
Incident HD	2	253	253	82%, 0.02	−0.43 (−0.72 to −0.15)	0.002	
Chronic PD	2	110	59	82%, 0.02	−0.28 (−1.06–0.49)	0.47	
NDD-CKD	108	334 298	334 298	8273%, 0.0006	−0.22 (−0.54–0.10)	0.17	
Ethnicity							0%, 0.79
White	220	211 843	20 071 800	8381%, <0.0001	0.04 (−0.14–0.22)	0.69	
Asian	15	419 177	450 187	339%, 0.13	−0.08 (−0.42–0.27)	0.67	
Other	5	158	146	86%, <0.0001	−0.11 (−0.69–0.48)	0.72	
Dosing modality							0%, 0.33
Fixed	3525	262 089	24 692 049	80%, <0.0001	0.03 (−0.11–0.16)	0.73	
Variable	5	129 109	134 114	0%, 0.93	0.14 (−0.14–0.16)	0.0.26	
Intact parathyroid hormone, pg/mL							
Dialysis status							48%, 0.12
Chronic HD	1612	666 466	665 461	6574%, <0.0001	51.9 (6.67–97.0)	0.02	
Incident HD	1	54	55	–	54.3 (0.68–108)		
Chronic PD	1	15	15	–	58.6 (33.9–83.3)	–	
NDD-CKD	43	11 599	119 103	5164%, 0.06	−5.43 (−52.4–41.5)	0.82	
Ethnicity							0%, 0.56
White	1512	481 426	480 429	881%, <0.0001	40.4 (2.28–78.5)	0.04	
Asian	62	304 134	325 134	190%, 0.51	55.6 7.29 (−50.2–64.8)	0.8	
Other	3	107	101	79%, 0.008	57.9 (−38.6–154)	0.24	

MD, mean difference; CI, confidence interval; iPTH, intact parathyroid hormone; hemodialysis (HD) and peritoneal dialysis (PD) studies were restricted to >2 months of dialysis; NDD-CKD, non-dialysis-dependent chronic kidney disease; *N*, number of studies with events or poolable data; CBPB, calcium-based phosphate binder.
[a]Test for subgroup differences using Higgin's I^2 and Cochrane's Q (P-value).

Adverse events (gastrointestinal events, hypercalcemia, pruritis, calciphylaxis)

Gastrointestinal problems (i.e. vomiting, diarrhea, constipation, abdominal pain, flatulence) were the most common complaints reported. The incidence of gastrointestinal adverse events did not differ between sevelamer (274/1406 events) and CBPBs (215/1330 events) [RR 1.27 (95% CI 0.97–1.66)], but was significantly higher for patients receiving lanthanum (381/834 events) than CBPBs (155/575 events) [RR 1.74 (95% CI 1.16–2.63)] (Figure 3). There was evidence of publication bias (P = 0.03; Supplementary data, Figure S2B). Beta-binomial estimates were RR = 1.27 (95% CI 0.72–2.24) for sevelamer, RR = 3.02 (95% CI 1.03–8.81) for lanthanum and RR 1.61 (95% CI 0.97–2.65) combined.

Hypercalcemic events were less likely for patients treated with sevelamer (73/1562 events) versus CBPBs (282/1493 events) [RR 0.27 (95% CI 0.17–0.42)]. Similarly, hypercalcemic events were decreased with lanthanum (13/797 events) versus CBPBs (126/538 events) [RR 0.12 (95% CI 0.05–0.32)] (Figure 4). There was no difference by the choice of calcium-free binder (P = 0.15; Table 2). Funnel plot analysis was suggestive of publication bias [P = 0.08 for Egger's test (Supplementary data, Figure S2C)]. Combined beta-binomial analysis was RR = 0.33 (95% CI 0.19–0.59).

Pruritis was reported in seven trials, with a higher risk with sevelamer (21/226 events) compared with CBPBs (11/227 events) [RR 1.87 (95% CI 0.93–3.77)] (Figure 5A). Reporting was too sparse to reliably include double-zero studies. Calciphylaxis developed in three CBPB patients [53]. Hyperchloremic acidosis was reported in one study participant receiving CBPB and one receiving lanthanum [49].

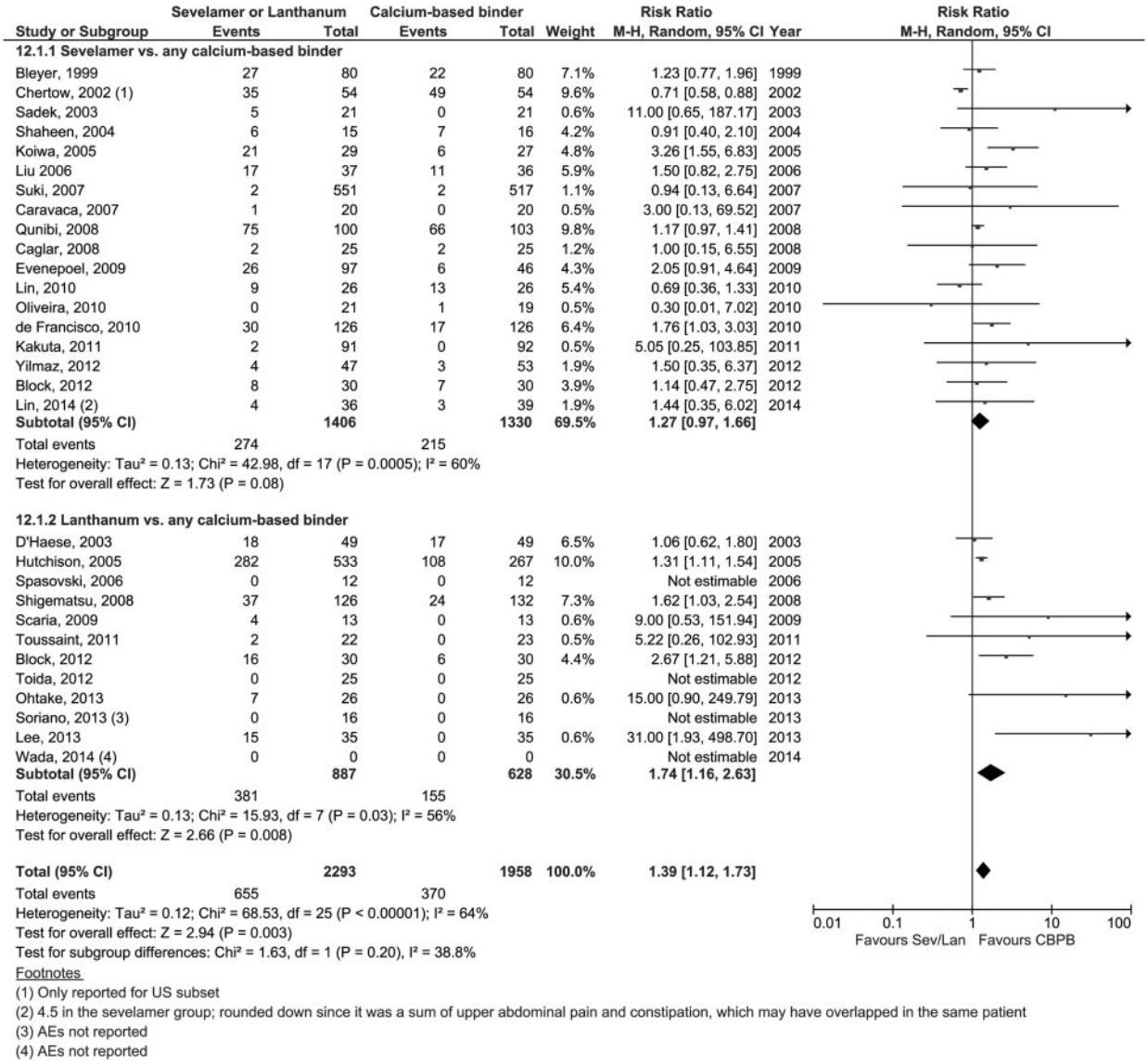

FIGURE 3: Forest plot comparing gastrointestinal adverse event rates over the study duration between patients treated with sevelamer or lanthanum (Sev/Lan) and calcium-based phosphate binders (CBPB). AE - adverse event.

Loss to follow-up

Fewer patients receiving sevelamer than CBPBs were lost to follow-up (736/2594 versus 804/2572) [RR 0.91 (95% CI 0.85–0.99)] but not lanthanum (142/908) versus CBPBs (103/650) [RR 1.19 (95% CI 0.75–1.88)] (Supplementary data, Figure S3). Using beta-binomial methods, the risk of attrition was RR = 0.95 (95% CI 0.61–1.47) for sevelamer, RR = 1.41 (95% CI 0.74–2.69) for lanthanum and RR = 1.07 (95% CI 0.75–1.54) combined.

Serum phosphorus

Meta-analyses of end-of-study biochemical parameters are presented in the Supplementary figures and summarized in Table 2. Sevelamer reduced serum phosphorus ($n = 2178$) to a similar extent to CBPBs ($n = 2133$) [MD −0.01 (95% CI −0.16–0.14)], irrespective of the type of CBPB used (Supplementary data, Figure S3). Lanthanum ($n = 581$) provided slightly less effective phosphate reduction than CBPBs ($n = 500$) [MD 0.18 (95% CI 0.10–0.27)]. No evidence of publication bias was found [Egger's P = 0.15 (Supplementary data, Figure S2D)].

The heterogeneity observed among sevelamer trials was not explained by the type of CBPB used as the comparator (P = 0.85), ethnicity (P = 0.79) or dosage strategy (P = 0.33) (Table 3). A significant difference was found in subgroup analysis by dialysis modality (P = 0.0005), whereby sevelamer was less effective than CBPBs in chronic HD patients.

Serum calcium

Lower end-of-study serum calcium was observed with sevelamer ($n = 2078$) versus CBPBs ($n = 2055$) [MD −0.35 (95% CI −0.50 to −0.21)] and lanthanum ($n = 579$) [MD −0.26 (95% CI −0.46 to −0.07)] versus CBPBs ($n = 499$). Despite significant heterogeneity between studies ($I^2 = 88\%$), results were

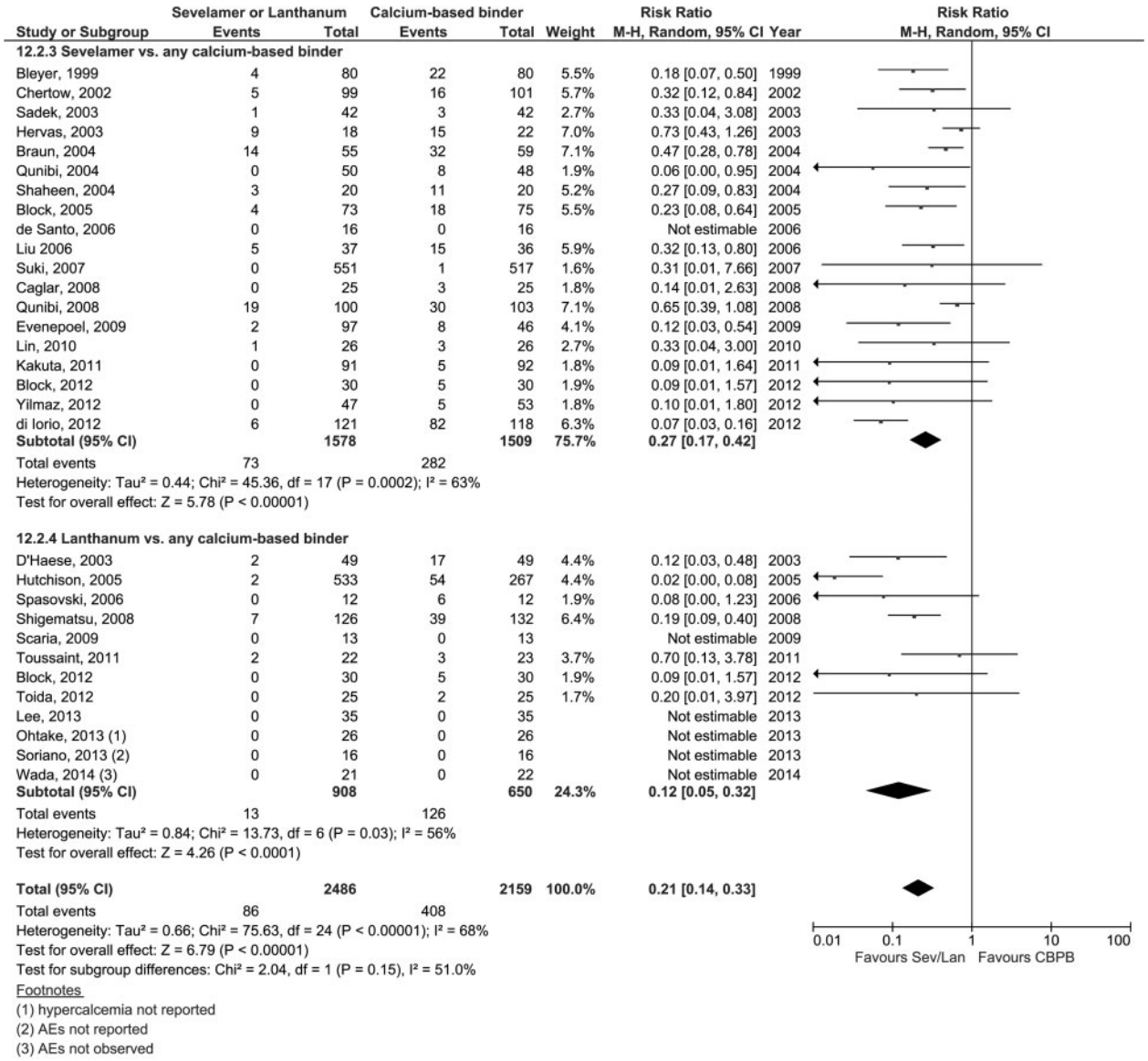

FIGURE 4: Forest plot comparing hypercalcemia event rates over the study duration between patients treated with sevelamer or lanthanum (Sev/Lan) and calcium-based phosphate binders (CBPB). AE - adverse event.

consistently in the same direction across all studies (Supplementary data, Figure S4).

Low-density lipoprotein

Sevelamer use (n = 974) was associated with significantly lower LDL levels by 20.9 (95% CI 18.6–23.3) mg/dL compared with CBPBs (n = 979) (Supplementary data, Figure S5). Although there was significant heterogeneity between studies (I^2= 69%), all point estimates were in favor of sevelamer, except one non-significant report [36]. Similar reductions were not observed with lanthanum (n = 47) versus CBPBs (n = 53), although only two studies provided data on LDL (Table 2).

Intact parathyroid hormone

Sevelamer (n = 634) and lanthanum (n = 276) were both associated with significantly higher iPTH levels: MD 43.5 (95% CI 11.1–75.9) pg/mL, n = 634 and MD 63.3 (95% CI 11.5–115) pg/mL, n = 294, respectively (Supplementary data, Figure S6). Differences were not observed in subgroup analyses (Table 3). Three studies that measured end-of-study iPTH levels in NDD-CKD patients could not be pooled since results were presented as medians, but all three trials reported lower end-of-study iPTH with sevelamer. We did not observe subgroup differences by the type of CBPB used as a comparator, ethnicity or dosing regimen.

Coronary artery calcification

By the end of the study, CAC was significantly lower among sevelamer-treated patients (n = 412) compared with CBPBs (n = 383) [MD −101 (95% CI −160 to −41.7)]. Heterogeneity between studies was observed (I^2= 74%), but all estimates were in the same direction. Among the two studies whose data could not be pooled, the increase in CAC was also higher among CBPB-treated patients [29, 49]. Only one study reported CAC

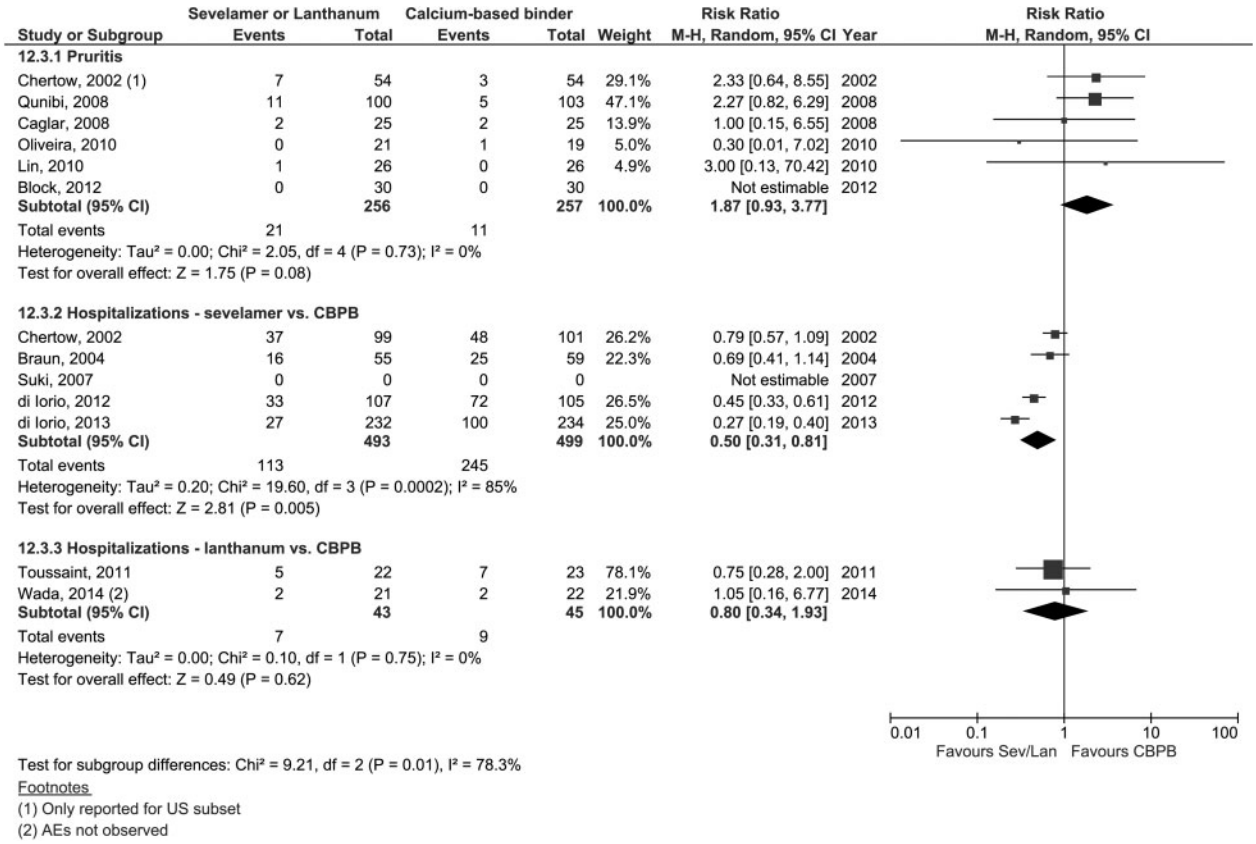

FIGURE 5: Forest plot comparing hospitalization events and pruritis events over the study duration between patients treated with sevelamer or lanthanum (Sev/Lan) and calcium-based phosphate binders (CBPB). AE - adverse event; US - United States.

following lanthanum treatment, but conclusions were drawn from a subgroup analysis ($n = 21$) [63].

Head-to-head comparisons for noncalcium binders

Sevelamer hydrochloride was compared with sevelamer carbonate in three head-to-head trials ($n = 207$): no differences were observed for end-of-study serum phosphorus, serum calcium or LDL, but no study reported on hyperchloremic acidosis (primary motivator for introducing sevelamer carbonate) [57–59]. Two trials ($n = 295$) comparing sevelamer hydrochloride with magnesium carbonate obtained conflicting results on end-of-study phosphorus levels, although no difference in serum calcium was observed [50, 56]. Three studies compared sevelamer directly with lanthanum carbonate ($n = 314$ patients): similar end-of-study phosphorus and calcium levels were observed, but sevelamer was associated with lower LDL [MD −20.9 (95% CI −29.9 to −11.9) mg/dL] [49, 54, 55].

Sevelamer was compared with iron-based binders in three studies ($n = 1492$) (Supplementary data, Figure S9) [73–75]. All-cause mortality [(RR 1.07 (95% CI 0.38–2.99), $I^2 = 0\%$], patient attrition [RR 1.03 (95% CI 0.49–2.13), $I^2 = 83\%$] and incidence of gastrointestinal adverse events [RR 1.30 (95% CI 0.61–2.78), $I^2 = 96\%$] were similar. Similar end-of-study phosphate [MD 0.07 (95% CI −0.42–0.56) mg/dL, $n = 1206$], calcium [MD −0.03 (95% CI −0.12–0.05) mg/dL, $n = 398$] and iPTH (only medians reported) were observed. Hypercalcemic events and hospitalization rates were not reported.

Meta-regression of relationship between biochemical parameters and mortality risk

The RR of mortality across studies was not associated with trial duration (P = 0.52) or the proportion of patients lost to follow-up in the intervention arm (P = 0.18) or CBPB arm (P = 0.26). A greater reduction in mortality risk was observed among studies with a greater reduction in end-of-study calcium (P < 0.0001), but not phosphorus (P = 0.27), LDL (P = 0.51) or CAC (P = 0.10) (Supplementary data, Figure S8).

DISCUSSION

When all available randomized evidence is considered, very few clinically relevant advantages have been proven for any particular phosphate binder. Confidence in any significant differences found is eroded by the shortcomings in the existing evidence base (lack of reporting clinically important outcomes, lack of blinding, selective reporting, publication bias and significant loss to follow-up). Despite >51 randomized trials of phosphate binders, there are few definitive answers, largely because the majority of the studies were focused on surrogate (biochemical) outcomes and not designed to study clinically relevant outcomes. In fact, few of the studies reported on the very reason that phosphate binders are given to patients with CKD: to prevent clinically important adverse events that (theoretically) may be due to hyperphosphatemia, such as bone events (bone

deformity, fractures), cardiac events and ultimately all-cause mortality and overall quality of life.

The most contentious finding is whether sevelamer reduces the risk of all-cause mortality compared with CBPBs. In our meta-analysis, we found that the RR for all-cause mortality for sevelamer versus CBPBs was 0.62 (95% CI 0.35–1.08). The CIs show results that are compatible with both a 65% reduction and an 8% increase in the risk of death. As a result, the conclusions cannot be definitive about whether sevelamer reduces, has no impact or increases the risk of death. Our conclusions regarding mortality agree with some recent meta-analyses [82] and contrast with others that purport to show that sevelamer significantly reduces the risk of all-cause mortality [13, 16, 17]. We explore these reasons next.

We used imputation and digitization to include data from more trials than previous meta-analyses [13, 16, 17]. The most recent systematic review [14] obtained a risk for all-cause mortality of RR = 0.54 (95% CI 0.32–0.93) from 13 studies, which we believe is optimistic. Deaths were not reported in 4 of these studies [30, 38, 39, 47] (so only 9/13 studies contributed to the RR estimate). Moreover, we identified three additional studies [25, 32, 34] that were not included in previous reviews [14, 83]. By including more trial data, our numerical results are less biased and more representative of the evidence base than other recent reviews [13, 14, 83]. Differences in how the treatment of observational studies (or observational periods postrandomization) was considered may explain some of the numerical differences between meta-analyses. For example, the mortality risk of RR = 0.53 (95% CI 0.28–1.03) in favor of sevelamer from the study by Block *et al.* [51, 84] was based on continued observation of patients who were no longer on assigned treatment for up to 3 years, a period we omitted [84]. We also conduct a sensitivity analysis to exclude the sevelamer trial whose loss to follow-up renders the comparability of the groups questionable [52]. Finally, a recent network meta-analysis [83] incidentally included a non-randomized trial (Takei, 2008) [85].

Numerical differences may also be due to data abstraction decisions based on intenion to treat: Di Lorio *et al.* [28] randomized 239 patients, but 212 were used as the denominator by both prior reviews [13, 14]. To further account for potential bias, secondary analyses trials with double-zero counts were included because data from trials reporting zero deaths are not uninformative (they suggest that mortality is infrequent and is similar between treatments) [23]. Excluding double-zero trials may overestimate treatment effects. Also, pooling of sparse-event studies using this methodology negates concern about the continuity correction. Since fewer lanthanum trials reported mortality and trials were generally small, there was a large proportion of trials with very few deaths, leading to spuriously high RR estimates due to the continuity correction [i.e. RR 5.23 (95% CI 0.27–103) for Wada and Wada [63] in Figure 3]. Finally, our meta-analysis was investigator driven, which may provide less bias than perspectives from industry-sponsored syntheses [86].

Much of the apparent 'controversy' between meta-analyses can be resolved through a more rational understanding of the numbers rather than overinterpretation of P-values as bluntly indicating 'significant' versus not significant at the magical threshold of P = 0.05. In fact, interpreting the effect size and the CIs should be the focus rather than the P-value. The most clinically useful interpretation is likely through NNT. When we consider the absolute difference in mortality between sevelamer and CBPBs with the RR = 0.65 (nntonline.net), NNT = 16, suggesting that on average a total 16 patients would need to be treated chronically with sevelamer instead of CBPBs for up to 3 years in order to prevent one death. This is likely an underestimate since NNT=35 if RR=0.85 (beta-binomial estimate) is used. This NNT estimate would be similar across all meta-analyses, but the CIs around NNT would differ (ranging from benefit to harm in our analysis). Thus, we can conclude that sevelamer might provide a reduced risk of death, though at best this difference applies to an average of only 1/16 patients treated with the drug. The other 15 patients would have similar survival regardless of which phosphate binder they used. Furthermore, the confidence in this effect estimate for sevelamer on mortality is sensitive to inclusion of the largest trial (yet most biased due to large loss to follow-up). Finally, it is important to consider that only three studies drive most of this potential difference in mortality. As a result of these limitations, the evidence base does not allow us to be more definitive than this; the loss to follow-up across the most pivotal trials makes any attempt at definitive conclusions suspect.

Patients receiving sevelamer (but not lanthanum) were less likely to drop out by the trials' end date. The reasons for differential attrition are likely mixed (i.e. due to the open-label nature of most studies, the effect of adverse events or side effects, pill burden), making conclusions difficult to draw. Other outcomes that were significantly improved with sevelamer versus CBPBs included fewer hospitalizations and hypercalcemic events. However, other important outcomes (bone fractures, cardiac events, calciphylaxis, surgeries and overall quality of life) remain largely unstudied. Sevelamer and lanthanum were associated with a higher risk of gastrointestinal events but lower risk of hypercalcemia (and lower serum calcium) compared with CBPBs. Another limitation is the paucity of reporting on hyperchloremic acidosis in head-to-head trials of sevelamer hydrochloride with sevelamer carbonate, lanthanum or iron-based binders—the very basis for the attempt to supplant sevelamer hydrochloride. If calcium-free phosphate binders are indeed the future of phosphate binder treatment [87], trials should focus on the relevant outcomes attributable to the specific binders to determine whether their balance of benefits and risks is worthy of supplanting the cheaper CBPBs. If randomized trials are unable to provide data that require long-term follow-up (particularly for rare outcomes like calciphylaxis [88] or long-term effects of lanthanum storage in the body [11]), methodologically sound large-scale observational studies may help fill this gap.

Sevelamer was as effective as CBPBs at reducing serum phosphorus, while lanthanum was less effective. Sevelamer also had significantly greater reductions in LDL, serum calcium, and CAC than CBPBs, and increased iPTH. However, the clinical relevance of these differences is unknown. Lanthanum generally did not have significant effects on these biochemical parameters. Results from observational studies suggest that mortality is elevated with higher serum phosphorus, LDL and calcification scores in a dose-dependent manner [89–92]. However, as is often the case with surrogate outcomes, these effects may not translate to better clinical outcomes [90, 93–96]. Although the relationship between

lower serum calcium and survival is supported by our meta-regression, this is hypothesis-generating only and needs to be the focus of clinical trials designed to test the relationship prospectively. Furthermore, studies provided short-term follow-up (maximum 3 years), which reduces our confidence in adequately studying relationships between biochemical parameters and risk of death. Our meta-regressions did not show a relationship with other biochemical parameters, including phosphate, LDL and CAC, and risk of mortality.

Most trials employed treat-to-target methodology, whereby the dose of the phosphate binder could be adjusted throughout the study. Although the recommended phosphate target of 3.5–5.5 mg/dL established by the Kidney Disease: Improving Global Outcomes guideline [97] was often used, some studies aimed as low as 2.5 mg/dL [34, 39] or as high as 6.5 mg/dL [51]. Given such differences in methodology, a random effects model was used to calculate pooled estimates. One limitation to pooling data may arise due to differences in how results are presented. Phosphorus control may be more appropriately measured as a time-weighted average to reflect the differences between groups over the entire course of follow-up. End-of-study phosphorus levels may not be representative of the general trends, as was the case with Lin *et al.* [44]. The extent to which these different measurement strategies impact conclusions depends on the temporal variation in phosphorus control throughout the study.

In conclusion, in this comprehensive update on the efficacy and safety of calcium-free binders compared with cheaper alternatives (i.e. CBPBs), sevelamer was associated with lower hospitalization rates, lower rates of hypercalcemia and a nonsignificant reduction in mortality. However, differences in some of the most important outcomes (cardiac events, fractures, calciphylaxis, hyperchloremic acidosis and health-related quality of life) remain unstudied. While sevelamer resulted in favorable biochemical outcomes, the importance of these surrogate outcomes remains unknown due to a lack of follow-up for associated clinically relevant outcomes. Future randomized trials should be of adequate power and duration to measure clinically important outcomes (the reason why phosphate binders are prescribed in the first place). Future studies that fail to address these outcomes will be wasteful.

ETHICS APPROVAL

This is a secondary analysis of publicly available data. No ethical approval was required.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

Dr Amit X Garg was supported by the Dr Adam Linton Chair in Kidney Health Analytics. S.H., S.P. and R.A. were supported by the Lilibeth Caberto Kidney Clinical Research Unit.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

(See related article by Elder. Calcium-based phosphate binders; down, but not out. *Nephrol Dial Transplant* 2017; 32: 5–8)

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Received for publication: 29.3.2016; Accepted in revised form: 13.7.2016