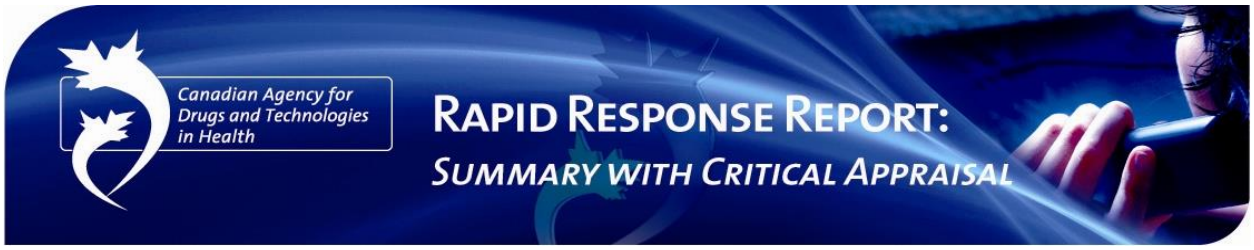

TITLE: Sevelamer for the Treatment of Patients with Chronic Kidney Disease: A Review of Clinical and Cost-Effectiveness

DATE: 21 September 2016

CONTEXT AND POLICY ISSUES

An estimated 12.5% of the Canadian population suffer from chronic kidney disease (CKD), defined by reduced kidney function for a period exceeding three months accompanied by a low glomerular filtration rate (GFR) or high GFR and renal abnormalities.[1,2]

CKD can lead to diabetes, cardiovascular disease, or death.[2] CKD is associated with phosphorus retention which leads to hyperphosphatemia, an abnormally high level of phosphate in serum. Hyperphosphatemia is a cardiovascular risk factor and a contributor to CKD-mineral and bone disorder (CKD-MBD).[3,4] In the early stages of CKD, increased secretions of parathyroid hormone and fibroblast growth factor-23 help to manage the levels of serum phosphate.[3] As the disease progresses, however, it becomes increasingly challenging to maintain phosphate levels. Diet restrictions, dialysis, oral phosphate binders, or a combination of therapies may be used depending on how far the disease has progressed.[4,5] Phosphate binders are needed when dietary restriction and dialysis are ineffective at controlling hyperphosphatemia.[4,6]

Phosphate binders are calcium-, iron-, aluminum- and magnesium-based or synthetic compounds. Aluminum- and magnesium-based phosphate binders have been widely replaced due to concern for toxicity and related adverse events.[3,4,6] Calcium-based phosphate binders may be used by patients with stage 4 CKD, but they are associated with hypercalcemia (i.e., elevated levels of calcium in serum) which is a risk factor for cardiovascular disease in patients with stage 5 CKD.[3] Alternatives to calcium-based phosphate binders include sevelamer hydrochloride (HCL), sevelamar carbonate, lanthanum carbonate, and iron-based phosphate binders.[5] Sevelamer HCL and sevelamer carbonate are synthetic, non-calcium-based, and non-absorbable phosphate binders. Although sevelamer is expensive, it is associated with controlling hypercalcemia and lowering the associated risk of cardiovascular disease.[3,5]

A 2009 CADTH rapid review of the clinical effectiveness of sevelamer HCL for the treatment of CKD found that sevelamer HCL appeared to be as effective as calcium-based phosphate

binders in the management of hyperphosphatemia in CKD patients on dialysis without inducing hypercalcemia.[6] While there was evidence to suggest that sevelamer HCL may slow down the progression of vascular calcification, there was no evidence on its impact on mortality outcomes, and the evidence on its effectiveness on aortic calcification was inconsistent.[6] The report concluded that the published literature at the time did not appear to support the routine use of sevelamer HCL in patients on dialysis.[6]

This report reviews the clinical and cost-effectiveness of sevelamer (i.e., HCL or carbonate) for use in patients with CKD.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of sevelamer for the treatment of patients with chronic kidney disease?

2. What is the cost-effectiveness of sevelamer for the treatment of patients with chronic kidney disease?

KEY FINDINGS

Overall, the evidence suggests that sevelamer is more effective at reducing serum calcium levels and lowering the attendant risk of hypercalcemia in patients with CKD stages 3 to 5D compared to calcium-based phosphate binders, but may be less effective at lowering serum phosphate levels. The results on the impact of sevelamer on vascular calcification are mixed. With respect to safety, sevelamer may be more effective at reducing the risks of all-cause mortality and cardiovascular mortality in patients with CKD stages 3 to 5D relative to calcium-based phosphate binders. Sevelamer increases the risk of diarrhea, constipation, abdominal bloating, and combined gastrointestinal events. The trends are statistically significant for constipation, and combined gastrointestinal events. The evidence on nausea is mixed. There is no evidence on the safety of sevelamer relative to calcium-based phosphate binders specific to patients with non-dialysis-dependent (NDD)-CKD.

Sevelamer is cost-effective relative to calcium carbonate based on a range of willingness-to-pay (WTP) ratios and a variety of hypothetical and patient-based scenarios involving patients in CKD stages 3 to 5D. In addition, sevelemar is cheaper and more clinically effective than calcium-carbonate in all scenarios involving a subset of pre-dialysis or NDD-CKD patients.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Embase, Medline, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and August 18, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with chronic kidney disease (subgroups of interest: dialysis and pre-dialysis patients)
Intervention	Sevelamer (hydrochloride and carbonate)
Comparator	Calcium-based phosphate binders (e.g., calcium carbonate, calcium acetate)
Outcomes	Q1: Clinical effectiveness (e.g., serum phosphate levels) and safety (e.g., mortality, hypercalcemia, coronary artery calcification score, other adverse events) Q2: Cost-effectiveness (e.g. cost per case, net benefit, incremental cost per life year gained [LYG], incremental cost per quality adjusted life year [QALY])
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), economic studies

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 1, 2011, if they were duplicate publications of the same study, or if they were referenced in a selected SR.

Critical Appraisal of Individual Studies

The included SRs were critically appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR),[7] RCTs were critically appraised using the Downs and Black checklist,[8] and economic studies were critically appraised using Drummond's checklist.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 299 citations were identified in the literature search. Following screening of titles and abstracts, 242 citations were excluded and 57 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the 57 potentially relevant articles, 46 publications were excluded for various reasons, while 11 publications met the inclusion criteria. Five SRs,[10-14] one RCT,[15] and five economic studies[16-20] were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5 – Additional References of Potential Interest.

Summary of Study Characteristics

A detailed summary of the included study designs, populations, interventions and comparators, and outcomes is provided in Appendix 2, tables A1 to A3.

Study Design
Three SRs included overlapping sets of studies.[10,11,14] One SR each was published in 2011,[14] and 2015,[13] and three were published in 2016.[10-12] The SRs included MAs of RCTs with follow-up time periods of three to 16 months,[10] two to at least 36 months,[11] at least four weeks,[12] and at least eight weeks.[13] One SR did not disclose the follow-up time periods of its studies.[14] Two SRs included network MAs of RCTs with follow-up time periods of at least four weeks.[10,12]

The RCT was published in 2012 and followed patients for eight weeks.[15]

Three of the economic studies had the same supervising author who also served as the primary author of two RCTs on which these studies were based.[18-20] The sources of data were extracted from the literature,[16,20] patient-level data,[16-20] manufacturing companies,[16] public healthcare systems,[16-20] and a hospital pharmacy.[18,19] The maximum WTP ratios included in the analyses varied as follows: €25,000 per LYG,[18] €10,000 to €100,000 per LYG,[19] €40,000 per LYG,[17] and £30,000 per QALY gained.[16,20] The economic studies were published in 2013,[20] 2014,[19] 2015,[17,18] and 2016,[16] and the studies modeled data over a 3-year time horizon,[18,19] over a 7-year time horizon,[17] and over a lifetime.[16,20]

Country of Origin
The SRs were published by authors in Italy,[10] Australia and Canada,[11] Canada and Saudi Arabia,[12] China,[13] and United States, New Zealand, Italy, Australia, and Sweden.[14] The RCT enrolled patients in Italy and was published by authors from Turkey and Italy.[15] Four of the economic studies involved data from patients in Italy[17-20] and one from patients in Singapore.[16] Two of the economic studies included authors from Italy as well as from the United States[18] and from Canada and the United Kingdom.[20]

Patient Population
One SR included adult patients with end-stage renal disease and on dialysis[13] while the remainder enrolled a mix of adult patients with CKD on dialysis or pre-dialysis.[10-12,14] Two SRs excluded transplant patients.[11,14] The SRs ranged in size from 3,481[10] to 7,631[14] patients although outcomes were generally reported for sub-sets of the respective populations. The RCT enrolled 100 hyperphosphatemic (i.e., serum phosphate level > 6.0 mg/dL) patients with stage 4 CKD.[15] The median ages were 45 years for patients randomized to receive sevelamer and 46 years for those randomized to receive calcium acetate. The RCT excluded patients with diabetes mellitus, hypercalcemia (i.e., serum calcium level > 11 mg/dL), history of coronary heart disease, smokers, and patients on statins, renin-angiotensin blockers, or vitamin D. In three economic studies all patients were either pre-dialysis (i.e., NDD-CKD)[16] or on hemodialysis at enrollment.[17,18] In the remaining economic studies, 34% of patients transitioned from stages 3-4 NDD-CKD to dialysis during the course of the study.[19,20] One of the studies incorporated data from stage 5D CKD patients enrolled in the RISCAVID RCT,[17] one incorporated data from stage 5 CKD patients enrolled in the INDEPENDENT – Reduce

Cardiovascular Calcifications to Reduce QT Interval in Dialysis RCT,[18] and one incorporated data from patients enrolled in the INDEPENDENT-CKD RCT.[19]

Interventions and Comparators
All studies compared sevelamer to calcium carbonate or calcium acetate. When the studies included other comparators, data relevant to sevelamer and calcium-based phosphate binders only were extracted.[10,12] In two SRs, the intervention was sevelamer HCL.[10,14] The remaining SRs and economic studies did not disclose whether sevelamer referred to its HCL or carbonate form. The RCT compared sevelamer HCL and calcium acetate.[15]

Outcomes
The clinical effectiveness outcomes included serum phosphate level,[11,13-15] serum calcium level,[11,13-15] hypercalcemia,[10,11,13,14] achievement of serum phosphate target levels,[10] and vascular calcification.[13,14]

The safety outcomes were all-cause mortality,[10-14] cardiovascular mortality,[10,11,13] and gastrointestinal adverse events, such as nausea, constipation, and diarrhea.[11,14]

The economic studies reported on incremental cost-effectiveness ratios in the form of cost per LYG[17-19] or cost per QALY gained.[16,20]

Summary of Critical Appraisal

Details of the strengths and limitations of the included studies are summarized in Appendix 3, tables A4 to A6.

Systematic reviews and meta-analyses
The included SRs completed a comprehensive literature search, disclosed their search strategy, had two independent reviewers perform the study selection and data extraction, provided a list of included studies, assessed the quality and risk of bias of included studies, and quantitatively synthesized data through a MA or network meta-analysis (NMA).[10-14] Other strengths were as follows: presented the keywords and search terms,[11-13] imposed no limits on publication status[11,13] or language,[10-14] and used Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology to assess the overall quality of evidence.[12,13] The authors of two studies declared that they had no conflicts of interest.[12,13]

The limitations were as follows: a list of excluded studies was not provided,[10-14] the publication status was not used as an inclusion criterion,[10,12,14] keywords and search terms were not disclosed in one SR,[10] publication bias and sub-group analysis had to be omitted due to the paucity of data,[14] and authors had a history of receiving funding from pharmaceutical companies.[10,11,14] In addition, follow-up time periods were inconsistently disclosed for the included primary studies.[12-14]

Randomized controlled trial
The RCT had more strengths than limitations.[15] The authors explicitly stated the objectives in the introduction and described the interventions, outcome measures, and characteristics of the included patients. There was reliable compliance with the intervention and all patients completed the trial. Patients in both study arms were selected from the same population. Appropriate statistical tests were used, and the statistical significance of the differences between the patient groups was calculated for each outcome of interest.

The primary limitation of the RCT was that the outcome measures were differences in percent change in serum phosphate and serum calcium levels rather than the difference in the absolute change in serum phosphate and serum calcium levels. As well, patients on dialysis and those that were hypercalcemic (i.e. with serum calcium levels exceeding 11 mg/dL) were excluded and outcome assessors were not blinded to treatment allocation, suggesting patient selection bias.

Economic studies

All of the economic studies described the assumptions, such as the sources and methods of calculating included costs, used in their models. They also defined the intervention, comparators and primary outcome measures, described the approach to sensitivity analysis, and provided a time horizon for the analysis.

In terms of limitations, three economic studies incorporated clinical trial data collected from a common group of investigators, but did not apply a discount rate to either outcomes or costs in the base case.[17-19] Two studies calculated the incremental cost-effectiveness ratio (ICER) as cost per life year gained instead of cost per QALY gained.[18,19] One study combined multiple treatment options into the comparator group.[17] Another study incorporated data from a primary study in which 11% of patients were lost to follow-up without an explanation.[20]

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4, tables A7 to A9.

1. What is the clinical effectiveness of sevelamer for the treatment of patients with chronic kidney disease?

Serum Phosphate and Calcium Levels

Three SRs and one RCT reported this outcome.[11,13-15] One SR explicitly stated that the intervention was sevelamer HCL[14] but the others did not.[11,13] When compared with calcium-based phosphate binders, sevelamer appeared to be less effective at lowering serum phosphate levels,[11,13,14] The difference in change in serum phosphate levels was marginally significant in two SRs,[13,14] and not assessed in the third one.[11] Sevelamer was reported to be more effective at lowering serum calcium levels,[11,13,14] and the difference was statistically significant in two SRs.[13,14] According to the RCT, both sevelamer (n=47) and calcium acetate (n=53) lowered serum phosphate and serum calcium levels significantly following eight weeks of treatment; however the decrease in levels were more significant in the sevelamer group.[15]

Serum Phosphate Level Target Achievement

One SR reported that the odds of achieving a target serum phosphate level was higher with sevelamer HCL than with calcium-based phosphate binders.[10] This result was based on data from one RCT that followed 139 patients over three months.

Incidence of Hypercalcemia

Four SRs reported this outcome.[10,11,13,14] Relative to calcium-based phosphate binders, sevelamer was found to reduce the odds[10,11,13] and the risk[14] of patients becoming hypercalcemic. Patients were considered hypercalcemic when their serum calcium levels exceeded an upper threshold of 10.2 mg/dL,[14] between 10.2 and 10.5 mg/dL,[13] or 11.0

mg/dL,[11,13] or as described by the individual study investigators.[14] Irrespective of the definition of hypercalcemic, the reduction in odds[13] and risk[14] were statistically significant in both studies.

Calcification
The results on calcification were mixed.[10,13,14] In one SR involving patients with end-stage renal disease and on dialysis, sevelamer was significantly more effective at preventing calcification relative to calcium acetate and calcium carbonate.[13] The impact on calcification was determined based on a reduction in the coronary artery calcification score in six RCTs (n=679) and the reduction in aortic calcification score in three RCTs (n=266).[13] Another SR reported that sevelamer HCL led to a slower progression of coronary artery calcification in two primary studies, yet two other studies reported no difference.[14] The data available on dialysis patients were inadequate to inform clinical recommendations on phosphate binders.[14] In another SR of eight RCTs involving mostly patients on dialysis, sevelamer was less effective at lowering coronary artery calcification relative to calcium-based phosphate binders.[10]

Mortality
All SRs reported on the incidence of all-cause mortality,[10-14] and three reported on the incidence of cardiovascular mortality.[10,11,13] Relative to calcium-based phosphate binders, sevelamer reduced the odds or the risk of all-cause mortality[10-14] and cardiovascular mortality.[10,11,13] The difference in all-cause mortality was statistically significant in three SRs,[10-12] but not statistically significant otherwise.[13,14] The difference in cardiovascular mortality was not statistically significant in patients with CKD stages 3 to 5D.[10,11] The NMA did not change the conclusions derived from the MAs.[10,12]

Gastrointestinal-related Adverse Events
Sevelamer HCL increased the risk of constipation, diarrhea, abdominal bloating, and combined gastrointestinal events combined.[11,14] Furthermore, sevelamer increased the risk of nausea in one SR[14] but decreased the risk in a second SR.[11] Except for constipation and combined gastrointestinal events, the differences were not statistically significant.

Patients on Dialysis
The impact of sevelamer on all-cause mortality and cardiovascular mortality is not statistical significant over calcium-based phosphate binders when data from patients on dialysis are considered.[11,13]

NDD-CKD Patients
The RCT involving patients with stage 4 CKD reported that both sevelamer HCL (n=47) and calcium acetate (n=53) lowered serum phosphate and serum calcium levels significantly; however the decrease in levels were more significant in the sevelamer group.[15]

2. What is the cost-effectiveness of sevelamer for the treatment of patients with chronic kidney disease?

The economic studies reported outcomes based on the perspective of the governments of Singapore[16] or Italy.[17-20] Four studies[16,18-20] compared sevelamer to calcium carbonate while one included calcium acetate and vitamin D in the comparator group.[17] All of the studies found sevelamer to be cost-effective below various WTP thresholds.

From the perspective of a third-party payer in Singapore, sevelamer was cost-effective relative to calcium carbonate in a model of 1000 hypothetical, pre-dialysis patients with CKD with a drug

cost SGD1.69 (Singapore dollar) per gram or less.[16] The model involved three stages: i) NDD-CKD, ii) end-stage renal disease with dialysis, and iii) all-cause mortality. Patients who entered dialysis stayed on dialysis until death. The model was run with a lifetime horizon of multiple one-year cycles. The sensitivity analysis accounted for the treatment dose, cost, and effectiveness. Data sources included the literature, the Singapore Ministry of Health, and a pharmaceutical manufacturer.

In another economic evaluation, sevelamer was found to be cost-effective in comparison to patients on calcium carbonate, calcium acetate or vitamin D, with a time horizon of seven years.[17] The results suggest that the ICER was below €40,000/life years gained (LYG). The sensitivity analyses accounted for transition probabilities, drug costs, hemodialysis and other costs. The study was based on data from the RISCAVID RCT involving hemodialysis patients under the care of the Italian National Health System.

Based on data from patients who had been on dialysis for less than four months and were enrolled in the INDEPENDENT-CKD, sevelamer treatment (n=107) was cheaper and more effective than calcium carbonate (n=105).[19] Hospitalization and dialysis costs were included. At enrollment, all patients in the INDEPENDENT-CKD RCT had NDD-CKD and 34% transitioned to dialysis within three years. In a later study (the INDEPENDENT RCT) by the same group of authors, sevelamer (n=232) was found to be cost-effective relative to calcium carbonate (n=234) for a time horizon of three years.[18] The ICER fell between €30,000/LYG to €50,000/LYG based on the results of the simulations. The third economic evaluation analyzed data from the same set of patients using a lifetime horizon rather than a 3 year horizon, and a discount rate of 3.5%.[20] The results suggest that sevelamer was cost-effective compared to calcium carbonate.

NDD-CKD patients
In a sub-group analysis of 73 NDD-CKD patients, sevelamer (n=31) was found to be cheaper and more effective than calcium carbonate (n=42).[19] A one-way sensitivity analysis demonstrated that sevelamer was more cost-effective than calcium carbonate in NDD-CKD patients.[20]

Limitations

One important limitation in this review is the heterogeneity across the body of evidence. The SRs included studies with calcium carbonate or calcium acetate as comparators. Two SRs reported on gastrointestinal-related adverse events[11,14] and three reported on calcification.[10,13,14] Follow-up periods were inconsistently reported in the SRs. There was considerable overlap in three SRs with two covering the same patient data.[10,11,14] The economic studies varied in the types of costs included in the analysis, the time horizons, discount rates, and the WTP thresholds. The collective body of evidence was not globally representative; rather the majority of the studies focused on data collected and analyzed in Italy. In particular, the results of the economic studies may not be transferable to the Canadian health care setting where treatment costs and options are different from those found in Italy.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Overall, the evidence suggests that sevelamer may be more effective relative to calcium-based phosphate binders in reducing serum calcium levels, and all-cause and cardiovascular mortality rates in patients enrolled with stages 3 through 5D CKD. However, sevelamer is less effective at controlling serum phosphate levels. The evidence on the impact of sevelamer on calcification, and the risk of adverse events (e.g., all-cause mortality rates, cardiovascular mortality rates, and gastrointestinal adverse events) remains inconclusive. The findings from one RCT of patients enrolled with stage 4 CKD suggests that sevelamer HCL is more effective at lowering both serum phosphate and calcium levels compared with calcium-based phosphate binders.

Sevelemar is considered to be cost-effective compared with calcium-based phosphate binders in NDD-CKD patients or in a mixed group of patients (i.e., on dialysis and NDD-CKD at enrollment). The cost-effectiveness of sevelamar is negatively impacted by the cost of dialysis and the length of time patients need to be treated. The results of the economic studies may not be directly applicable to the Canadian context as these studies were conducted in Italy and in Singapore.

The 2009 report by CADTH found that sevelamer HCL appeared to be as effective as calcium-based phosphate binders in the management of hyperphosphatemia in dialysis patients without elevating serum calcium levels. The current report differs from the 2009 report as it includes studies that enrolled patients on dialysis and NDD-CKD patients, and included both forms of sevelamer as the intervention.

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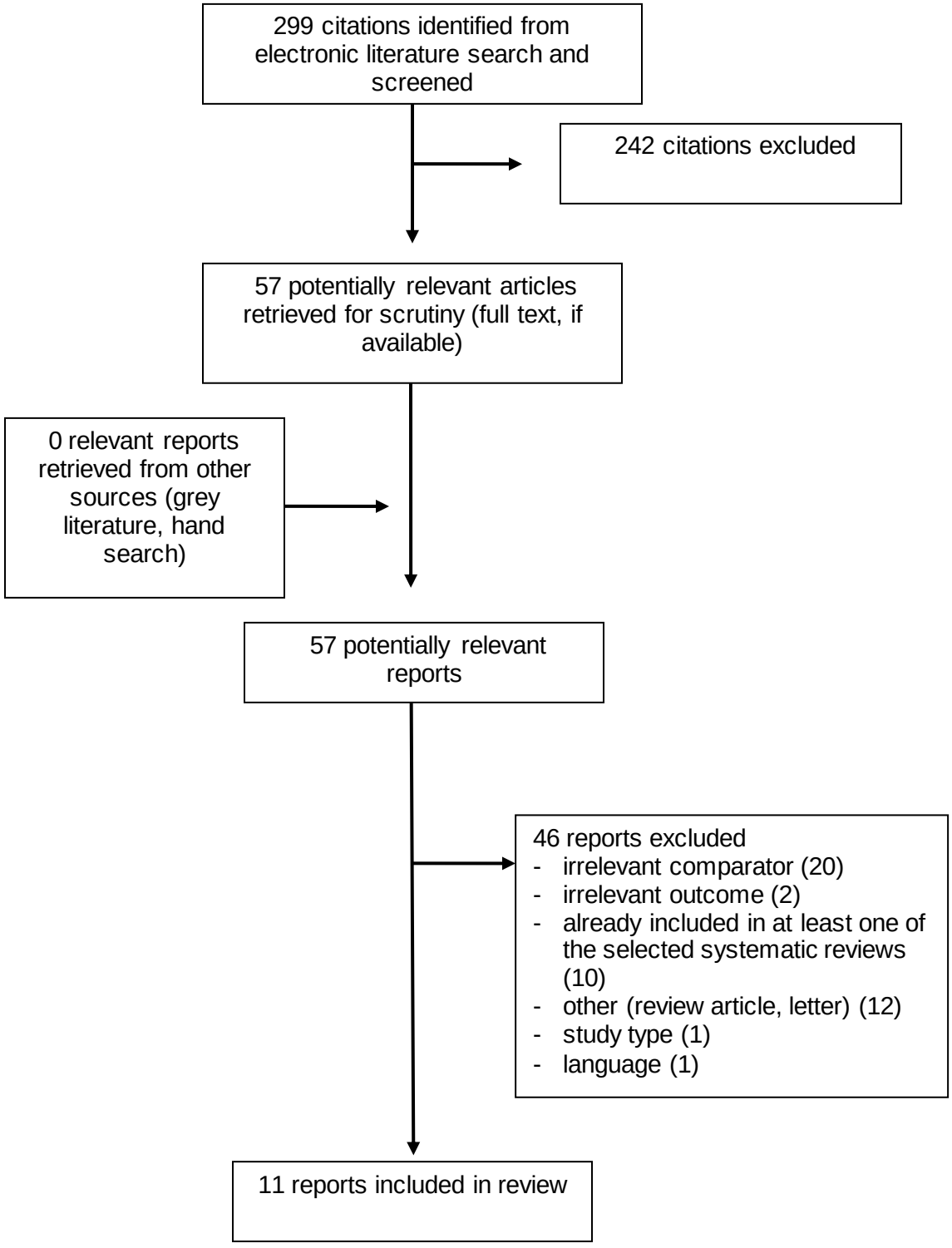
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Palmer, 2016,[10] Italy	SR and MA of 8 RCTs	n = 3,481 adult patients with CKD (stage 5D, n = 3,269; stages 3 and 4 without dialysis, n = 212); mean age range 47 to 65.6	Sevelamer HCL	Calcium carbonate, calcium acetate	Incidence of serum phosphate level target achievement; hypercalcemia, all-cause mortality, cardiovascular mortality, GI AEs F/u: 5 – 36 months
	SR and NMA of sub-sets of 27 parallel-group RCTs	n = 7,862 adult patients with CKD; dialyzed or non-dialyzed	Sevelamer (HCL, carbonate)	Calcium carbonate, calcium acetate, SBR759, PA21, sucroferric oxyhydroxide, colestilan	F/u: ≥ 4 weeks
Patel, 2016,[11] Australia and Canada	SR and MA of sub-sets of 25 RCTs and quasi-RCTs	n = 4,770 adult patients with CKD (on dialysis, n = 4,368; without dialysis, n = 402); majority with hyperphosphatemia; excluded transplant patients	Sevelamer (HCL, carbonate)	Calcium carbonate, calcium acetate, Sevelamar HCL + calcium carbonate	Serum phosphate level, serum calcium level, hypercalcemia, all-cause mortality, cardiovascular mortality, GI AEs F/u: > 8 weeks
Sekercioglu, 2016,[12] Canada and Saudi Arabia	SR and MA of 10 RCTs	n = 3,665 adult patients aged ≥ 18 years with CKD with or without dialysis	Calcium carbonate, calcium acetate, calcium citrate	Sevelamer (HCL, carbonate)	All-cause mortality F/u: ≥ 4 weeks
	SR and NMA of sub-sets of 28 RCTs	n = 8,335 adult patients aged ≥ 18 years with CKD			

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
		(stages 3 to 5 without dialysis, 25%); mean age range 47 to 69			
Wang, 2015,[13] China	SR and MA of sub-sets of 23 RCTs	n = 4,395 adults aged ≥ 18 years with end-stage renal disease; 100% on hemodialysis for 3 months to 18 years; mean age 57.9 years	Sevelamer (HCL, carbonate)	Calcium carbonate, calcium acetate	Serum phosphate level, serum calcium level, hypercalcemia, coronary artery calcification, all-cause mortality, cardiovascular mortality F/u: 8 to 193 weeks
Navaneethan, 2011,[14] United States, New Zealand, Italy, Australia, and Sweden	SR and MA of sub-sets of 60 RCTs	n = 7,631 adults aged > 18 years with CKD in stage 3 to 5D; excluded transplant patients	Sevelamer HCL	Calcium-based PBs	Serum phosphate level, serum calcium level, hypercalcemia, vascular calcification, all-cause mortality, GI AEs F/u: NR

AE(s) = adverse event(s); CKD = chronic kidney disease; f/u = follow -up; GI = gastrointestinal; HCL = hydrochloride; MA = meta-analysis; NMA = netw ork meta-analysis; PB(s) = phosphate binder(s); RCT(s) = randomized controlled trial(s); SR = systematic review

Table A2: Characteristics of the Included RCT

First author, Publication Year, Country,	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Yilmaz, 2012,[15] Italy and Turkey	RCT, 2-arm F/u: 8 weeks	n = 100 hyperphosphatemic (serum phosphate level > 6.0 mg/dL) patients with stage 4 CKD referred from March 2005 to April	Sevelamer HCL	Calcium acetate	Serum phosphate level, serum calcium level

Table A2: Characteristics of the Included RCT					
First author, Publication Year, Country,	**Study Design, Length of Follow-up**	**Patient Characteristics, Sample Size (n)**	**Intervention**	**Comparator(s)**	**Clinical Outcomes**
		2010; % female NR; excluded patients with diabetes mellitus, hypercalcemia (serum calcium > 11 mg/dL), history of coronary heart disease, smokers, patients on statins, renin-angiotensin blockers, or vitamin D			

RCT = randomized controlled trial; CKD = chronic kidney disease; NR = not reported

Table A3: Characteristics of Included Economic Studies					
First author, Publication Year, Country	**Type of Analysis, Perspective**	**Intervention, Comparator**	**Study Population**	**Time Horizon**	**Main Assumptions**
Nguyen, 2016[16] Singapore	CEA based on a Markov model, third party payer perspective	Sevelamer, calcium carbonate	n = 1000 incident CKD, pre-dialysis patients; mean age = 60 years; 0% on dialysis	Lifetime: multiple one-year cycles until all cohort members died	Discount rate of 3.5% for future costs and utilities Health states: NDD-CKD, ESRD, and death When patients in the NDD-CKD state transition to dialysis they are assumed to continue with dialysis until death. There were no transplants

Table A3: Characteristics of Included Economic Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Panichi, 2015[17] Italy	CEA based on a Markov model and data from patients enrolled in the RISCAVID study, government payer (Italian National Health System) perspective	Sevelamer, calcium carbonate/calcium acetate/vitamin D	n = 749 hemodialysis patients; 100% on dialysis Sevelamer (n = 242): mean daily dosage of 5.2 ± 2.1 g; non-sevelamer (n = 507; calcium carbonate at a mean daily dosage of 4.2 ± 2.1 g; calcium acetate at a mean daily dosage of 4.6 ± 1.8 g; vitamin D) Medication was given as monotx or in combination with other agents.	7 years	Estimated the transition rates between 3 health states: cardiovascular events, circulation problems, and stroke Data was extracted from patient information
Ruggeri, 2015[18] Italy and United States	CEA using data from patients enrolled in the INDEPENDENT-Reduce Cardiovascular Calcifications to Reduce QT Interval in Dialysis study, government payer (Italian National Health System) perspective	Sevelamer, calcium carbonate	n = 466 adult patients with stage 5D CKD; 100% on hemodialysis for < 120 days; mean age 65 (SD 14.8) years; 51% female; tx'd with sevelamer (n = 232) or calcium carbonate (n = 234); hypertension (79%); atherosclerotic cardiovascular disease (36%); diabetic (29%)	3 years	Excluded cost of dialysis from base case analysis

Table A3: Characteristics of Included Economic Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Ruggeri, 2014[19] Italy	CEA using data from patients enrolled in the 2012 INDEPENDENT-CKD study, government payer (Italian National Health System) perspective	Sevelamer, calcium carbonate	n = 239 adult patients aged ≥ 18 years with stages 3-4 NDD-CKD; 34% transitioned to dialysis in 3 years; tx'd with starting dose of 1,600 mg/day sevelamer HCL (n = 107; mean age 57.4±12.0) or 2,000 mg/day calcium carbonate (n = 105; mean age 58.5±12.4) or lost to f/u (n = 27)	3 years	Included direct medical costs (medication, hospitalizations, and dialysis) Excluded costs associated with outpatient visits, concomitant medications, and adverse events
Thompson, 2013[20] Canada, United Kingdom, Italy	CEA using data from patients enrolled in the 2012 INDEPENDENT-CKD study, government payer (Italian National Health System) perspective	Sevelamer, calcium carbonate	n = 239 adult patients aged ≥ 18 years with stages 3-4 NDD-CKD; 34% transitioned to dialysis in 3 years; tx'd with sevelamer HCL (n = 107; mean daily dose of 2,184 (SD 592) mg/day) or calcium carbonate (n = 105; mean daily dose 2,950 (SD 703) mg/day) or lost to f/u (n = 27)	Lifetime	Discount rate of 3.5%; used Weibull regression analysis to extrapolate survival beyond the duration of the clinical trial to a lifetime horizon Excluded costs associated with hospitalizations, outpatient visits, concomitant medications, and adverse events

CEA = cost-effectiveness analysis; CKD = chronic kidney disease; ESRD = end-stage renal disease; f/u = follow up; HCL = hydrochloride; NDD = non-dialysis-dependent; SD = standard deviation; tx = treatment or therapy

Appendix 3: Summary of Critical Appraisal of Included Study

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[7]

Strengths	Limitations
Palmer, 2016[10]	
• Research objectives were pre-determined by a panel of experts following the development of a study protocol • Conducted a comprehensive literature search on multiple databases • Did not impose language restrictions • Two independent reviewers performed study selection and data extraction. Disagreements were resolved through consensus • Provided a list of included studies as well as study characteristics • Qualitatively assessed publication bias using the Cochrane Collaboration Tool for Assessing Risk of Bias • The study was supported by unaffiliated funds • Provided quantitative comparisons through a network MA	• Did not use status of publication as inclusion criteria • Did not provide a list of excluded studies • Did not disclose keywords and search terms • Four out of nine authors previously received financial support from pharmaceutical companies
Patel, 2016[11]	
• Followed Cochrane methods and quality of reporting guidelines • Conducted a comprehensive literature search on multiple databases • Did not impose limits on publication status or language • Two independent reviewers performed study selection and data extraction. Disagreements on study selection were resolved through consensus involving a third author • Provided a list of included studies as well as study characteristics • Evaluated risk of bias by assessing randomization, allocation concealment, intent to treat analysis, follow-up completeness, and masking, using the Cochrane Renal Group checklist • Tested publication bias for all-cause mortality and serum phosphate level using funnel plots • Provided quantitative comparisons through a MA	• Did not provide a list of excluded studies as well as reasons for exclusion • All authors were supported by pharmaceutical manufacturers
Sekercioglu, 2016[12]	
• Research objectives were pre-determined by a panel of experts following the development of a study protocol and following PRISMA guidelines • Conducted a comprehensive literature search on multiple databases • Did not impose language restrictions	• Did not use status of publication as inclusion criteria • Articles selected by either reviewer were retrieved. Disagreements were not resolved through consensus. • Did not provided a list of excluded studies

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[7]

Strengths	Limitations
• Two independent reviewers performed study selection and data extraction. • Provided a list of included studies as well as study characteristics • Used a modified version of the Cochrane Collaboration Tool for Assessing Risk of Bias • Used GRADE methodology to assess the quality of evidence • Provided quantitative comparisons through a network MA • The authors declared they had no conflicts of interest	
Wang, 2015[13]	
• Followed PRISMA guidelines • Conducted a comprehensive literature search on multiple databases • Did not impose language or date restrictions • Included only published studies • Two independent reviewers performed study selection and data extraction. A third reviewer checked extracted data for accuracy and resolved disagreements • Provided list of included studies as well as study characteristics • Qualitatively assessed publication bias using the Cochrane Collaboration Tool for Assessing Risk of Bias • Used GRADE methodology to assess the quality of evidence • Provided quantitative comparison through a MA • The authors declared they had no conflicts of interest • Disclosed source of funding	• Did not provide a list of excluded studies
Navaneethan, 2011[14]	
• Research objectives were pre-determined by a panel of experts following the development of a study protocol • Conducted a comprehensive literature search on multiple databases • Did not impose language restrictions • Two independent reviewers performed study selection and data extraction. Disagreements were resolved through consultation with an arbitrator • Provided a list of included studies as well as study characteristics • Assessed the risk of bias of each study through an assessment of: allocation concealment; blinding of investigators, participants, outcome	• Did not use status of publication as inclusion criteria • One author disclosed prior relationships with pharmaceutical manufacturing companies • Did not provide a list of excluded studies • Did not assess publication bias due to paucity of studies • Did not conduct sub-group analysis due to limited number of studies

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[7]

Strengths	Limitations
assessors, and data analysis; intention-to-treat analysis and completeness to follow-up • Provided quantitative comparisons through a MA • Disclosed source of financial support	

MA = meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses

Table A5: Strengths and Limitations of the RCT using the Downs and Black Checklist[8]

Strengths	Limitations
Yilmaz, 2012[15]	
Reporting • Explicitly stated the objective(s) in the introduction • Described interventions, outcomes, and characteristics of included patients • Provided a list of confounders • Provided estimates of the random variability in the data for the main outcomes using confidence intervals • All patients completed the study • Made a comprehensive attempt to report tx-related adverse events • Described main findings • Reported probability values for main outcomes *External Validity* • Described the tx environment *Internal Validity – Bias* • Patients and outcome assessors were blinded to tx allocation • F/u time was 8 weeks following randomization • Appropriate statistical tests were used to assess main outcomes • There was reliable compliance with the intervention • Valid and reliable main outcomes measures were used *Internal Validity – Confounding* • Participants were selected from the same population • All multivariate models had sufficient statistical power	*External Validity* • Invited participants were not representative of the population. Hypercalcemic patients were excluded because of the impact on vascular function and baseline serum phosphate levels were restricted to the low end. Patients on dialysis were excluded • Randomization was interrupted starting with the 97th patient due to shortage of sevelamer at the tx site *Internal Validity – Bias* • Outcome assessors were not blinded to tx allocation

f/u= follow-up; tx = treatment; RCT = randomized controlled trial

Table A6: Strengths and Limitations of Economic Studies using Drummond's checklist[9]

Strengths	Limitations
Nguyen, 2016[16]	
• Described assumptions used in the model • Described the form of economic evaluation • Defined the intervention and comparator	• No limitations were observed

Table A6: Strengths and Limitations of Economic Studies using Drummond's checklist[9]	
Strengths	**Limitations**
• Described the approach to sensitivity analysis • Provided primary outcome measures • Provided a detailed decision tree model • Provided a source and method for calculating costs • Stated the discount rate • Provided the time horizon of costs and benefits	
Panichi, 2015[17]	
• Described assumptions used in the model • Described the form of economic evaluation • Defined the intervention and comparators • Described the approach to sensitivity analysis • Provided primary outcome measures • Provided a detailed decision tree model • Provided multiple sources and method for calculating costs • Provided the time horizon of costs and benefits	• Did not apply a discount rate to either outcomes or costs • Compared sevelamer to multiple comparators as a group • Calculated savings per LYG instead of savings per QALY gained
Ruggeri, 2015[18]	
• Minimized the use of assumptions by using patient-level data • Described the form of economic evaluation • Defined the intervention and comparators • Described the approach to sensitivity analysis • Provided primary outcome measures • Did not provide a decision tree model • Provided sources and method for calculating costs • Provided the time horizon of costs and benefits	• Did not apply a discount rate to either outcomes or costs • Calculated savings per LYG instead of savings per QALY gained
Ruggeri, 2014[19]	
• Described assumptions used in the model • Described the form of economic evaluation • Defined the intervention and comparator • Described the approach to sensitivity analysis • Provided primary outcome measures • Did not provide a decision tree model • Provided sources and method for calculating costs • Provided the time horizon of costs and benefits	• Did not apply a discount rate to either outcomes or costs • Calculated savings per LYG instead of savings per QALY gained
Thompson, 2013[20]	
• Described assumptions used in the model • Described the form of economic evaluation • Defined the intervention and comparator • Described the approach to sensitivity analysis • Provided primary outcome measures • Provided a simplified decision tree model • Provided sources and method for calculating costs • Provided the time horizon of costs and benefits	• Approximately 11% of patients in primary study were lost to follow-up without explanation

LYG = life year gained; QALY = quality-adjusted life year

Appendix 4: Main Study Findings and Authors' Conclusions

Table A7: Summary of Findings of Systematic Reviews and Meta-Analyses

Outcome	Intervention Group	Comparator Group	Pooled Estimates of Effect or Narrative Findings of Primary Studies	Author's Conclusions or Interpretations
Palmer, 2016[10]				
Pair-wise MA of head-to-head comparisons				
Serum phosphate level target achievement (n=139, 1 RCT; f/u 3 months)	Sevelamer HCL	Calcium (carbonate, acetate)	OR 1.25 (CI 0.60 to 2.57)	
Hypercalcemia (not defines) (n=3560, 13 RCTs; median f/u 9 months)			OR 0.14 (CI 0.07 to 0.29)	
All-cause mortality (n = 3481, 8 RCTs; median f/u 15 months)			OR 0.38 (CI 0.17 to 0.86)	
Cardiovascular mortality (n = 2712, 4 RCTs; median f/u 16 months)			OR 0.32 (CI 0.06 to 1.63)	
GI AE (nausea) (n = 2518, 5 RCTs; median f/u of 9 months)			OR 0.93 (CI 0.47 to 1.82)	
GI AE (abdominal pain) (n = 363, 3 RCTs; median f/u 9 months)			OR 2.1 (CI 0.72 to 5.60)	
GI AE (constipation) (n = 2602, 5 RCTs; median f/u 12 months)			OR 1.56 (CI 0.64 to 3.82)	
GI AE (diarrhea) (n = 315, 3 RCTs; median f/u 9 months)			OR 1.03 (CI 0.50 to 2.14)	
NMA				
Hypercalcemia (not defined) (n = 5,159, 21 RCTs; median f/u NR)	Sevelamer (HCL, carbonate)	Calcium-based PBs	OR 0.14 (CI 0.07 to 0.29)	"Sevelamer appeared to reduce all-cause mortality compared to calcium"[10] Page 5

Table A7: Summary of Findings of Systematic Reviews and Meta-Analyses

Outcome	Intervention Group	Comparator Group	Pooled Estimates of Effect or Narrative Findings of Primary Studies	Author's Conclusions or Interpretations
Change in coronary artery calcification (n = 456, 5 RCTs; median f/u 5730 patient-months)			SMD -0.20 (CI -0.40 to -0.01)	
All-cause mortality (n = 6,376, 20 RCTs; median f/u NR)			OR 0.39 (CI 0.21 to 0.74) Fixed effects model OR 0.74 (CI 0.62 to 0.89)	
Cardiovascular mortality (n = 2,913, 5 RCTs; median f/u 61,491 patient-months)			OR 0.33 (CI -0.08 to 1.41)	
GI AE (constipation) (n = 7,862, 27 RCTs; median f/u NR)			OR 2.12 (1.01 to 4.45)	
GI AE (diarrhea) (n = 4,894, 23 RCTs; median f/u NR)			OR 1.18 (0.38 to 3.66)	
Patel, 2016[11]				
MA of pair-wise head -to-head comparisons				
Serum phosphate level (n = 4,010, 23 RCTs; f/u 2 to 36 f/u months)	Sevelamer (HCL, carbonate)	Calcium (carbonate, acetate), sevelamar HCL + calcium carbonate	MD 0.1 mg/dL (CI -0.1 to 0.2)	"…this MA showing lower mortality with sevelamer … [suggests] a need to re-evaluate the recommendations of international guidelines for the management of hyperphosphatemia in CKD-mineral and bone disorder. ."[11] Page 243
Serum calcium level (n = 3,933, 22 RCTs; f/u 2 to 36 months)			MD -0.4 mg/dL (CI -0.6 to -0.2)	
Hypercalcemia (serum calcium > 11 mg/dL) (n = 1,537, 15 RCTs; f/u 2 to 36 months)			RR 0.30 (CI 0.19 to 0.48)	
All-cause mortality (n = 3,799, 13			RR 0.54 (CI 0.32 to 0.93)	

Table A7: Summary of Findings of Systematic Reviews and Meta-Analyses				
Outcome	**Intervention Group**	**Comparator Group**	**Pooled Estimates of Effect or Narrative Findings of Primary Studies**	**Author's Conclusions or Interpretations**
RCTs; f/u 2 to 36 months)				
All-cause mortality for patients on dialysis (n = 3,587, 12 RCTs; f/u 2 to 24 months)			RR 0.54 (CI 0.29 to 1.01)	
Cardiovascular mortality (n = 2,712, 4 RCTs; f/u 5 to ≥ 36 months)[a]			RR 0.33 (CI 0.07 to 1.64)	
GI AE (nausea and/or vomiting) (n = 255, 2 RCTs; f/u 2 to 20 months)			RR 0.64 (CI 0.12 to 3.45)	
GI AE (constipation) (n = 554, 5 RCTs; f/u 2 to 12 months)			RR 1.70 (CI 0.69 to 4.15)	
GI AE (diarrhea) (n = 255, 2 RCTs; f/u 2 to 20 months)			RR 1.03 (CI 0.55 to 1.91)	
GI AE (abdominal bloating) (n = 56, 1 RCT; f/u 3 months)			RR 2.33 (CI 0.49 to 11.01)	
GI AE (combined) (n = 384, 4 RCTs; f/u 2 to 12.5 months)			RR 1.42 (CI 0.97 to 2.08)	
Sekercioglu, 2016[12]				
Direct pair-wise MA				
All-cause mortality (n = 3665, 10 RCTs; f/u ≥ 4 weeks)	Calcium-based PBs	Sevelamer (HCL, carbonate)	RR 1.89 (CI 1.02 to 3.50)	"…calcium, as compared to non-calcium-based PBs in general and sevalamer in particular, increases all-cause mortality among CKD-mineral bone density patients."[12] Page 13
NMA				
All-cause mortality (n = 8335; 28 RCTs; f/u ≥ 4 weeks)	Calcium-based PBs	Sevelamer (HCL, carbonate)	RR 1.35 (CI 1.14 to 1.60)	
Wang, 2015[13]				
MA				
Serum phosphate level	Sevelamer (HCL,	Calcium (acetate,	MD 0.17 mg/dL (CI 0.03 to 0.31;	"…compared with calcium-based PBs, sevelamer has virtually no

Table A7: Summary of Findings of Systematic Reviews and Meta-Analyses				
Outcome	**Intervention Group**	**Comparator Group**	**Pooled Estimates of Effect or Narrative Findings of Primary Studies**	**Author's Conclusions or Interpretations**
(n = 3327, 18 RCTs; f/u 2 to 45 months)	carbonate)	carbonate)	*P* = 0.02)	advantage in terms of the control of serum levels of phosphate, but it can decrease [] the prevalence of hypercalcemia, and benefits vascular calcification in the long-term."[13] Page 12 "All RCTs showed that calcium-based PBs were better than sevelamer for the control of serum levels of phosphate."[13] Page 6
Serum calcium level (n = 3425, 18 RCTs; f/u 2 to 45 months)			MD -0.24 mg/dL (CI -0.34 to -0.14; *P* = NR)	
Hypercalcemia (exceeded serum calcium levels thresholds between 10.2 to 10.5 mg/dL) (n = 957, 10 RCTs; f/u NR)			RR 0.43 (CI -0.32 to 0.56; *P* < 0.00001)	
Hypercalcemia (serum calcium levels > 11.0 mg/dL) (n = 605, 8 RCTs; f/u NR)			RR 0.22 (CI 0.13 to 0.37; *P* < 0.00001)	
Coronary artery calcification (change in CACS) (n = 679, 6 RCTs; f/u 26 to 104 weeks)			MD -102.66 (CI -159.51 to -45.80; *P* = 0.0004)	"All RCTs analyzed showed that sevelamer was better for preventing calcification of coronary arteries than calcium-based PB."[13] Page 6
Aortic calcification (change in ACS) (n = 266, 3 RCTs; f/u 52 to 104 weeks)			MD -1008.26 (CI -1664.75 to -352.72; *P* = 0.003)	
All-cause mortality (n = 3000, 9 RCTs; f/u 5 to 45 months)			RR 0.91 (CI 0.79 to 1.04; *P* = 0.44)	"…no significant difference was found in all-cause mortality and cardiovascular mortality."[13] Page 8
Cardiovascular mortality (n = 2102, 3 RCTs; f/u NR)			RR 0.94 (CI 0.76 to 1.16; *P* = 0.80)	
Navaneethan, 2011[14]				
MA				
Serum phosphate level (n = 3126, 16	Sevelamer HCL	Calcium-based PBs	MD 0.23 (CI 0.04 to 0.42; *P* = 0.019)	"…the novel PBs such as sevelamer HCL [] are not superior to calcium salts for the control of

Table A7: Summary of Findings of Systematic Reviews and Meta-Analyses				
Outcome	**Intervention Group**	**Comparator Group**	**Pooled Estimates of Effect or Narrative Findings of Primary Studies**	**Author's Conclusions or Interpretations**
RCTs; f/u NR)				phosphorus levels in dialysis patients and their impact on morbidity and mortality is unknown. The primary advantage of more recently developed PBs (…sevelamer HCL) is a reduction in hypercalcaemia. Data for patient focused end-points in dialysis patients are inadequate to inform clinical recommendations for any PB"[14] Page 15
Serum calcium level (n = 3039, 15 RCTs; f/u NR)			MD -0.34 (CI -0.45 to -0.24; *P* < 0.00001)	
Hypercalcemia (n = 1144, 12 RCTs; f/u NR)			RR 0.45 (CI 0.35 to 0.59; *P* < 0.00001)	
Coronary artery calcification (n = 655, 5 RCTs): Scores NR			Two studies reported that sevelamer HCL led to a slower progression of coronary artery calcification (one of the studies was limited to patients on hemodialysis). Two studies reported no difference (one of the studies involved patients on dialysis).	
All-cause mortality (n = 3079, 10 RCTs; f/u NR)			RR 0.73 (CI 0.46 to 1.16; *P* = 0.19)	
GI AE (nausea) (n = 203, 1 RCT; f/u NR)			RR 1.03 (CI 0.57 to 1.86)	
GI AE (constipation) (n = 259, 2 RCTs; f/u NR)			RR 2.63 (CI 1.29 to 5.35)	
GI AE (diarrhea) (n = 203, 1 RCT; f/u NR)			RR 1.03 (CI 0.55 to 1.95)	
GI AE (abdominal bloating) (n = 56, 1 RCT; f/u NR)			RR 2.33 (CI 0.49 to 11.01)	
GI AE (combined) (n = 498, 5 RCTs; f/u NR)			RR 1.58 (CI 1.11 to 2.25)	

ACS = aortic calcification score; AE= adverse event; CACS = coronary artery calcification score; CKD = chronic kidney disease; CI = confidence interval; GI = gastrointestinal; HCL = hydrochloride; MA = meta-analysis; MD = mean difference; OR = odds ratio; PB(s) = phosphate binders; RR = risk ratio; SMD = standardized mean difference

[a] F/u for the INDEPENDENTRCT was listed as 24 months in Table 1 of the SR but as ≥ 36 months in the text

Table A8: Summary of Findings of the Included RCT	
Main Study Findings	**Author's Conclusions**
Yilmaz, 2012[15]	
Median age: 45 years (sevelamer) versus 46 years (calcium acetate) *Efficacy outcomes at week 8 for sevelamer (n = 47) versus calcium acetate (n = 53)* Differences between % decrease in serum phosphate: -16.2 (-15.8 to -6.3); *P* < 0.001 Differences between % decrease in serum calcium: -3.2 (-3.1 to -3.3); *P* = 0.03	• "…serum phosphate levels decreased with both sevelamer and calcium acetate, but the decrease was more marked with sevelamer (P < 0.001)."[15] Page 180

RCT = randomized controlled trial

Table A9: Summary of Findings of Included Economic Studies	
Main Study Findings	**Author's Conclusions**
Nguyen, 2016[16]	
Perspective: Third party payer Time horizon: Lifetime (range 2 to 40) <u>Base case (sevelamer versus calcium carbonate)</u> Discount rate: 1.5% WTP threshold: SGD61,000 or £30,000/QALY gained # patients: 1,000 (study did not specify how many were in each group) Tx costs (including drug, hospitalization, and dialysis): SGD180,724 versus SGD152,988 QALY: 6.34 versus 5.81 Mean incremental tx cost: SGD27,736 QALY gained: 0.53 ICER: SGD51,756/QALY gained <u>Sensitivity analysis (tx dose, tx cost, and tx effectiveness)</u> Sevelamer remained cost effective when its cost is ≤ SGD1.69/g. Beyond a time horizon of 6 years, the cost of sevalamer and dialysis increased at a rate faster than the QALY.	• "Compared with a CE threshold of £30,000 or SGD61,000 per QALY (based on the exchange rate as of Nov. 24, 2012), sevelamer is cost effective relative to calcium carbonate"[16] Page 5 • "From a third party payer perspective and considering a lifetime time horizon, sevelamer is likely to be cost effective relative to calcium carbonate as a treatment for hyperphosphatemia in CKD patients in Singapore and in countries with similar health systems."[16] Page 8
Panichi, 2015[17]	
Perspective: Government payer Time horizon: 7 years <u>Base case (sevelamer versus calcium carbonate/calcium acetate/vitamin D</u> Discount rate: NR WTP threshold: €40,000/LYG # patients: 242 versus 507 *Patients without co-morbidities*	• "Economical analysis confirms the cost effectiveness of sevelamer in patients with and without comorbidities. Probabilistic sensitivity analysis associated to our results a probability of 94% of being below €40,000/LYG."[17] Page 179

Table A9: Summary of Findings of Included Economic Studies	
Main Study Findings	**Author's Conclusions**
Mean incremental tx cost: €30,144 LYG:1.3 ICER: €23,272/LYG *Patients with co-morbidities* Mean incremental tx cost: €18,424 LYG: 0.552 ICER: €28,257/LYG[a] <u>Sensitivity analysis (transition probabilities, drug costs, hemodialysis and other costs)</u> In 94% of 10,000 simulations, sevelamer was cost-effective	
Ruggeri, 2015[18]	
Perspective: Government payer Time horizon: 3 years <u>Base case</u> Discount rate: None WTP threshold: €25,000/LYG # patients: 232 versus 234 Mortality rate: 12% (28/232) versus 43% (100/234); *P* = 0.0001 Mean incremental tx cost (including hospitalization, excluding dialysis costs): €1,261.73 (CI 666.16 to 1,857.30); *P* = 0.0001 LYG: 0.26 (CI 0.11 to 0.41); *P* = 0.05[b] ICER: €4,897/LYG[c] *Bootstrap simulations* Mean incremental tx cost: €1,262.92 (CI 1,224.24 to 1,301.60) LYG: 0.26 (CI 0.25 to 0.27) ICER: €4,857.38/LYG In 99.6% of 10,000 simulations, the ICER fell below the WTP threshold of €25,000/LYG In 94.9% of 10,000 simulations, the ICER fell below the WTP threshold of €10,000/LYG <u>Sensitivity analysis</u> Mean incremental tx cost (including hospitalization and dialysis costs*): €8,375.04 (CI 4,073.62 to 12,676.47); *P* = 0.02 LYG: 0.26 (CI 0.25 to 0.27) ICER: €32,506/LYG * Assuming 3 times weekly hemodialysis sessions at a cost of €176.98/session *Bootstrap simulations* Mean incremental tx cost (including hospitalization and dialysis):	• "Using patient-level data from the recently published INDEPENDENT study, this CEA demonstrated that sevelamer versus calcium carbonate represents good value for money in the first-line treatment of hyperphosphatemia in CKD patients initiating dialysis."[18] Page 601

Table A9: Summary of Findings of Included Economic Studies	
Main Study Findings	**Author's Conclusions**
€8,350.67 (CI 8,068.35 to 8,632.98) LYG: 0.26 (CI 0.25 to 0.27) In 96.8% of simulations, the ICER fell between €30,000/LYG to €50,000/LYG	
Ruggeri, 2014[19]	
Perspective: Government payer Time horizon: 3 years <u>Base case</u> Discount rate: None WTP threshold: €10,000 to €100,000/LYG # patients: 107 versus 105 Mortality rate: 11% (12/107) versus 21% (22/105); *P* = 0.009 Mean incremental tx cost (including hospitalization and dialysis): -€5,615 (CI -10,066 to -1,164); *P* = 0.038 LYG: 0.06 (CI -0.04 to 0.16); *P* = 0.23 *Bootstrap simulations* Mean incremental tx cost (including hospitalization and dialysis): -€5,651 (CI -6,083 to -5,219); *P* = NR LYG: 0.06 (CI 0.05 to 0.07); *P* = NR In 87.1% of 10,000 simulations, sevelamer was less costly and more effective <u>Subgroup analysis (NDD-CKD patients)</u> Mortality rate: 10.5% (8/76) versus 25.4% (16/63); *P* = 0.025 Mean incremental tx cost: €2,472.24 (CI -948 to 3,996); *P* < 0.0001 LYG: 0.11 (CI -0.01 to 0.22); *P* = 0.008 *Bootstrap simulations* Mean incremental tx cost: -€2,468 (CI -2,657 to -2,279); *P* = NR LYG: 0.11 (CI 0.09 to 0.12); *P* = NR In 91.6% of simulations, sevelamer was less costly and more effective	• "Using patient-level data from the recently published INDEPENDENT-CKD study, this analysis demonstrates that sevelamer provides more LYs and is less costly than calcium carbonate in the treatment of hyperphosphatemia in patients with NDD-CKD in Italy."[19] Page 323
Thompson, 2013[20]	
Perspective: Government payer Time horizon: Lifetime <u>Base case</u> Discount rate: 3.5% WTP threshold: £30,000/QALY gained # patients: 107 versus 105 Transitioned to dialysis: 31 versus 42 All-cause mortality (at 3 years): *P* < 0.01 Extrapolated mortality rate (at 10 years): 76%	• "…sevelamer represents a cost-effective alternative to calcium carbonate for the tx of hyperphosphatemia in patients with [NDD-CKD] in the UK."[20] Page 754

Table A9: Summary of Findings of Included Economic Studies	
Main Study Findings	**Author's Conclusions**
versus 96% Mean incremental tx cost (including dialysis, excluding hospitalization): £37,282 LYG: 2.0493 QALY gained: 1.5613 ICER: £18,193/LYG ICER: £23,878/QALY gained <u>Sensitivity analysis (one-way)</u> ICER (time horizon of 3 years): sevelamer was more effective and less costly than calcium carbonate ICER (mean daily dose of 14.4g): £38,490/QALY gained ICER (excluding impact of tx on initiation of dialysis): £2,108/QALY gained ICER (dialysis cost of £31,479.26): £30,348/QALY gained ICER (health utility of 0.70 for NDD-CKD patients): £25,990/QALY gained <u>Sensitivity analysis (probabilistic)</u> Mean ICER of £23,035 (SD = £6,238) Sevelamer was cost-effective in approximately 93% of 10,000 simulations	

CE = cost-effectiveness; CI = 95% confidence interval; CKD = chronic kidney disease; ICER = incremental cost-effectiveness ratio; LYG = life year gained; NDD = non-dialysis-dependent; QALY = quality-adjusted life year; SD = standard deviation; SGD = Singapore dollar; tx = treatment or therapy; WTP = willingness-to-pay

[a] At an incremental cost of €18,424 and LYG of 0.552, the ICER = €33,376/LYG[17]
[b] P<0.005 in the text on page 597[18]
[c] At an incremental cost of €1,261.73 and LYG of 0.26, the ICER = €4,852/LYG[18]

Appendix 5: Additional References of Potential Interest

List of Studies with Other Comparators

Lanthanum carbonate

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Other PBs

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