METHODOLOGICAL ISSUES IN EVIDENCE SUMMARIES AND GUIDELINES IN MINERAL AND BONE DISORDERS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

METHODOLOGICAL ISSUES IN EVIDENCE SUMMARIES AND GUIDELINES IN MINERAL AND BONE DISORDERS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

By

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ABSTRACT

Background and objectives: Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a systemic condition defined by an increase in cardiovascular calcifications and bone fragility. The condition is diagnosed by abnormal serum concentrations of calcium, phosphorus, parathyroid hormone and vitamin D. These biochemical abnormalities have been linked to abnormal bone metabolism as well as cardiovascular calcifications if left untreated.

Phosphate binders are known to cause phosphate reduction through mechanisms involve the gastrointestinal route. Their relative effects remain uncertain. Controversy arises because of concerns related to systematic effects, tolerability, costs and impact on patient important outcomes. The objective of Chapters 2 and 3 was to explore the relative effectiveness of phosphate binders on patient-important outcomes and laboratory outcomes in patients with CKD-MBD using the frequentist and Bayesian approaches, respectively. The purpose of Chapter 4 was to critically appraise clinical practice guidelines addressing CKD-MBD.

Methods and results

Chapter 2: We performed network meta-analyses for all cause-mortality for individual agents (seven-node analysis) and conventional meta-analysis of calcium vs. non-calcium based phosphate binders (NCBPB) for all-cause mortality, cardiovascular mortality and hospitalization. Our results suggested higher mortality with calcium than either sevelamer in our network meta-analysis or NCBPB in our conventional meta-analysis. Conventional

meta-analysis suggested no statistically difference in cardiovascular mortality between calcium and NCBPBs.

Chapter 3: We performed Bayesian network meta-analyses to calculate the effect estimates (mean differences) and 95% credible intervals for serum levels of phosphate, calcium and parathyroid hormone. Moderate-quality evidence suggests superior effect of active treatment categories as compared to placebo for reducing serum phosphate. Our NMA results did not find statistically significant difference between active treatment categories in lowering serum phosphate.

Chapter 4: We performed a systematic survey to critically appraise clinical practice guidelines addressing CKD-MBD. Most guidelines assessing CKD-MBD suffer from serious shortcomings using the Advancing Guideline Development, Reporting and Evaluation in Health Care instrument II (AGREE) criteria; a minority, however, fulfill the criteria. Limitations with respect to AGREE criteria do not, however, necessarily lead to inappropriate recommendations.

Conclusion: Given the likely mortality reduction with sevelamer versus calcium, the results suggest that higher calcium levels associated with calcium based phosphate binders may contribute to the mortality differential. We found that most clinical practice guidelines related to CKD-MBD were not satisfactory with major problems with rigor, update and implementation. Recommendations were consistent and thus unassociated with guideline quality. In other instances, however, this may not be the case, and ensuring trustworthiness of guidelines will require adherence to methodological standards.

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LIST OF ABBREVIATIONS

AGREE: Appraisal of Guidelines for Research and Evaluation Instrument –

CBPB: Calcium Based Phosphate Binders

CKD: Chronic Kidney Disease

CKD-MBD: Chronic Kidney Disease Mineral and Bone Disorders

CPG: Clinical Practice Guidelines

CI: Confidence Interval

CrI: Credible Interval

df : Degrees of Freedom

DIC: Deviance Information Criterion

EMBASE: Excerpta Medica Database

eGFR: Estimated Glomerular Filtration Rate

EBRP: European Renal Best Practice

FGF-23: Fibroblast Growth Factor

GRADE: The Grading of Recommendations Assessment, Development and Evaluation – GRADE

IQR: Interquartile Range

KDOQ/I: The Kidney Disease Outcomes Quality Initiative

KDIGO: Kidney Disease Improving Global Outcomes

MD: Mean Difference

MEDLINE: Medical Literature Analysis and Retrieval System Online

MeSH: Medical Subject Headings

MTC: Multiple Treatment Comparison

NA: Not Available

NICE: National Institute for Health and Care Excellence

NMA: Network Meta-analysis

NCBPB: Non-Calcium Based Phosphate Binders

NR: Not Reported

OR: Odds Ratio

OIS: Optimal Information Size

PrI: Predictive Intervals

PRISMA-NMA: Preferred Reporting Items for Systematic Review and Meta-analysis for Network Meta-analysis

RCT: Randomized Controlled Trials

ROC Curve: Receiver Operating Characteristic Curve

RR: Relative Risk

HPT: Renal Hyperparathyroidism

SD: Standard Deviation

SUCRA: Surface under the cumulative ranking curve

DECLARATION OF ACADEMIC ACHIEVEMENT

This is a "sandwich" thesis consisting of five chapters, one of which has been published in a peer-reviewed medical journal (Chapter 2), and other two have been submitted to a peer-reviewed medical journals and are under review (Chapter 4). I was the first author and main contributor for each chapter. My independent contributions involved leading each chapter's conception and design; performing acquisition, analysis, and/or interpretation of data; drafting the manuscripts and revising them critically for important intellectual content; providing final approval of the versions published or submitted; and agreeing to be accountable for all aspects of each work. I completed all aspects of this thesis between March 2015 and June 2016.

Chapter 1

INTRODUCTION

Chronic kidney disease mineral and bone disorders: an overview and management

Chronic kidney disease (CKD) can be defined as structural or functional abnormalities of the kidney that persist for at least three months [1]. CKD is often classified into five stages, according to the estimated glomerular filtration rate (eGFR)—a tool for defining CKD from a functional perspective (Table 1) [2]. Stage 5 status may require dialysis treatment (stage 5D) or a kidney transplant (stage 5T), collectively called renal replacement therapy [2].

CKD is a global public health problem that affects 8-10% of people worldwide. Diabetes mellitus and vascular/hypertension related disorders are the most common causes of CKD in high income countries [3-6]. Health care resource use and associated costs are considerably higher in CKD patients than in those not suffering from the condition, especially for those who are on dialysis or have a kidney transplant [7].

CKD has been associated with high mortality as well as morbidity; the leading cause of death among patients is cardiovascular disease [8-13]. Since CKD affects all organ systems, management requires a systematic approach and detailed considerations to prevent progression of CKD and extra-renal complications [2]. The goals of the treatment of CKD includes: (1) disease specific treatment if indicated; and (2) management of anemia, acidosis, blood pressure, dialysis dose, dialysis volume, proteinuria and markers of bone and mineral metabolism.

Markers of bone and mineral metabolism include phosphate, calcium and parathyroid hormone. High phosphate levels lead to chronic disturbances in calcium-phosphate homeostasis and cardiovascular calcifications in the intima and media layers of the arteries and subsequent cardiovascular events [8, 11-13]. Impaired bone density and quality—abnormal bone turnover, architecture and mineralization—lead to increased fracture risk in CKD patients [8]. The

phenomenon is called CKD mineral and bone disorder (CKD-MBD) and includes a spectrum of diseases that may result in cardiovascular consequences or adverse bone outcomes.

The pathogenesis of cardiovascular calcifications has been well-studied, and *in vitro* studies have demonstrated that vascular tissues are capable of producing structures similar to the bones [8]. Vascular smooth muscle cells have the potential to transform into chondrocyte–osteoblast cell types through a phosphorous mediated system that employs a transcription factor and a non-phosphorous mediated system that employs osteopontin [8, 14]. Elevated calcium, parathyroid hormone and parathyroid hormone-like peptides are other substances that provoke and promote the abnormal calcification process and accelerate atherosclerosis and cardiovascular diseases [15, 16].

In the early stages of CKD, high phosphate levels cause an increase in phosphaturic hormones, parathyroid hormone and fibroblast growth factor-23 (FGF-23) as well as a reduction in klotho and active vitamin D [17]. Klotho is a co-receptor of FGF-23 that enables the phosphaturic effect of FGF-23 [17, 18]. Klotho also plays a role in calcium and phosphate excretion, cardio-protection and anti-oxidation [19].

FGF-23—a more reliable indicator of calcium-phosphate homeostasis due to less diurnal variability as compared to parathyroid hormone and phosphate—increases phosphate excretion by the kidneys and decreases 1-alpha hydroxylase activity which is responsible for activation of vitamin D [20, 21]. Dialysis vintage—defined as length of time on dialysis treatment—and residual renal functions have been linked to FGF-23 levels (positively correlated with dialysis vintage and negatively correlated with residual renal function) [21].

High serum phosphate levels—a common finding in CKD patients— are associated with decreased patient and renal survival [22-25]. As a result, phosphate binders are perceived to have a pivotal role in the management of CKD-MBD. Calcium-based phosphate binders are inexpensive but may cause hypercalcemia. Non-calcium-based phosphate binders, sevelamer and lanthanum, are costlier drugs, but calcium-free. Recently, iron has been shown to be effective in lowering phosphate (e.g., ferric citrate and sucroferric oxyhydroxide) [26].

An overview of meta-analysis and its applications in health care

Pooling effectiveness measures using direct, indirect and mixed comparisons

Meta-analysis is a powerful tool to combine randomized or non-randomized effectiveness data from different studies to facilitate clinical decision making [27]. Conventional meta-analysis—also called head-to-head comparisons—indirect comparisons or combination of the two (network meta-analysis) are established methods to explore treatment effects from different studies.

Network meta-analysis (NMA) is conducted either in a frequentist or Bayesian framework. Bayesian analysis may employ non-informative priors (e.g., mean is equal to zero and precision is equal to 0.001) in order to draw conclusions fully driven by the study data [28, 29]. Another approach employs informative priors using prior knowledge in the form of expert opinion or published data. The frequentist approach does not allow assumptions to be incorporated based on what is known in the area [29]. Both approaches should yield similar results in terms of the magnitude, direction and significance of effect estimates in cases where non-informative priors are employed in the Bayesian framework [29].

A further refinement can be obtained using additive main effect models in complex treatments to decompose individual treatment effects. In addition to the NMA assumptions, additivity assumption maintains that interactions between treatment components are nonexistent.

Pooling diagnostic accuracy indices

Diagnostic tests are commonly used for screening, diagnosis and estimation of prognosis as well as treatment response in clinical practice. Reliability and validity are indicators of overall accuracy of a diagnostic test [30]. The extent of agreement of an index test with itself implies reliability while the agreement of an index test with the reference standard indicates validity of the instrument [31]. Sensitivity, specificity, Youden's index, positive and negative predictive values are indices of validity [31, 32]. The added value of an index test can be measured using a summary Receiver Operating Characteristic (ROC) curve or net reclassification improvement. Nevertheless, sensitivity and specificity are the most common measures of diagnostic accuracy studies [33].

Meta-analysis of diagnostic accuracy studies should account for between- and within-study variability which requires hierarchical random-effect models. Fixed-effect models only consider within-study variations [33, 34]. However, the differences in cut-off values, study populations, verification techniques (complete, partial or differential verification) and diagnostic test properties result in between study variations in performance indices [33].

Pooling summary measures of diagnostic studies: Two-dimensional parameters

One technique to pool the performance indices of diagnostic accuracy studies is to adopt a univariate approach using a diagnostic odds ratio for each study or reporting sensitivity and specificity separately [33]. This method ignores the negative correlation between sensitivity and

specificity and loses valuable information [33]. Moreover, an arbitrary threshold needs to be employed to create categories and achieve the values for sensitivity and specificity [33].

However, studies may use different thresholds due to differences in study populations, techniques, or by choice, which is reflected on sensitivity and specificity[33]. In order to remove the threshold effect and to compare overall accuracy between tests, a summary ROC curve with Q points (the corresponding point of sensitivity is equal to specificity on the ROC curve) is created using a univariate approach [33]. Nevertheless, two dimensions of the original data are lost.

The bivariate approach is considered an ideal method for pooling single test diagnostic accuracy studies. Bivariate meta-analysis is defined as, "*two outcomes per study are modelled simultaneously*" [35]. The parameter of interest in bivariate meta-analysis is the difference in performance indices between two tests [35]. A logarithmic transformation is applied to sensitivity and specificity, both of which will then assume a normal distribution. Subsequently, bivariate normal distribution is created. Bivariate models incorporate precision of the study (i.e., studies are weighed according to their precision), "*between study variation in true underlying sensitivity and specificity*" and negative correlation between sensitivity and specificity [35]. A summary ROC curve can be created with a confidence ellipse and sources of heterogeneity can be explored, including covariates using meta-regression techniques [35]. The main drawback of this technique is that it ignores covariance between dependent and independent variables [35].

<u>Another application of the bivariate approach: pooling correlation indices</u>

Correlation between patient important outcomes and laboratory outcomes can be estimated using a bivariate approach. First, logarithmic transformation of end of treatment mean value and its precision (or logarithmic transformation of proportion of those who achieved the targets) as well

as logarithmic transformation of relative risk of patient important outcomes need to be calculated. Afterwards, patient important outcomes and laboratory outcomes can be correlated using a scatter plot. Grading quality of evidence will rely on both sources of information.

Thesis description & objectives

Although the most recent systematic review and meta-analysis suggests higher mortality with calcium than with non-calcium based phosphate binders (NCBPB), there is no NMA to inform the comparative effectiveness of phosphate binders [36]. This thesis explores the comparative effectiveness of phosphate binders on both patient important and laboratory outcomes, and critically appraises clinical practice guidelines for management of CKD-MBD [37].

The purpose of this thesis is (1) to apply latest developments in NMA and application of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to NMA; (2) to explore the comparative effectiveness of phosphate binders; and (3) to critically appraise clinical practice guidelines addressing mineral and bone disorders. We hypothesized that reductions in phosphate levels using NCBPBs may be associated with reduced vascular stiffness and regression of left ventricular hypertrophy and consequently lowers cardiovascular events, cardiovascular calcifications and mortality. This thesis has made a unique contribution to the body of literature regarding CKD-MBD management by estimating relative effectiveness of phosphate binders and quality of CKD-MBD clinical practice guidelines.

This thesis consists of five chapters, including an introduction and conclusion. Chapter 1provides an overview of CKD-MBD, its management and different applications of meta-analysis in health care. Chapters 2 and 3 present NMAs examining comparative effectiveness of phosphate binders in CKD patients.

Chapter 2 examines the effectiveness of phosphate binders on patient-important outcomes. Chapter 3 examines the comparative effectiveness of phosphate binders on laboratory outcomes. Chapter 4 critically appraises clinical practice guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument.

REFERENCES

1.Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Annals of internal medicine. 2003;139(2):137-47. Epub 2003/07/16. PubMed PMID: 12859163.

2.Group. KDIGOKCW. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter. 2013;(3):1-150.

3.Wijewickrama ES, Weerasinghe D, Sumathipala PS, Horadagoda C, Lanarolle RD, Sheriff RM. Epidemiology of chronic kidney disease in a Sri Lankan population: experience of a tertiary care center. Saudi journal of kidney diseases and transplantation: an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2011;22(6):1289-93. Epub 2011/11/18. PubMed PMID: 22089806.

4.Liu H, Peng Y, Li J, Liu Y, Cheng M, Yuan F, et al. [Stages of 3,547 patients with chronic kidney disease and relevant factor analysis]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2010;35(5):499-510. Epub 2010/06/15. doi: 10.3969/j.issn.1672-7347.2010.05.016. PubMed PMID: 20543476.

5.Khader MI, Snouber S, Alkhatib A, Nazzal Z, Dudin A. Prevalence of patients with end-stage renal disease on dialysis in the West Bank, Palestine. Saudi journal of kidney diseases and transplantation: an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2013;24(4):832-7. Epub 2013/07/03. PubMed PMID: 23816745.

6.Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-72. Epub 2013/06/04. doi: 10.1016/s0140-6736(13)60687-x. PubMed PMID: 23727169.

7.Smith DH, Gullion CM, Nichols G, Keith DS, Brown JB. Cost of medical care for chronic kidney disease and comorbidity among enrollees in a large HMO population. Journal of the American Society of Nephrology : JASN. 2004;15(5):1300-6. Epub 2004/04/22. PubMed PMID: 15100370.

8.Moe SM. Vascular calcification and renal osteodystrophy relationship in chronic kidney disease. European Journal of Clinical Investigation. 2006;36:51-62. doi: 10.1111/j.1365-2362.2006.01665.x.

9.Arterial calcification and pathology in uremic patients undergoing dialysis. Am J Med. 1979;66(5):790-6.

10.Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000;58(1):353-62.

11.Valvular calcification upon initiating dialysis predict the appearance of cardiovascular events in patient evolution. Nefrologia. 2015;35(2):157-63. doi: 10.1016/j.nefro.2015.05.017. Epub Jun 23.

12.Valvular calcification and left ventricular modifying in peritoneal dialysis patients. Renal failure. 2015;19:1-7.

13.Coronary artery calcification, cardiovascular events, and death: a prospective cohort study of incident patients on hemodialysis. Can J Kidney Health Dis. 2015;2:29.(doi):10.1186/s40697-015-0065-6. eCollection 2015.

14.Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000;87(7):E10-7.

15.Parathyroid hormone-related peptide as a local regulator of vascular calcification. Its inhibitory action on in vitro calcification by bovine vascular smooth muscle cells. Arterioscler Thromb Vasc Biol. 1997;17(6):1135-42.

16.Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization in vitro. Kidney Int. 2004;66(6):2293-9.

17.Buiten MS, de Bie MK, Bouma-de Krijger A, van Dam B, Dekker FW, Jukema JW, et al. Soluble Klotho is not independently associated with cardiovascular disease in a population of dialysis patients. BMC Nephrology. 2014;15:197. doi: 10.1186/1471-2369-15-197. PubMed PMID: PMC4293085.

18.Regulation of oxidative stress by the anti-aging hormone klotho. J Biol Chem. 2005;280(45):38029-34. Epub 2005 Sep 26.

19.Soluble Klotho is not independently associated with cardiovascular disease in a population of dialysis patients. BMC Nephrol. 2014;15:197.(doi):10.1186/471-2369-15-197.

20.[FGF23 and Klotho protein--the role in the pathogenesis of hypertension]. Wiad Lek. 2015;68(1):67-70.

21.Isakova T, Xie H, Barchi-Chung A, Vargas G, Sowden N, Houston J, et al. Fibroblast growth factor 23 in patients undergoing peritoneal dialysis. Clin J Am Soc Nephrol. 2011;6(11):2688-95. Epub 2011/09/10. doi: 10.2215/cjn.04290511. PubMed PMID: 21903990; PubMed Central PMCID: PMC3206004.

22.Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31(4):607-17.

23.Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1(4):825-31. Epub 2006 May 17.

24.Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease. Nephrol Dial Transplant. 2011;26(9):2885-90. doi: 10.1093/ndt/gfq808. Epub 2011 Feb 3.

25.High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909-16. Epub 007 May 21.

26.Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. J Nephrol. 2015;28(1):105-13. doi: 10.1007/s40620-014-0108-6. Epub 2014 May 20.

27.Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-91. Epub 1997/06/01. PubMed PMID: 9250266.

28.Luce B, Anthony OH, Dennis F. A Primer on Bayesian Statistics in Health Economics and Outcomes Research: MEDTAP International, Incorporated; 2003.

29.Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):597-606. Epub 2013/06/28. doi: 10.1177/0272989x13487604. PubMed PMID: 23804506; PubMed Central PMCID: PMCPMC3704205.

30.Rutjes AW, Reitsma JB, Vandenbroucke JP, Glas AS, Bossuyt PM. Case-control and two-gate designs in diagnostic accuracy studies. Clin Chem. 2005;51(8):1335-41. Epub 2005/06/18. doi: 10.1373/clinchem.2005.048595. PubMed PMID: 15961549.

31.Whiting PF, Rutjes AW, Westwood ME, Mallett S. A systematic review classifies sources of bias and variation in diagnostic test accuracy studies. J Clin Epidemiol. 2013;66(10):1093-104. Epub 2013/08/21. doi: 10.1016/j.jclinepi.2013.05.014. PubMed PMID: 23958378.

32.Linnet K, Bossuyt PM, Moons KG, Reitsma JB. Quantifying the accuracy of a diagnostic test or marker. Clin Chem. 2012;58(9):1292-301. Epub 2012/07/26. doi: 10.1373/clinchem.2012.182543. PubMed PMID: 22829313.

33.Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of clinical epidemiology. 2005;58(10):982-90. Epub 2005/09/20. doi: 10.1016/j.jclinepi.2005.02.022. PubMed PMID: 16168343.

34.van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Statistics in medicine. 2002;21(4):589-624. Epub 2002/02/12. PubMed PMID: 11836738.

35.Moreau E, Bacher S, Mery S, Goff CL, Piga N, Vogeser M, et al. Performance characteristics of the VIDAS 25-OH Vitamin D Total assay - Comparison with four immunoassays and two liquid chromatography-tandem mass spectrometry methods in a multicentric study. Clinical Chemistry and Laboratory Medicine. 2016;54(1):45-53. doi: http://dx.doi.org/10.1515/cclm-2014-1249. PubMed PMID: 20160050923.

36.Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet (London, England). 2013;382(9900):1268-77. Epub 2013/07/23. doi: 10.1016/s0140-6736(13)60897-1. PubMed PMID: 23870817.

37.Brandenburg VM, Floege J. Adynamic bone disease-bone and beyond. NDT plus. 2008;1(3):135-47. Epub 2008/06/01. doi: 10.1093/ndtplus/sfn040. PubMed PMID: 25983860; PubMed Central PMCID: PMCPMC4421169.

Table 1: Stages of CKD according to eGFR [1]

Stages of CKD	**eGFR, ml/min/1.73 m^2**
Stage 1	≥90
Stage 2	60–89
Stage 3	30–59
Stage 4	15–29
Stage 5	< 15

Abbreviations: eGFR: estimated Glomerular Filtration Rate; CKD: Chronic Kidney Disease.

Chapter 2

Comparative effectiveness of phosphate binders in patients with chronic kidney disease: A systematic review and network meta-analysis

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COLLECTION REVIEW

Comparative Effectiveness of Phosphate Binders in Patients with Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis

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Abbreviations: CBPB, Calcium based phosphate binders; CI, Confidence intervals; CKD-MBD, Chronic kidney disease-mineral and bone disorders; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; NCBPB, Non-calcium based phosphate binders; NMA, Network meta-analysis; RCT, Randomized controlled trail; OR, odds ratio.

Abstract

Background

Chronic kidney disease-mineral and bone disorder (CKD-MBD) has been linked to poor health outcomes, including diminished quality and length of life. This condition is characterized by high phosphate levels and requires phosphate-lowering agents—phosphate binders. The objective of this systematic review is to compare the effects of available phosphate binders on patient-important outcomes in patients with CKD-MBD.

Methods

Data sources included MEDLINE and EMBASE Trials from 1996 to February 2016. We also searched the Cochrane Register of Controlled Trials up to April 2016. Teams of two reviewers, independently and in duplicate, screened titles and abstracts and potentially eligible full text reports to determine eligibility, and subsequently abstracted data and assessed risk of bias in eligible randomized controlled trials (RCTs). Eligible trials enrolled patients with CKD-MBD, randomized them to receive calcium (delivered as calcium acetate, calcium citrate or calcium carbonate), non-calcium-based phosphate binders (NCBPB) (sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, sucroferric oxyhydroxide and ferric citrate), phosphorus restricted diet, placebo or no treatment, and

reported effects on all-cause mortality, cardiovascular mortality or hospitalization at ≥4 weeks follow-up. We performed network meta-analyses (NMA) for all cause-mortality for individual agents (seven-node analysis) and conventional meta-analysis of calcium vs. NCBPBs for all-cause mortality, cardiovascular mortality and hospitalization. In the NMAs, we calculated the effect estimates for direct, indirect and network meta-analysis estimates; for both NMA and conventional meta-analysis, we pooled treatment effects as risk ratios (RR) and calculated 95% confidence intervals (CIs) using random effect models. We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to rate the quality of evidence for each paired comparison.

Results

Our search yielded 1190 citations, of which 71 RCTs were retrieved for full review and 15 proved eligible. With 13 eligible studies from a prior review, we included 28 studies with 8335 participants; 25 trials provided data for our quantitative synthesis. Results suggest higher mortality with calcium than either sevelamer (NMA RR, 1.89 [95% CI, 1.02 to 3.50], moderate quality evidence) or NCBPBs (conventional meta-analysis RR, 1.76 [95% CI, 1.21 to 2.56, moderate quality evidence). Conventional meta-analysis suggested no difference in cardiovascular mortality between calcium and NCBPBs (RR, 2.54 [95% CI, 0.67 to 9.62 low quality evidence). Our results suggest higher hospitalization, although non-significant, with calcium than NCBPBs (RR, 1.293 [95% CI, 0.94 to 1.74, moderate quality evidence).

Discussion/Conclusions

Use of calcium results in higher mortality than either sevelamer in particular and NCBPBs in general (moderate quality evidence). Our results raise questions about whether administration of calcium as an intervention for CKD- MBD remains ethical. Further research is needed to explore the effects of different types of phosphate binders, including novel agents such as iron, on quality and quantity of life.

Systematic Review Registration

PROSPERO CRD-42016032945

Introduction

Patients with chronic kidney disease (CKD) [1] are at higher risk of death, often due to cardiovascular disease [2–7]. CKD leads to hyperphoshatemia and a number of chronic disturbances of calcium-phosphate homeostasis collectively referred to as CKD mineral and bone disorder (CKD-MBD). This constellation of metabolic abnormalities leads to arterial intimal and medial calcification that are associated with cardiovascular events [2], while abnormal bone turnover, architecture and mineralization result in reduced bone quality and density, with increased risk of fracture [2].

Phosphate has long been considered an important target for managing CKD-MBD and its sequelae. Because of the adverse impact of high serum phosphate levels on cardiovascular and bone outcomes and on survival [8–11], and because elevated serum phosphate is common in CKD patients, phosphate binders have a pivotal role in the management of CKD. Calcium—delivered as calcium acetate, calcium citrate or calcium carbonate—is less expensive, but more

likely to cause hypercalcemia [8–11]. Non-calcium-based phosphate binders (NCBPB), sevelamer and lanthanum, are costlier but do not cause hypercalcemia [8–11].

Through different mechanisms, all phosphate binders prevent phosphate absorption from the gastrointestinal system [12]. Sevelamer is a resin-based binder with an anion exchange mechanism [13]. Lanthanum binds phosphate through its trivalent cation [13]. Recently, iron (e.g., ferric citrate and sucroferric oxyhydroxide) has also proved effective in lowering phosphate by impeding the absorption of phosphate in the stomach without evidence of toxicity [14,15]. The crucial question, however, is the relative impact of these agents on patient-important outcomes, particularly on mortality.

Jamal et al. conducted a meta-analysis of 15 randomized control trials (RCTs) examining CBPBs versus NCBPBs in patients with hyperphosphatemia and CKD. The results suggest higher mortality with CBPBs than with NCBPBs[16]. Inferences from this review are limited because the review did not address individual NCBPBs and because of imprecision of the main finding: results were consistent with either a moderate relative reduction in mortality (23%) or a very small relative reduction (3%). Moreover, the quality appraisal was limited, reducing overall confidence in the estimates of effect and conclusions [16].

The objective of this systematic review was (1) to update the Jamal et al. systematic review [16] using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and (2) to provide estimates of effect of individual agents by combining direct and indirect estimates through a network meta-analysis (NMA).

Methods

We registered our protocol with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016032945). We adhered to the PRISMA NMA guidelines in drafting our manuscript (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx) (S1 File).

Eligibility criteria

We included studies that (1) enrolled adult patients (≥18 years of age) with chronic kidney disease, defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2, including dialysis CKD patients (CKD stage 5D) and non-dialysis CKD patients (stages 3 through 5) [1, 17]; (2) randomized patients to a phosphate binder or a control. Phosphate binders included CBPBs (calcium acetate, calcium citrate or calcium carbonate) and NCBPDs (sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, sucroferric oxyhydroxide or ferric citrate). A control included phosphorus restricted diet, placebo or no intervention; (3) reported at least one of the following outcomes: all-cause mortality, cardiovascular mortality or hospitalization due to any cause; and (4) had a minimum follow-up of 4 weeks. We excluded studies that included pediatric patients if outcomes of adults were not reported separately.

Data sources and search strategy

We included all trials identified in a prior review and updated the search for the subsequent period [16]; specifically, we searched MEDLINE and EMBASE from January 2013 until February 2016 without language restrictions. We also searched the Cochrane Register of Controlled Trials up to April 2016. We used controlled vocabulary and text words and restricted our search to RCTs. We scanned the bibliographies of all prior systematic reviews and meta-analyses as well as all eligible primary studies for additional relevant articles. Our full search strategy is depicted in S2 File in supporting information.

Study selection

Teams of two reviewers independently screened each title and abstract. If either reviewer identified a citation as potentially relevant, we obtained the full text of the article. Two reviewers independently determined the eligibility of all studies that underwent full text evaluation. If we found more than one publication for a study, and if supplementary reports included eligible outcome measures not provided in the main report, we included complementary information from the second or third report.

Data abstraction

We extracted study data using a customized data collection form accompanied by a detailed instruction manual. We abstracted the following information from each study: author, year of publication, baseline characteristics of participants, number of participants in each arm at study onset and completion, trial duration and treatment effects. We recorded the last measurement if multiple measurements were provided during the follow-up period.

Risk of bias of included studies

Two independent reviewers used a modified version of the Cochrane risk for bias tool in order to assess the risk of bias on the basis of randomization, allocation concealment, blinding, incomplete outcome data, selective reporting (by comparing the methods and results sections of the manuscript) as well as stopping early for benefit [18]. Reviewers chose among response options of "definitely yes", "probably yes", "probably no", and "definitely no" for each of the domains, with "definitely yes" and "probably yes" ultimately assigned low risk of bias and "definitely no" and "probably no" assigned high risk of bias [19]. For eligibility and risk of bias, reviewers resolved disagreements by discussion.

Quality assessment of bodies of evidence

Quality assessment of direct evidence. We assessed the quality of evidence in effect estimates for each outcome as high, moderate, low or very low using the GRADE rating system [20]. In the GRADE system, RCTs begin as high quality evidence, but may be rated down by one or more of five categories of limitations [19]: risk of bias, precision, consistency, directness and publication bias [21].

Clinical heterogeneity was assessed in terms of differences in population, intervention, outcomes and settings (primary vs secondary vs tertiary care settings) and was used to judge directness. Statistical heterogeneity was assessed by visual inspection of forest plots for the degree of proximity in point estimates and overlap in 95% confidence intervals (95% CIs) and by the Chi-Square test of homogeneity, and the I^2 statistic for which 0–40% may be unimportant heterogeneity, 30–60% moderate, 50–90% substantial and 75–100% considerable heterogeneity [22].

With respect to precision, we assessed the width of the 95% CIs for inclusion of values that would alter clinical decision-making [23]. Publication bias was considered undetected unless the effect measure was asymmetrically distributed around the pooled effect [24, 25].

After considering these reasons for rating down, we judged the overall confidence in estimates of effect for all-cause mortality, cardiovascular mortality and hospitalization for each direct comparison as follows: 'high' quality of evidence (we are very confident that the true effect lies close to that of the estimate of the effect); 'moderate' quality of evidence (we are moderately confident in the effect estimate and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); 'low' quality of evidence

(our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); and 'very low' quality of evidence (we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect) [19].

Quality assessment of indirect evidence. We also applied the GRADE methodology to rate the confidence of indirect effect estimates. Indirect effect estimates are calculated from available 'loops' of evidence, which includes first order (based on a single common comparator treatment, the difference between the treatment A and B is based on comparisons of A and C as well as B and C, as with $\hat{d}^{I}_{AB} = \hat{d}^{D}_{AC} - \hat{d}^{D}_{BC}$) or higher order (more than one intervening treatment connecting the two interventions that constitute the comparison of interest) [26].

To judge the quality of the indirect comparison we chose the first order loop with the lowest variance in those without a common comparator. The quality of evidence rating for indirect comparisons was the lower of the ratings of quality for the two direct estimates that contribute to the first order loop of the indirect comparison. For instance, if one of the direct comparison was rated as low and other was rated as moderate evidence, we rated the quality of indirect evidence as low [27].

We also considered further rating down the quality of the indirect comparison for intransitivity. The transitivity assumption implies similarity of trials in terms of population, intervention (type and dosing frequency), settings and trial methodology. If the transitivity assumption was violated, we rated down indirect comparison one further level.

Quality assessment of NMA mixed estimates. If both direct and indirect evidence were available, the NMA mixed estimate quality rating came from the higher quality of the two. We also considered coherence (degree of consistency between direct and indirect effect estimates) in our final quality rating. We examined the magnitude of the difference between direct and indirect effect estimates and the extent to which confidence intervals overlapped and rated down confidence the quality of the NMA effect if we found large incoherence defined as inconsistency between direct and indirect effect estimates.

Asymmetrical funnel plots indicate reporting biases due to publication bias or small study effect [24]. We employed the comparison-adjusted funnel plot using fixed effect models. The black dashed line indicates the estimated small-study effects line—also called the regression line.

Thus, the quality of evidence for each paired network comparison included assessment of transitivity (similarity between populations, interventions, comparators and outcomes of trials in the direct comparisons that contribute to the indirect comparison estimate); coherence (similarity between direct and indirect effects); and homogeneity (similarity of effect estimates between trials in direct comparisons).

Data synthesis and statistical analysis

For conventional meta-analyses (all individual paired comparisons and comparison of calcium versus NCBPBs for all-cause and cardiovascular mortality, and for hospitalization) we calculated risk rations (RRs) and 95% confidence intervals (CIs) using random effects models. For our NMA, we synthesised the results from RCTs using the frequentist approach. The relevant analysis was a seven-node network meta-analysis (NMA) (sevelamer hydrochloride vs. calcium carbonate vs. lanthanum carbonate vs. iron vs. phosphorus restricted diet vs. placebo vs. sevelamer-plus-calcium-plus-magnesium). We report pooled RRs for direct, indirect and mixed network meta-analysis estimates and associated 95% CIs. We present the direct, indirect and network effect estimates. We summarized the overall network heterogeneity using the global test [28]. We used the inconsistency factor for the assessment of loop inconsistency in our

triangular loop [28–30]. The contribution plot indicates the contribution of each direct comparison to indirect and network estimates [28].

To estimate absolute benefit for statistically significant mortality benefit we used the median baseline risk of all studies with a calcium arm and applied the relative effect from the NMA mixed comparisons. We performed all analyses with Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) using the **mvmeta** command.

Results

Trial identification

Our updated search yielded 1190 citations, of which 71 were retrieved for full review; 15 RCTs proved eligible with 3576 (Fig 1). We included 13 RCTs from the previous systematic review [16]. Therefore, we included a total of 28 studies with 8335 participants; 25 provided data that allowed inclusion in our quantitative synthesis (Fig 1).

Trial and population characteristics

S1 Table in the supporting information presents the characteristics of all eligible studies, of which 25 reported all-cause mortality [31–58]. Seven of the 28 studies (25%) included non-dialysis patients. Year of publication ranged from 2002 to 2015. Most of the trials were multinational (11 studies) and all were multi-centre. The mean age of participants ranged from 47 to 69.

Our assessment indicated low risk of bias for missing data and selective reporting in about 75% of the trials; blinding was adequate in only about 25% of the studies (Fig 2 and S1 Fig in the supporting information).

Seven-node analysis

Fig 3 presents the network geometry of all-cause mortality and provides 8 direct and 13 indirect comparisons for seven interventions: sevelamer, lanthanum, iron, calcium, phosphorus restricted diet, sevelamer-plus-calcium-plus-magnesium and placebo. One trial compared three treatments [59]. Pairwise comparisons demonstrated I^2 values from 0% to 81.6% (Table 1).

For the seven-node comparison, Table 1 presents direct comparisons that contributed to the NMA, Table 2 the indirect comparisons with the associated quality of evidence ratings, and Table 3 the summary of results and quality of evidence. Moderate quality of evidence suggests higher mortality with calcium versus sevelamer (NMA RR, 1.89 [95% CI, 1.02 to 3.50]). Given a baseline mortality of 23% over a year this relative effect translates into an absolute mortality increase with calcium of 43 per 1000 (95% CI 23 to 80 more. Confidence intervals for all other comparisons included no effect. Fig 4 presents the confidence interval plot. S2 Fig in the supporting information depicts the contribution plot indicating the contribution of each direct comparison to indirect and network estimates.

S3 Fig depicts the comparison-adjusted funnel plot using random effect models. The comparison-adjusted funnel plot does not indicate the presence of small study effects.

Additionally, using visual interpretation, we compared RRs and 95% CIs from the consistency and inconsistency models (Table 3). The proximity of the RRs and overlap between 95% CIs were not satisfactory for the comparisons of calcium with sevelamer and iron with sevelamer. We therefore rated down quality of network evidence for incoherence.

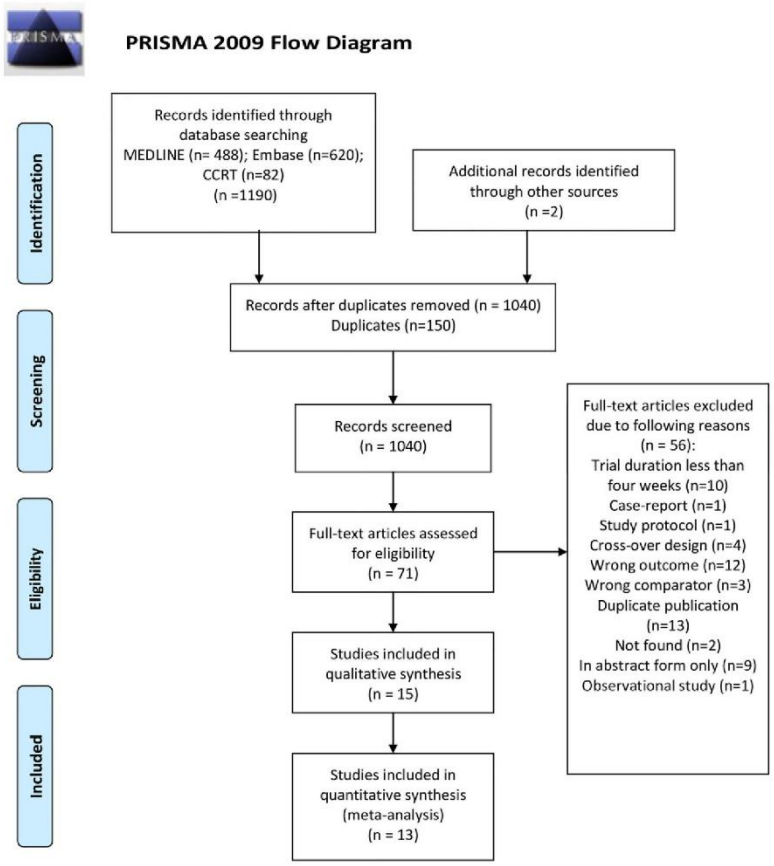

Fig 1. PRISMA Flow Diagram of Search Results. *From*: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit www.prisma-statement.org.

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Two-node analysis: Calcium-based phosphate binders versus non-calcium based phosphate binders

S4, S5 and S6 Figs present the results of our conventional meta-analysis of all-cause mortality, cardiovascular mortality and hospitalization. Fifteen studies that randomized patients to calcium versus NCBPBs showed an increase in all-cause mortality with calcium (RR 1.760 [95% CI, 1.21 to 2.56], moderate quality evidence) (S4 Fig). The outcome of cardiovascular mortality was based on five studies and did not prove significant (RR, 2.54 [95% CI, 0.67 to 9.62; low quality of evidence) (S5 Fig). The results of 3 studies suggest higher, although non-significant,

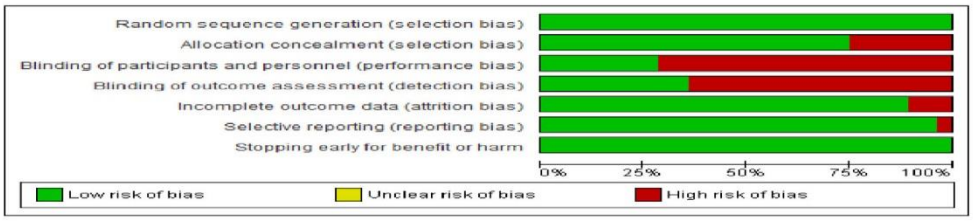

Fig 2. Risk of bias assessment; outcome: all-cause mortality. Legend: Our assessment indicated low risk of bias for missing data in about 75% of trials. The level of blinding was adequate in only about 25% of the studies.

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hospitalization with calcium than NCBPBs (RR, 1.28 [95% CI,0.94 to 1.74]; moderate quality of evidence) (S6 Fig). S2 Table presents the GRADE evidence profile associated with these results.

Discussion

Summary of main results

The results of this NMA provide moderate quality evidence that calcium causes higher rates of mortality versus sevelamer among CKD-MBD patients (NMA RR, 1.89 [95% CI, 1.02to 3.50]). This is consistent with our finding of an increase in mortality with calcium versus NCBPB in general from a conventional meta-analysis, and translates into an absolute increase in mortality

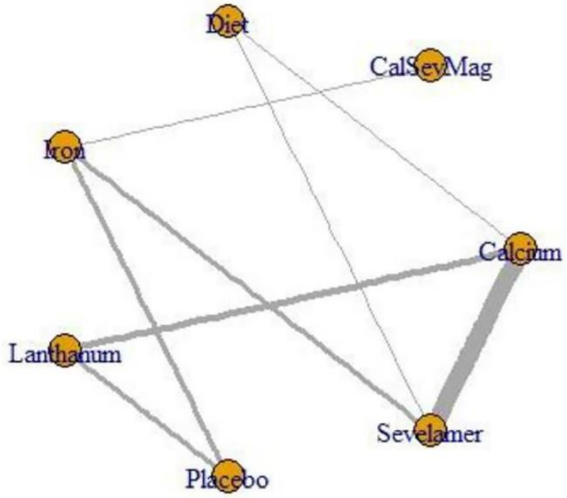

Fig 3. The network map of seven-node analysis; outcome: all-cause mortality. Legend: Edges are weighted by precision.

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Table 1. GRADE quality assessment of direct evidence of each pairwise treatment comparison for all-cause mortality.

Treatment comparison	Number of head-to-head trials; n	Study Limitations	Precision	Consistency	Directness	Publication bias	Overall quality of evidence	Direct estimate[2]; RR (95% CI)	Absolute effect per 100 treated (95% CI)
Sevelamer vs. Calcium	10;3665	Not serious	Not serious	Serious (I^2, 81.6%)	Not serious	Not serious	Moderate	1.89 (1.02 to 3.50)	43 cases more (23 more to 80 more)
Sevelamer vs. Iron	3; 1303	Serious (due to allocation concealment)	Serious	Not serious (I^2, 0%)	Not serious	Not serious	Low	1.24 (0.48 to 3.18)	28 cases more (11less to 73 more)
Sevelamer vs. diet	1; 60	Not serious	Very serious[1]	Not serious	Not serious	Not serious	Low	0.33 (0.01 to 7.87)	8 cases less (1less to 181 more)
Lanthanum vs. Calcium	4; 1494	Serious (due to allocation concealment)	Not serious	Not serious (I^2, 0%)	Not serious	Not serious	Moderate	1.17 (0.96 to 1.43)	27 cases more (22 less to 33 more)
Lanthanum vs Placebo	3; 408	Not serious	Very serious[1]	Not serious (I^2, 0%)	Not serious	Not serious	Low	0.92 (0.11 to 7.31)	21 cases less (3 less to 168 more)
Calcium vs diet	1; 60	Not serious	Very serious[1]	Not serious (I^2, 0%)	Not serious	Not serious	Low	0.33 (0.01 to 7.87)	8 cases less (1 less to 181more)
Iron vs. placebo	3; 561	Not serious	Very serious[1]	Not serious (I^2, 0%)	Not serious	Not serious	Low	3.04 (0.40 to 23.31)	64 cases more (9 less to 529 more)
Iron vs. Sevelamer-plus-calcium-magnesium	1; 441	Not serious	Serious	Not serious	Not serious	Not serious	Moderate	0.81 (0.35 to 1.87)	19 less (8 cases less to 43 more)

For domains "Study Limitations", "Precision", "Consistency", and "Directness": Not serious, Serious, or Very serious issues. For the domain "Publication bias": Not likely or Likely to exist. Reasons are provided when rating down. All direct comparisons begin with a "High" rating.

[1]Rated down two levels for imprecision;

[2]We employed random effect models.

CI: Confidence interval; RR: Risk ratio.

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of 43 cases per 1000 (95% CI 23 to 80 more). Although not statistically significant, conventional meta-analysis results also suggest an increase in cardiovascular mortality and hospitalization with calcium versus NCBPBs.

Underlying hypothesis related to the link between type of phosphate binders and the cardiovascular risk

Vascular smooth muscle cells can assume an osteoblast phenotype through phosphorous mediated and non-phosphorous mediated systems [2,62–64]. This leads to an increase in vascular stiffness, afterload, and promotes left ventricular hypertrophy [2, 60–62]. Elevated calcium, parathyroid hormone and parathyroid hormone-like peptides provoke and promote the abnormal calcification process and cardiovascular diseases[63, 64]. Calcium-based phosphate binders can cause hypercalcemia and contribute to cardiovascular calcification[13]. This condition eventually leads to cardiovascular mortality which is the leading cause of death in patients with CKD[65, 66]. Recently, a systematic review of the 11 RCTs including 1501 patients found that lanthanum reduced the incidence of hypercalcemia relative to calcium [67].

Table 2. GRADE confidence assessments of indirect estimates per pairwise treatment comparison for all-cause mortality.

	Treatment comparisons	Common comparator treatment in thedominant first order loop (in the absence of the first order loop, higher order loop with the lowest variance)	GRADE of first contributing direct comparison	GRADE of second contributing direct comparison	Assessment of transitivity	Final GRADE of Indirect Comparison
1	Sevelamer vs. placebo	Iron	Low (sevelamer vs. iron)	Low (placebo vs. iron)	Not serious	Low
2	Sevelamer vs. Lanthanum	Calcium	Moderate (sevelamer vs. calcium)	Moderate (lanthanum vs. calcium)	Not serious	Moderate
3	Sevelamer vs. sevelamer plus calcium plus magnesium	Iron	Low (sevelamer vs. iron)	Moderate (iron vs. sevelamer-plus-calcium)	Not serious	Low
4	Calcium vs. placebo	Lanthanum	Moderate (calcium vs. lanthanum)	Low (lanthanum vs. placebo)	Not serious	Low
5	Calcium vs. Iron	Lanthanum placebo	Moderate (calcium vs. lanthanum)	Low (placebo vs. iron)	Not serious	Low
6	Calcium vs. sevelamer plus calcium plus magnesium	Lanthanum placebo	Moderate (calcium vs. lanthanum)	Low (placebo vs. iron)	Not serious	Low
7	Placebo vs. diet	Lanthanum placebo	Low (Calcium vs. diet)	Low (Lanthanum vs. placebo)	Not serious	Low
8	Placebo vs. sevelamer plus calcium plus magnesium	Iron	Low (placebo vs iron)	Moderate (Iron vs. sevelamer plus calcium)	Not serious	Low
9	Lanthanum vs. Iron	Placebo	Low (iron vs. placebo)	Low (lanthanum vs. placebo)	Not serious	Low
10	Lanthanum vs. diet	Calcium	Moderate (calcium vs. lanthanum)	Low (calcium vs. diet)	Not serious	Low
11	Lanthanum vs. sevelamer plus calcium plus magnesium	Lanthanum placebo	Moderate (calcium vs. lanthanum)	Low (placebo vs. iron)	Not serious	Low
12	Iron vs. diet	Sevelamer	Low (sevelamer vs. diet)	Low (sevelamer vs. iron)	Not serious	
13	Diet vs. sevelamer plus calcium plus magnesium	Lanthanum placebo	Low (Lanthanum vs. placebo)	Low (placebo vs. iron)	Not serious	Low

A single first order loop for each pairwise comparison is used to GRADE indirect estimates. All indirect comparisons begin with the lower of the two contributing direct estimates and undergo an assessment of transitivity. For the transitivity assumption: Not serious or serious to exist.

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Comparative effectiveness studies of NCBPBs have used calcium as the comparator [16]. While our meta-analysis, and that of Jamal et el. suggests increased all-cause mortality with calcium compared with NCBPBs [16], this apparent benefit may be due to harmful effects of calcium, rather than beneficial effects with NCBPBs. The harmful effect of calcium is consistent with the role of calcium in the pathophysiology of vascular calcification [63, 64] and is also supported by studies in the general population suggesting increased cardiovascular risk with higher levels of calcium exposure [68].

Whether the increase in mortality with calcium versus NCBPBs represents a harmful effect of calcium versus no treatment for hyperphosphatemia, or a beneficial effect of NCBPBs,

Table 3. Direct, indirect, and NMA estimates of all-cause mortality with 95% confidence intervals and GRADE assessments for each pairwise comparison within the network of seven phosphate binders.

	Comparison	Direct estimate; RR (95% CI)	Quality of evidence	Indirect estimate; RR (95% CI)	Quality of evidence	NMA estimate; RR (95% CI)	Quality of evidence
1	Placebo vs. sevelamer	Not available	Not available	1.38(0.11 to 17.44)	Low	1.38(0.11 to 17.44)	Low
2	Lanthanum vs. sevelamer	Not available	Not available	1.80 (0.47 to 6.82)	Moderate	1.80 (0.47 to 6.82)	Moderate
3	CalSevMag vs. sevelamer	Not available	Not available	0.76 (0.27 to 2.15)	Low	0.76 (0.27 to 2.15)	Low
4	Placebo vs. calcium	Not available	Not available	0.72 (0.06 to 9.10)	Low	0.72 (0.06 to 9.10)	Low
5	Iron vs. Calcium	Not available	Not available	0.89 (0.41 to 1.95)	Low	0.89 (0.41 to 1.95)	Low
6	CalSevMag vs. calcium	Not available	Not available	0.40 (0.13 to 1.19)	Low	0.40 (0.13 to 1.19)	Low
7	Diet vs. placebo	Not available	Not available	0.69 (0.03 to 14.3)	Low	0.69 (0.03 to 14.3)	Low
8	Placebo vs. CalSevMag	Not available	Not available	1.83 (0.12 to 28)	Low	1.83 (0.12 to 28)	Low
9	Iron vs. lanthanum	Not available	Not available	0.95 (0.26 to 3.41)	Low	0.95 (0.26 to 3.41)	Low
10	Diet vs. lanthanum	Not available	Not available	0.53 (0.09 to 3.25)	Low	0.53 (0.09 to 3.25)	Low
11	CalSevMag vs. lanthanum	Not available	Not available	0.42 (0.12 to 1.47)	Low	0.42 (0.12 to 1.47)	Low
12	Diet vs. iron	Not available	Not available	0.56 (0.09 to 3.4)	Low	0.56 (0.09 to 3.4)	Low
13	Diet vs. CalSevMag	Not available	Not available	1.26 (0.34 to 4.69)	Low	1.26 (0.34 to 4.69)	Low
14	Calcium vs. sevelamer	1.89 (1.02 to 3.50)	Moderate	0.51 (0.03 to 9.89)	Moderate	1.35 (1.14 to 1.60)	Low[1]
15	Iron vs. sevelamer	1.24 (0.48 to 3.18)	Low	0.81 (0.05–11.94)	Low	1.71 (0.71 to 4.11)	Very low[1]
16	Diet vs. sevelamer	0.33 (0.01 to 7.87)	Low	0.73 (0.23 to 2.35)	Low	0.95 (0.18 to 5.11)	Low
17	Lanthanum vs. Calcium	1.17 (0.96 to 1.43)	Moderate	1.03 (0.17 to 6.33)	Moderate	0.94 (0.25 to 3.55)	Moderate
18	Placebo vs. lanthanum	0.92 (0.11 to 7.31)	Low	0.50 (0.02 to 16.08)	Low	0.77 (0.04 to 13.22)	Low
19	Diet vs.calcium	0.33 (0.01 to 7.87)	Low	0.47 (0.07 to 2.96)	Low	0.50 (0.09 to 2.77)	Low
20	Placebo vs.iron	3.04 (0.40 to 23.31)	Low	0.56 (0.03 to 12.24)	Low	0.81 (0.06 to 11.46)	Low
21	CalSevMag vs. Iron	0.81 (0.35 to 1.87)	Moderate	0.41 (0.09 to 1.87)	Moderate	0.44 (0.13 to 1.53)	Moderate

[1]Rated down one level for incoherence.

CalSevMag: Calcium and sevelamer and magnesium; CI: Confidence interval; RR: Risk ratio.

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should ideally be informed by trials of NCBPBs versus placebo, no treatment, or a phosphorus restricted diet. Unfortunately, our NMA provides little information in this regard: although we were able to adduce estimates, the confidence intervals are sufficiently wide as to be uninformative (Table 3).

Thus, additional evidence is required to address this issue. Potential benefits of NCBPBs may be particularly difficult to prove in the context of a moderate-sized randomized trial. Since vascular medial calcification is a result of cellular differentiation, the degree to which it is reversible is likely limited. Long nocturnal hemodialysis, for example, provides excellent biochemical control and can induce negative calcium and phosphorus balance, but does not consistently promote regression of vascular calcification [69–71]. Therefore, in clinical trials with relatively short follow-up, and high attrition rates, one might not expect to see significant reversal of established vascular calcification or major effects on cardiovascular and all-cause mortality.

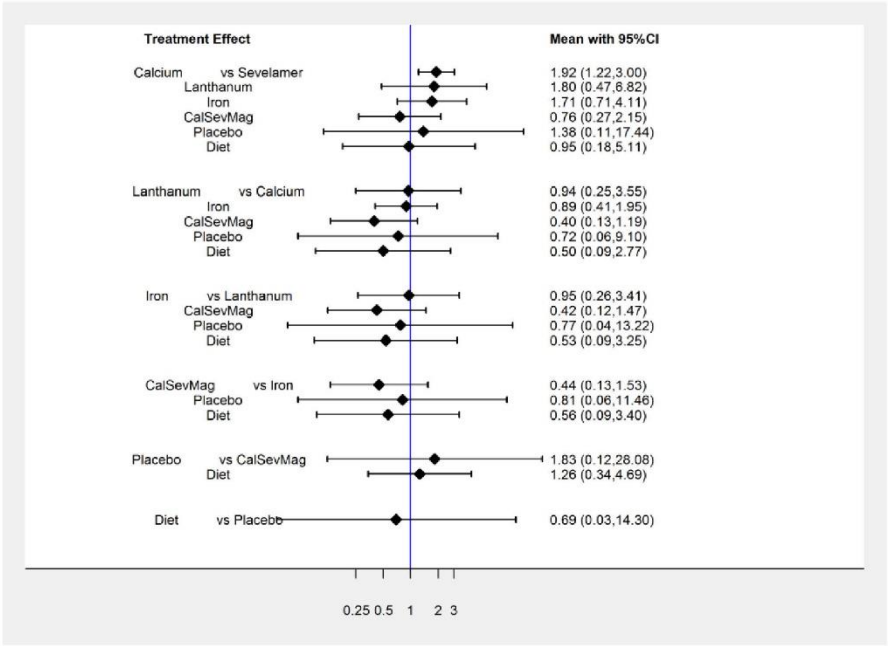


Fig 4. The predictive interval consistency plot from the consistency model of seven-node analysis; outcome: all-cause mortality without a reference standard.

doi:10.1371/journal.pone.0156891.g004

Consistency of our findings with the existing evidence

Our finding that calcium leads to increased mortality versus NCBPBs is congruent with results reported with previous systematic reviews using head-to-head comparisons [16]. Although there are strong associations between calcium, phosphate and parathyroid hormone with survival and cardiovascular events, these measures may simply represent vigilance of care and are not necessarily causally related to these outcomes [72, 73]. A recent systematic review examined the correlation between CKD-MBD biochemical markers and mortality and indicated a significant negative correlation between parathyroid hormone and all-cause mortality [74]. Nevertheless, the correlation between serum calcium and phosphorus concentration and mortality did not prove significant [74].

Strengths and limitations of this study

Strengths of our review include explicit eligibility criteria, a comprehensive search, and independent duplicate assessment of eligibility. Our analysis incorporates the latest developments in NMA statistical analysis and we applied the recently developed GRADE approach to NMA that included assessment of transitivity assumptions for indirect evidence as well as coherence

for combining direct and indirect evidence. This is the first systematic review and network meta-analysis that includes iron-based phosphate binders.

The main weakness of our study was limited statistical power for a number of comparisons. With the exception of sevelamer, we were unable to establish the impact of individual NCBPBs on all-cause mortality in relation to calcium, nor were we able to inform the impact of any NCBPB on mortality relative to placebo, or phosphorus diet restriction.

As previously mentioned, inadequate follow-up time in some of the trials was another weakness of our data. Overall, the lack of long-term outcome data of patients with CKD-MBD necessitates conduct of large RCTs with longer follow-up. Another option would be observational studies with longer follow-up that capture mortality if long-term RCTs are unfeasible.

Conclusions and Future Directions

CKD-MBD is a systematic condition defined by an increase in cardiovascular calcifications and bone fragility [75]. A consensus exists regarding the need for CKD-MBD treatment to maintain guideline recommended targets for calcium, phosphorus and parathyroid hormone in the presumption that meeting these targets will improve quality and quantity of life [76].

Our systematic review suggests that calcium, as compared to NCBPBs in general and sevalamer in particular, increases all-cause mortality among CKD-MBD patients. Future studies should start at earlier stages of CKD, before irreversible calcification is established.

The finding of higher mortality with calcium than alternative phosphate binders, and the possibility that this increase in mortality represents an adverse effect of calcium rather than any benefit with NCBPB, raises serious questions about the advisability, and perhaps the ethical acceptability, of calcium administration in patients with CKD-MBD.

Supporting Information

S1 Fig. Risk of bias assessment; outcome: all-cause mortality. Low risk of bias for missing data and selective reporting in about 75% of the trials.
(TIF)

S2 Fig. Contribution plot of phosphate binders for CKD-MBD; outcome: all-cause mortality.
(TIF)

S3 Fig. The comparison-adjusted funnel plot for the phosphate binder network; outcome: all-cause mortality.
(TIF)

S4 Fig. Forest plot, calcium-based versus non-calcium-based phosphate binders; outcome: all-cause mortality.
(TIF)

S5 Fig. Forest plot, calcium based vs. non-calcium based phosphate binders; outcome: cardiovascular mortality.
(TIF)

S6 Fig. Forest plot, calcium based vs. non-calcium based phosphate binders; outcome: hospitalization.
(TIF)

S1 File. PRISMA NMA checklist.
(DOCX)

S2 File. Search strategies.
(DOCX)

S1 Table. Study Characteristics.
(DOCX)

S2 Table. GRADE quality assessments of direct evidence per pairwise treatment comparison for all-cause mortality, cardiovascular mortality and hospitalization due to any reason.
(DOCX)

Author Contributions

Conceived and designed the experiments: NS GG JB LT AI NAD CJL AA RA GN JPDM. Analyzed the data: NS. Contributed reagents/materials/analysis tools: NS LT GG AI. Wrote the paper: NS. Critically revised the manuscript: NS GG JB LT NAD CJL AI AA RA GN JPDM. Read and approved the final manuscript: NS GG JB LT NAD CJL AI AA RA GN JPDM. Interpretation of data: NS GG JB LT AI NAD CJL AA RA GN JPDM.

References

1. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Annals of internal medicine. 2003; 139(2):137–47. Epub 2003/07/16. PMID: 12859163.
2. Moe SM. Vascular calcification and renal osteodystrophy relationship in chronic kidney disease. European Journal of Clinical Investigation. 2006; 36:51–62. doi: 10.1111/j.1365-2362.2006.01665.x PMID: 16884398
3. Ibels LS, Alfrey AC, Huffer WE, Craswell PW, Anderson JT, Weil R 3rd. Arterial calcification and pathology in uremic patients undergoing dialysis. Am J Med. 1979; 66(5):790–6. Epub 1979/05/01. PMID: 443254.
4. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000; 58(1):353–62. Epub 2000/07/08. doi: 10.1046/j.1523-1755.2000.00173.x PMID: 10886582.
5. Sanchez-Perales C, Vazquez Ruiz de Castroviejo E, Garcia-Cortes MJ, Biechy Mdel M, Gil-Cunquero JM, Borrego-Hinojosa J, et al. Valvular calcifications at the start of dialysis predict the onset of cardiovascular events in the course of follow-up. Nefrologia. 2015; 35(2):157–63. Epub 2015/08/25. PMID: 26300509.
6. Rebic D, Rasic S, Hamzic-Mehmedbasic A, Dzemidzic J, Kurtalic E. Valvular calcification and left ventricular modifying in peritoneal dialysis patients. Ren Fail. 2015:1–7. Epub 2015/08/15. PMID: 26275111.
7. Wilkieson TJ, Rahman MO, Gangji AS, Voss M, Ingram AJ, Ranganath N, et al. Coronary artery calcification, cardiovascular events, and death: a prospective cohort study of incident patients on hemodialysis. Can J Kidney Health Dis. 2015; 2:29. Epub 2015/08/14. doi: 10.1186/s40697-015-0065-6 PMID: 26269747; PubMed Central PMCID: PMCPMC4534029.
8. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998; 31(4):607–17. Epub 1998/04/08. PMID: 9531176.
9. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006; 1(4):825–31. Epub 2007/08/21. doi: 10.2215/cjn.02101205 PMID: 17699293.
10. O'Seaghdha CM, Hwang SJ, Muntner P, Melamed ML, Fox CS. Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease. Nephrol Dial Transplant. 2011; 26(9):2885–90. Epub 2011/02/05. doi: 10.1093/ndt/gfq808 PMID: 21292817; PubMed Central PMCID: PMCPMC3175050.
11. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007; 22(10):2909–16. Epub 2007/05/23. doi: 10.1093/ndt/gfm286 PMID: 17517792.
12. Cernaro V, Santoro D, Lacquaniti A, Costantino G, Visconti L, Buemi A, et al. Phosphate binders for the treatment of chronic kidney disease: role of iron oxyhydroxide. International journal of nephrology and

renovascular disease. 2016; 9:11–9. Epub 2016/02/20. doi: 10.2147/ijnrd.s78040 PMID: 26893577; PubMed Central PMCID: PMCPMC4749089.

13. Locatelli F, Del Vecchio L, Violo L, Pontoriero G. Phosphate binders for the treatment of hyperphosphatemia in chronic kidney disease patients on dialysis: a comparison of safety profiles. Expert opinion on drug safety. 2014; 13(5):551–61. Epub 2014/04/08. doi: 10.1517/14740338.2014.907791 PMID: 24702470.

14. Cozzolino M, Funk F, Rakov V, Phan O, Teitelbaum I. Preclinical Pharmacokinetics, Pharmacodynamics and Safety of Sucroferric Oxyhydroxide. Current drug metabolism. 2014; 15(10):953–65. Epub 2015/02/07. PMID: 25658128.

15. Lee CT, Wu IW, Chiang SS, Peng YS, Shu KH, Wu MJ, et al. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. J Nephrol. 2015; 28(1):105–13. Epub 2014/05/21. doi: 10.1007/s40620-014-0108-6 PMID: 24840781.

16. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet (London, England). 2013; 382 (9900):1268–77. Epub 2013/07/23. doi: 10.1016/s0140-6736(13)60897-1 PMID: 23870817.

17. Group. KDIGOKCW. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter. 2013;(3:):1–150.

18. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society Series A, (Statistics in Society). 2009; 172(1):137–59. Epub 2009/04/22. doi: 10.1111/j.1467-985X.2008.00552.x PMID: 19381330; PubMed Central PMCID: PMCPMC2667312.

19. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008; 336(7650):924–6. Epub 2008/04/26. doi: 10.1136/bmj.39489.470347.AD PMID: 18436948; PubMed Central PMCID: PMCPmc2335261.

20. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004; 328(7454):1490. Epub 2004/06/19. doi: 10.1136/bmj.328.7454.1490 PMID: 15205295; PubMed Central PMCID: PMCPMC428525.

21. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013; 66(2):158–72. Epub 2012/05/23. doi: 10.1016/j.jclinepi.2012.01.012 PMID: 22609141.

22. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. J Clin Epidemiol. 2011; 64(12):1294–302. Epub 2011/08/02. doi: 10.1016/j.jclinepi.2011.03.017 PMID: 21803546.

23. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. Journal of clinical epidemiology. 2011; 64(12):1283–93. Epub 2011/08/16. doi: 10.1016/j.jclinepi.2011.01.012 PMID: 21839614.

24. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Research Synthesis Methods. 2012; 3(2):161–76. doi: 10.1002/jrsm.57 PMID: 26062088

25. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. J Clin Epidemiol. 2011; 64(12):1277–82. Epub 2011/08/02. doi: 10.1016/j.jclinepi.2011.01.011 PMID: 21802904.

26. Lumley T. Network meta-analysis for indirect treatment comparisons. Statistics in medicine. 2002; 21 (16):2313–24. Epub 2002/09/05. doi: 10.1002/sim.1201 PMID: 12210616.

27. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014; 349:g5630. doi: 10.1136/bmj.g5630 PMID: 25252733

28. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical Tools for Network Meta-Analysis in STATA. PLoS ONE. 2013; 8(10). doi: 10.1371/journal.pone.0076654 PMID: 24098547; PubMed Central PMCID: PMCPMC3789683.

29. Cosmai L, Gallieni M, Porta C. Renal toxicity of anticancer agents targeting HER2 and EGFR. J Nephrol. 2015; 28(6):647–57. doi: 10.1007/s40620-015-0226-9

30. Ng KP, Arnold J, Sharif A, Gill P, Townend JN, Ferro CJ. Cardiovascular actions of mineralocorticoid receptor antagonists in patients with chronic kidney disease: A systematic review and meta-analysis of randomized trials. JRAAS—Journal of the Renin-Angiotensin-Aldosterone System. 2015; 16(3):599–613. doi: 10.1177/1470320315575849

31. Barreto DV, Barreto Fde C, de Carvalho AB, Cuppari L, Draibe SA, Dalboni MA, et al. Phosphate binder impact on bone remodeling and coronary calcification—results from the BRiC study. Nephron Clinical practice. 2008; 110(4):c273–83. Epub 2008/11/13. doi: 10.1159/000170783 PMID: 19001830.

32. Block GA, Fishbane S, Rodriguez M, Smits G, Shemesh S, Pergola PE, et al. A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD Stages 3–5. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2015; 65(5):728–36. Epub 2014/12/04. doi: 10.1053/j.ajkd.2014.10.014 PMID: 25468387.

33. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney international. 2007; 71(5):438–41. Epub 2007/01/04. doi: 10.1038/sj.ki.5002059 PMID: 17200680.

34. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, et al. Effects of phosphate binders in moderate CKD. Journal of the American Society of Nephrology: JASN. 2012; 23(8):1407–15. Epub 2012/07/24. doi: 10.1681/asn.2012030223 PMID: 22822075; PubMed Central PMCID: PMCPMC3402292.

35. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney international. 2002; 62(1):245–52. Epub 2002/06/26. doi: 10.1046/j.1523-1755.2002.00434.x PMID: 12081584.

36. de Francisco AL, Leidig M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2010; 25(11):3707–17. Epub 2010/06/10. doi: 10.1093/ndt/gfq292 PMID: 20530499; PubMed Central PMCID: PMCPmc2957591.

37. Di Iorio B, Bellasi A, Russo D. Mortality in kidney disease patients treated with phosphate binders: a randomized study. Clinical journal of the American Society of Nephrology: CJASN. 2012; 7(3):487–93. Epub 2012/01/14. doi: 10.2215/cjn.03820411 PMID: 22241819.

38. Di Iorio B, Molony D, Bell C, Cucciniello E, Bellizzi V, Russo D, et al. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2013; 62(4):771–8. Epub 2013/05/21. doi: 10.1053/j.ajkd.2013.03.023 PMID: 23684755.

39. Floege J, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney international. 2014; 86(3):638–47. Epub 2014/03/22. doi: 10.1038/ki.2014.58 PMID: 24646861; PubMed Central PMCID: PMCPmc4150998.

40. Kakuta T, Tanaka R, Hyodo T, Suzuki H, Kanai G, Nagaoka M, et al. Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2011; 57(3):422–31. Epub 2011/01/18. doi: 10.1053/j.ajkd.2010.10.055 PMID: 21239096.

41. Lee CT, Wu IW, Chiang SS, Peng YS, Shu KH, Wu MJ, et al. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. Journal of nephrology. 2015; 28(1):105–13. Epub 2014/05/21. doi: 10.1007/s40620-014-0108-6 PMID: 24840781.

42. Lee YK, Choi HY, Shin SK, Lee HY. Effect of lanthanum carbonate on phosphate control in continuous ambulatory peritoneal dialysis patients in Korea: a randomized prospective study. Clinical nephrology. 2013; 79(2):136–42. Epub 2012/12/06. doi: 10.5414/cn107362 PMID: 23211335.

43. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. Journal of the American Society of Nephrology: JASN. 2015; 26(2):493–503. Epub 2014/07/26. doi: 10.1681/asn.2014020212 PMID: 25060056; PubMed Central PMCID: PMCPmc4310662.

44. Ohtake T, Kobayashi S, Oka M, Furuya R, Iwagami M, Tsutsumi D, et al. Lanthanum carbonate delays progression of coronary artery calcification compared with calcium-based phosphate binders in patients on hemodialysis: a pilot study. Journal of cardiovascular pharmacology and therapeutics. 2013; 18(5):439–46. Epub 2013/04/26. doi: 10.1177/1074248413486355 PMID: 23615577.

45. Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2008; 51(6):952–65. Epub 2008/04/22. doi: 10.1053/j.ajkd.2008.02.298 PMID: 18423809.

46. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney international. 2007; 72(10):1255–61. Epub 2007/09/07. doi: 10.1038/sj.ki.5002518 PMID: 17805238.

47. Sadek T, Mazouz H, Bahloul H, Oprisiu R, El Esper N, El Esper I, et al. Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: an open-label, randomized study. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2003; 18(3):582–8. Epub 2003/02/14. PMID: 12584283.

48. Suki WN. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. Journal of renal nutrition: the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2008; 18(1):91–8. Epub 2007/12/20. doi: 10.1053/j.jrn.2007.10.019 PMID: 18089452.

49. Takahara Y, Matsuda Y, Takahashi S, Shigematsu T. Efficacy and safety of lanthanum carbonate in pre-dialysis CKD patients with hyperphosphatemia: a randomized trial. Clinical nephrology. 2014; 82 (3):181–90. Epub 2014/08/01. PMID: 25079863.

50. Takei T, Otsubo S, Uchida K, Matsugami K, Mimuro T, Kabaya T, et al. Effects of sevelamer on the progression of vascular calcification in patients on chronic haemodialysis. Nephron Clinical practice. 2008; 108(4):c278–83. Epub 2008/04/25. doi: 10.1159/000127361 PMID: 18434749.

51. Toussaint ND, Lau KK, Polkinghorne KR, Kerr PG. Attenuation of aortic calcification with lanthanum carbonate versus calcium-based phosphate binders in haemodialysis: A pilot randomized controlled trial. Nephrology (Carlton, Vic). 2011; 16(3):290–8. Epub 2011/02/24. doi: 10.1111/j.1440-1797.2010.01412.x PMID: 21342323.

52. Urena-Torres P, Prie D, Keddad K, Preston P, Wilde P, Wan H, et al. Changes in fibroblast growth factor 23 levels in normophosphatemic patients with chronic kidney disease stage 3 treated with lanthanum carbonate: results of the PREFECT study, a phase 2a, double blind, randomized, placebo-controlled trial. BMC nephrology. 2014; 15:71. Epub 2014/06/03. doi: 10.1186/1471-2369-15-71 PMID: 24885942; PubMed Central PMCID: PMCPmc4107721.

53. Wada K, Wada Y. Evaluation of aortic calcification with lanthanum carbonate vs. calcium-based phosphate binders in maintenance hemodialysis patients with type 2 diabetes mellitus: an open-label randomized controlled trial. Therapeutic apheresis and dialysis: official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2014; 18(4):353–60. Epub 2014/01/15. doi: 10.1111/1744-9987.12153 PMID: 24417760.

54. Wilson R, Zhang P, Smyth M, Pratt R. Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. Current medical research and opinion. 2009; 25(12):3021–8. Epub 2009/10/23. doi: 10.1185/03007990903399398 PMID: 19845495.

55. Wuthrich RP, Chonchol M, Covic A, Gaillard S, Chong E, Tumlin JA. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. Clinical journal of the American Society of Nephrology: CJASN. 2013; 8(2):280–9. Epub 2012/11/06. doi: 10.2215/cjn.08230811 PMID: 23124782; PubMed Central PMCID: PMCPmc3562865.

56. Xu J, Zhang YX, Yu XQ, Liu ZH, Wang LN, Chen JH, et al. Lanthanum carbonate for the treatment of hyperphosphatemia in CKD 5D: multicenter, double blind, randomized, controlled trial in mainland China. BMC nephrology. 2013; 14:29. Epub 2013/02/06. doi: 10.1186/1471-2369-14-29 PMID: 23379590; PubMed Central PMCID: PMCPmc3570485.

57. Yokoyama K, Akiba T, Fukagawa M, Nakayama M, Sawada K, Kumagai Y, et al. A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2014; 29(5):1053–60. Epub 2014/01/01. doi: 10.1093/ndt/gft483 PMID: 24376274.

58. Yokoyama K, Hirakata H, Akiba T, Fukagawa M, Nakayama M, Sawada K, et al. Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. Clinical journal of the American Society of Nephrology: CJASN. 2014; 9(3):543–52. Epub 2014/01/11. doi: 10.2215/cjn.05170513 PMID: 24408120; PubMed Central PMCID: PMCPmc3944759.

59. Spasovski G. Advances in pharmacotherapy for hyperphosphatemia in renal disease. Expert Opin Pharmacother. 2015; 16(17):2589–99. doi: 10.1517/14656566.2015.1092521

60. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, et al. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000; 87(7):E10–7. Epub 2000/09/29. PMID: 11009570.

61. Lee WH, Hsu PC, Chu CY, Chen SC, Lee HH, Lee MK, et al. Estimated Glomerular Filtration Rate and Systolic Time Intervals in Risk Stratification for Increased Left Ventricular Mass Index and Left Ventricular Hypertrophy. Medicine. 2016; 95(10):e2917. Epub 2016/03/11. PMID: 26962788.

62. Shroff RC, McNair R, Figg N, Skepper JN, Schurgers L, Gupta A, et al. Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. Circulation. 2008; 118(17):1748–57. Epub 2008/10/08. doi: 10.1161/circulationaha.108.783738 PMID: 18838561.

63. Yang H, Curinga G, Giachelli CM. Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization in vitro. Kidney Int. 2004; 66(6):2293–9. Epub 2004/12/01. doi: 10.1111/j.1523-1755.2004.66015.x PMID: 15569318.

64. Jono S, Nishizawa Y, Shioi A, Morii H. Parathyroid hormone-related peptide as a local regulator of vascular calcification. Its inhibitory action on in vitro calcification by bovine vascular smooth muscle cells. Arterioscler Thromb Vasc Biol. 1997; 17(6):1135–42. Epub 1997/06/01. PMID: 9194765.

65. Granata A, Clementi A, Virzi GM, Brocca A, de Cal M, Scarfia VR, et al. Cardiorenal syndrome type 4: From chronic kidney disease to cardiovascular impairment. European journal of internal medicine. 2016. Epub 2016/03/11. doi: 10.1016/j.ejim.2016.02.019 PMID: 26961461.

66. System USRD. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD2013.

67. Zhai CJ, Yang XW, Sun J, Wang R. Efficacy and safety of lanthanum carbonate versus calcium-based phosphate binders in patients with chronic kidney disease: a systematic review and meta-analysis. Int Urol Nephrol. 2015; 47(3):527–35. doi: 10.1007/s11255-014-0876-x PMID: 25399356.

68. Bolland MJ, Grey A, Reid IR. Calcium supplements and cardiovascular risk: 5 years on. Therapeutic Advances in Drug Safety. 2013; 4(5):199–210. doi: 10.1177/2042098613499790. PMC4125316. PMID: 25114781

69. Chan CT, Lovren F, Pan Y, Verma S. Nocturnal haemodialysis is associated with improved vascular smooth muscle cell biology. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2009; 24(12):3867–71. Epub 2009/09/19. doi: 10.1093/ndt/gfp495 PMID: 19762602.

70. Kooienga L. Phosphorus balance with daily dialysis. Seminars in dialysis. 2007; 20(4):342–5. Epub 2007/07/20. doi: 10.1111/j.1525-139X.2007.00304.x PMID: 17635826.

71. Toussaint N, Boddington J, Simmonds R, Waldron C, Somerville C, Agar J. Calcium phosphate metabolism and bone mineral density with nocturnal hemodialysis. Hemodialysis international International Symposium on Home Hemodialysis. 2006; 10(3):280–6. Epub 2006/06/30. doi: 10.1111/j.1542-4758.2006.00109.x PMID: 16805890.

72. Wu HC, Lee LC, Wang WJ. Associations among time-average mineral values, mortality and cardiovascular events in hemodialysis patients. Renal failure. 2015; 37(10):343–53. Epub 2015/09/17. doi: 10.3109/0886022x.2015.1087862 PMID: 26375759.

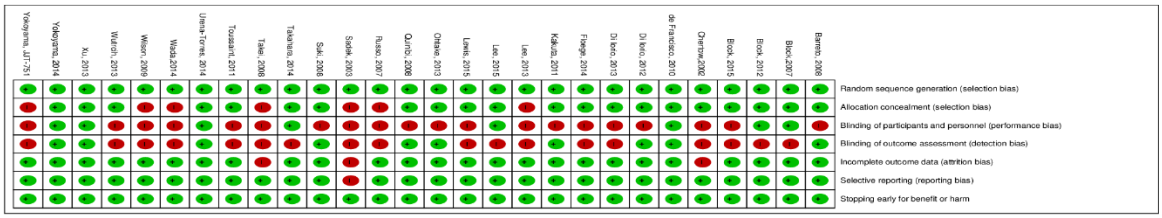
73. Tagawa M, Hamano T, Nishi H, Tsuchida K, Hanafusa N, Fukatsu A, et al. Mineral Metabolism Markers Are Associated with Myocardial Infarction and Hemorrhagic Stroke but Not Ischemic Stroke in Hemodialysis Patients: A Longitudinal Study. PloS one. 2014; 9(12):e114678. Epub 2014/12/11. doi: 10.1371/journal.pone.0114678 PMID: 25494334; PubMed Central PMCID: PMCPmc4262415.

74. Association of Drug Effects on Serum Parathyroid Hormone, Phosphorus, and Calcium Levels With Mortality in CKD: A Meta-analysis. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2015; 20(15):00633–2.

75. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006; 69(11):1945–53. PMID: 16641930.

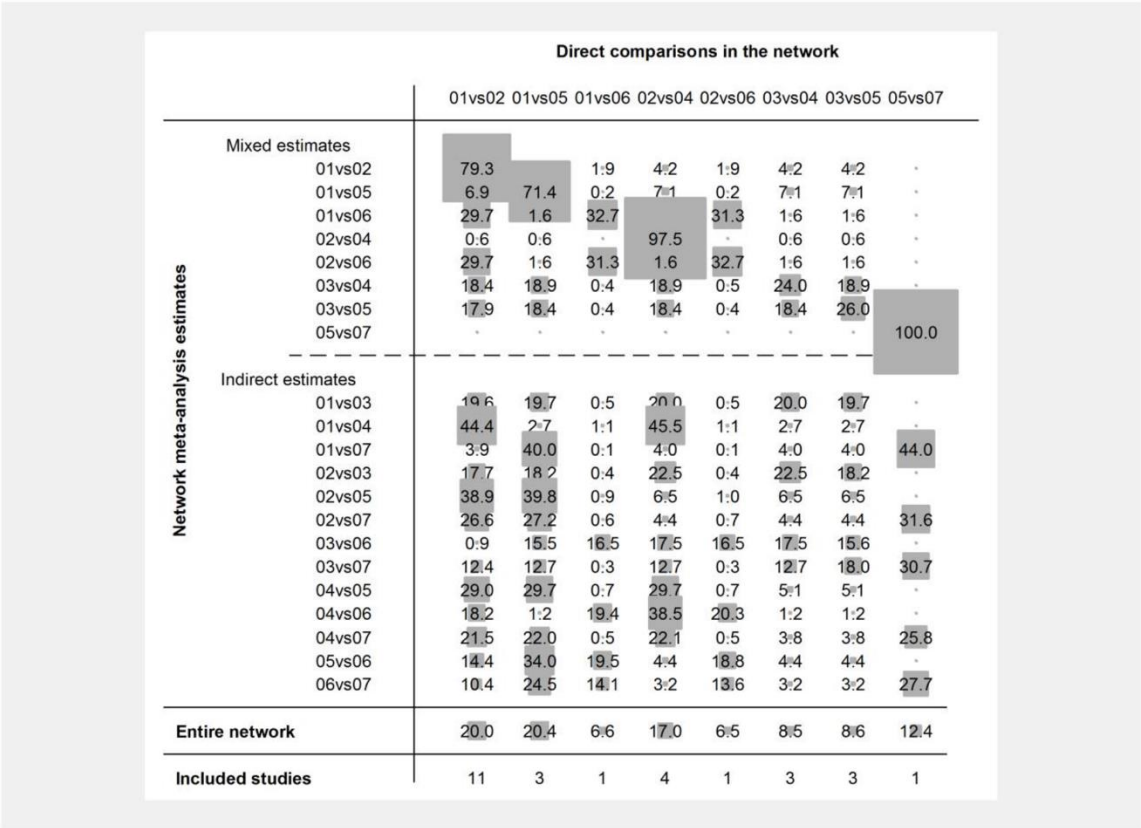
76. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol. 2011; 6(4):913–21. doi: 10.2215/CJN.06040710 PMID: 21454719.

S1 Figure. Risk of bias assessment; outcome: all-cause mortality



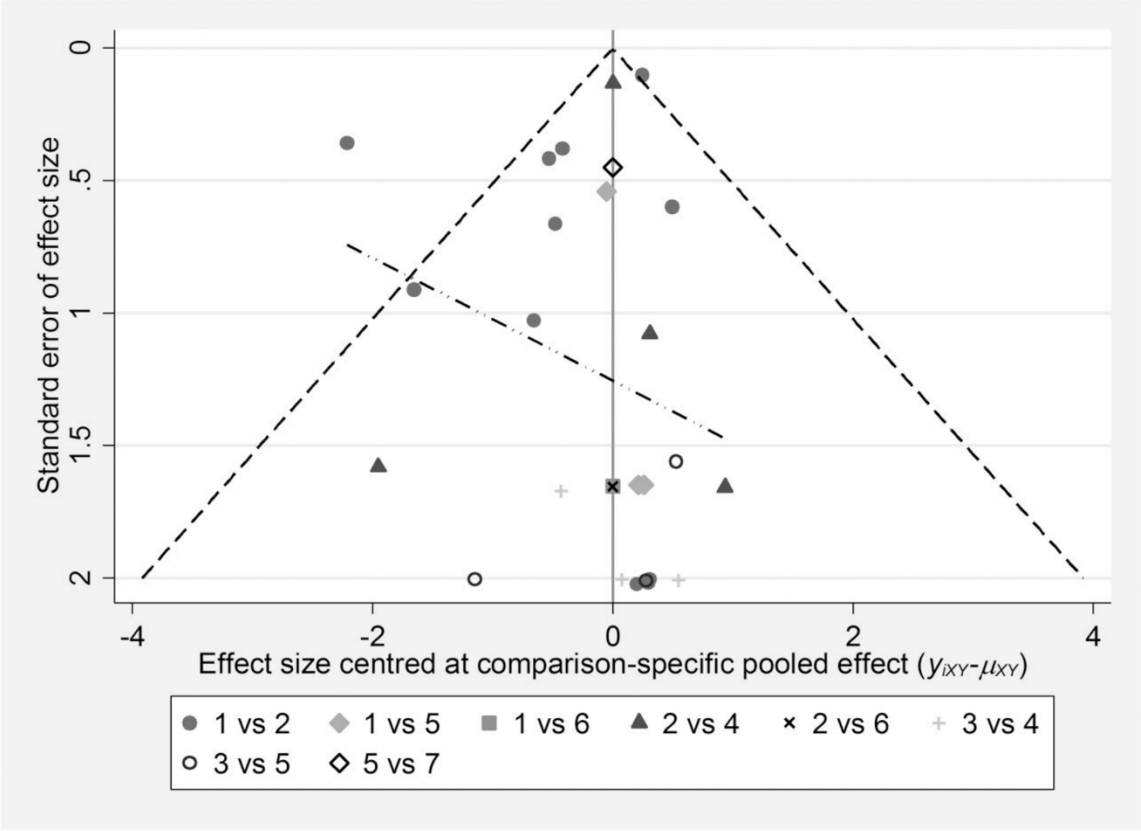
Legend: Low risk of bias for missing data and selective reporting in about 75% of the trials. The level of blinding was adequate in only about 25% of the studies.

S2 Figure. Contribution plot of phosphate binders for CKD-MBD; outcome: all-cause mortality.



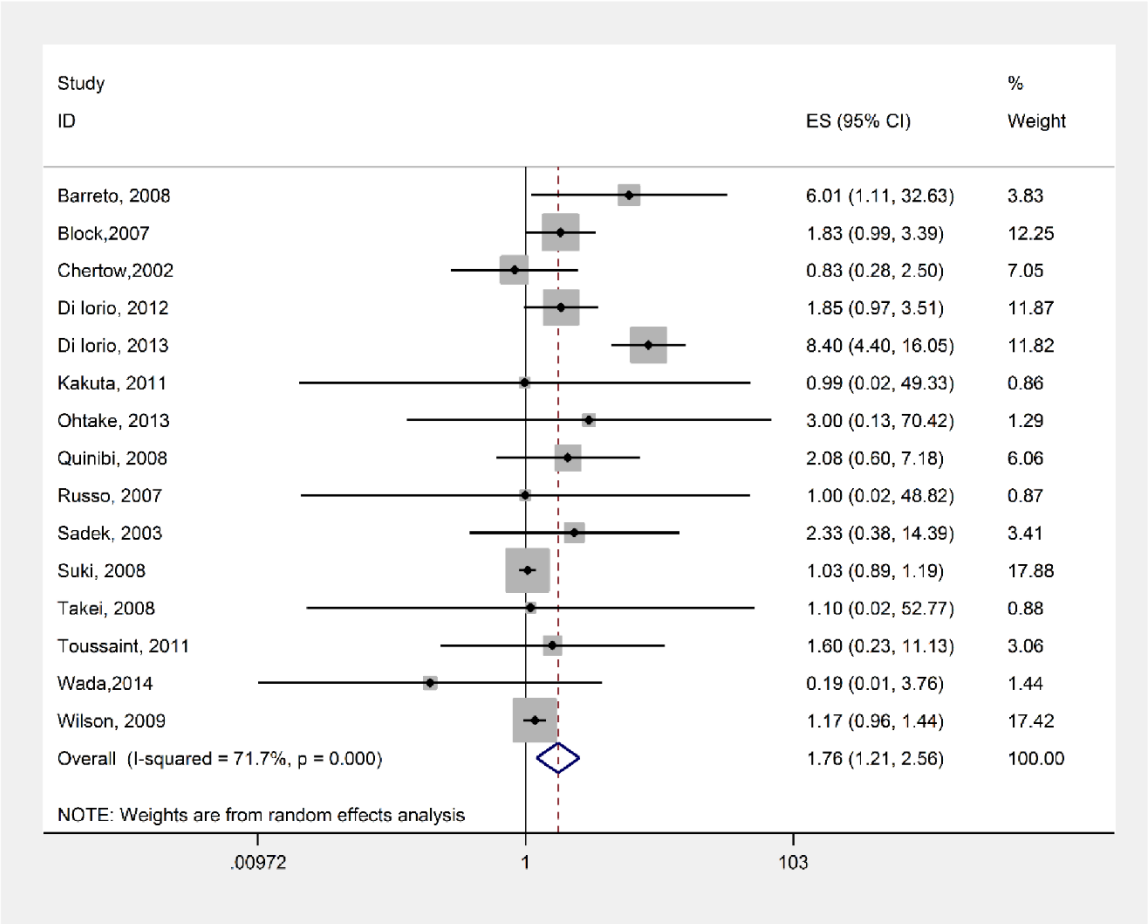
Legend: The size of each square is proportional to the weight of each direct summary effect plotted on the horizontal axis. It is used to estimate each network summary effects plotted on the vertical axis. The numbers indicate the weights as percentage [29]. Note: 1=Sevelamer; 2=Calcium; 3=Placebo; 4=Lanthanum; 5=Iron; 6=Phosphorous restricted diet; 7= Calcium-plus-sevelamer-plus-magnesium.

S3 Figure. The comparison-adjusted funnel plot to assess publication bias for the phosphate binder network; outcome: all-cause mortality.

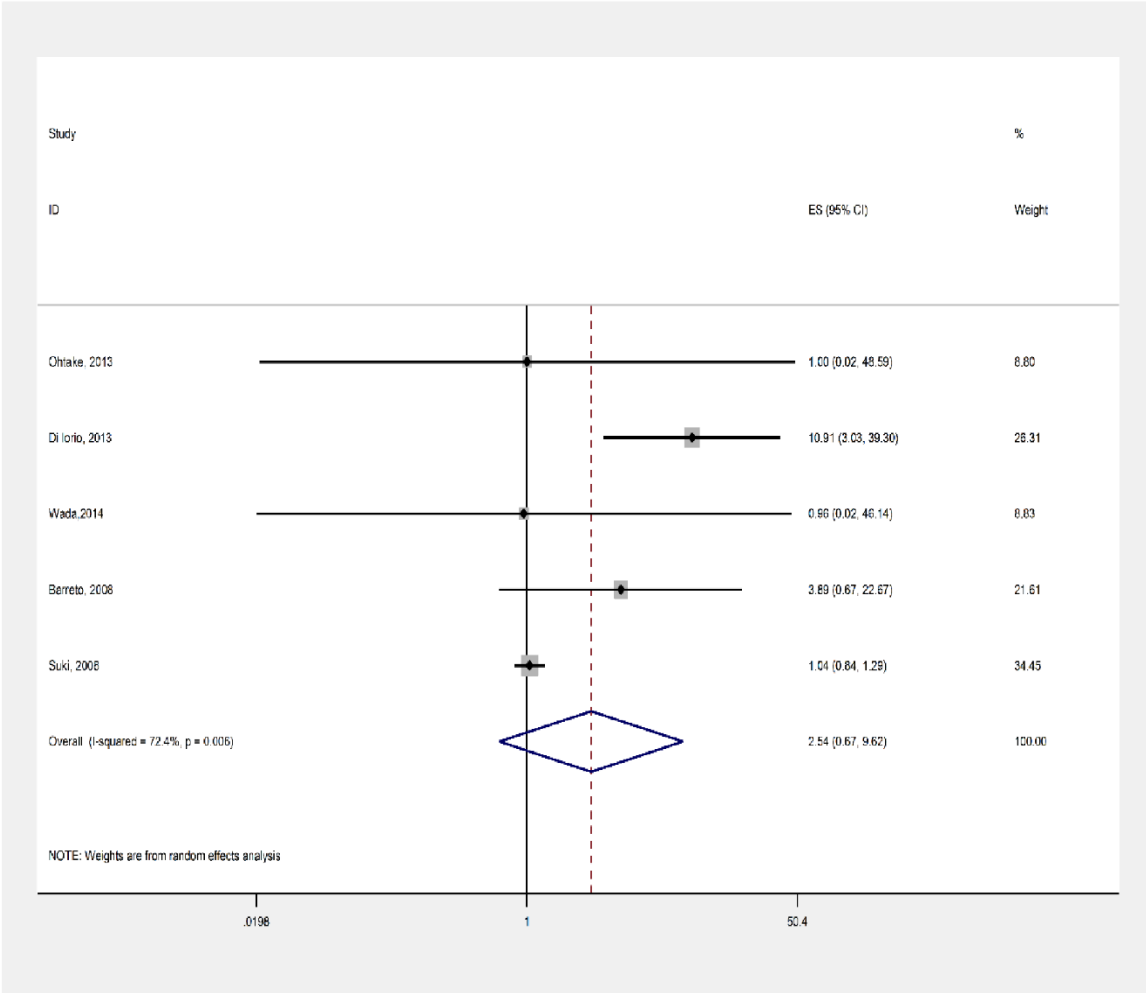


Legend: Black dashed line indicates the estimated small-study effects line also called the regression line. The red solid line depicts the summary ln(OR) (mXY) of each comparison estimated from the network meta-analysis model and represents the null hypothesis. The null hypothesis implies that there is no significant relationship between comparison-specific pooled effect estimates and study-specific effect sizes. Note: 1=Sevelamer; 2=Calcium; 3=Placebo; 4=Lanthanum; 5=Iron; 6=Phosphorous restricted diet; 7= calcium-plus-sevelamer-plus-magnesium.

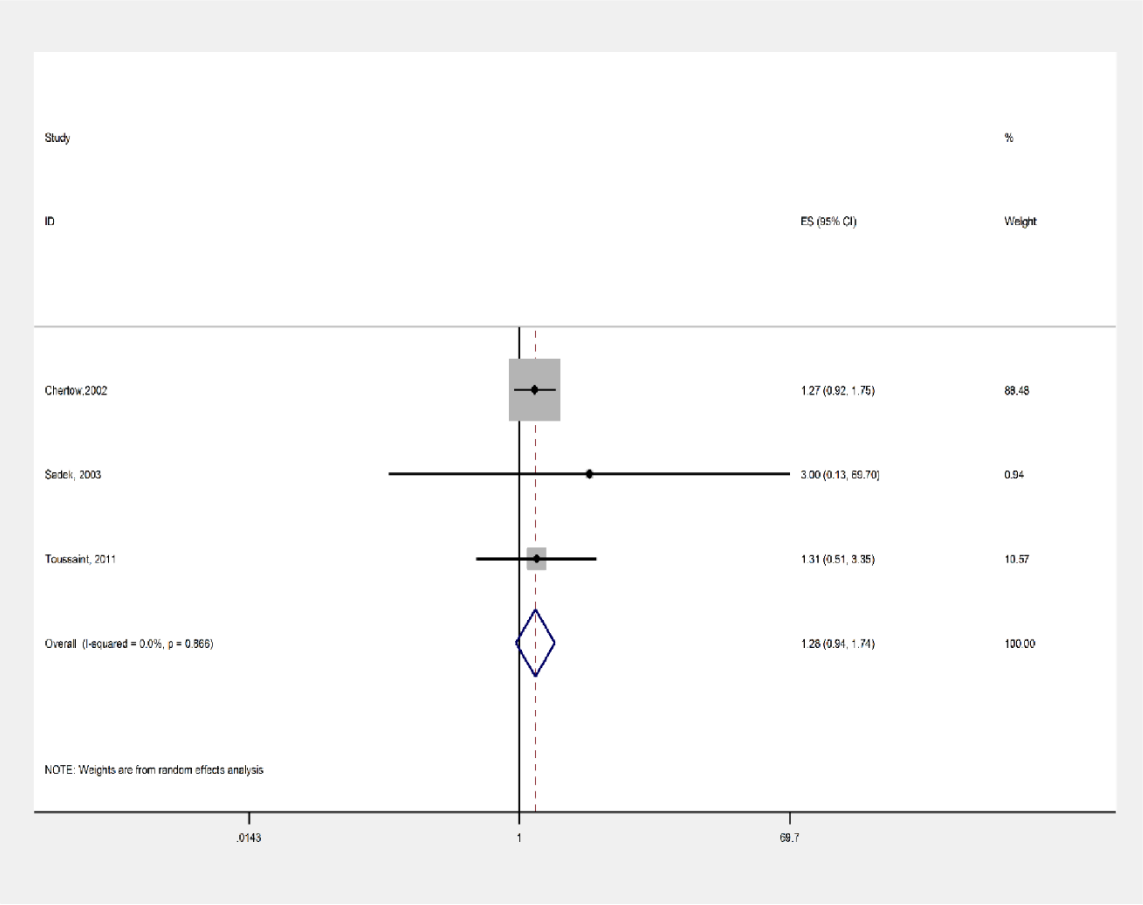
S4 Figure. Forest plot, calcium-based versus non-calcium-based phosphate binders; outcome: all-cause mortality



S5 Figure. Forest plot, calcium based vs. non-calcium based phosphate binders; outcome: cardiovascular mortality



S6 Figure. Forest plot, calcium based vs. non-calcium based phosphate binders; outcome: hospitalization



S1 Table. Study Characteristics

Study, Year (Reference)	Country	Randomly assigned patients, n	Number of arms	Women, %	Age, y (SD)	Stage of CKD	Comparison	Diabetes, n (%)	Hypertension, n (%)	Follow-up duration in months
Chertow et al, 2002[38]	United States, Austria and Germany	99 101	2	70, 35%	57 (14) 56 (16)	Stage 5D	Sevelamer vs. calcium	32% 33%	86% 83%	12
Sadek et al, 2003[39]	France	21 21	2	-	-	Stage 5D	Sevelamer vs. calcium	-	-	5
Block et al, 2007 [40]	United States and Italy	60 67	2	42% 36%	56 (14) 58 (14)	Stage 5D	Sevelamer vs. calcium	60% 56%	95% 98%	60
Russo et al, 2007 [41]	Italy	30 30 30	3	3 (10%) 5 (16%)	55 (13) 54 (12)	Non-dialysis	Sevelamer vs. calcium vs. diet	-	-	24
Barreto et al, 2008 [42]	Brazil	52 49	2	34% 30%	47 (13)	Stage 5D	Sevelamer vs. calcium	15% 13%	66% 73%	12

					47 (14)					
Qunibi et al, 2008 [43]	United States	100 103	2	54% 42%	60 (12) 58 (12)	Stage 5D	Sevelamer vs. calcium	57% 57%	31% 31%	12
Suki et al, 2008[44]	United States	1053 1050	2	479 (45%) 481(48%)	59 (14) 60 (15)	Stage 5D	Sevelamer vs. calcium	50% 50%	33% 33%	45
Takei et al, 2008[45]	Japan	22 20	2	50% 45%	54 (10) 54 (9)	Stage 5D	Sevelamer vs. calcium	36% 36%	-	6
Wilson et al, 2009 [46]	United States and United Kingdom	680 674	2	42% 38%	54 (14) 60 (14)	Stage 5D	Lanthanum vs. Standard treatment	34% 34%	31% 28%	24
De Francisco et al,[47] 2010[48]	Spain, Portugal, Germany, Italy, Romania and Poland	127 125	2	49% 47%	56 (12) 59 (14)	Stage 5D	Sevelamer vs. calcium	20% 24%	-	6

Kakuta et al, 2011 [49]	Japan	91 92	2	43% 49%	59 (12) 57 (12)	Stage 5D	Sevelamer vs. calcium	-	60% 64%	12
Toussaint et al, 2011 [50]	Australia	22 23	2	45% 26%	56 (15) 59 (15)	Stage 5D	Lanthanum vs calcium	32% 35%	9% 9%	18
Block et al, 2012[47]	United States, Germany and United Kingdom	57 28 30 30	4	21% 18% 20% 20%	65 (12) 70 (10) 66 (12) 68 (12)	Non-dialysis	Placebo vs. Lanthanum vs. Sevelamer vs. Calcium	58% 57% 53% 57%	100% 100% 97% 97%	10 (median follow-up time 249 days)
Di Iorio et al, 2012[51]	United States and Italy	232 234	2	50% 52%	67 (14) 65 (15)	Stage 5D	Sevelamer vs. calcium	30% 29%	78% 81%	24
Di Iorio et al, 2013 [52]	Italy	121 118	2	39% 39%	57 (12)	Non-dialysis	Sevelamer vs. calcium	27% 29%	73% 76%	36

					59 (12)					
Lee et al, 2013 [53]	Korea	50	2	45% 63%	48 (11) 52 (11)	Stage 5D	Lanthanum vs calcium	30% 17%	35% 37%	6
Ohtake et al, 2013 [54]	Japan	26 26	2	40%	68 (6)	Stage 5D	Lanthanum vs calcium	43%	-	12
Wuthrich et al, 2013 [55]	Canada, United States, Romania, and Switzerland	24 126	2	58% 37%	60 (13) 62 (11)	Stage 5D	Sevelamer vs. sucroferric oxyhydroxide	38% 32%	67% 75%	1.5
Xu et al, 2013 [56]	China	115 115	2	47% 36%	48 (13) 48 (12)	Stage 5D	Lanthanum vs. Placebo	-	-	2
Floege et al, 2014[57]	United States, Romania, Germany and Switzerland	349 710	2	37% 45%	56 (15) 56 (13)	Stage 5D	Sevelamer vs. sucroferric oxyhydroxide	-	-	6

Takahara et al, 2014 [58]	Japan	86 55	2	55% 27%	61 (11) 62 (13)	Non-dialysis	Lanthanum vs. Placebo	-	-	2
Urena-Torres et al, 2014 [59]	France	17 12	2	41% 58%	66 (15) 69 (13)	Non-dialysis	Lanthanum vs. Placebo	-	-	3
Wada et al, 2014 [60]	Japan	21 22	2	23% 21%	66 (10) 66 (8)	Stage 5D	Lanthanum vs calcium	100% 100%	-	12
Yokoyama et al, 2014 [61]	Japan and Unites States	110 115	2	35% 37%	62 (10) 60 (11)	Stage 5D	Sevelamer vs JTT-751	-	-	3
Yokoyama et al, 2014 [62]	Japan and Unites States	60 30	2	42% 41%	65 (10) 65 (14)	Non-dialysis and dialysis	Ferric citrate vs. Placebo	-	-	3
Block et al, 2015[63]	United States, Germany and Spain	75 74	2	69% 62%	66 (12) 64 (14)	Non-dialysis and dialysis	Ferric citrate vs. Placebo	67% 71%	-	3

Lee et al, 2015 [64]	Taiwan	36 75 72	3	37% 43% 31%	53 (12) 53 (11) 53 (12)	Stage 5D	Ferric citrate vs. Placebo	-	-	2
Lewis et al, 2015 [65]	United States	292 149	2	37% 42%	56 (45-63) 54 (45-63)	Stage 5D	Ferric citrate vs. Active control (calcium acetate and sevelamer)	-	-	12

Note: Diet indicates phosphorus restricted diet.

S2 Table. GRADE quality assessments of direct evidence per pairwise treatment comparison for all-cause mortality, cardiovascular mortality and hospitalization due to any reason.

Outcome	Number of studies number of participants	Study Limitations	Precision	Consistency	Directness	Publication bias	Overall quality of evidence	Relative effect estimate[1]; OR (95% CI)
All-cause mortality	15;5260	Not serious	Not serious	Serious (I^2, 74.3%)	Not serious	Not serious	Moderate	1.76 (1.21 to 2.56)
Cardiovascular mortality	5,2765	Not serious	Serious	Serious (I^2, 73.4%)	Not serious	Not serious	Low	2.54 (0.67 to 9.62)
Hospitalization due to any reason	3; 287	Not serious	Serious	Not serious (I^2, 0%)	Not serious	Not serious	Moderate	1.28 (0.94 to 1.74)

Legend: Ratings for domains "Study limitations", "Precision", "Consistency", and "Directness" were: Not serious, Serious, or Very serious issues. For the domain "Publication bias": Not likely or Likely to exist. Reasons are provided when rating down. All direct comparisons begin with a "High" quality rating.[1]We employed random effect models.

Chapter 3

Effects of phosphate binders in patients with chronic kidney disease on laboratory outcomes: A systematic review and network meta-analysis

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Effects of phosphate binders in patients with chronic kidney disease on laboratory outcomes: A systematic review and network meta-analysis

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Abstract

Background: Chronic kidney disease-mineral and bone disorder (CKD-MBD), a complication of chronic kidney disease, results in reduction in quality and length of life. High serum phosphate levels that result from CKD-MBD require phosphate-lowering agents, also known as phosphate binders. The objective of this systematic review is to compare the effects of available phosphate binders on laboratory outcomes in patients with CKD-MBD.

Methods: Data sources included MEDLINE and EMBASE from January 1996 to April 2016, and the Cochrane Register of Controlled Trials up to April 2016. Teams of two reviewers, independently and in duplicate, screened titles and abstracts and potentially eligible full text reports to determine eligibility, and subsequently abstracted data and assessed risk of bias in eligible randomized controlled trials (RCTs). Eligible trials enrolled patients with CKD-MBD and randomized them to receive calcium-based phosphate binders (delivered as calcium acetate, calcium citrate or calcium carbonate), non-calcium-based phosphate binders (NCBPB) (sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, sucroferric oxyhydroxide and ferric citrate), phosphorus restricted diet (diet), placebo or no treatment and reported effects on serum levels of phosphate, calcium and parathyroid hormone.

We performed Bayesian network meta-analyses (NMA) to calculate the effect estimates (mean differences) and 95% credible intervals for serum levels of phosphate, calcium and parathyroid hormone. We calculated direct, indirect and network meta-analysis estimates using random-effects models. We applied the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to rate the quality of evidence for each pairwise comparison.

Results: Our search yielded 1108 citations; 71 RCTs were retrieved for full review and 16 proved eligible. Including an additional 13 studies from a previous review, 29 studies that enrolled 8335 participants proved eligible; 26 trials provided data for quantitative synthesis. Sevelamer, lanthanum, calcium, iron, diet and combinations of active treatments (calcium or sevelamer or lanthanum and combination of calcium and sevelamer) resulted in significantly lower serum phosphate as compared to placebo (moderate to very low quality of evidence). We found no statistically significant differences between active treatment categories in lowering serum phosphate. Sevelamer, lanthanum and diet resulted in lower serum calcium compared to calcium (moderate quality evidence for lanthanum and diet; low quality evidence for Sevelamer). Iron, sevelamer and calcium yielded lower parathyroid hormone levels as compared to lanthanum. Meta-regression analyses did not yield a statistically significant association between treatment effect and trial duration.

Discussion/Conclusions: We found few differences between treatments in impact on phosphate and differences in parathyroid hormone were in most instances moderate, low or very low quality. Results suggest the possibility that higher serum calcium may contribute to the previously demonstrated lower mortality in sevelamer versus calcium binders. Treatment recommendations should be based on impact on patient-important outcomes rather than on surrogate outcomes.

Systematic review registration: PROSPERO CRD-42016032945

Key words: Chronic kidney disease, phosphate binders, mortality, network meta-analysis

Background

Chronic kidney disease (CKD) has been linked to negative patient outcomes, including mortality, often due to cardiovascular diseases [1-7]. CKD also contributes to comorbid conditions with extra-renal manifestations, such as disturbances of calcium-phosphate homeostasis collectively referred to as CKD mineral and bone disorder (CKD-MBD). CKD-MBD is a systematic disorder that results in adverse bone outcomes (e.g., fractures due to abnormal structure and composition of bones) and cardiovascular outcomes (i.e., cardiovascular calcifications and subsequent cardiovascular events) [2].

In patients suffering from CKD-MBD, clinical practice guidelines suggest maintaining targets for serum phosphate, calcium and parathyroid hormone [8-10]. Dietary restrictions and phosphate binders are commonly used to prevent long-term complications of high serum phosphate (i.e., cardiovascular and soft tissue calcifications) [11-14]. Calcium-based phosphate binders (henceforth referred to as calcium), such as calcium acetate, calcium citrate and calcium carbonate, may lead to positive calcium balance and hypercalcemia [11-14]. Non-calcium-based phosphate binders (NCBPB) include sevelamer, lanthanum and iron (e.g., ferric citrate and sucroferric oxyhydroxide) [11-14]. The combination of calcium carbonate and magnesium carbonate is a new phosphate binding agent [15]. All phosphate binders work in the gastrointestinal system by increasing the excretion of phosphate [16-19].

Previous systematic reviews have addressed the impact of alternative interventions for CKD-MBD on outcomes of important to patients, including all-cause mortality [20, 21]. Jamal et al. conducted a systematic review and explored the effectiveness of calcium versus NCBPBs in patients with CKD-MBD. The results suggest higher mortality with calcium binders than with NCBPBs [21].

Consistent with Jamal's review, our systematic review and network meta-analysis (NMA) found that calcium versus sevelamer resulted in higher mortality among CKD-MBD patients [22]. Our NMA results were congruent with our conventional meta-analysis in terms of the direction, magnitude and statistical significance of the effects of phosphate binders on mortality [22]. Although not statistically significant, conventional meta-analysis results also showed higher cardiovascular mortality and hospitalization with calcium binders relative to NCBPBs [22].

The association between drug effects on laboratory outcomes and patient survival has been explored with mixed results [23, 24]. Nevertheless, the impact of the interventions on patient-important outcomes is likely to be mediated through effects on target physiological variables: phosphate, calcium, and parathyroid hormone. This line of thinking is consistent with the majority of clinical practice guidelines, which base their recommendations regarding the management of CKD-MBD on laboratory outcomes [8, 25-28].

Knowledge of the impact of interventions on these surrogate outcomes may provide insight into understanding of the results of randomized controlled trials (RCTs) that address patient-important outcomes, and might provide clues regarding the comparative effectiveness of NCBPB agents on patient-important outcomes, currently unestablished. The objective of this study was therefore to systematically review and synthesize evidence from RCTs addressing the effectiveness of phosphorus restricted diet (diet) and different phosphate binders on serum levels of phosphate, calcium and parathyroid hormone by combining direct and indirect estimates in a NMA. We updated the Jamal systematic review [21] and applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence on an outcome-by-outcome basis.

Methods

We registered our protocol on PROSPERO (CRD42016032945) and we adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis for Network Meta-analysis (PRISMA NMA) guidelines in drafting our manuscript (S1 File) [29].

Eligibility criteria

We included studies that: (1) enrolled patients with CKD, defined as an estimated glomerular filtration rate <60 ml/min/1.73 m2, including dialysis and non-dialysis CKD patients; (2) randomized patients to a diet or phosphate binder versus a control; (3) reported at least one of the following outcomes: serum phosphate, calcium or parathyroid hormone; and (4) had a minimum follow-up of 4 weeks. Phosphate binders included calcium (calcium acetate, calcium citrate or calcium carbonate) or NCBPBs (sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, sucroferric oxyhydroxide or ferric citrate). A control included placebo or no intervention; we excluded non-randomized controlled trials, observational studies and conference abstracts.

Data sources and search strategy

We used the search of MEDLINE and EMBASE that we performed in our recently published review [22] which was based on a prior review [21], and updated the search for the subsequent period. We scanned references of all prior systematic reviews and meta-analyses as well as all eligible primary studies for additional relevant articles [21]. We established search alerts for monthly notification and repeated the search before thesis submission to identify any new relevant trials from the MEDLINE and EMBASE databases. S2 File in the supporting information file presents the full search strategy.

Study selection

Teams of two reviewers independently screened each title and abstract. If either reviewer identified a citation as potentially relevant, we obtained the full text of the article. Two reviewers independently determined the eligibility of all studies that underwent full text evaluation and resolved discrepancies by discussion.

Data abstraction

We extracted study data using a customized data collection form accompanied by a detailed instruction manual. Two independent reviewers abstracted the following information from each study: (1) author, (2) year of publication, (3) summary of baseline characteristics of the participants, (4) trial duration, and (5) serum levels of phosphate, parathyroid hormone or calcium. We recorded the last measurement if multiple measurements were provided during the follow-up period.

Risk of bias of included studies

Two reviewers used a modified version of the Cochrane risk for bias tool in order to assess the risk of bias on the basis of randomization, allocation concealment, blinding, incomplete outcome data, selective reporting (by comparing the methods and results sections of the manuscript) as well as stopping early for benefit [30]. Reviewers chose among response options of “definitely yes”, “probably yes”, “probably no”, and “definitely no” for each of the domains, with “definitely yes” and “probably yes” ultimately assigned low risk of bias and “definitely no” and “probably no” assigned high risk of bias [31].

Quality assessment of evidence

We assessed the quality of evidence in effect estimates for each outcome as high, moderate, low or very low using the GRADE rating system [32] in which RCTs begin as high quality evidence, but may be rated down by one or more of five categories of limitations [31]: risk of bias, precision, consistency, directness or publication bias [33].

After considering these reasons for rating down, we judged the overall confidence in estimates of effect for change in serum phosphate, calcium and parathyroid hormone from baseline for each pairwise comparison as follows: 'high' quality of evidence (we are very confident that the true effect lies close to that of the estimate of the effect); 'moderate' quality of evidence (we are moderately confident in the effect estimate and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); 'low' quality of evidence (our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); and 'very low' quality of evidence (we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect) [31].

We also applied the GRADE methodology to rate the confidence of indirect effect estimates. In relation to the treatment comparisons, we visually examined the network graphs and identified first order (one intervention connecting to two interventions, also called a single common comparator) and higher order loops (more than one interventions connecting to the two interventions). The quality of evidence rating for the indirect comparisons informing each pairwise comparison was the lower of the ratings of quality for the two direct estimates contributing to the first order loop. For instance, if one contributing direct comparison was rated as low and other

rated as moderate evidence, we rated the quality of indirect evidence as low [34]. In the absence of a first order loop, a higher order loop was used to rate quality of evidence. In a higher order loop, we identified all contributing comparisons and quality of evidence in each comparison. The quality of evidence rating for the indirect comparisons in each higher order loop was the lower of the ratings of quality for the direct estimates contributing to the higher order loop.

In the GRADE system for NMA, indirect effect estimates may be further rated down for intransitivity. The transitivity assumption implies similarity of trials in terms of population, intervention (type and dosing frequency), settings and trial methodology across the treatment comparisons included in the network. If the transitivity assumption was deemed to be violated, we planned to rate down the indirect comparison by one further level (if possible), as well as to explore this meta-regression analysis. Trial duration was the only effect modifier that we assessed for this assumption. All other potential effect modifiers, indeed, were not assessed using meta-regression due to unavailability of the data, such as mean age.

If both direct and indirect evidence were available, the NMA quality rating came from the higher of the two. If there was direct evidence, but no indirect evidence because of no closed loop or if there was a closed loop formed by a multi-arm trial, the NMA was graded according to the direct evidence. If there was no direct evidence, the NMA received the GRADE assessment of the indirect estimate.

We also considered coherence (degree of consistency between direct and indirect effect estimates) in our final quality rating of network estimates. We visually examined the magnitude of the difference between direct and indirect effect estimates and the extent to which their confidence intervals overlapped and planned to rate down the quality of the NMA effect if we found

meaningfully large incoherence. We calculated indirect effect estimates using the node-splitting approach [35]. We used the design-by-treatment interaction model that provides an omnibus test for loop and design inconsistency in the entire network [36, 37]. If the NMA evidence was substantially more precise than the higher quality of the direct or indirect estimates, we rated that estimate up due to improved precision.

We used a funnel plot to explore publication bias for comparisons with more than 10 studies in the direct comparisons. Asymmetrical funnel plots indicate reporting biases due to publication bias or small-study effect [38, 39].

In summary, the quality of evidence for each pairwise network comparison included assessment of transitivity (similarity between populations, interventions, comparators and outcomes of trials in the direct comparisons that contribute to the indirect comparison estimate); coherence (similarity between direct and indirect effect estimates); and homogeneity (similarity of effect estimates between trials in direct comparisons).

Data synthesis and statistical analysis

We used aggregate data (i.e., summary point estimates for all patients included in each study) to perform pairwise and network meta-analyses. In our conventional meta-analysis, we calculated pooled mean differences (MD) and the associated 95% credible intervals (CrIs) for each outcome using random-effects models in a Bayesian framework.

For Bayesian analyses, we used non-informative normal priors for means and a half-normal prior distribution for the between-study standard deviation ($\tau \sim N(0,1)$, $\tau > 0$). Posterior distributions were produced using Markov chain Monte Carlo methods. Two sets of initial values were produced for each chain with 100,000 iterations. We planned to increase the number of iterations if the data did

not converge. The first 10,000 iterations were discarded as burn-in and a thinning of 10 was also applied [40].

We employed fixed-effect and random-effects models and compared model fit and parsimony using the deviance information criterion (DIC). We reported our final results based on random-effect models because they indicated lower DIC values.

For each outcome, we reported the pooled MD and associated 95% CrIs based on the posterior distributions of Bayesian NMAs We also calculated predictive intervals (PrIs) to capture the magnitude of the between-study variance for each outcome per phosphate binder. PrIs present the intervals within which we would expect the treatment effect of a future study to lie [30]. For each outcome, we present network graphs, the NMA effect estimates and ranking of treatments according to their effectiveness using the surface under the cumulative ranking probabilities (SUCRA) curve [41]. We present SUCRA values from all outcomes in a single diagram using a rank-heat plot [42, 43].

Modified Gelman-Rubin statistics and graphical assessment of trace plots were used to examine model convergence. The analysis was performed using OpenBUGS 3.2.3 (MRC Biostatistics unit, Cambridge, UK), which generated inferences using the Gibbs sampler. We performed analysis for indirect estimates in R studio using the gemtc package [44]. We assessed consistency using the network command in Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) [37].

We employed a network meta-regression in order to examine an association between treatment effect using trial duration as a continuous variable measured in months.

Results

Trial identification

Our updated search yielded 1108 citations, of which 71 were retrieved for full review; 16 RCTs including 3576 patients proved eligible (Figure 1). We included 13 RCTs from the previous systematic review [21] for a total of 29 eligible studies with 8397 participants; 26 provided data (n=6760) that allowed inclusion in our quantitative synthesis (Figure 1).

Trial and population characteristics

Table S1in the supplemental file presents the characteristics of all eligible studies [45-73]. Eight of the twenty-nine studies (28%) included non-dialysis patients. Year of publication ranged from 2002 to 2015. A total of 11 trials were multinational and all were multi-centre. The mean age of participants ranged from 47 to 69.

Assessment of consistency between direct and indirect estimates

The omnibus test of consistency between direct and indirect estimates did not approach significance for any of the three outcomes (degrees of freedom [d.f.]= 3, chi-square test= 1.76, p= 0.62 for phosphate, d.f.= 6, chi-square test= 3.77, p=0.70 for calcium and d.f.= 6, chi-square test= 6.35, p=0.38 for parathyroid hormone).

Assessment of risk of bias in individual studies and quality of evidence in conventional pair-wise meta-analyses

Our assessment indicated low risk of bias for missing data and selective reporting in about 95% of the trials; blinding was adequate in only about 25% of the studies (Figure 2). Of the ten pairwise

comparisons for phosphate, we classified one as high quality, four as moderate quality, three as low quality and two very low quality (S4 Table). Of the eleven pairwise comparisons for calcium, we classified five as high quality, four as moderate quality, one as low quality and one as very low quality (S7 Table). Of the twelve pairwise comparisons, we classified seven as high quality, two as moderate quality, two as low quality and one as very low quality (S10 Table).

Direct treatment comparisons from conventional pair-wise meta-analysis

Lanthanum was associated with significant reductions in serum phosphate level as compared to placebo (-0.88 mg/dl [95% CrI, -1.63 to -0.84]) as was iron (-1.43 mg/dl [95% CrI, -2.20 to -0.70]) (S4 Table in the supporting information file). In the comparison of diet and calcium, the results indicated significant lower phosphate levels with diet (-0.80 mg/dl [95% CrI, -1.43 to -0.18]). No other differences reached statistical significance (S4 Table).

Reductions in serum calcium were observed with sevelamer vs. diet (-0.60 mg/dl [95% CrI, -0.74 to -0.46] and sevelamer vs calcium (-0.30 mg/dl [95% CrI, -0.08 to -0.52] (S7 Table in the supporting information file). No other MDs achieved statistical significance.

All phosphate binder comparisons except calcium vs. sevelamer, lanthanum vs. sevelamer, diet vs. sevelamer achieved significantly different mean reduction in serum parathyroid hormone levels (S10 Table in the supporting information file). Iron, as compared to sevelamer, led to greater parathyroid hormone reduction (-8 pg/ml [95% CrI, -17 to -0.52]). Calcium was associated with significant reductions in serum parathyroid hormone as compared to placebo (-67 pg/ml [95% CrI, -131 to - 4]) as was lanthanum (-45 mg/dl [95% CrI, -83 to -11]).

Network meta-analysis: phosphate

Figure 3 presents the network plot for phosphate. Of the twenty-six RCTs evaluating nine treatments or treatment combinations of phosphate binders from seven pharmacological and non-pharmacological interventions reported data on the change in serum phosphate levels. Figure 4 displays a forest plot of the mean changes and 95% CrIs and 95% and PrIs of reduction in serum phosphate levels for all pairwise comparisons from the network.

Relative to placebo, sevelamer, lanthanum, calcium, iron, diet and combination of active treatments (calcium or sevelamer or lanthanum and combination of calcium and sevelamer) showed significant reduction in serum phosphate level (Table 1). No other pairwise comparisons showed statistically significant differences, except iron versus combination of sevelamer or calcium or lanthanum category (1.31 mg/dl [95% CrI, 0.01 to 2.67], [95% PrI, -0.43 to 3.14]) (moderate quality evidence). Of the 29 comparisons that failed to reach statistical significance in the network estimate, we classified six as moderate quality, ten as low quality, and 13 as very low quality evidence.

SUCRA ranking suggested diet as the optimal treatment for reducing serum phosphate (SUCRA, 0.75; 95% CrI, 0.25 to 1.00) (Figure 9). However, credible intervals of the SUCRA value were large. The between-study variance was 0.33 (95% CrI, 0.15 to 0.76).

Network meta-analysis: calcium

Figure 5 presents the network plot for calcium is depicted in Figure 5. Twenty-six RCTs evaluating eight treatments or treatment combinations of phosphate binders from seven pharmacological and non-pharmacological categories reported data on the change in calcium level from baseline.

Figure 6 displays a forest plot of the mean changes and 95% CrIs and 95% PrIs of reduction in serum calcium levels for all head-to-head comparisons from the network. Relative to calcium, sevelamer, lanthanum and diet showed significant reduction in serum calcium from baseline (-0.30 mg/dl [95% CrI, -0.51 to -0.07] for sevelamer vs. calcium; -0.31 mg/dl [95% CrI, -0.62 to 0] for lanthanum vs. calcium; -0.89 mg/dl [95% CrI, -1.63 to -0.17] for diet vs. calcium) (in comparisons with calcium moderate quality evidence for lanthanum and diet; low quality evidence for sevelamer). There was no statistically significant difference between other drug categories (Table 2).

Of the 25 comparisons that failed to reach statistical significance in the network estimate, we classified eight as high quality, eight as moderate quality and nine as very low quality evidence (Table 2).

Patients treated with diet had a higher likelihood of reduction in serum calcium as compared to those treated with other treatment categories (SUCRA, 1; 95% CrI, 0.29 to 1.00) (Figure 9). However, credible intervals of the SUCRA value were large. The between-study variance was 0.11 (95% CrI, 0.06 to 0.24).

Network meta-analysis: parathyroid hormone

Figure 7 presents the network plot for parathyroid hormone. Twenty-six RCTs evaluating eight treatments, or treatment combinations, of phosphate binders from seven pharmacological and non-pharmacological categories reported data on the change in serum parathyroid hormone level from baseline. Figure 8 displays a forest plot of the mean changes and 95% CrIs and 95% PrIs of reduction in serum parathyroid hormone levels for all head-to-head comparisons from the phosphate-binder network.

In individual interventions tested, iron, diet, sevelamer and calcium yielded lower parathyroid hormone levels as compared to lanthanum. Iron was more effective in reducing parathyroid hormone than sevelamer, calcium, lanthanum and placebo (Iron vs sevelamer -8.6 pg/ml [95% CrI, -17.60 to -0.45], [95% PrI, -18.36 to 0.03]; moderate quality evidence) (Table 3).

Combination treatment with magnesium yielded significantly higher parathyroid hormone levels than iron and calcium-and-sevelamer combination. Combination treatment with sevelamer and calcium showed lower parathyroid hormone levels as compared to single treatment with sevelamer, calcium, lanthanum and iron.

Of the 28 comparisons, 11 failed to reach statistical significance in the network estimate. We classified eight as high quality, eight as moderate quality, three as low quality evidence an nine very low quality (Table 3).

Patients treated with sevelamer and calcium combination had a higher likelihood of reduction in serum parathyroid hormone as compared to those treated with other treatment categories (median SUCRA, 1; 95% CrI, 0.86 to 1) (Figure 9). The between-study variance was 1.29 (95% CrI, 0.00 to 12.00) and considered as high heterogeneity.

Assessment of robustness of our findings

In meta-regression analysis, trial duration is not associated with a significant change in phosphate, calcium and parathyroid hormone levels (regression coefficient for phosphate, 0.009 [95% CrI, -0.019 to 0.038]; regression coefficient for calcium, 0.011 [95% CrI, -0.005 to 0.027]; regression coefficient for parathyroid hormone, -0.186 [95% CrI, -1.847 to 1.338]).

Discussion

Summary of main findings

This NMA of 8397 participants from twenty-nine trials provide evidence for effectiveness of phosphate binders on laboratory outcomes in patients with CKD using both placebo-controlled and active-controlled trials. Our results indicate that all treatments likely result in reductions of serum phosphate relative to placebo (moderate to very low quality of evidence). Our NMA results find no statistically significant difference between active treatment categories in lowering serum phosphate. Further, combination therapy provides no benefits relative to monotherapy in lowering serum phosphate.

In terms of reducing serum calcium levels, we find no statistically significant difference between those who receive placebo or active treatment. Calcium binders likely increase serum calcium levels relative to other interventions (moderate quality evidence for lanthanum and diet; low quality evidence for sevelamer).

The use of lanthanum increases parathyroid hormone as compared to sevelamer, calcium, iron, diet and placebo (high to very low quality of evidence). Our results show combination therapy with sevelamer and calcium will likely reduce parathyroid hormone as compared to single drug regimen which includes sevelamer, calcium, lanthanum or iron. Combination therapy with magnesium relative to iron and calcium-and-sevelamer combination yields an increase in parathyroid hormone levels with very low quality of evidence (66 pg/ml [95% CrI 11 to 124] for iron and 87 pg/ml [95% CrI, 31 to 145] for calcium-and-sevelamer).

Strengths and limitations of this study

This is the first network meta-analysis within a Bayesian framework that examined effectiveness of phosphate binders on laboratory outcomes in patients with CKD. The most recent systematic review addressing phosphate binders in patients with CKD did not report the effectiveness of calcium and NCBPBs on laboratory outcomes [21].

Strengths of our systematic review and meta-analysis include explicit eligibility criteria, a comprehensive search, independent duplicate assessment of eligibility, and use of the GRADE approach to assess quality of evidence an outcome-by-outcome basis for direct, indirect and network evidence. Limitations of our review included low and very low quality evidence for some treatment comparisons.

Current knowledge and prior recommendations

Previous evidence had demonstrated that phosphate binders lower serum phosphate levels by diminishing phosphate reabsorption from the gastrointestinal system. Clinical practice guidelines recommend calcium as first line treatment for stages 4 and 5 CKD patients [9, 10] and suggest that serious gastrointestinal side effects, hypercalcemia and low parathyroid hormone at the lowest extreme (<100 pg/ml for hemodialysis patients) are main indications for a switch to NCBPs or a combination treatment [48, 74]. These recommendations ignore evidence that sevelamer results in decreased mortality relative to calcium [21, 75].

The association between laboratory outcomes and patient-important outcomes has been an area of interest for many researchers. A recent systematic review failed to show a significant association between drug effects on the laboratory outcomes and survival in CKD-MBD [23]. The trials included in this systematic review had low event rates in mortality due to inadequate trial duration

and had flaws in the design and execution. Nevertheless, clinical practice guidelines still make recommendations for laboratory outcomes in the management of CKD-MBD [8, 25-28].

Comparative effectiveness of phosphate binders on markers of bone and mineral metabolism including phosphate, calcium and parathyroid hormone have been investigated in vivo and in vitro studies. An association between calcium phosphate binders and cardiovascular calcifications, positive calcium balance and hypercalcemia have been previously reported [16, 17, 76].

In animal models, iron has been associated with a significant decline in serum parathyroid levels [77]. In contrary to those findings, iron administration has been linked to an increase in parathyroid hormone levels in a small-scale observational study over a 12-week follow-up in dialysis patients [78].

Magnesium has been inversely correlated with parathyroid hormone and plays a role in the causation of adynamic bone disorder [79-81]. Therefore, magnesium is not recommended as first line treatment for hyperphosphatemia. However, our review with one trial and 252 participants did not find statistical evidence of an increase in parathyroid hormone with magnesium intake.

Implications of the review for mechanisms

Sevelamer reduces mortality relative to calcium [22], but results did not indicate a superior effect in lowering phosphate or parathyroid hormone. This review also supported previous findings related to the link between the use of calcium and hypercalcemia. Therefore, the only link between laboratory values and mortality reduction may be serum calcium levels.

Implications of the review for research

According to our previous systematic review, the effects of various types of NCBPs have not been linked to mortality, although the sevelamer and calcium comparison yielded significant results supporting the mortality benefit of sevelamer [22]. Further research is needed with adequate trial duration and size to address the relative impact of phosphate binders on mortality and other patient-important outcomes.

Some RCTs are designed and executed to assess the impacts of treatments on laboratory outcomes rather than mortality or quality of life. They often report events during the trial period, but study durations are not long enough to capture the effects on patient important outcomes. Since it is not always possible and practical to design and conduct an RCT to capture information about patient important outcomes, laboratory outcomes are used instead. The main problem with this approach is that it is difficult to relate laboratory outcomes to patient-important outcomes.

Conclusion and future directions

This NMA showed only small and unconvincing differences between phosphate binding agents with low to very low quality of evidence. The treatment of hyperphosphatemia with calcium will likely induce hypercalcemia. The combination therapy with sevelamer and calcium will likely cause a decrease in serum parathyroid hormone.

The only result possibly explaining the previously demonstrated reduction in mortality with sevelamer versus calcium binders was a lower serum calcium with sevelamer. Our findings emphasize the necessity for trials focusing on patient-important outcomes to establish the relative benefit and harm of alternative management strategies for CKD-MBD.

In order to fully explore the return on investment and risk of investment, cost and effectiveness data should be incorporated in a network meta-analyses. This will guide policy-makers in drug coverage making decisions, especially in countries with taxed-based heath care financing systems, such as Canada.

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Authors' contributions:

Conception and design: NS, GHG, LT, JWB, NAD, AI, AAV

Paper selection: NS, LCL

Data abstraction: NS, LCL

Data synthesis: NS, AAV

Interpretation of results: NS, AAV, GHG, LT, JWB, NAD, AI

Manuscript drafting: NS, GHG

Manuscript review and approval: NS, GHG, LT, JWB, NAD, AI, AAV, LCL

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REFERENCES

1. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Annals of internal medicine. 2003;139(2):137-47. Epub 2003/07/16. PubMed PMID: 12859163.

2. Moe SM. Vascular calcification and renal osteodystrophy relationship in chronic kidney disease. European Journal of Clinical Investigation. 2006;36:51-62. doi: 10.1111/j.1365-2362.2006.01665.x.

3. Ibels LS, Alfrey AC, Huffer WE, Craswell PW, Anderson JT, Weil R, 3rd. Arterial calcification and pathology in uremic patients undergoing dialysis. Am J Med. 1979;66(5):790-6. Epub 1979/05/01. PubMed PMID: 443254.

4. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000;58(1):353-62. Epub 2000/07/08. doi: 10.1046/j.1523-1755.2000.00173.x. PubMed PMID: 10886582.

5. Sanchez-Perales C, Vazquez Ruiz de Castroviejo E, Garcia-Cortes MJ, Biechy Mdel M, Gil-Cunquero JM, Borrego-Hinojosa J, et al. Valvular calcifications at the start of dialysis predict the onset of cardiovascular events in the course of follow-up. Nefrologia. 2015;35(2):157-63. Epub 2015/08/25. doi: 10.1016/j.nefro.2015.05.017. PubMed PMID: 26300509.

6. Rebic D, Rasic S, Hamzic-Mehmedbasic A, Dzemidzic J, Kurtalic E. Valvular calcification and left ventricular modifying in peritoneal dialysis patients. Ren Fail. 2015:1-7. Epub 2015/08/15. PubMed PMID: 26275111.

7. Wilkieson TJ, Rahman MO, Gangji AS, Voss M, Ingram AJ, Ranganath N, et al. Coronary artery calcification, cardiovascular events, and death: a prospective cohort study of incident patients on hemodialysis. Can J Kidney Health Dis. 2015;2:29. Epub 2015/08/14. doi: 10.1186/s40697-015-0065-6. PubMed PMID: 26269747; PubMed Central PMCID: PMCPMC4534029.

8. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2003;42(4 Suppl 3):S1-201. Epub 2003/10/02. PubMed PMID: 14520607.

9. Centre for Clinical Practice at N. National Institute for Health and Clinical Excellence: Guidance. Hyperphosphataemia in Chronic Kidney Disease: Management of Hyperphosphataemia in Patients with Stage 4 or 5 Chronic Kidney Disease. Manchester: National Institute for Health and Clinical Excellence (UK)

Copyright (c) National Institute for Health and Clinical Excellence, 2013.; 2013.

10. Hyperphosphataemia in chronic kidney disease Evidence Update December 2014. NICE guidelines [Internet]. 2014.

11. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31(4):607-17. Epub 1998/04/08. PubMed PMID: 9531176.

12. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1(4):825-31. Epub 2007/08/21. doi: 10.2215/cjn.02101205. PubMed PMID: 17699293.

13. O'Seaghdha CM, Hwang SJ, Muntner P, Melamed ML, Fox CS. Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease. Nephrol Dial Transplant. 2011;26(9):2885-90. Epub 2011/02/05. doi: 10.1093/ndt/gfq808. PubMed PMID: 21292817; PubMed Central PMCID: PMCPMC3175050.

14. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909-16. Epub 2007/05/23. doi: 10.1093/ndt/gfm286. PubMed PMID: 17517792.

15. Meyer C, Cameron K, Battistella M. New agent to treat elevated phosphate levels: magnesium carbonate/calcium carbonate tablets. CANNT journal = Journal ACITN. 2012;22(4):33-5; quiz 6-7. Epub 2013/02/19. PubMed PMID: 23413537.

16. Cernaro V, Santoro D, Lacquaniti A, Costantino G, Visconti L, Buemi A, et al. Phosphate binders for the treatment of chronic kidney disease: role of iron oxyhydroxide. International journal of nephrology and renovascular disease. 2016;9:11-9. Epub 2016/02/20. doi: 10.2147/ijnrd.s78040. PubMed PMID: 26893577; PubMed Central PMCID: PMCPMC4749089.

17. Locatelli F, Del Vecchio L, Violo L, Pontoriero G. Phosphate binders for the treatment of hyperphosphatemia in chronic kidney disease patients on dialysis: a comparison of safety profiles. Expert opinion on drug safety. 2014;13(5):551-61. Epub 2014/04/08. doi: 10.1517/14740338.2014.907791. PubMed PMID: 24702470.

18. Cozzolino M, Funk F, Rakov V, Phan O, Teitelbaum I. Preclinical Pharmacokinetics, Pharmacodynamics and Safety of Sucroferric Oxyhydroxide. Current drug metabolism. 2014;15(10):953-65. Epub 2015/02/07. PubMed PMID: 25658128.

19. Lee CT, Wu IW, Chiang SS, Peng YS, Shu KH, Wu MJ, et al. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. J Nephrol. 2015;28(1):105-13. Epub 2014/05/21. doi: 10.1007/s40620-014-0108-6. PubMed PMID: 24840781.

20. Zhai CJ, Yang XW, Sun J, Wang R. Efficacy and safety of lanthanum carbonate versus calcium-based phosphate binders in patients with chronic kidney disease: a systematic review and meta-analysis. Int Urol Nephrol. 2015;47(3):527-35. doi: http://dx.doi.org/10.1007/s11255-014-0876-x. PubMed PMID: 25399356.

21. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet (London, England). 2013;382(9900):1268-77. Epub 2013/07/23. doi: 10.1016/s0140-6736(13)60897-1. PubMed PMID: 23870817.

22. Sekercioglu N, Thabane L, Diaz Martinez JP, Nesrallah G, Longo CJ, Busse JW, et al. Comparative Effectiveness of Phosphate Binders in Patients with Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis. PLoS One. 2016;11(6):e0156891. Epub 2016/06/09. doi: 10.1371/journal.pone.0156891. PubMed PMID: 27276077.

23. Palmer SC, Teixeira-Pinto A, Saglimbene V, Craig JC, Macaskill P, Tonelli M, et al. Association of Drug Effects on Serum Parathyroid Hormone, Phosphorus, and Calcium Levels With Mortality in CKD: A Meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2015;66(6):962-71. Epub 2015/05/25. doi: 10.1053/j.ajkd.2015.03.036. PubMed PMID: 26003472.

24. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1998;31(4):607-17. Epub 1998/04/08. PubMed PMID: 9531176.

25. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney international Supplement. 2009;(113):S1-130. Epub 2009/08/01. doi: 10.1038/ki.2009.188. PubMed PMID: 19644521.

26. Fukagawa M, Yokoyama K, Koiwa F, Taniguchi M, Shoji T, Kazama JJ, et al. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2013;17(3):247-88. Epub 2013/06/06. doi: 10.1111/1744-9987.12058. PubMed PMID: 23735142.

27. Jindal K, Chan CT, Deziel C, Hirsch D, Soroka SD, Tonelli M, et al. Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. Journal of the American Society of Nephrology : JASN. 2006;17(3 Suppl 1):S1-27. Epub 2006/02/25. doi: 10.1681/asn.2005121372. PubMed PMID: 16497879.

28. Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, et al. Guidelines for the management of chronic kidney disease. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008;179(11):1154-62. Epub 2008/11/19. doi: 10.1503/cmaj.080351. PubMed PMID: 19015566; PubMed Central PMCID: PMCPmc2582781.

29. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Annals of internal medicine. 2015;162(11):777-84. Epub 2015/06/02. doi: 10.7326/m14-2385. PubMed PMID: 26030634.

30. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society Series A, (Statistics in Society). 2009;172(1):137-59. Epub 2009/04/22. doi: 10.1111/j.1467-985X.2008.00552.x. PubMed PMID: 19381330; PubMed Central PMCID: PMCPMC2667312.

31. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008;336(7650):924-6. Epub 2008/04/26. doi: 10.1136/bmj.39489.470347.AD. PubMed PMID: 18436948; PubMed Central PMCID: PMCPmc2335261.

32. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490. Epub 2004/06/19. doi: 10.1136/bmj.328.7454.1490. PubMed PMID: 15205295; PubMed Central PMCID: PMCPMC428525.

33. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72. Epub 2012/05/23. doi: 10.1016/j.jclinepi.2012.01.012. PubMed PMID: 22609141.

34. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.(doi):10.1136/bmj.g5630.

35. Lumley T. Network meta-analysis for indirect treatment comparisons. Statistics in medicine. 2002;21(16):2313-24. Epub 2002/09/05. doi: 10.1002/sim.1201. PubMed PMID: 12210616.

36. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Research synthesis methods. 2012;3(2):111-25. Epub 2012/06/01. doi: 10.1002/jrsm.1045. PubMed PMID: 26062085; PubMed Central PMCID: PMCPMC4433771.

37. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Research synthesis methods. 2012;3(2):98-110. Epub 2012/06/01. doi: 10.1002/jrsm.1044. PubMed PMID: 26062084; PubMed Central PMCID: PMCPMC4433772.

38. Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Research Synthesis Methods. 2012;3(2):161-76. doi: 10.1002/jrsm.57.

39. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PloS one. 2013;8(10):e76654. Epub 2013/10/08. doi: 10.1371/journal.pone.0076654. PubMed PMID: 24098547; PubMed Central PMCID: PMCPMC3789683.

40. Warn DE, Thompson SG, Spiegelhalter DJ. Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. Stat Med. 2002;21(11):1601-23. Epub 2002/07/12. doi: 10.1002/sim.1189. PubMed PMID: 12111922.

41. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71. Epub 2010/08/07. doi: 10.1016/j.jclinepi.2010.03.016. PubMed PMID: 20688472.

42. Veroniki AA, Straus SE, Fyraridis A, Tricco AC. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. Journal of clinical epidemiology. 2016. Epub 2016/03/05. doi: 10.1016/j.jclinepi.2016.02.016. PubMed PMID: 26939929.

43. Gert van Valkenhoef, Kuiper J. gemtc: Network Meta-Analysis Using Bayesian Methods. R package version 0.8.

. gemtc: Network Meta-Analysis Using Bayesian Methods R package version 08 [Internet]. 2016.

44. team Rc. R: A language and environment for statistical computing. R Foundation for Statistical Computing, . Vienna, Austria: R core team; 2015.

45. Barreto DV, Barreto Fde C, de Carvalho AB, Cuppari L, Draibe SA, Dalboni MA, et al. Phosphate binder impact on bone remodeling and coronary calcification--results from the BRiC study. Nephron Clinical practice. 2008;110(4):c273-83. Epub 2008/11/13. doi: 10.1159/000170783. PubMed PMID: 19001830.

46. Block GA, Fishbane S, Rodriguez M, Smits G, Shemesh S, Pergola PE, et al. A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD Stages 3-5. American journal of kidney

diseases : the official journal of the National Kidney Foundation. 2015;65(5):728-36. Epub 2014/12/04. doi: 10.1053/j.ajkd.2014.10.014. PubMed PMID: 25468387.

47. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney international. 2007;71(5):438-41. Epub 2007/01/04. doi: 10.1038/sj.ki.5002059. PubMed PMID: 17200680.

48. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, et al. Effects of phosphate binders in moderate CKD. Journal of the American Society of Nephrology : JASN. 2012;23(8):1407-15. Epub 2012/07/24. doi: 10.1681/asn.2012030223. PubMed PMID: 22822075; PubMed Central PMCID: PMCPMC3402292.

49. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney international. 2002;62(1):245-52. Epub 2002/06/26. doi: 10.1046/j.1523-1755.2002.00434.x. PubMed PMID: 12081584.

50. de Francisco AL, Leidig M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(11):3707-17. Epub 2010/06/10. doi: 10.1093/ndt/gfq292. PubMed PMID: 20530499; PubMed Central PMCID: PMCPmc2957591.

51. Di Iorio B, Bellasi A, Russo D. Mortality in kidney disease patients treated with phosphate binders: a randomized study. Clinical journal of the American Society of Nephrology : CJASN. 2012;7(3):487-93. Epub 2012/01/14. doi: 10.2215/cjn.03820411. PubMed PMID: 22241819.

52. Di Iorio B, Molony D, Bell C, Cucciniello E, Bellizzi V, Russo D, et al. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;62(4):771-8. Epub 2013/05/21. doi: 10.1053/j.ajkd.2013.03.023. PubMed PMID: 23684755.

53. Floege J, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney international. 2014;86(3):638-47. Epub 2014/03/22. doi: 10.1038/ki.2014.58. PubMed PMID: 24646861; PubMed Central PMCID: PMCPmc4150998.

54. Kakuta T, Tanaka R, Hyodo T, Suzuki H, Kanai G, Nagaoka M, et al. Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2011;57(3):422-31. Epub 2011/01/18. doi: 10.1053/j.ajkd.2010.10.055. PubMed PMID: 21239096.

55. Lee CT, Wu IW, Chiang SS, Peng YS, Shu KH, Wu MJ, et al. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. Journal of nephrology. 2015;28(1):105-13. Epub 2014/05/21. doi: 10.1007/s40620-014-0108-6. PubMed PMID: 24840781.

56. Lee YK, Choi HY, Shin SK, Lee HY. Effect of lanthanum carbonate on phosphate control in continuous ambulatory peritoneal dialysis patients in Korea: a randomized prospective study. Clinical nephrology. 2013;79(2):136-42. Epub 2012/12/06. doi: 10.5414/cn107362. PubMed PMID: 23211335.

57. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. Journal of the American Society of Nephrology : JASN. 2015;26(2):493-503. Epub 2014/07/26. doi: 10.1681/asn.2014020212. PubMed PMID: 25060056; PubMed Central PMCID: PMCPmc4310662.

58. Ohtake T, Kobayashi S, Oka M, Furuya R, Iwagami M, Tsutsumi D, et al. Lanthanum carbonate delays progression of coronary artery calcification compared with calcium-based phosphate binders in patients on hemodialysis: a pilot study. Journal of cardiovascular pharmacology and therapeutics. 2013;18(5):439-46. Epub 2013/04/26. doi: 10.1177/1074248413486355. PubMed PMID: 23615577.

59. Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2008;51(6):952-65. Epub 2008/04/22. doi: 10.1053/j.ajkd.2008.02.298. PubMed PMID: 18423809.

60. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney international. 2007;72(10):1255-61. Epub 2007/09/07. doi: 10.1038/sj.ki.5002518. PubMed PMID: 17805238.

61. Sadek T, Mazouz H, Bahloul H, Oprisiu R, El Esper N, El Esper I, et al. Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: an open-label, randomized study. Nephrology, dialysis, transplantation : official

publication of the European Dialysis and Transplant Association - European Renal Association. 2003;18(3):582-8. Epub 2003/02/14. PubMed PMID: 12584283.

62. Suki WN. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2008;18(1):91-8. Epub 2007/12/20. doi: 10.1053/j.jrn.2007.10.019. PubMed PMID: 18089452.

63. Takahara Y, Matsuda Y, Takahashi S, Shigematsu T. Efficacy and safety of lanthanum carbonate in pre-dialysis CKD patients with hyperphosphatemia: a randomized trial. Clinical nephrology. 2014;82(3):181-90. Epub 2014/08/01. PubMed PMID: 25079863.

64. Takei T, Otsubo S, Uchida K, Matsugami K, Mimuro T, Kabaya T, et al. Effects of sevelamer on the progression of vascular calcification in patients on chronic haemodialysis. Nephron Clinical practice. 2008;108(4):c278-83. Epub 2008/04/25. doi: 10.1159/000127361. PubMed PMID: 18434749.

65. Toussaint ND, Lau KK, Polkinghorne KR, Kerr PG. Attenuation of aortic calcification with lanthanum carbonate versus calcium-based phosphate binders in haemodialysis: A pilot randomized controlled trial. Nephrology (Carlton, Vic). 2011;16(3):290-8. Epub 2011/02/24. doi: 10.1111/j.1440-1797.2010.01412.x. PubMed PMID: 21342323.

66. Urena-Torres P, Prie D, Keddad K, Preston P, Wilde P, Wan H, et al. Changes in fibroblast growth factor 23 levels in normophosphatemic patients with chronic kidney disease stage 3 treated with lanthanum carbonate: results of the PREFECT study, a phase 2a, double blind, randomized, placebo-controlled trial. BMC nephrology. 2014;15:71. Epub 2014/06/03. doi: 10.1186/1471-2369-15-71. PubMed PMID: 24885942; PubMed Central PMCID: PMCPmc4107721.

67. Wada K, Wada Y. Evaluation of aortic calcification with lanthanum carbonate vs. calcium-based phosphate binders in maintenance hemodialysis patients with type 2 diabetes mellitus: an open-label randomized controlled trial. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2014;18(4):353-60. Epub 2014/01/15. doi: 10.1111/1744-9987.12153. PubMed PMID: 24417760.

68. Wilson R, Zhang P, Smyth M, Pratt R. Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. Current medical research and opinion. 2009;25(12):3021-8. Epub 2009/10/23. doi: 10.1185/03007990903399398. PubMed PMID: 19845495.

69. Wuthrich RP, Chonchol M, Covic A, Gaillard S, Chong E, Tumlin JA. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. Clinical journal of the American Society of Nephrology : CJASN. 2013;8(2):280-9. Epub 2012/11/06. doi: 10.2215/cjn.08230811. PubMed PMID: 23124782; PubMed Central PMCID: PMCPmc3562865.

70. Xu J, Zhang YX, Yu XQ, Liu ZH, Wang LN, Chen JH, et al. Lanthanum carbonate for the treatment of hyperphosphatemia in CKD 5D: multicenter, double blind, randomized, controlled trial in mainland China. BMC nephrology. 2013;14:29. Epub 2013/02/06. doi: 10.1186/1471-2369-14-29. PubMed PMID: 23379590; PubMed Central PMCID: PMCPmc3570485.

71. Yokoyama K, Akiba T, Fukagawa M, Nakayama M, Sawada K, Kumagai Y, et al. A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant

Association - European Renal Association. 2014;29(5):1053-60. Epub 2014/01/01. doi: 10.1093/ndt/gft483. PubMed PMID: 24376274.

72. Yokoyama K, Hirakata H, Akiba T, Fukagawa M, Nakayama M, Sawada K, et al. Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. Clinical journal of the American Society of Nephrology : CJASN. 2014;9(3):543-52. Epub 2014/01/11. doi: 10.2215/cjn.05170513. PubMed PMID: 24408120; PubMed Central PMCID: PMCPmc3944759.

73. Gulati A, Sridhar V, Bose T, Hari P, Bagga A. Short-term efficacy of sevelamer versus calcium acetate in patients with chronic kidney disease stage 3-4. International urology and nephrology. 2010;42(4):1055-62. Epub 2009/12/19. doi: 10.1007/s11255-009-9688-9. PubMed PMID: 20020207.

74. Chertow GM, Burke SK, Lazarus JM, Stenzel KH, Wombolt D, Goldberg D, et al. Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1997;29(1):66-71. Epub 1997/01/01. PubMed PMID: 9002531.

75. N S, L T, JP MD, G N, C L. Comparative Effectiveness of Phosphate Binders in Patients with Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis. PLOS ONE. 2016. Epub Accepted for publication.

76. Wu HC, Lee LC, Wang WJ. Associations among time-average mineral values, mortality and cardiovascular events in hemodialysis patients. Renal failure. 2015;37(10):343-53. Epub 2015/09/17. doi: 10.3109/0886022x.2015.1087862. PubMed PMID: 26375759.

77. Phan O, Maillard M, Malluche HH, Stehle JC, Funk F, Burnier M. Effects of Sucroferric Oxyhydroxide Compared to Lanthanum Carbonate and Sevelamer Carbonate on Phosphate Homeostasis and Vascular Calcifications in a Rat Model of Chronic Kidney Failure. BioMed research international. 2015;2015:515606. Epub 2015/07/30. doi: 10.1155/2015/515606. PubMed PMID: 26221597; PubMed Central PMCID: PMCPMC4499607.

78. Iguchi A, Kazama JJ, Yamamoto S, Yoshita K, Watanabe Y, Iino N, et al. Administration of Ferric Citrate Hydrate Decreases Circulating FGF23 Levels Independently of Serum Phosphate Levels in Hemodialysis Patients with Iron Deficiency. Nephron. 2015;131(3):161-6. Epub 2015/11/10. doi: 10.1159/000440968. PubMed PMID: 26551233.

79. Navarro JF, Mora C, Macia M, Garcia J. Serum magnesium concentration is an independent predictor of parathyroid hormone levels in peritoneal dialysis patients. Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis. 1999;19(5):455-61. Epub 2001/05/31. PubMed PMID: 11379859.

80. Cho MS, Lee KS, Lee YK, Ma SK, Ko JH, Kim SW, et al. Relationship between the serum parathyroid hormone and magnesium levels in continuous ambulatory peritoneal dialysis (CAPD) patients using low-magnesium peritoneal dialysate. The Korean journal of internal medicine. 2002;17(2):114-21. Epub 2002/08/08. PubMed PMID: 12164088; PubMed Central PMCID: PMCPMC4531662.

81. Wei M, Esbaei K, Bargman JM, Oreopoulos DG. Inverse correlation between serum magnesium and parathyroid hormone in peritoneal dialysis patients: a contributing factor to adynamic bone disease? International urology and nephrology. 2006;38(2):317-22. Epub 2006/07/27. doi: 10.1007/s11255-006-0082-6. PubMed PMID: 16868704.

Table 1. Direct, indirect, and NMA estimates of phosphate with 95% credible intervals and GRADE assessments from each pairwise comparison within the phosphate-binder network.

Treatment Comparison		Direct estimate; MD (95% CrI)	Quality of evidence	Indirect estimate; MD (95% CrI)	Quality of evidence	NMA estimate; MD (95% CrI)	Quality of evidence
Sevelamer	Calcium	0.05 (-0.36, 0.46)	Low	0.11 (-1.40, 1.61)	Low	0.09 (-0.29, 0.47)	Low
Sevelamer	Placebo	NA	NA	1.13 (0.35, 1.90)	Very Low	1.13 (0.35, 1.90)	Very Low
Calcium	Placebo	NA	NA	1.03 (0.26, 1.81)	Low	1.03 (0.26, 1.81)	Low
Lanthanum	Sevelamer	NA	NA	0.24 (-0.49, 0.98)	Low	0.24 (-0.49, 0.98)	Low
Lanthanum	Calcium	0.15 (-0.69, 0.98)	Low	0.17 (-1.20, 1.56)	Very Low	0.15 (-0.54, 0.85)	Low
Lanthanum	Placebo	-0.87 (-1.6, -0.14)	Moderate	-0.90 (-2.34, 0.52)	Very Low	-088 (-1.52, -0.25)	Moderate
Sevelamer	Iron	-0.28 (-1.06, 0.45)	Very Low	-0.31 (-1.77,1.10)	Low	-0.28 (-0.95, 0.34)	Low
Iron	Calcium	NA	NA	-0.38 (-1.09, 0.31)	Very Low	-0.38 (-1.09, 0.31)	Very Low
Iron	Placebo	-1.49 (-2.2, -0.69)	Moderate	-1.42 (-2.85, 0)	Very Low	-1.41 (-2.07, -0.79)	Moderate
Iron	Lanthanum	NA	NA	-0.53 (-1.30, 0.21)	Very Low	-0.53 (-1.30, 0.21)	Very Low
Sevelamer	Diet	-0.20 (-1.12, 0.71)	Very Low	Closed loop formed by a multi-arm trial; not estimated	Not available	-0.24 (-1.08, 0.58)	Very Low
Calcium	Diet	-0.79 (-1.42, -0.17)	High	0.42 (-0.89,1.75)	Very Low	-0.33 (-1.22, 0.54)	Moderate[1]

Diet	Placebo	NA	NA	-1.37 (-2.5, -0.26)	Very Low	-1.37 (-2.5, -0.26)	Very Low
Lanthanum	Diet	NA	NA	-0.49 (-1.58, -0.59)	Low	-0.49 (-1.58, -0.59)	Low
Iron	Diet	NA	NA	0.04 (-0.9, 1.1)	Very Low	0.04 (-0.9, 1.1)	Very Low
Sevelamer	Calsev	NA	NA	-0.26 (-1.62, 1.05)	Very Low	-0.26 (-1.62, 1.05)	Very Low
Calcium	Calsev	NA	NA	-0.36 (-1.75, 0.98)	Very Low	-0.36 (-1.75, 0.98)	Very Low
Placebo	Calsev	NA	NA	-1.39 (-2.76, -0.08)	Moderate	-1.39 (-2.76, -0.08)	Moderate
Lanthanum	Calsev	NA	NA	-0.51 (-1.93, 0.87)	Moderate	-0.51 (-1.93, 0.87)	Moderate
Iron	Calsev	0.01 (-0.003 to 0.04)	Moderate	No closed loop; not estimated	Not available	0.02 (-1.15, 1.19)	Moderate
Calsev	Diet	NA	NA	-0.02 (-1.61, 1.53)	Very Low	-0.02 (-1.61, 1.53)	Very Low
Sevelamer	Calmag	-0.17 (-0.59 to 0.23)	Low	No closed loop; not estimated	Not available	-0.18 (-1.42, 1.05)	Low
Calmag	Calcium	NA	NA	-0.27 (-1.57, 1.03)	Low	-0.27 (-1.57, 1.03)	Low
Calmag	Placebo	NA	NA	-1.31 (-2.77, 0.14)	Low	-1.31 (-2.77, 0.14)	Low
Calmag	Lanthanum	NA	NA	-0.43 (-1.87, 1.02)	Low	-0.43 (-1.87, 1.02)	Low
Calmag	Iron	NA	NA	0.10 (-1.27, 1.52)	Very Low	0.10 (-1.27, 1.52)	Very Low
Calmag	Diet	NA	NA	0.06 (-1.43, 1.56)	Very Low	0.06 (-1.43, 1.56)	Very Low
Calmag	Calsev	NA	NA	0.08 (-1.72, 1.93)	Very Low	0.08 (-1.72, 1.93)	Very Low
Calsevlant	Sevelamer	NA	NA	1.03 (-0.37, 2.44)	Very Low	1.03 (-0.37, 2.44)	Very Low

Calsevlant	Calcium	NA	NA	0.93 (-0.46, 2.35)	Low	0.93 (-0.46, 2.35)	Low
Calsevlant	Placebo	-0.09 (-0.23, 0.03)	Moderate	No closed loop; not estimated	Not available	-0.09 (-1.28, 1.07)	Moderate
Calsevlant	Lanthanum	NA	NA	0.78 (-0.55, 2.13)	Moderate	0.78 (-0.55, 2.13)	Moderate
Calsevlant	Iron	NA	NA	1.31 (0.01, 2.67)	Moderate	1.31 (0.01, 2.67)	Moderate
Calsevlant	Diet	NA	NA	1.27 (-0.34, 2.91)	Very Low	1.27 (-0.34, 2.91)	Very Low
Calsevlant	Calsev	NA	NA	1.29 (-0.45, 3.1)	Moderate	1.29 (-0.45, 3.1)	Moderate
Calsevlant	Calmag	NA	NA	1.21 (-0.65, 3.09)	Very Low	1.21 (-0.65, 3.09)	Very Low

Legend:[1]Rated down for incoherence**.** Abbreviations: CrI: Credible interval; MD: Mean difference; calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum; NA: not available.

Table 2. Direct, indirect, and NMA estimates of calcium with 95% credible intervals and GRADE assessments from each pairwise comparison within the phosphate-binder network.

Treatment Comparison		Direct estimate; MD (95% CrI)	Quality of evidence	Indirect estimate; MD (95% CrI)	Quality of evidence	NMA estimate; MD (95% CrI)	Quality of evidence
Calcium	Sevelamer	0.30 (0.08 to 0.51)	Moderate	0.08 (-0.82 to 0.97)	Moderate	0.29 (0.07 to 0.51)	Moderate
Sevelamer	Placebo	0.10 (0.39 to 0.59)	High	-0.24 (-0.73 to 0.24)	Low	-0.03 (-0.37 to 0.29)	High
Placebo	Calcium	-0.01 (-0.5 to 0.5)	Low	-0.60 (-1.08 to -0.11)	Moderate	-0.33 (-0.67 to 0.01)	Moderate
Sevelamer	Lanthanum	-0.09 (-0.33 to 0.13)	Moderate	0 (-0.42 to 0.41)	Moderate	-0.01 (-0.36 to 0.32)	Moderate
Lanthanum	Calcium	-0.33 (-0.67 to 0.01)	Moderate	-0.20 (-0.90 to 0.53)	Low	-0.31 (-0.62 to 0)	Moderate
Lanthanum	Placebo	0.07 (-0.33 to 0.48)	Moderate	-0.10 (-0.78 to 0.57)	Low	0.02 (-0.33 to 0.36)	Moderate
Sevelamer	Iron	-0.15 (-0.64 to 0.34)	Very Low	0.30 (-0.28 to 0.87)	High	0.04 (-0.33 to 0.43)	High
Iron	Calcium	NA	NA	-0.24 (-0.65 to 0.16)	Very Low	-0.24 (-0.65 to 0.16)	Very Low

Iron	Placebo	0.22 (-0.18 to 0.62)	High	-0.24 (-0.88 to 0.41)	Very Low	0.09 (-0.27 to 0.45)	High
Iron	Lanthanum	NA	NA	0.06 (-0.37 to 0.51)	Very Low	0.06 (-0.37 to 0.51)	Very Low
Sevelamer	Diet	-0.60 (-0.74 to -0.45)	Moderate	No closed loop	Not available	-0.6 (-1.3 to 0.10)	Moderate
Diet	Calcium	NA	NA	-0.89 (-1.62 to -0.15)	Moderate	-0.89 (-1.62 to -0.15)	Moderate
Placebo	Diet	NA	NA	-0.56 (-1.33 to 0.22)	Moderate	-0.56 (-1.33 to 0.22)	Moderate
Lanthanum	Diet	NA	NA	-0.58 (-1.36 to 0.20)	Moderate	-0.58 (-1.36 to 0.20)	Moderate
Iron	Diet	NA	NA	-0.64 (-1.44 to 0.15)	Very Low	-0.64 (-1.44 to 0.15)	Very Low
Sevelamer	Calsev	NA	NA	0.20 (-0.59 to 0.98)	Very Low	0.20 (-0.59 to 0.98)	Very Low
Calcium	Calsev	NA	NA	-0.09 (-0.89 to 0.70)	Very Low	-0.09 (-0.89 to 0.70)	Very Low
Placebo	Calsev	NA	NA	0.23 (-0.54 to 1.01)	High	0.23 (-0.54 to 1.01)	High
Lanthanum	Calsev	NA	NA	0.21 (-0.60 to 1.04)	Very Low	0.21 (-0.60 to 1.04)	Very Low

Iron	Calsev	0.15 (0.13 to 0.16)	High	No closed loop	Not available	0.15 (-0.54 to 0.84)	High
Diet	Calsev	NA	NA	0.80 (-0.26 to 1.86)	Very Low	0.80 (-0.26 to 1.86)	Very Low
Sevelamer	Calmag	-012 (-0.26 to 0.02)	High	No closed loop	Not available	-0.12 (-0.82 to 0.58)	High
Calcium	Calmag	NA	NA	-0.41 (-1.14 to 0.32)	Moderate	-0.41 (-1.14 to 0.32)	Moderate
Placebo	Calmag	NA	NA	-0.08 (-0.86 to 0.70)	High	-0.08 (-0.86 to 0.70)	High
Lanthanum	Calmag	NA	NA	-0.10 (-0.87 to 0.68)	Moderate	-0.10 (-0.87 to 0.68)	Moderate
Iron	Calmag	NA	NA	-0.17 (-0.96 to 0.63)	Very Low	-0.17 (-0.96 to 0.63)	Very Low
Diet	Calmag	NA	NA	0.47 (-0.50 to 1.47)	Moderate	0.47 (-0.50 to 1.47)	Moderate
Calmag	Calsev	NA	NA	-0.32 (-1.37 to 0.74)	Very Low	-0.32 (-1.37 to 0.74)	Very Low

Legend: Abbreviations: CrI: Credible interval; MD: Mean difference; calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum.

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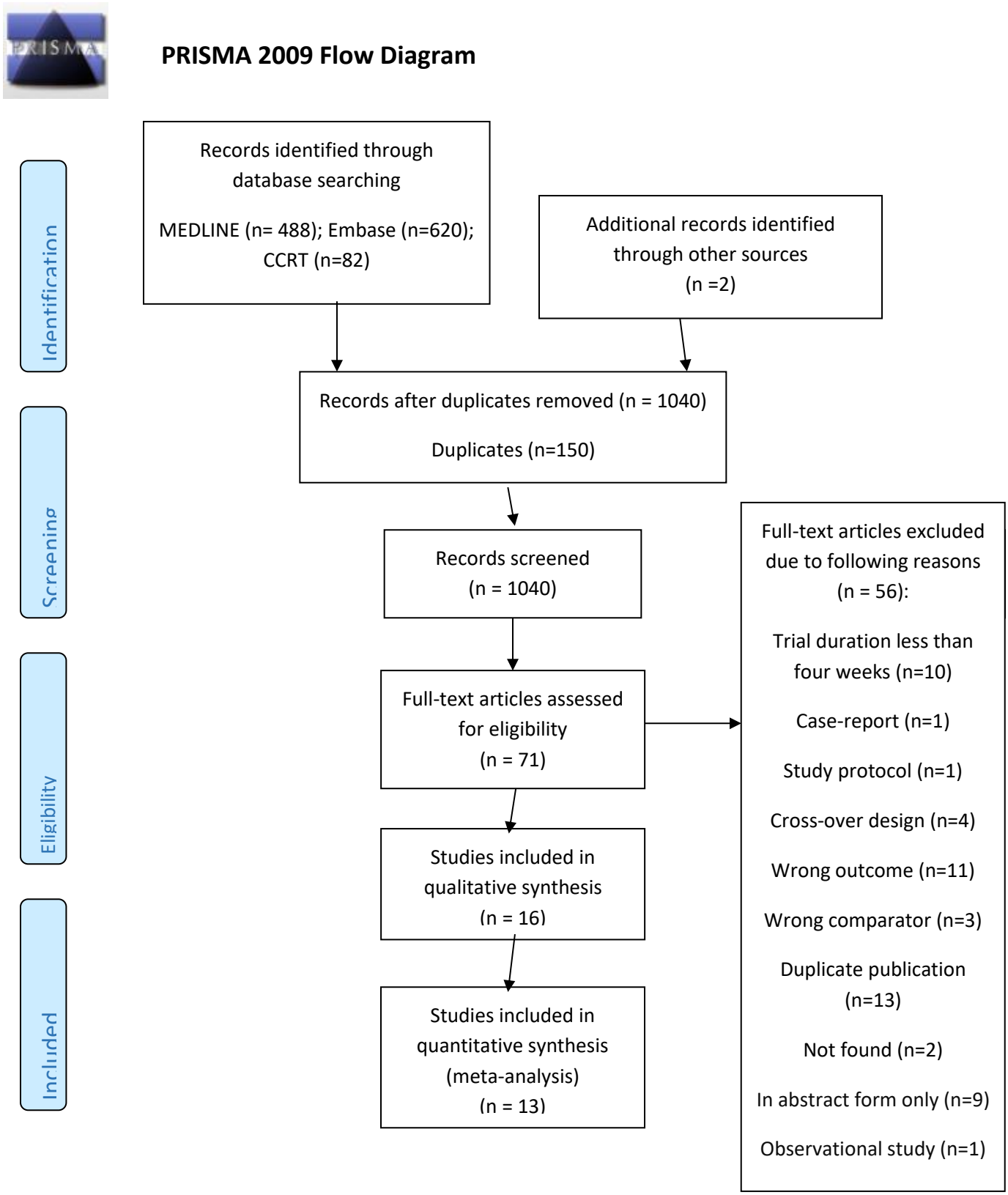
Table 3. Direct, indirect, and NMA estimates of parathyroid hormone with 95% credible intervals and GRADE assessments from each pairwise comparison within the phosphate-binder network.

Treatment Comparison		Direct estimate; MD (95% CrI)	Quality of evidence	Indirect estimate; MD (95% CrI)	Quality of evidence	NMA estimate; MD (95% CrI)	Quality of evidence
Sevelamer	Calcium	12 (-6.89 to 31)	Low	15 (-131 to 163)	Low	13 (-5.18 to 30)	Low
Placebo	Sevelamer	66 (4 to 129)	High	6.65 (-73 to 84)	Very Low	26 (0.71 to 53)	Moderate[1]
Lanthanum	Sevelamer	54 (-18 to 127)	High	29.74 (-44 to 101)	High	66 (39 to 94)	High
Iron	Sevelamer	-8.7 (-17 to -0.26)	Very low	-13 (-135 to 105)	High	-8.6(-17 to -0.2)	High
Diet	Sevelamer	11 (-23 to 47)	High	Closed loop formed by a multi-arm trial	Not available	-5.4 (-37 to 26)	High
Calmag	Sevelamer	59 (1.7 to 116)	Moderate	No closed loop	Not available	58 (2.8 to 115)	Moderate
Placebo	Calcium	67 (3.6 to 131)	Moderate	-14 (-64 to 92)	Low	13 (-12 to 41)	Low[1]
Lanthanum	Calcium	44 (9.2 to 80)	Low	76 (-47 to 200)	Low	53 (26 to 81)	Low
Diet	Calcium	-26 (-59 to 6.8)	High	-159 (-348 to 26)	Low	-18 (-49 to 13)	High
Lanthanum	Placebo	40 (29 to 50)	High	-5 (-148 to 136)	Low	39 (28 to 50)	High
Iron	Placebo	-30 (-68 to 6.3)	High	-36 (-141 to 70)	Very Low	-35 (-62 to -9.3)	High
Calsev	Iron	-20 (-26 to -15)	High	No closed loop	Not available	-20 (-27 to -14)	High
Iron	Calcium	NA	NA	-21 (-40 to -1.8)	Very Low	-21 (-40 to -1.8)	Very Low

Iron	Lanthanum	NA	NA	-75 (-102 to -50)	Very Low	-75 (-102 to -50)	Very Low
Diet	Placebo	NA	NA	-32 (-72 to 7)	Moderate	-32 (-72 to 7)	Moderate
Diet	Lanthanum	NA	NA	-71 (-111 to -31)	High	-71 (-111 to -31)	High
Diet	Iron	NA	NA	3.2 (-29 to 35)	Very Low	3.2 (-29 to 35)	Very Low
Calsev	Sevelamer	NA	NA	-29 (-40 to -19)	Very Low	-29 (-40 to -19)	Very Low
Calsev	Calcium	NA	NA	-42 (-62 to -21)	Very Low	-42 (-62 to -21)	Very Low
Calsev	Placebo	NA	NA	-56 (-84 to -29)	High	-56 (-84 to -29)	High
Calsev	Lanthanum	NA	NA	-95 (-124 to -68)	High	-95 (-124 to -68)	High
Calsev	Diet	NA	NA	-24 (-57 to 9.3)	Very Low	-24 (-57 to 9.3)	Very Low
Calmag	Calcium	NA	NA	45 (-13 to 105)	Low	45 (-13 to 105)	Low
Calmag	Placebo	NA	NA	31 (-29 to 94)	Moderate	31 (-29 to 94)	Moderate
Calmag	Lanthanum	NA	NA	-8.2 (-69 to 55)	Moderate	-8.2 (-69 to 55)	Moderate
Calmag	Iron	NA	NA	66 (11 to 124)	Very Low	66 (11 to 124)	Very Low
Calmag	Diet	NA	NA	63 (-0.3 to 128)	Moderate	63 (-0.3 to 128)	Moderate
Calmag	Calsev	NA	NA	87 (31 to 145)	Very Low	87 (31 to 145)	Very Low

Note: [1]Rated down for incoherence. Abbreviations: CrI: Credible interval; MD: Mean difference; calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum.

Figure 1. PRISMA Flow Diagram



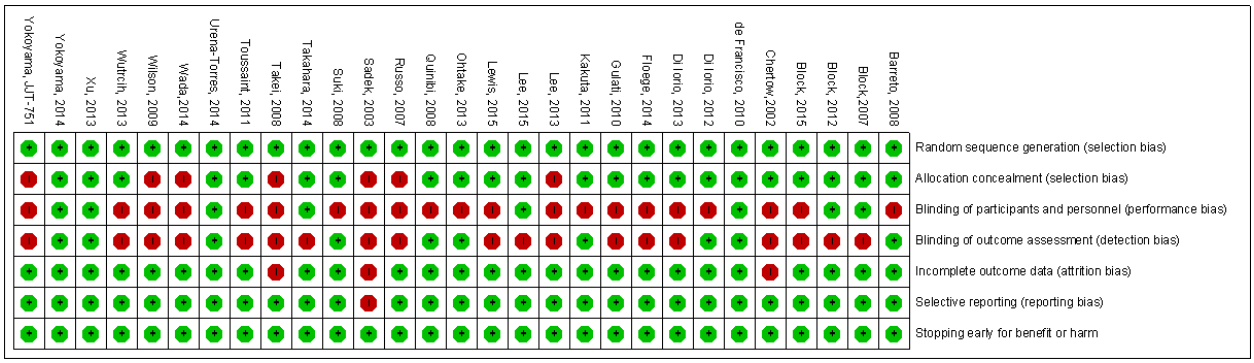


Figure 2. Risk of bias assessment for surrogate outcomes

Legend: Low risk of bias for missing data and selective reporting in about 95% of the trials. The level of blinding was adequate in only about 25% of the studies.

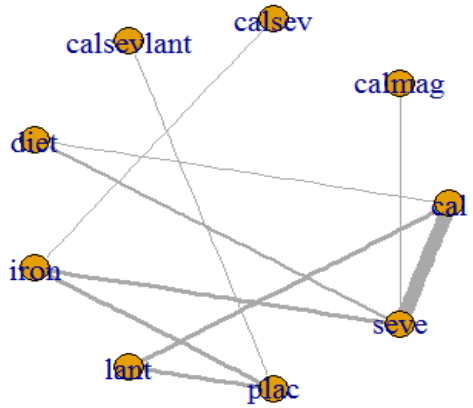


Figure 3. Network of clinical trials of phosphate binders in patients with chronic kidney disease: outcome mean change from baseline in serum phosphate concentration

Legend: Netplot of effectiveness outcome for mean phosphate reduction at the end of the study period. Network of randomized controlled trials comparing different phosphate binders for mean change in serum phosphate. Lines connect different phosphate binder categories with direct evidence. The width of lines correlates the number of RCTs for each direct comparison while the size of the nodes correlates with the total sample size. Abbreviations: cal: calcium; calmag: calcium and magnesium; calsev: calcium and Sevelamer; calsevlant: calcium or sevelamer or lanthanum; lant: lanthanum; seve: Sevelamer.

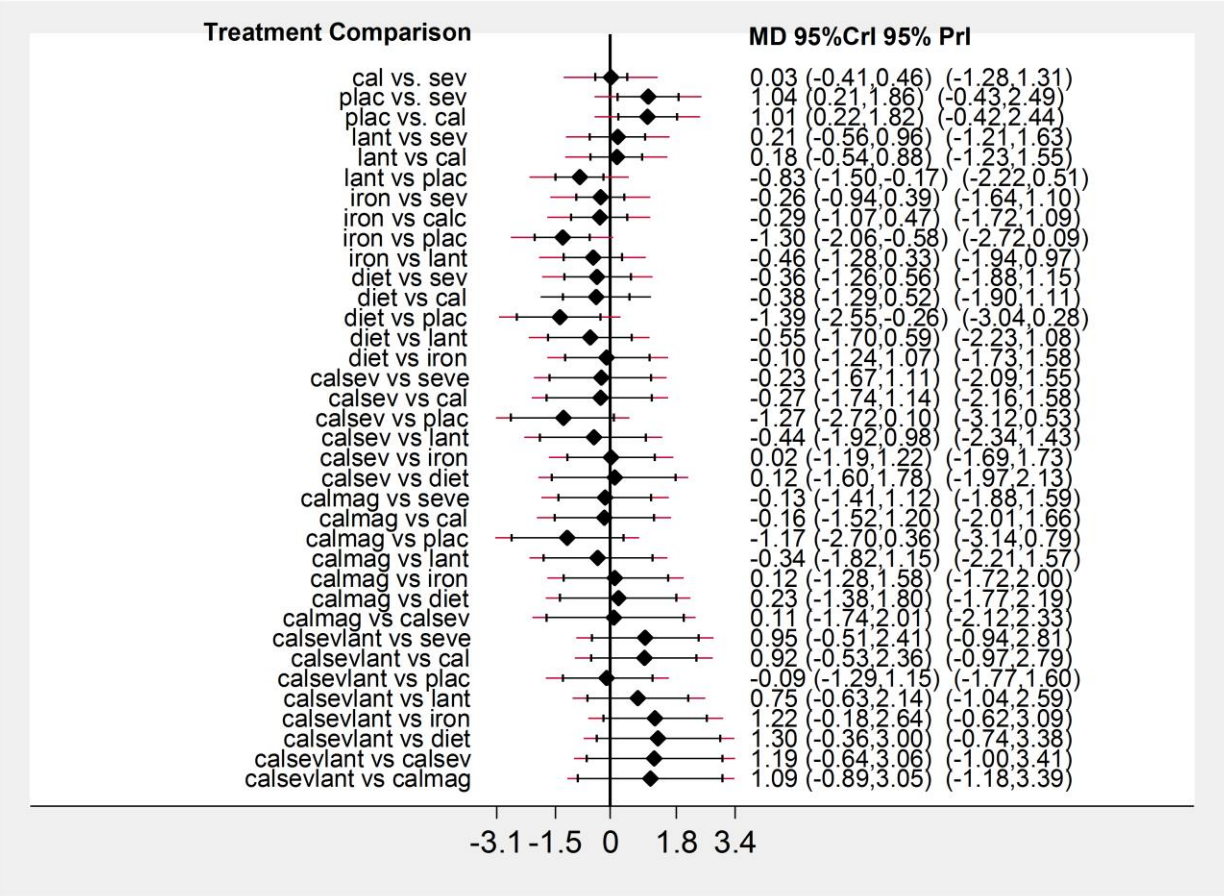


Figure 4. Network meta-analysis results for serum phosphate

Legend: Forest plot of effectiveness outcome for mean phosphate reduction at the end of the study period. MD: Mean difference; CrI: Credible interval; PrI: predictive intervals.

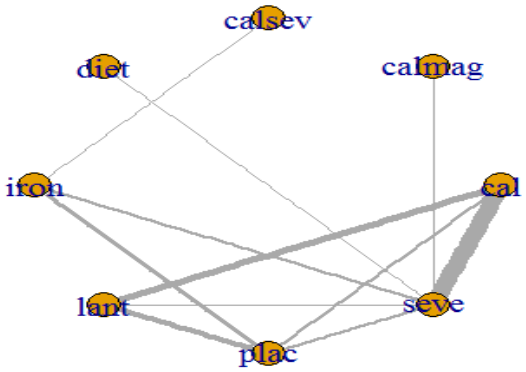


Figure 5. Network of clinical trials of phosphate binders in patients with chronic kidney disease: outcome mean change from baseline in serum calcium concentration

Legend: Netplot of effectiveness outcome for mean calcium reduction at the end of the study period. Network of randomized controlled trials comparing different phosphate binders for mean change in serum calcium. Lines connect different phosphate binder categories with direct evidence. The width of lines correlates the number of RCTs for each direct comparison while the size of the nodes correlates with the total sample size. Abbreviations: cal: calcium; calmag: calcium and magnesium; calsev: calcium and Sevelamer; Lant: lanthanum; seve: Sevelamer.

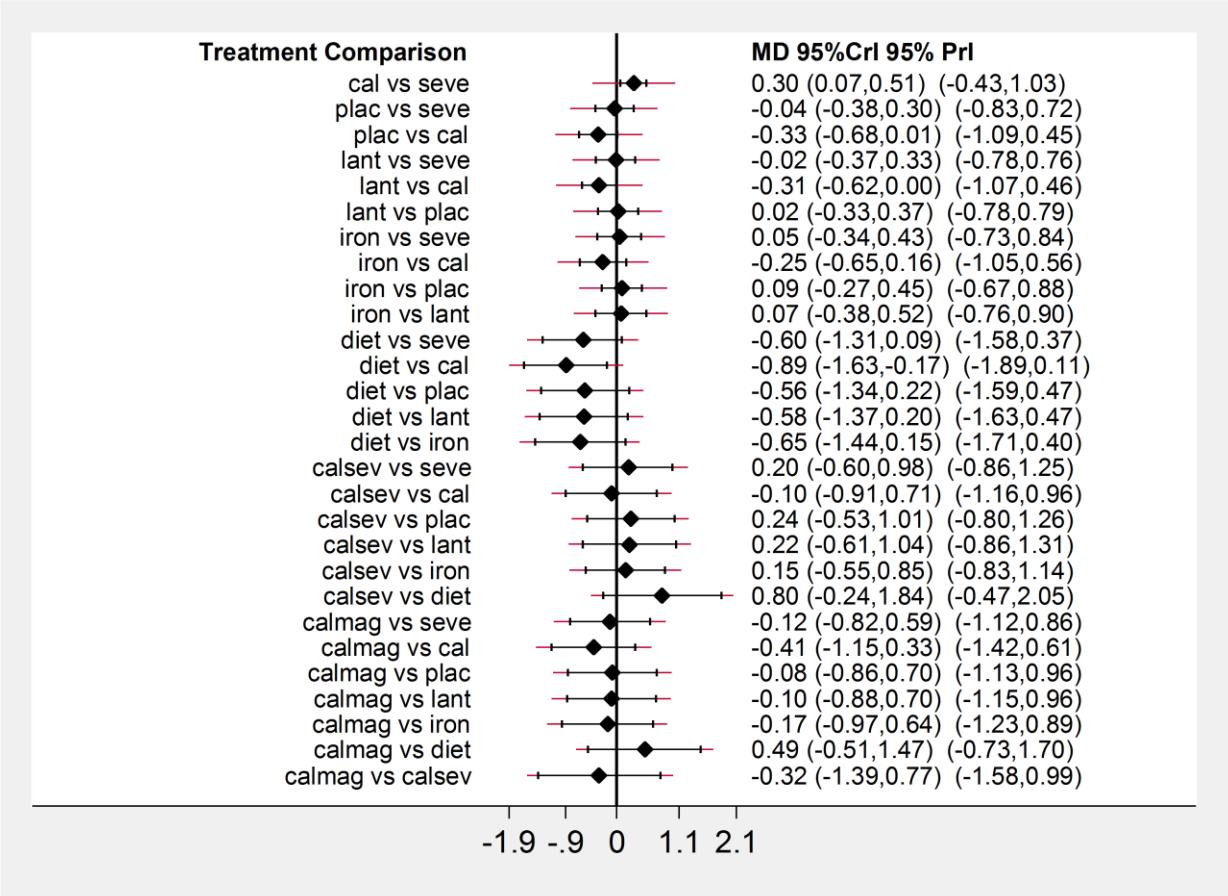


Figure 6. Network meta-analysis results for serum calcium

Legend: Forest plot of effectiveness outcome for mean calcium reduction at the end of the study period; MD: Mean difference; CrI: Credible interval; PrI: predictive intervals.

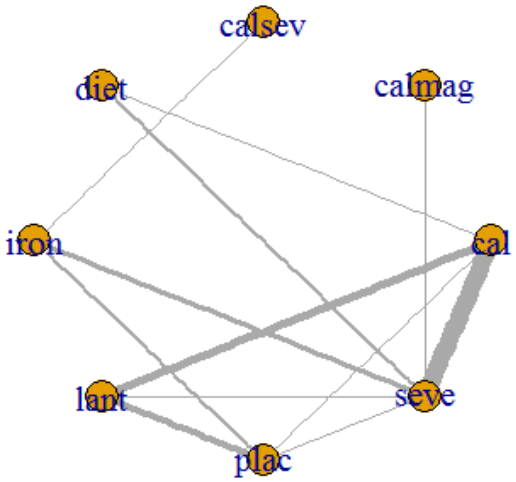


Figure 7. Network of clinical trials of phosphate binders in patients with chronic kidney disease: outcome mean change from baseline in serum parathyroid hormone concentration

Legend: Netplot of effectiveness outcome for mean parathyroid hormone reduction at the end of the study period. Network of randomized controlled trials comparing different phosphate binders for mean change in serum parathyroid hormone Lines connect different phosphate binder categories with direct evidence. The width of lines correlates the number of RCTs for each direct comparison while the size of the nodes correlates with the total sample size. Abbreviations: cal: calcium; calmag: calcium and magnesium; calsev: calcium and Sevelamer; Lant: lanthanum; seve: Sevelamer.

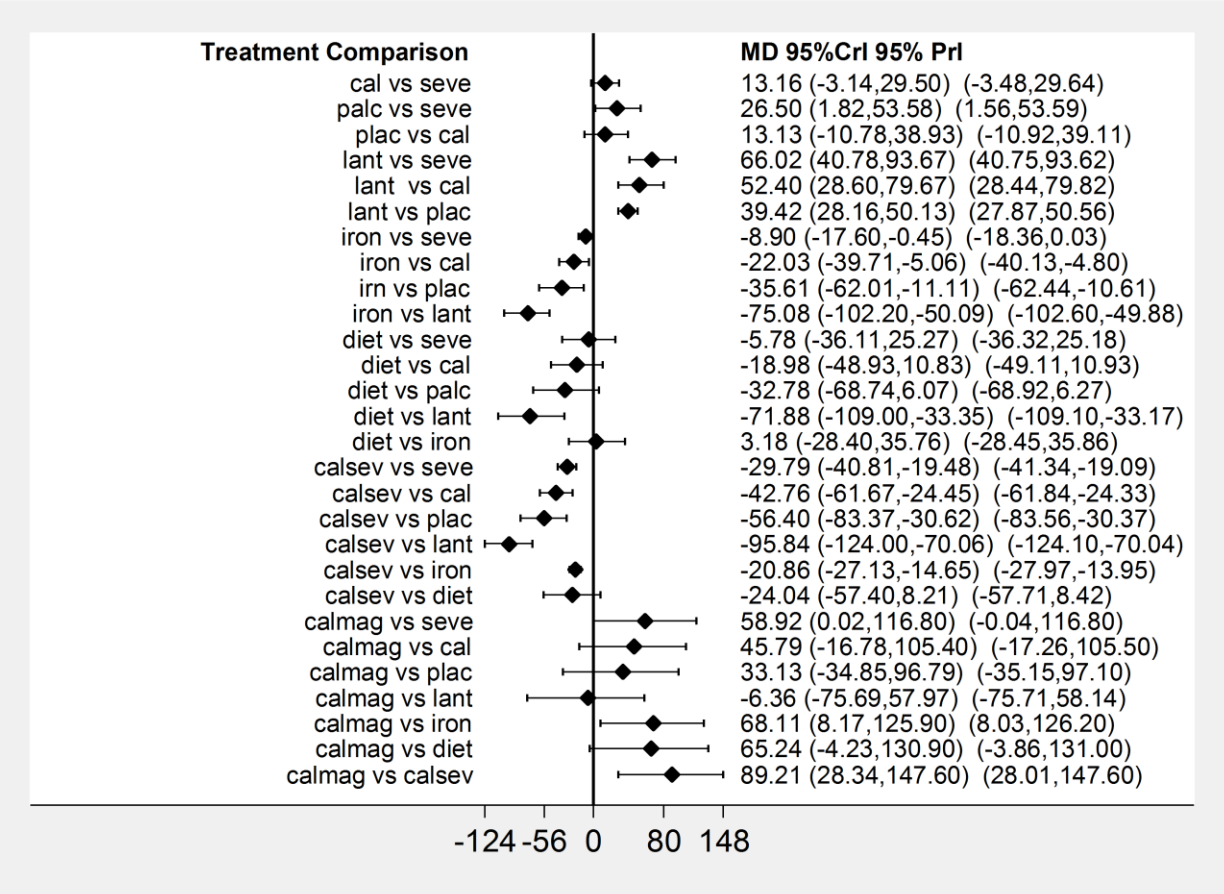


Figure 8 Network meta-analysis results for serum parathyroid hormone

Legend: Forest plot of effectiveness outcome for mean parathyroid hormone reduction at the end of the study period; MD: Mean difference; CrI: Credible interval; PrI: predictive interval.

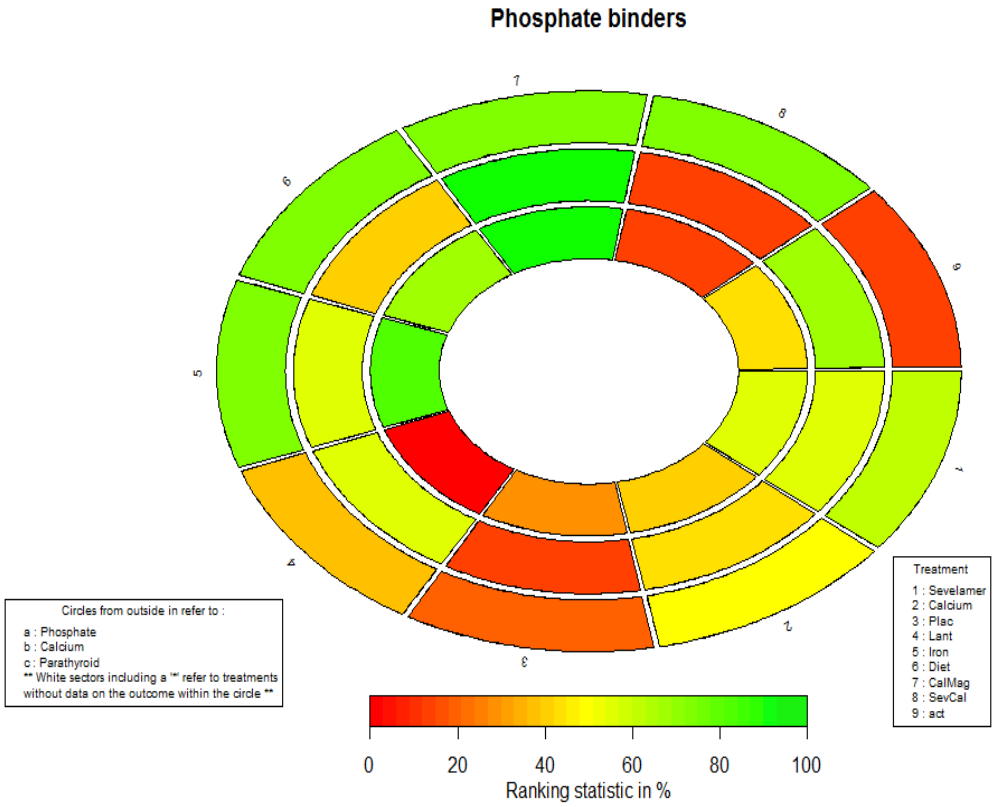


Figure 9. Rank-heat plot of the phosphate binder network for laboratory outcomes

Supplementary content

Comparative effectiveness of phosphate binders in patients with chronic kidney disease: A systematic review and network meta-analysis. Nigar Sekercioglu, Areti Angeliki Veroniki, Lehana Thabane, Jason W. Busse, Noori Akhtar-Danesh, Alfonso Iorio, Luciane Cruz Lopes, Gordon H. Guyatt.

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

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S1. File Search strategies MEDLINE OVID, EMBASE OVID

(((kidney* or nephro* or renal or home or peritoneal or intermittent or chronic or extracorporeal or ambulatory) adj2 (haemodialys* or hemodialys* or dialys*)) or hemorenodialysis or hemodialyse or CAPD).ti,ab.

renal dialysis/ or hemodialysis, home/ or peritoneal dialysis/ or peritoneal dialysis, continuous ambulatory/

renal insufficiency, chronic/ or kidney failure, chronic/

(((chronic or "end-stage" or "end stage") adj3 (kidney* or renal or nephro*) adj3 (insufficien* or disease*)) or esrd).ti,ab.

renal osteodystrophy/ or ((renal or kidney* or nephro*) adj2 (osteodystroph* or ricket*)).mp.

azotemia/ or azotemi*.mp

uremia/ or uremi*.mp.

1 or 2 or 3 or 4 or 5 or 6 or 7

controlled clinical trial.pt. or controlled clinical trials as topic/ or meta analysis.pt. or meta analysis as topic/ or multicentre study.pt. or multicenter studies as topic/ or randomized controlled trial.pt. or randomized controlled trials as topic/ or pragmatic clinical trial.pt. or Pragmatic Clinical Trials as Topic/ or ((preference or practical or pragmatic or "real world" or naturalistic) adj5 trial*).ti,ab. or Comparative Effectiveness Research/ or ((comparative adj2 effectiveness) or (CER adj5 (research* or method* or framework* or compari* or statement*))).ti,ab. or ((singl: or doubl: or tripl: or trebl:) and (mask: or blind:)).ti,ab. or ((random: adj5 trial:) or rct or rcts).ti,ab.

calcium/ or (calc* or calc* acet* or Calc* acet* or Cal* car* or Cal*Car).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

(phosphate binders or phosphate lowering agent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

(lanthanum or lanthanum carbonate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

(sevelamer or sevela*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

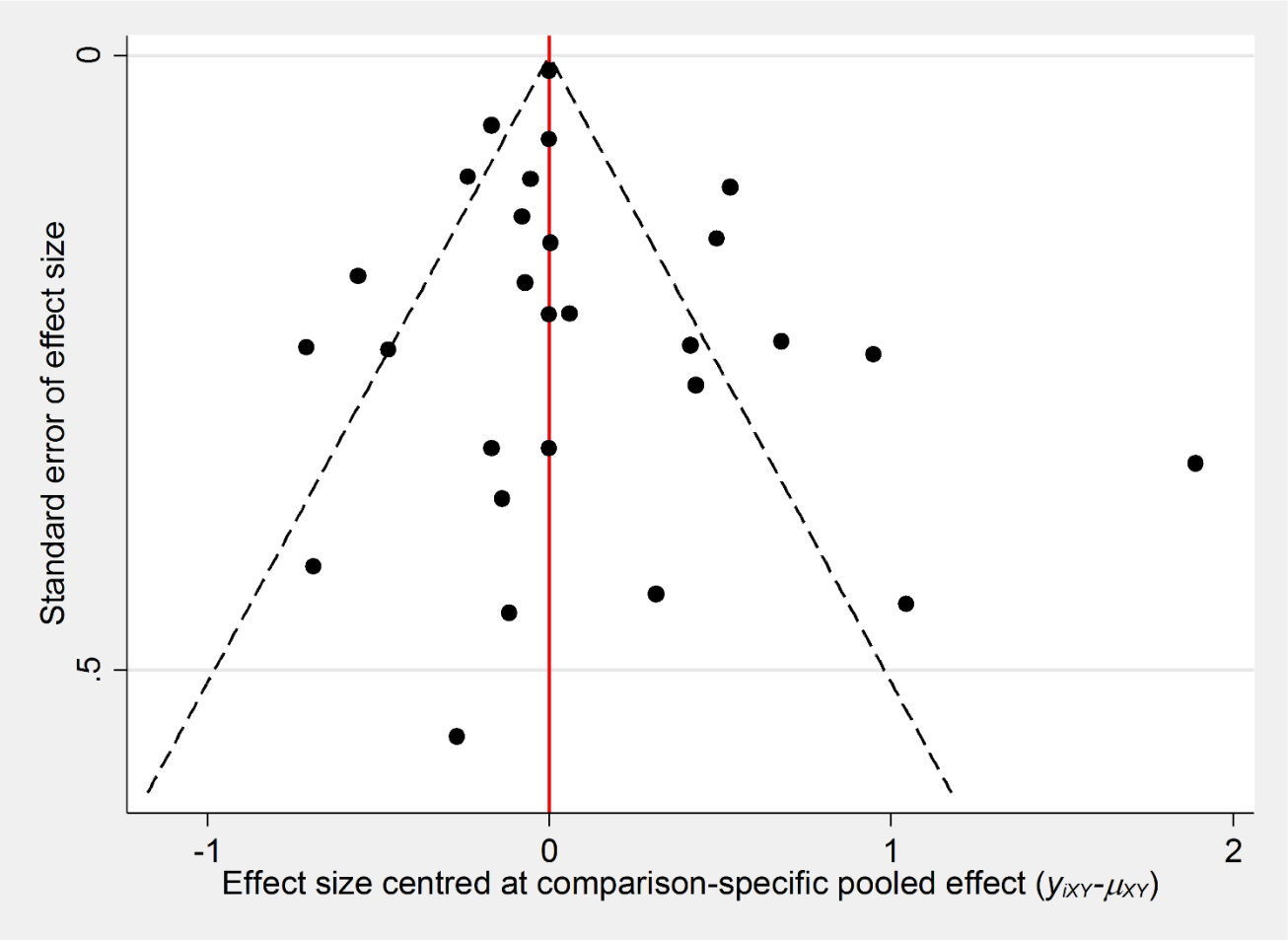
(iron or ferrous citrate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

10 or 11 or 12 or 13 or 14

8 and 9 and 14

limit 25 to yr="2013 -Current"

S1 Figure. Assessment of publication bias by funnel plots for phosphate outcome



Note: Funnel plot of effectiveness outcome for mean phosphate reduction at the end of the study period

S1 Table. Study Characteristics

Study, Year (Reference)	Country	Randomly assigned patients, n	Number of arms	Women, %	Age, y (SD)	Stage of CKD	Comparison	Follow-up duration in months
Chertow et al, 2002[38]	United States, Austria and Germany	99 101	2	70, 35%	57 (14) 56 (16)	Stage 5D	Sevelamer vs. calcium	12
Sadek et al, 2003[39]	France	21 21	2	-	-	Stage 5D	Sevelamer vs. calcium	5
Block et al, 2007 [40]	United States and Italy	60 67	2	42% 36%	56 (14) 58 (14)	Stage 5D	Sevelamer vs. calcium	60
Russo et al, 2007 [41]	Italy	30 30 30	3	3 (10%) 5 (16%)	55 (13) 54 (12)	Non-dialysis	Sevelamer vs. calcium vs. phosphorus restricted diet	24
Barreto et al, 2008 [42]	Brazil	52 49	2	34% 30%	47 (13) 47 (14)	Stage 5D	Sevelamer vs. calcium	12
Qunibi et al, 2008 [43]	United States	100 103	2	54% 42%	60 (12) 58 (12)	Stage 5D	Sevelamer vs. calcium	12
Suki et al, 2008[44]	United States	1053 1050	2	479 (45%) 481(48%)	59 (14) 60 (15)	Stage 5D	Sevelamer vs. calcium	45
Takei et al, 2008[45]	Japan	22 20	2	50% 45%	54 (10) 54 (9)	Stage 5D	Sevelamer vs. calcium	6
Wilson et al, 2009 [46]	United States and United Kingdom	680 674	2	42% 38%	54 (14) 60 (14)	Stage 5D	Lanthanum vs. Standard treatment	24
De Francisco	Spain, Portugal, Germany,	127 125	2	49% 47%	56 (12)	Stage 5D	Sevelamer vs. calcium	6

et al, 2010[48]	Italy, Romania and Poland				59 (14)			
Gulati et al, 2010[66]	India	11 11	2	50% 45%	10 (5) 10(5)	Non-dialysis	Sevelamer vs. calcium	3
Kakuta et al, 2011 [49]	Japan	91 92	2	43% 49%	59 (12) 57 (12)	Stage 5D	Sevelamer vs. calcium	12
Toussaint et al, 2011 [50]	Australia	22 23	2	45% 26%	56 (15) 59 (15)	Stage 5D	Lanthanum vs calcium	18
Block et al, 2012[47]	United States, Germany and United Kingdom	57 28 30 30	4	21% 18% 20% 20%	65 (12) 70 (10) 66 (12) 68 (12)	Non-dialysis	Placebo vs. Lanthanum vs. Sevelamer vs. Calcium	10 (median follow-up time 249 days)
Di Iorio et al, 2012[51]	United States and Italy	232 234	2	50% 52%	67 (14) 65 (15)	Stage 5D	Sevelamer vs. calcium	24
Di Iorio et al, 2013 [52]	Italy	121 118	2	39% 39%	57 (12) 59 (12)	Non-dialysis	Sevelamer vs. calcium	36
Lee et al, 2013 [53]	Korea	50	2	45% 63%	48 (11) 52 (11)	Stage 5D	Lanthanum vs calcium	6
Ohtake et al, 2013 [54]	Japan	26 26	2	40%	68 (6)	Stage 5D	Lanthanum vs calcium	12
Wuthrich et al, 2013 [55]	Canada, United States, Romania, and Switzerland	24 126	2	58% 37%	60 (13) 62 (11)	Stage 5D	Sevelamer vs. sucroferric oxyhydroxide	1.5
Xu et al, 2013 [56]	China	115 115	2	47% 36%	48 (13) 48 (12)	Stage 5D	Lanthanum vs. Placebo	2

Floege et al, 2014[57]	United States, Romania, Germany and Switzerland	349 710	2	37% 45%	56 (15) 56 (13)	Stage 5D	Sevelamer vs. sucroferric oxyhydroxide	6
Takahara et al, 2014 [58]	Japan	86 55	2	55% 27%	61 (11) 62 (13)	Non-dialysis	Lanthanum vs. Placebo	2
Urena-Torres et al, 2014 [59]	France	17 12	2	41% 58%	66 (15) 69 (13)	Non-dialysis	Lanthanum vs. Placebo	3
Wada et al, 2014 [60]	Japan	21 22	2	23% 21%	66 (10) 66 (8)	Stage 5D	Lanthanum vs calcium	12
Yokoyama et al, 2014 [61]	Japan and Unites States	110 115	2	35% 37%	62 (10) 60 (11)	Stage 5D	Sevelamer vs JTT-751	3
Yokoyama et al, 2014 [62]	Japan and Unites States	60 30	2	42% 41%	65 (10) 65 (14)	Non-dialysis and dialysis	Ferric citrate vs. Placebo	3
Block et al, 2015[63]	United States, Germany and Spain	75 74	2	69% 62%	66 (12) 64 (14)	Non-dialysis and dialysis	Ferric citrate vs. Placebo	3
Lee et al, 2015 [64]	Taiwan	36 75 72	3	37% 43% 31%	53 (12) 53 (11) 53 (12)	Stage 5D	Ferric citrate vs. Placebo	2
Lewis et al, 2015 [65]	United States	292 149	2	37% 42%	56 (45-63) 54 (45-63)	Stage 5D	Ferric citrate vs. Active control (calcium acetate and sevelamer)	12

S2 Table. Treatment codes, treatment categories and abbreviations used in the analysis

Code	Treatment name	Abbreviation
1	sevelamer	seve
2	calcium	cal
3	placebo	plac
4	lanthanum	lant
5	iron	iron
6	Low phosphorus diet	Diet
7	Calcium and sevelamer	calsev
8	Calcium and magnesium	calmag
9	Calcium or Sevelamer or lanthanum	calsevlant

S3 Table. Treatment comparisons, number of studies and number of patients for phosphate outcome

Treatment Comparison	Coded Treatment Comparison	Number of studies	Number of patients
Cal vs. sev	2 vs 1	10	3560
Iron vs. sev	5 vs 1	3	1336
Diet vs. sev	6 vs 1	2	120
Calmag vs. sev	8 vs 1	1	252
Lant vs. cal	4 vs 2	3	140
Diet vs. cal	6 vs 2	1	60
Lant vs. plac	4 vs 3	3	408
Iron vs. plac	5 vs 3	3	418
Calsevlant vs plac	9 vs 3	1	145
Calsev vs. iron	7 vs 5	1	441

S4 Table. GRADE quality assessment of direct evidence from each pairwise treatment comparison for phosphate outcome

Treatment comparison	Number of head-to-head trials; n	Study Limitations	Precision	Consistency	Directness	Publication bias	Overall quality of evidence	Direct estimate[2,3]; MD (95% CrI)	Direct estimate[2,4;] MD (95% CI)
Sevelamer vs. Calcium	10;3560	Not serious	Serious limitations	Serious limitations (I^2:84%)	Not serious	Not likely	Low	0.05 (-0.36 to 0.46)	0.09 (-0.17 to 0.34)
Sevelamer vs. Iron	3; 1303	Serious (due to allocation concealment)	Serious limitations	Serious limitations (I^2:65%)	Not serious	N/A	Very Low	-0.28 (-1.06 to 0.45)	-0.16 (-0.51 to 0.19)
Sevelamer vs. diet	1; 60	Not serious	Very serious limitations[1]	Serious limitations (I^2:94%)	Not serious	N/A	Very Low	-0.20 (-1.12 to 0.71)	-0.21 (-1.57 to 1.16)
Sevelamer vs. calmag	1; 252	Not serious	Very serious limitations[1]	N/A	Not serious	N/A	Low	-0.17 (-0.59 to 0.23)	-0.18 (-0.59 to 0.23)
Lanthanum vs. Calcium	3; 140	Serious (due to allocation concealment)	Serious limitations	Not serious limitations (I^2:0%)	Not serious	N/A	Low	0.15 (-0.69 to 0.98)	0.16 (-0.30 to0.63)
Calcium vs. diet	1; 30	Not serious	No serious limitations	N/A	Not serious	N/A	High	-0.79 (-1.42 to -0.17)	-0.80 (-1.43 to -0.17)

Lanthanum vs Placebo	3; 408	Not serious	No serious limitations	Serious limitations (I^2:92%)	Not serious	N/A	Moderate	-0.87 (-1.6 to -0.14)	-0.89 (-1.73 to -0.05)
Iron vs. placebo	3; 418	Not serious	No serious limitations	Serious limitations (I^2:95%)	Not serious	N/A	Moderate	-1.49 (-2.2 to -0.69)	-1.49 (-2.58 to -0.40)
Placebo vs. calsevlant	1; 145	Not serious	Serious limitations	N/A	Not serious	N/A	Moderate	-0.09 (-0.23 to 0.03)	-0.10 (-0.23 to 0.03)
Iron vs Calsev	1; 441	Not serious	Serious limitations	N/A	Not serious	N/A	Moderate	0.01 (-0.003 to 0.04)	0.02 (-0.001 to 0.04)
Common within network between-study variance (95% Crl) = 0.15 (0.34 to 0.78)									

Note: For domains "Study Limitations", "Precision", "Consistency", and "Directness": No serious limitations, Serious limitations or Very serious limitations. For the domain "Publication bias": Not likely, Likely to exist or not applicable if the comparison has less than ten trials. Reasons are provided when rating down. All direct comparisons begin with a "High" rating.[1]Rated down two levels for imprecision;[2]We employed random effect models, [3]Bayesian methods used, [4]The frequentist method used. CI: Confidence interval; Crl: credible intervals; MD: mean difference; N/A: not applicable. I^2 indicates the expected degree of change in the effect estimates due to between-study variance.

S5 Table. GRADE confidence assessments of indirect estimates per pairwise treatment comparison for phosphate in cases when direct comparisons are available

Treatment comparisons	Is a first order loop available?	Common comparator treatment in dominant first order loop (in the absence of first order loop, possible comparisons in higher order loop)	GRADE of first contributing direct comparison: name of the contributors (quality of evidence)	GRADE of second contributing direct comparison (quality of evidence)	Final GRADE of indirect comparison
Sevelamer vs. Calcium	Yes	Diet	Diet calcium (H)	Diet sevelamer (L)	Low
Sevelamer vs. Iron	No	Iron placebo (M) Placebo lanthanum (M) Lanthanum calcium (L) Calcium Sevelamer (L)	Not available	Not available	Low
Sevelamer vs. diet	Closed loop formed by a multi-arm trial	Not available	Not available	Not available	Not available
Sevelamer vs. calmag	Unconnected comparison	Unconnected comparison	Not available	Not available	Not available
Lanthanum vs. Calcium	No	Calcium sevelamer (L) Sevelamer iron (VL)	Not available	Not available	Very Low

		Iron placebo (M) Placebo lanthanum (M)			
Calcium vs. diet	Yes	Sevelamer	Diet sevalamer (VL)	Calcium sevalamer (L)	Very Low
Lanthanum vs. Placebo	No	Placebo Iron (M) Iron sevelamer (VL) Sevelamer calcium (L) Calcium lanthanum (L)	Not available	Not available	Very Low
Iron vs. placebo	No	Placebo lanthanum (M) Lanthanum calcium (L) Calcium Sevelamer (L) Sevelamer iron (VL)	Not available	Not available	Very Low
Placebo vs. Calsevlant	Unconnected comparison	Unconnected comparison	Not available	Not available	Not available
Iron vs. Calsev	Unconnected comparison	Unconnected comparison	Not available	Not available	Not available

Note: A single first order loop for each pairwise comparison is used to GRADE indirect estimates. All indirect comparisons begin with the lower of the two contributing direct estimates and undergo an assessment of transitivity.; The quality of evidence rating for the indirect comparisons informing each paired comparison was the lower of the ratings of quality for the direct estimates contributing to the first or higher order loop. Abbreviations:

calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum; H: high; Low: low; M: moderate; VL: very low.

S6 Table. GRADE confidence assessments of indirect estimates per pairwise treatment comparison for phosphate in cases when direct comparisons are unavailable

Treatment comparisons	First order loop available	Common comparator treatment in the dominant first order loop (in the absence of the first order loop, possible comparisons in higher order loop)	GRADE of first contributing direct comparison: name of the contributors (quality of evidence)	GRADE of second contributing direct comparison	Final GRADE of Indirect Comparison
Sevelamer vs. placebo	Yes	Iron	Sevelamer iron (VL)	Placebo iron (M)	Very Low
Lanthanum vs. sevelamer	Yes	calcium	Calcium sevelamer (L)	Calcium lanthanum (L)	Low
Calcium vs. placebo	Yes	Lanthanum	Placebo lanthanum (M)	Calcium lanthanum (L)	Low

Iron vs. lanthanum	No	Lanthanum placebo (M) Placebo iron (M) Iron Sevelamer (VL) Sevelamer calcium (L) Calcium lanthanum (L)	Not available	Not available	Very Low
Iron vs. calcium	Yes	Iron	Iron sevelamer (L)	Calcium sevelamer (VL)	Very low
Diet vs. placebo	No	Placebo lanthanum (M) Lanthanum calcium (L) Calcium Sevelamer (L) Sevelamer diet (VL)	Not available	Not available	Very Low

Diet vs. lanthanum	Yes	Calcium	Diet calcium (H)	Lanthanum calcium (L)	Low
Iron vs. diet	Yes	Sevelamer	Iron sevelamer (VL)	Diet sevelamer (VL)	Very Low
Cal vs. calsev	No	Calcium Sevelamer (L) Sevelamer iron (VL) Iron calsev (M)	Not available	Not available	Very Low
Calsev vs. sevelamer	Yes	Iron	Calsev iron (M)	Iron sevelamer (VL)	Very Low
Calsev vs. placebo	Yes	Iron	Calsev iron (M)	Placebo iron (M)	Moderate
Calsev vs. lanthanum	No	Lanthanum placebo (M) Placebo iron (M) Iron calsev (M)	Not available	Not available	Moderate
Calsev vs. diet	No	Diet Sevelamer (VL)	Not available	Not available	Very Low

		Sevelamer iron (VL) Iron calsev (M)			
Calmag vs. calcium	Yes	Sevelamer	Calcium vs. Sevelamer (L)	Calmag vs. Sevelamer (L)	Low
Calmag vs. placebo	No	Placebo lanthanum (M) Lanthanum calcium (L) Calcium Sevelamer (L) Sevelamer calmag (L)	Not available	Not available	Low
Calmag vs. lanthanum	No	Lanthanum calcium (L) Calcium Sevelamer (L) Sevelamer calmag (L)	Not available	Not available	Low
Calmag vs. iron	Yes	Sevelamer	Calmag vs. Sevelamer	Iron vs. Sevelamer (VL)	Very Low

			(L)		
Calmag vs. diet	Yes	Sevelamer	Calmag vs. Sevelamer (L)	Diet vs. Sevelamer (VL)	Very Low
Calmag vs. calsev	No	Calmag Sevelamer (L) Sevelamer iron (VL) Iron calsev (M)	Not available	Not available	Very Low
Calsevlant vs. sevelamer	No	Sevelamer iron (VL) Iron placebo (M) Placebo calsevlant (M)	Not available	Not available	Very Low
Calsevlant vs. calcium	No	Calcium lanthanum (L) Lanthanum placebo (M) Placebo calsevlant (M)	Not available	Not available	Low

Calsevlant vs. lanthanum	Yes	Placebo	Placebo vs. lanthanum (M)	Calsevlant vs. placebo (M)	Moderate
Calsevlant vs. iron	Yes	Placebo	Placebo vs. iron (M)	Calsevlant vs. placebo (M)	Moderate
Calsevlant vs. diet	No	Diet Sevelamer (VL) Sevelamer iron (VL) Iron placebo (M) Placebo calsevlant (M)	Not available	Not available	Very Low
Calsevlant vs. calsev	No	Calsev iron (M) iron vs. placebo (M) Placebo calsevlant (M)	Not available	Not available	Moderate
Calsevlant vs. calmag	No	Calmag Sevelamer (L) Sevelamer iron (VL)	Not available	Not available	Very Low

		Iron placebo (M) Placebo calsevlant (M)			

Note: A single first order loop for each pairwise comparison is used to GRADE indirect estimates. All indirect comparisons begin with the lower of the two contributing direct estimates and undergo an assessment of transitivity.; The quality of evidence rating for the indirect comparisons informing each paired comparison was the lower of the ratings of quality for the direct estimates contributing to the first or higher order loop.
Abbreviations: calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum; H: high; Low: low; M: moderate; VL: very low.

S7 Table. GRADE quality assessment of direct evidence from each pairwise treatment comparison for calcium outcome

Treatment comparison	Number of head-to-head trials; n	Study Limitations	Precision	Consistency	Directness	Publication bias	Overall quality of evidence	Direct estimate[2]; MD (95% CrI)	Direct estimate[2],[4]; MD (95% CI)
Sevelamer vs. Calcium	11;3620	Not serious	Not serious	Serious limitations (I^2:95%)	Not serious	Not serious	Moderate	0.30 (0.08 to 0.51)	0.29 (0.04 to 0.55)
Sevelamer vs. placebo	1; 60	Not serious	Not serious	N/A	Not serious	N/A	High	0.10 (0.39 to 0.59)	0.60 (0.46 to 0.74)
Sevelamer vs. Lanthanum	1; 58	Not serious	Serious limitations	N/A	Not serious	N/A	Moderate	-0.09 (-0.33 to 0.13)	-0.10 (-0.33 to 0.13)
Sevelamer vs. Iron	2; 381	Serious (due to allocation concealment)	Serious limitations	Serious limitations (I^2:91%)	Not serious	N/A	Very low	-0.15 (-0.64 to 0.34)	-0.16 (-0.73 to 0.41)
Sevelamer vs. diet	1; 60	Not serious	Not serious	N/A	Not serious	N/A	Moderate	-0.60 (-0.74 to -0.45)	-0.60 (-0.74 to -0.46)

Sevelamer vs. calcium and magnesium	1; 252	Not serious	Not serious	N/A	Not serious	N/A	High	-012 (-0.26 to 0.02)	-012 (-0.27 to 0.03)
Placebo vs. calcium	2; 147	Not serious	Serious limitations	Serious limitations (I^2:72%)	Not serious	N/A	Low	-0.01 (-0.5 to 0.5)	-0.02 (-0.41 to 0.37)
Lanthanum vs. Calcium	5; 248	Serious (due to allocation concealment)	No serious limitations	No serious limitations (I^2:0%)	Not serious	N/A	Moderate	-0.33 (-0.67 to 0.009)	-0.30 (-0.47 to -0.14)
Lanthanum vs Placebo	3; 408	Not serious	Serious limitations	No serious limitations (I^2:0%)	Not serious	N/A	Moderate	0.07 (-0.33 to 0.48)	0.12 (-0.09 to 0.33)
Iron vs. placebo	3; 418	Not serious	No serious limitations	No serious limitations (I^2:0%)	Not serious	N/A	High	0.22 (-0.18 to 0.62)	0.24 (-0.11 to 0.37)
Iron vs Calsev	1; 441	Not serious	No serious limitations	N/A	Not serious	N/A	High	0.15 (0.13 to 0.16)	0.15 (0.14 to 0.16)
Common within network between-study variance 0.10 (0.05 to 0.22)									

Note: For domains “Study Limitations”, “Precision”, “Consistency”, and “Directness”: No serious limitations, Serious limitations or Very serious limitations. For the domain “Publication bias”: Not likely, Likely to exist or not applicable if the comparison has less than ten trials. Reasons are provided when rating down. All direct comparisons begin with a “High” rating. [1]Rated down two levels for imprecision; [2]We employed random effect models, [3]Bayesian methods used, [4]The frequentist method used. CI: Confidence interval; Crl: credible intervals; MD: mean difference; N/A: not applicable. I^2 indicates the expected degree of change in the effect estimates due to between-study variance.

S8 Table. GRADE confidence assessments of indirect estimates per pairwise treatment comparison for calcium when direct comparisons are available

Treatment comparisons	First order loop available	Common comparator treatment in the dominant first order loop (in the absence of the first order loop, possible comparisons in higher order loop)	GRADE of first contributing direct comparison; name of the contributors (quality of evidence)	GRADE of second contributing direct comparison	Final GRADE of Indirect Comparison
Sevelamer vs. Calcium	Yes	Lanthanum	Calcium vs. lanthanum (M)	Sevelamer vs. lanthanum (M)	Moderate
Sevelamer vs. placebo	Yes	Calcium	Placebo calcium (L)	Sevelamer vs. calcium (M)	Low
Sevelamer vs. Lanthanum	Yes	Calcium	Sevelamer calcium (M)	Calcium lanthanum (M)	Moderate

Sevelamer vs. Iron	Yes	Placebo	Placebo Sevelamer (H)	Placebo iron (H)	High
Sevelamer vs. diet	Unconnected comparison	Not available	Not available	Not available	Not available
Sevelamer vs. calmag	Unconnected comparison	Not available	Not possible	Not possible	Not available
Placebo vs. calcium	Yes	Lanthanum	Lanthanum placebo (H)	Calcium lanthanum (M)	Moderate
Lanthanum vs. Calcium	Yes	Placebo	Lanthanum placebo (H)	Calcium placebo (L)	Low
Lanthanum vs. Placebo	Yes	Calcium	Calcium placebo (L)	Calcium lanthanum (M)	Low
Iron vs. placebo	Yes	Sevelamer	Iron sevelamer (VL)	Placebo sevelamer (H)	Very Low
Iron vs. Calsev	Unconnected comparison	Not available	Not possible	Not possible	Not available

Note: A single first order loop for each pairwise comparison is used to GRADE indirect estimates. All indirect comparisons begin with the lower of the two contributing direct estimates and undergo an assessment of transitivity.; The quality of evidence rating for the indirect comparisons

informing each paired comparison was the lower of the ratings of quality for the direct estimates contributing to the first or higher order loop. Abbreviations: calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum; H: high; Low: low; M: moderate; VL: very low.

S9 Table. GRADE confidence assessments of indirect estimates per pairwise treatment comparison for calcium when direct comparisons are unavailable

Treatment comparisons	First order loop available	Common comparator treatment in the dominant first order loop (in the absence of the first order loop, possible comparisons in higher order loop)	GRADE of first contributing direct comparison; name of the contributors (quality of evidence)	GRADE of second contributing direct comparison	Final GRADE of Indirect Comparison
Iron vs. calcium	Yes	Sevelamer	Iron sevelamer (VL)	Calcium sevelamer (M)	Very Low
Iron vs. lanthanum	Yes	Sevelamer	Iron sevelamer (VL)	Lanthanum sevelamer (M)	Very Low
Diet vs. calcium	Yes	Sevelamer	Diet sevelamer (M)	Calcium sevelamer (M)	Moderate
Diet vs. placebo	Yes	Sevelamer	Diet sevelamer	Placebo sevelamer	Moderate

			(M)	(H)	
Diet vs. lanthanum	Yes	Sevelamer	Diet sevelamer (M)	Lanthanum sevelamer (M)	Moderate
Diet vs. Iron	Yes	Sevelamer	Diet sevelamer (M)	Iron sevelamer (VL)	Very Low
Calsev vs. sevelamer	Yes	Iron	Sevelamer iron (VL)	Iron calsev (H)	Very Low
Calsev vs. calcium	No	Calcium Sevelamer (M) Sevelamer iron (VL) Iron calsev (H)	Not available	Not available	Very Low
Calsev vs. placebo	Yes	Iron	Placebo iron (H)	Calsev iron (H)	High
Calsev vs. lanthanum	No	Lanthanum calcium (M) Calcium Sevelamer (M) Sevelamer iron (VL)	Not available	Not available	Very Low

		Iron calsev (H)			
Calsev vs. diet	No	Diet Sevelamer (M) Sevelamer iron (VL) Iron calsev (H)	Not available	Not available	Very Low
Calmag vs. calcium	Yes	Sevelamer	Calcium sevelamer (M)	Calmag sevelamer (H)	Moderate
Calmag vs. placebo	Yes	Sevelamer	Placebo sevelamer (H)	Calmag sevelamer (H)	High
Calmag vs. lanthanum	Yes	Sevelamer	Lanthanum sevelamer (M)	Calmag sevelamer (H)	Moderate
Calmag vs. iron	Yes	Sevelamer	Sevelamer iron (VL)	Calmag vs. Sevelamer (H)	Very Low
Calmag vs. diet	Yes	Sevelamer	Diet sevelamer (M)	Calmag vs. Sevelamer (H)	Moderate

Calmag vs. calsev[a]	No	Calmag Sevelamer (H) Sevelamer iron (VL) Iron calsev (H)	Not available	Not available	Very Low

Note: A single first order loop for each pairwise comparison is used to GRADE indirect estimates. All indirect comparisons begin with the lower of the two contributing direct estimates and undergo an assessment of transitivity.; The quality of evidence rating for the indirect comparisons informing each paired comparison was the lower of the ratings of quality for the direct estimates contributing to the first or higher order loop.
Abbreviations: calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum; H: high; Low: low; M: moderate; VL: very low.

S10 Table. GRADE quality assessment of direct evidence from each pairwise treatment comparison for parathyroid hormone outcome

Treatment comparison	Number of head-to-head trials; n	Study Limitations	Precision	Consistency	Directness	Publication bias	Overall quality of evidence	Direct estimate[2]; MD (95% CrI)	Direct estimate[2],[4;] MD (95% CI)
Sevelamer vs. calcium	11; 3620	Not serious	Serious limitations	Serious limitations; (I^2: 58%)	No serious limitations	No serious limitations	Low	12 (-6.89 to 31)	4.63 (-31 to 41)
Placebo vs. sevelamer	1; 60	Not serious	No serious limitations	N/A	No serious limitations	N/A	High	66 (4 to 129)	172 (20 to 323)
Lanthanum vs. sevelamer	1; 58	Not serious	Serious limitations	N/A	No serious limitations	N/A	High	54 (-18 to 127)	48 (-31 to 127)
Iron vs. sevelamer	3; 1440	Serious (due to allocation concealment)	Serious limitations	Serious limitations; (I^2: 58%)	No serious limitations	N/A	Very low	-13 (-135 to 105)	-13 (-91 to 65)
Diet vs. sevelamer	1; 60	Not serious	No serious limitations	N/A	No serious limitations	N/A	High	11 (-23 to 47)	172 (20 to 323)
Calmag vs. sevelamer	1; 252	Not serious	Serious limitations	N/A	No serious limitations	N/A	Moderate	59 (1.7 to 116)	47 (-13 to 107)
Placebo vs calcium	1;87	Not serious	Serious limitations	N/A	No serious limitations	N/A	Moderate	67 (3.6 to 131)	59 (-10 to 126)

Lanthanum vs. calcium	4; 190	Serious (due to allocation concealment)	Serious limitations	No serious limitations; (I^2: 37%)	No serious limitations	N/A	Low	44 (9.2 to 80)	26 (-32 to 84)
Diet vs. calcium	1; 60	Not serious	No serious limitations	N/A	No serious limitations	N/A	High	-26 (-59 to 6.8)	-29 (-62 to 4)
Lanthanum vs. placebo	3; 408	Not serious	No serious limitations	No serious limitations; (I^2: 0%)	No serious limitations	N/A	High	40 (29 to 50)	40 (29 to 50)
Iron s placebo	2; 235	Not serious	No serious limitations	No serious limitations; (I^2: 0%)	No serious limitations	N/A	High	-30 (-68 to 6.3)	-39 (-77 to 0.57)
Calcium and Sevelamer vs. iron	1; 441	Not serious	No serious limitations	N/A	No serious limitations	N/A	High	-20 (-26 to -15)	-21 (-26 to -15)
Common within network between-study variance 0.15 (0.34 to 0.78)									

Note: For domains "Study Limitations", "Precision", "Consistency", and "Directness": No serious limitations, Serious limitations or Very serious limitations. For the domain "Publication bias": Not likely, Likely to exist or not applicable if the comparison has less than ten trials. Reasons are provided when rating down. All direct comparisons begin with a "High" rating.[1]Rated down two levels for imprecision;[2]We employed random effect models, [3]Bayesian methods used, [4]The frequentist method used. CI: Confidence interval; Crl: credible intervals; MD: mean difference; N/A: not applicable. I^2 indicates the expected degree of change in the effect estimates due to between-study variance.

S11 Table. GRADE confidence assessments of indirect estimates per pairwise treatment comparison for parathyroid hormone when direct comparisons are available

Treatment comparisons	First order loop available	Common comparator treatment in the dominant first order loop (in the absence of the first order loop, possible comparisons in higher order loop)	GRADE of first contributing direct comparison; name of the contributors (quality of evidence)	GRADE of second contributing direct comparison	Final GRADE of Indirect Comparison
Sevelamer vs. calcium	Yes	Lanthanum	Calcium lanthanum (L)	Sevelamer lanthanum (H)	Low
Placebo vs. sevelamer	Yes	Iron	Placebo vs. iron (H)	Sevelamer vs. iron (VL)	Very Low
Lanthanum vs. sevelamer	Yes	Calcium	Sevelamer placebo (H)	Lanthanum placebo (H)	H
Iron vs. sevelamer	Yes	Placebo	Sevelamer vs. placebo (H)	Iron vs. placebo (H)	High

Diet vs. sevelamer	Closed loop formed by a multi-arm trial	Not available	Not available	Not available	Not available
Calmag vs. sevelamer	Unconnected comparison	Not available	Not available	Not available	Not available
Placebo vs. calcium	Yes	Lanthanum	Calcium vs. lanthanum (L)	Placebo vs. lanthanum (H)	Low
Lanthanum vs. calcium	Yes	Sevelamer	Calcium vs. Sevelamer (L)	Lanthanum vs. Sevelamer (H)	Low
Diet vs. calcium	Yes	Sevelamer	Calcium vs. Sevelamer (L)	Diet vs. Sevelamer (H)	Low
Lanthanum vs. placebo	Yes	Calcium	Calcium vs placebo (M)	Lanthanum vs. calcium (L)	Low
Iron vs. placebo	Yes	Sevelamer	Iron vs. Sevelamer (VL)	Placebo vs. Sevelamer (H)	Very Low
Calsev vs. iron	Unconnected comparison	Not available	Not available	Not available	Not available

Note: A single first order loop for each pairwise comparison is used to GRADE indirect estimates. All indirect comparisons begin with the lower of the two contributing direct estimates and undergo an assessment of transitivity.; The quality of evidence rating for the indirect comparisons informing each paired comparison was the lower of the ratings of quality for the direct estimates contributing to the first or higher order loop. Abbreviations: calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum; H: high; Low: low; M: moderate; VL: very low.

S12 Table. GRADE confidence assessments of indirect estimates per pairwise treatment comparison for parathyroid hormone when direct comparisons are unavailable[c]

Treatment comparisons	First order loop available	Common comparator treatment in the dominant first order loop (in the absence of the first order loop, possible comparisons in higher order loop)	GRADE of first contributing direct comparison; name of the contributors (quality of evidence)	GRADE of second contributing direct comparison	Final GRADE of Indirect Comparison
Iron vs. calcium	Yes	Sevelamer	Calcium sevelamer (L)	Iron sevelamer (VL)	Very Low
Iron vs. lanthanum	Yes	Sevelamer	Lanthanum sevelamer	Iron sevelamer	Very Low

			(H)	(VL)	
Diet vs. placebo	Yes	Sevelamer	Diet calcium (H)	Placebo calcium (M)	Moderate
Diet vs. lanthanum	Yes	Sevelamer	Diet sevelamer (H)	Lanthanum sevelamer (H)	High
Diet vs. Iron	Yes	Sevelamer	Diet sevelamer (H)	Iron sevelamer (VL)	Very Low
Calsev vs. sevelamer	Yes	Iron	Calsev iron (H)	Iron sevelamer (VL)	Very Low
Calsev vs. calcium	No	Calcium Sevelamer (L) Iron Sevelamer (VL) Calcium calsev (H)	Not available	Not available	Very Low
Calsev vs. Placebo	Yes	Iron	Calsev iron (H)	Placebo iron (H)	High
Calsev vs. Lanthanum	No	Lanthanum placebo (H)	Not available	Not available	High

		Placebo iron (H) Iron calsev (H)			
Calsev vs. diet	No	Diet Sevelamer (H) Sevelamer iron (VL) Iron calsev (H)	Not possible	Not possible	Very Low
Calmag vs. calcium	Yes	Sevelamer	Calcium sevelamer (L)	Calmag sevelamer (M)	Low
Calmag vs. placebo	Yes	Sevelamer	Placebo sevelamer (H)	Calmag sevelamer (M)	Moderate
Calmag vs. lanthanum	Yes	Sevelamer	Lanthanum sevelamer (H)	Calmag sevelamer (M)	Moderate
Calmag vs. Iron	Yes	Sevelamer	Iron sevelamer (VL)	Calmag sevelamer (M)	Very Low
Calmag vs. diet	Yes	Sevelamer	Diet sevelamer (H)	Calmag sevelamer (M)	Moderate

Calmag vs. calsev	No	Calmag Sevelamer (M) Sevelamer iron (VL) Iron calsev (H)	Not available	Not available	Very Low

Note: A single first order loop for each pairwise comparison is used to GRADE indirect estimates. All indirect comparisons begin with the lower of the two contributing direct estimates and undergo an assessment of transitivity.; The quality of evidence rating for the indirect comparisons informing each paired comparison was the lower of the ratings of quality for the direct estimates contributing to the first or higher order loop.
Abbreviations: calmag: calcium and magnesium; calsev: calcium and sevelamer; calsevlant: calcium or sevelamer or lanthanum; H: high; Low: low; M: moderate; VL: very low.

S13 Table. SUCRA rankings of phosphate binders

	Phosphorus; median (95% Crl)	Calcium; median (95% Crl)	Parathyroid hormone; median (95% Crl)
Sevelamer	0.63 (0.25 to 0.88)	0.57 (0.14 to 0.86)	0.57 (0.43 to 0.71)
Calcium	0.50 (0.25 to 0.88)	0.14 (0 to 0.43)	0.43 (0.29 to 0.57)
Placebo	0 (0 to 0.25)	0.57 (0.14 to 0.86)	0.29 (0.14 to 0.57)
Lanthanum	0.38 (0.13 to 0.88)	0.57 (0.14 to 0.86)	0.00 (0.00 to 0.14)
Iron	0.75 (0.38 to 1)	0.43 (0 to 0.86)	0.86 (0.71 to 0.86)
Diet	0.75 (0.25 to 1)	1.00 (0.29 to 1)	0.71 (0.29 to 1.00)
Calcium and sevelamer	0.75 (0.13 to 1.00)	0.14 (0 to 1)	1 (0.86 to 1)
Calcium and magnesium	0.75 (0 to 1)	0.71 (0 to 1)	0.14 (0 to 0.57)

Note: The results of surface under the cumulative ranking curve of eight phoshate binders; CrI: Credible interval; MD: Mean difference; SUCRA: surface under the cumulative ranking curve.

S14 Table. Effectiveness outcome for mean phosphate, calcium and parathyroid hormone reductions at the end of the study period using network meta-regression analysis for trial duration

	Phosphate; MD (95% Crl)	Calcium; MD (95% Crl)	Parathyroid hormone; MD (95% Crl)
Meta-regression coefficient	0.009 (-0.019 to 0.038)	0.011 (-0.005 to0.027)	-0.186 pg/ml (-1.847 to 1.338)
Calcium vs. sevelamer	0.03 mg/dl (-0.41 to 0.46)	0.23 mg/dl (-0.01 to 0.46)	11.13 pg/ml (-7.06 to 30.89)
Placebo vs. sevelamer	1.04 mg/dl (0.21 to 1.86)	-0.11 mg/dl (-0.47 to 0.24)	26.95 pg/ml (-2.13 to 55.27)
Placebo vs. calcium	1.01 mg/dl (0.22 to 1.82)	-0.34 mg/dl (-0.67 to 0.00)	16.04 pg/ml (-14.50 to 42.90)
Lanthanum vs. sevelamer	0.21 mg/dl (-0.56 to 0.96)	-0.05 mg/dl (-0.41 to 0.28)	63.83 pg/ml (35.49 to 91.98)
Lanthanum vs. calcium	0.18 mg/dl (-0.54 to 0.88)	-0.28 mg/dl (-0.59 to 0.03)	53.76 pg/ml (23.53 to 79.92)
Lanthanum vs. placebo	-0.83 mg/dl (-1.50 to -0.17)	0.06 mg/dl (-0.30 to 0.41)	37.96 pg/ml (18.65 to 54.67)
Iron vs. sevelamer	-0.26 mg/dl (-0.94 to 0.39)	0.10 mg/dl (-0.28 to 0.48)	-10.34 pg/ml (-26.54 to 4.48)
Iron vs. calcium	-0.29 mg/dl (-1.07 to 0.47)	-0.12 mg/dl (-0.57 to 0.31)	-21.87 pg/ml (-46.56 to 2.61)
Iron vs. placebo	-1.30 mg/dl (-2.06 to -0.58)	0.21 mg/dl (-0.18 to 0.60)	-37.27 pg/ml (-74.29 to -2.22)
Iron vs. lanthanum	-0.46 mg/dl (-1.28 to 0.33)	0.16 mg/dl (-0.30 to 0.61)	-75.15 pg/ml (-103.60 to -45.48)

Note: There is no significant association between treatment effect and trial duration as credible intervals include zero; MD: Mean difference; CrI: Credible interval.

S17 Table. Assessing the global consistency in networks for each labaoraty outcome using the design-by-treatment interaction model

Outcome	Chi-square	Degrees of freedom	P value for the global inconsistency test
Phosphate	1.76	3	0.62
Calcium	3.77	6	0.70
Parathyroid hormone	6.35	6	0.38

Chapter 4

A critical appraisal of chronic kidney disease mineral and bone disorders clinical practice guidelines using the AGREE II instrument

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A critical appraisal of chronic kidney disease mineral and bone disorders clinical practice guidelines using the AGREE II instrument

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Abstract

Background: Patients with chronic kidney disease mineral and bone disorders (CKD-MBD) suffer high rates of morbidity and mortality, in particular related to bone and cardiovascular outcomes. The management of CKD-MBD remains challenging. The objective of this systematic survey is to critically appraise clinical practice guidelines (CPG) addressing CKD-MBD.

Methods/Design: Data sources included MEDLINE, EMBASE, the National Guideline Clearinghouse, Guideline International Network and Turning Research into Practice up to May 2016. Teams of two reviewers, independently and in duplicate, screened titles and abstracts and potentially eligible full text reports to determine eligibility, and subsequently appraised the guidelines using the Advancing Guideline Development, Reporting and Evaluation in Health Care instrument II (AGREE).

Results: Sixteen CPGs published from 2003 to 2015 addressing the diagnosis and management of CKD-MBD in adult patients (eleven English, two Spanish, one Italian, one Portuguese and one Slovak) proved eligible. The National Institute for Health and Care Excellence (NICE) guideline performed best with respect to AGREE II criteria; only three other CPGs warranted high scores on all domains. All other guidelines received scores of under 60% on one or more domains. Major discrepancies in recommendations were not, however, present, and we found no association between quality of CPGs and resulting recommendations.

Conclusions: Most guidelines assessing CKD-MBD suffer from serious shortcomings using AGREE criteria although limitations with respect to AGREE criteria do not necessarily lead to inappropriate recommendations.

Key words: Chronic kidney disease, Advancing Guideline Development, Reporting and Evaluation in Health Care instrument, clinical practice guidelines, mineral and bone disorder.

Background

Chronic kidney disease (CKD) is a growing concern around the world that affects 8–16% of the general population[1]. CKD is associated with high mortality and morbidity, high rates of hospitalization and rehospitalisation, reduced quality of life, and high health care costs related both to CKD itself and associated comorbidity[2-4]. Poorly managed patients suffer worse health outcomes and generate greater healthcare costs[5-7].

Since CKD affects all organ systems, management requires a systematic approach and detailed considerations to prevent progression of CKD and extra-renal complications[8]. The goals of the treatment of CKD includes: (1) disease specific treatment if indicated; and (2) management of anemia, acidosis, blood pressure, dialysis dose, dialysis volume, proteinuria and disorders of bone and mineral metabolism.

Patients with CKD often suffer from chronic kidney disease mineral and bone disorder (CKD-MBD), a condition that is associated with higher risk of cardiovascular events and bone fractures[9-12]. Both abnormally high or low parathyroid hormone levels and elevated phosphate levels result in disturbances in calcium-phosphate homeostasis and cardiovascular calcifications in the media layers of the arteries that may lead to cardiovascular events[9-12]. The association between CKD-MBD and increased fracture risk results from abnormal bone turnover, architecture and mineralization[9].

Persistently elevated serum parathyroid hormone concentration associated with CKD-MBD indicates the presence of renal hyperparathyroidism (HPT). In severe forms of the disease, medical management requires combination therapy: the use of active vitamin D analogs, which works through vitamin D receptors, and calcimimetic agents that work through calcium sensing

receptors[13,14,15]. On the other hand, the management of abnormally low parathyroid hormone levels and the associated adynamic bone disease is often more challenging. An alternative approach to the management of renal HPT is the removal of the parathyroid glands[16].

CKD-MBD also involves disturbances of phosphate metabolism that lead to increased phosphate levels. Through a variety of mechanisms, phosphate binders prevent phosphate absorption from the gastrointestinal system[17]. Calcium-based phosphate binders have been associated with an increased risk of all-cause mortality[18-20]. Overall the pathophysiology of CKD-MBD is complex and the management requires close monitoring of clinical and laboratory parameters (i.e., serum phosphate, parathyroid hormone and calcium) because of potential problems related to safety and tolerability of interventions. CKD-MBD CPGs include recommendations based on evidence and expert opinions. The role of clinical practice guidelines (CPGs) is to summarize the available evidence and provide guidance for health care providers. If developed systematically with adequate rigour, CPGs effectively support the knowledge to action cycle[21]. By closing gaps between evidence and policy that limit the utilization of effective interventions or lead to futile interventions, CPGs can improve patient-important outcomes, patient satisfaction and quality of health care[22]. Another potential positive impact of CPGs is prioritization of future research.

A 2005 systematic review of CPG assessment tools included 24 instruments of which only two had a validated scoring system[23]. The most widely used of these instruments, AGREE (Advancing Guideline Development, Reporting and Evaluation in Health Care)[24], has 23 questions aggregated in six domains[25]. The AGREE II instrument provides an online tutorial for reviewers and, while shorter, is as comprehensive as the other instrument with a validated scoring system[25].

Guidelines are expected to minimize variations in health care and improve health outcomes which can be achieved by well-developed guidelines with valid recommendations. Therefore, it is important to assess the existing guidelines to address their strengths and limitations.

The objective of this study was to critically appraise existing CPGs related to CKD-MBD using the AGREE II instrument. Since the quality of CKD-MBD CPGs have not been examinedpreviously and the condition has a significant negative impacts on patients' quality of life and survival, we decided to appraise CPGs on CKD-MBD to address areas for further research and clarification. Our aim also included to explore the direction of CPG recommendations in terms of diagnosis and management.

Methods/Design

Eligibility criteria

We included CPGs addressing screening, diagnosis, monitoring or management of CKD-MBD, including both pharmacological and non-pharmacological interventions. CPGs were excluded if they addressed only a pediatric patient population.

We included CPGs that: (1) were based on systematic evidence synthesis with an explicit research question; (2) employed a grading system to rate the quality of evidence; (3) were published in a peer reviewed journal or in a guideline database. We excluded position statements or consensus statements defined as an organizational policy related to screening, diagnosis or management of CKD-MBD rather than a set of directions and principles developed by a rigorous methodology. We also excluded commentaries that summarized the evidence from a published CPG and made recommendations according to local factors. We evaluated the most current version of each CPG.

Data sources and search strategy

We conducted electronic literature searches of MEDLINE and EMBASE + EMBASE Classic, from inception of each database to February 8, 2016. Subject and text-word terms were selected for (Chronic Kidney diseases or hemodialysis) and (demineralization or bone diseases) and (guidelines), without language restrictions. We established search alerts for monthly notification, and repeated our search before the final manuscript submission to identify any new relevant CPGs.

We scanned the bibliographies of all eligible CPGs for additional relevant guidelines. We also hand-searched the National Guideline Clearinghouse, Guideline International Network and Turning Research into Practice (see eSearch strategies in the supplement for our full search strategy).

All references were saved in the Covidence online software program. Teams of two reviewers independently screened each title and abstract from our literature search (NS, RA). If either reviewer identified a citation as potentially relevant, we obtained the full text of the article. Two reviewers independently determined the eligibility of all CPGs that underwent full text evaluation (NS, RA). Disagreements were resolved through discussion between reviewers.

Data abstraction

Teams of reviewers (NS, RA, JEE, RME, JPDM, TI, IF) extracted data from all eligible CPGs using a standardized, pilot-tested, data collection form accompanied by a detailed instruction manual. Reviewers abstracted the following information from each CPG: (1) author, (2) year of

publication, (3) main recommendations for the management of CKD-MBD, (4) target population, (5) outcomes, and (6) type of meta-analysis (direct, indirect only or mixed evidence).

Analysis Plan

We generated a measure of central tendency and dispersion for each AGREE II domain. We used mean values (SD) for normally distributed and median values (inter-quartile range; IQR) for non-normally distributed variables. We employed the Shapiro-Wilk normality test to examine distributions of domain scores. We compared performance of English vs. non-English CPGs using the t-test. Previous CPG appraisal studies on other topics applied language restrictions. We tested the difference in quality between English and non-English CPGs using the scale domain scores for the comparison.

All analyses were performed in Microsoft® Excel and Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). We made calculation for agreement of full text articles using Kappa with linear weighting (http://vassarstats.net/).

The quality assessment instrument and methods

The AGREE II instrument (www.agreetrust.org) contains 23 items divided into six domains: scope and purpose (questions 1-3); stakeholder involvement (questions 4-6); rigour of development (questions 7-14), clarity of presentation (questions 15-17); applicability (questions 18-21) and editorial independence (questions 22-23) (eTable1 in the supplemental file)[24]. A seven point scale is used to answer each question with a range of options from 1 (strongly disagree) to 7 (strongly agree)[24]. A standardized score ranging from 0% to 100% was then calculated for each domain[24]. eMethods in the supplement present a detailed description of the scoring system of the AGREE II instrument.

After assessing all domains, we judged the overall confidence in each CPG as follows: 'the CPG was strongly recommended (four of six domains were >=60%); 'the CPG was recommended with alterations (at least two domain scores were above 60%) and 'the CPG is not recommended due to very serious problems according to AGREE II criteria' (three of six domains scores were less than 30% or none of the domains was above 60%)26. Mean domain scores are categorized as good (≥80%), acceptable (60-79%), moderate (40-59%) or low (<40%).

All reviewers completed the online tutorial before starting quality assessment (http://www.agreetrust.rog/resouce-center/training/). In order to improve reliability of assessment, each CPG was assessed by three reviewers. Reviewers first read the CPGs in their entirety and reviewed all relevant information regarding the guideline development process, including supplementary material related to the CPG.

Results

CPG identification

The strategy retrieved a total of 3043 references. Our search yielded 2561 unique citations, of which 101 were retrieved for full text review; sixteen CPGs proved eligible (Figure 1). We included two additional Canadian CPGs identified from the reference list of a commentary[27]. Weighted Kappa with linear weights was 0.96 for full-text eligibility. The Shapiro-Wilk test indicated that domain 2 and 5 did not pass the normality test and we reported median and interquartile ranges (p=0.04, p=0.0005, domain 2 and domain 5, respectively).

Characteristics of CPGs

Table 1 presents characteristics of all eligible CPGs. Year of publication ranged from 2003 to 2015; 11 CPGs were in English[28-39], 2 in Spanish[40,41], 1 in Italian[42], 1 in Portuguese[43], and 1 in Slovak[44]. The target population was dialysis patients in two CPGs, non-dialysis patients in one, and kidney transplant patients in three CPGs. Ten CPGs made recommendations for both dialysis and non-dialysis patient populations.

Table 2 presents AGREE II quality scores for each CPG28-30,32-37,40-44. All but three CPGs recommended targets for parathyroid hormone, calcium and phosphorus serum levels (Table 3)[30-33]. Two CARI guidelines and the NICE guideline made recommendations regarding drugs to ameliorate biochemical abnormalities (Table 1). The NICE guideline also included potential effects of different drug choices on biochemical markers, cardiovascular and bone outcomes (Table 1).

The NICE guideline did not provide any specific recommendation about the targets for parathyroid hormone, phosphate or calcium. The main focus was on different treatment options (i.e., phosphate-binders) and their effectiveness and cost—effectiveness on biochemical abnormalities, bone and cardiovascular outcomes as well as on mortality. Table1 includes the summary of main features of the CPGs including whether they focused on thresholds, drugs or both.

Reporting quality of CKD-MBD CPGs

Domain 1 Scope and purpose. The AGREE II quality scores for domain 1 ranged from 0% to 100% with a mean score of 62% (SD=33%) (Table 2, eFigure 1). Scores of all CPGs were greater than 60% in the domain 1 with the following exceptions: European Best Practice Guidelines (EBPG) for bone disease guideline[35], Steddon et al[36], Jindal et al[38], Carvalho et al[43], Prados-Garrido et al[41]

and the Slovak Republic CPG[44]. The lack of adequate description of objectives, health questions and study populations resulted in low scores for these CPGs.

Domain 2 Stakeholder involvement. The AGREE II quality scores of domain 2 ranged from 1% to 89% with a median score (IQR) of 21% (12% to 54%) (Table 2, eFigure 2). K/DOQI28, KDIGO29 and NICE30 CPGs reported stakeholder involvement. The majority of the CPGs did not provide adequate information related to patient preferences or target users and subsequently were assigned low scores. The following CPGs obtained a score higher than 60%: K/DOQI[28], KDIGO[29], NICE[30] and Levin et al[39].

Domain 3 Rigour of development. The AGREE II quality scores for domain 3 ranged from 1% to 94% with a mean score of 44% (SD=28%) (Table 2, eFigure 3). Eleven CPGs received less than 60% in this domain. Procedures for update and external review were the most common weaknesses across all included CPGs. The following CPGs received a score higher than 60%: K/DOQI[28], KDIGO[29], NICE[30], Levin et al[39] and Mazzaferro et al[42].

Domain 4 Clarity of presentation. The AGREE II quality scores of domain 4 ranged from 61% to 100% with a mean score of 83% (SD=11%) (Table 2, eFigure 4). This domain was well-addressed in all included CPGs. Recommendations were specific and easily identifiable in all CPGs, expect one Canadian guideline38. The highest mean score with small variability was in this domain (mean=83%, SD= 11%).

Domain 5 Applicability. The AGREE II quality scores for domain 5 ranged from 0% to 100% with a median score (IQR) of 21% (10% to 27%) (Table 2, eFigure 5). The NICE guideline received the highest score and it was the only CPG received a score above 60%. Most of the CPGs did not

mention a knowledge translation plan. Barriers, facilitators, monitoring and auditing criteria were not addressed by most of the CPGs. As a result, 15 CPGs received a score below 60%.

Domain 6 Editorial independence. The AGREE II quality scores for domain 6 ranged from 0% to 95% with a mean score of 40% (SD=33%) (Table 2, eFigure 6). This domain yielded poor scores for many CPGs. Competing interests, including financial and intellectual, were poorly addressed in ten guidelines that received a score of less than 60%.

We tested the reporting quality of English-language versus other CPGs. The results indicated that there was not a statistically significant difference in domain scores between English and non-English CPGs (Table 4). Published CPG appraisal studies applied language restrictions. Therefore, we explored the difference in quality between English and non-English CPGs as an hypothesis generating approach.

Overall the NICE guideline scored the highest domain percentages with the AGREE II instrument. Four out of sixteen CPGs proved acceptable by our criteria; the remainder did not. All of the CPGs relied on pairwise comparisons and did not include multiple treatment comparison (MTC) meta-analysis, except the NICE guideline.

Information on the recommendations

The included CPGs provided consistent recommendations (Tables 4). We found no suggestion of an association between adherence to AGREE criteria and the recommended management strategies. Of 16 CPGs, four CPGs were strongly recommended and four CPGs were recommended with alterations. Etables 2 and 3 in the supplemental file present additional information related to included CPGs. The consistency in recommendations despite varying

quality of CPGs may reflect a consensus in the clinical community despite the absence of high quality evidence.

Discussion

Our review identified sixteen CPGs that focused on the management of CKD-MBD, either by making recommendations for target values of parathyroid hormone, calcium and phosphorus or recommending drugs for patients suffering from hyperphosphatemia or renal HPT. Only four of these guidelines, including the K/DOQI, KDIGO and NICE guidelines, met most criteria of the AGREE II instrument (Figures 1 through 6), and only the NICE CPG reported an analytical framework and economic modelling with cost-effectiveness analysis. However, guideline recommendations were consistent across all 16 CPGs, suggesting that reporting quality does not necessarily result in problematic recommendations.

The domain scores of clarity of presentation were highest (83%) with the lowest variability (11%). The proportion that scored over the threshold of 80% was 68%. The domain related the scope and purpose yielded the second best scores. Applicability scored poorly in the majority of CPGs. This is an expected finding as most of the CPGs did not make a recommendations related to management strategies in terms of pharmacological and nonpharmacological interventions, but management of biochemical targets. In general, more guidance is needed for providers related to management strategies to achieve the proposed targets. The issue was adequately addressed by the NICE guideline which can inform clinical practice in CKD-MBD.

Eleven CPGs applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence, which considers the overall risk of bias, precision, consistency, directness and publication bias[45]. Precision requires the

assessment of the optimal information size (OIS; the number of patients generated by a conventional sample size calculation for a single trial) and the width of the 95% CIs. With respect to directness, differences in population, intervention, outcomes and settings (primary vs secondary vs tertiary care settings) need to be considered. Consistency requires assessment of clinical, methodological and statistical heterogeneity.

After considering these reasons for rating down, the overall quality of evidence in estimates of effect for each outcome is reported as follows: "high" quality of evidence (we are very confident that the true effect lies close to that of the estimate of the effect); "moderate" quality of evidence (we are moderately confident in the effect estimate and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); "low" quality of evidence (our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); and "very low" quality of evidence (we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect) [46]. A total of eleven CPGs employed the GRADE methodology to assess the quality of evidence.

Two CPGs developed by the Canadian Society of Nephrology used a grading system from A through D that was developed based on the width of the confidence intervals of effect estimates by the Canadian Hypertension Education Program[38,39]. The system assesses internal validity, precision (the width of confidence intervals) and external validity [47]. In this system, RCTs begin as grade A, but may be rated down by one or more after being examined for adequate power and applicability of the results[47]. Observational studies begin as Grade C and can be rated down for issues related to applicability and precision[47].

Since decision making in health care is largely decentralised, a substantial variation between decisions made by health care providers is not surprising in situations when evidence does not show definitive conclusions regarding optimal practice. CPGs facilitate standardized approaches across health care providers and health care systems using retrieved, appraised and summarized best available evidence – but only when evidence is high quality. When evidence is not high quality, variable practice may be reasonable, appropriate and inevitable[48].

CPGs are considered as basic units of knowledge translation and require expertise and a team-work for successful implementation and sustainability with careful identifications of barriers and facilitators. One should take advantage of facilitators to overcome barriers. Clinical pathways provided by well-developed CPGs based on best current evidence can provide great benefit for patients with CKD-MBD.

Relation to other studies

The AGREE II instrument was employed to appraise CPGs in the past. Several studies defined similar shortcomings in terms of validity of the recommendations and methods of the development process related to CPGs on osteoarthritis[49-51]. The assessment of CPGs on peripheral artery disease indicated a positive change in methodological quality after publication of the AGREE II instrument[52]. One study compared AGREE II tool and GRADE methodology in patients with rheumatoid arthritis and found that the AGREE II tool was not comprehensive enough to accommodate all GRADE criteria[53].

Strengths and limitations

This is the first study to employ the AGREE II instrument for critical appraisal of CPGs related to CKD-MBD. Strengths of our review include explicit eligibility criteria, a comprehensive search

(no restrictions in terms of language and thus are able to present an overview of worldwide guidelines) and independent duplicate assessment of eligibility. We used AGREE II, a rigorously developed and tested instrument, to assess the quality of the CPGs related to CKD-MBD. Lastly, our review was performed by methodologists and clinical experts with substantial expertise on quality appraisal and synthesis of evidence.

One limitation of the choice to use AGREE II is that the instrument does not comprehensively address all aspects of a guideline that are important – in particular, some issues highlighted by the GRADE approach to developing guidelines[51]. In particular, AGREE II does not address whether the evidence summary in the guideline addresses all important issues related to quality of the evidence – risk of bias, precision, consistency, directness and publication bias. Equally important, AGREE II does not assess the extent to which the guideline makes underlying value and preference judgments explicit – a key aspect crucial to the use of the guideline in clinical care. Finally, AGREE II does not explicitly label the issue of the recommendations being consistent with the evidence (i.e. that generally moderate or high quality evidence is necessary to justify strong recommendations).

The quality of the guideline (the extent to which the guideline meets AGREE II criteria and other criteria not included in AGREE II) is a separate issue from the certainty (quality, confidence) in the evidence underlying the recommendations the guideline offers. That is, a guideline may conduct its process optimally, but limitations in the underlying evidence may justify only weak recommendations.[54,55] We did not describe the guidelines' assessment of the quality of the underlying evidence; when assessed, we did not describe the guidelines' conclusions about quality of evidence; nor did we make such an assessment ourselves.

One could also question our choice of a threshold of 60% for adequate domain scores. One could, for instance, argue that 80% is preferable. One of the limitations of our study is a possible selection bias towards higher quality CPGs.

Implications

We showed there was a wide variation in the quality of CPGs, with most suffering from substantial limitations; these limitations were not, however, associated with differing recommendations. Possible explanations for the consistency in recommendations despite varying guideline adherence to AGREE II criteria include the evidence being extremely clear and thus, whatever the methodology, conclusions would be evident. This does not appear to be the case, however, because evidence in most instances was not high quality. The consistency of the recommendations appears to reflect a consensus in the clinical community despite the absence of high quality evidence.

Conclusions

Evidence-based management of CKD-MBD requires rigorously developed CPGs with well-justified valid recommendations based on the best available evidence. We found that most CPGs related to CKD-MBD was not satisfactory with major problems with rigor, update and implementation. In this instance, recommendations were consistent and thus unassociated with guideline quality. In other instances, however, this may not be the case, and ensuring trustworthiness of guidelines will require adherence to methodological standards.

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REFERENCES

1. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-272.

2. National Institutes of Health NIoDaDaKD. United States Renal Data System. 2015 USRDS annual data report: Epidemiology of kidney disease in the United States. . Bathesda, MD: United States Renal Data System; 2015.

3. Smith DH, Gullion CM, Nichols G, Keith DS, Brown JB. Cost of medical care for chronic kidney disease and comorbidity among enrollees in a large HMO population. Journal of the American Society of Nephrology : JASN. 2004;15(5):1300-1306.

4. Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. Kidney international. 2007;72(3):247-259.

5. Cortes-Sanabria L, Rodriguez-Arreola BE, Ortiz-Juarez VR, et al. Comparison of direct medical costs between automated and continuous ambulatory peritoneal dialysis. Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis. 2013;33(6):679-686.

6. Suja A, Anju R, Anju V, Neethu J, Peeyush P, Saraswathy R. Economic evaluation of end stage renal disease patients undergoing hemodialysis. Journal of pharmacy & bioallied sciences. 2012;4(2):107-111.

7. Laliberte F, Bookhart BK, Vekeman F, et al. Direct all-cause health care costs associated with chronic kidney disease in patients with diabetes and hypertension: a managed care perspective. Journal of managed care pharmacy : JMCP. 2009;15(4):312-322.

8. Group. KDIGOKCW. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter. 2013(3):1-150.

9. Moe SM. Vascular calcification and renal osteodystrophy relationship in chronic kidney disease. European Journal of Clinical Investigation. 2006;36:51-62.

10. Valvular calcification upon initiating dialysis predict the appearance of cardiovascular events in patient evolution. Nefrologia. 2015;35(2):157-163. doi: 110.1016/j.nefro.2015.1005.1017. Epub 2015 Jun 1023.

11. Valvular calcification and left ventricular modifying in peritoneal dialysis patients. Renal failure. 2015;19:1-7.

12. Coronary artery calcification, cardiovascular events, and death: a prospective cohort study of incident patients on hemodialysis. Can J Kidney Health Dis. 2015;2:29.(doi):10.1186/s40697-40015-40065-40696. eCollection 42015.

13. Arenas MD, Alvarez-Ude F, Gil MT, et al. Implementation of 'K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease' after the introduction of cinacalcet in a population of patients on chronic haemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2007;22(6):1639-1644.

14. Wetmore JB, Quarles LD. Calcimimetics or vitamin D analogs for suppressing parathyroid hormone in end-stage renal disease: time for a paradigm shift? Nat Clin Pract Nephrol. 2009;5(1):24-33.

15. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol. 2011;6(4):913-921.

16. Pitt SC, Sippel RS, Chen H. Secondary and tertiary hyperparathyroidism, state of the art surgical management. The Surgical clinics of North America. 2009;89(5):1227-1239.

17. Cernaro V, Santoro D, Lacquaniti A, et al. Phosphate binders for the treatment of chronic kidney disease: role of iron oxyhydroxide. International journal of nephrology and renovascular disease. 2016;9:11-19.

18. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet. 2013;382(9900):1268-1277. doi: 1210.1016/S0140-6736(1213)60897-60891. Epub 62013 Jul 60819.

19. Efficacy and safety of lanthanum carbonate versus calcium-based phosphate binders in patients with chronic kidney disease: a systematic review and meta-analysis. Int Urol Nephrol. 2015;47(3):527-535. doi: 510.1007/s11255-11014-10876-x. Epub 12014 Nov 11216.

20. Sevelamer Versus Calcium-Based Binders for Treatment of Hyperphosphatemia in CKD: A Meta-Analysis of Randomized Controlled Trials. Clin J Am Soc Nephrol. 2015;14:06800615.

21. Meyer C, Cameron K, Battistella M. New agent to treat elevated phosphate levels: magnesium carbonate/calcium carbonate tablets. CANNT journal = Journal ACITN. 2012;22(4):33-35; quiz 36-37.

22. Field B, Booth A, Ilott I, Gerrish K. Using the Knowledge to Action Framework in practice: a citation analysis and systematic review. Implementation science : IS. 2014;9:172.

23. A systematic review of appraisal tools for clinical practice guidelines: multiple similarities and one common deficit. Int J Qual Health Care. 2005;17(3):235-242. Epub 2005 Mar 2002.

24. AGREE II: advancing guideline development, reporting, and evaluation in health care. Prev Med. 2010;51(5):421-424. doi: 410.1016/j.ypmed.2010.1008.1005. Epub 2010 Aug 1020.

25. Development and application of a generic methodology to assess the quality of clinical guidelines. Int J Qual Health Care. 1999;11(1):21-28.

26. Yan J, Min J, Zhou B. Diagnosis of pheochromocytoma: a clinical practice guideline appraisal using AGREE II instrument. Journal of evaluation in clinical practice. 2013;19(4):626-632.

27. Manns BJ, Hodsman A, Zimmerman DL, et al. Canadian Society of Nephrology commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD). American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(5):800-812.

28. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2003;42(4 Suppl 3):S1-201.

29. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney international. Supplement. 2009(113):S1-130.

30. Centre for Clinical Practice at N. National Institute for Health and Clinical Excellence: Guidance. Hyperphosphataemia in Chronic Kidney Disease: Management of Hyperphosphataemia in Patients with Stage 4 or 5 Chronic Kidney Disease. Manchester: National Institute for Health and Clinical Excellence (UK)

31. Hyperphosphataemia in chronic kidney disease Evidence Update December 2014. NICE guidelines. 2014.

32. Chadban S, Chan M, Fry K, et al. The CARI guidelines. Nutritional interventions for the prevention of bone disease in kidney transplant recipients. Nephrology (Carlton, Vic.). 2010;15 Suppl 1:S43-47.

33. Elder G, Faull R, Branley P, Hawley C. The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. Nephrology (Carlton, Vic.). 2006;11 Suppl 1:S230-261.

34. Hawley C, Elder G. The CARI guidelines. Biochemical targets. Nephrology (Carlton, Vic.). 2006;11 Suppl 1:S198-216.

35. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.8. Bone disease. Nephrology, dialysis, transplantation

: official publication of the European Dialysis and Transplant Association - European Renal Association. 2002;17 Suppl 4:43-48.

36. Steddon S. CLINICAL PRACTICE GUIDELINE CKD-MINERAL AND BONE DISORDERS (CKD-MBD). 2015.

37. Fukagawa M, Yokoyama K, Koiwa F, et al. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2013;17(3):247-288.

38. Jindal K, Chan CT, Deziel C, et al. Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. Journal of the American Society of Nephrology : JASN. 2006;17(3 Suppl 1):S1-27.

39. Levin A, Hemmelgarn B, Culleton B, et al. Guidelines for the management of chronic kidney disease. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008;179(11):1154-1162.

40. Torregrosa JV, Cannata Andia J, Bover J, et al. [SEN Guidelines. Recommendations of the Spanish Society of Nephrology for managing bone-mineral metabolic alterations in chronic renal disease patients]. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia. 2008;28 Suppl 1:1-22.

41. Prados-Garrido MD, Bover J, Teresa González-Álvarez M, J H. Clinical practice guideline for chronic kidney disease-mineral and bone disease (2010 version). Dialisis Transplante. 2011;32(3):108-118.

42. Mazzaferro S, Cozzolino M, Marangella M, Strippoli GF, Messa P. [Calcimimetics, phosphate binders, vitamin D and its analogues for treating secondary hyperparathyroidism in chronic kidney disease: guideline from the Italian Society of Nephrology]. Giornale italiano di nefrologia : organo ufficiale della Societa italiana di nefrologia. 2007;24 Suppl 37:S107-124.

43. Carvalho AB, Gueiros AP, Gueiros JE, et al. [Guidelines on bone mineral disorder in chronic kidney disease--addendum chapter 2]. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia. 2012;34(2):199-205.

44. Anonymous. Guidelines of the Ministry of Health of the Slovak Republic for the treatment of bone and mineral metabolism disorders in patients with chronic kidney disease. . Aktuality v Nefrologii 2009;15(3):121-127.

45. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-172.

46. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed.). 2008;336(7650):924-926.

47. Zarnke KB, Campbell NR, McAlister FA, Levine M. A novel process for updating recommendations for managing hypertension: rationale and methods. The Canadian journal of cardiology. 2000;16(9):1094-1102.

48. Djulbegovic B, Guyatt GH. Evidence-based practice is not synonymous with delivery of uniform health care. Jama. 2014;312(13):1293-1294.

49. Smith CA, Toupin-April K, Jutai JW, et al. A Systematic Critical Appraisal of Clinical Practice Guidelines in Juvenile Idiopathic Arthritis Using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument. PloS one. 2015;10(9):e0137180.

50. Brosseau L, Rahman P, Poitras S, et al. A systematic critical appraisal of non-pharmacological management of rheumatoid arthritis with Appraisal of Guidelines for Research and Evaluation II. PloS one. 2014;9(5):e95369.

51. Brosseau L, Rahman P, Toupin-April K, et al. A systematic critical appraisal for non-pharmacological management of osteoarthritis using the appraisal of guidelines research and evaluation II instrument. PloS one. 2014;9(1):e82986.

52. Barriocanal AM, Lopez A, Monreal M, Montane E. Quality assessment of peripheral artery disease clinical guidelines. Journal of vascular surgery. 2016;63(4):1091-1098.

53. Hazlewood GS, Akhavan P, Schieir O, et al. Adding a "GRADE" to the quality appraisal of rheumatoid arthritis guidelines identifies limitations beyond AGREE-II. Journal of clinical epidemiology. 2014;67(11):1274-1285.

54. Vlayen J, Aertgeerts B, Hannes K, Sermeus W, Ramaekers D. A systematic review of appraisal tools for clinical practice guidelines: multiple similarities and one common deficit. International journal for quality in health care : journal of the International Society for Quality in Health Care / ISQua. 2005;17(3):235-242.

55. Watine J, Friedberg B, Nagy E, et al. Conflict between guideline methodologic quality and recommendation validity: a potential problem for practitioners. Clinical chemistry. 2006;52(1):65-72.

Table 1. General characteristics of eligible CPGs

Title of the CPG	Country and year of publication	Short name	Organization	Language of publication	Purposes of the guideline (screening, diagnosis or management)	Evidence summary tables	Quality tables
K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease[67]	USA, 2003	K/DOQI	National Kidney Foundation	English	Diagnosis and management	Yes	Yes
KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)[68]	USA, 2009	KDIGO	Kidney Disease Outcomes Quality Initiative	English	Diagnosis and management	Yes	Yes
National Institute for Health and Care Excellence[69, 70]	United Kingdom, 2014	NICE	National Institute for Health and Care Excellence	English	Diagnosis and management	Yes	Yes
Caring for Australasians with Renal Impairment,	Australia, 2010	CARI for nutritional interventions	Caring for Australasians	English	Diagnosis and management	Yes	Yes

for nutritional interventions [71]			with Renal Impairment				
Caring for Australasians with Renal Impairment management of bone disease, calcium, phosphate and parathyroid hormone[72]	Australia, 2006	CARI management of bone disease, calcium, phosphate and parathyroid hormone;	Caring for Australasians with Renal Impairment	English	Diagnosis and management	Yes	Yes
Caring for Australasians with Renal Impairment biochemical targets[73]	Australia, 2006	CARI biochemical targets	Caring for Australasians with Renal Impairment	English	Diagnosis and management	No	No
European renal best practice guidelines for renal transplantation for bone disease[74]	European countries, 2003	ERBP for bone disease	European Renal Best Practice	English	Diagnosis and management	No	No
Clinical practice guideline and bone disorders (CKD-MBD).[75]	United Kingdom, 2015	N/A	Renal Association clinical practice guidelines	English	Diagnosis and management	No	No
Clinical Practice Guideline for the Management of Chronic Kidney	Japan, 2013	N/A	Japanese society of Nephrology	English	Diagnosis and management	No	No

Disease-Mineral and Bone Disorder[76]							
Jindal et al, 2006[77]	Canada, 2006	N/A	Canadian Society of Nephrology	English	Management	No	No
Levin et al, 2008[78]	Canada, 2008	N/A	Canadian Society of Nephrology	English	Management	No	No
Guidelines on Bone Mineral Disorder in Chronic Kidney Disease[79]	Brazil, 2012	N/A	Brazilian Society of Nephrology	Portuguese	Management	No	No
Clinical practice guideline for chronic kidney disease-mineral and bone disease[80]	Spain, 2011	N/A	Spanish Dialysis and Transplant Society	Spanish	Diagnosis and management	No	No
Recommendations of the Spanish Society of Nephrology for managing bone-mineral metabolic alterations in chronic renal disease [81]	Spain, 2008	SEN guidelines	Spanish Society of Nephrology	Spanish	Diagnosis and management	No	No
Calcimimetics, phosphate binders, vitamin D and its analogues for treating secondary	Italy, 2007	N/A	Italian Society of Nephrology	Italian	Management	Yes	No

hyperparathyroidism in chronic kidney disease: guideline from the Italian Society of Nephrology[82]							
The Slovak Republic CPG[83]	Slovak, 2009	N/A	Slovak	Slovak	Management	No	No

Table 2. Quality of clinical practice guidelines on CKD-MBD using the AGREE II tool (expressed as percentage)

	CPG ID, year of publication	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Total AGREE II score; mean (SD)	The CPG recommended for use
1	K/DOQI 2003[67]	100	70	80	100	40	67	76 (22)	Strongly recommended
2	KDIGO 2009[68]	100	80	94	100	23	95	82(29)	Strongly recommended
3	NICE 2013[69, 70]	100	89	88	100	10	83	92 (8)	Strongly recommended
4	CARI for nutritional interventions, 2010[71]	80	17	40	70	0	67	46 (32)	Recommended with alterations
5	CARI management of bone disease, calcium, phosphate and parathyroid hormone 2006[72]	77	15	34	87	18	13	41 (33)	Not recommended
6	CARI biochemical targets 2006[73]	81	7	40	80	17	14	40 (33)	Not recommended
7	EBPG for bone disease, 2003[74]	1	1	4	61	0	0	11 (24)	Not recommended
8	Steddon et al., 2015[75]	26	10	44	77	21	33	35 (23)	Not recommended
9	Fugakawa et al. 2013[76]	69	35	33	87	7	50	47 (28)	Recommended with alterations
10	Jindal et al[77], 2006	52	44	40	83	14	39	45 (22)	Recommended with alterations

11	Levin et al, 2008[78]	85	64	64	89	21	83	68 (25)	Strongly recommended
12	Carvalho et al, 2012[79]	33	20	17	87	27	25	35 (26)	Not recommended
13	Prados-Garrido et al, 2011[80]	27	16	22	77	26	11	30 (24)	Not recommended
14	Torregrosa et al, 2008[81]	74	45	38	83	33	72	58 (21)	Recommended with alterations
15	Mazzaferro et al, 2007[82]	79	22	72	83	24	0.08	47 (35)	Not recommended
16	The Slovak Republic CPG. [83]	0	1	1	66	1	1	12 (26)	Not recommended
Overall domain score; mean(SD)	---------	62 (33)	34 (29)	44 (28)	83 (11)	23 (23)	33 (41)	----------	----------

Legend: Domain 1: Scope and purpose; Domain 2: Stakeholder involvement; Domain 3: Rigour of development; Domain 4: Clarity of presentation; Domain 5: Applicability; Domain 6: Editorial independence; Overall quality of CPG: Using a scoring system (1 through 7) overall quality was assessed; AGREE II: Appraisal of Guidelines, REsearch and Evaluation II; K/DOQI: Kidney Disease Outcomes Quality Initiative; KDIGO: Kidney Disease Improving Global Outcomes; NICE: National Institute for Health and Clinical Excellence; CARI: Caring for Australian with Renal Impairment; EBPG: European Best Practice Guidelines for Renal Transplantation, Scores ranges between 0% to 100%; SD: Standard deviation. Domain scores>=80%: good; 60-79%: acceptable; 40-59%: moderate; <40% low[84].

Table 3. Recommendations for the management of CKD-MBD

CPG ID, year of publication	Calcium	Phosphate	Parathyroid hormone	Calcium and phosphate product
K/DOQI; 2003[67]	Corrected calcium should be maintained within normal range (2.09-2.37 mmol/L)	1.13-1.77 mmol/L	35-70 pg/ml for stage 3 CKD; 70-110 pg/ml for stage 4 CKD; 150-300pg/ml for stage 5 CKD	$<55 mg^2/dl^2$
KDIGO; 2009[68]	Within the normal range	Within the normal range	2-9 times upper limit of the normal value	N/A
NICE; 2014[69, 70]	N/A	N/A	N/A	N/A
CARI for nutritional interventions ;2010[71]	N/A	N/A	N/A	
CARI management of bone disease, calcium, phosphate and parathyroid hormone; 2006[72]	N/A	N/A	N/A	
CARI biochemical targets 2006[73]	2.1-2.4mmol/L	0.8-1.6mmol/L	2-3 times upper limit of the normal value	<4mmol/L
EBPG for bone disease, 2003[74]	N/A	N/A	N/A	N/A
Steddon et al., 2015[75]	2.2-2.5mmol/L	1.1-1.7mmol/L	2-9 times upper limit of the normal value	
Fugakawa et al, 2013[76]	2.09-2.49 mmol/L	1.13-1.93 mmol/L	60-240pg/ml	N/A

Jindal et al[77], 2006	Within the normal range calcium levels	Within the normal phosphate level	100-500pg/ml	
Levin et al. 2008[78]	Within the normal range calcium levels	Within the normal phosphate level	N/A	
Carvalho et al, 2012[79]	Within the normal value of reference	Within the normal value of reference for eGFR < 60 ml/min/1.73 ^{2}; if on dialysis: reduce toward the normal value	35-70pg/ml if eGFR <60 ml/min/1.73 ^{2}; 70-110pg/ml if eGFR 15-29 ml/min/1.73 ^{2}; 2-9 times higher than superior limit of reference for CKD 5	< 55mg^2/dl^2 for adults
Prados-Garrido et al, 2011[80]	2.09-2.37 mmol/L for all stages of CKD	0.87-1.48mmol/L for stages 3 and 4 CKD	Within the normal value of reference for CKD 3; 2 times the upper normal limit for CKD 4; 2-5 times the upper normal limit for CKD 5	N/A
Torregrosa et al, 2008[81]	2-2.37 mmol/L for all stages of CKD	0.87-1.48mmol/L for stages 1,2,3 and 4 CKD; 0.87-1.61mmol/L for stage 5 CKD	<65pg/ml for CKD 2 and 3; <110 pg/ml for CKD 4; 150-300 pg/ml for CKD 5	N/A
Mazzaferro et al, 2007[82]	2.09-2.37 mmol/L for CKD 5	0.87-1.48mmol/L for stages 3 and 4 CKD; 1.13-1.77 mmol/L for CKD stage 5	35-70pg/ml for CKD 3, 70-100pg/ml for CKD 4, and 150-300pg/ml for CKD 5	<55 mg^2/dl^2
The Slovak Republic guideline[83]	2.1-2.4 mmol/L for all stages of CKD	0.9-1.5mmol/L for CKD 3, 1.1-1.8mmol/L for CKD 5	35-70pg/ml for CKD 3, 150-300pg/ml for CKD 5	

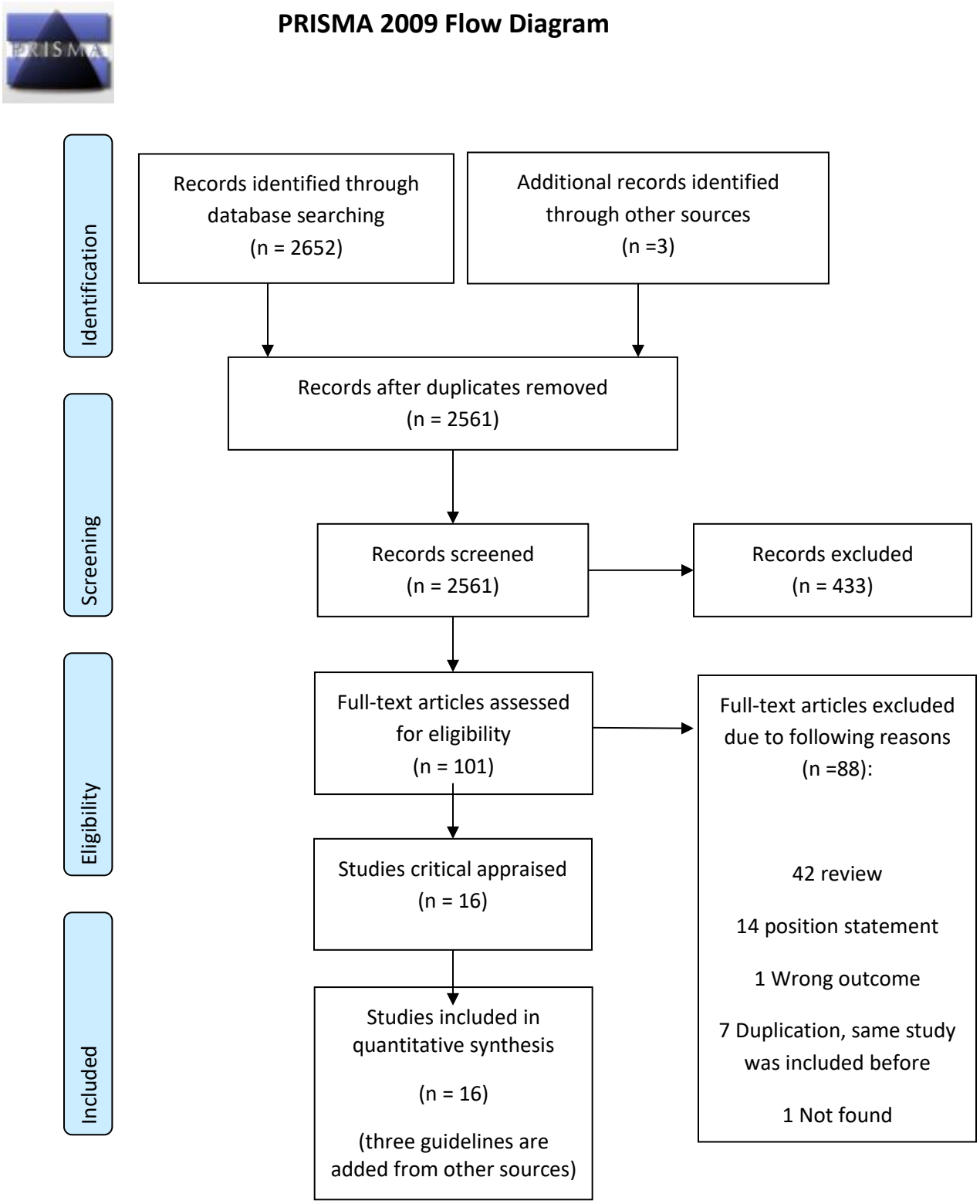
Legend: CARI: Caring for Australian with Renal Impairment; CKD-MBD: Chronic kidney disease mineral and bone disorders; CPG: Clinical practice guidelines; EBPG: European Best Practice Guidelines for Renal Transplantation; K/DOQI: Kidney Disease Outcomes Quality Initiative; KDIGO: Kidney Disease Improving Global Outcomes; NICE: National Institute for Health and Clinical Excellence; N/A: Not available. Conversion factor[68] for PTH 0.106; calcium 0.2495; phosphorus 0.3229.

Table 4. The performance of English-language versus non-English CPGs (expressed as percentage)

	English CPGs; mean domain score (SD)	Non-English CPGs; mean domain score (SD)
Domain 1	70 (31)	43 (33)
Domain 2	39 (31)	21 (15)
Domain 3	51 (27)	30 (24)
Domain 4	85 (12)	79 (8)
Domain 5	24 (27)	22 (12)
Domain 6	49 (32)	22 (29)

Legend: CPG: Clinical practice guidelines; SD: standard deviation

Figure 1. PRISMA Flow Diagram of Search Results



Supplementary content

A critical appraisal of clinical practice guidelines for chronic kidney disease mineral and bone disorders. Nigar Sekercioglu, Reem Al-Khalifah, Joycelyne Efua Ewusie, Rosilene M. Elias, Lehana Thabane, Jason W. Busse, Noori Akhtar-Danesh, Alfonso Iorio, Tetsuya Isayama, Juan Pablo Díaz Martínez, Ivan Florez, Gordon H. Guyatt

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

Expanded Search strategies

Expanded Methods

Expanded Table 1. AGREE assessment: on a seven-point scale from strongly disagree to strongly agree

Expanded Table 2. Characteristics of recommendations of the CPGs

Expanded Table 3. Other characteristics of included CPGs

Expanded Figure 1-6. The scale domain scores

Expanded search strategies

MEDLINE:

The search strategy for OvidSP MEDLINE (1946 to **January Week 4 2016**) retrieved a total of **951** of which **939** were unique references not duplicated in our other searches. The strategy includes a combination of MeSH descriptors and free text terms for

Ovid MEDLINE(R) 1946 to January Week 4 2016			
u	**Searches**	**Results**	**Comment**
1	(((kidney* or nephro* or renal or home or peritoneal or intermittent or chronic or extracorporeal or ambulatory) adj2 (haemodialys* or hemodialys* or dialys*)) or hemorenodialysis or hemodialyse or CAPD).ti,ab.	36648	
2	renal replacement therapy/ or renal dialysis/ or hemodiafiltration/ or hemodialysis, home/ or peritoneal dialysis/ or peritoneal dialysis, continuous ambulatory/ or kidney transplantation/	176178	
3	renal insufficiency, chronic/ or kidney failure, chronic/	90213	
4	(((chronic or "end-stage" or "end stage") adj3 (kidney* or renal or nephro*) adj3 (insufficien* or disease*)) or esrd).ti,ab.	51588	
5	frasier syndrome/ or ("frasier* syndrome*" or (frasier* adj2 syndrome*)).mp.	111	
6	azotemia/ or azotemi*.mp.	2792	
7	uremia/ or uremi*.mp.	31004	
8	or/1-7	251637	Kidney disease terms
9	renal osteodystrophy/ or ((renal or kidney* or nephro*) adj2 (osteodystroph* or ricket*)).mp. [****renal osteodystrophy terms****]	3819	
10	"bone and bones"/ or bone-implant interface/ or "bones of lower extremity"/ or foot bones/ or metatarsal bones/ or tarsal bones/ or calcaneus/ or talus/ or toe phalanges/ or leg bones/ or femur/ or femur head/ or femur neck/ or fibula/ or patella/ or tibia/ or pelvic bones/ or acetabulum/ or ilium/ or ischium/ or pubic bone/ or "bones of upper extremity"/ or arm bones/ or humerus/ or humeral head/ or radius/ or ulna/ or olecranon process/ or clavicle/ or hand bones/ or carpal bones/ or capitate bone/ or hamate bone/ or lunate bone/ or pisiform bone/ or scaphoid bone/ or trapezium bone/ or trapezoid bone/ or triquetrum bone/ or finger phalanges/ or metacarpal bones/ or scapula/ or acromion/ or glenoid cavity/ or diaphyses/ or epiphyses/ or growth plate/ or hyoid bone/ or sesamoid bones/ or skull/ or cranial fontanelles/ or cranial sutures/ or ethmoid bone/ or facial bones/ or jaw/ or alveolar process/ or tooth socket/ or dental arch/ or mandible/ or chin/ or mandibular condyle/ or maxilla/ or palate, hard/ or nasal bone/ or orbit/ or	530906	

	turbinates/ or vomer/ or zygoma/ or frontal bone/ or occipital bone/ or foramen magnum/ or parietal bone/ or pterygopalatine fossa/ or skull base/ or cranial fossa, anterior/ or cranial fossa, middle/ or cranial fossa, posterior/ or sphenoid bone/ or sella turcica/ or temporal bone/ or mastoid/ or petrous bone/ or spine/ or cervical vertebrae/ or axis, cervical vertebra/ or odontoid process/ or cervical atlas/ or coccyx/ or intervertebral disc/ or lumbar vertebrae/ or sacrum/ or spinal canal/ or epidural space/ or thoracic vertebrae/ or thorax/ or ribs/ or cervical rib/ or sternum/ or manubrium/ or xiphoid bone/		
11	(bone or bones or osteo).ti,ab,kw.	520410	
12	bone diseases, endocrine/ or osteitis fibrosa cystica/ or bone diseases, metabolic/ or bone demineralization, pathologic/ or decalcification, pathologic/ or osteoporosis/ or osteoporosis, postmenopausal/ or pseudopseudohypoparathyroidism/ or rickets/ or alveolar bone loss/	67334	
13	Bone Density/	43200	
14	Calcium/	247557	
15	vitamin d/ or exp cholecalciferol/ or exp ergocalciferols/	46977	
16	exp Vitamin D Deficiency/	22006	
17	Phosphorus/	35915	
18	parathyroid hormone/ or teriparatide/ or parathyroid hormone-related protein/	28115	
19	calcium metabolism disorders/ or calcinosis/ or vascular calcification/ or monckeberg medial calcific sclerosis/	36890	
20	exp fractures, bone/ or fractures, cartilage/	154673	
21	exp Bone Density Conservation Agents/	108344	
22	calcimimetic agents/ or cinacalcet hydrochloride/	741	
23	Sevelamer/	547	
24	Lanthanum/	4330	
25	or/9-24	1321859	Bone Diseases or demineralization
26	8 and 25	20294	Base Clinical set
27	(consensus development conference or consensus development conference, nih or guideline or practice guideline).pt.	34884	
28	practice guideline/ or guideline/ or guidelines as topic/ or practice guidelines as topic/ or consensus development conferences as topic/ or consensus development conferences, nih as topic/ or clinical protocols/	169586	
29	meta analysis.pt. or meta analysis/ or "meta analysis (topic)"/ or (metaanalys* or "meta-analys*" or (meta adj2 analys*)).mp.	93051	
30	Critical Pathways/ or (guideline* or (standard adj2 care) or consensus).mp.	410242	
31	advance directive adherence/	476	
32	guideline adherence/	23558	

33	clinical protocols/ or antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/	135158	
34	nursing process/ or patient care planning/ or advance care planning/ or advance directives/ or living wills/ or critical pathways/ or patient-centered care/	65277	
35	"consensus development conference".pt.	9648	
36	(guideline: or (standard adj2 care) or consensus).mp.	406317	
37	or/27-34	675922	Practice guideline terms
38	26 and 37	951	Final results

EMBASE

The search strategy for OvidSP Embase Classic+Embase 1947 to 2016 Week 06 retrieved a total of **2092** of which **1649** were unique references not duplicated in our other searches. The strategy included a combination of EMBASE descriptor and free text terms for

Embase Classic+Embase 1947 to 2016 Week 06			
#	**Searches**	**Results**	**Comment**
1	(((kidney* or nephro* or renal or home or peritoneal or intermittent or chronic or extracorporeal or ambulatory) adj2 (haemodialys* or hemodialys* or dialys*)) or hemorenodialysis or hemodialyse or CAPD).ti,ab.	51081	
2	dialysis/ or dialysis catheter/	46479	
3	renal replacement therapy/ or continuous ambulatory peritoneal dialysis/ or continuous renal replacement therapy/ or continuous hemodiafiltration/ or continuous hemodialysis/ or continuous hemofiltration/ or modified ultrafiltration/ or slow continuous ultrafiltration/ or extended daily dialysis/ or hemodiafiltration/ or hemodialysis/ or hemofiltration/ or home dialysis/ or peritoneal dialysis/	154398	
4	kidney failure/ or chronic kidney failure/ or renal replacement therapy-dependent renal disease/	176385	
5	(((chronic or "end-stage" or "end stage") adj3 (kidney* or renal or nephro*) adj3 (insufficien* or disease*)) or esrd).ti,ab.	85770	
6	frasier syndrome/ or ("frasier* syndrome*" or (frasier* adj2 syndrome*)).mp.	195	
7	(azotaemia* or azotemia* or hyperazotemia* or hyperuraemia* or hyperuremia*).mp.	4433	
8	uremia/ or (uremi* or uraemi*).mp.	52454	
9	or/1-8	375604	Kidney disease terms
10	renal osteodystrophy/ or ((renal or kidney* or nephro*) adj2 (osteodystroph* or ricket*)).mp. [****renal osteodystrophy terms****]	5699	
11	bone/ or "bones of the extremities"/ or "bones of the arm and hand"/ or hand bone/ or exp carpal bone/ or finger phalanx/ or	705769	

	metacarpal bone/ or humerus/ or humerus head/ or olecranon/ or radius/ or ulna/ or "bones of the leg and foot"/ or calcaneus/ or femur condyle/ or femur diaphysis/ or femur epiphysis/ or femur head/ or femur metaphysis/ or femur neck/ or femur shaft/ or greater trochanter/ or lesser trochanter/ or "ligament of head of femur"/ or tibia/ or tibia epiphysis/ or tibia shaft/ or tibia tuberosity/ or distal phalanx/ or long bone/ or exp diaphysis/ or exp epiphysis/ or epiphysis plate/ or fibula/ or humerus/ or humerus head/ or exp metaphysis/ or olecranon/ or radius/ or ulna/ or phalanx/ or sesamoid bone/ or pelvic girdle/ or coccygeal bone/ or iliac bone/ or iliac crest/ or ischial tuberosity/ or ischium/ or pubic bone/ or pubis symphysis/ or sacrum/ or rib/ or shoulder girdle/ or clavicle/ or scapula/ or acromion/ or glenoid cavity/ or sternum/ or skull/ or alveolar bone/ or alveolar ridge/ or anterior cranial fossa/ or bregma/ or calvaria/ or clivus/ or cranial suture/ or ethmoid bone/ or facial bone/ or foramen magnum/ or frontal bone/ or hyoid bone/ or infratemporal fossa/ or jaw/ or mandible/ or mastoid/ or maxilla/ or middle cranial fossa/ or nasal bone/ or occipital bone/ or orbit/ or petrous bone/ or posterior fossa/ or pterygopalatine fossa/ or sella turcica/ or skull base/ or skull suture/ or sphenoid/ or temporal bone/ or tooth arch/ or tooth socket/ or turbinate/ or vomer/ or zygoma/ or skeleton/ or spine/ or exp cervical spine/ or exp intervertebral disk/ or lumbar disk/ or lumbar spine/ or lumbar vertebra/ or lumbosacral spine/ or odontoid process/ or thoracic spine/ or thoracolumbar spine/ or vertebra/ or vertebra arch/ or vertebra body/ or vertebra spinous process/ or vertebral canal/		
12	(bone or bones or osteo).ti,ab,kw.	800642	
13	metabolic bone disease/ or bone demineralization/ or osteoporosis/ or corticosteroid induced osteoporosis/ or primary osteoporosis/ or secondary osteoporosis/ or postmenopause osteoporosis/ or senile osteoporosis/ or hajdu cheney syndrome/ or hypophosphatasia/ or pseudopseudohypoparathyroidism/ or rickets/ or hypophosphatemic rickets/ or familial hypophosphatemic rickets/ or autosomal dominant hypophosphatemic rickets/ or hereditary hypophosphatemic rickets with hypercalciuria/ or x linked hypophosphatemic rickets/ or oncogenic osteomalacia/	121267	
14	bone density/ or bone destruction/	71969	
15	Calcium/	264181	
16	vitamin d/ or 24,25 dihydroxyvitamin d/ or 25 hydroxyvitamin d/ or "9,10 secocholesta 5,7,10(19) trien 23 yne 1,3,25 triol"/ or "9,10 secocholesta 5,7,10(19) trien 23 yne 3,25 diol"/ or "9,10 secocholesta 5,7,10(19),16 tetraen 23 yne 1,3,25 triol"/ or "9,10 secocholesta 5,7,10(19),22 tetraene 1,3,25,26 tetrol"/ or ascorbic acid plus fluoride plus retinol plus vitamin d/ or calcium	109208	

	carbonate plus ferrous fumarate plus vitamin d/ or calcium phosphate dibasic plus ferrous sulfate plus manganese sulfate plus nicotinic acid plus riboflavin plus thiamine plus vitamin d/ or exp colecalciferol derivative/ or dihydrotachysterol/ or exp ergocalciferol derivative/ or lunacalcipol/ or vitamin d derivative/		
17	exp Vitamin D Deficiency/	19800	
18	Phosphorus/	70986	
19	parathyroid hormone derivative/ or parathyroid hormone/ or parathyroid hormone related protein/ or "parathyroid hormone[1-31][27 leucine] amide 22,26 amide"/ or "parathyroid hormone[1-34]"/ or recombinant parathyroid hormone/ or semparatide/ or parathyroid hormone i 125/ or teriparatide*.mp. or parathyroid hormone blood level/ or parathyroid hormone related protein/	56044	
20	electrolyte disturbance/ or hyperkalemia/ or hypernatremia/ or hypokalemia/ or hypokalemic periodic paralysis/ or hyponatremia/ or calcinosis/ or ligament calcinosis/ or calcification/	121468	
21	fracture/ or exp arm fracture/ or avulsion fracture/ or catheter fracture/ or clavicle fracture/ or comminuted fracture/ or exp face fracture/ or foot fracture/ or fracture dislocation/ or exp fracture healing/ or fragility fracture/ or intraarticular fracture/ or joint fracture/ or exp leg fracture/ or limb fracture/ or open fracture/ or pathologic fracture/ or exp pelvis fracture/ or periprosthetic fracture/ or exp rib fracture/ or exp skull fracture/ or exp spine fracture/ or stress fracture/ or cartilage fracture/	245025	
22	bone density conservation agent/	2717	
23	calcimimetic agent/ or cinacalcet/	2625	
24	sevelamer/ or sevelamer carbonate/ or Sevelamer.mp.	2165	
25	Lanthanum/ or lanthanum.mp.	9690	
26	or/10-25	1854407	Bone Diseases or demineralization
27	9 and 26	47666	Base Clinical set
28	practice guideline/ or clinical protocol/	335249	
29	meta analysis/ or "meta analysis (topic)"/ or (metaanalys* or "meta-analys*" or (meta adj2 analys*)).mp.	163249	
30	consensus development/ or good clinical practice/	17949	
31	clinical pathway/	6852	
32	nursing protocol/ or nursing care plan/	271	
33	(guideline* or (standard adj2 care) or consensus).mp.	659907	
34	"systematic review"/ or "systematic review (topic)"/ or (cochrane or medline or cinahl or embase or CCTR or scopus or "web of science" or lilacs or (systematic* adj2 review*)).mp.	227708	
35	or/28-32	508287	Practice guideline terms
36	27 and 35	2092	Final results

National Guideline Clearinghouse:

Searched by disease topic. 18 guidelines including the KDIGO guidelines.

Expanded methods

Methods for scoring of the AGREE II instrument

High scores indicate better quality of the CPG. We employed the following technique to calculate the scale domain scores:

Domain1: Scope and purpose

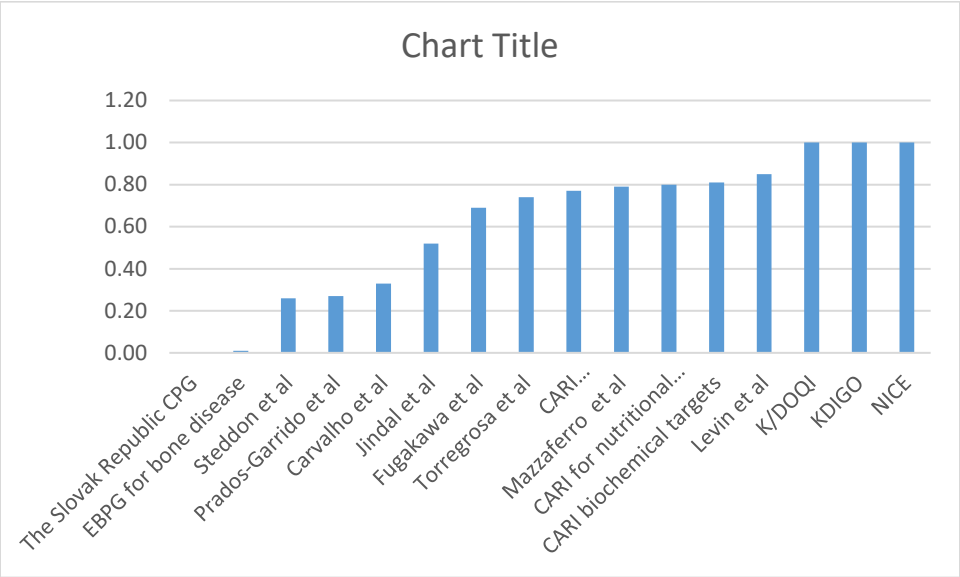
	Item 1 Objectives are specifically described	Item 2 The health question is specifically described.	Item 3 The population to whom the guideline is meant to apply is specifically described.	Total
Appraiser 1				
Appraiser 2				
Appraiser 3				

Maximum possible score=7(strongly agree) *3 (items)*3(appraisers)=

Minimum possible score=1(strongly disagree) *3(items)*3(appraisers)=

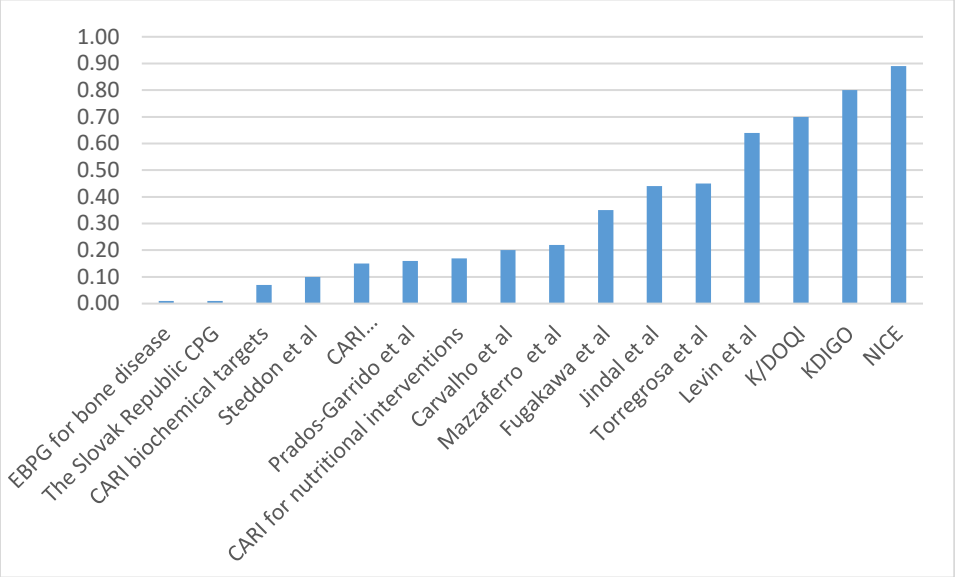
The scale domain score= (Obtained score-minimum possible score) / (Maximum possible score-Minimum possible score)

eFigure 1 The domain 1 score distribution of the 16 included CPGs



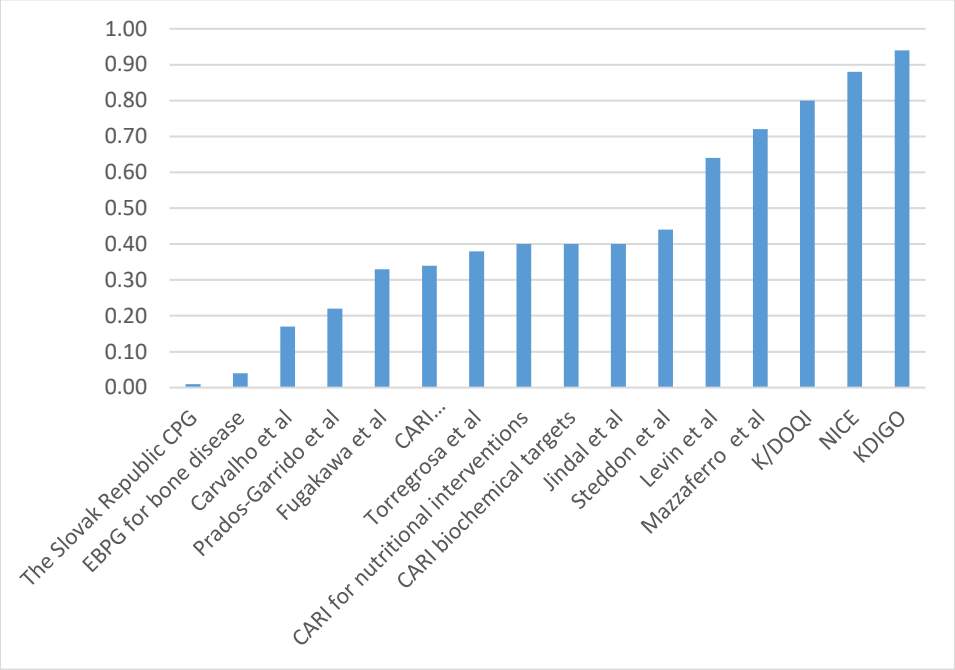
Legend: Bar chart depicting the percentage distribution of the 16 included CPGs according to the scores from the domain 1. The K/DOQI, KDIGO and NICE CPGs receive the highest scores of 1.

eFigure 2 The domain 2 score distribution of the 16 included CPGs



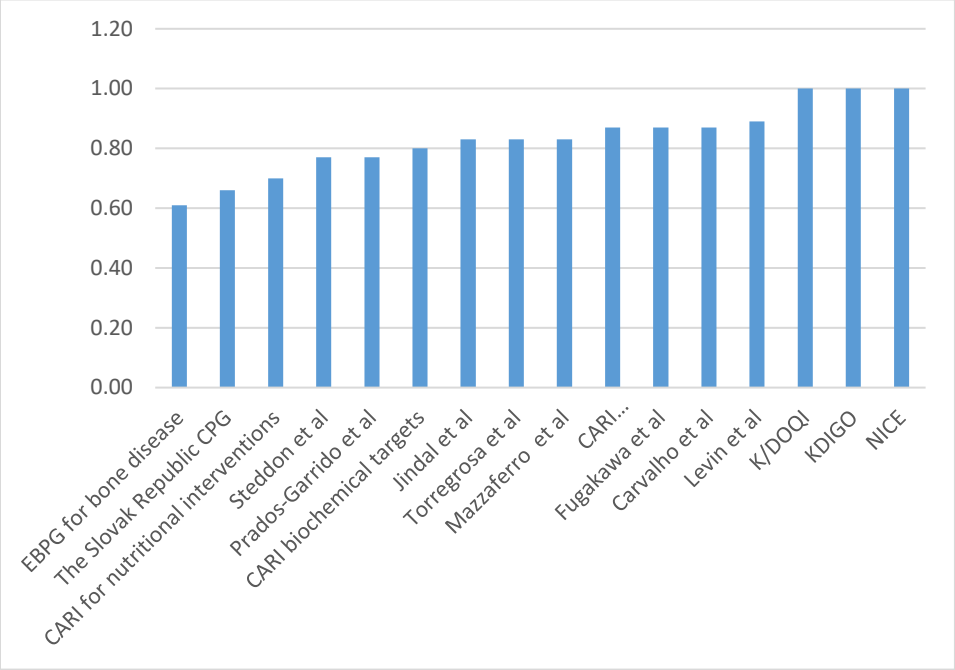
Legend: Bar chart depicting the percentage distribution of the 16 included CPGs according to the scores from the domain 2. The NICE CPG indicates the highest score.

eFigure 3 The domain 3 score distribution of the 16 included CPGs



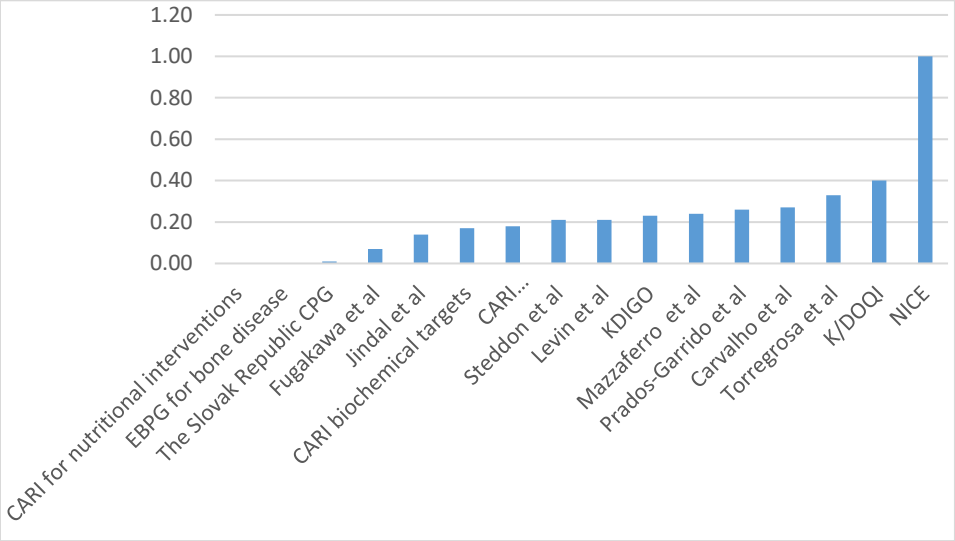
Legend: Bar chart depicting the percentage distribution of the 16 included CPGs according to the scores from the domain 3. The KDIGO CPG indicates the highest score.

eFigure 4 The domain 4 score distribution of the 16 included CPGs



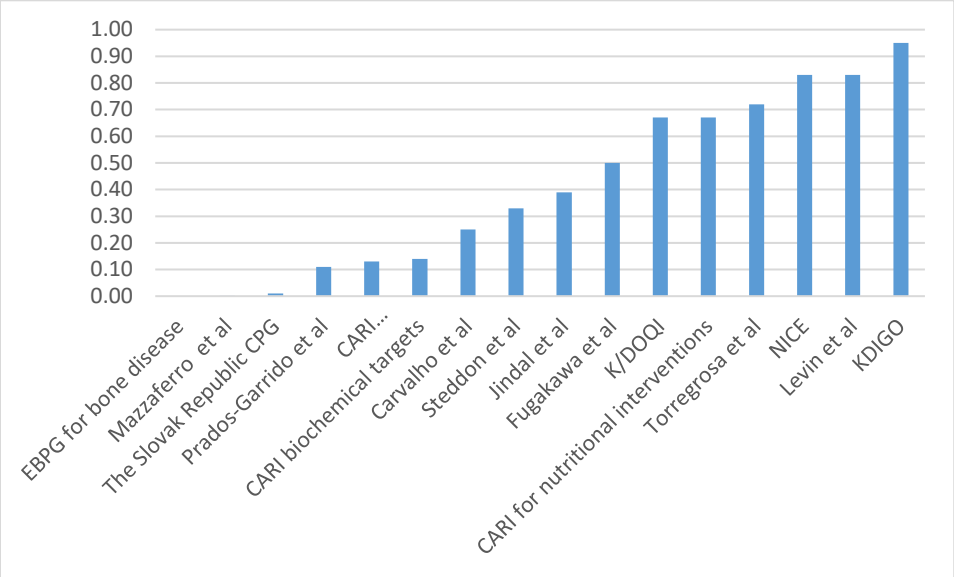
Legend: Bar chart depicting the percentage distribution of the 16 included CPGs according to the scores from the domain 4. The K/DOQI, KDIGO and NICE CPGs indicate the highest scores of 100%.

eFigure 5 The domain 5 score distribution of the 16 included CPGs



Legend: Bar chart depicting the percentage distribution of the 16 included CPGs according to the scores from the domain 5. The NICE CPG indicates the highest score of 100%.

eFigure 6 The domain 6 score distribution of the 16 included CPGs



Legend: Bar chart depicting the percentage distribution of the 16 included CPGs according to the scores from the domain 6. The K/DOQI CPG indicates the highest score.

eTable 1 AGREE assessment: on a seven-point scale from strongly disagree to strongly agree

Domain 1. Scope and Purpose
1. The overall objective(s) of the guideline is (are)specifically described
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described**.**
Domain 2. Stakeholder Involvement
4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
Domain 3. Rigour of development
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
Domain 4. Clarity of Presentation
15. The recommendations are specific and unambiguous
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
Domain 5. Applicability
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.
Domain 6. Editorial Independence
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.
Overall Assessment
A. The rating of the overall quality of the guideline
B. The guideline would be recommended for use in practice.

Legend: 7 strongly agree; 1 strongly disagree.

eTable 2. Characteristics of recommendations of the CPGs

CPG ID, year of publication	Evidence identification	Number of recommendations total	Number of recommendations evidence based	Number of recommendations with completely opinion based or includes opinion based statements	Evidence based vs. non-evidence based stated explicitly (Yes/No)	Research Recommendations provided	Economic report provided
K/DOQI; 2003[67]	Comprehensive search	111	One third	Two thirds	Yes	Yes	No
KDIGO; 2009[68]	Comprehensive search	39	29	10	Yes	Yes	No
NICE; 2014[69, 70]	Updated comprehensive search up to July 2014					Yes	Yes
CARI for nutritional interventions ;2010[71]	Stated as comprehensive search up to September 2006	5	Unclear	Unclear	Included only strength of recommendations, but not quality of evidence	Yes	No
CARI management of bone disease, calcium, phosphate and parathyroid hormone ; 2006[72]	Stated as comprehensive search up to January 2005	37	28	9	Yes	Yes	No
CARI biochemical targets 2006[73]	Stated as comprehensive search up to April 2005	19	9	10	Yes	Yes	No

EBPG for bone disease, 2003[74]	Not specified	6	6	0	No, we considered all as evidence based as there was no opinion based or non-graded evidence	No	No
Steddon et al., 2015[75]	Updated comprehensive search with language limits from October 2013	7	6	1	No, we considered as opinion based if the evidence is non-graded	No	No
Fugakawa et al, 2013[76]	Updated comprehensive search with language limits	55	38	17	No, we considered as opinion based if the evidence is non-graded	No	No
Jindal et al[77], 2006	Focused search with language limits	8	5	3	Yes	Yes	No
Levin et al. 2008[78]	Stated as comprehensive search	10	4	6	Yes	No	No
Carvalho et al, 2012[79]	Not specified	201	89	121	Yes	No	No
Prados-Garrido et al, 2011[80]	Not specified	6	unclear	unclear	No	No	No
Torregrosa et al, 2008[81]	Stated as comprehensive search	12	unclear	unclear	No	No	No

Mazzaferro et al, 2007[82]	Stated as comprehensive search up to September 2005	9	8	1	Yes	No	No
The Slovak Republic guideline [83]	Not specified	49	unclear	unclear	Not applicable		No

eTable 3. Other characteristics of included CPGs

CPG ID, year of publication	Main focus of the CPG	Population	Outcomes	The methodology Used (Grade vs. non-GRADE vs. none)
K/DOQI; 2003[67]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities and bone outcomes	GRADE
KDIGO; 2009[68]	Management of CKD-MBD	Non-dialysis, dialysis and patients with a kidney transplant	Biochemical abnormalities, bone and cardiovascular outcomes	GRADE
NICE; 2014[69, 70]	Management of CKD-MBD using pharmacological and non-pharmacological interventions	Non-dialysis and dialysis	Biochemical abnormalities with different treatment choices; bone outcomes; cardiovascular outcomes and mortality	GRADE
CARI for nutritional interventions ;2010[71]	Diet (vitamin D and calcium supplementation)	Patients with a kidney transplant	Bone outcomes	GRADE
CARI management of bone disease, calcium, phosphate and parathyroid hormone; 2006[72]	The use of vitamin D and calcimimetics, phosphate binders	Dialysis patients	Treatment recommendations to achieve targets for PTH, Ca and P	GRADE
CARI biochemical targets 2006[73]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities	GRADE

EBPG for bone disease, 2003[74]	Management of CKD-MBD	Patients with a kidney transplant	Biochemical abnormalities and bone outcomes	GRADE
Steddon et al., 2015[75]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities	GRADE
Fugakawa et al, 2013[76]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities, bone and cardiovascular outcomes	GRADE
Jindal et al[77], 2006	Management of CKD-MBD in hemodialysis	Dialysis	Biochemical abnormalities	Non-GRADE; Canadian Hypertension Education grading system[85]
Levin et al. 2008[78]	Management of CKD-MBD in the non-dialysis patient population	Non-dialysis	Biochemical abnormalities	Non-GRADE; Canadian Hypertension Education grading system[85]
Carvalho et al, 2012[79]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities	GRADE
Prados-Garrido et al, 2011[80]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities	None
Torregrosa et al, 2008[81]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities	None
Mazzaferro et al, 2007[82]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities	GRADE
The Slovak Republic guideline[83]	Management of CKD-MBD	Non-dialysis and dialysis	Biochemical abnormalities	None

REFERENCES

1. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Annals of internal medicine. 2003;139(2):137-47. Epub 2003/07/16. PubMed PMID: 12859163.
2. Group. KDIGOKCW. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter. 2013;(3):1-150.
3. Wijewickrama ES, Weerasinghe D, Sumathipala PS, Horadagoda C, Lanarolle RD, Sheriff RM. Epidemiology of chronic kidney disease in a Sri Lankan population: experience of a tertiary care center. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2011;22(6):1289-93. Epub 2011/11/18. PubMed PMID: 22089806.
4. Liu H, Peng Y, Li J, Liu Y, Cheng M, Yuan F, et al. [Stages of 3,547 patients with chronic kidney disease and relevant factor analysis]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2010;35(5):499-510. Epub 2010/06/15. doi: 10.3969/j.issn.1672-7347.2010.05.016. PubMed PMID: 20543476.
5. Khader MI, Snouber S, Alkhatib A, Nazzal Z, Dudin A. Prevalence of patients with end-stage renal disease on dialysis in the West Bank, Palestine. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2013;24(4):832-7. Epub 2013/07/03. PubMed PMID: 23816745.
6. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-72. Epub 2013/06/04. doi: 10.1016/s0140-6736(13)60687-x. PubMed PMID: 23727169.
7. Smith DH, Gullion CM, Nichols G, Keith DS, Brown JB. Cost of medical care for chronic kidney disease and comorbidity among enrollees in a large HMO population. Journal of the American Society of Nephrology : JASN. 2004;15(5):1300-6. Epub 2004/04/22. PubMed PMID: 15100370.
8. Moe SM. Vascular calcification and renal osteodystrophy relationship in chronic kidney disease. European Journal of Clinical Investigation. 2006;36:51-62. doi: 10.1111/j.1365-2362.2006.01665.x.
9. Arterial calcification and pathology in uremic patients undergoing dialysis. Am J Med. 1979;66(5):790-6.
10. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000;58(1):353-62.
11. Valvular calcification upon initiating dialysis predict the appearance of cardiovascular events in patient evolution. Nefrologia. 2015;35(2):157-63. doi: 10.1016/j.nefro.2015.05.017. Epub Jun 23.
12. Valvular calcification and left ventricular modifying in peritoneal dialysis patients. Renal failure. 2015;19:1-7.
13. Coronary artery calcification, cardiovascular events, and death: a prospective cohort study of incident patients on hemodialysis. Can J Kidney Health Dis. 2015;2:29.(doi):10.1186/s40697-015-0065-6. eCollection 2015.
14. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000;87(7):E10-7.
15. Parathyroid hormone-related peptide as a local regulator of vascular calcification. Its inhibitory action on in vitro calcification by bovine vascular smooth muscle cells. Arterioscler Thromb Vasc Biol. 1997;17(6):1135-42.
16. Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization in vitro. Kidney Int. 2004;66(6):2293-9.
17. Buiten MS, de Bie MK, Bouma-de Krijger A, van Dam B, Dekker FW, Jukema JW, et al. Soluble Klotho is not independently associated with cardiovascular disease in a population of dialysis patients. BMC Nephrology. 2014;15:197. doi: 10.1186/1471-2369-15-197. PubMed PMID: PMC4293085.
18. Regulation of oxidative stress by the anti-aging hormone klotho. J Biol Chem. 2005;280(45):38029-34. Epub 2005 Sep 26.

19. Soluble Klotho is not independently associated with cardiovascular disease in a population of dialysis patients. BMC Nephrol. 2014;15:197.(doi):10.1186/471-2369-15-197.
20. [FGF23 and Klotho protein--the role in the pathogenesis of hypertension]. Wiad Lek. 2015;68(1):67-70.
21. Isakova T, Xie H, Barchi-Chung A, Vargas G, Sowden N, Houston J, et al. Fibroblast growth factor 23 in patients undergoing peritoneal dialysis. Clin J Am Soc Nephrol. 2011;6(11):2688-95. Epub 2011/09/10. doi: 10.2215/cjn.04290511. PubMed PMID: 21903990; PubMed Central PMCID: PMC3206004.
22. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31(4):607-17.
23. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1(4):825-31. Epub 2006 May 17.
24. Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease. Nephrol Dial Transplant. 2011;26(9):2885-90. doi: 10.1093/ndt/gfq808. Epub 2011 Feb 3.
25. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909-16. Epub 007 May 21.
26. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. J Nephrol. 2015;28(1):105-13. doi: 10.1007/s40620-014-0108-6. Epub 2014 May 20.
27. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-91. Epub 1997/06/01. PubMed PMID: 9250266.
28. Luce B, Anthony OH, Dennis F. A Primer on Bayesian Statistics in Health Economics and Outcomes Research: MEDTAP International, Incorporated; 2003.
29. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):597-606. Epub 2013/06/28. doi: 10.1177/0272989x13487604. PubMed PMID: 23804506; PubMed Central PMCID: PMCPMC3704205.
30. Rutjes AW, Reitsma JB, Vandenbroucke JP, Glas AS, Bossuyt PM. Case-control and two-gate designs in diagnostic accuracy studies. Clin Chem. 2005;51(8):1335-41. Epub 2005/06/18. doi: 10.1373/clinchem.2005.048595. PubMed PMID: 15961549.
31. Whiting PF, Rutjes AW, Westwood ME, Mallett S. A systematic review classifies sources of bias and variation in diagnostic test accuracy studies. J Clin Epidemiol. 2013;66(10):1093-104. Epub 2013/08/21. doi: 10.1016/j.jclinepi.2013.05.014. PubMed PMID: 23958378.
32. Linnet K, Bossuyt PM, Moons KG, Reitsma JB. Quantifying the accuracy of a diagnostic test or marker. Clin Chem. 2012;58(9):1292-301. Epub 2012/07/26. doi: 10.1373/clinchem.2012.182543. PubMed PMID: 22829313.
33. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of clinical epidemiology. 2005;58(10):982-90. Epub 2005/09/20. doi: 10.1016/j.jclinepi.2005.02.022. PubMed PMID: 16168343.
34. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Statistics in medicine. 2002;21(4):589-624. Epub 2002/02/12. PubMed PMID: 11836738.
35. Moreau E, Bacher S, Mery S, Goff CL, Piga N, Vogeser M, et al. Performance characteristics of the VIDAS 25-OH Vitamin D Total assay - Comparison with four immunoassays and two liquid chromatography-tandem mass spectrometry methods in a multicentric study. Clinical Chemistry

and Laboratory Medicine. 2016;54(1):45-53. doi: http://dx.doi.org/10.1515/cclm-2014-1249. PubMed PMID: 20160050923.
36. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet (London, England). 2013;382(9900):1268-77. Epub 2013/07/23. doi: 10.1016/s0140-6736(13)60897-1. PubMed PMID: 23870817.
37. Brandenburg VM, Floege J. Adynamic bone disease-bone and beyond. NDT plus. 2008;1(3):135-47. Epub 2008/06/01. doi: 10.1093/ndtplus/sfn040. PubMed PMID: 25983860; PubMed Central PMCID: PMCPMC4421169.
38. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney international. 2002;62(1):245-52. Epub 2002/06/26. doi: 10.1046/j.1523-1755.2002.00434.x. PubMed PMID: 12081584.
39. Sadek T, Mazouz H, Bahloul H, Oprisiu R, El Esper N, El Esper I, et al. Sevelamer hydrochloride with or without alphacalcidol or higher dialysate calcium vs calcium carbonate in dialysis patients: an open-label, randomized study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2003;18(3):582-8. Epub 2003/02/14. PubMed PMID: 12584283.
40. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney international. 2007;71(5):438-41. Epub 2007/01/04. doi: 10.1038/sj.ki.5002059. PubMed PMID: 17200680.
41. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney international. 2007;72(10):1255-61. Epub 2007/09/07. doi: 10.1038/sj.ki.5002518. PubMed PMID: 17805238.
42. Barreto DV, Barreto Fde C, de Carvalho AB, Cuppari L, Draibe SA, Dalboni MA, et al. Phosphate binder impact on bone remodeling and coronary calcification--results from the BRiC study. Nephron Clinical practice. 2008;110(4):c273-83. Epub 2008/11/13. doi: 10.1159/000170783. PubMed PMID: 19001830.
43. Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2008;51(6):952-65. Epub 2008/04/22. doi: 10.1053/j.ajkd.2008.02.298. PubMed PMID: 18423809.
44. Suki WN. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2008;18(1):91-8. Epub 2007/12/20. doi: 10.1053/j.jrn.2007.10.019. PubMed PMID: 18089452.
45. Takei T, Otsubo S, Uchida K, Matsugami K, Mimuro T, Kabaya T, et al. Effects of sevelamer on the progression of vascular calcification in patients on chronic haemodialysis. Nephron Clinical practice. 2008;108(4):c278-83. Epub 2008/04/25. doi: 10.1159/000127361. PubMed PMID: 18434749.
46. Wilson R, Zhang P, Smyth M, Pratt R. Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. Current medical research and opinion. 2009;25(12):3021-8. Epub 2009/10/23. doi: 10.1185/03007990903399398. PubMed PMID: 19845495.
47. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, et al. Effects of phosphate binders in moderate CKD. Journal of the American Society of Nephrology : JASN.

2012;23(8):1407-15. Epub 2012/07/24. doi: 10.1681/asn.2012030223. PubMed PMID: 22822075; PubMed Central PMCID: PMCPMC3402292.
48. de Francisco AL, Leidig M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(11):3707-17. Epub 2010/06/10. doi: 10.1093/ndt/gfq292. PubMed PMID: 20530499; PubMed Central PMCID: PMCPmc2957591.
49. Kakuta T, Tanaka R, Hyodo T, Suzuki H, Kanai G, Nagaoka M, et al. Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2011;57(3):422-31. Epub 2011/01/18. doi: 10.1053/j.ajkd.2010.10.055. PubMed PMID: 21239096.
50. Toussaint ND, Lau KK, Polkinghorne KR, Kerr PG. Attenuation of aortic calcification with lanthanum carbonate versus calcium-based phosphate binders in haemodialysis: A pilot randomized controlled trial. Nephrology (Carlton, Vic). 2011;16(3):290-8. Epub 2011/02/24. doi: 10.1111/j.1440-1797.2010.01412.x. PubMed PMID: 21342323.
51. Di Iorio B, Bellasi A, Russo D. Mortality in kidney disease patients treated with phosphate binders: a randomized study. Clinical journal of the American Society of Nephrology : CJASN. 2012;7(3):487-93. Epub 2012/01/14. doi: 10.2215/cjn.03820411. PubMed PMID: 22241819.
52. Di Iorio B, Molony D, Bell C, Cucciniello E, Bellizzi V, Russo D, et al. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;62(4):771-8. Epub 2013/05/21. doi: 10.1053/j.ajkd.2013.03.023. PubMed PMID: 23684755.
53. Lee YK, Choi HY, Shin SK, Lee HY. Effect of lanthanum carbonate on phosphate control in continuous ambulatory peritoneal dialysis patients in Korea: a randomized prospective study. Clinical nephrology. 2013;79(2):136-42. Epub 2012/12/06. doi: 10.5414/cn107362. PubMed PMID: 23211335.
54. Ohtake T, Kobayashi S, Oka M, Furuya R, Iwagami M, Tsutsumi D, et al. Lanthanum carbonate delays progression of coronary artery calcification compared with calcium-based phosphate binders in patients on hemodialysis: a pilot study. Journal of cardiovascular pharmacology and therapeutics. 2013;18(5):439-46. Epub 2013/04/26. doi: 10.1177/1074248413486355. PubMed PMID: 23615577.
55. Wuthrich RP, Chonchol M, Covic A, Gaillard S, Chong E, Tumlin JA. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. Clinical journal of the American Society of Nephrology : CJASN. 2013;8(2):280-9. Epub 2012/11/06. doi: 10.2215/cjn.08230811. PubMed PMID: 23124782; PubMed Central PMCID: PMCPmc3562865.
56. Xu J, Zhang YX, Yu XQ, Liu ZH, Wang LN, Chen JH, et al. Lanthanum carbonate for the treatment of hyperphosphatemia in CKD 5D: multicenter, double blind, randomized, controlled trial in mainland China. BMC nephrology. 2013;14:29. Epub 2013/02/06. doi: 10.1186/1471-2369-14-29. PubMed PMID: 23379590; PubMed Central PMCID: PMCPmc3570485.
57. Floege J, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney international. 2014;86(3):638-47. Epub 2014/03/22. doi: 10.1038/ki.2014.58. PubMed PMID: 24646861; PubMed Central PMCID: PMCPmc4150998.
58. Takahara Y, Matsuda Y, Takahashi S, Shigematsu T. Efficacy and safety of lanthanum carbonate in pre-dialysis CKD patients with hyperphosphatemia: a randomized trial. Clinical nephrology. 2014;82(3):181-90. Epub 2014/08/01. PubMed PMID: 25079863.

59. Urena-Torres P, Prie D, Keddad K, Preston P, Wilde P, Wan H, et al. Changes in fibroblast growth factor 23 levels in normophosphatemic patients with chronic kidney disease stage 3 treated with lanthanum carbonate: results of the PREFECT study, a phase 2a, double blind, randomized, placebo-controlled trial. BMC nephrology. 2014;15:71. Epub 2014/06/03. doi: 10.1186/1471-2369-15-71. PubMed PMID: 24885942; PubMed Central PMCID: PMCPmc4107721.
60. Wada K, Wada Y. Evaluation of aortic calcification with lanthanum carbonate vs. calcium-based phosphate binders in maintenance hemodialysis patients with type 2 diabetes mellitus: an open-label randomized controlled trial. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2014;18(4):353-60. Epub 2014/01/15. doi: 10.1111/1744-9987.12153. PubMed PMID: 24417760.
61. Yokoyama K, Akiba T, Fukagawa M, Nakayama M, Sawada K, Kumagai Y, et al. A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2014;29(5):1053-60. Epub 2014/01/01. doi: 10.1093/ndt/gft483. PubMed PMID: 24376274.
62. Yokoyama K, Hirakata H, Akiba T, Fukagawa M, Nakayama M, Sawada K, et al. Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. Clinical journal of the American Society of Nephrology : CJASN. 2014;9(3):543-52. Epub 2014/01/11. doi: 10.2215/cjn.05170513. PubMed PMID: 24408120; PubMed Central PMCID: PMCPmc3944759.
63. Block GA, Fishbane S, Rodriguez M, Smits G, Shemesh S, Pergola PE, et al. A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD Stages 3-5. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2015;65(5):728-36. Epub 2014/12/04. doi: 10.1053/j.ajkd.2014.10.014. PubMed PMID: 25468387.
64. Lee CT, Wu IW, Chiang SS, Peng YS, Shu KH, Wu MJ, et al. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. Journal of nephrology. 2015;28(1):105-13. Epub 2014/05/21. doi: 10.1007/s40620-014-0108-6. PubMed PMID: 24840781.
65. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. Journal of the American Society of Nephrology : JASN. 2015;26(2):493-503. Epub 2014/07/26. doi: 10.1681/asn.2014020212. PubMed PMID: 25060056; PubMed Central PMCID: PMCPmc4310662.
66. Gulati A, Sridhar V, Bose T, Hari P, Bagga A. Short-term efficacy of sevelamer versus calcium acetate in patients with chronic kidney disease stage 3-4. International urology and nephrology. 2010;42(4):1055-62. Epub 2009/12/19. doi: 10.1007/s11255-009-9688-9. PubMed PMID: 20020207.
67. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2003;42(4 Suppl 3):S1-201. Epub 2003/10/02. PubMed PMID: 14520607.
68. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney international Supplement. 2009;(113):S1-130. Epub 2009/08/01. doi: 10.1038/ki.2009.188. PubMed PMID: 19644521.
69. Centre for Clinical Practice at N. National Institute for Health and Clinical Excellence: Guidance. Hyperphosphataemia in Chronic Kidney Disease: Management of Hyperphosphataemia in Patients with Stage 4 or 5 Chronic Kidney Disease. Manchester: National Institute for Health and Clinical Excellence (UK)

70. Hyperphosphataemia in chronic kidney disease Evidence Update December 2014. NICE guidelines [Internet]. 2014.
71. Chadban S, Chan M, Fry K, Patwardhan A, Ryan C, Trevillian P, et al. The CARI guidelines. Nutritional interventions for the prevention of bone disease in kidney transplant recipients. Nephrology (Carlton, Vic). 2010;15 Suppl 1:S43-7. Epub 2010/04/01. doi: 10.1111/j.1440-1797.2010.01233.x. PubMed PMID: 20591043.
72. Elder G, Faull R, Branley P, Hawley C. The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. Nephrology (Carlton, Vic). 2006;11 Suppl 1:S230-61. Epub 2006/05/11. doi: 10.1111/j.1440-1797.2006.00508.x. PubMed PMID: 16684078.
73. Hawley C, Elder G. The CARI guidelines. Biochemical targets. Nephrology (Carlton, Vic). 2006;11 Suppl 1:S198-216. Epub 2006/05/11. doi: 10.1111/j.1440-1797.2006.00504.x. PubMed PMID: 16684076.
74. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.8. Bone disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2002;17 Suppl 4:43-8. Epub 2002/07/02. PubMed PMID: 12091645.
75. Steddon S. CLINICAL PRACTICE GUIDELINE CKD-MINERAL AND BONE DISORDERS (CKD-MBD)2015.
76. Fukagawa M, Yokoyama K, Koiwa F, Taniguchi M, Shoji T, Kazama JJ, et al. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2013;17(3):247-88. Epub 2013/06/06. doi: 10.1111/1744-9987.12058. PubMed PMID: 23735142.
77. Jindal K, Chan CT, Deziel C, Hirsch D, Soroka SD, Tonelli M, et al. Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. Journal of the American Society of Nephrology : JASN. 2006;17(3 Suppl 1):S1-27. Epub 2006/02/25. doi: 10.1681/asn.2005121372. PubMed PMID: 16497879.
78. Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, et al. Guidelines for the management of chronic kidney disease. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008;179(11):1154-62. Epub 2008/11/19. doi: 10.1503/cmaj.080351. PubMed PMID: 19015566; PubMed Central PMCID: PMCPmc2582781.
79. Carvalho AB, Gueiros AP, Gueiros JE, Neves CL, Karohl C, Sampaio E, et al. [Guidelines on bone mineral disorder in chronic kidney disease--addendum chapter 2]. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia. 2012;34(2):199-205. Epub 2012/08/02. PubMed PMID: 22850924.
80. Prados-Garrido MD, Bover J, Teresa González-Álvarez M, J H. Clinical practice guideline for chronic kidney disease-mineral and bone disease (2010 version). Dialisis Transplante. 2011;32(3):108-18.
81. Torregrosa JV, Cannata Andia J, Bover J, Caravaca F, Lorenzo V, Martin de Francisco AL, et al. [SEN Guidelines. Recommendations of the Spanish Society of Nephrology for managing bone-mineral metabolic alterations in chronic renal disease patients]. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia. 2008;28 Suppl 1:1-22. Epub 2008/05/28. PubMed PMID: 18338978.
82. Mazzaferro S, Cozzolino M, Marangella M, Strippoli GF, Messa P. [Calcimimetics, phosphate binders, vitamin D and its analogues for treating secondary hyperparathyroidism in chronic kidney disease: guideline from the Italian Society of Nephrology]. Giornale italiano di nefrologia : organo ufficiale della Societa italiana di nefrologia. 2007;24 Suppl 37:S107-24. Epub 2007/03/10. PubMed PMID: 17347960.

83. Anonymous. Guidelines of the Ministry of Health of the Slovak Republic for the treatment of bone and mineral metabolism disorders in patients with chronic kidney disease. . Aktuality v Nefrologii 2009;15(3):121-7.
84. Barriocanal AM, Lopez A, Monreal M, Montane E. Quality assessment of peripheral artery disease clinical guidelines. Journal of vascular surgery. 2016;63(4):1091-8. Epub 2016/03/29. doi: 10.1016/j.jvs.2015.12.040. PubMed PMID: 27016858.
85. Zarnke KB, Campbell NR, McAlister FA, Levine M. A novel process for updating recommendations for managing hypertension: rationale and methods. The Canadian journal of cardiology. 2000;16(9):1094-102. Epub 2000/10/06. PubMed PMID: 11021953.

Chapter 5
CONCLUSION

Conclusion

Summary of main findings

Chapter 1 presented an introduction on chronic kidney disease-mineral and bone disorder (CKD-MBD) which is a systematic condition defined by an increase in cardiovascular calcifications and bone fragility. The condition is diagnosed by abnormal serum concentrations of calcium, phosphorus, parathyroid hormone and vitamin D [1]. These biochemical abnormalities have been linked to abnormal bone metabolism as well as cardiovascular calcifications if left untreated [1, 2]. Cardiovascular calcifications have been related to cardiovascular events and cardiovascular mortality which is the leading cause of death in patients with CKD [3, 4].

Phosphate binders are known to cause phosphate reduction through mechanisms that involve the gastrointestinal route [5, 6]. Their relative effects remain uncertain. Controversy arises because of concerns related to systematic effects, tolerability and costs of and impact on patient important outcomes.

Chapter 2 presented a network meta-analysis on relative effectiveness of phosphate binders on patient important outcomes using the frequentist approach. Our results suggested higher mortality with calcium than either sevelamer in our network meta-analysis or NCBPBs in our conventional meta-analysis. Conventional meta-analysis suggested no difference in cardiovascular mortality between calcium and NCBPBs. Our results suggest higher hospitalization, although non-significant, with calcium than NCBPBs. Our results raise questions about whether administration of calcium as an intervention for CKD- MBD remains ethical. Further research is needed to explore the effects of different types of phosphate binders, including novel agents such as iron, on quality and quantity of life in a large scale randomized controlled trial.

Chapter 3 presented a Bayesian network meta-analyses addressing the relative effectiveness of phosphate binders on laboratory outcomes. We calculated the effect estimates (mean differences) and 95% credible intervals for serum levels of phosphate, calcium and parathyroid hormone. Moderate-quality evidence suggests superior effect of each of the active treatment categories as compared to placebo for reducing serum phosphate. However, there was no significant difference between phosphate binders in terms of reducing serum phosphate. Results emphasize uncertainties regarding the mechanisms of sevelamer's reduction in mortality relative to calcium binders (the only difference in impact on biochemical variables was higher serum calcium with the calcium binders) and the necessity for basing recommendations on impact on patient-important outcomes.

Chapter 4 illustrated a systematic survey of critically appraisal of clinical practice guidelines addressing CKD-MBD. Most guidelines assessing CKD-MBD suffer from serious shortcomings using the Advancing Guideline Development, Reporting and Evaluation in Health Care instrument II (AGREE) criteria; a minority, however, fulfill the criteria. Limitations with respect to AGREE criteria do not, however, necessarily lead to inappropriate recommendations.

The most compelling implications for clinical practice come from Chapter 2, the meta-analysis addressing the relative impact of strategies to address the adverse consequences of CKD-BMD. Evidence should discourage physicians from prescribing calcium rather than NCBPB, and in particular sevalamer, due to a possible increased mortality with calcium binders relative to NCBPBs mortality.

Methodological issues

A. Probability of being best versus highest expected treatment benefit

Not highlighted in chapters 2 and 3, which present a published paper and a paper will be submitted for publication directed toward clinicians, are methodological issues arising from the network meta-analyses. One of these issues that arises when ranking treatments: i) the highest expected benefit; ii) the highest probability of showing the most favourable treatment effect; and iii) the cumulative effectiveness ranking. The highest expected benefit would be the total proportion of successes or (as in the example that follows) mean difference at study completion, across all simulations. The highest probability of showing the most favourable treatment effect is based on the ranks in each simulation (irrespective of the difference in results in treatments in adjacent ranks). This probability can be summarized cumulatively as an area under the curve or as a single statistic—surface under the cumulative ranking curve (SUCRA). We present a hypothetical example to explain the phenomena in Table 1. The outcome of interest is the mean difference in serum phosphate.

According to our hypothetical example, the highest expected benefit is achieved by treatment C, but highest probability of being best is equal with treatments B and C (4/10=40%). Therefore, we did not present rankograms based on ranking probabilities of being best treatment (Figure 1).

We confronted this problem of discrepant messages from the effect estimates and the ranking probabilities of being best in Chapter 2. Our judgement was that the effect estimate more accurately conveyed the relative merit of the treatments than did the ranking. Therefore, in Chapter 2 we did not present the SUCRA values. For illustrative purposes, we presented SUCRA values in our NMA on laboratory outcomes.

Other considerations

We assessed visually the congruence assumption which implies the extent of agreement between direct and indirect estimates: the proximity of point estimates and the degree of overlap between confidence or credible intervals, whichever is applicable.

We planned to rate down for imprecision when we observe wider confidence or credible intervals in our network estimates as compared to the contributing direct and indirect estimates. This could happen in theory because random-effect models include the difference between direct and indirect estimates in the error variance. We did not, however, observe this phenomenon in any of our analyses.

Bayesian analysis employs two sources of information: the prior information (also called the prior) and likelihood (study data) [9]. The prior and likelihood are used to create posterior distributions [9]. When conducting meta-regression, the Bayesian framework provides a common coefficient for all treatment comparisons. For instance, in Chapter 3 we addressed the possibility that duration of follow-up influenced the magnitude of effect consistently in all treatment comparisons. It is not possible to produce a common coefficient in the frequentist framework. We found no statistically significant association between trial duration and treatment effect in our meta-regression.

Summary of Contribution

This thesis has contributed to knowledge through the application of a novel methodology, NMA, to an important clinical issue in nephrology, the management of patients with CKD-BMD. The clinically important finding was mortality advantage of NCPB, and particularly sevelamer, over calcium binders. In addition, the application encountered previously unaddressed issues in the application of GRADE to NMA, issues for which the NMAs provided solutions. Finally, the thesis

identified limitations in the practice guidelines addressing CKD-BMD, but noted that methodological limitations don't always lead to different recommendations.

REFERENCES

1. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69(11):1945-53. Epub 2006/04/28. doi: 10.1038/sj.ki.5000414. PubMed PMID: 16641930.

2. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2005;67(3):1179-87.

3. Noordzij M, Korevaar JC, Boeschoten EW, Dekker FW, Bos WJ, Krediet RT. The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guideline for Bone Metabolism and Disease in CKD: association with mortality in dialysis patients. Am J Kidney Dis. 2005;46(5):925-32. Epub 2005/10/29. doi: 10.1053/j.ajkd.2005.08.013. PubMed PMID: 16253734.

4. Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. Kidney Int. 2010;78(6):578-89. doi: 10.1038/ki.2010.167. Epub Jun 16.

5. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, et al. Effects of phosphate binders in moderate CKD. Journal of the American Society of Nephrology : JASN. 2012;23(8):1407-15. Epub 2012/07/24. doi: 10.1681/asn.2012030223. PubMed PMID: 22822075; PubMed Central PMCID: PMCPMC3402292.

6. Chertow GM, Burke SK, Lazarus JM, Stenzel KH, Wombolt D, Goldberg D, et al. Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1997;29(1):66-71. Epub 1997/01/01. PubMed PMID: 9002531.

7. Sekercioglu N, Thabane L, Diaz Martinez JP, Nesrallah G, Longo CJ, Busse JW, et al. Comparative Effectiveness of Phosphate Binders in Patients with Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis. PLoS One. 2016;11(6):e0156891. Epub 2016/06/09. doi: 10.1371/journal.pone.0156891. PubMed PMID: 27276077.

8. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):597-606. Epub 2013/06/28. doi: 10.1177/0272989x13487604. PubMed PMID: 23804506; PubMed Central PMCID: PMCPMC3704205.

9. McCarron CE, Pullenayegum EM, Thabane L, Goeree R, Tarride JE. The impact of using informative priors in a Bayesian cost-effectiveness analysis: an application of endovascular versus open surgical repair for abdominal aortic aneurysms in high-risk patients. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(3):437-50. Epub 2012/10/12. doi: 10.1177/0272989x12458457. PubMed PMID: 23054366.

Table 1. An illustration of expected treatment benefit versus probability of being best

Simulation	Treatment A vs. placebo	Treatment B vs. placebo	Treatment C vs. placebo	Treatment D vs. placebo	Best treatment according to the highest mean difference achieved at the end of study
1	0.19	-1.15	-0.51	-0.25	B
2	-1.49	0.13	-0.37	-0.51	A
3	0.36	-0.19	-0.59	-1.34	D
4	0.35	-1.02	-1.61	-0.28	C
5	0.41	-0.02	-0.80	0.20	C
6	0.07	1.3	-0.63	0.14	C
7	0.03	0.02	-1.03	0.10	C
8	0.43	-1.50	-0.95	-0.18	B
9	0.22	-0.7	-0.50	-0.007	B
10	-0.05	-1.19	-0.03	-0.46	B
MD	0.52	-1.5	-2.8	-0.28	

Legend: The numbers in the Treatment A, B, C and D columns represent the mean difference in serum phosphate between treatments and placebo for patients in that treatment in that simulation. Minus values indicate lower serum phosphate at the end of the study period and positive outcome; MD: mean difference

Figure 1. Rankogram are based on ranking probabilities

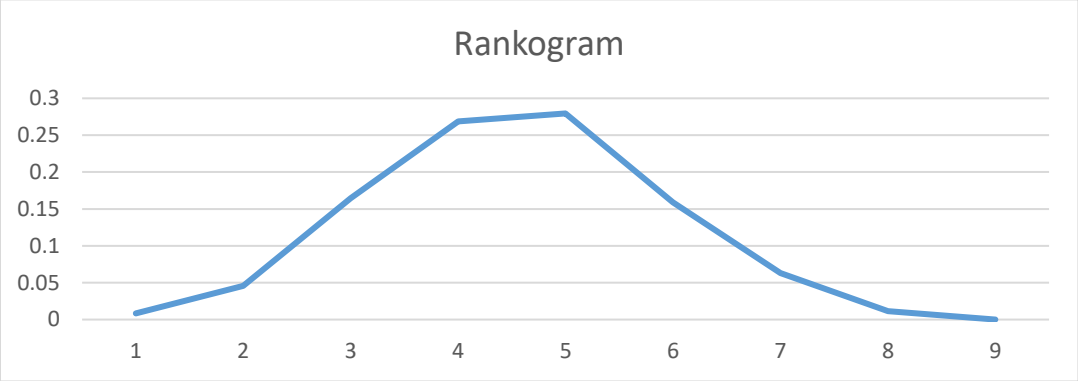


Figure 2. Cumulative ranking curve of sevelamar for serum phosphate. The area under the curve indicates the SUCRA value associated with the treatment