Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

## Vorgang: 2014-10-01-D-136 Sucroferric Oxyhydroxid

Stand: Juni 2014

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

## Inhalt



### Indikation für die Recherche bei Wirkstoff Sucroferric (Velphoro®):

Zur Kontrolle des Serumphosphorspiegels bei erwachsenen Patienten mit chronischer Niereninsuffizienz unter Hämodialyse oder Peritonealdialyse

### Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s.: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

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## I. Zweckmäßige Vergleichstherapie: Kriterien gemäß § 6 5. Kapitel VerfO G-BA

Sucroferric Oxyhydroxid

Zur Kontrolle des Serumphosphorspiegels bei erwachsenen Patienten mit chronischer Niereninsuffizienz unter Hämodialyse oder Peritonealdialyse

| Kriterien gemäß 5. Kapitel § 6 VerfO | |
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| 1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | Calciumacetat,<br>Calciumcarbonat<br>Calciumacetat und Magnesiumcarbonat<br>Aluminiumchloridhydroxid<br>Aluminiumhydroxid<br><br>Sevelamercarbonat/Sevelamerhydrochlorid<br>Lanthan(III)carbonat<br><br>Colestilan |
| 2. Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | *Nicht angezeigt* |
| 3. Als Vergleichstherapie sollen bevorzugt Arzneimittelanwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist. | Beschluss über die Nutzenbewertung von Colestilan nach § 35 a SGB V vom 20.02.2014<br><br>AM-RL/ Anlage 1:<br>Nr. 37. Phosphatbinder nur zur Behandlung der Hyperphosphataemie bei chronischer Niereninsuffizienz und Dialyse. |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
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| Wirkstoff<br>ATC-Code<br>Handelsname | Anwendungsgebiet<br>(Text aus Fachinformation/Beratungsanforderung) |
| Sucroferric Oxyhydroxid | Velphoro wird bei Erwachsenen mit chronischer Niereninsuffizienz unter Hämodialyse oder Peritonealdialyse zur Kontrolle des Serumphosphorspiegels angewendet.<br>Velphoro sollte im Rahmen eines umfassenden therapeutischen Ansatzes angewendet werden, der ein Calciumergänzungsmittel, 1,25-dihydoxy Vitamin D3 oder eines seiner Analoga oder Kalzimimetika umfassen könnte, um die Entwicklung renaler Knochenerkrankungen zu kontrollieren. |
| Colestilan BindRen® | BindRen® wird angewendet zur Behandlung der Hyperphosphatämie bei Erwachsenen mit chronischer Nierenerkrankung (Chronic Kidney Disease, CKD) im Stadium 5, die sich einer Hämodialyse oder Peritonealdialyse unterziehen. |
| Sevelamer (carbonat bzw. hydroxid)<br>V03AE02<br>Renagel® / Renvela® | Renagel ist indiziert zur Behandlung von Hyperphosphatämie bei erwachsenen Patienten, die eine Hämodialyse oder eine Peritonealdialyse erhalten. Renagel sollte innerhalb einer Mehrfachtherapie angewendet werden, die zur Kontrolle der Entwicklung von renaler Knochenerkrankung Kalziumzusätze, 1,25-Dihydroxy-Vitamin D3 oder einen Analogstoff desselben enthalten könnte. |
| Lanthan(III)-carbonat<br>V03AE03<br>Fosrenol® | Fosrenol ist indiziert als phosphatbindendes Mittel zur Vermeidung einer Hyperphosphatämie bei Patienten mit chronischer Niereninsuffizienz, die eine Hämodialysebehandlung oder eine kontinuierliche, ambulante Peritonealdialyse (CAPD) erhalten.. |
| Calciumacetat und Magnesiumcarbonat<br>V03AE04<br>OsvaRen® | Behandlung von Hyperphosphatämie in Zusammenhang mit chronischer Niereninsuffizienz bei Dialysepatienten (Hämodialyse, Peritonealdialyse). |
| Calciumacetat<br>V03AE07 Calciumacetat-Nefro® | Hyperphosphatämie, verursacht durch chronische Niereninsuffizienz bei Patienten unter Dialysebehandlung. |
| Calciumcarbonat<br>V03AE08 | Erhöhtes Serumphosphat (Hyperphosphatämie) bei chronischer Niereninsuffizienz, insbesondere bei Patienten unter Dialysebehandlung. |

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| CC-Nefro® | |
| Aluminiumhydroxid<br>V03AE05<br>Antiphosphat® | Verminderung der Phosphatresorption bei niereninsuffizienten Patienten mit erhöhten Phosphatblutspiegeln und sekundärem Hyperparathyreoidismus (zur Verminderung der Aufnahme von Phosphat aus dem Darm bei Patienten mit eingeschränkter Nierenfunktion, bei denen das Phosphat nicht ausreichend ausgeschieden wird, sodass der Phosphatblutspiegel ansteigt).. |
| Aluminiumchlorid-hydroxid<br>V03AE09<br>Phosphonorm® | Zur Verminderung der Phosphataufnahme aus dem Darm bei Patienten mit Niereninsuffizienz und erhöhten Serumphosphatspiegeln insbesondere bei Patienten im Dialyseprogramm |

Gemeinsamer Bundesausschuss

**Systematische Recherche:**

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Kontrolle des Serumphosphorspiegels bei Erwachsenen mit chronischer Niereninsuffizienz, die Hämodialyse oder Peritonealdialyse erhalten“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am **02.06.2014** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **435** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies **13** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Ergänzend wurden

– 2 Dokumente anderer Organisationen zu möglichen Komparatoren von Sucroferric Oxyhydroxid identifiziert und eingeschlossen (SMC).

Abkürzungen

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| ÄZQ | Ärztliches Zentrum für Qualität in der Medizin |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| CKD | Chronic kidney disease |
| DAHTA | Deutsche Agentur für Health Technology Assessment |
| G-BA | Gemeinsamer Bundesausschuss |
| GFR | Glomeruläre Filtrationsrate |
| GIN | Guidelines International Network |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| LC | Lanthancarbonat |
| NGC | National Guideline Clearinghouse |
| NHS CRD | National Health Services Center for Reviews and Dissemination |
| NICE | National Institute for Health and Care Excellence |
| RCT | Randomisierte kontrollierte Studie |
| SH | Sevelamerhydrochlorid |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |

## G-BA Beschlüsse/IQWiG-Bewertung

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| **Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V**<br>**Beschluss vom 20.02.2014: Colestilan zur Behandlung der Hyperphosphatämie bei Dialysepatienten** | **Zweckmäßige Vergleichstherapie** zur Behandlung der Hyperphosphatämie bei Erwachsenen mit chronischer Nierenerkrankung (Chronic Kidney Disease, CKD) im Stadium 5, die sich einer Hämodialyse oder Peritonealdialyse unterziehen:<br>- kalziumhaltige Phosphatbinder (einzeln oder in Kombination) oder Sevelamer oder Lanthankarbonat<br>- bei Patienten bei denen kalziumhaltige Phosphatbinder laut Fachinformation kontra-indiziert sind (z. B. Hyperkalzämie): Sevelamer oder Lanthankarbonat.<br><br>Ausmaß und Wahrscheinlichkeit des **Zusatznutzens** gegenüber der zweckmäßigen Vergleichstherapie (kalziumhaltige Phosphatbinder oder Sevelamer oder Lanthankarbonat):<br>a) <u>Patienten, für die eine Behandlung mit kalziumhaltigen Phosphatbindern geeignet ist:</u><br>Ein Zusatznutzen ist nicht belegt.<br>b) <u>Patienten, bei denen kalziumhaltige Phosphatbinder laut Fachinformation kontraindiziert sind:</u><br>Ein Zusatznutzen ist nicht belegt. |
| **IQWiG-Berichte – Nr. 173 Colestilan – Nutzenbewertung gemäß § 35a SGB V**<br>**Stand: 27.06.2013** | Für erwachsene Patienten mit CKD 5D mit Kontraindikation für calcium- und aluminiumhaltige Phosphatbinder (auch in Kombination) (Teilanwendungsgebiet AII) liegt in der Kategorie nicht schwere / nicht schwerwiegende Nebenwirkungen ein größerer Schaden von Colestilan mit der Wahrscheinlichkeit „Anhaltspunkt“ und dem Ausmaß „nicht quantifizierbar“ vor (Endpunkt: Therapieabbrüche wegen UEs). Positive Effekte liegen nicht vor.<br>Damit ergibt sich insgesamt ein **Anhaltspunkt für einen geringeren Nutzen von Colestilan gegenüber der zweckmäßigen Vergleichstherapie Sevelamerhydrochlorid**. |

**Cochrane Reviews**

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| **Navaneethan SD et al. 2011**<br><br>Phosphate binders for preventing and treating bone disease in chronic kidney disease patients. Cochrane Database Syst Rev 2: CD006023 | 1. Fragestellung<br><br>Effekte verschiedener Phosphatbinder auf biochemische und patientenrelevante Endpunkte bei Patienten mit Niereninsuffizienz im Stadium 3-5D [D=Dialyse] |
| | 2. Methodik<br><br><u>Population</u><br>*People with CKD in stage 3, 4, 5 and 5D as defined by the K/DOQI guidelines (stage 3: GFR 30-59 mL/min; stage 4: GFR 15-29 mL/min; stage 5: GFR < 15 mL/min; stage 5D: on dialysis) and older than 18 years.*<br><br><u>Intervention</u><br>*Studies greater than eight weeks duration of phosphate binders such as aluminium hydroxide, calciumacetate, calciumcarbonate, calcium ketoglutarate, sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, and magnesium carbonate compared with placebo or to other phosphate binder were included.*<br><br><u>Komparator</u><br>*Comparisons were categorised as:*<br>*1. Calcium salts versus other calcium salts or placebo or other agents.*<br>*2. Sevelamer versus calcium salts or placebo or other agents.*<br>*3. Lanthanum carbonate versus calcium salts or placebo or other agents.*<br>*4. Miscellaneous agents versus placebo or other agents.*<br><br><u>Endpunkte</u> (keine Unterscheidung in primäre oder sekundäre)<br>*1. All-cause mortality, cardiovascular mortality, cardiovascular events, hospitalisation (incidence or duration of hospitalisation), or fracture (incidence of fracture at any site; vertebral compression fractures; fracture of femur, hip, and any long bones identified by radiographic studies).*<br>*2. Incidence and nature of treatment-related adverse effects including gastrointestinal (gastritis, diarrhoea, constipation, abdominal bloating), electrolyte imbalance (hypomagnesaemia, hyperkalaemia), accumulation of drug deposits as demonstrated by bone biopsies or anaemia.*<br>*3. Hypercalcaemia (defined as serum calcium level > 10.2 mg/dL or as defined by the study investigators)*<br>*4. Hyperphosphataemia.*<br>*5. Serum phosphorus (mg/dL), serum calcium (mg/dL), Ca x P* |

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| | *product (mg²/dL²), PTH (intact (iPTH), or PTH (1-84)); alkaline phosphatase (IU/L), serum bicarbonate (mEq/L).*<br>*6. Total serum cholesterol (mg/dL).*<br>*7. Vascular calcification, soft tissue or valvular calcification, or incidence of calciphylaxis.*<br>*8. Bone mineral density assessed by DEXA or QCT (change in BMD using Z-scores or per cent change (g/cm²) at the lumbar spine, femoral neck, or radius).*<br>*9. Bone turnover and mineralisation based on histomorphometry and histology.*<br><br><u>Suchzeitraum</u> (Aktualität der Recherche): Recherche bis März 2010<br>Recherche im Studienregister der Cochrane Renal Group (regelmäßige Suche in Medline mit Cochrane-Suchfilter für RCTs und in CENTRAL sowie Handsuche), MEDLINE und EMBASE<br><br>Anzahl eingeschlossene Studien/Patienten (gesamt): 60 RCTs (67 Publikationen) (n=7.631)<br>- Sevelamer vs. kalziumhaltige Phosphatbinder oder Plazebo (21 RCTs, 4.045 Pat.)<br>- Kalziumacetat vs. Kalziumkarbonat (13 RCTs, 501 Pat.)<br>- Lanthan vs. Plazebo / Kalziumkarbonat (12 RCTs, 2.541 Pat.)<br>- Sonstige Vergleiche (14 RCTs, 544 Pat.)<br><br><u>Qualitätsbewertung</u><br>*The quality items assessed were allocation concealment; blinding of investigators, participants, outcome assessors, and data analysis; intention-to-treat analysis and completeness to follow-up.*<br><br>*Reported study quality was variable.*<br>*• Allocation concealment was adequate in 11/60 (18%) studies and unclear in other studies.*<br>*• Participants and investigators were blinded in 10/60 (17%) studies and outcome assessors were blinded in none of the studies.*<br>*• Only 13/60 (22%) studies were analysed on an intention-to-treat basis.*<br>*• The number of participants lost to follow-up ranged from 0% to 31% but did not differ between the treatment and control groups of the studies.* |
| | 3. Ergebnisdarstellung<br><br>• *There was no significant reduction in all-cause mortality (10 studies, 3079 participants: RR 0.73, 95%CI 0.46 to 1.16), or serum calcium by phosphorus (Ca x P) product with sevelamer* |

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| | *hydrochloride compared to calcium-based agents.*<br><br>• *There was a significant reduction in serum phosphorus (16 studies, 3126 participants: MD 0.23 mg/dL, 95% CI 0.04 to 0.42) and parathyroid hormone (PTH) (12 studies, 2551 participants; MD 56 pg/mL, 95% CI 26 to 84) but a significant increase in the risk of hypercalcaemia (12 studies, 1144 participants: RR 0.45, 95% CI 0.35 to 0.59) with calcium-based agents compared to sevelamer hydrochloride.*<br><br>• *There was a significant increase in the risk of adverse gastrointestinal events with sevelamer hydrochloride in comparison to calcium salts (5 studies, 498 participants: RR 1.58, 95% CI 1.11 to 2.25).*<br><br>• *Compared with calcium-based agents, lanthanum significantly reduced serum calcium (2 studies, 122 participants: MD -0.30 mg/dL, 95% CI -0.64 to -0.25) and the Ca x P product, but not serum phosphorus levels.*<br><br>• *The effects of calcium acetate on biochemical end-points were similar to those of calcium carbonate.*<br><br>• *there are insufficient data to establish the comparative superiority of novel non-calcium binding agents over calcium-containing phosphate binders for patient-level outcomes such as all-cause mortality and cardiovascular end-points in CKD.* |
| | 4. Anmerkungen/Fazit der Autoren<br><br>*Our review supports the conclusion that the novel phosphate binders such as sevelamer hydrochloride and lanthanum carbonate are not superior to calcium salts for the control of phosphorus levels in dialysis patients and their impact on morbidity and mortality is unknown. The primary advantage of more recently developed phosphate binders (lanthanum carbonate and sevelamer hydrochloride) is a reduction in hypercalcaemia. Data for patient focused end-points in dialysis patients are inadequate to inform clinical recommendations for any phosphate binder.* |

**Systematische Reviews**

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| **Jamal et al. 2013**<br><br>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 382:1268-77 | 1. Fragestellung<br><br>We aimed to update our meta-analysis on the effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease.<br><br>(Update einer früheren Metaanalyse) |
| | 2. Methodik<br><br><u>Population</u><br>*patients (men or women irrespective of menopausal status) with chronic kidney disease (irrespective of stage of chronic kidney disease or type of dialysis)*<br><br><u>Intervention</u><br>*calcium-based phosphate binders (calcium carbonate or calcium acetate)*<br><br><u>Komparator</u><br>*non-calcium-based binders (sevelamer hydrochloride, sevelamer carbonate, or lanthanum)*<br><br><u>Endpunkte</u><br>Primär: *all-cause mortality*<br>Sekundär: kardiovaskuläre Ereignisse (*fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, and sudden death*), Gefäßverkalkungen, Frakturen, *vascular compliance*<br><br><u>Suchzeitraum</u> (Aktualität der Recherche: 10/2012)<br>*…searched for clinical trials published after Aug 1, 2008 (when our previous systematic review ended), up until Oct 22, 2012 (the date of the last search). They searched the electronic databases Ovid Medline (articles published between 1946 and October, 2012, including those in the process of being added to the database and other citations from journals listed in PubMed but not included in Medline), Ovid Embase (1974 to October, 2012), Ovid International Pharmaceutical Abstracts (1970 to September, 2012), Wiley Cochrane Central Register of Controlled Trials (inception to October, 2012), and EBSCO Cumulative Index to Nursing and Allied Health Literature (inception to October, 2012). Keywords included "phosphate binders", "calcium", "kidney disease", "dialysis", "cardiovascular events", and "mortality".*<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 Studien, darunter 5 RCTs neu identifiziert (n=3.230) |

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| | - 1.726 Pat. erhielten Kalziumkarbonat oder Kalziumacetat<br>- 774 erhielten Sevelamer<br>- 730 erhielten Lanthan<br>Insgesamt 14 RCTs, 2 Beobachtungsstudien, 1 Querschnittsstudie, 1 Kohortenstudie (retrospektiv) im Studienpool; Auswertung des primären Endpunkts nur mittels der RCTs<br><br>Qualitätsbewertung der Studien:<br>*We used the Cochrane risk of bias method to appraise study quality*<br><br>5 RCTs mit niedrigem Biasrisiko, 6 mit hohem, 3 mit unklarem Biasrisiko |
| | 3. Ergebnisdarstellung<br>Primärer Endpunkt:<br>11 RCTs (N=4.622) ausgewertet, die Mortalität berichteten (936 Todesfälle)<br>RR 0,78 (95%-KI 0,61;0,98) zugunsten von Sevelamer / Lanthan bei mäßiger Heterogenität $I^2$=43%) [aber nicht signifikant, wenn für Sevelamer {RR 0,89; 95%-KI 0,78;1,01} oder Lanthan {RR 0,74; 95%-KI 0,49;1,13} separat ausgewertet wird]<br>Sekundäre Endpunkte:<br>- *None of the eight newly added studies included data for cardiovascular events, therefore our estimate of effect is the same as in our previous paper: a non-significant reduction in mortality of 15% (RR 0·85, 95% CI 0·35–2·03)*<br>- *Coronary artery calcification was reported in seven randomised (five of these were included in our previously published meta-analysis). Data for coronary artery calcification was reported in 704 patients; 235 patients were newly added. The reduction in vascular calcification was greater in patients assigned to non-calcium- based phosphate binders than in those assigned to calcium binders at all timepoints. mean difference in Agatston score −95.26, 95% CI −146.68 to −43.84*<br>- *As in our previous meta-analysis, none of the studies reported on fractures or vascular compliance* |
| | 4. Anmerkungen/Fazit der Autoren<br>*Calcium-based phosphate binders are inexpensive; however, based on our systematic review, the best evidence available so far suggests that they might be harmful. The mechanism of the benefits of non-calcium-based phosphate binders seems to be a slower progression of vascular calcification.* |

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| | Anmerkung FBMed:<br><br>Hinweis auf Publikationsbias im Funnel Plot, signifikanter Egger-Test |
| **Abbasi et al. 2010**<br><br>Clinical Evidence: End-stage renal disease<br><br>Search date October 2009 | 1. Fragestellung<br><br>*We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of different doses for peritoneal dialysis? What are the effects of different doses and membrane fluxes for haemodialysis?* ***What are the effects of interventions aimed at preventing secondary complications?*** |
| | 2. Methodik<br><br><u>Population</u><br>Patienten mit terminaler Niereninsuffizienz<br><br><u>Intervention</u><br>Sevelamer<br><br><u>Komparator</u><br>Kalziumsalze<br><br><u>Endpunkte</u><br>*Outcomes of interest include: mortality; cardiovascular complications (incidence of MI, congestive heart failure, stroke, and hypertension); quality of life; adverse effects. For the question on interventions aimed at reducing secondary complications, we have also reported non-cardiovascular complications (anaemia, calcium-phosphorous homeostasis [including serum calcium, serum phosphorous, serum parathyroid hormone levels, vascular calcification], and infections).*<br><br><u>Suchzeitraum</u> (Aktualität der Recherche)<br>*Medline 1966 to October 2009, Embase 1980 to October 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 3 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA).*<br><br>Anzahl eingeschlossene Studien/Patienten (nur Fragestellung Sevelamer vs. Kalziumsalze): 2 Systematischer Reviews (10 RCTs mit n= 3.079 bzw. 1 RCT mit n=200)<br><br>Qualitätsbewertung der Studien:<br>Bewertung der Qualität der Evidenz nach GRADE<br>- Qualität der Evidenz bzgl. Mortalität: moderat (*Directness point deducted for large variation in study duration*)<br>- Qualität der Evidenz bzgl. nicht kardiovaskuläre Komplikationen: |

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| | 3. Ergebnisdarstellung<br>- Auswertung des Cochrane-Reviews von Navaneethan et al. bzgl. Mortalität: *Compared with calcium salts Sevelamer seems no more effective at reducing mortality in people with end-stage renal disease*<br>*8- to 156-week follow-up (10 RCTs; 3079 people on renal replacement therapy: 290/1532 [19%] with sevelamer v 320/1547 [21%] with calcium salts; RR 0.73, 95% CI 0.46 to 1.16)*<br>- Auswertung eines systematischen Reviews zu nicht kardiovaskulären Komplikationen: *Compared with calcium salts Sevelamer is more effective at 52 weeks at reducing the progression of coronary artery and aortic calcification in people with end-stage renal disease*<br>*Agatston score: –46 with sevelamer v +151 with calcium salts; P = 0.04* |
| | 4. Anmerkungen/Fazit der Autoren<br>*Likely to be beneficial:*<br>*Sevelamer (reduces progression of coronary artery and aortic calcification compared with calcium salts)*<br>*Phosphate binders (sevelamer) may slow down arterial calcification, and may reduce serum low-density lipoprotein cholesterol levels, but we don't yet know whether this reduces cardiovascular events or mortality.* |
| **Huang et al., 2014**<br>Efficacy and tolerability of lanthanum carbonate in treatment of hyperphosphatemia patients receiving dialysis – a systematic review and meta-analysis of randomized controlled trials. Current Medical Research & Opinion 30;99–108 | 1. Fragestellung<br>*The aim of this meta-analysis was to systematically assess and compare the effectiveness and safety of LC with placebo for the treatment of hyperphosphatemia in patients with ESRD receiving dialysis.* |
| | 2. Methodik<br><u>Population</u><br>*Studies enrolling adult patients (age ≥18 years) with CKD stages 5 (dialysis) were included*<br><u>Intervention</u><br>*Lanthanum carbonate for the treatment of hyperphosphatemia*<br><u>Komparator</u><br>Plazebo<br><u>Endpunkte</u> |

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| | primärer Endpunkt:<br>*predialysis serum phosphorus concentration [PSPL] during and following treatment with lanthanum carbonate*<br>sekundäre Endpunkte:<br>*biochemical or hematological parameters and adverse events: serum calcium (Ca), calcium x phosphorus (Ca x Pi) product, parathyroid hormone (PTH), blood lanthanum concentrations, safety and tolerability*<br><br><u>Suchzeitraum</u> (Aktualität der Recherche: März 2013)<br>*Literature searches of all publication years (from inception to March 2013) were conducted using PubMed, EMBASE, the Science Citation Index, the Cochrane library, the Chinese Biological Medical Database, the Chinese National Knowledge Infrastructure, and the VIP Database for Chinese Technical Periodicals.*<br>*search terms: Lanthanum carbonate OR Fosrenol in English and Tan Suan Lan OR Fu Si Li Nuo in Chinese. We also hand-searched the reference lists of every primary study for additional publications.*<br>*No language restriction was used.*<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 RCTs (n=950)<br><br><u>Qualitätsbewertung der Studien</u>:<br>*Each included trial is assessed independently to ascertain the following methodological qualities: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. To assess the effect of trial quality on the effect size, sensitivity analysis was done by comparing studies whether they fulfilled quality criteria or not.*<br><br>Klinische Heterogenität zwischen den Studien mit Ausnahme der Art der Dialyse gering.<br>Nur eine Studie mit niedrigem Biasrisiko: *Only one study described an adequate random sequence generation. Allocation concealment and blinding were uncertain in almost all studies.*<br>Alle Studien waren doppelt verblindet; ITT-Analyse in 5 Studien; selektives Berichten von Outcomes in allen Studien. |
| | 3. Ergebnisdarstellung<br><br>Primärer Endpunkt:<br><br>*significant difference in PSPL between the lanthanum carbonate and placebo groups (SMD -1.06, 95% CI -1.27;-0.86, p<0.00001),* 4 |

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| | RCTs (n=417), $I^2$=32%<br><br>sekundäre Endpunkte:<br><br>- *There were no significant differences in serum calcium changes from baseline between the lanthanum carbonate and placebo groups (SMD 0.12, 95% CI -0.10;0.34, P=0.28)* (2 RCTs, n=311)<br>- *There was a significant difference in Ca x Pi changes from baseline between the lanthanum carbonate and placebo groups. The increase in Ca x Pi product from baseline was significantly lower in lanthanum carbonate treated patients than that in placebo treated patients (SMD -0.90, 95% CI -1.13;-0.66, P<0.00001).* (2 RCTs, n=310)<br>- *increase of serum PTH from baseline was significantly lower in lanthanum carbonate treated patients than in placebo treated patients (SMD -0.27, 95% CI -0.46;-0.06, P<0.007)* (3 RCTs, n=454)<br>- *The treatment related side-effects that occurred more frequently in LC treated patients, compared with placebo treated patients, were vomiting and nausea (OR 3.10, 95% CI 1.35–7.08, P<0.007; OR 2.74, 95% CI 1.22–6.19, P=0.02, respectively). (*6 bzw. 5 RCTs)<br>- *The mean lanthanum concentrations in plasma were higher in the lanthanum carbonate treated group compared with the placebo group (SMD 0.80, 95% CI 0.54–1.06, P<0.00001). Mean lanthanum levels were 0.67±0.98 ng/g in the lanthanum carbonate treated group and 0.14±0.26 ng/g in the placebo group.* (3 RCTs, n=298) |
| | 4. Anmerkungen/Fazit der Autoren<br><br>*In the treatment of hyperphosphatemia in patients with chronic renal failure requiring dialysis, lanthanum carbonate is generally well tolerated and more effective than placebo during short-term trials. Furthermore, it help to maintain PTH and Ca x Pi product levels within recommended limits, indicating that lanthanum carbonate treatment may contribute to the reduction of cardiovascular morbidity and mortality risk in patients with ESRD.*<br><br>5. Hinweise durch FB Med:<br>- Publikationsbias nicht untersucht<br>- einige Metaanalysen nicht vorab spezifiziert, daher hier nicht dargestellt (u.a. Dosis, Responder)<br>- Dauer der Studien 4-6 Wochen<br>- nur Surrogatendpunkte<br>- nur Plazebovergleiche |

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| **Zhang Q et al. 2010**<br><br>Meta-analysis comparing sevelamer and calcium-based phosphate binders on cardiovascular calcification in hemodialysis patients. Nephron Clinical Practice 115:c259-c267 | 1. Fragestellung<br><br>Effekt von Sevelamer-Hydrochlorid vs. kalziumbasierte Phosphatbinder auf den *coronary artery calcification score*, C-reaktives Protein, alkalische Phosphatase und intaktes Parathormon bei Dialysepatienten |
| | 2. Methodik<br><br><u>Population</u><br>*adult human subjects undergoing HD who were treated with sevelamer or calcium-based phosphate binders (CBPBs).*<br><br><u>Intervention</u><br>Sevelamer<br><br><u>Komparator</u><br>Kalziumbasierte Phosphatbinder<br><br><u>Endpunkte</u><br>*The primary outcome was change in CAC [coronary artery calcium] level from baseline to end of treatment. When data were unavailable, CAC level at the end of the study was used. Secondary outcomes included CRP, iPTH, AKP, bone-specific alkaline phosphatase (BSAP), mineral metabolism, and lipid profiles.*<br><br><u>Suchzeitraum</u> (Aktualität der Recherche)<br>*We searched for the terms 'sevelamer' or 'Renagel' on MEDLINE (January 1969 to April 2009), EMBASE (January 1969 to April 2009), and CENTRAL (The Cochrane Library up to 2008, issue 4)*<br><br><u>Anzahl eingeschlossene Studien/Patienten</u> (Gesamt): 14 RCTs (n=3.271)<br><br><u>Qualitätsbewertung der Studien:</u><br>Jadad-Score<br>6 RCTs mit Jadad Score ≥3 |
| | 3. Ergebnisdarstellung<br><br>Primärer Endpunkt:<br>- *Effects on Cardiovascular Calcification: Four trials reported changes in the CAC score from baseline. Taken together, no significant difference was found between the sevelamer group and the CBPB group (WMD -74.87; 95% CI -159.96 to 10.22) (fig. 2). There was no significant heterogeneity of trial results ($X^2$ = 3.56, P = 0.31, $I^2$ = 15.7%).* 4 RCTs, n=652 |

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| | Sekundäre Endpunkte:<br>- Phosphatspiegel unter Sevelamer tendenziell (nicht signifikant) höher (WMD 0,18 mg/dl 95%-CI -0,02;0,37, p=0,08, mäßige Heterogenität [p=0,005, $I^2$ 56%])<br>- Calciumspiegel unter Sevelamer niedriger (WMD -0.38 mg/dl 95%-CI -0,62;-0,14, p<0,00001, mäßige Heterogenität [p=0,002, $I^2$ 50%])<br>- iPTH, CRP und Lipide unter Sevelamer signifikant niedriger<br>- AKP und BSAP unter Sevelamer signifikant höher<br>- Ca x P, HDL, Triglyceride: keine signifikanten Unterschiede |
| | 4. Anmerkungen/Fazit der Autoren<br>*In conclusion, the results of this meta-analysis indicate that there is no difference between sevelamer and CBPBs in reducing vascular calcification in patients undergoing HD.*<br><br>5. Hinweise durch FB Med:<br>- Studiendauer 8 Wochen bis 45 Monate<br>- ausschließlich Surrogatendpunkte<br>- kein Hinweis auf Publikationsbias |
| **Zhang et al. 2013**<br>Efficacy and safety of lanthanum carbonate on chronic kidney disease – mineral and bone disorder in dialysis patients: a systematic review. BMC Nephrology 2013:14:226. | 1. Fragestellung<br>*We conducted a systematic review of the efficacy and safety of LC in ESRD patients undergoing dialysis, particularly in terms of long-term outcomes such as mortality, CV calcification, and bone disorder.* |
| | 2. Methodik<br><br><u>Population</u><br>*ESRD patients who regularly receive HD or PD, aged ≥18 years old, and did not use LC previously (at least > 1 week) were included in this study.*<br><br><u>Intervention</u><br>Lanthancarbonat<br><br><u>Komparator</u><br>*The comparisons were as follows:*<br>*1. LC + routine treatment versus placebo + routine treatment.*<br>*2. LC + routine treatment versus calcium-based binders (CBBs) + routine treatment.*<br>*3. LC + routine treatment versus SH + routine treatment.*<br>*4. LC + routine treatment versus other non-calcium binders (NCBs) or previous phosphate binders + routine treatment.*<br><br><u>Endpunkte</u><br><u>Primare Endpunkte</u> |

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| | *1. All-cause mortality.*<br>*2. Cardiovascular events.*<br>*Cardiovascular events were defined as fatal or nonfatal myocardial infarction, fatal or nonfatal cerebrovascular event (stroke), or the development of coronary artery disease.*<br><br>Sekundäre Endpunkte<br>*1. Vessel calcification (VC), including those of the aorta, coronary artery, and cardiac valves, as determined by spiral computed tomography.*<br>*2. Biochemical outcomes such as levels of serum phosphorus, serum calcium, calcium × phosphate product (Ca × P), intact parathyroid hormone (iPTH), 1,25-(OH)D 3 , 25-(OH) 2 D 3 , total alkaline phosphatase (TAP), bone-specific alkaline phosphatase (BAP), and blood lipid.*<br>*3. Bone disorder (including bone morphology and bone metabolism).*<br>*4. Lanthanum contents in bone, liver, and blood.*<br>*5. Inflammatory biomarker such as C-reactive protein (CRP).*<br>*6. Side effects of medications.*<br><br>Suchzeitraum (Aktualität der Recherche)<br>*MEDLINE, EMBASE, the Cochrane Renal Group Specialised Register, and the Cochrane Central Register of Controlled Trials (CENTRAL) using the following criteria without any language restrictions: "lanthanum carbonate OR Fosrenol AND (dialysis OR hemodialysis OR peritoneal dialysis OR end stage renal disease"*<br>*The latest date for the search was March 31, 2013.*<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 16 RCTs (n=3.789), 6 plazebokontrolliert<br><br>Qualitätsbewertung der Studien:<br>Qualitätscheckliste der Cochrane Renal Group: *The quality items assessed were the allocation concealment, blinding, intention-to-treat analysis, and completeness of follow-up. Blinding was assessed for investigators, participants, outcome assessors, and data analysts.*<br>*All 16 studies performed random allocation, but only 2 described the use of randomization. A considerable part of the studies included in this review were not blinded. Only 8 studies reported blinding of patients and physicians, and 1 reported blinding of outcome assessors. Intention-to-treat analysis was performed in 10 of the 16 studies, and fulfillment of follow-up was high in most of the studies except for two, which had long follow-up durations.* |

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| | 3. Ergebnisdarstellung<br><br><u>Primäre Endpunkte</u><br><br>*Effect on all-cause mortality*<br><br>- *No significant difference was observed between the LC and the control in the risk of lowering all-cause mortality (2 studies, 1404 patients, RR: 0.85, 95% CI: 0.69 to 1.04).*<br><br>*Effect on cardiovascular events*<br><br>- *No significant difference was observed between the LC and CBB groups in terms of the risk of lowering cardiovascular events (1 study, 45 patients, RR: 0.78, 95% CI: 0.20 to 3.11).*<br><br><u>Sekundäre Endpunkte</u><br><br>- Vessel calcification (VC): *Patients in the LC group showed significantly less aortic VC progression than those in the CC group (difference from baseline − 99.6 HU, 95% CI: – 150.5 to − 48.8, p < 0.001).* 1 RCT, n=45<br>- Biochemical outcomes: *Meta-analysis showed that LC significantly lowered the serum phosphorus level compared with the placebo (5 studies, 562 patients, MD: – 0.64, 95% CI: – 0.78 to − 0.50), whereas no difference was observed between the LC and CC groups (4 studies, 377 patients, MD: 0.09, 95% CI: 0.00 to 0.19) and between the LC and SH groups (1 study, 84 patients, MD: – 0.09, 95% CI: –0.19 to 0.01)*<br>*CC-treated patients had higher calcium levels than those treated with LC (4 studies, 1099 patients, MD: – 0.12, 95% CI: – 0.15 to − 0.09)*<br>*The results also showed that when compared with the SH* [Sevelamerhydrochlorid] *group, the LC group had higher levels of total cholesterol (1 study, 84 patients, MD: 25.00, 95% CI: 12.17 to 37.83) and LDL cholesterol (1 study, 84 patients, MD: 20.00, 95% CI: 10.16 to 29.84)*<br>[Ergebnisse für andere biochemische Endpunkte nicht dargestellt; keine signifikanten Gruppenunterschiede vorhanden]<br>- Bone disorder: *Two trials found improvements in renal osteodystrophy in lanthanum-treated patients compared with those treated with CC or with their previous phosphate binders (without lanthanum). However, another trial showed no difference between the two binders.*<br>- Lanthanum contents in bone, liver, and blood: *Seven studies measured the plasma or serum lanthanum level. Most of the results showed slightly increased lanthanum levels in the blood of the LC groups but did not indicate any statistical difference*<br>- Inflammatory biomarker such as C-reactive protein (CRP): *None* |

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| | *of trials reported any inflammatory biomarker such as CRP.*<br>- Side effects of medications: *Results showed that LC had a lower risk of diarrhea when compared with placebo (4 studies, 395 patients, RR 0.31, 95% CI 0.15 to 0.65). When compared with CBBs, there was a higher rate of vomiting (2 studies, 1058 patients, RR 1.51, 95% CI 1.08 to 2.12) and a lower rate of hypercalcaemia (5 studies, 1220 patients, RR 0.12, 95% CI 0.04 to 0.38) in patient treated with LC.* |
| | 4. Anmerkungen/Fazit der Autoren<br>*The results of this meta-analysis show that lanthanum efficiently lowers the serum phosphorous and iPTH levels without elevating the serum calcium level. Apart from a higher incidence of vomiting, LC did not demonstrate higher incidence rates of other adverse effects compared with other treatments.*<br>*Current evidence is insufficient to demonstrate that lanthanum is superior to other phosphate binders in terms of lowering mortality, cardiovascular events, and vascular calcification as well as of improving bone disorder.*<br>5. Hinweise durch FB Med)<br>- Studiendauer zwischen 4 und 104 Wochen |

**Leitlinien**

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| **KDIGO, 2009**<br>KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD).<br>Kidney International 76 (Suppl 113): S1–S130 | Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group |
| | Methodik<br>Grundlage der Leitlinie<br>Anwendung der GRADE-Methodik, basierend auf einem Endpunktmodell und einer systematischen Literaturrecherche. Empfehlungen Level 1 (starke Empfehlungen) und Level 2 (schwache Empfehlungen) in Kombination mit Angabe der Qualität der (endpunktbezogenen) Evidenz (hoch, mittel, niedrig, sehr niedrig).<br>Medline-Recherche bis Dez. 2008 und in Referenzlisten der KDOQI-Leitlinien sowie in systematischen Reviews; Restriktion auf englischsprachige Publikationen. Update der Leitlinie von 2003.<br>Einschlusskriterien für Studien zu Phosphatbindern:<br>*Any P Binder vs placebo/active control (except Ca vs placebo), CKD stages 3–5, 5D, or 1–5T, RCTs, N≥25 per arm (≥10 per arm for bone biopsy), F/U ≥6 months*<br>LoE und GoR:<br>**NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS**<br>Each chapter contains recommendations that are graded as **level 1** or **level 2**, and by the quality of the supporting evidence **A**, **B**, **C**, or **D** as shown. In addition, the Work Group could also make ungraded statements (see Chapter 2 section on ungraded statements).<br>Implications<br>Grade / Patients / Clinicians / Policy<br>**Level 1** 'We recommend' — Most people in your situation would want the recommended course of action and only a small proportion would not — Most patients should receive the recommended course of action — The recommendation can be adopted as a policy in most situations<br>**Level 2** 'We suggest' — The majority of people in your situation would want the recommended course of action, but many would not — Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences — The recommendation is likely to require debate and involvement of stakeholders before policy can be determined<br>Grade / Quality of evidence / Meaning<br>A / High / We are confident that the true effect lies close to that of the estimate of the effect<br>B / Moderate / The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different<br>C / Low / The true effect may be substantially different from the estimate of the effect<br>D / Very low / The estimate of effect is very uncertain, and often will be far from the truth<br>Sonstige methodische Hinweise:<br>Limitationen der Literaturrecherche (Medline, nur englische Sprache) |
| | Empfehlungen:<br>- *Recommendation 4.1.4: In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of* |

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| | *phosphate binder takes into account CKD stage, presence of other components of CKD–MBD, concomitant therapies, and side-effect profile (not graded).*<br>- *Recommendation 4.1.5: In patients with CKD stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B).*<br>- *Recommendation 4.1.6: In patients with CKD stages 3–5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).*<br>- *Vascular calcification: The use of sevelamer-HCl attenuates the progression of arterial calcification in patients with CKD stages 3–5 and stage 5D when compared with the use of calcium-based salts in some, but not all, studies. The effect of other binders on progression of vascular calcification has not been systematically studied. Most important, it is not clear whether slowing vascular calcification translates into improvements in clinical outcomes (S. S56).*<br>- *Overall, there is insufficient comparative efficacy data on clinical outcomes to make a recommendation for the use of a specific binder for all patients (S. S54).*<br><br>Evidenzprofile: siehe Anhang |
| **NICE, 2013**<br><br>Hyperphosphataemia in chronic kidney disease. Management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease. NICE clinical guideline 157 | National Institute for Health and Care Excellence |
| | Methodik<br><br>Grundlage der Leitlinie<br><br>Grundlage der Leitlinie: Systematische Evidenzaufbereitung ohne Konsensusprozesse - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen nieder – Konsultationsphase vor Veröffentlichung - keine formalen Konsensusprozesse<br><br>Fragestellung 3.5: *For people with stage 5 CKD who are on dialysis, are phosphate binders effective compared to placebo or other treatments in managing serum phosphate and its associated outcomes? Which is the most effective phosphate binder?*<br><br>*For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews and the Centre for Reviews and Dissemination) using a broad search strategy, pulling in all papers relating to the use of phosphate binders in the management of hyperphosphataemia in CKD. Only RCTs that compared a phosphate binder with either a placebo or another comparator in patients with* |

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| | *stage 5 CKD who are on dialysis were considered for inclusion.*<br><br>45 RCTs ausgewertet (Erwachsene), Daten in Summary of Findings-Tabellen; multiple treatment comparisons (Netzwerk-Metaanalysen) für Phosphat- und Kalziumspiegel sowie Phosphatkontrolle und Risiko für Hyperkalziämie sowie gesundheitsökonomisches Modell<br><br>LoE entsprechend GRADE<br><br>GoR<br><br>- *Interventions that must (or must not) be used: We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.*<br>- *Interventions that should (or should not) be used – a 'strong' recommendation: We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.*<br>- *Interventions that could be used: We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.*<br><br>Sonstige methodische Hinweise<br><br>Keine Angaben zum Recherchezeitraum<br><br>Qualität der Evidenz insgesamt niedrig |
| | Empfehlungen:<br><br>*Phosphate binders: adults*<br><br><u>First line</u><br><br>*1.1.8 For adults, offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management.*<br><br>*1.1.9 For adults, consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable.*<br><br><u>Second line</u> |

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| | *1.1.11 For adults with stage 5 CKD who are on dialysis and remain hyperphosphataemic despite adherence to the maximum recommended or tolerated dose of calcium-based phosphate binder, consider either combining with, or switching to, a non-calcium-based binder.*<br><br>*1.1.12 For adults with stage 5 CKD who are on dialysis and who are taking a calcium-based binder, if serum phosphate is controlled by the current diet and phosphate binder regimen but:*<br><br>*- serum calcium goes above the upper limit of normal, or*<br><br>*- serum parathyroid hormone levels are low,*<br><br>*consider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having taken into account other causes of raised calcium.*<br><br>*Evidence to recommendations:*<br><br>*The evidence showed that the phosphate binders examined were all effective in lowering serum phosphate compared with placebo. According to the results of the MTC, no binder was clearly the most effective in terms of impact on serum phosphate levels at the time-points considered, although calcium acetate consistently did well.[…] Both sevelamer hydrochloride and lanthanum carbonate appear to reduce the risk of death in those older than 65 years. […] Non-calcium-based binders were associated with lower serum calcium levels, with sevelamer hydrochloride and magnesium carbonate performing particularly well. Calcium carbonate consistently performed least well. Calcium carbonate was also associated with a greater risk of hypercalcaemia compared with the other calcium-based phosphate binder, calcium acetate. […] Sevelamer hydrochloride was better than calcium-based binders in controlling coronary calcification scores. However, when the effectiveness of the 2 calcium-based binders was considered separately, sevelamer hydrochloride was only better than calcium carbonate; there was no statistically significant difference in coronary calcification scores between sevelamer hydrochloride and calcium acetate. […]* |

**Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren**

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| **SMC 2011 Ref ID 471 (Lanthancarbonat)** | Calcium carbonate (Calcichew, Calcichew Forte, Calcium 500 and Adcal), calcium acetate (Phosex and PhosLo), aluminium hydroxide (Alu-cap), sevelamer hydrochloride (Renagel), sevelamer carbonate (Renvela) and lanthanum carbonate (Fosrenol) can all be used to treat hyperphosphataemia. For the patient population in the submitting company's proposed positioning (i.e. those with hyperphosphataemia insufficiently controlled by calcium-containing phosphate binders alone or in whom there are concerns about calcification with calcium-containing phosphate binders) relevant comparators would be aluminium hydroxide, sevelamer hydrochloride, sevelamer carbonate and lanthanum carbonate. |
| **SMC 2014 Ref ID 468 (Colestilan)** | Hyperphosphataemia can be treated with calcium-based phosphate binders (e.g. Calcichew ®); lanthanum carbonate (Fosrenol®); aluminium hydroxide (Alu-Cap®); sevelamer hydrochloride (Renagel®) and sevelamer carbonate (Renvela®). |
| **Tran K & Banks R. 2009.** Sevelamer hydrochloride for the treatment of patients with chronic kidney disease: a review of the clinical effectiveness. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). | • HTA-Bericht von CADTH, übergeordnete Fragestellung: klinische Wirksamkeit von Sevelamer-Hydrochlorid zur Behandlung der Hyperphosphatämie bei Dialyse-Patienten, sowie Vergleich der Wirksamkeit von Sevelamer und Lanthan-Carbonat<br>• Literaturrecherche: *PubMed, The Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and August, 2009.*<br>• 1 systematischer Review und 18 RCTs eingeschlossen: *sevelamer hydrochloride with calcium acetate (nine trials), calcium carbonate (six trials), both calcium salts (two trials), or aluminum hydroxide (one trial). Trials with direct comparison of sevelamer hydrochloride and lanthanum carbonate were not identified.*<br>• *Ergebnisse:*<br>*- Serum calcium: In comparison with calcium salts, treatment with sevelamer was associated with significantly lower serum calcium levels in nine trials and a non-significant difference in six trials. There was no significant difference in serum calcium levels in sevelamer compared with aluminum hydroxide.*<br>*- Serum phosphorus: Four trials showed that sevelamer therapy was associated with slightly and significantly higher serum phosphorus levels compared with calcium salt therapy, while 11 trials showed no significant difference between treatment groups. There was no significant difference in serum phosphorous levels between sevelamer and aluminum hydroxide therapies.*<br>*- The published literature shows that sevelamer appears to as effective as calcium-based phosphate binders in the management of hyperphosphatemia in dialysis patients without elevating serum calcium levels, although the phosphate levels in sevelamer treated patients were slightly higher than those receiving calcium based agents.*<br>*- Aortic calcification: Patients treated with sevelamer had a* |

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| | *lower progression of aortic calcification compared with patients treated with calcium salts, particularly in diabetic patients. One trial found no significant difference in coronary calcification scores between sevelamer and calcium acetate therapy.*<br>*- Mortality: The DECOR study with the largest population of hemodialysis patients (N=2103) found no significant difference in all-cause mortality or cardiovascular mortality between sevelamer and calcium salt treated groups. The numbers of hospitalizations were also not significantly different between interventions. However, older patients (≥65 years) who received sevelamer had lower risk of death compared with calcium group.*<br>*- Adverse events: One trial reported that more patients treated with sevelamer experienced gastrointestinal disturbances compared with calcium acetate group. One trial reported that sevelamer therapy was associated with higher events of dyspepsia compared with calcium carbonate. However, two trials found similar rates of adverse events between sevelamer and calcium acetate group.*<br><br>Schlussfolgerungen der Autoren:<br>*Taken together, apart from its comparable control of serum phosphate levels with a lower risk of hypercalcemia compared with calcium-based agents, there is no evidence in the published literature that sevelamer improves morbidity and mortality in dialysis patients. Studies on direct comparison of sevelamer and lanthanum carbonate were not identified and therefore conclusions about comparative clinical effectiveness are not possible. One trial suggested that sevelamer may be beneficial for patients over 65 years of age, but further information about effectiveness in other subgroups was not identified. The studies did not indicate a difference in outcomes between patients on hemodialysis or peritoneal dialysis. The inconsistent data are a consideration and the routine use of sevelamer in dialysis patients does not appear to be supported by the current literature.* |

**Detaillierte Darstellung der Recherchestrategie:**

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 2.6.2014

| Suchschritt | Suchfrage |
|---|---|
| #1 | MeSH descriptor: [Kidney Failure, Chronic] explode all trees |
| #2 | MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees |
| #3 | ((kidney next disease*) or (renal next disease*) or (kidney next insufficien*) or (renal next insufficien*) or (kidney next failure*) or (renal next failure*) or (kidney next injur*) or (renal next injur*) or ckd or crd or cki or cri or esrd or esrf):ti,ab,kw (Word variations have been searched) |
| #4 | MeSH descriptor: [Renal Dialysis] explode all trees |
| #5 | (dialysis or dialyses or hemodialys* or haemodialys*):ti,ab,kw (Word variations have been searched) |
| #6 | #1 or #2 or #3 or #4 or #5 |
| #7 | MeSH descriptor: [Hyperphosphatemia] explode all trees |
| #8 | MeSH descriptor: [Phosphorus] explode all trees |
| #9 | (phosphorus or phosphate* or hyperphosphatemi* or hyperphosphataemi*):ti,ab,kw (Word variations have been searched) |
| #10 | #7 or #8 or #9 |
| #11 | #6 and #10 Publication Date from 2009 to 2014 |

MEDLINE (PubMed) am 2.6.2014

| Suchschritt | Suchfrage |
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| #1 | chronic kidney failure[MeSH Terms] |
| #2 | chronic renal insufficiency[MeSH Terms] |
| #3 | ((((((((((((kidney disease*[Title/Abstract]) OR renal disease*[Title/Abstract]) OR kidney insufficien*[Title/Abstract]) OR renal insufficien*[Title/Abstract]) OR kidney failure*[Title/Abstract]) OR renal failure*[Title/Abstract]) OR kidney injur*[Title/Abstract]) OR renal injur*[Title/Abstract]) OR ckd[Title/Abstract]) OR crd[Title/Abstract]) OR cki[Title/Abstract]) OR cri[Title/Abstract]) OR esrd[Title/Abstract]) OR esrf[Title/Abstract] |
| #4 | renal dialysis[MeSH Terms] |
| #5 | (((dialysis[Title/Abstract]) OR dialyses[Title/Abstract]) OR hemodialys*[Title/Abstract]) OR haemodialys*[Title/Abstract] |
| #6 | ((((#1) OR #2) OR #3) OR #4) OR #5 |
| #7 | hyperphosphatemia[MeSH Terms] |
| #8 | phosphorus[MeSH Terms] |
| #9 | (((phosphorus[Title/Abstract]) OR phosphate*[Title/Abstract]) OR hyperphosphatemi*[Title/Abstract]) OR hyperphosphataemi*[Title/Abstract] |
| #10 | ((#7) OR #8) OR #9 |
| #11 | (#6) AND #10 |

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| #12 | (#11) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) |
| #13 | ((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))) |
| #14 | (#11) AND #13 |
| #15 | (#12) OR #14 |
| #16 | (#15) AND (“2009/06/01”[PDAT] : “2014/06/02”[PDAT]) |

MEDLINE (PubMed) nach Leitlinien am 2.6.2014

| Suchschritt | Suchfrage |
|---|---|
| #1 | chronic kidney failure[MeSH Major Topic] |
| #2 | chronic renal insufficiency[MeSH Major Topic] |
| #3 | ((((((((((((kidney disease*[Title]) OR renal disease*[Title]) OR kidney insufficien*[Title]) OR renal insufficien*[Title]) OR kidney failure*[Title]) OR renal failure*[Title]) OR kidney injur*[Title]) OR renal injur*[Title]) OR ckd[Title]) OR crd[Title]) OR cki[Title]) OR cri[Title]) OR esrd[Title]) OR esrf[Title] |
| #4 | ((#1) OR #2) OR #3 |
| #5 | ((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title] |
| #6 | (#4) AND #5 |
| #7 | (#6) AND (“2009/06/01”[PDAT] : “2014/06/02”[PDAT]) |

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Gemeinsamer Bundesausschuss

**Anhang: Evidenzprofile aus der KDOQI-Leitlinie**

**Table 23 | Evidence matrix for sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D**

| | Methodological quality | | | | | | | | | Adverse event reporting | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | | | B | | | C | | | | | |
| Outcome | Author | *N* (on agent) | F/U | Author | *N* (on agent) | F/U | Author | *N* (on agent) | F/U | Author | *N* (on agent) | F/U |
| Mortality | — | — | — | Block (2007)[265] | 127 (60) | 44 months median | — | — | — | Chertow (2002)[284] | 200 (99) | 12 months |
| | | | | St Peter (2008)[267a] | 2102 (1051) | 28 months | | | | Braun (2004)[343] | +⩽21 (+ ⩽11[b]) | 12 months |
| Clinical CVD | — | — | — | | | | — | — | — | — | — | — |
| Hospitalization | — | — | — | — | — | — | Suki (2007)[266 c] | 2103 (1053) | 20 months | Chertow (2002)[284] | 200 (99) | 12 months |
| | | | | | | | | | | Braun (2004)[343] | + ⩽21 (+ ⩽11[b]) | 12 months |
| QoL | — | — | — | — | — | — | — | — | — | — | — | — |
| Fractures | — | — | — | — | — | — | — | — | — | — | — | — |
| PTx | — | — | — | — | — | — | — | — | — | — | — | — |
| Bone density | — | — | — | — | — | — | Raggi (2005)[346] | 111 (51) | 12 months | — | — | — |
| | | | | | | | Asmus (2005)[344] | + ⩽21 (+ ⩽11[b]) | 21 months | | | |
| Bone histology | Ferreira (2008)[104] | 91 (44) | 13.5 months | Salusky (2005)[17] | 29 (15) | 8 months | — | — | — | — | — | — |
| | Barreto (2008)[288] | 101 (41) | 12 months | | | | | | | | | |
| Vascular/valvular calcification | — | — | — | Qunibi (2008)[287] | 203 (103) | 12 months | Asmus (2005)[344] | + ⩽21 (+ ⩽11[b]) | 21 months | — | — | — |
| | | | | Chertow (2002)[284] | 132 (62) | 12 months | | | | | | |
| | | | | Block (2005)[285] | 148 (73) | 18 months | Barreto (2008)[288] | 101 (41) | 12 months | | | |
| Lab: Ca, P, PTH | — | — | — | Qunibi (2008)[287] | 203 (103) | 12 months | Suki (2007)[266] | 2103 (1053) | 20 months | — | — | — |
| | | | | Chertow (2002)[284] | 200 (99) | 12 months | Asmus (2005)[344] | + ⩽21 (+ ⩽11[b]) | 24 months | | | |
| | | | | Block (2005)[285] | 148 (73) | 18 months | Barreto (2008)[288] | 101 (41) | 12 months | | | |
| | | | | Ferreira (2008)[104] | 91 (44) | 13.5 months | | | | | | |
| Lab: ALP, b-ALP | — | — | — | Qunibi (2008)[287] | 203 (103) | 12 months | Raggi (2005)[346] | 111 (51) | 12 months | — | — | — |
| | | | | Ferreira (2008)[104] | 91 (44) | 13.5 months | Barreto (2008)[288] | 101 (41) | 12 months | | | |
| Lab: Bicarbonate | — | — | — | Qunibi (2008)[287] | 203 (103) | 12 months | — | — | — | — | — | — |
| | | | | Chertow (2002)[284] | 200 (99) | 12 months | | | | | | |
| | | | | Ferreira (2008)[104] | 91 (44) | 13.5 months | | | | | | |
| Adverse events | — | — | — | — | — | — | — | — | — | Suki (2007)[266] | 2103 (1053) | 20 months |
| | | | | | | | | | | Qunibi (2008)[287] | 203 (103) | 12 months |
| | | | | | | | | | | Chertow (2002, 2003)[284,357] | 200 (99) | 12 months |
| | | | | | | | | | | Braun (2004)[343] | + ⩽21 (+ ⩽11[b]) | 12 months |
| | | | | | | | | | | Block (2005)[285] | 148 (73) | 18 months |
| | | | | | | | | | | Ferreira (2008)[104] | 91 (44) | 13.5 months |

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; *N*, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QOL, quality of life.

Number randomized may be higher than number analyzed; this evidence profile does not include studies of sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3–5 (refer to summary table entry for Russo (2007)[286]) or studies in pediatric population (refer to summary table entry for Salusky (2005)[17]).

[a]See also report by Suki (2007)[266]

[b]Unclear reporting regarding the number of individuals who received study drug.

[c]See also report by St Peter (2008).[267]

**Table 24 | Evidence profile[a] for the treatment of CKD-MBD with sevelamer-HCl vs calcium-containing phosphate binders in CKD stage 5D**

| Outcome | No. of studies and study design | Total *N* (*N* on study drug) | Methodological quality of studies | Consistency across studies | Directness of the evidence (generalizability/ applicability) | Other considerations[b] | Summary of findings: Quality of evidence for outcome | Summary of findings: Qualitative and quantitative description of effect | Summary of findings: Importance of outcome |
|---|---|---|---|---|---|---|---|---|---|
| Mortality | 2 RCTs | 2230 (1126) | Serious limitations (−1)[c] | Important inconsistencies[d] (−1) | Direct | — | Low | No difference in one moderate quality study in prevalent HD patients. Borderline statistically significant benefit for sevelamer-HCl in one moderate quality study in incident HD patients | Critical |
| | AE from 1+ RCTs[e] | 221 (99+?) | Very serious limitations (−2) | — | — | — | | | |
| Clinical CVD and CeVD | — | — | — | — | — | — | — | — | Critical |
| All-cause hospitalization | 1 RCT | 2103 (1053) | Very serious limitations (−2)[f] | NA | Direct | — | Low | Trend to lower all-cause hospitalization in one low-quality study | High |
| | AE from 1+ RCTs[e] | 221 (99+?) | Very serious limitations (−2) | — | — | — | | | |
| Quality of life | — | — | — | — | — | — | — | — | High |
| Fractures | — | — | — | — | — | — | — | — | High |
| PTx | — | — | — | — | — | — | — | — | High |
| X-ray bone assessment | 1+ RCTs[e] | 111+? (51+?) | Very serious limitation (−2)[g] | NA | Major uncertainty (−2)[h] | Sparse (−1) | Very Low | Unable to assess | Moderate |
| Bone histology | 2 RCTs | 192 (85) | No limitations | NA | Direct | Sparse (−1) | Moderate | Overall not much difference between groups | Moderate |
| Vascular/valvular calcification | 4+ RCTs[e] | 673 (316 +?) | Serious limitations (−1)[i] | Important inconsistencies[j] (−1) | Direct | — | Low | Trend toward less progression with sevelamer, but inconsistency regarding statistical significance and size of difference assessed with different metrics at different time points and at different sites | Moderate |
| *Laboratory measurements* | | | | | | | | | |
| Calcium | 6+ RCTs[e] | 2867 (1413+?) | Serious limitations (−1)[k] | No important inconsistencies | Direct | — | Moderate | Higher with calcium | Moderate |
| Phosphorus | | | Serious limitations (−1)[k] | No important inconsistencies | Direct | — | Moderate | No consistent difference | |
| Ca × P | | | Serious limitations (−1)[k] | No important inconsistencies | Direct | — | Moderate | No consistent difference | |
| PTH | | | Serious limitations (−1)[k] | No important inconsistencies | Direct[l] | — | Moderate | Lower with calcium | |
| ALP, b-ALP | 4 RCTs | 595 (287) | Serious limitations (−1)[m] | NA | Direct | Sparse (−1) | Low | Unable to assess | |
| Bicarbonate | 3 RCTs | 494 (246) | Serious limitations (−1)[m] | NA | Direct | Sparse (−1) | Low | Lower with sevelamer | |
| Adverse events | 6+ RCTs[e] | 2867 (1413+?) | | | | | | Inconsistent trend in GI and CVD events when using sevelamer-HCl vs Ca-containing P binders. More hypercalcemia with Ca-containing P binders | Depends on outcome |

**Balance of potential benefits and harm:**
Sevelamer-HCl is as effective as calcium-based binders in terms of target-driven attainment of biochemical values. There is a trend towards slower progression of vascular calcification (sevelamer-HCl vs calcium-containing phosphate binders); there is no robust statistically significant difference for mortality or hospitalizations

**Quality of overall evidence:**
Moderate for biochemical outcomes
Low to very low for other surrogate outcomes
Low for patient-centered outcomes

**Table 24 | Continued**

AE, adverse event, ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium–phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CVD, cardiovascular disease; GI, gastrointestinal, HD, hemodialysis; *N*, number of subjects; NA, not applicable; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.
? Unclear number of patients studied for outcome.
[a]This evidence profile does not include studies of sevelamer-HCl vs calcium-containing phosphate binders in CKD stages 3–5 (refer to summary table entry for Russo (2007)[286]) or studies in pediatric population (refer to summary table entry for Salusky (2005)[17]).
[b]Other considerations include imprecise or sparse data (−1), high probability of reporting bias (−1). For observational studies, other considerations include strong association (+1 or +2), dose-response gradient (+1), and all plausible confounders would have reduced the effect (+1).
[c]2 grade B.
[d]One study showed a trend toward benefit in terms of all-cause mortality, whereas the other showed not statistically significant difference.
[e]Braun (2004)[343] and Asmus (2005)[344] have considerable patient overlap (*N*=93 out of 114) with Chertow (2002)[284] and Raggi (2005)[346] respectively.
[f]One grade C, inconsistency for statistical significance for all-cause hospitalization between reports for same study (Suki (2007)[266], St Peter (2008)[267]).
[g]One plus grade C.
[h]Nonvalidated method.
[i]Three grade B, one grade C.
[j]Heterogeneity in the study designs.
[k]Four grade B, two grade C.
[l]However, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.
[m]Two grade B, two grade C.

**Table 26 | Evidence profile of lanthanum carbonate vs other phosphate binders in CKD stages 5D**

| Outcome | No. of studies and study design | Total *N* (*N* on study drug) | Methodological quality of studies | Consistency across studies | Directness of the evidence generalizability/ applicability | Other considerations[a] | Summary of findings: Quality of evidence for outcome | Summary of findings: Qualitative and quantitative description of effect | Summary of findings: Importance of outcome |
|---|---|---|---|---|---|---|---|---|---|
| Mortality | AE from 2 RCTs | 1383 (694) | Very serious limitations (−2) | — | — | — | Very low | Unable to assess | Critical |
| Clinical CVD and CeVD | — | — | — | — | — | — | — | — | Critical |
| All-cause hospitalization | — | — | — | — | — | — | — | — | High |
| Quality of life | — | — | — | — | — | — | — | — | High |
| Fractures | — | — | — | — | — | — | — | — | High |
| PTx | — | — | — | — | — | — | — | — | High |
| Bone density | — | — | — | — | — | — | — | — | Moderate |
| Bone histology | 3 RCTs | 333 (63) | Serious limitations (−1)[b] | No major inconsistencies | Direct | — | Moderate | Lanthanum biopsies showed overall better turnover with no differences in mineralization, and possible higher volume | Moderate |
| Vascular/valvular calcification | — | — | — | — | — | — | — | — | Moderate |
| *Laboratory measurements* | | | | | | | | | |
| Calcium | 3 RCTs | 1668 (782) | Very serious limitations (−2)[c] | No major inconsistencies | Direct | — | Low | Tendency toward lower Ca and lower rates for hypercalemic episodes | Moderate |
| Phosphorus | 3 RCTs | 1668 (782) | Very serious limitations (−2)[c] | No major inconsistencies | Direct | — | Low | Similar P control | |
| Ca × P | 1 RCT | 98 (49) | Very serious limitations (−2)[d] | NA | Direct | Sparse | Very low | Tendency toward higher Ca × P | |
| PTH | 3 RCTs | 1668 (782) | Very serious limitations (−2)[c] | No major inconsistencies | Direct[e] | — | Low | Tendency toward higher PTH | |
| ALP, b-ALP | 2 RCT | 1570 (733) | Very serious limitations (−2)[f] | NA | Direct | — | Low | Tendency toward higher b-ALP | |
| Bicarbonate | 1 RCT | 1359 (682) | Very serious limitations (−2)[g] | NA | Direct | — | Low | No difference in bicarbonate | |
| Adverse events | 5 RCTs | 2492 (1327) | | | | | | One study showed no worse decline in cognitive function with lanthanum. Bone and plasma lanthanum levels were higher in lanthanum groups | Depends on outcome |

**Balance of potential benefits and harm:**
No evidence of benefit or harm on clinical and calcification outcomes. Uncertain effect on bone laboratory outcomes. Bone histology was improved more often in lanthanum group but formal statistical comparisons were not done.

**Quality of overall evidence:**
Low for biochemical outcomes
Moderate for other surrogate outcomes
Very Low for patient-centered outcomes

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium–phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; *N*, number of subjects; NA, not applicable; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.
[a]Other considerations include imprecise or sparse data (−1), high probability of reporting bias (−1). For observational studies, other considerations include strong association (+1 or +2), dose–response gradient (+1), all plausible confounders would have reduced the effect (+1).
[b]Three grade B.
[c]Two grade B and one grade C in studies not designed for comparative efficacy.
[d]One grade B in study not designed for comparative efficacy.
[e]However, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.
[f]One grade B and one grade C.
[g]One grade C.