Strategies Aiming to Reduce Hyperphosphatemia in Chronic Kidney Disease: Dialysis Patients

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Honoraria: none

Board position: CKD-MBD ERA-EDTA Working Group
The most abundant anion in the body (700 g = 23 000 mmol)
- Intracellular (80-120 mmol/l IC and only 1-1.5 mmol/l plasma)
- Minimum needs in a healthy adult: 300 mg/day
Regulation of Serum Phosphate

- FGF23 Synthesis by Bone Cells
- Calcitriol Synthesis by the Kidney
- PTH Synthesis by Parathyroid Cells

Intestinal Absorption of Phosphate

Intestinal lumen

- 3 PO₄
- 1 Na⁺
- Na⁺
- H⁺

Enterocyte

- NPT2b
- NHE3
- PiT1
- PiT2

Basolateral side

- PO₄
- Na⁺
- K⁺

pH < 7.0

- 2 PO₄
- 1 Na⁺
- 2 PO₄
- 1 Na⁺

GI intake 1400 mg/d

Serum Phosphorus (Pi)

Digestive juice phosphorus 210 mg/d

Formation 210 mg/d

Total absorbed intestinal phosphorus 1120 mg/d

Bone

Resorption 210 mg/d

Urine 910 mg/d

Stool 490 mg/d
Intestinal Phosphate Absorption

Net Intestinal PO4 Absorption (mmol/day) vs. Dietary PO4 (mg/day)

Net PO4 Abs, mmol/day = -5 + 0.77 * dietary PO4, mmol/day

r = 0.95

Lemann J and Favus M, Primer JBMR 1999
Phosphate Intake, Demography, Cardiovascular Risk Factors, and Kidney Function Explain Only 12% of Variation in Serum Phosphate Levels (NHANES III)

Reasons:
1- Underestimation of phosphate content in foods (hidden phosphate in additives)
2- Differences in phosphate bioavailability. Type of phosphates (plants versus animals derived phosphates)
3- The ratio calcium:phosphate in foods
4- Other factors presents in the intestine (Mg, Na, pH, binders, etc)
5- Diurnal and circadian variation of phosphatemia
6- Age, Race, Gender

15,513 subjects

De Boer IH, et al., AJKD 53:399-407, 2009
Common Genetic Variants Associate with Serum Phosphorus Concentration

Figure 1. Single nucleotide polymorphisms on chromosomes 1, 3, 5, 6, and 12 associate with the serum phosphorus concentration. Log (P values) for individual SNPs plotted for each chromosome in the discovery sample. Horizontal line represents genome-wide significance level of $4 \times 10^{-7}$. 

Serum Phosphate Concentration and Longevity

Fig. 2. Relation between longevity and serum phosphate in mammals. 1: Klotho−/− mouse, 2: Mouse, 3: Rat, 4: Hamster, 5: Gerbil, 6: Nutria, 7: Rabbit, 8: Guinea pig, 9: Sheep, 10: Squirrel, 11: Porcupine, 12: Naked mole rat, 13: Flying fox, 14: Bear, 15: Rhinoceros, 16: Elephant, 17: Human, 18: Human (centenarian). Serum phosphate levels are average or median values, whichever available in literatures (Asadi et al., 2007; Feldhamer et al., 2003; Field et al., 1998; Gorbunova et al., 2008; Heard et al., 2006; Holliday, 1995; Kuro-o et al., 1997; Moreau et al., 2003; Munson et al., 1998; Passeri et al., 2008; Pugh, 2002; Ramsay, 2003; Segawa et al., 2007; Thrall et al., 2004; Tuntasuvan et al., 2002; Yahav et al., 1993).
Serum Phosphate Concentration and Risk of Mortality in Subjects with Normal Renal Function

Tonelli M et al., Circulation 112:2627-2633, 2005

- Post-hoc analysis from CARE study
- 60-month follow-up
- Pravastatin vs Placebo
- 375 death over 60 months
- Baseline serum PO₄ vs adjusted mortality risk

- A grade risk of death rate vs serum PO₄ seen
- Serum PO₄ < 3.5 mg/L (1.13 mM) hazard ratio = 1.27 (1.02-1.59) compared to serum PO₄ > 3.5
- Higher levels of serum PO₄ associated with new heart failure, myocardial infarction, and coronary death or nonfatal MI
Phosphate Concentration and Risk of Mortality in CKD Patients

Kestenbaum, B., et al. JASN 16:520-528, 2005

3490 CKD patients (veterans)
23% du HR x 1 mg/dl


< 10%
0.71
1.98

Dialysis patients
Phosphate Concentration and Risk of Mortality in CKD Patients

Tentori F. et al. DOPPS 2008
Changes in Serum Phosphate Concentration and Risk of Mortality in CKD Patients: Cosmos

Guideline 4.1.1: In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the normal range (2C). In patients with CKD stage 5D, we suggest lowering elevated phosphorus levels toward the normal range (2C).

Normal range: 2.7 – 4.5 mg/dl (0.87 – 1.45 mmol/L)

AJKD 42 (4), Suppl 3 (Oct) 2003

KDIGO CKD-MBD guidelines, KI 2009, 76 (Suppl. 113)
Serum Phosphate Concentration in Dialysis Patients

Most recent (single) monthly value
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods"). Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

Serum Phosphate Concentration in Dialysis Patients

Pour Quoi ?
HIGH 33 %

NORMAL 58 %

Most recent (single) monthly value
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods"). Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").
Phosphate binder: Approximately 50% of daily pill burden in dialysis patients

The daily tablet load in dialysis patients is one of the highest of all chronic illnesses (~19 tablets/day)

Phosphate binders (49%)  
Anti-HTA drugs (18%)  
Others

N = 233  
Median number of tablets for phosphate binders: 
Calcium acetate/carb. = 9  
Sevelamer = 9  
Lanthanum = 6
Why are phosphate binders not taken?
- A Welsh analysis -

919 HD patients

25% report problems when taking PO₄ binders

38% forget to take it at least 1x/week

Reasons for not taking

- Forgot
- Size
- Swallowing problems
- Too many
- Chewing problems
- Taste
- Not effective

[Graph showing reasons for not taking phosphate binders with percentages for each reason]
Phosphate Metabolism in Dialysis Patients

- GI intake: 1400 mg/d
- Digestive juice phosphorus: 210 mg/d
- Total absorbed intestinal phosphorus: 1120 mg/d
- Stool: 490 mg/d
- Bone:
  - Formation: 210 mg/d
  - Resorption: 210 mg/d
- Serum Phosphorus (Pi)
- Urine: 910 mg/d

CKD-DIALYSIS PATIENT

Note: The diagram illustrates the typical phosphate metabolism in dialysis patients, highlighting the increased load of phosphorus due to renal failure compared to a healthy individual.
Principles for the Treatment of Hyperphosphatemia

1. Control of PTH and bone remodeling
2. Control of inter-compartment exchanges
3. Optimizing phosphate removal by the dialysis
4. Decreasing dietary phosphate
5. Blocking intestinal phosphate transporter(s)
6. Intestinal phosphate binders

1- Control of PTH and bone remodeling

69,355 patients
From the DaVita Database

1- Control of PTH and bone remodeling

Increasing Serum PTH Levels Were Associated with a Higher Incidence of Elevated Serum Phosphate Levels (OutcomesPlus)

![Bar chart showing the incidence of elevated serum phosphate levels with increasing PTH levels.](image)

**Explanation:**
- PTH (pg/ml)
  - < 150 (N = 30,628): 19%
  - 150-400 (N = 97,572): 25%
  - > 400-60 (N = 47,656): 34%
  - > 600 (N = 51,204): 49%

**Data Source:**
- Data on file, AMGEN 2015
- OutcomesPlus database; October 2014.
1- Control of PTH and bone remodeling

PTX
Calcimimétiques
Calcitonine
Bisphosphonates
Anti-RANKL

Fig. 1. Daily variations of plasma total calcium (○), phosphorus (○).
1- Control of PTH and bone remodeling

Calcimimetic Effects on Serum Calcium and Phosphate

PTH 1855 pg/ml

PTH 158 pg/ml

Serum Calcium (mM)
Serum Phosphorus (mM)

Calcimimetic Effects on Serum Calcium and Phosphate

1 - Control of PTH and bone remodeling

Calcimimetic Effects on Serum Calcium and Phosphate

Urena P et al. Orangerie data 2008 (COH)
2- Control of inter-compartment exchanges

- Correction of acido-cetosis states

- Hormones: insulin, agonists b-adrenergics, cathecholamines, cortisol

- Renutrition syndrome
### 3- Optimizing phosphate removal by the dialysis

<table>
<thead>
<tr>
<th>Dialysis Technique</th>
<th>Quantity of Phosphate Removed (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous Ambulatory Peritoneal Dialysis (CAPD)</td>
<td>350 mg/day</td>
</tr>
<tr>
<td>Hemofiltration, Acetate Free Biofiltration (AFB)</td>
<td>350 mg/day</td>
</tr>
<tr>
<td>Nocturnal Hemodialysis (8h/3x week)</td>
<td>340 mg/day</td>
</tr>
<tr>
<td>Short daily hemodialysis (2h/day/6-7 days x week)</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Standard hemofiltration (HF) (3-4h/3 x week)</td>
<td>250 mg/day</td>
</tr>
<tr>
<td>Standard hemodialysis (HD) (3-4h/3 x week)</td>
<td>250 mg/day</td>
</tr>
<tr>
<td>Daily Nocturnal hemodialysis (6-8h/6-7 days x week)</td>
<td>350 mg/day</td>
</tr>
<tr>
<td>Nocturnal Hemodialysis (8h/3x week)</td>
<td>350 mg/day</td>
</tr>
<tr>
<td>Short daily hemodialysis (2h/day/6-7 days x week)</td>
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</tr>
<tr>
<td>Standard hemofiltration (HF) (3-4h/3 x week)</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Standard hemodialysis (HD) (3-4h/3 x week)</td>
<td>250 mg/day</td>
</tr>
</tbody>
</table>

**Diet Protein Intake**
- 1.1 to 1.4 g/kg/day
- 77 to 98 g/day (h-70 kg)

**Phosphate Content**
- 12 to 17 mg/kg/day
- 840 to 1190 mg/day
- 5880 to 8330 mg/week

**Intestinal absorption 60-70%**
- 3480 to 4980 mg/week

**Dialysis phosphate removal**
- 1750 to 2350 mg/week

**Positive balance**
- 1730 to 3230 mg/week

**Standard dialysis removes 20-30 mmole of PO₄ (620-930 mg/dialysis or 1860-2790 mg/week)**
4- Decreasing dietary phosphate

- < 0.8 g/kg/d protein
  - < 800 mg of PO$_4$/d
- > 1.2 g/kg/d protein
  - > 1000 mg of PO$_4$/d

**Denutrition**

**Hyperphosphatemia**
**Hyperparathyroidism**
**Augmentation Ca x P**
**CV Calcifications**
**Risk of morbi-mortality**
Nicotinamide Decreases Serum Phosphate Concentration in Dialysis Patients

Eto N et al., Nephrol Dial Transplant 20:1378-1385, 2004
5- Blocking intestinal phosphate transporter(s)

Serum Phosphate and PTH Concentrations in a Hemodialysis Patient Treated by Nicotinamide


- CaCO₃ 2.4 g/d
- Sevelamer 4.8 g/d
- NICOBION (mg/day) 1000
5- Blocking intestinal phosphate transporter(s)

Vascular calcification

Labonté E et al. JASN 26:1138-1149, 2015
5- Blocking intestinal phosphate transporter(s)

Block et al. CJASN 28, 2017
5- Blocking intestinal phosphate transporter(s)

Block et al. CJASN 28, 2017
Old and New Intestinal Phosphate Binders
<table>
<thead>
<tr>
<th>Year</th>
<th>Intestinal Phosphate Binder</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966</td>
<td>Carbonate de calcium</td>
</tr>
<tr>
<td>1972</td>
<td>Hydroxyde d’alumine (1976 - encéphalopathie)</td>
</tr>
<tr>
<td>1986</td>
<td>Carbonate de magnésium</td>
</tr>
<tr>
<td>1986</td>
<td>Alginate de calcium</td>
</tr>
<tr>
<td>1989</td>
<td>Acétate de calcium</td>
</tr>
<tr>
<td>1995</td>
<td>Chlorure de zirconyl</td>
</tr>
<tr>
<td>1996</td>
<td>Kétoglutarate de calcium</td>
</tr>
<tr>
<td>1999</td>
<td>Sulfate de fer hydrolysé</td>
</tr>
<tr>
<td>2000</td>
<td>Sevelamer (Hydrochloride)</td>
</tr>
<tr>
<td>2004</td>
<td>Carbonate de lanthane</td>
</tr>
<tr>
<td>2014</td>
<td>Sevelamer (Carbonate)</td>
</tr>
<tr>
<td>2015</td>
<td>Ferric Citrate (JTT-751 ou Zerenex)</td>
</tr>
<tr>
<td>2015</td>
<td>Sucroferric oxhydroxide ou PA21 (Velphoro)</td>
</tr>
<tr>
<td>2015</td>
<td>Fermagate, SBR759, PT20 (iron-magnesium hydroxycarbonate)</td>
</tr>
</tbody>
</table>

**Avant 1980**


**Après 2009 (KDIGO)**
Prescription of Intestinal Phosphate Binders

Phosphate binder use, last 1 month
National sample

Values for each month reflect prescription at end of study month (2010, 2011) or anytime during study month (2012+).
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods"). Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").
Prescription of Intestinal Phosphate Binders

Values for each month reflect prescription among patients prescribed a phosphate binder. Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").

Prescription of Intestinal Phosphate Binders

Values for each month reflect prescription among patients prescribed a phosphate binder. Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods"). Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods"). Source: US-DOPPS Practice Monitor, December 2016; http://www.dopps.org/DPM
## Mechanisms of Action of Intestinal Phosphate Binders

<table>
<thead>
<tr>
<th>Nom</th>
<th>Contenu</th>
<th>Mode d’action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Acetate</td>
<td>253 mg of calcium element per 1000 mg of calcium acetate</td>
<td>Formation of insoluble calcium-phosphate complexes</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>400 mg of calcium element per 1000 mg of calcium carbonate</td>
<td>Formation of insoluble calcium-phosphate complexes</td>
</tr>
<tr>
<td>Sevelamer HCl</td>
<td></td>
<td>Ionic liaison and interaction between H+ and intestinal phosphate</td>
</tr>
<tr>
<td>Carbonate de sevelamer</td>
<td></td>
<td>Ionic liaison and interaction between H+ and intestinal phosphate</td>
</tr>
<tr>
<td>Lanthane Carbonate</td>
<td></td>
<td>Formation of insoluble lanthane phosphate complexes</td>
</tr>
<tr>
<td>Ferric Citrate</td>
<td>210 mg of ferric iron per 1000 mg of ferric citrate</td>
<td>Iron liaison with phosphate</td>
</tr>
<tr>
<td>Sucroferric oxyhydroxide</td>
<td>500 mg of iron per 2500 mg of Velphoro</td>
<td>Liaison of phosphate with the hydroxyle group and with water contained in Velphoro</td>
</tr>
</tbody>
</table>
## Capacity of Intestinal Phosphate Binders

<table>
<thead>
<tr>
<th>Name</th>
<th>Mg of phosphate/gramme of binder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Carbonate</td>
<td>43</td>
</tr>
<tr>
<td>Calcium Acetate</td>
<td>106</td>
</tr>
<tr>
<td>Aluminium Hydroxyde</td>
<td>150</td>
</tr>
<tr>
<td>Lanthanum Carbonate</td>
<td>156</td>
</tr>
<tr>
<td>Sevelamer Hydrochloride</td>
<td>140</td>
</tr>
<tr>
<td>Ferric Citrate</td>
<td>87</td>
</tr>
<tr>
<td>Sucroferric Oxyhydroxide</td>
<td>116</td>
</tr>
</tbody>
</table>

Adapted from Ureña P et al. John Libbey, 2004; Hsu CH et al. JASN 10:1274-1280, 1999; and FDA and EMA reports 2015.
Capacity of Intestinal Phosphate Binders

Meal Phosphorous = 345 mg
Ca or Aluminum = 50 mEq

Sheikh M et al. JCI 83:66-73, 1989
Calcium-Based Intestinal Phosphate Binders

CaCO$_3$

An incongruous phosphate binder?

Needs a low gastric pH in order to facilitate its dissolution and a high pH to bind phosphate, similar to other calcium salts

Sheikh M et al. JCI 83:66-73, 1989
Calcium-Based versus Non-Calcium-Based Intestinal Phosphate Binders

Calcium Acetate

A more soluble calcium salt. 10,000 times more than CaCO3

Dissolution over a larger pH range than CaCO3

Maximal binding capacity obtained after one hour

Sheikh M et al. JCI 83:66-73, 1989
Effect of Phosphate Binders

Gastrointestinal Ca absorption $\uparrow$ ($^{47}\text{CaCl}_2$)

Results of prolonged phosphorus depletion using aluminum gels, in a normal subject

Bone demineralisation

Fecal Ca fell from control values $\pm$ 200 mg to 75-90 mg/day.

This decline represented a rise of Ca absorption, shown by $^{47}\text{CaCl}_2$ studies:

Control: 45% Ca abs.
Aluminum R: 75% Ca abs.
Calcium-Based Intestinal Phosphate Binders

“Calcium Absorption”

Figure 3b. Effect of ingestion of calcium carbonate or calcium acetate on absorption of ingested phosphorus and calcium by hemodialysis patients (n = 6). Absorption was measured with a one-meal balance technique. The dose of each medication contained 50 mEq of calcium. Calcium acetate bound more phosphorus and was associated with less calcium absorption (adapted from Mai et al.).

Effect of Phosphate Binders

Gastrointestinal Sodium Phosphate Cotransporter NPT2b ↑

Effects of Intestinal Calcium-Based, Calcium-Free, and Iron-Based Phosphate Binders on Classical and Non Classical Biochemical Parameters (PO4, CRP, Uric Acid, FGF23)
Efficacy of Phosphate Binders

Serum P (mg/dl) vs. Weeks

- Ca (TTG)*
- Ca (CARE)***
- Sevelamer/TTG*
- Lanthanum**

* TTG: Chertow GM. KI 2002
** Hutchison WCN 03. Berlin
*** Qunibi W. Kidney Int. 2004 65: 1914
Effect of Iron-Based Intestinal Phosphate Binders on Serum Phosphate Concentration

**Ferric citrate**
- Concentration: 1.0 g (elemental iron content: 210 mg)
- Dose: 6-8 tablets/day

**Sucroferric oxyhydroxide**
- **Floege J et al, Kidney Int 2014**
- Concentration: 500 mg (iron content: 500 mg (2.5 g tablet))
- Dose: 3 tablets/day
Autres Effets Biologiques des Chélateurs Non-Calciques (Sevelamer)

- Phosphate
- Acide urique
- CRP
- Acides biliaires
- Indoxyl-sulfate
- p-Crésol
Combined therapy with lanthanum carbonate and calcium carbonate for hyperphosphatemia decreases serum FGF-23 level independently of calcium and PTH (COLC Study)
Calcium/Acetate Magnesium Carbonate versus Sevelamer HCl and the effect on serum FGF-23 levels (Post-hoc CALMAG study)

104 HD patients
105 CaMg
99 Sevelamer
25 weeks

Both compounds
Significantly reduced FGF23
No difference Between groups
Serum FGF-23 levels and Iron-Based Intestinal Phosphate Binder (Ferric Citrate)

Block G et al. AJKD Oct, 2014
Serum FGF-23 levels and Iron-Based Intestinal Phosphate Binder (Sucroferric Oxyhydroxide)

Decreases from baseline in mean serum FGF-23 concentrations were observed over 1 year in both Velphoro and sevelamer treatment groups. Integrated analysis of mean (SD) FGF-23 and change from baseline (SS; N=1,055) over 1 year.

Sprague SM et al. ASN 2013. Poster
Effects of Intestinal Calcium-Based, Calcium-Free, and Iron-Based Phosphate Binders on Cardiovascular Calcifications
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treat-to-Goal-Study (TTG)</strong></td>
<td>▪ 200 patients, 1 year follow up</td>
<td>▪ No difference in sP and Ca × P</td>
</tr>
<tr>
<td>Chertow GM et al., KI 2002</td>
<td>▪ Patients on sevelamer or any CaPB (CaAc or CaCO₃)</td>
<td>▪ Significantly lower increase of CACS in Sevelamer pts</td>
</tr>
<tr>
<td></td>
<td>▪ PB doses to achieve sP and sCa target levels</td>
<td>▪ Significant decrease in LDL and total cholesterol in sevelamer group</td>
</tr>
<tr>
<td><strong>Renagel in New Dialysis (RIND)</strong></td>
<td>▪ 129 incident HD pts, sevelamer or any CaPB for 18 months</td>
<td>▪ Lower increase of CACS in sevelamer group</td>
</tr>
<tr>
<td>Block GA et al., KI 2005</td>
<td>▪ Management of parameters of bone metabolism at investigators’ discretion</td>
<td>▪ Significant decrease in LDL and total cholesterol in sevelamer group</td>
</tr>
<tr>
<td><strong>CARE II</strong></td>
<td>▪ 203 pts (52 weeks) on Ca Ac or Sevelamer, both + atorvastatin</td>
<td>▪ No difference in calcification</td>
</tr>
<tr>
<td>Qunibi et al, AJKD 2008</td>
<td>▪ No difference in LDL levels</td>
<td>▪ No difference in LDL levels</td>
</tr>
<tr>
<td><strong>BRiC</strong></td>
<td>▪ 71 pts, on Ca Ac or sevelamer for 12 months</td>
<td>▪ No difference in calcification</td>
</tr>
<tr>
<td>Barreto et al., Nephrol Clin Pract 2008</td>
<td>▪ dCa and vit D regimen changes during study</td>
<td>▪ No difference in bone turnover</td>
</tr>
<tr>
<td></td>
<td>▪ No difference in LDL levels</td>
<td>▪ No difference in LDL levels</td>
</tr>
</tbody>
</table>
Effects of Intestinal Calcium-Based, Calcium-Free, and Iron-Based Phosphate Binders on Mortality Risk
Effect of Sevelamer and Calcium-Based Intestinal Phosphates Binders on Survival in HD Patients “RIND Study”

- 129 incident HD pts, sevelamer or any CaPB for 18 months

Survival (%)

74%  
46%

11 deaths Renagel®  
23 deaths Calcium

$p = 0.016$

Effect of Sevelamer and Calcium-Based Intestinal Phosphates Binders on Survival in HD Patients “DCOR Study”

- 2013 prevalent dialysis patients
- 1053 sevelamer
- 1050 any CaPB
- follow-up 2 years

2013 prevalent dialysis patients
1053 sevelamer
1050 any CaPB
follow-up 2 years

HR = 0.93 (0.79 - 1.10)

Effect of Sevelamer and Calcium-Based Intestinal Phosphates Binders on Survival in HD Patients

“DCOR Study”

- 2013 prevalent dialysis patients
- 1053 sevelamer
- 1050 any CaPB
- follow-up 2 years

Effect of Sevelamer and Calcium-Based Intestinal Phosphates Binders on Survival in HD Patients

Meta-Analysis of 11 RCTs (4622 patients)
Patients assigned to non calcium-based phosphate binders had a 22% reduction in the risk of all-cause mortality compared with those assigned to calcium-based phosphate binders (risk ratio 0.78, 95% CI 0.61–0.98)

Side Effects of Intestinal Calcium-Based, Calcium-Free, and Iron-Based Phosphate Binders
<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tums, Os-Cal, Caltrate (calcium carbonate) and Phoslo, Eliphos</td>
<td><strong>Gastrointestinal effects</strong> in 22% of patients; <strong>hypercalcemia</strong> in 10% of patients (12–54); <strong>peritonitis</strong> in 4% of patients; <strong>pruritus</strong> in 10% of patients; <strong>xerostomia</strong> in 12% of patients; <strong>muscle cramping</strong> in 6% of patients</td>
</tr>
<tr>
<td>(calcium acetate)</td>
<td></td>
</tr>
<tr>
<td>Renagel (sevelamer hydrochloride) and Renvela (sevelamer carbonate)</td>
<td><strong>Gastrointestinal effects</strong> in 38% of patients; <strong>hypercalcemia</strong> in 13% of patients; <strong>metabolic acidosis</strong> in 34% of patients (Renagel); <strong>peritonitis</strong> in 11% of patients</td>
</tr>
<tr>
<td>Fosrenol (lanthanum carbonate)</td>
<td><strong>Peripheral edema</strong> in 24% of patients; <strong>gastrointestinal effects</strong> in 8% of patients; <strong>hypercalcemia</strong> in 6% of patients; <strong>muscular cramping</strong> in 7% of patients; <strong>myalgia</strong> in 21% of patients; <strong>peritonitis</strong> in 4% of patients</td>
</tr>
</tbody>
</table>
K-DOQI and KDIGO Recommendations.

How can they help us to choose the type of intestinal phosphate binder?
Choice of phosphate binder: No specific recommendation

CKD stage 5:
- Ca based binders and Sevelamer are effective
- Combination of both if sP remains above 5.5 mg/dl with either one P binder
- If sP > 7.0 mg/dl, Al-based P binders may be used for up to 4 weeks

Guidelines 4.1.4 and 4.1.6:
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 phosphate binder takes into account CKD stage, presence of other components of CKD–MBD, concomitant therapies, and side-effect profile (not graded). [...] recommend avoiding the long-term use of aluminum-containing phosphate binders [...].
Choice of phosphate binder: No specific recommendation

- Maximum dose of elemental Ca from P binders: **1500 mg/d** (opinion), total intake of elemental Ca incl. diet: **2000 mg/d**
- No Ca based P binders in pts with sCa > 10.2 mg/dl or with iPTH < 150 pg/ml on two consecutive measurements
- Non-Ca based binders in pts with severe vascular or other soft tissue calcification

AJKD 42 (4), Suppl 3 (Oct) 2003

Guidelines 4.1.6:

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 analogue in the presence of persistent or recurrent hypercalcemia (1B).

In patients with CKD stages 3–5D and hyperphosphatemia, we suggest **restricting** the dose of calcium based phosphate binders in the presence of **arterial calcification** (2C) and/or **adynamic bone disease** (2C) and/or if serum PTH levels are persistently low (2C).

KDIGO CKD-MBD guidelines, KI 2009, 76 (Suppl. 113)
In Practice: How to Choose An Intestinal Phosphate Binder?

1- Based on biochemical parameters (Calcemia, Phosphatemia and PTH)

2- Based on the presence or the absence of cardiovascular calcifications

3- Based on the bone biopsy data (presence or the absence of low bone turnover or an adynamic bone disease)
### In Practice: How to Choose An Intestinal Phosphate Binder?

<table>
<thead>
<tr>
<th></th>
<th>Calcemia</th>
<th>Vascular Calcifications</th>
<th>Ca-Based Phosphate Binder</th>
<th>Ca-Free Phosphate Binder</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH Normal/Low</td>
<td>N/Low</td>
<td>YES</td>
<td></td>
<td>+/+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>YES</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PTH High</td>
<td>N/Low</td>
<td>YES</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>YES</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
## Cost of Intestinal Phosphate Binders

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose Range</th>
<th>Cost per month (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Acetate</td>
<td>Variable</td>
<td>11 - 34</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>Variable</td>
<td>11 - 25</td>
</tr>
<tr>
<td>Calcium Acetate/Magnesium Carbonate (Osvaren)</td>
<td>3-10 Tablets</td>
<td>15-55</td>
</tr>
<tr>
<td>Aluminum Hydroxyde</td>
<td>4-20 Capsules</td>
<td>18 - 90</td>
</tr>
<tr>
<td>Sevelamer HC (Renagel)</td>
<td>1-5 Tablets 3 times a day</td>
<td>110 - 550</td>
</tr>
<tr>
<td>Sevelamer Carbonate (Renvela)</td>
<td>1-3 Tablets 3 times a day</td>
<td>110 - 330</td>
</tr>
<tr>
<td>Lanthanum Carbonate (Fosrenol)</td>
<td>1,500-3,000 mg per day</td>
<td>163 - 254</td>
</tr>
<tr>
<td>Sucroferric Oxohydroxide (Velphoro)</td>
<td>3-6 Tablets per day</td>
<td>235 - 471</td>
</tr>
</tbody>
</table>

THANK YOU VERY MUCH

MERCI BEAUCOUP