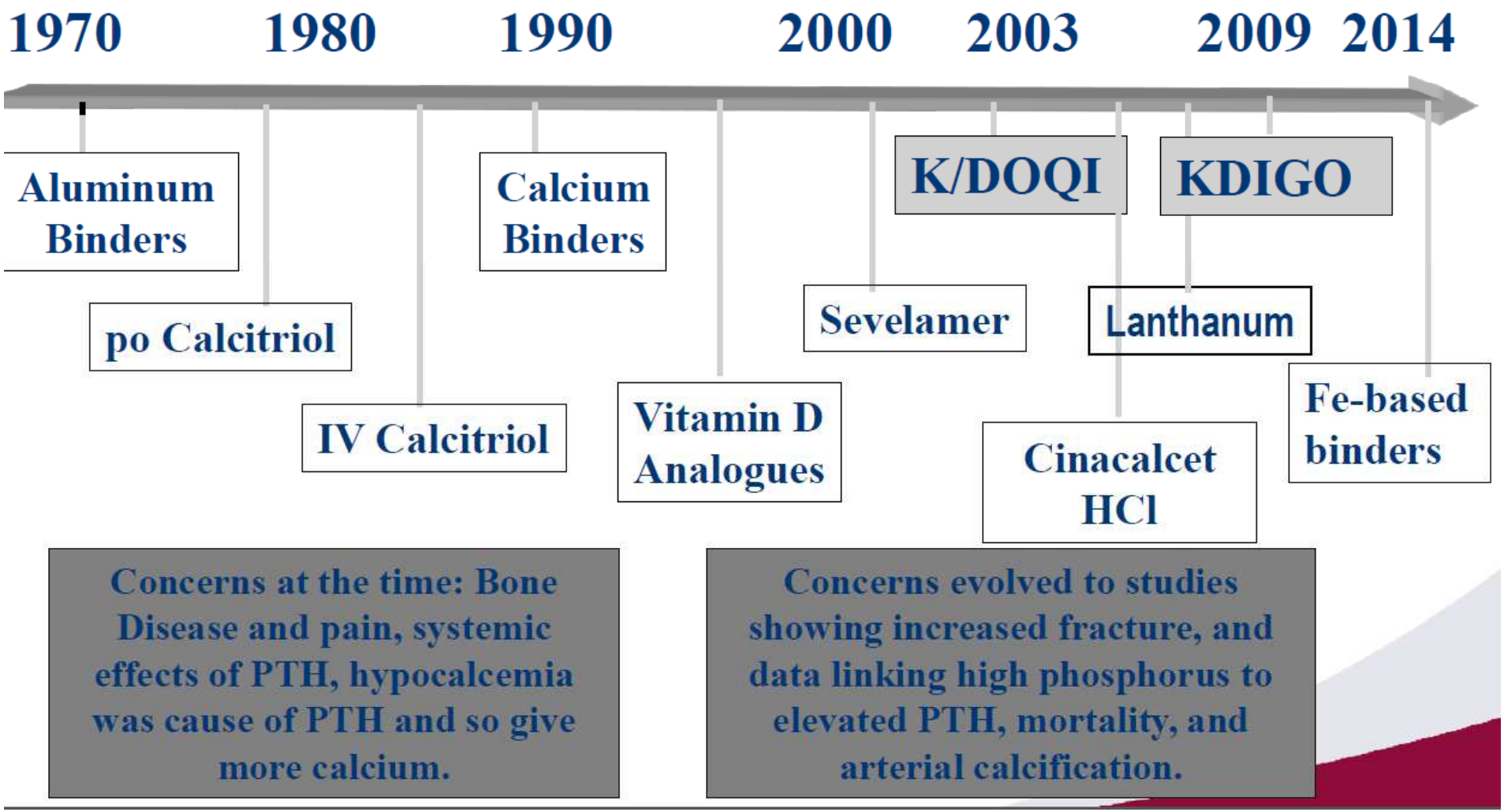
Phosphorus Management in ESRD

SKC In-service March 2016

History of Treatment Strategies for CKD-MBD



General Approach to Phosphorus Management in ESRD

- **Normalize serum phosphorus:** By diet, phosphorus binder therapy, and more dialysis
- **Normalize serum calcium:** Targeting the lower end of normal allows more flexibility in treatments
- **Treat elevated PTH:** With calcitriol or other "less hypercalcemic" vitamin D analogues

- **Ultimately want to improve biochemical parameters in order to**
  - Reduce cardiovascular calcification
  - Improve LVH
  - Treat renal osteodystrophy (bone abnormalities)
  - Reduce fractures

KDOQI (in red) and KDIGO (in blue) "Target" values

	CKD Stage 3	CKD Stage 4	CKD Stage 5
Phosph (mg/dl)	2.7-4.6 mg/dl (Opinion) "Normal" (2C)	2.7-4.6 mg/dl (Opinion) "Normal"(2C)	2.7-5.5 mg/dl (Evidence) Towards the normal range(2C)
Calcium (mg/dl)	Normal (Opinion) "Normal" (2D)	Normal (Opinion) "Normal" (2D)	8.4-9.5; Hypercalcemia = >10.2 (Evidence) "Normal"(2D)
Intact PTH (pg/ml)	35-70 pg/ml (Opinion) Ideal level unknown	70-110 pg/ml (Opinion) Ideal level unknown	150-300 pg/ml (Evidence) >2 and < 9 times the upper limit of normal [if TREND changing within that range, adjust RX (2C)]

Evidence Based?

- Animal and in vitro studies demonstrate that phosphorus is a direct vascular toxin, can induce LVH, and increases PTH.
- Many associative data demonstrate increased mortality when phosphorus is above a certain value; what the inflection point at which this risk increases depends in part on what the reference range was set at.
- Meta analysis of studies evaluating an association of phosphorus with adverse outcomes demonstrate a relative risk of 1.18(1.12-1.25 95% CI) per unit increase of phosphorus for all cause mortality, and 1.10 (1.06-1.13) per unit increase for phosphorus and cardiovascular mortality. (Palmer, JAMA 2011)
- No study has been done to demonstrate that lowering phosphorus to a specific level is associated with an improved outcome; thus the ideal 'target' is unknown and thus "toward the normal range" was used in the KDIGO guidelines
- Must individualize treatment in each patient to optimize phosphorus lowering while minimizing side effects

Will treatments with phosphate binders impact any of these end points?

Ca: Ca binder will cause hypercalcemia more than non Ca binder

PTH: Ca binder will suppress PTH more than non Ca binder

LVH and Vascular Calcification

PTH, Ca, Pi Bone Remodeling

Vascular Calcification: Studies evaluating arterial calcification in humans have compared sevelamer vs. calcium carbonate or acetate. Results are mixed and depend on study design

Bone Remodeling: Ca binder will suppress bone remodeling more than non Ca binder

Hospitalizations Quality of Life Mortality

(Evidence from RCTs summarized in grey boxes, see KDIGO guidelines for references)

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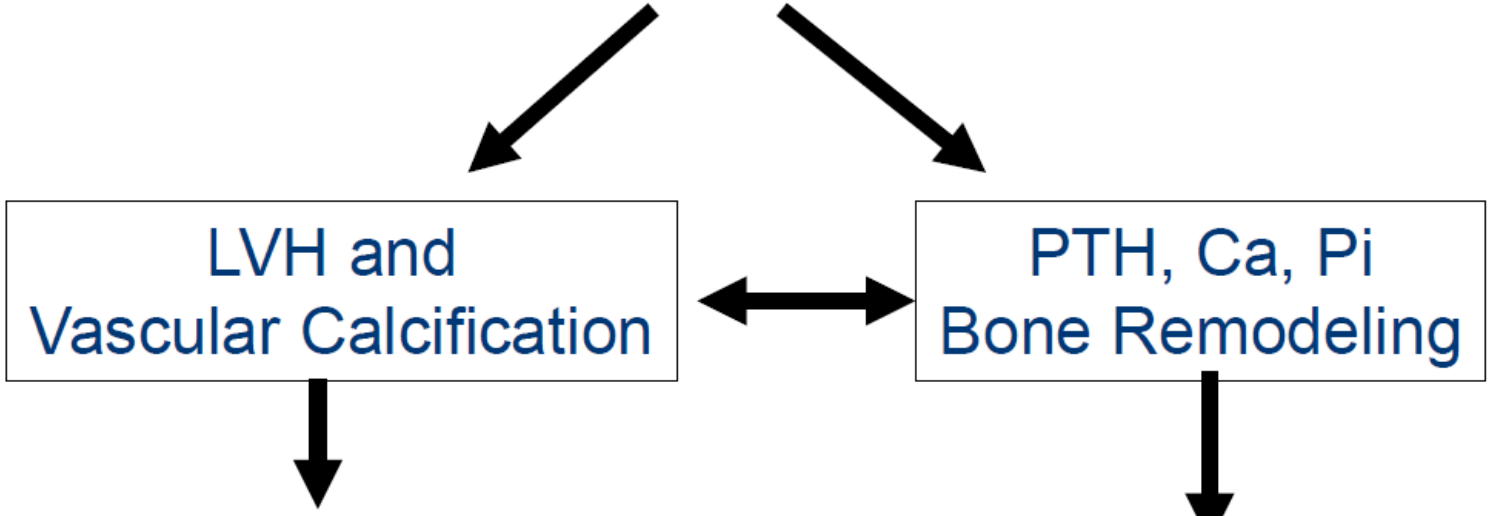


Mortality: In CKD 5 on dialysis, Block (KI 2006) showed reduced mortality with sevelamer compared to calcium, but Suki study (DCOR,KI 2007) did not. Meta analysis showed benefit of non calcium vs. calcium based binder on mortality (0.87; 95% CI 0.77-0.97; Jamal Lancet 2014)

Fractures

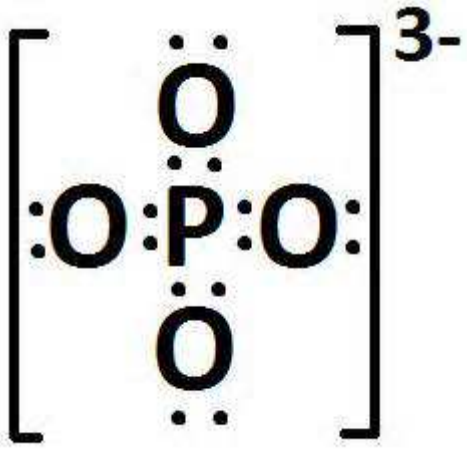
No data that any treatment improves fractures

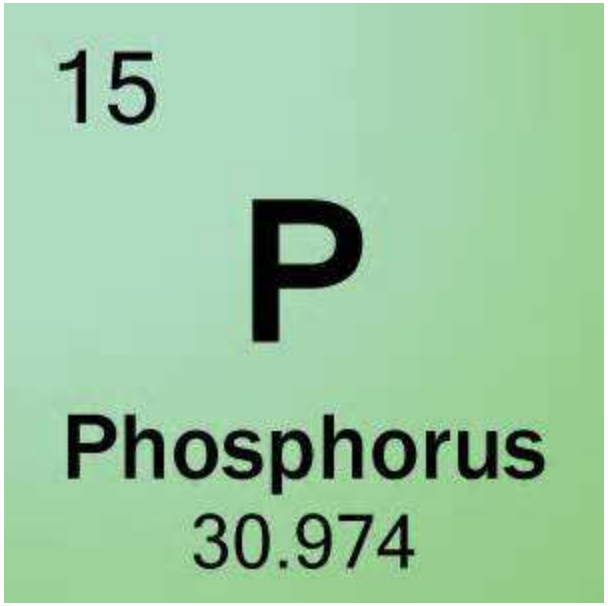
Hospitalizations Quality of Life
Mortality

(Evidence from RCTs summarized in grey boxes, see KDIGO guidelines for references)

Considerations for Phosphorus Control

1. Dietary Management of Phosphorus Intake
2. Removal of Phosphorus with RRT
3. Phosphorus Binder Management





Dietary Management of Phosphorus

Source	Examples	Phos Content*	Phos Type	Phos Absorbed**
Plant-based foods	Most fruits and vegetables	↓	Organic phytate or phytic acid	< 50%
	Nuts, seeds, legumes	↑		
Animal-based foods	Meat, fish, poultry, dairy products, eggs	↑	Organic phosphate	40 – 60%
Processed or enhanced foods	Certain beverages, processed meats and cheeses, bakery mixes, frozen meals, fast foods	↑↑	Inorganic phosphate salts (PO_4 additives)	> 90%

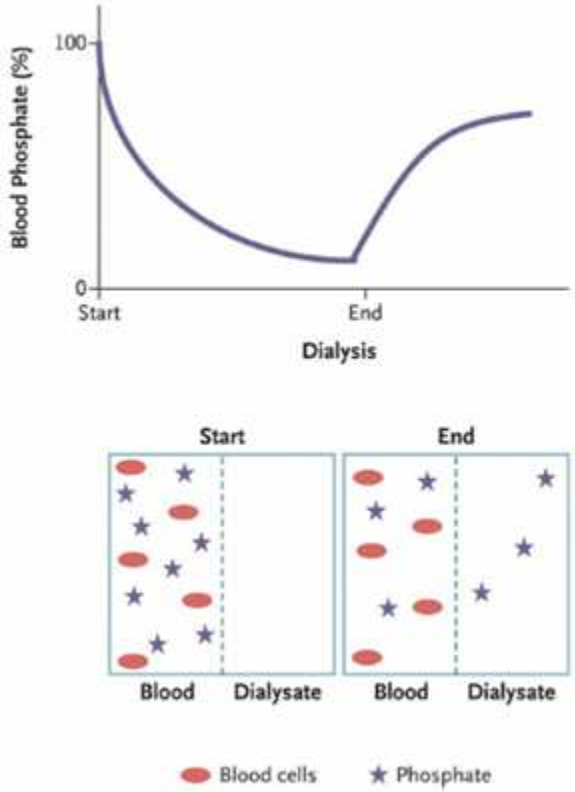
*Consider phosphorus to protein ratio

** Phosphorus absorption rates may vary, e.g. higher absorption can be observed upon vitamin D administration.

Kalantar-Zadeh K, et al. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010; 5:519-530.

Phosphorus removal with dialysis

- The majority of phosphorus is not in the extracellular space. Thus conventional hemodialysis will lower phosphorus, but with rebound after dialysis is done.
  - Dialysis with maximal convection and maximal time will yield greatest removal of phosphorus
  - Standard thrice weekly HD removes ~ 2.4 g/week
  - Hemodiafiltration removes ~3.6 g/week
  - Short daily HD (SDHD) removes ~2.5 g/week
  - Nocturnal HD removes ~ 8 g/week
  - CAPD removes ~2.8 g/week
  - CCPD removes ~2.8 g/week



- In the randomized trial of thrice weekly vs. SDHD, there was a greater reduction in pre dialysis phosphorus concentration over the 12 months in frequent compared to thrice weekly dialysis (-0.56 mg/dl (95% CI -0.91 to -0.22). (Chertow et al, NEJM 2010)

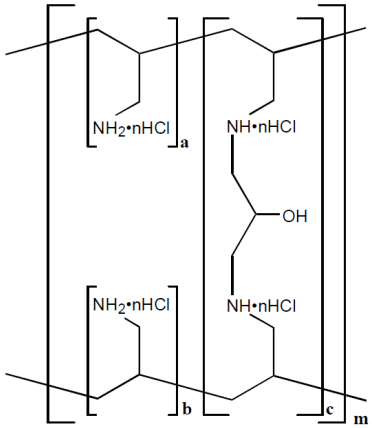
- The average person (in US) eats 1.4 g / day or ~ 9 to 10 g/wk!

Phosphorus Binders

- Calcium Based Binders
  - Calcium carbonate (Tums)
  - Elemental calcium equivalent:
    - 400 mg (161 mg)
    - 500 mg (200 mg)
    - 750 mg (300 mg)
    - 1000 mg (400 mg)
    - 1177 mg (470 mg)
  - Calcium acetate (PhosLo, Phoslyra = liquid form)
    - 667 mg caps or 667mg / 5mL
    - Calcium acetate 667mg = 169mg elemental calcium
    - Seems to be more available to bind phosphorus than calcium carbonate. Limited studies suggest similar phosphorus binding at around half the elemental calcium dose with calcium acetate compared to calcium carbonate. (Delmez, JASN 1992)

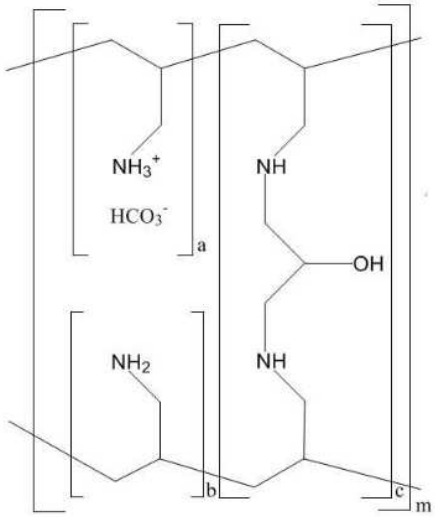
Phosphorus Binders

- Sevelamer
  - Renagel (Sevelamer HCl)
    - 800 mg tabs
  - Renvela (Sevelamer Carbonate)
    - 800 mg tabs
    - 800 mg or 2400 mg powder
  - Also binds bile acids
  - Not absorbed
  - Renvela can raise serum HCO3- level
  - Decreases bioavailability of MMF by ~30%
  - Decreases bioavailability of Cipro by ~50%
  - Most common side effect is GI upset
  - Can worsen constipation / fecal impaction
  - Contraindicated in bowel obstruction



a, b = number of primary amine groups a + b = 9
c = number of crosslinking groups c = 1
n = fraction of protonated amines n = 0.4
m = large number to indicate extended polymer network

Figure 1. Chemical Structure of Sevelamer Carbonate



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Other Phosphorus Binders

- Magnesium Hydroxide
- Aluminum Hydroxide
- Lanthanum Carbonate (Fosrenol)
- Sucroferric oxyhydroxide (Velphoro)

Cost (table 2009)

TABLE 1. Retail cost of commonly used phosphate binders

Generic name	Trade name	Dose	Quantity	Cost (US $)[a]
Calcium carbonate	TUMS®	500 mg	100 tabs	5.49
Calcium acetate	PhosLo®	667 mg	100 caps	62.49
Sevelamer hydrochloride	Renagel®	800 mg	100 tabs	184.40
Lanthanum carbonate	Fosrenol®	500 mg	100 tabs	233.06

Renvela 90 tabs ~ $150-300
Velphro 90 tabs ~ $800-900