Calcium-Based Phosphate Binders

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Object

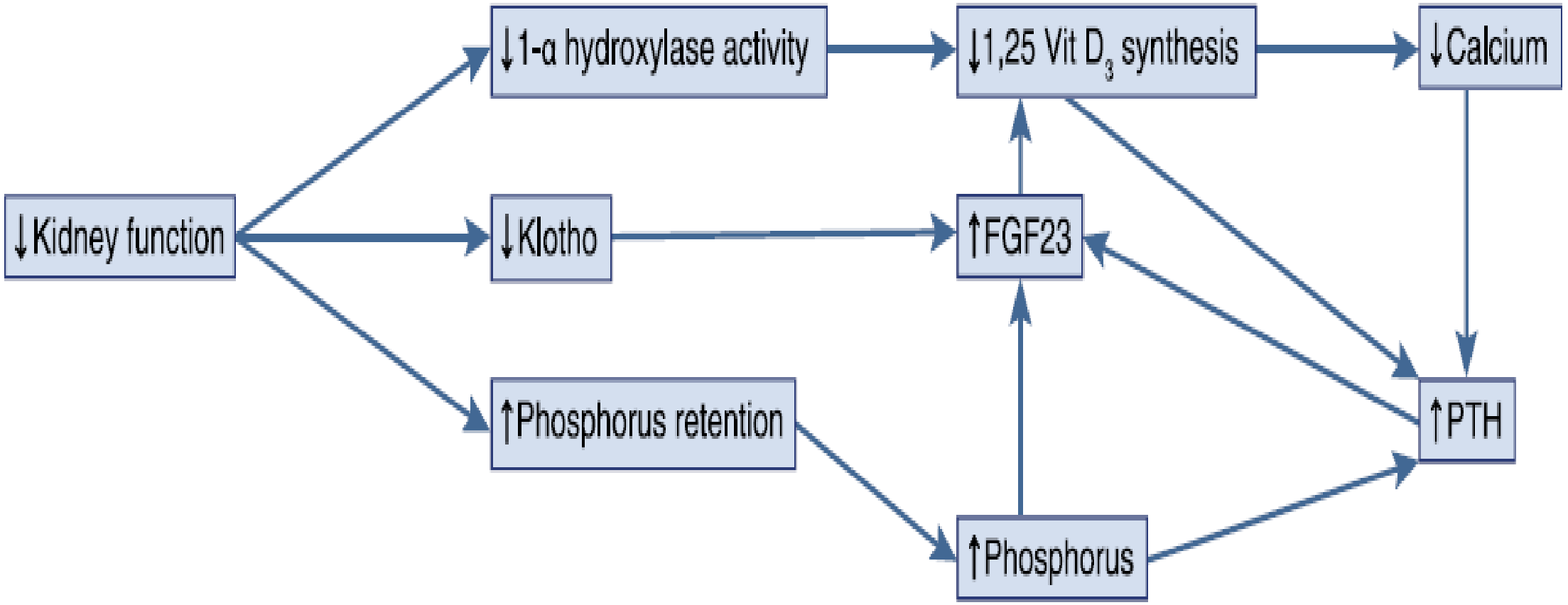
- Introduction
- Pathophysiology
- Causes of Hyperphosphatemia
- Control of Hyperphosphatemia
- Phosphorus binders
- Class selection
- Vascular calcification

Introduction

As kidney function declines, there is a progressive loss of the ability to maintain mineral homeostasis and normal bone turnover.

Three hormones are involved primarily in maintaining mineral bone homeostasis in early CKD:

- FGF23
- calcitriol
- PTH



Secondary Hyperparathyroidism in a Patient with CKD- Ryyan Hyder 2020

Causes of Hyperphosphatemia

- Decreased Kidny Excretion of phosphorus
- Exogenous phosphorus Administration
- Redistribution of phosphorus.
- PseudoHyperphosphatemia

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Causes of Hyperphosphatemia (Continue…)

Hyperphosphatemia, common in dialysis patients, contributes to
The development of hyperpara- thyroidism and bone disease,
The development and progression of cardiovascular disease.

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Control of Hyperphosphatemia

- The normal range for serum phosphorus is 2.7 to 4.6 mg/dL (0.9–1.5 mmol/L).

- In dialysis patients, the KDIGO bone guidelines recommend attempting to maintain predialysis phosphorus in the normal range,

Handbook of dialysis2015

Dietary restriction.

Restricting phosphorus in the diet to 800 to 1,200 mg per day is the key to controlling serum phosphorus.

Removal of phosphorus by dialysis

- Hemodialysis typically removes about 800 mg of phosphorus per treatment regardless of predialysis serum levels.

- For hemodialysis, the total weekly time on dialysis is the most important factor affecting phosphorus removal.

- Peritoneal dialysis removes approximately 300 mg per day

Foods Especially High in Phosphorusa

- Dairy products (milk, yogurt, cheese)
- Organ and processed meat
- Beans/peas
- Nuts/seeds
- Whole-grain breads, bran, and cereals
- Many soft drinks (particularly colas)

Residual kidney function

Patients with urine volumes >500 mL per day typically require substantially lower amounts of phosphorus binders.

Phosphorus binders

These agents work by binding phosphorus in the gastrointestinal tract, either by forming an insoluble complex or by binding it into a resin

Recent observational data have suggested that the use of phosphorus binders may also correlate with longer survival and better nutritional status

Phosphorus binders (Continue…)

Phosphorus binders in two broad categories:

- Those that contain calcium (calcium car-bonate and calcium acetate)

- Those that do not (sevelamer, lanthanum, magnesium carbonate, sucroferric oxyhydroxide, ferric citrate, and aluminum-containing compounds.

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Phosphorus binder equivalent dose:

This so-called phosphorus binding equivalent dose (PBED) allows one to compare dosages in patients taking multiple binders or different binders.

In U.S. patients with minimal residual kidney function being dialyzed according to typical U.S. practices, PBED averages around 6 g per day

Calcium load associated with some phosphorus binders.

- Calcium acetate, on a gram-per-gram basis, is about as effective as calcium carbonate as a phosphorus binder.

- Calcium acetate contains only 25% calcium by weight

- Calcium carbonate contains 40% calcium by weight.

Product	Trade Names	Dose (mg) per Tablet	Elemental Calcium	Maximum Dose per Day	Comments
Calcium carbonate	(Generic, Multiple Names)	Multiple doses	40% elemental calcium	1.5 g of elemental calcium/d	Administered with meals as binder; on empty stomach as supplement
	TUMS	500 mg	200 mg/tab	As above (7 tablets)	
	TUMS EX	750 mg	300 mg/tab	As above (5 tablets)	
	TUMS Ultra	1,000 mg	400 mg/tab	As above (3 tablets)	
	TUMS 500	1,250 mg	500 mg/tab	As above (3 tablets)	
	Os-Cal 500	1,250 mg	500 mg/tab	As above (3 tablets)	
	Os-Cal+D	1,250 mg	500 mg/tab	As above (3 tablets)	200 IU of vitamin D/tab
	Caltrate	600 mg	240 mg/tab	As above (6 tablets)	
Calcium acetate	PhosLo	667 mg	169 mg of elemental calcium/tab	As above (9 tablets)	More expensive than calcium carbonate. Prescription medication
Magnesium carbonate with calcium carbonate	MagneBind	200: 200 mg $MgCO_3$ with 400 mg $CaCO_3$	160 mg/tab	Dose limited by serum Mg levels and diarrhea	85 mg of elemental magnesium/tab. Dialysate magnesium concentrations should be adjusted
Magnesium carbonate with calcium carbonate	MagneBind	300: 300 mg $MgCO_3$ with 250 mg $CaCO_3$	100 mg/tab	Dose limited by serum Mg levels and diarrhea	85 mg of elemental magnesium/tab. Dialysate magnesium concentrations should be adjusted

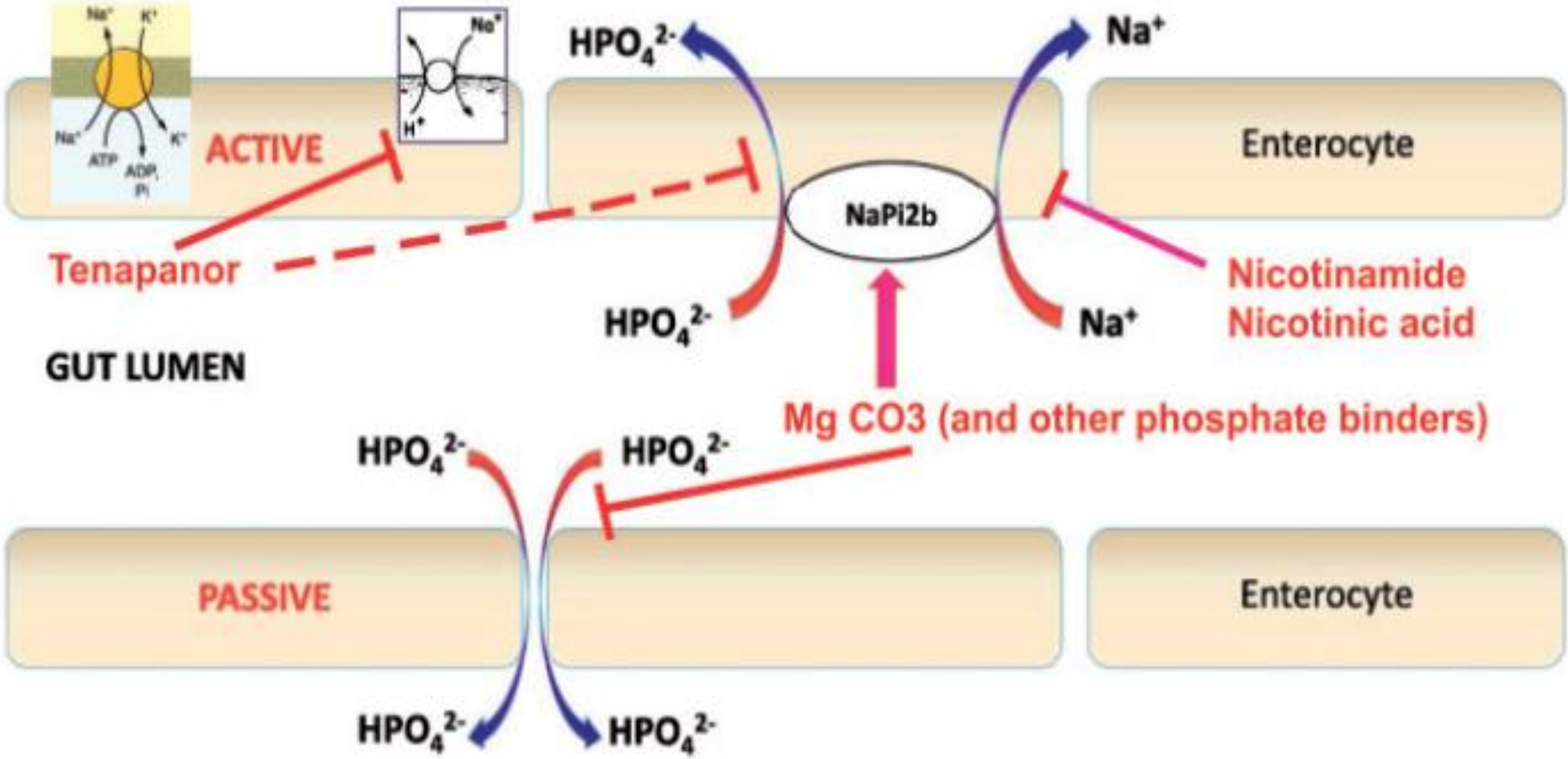
Magnesium carbonate + calcium acetate	Osvaren	435 mg of $MgCO_3$ and 235 mg of Ca acetate	60 mg/tab		Reduction of calcium load; Mg may have anticalcification properties; not available in the US
Lanthanum carbonate	Fosrenal	250-mg and 500-mg tablets	0	1,250 mg t.i.d. Higher doses have not been tested long-term	Significantly more expensive than other products.Must be chewed
Sevelamer carbonate	Renvela	400-mg and 800-mg tablets and powder	0	Has been tested to 14 g/d in normal individuals. Dose may be limited by side effect of GI discomfort	Significantly more expensive than other products
Sucroferric oxyhydroxide (PA21)	Velphoro	500 mg	0	3 g/d	Designed to minimize iron absorption from this iron-containing binder
Ferric citrate (JTT-751)	Not yet assigned	210 mg ferric iron	0	2.5 g/d ferric iron	210 mg elemental iron per tablet as 1 g ferric citrate. Associated with significant increase in serum iron markers

Niacin and nicotinamide

These compounds inhibit the intestinal sodiumdependent phosphate transporter NaPi2b and the renal sodium-dependent phosphate transporters NaPi2a and NaPi2c.

Several studies have shown that both niacin and nicotinamide are able to reduce hyperphosphataemia in dialysis patients, together with a lower pill burden than classic phosphate binders

Vascular calcification—any place left for nicotinamide-Tilman B (2020)


ACTIVE
Tenapanor
GUT LUMEN
HPO4 2-
Na+
NaPi2b
Enterocyte
Nicotinamide
Nicotinic acid
Mg CO3 (and other phosphate binders)
PASSIVE
Enterocyte

Calcium-containing compounds.

KDIGO recommendations that elemental calcium ingestion should generally not exceed 1.5 g per day.

Calcium Carbonate

Calcium carbonate dissociates best in an acidic environment its solubility can be inhibited by medications such as proton pump inhibitors.

Calcium Acetate

Administration is a swallowed tablet, and side effects include hypercalcemia, nausea, and constipation.

Use of more than one phosphorus binder.

Combined treatment with different types of phosphorus binders may be advantageous and cost effective.

Class Selection

Complication:

The accumulation of calcium in patients with CKD and kidney failure has limited enthusiasm for high doses of calcium-based phosphate binders. These concerns arise justifiably from observed vascular calcification present even in young.

State-of-the-Art Management of Hyperphosphatemia in Patients With CKD: An NKFKDOQI Controversies Perspective 2021

Complication (Continue…)

Hypercalcemia:

Hypercalcemia is usually due to excessive use of calcium-based binders or to use of vitamin D receptor agonists that increase gut calcium absorption.

Complication (Continue…)
Vascular calcification

- Vascular calcification is a serious complication of chronic kidney Disease.
- Its presence is associated with an increased risk of cardiovascular events and mortality.
- The pathogenesis of vascular calcification is complex ,soft tissue deposition of calcium and phosphate as a consequence of hypercalcaemia and hyperphosphataemia are the main underlying cause.

Vascular calcification—any place left for nicotinamide-Tilman B (2020)

Assesment of Vascular Calcification

Plain latral radiographs can be used to assess the presence or absence vascular Calcification.

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Complication (Continue…)

- Sevelamer, lanthanum, and iron-based binders may causegastrointestinal side effects, including constipation, vomiting, and diarrhea.

- the higher costs of non-calciumbased binders may not be outweighed by reduced health care costs.

Other Goals:

In addition to lowering serum phosphate, sevelamer-based binders also lower serum cholesterol and reduce inflammatory markers.

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Mortality

High degrees of heterogeneity in the mortality effects of calcium versus non-calcium-based binders has been noted in all systematic reviews of the topic.

Mortality (Continue…)

Finding of McCoullough's literature analysis is that only three of 30 studies implied any independent association between oral calcium load and cardiac and/or vascular calcifications.

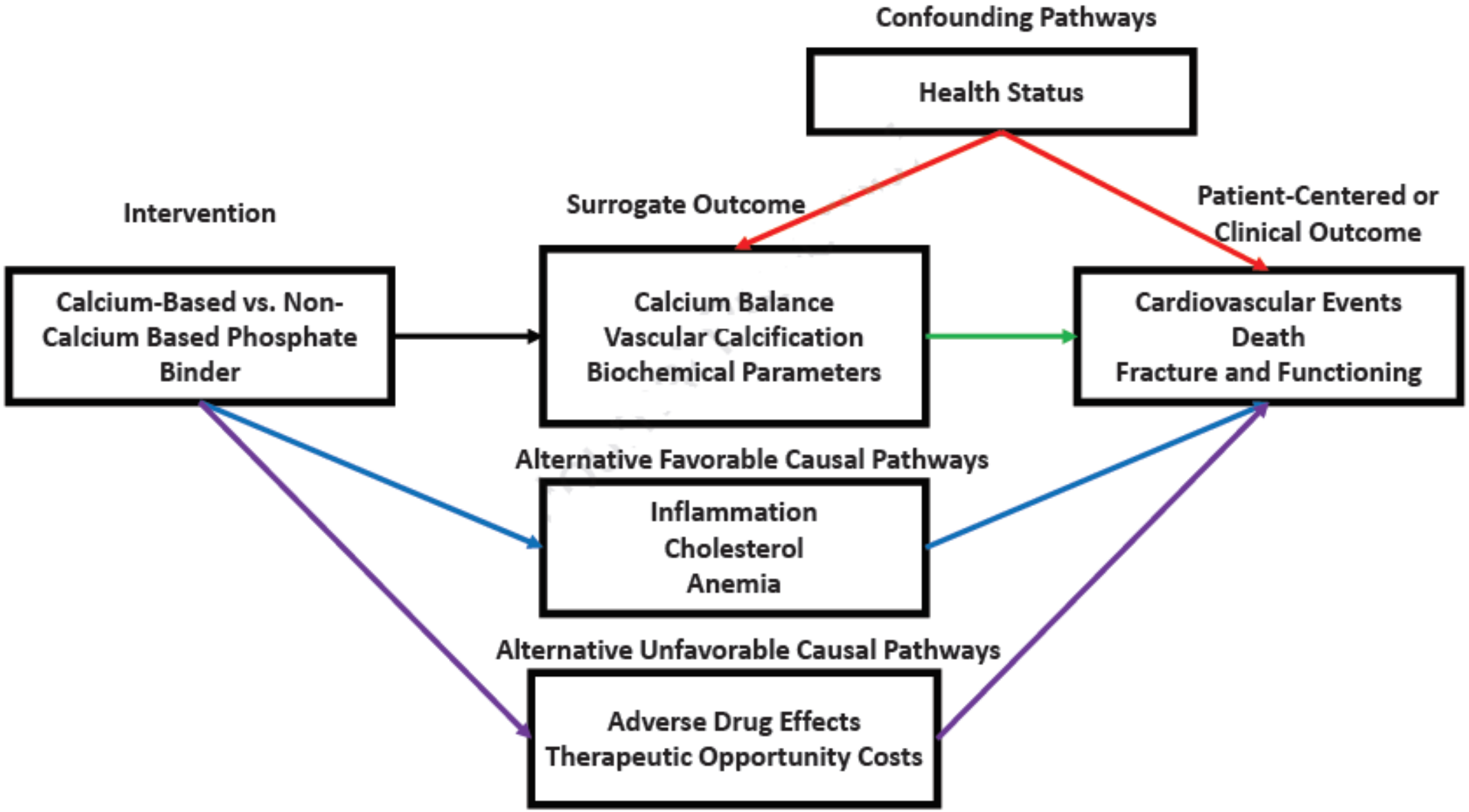
The main determinants of cardiac and vascular calcification discerned were patient age, duration of dialysis treatment, and, inconclusively, dyslipidemia.

State-of-the-Art Management of Hyperphosphatemia in Patients With CKD: An NKFKDOQI Controversies Perspective 2021

The upcoming KDOQI guideline on nutrition in CKD suggests that total elemental calcium intake including :

- dietary calcium
- calcium supplementation
- calcium-based phosphate binders

Be kept in the range of 800-1,000 mg/day for patients with CKD G3-4 in order to maintain a neutral calcium balance



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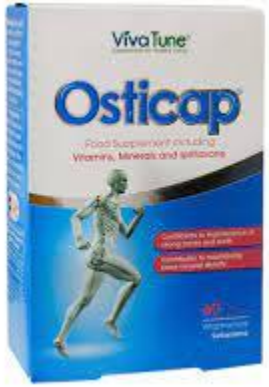

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Conclusions

It remains possible that in advanced stages of CKD hyperphosphataemia control by calcium-containing binders is still better than no hyperphosphataemia control at all.

The most worrisome issue with the prescription of classic phosphate binders is insufficient adherence since they are more or less bulky and may cause gastrointestinal intolerance.

Highdose calcium-based phosphate binders may induce calcium overload.


THANK
YOU