Vascular calcification treatment & prophylaxis

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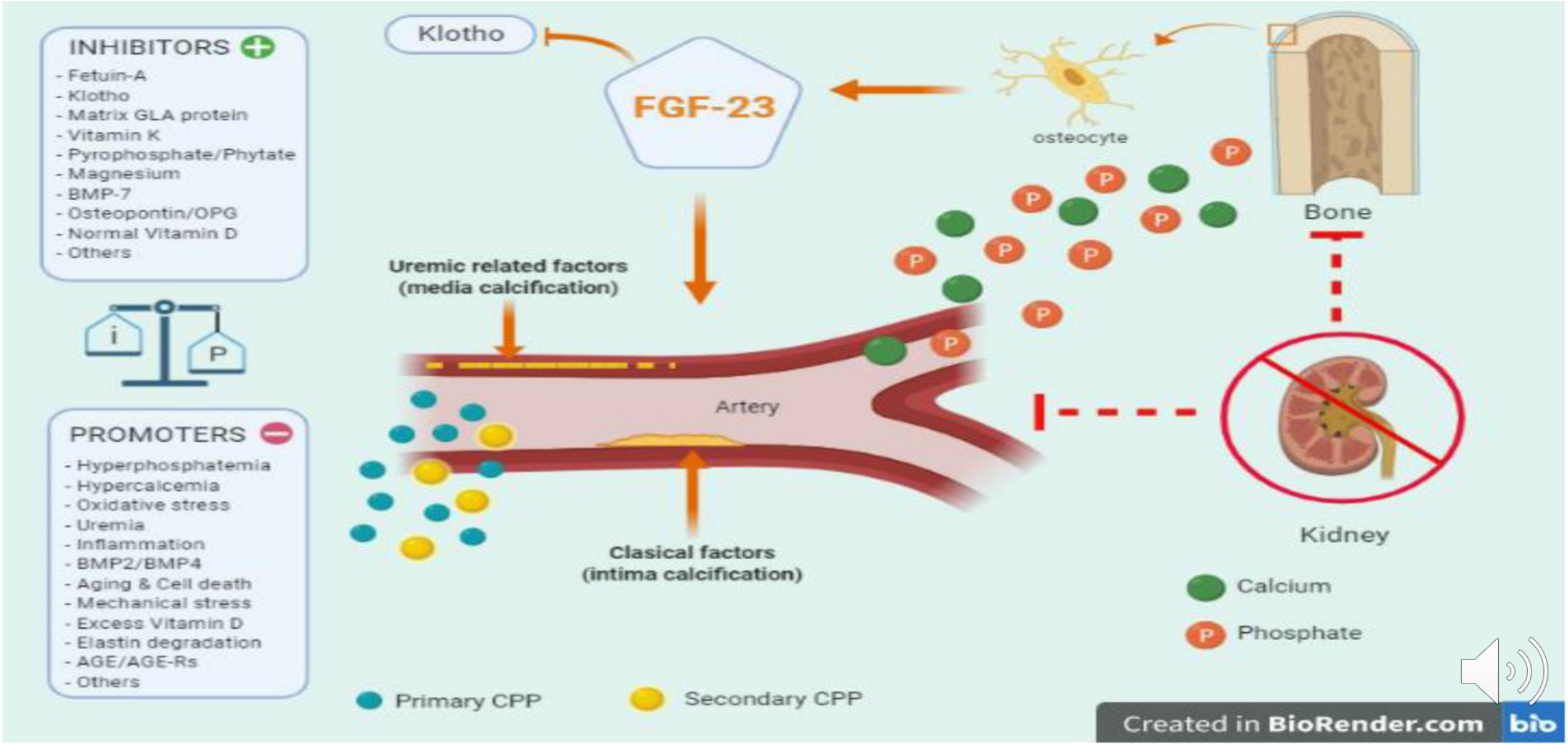
OUTLINE:

- Blood pressure management
- Lipid lowering agent
- Hyperphosphatemia

New agent: Sucroferric oxyhydroxide,Tenapanor, Nicotinamide

- Magnesium
- Calcimimetics
- Parathyroidectomy
- vitamin D
- vitamin K
- ACEI/ARB
- Iron
- SNF472
- Romosozumab
- Apabetalone
- Exogenous Parath Hormone

Vascular calcification



Blood pressure management

- No evidence that antihypertensive therapy affects VC but may reduce myocardial fibrosis and LVH
- retard the progression of CKD stages 2-5

- KDIGO guidelines recommend: target blood pressure in CKD

1. patients with albuminuria :≤140/ ≤90 mm Hg
2. patients without albuminuria: ≤130 /≤80 mm Hg

- Meta-analyses reported benefits of antihypertensive therapy compared to placebo for cardiovascular protection in hemodialysis patients

Lipid lowering agent

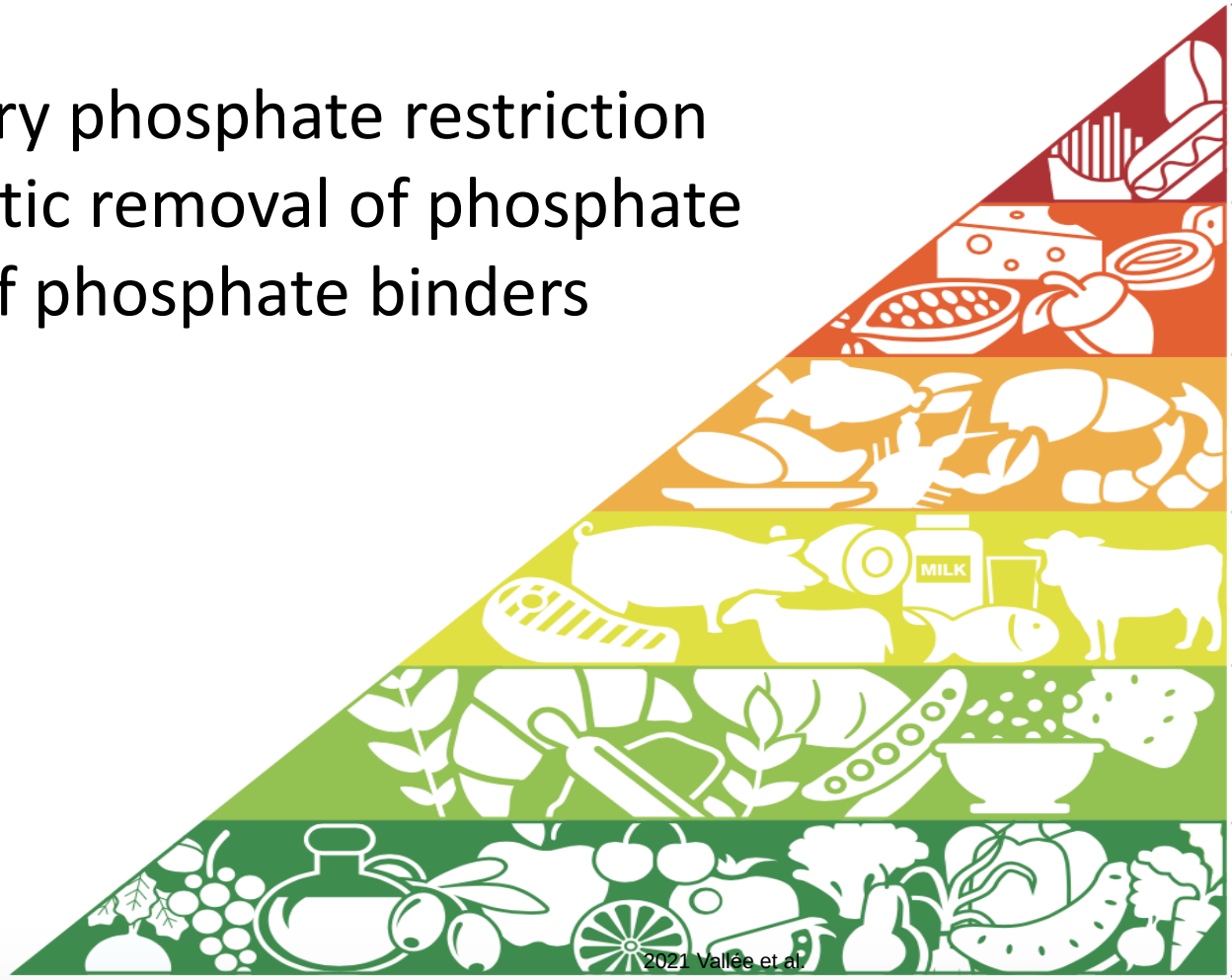
- **Statin therapy in patients with CKD**:
  Reduce cardiovascular mortality and cardiovascular event

- **Statins on dialysis** : inconsistently improving cardiovascular outcomes
  - Only RCT SHARP (using statin plus ezetemibe), :significant effect in dialysis patients
  - AURORA: No effect

- **Fibrates in patients with CKD**: No RCT supports usage

Strategies to Manage Hyperphosphatemia

Dietary phosphate restriction
Dialytic removal of phosphate
use of phosphate binders



Beverages and foods with phosphate additives:
Soft drinks; dehydrated milk; processed cheese and meats, packaged desserts, instant coffees

Hard cheeses: parmesan, cheddar, etc.
Nuts and egg yolk

Meat: sausages, organ meats (liver, brain)[a]
Turkey, shrimp; squid; salmon[a]
Soft cheeses: cottage cheese, mozzarella

Meat: rabbit, lamb, pork, veal, ham with no preservatives[b]
Chicken;[a] trout; tuna; cod; hake; sole
Milk; yogurt

Cereals: bread, pasta, rice, couscous, corn flour, etc.
Legumes: peas, broad beans, chickpeas, lentils, soy, etc.

Egg white, butter,[d] sugar,[e] protein-free products[f]
Fruits and vegetables:[c] olive oil and vegetable fats[d]

2021 Vallée et al.

Phosphate content of drug

Medication and Dosage (mg)	Phosphate Content (mg)*
Paroxetine	
10.0 mg 20.0 mg 30.0 mg 40.0 mg	17.1–147.9 mg 55.8–295.8 mg 443.7 mg 111.5 mg
Amlodipine	
2.5 mg 5.0 mg 10.0 mg	20.9–29.1 mg 3.8–82.8 mg 7.9–165.6 mg
Lisinopril	
5.0 mg 10.0 mg 20.0 mg 30.0 mg 40.0 mg	3.6–18.4 mg 21.4–32.6 mg 7.4–30.7 mg 27.4 mg 26.2–30.8 mg
Sitagliptin	
25.0 mg 50.0 mg	7.3 mg 13.2 mg
Acetaminophen	
8 mg Codeine 15 mg Codeine 30 mg Codeine	60 mg 60 mg 60 mg

Phosphate-Binding Agents

Type	Daily Dose	Daily Pill Burden	Advantages	Disadvantages
Aluminum hydroxide	No safe dose identified	–	Effective, inexpensive	Potential for aluminum toxicity. Patient requires careful monitoring
Calcium acetate	667 mg	6–12 capsules	Effective, potentially more so than calcium carbonate with less calcium absorption	Potential for hypercalcemia; extra-skeletal calcification; PTH suppression; GI side effects
Calcium carbonate	500–1250 mg	3–6 tablets	Effective, inexpensive	Potential for increased hypercalcemia – could lead to vascular calcification; GI side effects
Calcium citrate	4000–6000 mg (equivalent to 250 mg calcium per day)	4–6 pills	Effective, inexpensive	Enhancement of aluminum absorption; GI side effects; not recommended in CKD
Sevelamer hydrochloride	800 mg	6–12 capsules	Effective; lipid-lowering effect; no calcium	Cost; GI side effects; potential development of metabolic acidosis
Sevelamer carbonate	800 mg	6–12 capsules	Effective; lipid-lowering effect; no calcium	Cost; GI side effects
Lanthanum carbonate	250–1000 mg	3–6 chewable tablets	Effective; no calcium	Cost; GI side effects; systemic absorption may be a concern due to potential for accumulation
Sucroferric oxyhydroxide	500 mg	2–6 chewable tablets	Effective; no calcium; does not lead to iron overload	Cost; discolored feces; GI side effects

International Journal of Nephrology and Renovascular Disease 2021:14

Overall Evidence for Phosphate-Binding Therapy CKD G3-G5

Trial	N	Mean eGFR, mL/min/1.73 m²	Intervention Arms	Duration, mo	End Point	Results	Comment
Russo et al[65]	90	33 vs 26 vs 26	Diet, diet + $CaCO_3$, diet + sevelamer	24 ± 4.2	1. CAC score 2. Biochemical changes	1. CAC progression w/ diet + $CaCO_3$; stable w/ sevelamer 2. Urine P decreased in binder groups 3. ALP decreased in diet and diet + sevelamer group	Excluded those w/ diabetes; excluded previous coronary procedures; CONSORT criteria not described in publication
Block et al[9]	148	32	Calcium acetate, lanthanum, sevelamer, placebo	9	1. Biochemical changes 2. VC	1. Binders lowered serum P, urine P; PTH stable w/ binders and increased w/ placebo 2. Calcification increased w/ binders	Did not exclude previous coronary procedures; all patients received fixed dose vitamin D; high dropout rate (28%); only 96 patients had calcification data
Seifert et al[66]	38	CKD G3	Lanthanum, placebo	12	1. Biochemical changes 2. PWV, cIMT, and VC	None of the studied parameters were different between lanthanum and placebo	Pilot study; matching performed between the 2 groups
Ureña-Torres et al[12]	35	42 vs 48	Lanthanum, placebo	3	1. Biochemical changes	1. No sustained reduction in FGF-23 2. Decrease in urine P	GFR was measured; imbalance in characteristics between the 2 groups
Kovesdy et al[67]	120	32	Diet, lanthanum, calcium acetate	12	1. CAC, PWV, FMD 2. Biochemical changes	1. bALP lower after 1 y 2. No other changes compared to baseline 3. Calcium acetate suppressed PTH	Randomized, open-label, 2-center trial; predominantly men; powered to detect changes in bone-mineral parameters
Di Iorio et al[68]	212	32.7	Sevelamer, $CaCO_3$	36	1. Predialysis mortality 2. Dialysis start	1. Biochemical results more favorable w/ sevelamer 2. Mortality lower w/ sevelamer 3. Dialysis start less frequent w/sevelamer	Randomized nonblinded study; RCT was not registered; benefits implausibly large
Ix et al[10]	205	32	NAM + lanthanum, NAM + placebo, lanthanum + placebo, double placebo	12	1. Biochemical changes	No significant change in serum P or FGF-23 concentrations between the 4 arms	Randomized, blinded, placebo-controlled trial; suboptimal adherence due to GI side effects
Ruggiero et al[11]	53	49	Sevelamer, no sevelamer	3	1. Proteinuria 2. Biochemical changes	1. No change in proteinuria 2. Sevelamer reduced urine P; no change in serum P, FGF-23, klotho, PTH, vitamin D	Randomized, open label, 2-center, crossover trial; GFR was measured
Block et al[14]	199	CKD G4-G5	Ferric citrate, usual care	9	1. Biochemical changes 2. Hospitalization 3. Kidney failure, death	1. Iron parameters and Hb increased on ferric citrate 2. FGF-23 stabilized on ferric citrate compared to increasing on usual care 3. Event rates lower on ferric citrate	Randomized population imbalanced; high drop-out rate for biochemical end points due to dialysis transition; reported event end points were exploratory (not registered)

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Evidence for Phosphate-Binding Therapy CKD G3-G5

Patient-centered and clinical outcome studies are needed before use of phosphate binders of any type can be recommended in patients with CKD G3-G5 except to control symptomatic or severe hyperphosphatemia

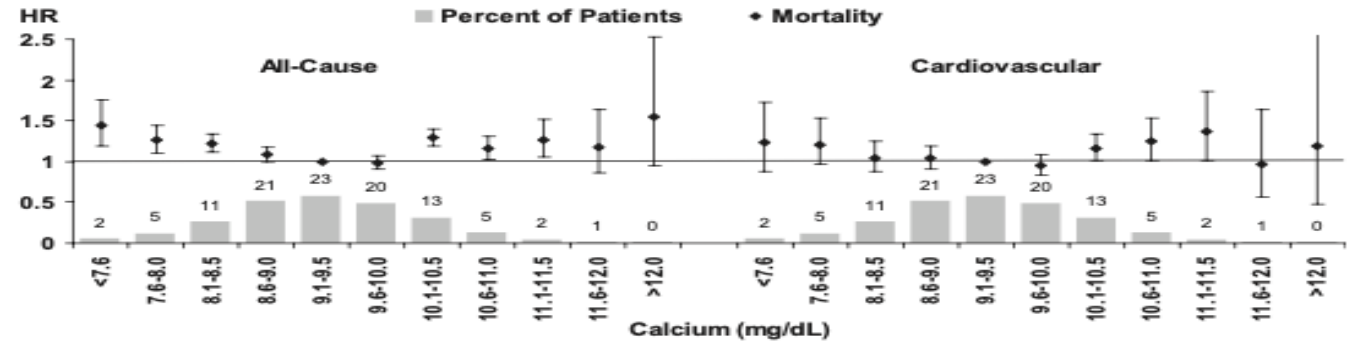
Evidence for Phosphate-Binding Therapy CKD 5D

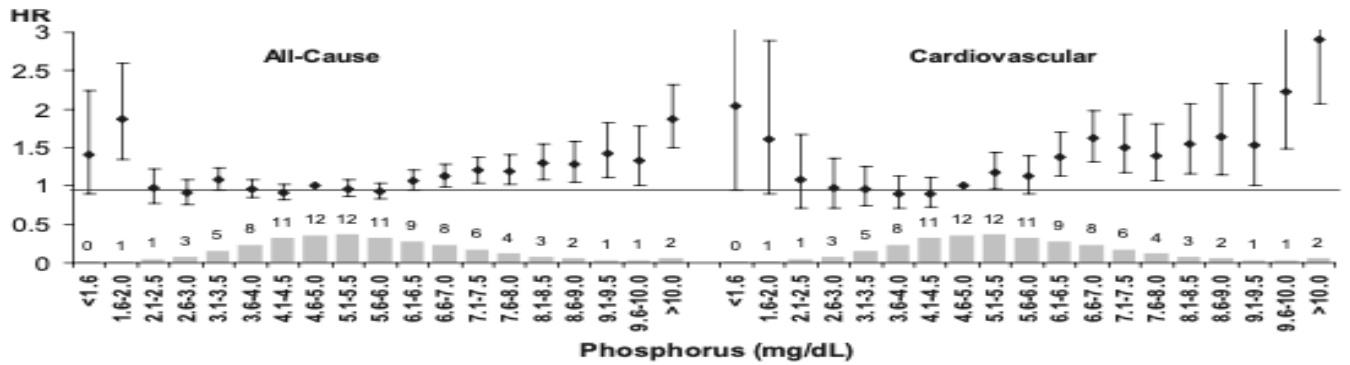
- No trials evaluate effects on clinical outcomes compared with placebo

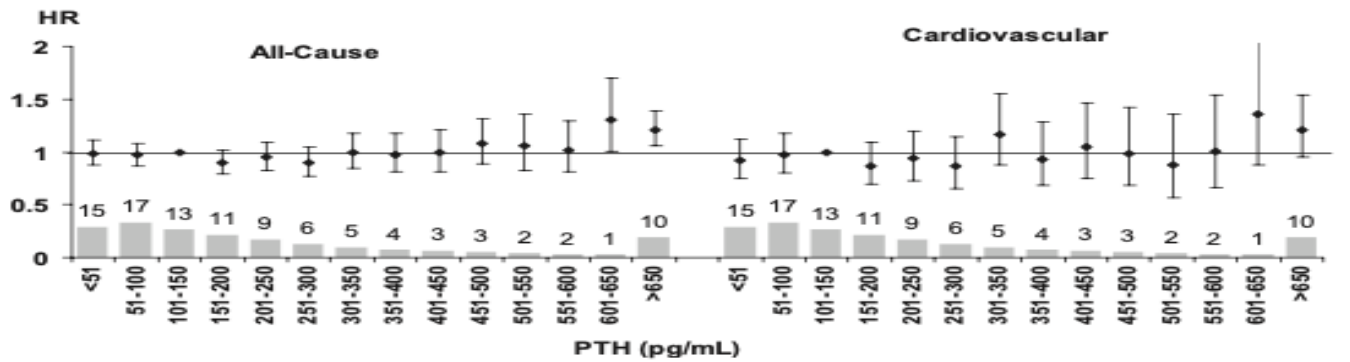
- Hyperphosphatemia may become severe in CKD G5D, resulting in symptoms and well-described clinical complications such as bone disease, calciphylaxis, and itching
- Use of binders to prevent clinically important hyperphosphatemia is justified

Mortality Risk for Dialysis Patients With Different Levels of Serum Calcium, Phosphorus, and PTH: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

Francesca Tentori, MD [1] Margaret J. Blayney, MS [1] Justin M. Albert, BA [1]

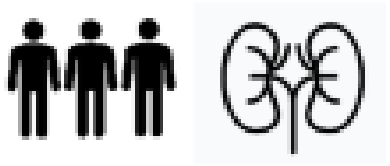






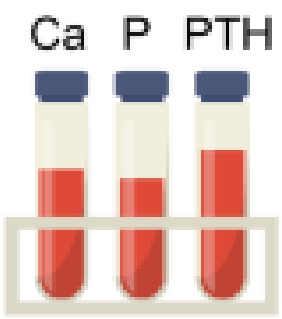
Disorders in bone-mineral parameters and the risk of death in persons with chronic kidney disease stages 4 and 5: the PECERA study

Patient Selection & Study Design



966 patients
-Age >18 years
-ND-CKD 4-5
-Prospective
-3y follow-up

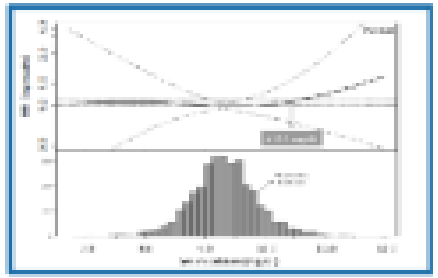
Study Exposure



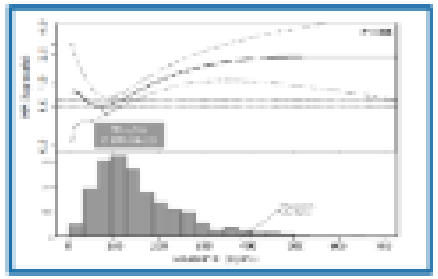
Serum levels of calcium, phosphate and iPTH with repeated measures every 6 months

Results: lowest mortality risk ranges

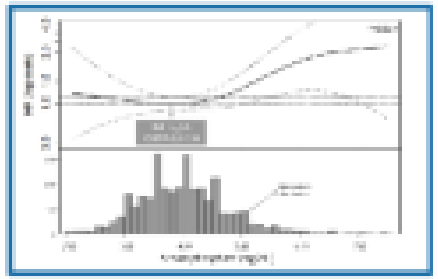
Calcium
≤ 10.5 mg/dL



Phosphate
2.8 to 5.0 mg/dL



iPTH
38 to 112 pg/mL



Conclusion. There was a non-linear association of serum calcium, phosphate and iPTH levels with mortality in stage 4 and 5 ND-CKD patien as previously reported for dialysis patients.

Journal of Nephrology

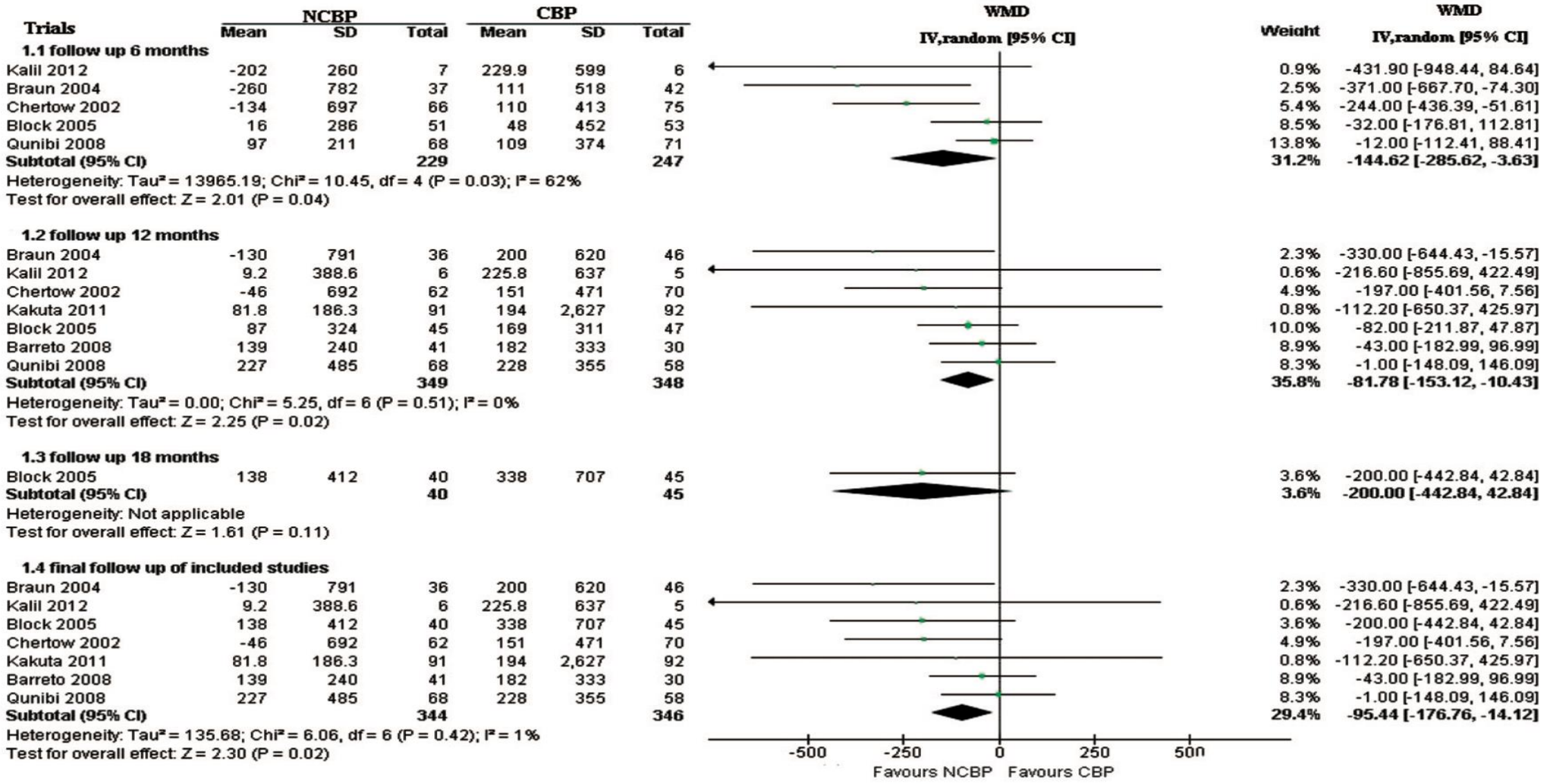
Molina *et al*, 2021

The effects of non-calcium-based phosphate binders versus calcium-based phosphate binders on cardiovascular calcification and bone remodeling among dialysis patients: a meta-analysis of randomized trials

Ling Liu, Yongjun Wang, Hongyu Chen, Xiaoling Zhu, Liusha Zhou & Yazhen Yang

Eighteen eligible randomized controlled trials totaling 3676 patients

- serum calcium levels significant lower in NCPB group than in CPB groups
- serum iPTH levels were significantly higher in NCPB groups



- NCBP could significantly attenuate progression of coronary artery calcification than CBP

Will early phosphate binder use confer any vascular protection in predialysis patients?

A Randomized Trial on the Effect of Phosphate Reduction on Vascular End Points in CKD (IMPROVE-CKD)

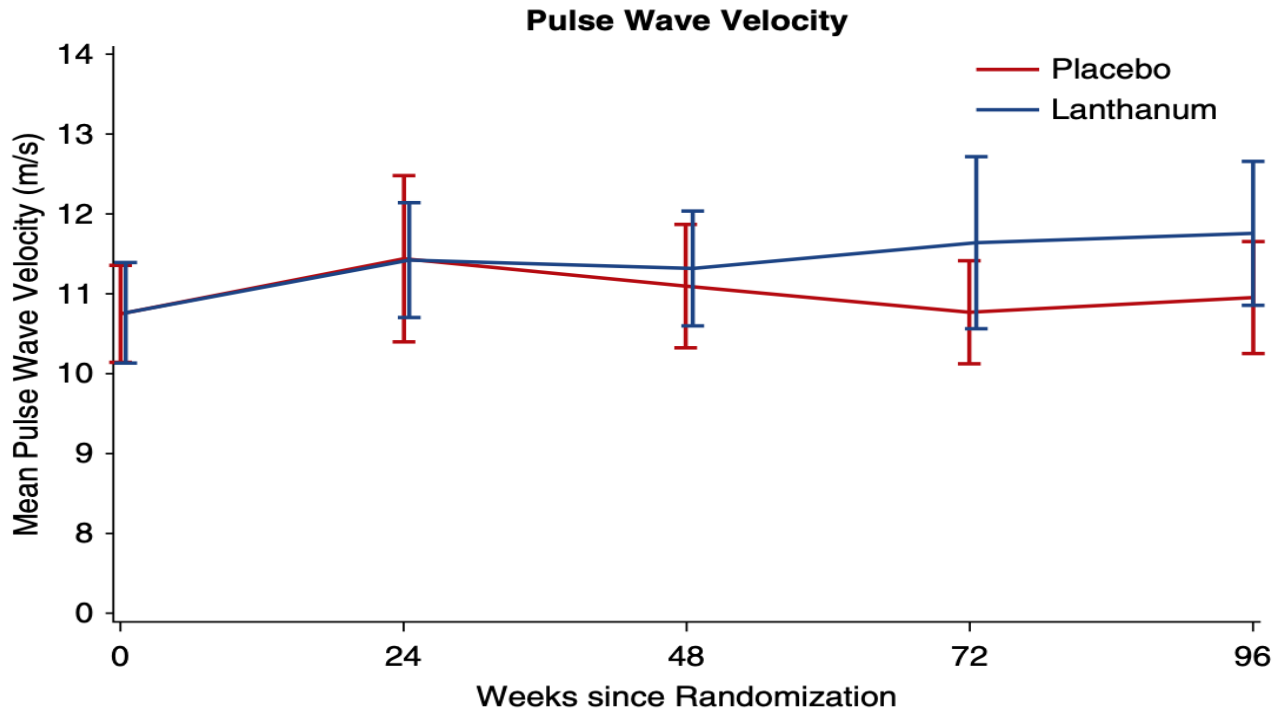
138 participants received lanthanum and 140 received placebo (mean age 63y Mean eGFR : 26.6 ml/min per 1.73 m2

Mean serum phosphate :3.87 mg/dl

At 96 weeks, pulse wave velocity and abdominal aortic calcification: no difference

phosphate,PTH, FGF23, and 24-hour urinary phosphate, Serious adverse events (46%) :No difference

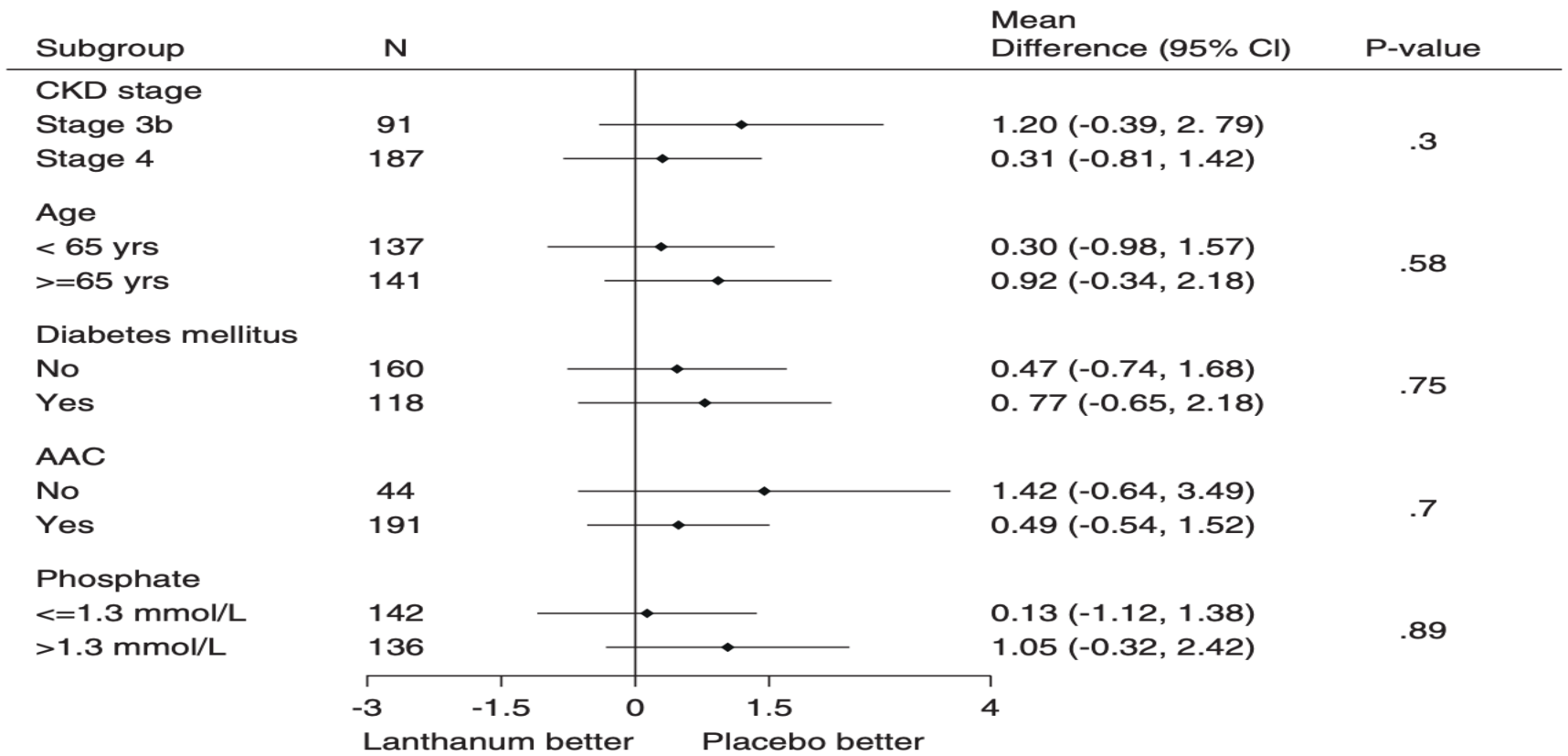
A Randomized Trial on the Effect of Phosphate Reduction on Vascular End Points in CKD (IMPROVE-CKD)



No.of Patients:					
Placebo	131	108	114	94	98
Lathanum	127	113	106	90	103

A Randomized Trial on the Effect of Phosphate Reduction on Vascular End Points in CKD (IMPROVE-CKD)

Abdominal aorta calcification



Article Type: Original Investigation

Safety and Efficacy of Tenapanor for Long-term Serum Phosphorus Control in Maintenance Dialysis: A 52-Week Randomized Phase 3 Trial (PHREEDOM)

DOI: 10.34067/KID.0002002021

- non-binder, sodium/hydrogen exchanger isoform 3 (NHE3) inhibitor
- 52-week , 564 HD patients
- Tenapanor 30 mg twice daily or sevelamer carbonate
- The most frequent Adverse event: Loosened stools (53%)
- Serious adverse events were reported more frequently for sevelamer carbonate (16–23% compared with tenapanor 11–17%)
- Conclusions: Tenapanor reduced serum phosphorus concentrations and maintained control of serum phosphorus with an acceptable safety and tolerability profile

Long-term effects of iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients

Article *in* Nephrology Dialysis Transplantation · February 2015

DOI: 10.1093/ndt/gfv006 · Source: PubMed

- Approved for the control of serum phosphate levels in patients with ESKD
- lower pill burden compared with sevelamer
- Well tolerated
- No evidence of Iron accumulation

Nicotinamide

- lower intestinal phosphate absorption by reducing NaPi2b expression

- Several studies in hemodialysis patients have suggested that nicotinamide treatment may lower serum phosphate levels, although patients in these studies experienced a high number of adverse event (including thrombocytopenia)

Effects of Nicotinamide and Lanthanum Carbonate on Serum Phosphate and Fibroblast Growth Factor-23 in CKD: The COMBINE Trial

JASN 30: 1096–1108, 2019.

RCT, 205 non dialysis CKD with GFR : 32ml/min per 1.73
serum phosphate was 3.7 mg/dl and median FGF23 was 99 pg/ml
Mean rates of change in phosphate , percent changes in FGF23 and adverse events rates were similar across arms . These agents appeared safe, intestinal symptoms limited adherence
Conclusions: LC and/or NAM treatment did not significantly lower serum phosphate or FGF23 in stage 3b/4 CKD

Magnesium

- Meta-analyses report serum magnesium is inversely associated with cardiovascular risk in both healthy and hemodialysis cohorts

- Mechanism:
- Prevents posttranscriptional changes in VSMC differentiation and apoptosis
- Up-regulates VC inhibitors (MGP and osteopontin)
- Counteracting expression of osteogenic transcription factors (BMP-2, RUNX2)

Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability

- RCT , 255 hemodialysis patients
- Comparison calcium acetate/magnesium carbonate with sevelamer hydrochloride (efficacy and tolerability)
- Efficacy and safety of magnesium carbonate in combination with calcium acetate was noninferior to sevelamer

Mg & Vascular calcification

Study	Study type	Population	Treatment	Duration	Primary outcome	Results
Mortazavi et al[152]	RCT	HD (n = 54)	440 mg Mg oxide thrice weekly versus placebo	6 mo	cIMT	Decrease in cIMT in Mg group (from 0.84 ± 0.13 mm to 0.76 ± 0.13 mm, *P* = .001)
Tzanakis et al[106]	RCT	HD (n = 72)	Mg carbonate + Ca acetate versus Ca acetate alone	12 mo	SVCS	Improvement in small proportion of Mg group (n = 4), no improvement in Ca group (n = 0). Remainder of population either stable or worsening VC (n = ns)
Turgot et al[153]	RCT	HD (n = 47)	Mg citrate (610 mg) alternate daily vs Ca acetate	2 mo	cIMT	Improvement in cIMT in Mg group (left cIMT *P* = .001, right cIMT *P* = .002)
Spiegel et al[154]	RCT	HD (n = 7)	Mg carbonate + Ca carbonate as phosphate binder	18 mo	CAC	No median percent change in CAC at completion (*P* = .07)
Molnar et al[109]	Cross-sectional	PD (n = 80)	N/A	N/A	Lateral lumbar X-rays	Higher serum Mg (>0.8 mmol/L) associated with lower AAC score (R^2 = .006, unstandardized coefficient [B] = −7.81, *P* = .003)
Ishimura et al[155]	Cross-sectional	Nondiabetic HD (n = 390)	N/A	N/A	Hand X-ray	Serum mg significantly lower in patients with VC than those without (*P* < .05)
Matias et al[156]	Prospective	Hemofiltration (n = 206)	N/A	48 mo	Plain X-ray	Significantly lower serum mg in patients with SVCS≥3 (*P* = .008)
Zaher et al[157]	Cross-sectional	Children on HD (n = 25)	N/A	N/A	cMIT	Higher cIMT in aorta and carotids in HD group than controls (*P* = .034 and *P* = .001 respec[illegible]ely)

RCT, randomized controlled trial; HD, hemodialysis; PD, peritoneal dialysis; cIMT, carotid intimal medial thickness; Ca, calcium; Mg, magnesium; CKD, chronic kidney disease; CAC, coronary artery calcification, SVCS, simple vascular calcification score; AE, adverse events

A Randomized Trial of Magnesium Oxide and Oral Carbon Adsorbent for Coronary Artery Calcification in Predialysis CKD

Am Soc Nephrol. 2019

- 2-year, open-label, RCT with oral magnesium oxide or oral carbon adsorbent AST-120
- CAC progression in stage 3–4 CKD (96 patients)

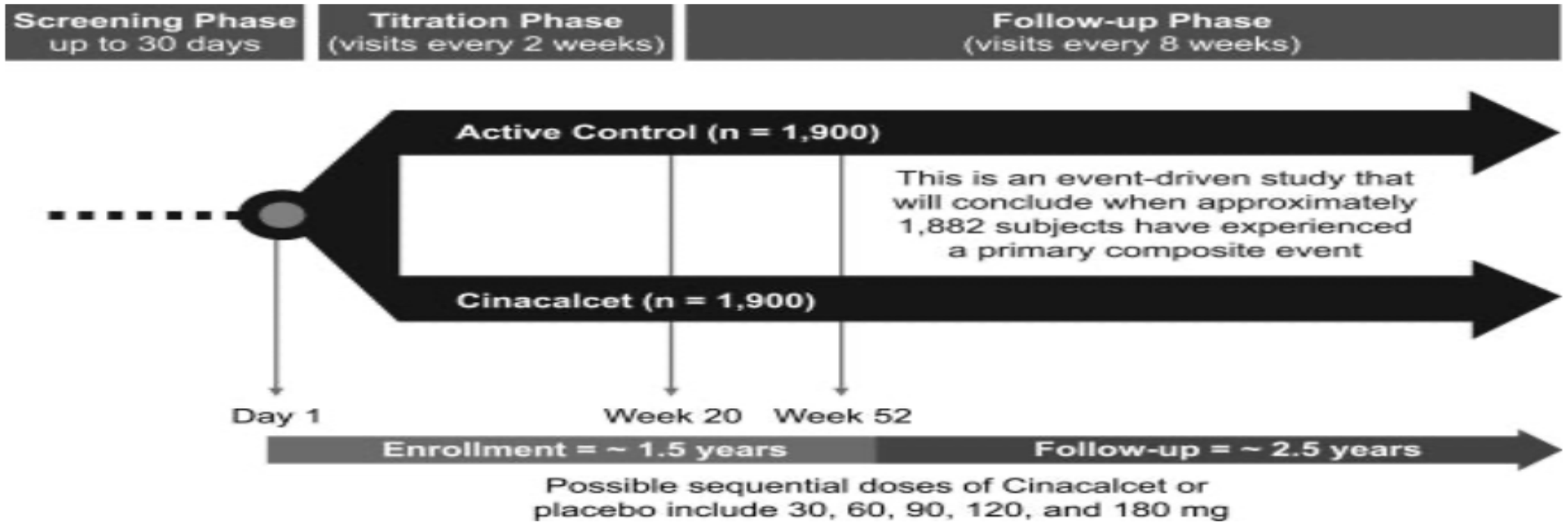
- Magnesium oxide : significantly smaller percentage change in CAC score compared with controls (11.3% versus 39.5%)
- AST-120 was not significant slowing of CAC

Calcimimetics

❑ADVANCE trial :

- 165 dialysis patients
- Effects of cinacalcet on progressive coronary artery, aortic, and valvular calcification
- Beneficial trend (approximately $P < 0.05$) for both arteries and cardiac valves

Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): Rationale and Design Overview



3883 participants, failed to show a difference in primary composite endpoint (death, myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event) in the cinacalcet compared to placebo group

post hoc analyses EVOLVE

reduced incidence of calcific uremic arteriolopathy (CUA)

reduced fracture rate

Decreased risk of death and cardiovascular events

RESEARCH ARTICLE

The shift from high to low turnover bone disease after parathyroidectomy is associated with the progression of vascular calcification in hemodialysis patients: A 12-month follow-up study

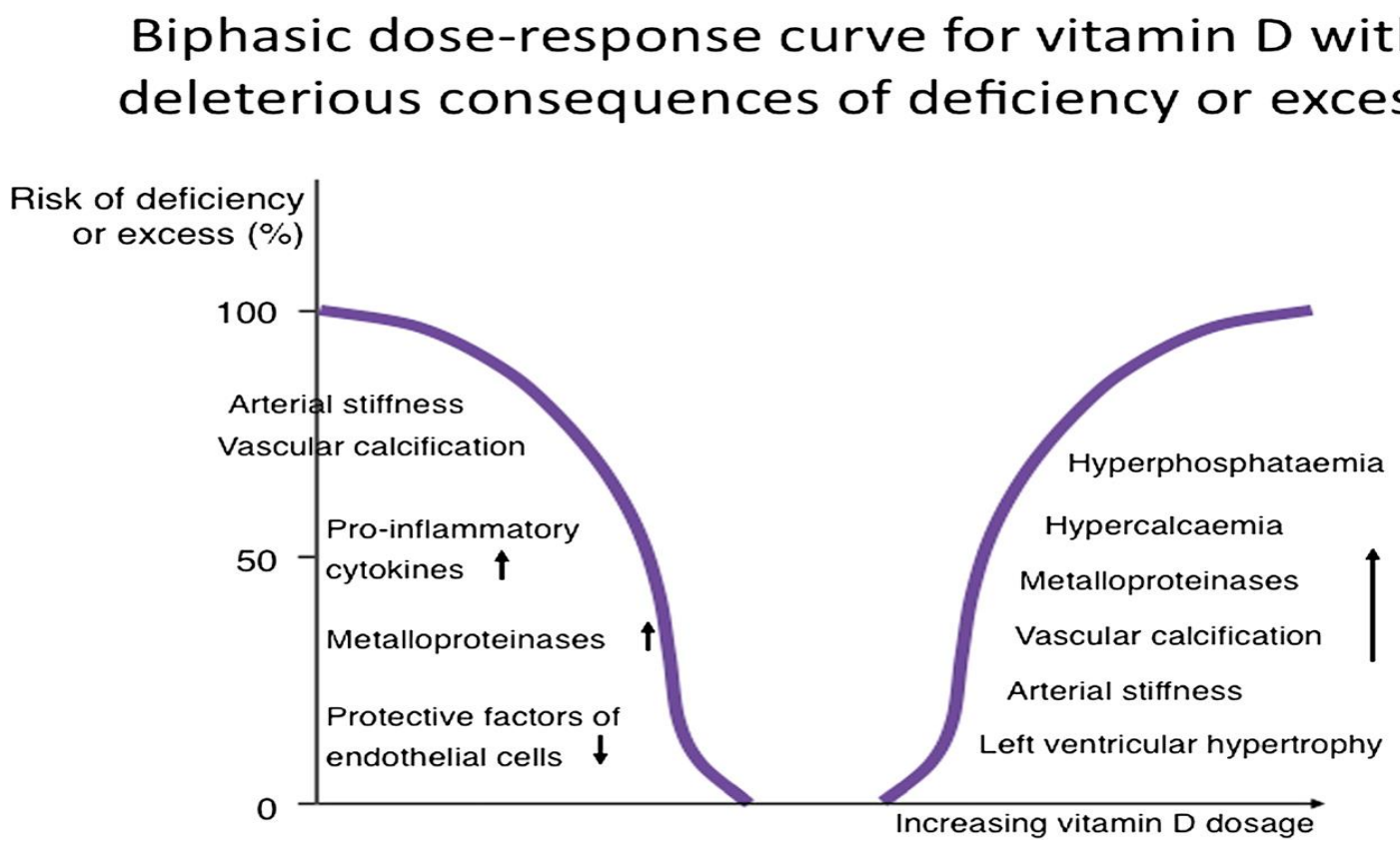
Prospective observational study ,12-month period

19 hemodialysis patients with severe SHPT

Result : Parathyroidectomy resulted increased CAC (P = .02) and a shift from high to low bone turnover disease on bone biopsy

vitamin D

Both low and high serum concentrations of vitamin D have been reported to be associated with VC in hemodialysis patients (U-shaped relationship)



Potential roles of vitamin D in preventing vascular calcification on endothelium and vascular smooth muscle.

- **Inhibition of foam cell and cholesterol efflux in macrophage**
  1. Activation of cholesterol 7-α-hydroxylase
  2. Decrease of oxidative LDL uptake by foamy cells

- **Enhancing vascular regeneration (RAAS system inactivation)**
- **Treatment on renal osteodystrophy**
  1. On high-turnover osteodystrophy: inhibition of parathyroid hormone
  2. On low-turnover osteodystrophy: restoring osteoblast activity
- **Restoring calcification inhibitors**
  1. Increase of fetuin-A concentration
  2. Restoring local klotho expression

Double-blind RCTs (PRIMO and OPERA studies) in nondialysis CKD stages 3–5

- With active vitamin D (paricalcitol)
- Failed to improvement in cardiac outcome
- An increased risk of hypercalcemia

Randomized Controlled Trial for the Effect of Vitamin D Supplementation on Vascular Stiffness in CKD

Clin J Am Soc Nephrol 12: 1447–1460, 2017. d

- 119 patients , eGFR of 15–45 ml/min per 1.73 m2

- Change in PWV after 6 months of treatment with a fixed dose of oral calcifediol (5000 IU), calcitriol (0.5 mg), or placebo, thrice weekly

- PWV decreased in the calcifediol group, remained unchanged in the calcitriol group, and increased in the placebo group

A Randomized Trial of Vitamin D Supplementation on Vascular Function in CKD

120 patients ,18–70 years, nondiabetic CKD stage 3–4 and vitamin D deficiency (25OH-D <20 ng/ml)
oral doses of cholecalciferol (300,000 IU) or placebo at baseline and 8week

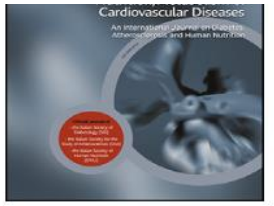
Significant favorable changes in PWV and circulating IL-6 levels
Vitamin D supplementation may improve vascular function

KDIGO CKD-MBD guidelines

nutritional vitamin D for treatment of 25(OH)D deficiency but not routine use of calcitriol or vitamin D receptor analogs in predialysis patients, given the risk of hypercalcemia and likely associated procalcific effects

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd



The impact of cholecalciferol on markers of vascular calcification in hemodialysis patients: A randomized placebo controlled study

Mona Alshahawey [a,*], Radwa El borolossy [a], Lamia El Wakeel [a], Tamer Elsaid [b], Nagwa Ali Sabri [a]

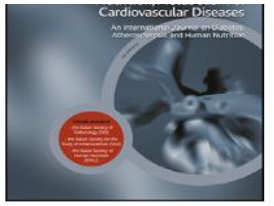
- Prospective, randomized, placebo-controlled study,60 HD
- Treatment group (Oral 200.000IU Cholecalciferol /month) or a placebo group, for 3 months
- Assesment of 25(OH)D, fetuin-A, FGF-23, osteoprotegerin (OPG), ca, p and iPTH levels, at baseline and at the end of study

Parameter	Drug group n = 30	Placebo group n = 30	P-value	
25(OH)D[a] ng/ml	Median (IQR)	Median (IQR)		
Before	17.9 (16.48–20)	18.7 (17.3–20.4)	0.312[b]	
After	32 (29.98–34.15)	18.7 (17.35–19.83)	**Treatment:**	**< 0.001**[**c]**
P-value	**< 0.001**[**a]**	0.66[a]	**Time:**	**< 0.001**[**c]**
			Treatment*Time:	**< 0.001**[**c]**
Fetuin-A (g/L)	Median (IQR)	Median (IQR)		
Before	0.168 (0.123–0.202)	0.168 (0.127–0.210)	0.796[b]	
After	0.199 (0.17–0.279)	0.165 (0.129–0.204)	**Treatment:**	**< 0.001**[**c]**
P-value	**< 0.001**[**a]**	0.819[a]	**Time:**	**< 0.001**[**c]**
			Treatment*Time:	**< 0.001**[**c]**
FGF-23[b] (pg/mL)	Mean ± SD	Mean ± SD		
Before	118.47 ± 10.23	118.49 ± 10.73	0.993[b]	
After	118.94 ± 11.14	118.86 ± 10.63	**Treatment:**	0.953[c]
P-value	0.521[a]	0.547[a]	**Time:**	0.405[c]
			Treatment*Time:	0.903[c]
OPG[c] (pmol/L)	Median (IQR)	Median (IQR)		
Before	19.88 (18.34–24.52)	19.99 (17.99–23.53)	0.941[b]	
After	19.9 (18–23.95)	19.88 (17.89–24.52)	**Treatment:**	0.902[c]
P-value	0.39[a]	0.44[a]	**Time:**	0.925[c]
			Treatment*Time:	0.147[c]

- Cholecalciferol significantly increased serum levels of 25(OH)D and fetuin-A in the treatment group while no significant difference was observed in the placebo group
- No adverse effects

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd



The impact of cholecalciferol on markers of vascular calcification in hemodialysis patients: A randomized placebo controlled study

Mona Alshahawey [a,*], Radwa El borolossy [a], Lamia El Wakeel [a], Tamer Elsaid [b], Nagwa Ali Sabri [a]

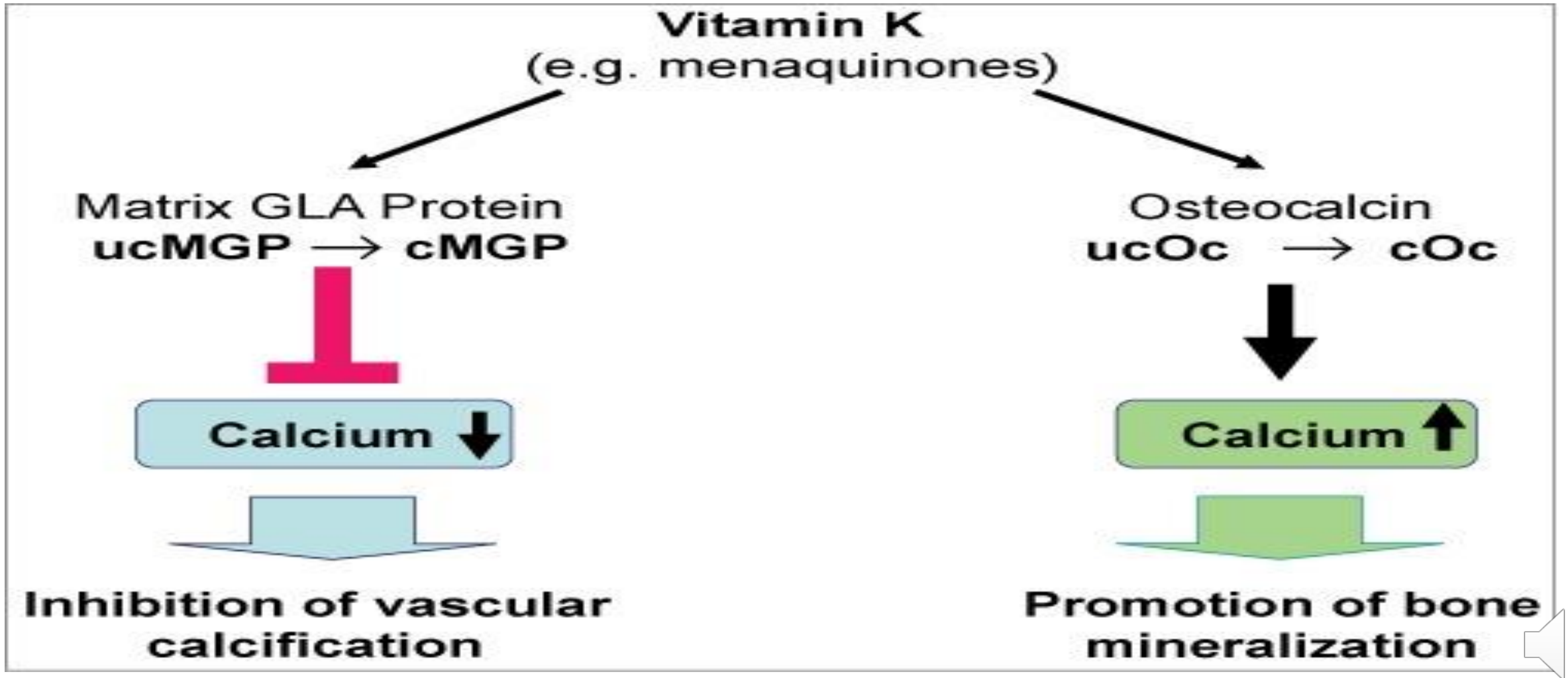
- Conclusion: Cholecalciferol was shown to be an effective, tolerable, inexpensive option to overcome vitamin D deficiency, with a possible modulating effect on fetuin-A, among hemodialysis patients

Nutritional vitamin D and active vitamin D treatment on vascular health

- Uncertain (inconsistent evidence)

- RCTs shows improvement in surrogate markers of vascular stiffness (pulse wave velocity [PWV]) with nutritional vitamin D supplementation but not active vitamin D

Effect of vitamin K on bone and vascular health



Vitamin K supplementation to improve vascular stiffness in chronic kidney disease – the K4Kidneys randomised controlled trial

Methods

Two centres (Scotland)

N=159 CKD 3b/4

12 months

1:1

- Vitamin K2 (MK7) 400micrograms
- Placebo

Vitamin K: n=80
67 (11) years
40% female

Placebo: n=79
67 (11) years
38% female

Outcomes

Vascular stiffness
(carotid-femoral Pulse Wave Velocity)

Treatment effect*
-0.12 (-0.93 to 0.69); p=0.77

**adjusted for age, sex and the baseline value*

Adherence
Vitamin K 91%
Placebo 91%

Adverse events
Vitamin K 72%
Placebo 72%

Conclusion: Vitamin K2 supplementation did not improve vascular stiffness or other measures of vascular health in this trial.

10.1681/ASN.2020020225

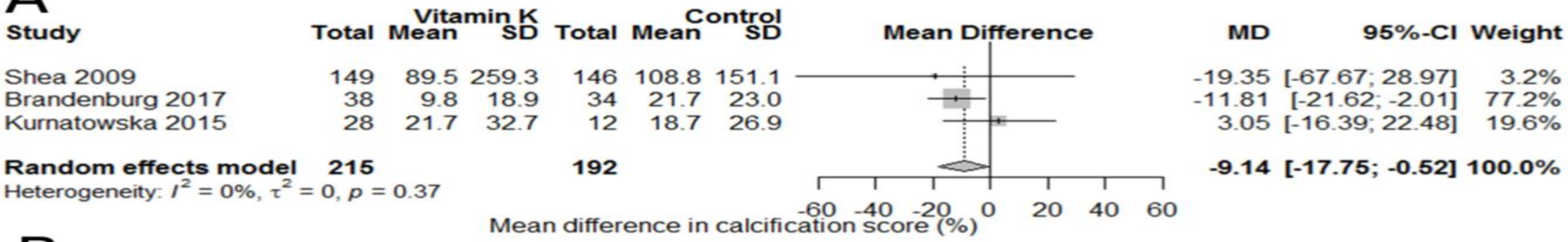
JASN

ORIGINAL RESEARCH ARTICLE

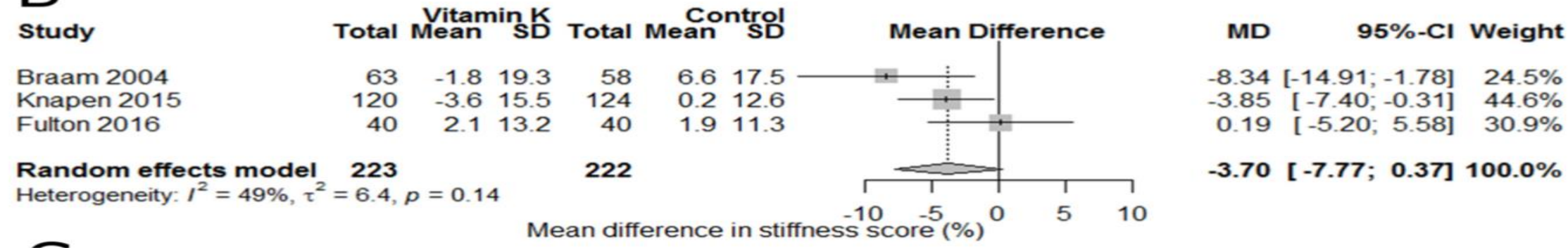
Vitamin K status, supplementation and vascular disease: a systematic review and meta-analysis

Jennifer Susan Lees,[1,2] Fiona A Chapman,[2] Miles D Witham,[3] Alan G Jardine,[1,2] Patrick B Mark[1,2]

A



B



No effect of vitamin K2 supplementation on vascular stiffness or vascular calcification measures

intervention trials evaluating effects of vitamin K supplementation in patients with advanced CKD

Patients/trial	Intervention	Duration of follow-up, mo	Relative reduction in ucMGP plasma levels at study end	Effect on calcification in vitamin K group	Effect on other outcomes in vitamin K group
Hemodialysis patients with atrial fibrillation (VALKYRIE)[126]	MK7, 2 mg, thrice weekly	18	47%	None	None on pulse-wave velocity, all-cause death, stroke, and cardiovascular event rates
CKD stage 3b–4 patients (K4Kidneys)[156]	MK7, 0.4 mg, daily	12	Uncertain[a]	None	None on pulse-wave velocity, augmentation index, blood pressure, B-type natriuretic peptide, or physical function
CKD stage 3–5 ND patients[157]	MK7, 0.09 mg, daily	9	19%	None	Reduced progression of common carotid artery intima-media thickness
Hemodialysis patients[158]	MK7, 0.2 mg, daily	12	47%	None	—
Hemodialysis patients[159]	MK7, 0.36 mg, daily	24	39% after 1 yr, 8% after 2 yr	None	None on pulse-wave velocity and blood pressure

Ongoing trials with vitamin K1

- K1, 5 mg, thrice weekly . 18 m, To be determined Hemodialysis patients (iPACK-HD)

- K1, 10 mg, thrice weekly , 12 m, To be determined Hemodialysis patients (VitaVasK)
- Treatment to reduce vascular calcification in hemodialysis patients using vitamin K (Trevasc-HDK) A study protocol for a randomized controlled tria

Takaori *et al. BMC Nephrology* (2021) 22:7
https://doi.org/10.1186/s12882-020-02198-6

BMC Nephrology

RESEARCH ARTICLE Open Access

User of angiotensin-converting-enzyme inhibitor and/or angiotensin II receptor blocker might be associated with vascular calcification in predialysis chronic kidney disease patients: a retrospective single-center observational study

ACEI/ARB and vascular calcification

121 predialysis CKD patients (age 71 ± 12 y)
Calculatation vascular calcification volume (Calc) ;three-dimensional imaging software and standardized by body surface area (BSA)
ACEI/ARB use is significantly and positively associated with log [Calc/BSA]

Takaori *et al. BMC Nephrology* (2021) 22:7
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BMC Nephrology

RESEARCH ARTICLE Open Access

User of angiotensin-converting-enzyme inhibitor and/or angiotensin II receptor blocker might be associated with vascular calcification in predialysis chronic kidney disease patients: a retrospective single-center observational study

ACEI/ARB and vascular calcification

- Conclusions: ACEI/ARB user was associated with vascular calcification in predialysis patients with low eGFR

Circulation

ORIGINAL RESEARCH ARTICLE

Slowing Progression of Cardiovascular Calcification With SNF472 in Patients on Hemodialysis

Results of a Randomized Phase 2b Study

(CaLIPSO)

•SNF472, a selective inhibitor of hydroxyapatite formation and growth

CaLIPSO : multinational, randomized, placebo-controlled, double-blind phase 2b trial ,6 months

HD with coronary artery calcium (CAC) Agatston score between 100 -3500 units , as measured on a non-contrast multidetector computed tomography (CT) scanner

Circulation

ORIGINAL RESEARCH ARTICLE

Slowing Progression of Cardiovascular Calcification With SNF472 in Patients on Hemodialysis

Results of a Randomized Phase 2b Study

- 1:1:1 ratio SNF472 300 mg, SNF472 600 mg, or placebo 3 times weekly

- SNF472 significantly attenuated the progression of coronary artery and aortic valve calcification in patients with ESKD receiving hemodialysis
- Prevents the initial development of CAC : ??

RCT Dialysis

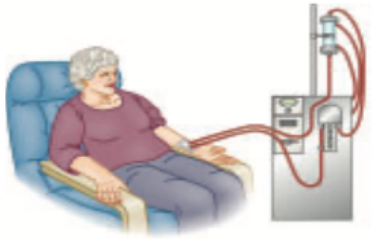
Sodium thiosulfate and calcification

In haemodialysis patients, over 6 months, sodium thiosulfate (NaTS) reduces progression of calcification in iliac arteries and heart valves but not abdominal aorta

HD

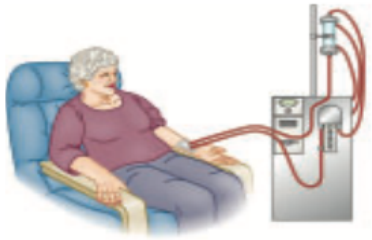
6 months

N = 26
56.7% ♂
63.8 years



NaTS →

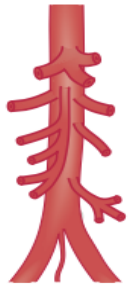
N = 29
70.0% ♂
64.1 years



Placebo →

Primary outcome

+264



+372

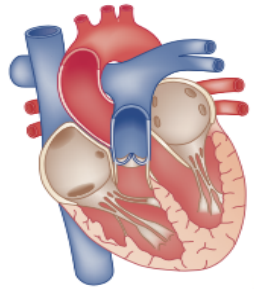
p = 0.592

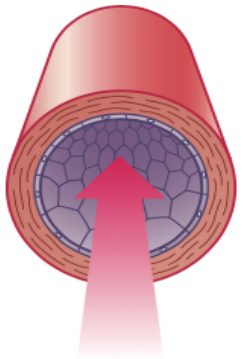
Secondary outcomes

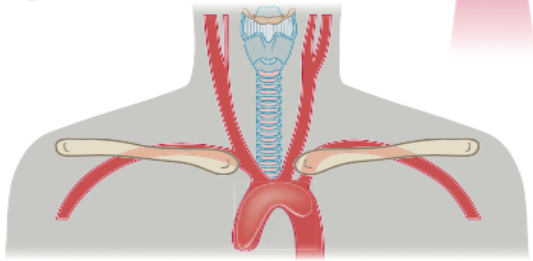
–137

+245

p = 0.049







ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Djuric P., Dimkovic N., Schlieper G., et al. NDT (2019)
@NDTSocial

Conclusions: NaTS failed to retard abdominal aortic calcification progress, it positively affected calcification progress in iliac arteries and heart valves as well as several other cardiovascular functional parameters

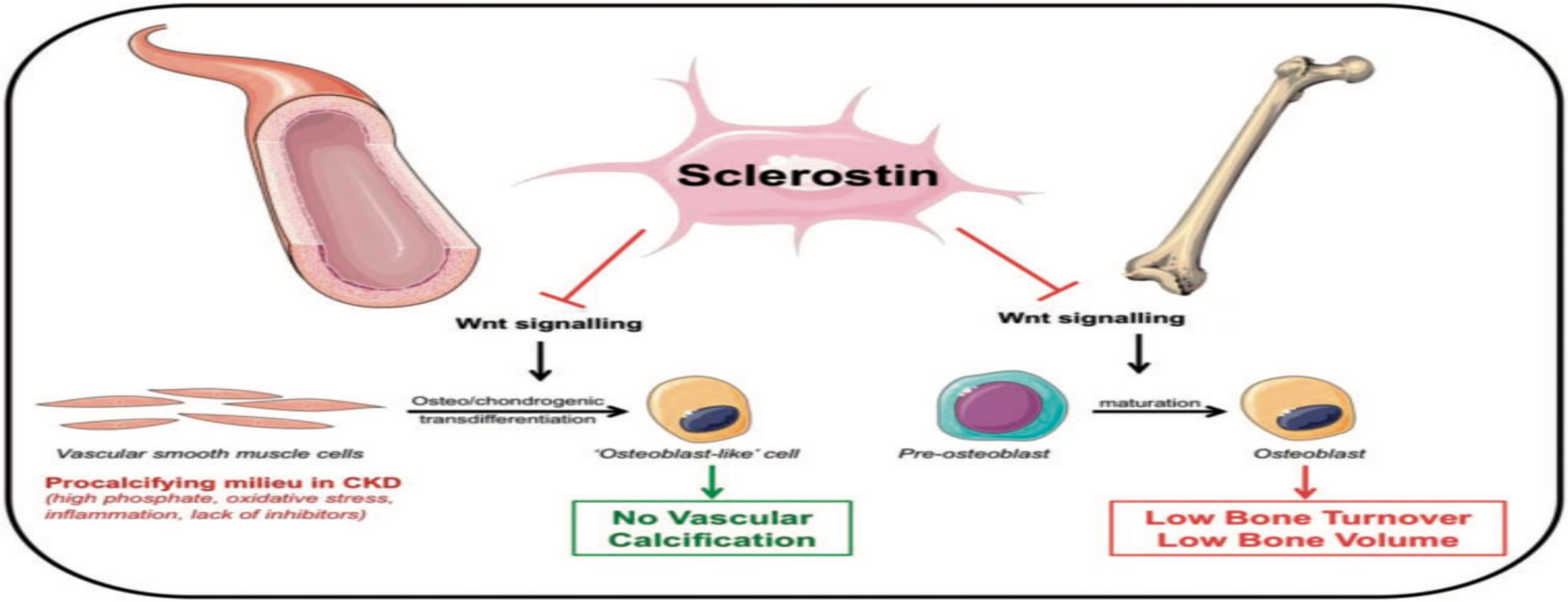
Role of Bisphosphonates in vascular calcification:

- ❑Synthetic analogues of pyrophosphate and inhibit osteoclast-mediated resorption as well as calcium-phosphate crystal deposition in bone
- ❑USAGE:
- Treatment of osteoporosis
- Inhibiting arterial calcification and macrophage suppression in atheromatous lesions

Role of Bisphosphonates in vascular calcification:

- General population(largest study 474 elderly osteoporotic women) : No effect on aortic calcification
- Patients with type 2 diabetes and osteopenia :Reduction in carotid intima-media thickness
- RCT in the pre dialysis CKD population: No difference in progression of aortic VC
- Use of low dose bisphosphonates on VC in hemodialysis patients Etidronate administration for 12 months reduced or inhibited CAC progression, but was associated with an increased risk of osteomalacia

Sclerostin and VC



Nephrol Dial Transplant (2019) 34: 408–

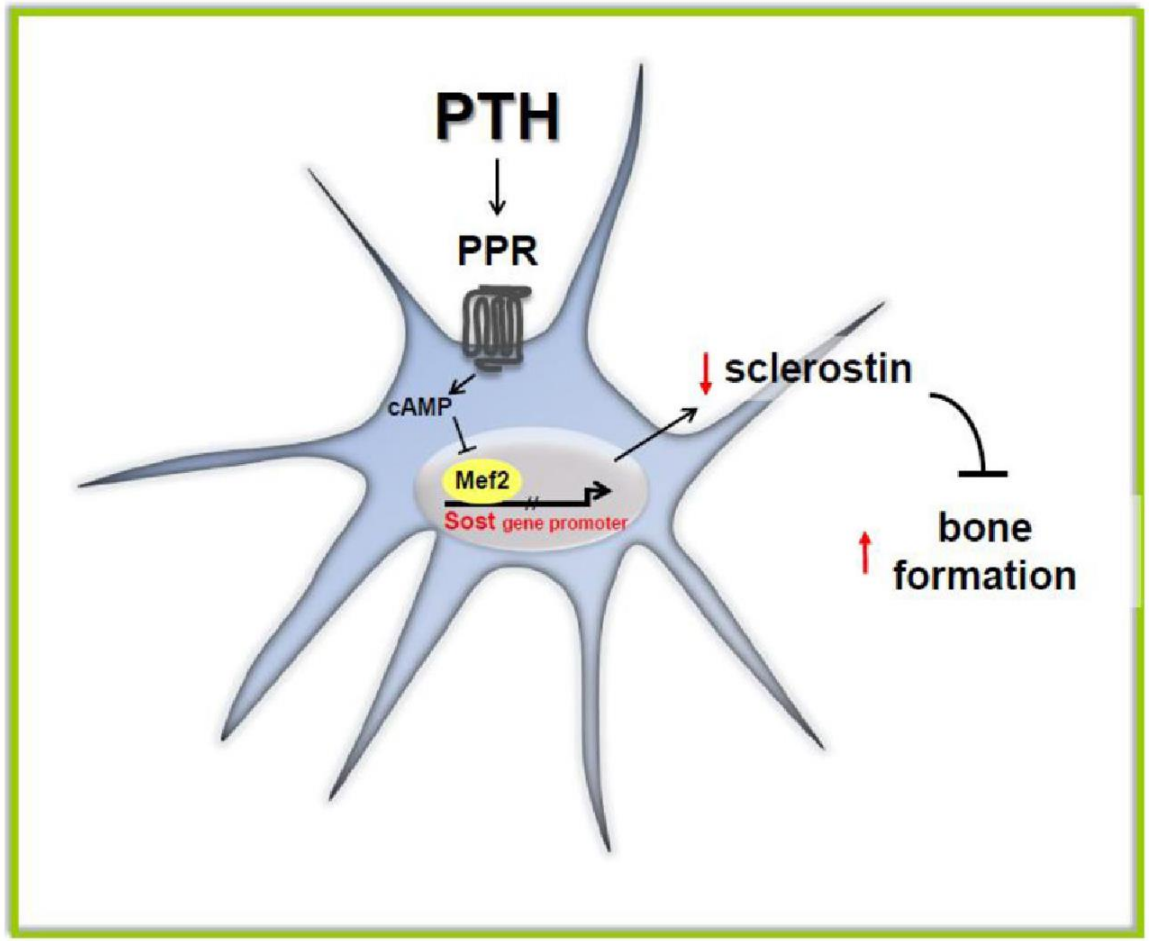
High Serum Sclerostin Levels Are Associated with a Better Outcome in Hemodialysis Patients

207 HD patients
Correlation serum sclerostin with aortic calcification score, BMD scores and survival rate

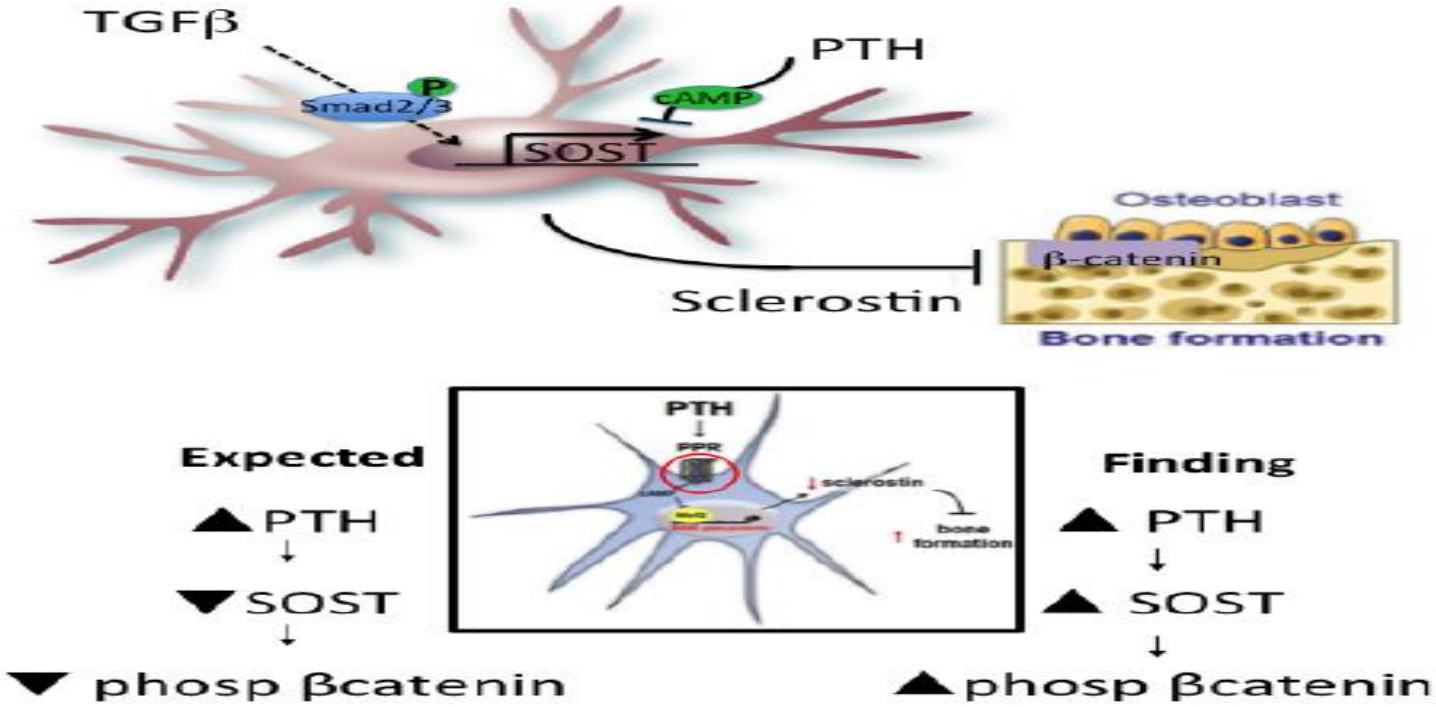
Conclusion: Our study of HD patients shows that higher serum sclerostin levels are associated with higher BMD, lower aortic calcification scores, and a better survival rate

https://doi.org/10.1159/000443845

PTH and sclerostin



PTH and sclerostin in CKD



Elevations in PTH usually are associated with sclerostin inhibition and decreased phosphorylation of b-catenin. However, in CKD, sclerostin and iphosphorylated b-catenin increased, despite high PTH levels

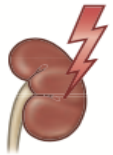
Clinical Kidney Journal

Sclerostin and DKK1 circulating levels associate with low bone turnover in patients with chronic kidney disease stages 3 and 4

Renal osteodystrophy (ROD) is evaluated by bone biopsy, which is an invasive procedure.
New bone biomarkers could be used to discriminate between turnover categories in pre-dialysis patients.

Methods

Cross-sectional study
n=56



CKD stage 3 and 4

Circulating levels:
sclerostin, DKK1, sRANKL, osteoprotegerin

+

Bone biopsy
Histomorphometry

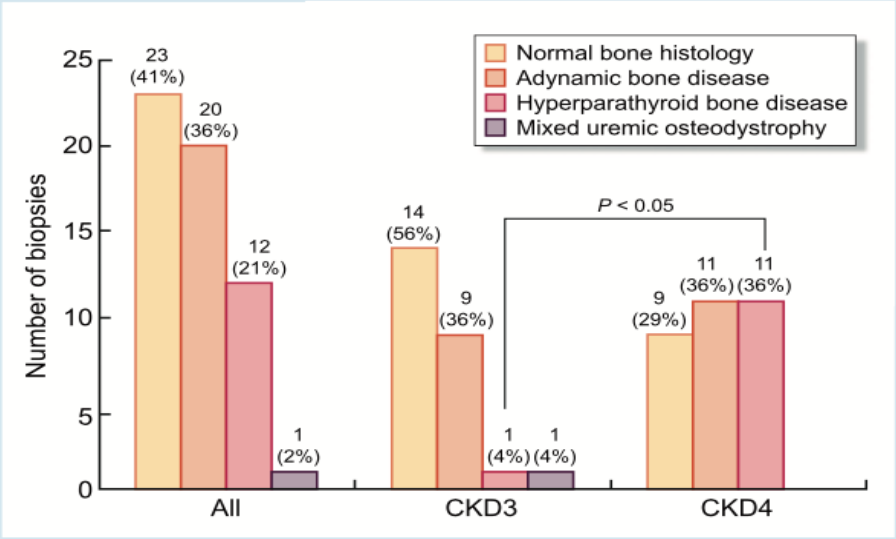
Results

Low-turnover bone disease

- Higher sclerostin levels
- Lower DKK1 levels

High-turnover bone disease

- No biomarker was found to be associated in multivariate analysis



Conclusion: Circulating levels of sclerostin and DKK1 are predictive of low-turnover bone disease in patients not yet on dialysis. Further research is needed to access the performance of these bone turnover biomarkers in diagnosis and treatment monitoring of ROD.

Neto R., et al
Clinical Kidney Journal (2021)
@CKJSocial

Sclerostin and vascular calcifications in CKD/ESRD patients

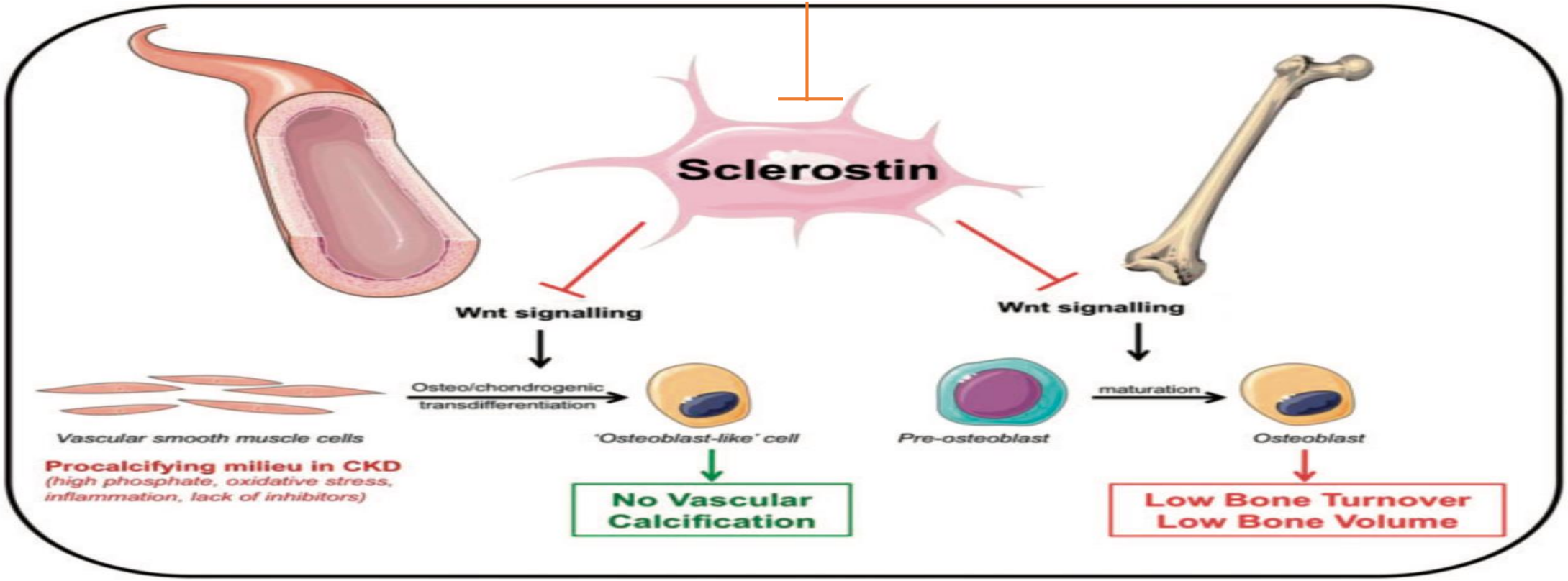
- Studies on correlation between sclerostin and vascular calcifications development

Authors and reference	Patients (n) Renal status	Type of calcifications detection and sclerostin assay	Association between sclerostin and VC
Claes et al. [70]	• 154 • CKD 1 – 5	• AAC by lateral X-ray • TECOmedical	• Univariate analysis: positive association • Multivariate analysis: negative association after adjustment for age, diabetes, CV history, hypertension, BMI, eGFR, CRP
Morena et al. [69]	• 241 • CKD 2 – 5	• CAC by CT scan • TECOmedical	• Univariate analysis: positive association • Multivariate analysis: positive association after adjustment for age, gender, diabetes, BMI and smoking
Lv et al. [75]	• 97 • CKD 3 – 4	• AAC by CT scan • Biomedica	• Univariate analysis: positive association • Multivariable analysis: positive association after adjustment for age and eGFR
Brandenburg et al. [54]	• 67 • HD patients	• CAC by CT scan • TECOmedical	• Univariate or multivariate analysis: no association • But high sclerostin level associated with aortic valvular calcification in univariate and multivariate model
Delanaye et al. [71]	• 164 • HD patients	• AAC by CT scan • TECOmedical	• Univariate analysis: no association • Multivariable analysis: negative association
Yang et al. [73]	• 125 • HD patients	• Aortic calcification by X-ray • R&D Systems	• Univariate analysis: negative association
Jean et al. [63]	• 207 • HD patients	• AAC by lateral X-ray • TECOmedical	• Univariate analysis: negative association
Qureshi et al. [68]	• 89 • HD patients	• CAC by CT scan • R&D Systems	• Univariate analysis: positive association • Multivariable analysis: no association after adjustment for age, gender and diabetes • But in multivariate analysis for calcification detected in the tissue: positive association after adjustment for age, gender
Bruzzese et al. [76]	• 21 • HD patients	• CAC by CT scan • TECOmedical	• Univariate analysis: no association
Wang et al. [77]	• 161 • CKD 3 – 5D (HD and PD)	• AAC by lateral X-ray • CUSABIO	• Binary logistic regression analysis: positive association • But lower sclerostin level when AAC are moderate to severe

USE OF ROMOSOZUMAB FOR OSTEOPOROSIS IN HEMODIALYSIS PATIENTS

Rie Kiyosumi, Naofumi Ikeda **Published:** 06 June 2020

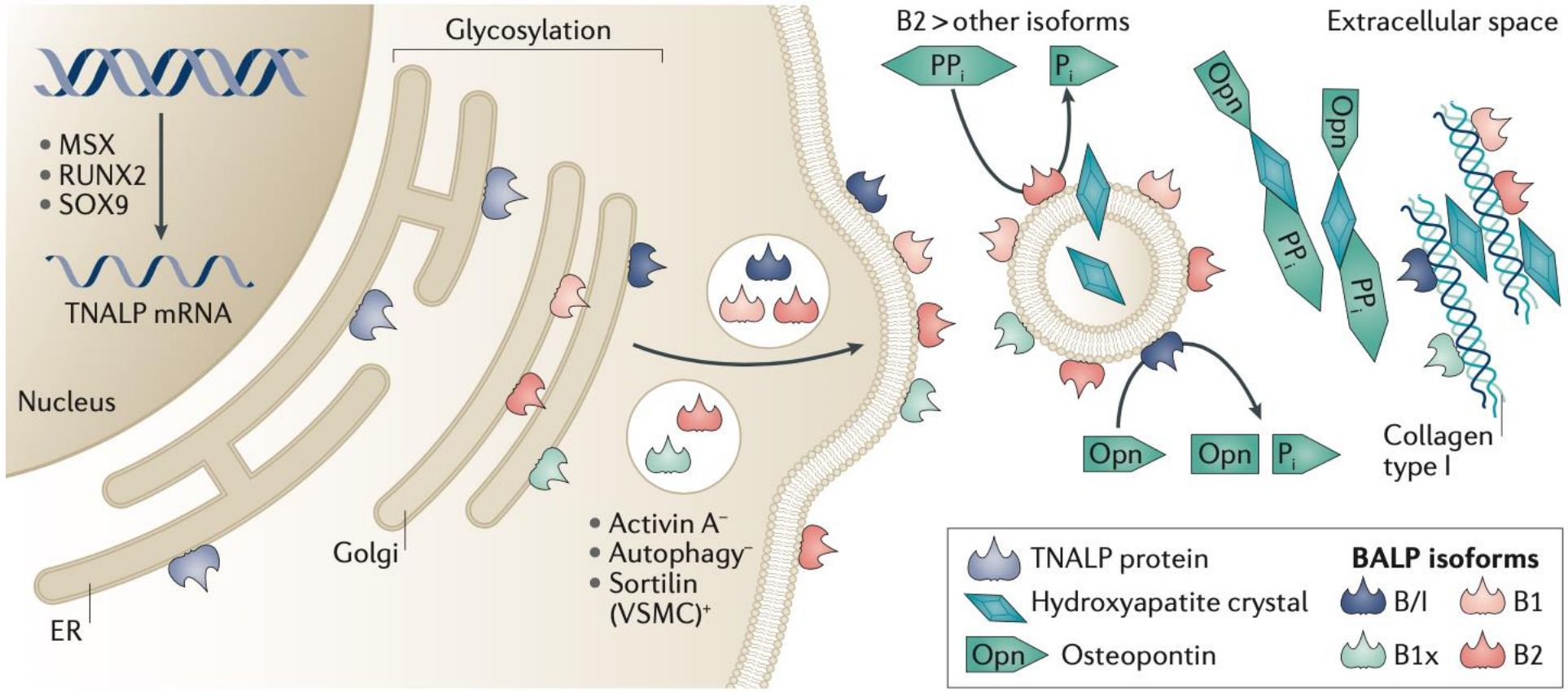
Romosozumab(sclerotin antibody)



Nephrol Dial Transplant (2019) 34: 408–

Romosozumab is a monoclonal antibody targeting sclerostin and was recently FDA approved for the treatment of osteoporosis

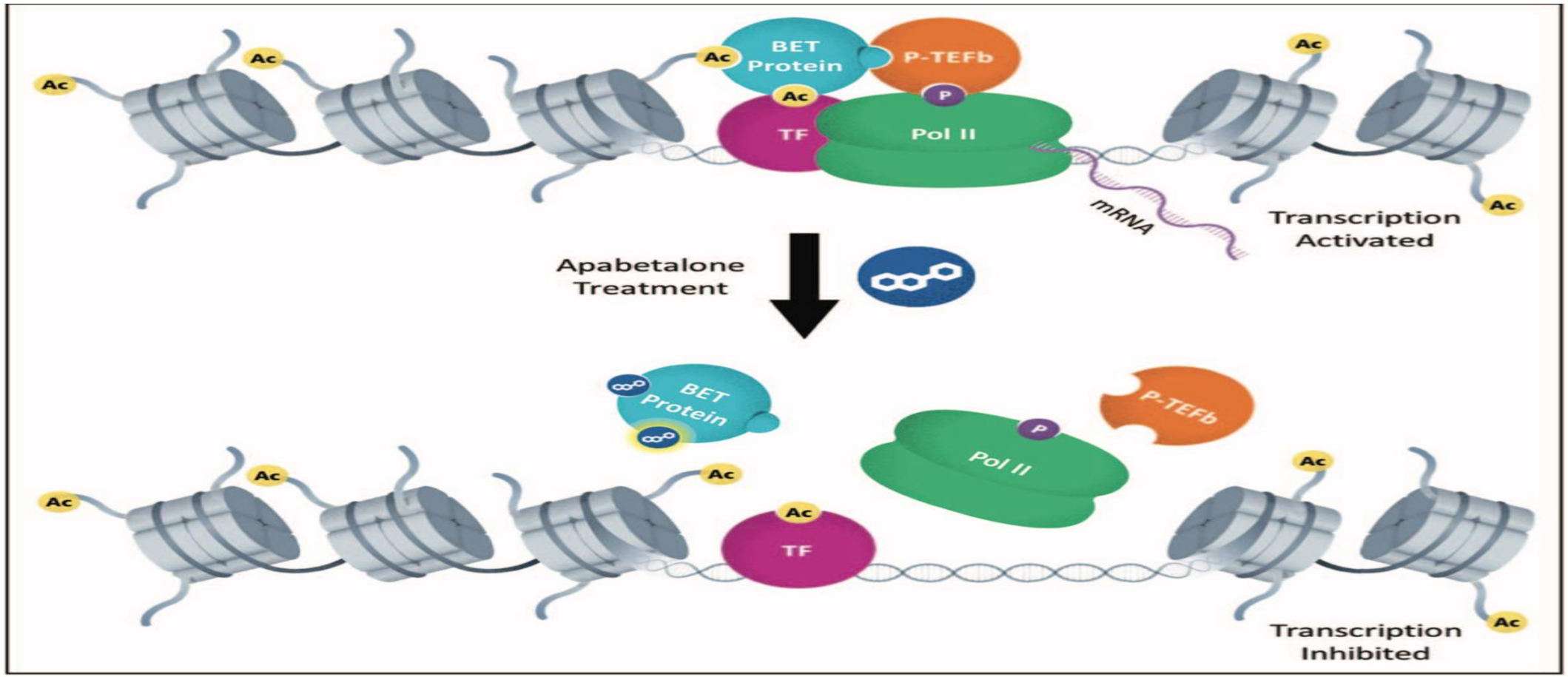
BALP and VC


Glycosylation
B2 > other isoforms
Extracellular space
• MSX
• RUNX2
• SOX9
TNALP mRNA
Nucleus
ER
Golgi
• Activin A⁻
• Autophagy⁻
• Sortilin
(VSMC)⁺
PPi
Pi
Opn
Opn
Opn
Pi
Collagen
type I
TNALP protein
Hydroxyapatite crystal
Opn Osteopontin
BALP isoforms
B/I
B1
B1x
B2

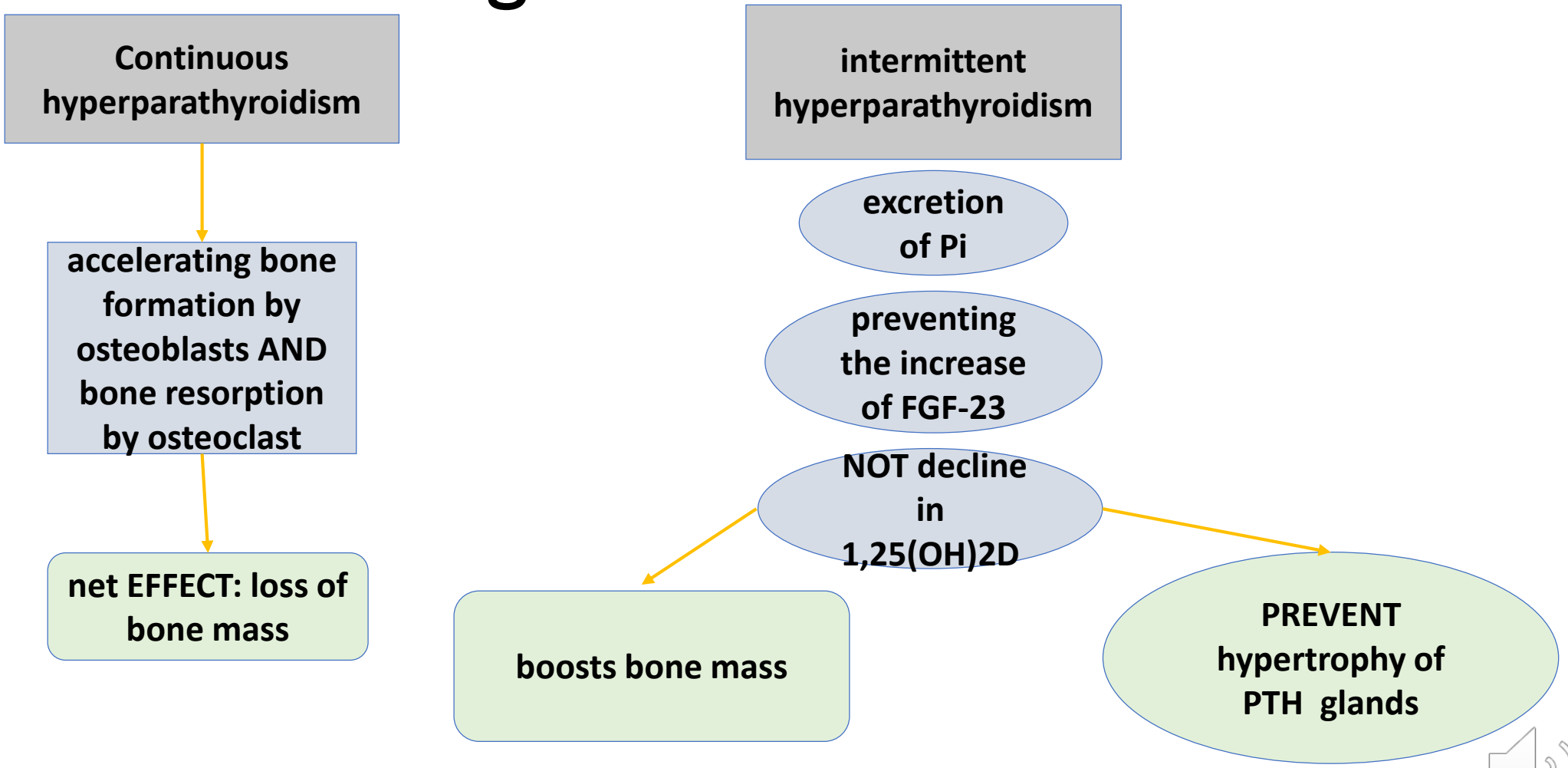
CURRENT OPINION

Pharmacologic epigenetic modulators of alkaline phosphatase in chronic kidney disease

Mathias Haarhaus[a,b,c], *Dean Gilham*[d], *Ewelina Kulikowski*[d], *Per Magnusson*[b], *and Kamyar Kalantar-Zadeh*[e,f,g]



Can we Use of Exogenous Parathyroid Hormone in Management of CKD-MBD



Continuous hyperparathyroidism causes net loss of bone mass, despite accelerating bon

Exogenous Parathyroid Hormone in VC

Intermittent PTH Administration could:

- Hand the **Control** of **Phosphate** levels back to PTH
- **Control** **FGF-23** levels
and **Eliminate** or **Reduce significantly** the risks
associated with increased circulating **FGF-23**
- **Achieve a better control** of **1,25(OH)$_2$D** levels
- **Reduce** the risk of **Atherosclerosis** and **Cardiovascular Disease**
- **Prevent** the elevation of **PTH**
- **Protect** the **Parathyroid Glands** from Hyperfunction
and **Prevent** Hyperplasia
- **Protect** the **Skeleton** from the Catabolic Effects caused
by the Continuously Elevated circulating **PTH**

https://doi.org/10.11005/jbm.2020.27.1.1

CONCLUSION:

- No evidence that antihypertensive therapy affects VC but may reduce myocardial fibrosis and LVH
- Phosphate-Binding Therapy in patients with CKD G3-G5 except to control symptomatic or severe hyperphosphatemia
- in CKD G5D, resulting in clinical complications such as bone disease, calciphylaxis, and itching,Use of binders to prevent clinically important hyperphosphatemia is justified
- NCBP could significantly attenuate progression of coronary artery calcification than CBP

- early phosphate binder use don’t any vascular protection in predialysis patients
- Magnesium oxide : significantly smaller percentage change in CAC score
- calcimimetic:Beneficial trend for both arteries and cardiac valves
- Parathyroidectomy may resulted increased CAC
- **Vitamin D supplementation may improve vascular function**
- No effect of vitamin K2 supplementation on vascular stiffness or vascular calcification measures
- ACEI/ARB user was associated with vascular calcification in predialysis patients with low eGFR
- SNF472 significantly attenuated the progression of coronary artery and aortic valve calcification in patients with ESKD