Why dialysis patients have such a high risk to develop vascular calcifications ?

Marc E. De Broe , Patrick Dhaese , Geert Behets

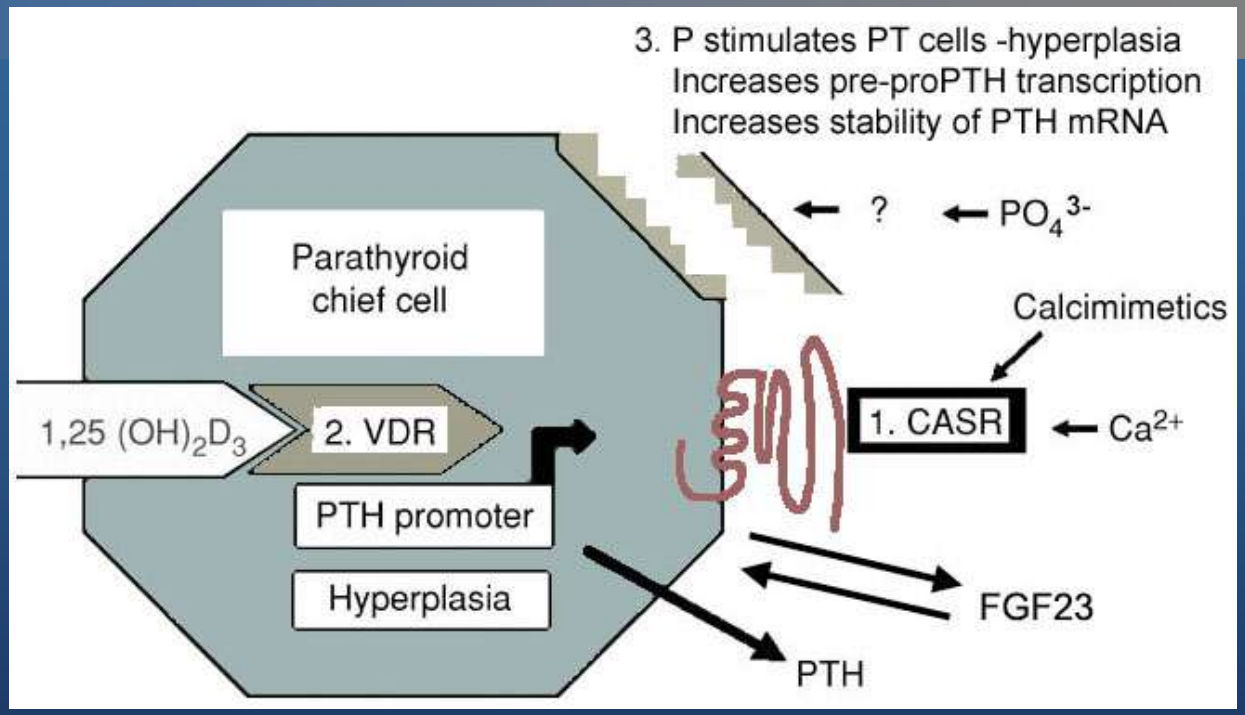
University of Antwerp, Belgium

Laboratory of Pathophysiology

Universiteit Antwerpen

Norwich november 2010

PTH secretion, PTH gene expression, parathyroid gland hyperplasia



1. CASR cell suface G protein – coupled receptor ;extrac. Ca^{++}
2. Vitamin D receptor nuclear receptor controlling gene transcription
3. Uncharacterized phosphate sensor
4. FGF23 is a negative regulator of parathyroid function

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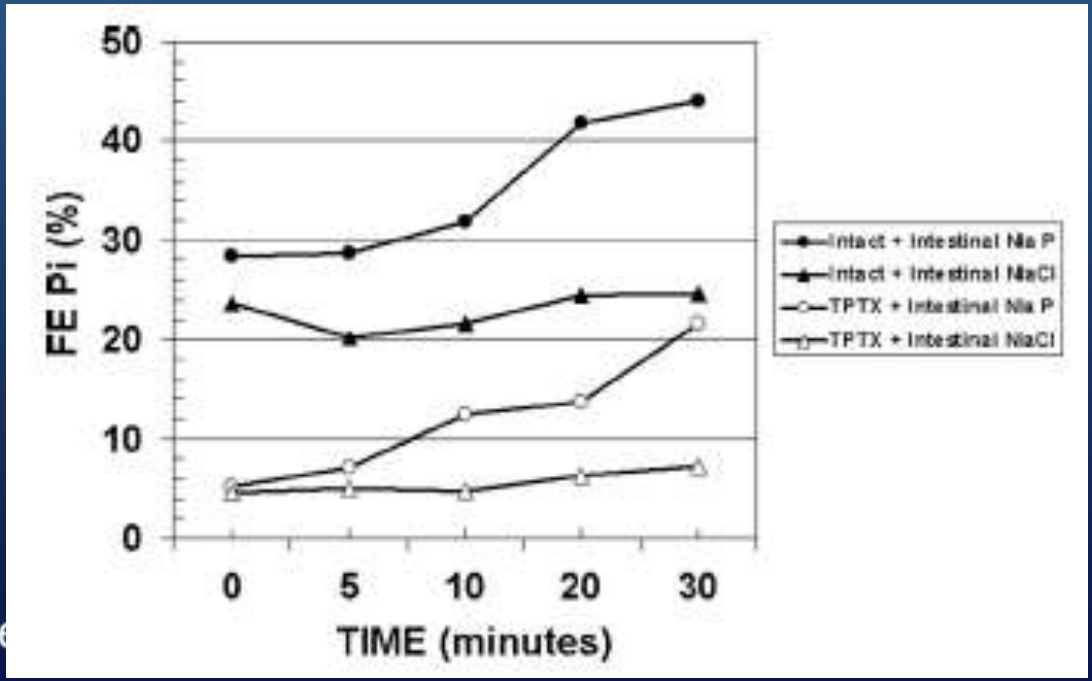
Quarles LD: Kidney Int 68 (S96): S24-S28, 2005

« Sensor » digestif du Phosphore

Evidence for a signaling axis by which intestinal phosphate rapidly modulates renal phosphate reabsorption

Theresa Berndt*, Leslie F. Thomas*, Theodore A. Craig*, Stacy Sommer*, Xujian Li†, Eric J. Bergstralh†, and Rajiv Kumar*‡§



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PNAS early online edition 2007

Importance of ionized calcium dependent signaling

Vitamin D dependent pathways play a 2ary role

	VDR –/– (Vit D deficiency)	1αOHase –/–
Calcemia	↓	↓
Phosphatemia	↓↓	↓↓
PTH	↑↑	↑↑
Osteomalacia	+	+
Gland hyperplasia	+	+
Calcitriol	↑↑	↓↓undetectable

Feeding 2% calcium normalizes everything; signaling through CaSR is sufficient to prevent SHPT and gland hyperplasia in tissues incapable to respond to Vit D

Calcitriol normalizes everything; Ca administration almost everything

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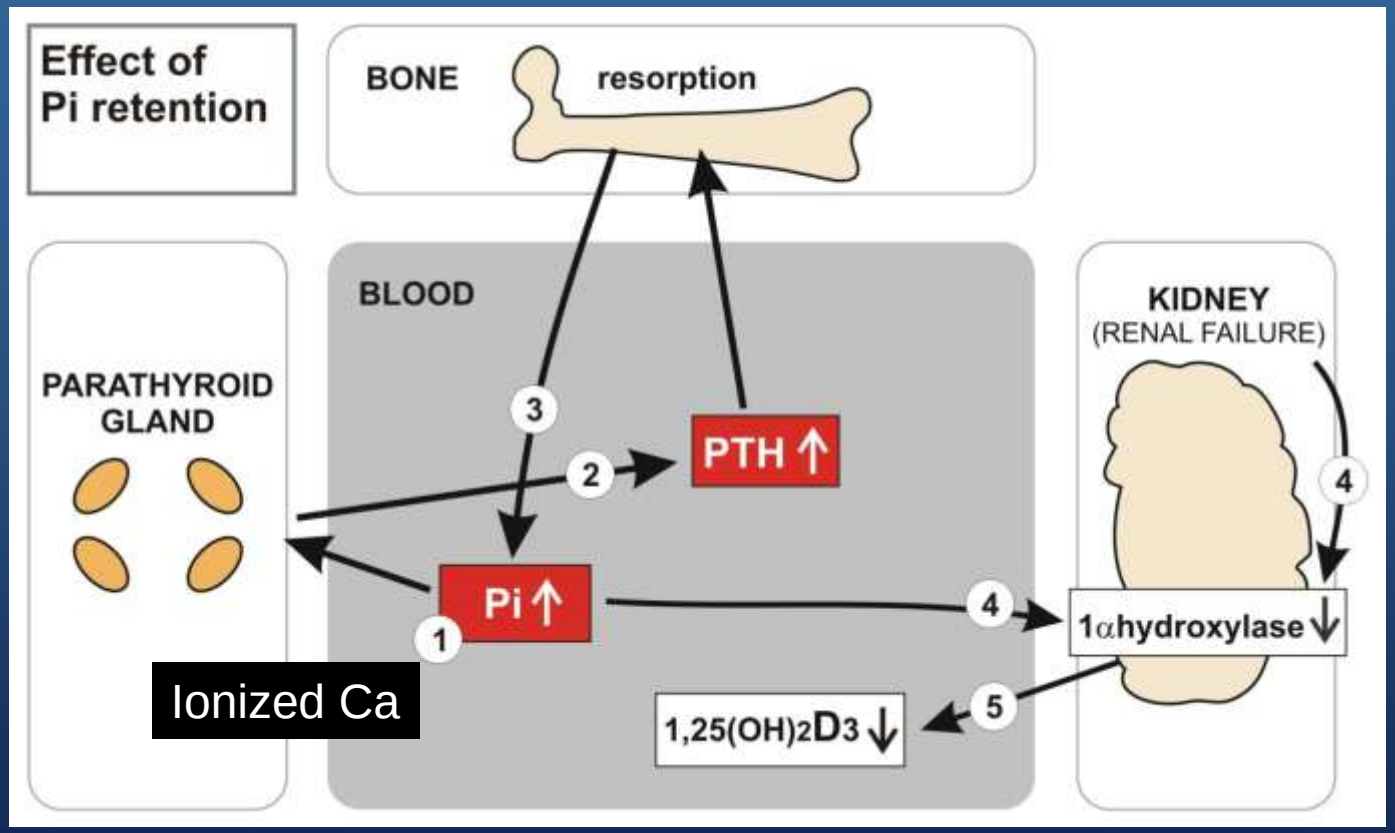
Consequences of phosphate accumulation in chronic renal failure. SECUNDARY HYPERPARATHYROIDISM

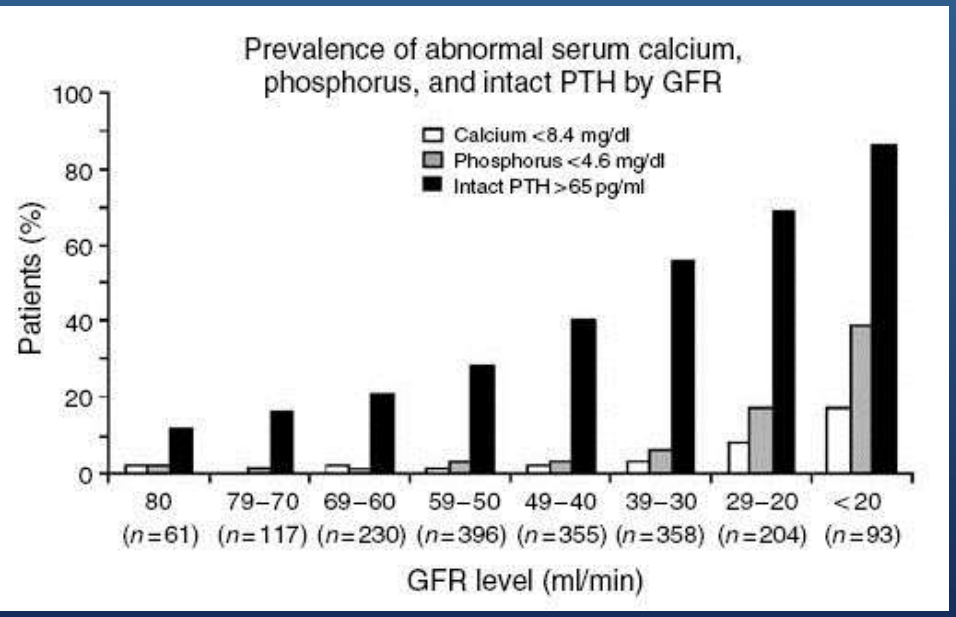


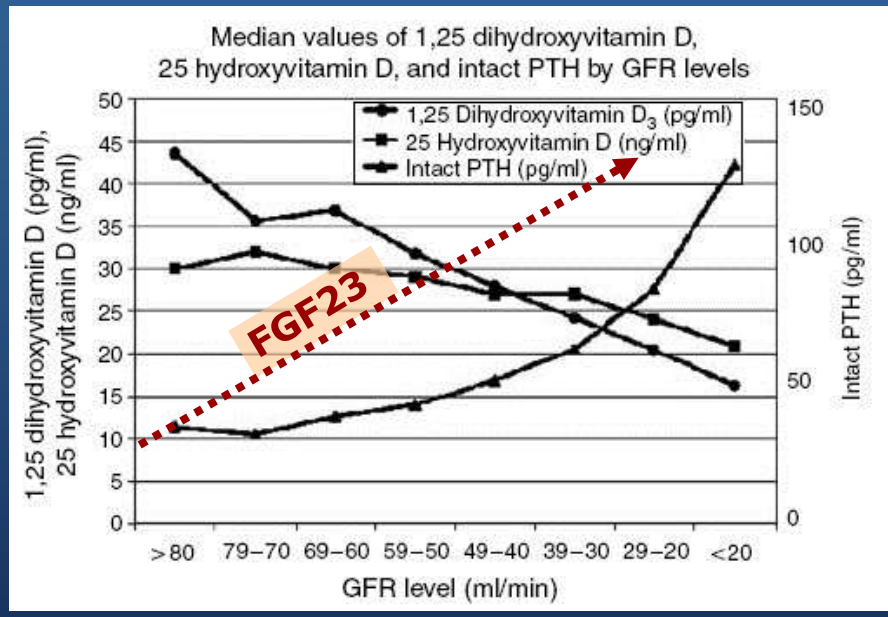
FGF23 increase
Decrease Vit D receptors
Decrease in Ca sens Rs.

High phosphate levels due to the phosphate accumulation in renal failure (1) increase the PTH secretion by the parathyroid glands (2). The resulting increase in osteoclast activity will raise the phosphate levels further (3). Renal failure itself, together with increased serum phosphate levels, leads to a decrease in 1-✂ hydroxylase activity (4), resulting in reduced 1,25-(OH)2 vitamin D3 levels (5)

DDW2078

Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: *Results of the study to evaluate early kidney disease*





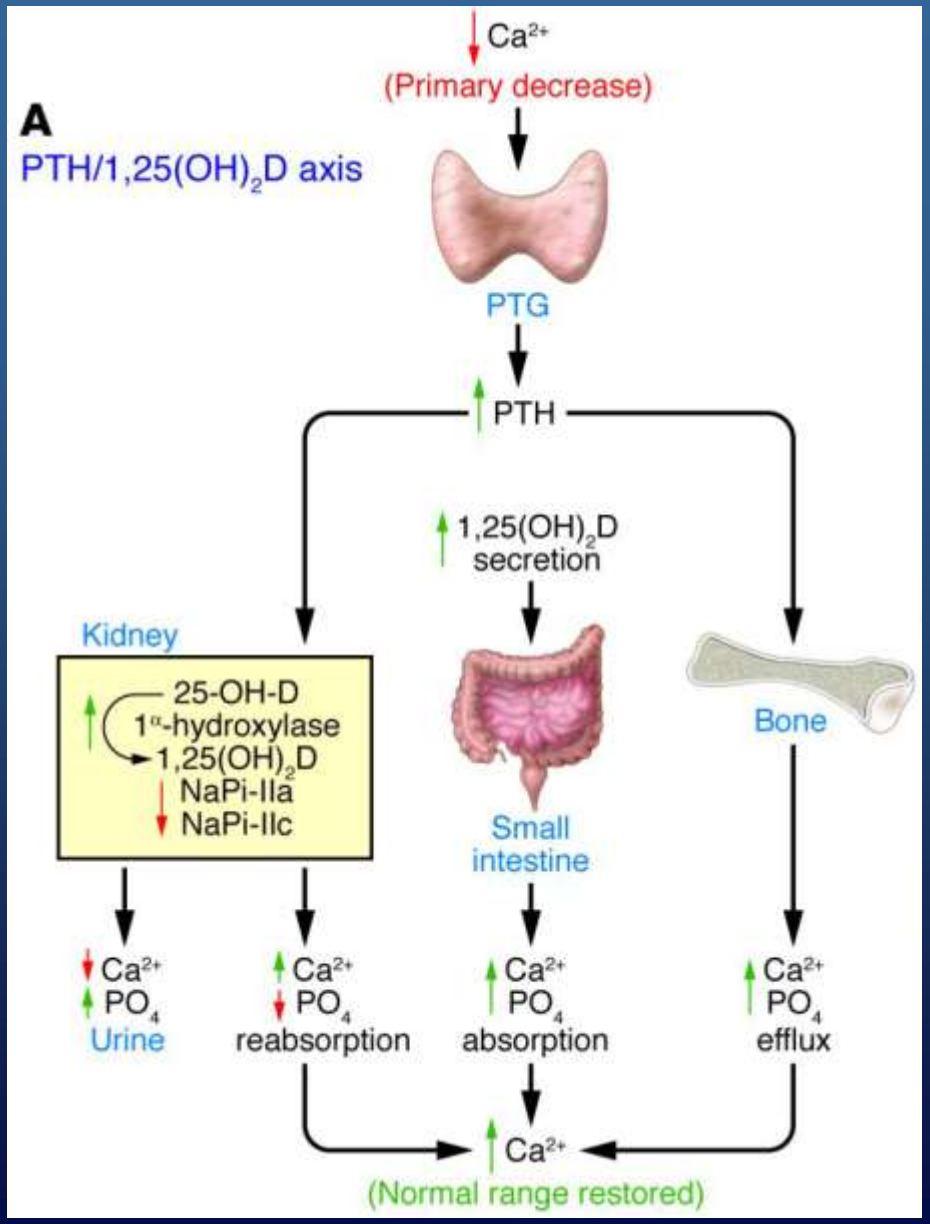
Decrease in Vit D receptors
Decrease in Ca sensing receptors on PTH gland

Early increase of FGF23
No relation to the renal mass
Hypocalciuria
Tendency to hypocalcemia

SECUNDARY HYPERPARATHYROIDISM

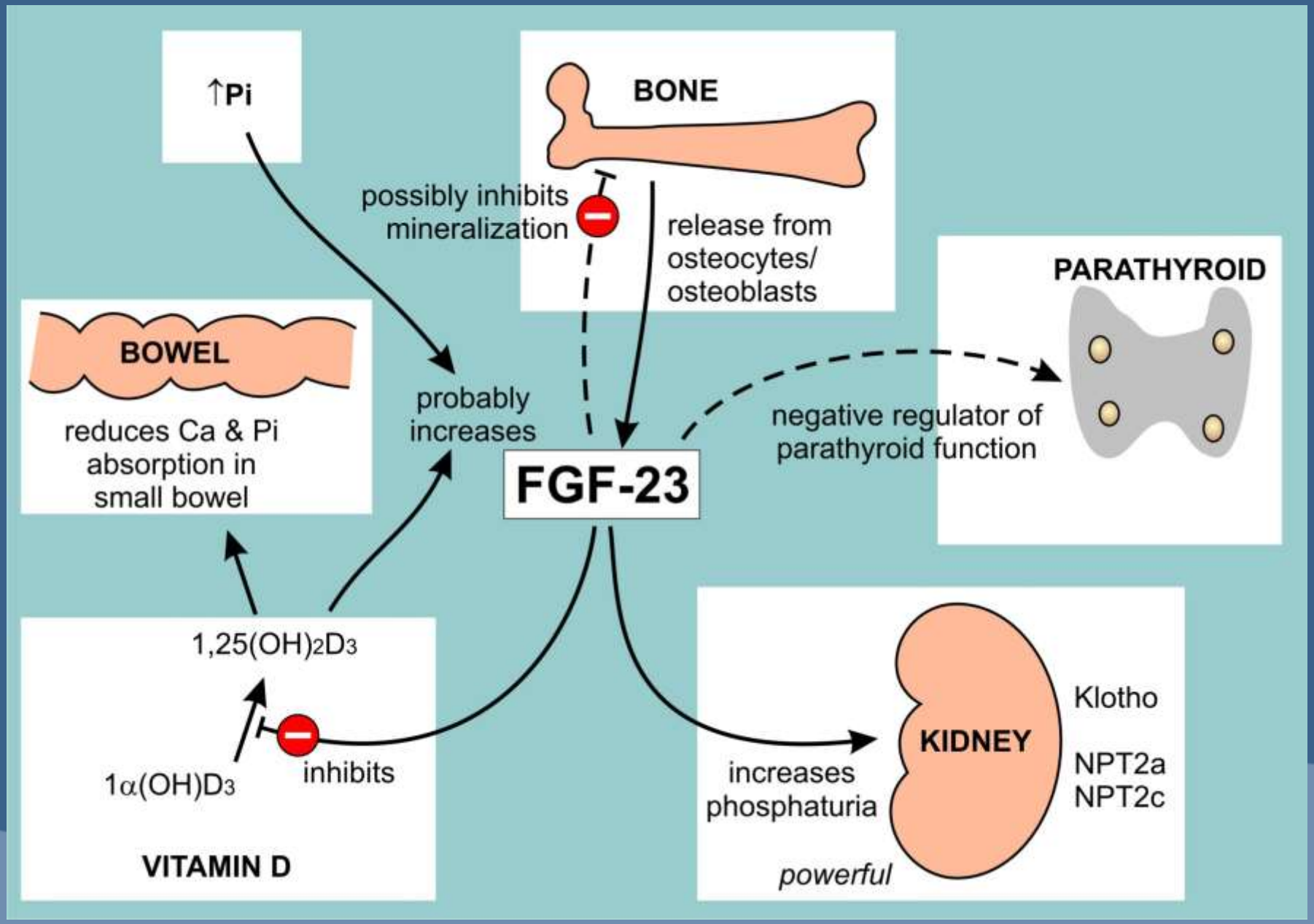
Levin A et al, Kidney Int 71: 31-38, 2007

Endocrine functions of bone in mineral metabolism regulation

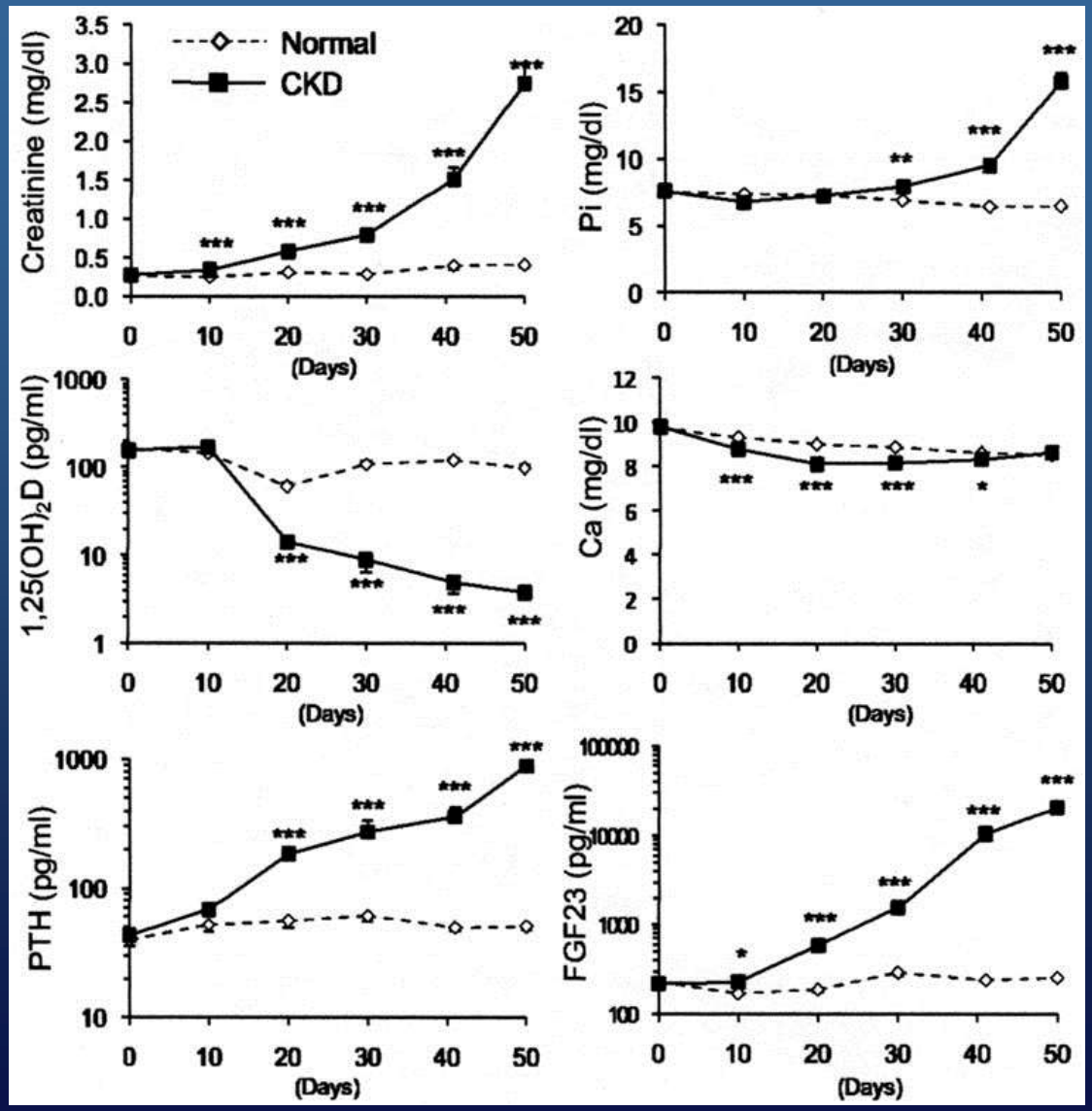


Quarles LD: JCI 118: 3820-8, 2008

Fibroblast growth factor 23



Direct evidence for a causative role of FGF23 in the abnormal renal phoshate handling and vitamin D metabolism in rats with end-stage CKD



Hasegawa H et al: Kidney Int: in press 2010

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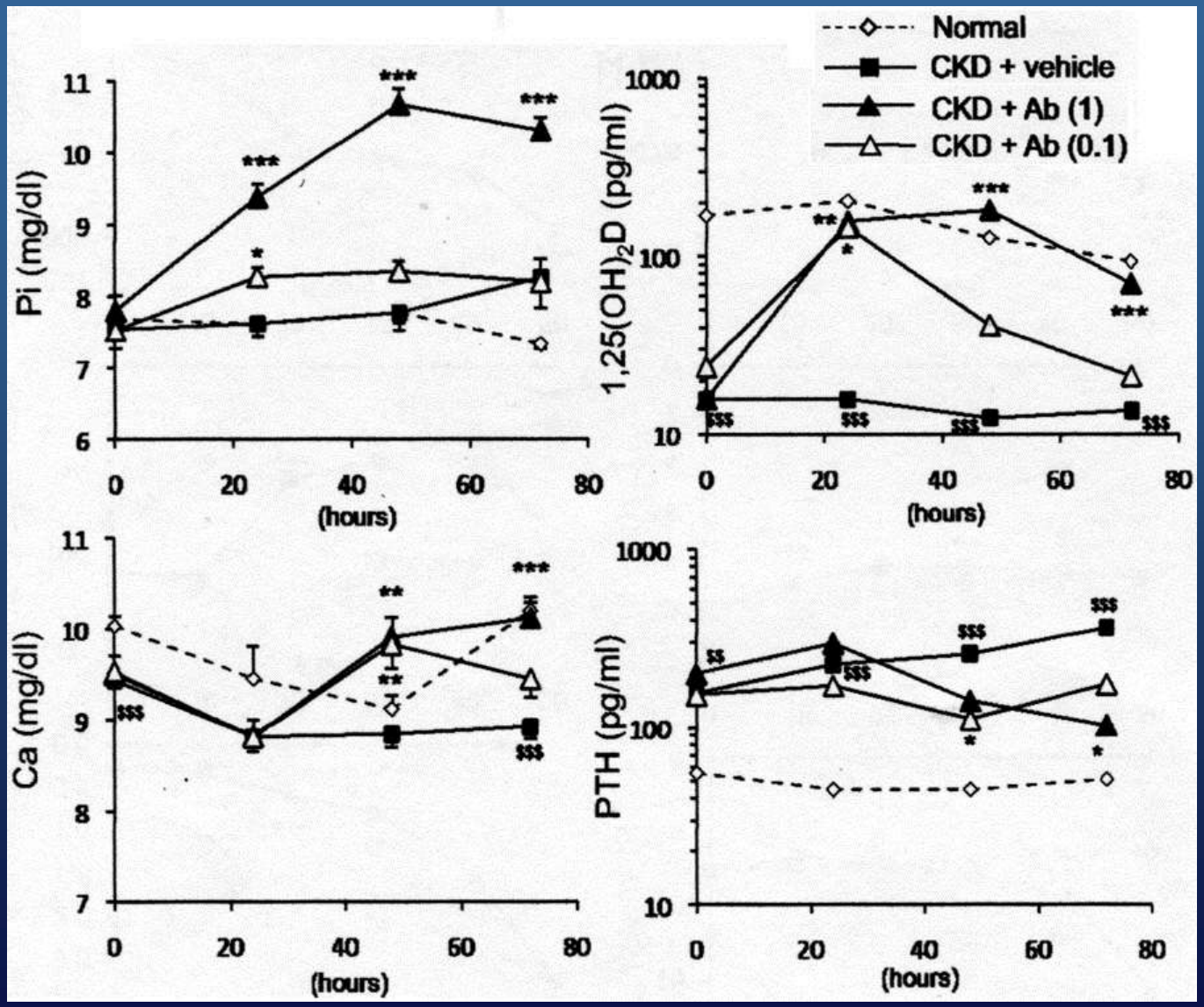

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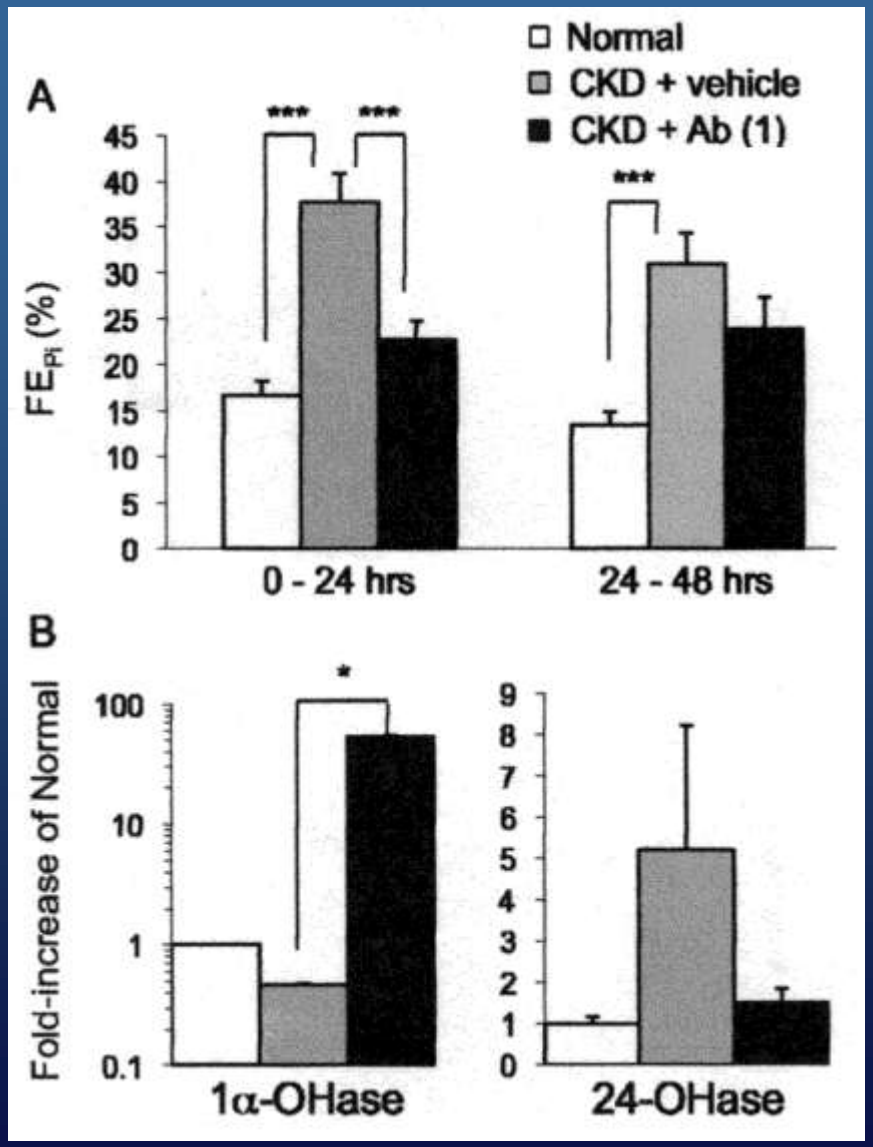
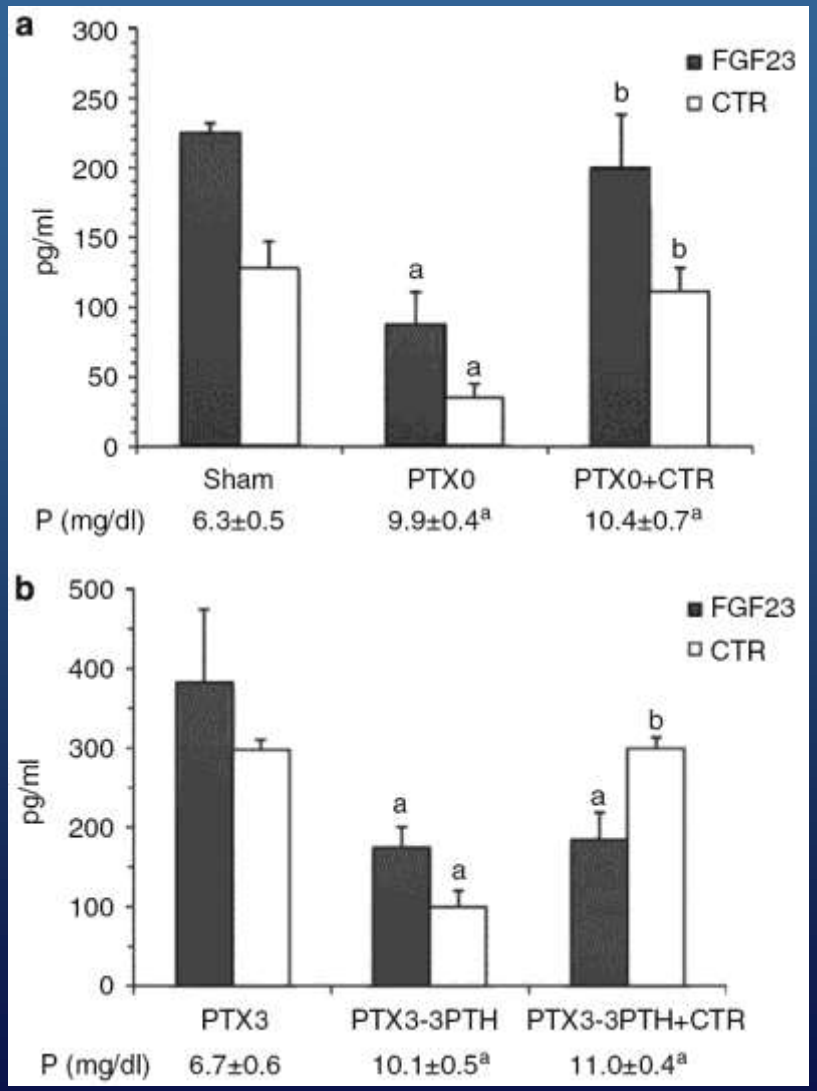


Hasegawa H et al: Kidney Int: in press 2010

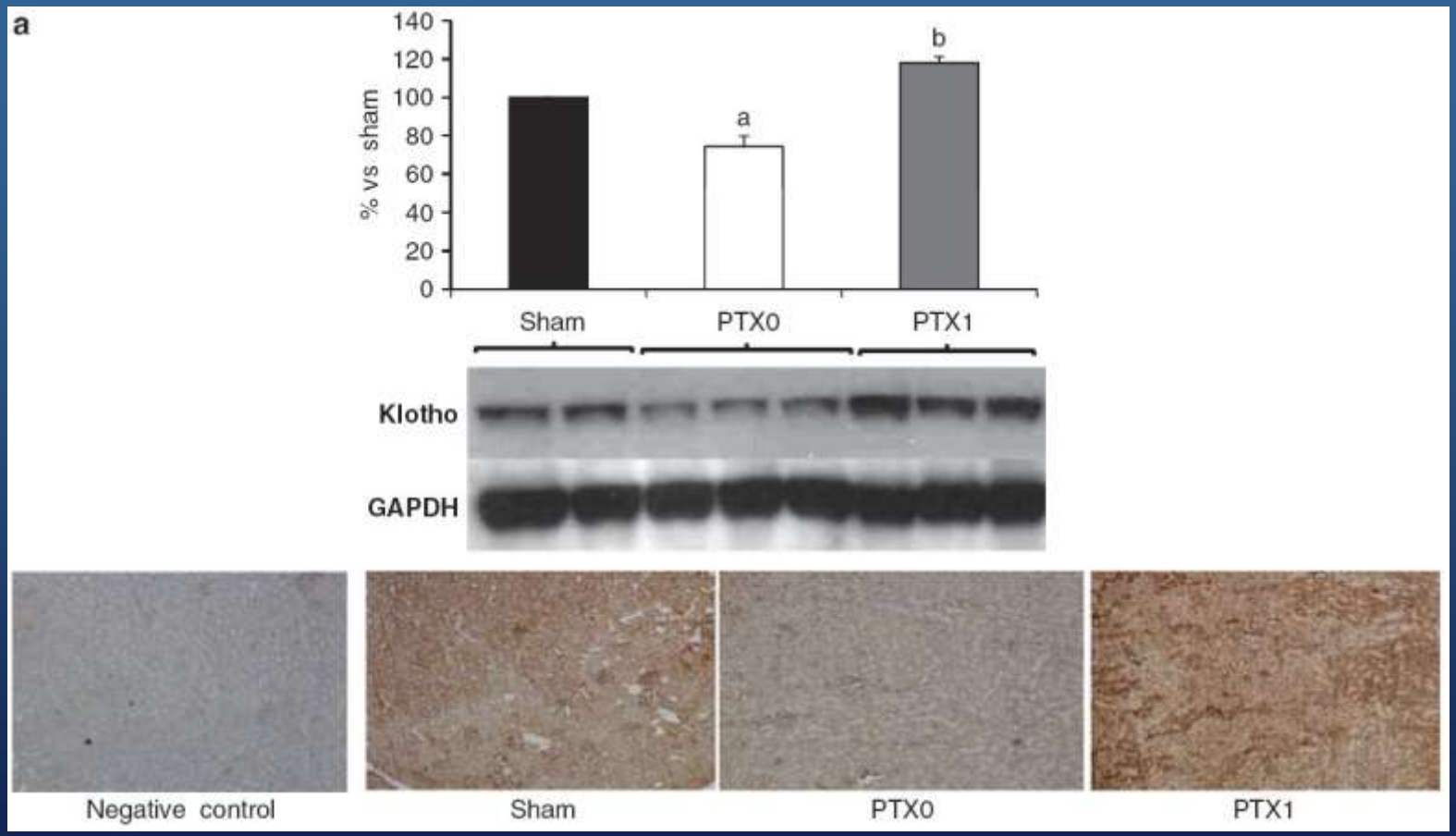
Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 *in vivo*



Plasma fibroblastic growth factor 23 (FGF23) and calcitriol (CTR) levels after calcitriol administration to parathyroidectomized (PTX) rats

Lopez I et al: Kidney Int 80, 475-480, 2011

Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 *in vivo*

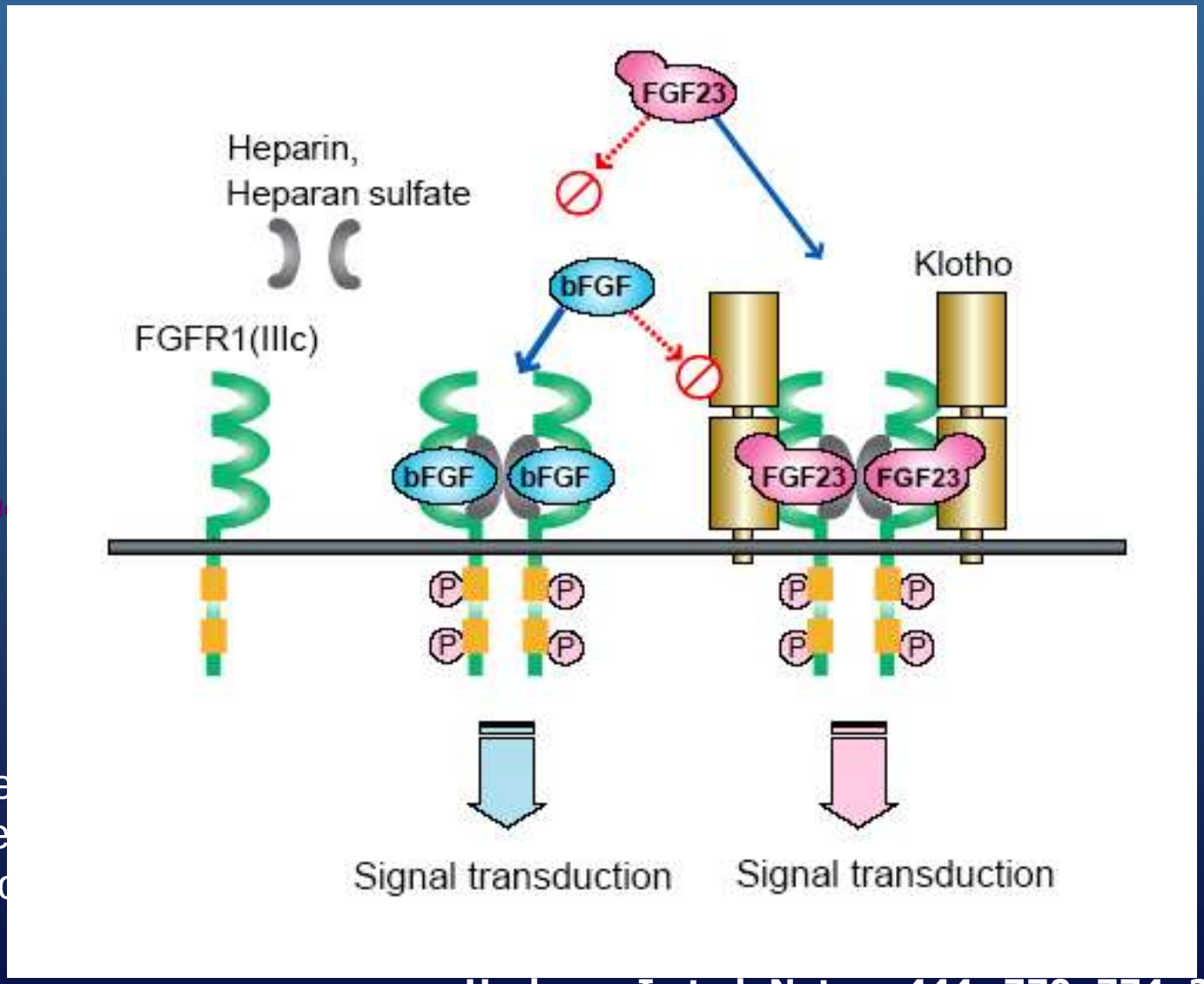


Klotho

Lopez I et al: Kidney Int 80, 475-480, 2011

Régulation de la Phosphatémie par l'action Concertée de FGF23/FGFR/Klotho

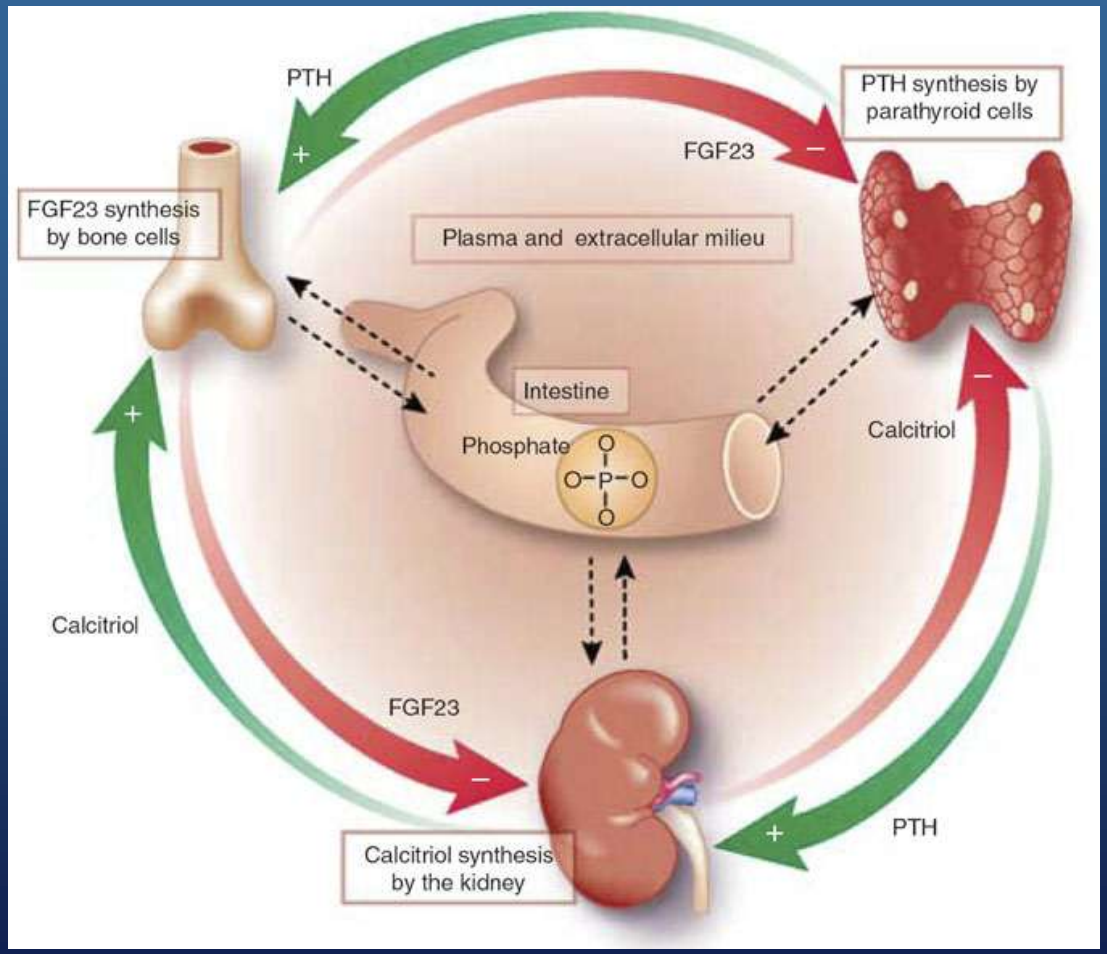
FGF23/FGFR1(IIIc)/Kl
Interaction



Klotho is a co-re
increasing the se
of FGF recepto
FGF23

Urakawa I et al. Nature 444:-770, 774, 2006

Three feedback loops precisely regulating serum phosphate concentration



Regulatory mechanisms of phosphate homeostasis

Parathyroid hormone (PTH) and vitamin D were considered the major factors regulating phosphate homeostasis.

Now, with the identification of fibroblast growth factor 23 (FGF23), a phosphaturic molecule inhibiting calcitriol and PTH, they need to be integrated into three feedback loops involving parathyroid, bone, and kidney.

PTH and calcitriol are required for the appropriate synthesis of FGF23 by bone cells.

PTH also regulates klotho expression in the kidney and thereby the phosphaturic action of FGF23.

Ureña Torres PA & De Brauwere DP: Kidney Int 80, 443-445, 2011

Parathyroid cell resistance to fibroblast growth factor 23 in secondary hyperparathyroidism of chronic kidney disease

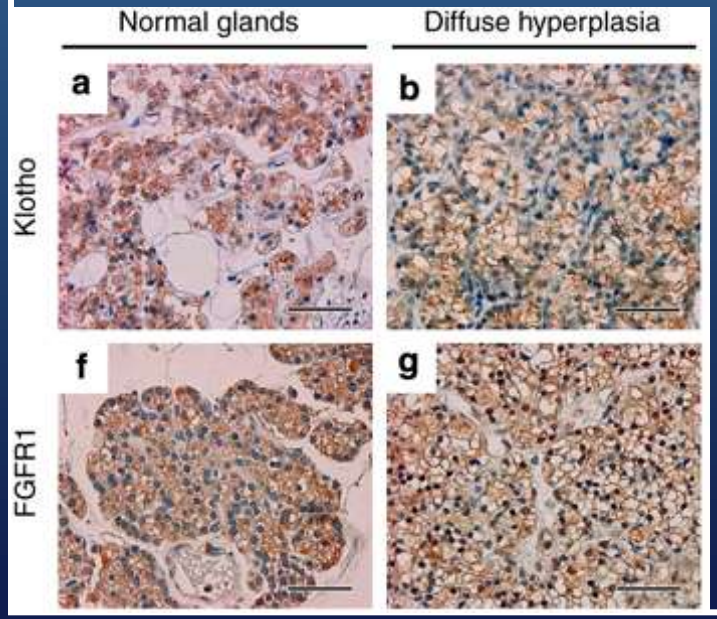
RATS (adenine)

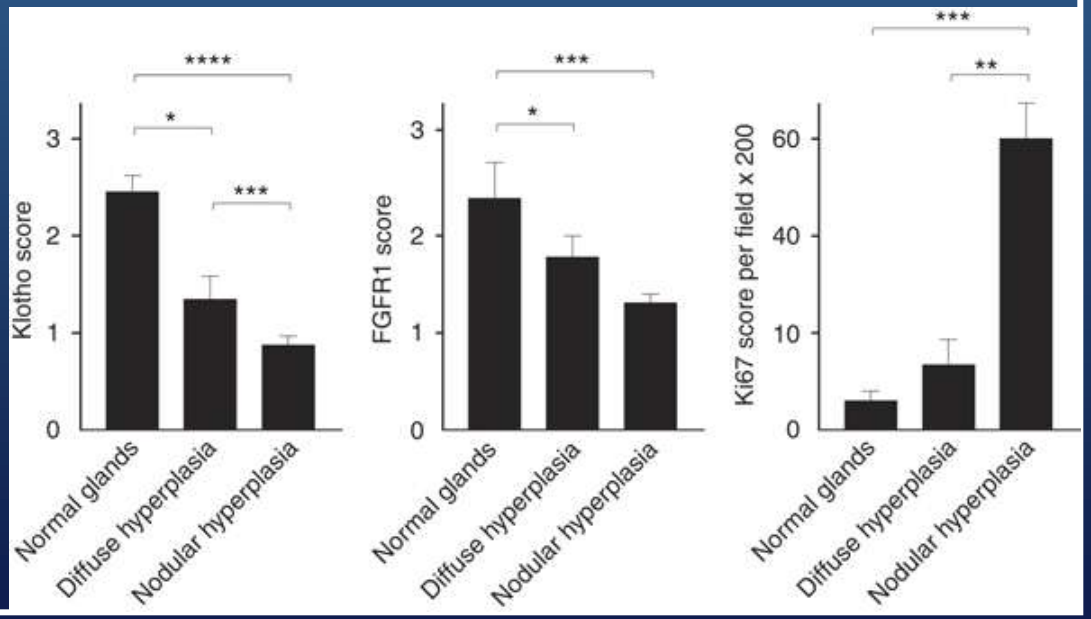
Gallitzer H et al: Kidney Int 77: 211-8, 2009

Depressed expression of Klotho and FGF receptor 1 in hyperplastic parathyroid glands from uremic patients

MAN (dialysis)

Komaba H et al: Kidney Int 77: 232-8, 2010





Kumata C et al: JASN 31: 230-8, 2010

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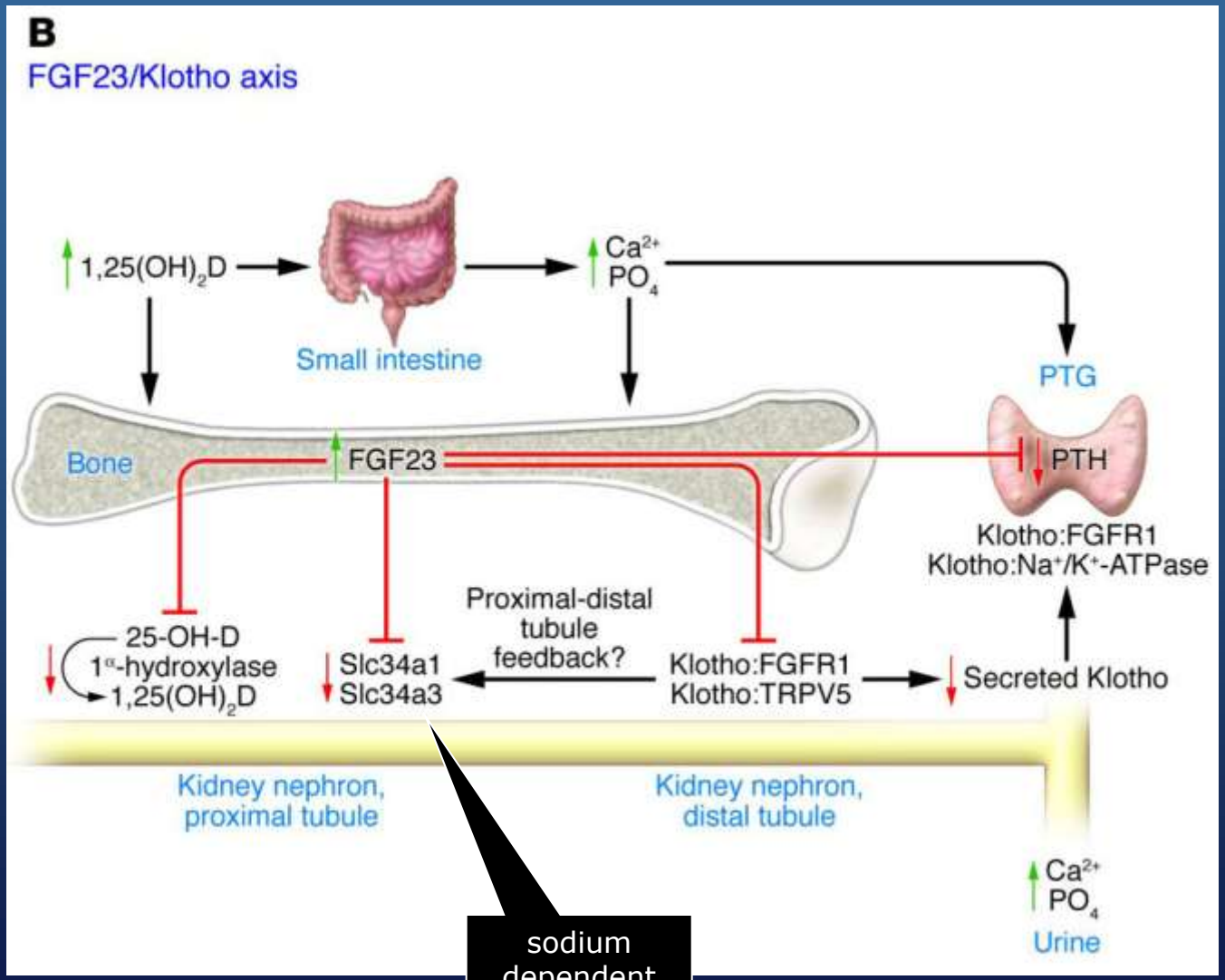
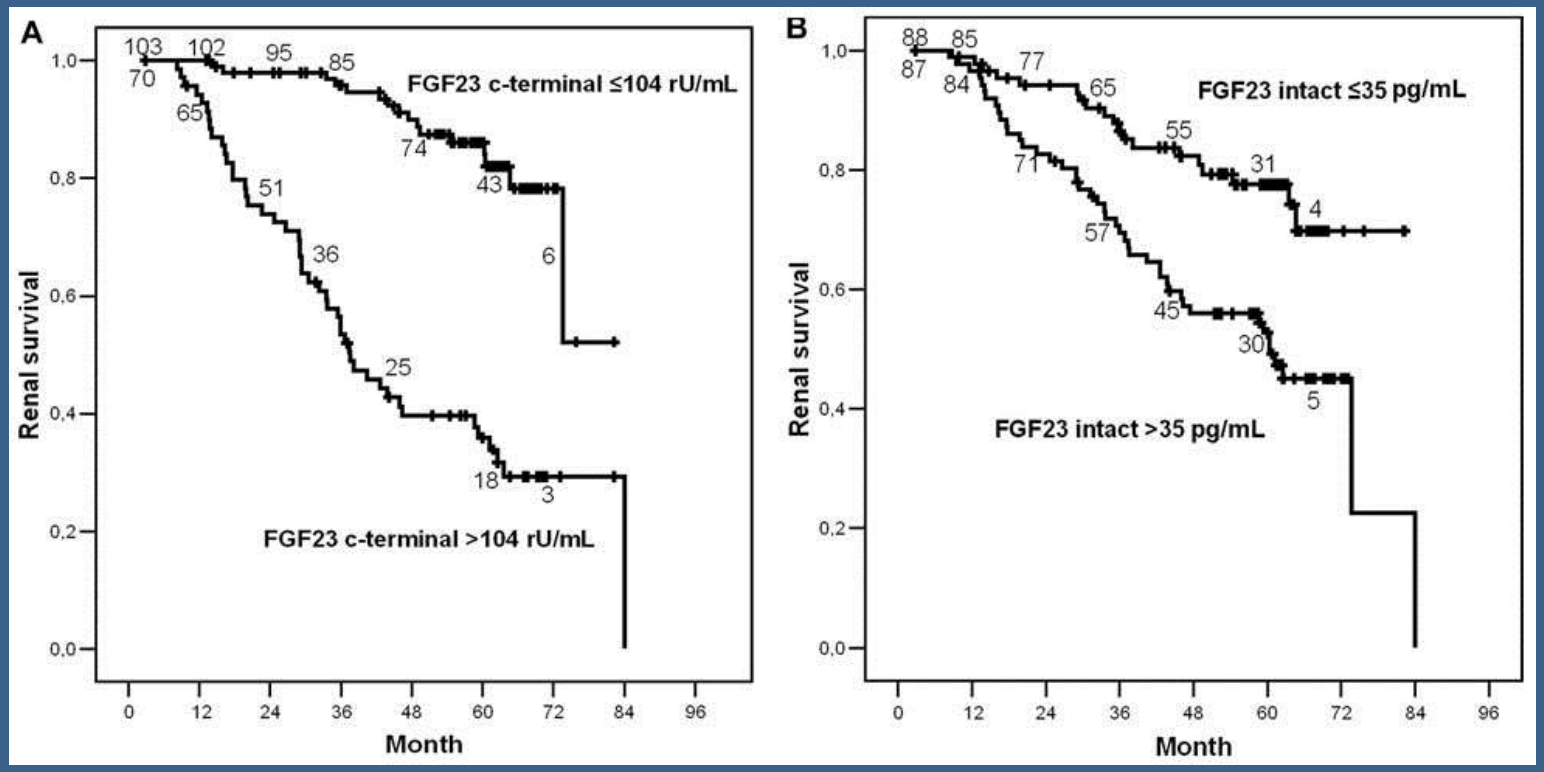


sodium dependent phosphate transporters

Quarles LD: JCI 118: 3820-8, 2008

FGF-23 predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease study



Kaplan-Meier curves of renal end points in patients with below and above optimal cutoff of plasma c-terminal (A) FGF23 concentrations and for intact (B) FGF23 concentrations below and above the median

Fliser D et al: JASN 18: 2600-2608, 2007

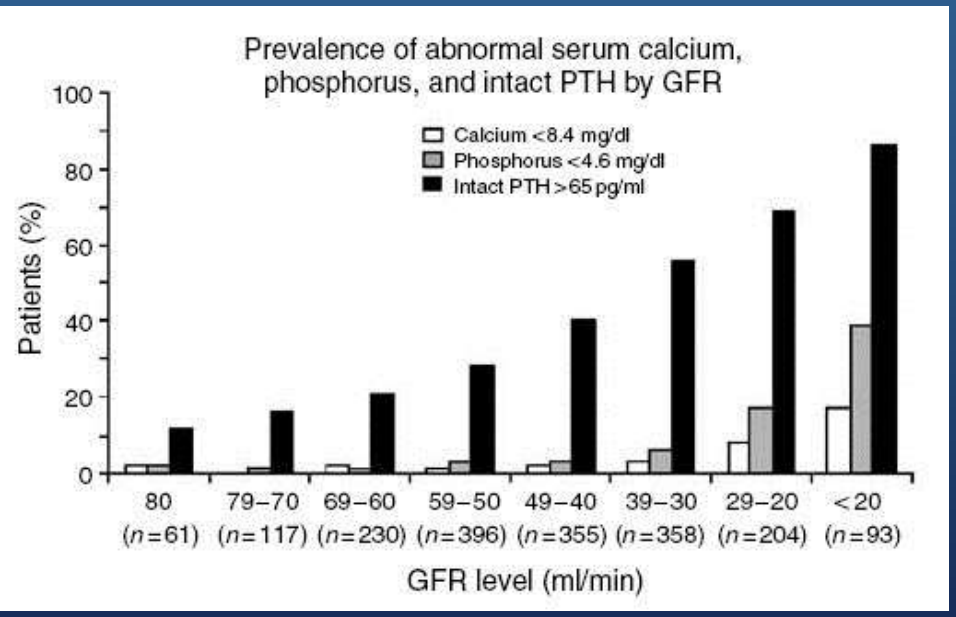
FGF 23 and Clinical Nephrology

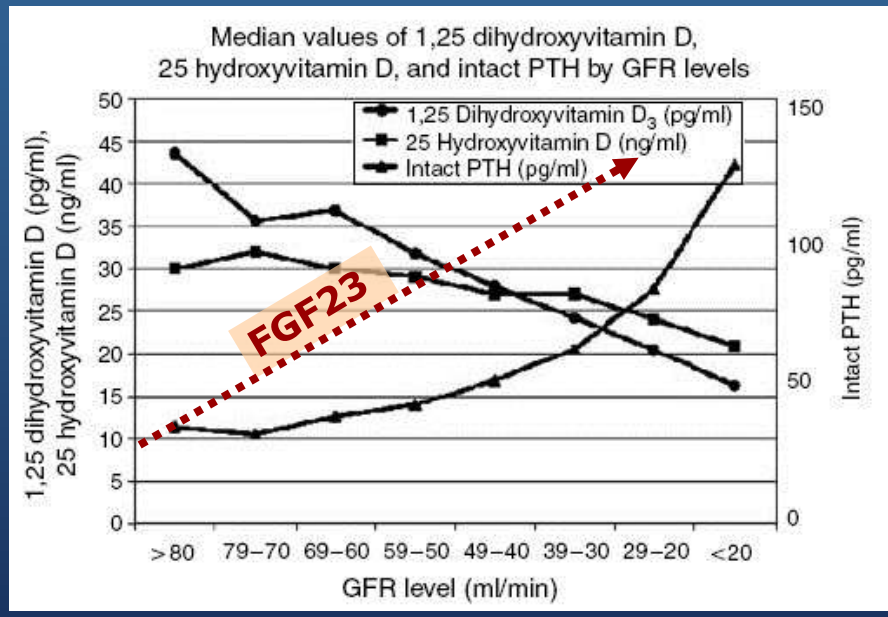
- FGF 23 early incr.--- normalization Ps
- Vitamin D Levels decrease--- FGF 23 excess ---renal mass?
- Postansplanttion hypophosphtemia

- FGF 23 may be a superior marker for disorders of P metabolism related CVD in CKD
- FGF23 as biomarker of CKD progression
- Dose dependent increase of mortality in CKD patients
- Phosphate binding decrease FGF 23 levels ?

NEJM 359 ,584 ,2008
JASN 18 , 2600 , 2007
Kidn Intern 69 , 531 , 2006
Atheros. 2009

Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: *Results of the study to evaluate early kidney disease*





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Levin A et al, Kidney Int 71: 31-38, 2007

PATIENTS with CKD 3/4/5/ NOT in DIALYSIS

1 **Hypocalciuria** is a hallmark of moderate to severe renal failure .

2 Inadequate renal calcitriol production provides physiological evidence for impaired intestinal calcium absorption hence hypocalciuria and modest **hypocalcemia** in untreated patients with CKD 3/4/5/ Arch Int Med 1969

3 **Secundary hyperparathyroidism**

- Patients in CKD 4-5 NOT yet in dialysis have a **negative Ca2+ balance** if no treatment with Vit D and calcium containing phosphate binders

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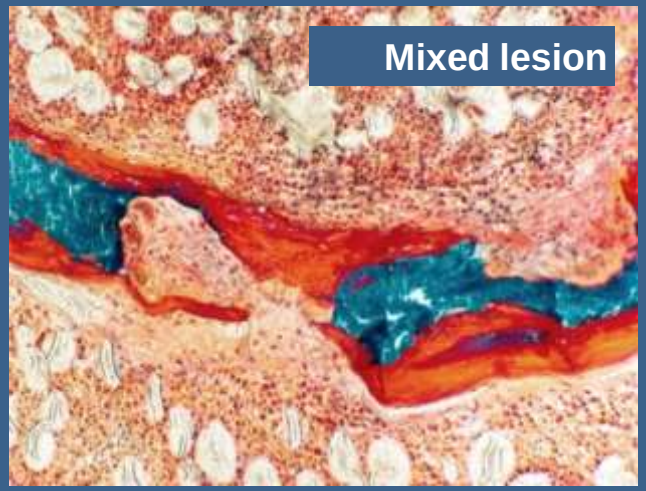
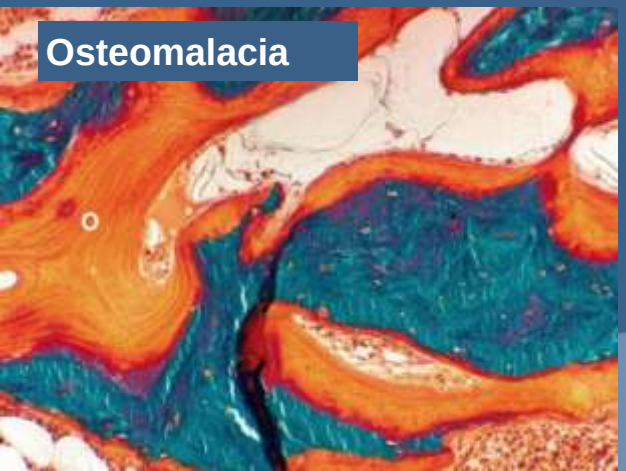
- Lack of good metabolic studies in CKD

Kidney Bone Disease
What happens when the kidney fails?

- ✓ Progression of kidney damage >> mineral metabolism
- ➢ Bone histology in ESRF
- o Concept of calcium loading in CKD
- o Non-calcium containing phosphate binders
- o Lanthanum: a safe phosphate binder?
- o Lanthanum and the calcium loading concept

Classification of renal osteodystrophy



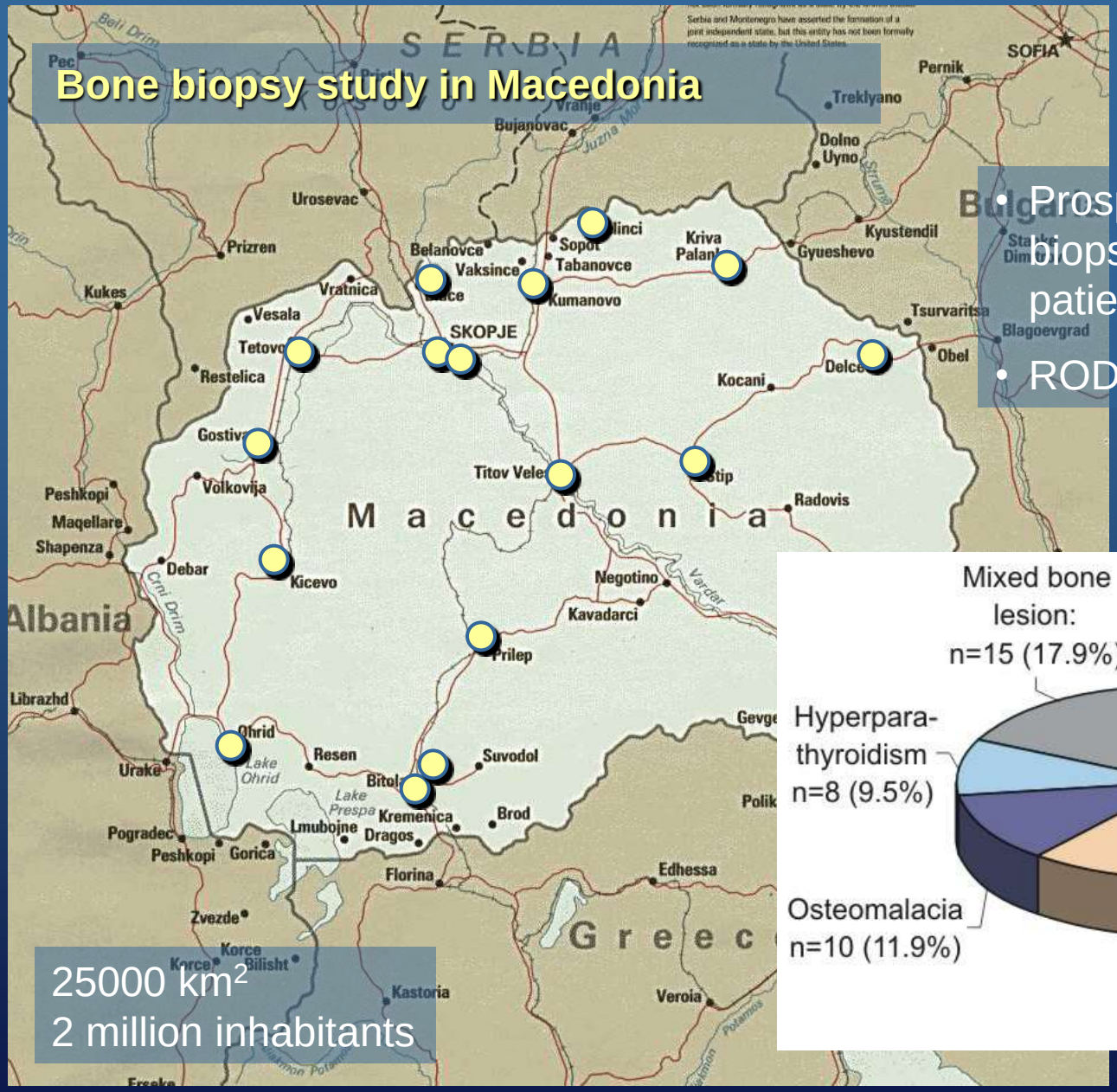


Summary of published prevalences (%) of different types of ROD over the years in *dialysis patients*

Reference (et al)	Type of patients	N	Index of Al presence	Prevalence			
				ABD	Normal	Osteomal.	OF/Mixed
Sherrard, 1972	HD	67		0%		24%	67%/9%
Liach, 1986	HD	142	Major. of OM & ABD	7%		25%	68%
Salusky, 1988	CAPD (children)	44	23%	11%	16%	9	64%/0%
Moriniere, 1989	HD	42	9.5%	24%		0	76%
Maluche, 1992	HD+CAPD	1803 1984y 1991y	 56.4% 62.2%	 5% 20%		 15% 2%	 27%/53% 22%/56%
Sherrard, 1993	HD CAPD	117 142	15% 25%	36% 60%		3% 6%	50%/11% 30%/4%
Torres, 1995	HD CAPD	49 32		32% 48%		12% 10%	44%/12% 32%/10%
Couttenye, 1996	HD	103	5%	37%	13%	10%	20%20%
Coen, 1998	HD	41	0%	11%		11%	56%/22%
Canavese,1998	HD	80	35%	9%		18%	36%/37%
Sanchez, 2000	CAPD	57	14%	63%		0%	37%
Gerakis, 2000	HD	62	34%	23%		3%	64%/10%
Changsirikul-chai, 2001	HD CAPD	39 17	3.5%	41%		4%	30%/25%
Ballanti, 2001	HD	37	0%	14%		19%	43%/24%

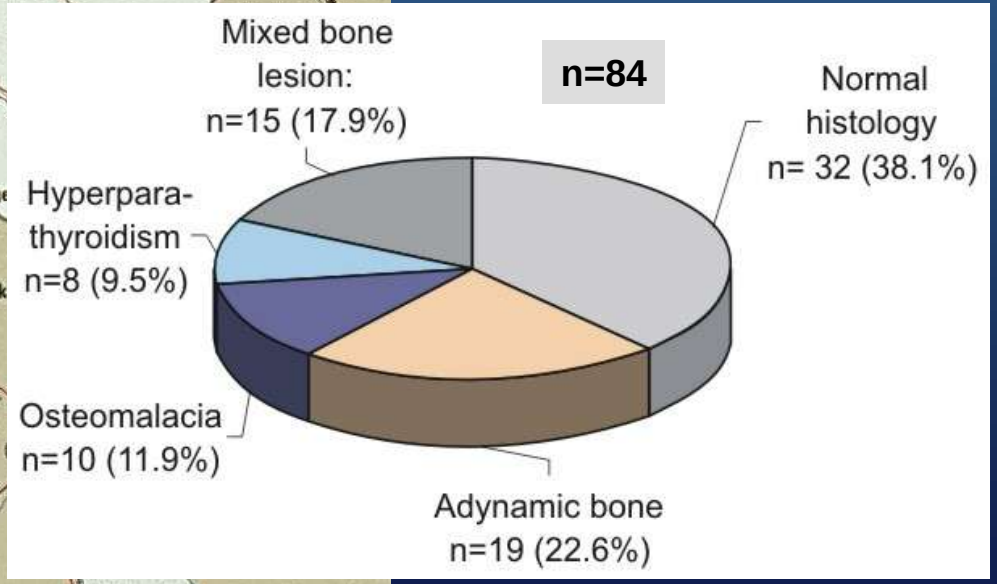
GS Spasovski, PhD thesis, University of Skopje, Macedonia, 2002

Bone biopsy study in Macedonia



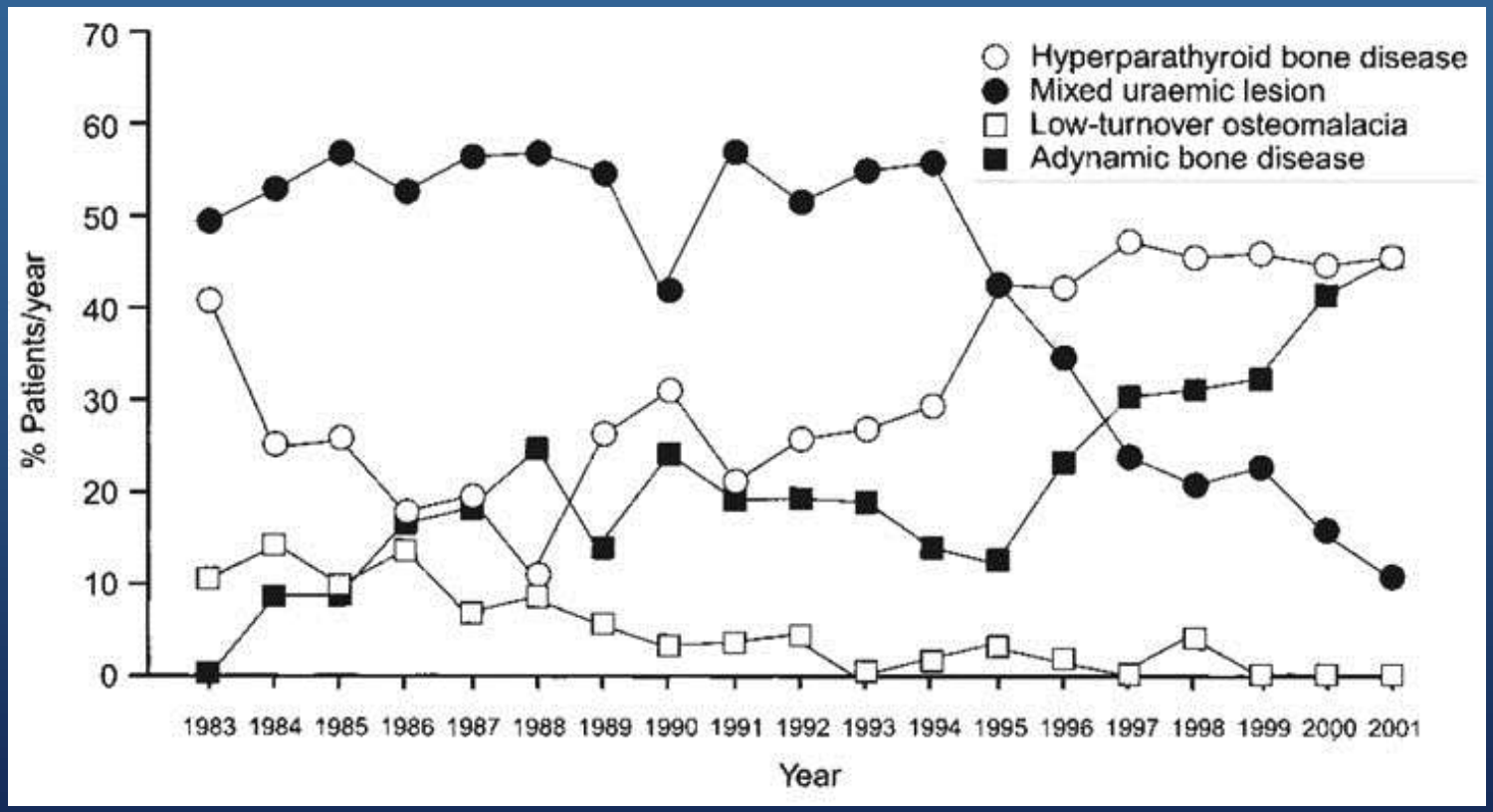
25000 km^2
2 million inhabitants

- Prospective unselected bone biopsy study of all pre-dialysis patients over 9 months
- ROD histology



Spasovski GB et al, Neprol Dial Transplant, 2003
Bervoets A et al: Am J Kidney Dis, 2003

Evolution of renal osteodystrophy



Malluche et al., Nephrol Dial Transplant 2004

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CALCIUM LOAD in END STAGE RENAL FAILURE PATIENTS

- No renal function,black box ,bone and ….vessels
- Administration of Vitamin D
- Use of Calcium containing Phospate binders (8 – 15 mEq/ dialysis day)
- Use of non calcium containing Phosphate binders
- Calcium load through dialysate
- peritoneal dialysis (2.5 – 3.0 mEq/l / serum iCa 1.8- 2.5 mEq/l)
- Diet

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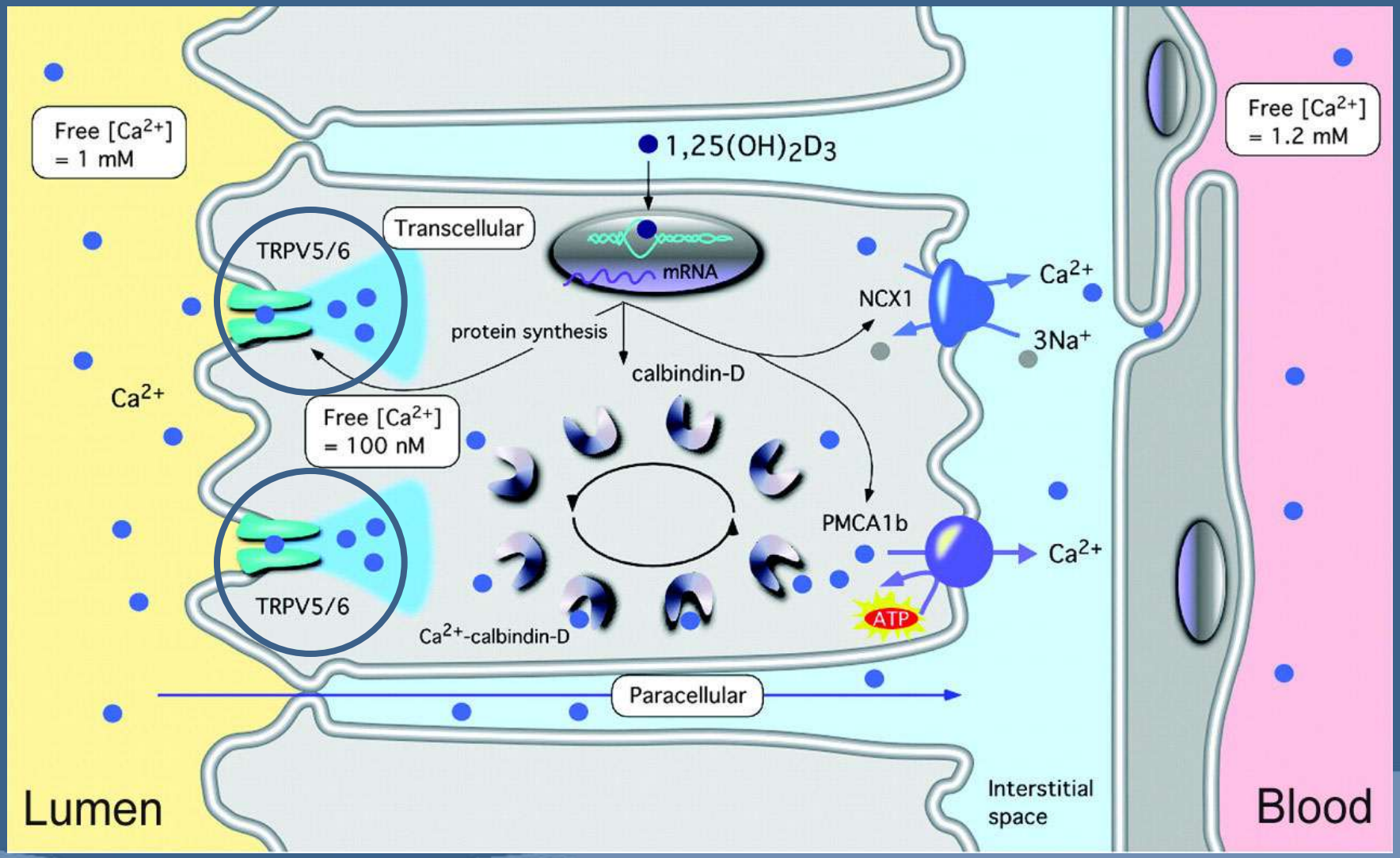
Calcium absorption across epithelia

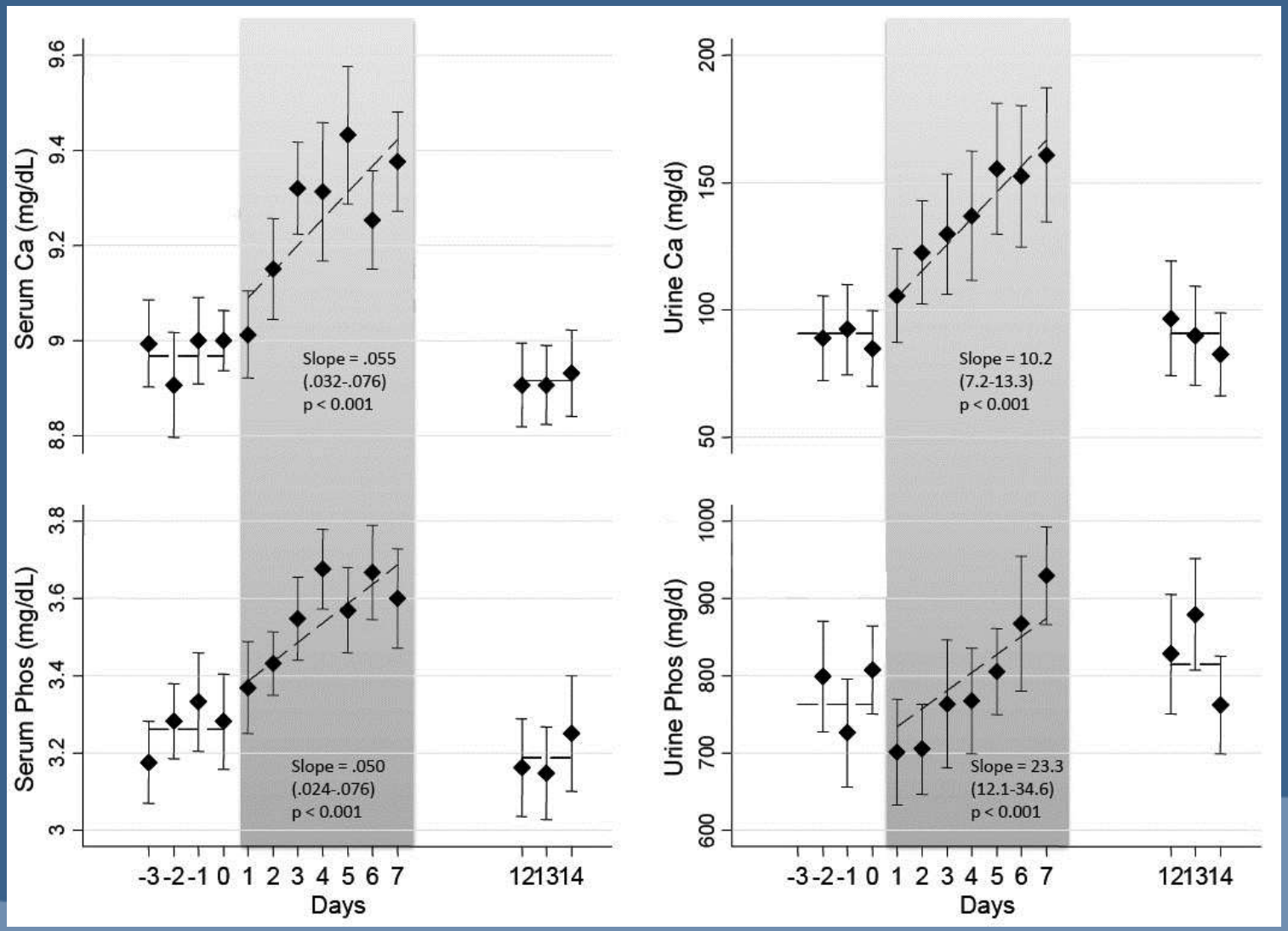
Mechanism of epithelial Ca^{2+} transport



Hoenderop JG et al: Physiol Rev 85: 373-422, 2005

Calcium sensing receptor

Short-term effects of vitamin D receptor activation on serum creatinine, creatinine generation, and glomerular filtration rate



Agarwal R et al: Kidney Int 2011 (In press)

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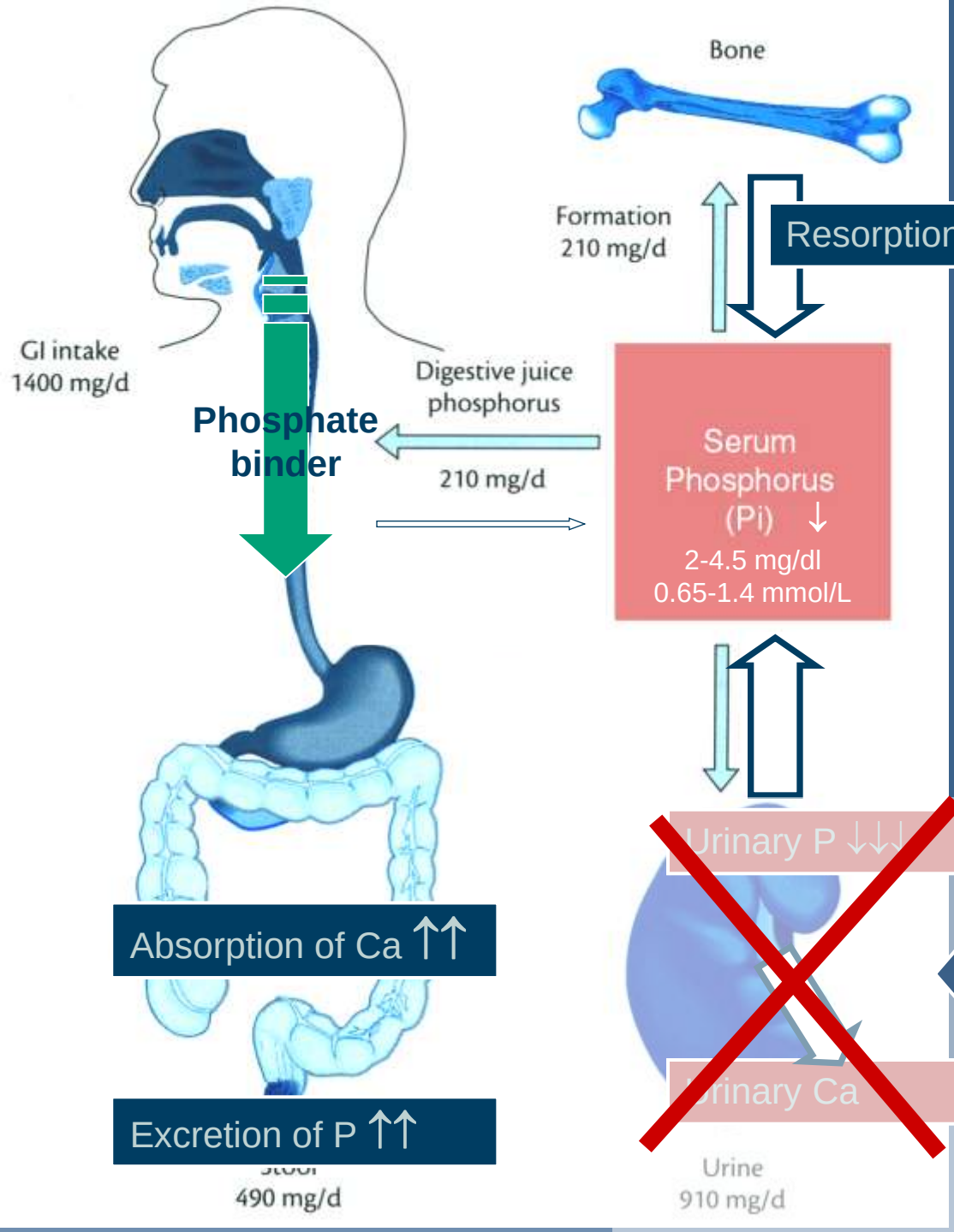
Effect of phosphate binder



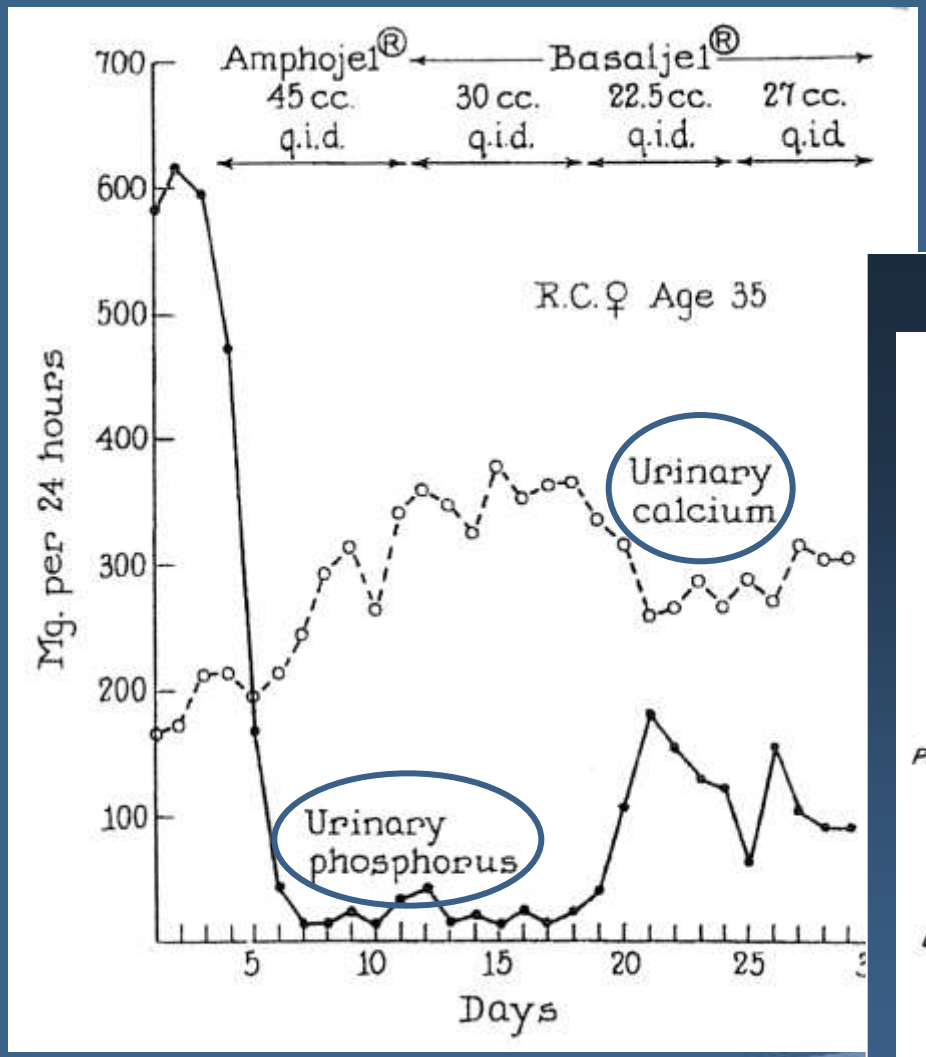
- Bone Demineralization
- Osteomalacia

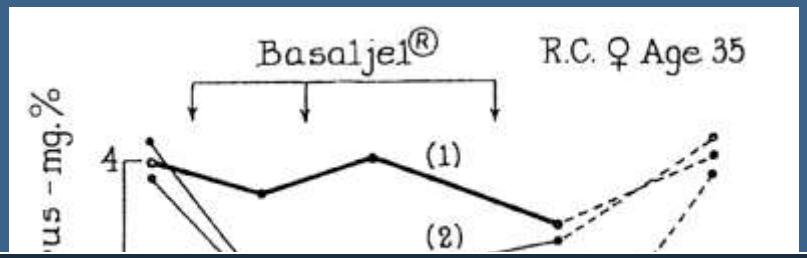
Foldes J et al: Bone 12: 67-71, 1991

DIALYSIS PATIENT

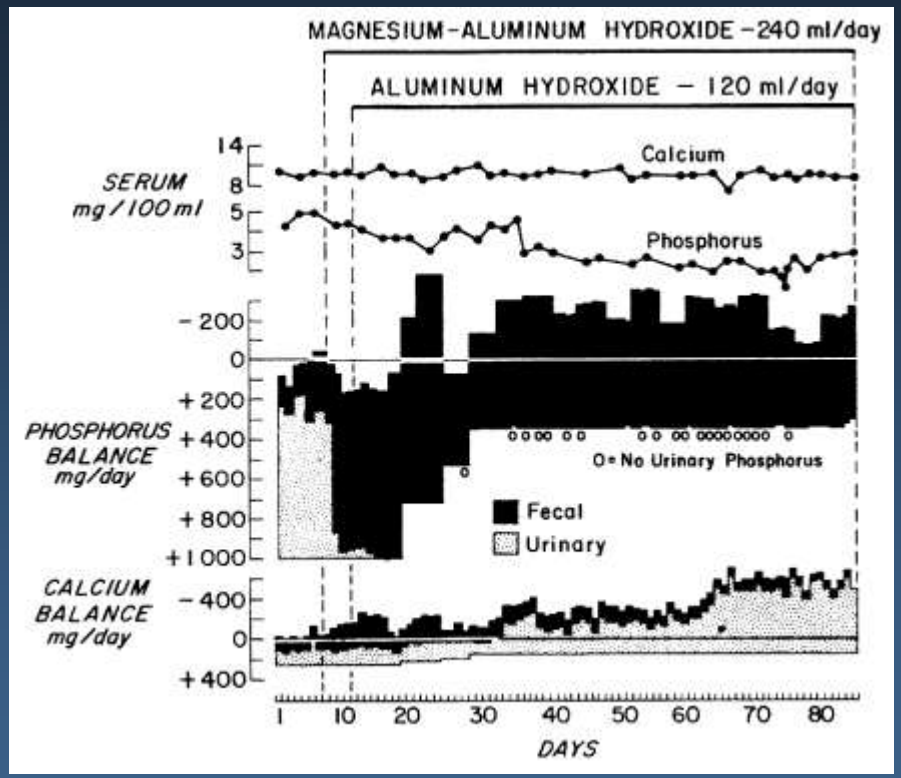
Evidence for a phosphorus-depletion syndrome in man.
New Engl J Med 278: 409-415, 1968

Aluminum gels in the management of renal phosphatic calculi





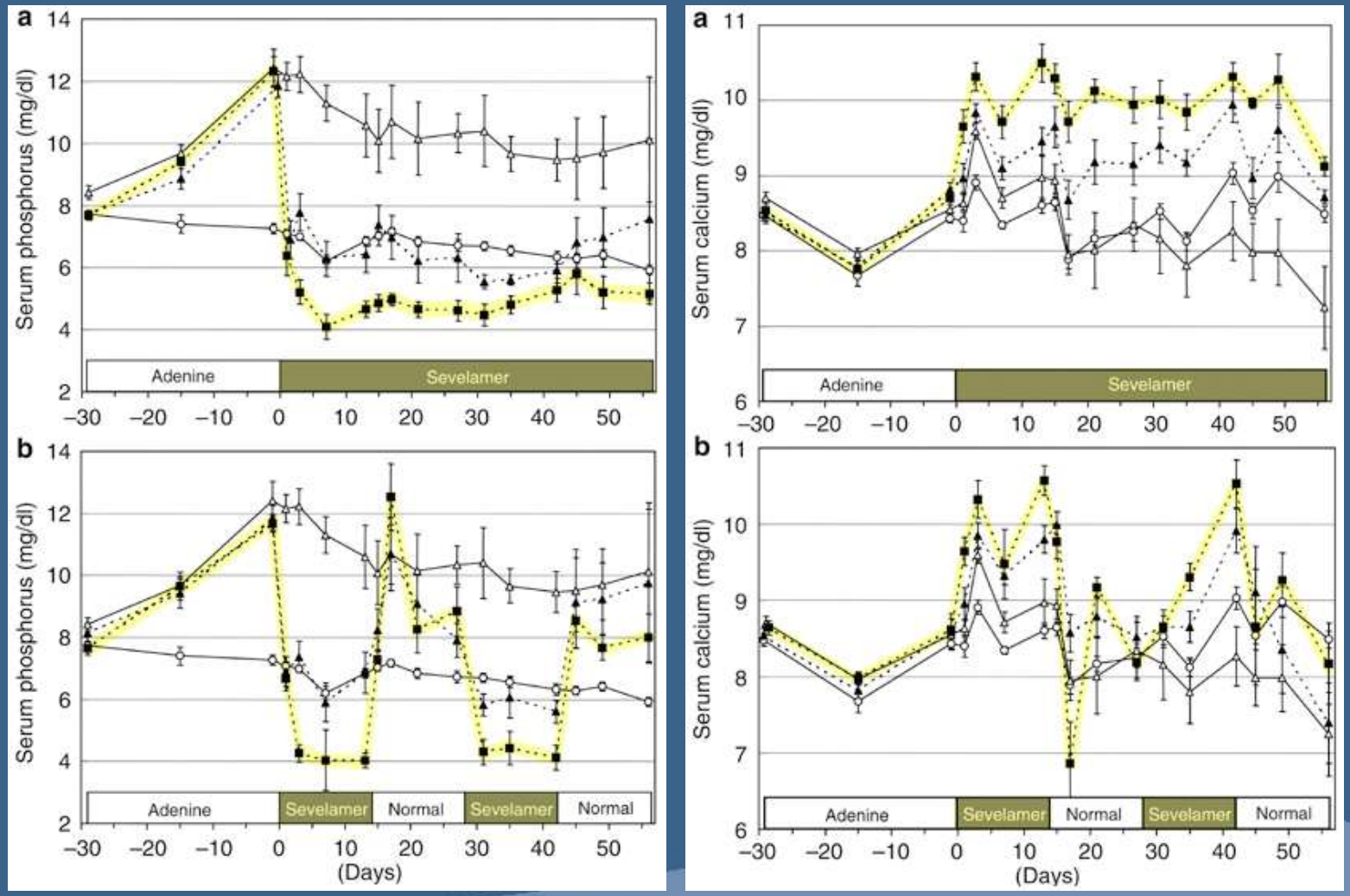
Gastrointestinal Ca absorption ↑ ($^{47}CaCl_2$)



Lotz M et al: New Engl J Med 278: 409-415, 1968

Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats

- ○ normal control
- △ disease control
- ▲ 1% sevelamer
- ■ 3% sevelamer



Nagano N et al: Kidney Int 69: 531-537, 2006

Effects of (a) continuous and (b) intermittent treatment with sevelamer on serum phosphorus (left) and calcium (right) levels

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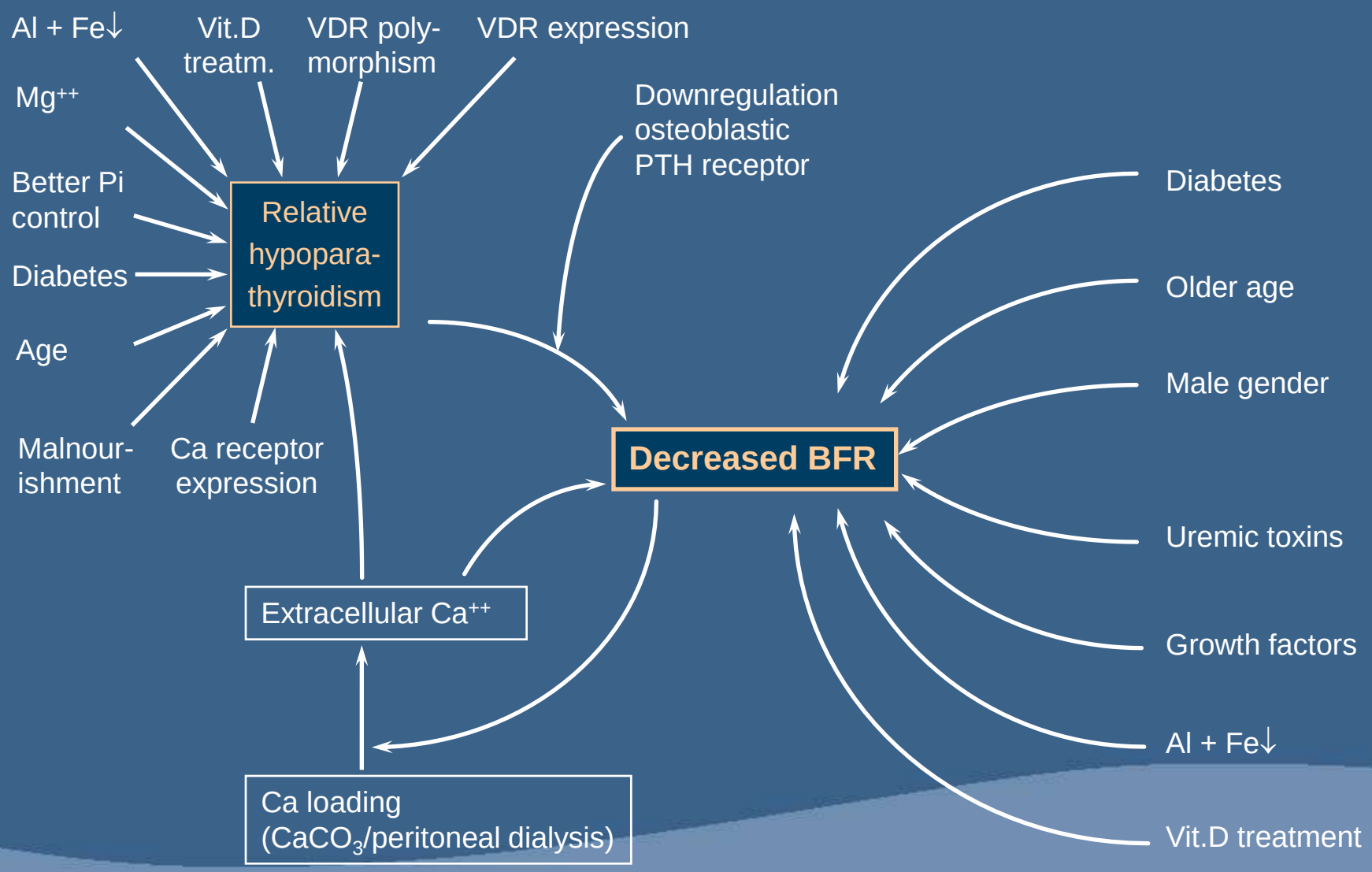
Adynamic Bone Disease

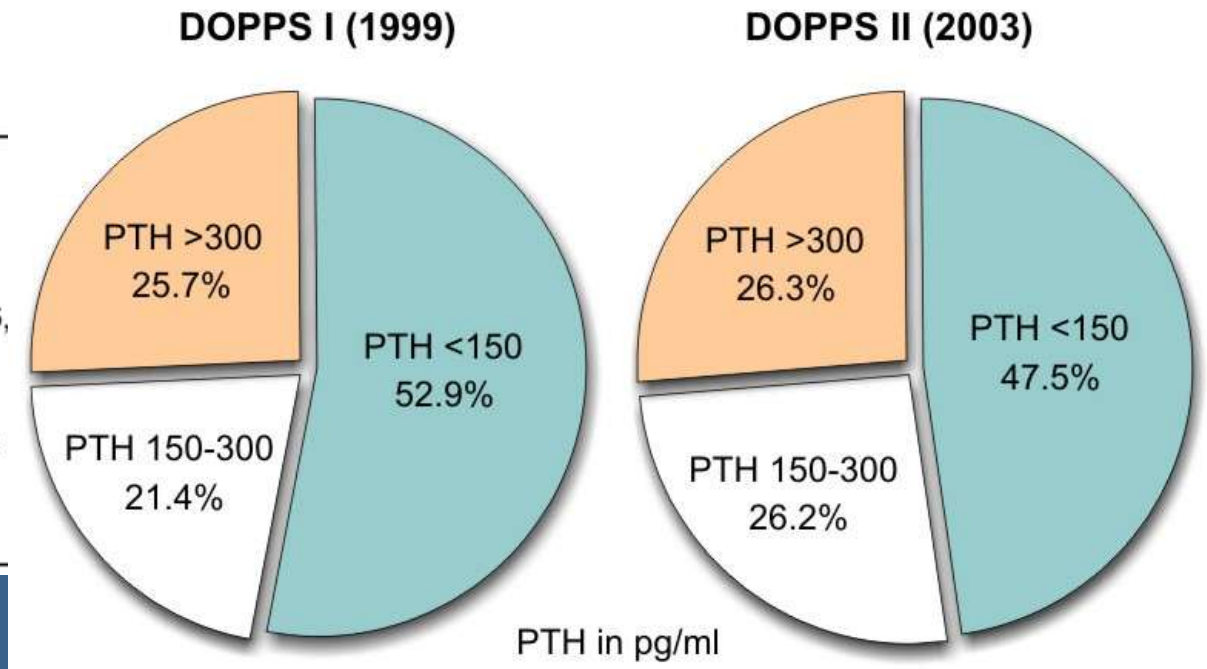


Couttenye MM et al: Kidney Int 56, S70, 1999

Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

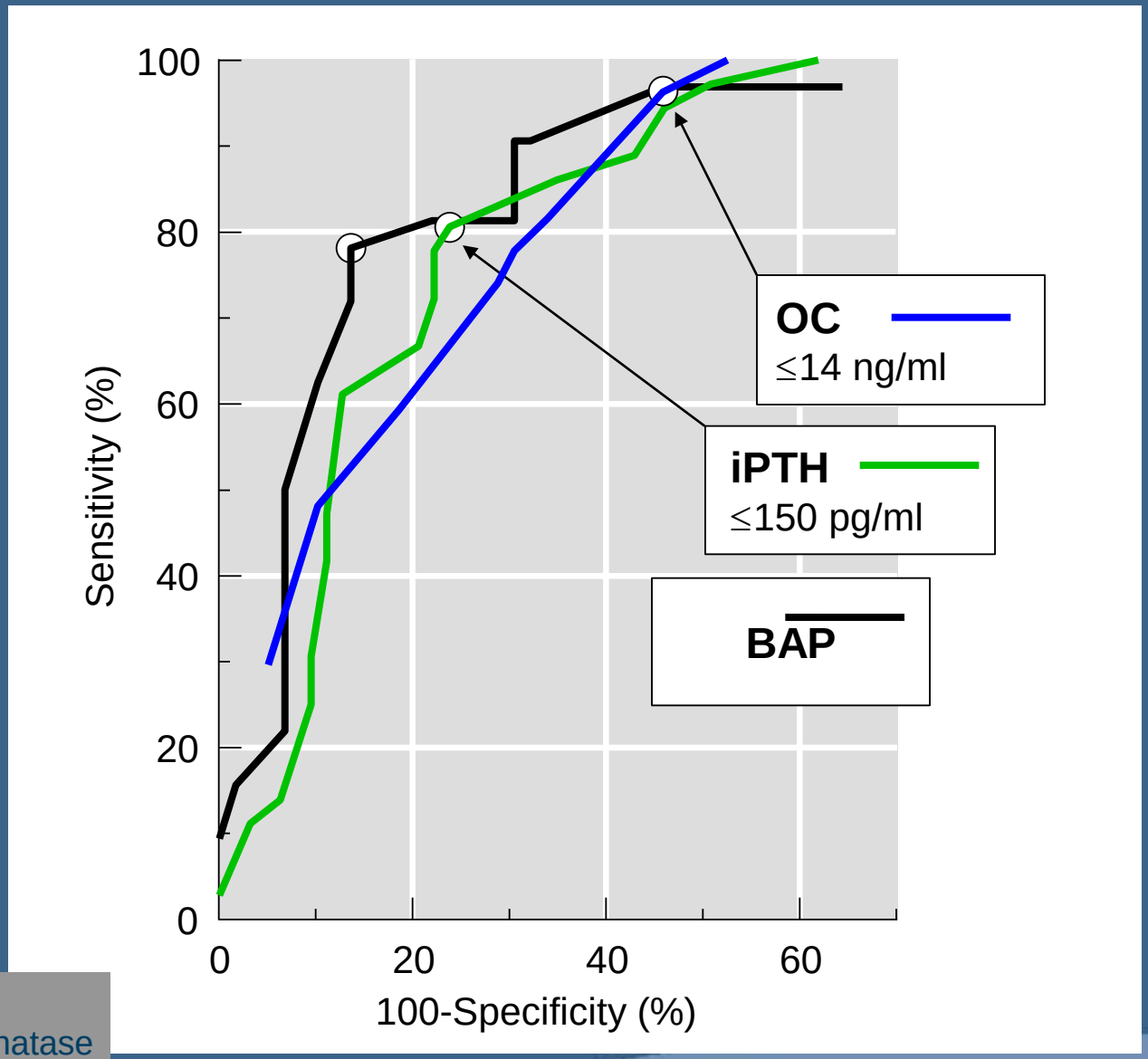
Overall Distribution of Mineral Metabolism Laboratory Values by Time (DOPPS I and DOPPS II)

Measurement (n_1/n_2)	P Value
PTH (pg/mL) (n_1/n_2 = 5,439/4,261)	<0.001
Serum calcium$_{Alb}$ (mg/dL) (n_1/n_2 = 6,	0.06
Serum phosphorus (mg/dL) (n_1/n_2 =	<0.001



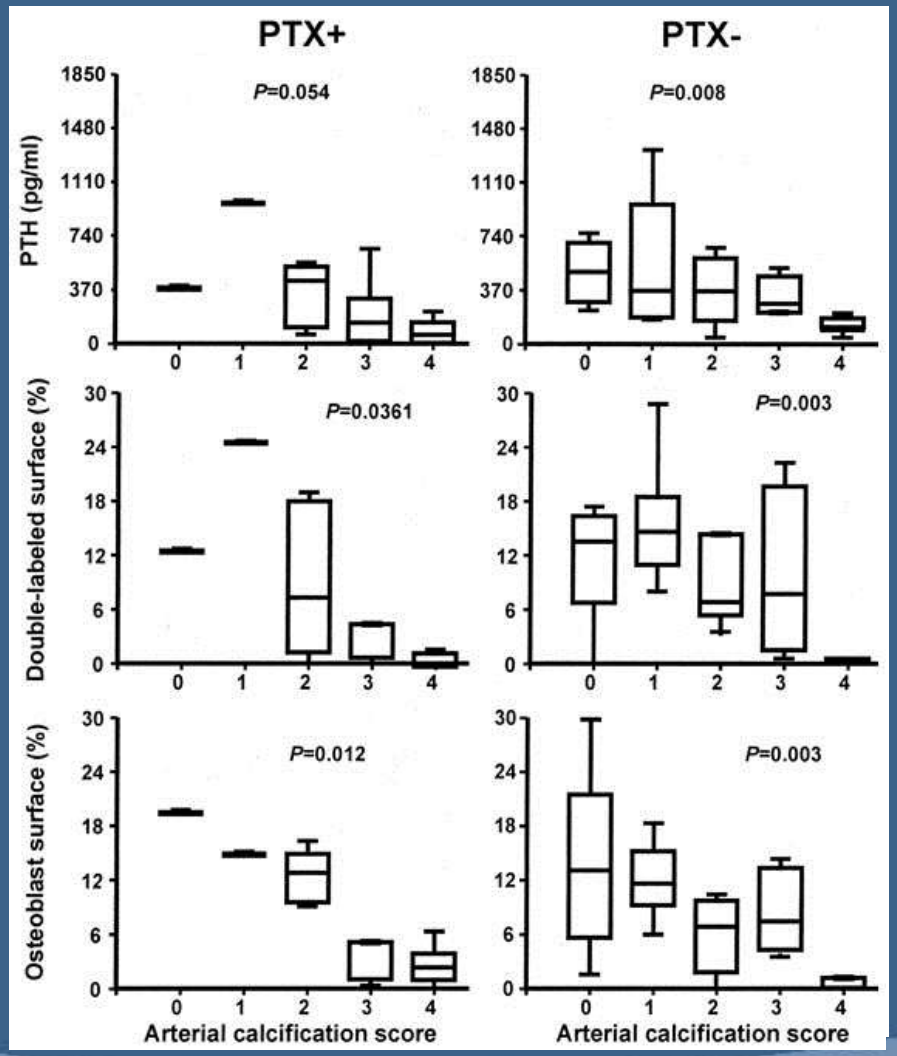
Young EW et al: AJKD 44: S34-S38, 2004

Diagnosis of adynamic bone disease in *hemodialysis* patients



OC: Osteocalcin
BAP: Bone alkaline phosphatase

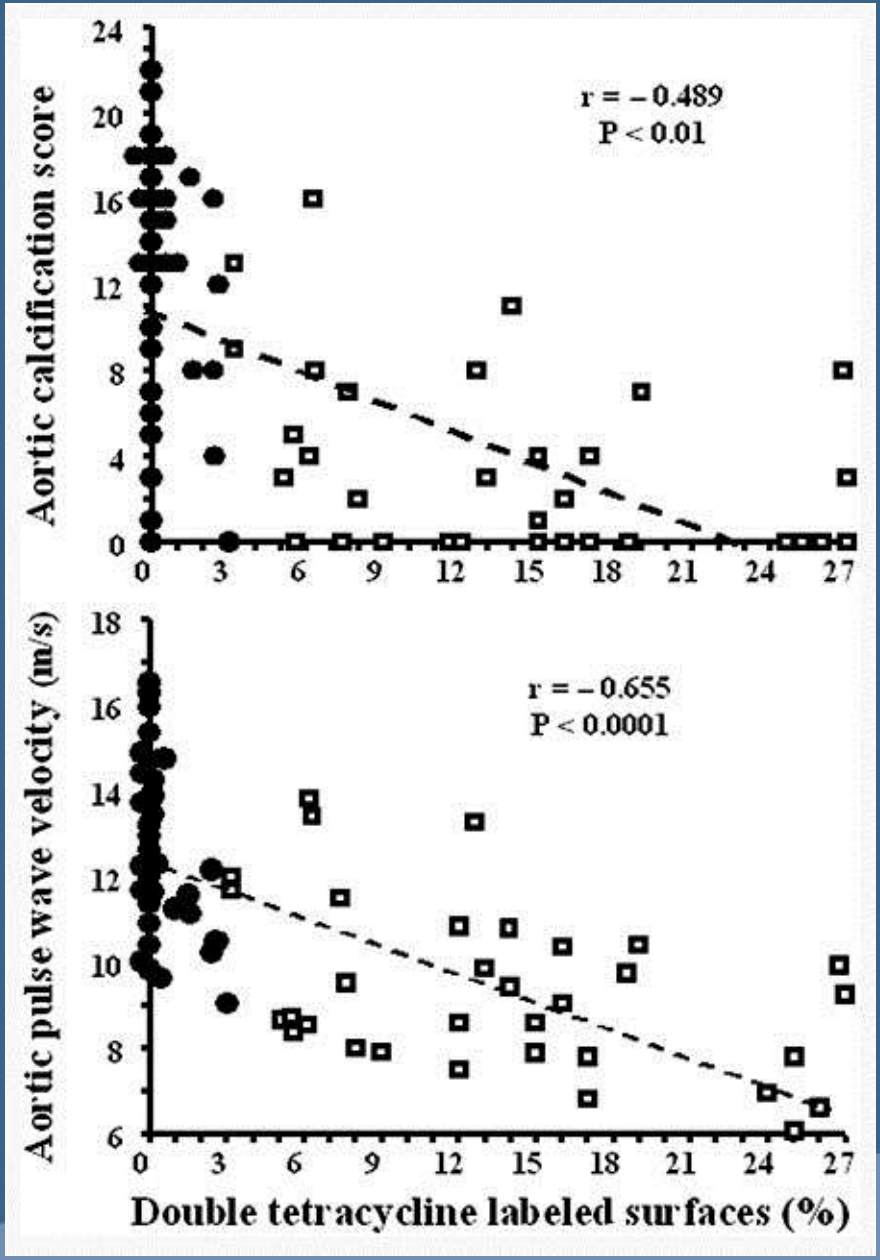
Arterial calcifications and bone histomorphometry in ESRD



Therapeutic interventions associated with excessive lowering of parathyroid activity (parathyroidectomy, excessive calcium or aluminum load) **favor lower bone turnover and adynamic bone disease,** which could influence the **development and progression of arterial calcification.**

London GM et al, JASN 15: 1943-1951, 2004

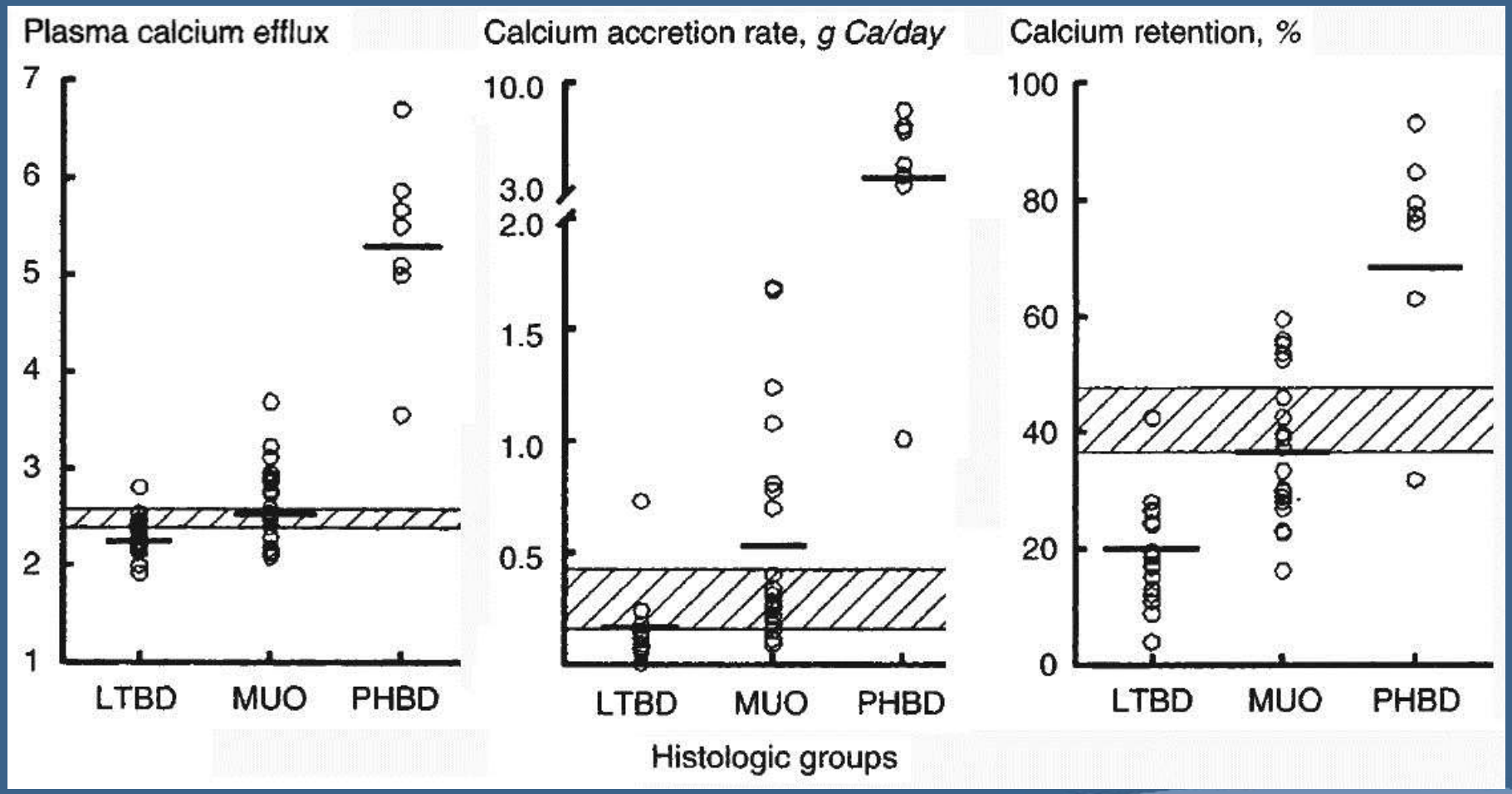
Association of bone activity, calcium load, aortic stiffness and calcifications in ESRD



Correlations (*n* = 66) between double tetracycline–labeled surfaces and abdominal aortic calcification score or aortic PWV.
• adynamic bone
□ active bone

London GM et al: JASN 19: 1827-1835, 2008

Evidence for abnormal calcium homeostasis in patients with adynamic bone disease

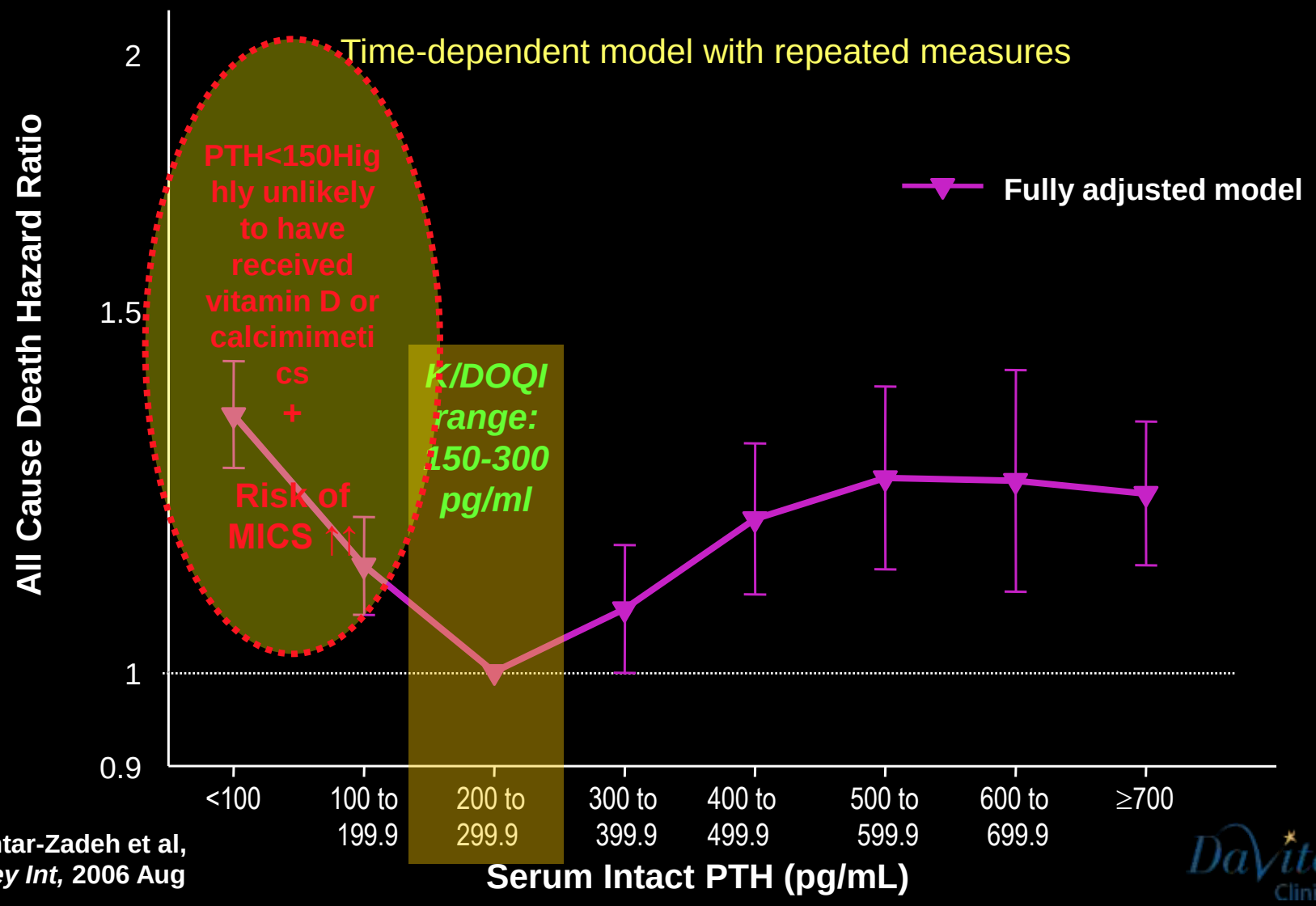


LTBD: low turnover bone disease
MUO: mixed uremic osteodystrophy
PHBD: predominant hyperparathyroid bone disease

Kurz P et al: Kidney Int 46: 855-861, 1994

Universiteit Antwerpen

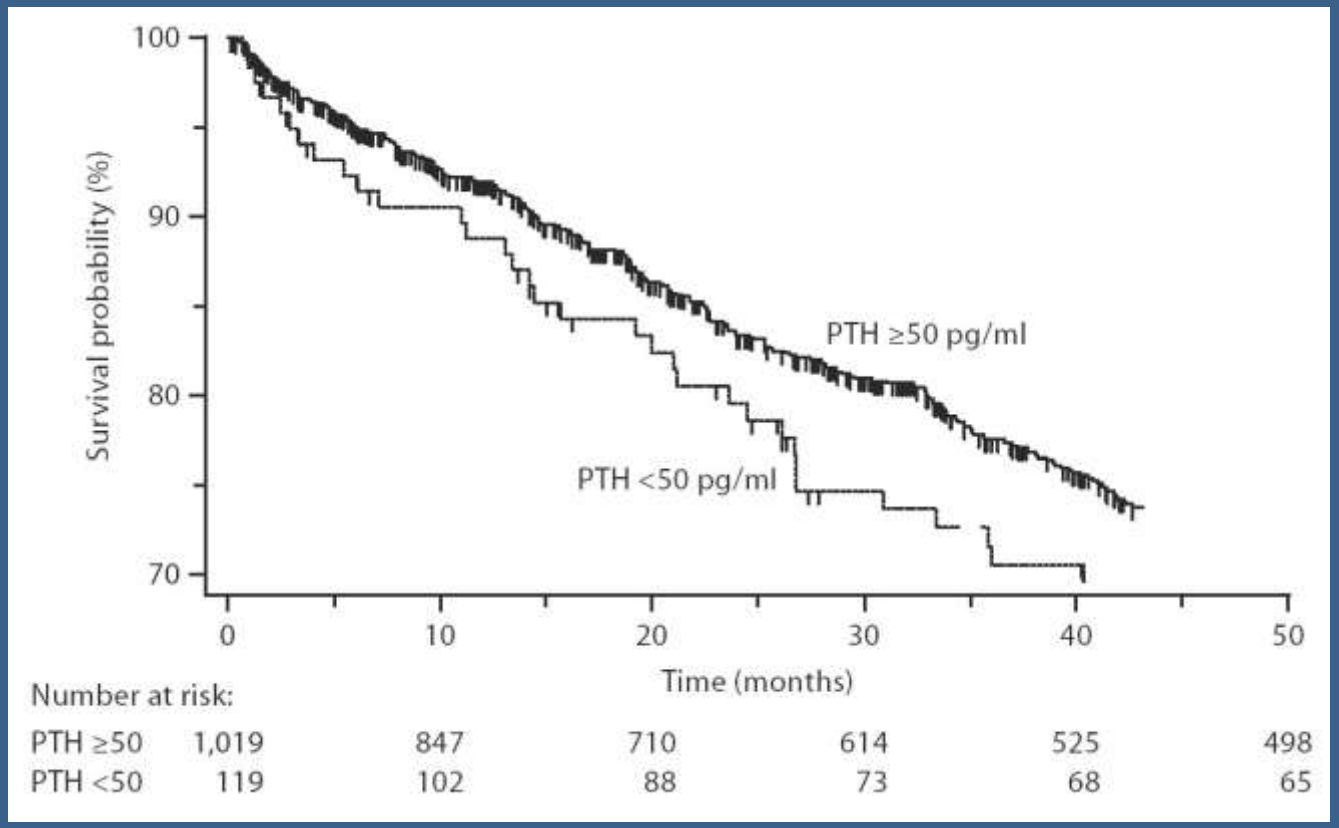
Risk of Death by Quarterly Varying PTH



Kalantar-Zadeh et al, *Kidney Int*, 2006 Aug

DaVita Clinical Research

Association between very low PTH levels and poor survival rates in hemodialysis patients: Results from the French ARNOS cohort

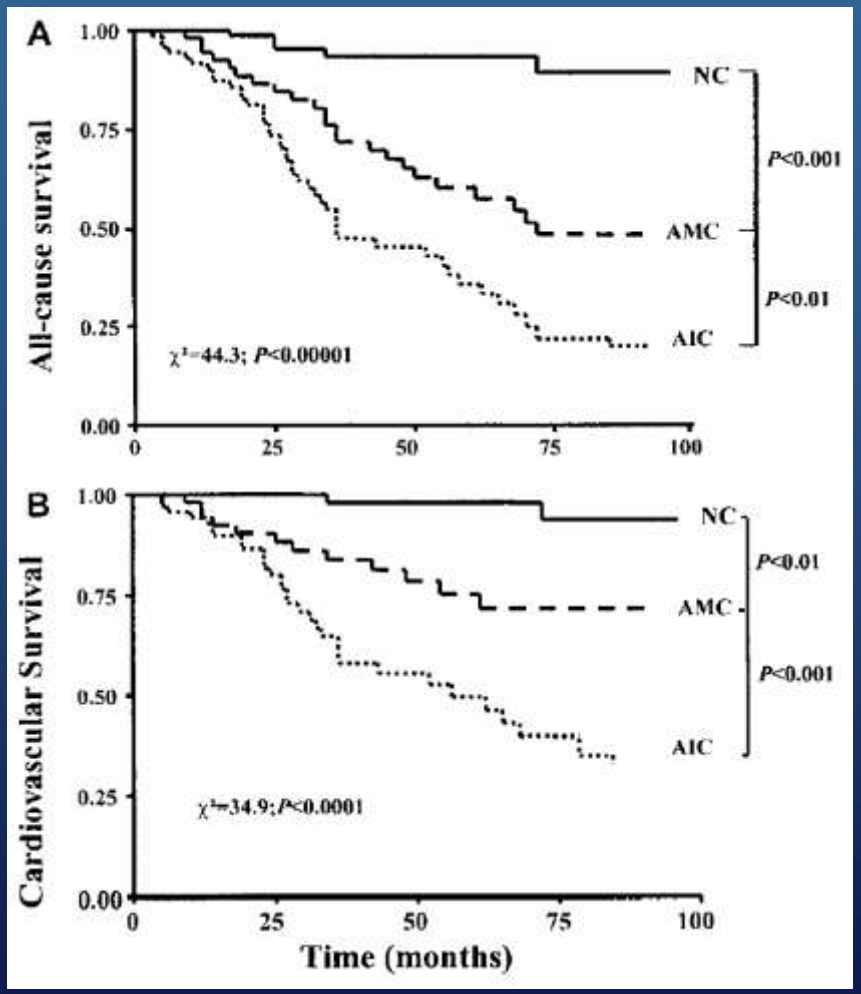


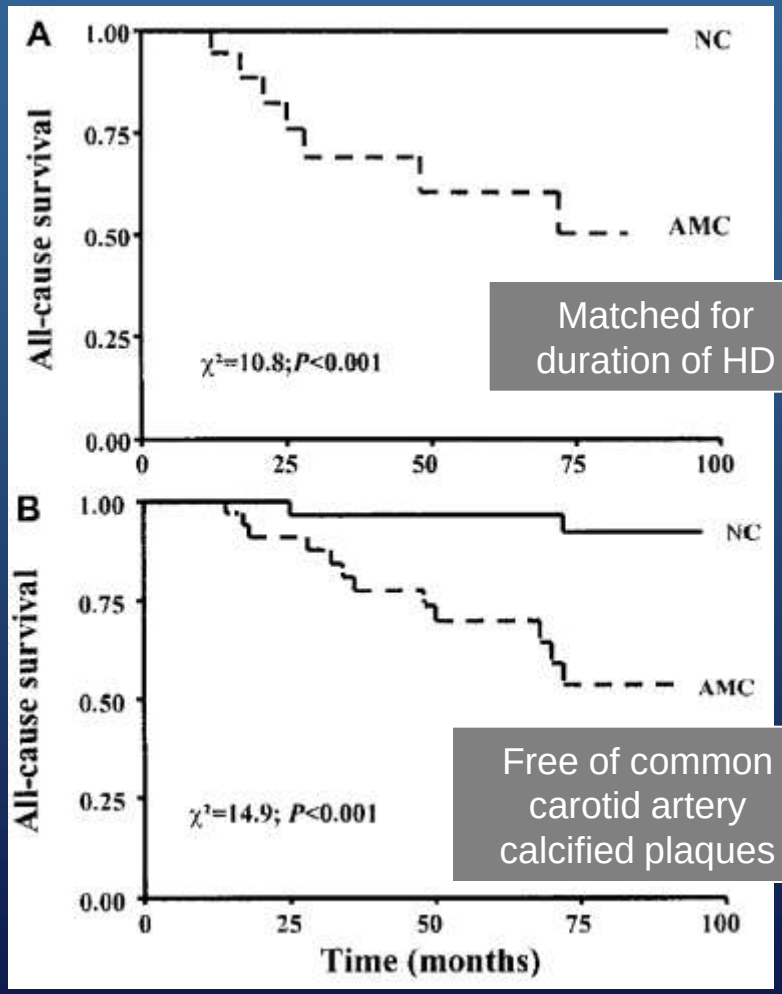
42-month survival curve acc. to the baseline serum PTH levels adjusted for age, dialysis vintage, gender and diabetes

Jean G et al: Nephron Clin Pract 2010 (In Press)

Arterial media calcification in ESRD: impact on all-cause and cardiovascular mortality

NC no calcification
AMC Arterial media calcification
AIC Arterial intima calcification



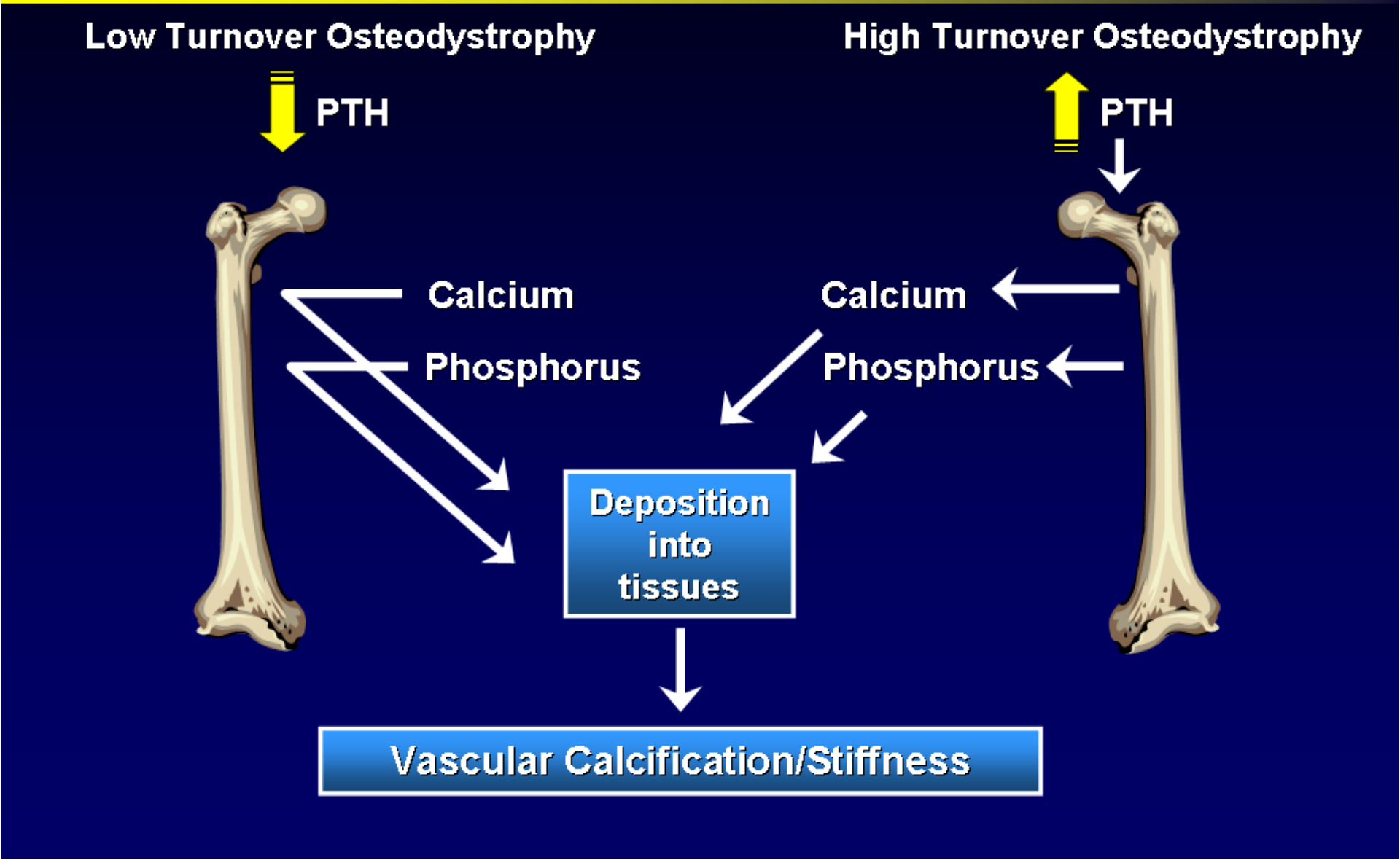


Matched for duration of HD

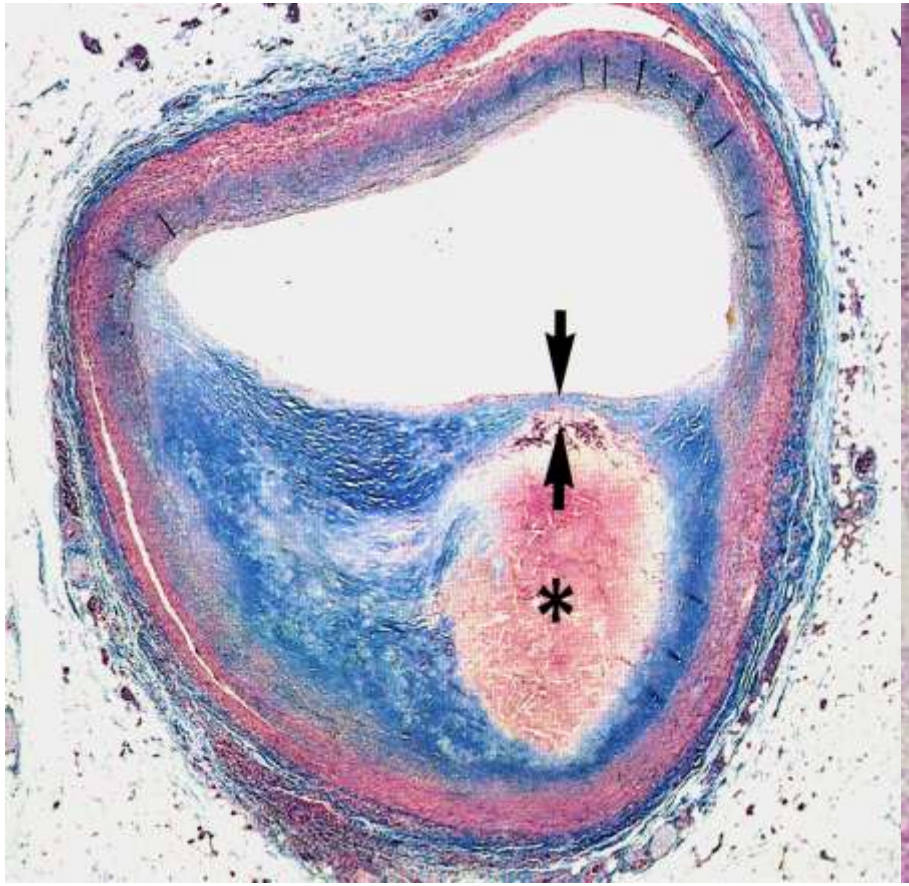
Free of common carotid artery calcified plaques

London GM et al: Nephrol Dial Transplant 18: 1731-1740, 2003

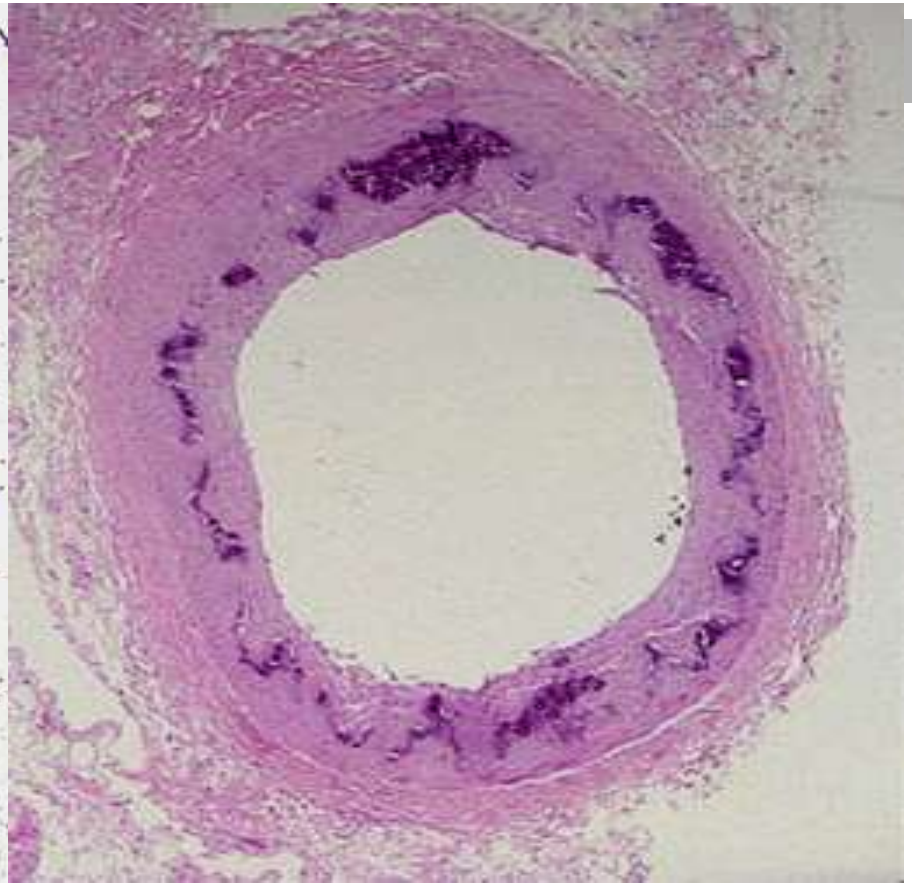
Both Forms of Osteodystrophy in CKD Contribute to Hyperphosphatemia



Atherosclerosis – intimal
Plaque calcification

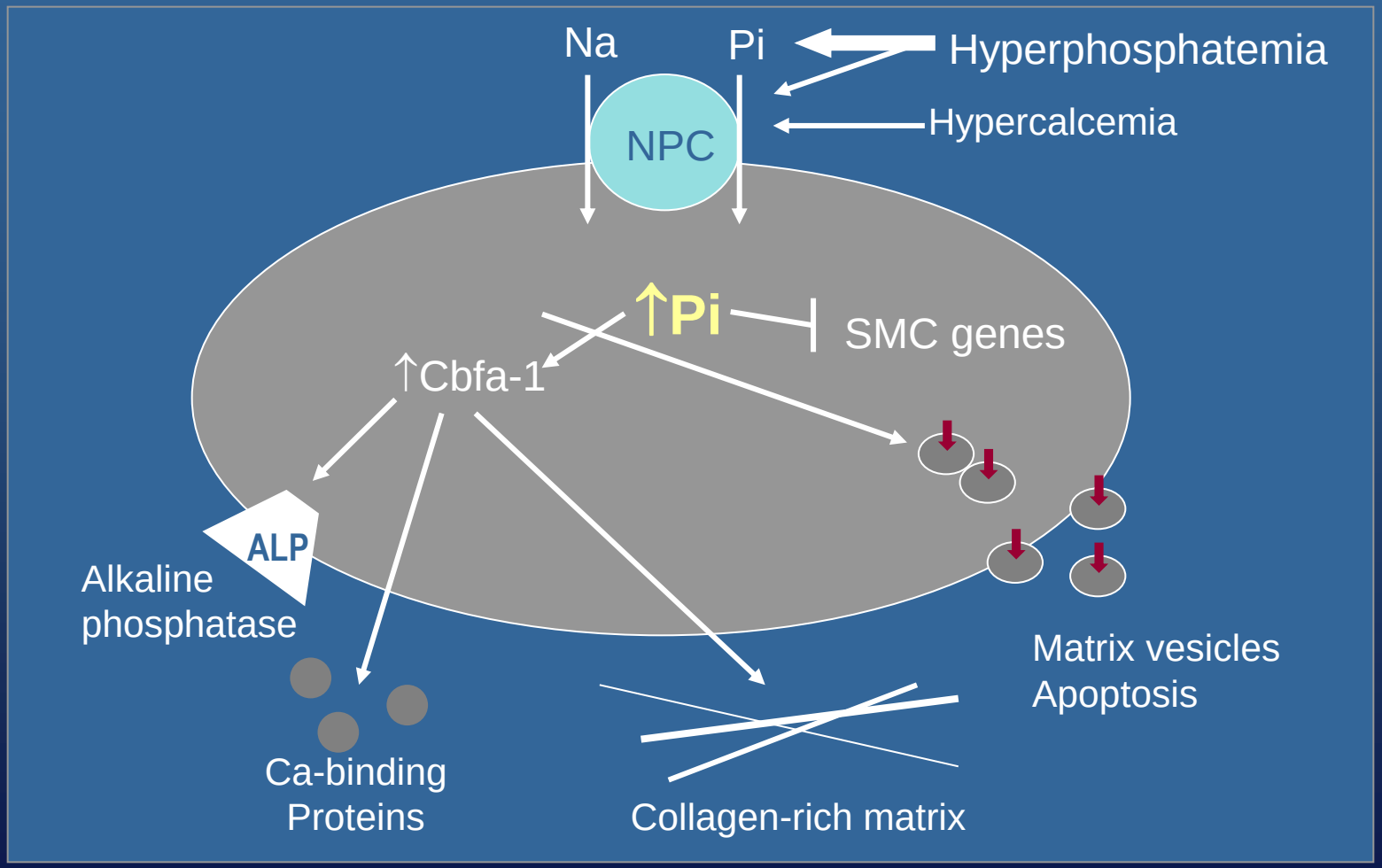


Medial calcifications
Monckeberg mediacalcosis



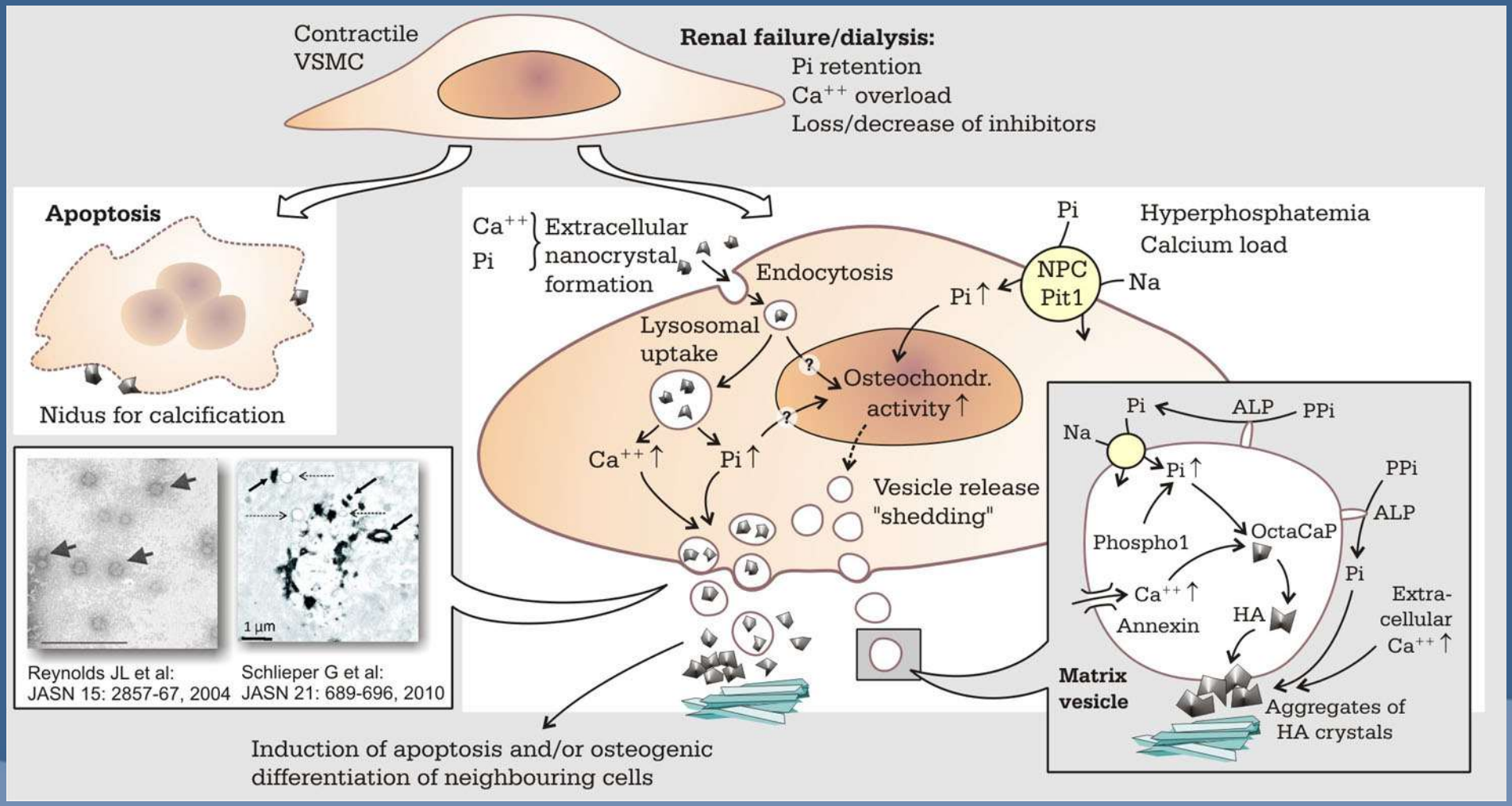
Cell biology of uremia-related vascular calcification

Transdifferentiation of vascular smooth muscle cells to an osteoblast phenotype

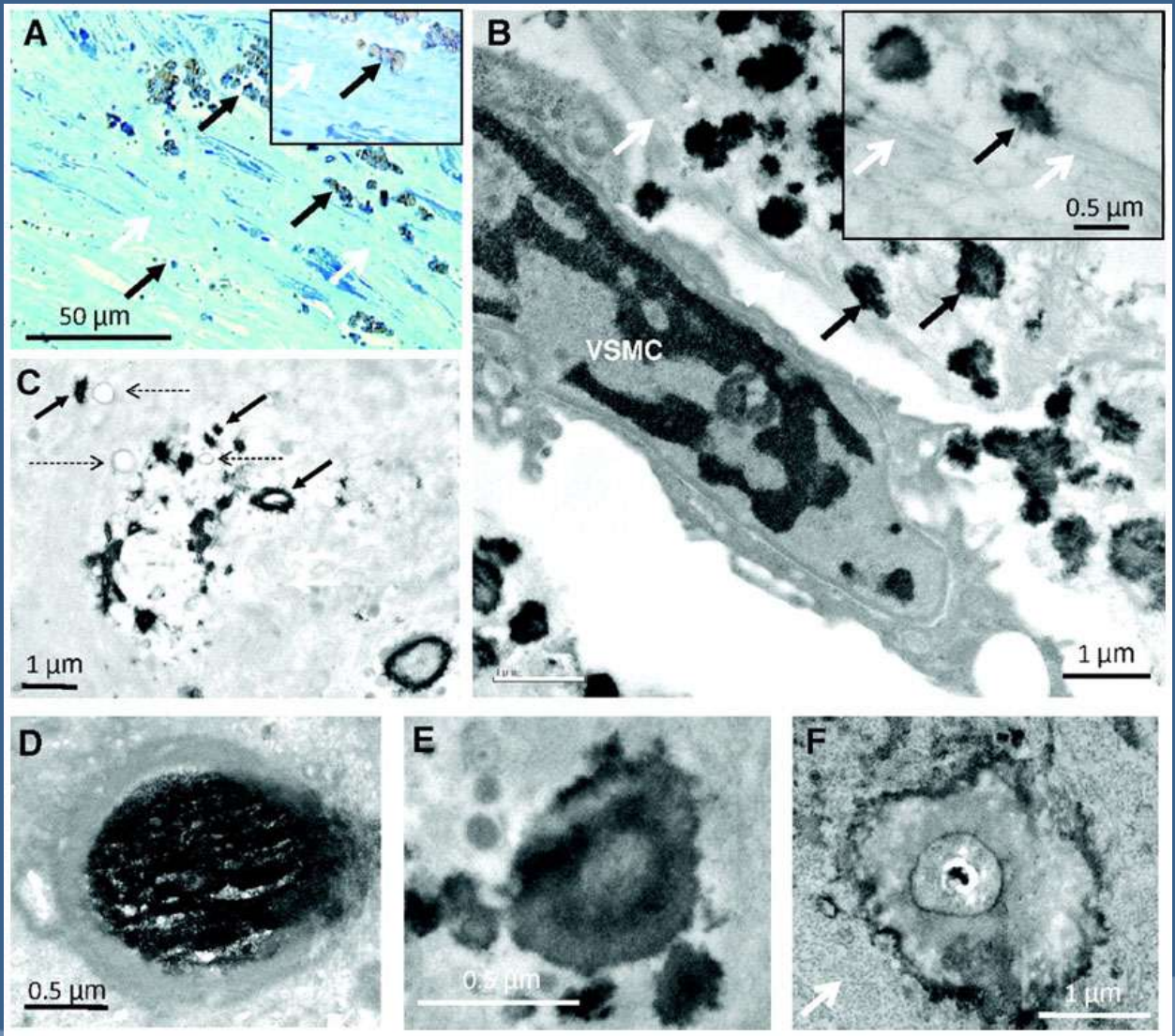


Steitz, Circ Res 2001; Giachelli, Kidney Int, 2003; Yang, Kidney Int 2004, K I 75 /890/2009, phosphonormic acid,Pit ko

Physiopathological mechanisms of vascular calcification



Ultrastructural analysis of vascular calcifications in uremia



Microcalcifications in uremic arteries, located ***extracellularly*** in the vicinity of collagen and vesicular structures.

(A) Undecalcified arterial samples: small ***mineralization foci of variable size*** (black arrows) near collagen fibrils (light blue staining, white arrows) (LM, Von Kossa).

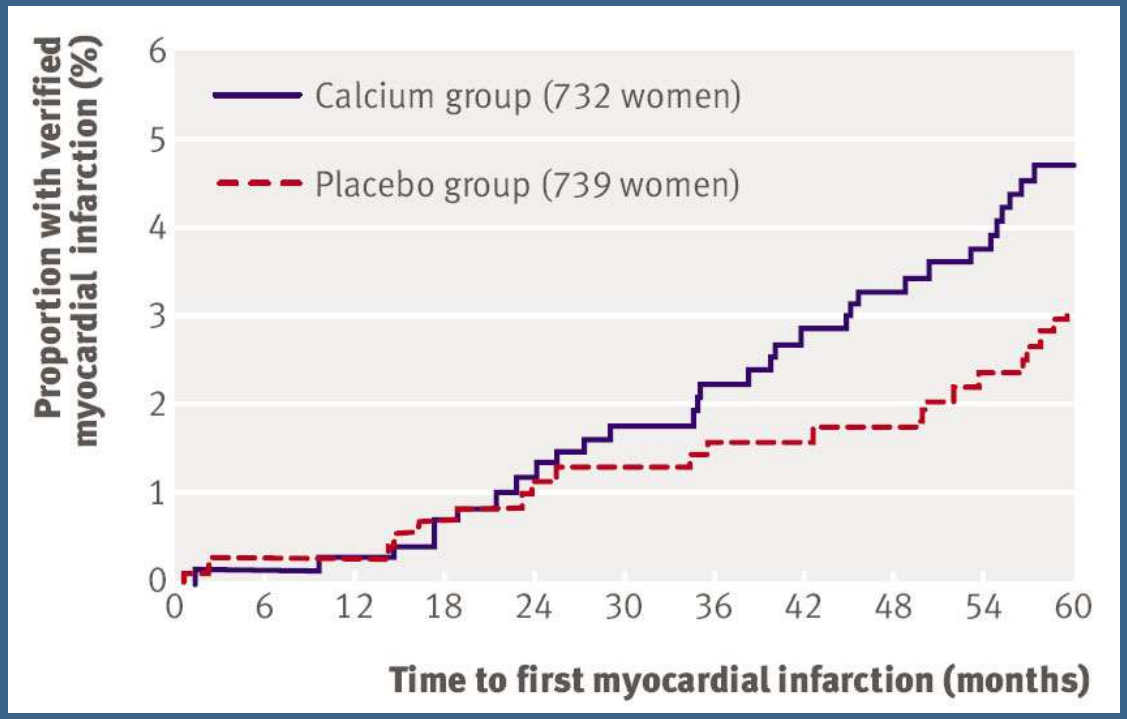
(B) VSMC surrounded by multiple small mineralization foci (black arrows) in the extracellular matrix. The white arrows indicate collagen fibrils (TEM).

(C) Mineralization foci (black solid arrows) in the vicinity of ***vesicular structures*** (black dashed arrows) and collagen fibrils (white arrows).

(D through F) Mineralization foci in the extracellular matrix (TEM).

Aachen,Antwerp,Erlangen,Montreal,
Schlieper G et al JASN,21,689,2010

Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial



Calcium supplementation in healthy postmenopausal women is associated with upward trends in cardiovascular event rates. This potentially detrimental effect should be balanced against the likely benefits of calcium on bone

Bolland MJ et al: BMJ 2009

CALCIUM LOAD in DIALYSIS PATIENTS

- Increase in serum calcium –ionized calcium
- Decrease in PTH secretion ,relative hypoparathyroidism
- Low bone turn over
- Less incorporation of calcium in bone
- Higher risk for development of vascular calcifications

EFFICIENT PHOSPHATE BINDING

AVOID EXCESIVE CALCIUM LOAD

How to Limit Calcium Load in Dialysis Patients

- Limited use of calcium containing phosphate binders
- KDIGO guidelines

- Avoid the development of adynamic bone disease
- follow up of PTH (more 150-200pg/ml) and bone ALP

- Decrease calcium concentration of dialysis fluids. Below
- 3.0 mEq/L if calcium containing P binders and Vit D are used

- Non- calcium- containing P binders

- Monitoring serum ionized calcium

Chronic Kidney Disease

	CKD 3 – 4 – 5	CKD 5 D
Hyperphosphatemia	+	+++
Vitamin D	insufficiency/deficiency	deficiency
Hypocalcemia	+	+
Hypocalciuria	++	irrelevant
PTH	+/++	+++ (35-40% PTH+)
FGF23	+/++	+++
Vascular calcifications	0/+	++/+++

Kidney Bone Disease
What happens when the kidney fails?

- ✓ Progression of kidney damage >> mineral metabolism
- ✓ Bone histology in ESRF
- ✓ Concept of calcium loading in CKD
- ➢ Non-calcium containing phosphate binders
- o Lanthanum: a safe phosphate binder?
- o Lanthanum and the calcium loading concept

L'arsenal thérapeutique

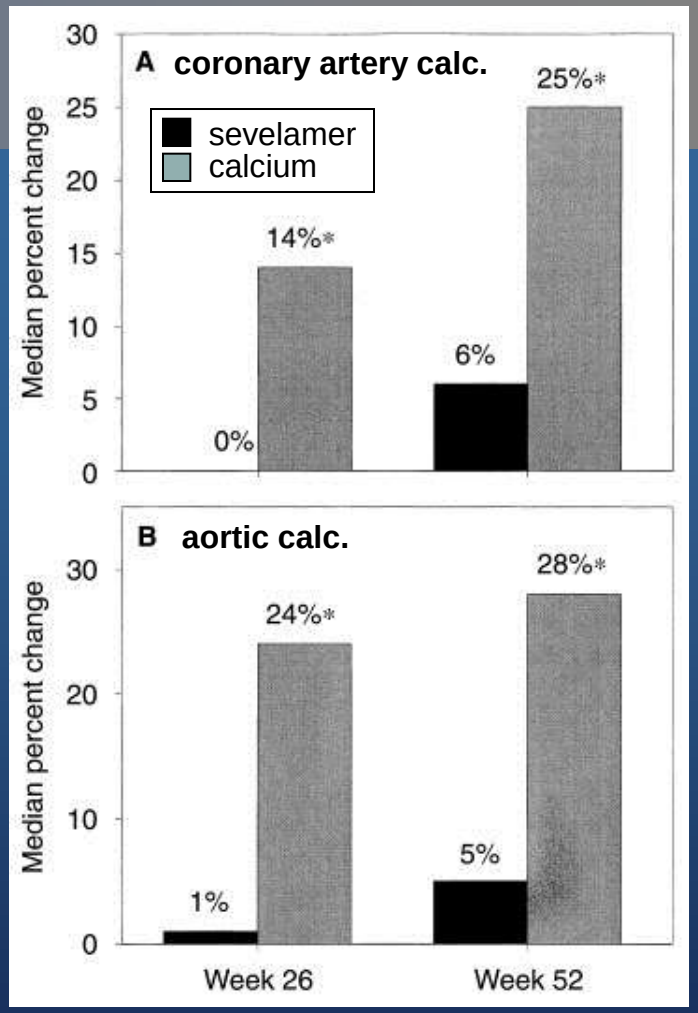
Tonelli N Engl J Med 2010;362:1312-24.

Table 1. Common Drug Interactions and Adverse Events with Phosphate Binders.

Drug*	Interaction	Adverse Effects†
Sevelamer hydrochloride (Renagel) and sevelamer carbonate (Renvela)		Gastrointestinal effects (nausea, vomiting, abdominal pain, bloating, diarrhea, and constipation) in 38% of patients (3.3–67)[31-42] Hypercalcemia in 13% of patients (0–22)[32,33,37,42] Metabolic acidosis in 34% of patients[43]‡ Peritonitis in 11% of patients[32]
Lanthanum (Fosrenol)		Gastrointestinal effects (nausea, vomiting, diarrhea, constipation, and dyspepsia) in 8% of patients (1.4–53)[44-51] Hypercalcemia in 6% of patients (0.0–6)[45,51,52] Muscular cramping in 7% of patients[44] Peripheral edema in 24% of patients[53] Myalgia in 21% of patients[53] Peritonitis in 4% of patients[44]
Calcium carbonate (Tums, Os-Cal, Caltrate) and calcium acetate (Phoslo, Eliphos)	Interference with absorption of aspirin, digoxin, isoniazid, quinolone, and tetracycline[54]	Gastrointestinal effects (nausea, vomiting, diarrhea, constipation, and epigastralgia) in 22% of patients (3.8–49)[36,37,42,51,55,56] Hypercalcemia in 10% of patients (12–54)[32,33,37,42-44,51,52,57] Peritonitis in 4% of patients[37] Pruritus in 10% of patients[56] Xerostomia in 12% of patients[56] Muscle cramping in 6% of patients[44]
Magnesium hydroxide (Milk of Magnesia) and magnesium carbonate (Gaviscon§)	Impaired absorption of oral iron[58]	Gastrointestinal effects (diarrhea and constipation) in 20% of patients (4–35)[55,59] Hypermagnesemia in 4% of patients[59]

Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients

Baseline characteristics	Sevelamer (N = 99)	Calcium (N = 101)	P value
Age *years* (mean ± SD)	57 ± 14	56 ± 16	0.88
Sex *% female*	36%	34%	0.77
Race			
Black	17%	23%	0.34
White	71%	66%	
Other	12%	11%	
Diabetes %	32%	33%	1.0
Hypertension %	86%	83%	0.70
Smoker %	3%	8%	0.21
Primary Cause of ESRD %			
Hypertension	16%	17%	0.66
Glomerulonephritis	26%	16%	
Diabetes	23%	28%	
Polycystic kidney disease	9%	11%	
Other	26%	28%	
Dialysis vintage *years, median*	3.6	2.9	0.24
Phosphate binder use prior to study entry %			0.81
Calcium carbonate	38%	44%	
Calcium acetate	33%	36%	
Calcium + aluminum	14%	13%	
Sevelamer	3%	1%	
Other combinations	12%	6%	
Vitamin D usage at study entry	56%	59%	0.67



Change in calcification scores from baseline to weeks 26 and 52 in pt with score>30 at baseline

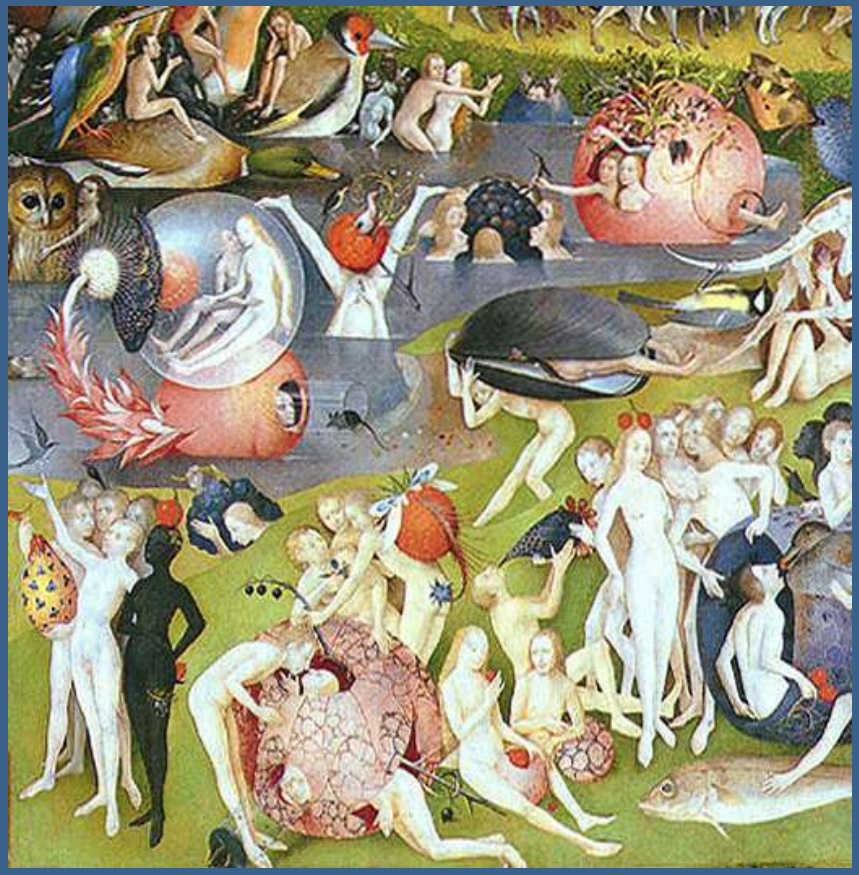
Compared with calcium-based phosphate binders, sevelamer is less likely to cause hypercalcemia, low levels of PTH, and progressive coronary and aortic calcification in hemodialysis patients

Chertow GM et al:
Kidney Int 62: 245-252, 2007

,Rind study 2007

2950

Metals and the kidney:
a relationship of love and hate

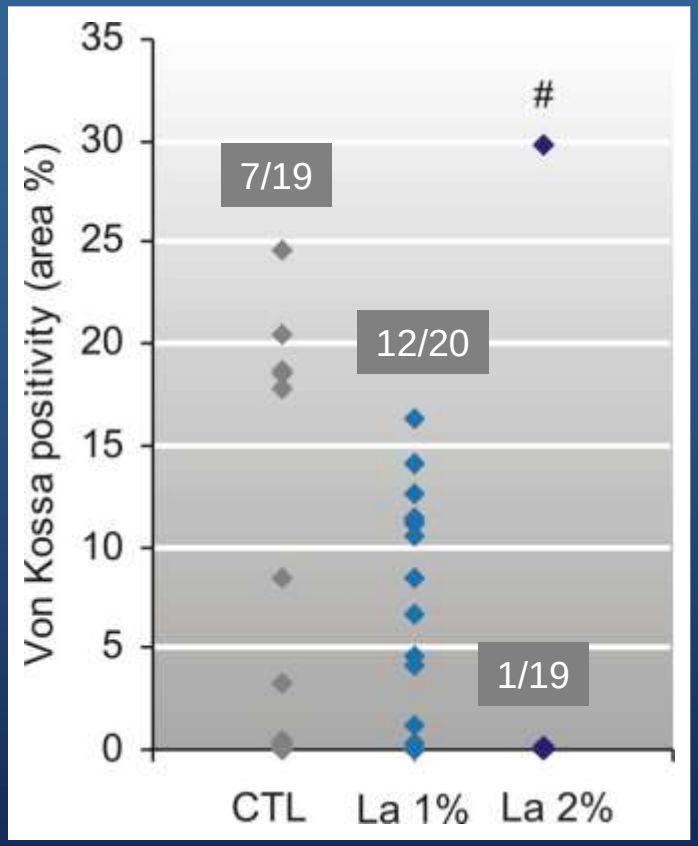


Hieronymus Bosch, 1469
De tuin der lusten, detail

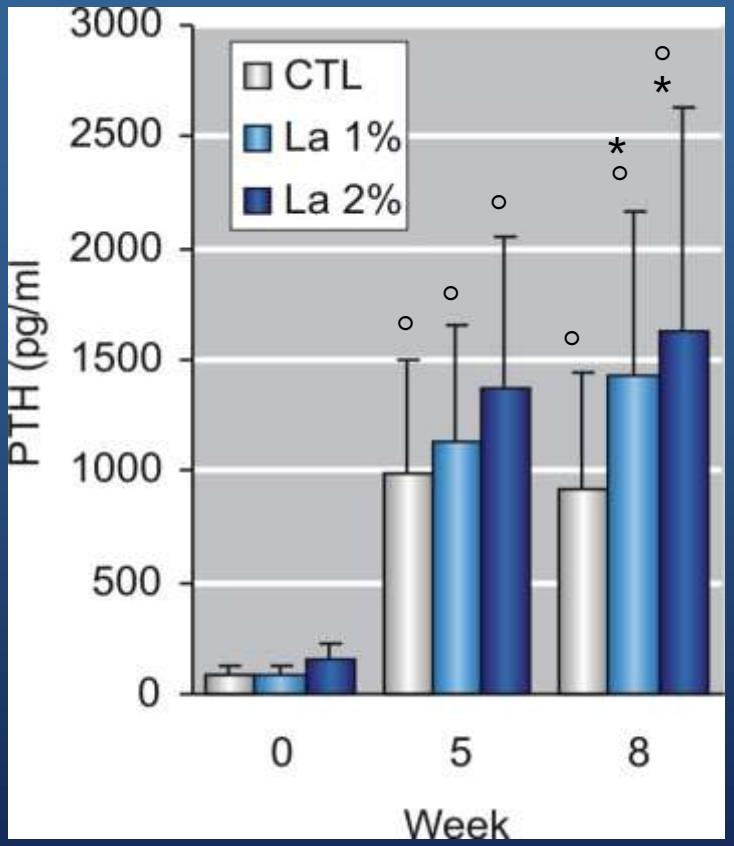
Hieronymus Bosch, 1510
De kruisdraging

Effect of lanthanum carbonate on adenine induced vascular calcification

DOSE FINDING ARM



#: p<0.05 vs. La 1%



°: p<0.05 vs week 0; *: p<0.05 vs CTL

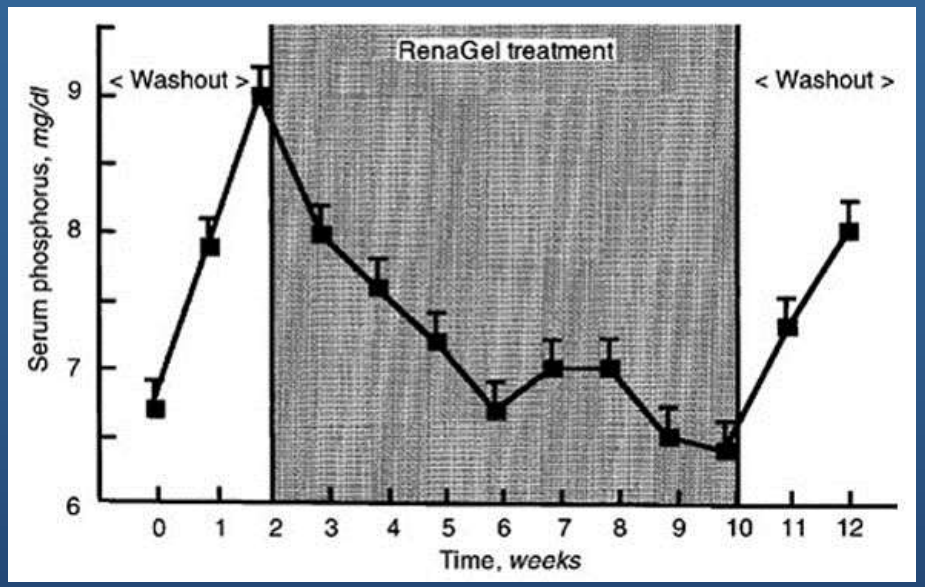
Neven et al. 2007 Nephr Dial Transp

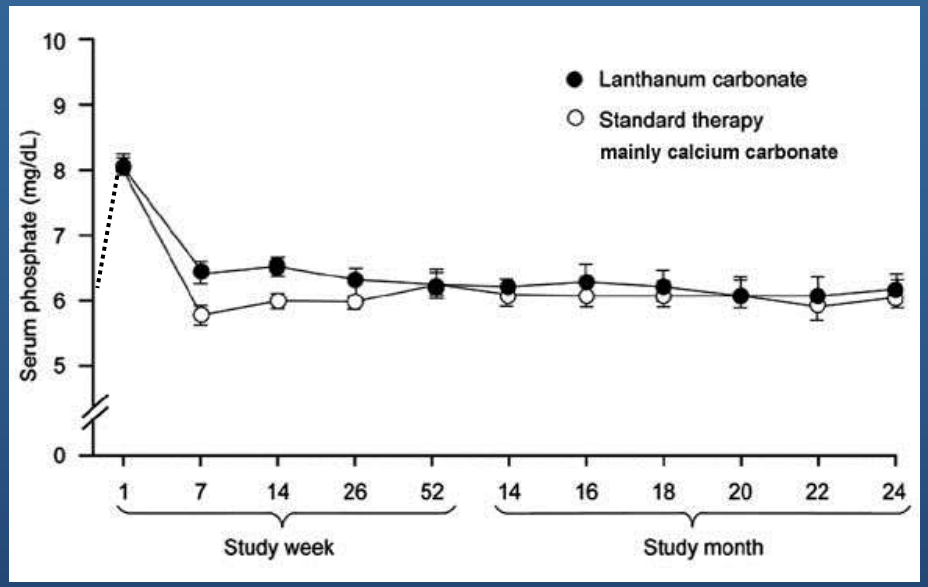
Non calcium containing phosphate binders

Renagel (n= 172)

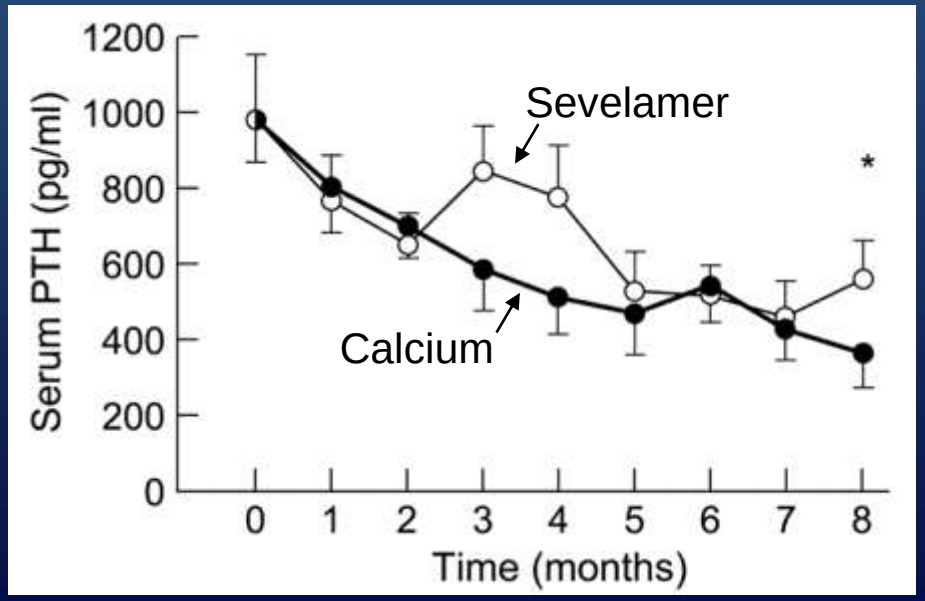
Lanthanum (n= 682 La, n=677 controls)

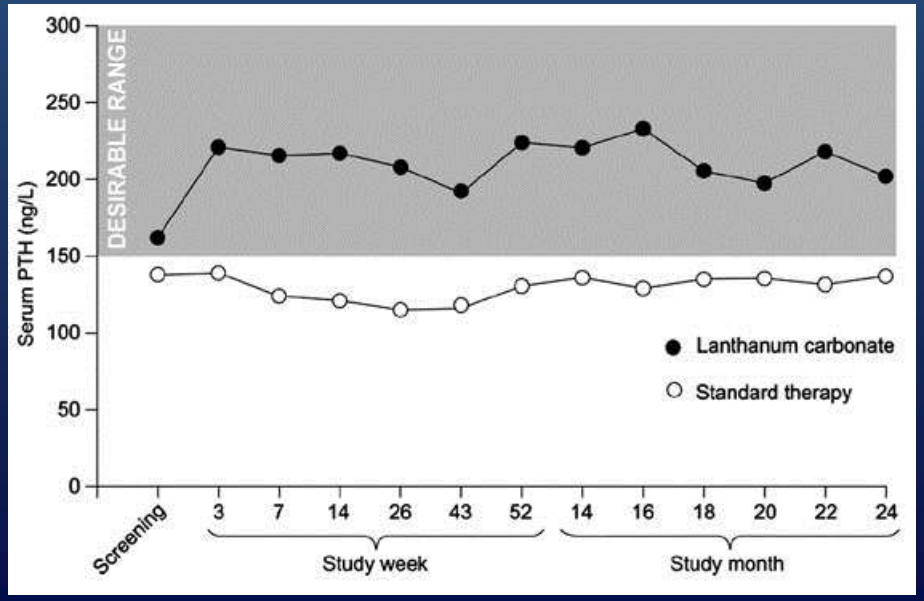
Serum P





Serum PTH



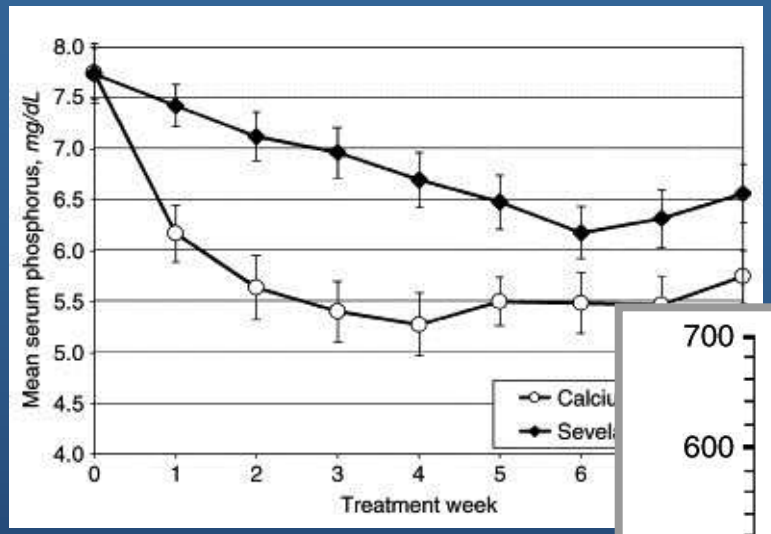


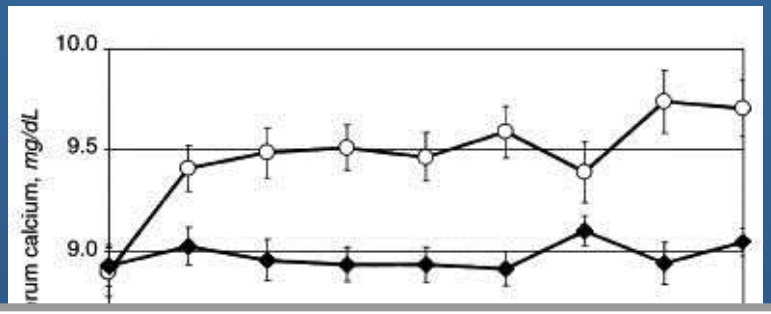
Slatopolsky EA et al: Kidney Int 55: 299-307, 1999

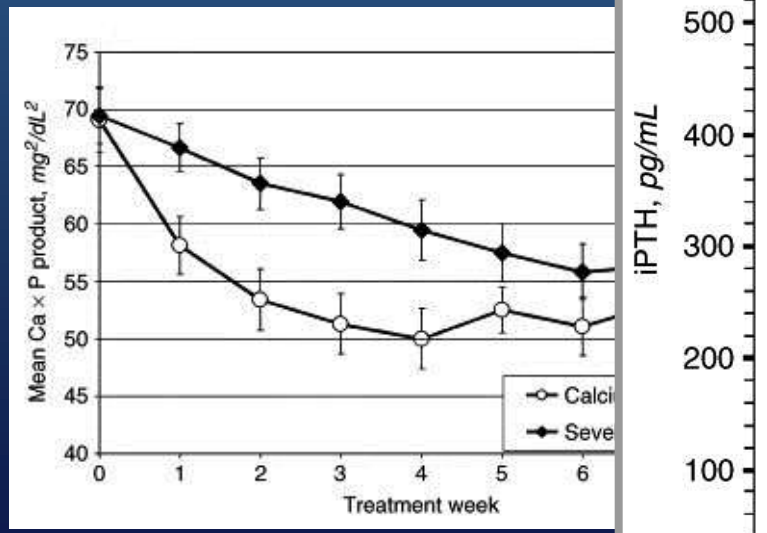
Finn WF et al: Clin Nephrol 65: 191-202, 2006

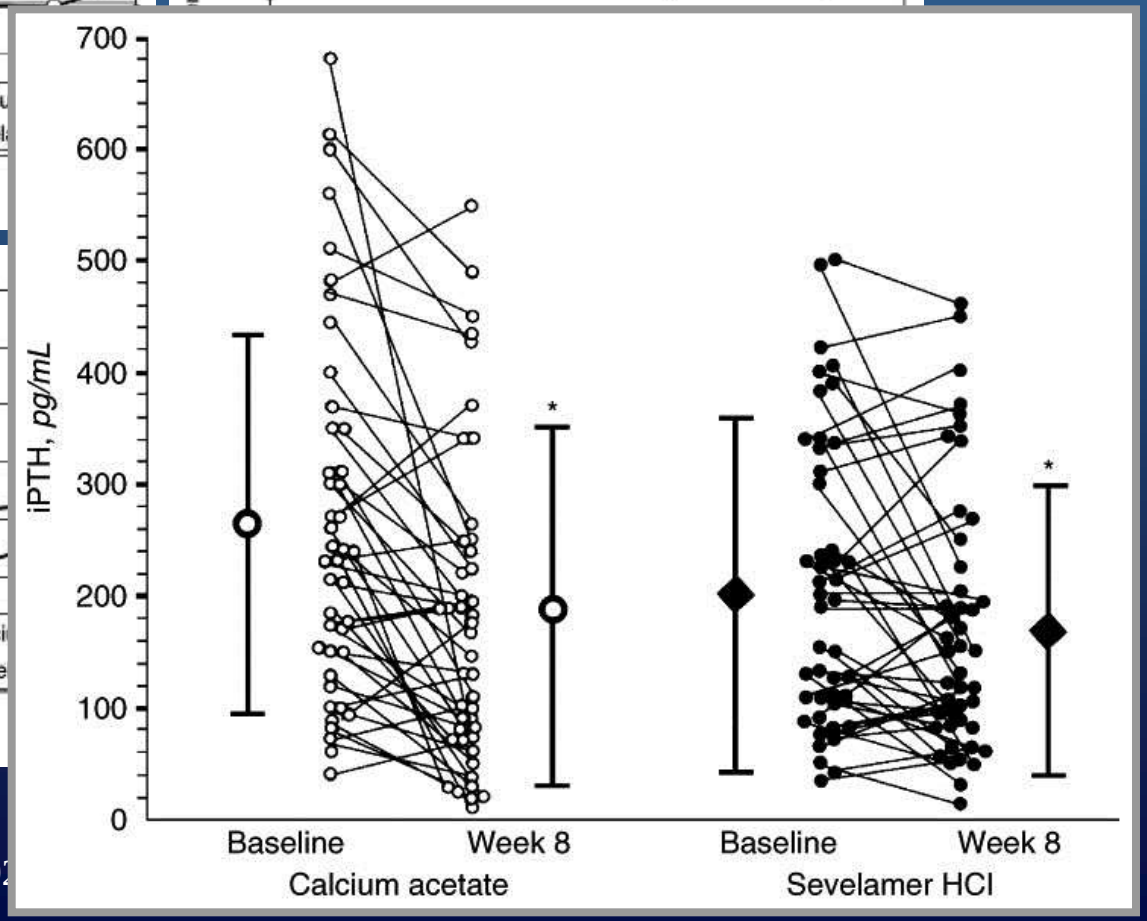
Treatment of hyperphosphatemia in hemodialysis patients:

The Calcium Acetate Renagel Evaluation (CARE Study)







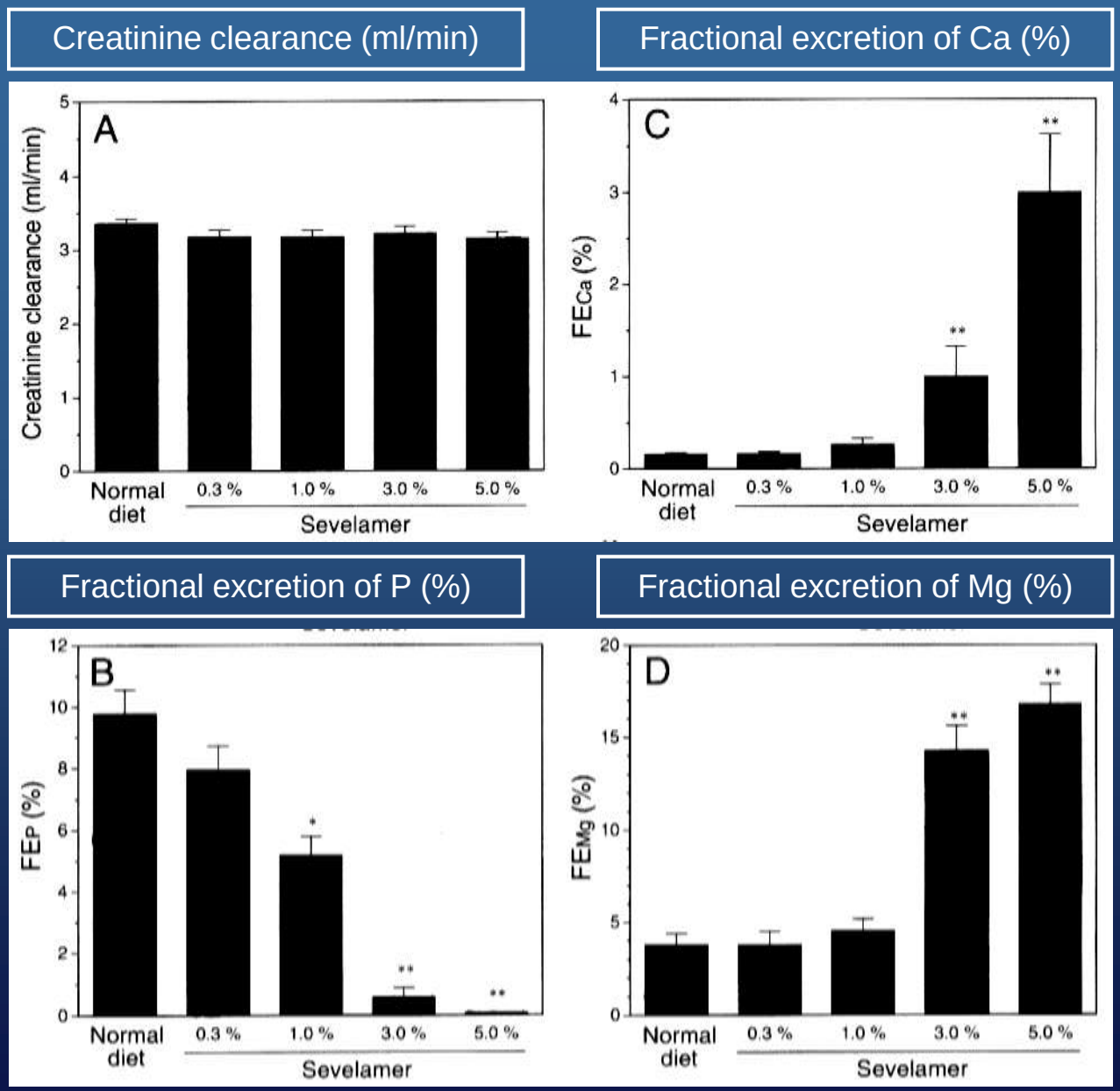


Qunibi WY et al: Kidney Int 65: 1914-192

Renal mineral handling in normal rats treated with sevelamer HCl, a non-calcemic phosphate binder

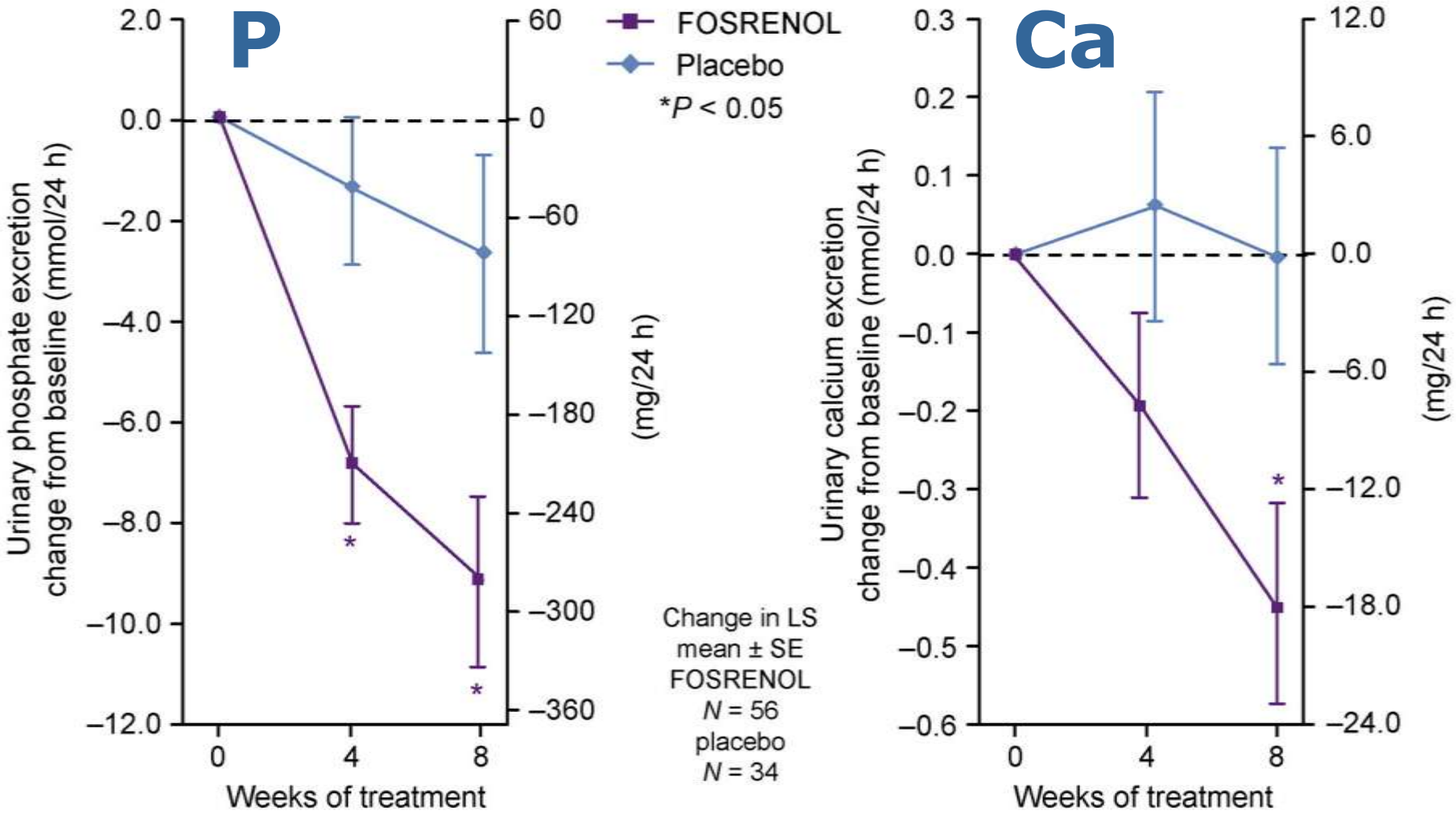
Nagano N et al:
Nephron 89: 321-328, 2001

Effects of sevelamer treatment for 8 days on creatinine clearance, FE_P, FE_{Ca} and FE_{Mg}



Phase 2 study in predialysis CKD: Fosrenol vs. Placebo (Shire SPD 405-206)

Change in urinary P and Ca



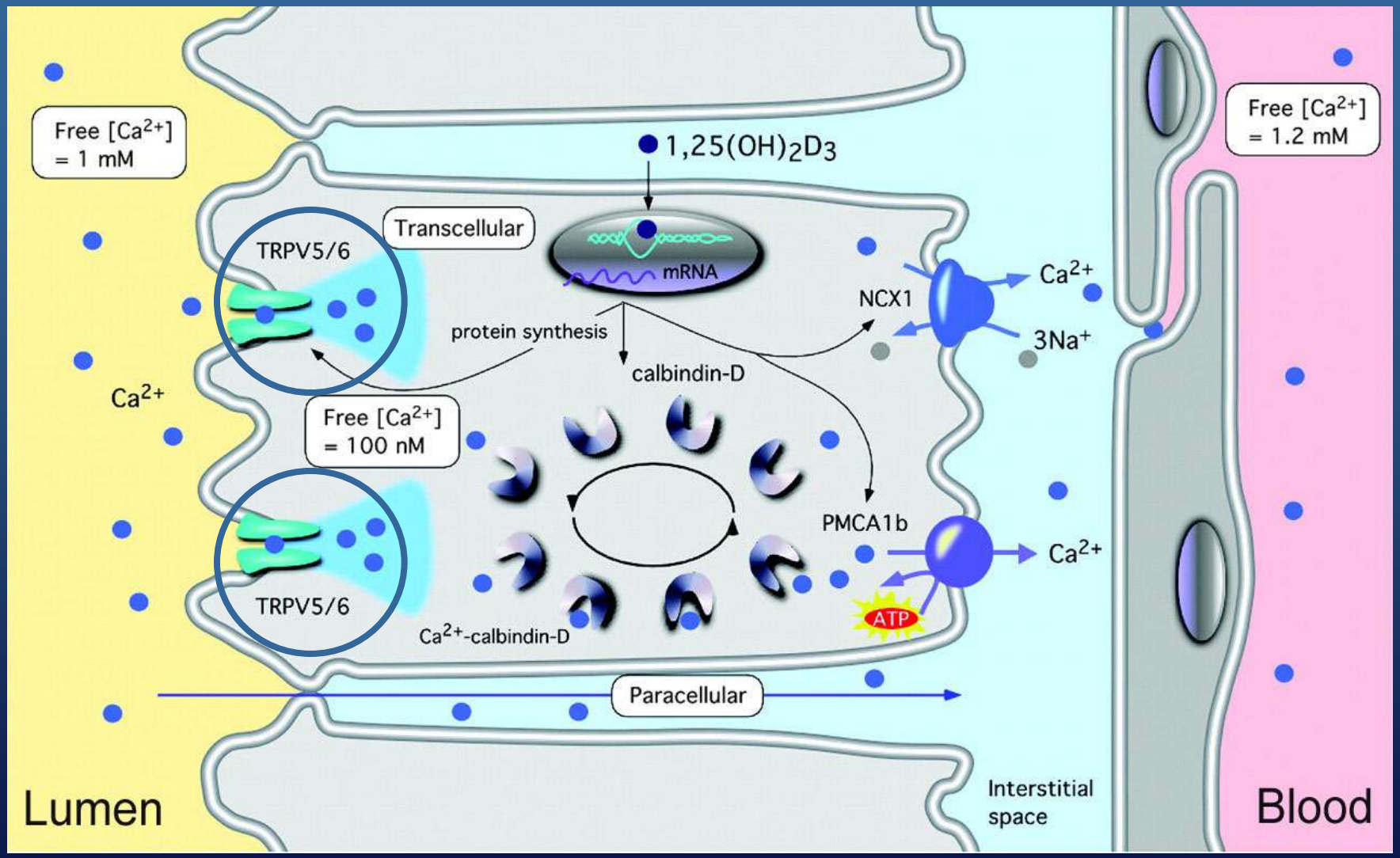
FOSRENOL (baseline P: 20.9 ± 1.50 mmol/24 h [836 ± 60 mg/24 h])
Placebo (baseline P: 19.6 ± 1.72 mmol/24 h [784 ± 69 mg/24 h])

FOSRENOL (baseline Ca: 1.01 ± 0.05 mmol/24 h [31.4 ± 6.1 mg/24 h])
Placebo (baseline Ca: 0.94 ± 0.17 mmol/24 h [29.3 ± 5.2 mg/24 h])

DDW3660

Mechanism of epithelial Ca^{2+} transport ,

Calcium absorption across epithelia



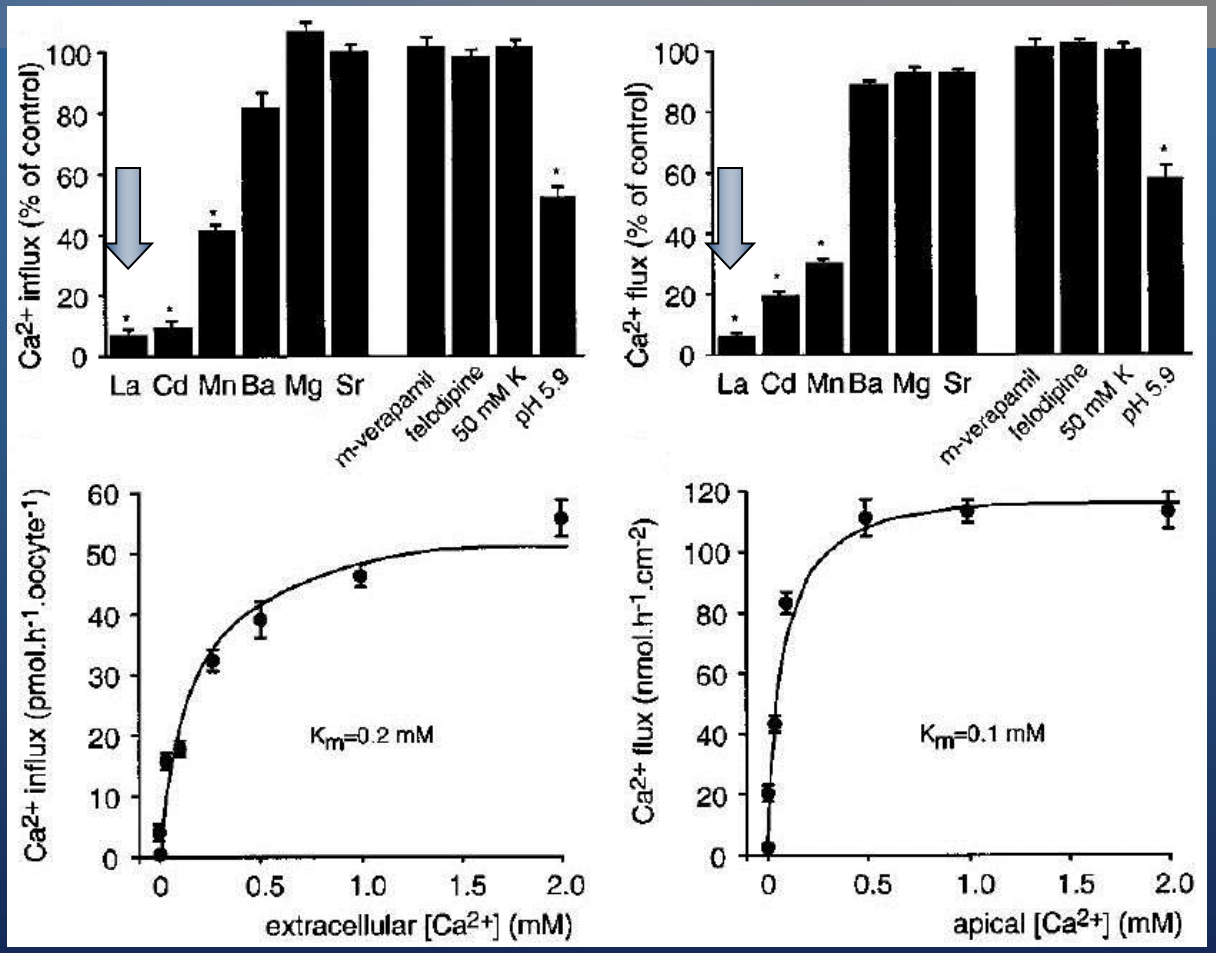
Hoenderop JG et al: Physiol Rev 85: 373-422, 2005

Calcium sensing receptor

Molecular identification of the apical Ca^{2+} channel in 1,25-dihydroxyvitamin D_3-responsive epithelia*

Hoenderop JG et al: J Biol Chem 274: 8375–8378, 1999

Functional characterization of the epithelial Ca^{2+} channel



La dose: 0.5 mM

Serum La = 3-15 nM

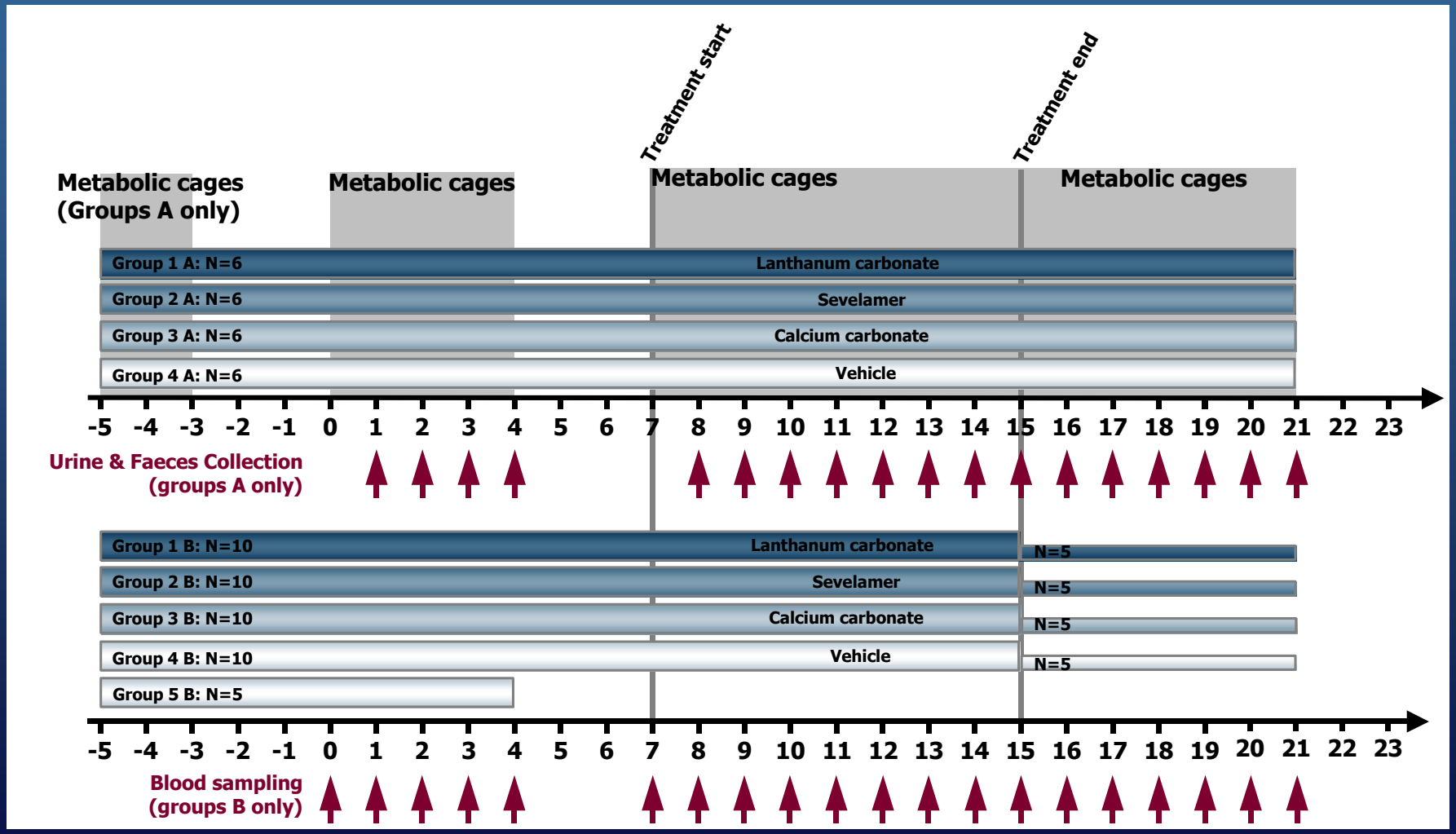
Fosrenol® (La carbonate) treatment: 2.5 – 4 g/day oral

La > 99% bound to serum proteins

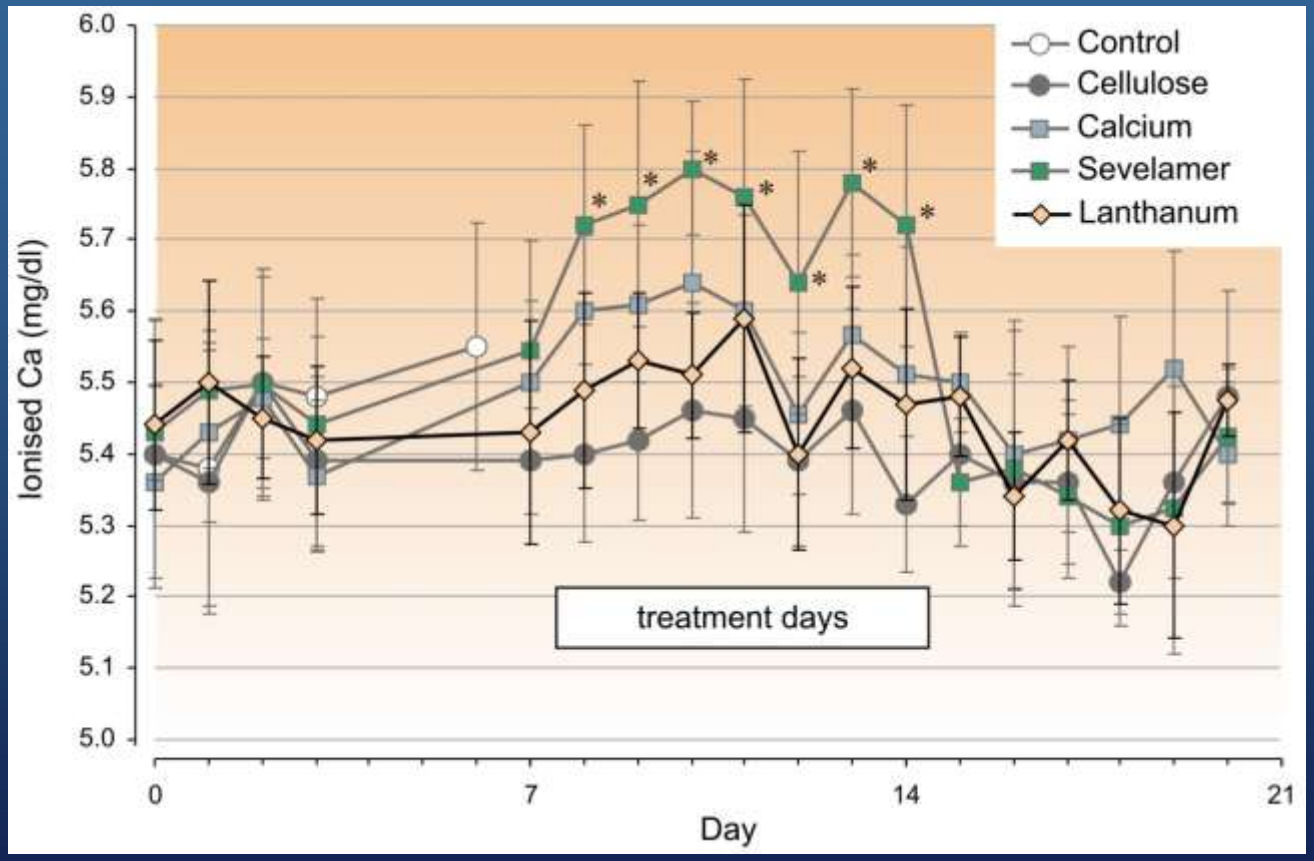
Free La < 0.03-0.15 nM

NO Calcium Channel Blocking Effect

Calcium balance study in rats receiving non-calcium-containing P binders



Serum ionised Ca levels

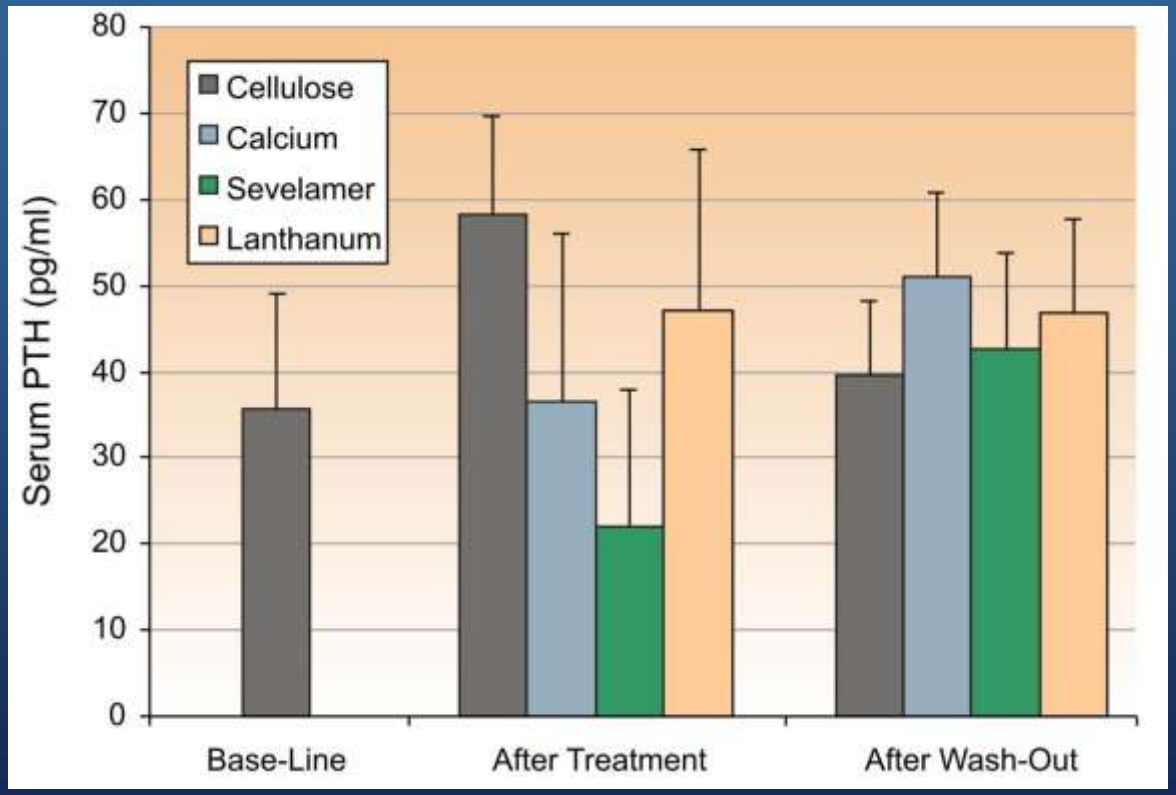


*: $p<0.05$ vs La

Total calcium in serum not signif. different

Behets G et al, 2008

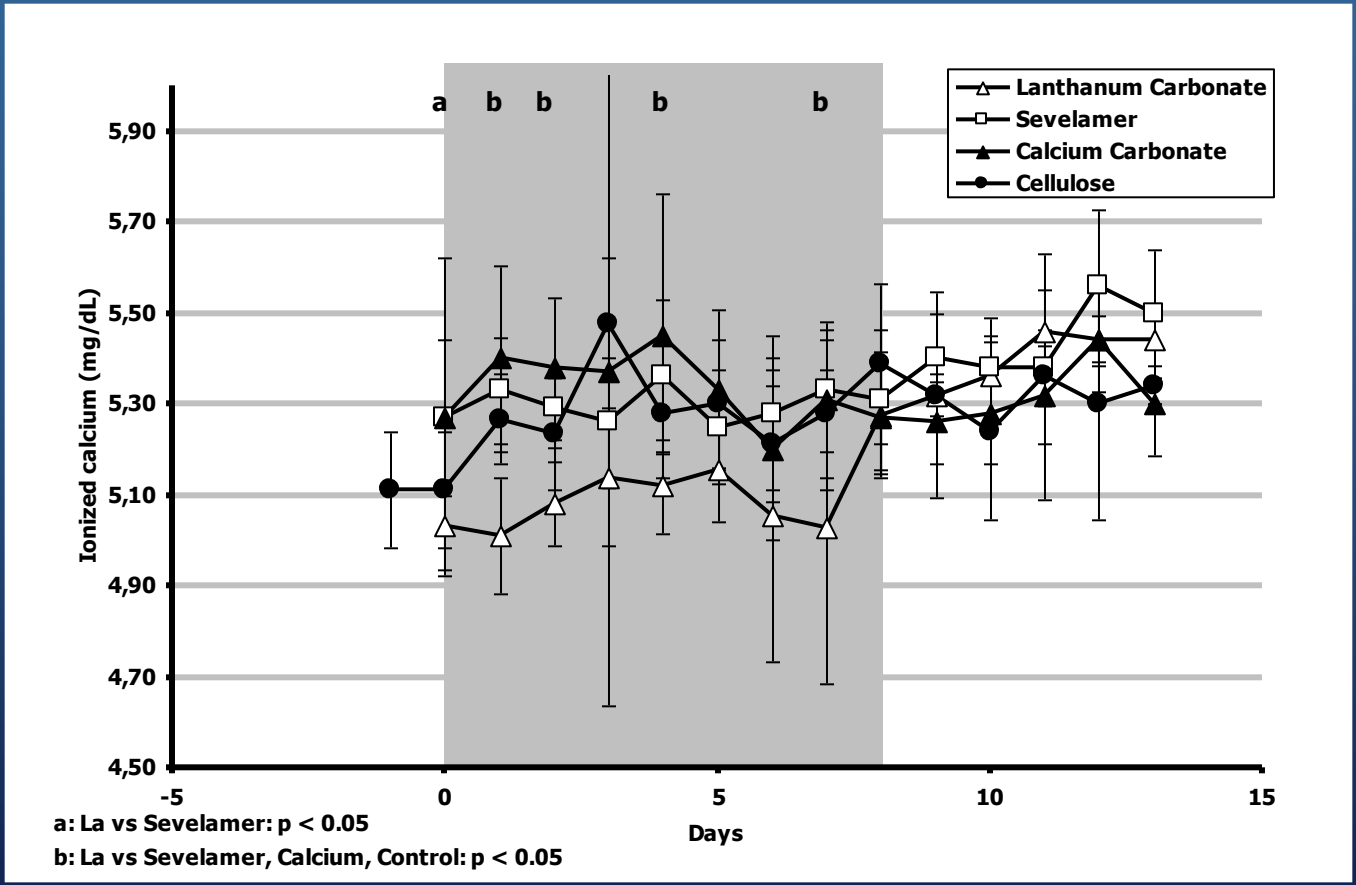
Serum PTH



Behets G et al, 2008

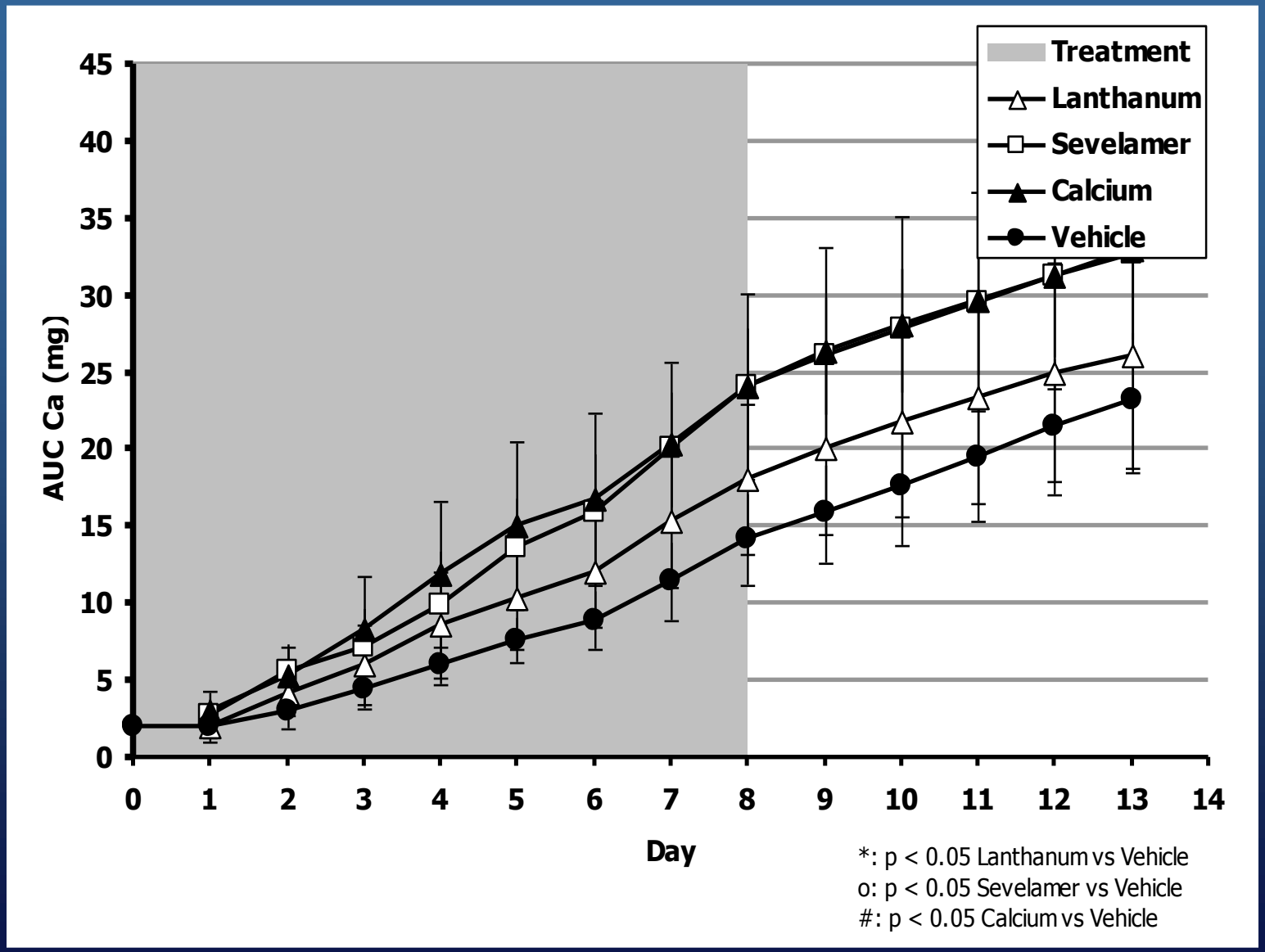
Serum ionised Ca levels

Balance study in human volunteers



Renal failure animals (5/6th nephrectomy)
Daily treatment by oral gavage (1000 mg/kg/day)
8 days of treatment, 6 days follow-up
N=10 animals per group

Area under curve per time point of calciuria



Balance study in human volunteers . 26% difference in Calcium absortion between Two non calcium containing P binders

Comparative study on the absorption of dietary phosphorus in healthy subjects after a single dose of lanthanum carbonate (1000mg) and a single dose of sevelamer carbonate (2400 mg)

Table 7: Analysis of Net Calcium Absorption after Lanthanum Carbonate and Sevelamer Carbonate (Pharmacodynamic Set)

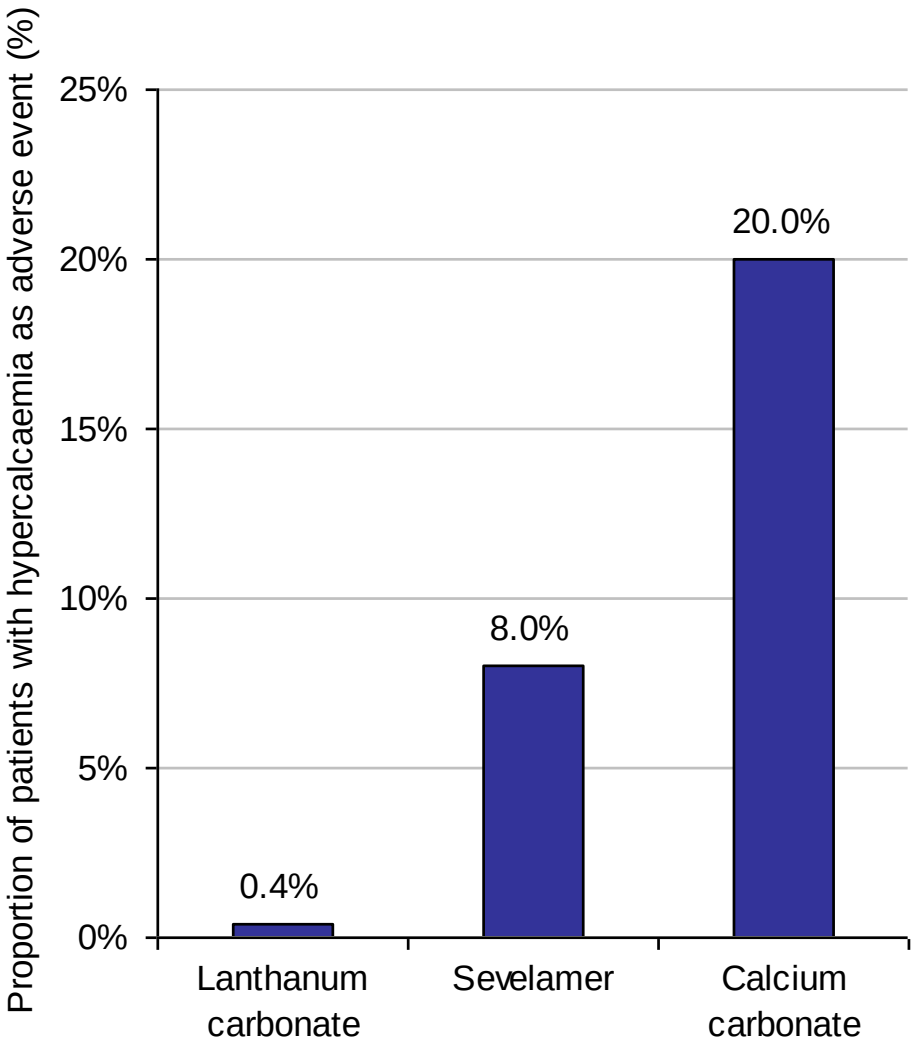
Net Calcium Absorption (mg)	Lanthanum Carbonate (N=18)	Sevelamer Carbonate (N=18)
N	18	18
Mean (SE)	49.2 (11.16)	70.4 (11.09)
Median	41.41	55.62
Min, Max	-43.5, 135.6	13.9, 156.4
LS Mean (SE)[a]	49.46 (10.480)	70.13 (10.450)
95% CI of the LS Mean	(28.11, 70.80)	(48.85, 91.42)
Difference between the LS Means[b]	-20.67	
95% CI of the Difference	(-41.22, -0.13)	
p-value	0.049	

[a] Net calcium absorption was analyzed using a mixed effect linear model with sequence group, period, and treatment regimen as fixed effects, and subject within sequence as a random effect.

[b] This is the LS mean of lanthanum carbonate minus the LS mean of sevelamer carbonate.

Shire Clinical Study report SPD 405-128

Incidence of hypercalcaemia based on a recent literature survey



Shire Pharmaceutical Contracts Ltd. Fosrenol® – Summary of Product Characteristics 2006
Hutchison A *et al. Nephron Clin Pract* 2005;100:8–19

Treatment of CKD–MBD targeted at lowering high serum phosphorus and maintaining serum calcium

- CKD stage 5D:
  dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2D)
- Ionized calcium in serum 1.8-2.5mEq/l 1.1-1.25mMol/L

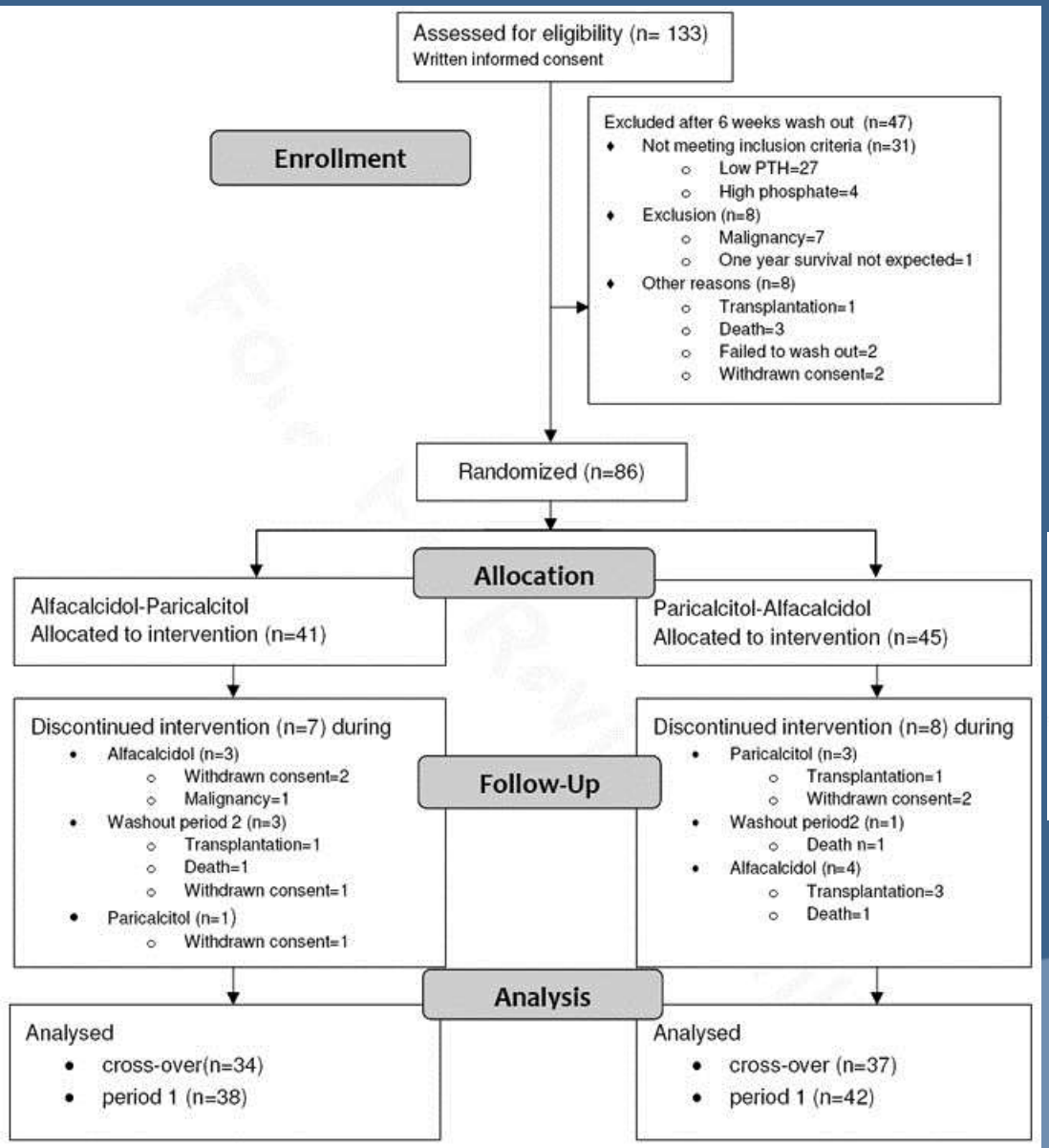
- CKD stages 3–5D and hyperphosphatemia:
  - **restrict the dose of calcium-based phosphate binders** and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B).
  - **restrict the dose of calcium-based phosphate binders**
    in the presence of arterial calcification (2C) and/or adynamic bone disease (2C)

Kidney Int 76: S50-S99, 2009

Chronic Kidney Disease

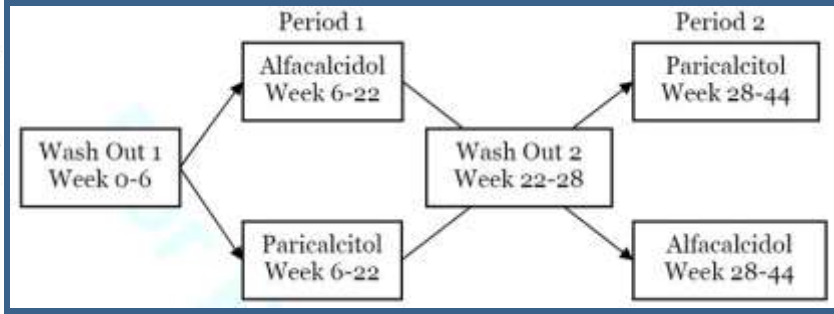
	CKD 3 – 4 – 5	CKD 5 D
Hyperphosphatemia	+	+++
Vitamin D	insufficiency/deficiency	deficiency
Hypocalcemia	+	+
Hypocalciuria	++	irrelevant
PTH	+/++	+++ (35-40% PTH+)
FGF23	+/++	+++
Vascular calcifications	0/+	++/+++

Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients.
A randomised cross-over study



Participants flow through the study

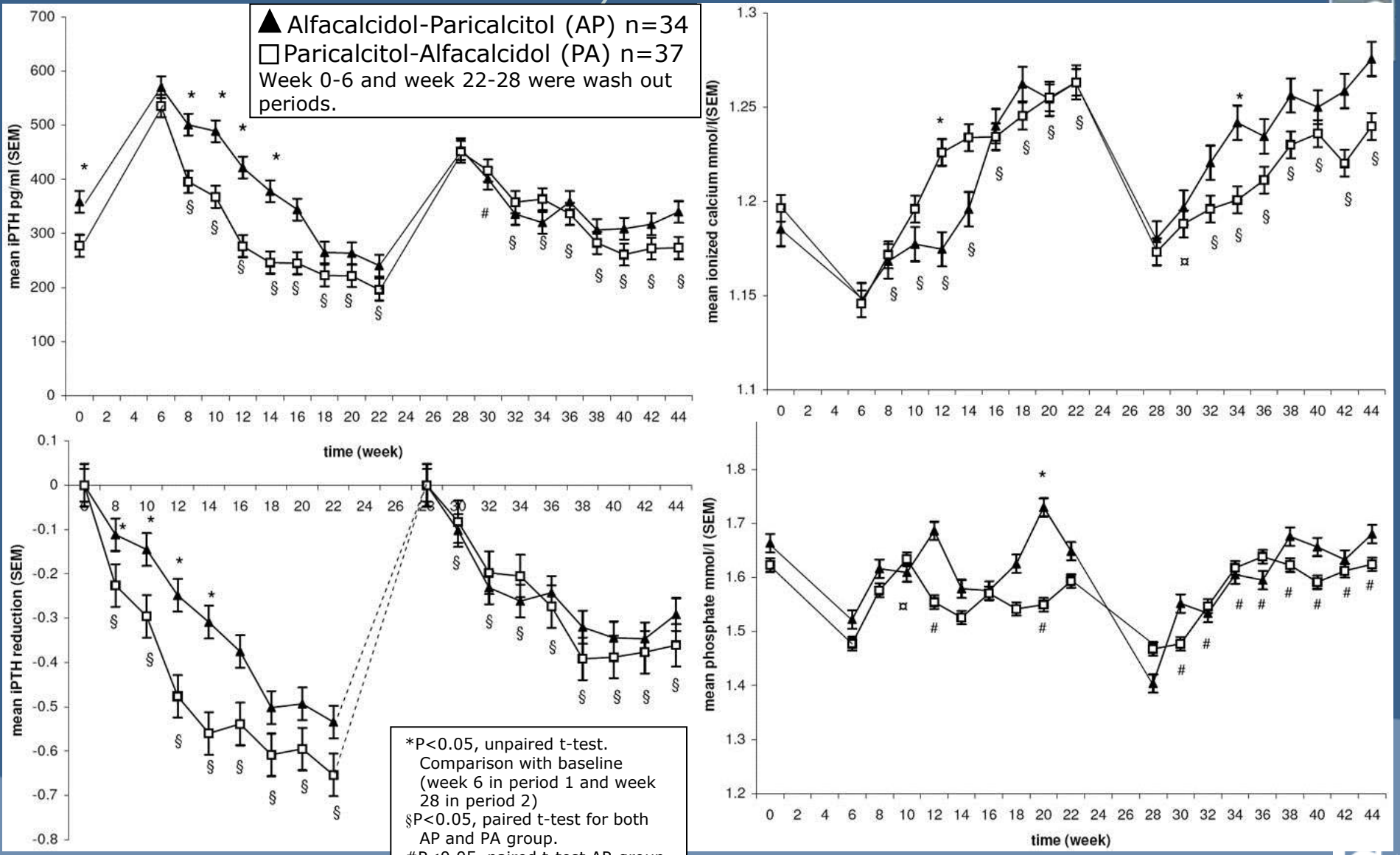
Treatment periods and treatment arms



Hansen D et al:
Kidney Int 2011 (In press)

Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients.

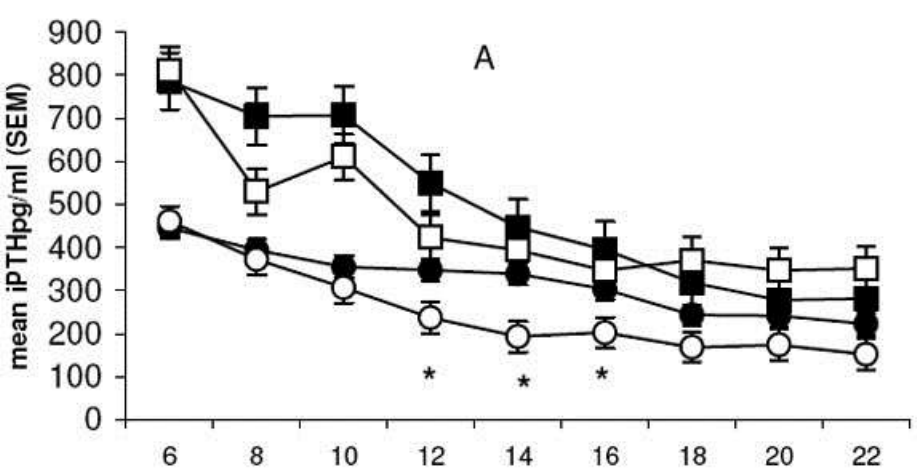
A randomised cross-over study

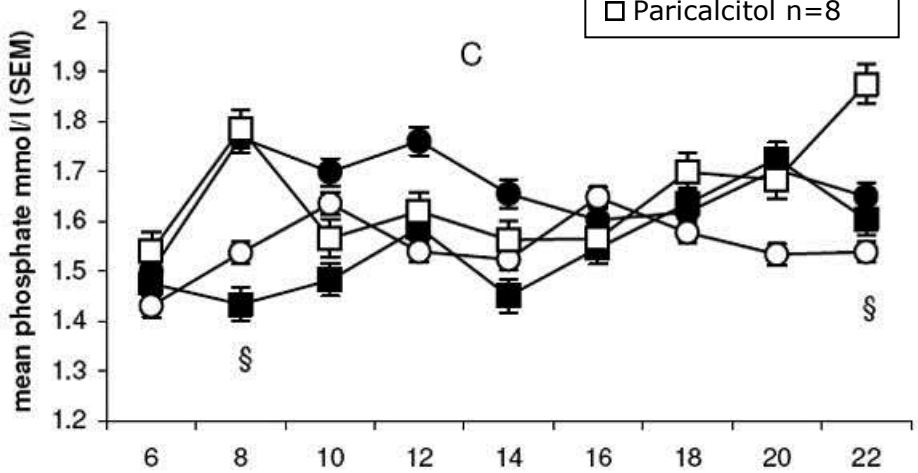


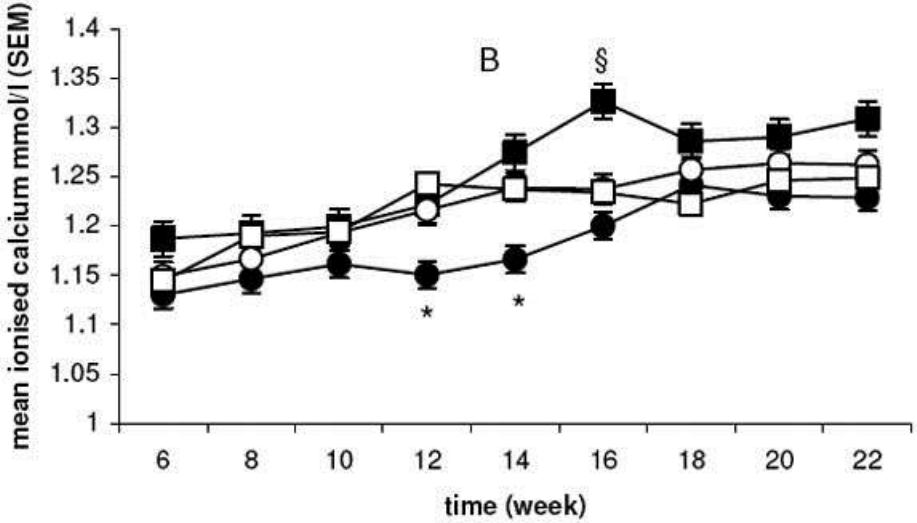
Hansen D et al: Kidney Int 2011 (In press)

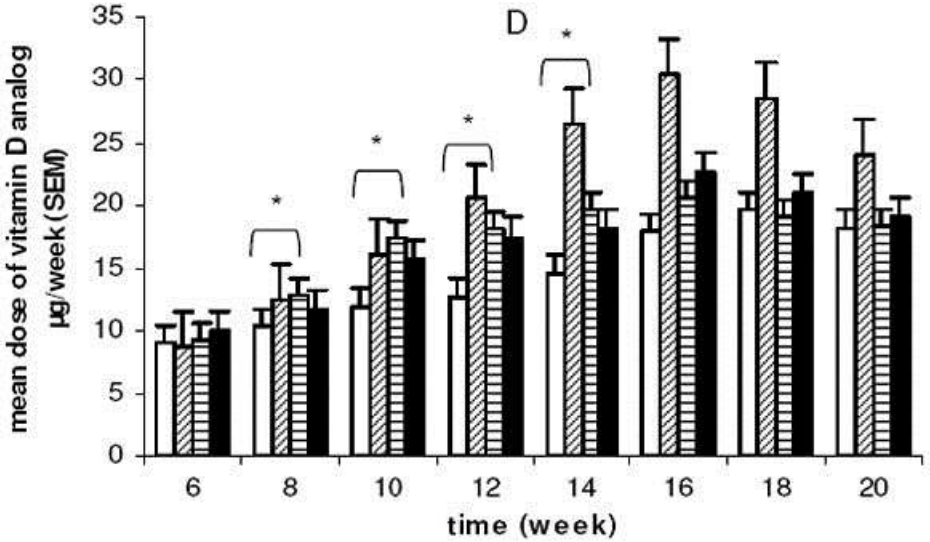
Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients. *A randomised cross-over study*

Low baseline PTH ≤ 600 pg/ml:
● Alfacalcidol n=24
○ Paricalcitol n=34
High baseline PTH >600 pg/ml:
■ Alfacalcidol n=14
□ Paricalcitol n=8





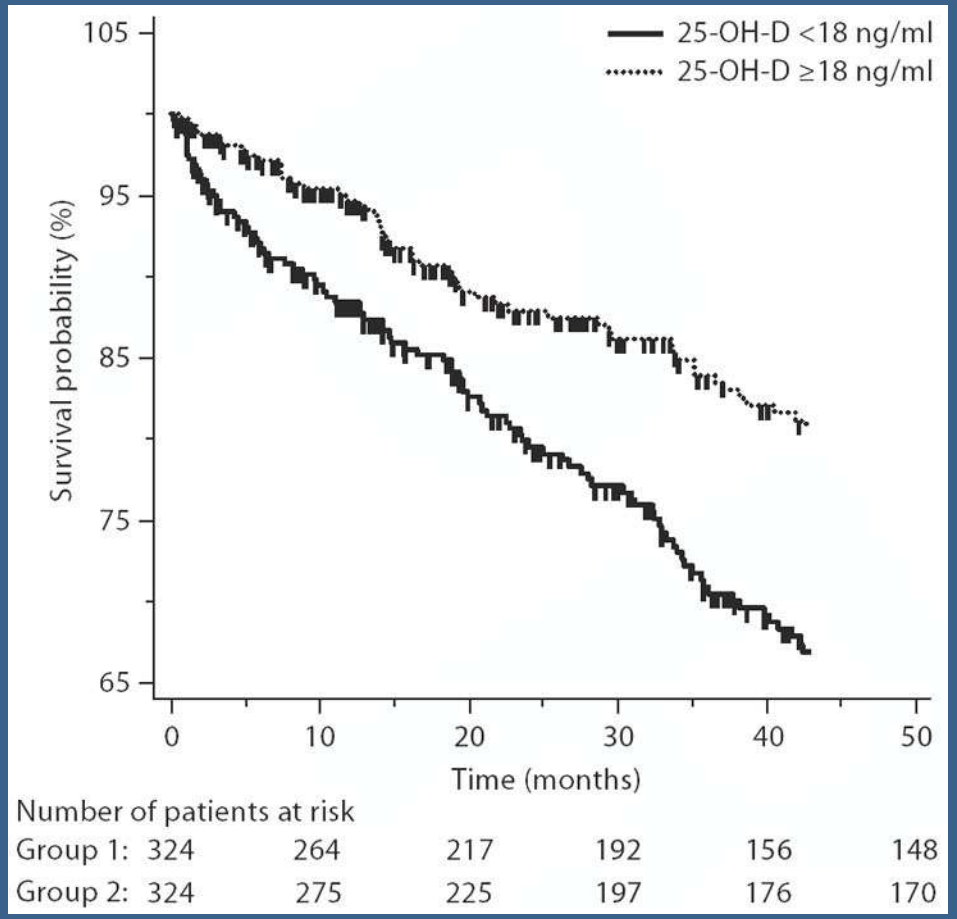




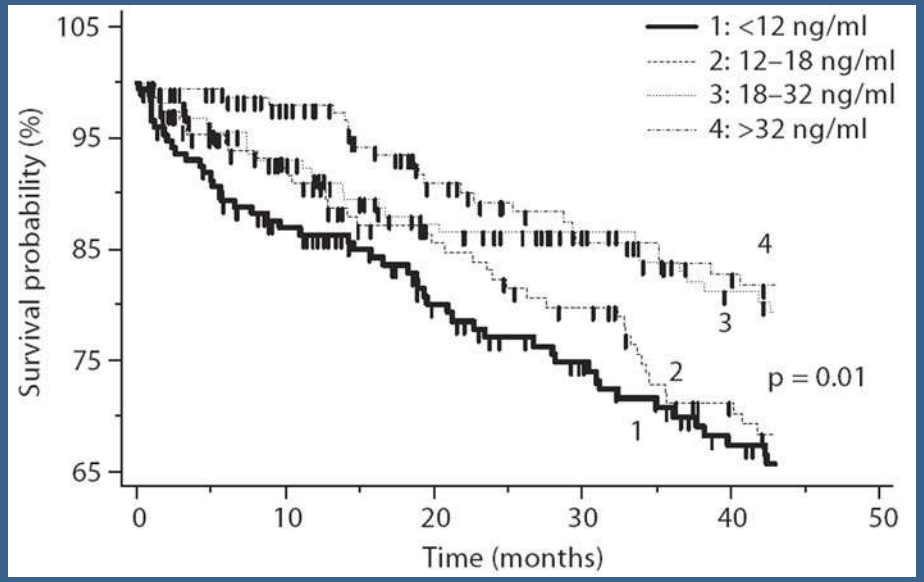
*P<0.05 and high PTH groups
§P<0.05 (unpaired t-test)

Hansen D et al:
Kidney Int 2011 (In press)

Impact of hypovitaminosis D and alfacalcidol therapy on survival of hemodialysis patients: Results from the French ARNOS study



42-month survival (Kaplan-Meier) acc. to the serum 25-OHD median level (18 ng/ml)



42-month survival (Kaplan-Meier) acc. to the serum 25-OHD quartile

Jean G et al: Nephron Clin Pract 2010 (In Press)

Effet du cholécalciférol 100 000 mensuel en dialyse

G Jean et al,NDT(2009) 24: 3799–3805

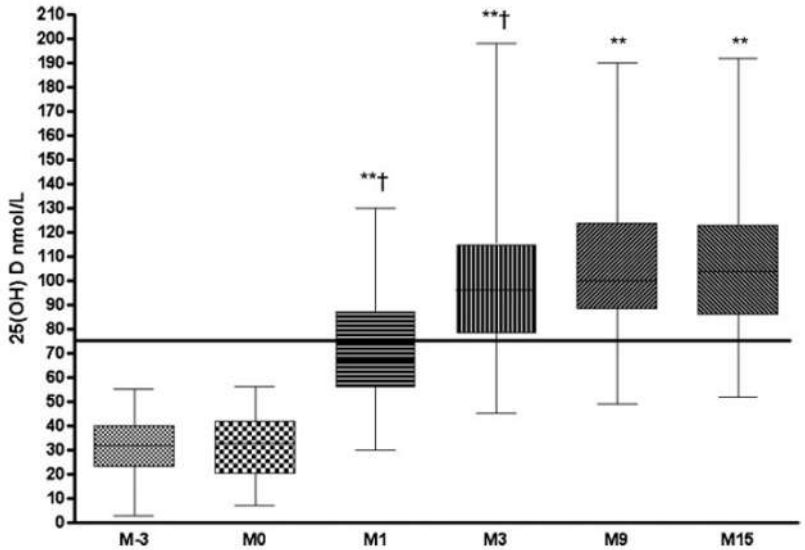


Fig. 1. Evolution of 25(OH)D serum levels (Box plot). $^{**}P < 0.001$ with baseline, $^{\dagger}P < 0.05$ with the previous value.

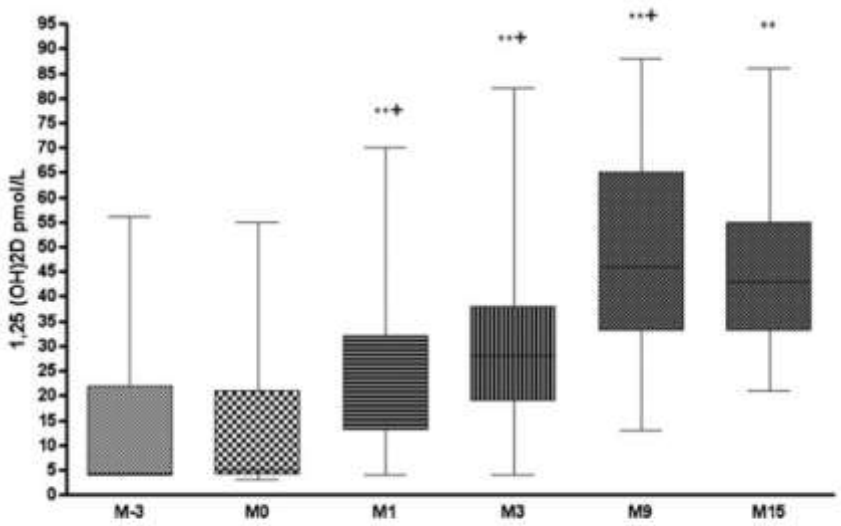


Fig. 2. Evolution of 1,25(OH)2D serum levels (Box plot). $^{**}P < 0.001$ with baseline, $^{\dagger}P < 0.05$ with the previous value.

Table 2. Changes in vitamin D and mineral metabolism parameters

Months	M-3	M0	M1	M3	M9	M15
25(OH)D (nmol/L) (range)	31 ± 11 (3–55)	32 ± 13 (7–56)	68.3 ± 19 (30–130)**,†	97.7 ± 28 (45–198)**,†	105.7 ± 28 (49–190)**	105.8 ± 27 (52–192)**
% 25(OH)D > 75 nmol/L	0	0	46**,†	82**,†	88**	91**
$1,25(OH)_2D$ (pmol/L) (range)	14 ± 14 (4–56)	13.7 ± 14 (4–55)	23.8 ± 14 (4–70)**,†	30.7 ± 14 (4–82)**,†	49.2 ± 17 (13–88)**,†	45 ± 13 (21–86)**
PTH (pg/mL) (median, inter-quartile range)	294 (180–435)	295 (190–450)	249 (158–378)*,†	220 (113–300)*	200 (145–280)*	190 (110–273)*
BALP (μg/L) (range)	21 ± 10 (6–45)	20.5 ± 9 (7–41)	18.7 ± 9 (6–37)	16.5 ± 6 (6–35)*,†	17 ± 6 (8–35)*	17.1 ± 7 (6–35)*
β-cross-laps (μg/L) (range)	2.5 ± 1 (0.8–6)	2.5 ± 1 (0.9–5)	2.27 ± 1 (0.6–5)	2.1 ± 1 (0.64.8)*,†	2.05 ± 0.8 (0.7–4.2)*	2.07 ± 0.8 (0.5–4.1)*
Calcaemia (mmol/L) (range)	2.27 ± 0.14 (1.9–2.53)	2.24 ± 0.12 (2–2.5)	2.28 ± 0.1 (2 –2.53)	2.28 ± 0.1 (2–2.5)	2.25 ± 0.1 (2–2.53)	2.25 ± 0.1 (2–2.58)
Phosphataemia (mmol/L) (range)	1.34 ± 0.3 (0.8–2.2)	1.32 ± 0.3 (0.8–2)	1.36 ± 0.3 (0.7–2.3)	1.33 ± 0.3 (0.7–1.9)	1.36 ± 0.3 (0.8–1.9)	1.31 ± 0.3 (0.8–2.1)

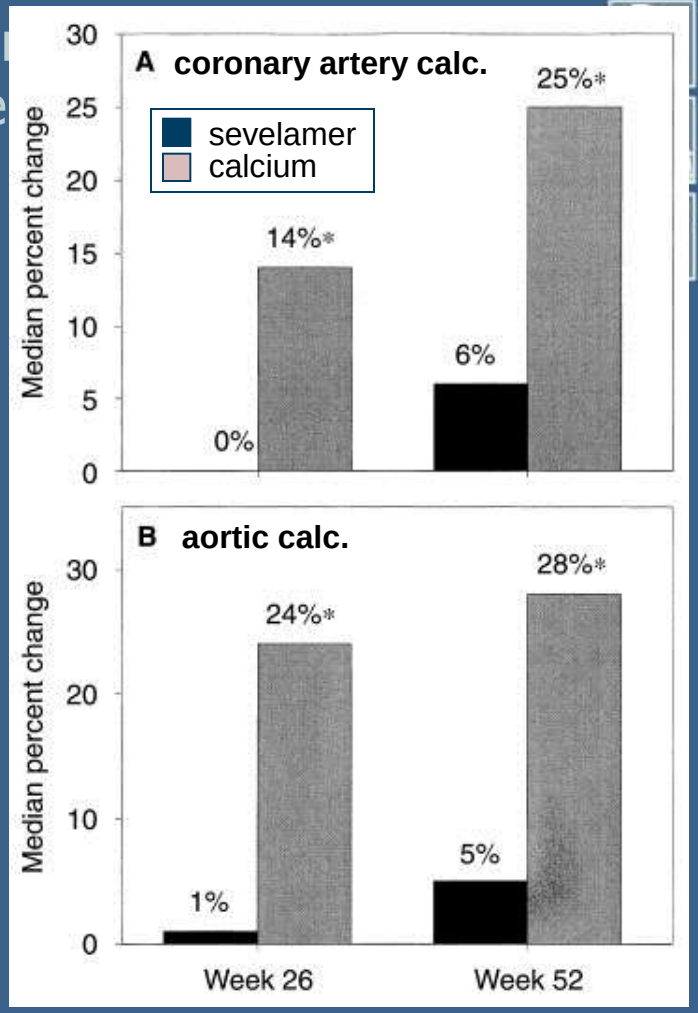
$^{*}P < 0.05$, $^{**}P < 0.001$ with the previous value, $^{\dagger}P < 0.05$ with the baseline value.

PARATHYROIDECTOMY in CKD5D

- Very elevated iPTH levels
- Vit D treatment resulting in bouts of hypercalcemia
- Cinacalcet treatment inadequate
- All glands have to be found (!!)
- Storage of PTH material for later implantation

Sevelamer attenuates the progression of co and aortic calcification in hemodialysis patie

Baseline characteristics	Sevelamer (N = 99)	Calcium (N = 101)	P value
Age *years* (mean ± SD)	57 ± 14	56 ± 16	0.88
Sex *% female*	36%	34%	0.77
Race			
Black	17%	23%	0.34
White	71%	66%	
Other	12%	11%	
Diabetes %	32%	33%	1.0
Hypertension %	86%	83%	0.70
Smoker %	3%	8%	0.21
Primary Cause of ESRD %			
Hypertension	16%	17%	0.66
Glomerulonephritis	26%	16%	
Diabetes	23%	28%	
Polycystic kidney disease	9%	11%	
Other	26%	28%	
Dialysis vintage *years, median*	3.6	2.9	0.24
Phosphate binder use prior to study entry %			0.81
Calcium carbonate	38%	44%	
Calcium acetate	33%	36%	
Calcium + aluminum	14%	13%	
Sevelamer	3%	1%	
Other combinations	12%	6%	
Vitamin D usage at study entry	56%	59%	0.67



Change in calcification scores from baseline to weeks 26 and 52 in pt with score>30 at baseline

Compared with calcium-based phosphate binders, sevelamer is less likely to cause hypercalcemia, low levels of PTH, and progressive coronary and aortic calcification in hemodialysis patients

Chertow GM et al:
Kidney Int 62: 245-252, 2007

,Rind study 20 7

CARE 2: Le sevelamer ne ralenti pas les calcifications vs calcium (avec statines)

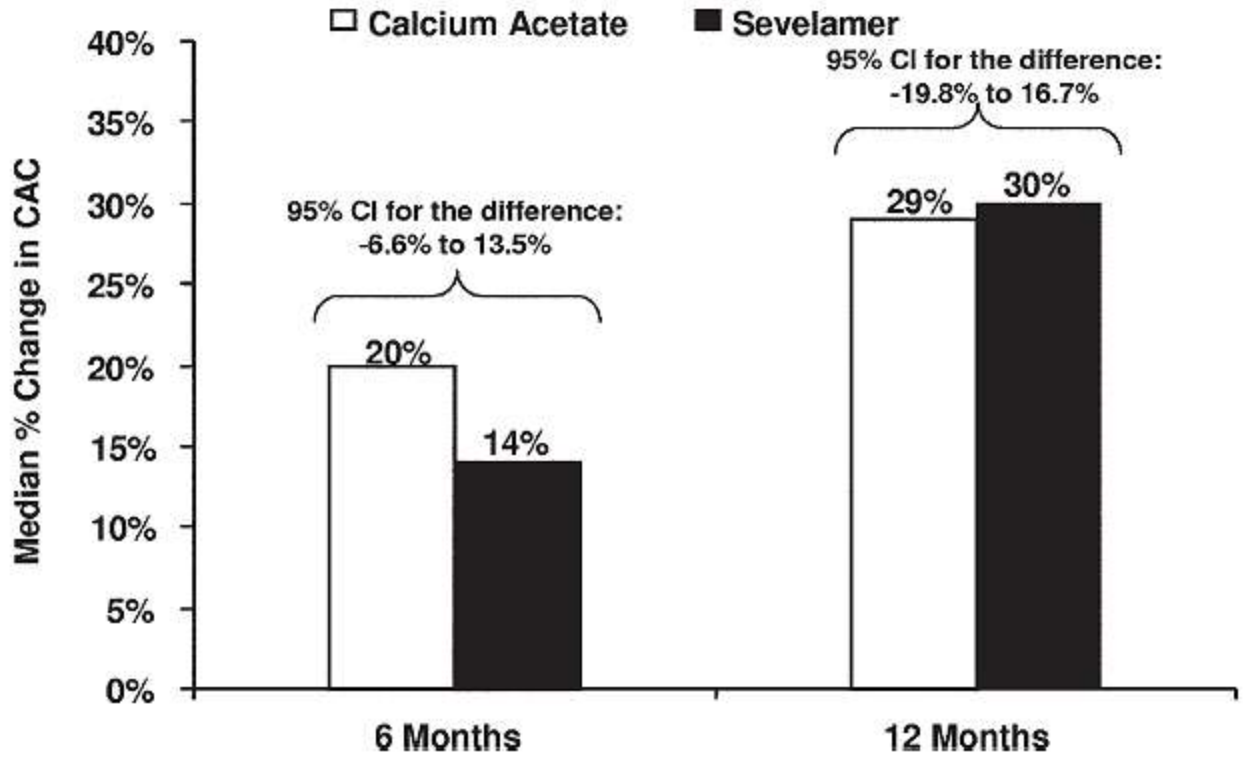


Figure 3. Median percentage of change in coronary artery calcium (CAC) scores from baseline to months 6 and 12 in patients with scores of 30 or higher at baseline and 95% confidence interval (CI) for the between-group difference (calcium acetate to sevelamer) in median percentage of change.

Qunibi et al, AJKD 2008

Potential therapies that indirectly and directly target vascular calcification

Treatment of hyperparathyroidism

Phosphate binders, calcimimetics, vit D

- Pyrophosphate , bisphosphonates
- Vitamin K
- Thiosulphate
- Matrix gla protein , Bone morphogenic protein 7,osteopontin
- Acidosis

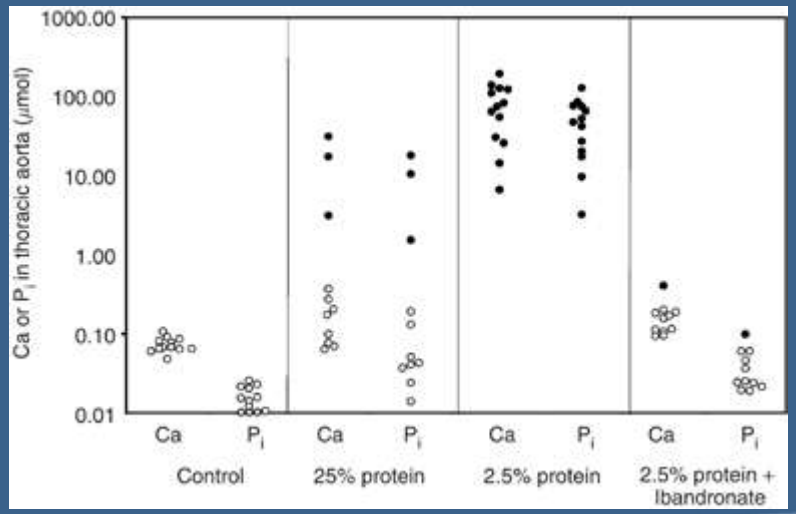
O'Neill WC & Lomashvili KA: Kidney Int 2010: In press

Effect of zoledronic acid in different experimental models of renal osteodystrophy

Perspectives in vivo research

Bisphosphonates

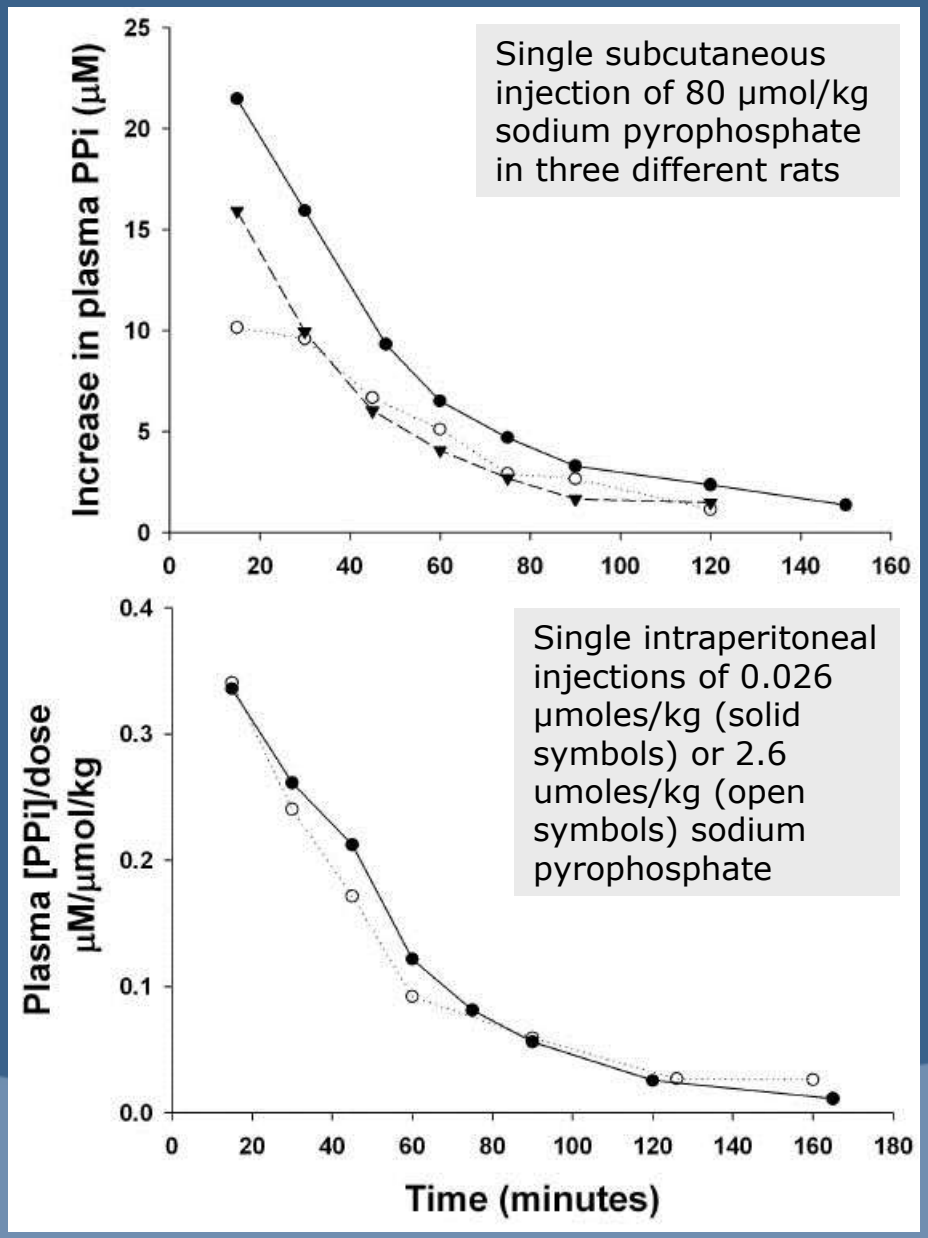
- Experimental studies
  - Warfarine induced VC ↓
    Price Arterioscler.Thromb.Vasc.Biol., 2001
  - Vitamin D induced VC ↓
    Price PA, et al., J.Nutr., 2001
  - Adenine induced VC ↓
    Price PA, et al., Kidney Int., 2006
- Patient studies
  - Uremia-related VC ↓
    Hashiba *Ther.Apher.Dial., 2005*
    Hashiba *Ther.Apher.Dial., 2006*

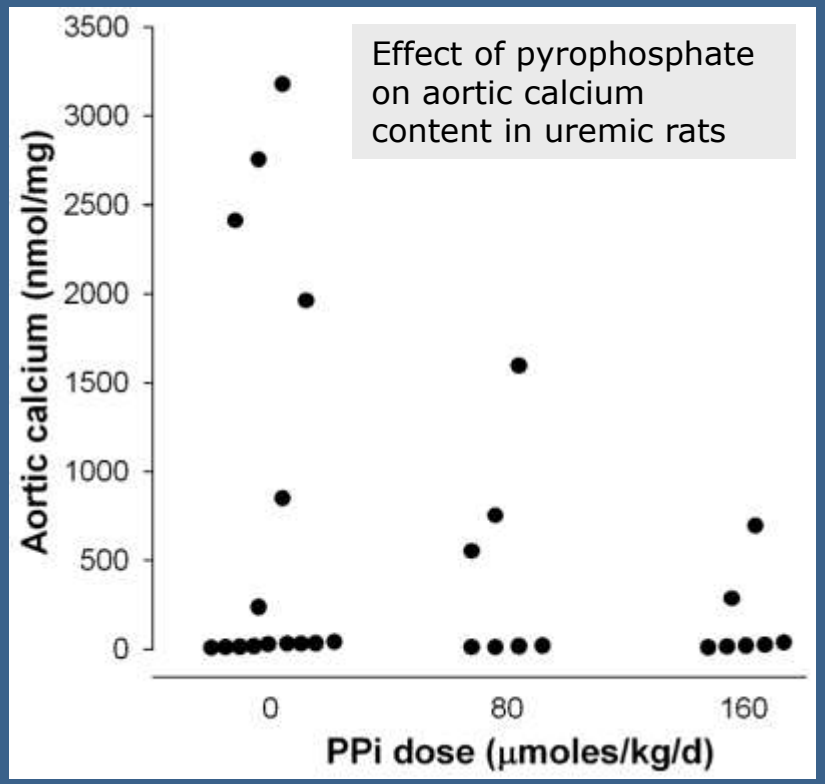


Mechanism of action?

- Indirect effect: inhibition of bone formation , pharmacokinetics!!!
- Direct effect on the vascular wall?

Treatment of uremic vascular calcification with pyrophosphate





Incorporation of Pi
in apatite crystals is blocked

O'Neill W et al: Kidney Int 2010

Potential therapies that indirectly and directly target vascular calcification

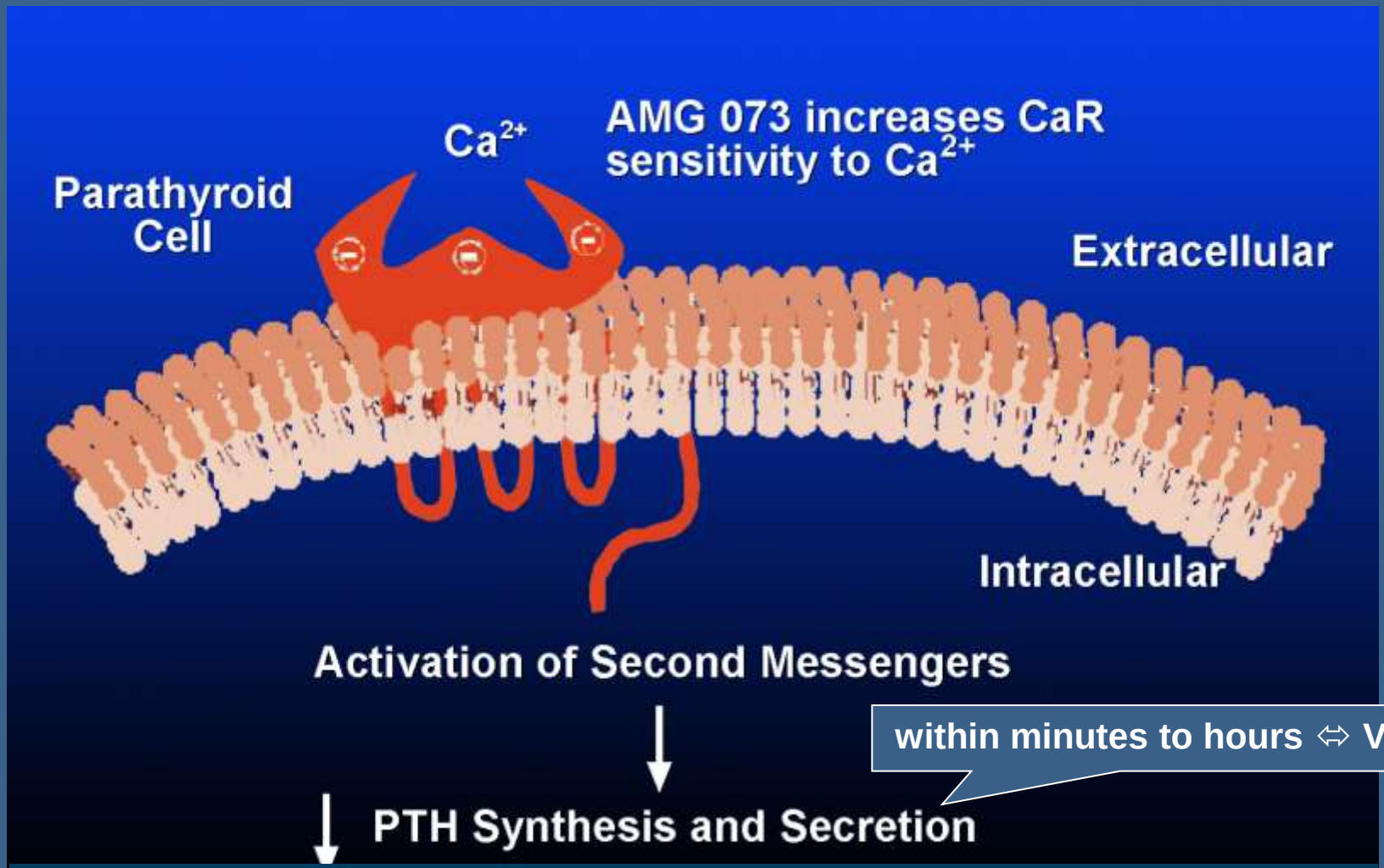
- Vitamin K is a cofactor in gamma-carboxylation s.a. matrix gla protein (MGP).
- Deletion of MGP causes massive calcification.
- Warfarin blocks vit K dependent gamma cbx.
- Warfarin has been associated with valvular calcification.
- Disparate results with vit K and calcifications in humans

Potential therapies that indirectly and directly target vascular calcification

- Thiosulphate prevents nephrolithiasis in humans
- Inhibits medial calcifications in rats.
- Slowed down progression of coronary calc. in small cohort of dialysis patients
- Mechanism calcium crystalization??
- Inhibition of bone formation ? Decrease in bone strenght.

Vascular alcifications in Renal Failure

- Substantial progress in unravelling different mechanisms
- Several potential interesting therapeutic approaches (???)
- Treat at early stage
- Control of hyperphosphatemia and calcium load.



within minutes to hours ⇔ Vit D

In the absence of in extracellular calcium

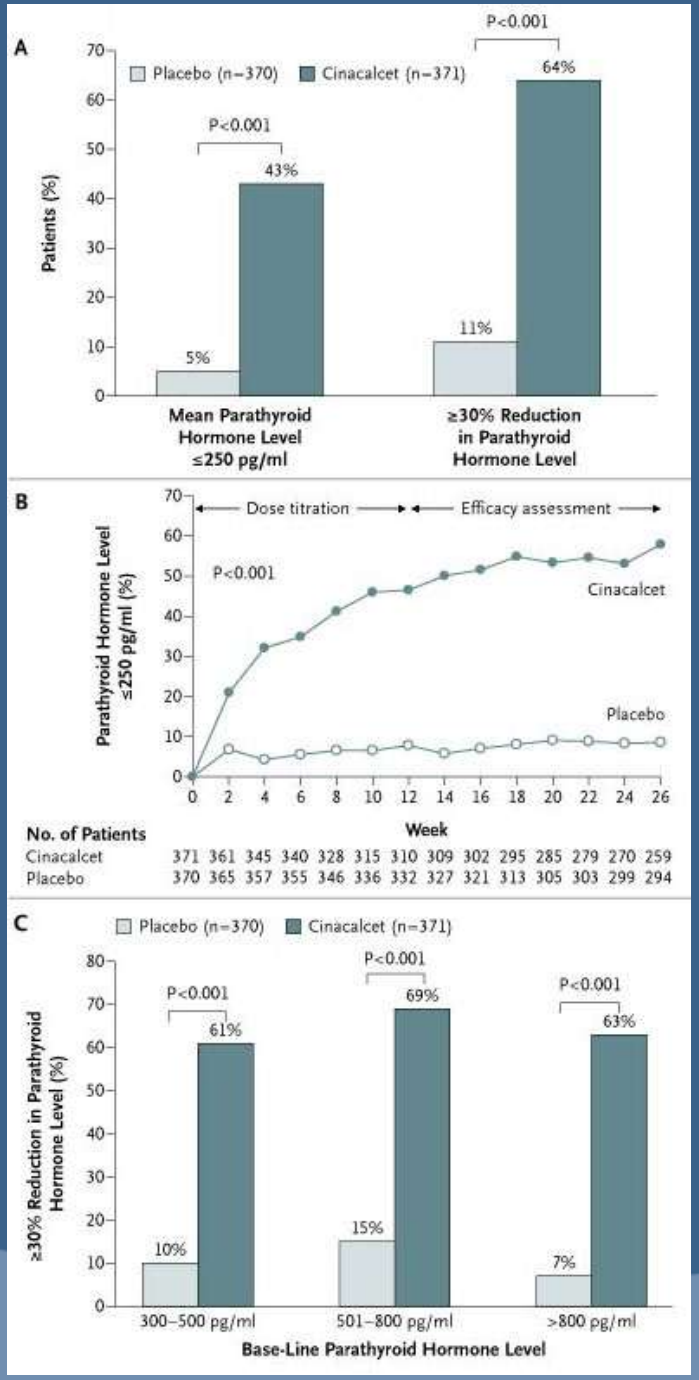
Serum calcium ↓

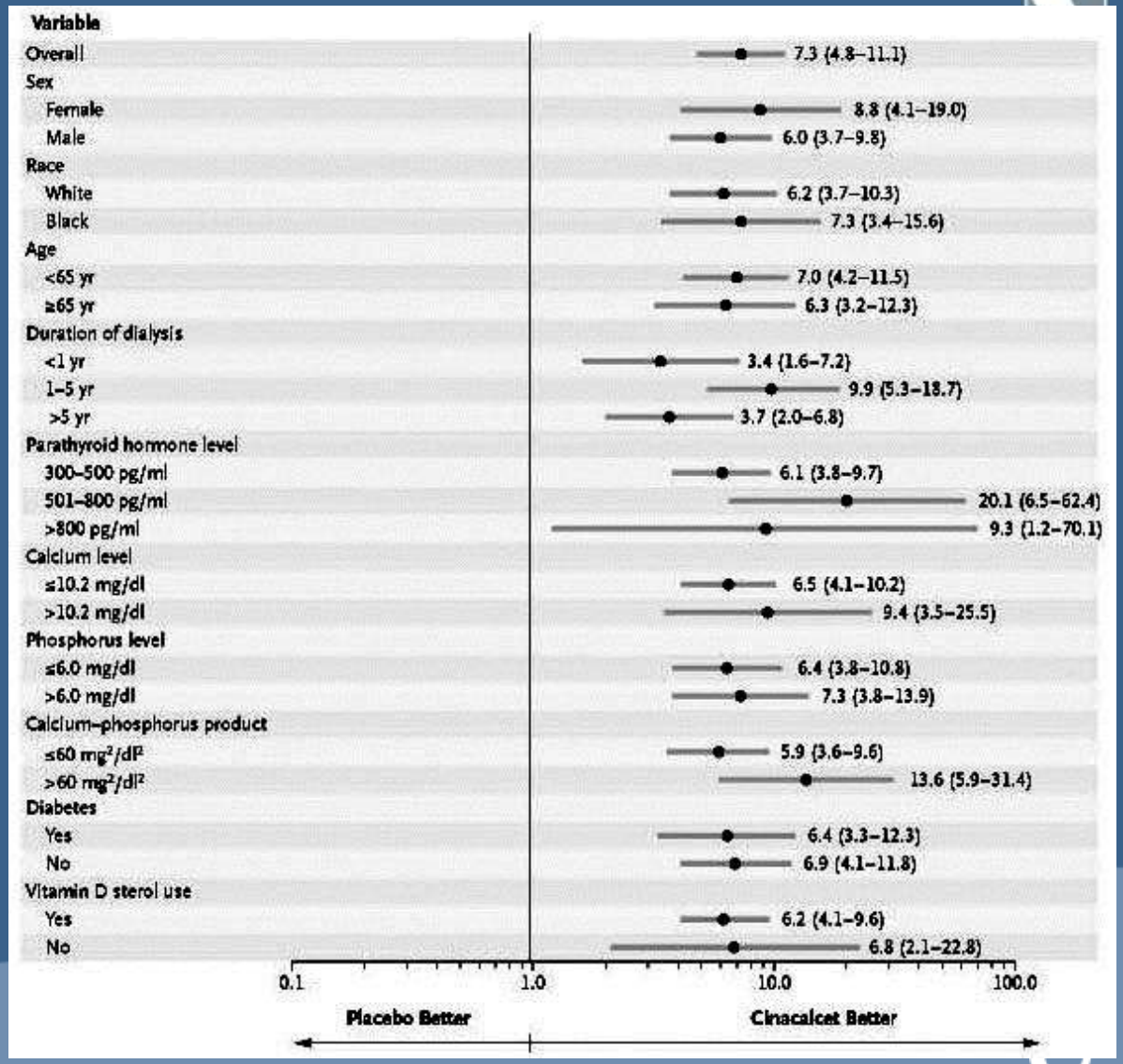
Renal calcium excretion

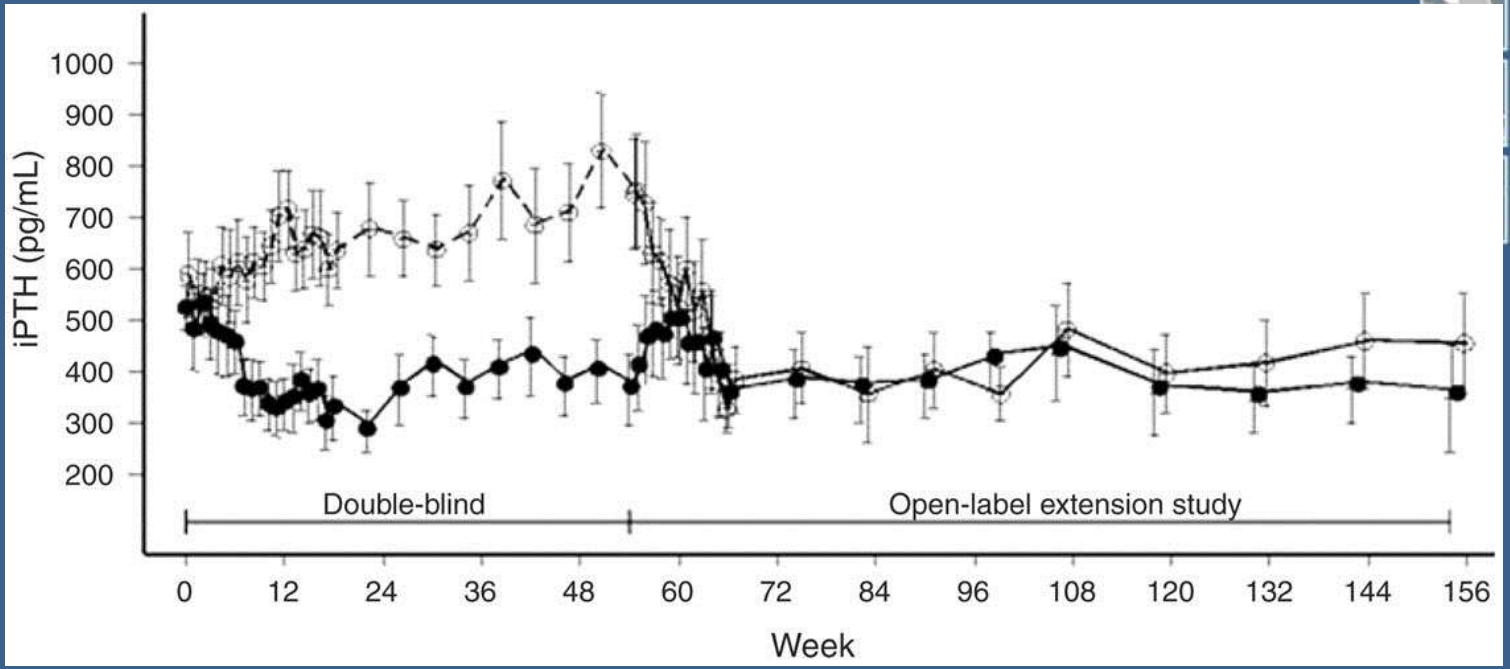
AMGEN

Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis

Block GA et al: New Engl J Med 350: 1516-1525, 2004







Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl

Table 3. The proportion of patients who achieved the NKF-K/DOQI™ targets

Recommended NKF-K/DOQI™ targets	Baseline of qualifying study *n* (%)	Week 52 *n* (%)	Week 100 *n* (%)
PTH ≤300 pg/ml	6 (10%)	30 (52%)[a]	35 (59%)[a]
Serum calcium ≥8.4 to ≤9.5 mg/dl	25 (42%)	23 (40%)	22 (37%)
Serum phosphorus ≥3.5 to ≤5.5 mg/dl	19 (32%)	21 (37%)	22 (37%)
Ca×P <55 mg^2/dl^2	25 (42%)	32 (56%)	31 (53%)

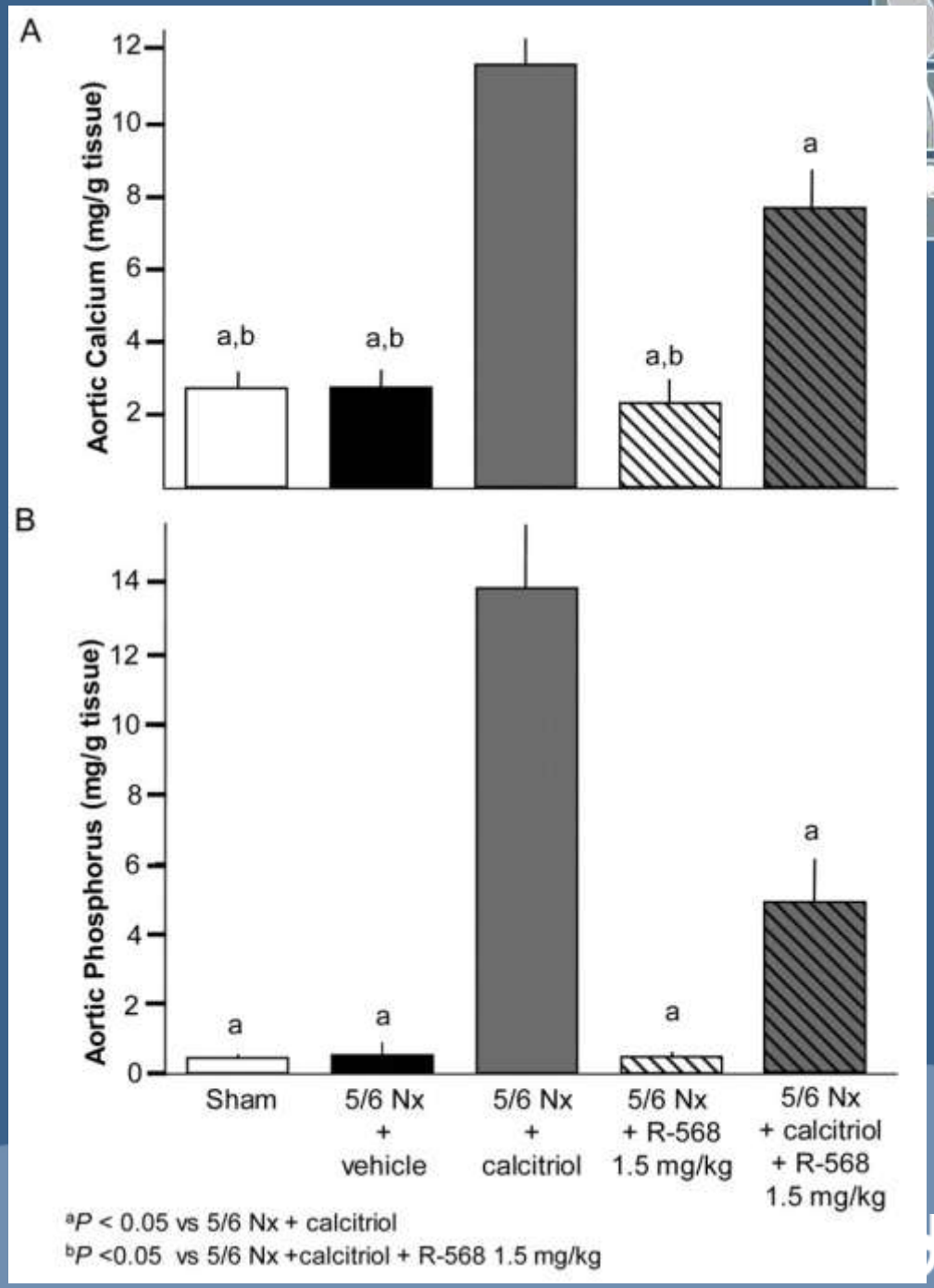
Moe SM et al: Nephrol Dial Transplant 20, 2186-2193, 2005

Calcimimetics – Secondary hyperparathyroidism

- Bioavailability is low
- Metabolism is variable – pharmacokinetics?
- Long term use
- Hypocalcemia – calcium load ? uptake in bone?
  5%: < 7.5 mg%
- Phosphate handling – dialysis – stage 3 - 4 CKD,hyperP
- Effects on bone – vascular calcification
- Effects on other systems – calciuria
- ←→ persistent effect of PTH

Calcimimetic R-568 decreases extraosseous calcifications in uremic rats treated with calcitriol

Weak effect



Lopez I et al: JASN 17: 795-804, 2006

Information from Surgical Parathyroidectomy (1)

1- Meema H, Oreopoulos D, deVeber G. Arterial calcifications in severe chronic renal disease and their relationship to dialysis treatment, renal transplant, and parathyroidectomy. Radiology 121:315-321, 1976

2- De Francisco A.M., Ellis H.A., Owen J.P. et coll. : Parathyroidectomy in chronic renal failure Q.J.Med. 55:289-315, 1985

Increase in cardiac calcification in 4 out of 6 pts

3- Girotto J, Harmon J, Ratner L, Nicol T, Wong L, Chen H. Parathyroidectomy promotes wound healing and prolongs survival in patients with calciphylaxis from secondary hyperparathyroidism. Surgery 130:645-651, 2001

Increase in peripheral arterial calcification in 56% of pts

4- DiLeo C, Gallieni M, Bestetti A, et al. Cardiac and pulmonary calcification in a hemodialysis patient : Partial regression 4 years after parathyroidectomy. Clin Nephrol 59:59-63, 2003

Healing of calciphylaxis in 6 out of 13 patients after PTX

No conclusive, limited by the use of radiological techniques that could only grossly quantify calcifications

Hypothesis of the ADVANCE Study

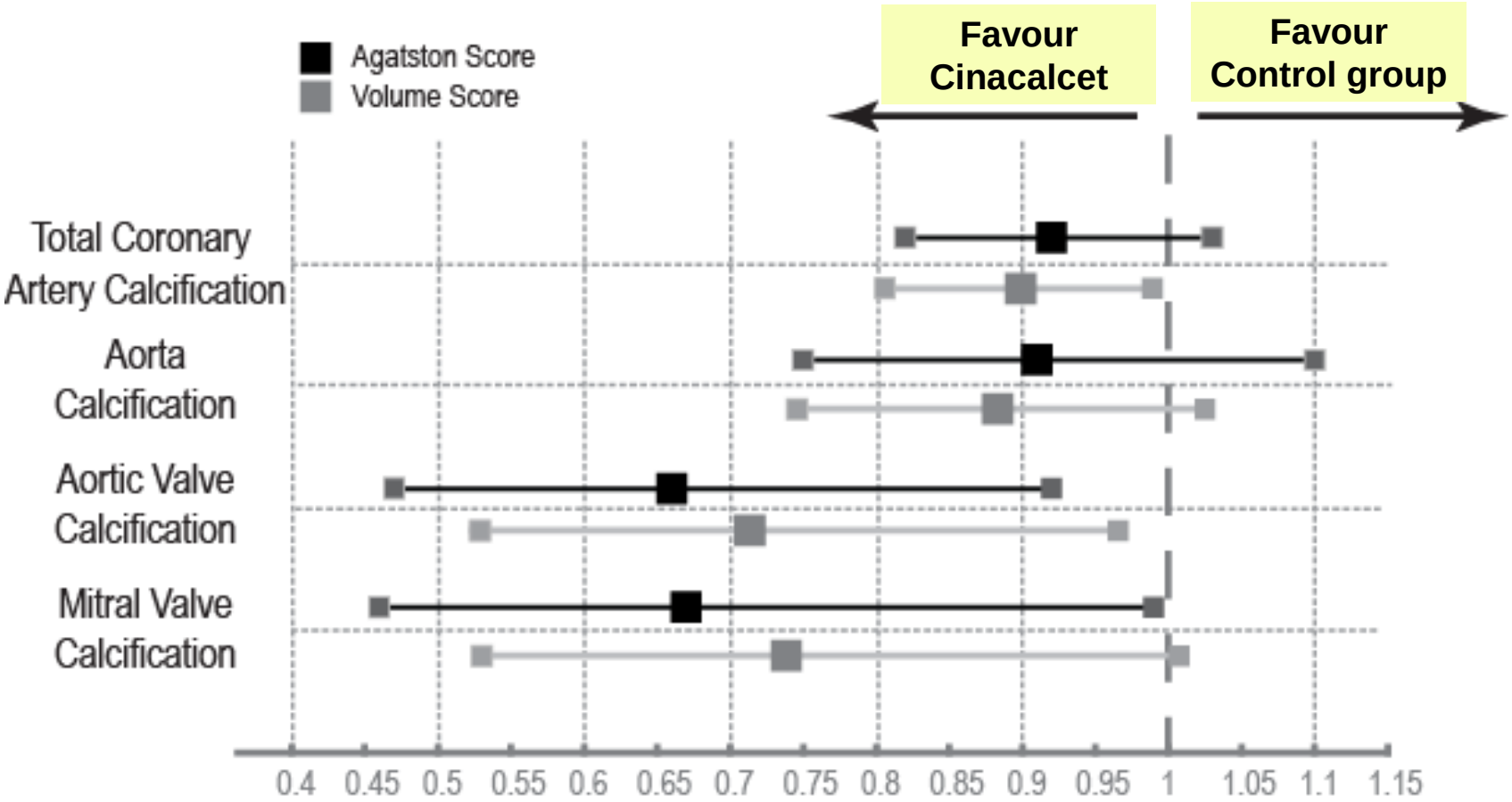
"A treatment with cinacalcet and low dose vitamin D will attenuate the progression of coronary artery calcification over a one year period compared with a treatment with flexible vitamin D dosing, in hemodialysis patients with secondary hyperparathyroidism"

The ADVANCE Study: A randomized study to evaluate the effects of cinacalcet plus low dose vitamin D on vascular calcification in patients on hemodialysis

- This prospective, randomized, controlled trial compared progression of vascular and cardiac valve calcification in 360 prevalent adult hemodialysis patients with secondary hyperparathyroidism treated either with cinacalcet plus low dose vitamin D sterols or flexible doses of vitamin D sterols alone
- The primary endpoint was percentage change in Agatston CAC score from baseline to week 52. Median (P10, P90) Agatston CAC scores increased 24% (-22%, 119%) in the cinacalcet group and 31% (-9%, 179%) in the flexible vitamin D group (P = 0.073). Corresponding changes in volume CAC scores were 22% (-12%, 105%) and 30% (-6%, 133%; P = 0.009).
- In hemodialysis patients with moderate to severe secondary hyperparathyroidism, cinacalcet plus low dose vitamin D sterols may attenuate vascular and cardiac valve calcification.

Raggi P et al

Summary of Treatment Comparison of Percent Change in Calcification (Agatston and Volume) from Baseline to Week 52 (adjusted for SCR CAC Strata)



Estimate hazard ratios of baseline to week 52 calcification scores (Agatston and Volume) and 95% confidence intervals.
Agatston: CAC: Table14-04-001-001-002; AC: Table 14-04-004-001-002; AVC: Table 14-04-017-001-002; MVC: Table 14-04-018-001-002
Volume: Tables to come

Amgen – Proprietary and Confidential

Chronic Kidney Disease

	CKD 3 – 4 – 5	CKD 5 D
Hyperphosphatemia	+	+++
Vitamin D	insufficiency/deficiency	deficiency
Hypocalcemia	+	+
Hypocalciuria	++	irrelevant
PTH	+/++	+++ (35-40% PTH+)
FGF23	+/++	+++
Vascular calcifications	0/+	++/+++

People Involved

21 September 2011

University of Antwerp, Belgium

- BEHETS Geert
- BERVOETS An
- DAMS Geert
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