Treatment Options for Chronic Kidney Disease: Metabolic Bone Disease

Goce Spasovski, R. Macedonia

Budapest, *August 29, 2011*

Session Objectives

- **Definition of the problem of CKD-MBD**
- **Clinical relevance and consequences**
  - ***increased morbidity and mortality***
- **Current therapeutical options-modification**
  - **Calcium and phosphate levels (bone)**
  - **Calcifications (vessels)**
  - **CVDs (outcome)**
  - ***phosphate binders***

Recent Patents on Cardiovascular Drug Discovery 2008; 3(3):222-8

New Strategies in Treatment of Mineral and Bone Disorders and Associated Cardiovascular Disease in Patients with Chronic Kidney Disease

Goce Spasovski*

Mineral & Bone Disorder (MBD) Systemic Complication in CKD

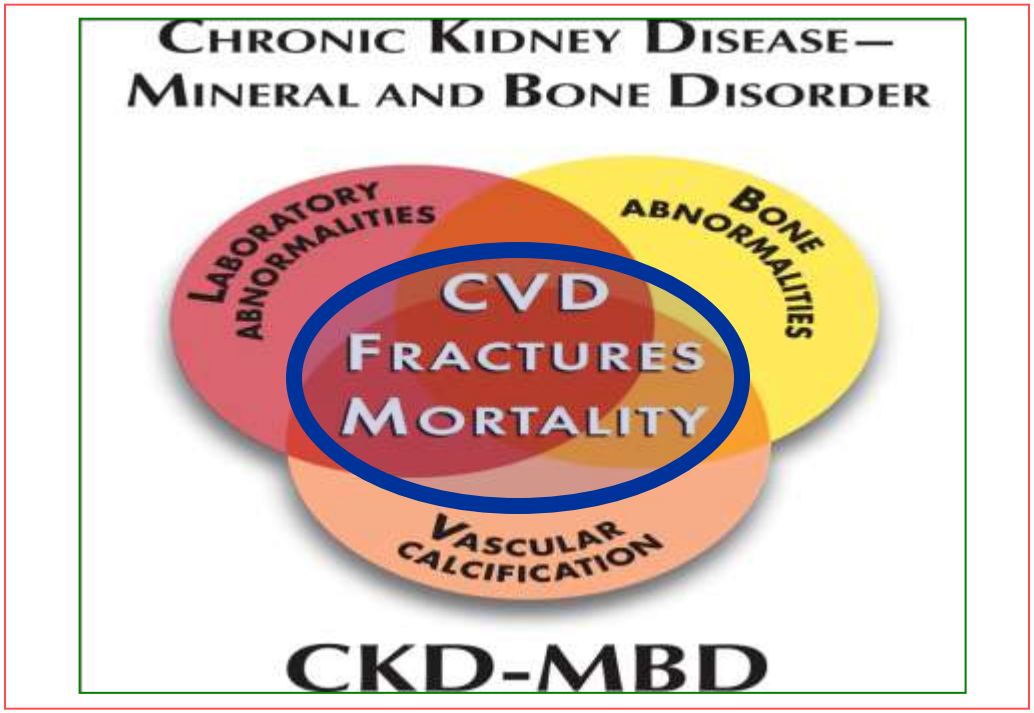
Mineral

Hormonal

Bone abnormalities,

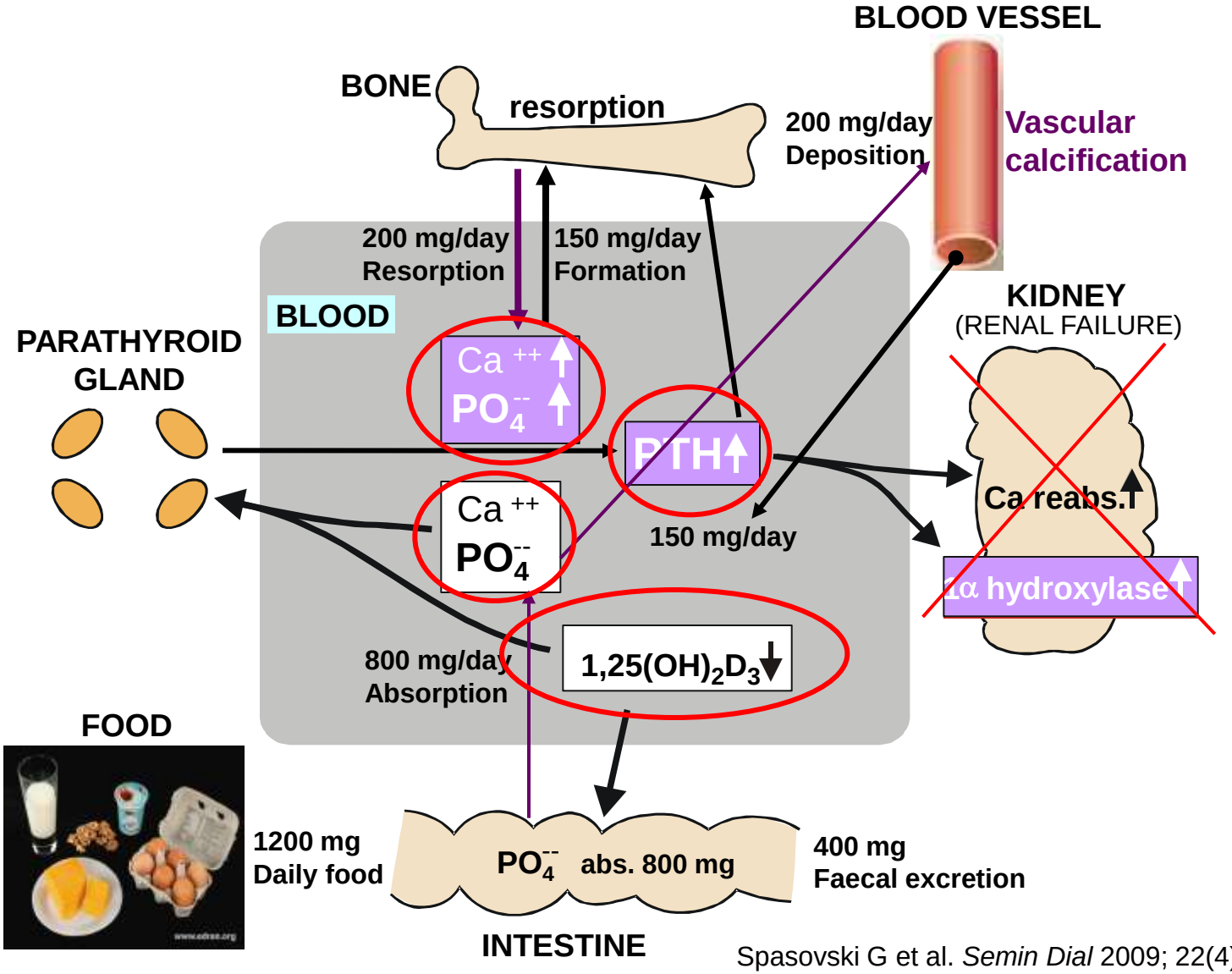
Vascular calcifications

Soft tissue calcifications



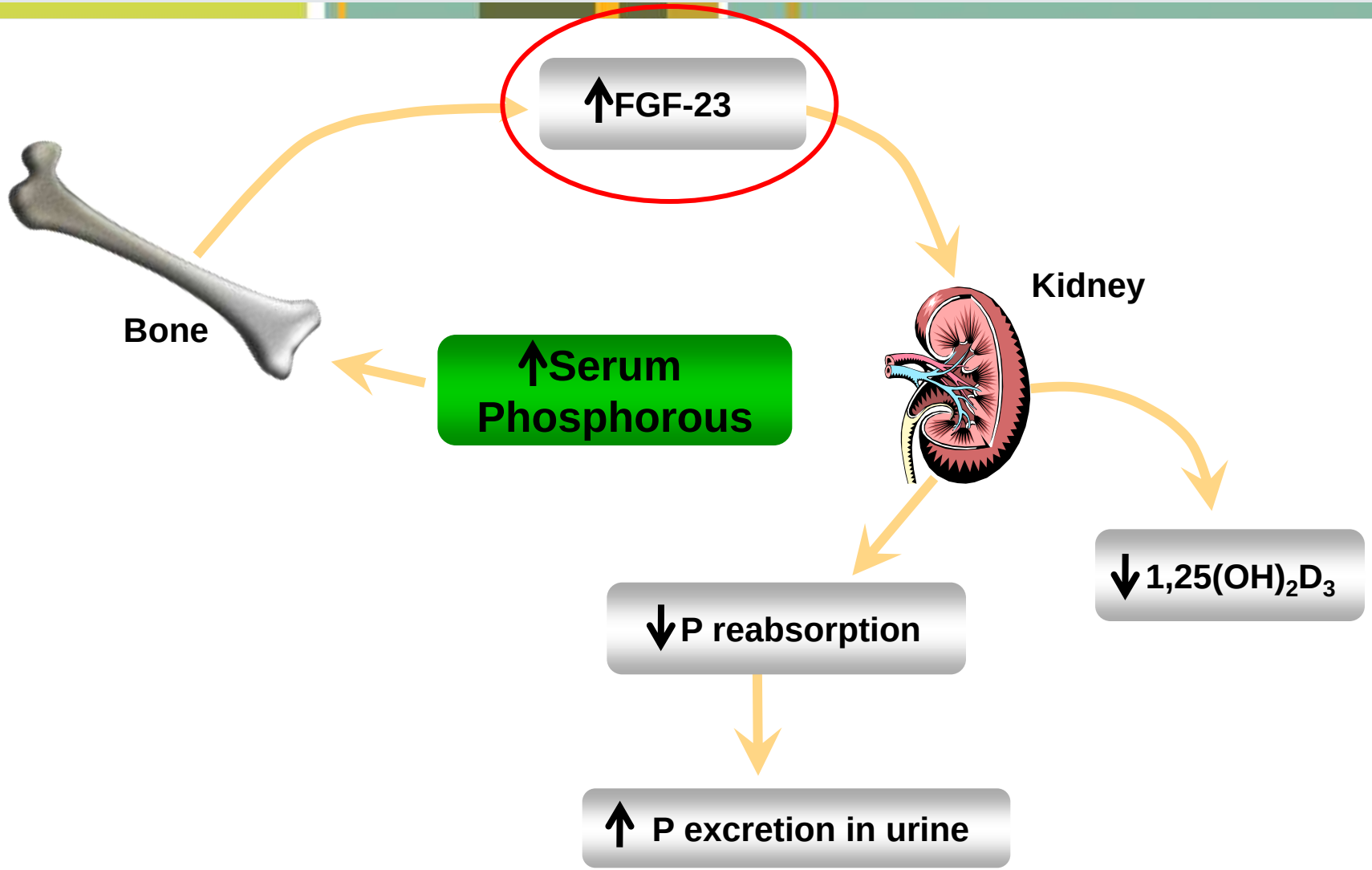
CVD, fractures, mortality

Pathophysiology of CKD - MBD



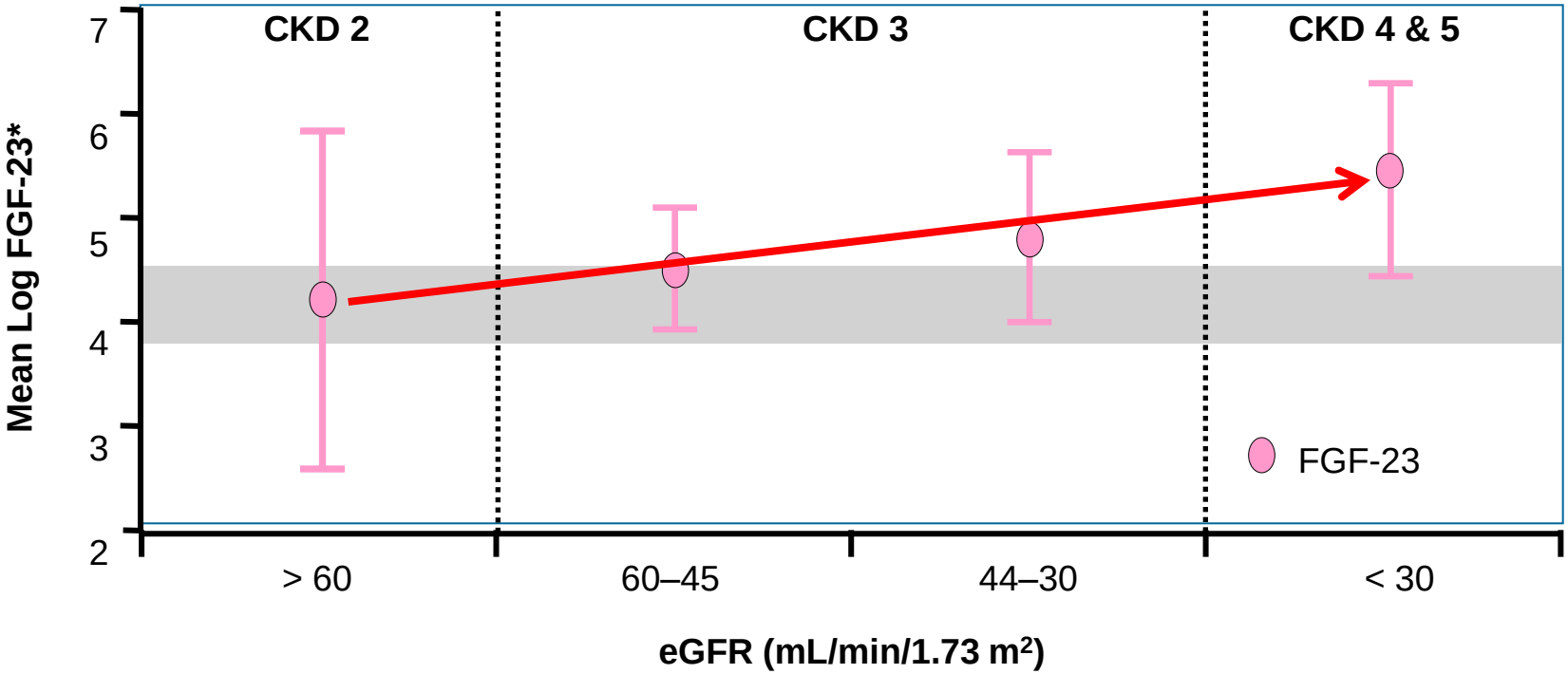
Spasovski G et al. *Semin Dial* 2009; 22(4): 357-362

FGF-23 Regulation of Phosphorous Homeostasis



Adapted from Stubbs J, et al. *Semin Dial.* 2007;20:302-308

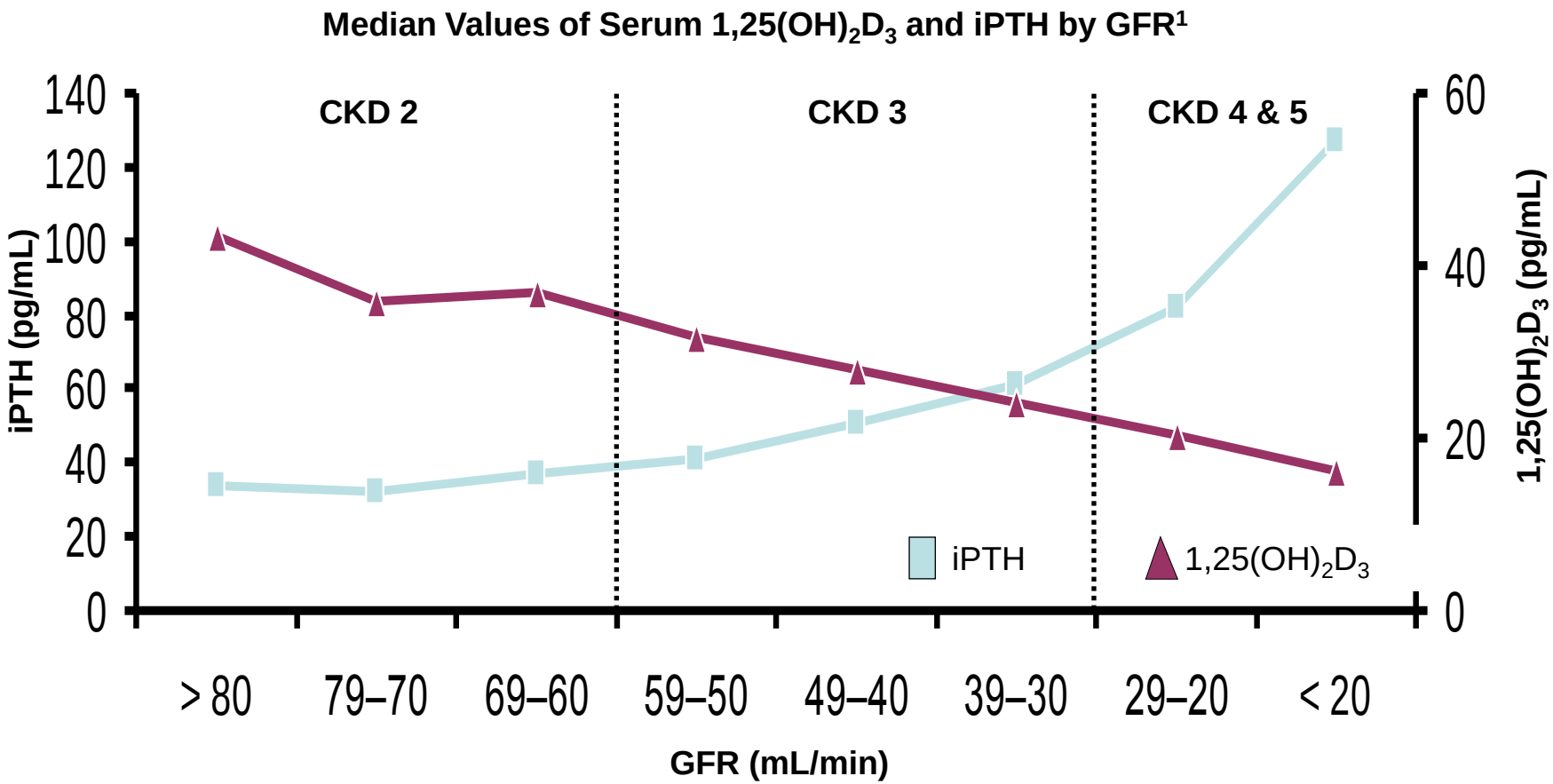
Changes in FGF-23 Levels With Decline in Kidney Function



N = 220

*Normal range for FGF-23 indicated by shaded area; GFR = glomerular filtration rate; eGFR = estimated GFR.
Adapted from Gutiérrez OM, et al. *Circulation*. 2009;119:2545-2552.

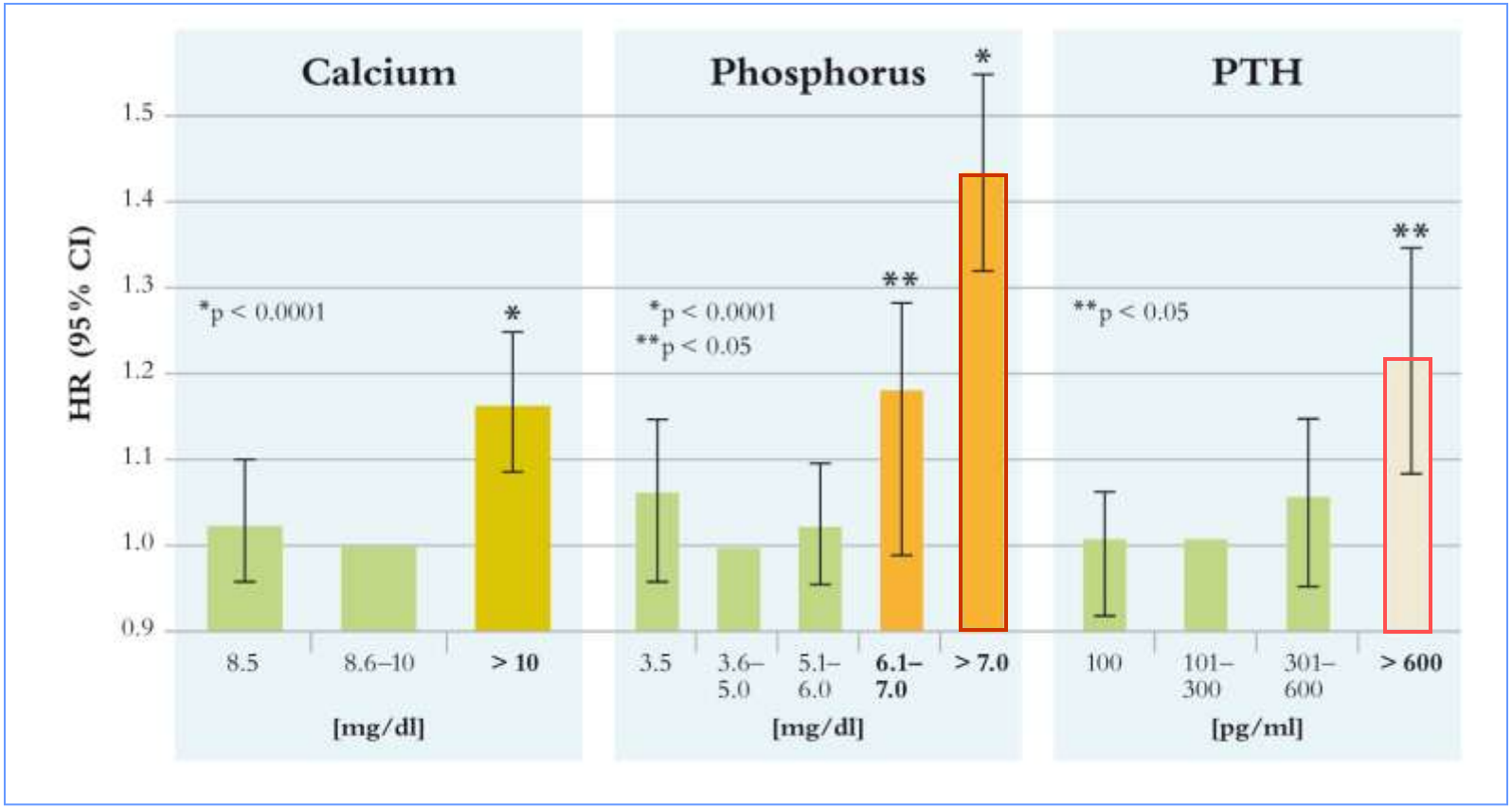
Changes in PTH and 1,25(OH)$_2$D$_3$ Levels With Decline in Kidney Function



N = 1,814

iPTH = intact PTH; GFR = glomerular filtration rate.
Levin A, et al. *Kidney Int*. 2007; 71:31-38.

Mineral Metabolism and Mortality Risk in the DOPPS



Disorders of mineral metabolism are associated with increased mortality

Prospective observational cohort study. 25.588 patients with ESRD on hemodialysis. Outcomes: Adjusted hazard ratios (HR) for all-cause and cardiovascular mortality using Cox models. Tentori F et al. *Am J Kidney Dis* 2008;52:519-530.

K/DOQI* guidelines for Bone Metabolism and Disease / Dislipidemia in Chronic Kidney Disease

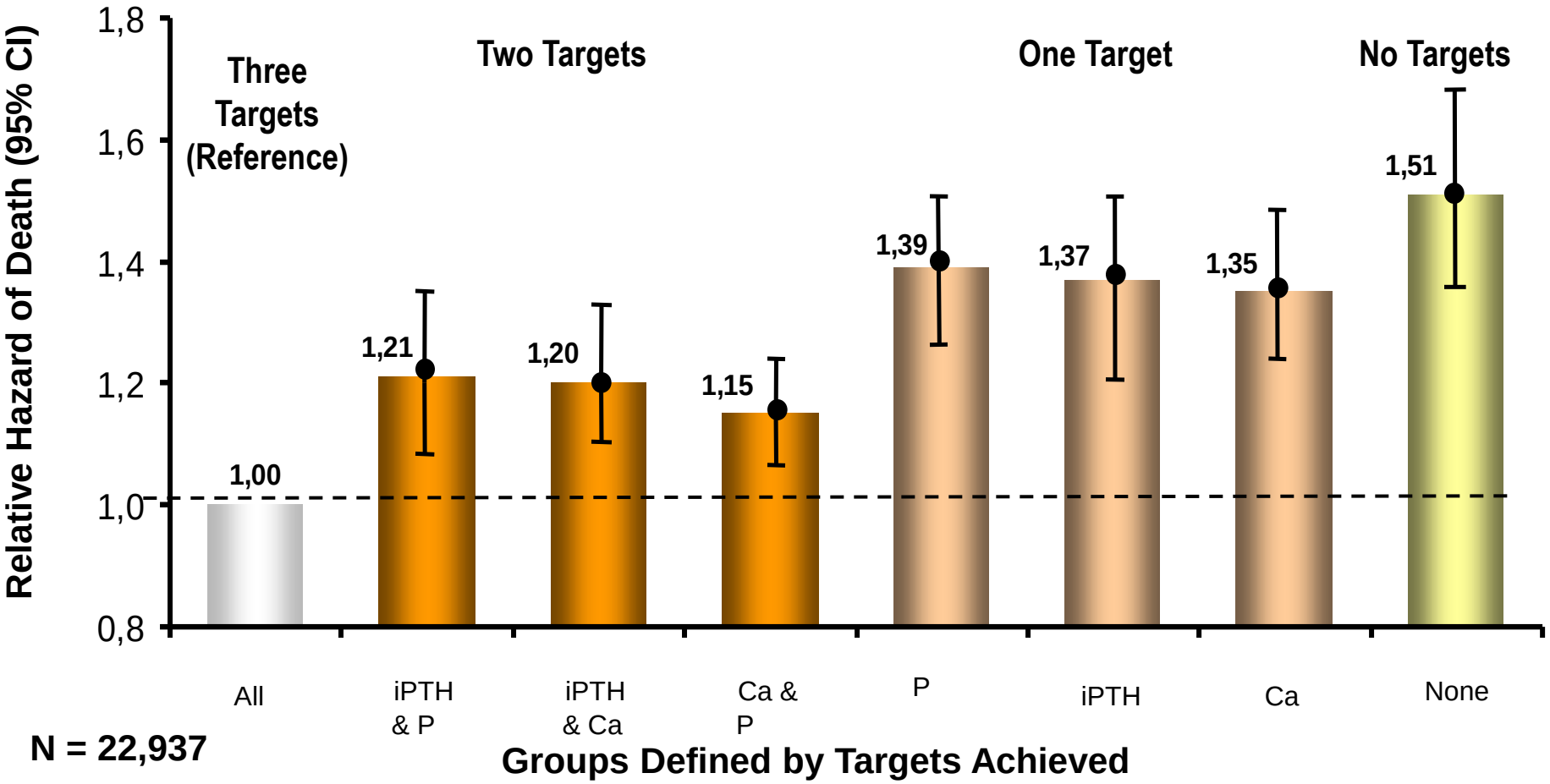
	K/DOQI Guidelines
P	3.5 – 5.5 mg/dL **(1.1 – 1.8 mmol/l)**
Ca x P	< 55 mg^2/dL^2 **(< 4.4 $mmol^2/l^2$)**
PTH	150 – 300 pg/mL
LDL cholesterol	< 100 mg/dL **(< 2.56 mmol/l)**
Total cholesterol	< 200 mg/dL **(< 5.12 mmol/l)**

*National Kidney Foundation K/DOQI (Kidney Disease Outcome Initiative)

The K/DOQI guidelines have become widely accepted and are basis of many national treatment guidelines in Eastern Europe

National Kidney Foundation K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 2003;42(Suppl 3):S1-S202. National Kidney Foundation K/DOQI Clinical Practice Guidelines for managing Dyslipidemias in Chronic Kidney Disease. *Am J Kidney Dis.* 2003;41(suppl 3):S1-91.

Mortality Risk Varies According to Number of Laboratory Targets* Achieved Concurrently



Time-dependent model. *Laboratory targets from National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI™). KDOQI™ is a trademark of the National Kidney Foundation, Inc.

Danese MD, et al. *Clin J Am Soc Nephrol.* 2008;3:1423-1429.

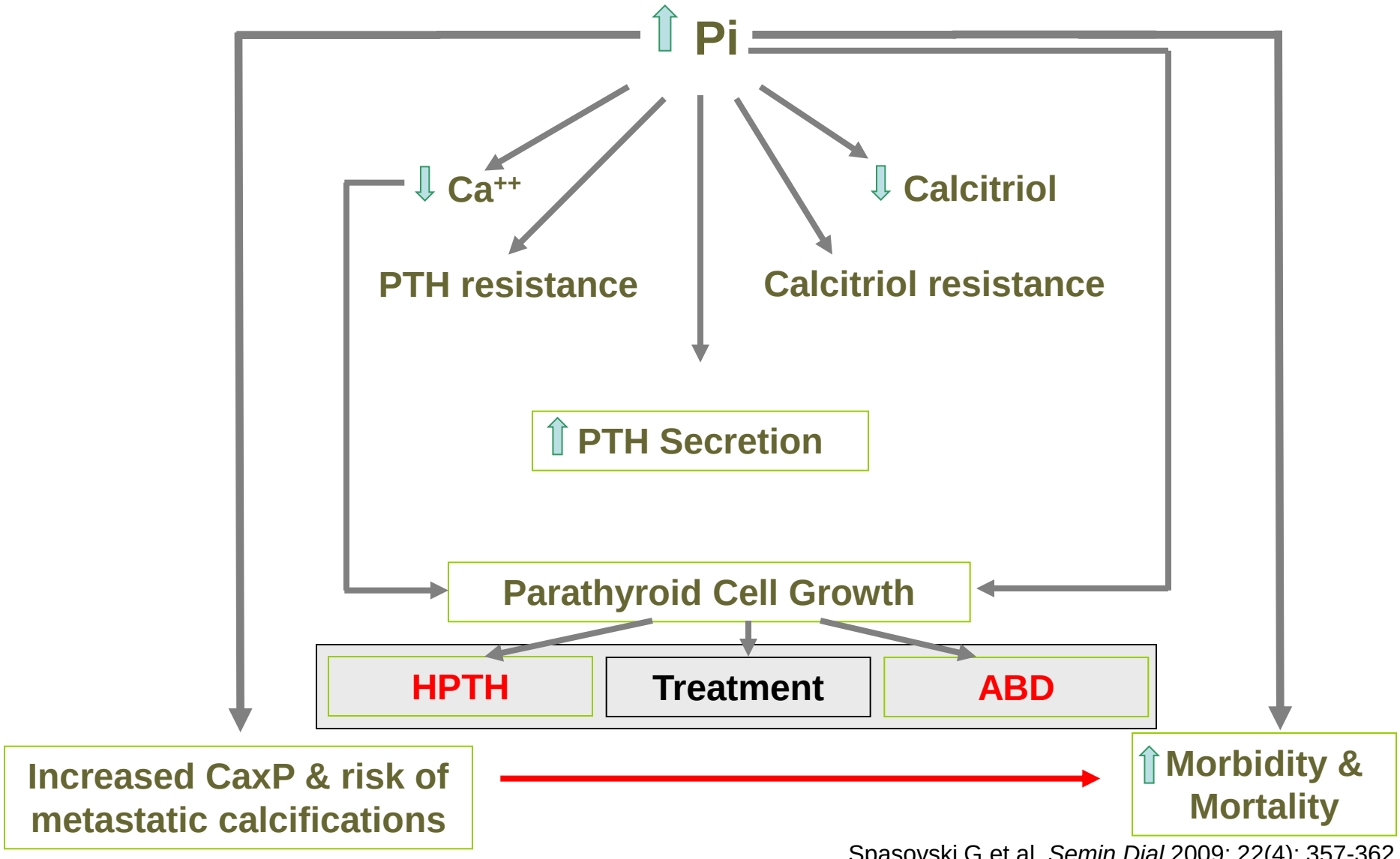
Bone as primary reservoir of calcium & phosphorus

Hydroxyapatite

	% of total body Ca	% of total body PO_4
Bone	99 %	29 %
Intracellular	0.9 %	70 % (exch.)
Interstitial	0.075 %	0.1 %
Plasma	0.025 %	0.9 %

Spasovski G et al. *Semin Dial* 2009; 22(4): 357-362

Consequences of Elevated Serum Phosphorus



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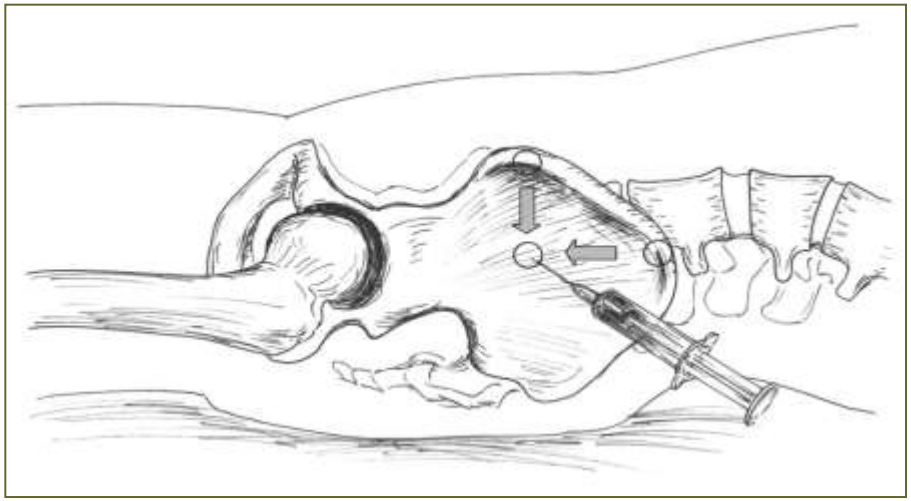
The International Journal of Artificial Organs / Vol. 27 / no. 11, 2004 / pp. 918-923

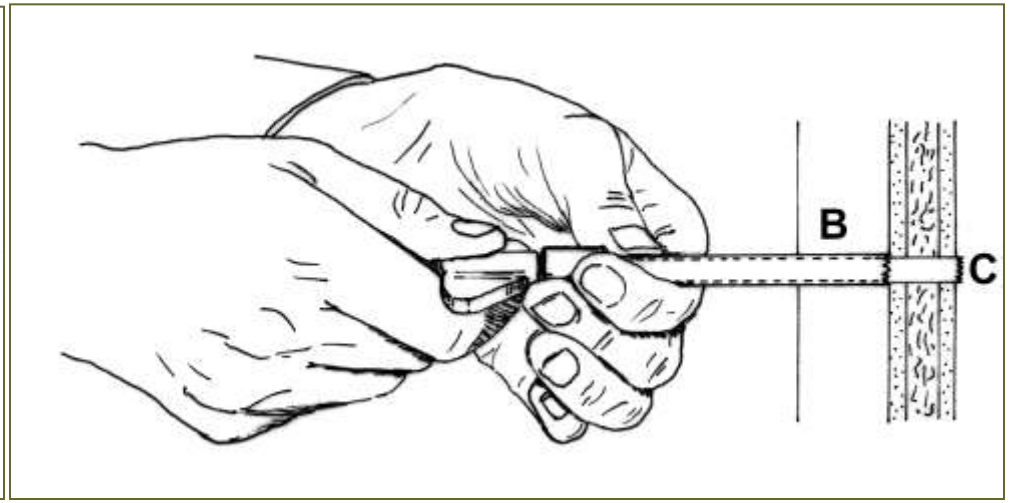
Editorial Review

Bone biopsy as a diagnostic tool in the assessment of renal osteodystrophy

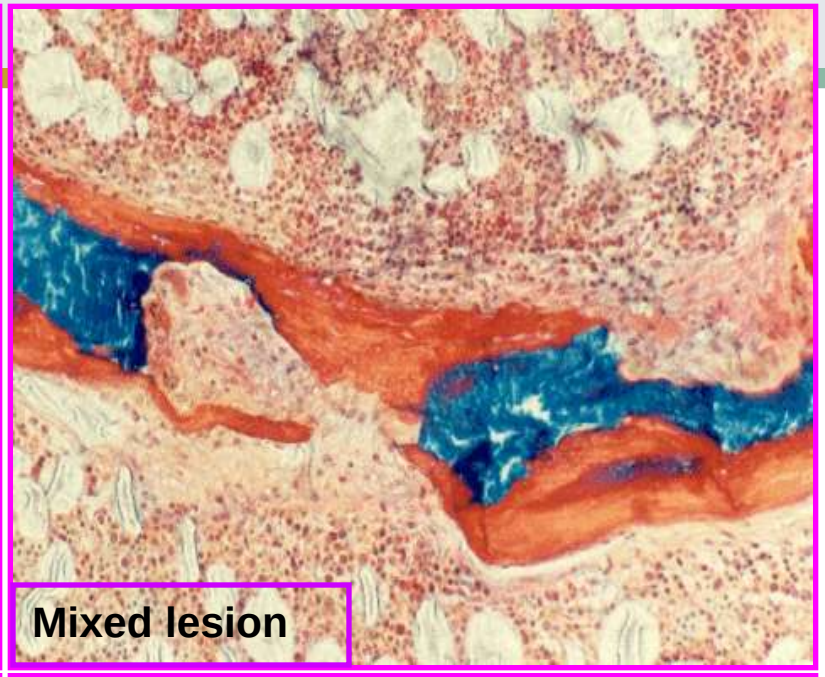
G.B. SPASOVSKI

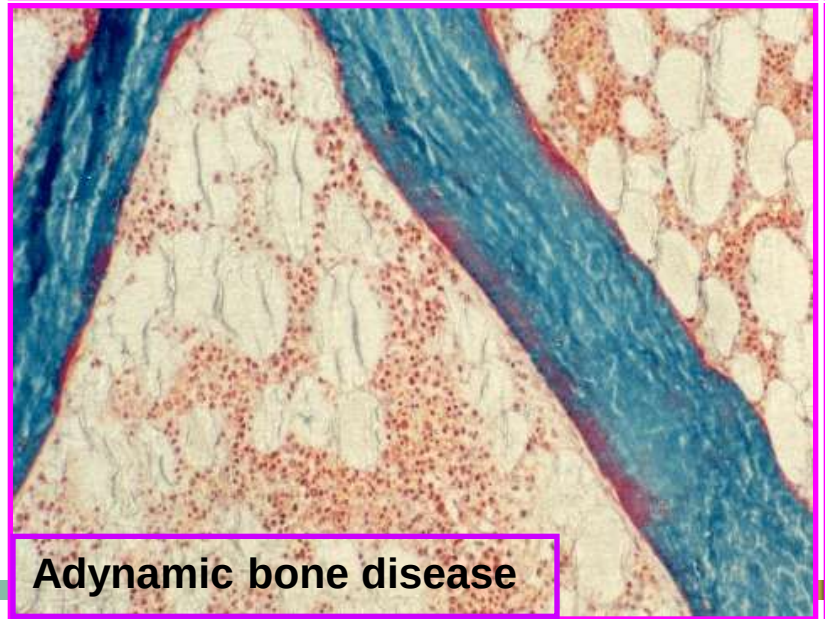
Department of Nephrology, Clinical Center Skopje, University of Skopje - Macedonia

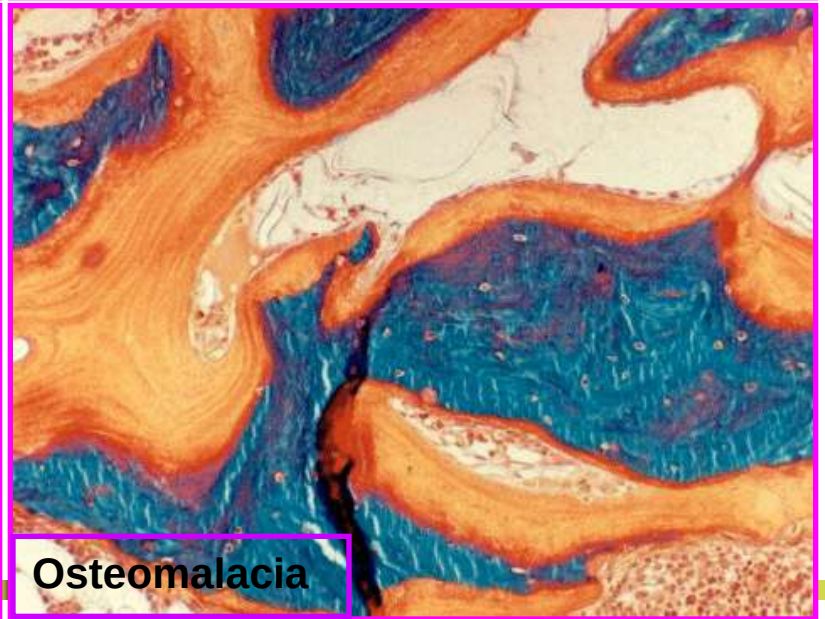




Bone Histology in ROD





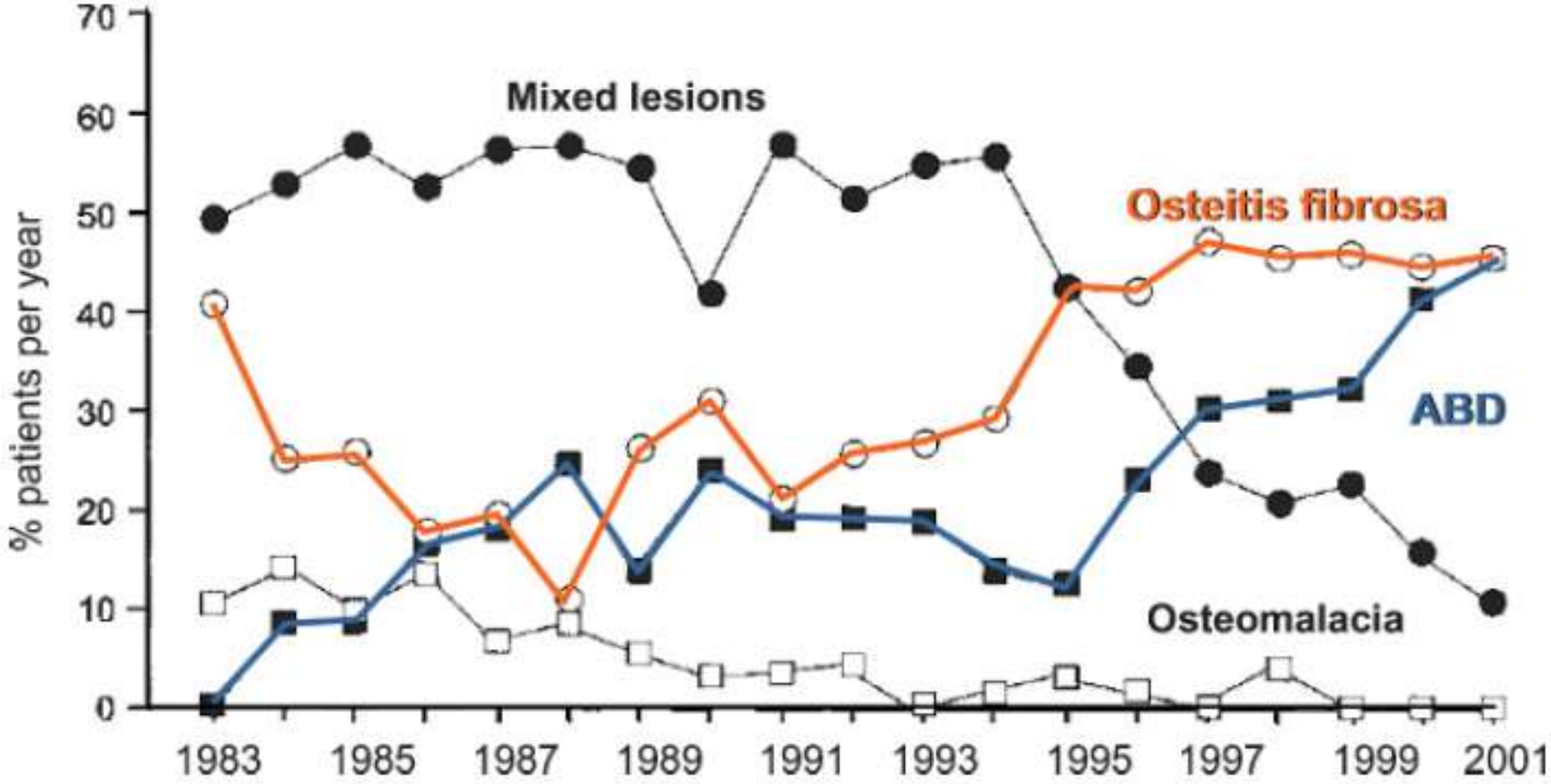


Changing Spectrum of ROD

- *Earliest reports*
- HPTH – most prevalent, followed by OM
  - Insufficient treatment of sHPTH
  - Vitamin D deficiency
  - Al intoxication
- *Last two decades*
- ABD
  - Older age of the patients
  - Diabetes
  - ***Calcium containing phosphate binder***
  - ***Vitamin D treatment***
  - ***High calcium dialysate concentration***

Adynamic Bone Disease - bone and beyond

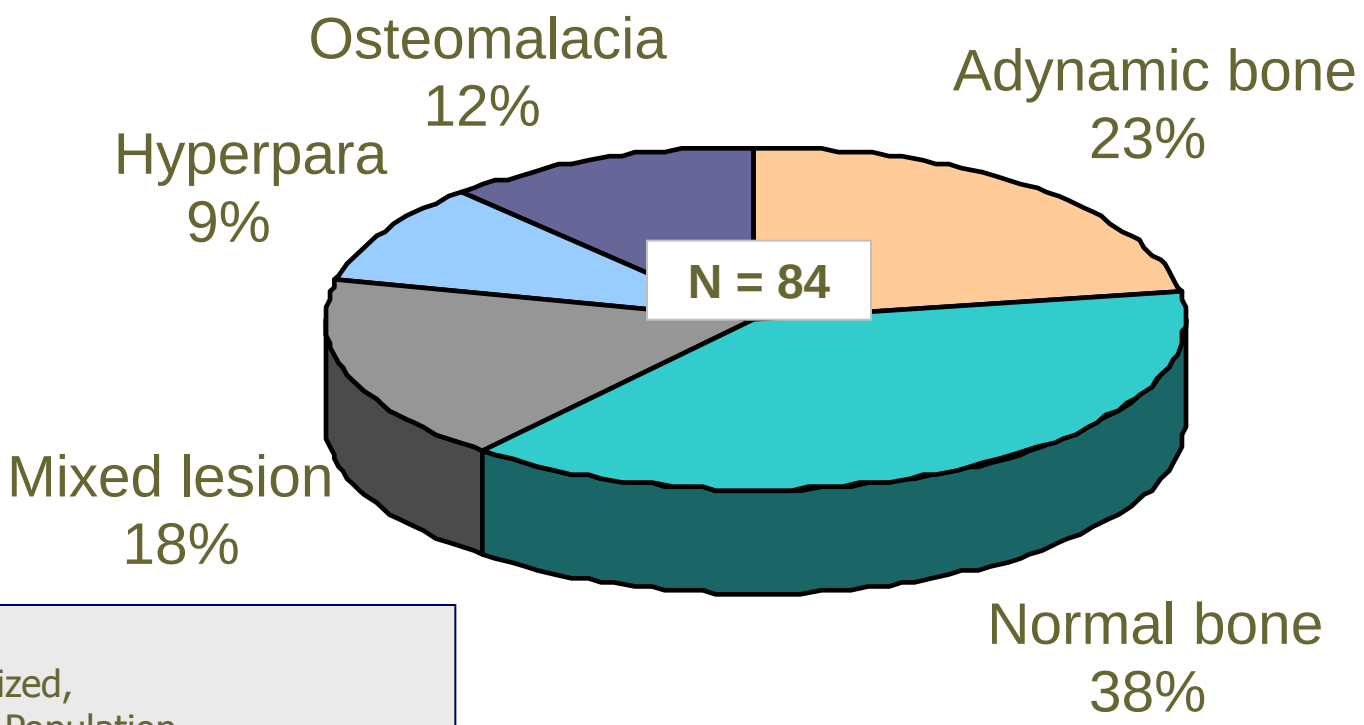
Changing spectrum of renal osteodystrophy



Evolution of ROD distribution pattern over time

Brandenburg VM & Floege J. NDT plus (2008) 3: 135–147
Malluche HH, Mawad H, Monier-Faugere MC. Nephrol Dial Transpl 2004; 19 Suppl 1: i9-13

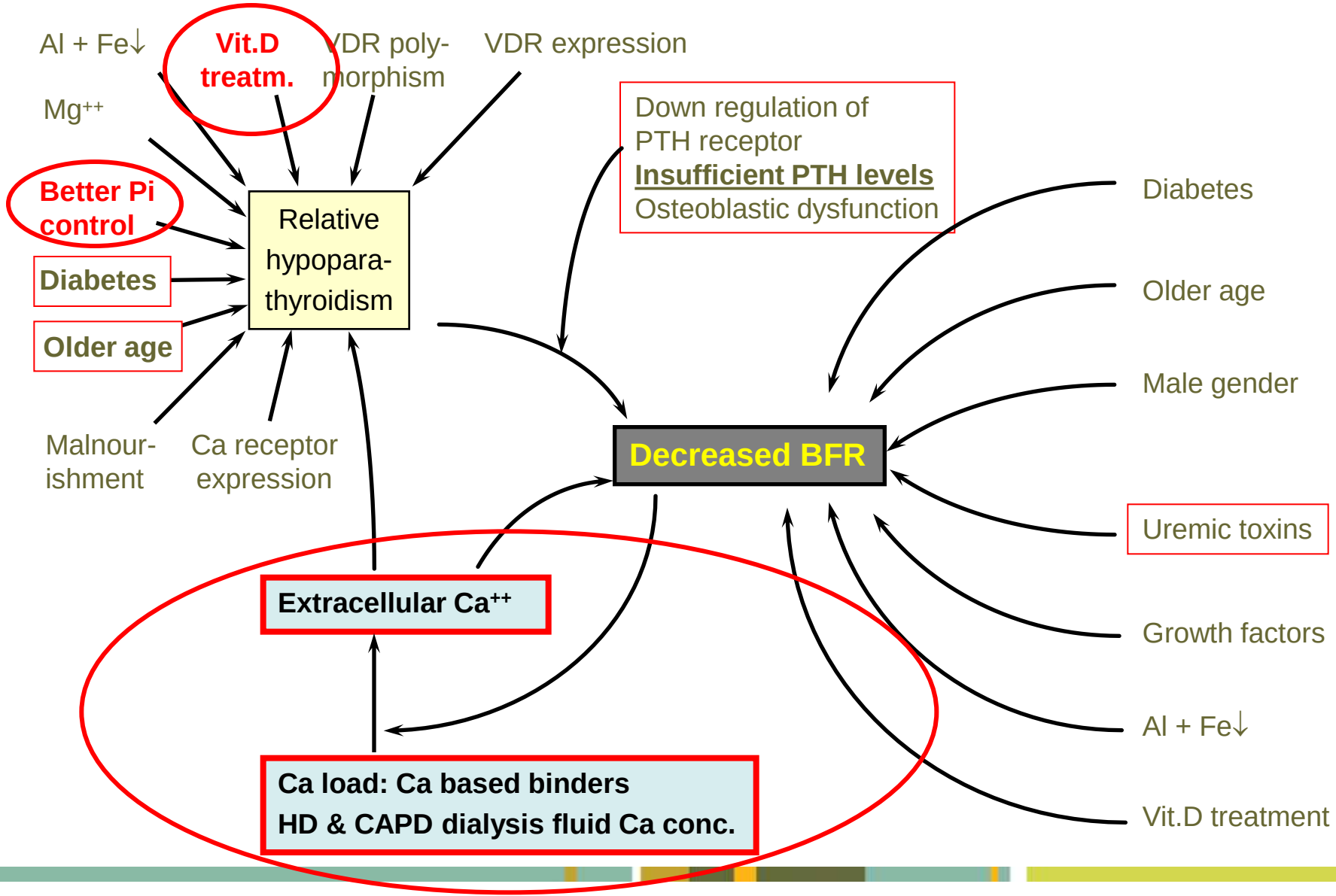
Spectrum of Renal Bone Disease in patients with end-stage renal bone disease not yet in dialysis



- Prospective,
- Non-randomized,
  Macedonian Population
- N = 84 patients
- Histomorphometric criteria
  according to:
  Salusky et al., Kidney Int.,33,1988
  Parfitt et al., Calcif Tissue Int 42, 1988

GB Spasovski et al. *Nephrol Dial Transpl* 2003; 18: 1159-66

Physiopathology of Adynamic Bone



Clinical Relevance and Consequences

Association in CKD patients between:

MBD (abnormal mineral metabolism & bone health)

&

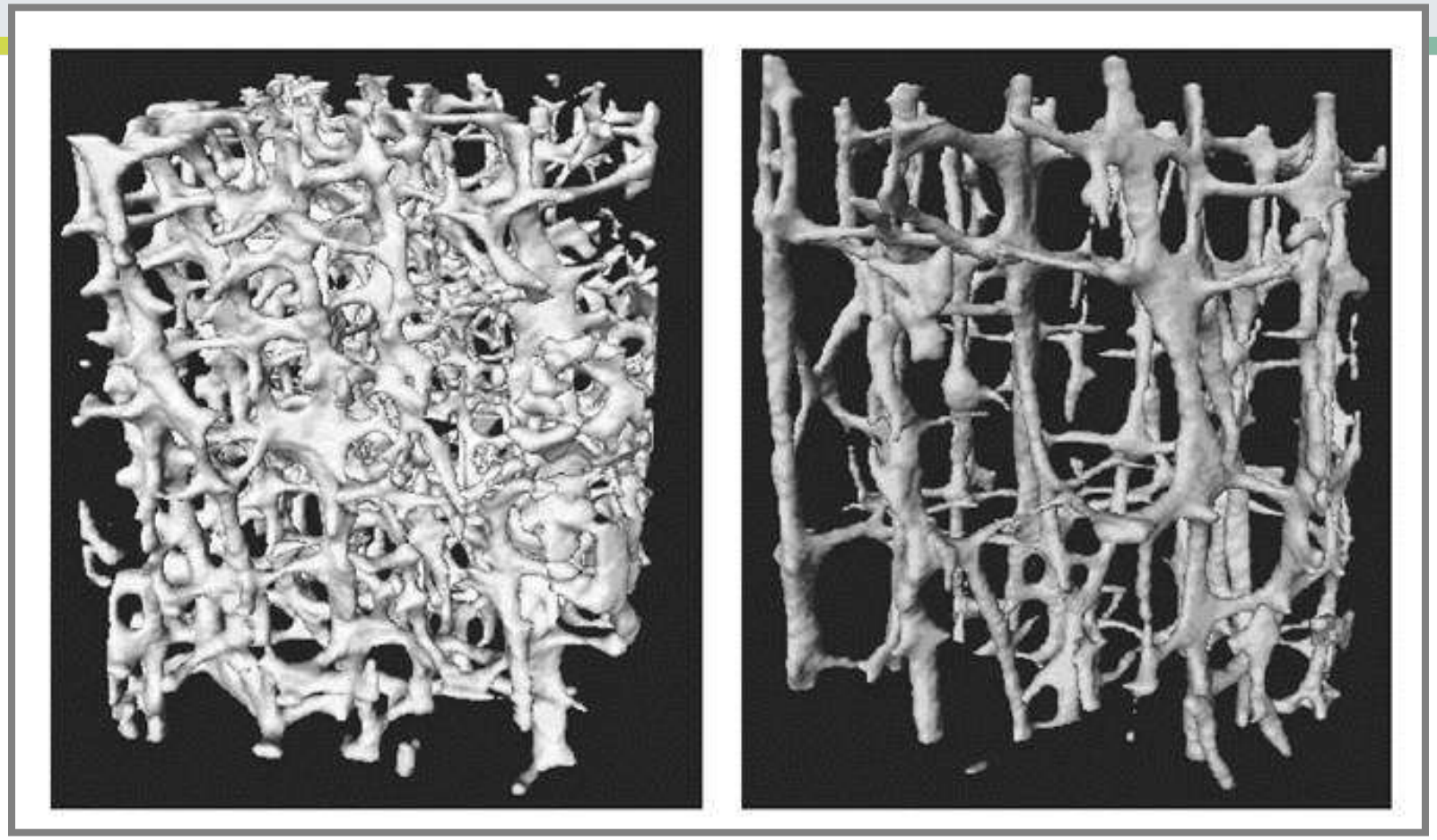
Fractures – decreased quality of life

VC – most important cause of morbidity

CVD – significant mortality

Bone health and vascular calcification relationship in chronic kidney disease
Spasovski G. *Int Urol Nephrol* 2007;39:1209–1216

CKD - MBD: Bone lose & fracture

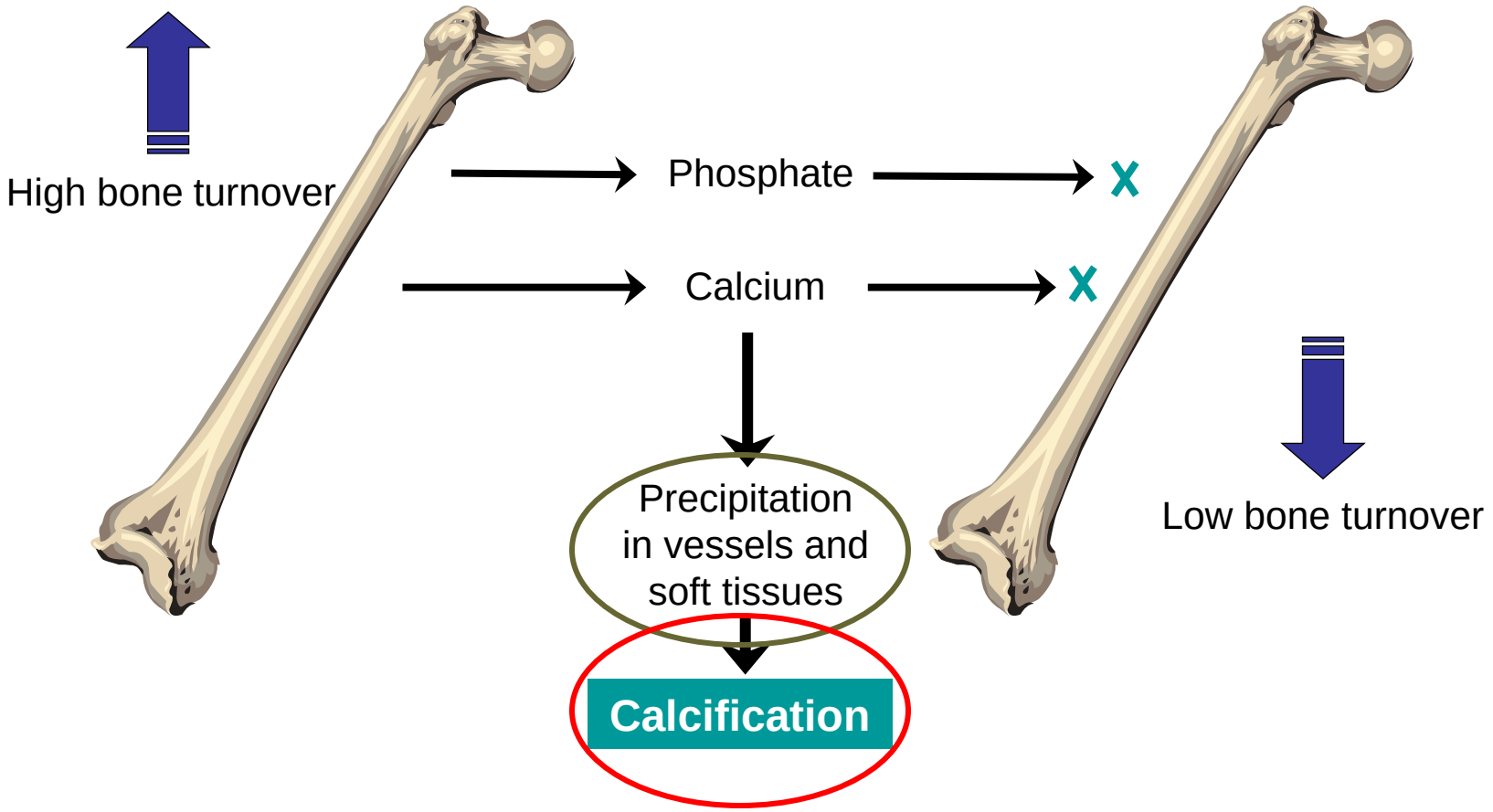


United States Renal Data System data (300,000 patients)

- The relative risk for hip fracture in dialysed patients is 4.4 times (men and women) that of age-matched controls.

Alem A et al. Kidney Int 2000, 58: 396-9

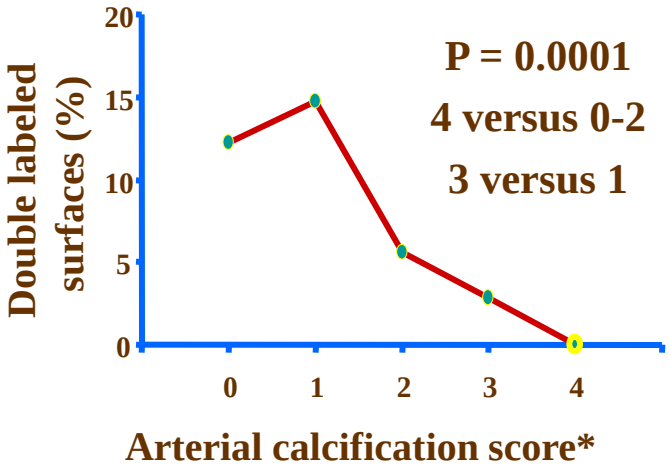
Disordered bone remodelling can induce vascular calcification

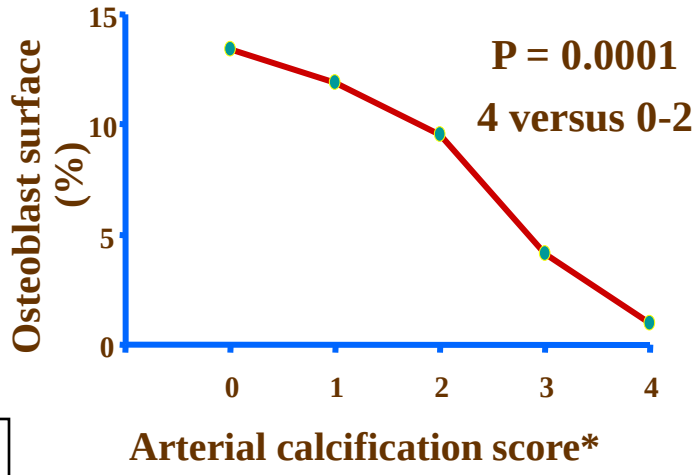


High bone turnover leads to release of Ca + P from bone. Low bone turnover hinders their emplacement in bone. Result is cardiovascular and soft tissue calcification.

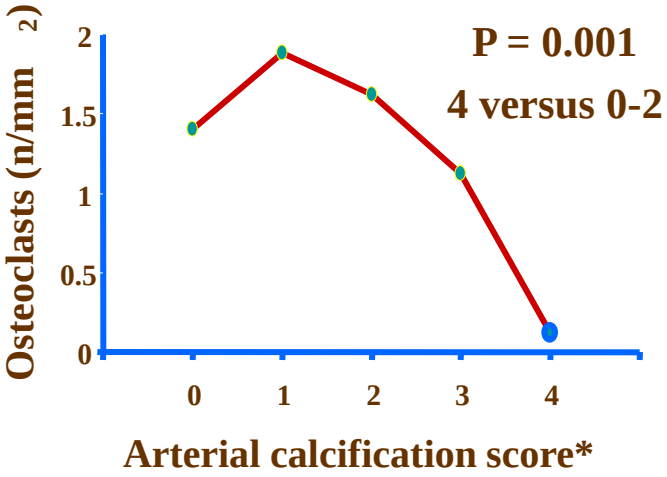
London et al. *J Am Soc Nephrol* 2004;15:1943–1951; Spasovski G. *Int Urol Nephrol* 2007;39:1209–1216

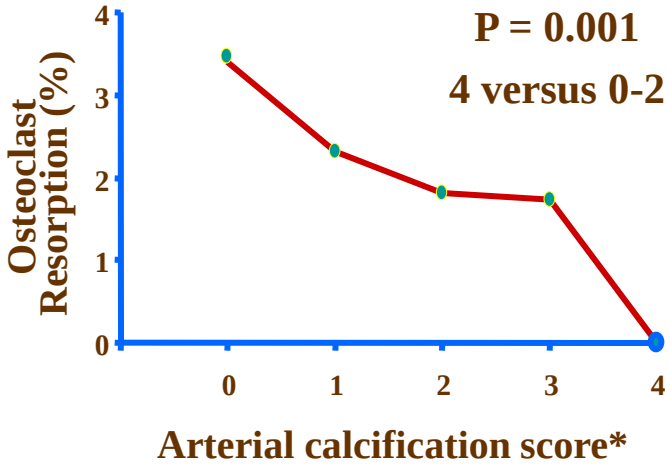
Arterial Calcifications and Bone Histomorphometry in ESRD





n = 58

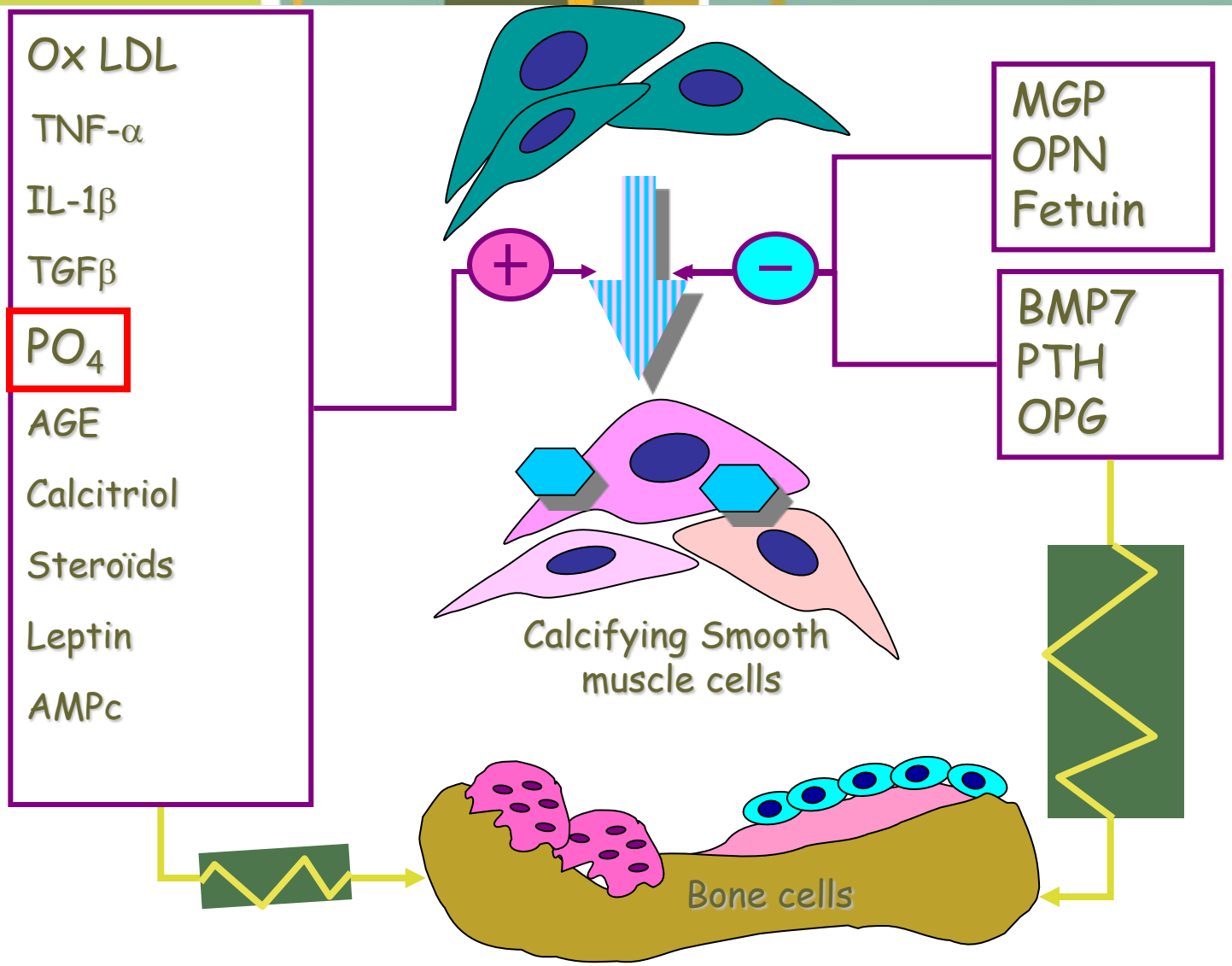




*Determined by ultrasonography

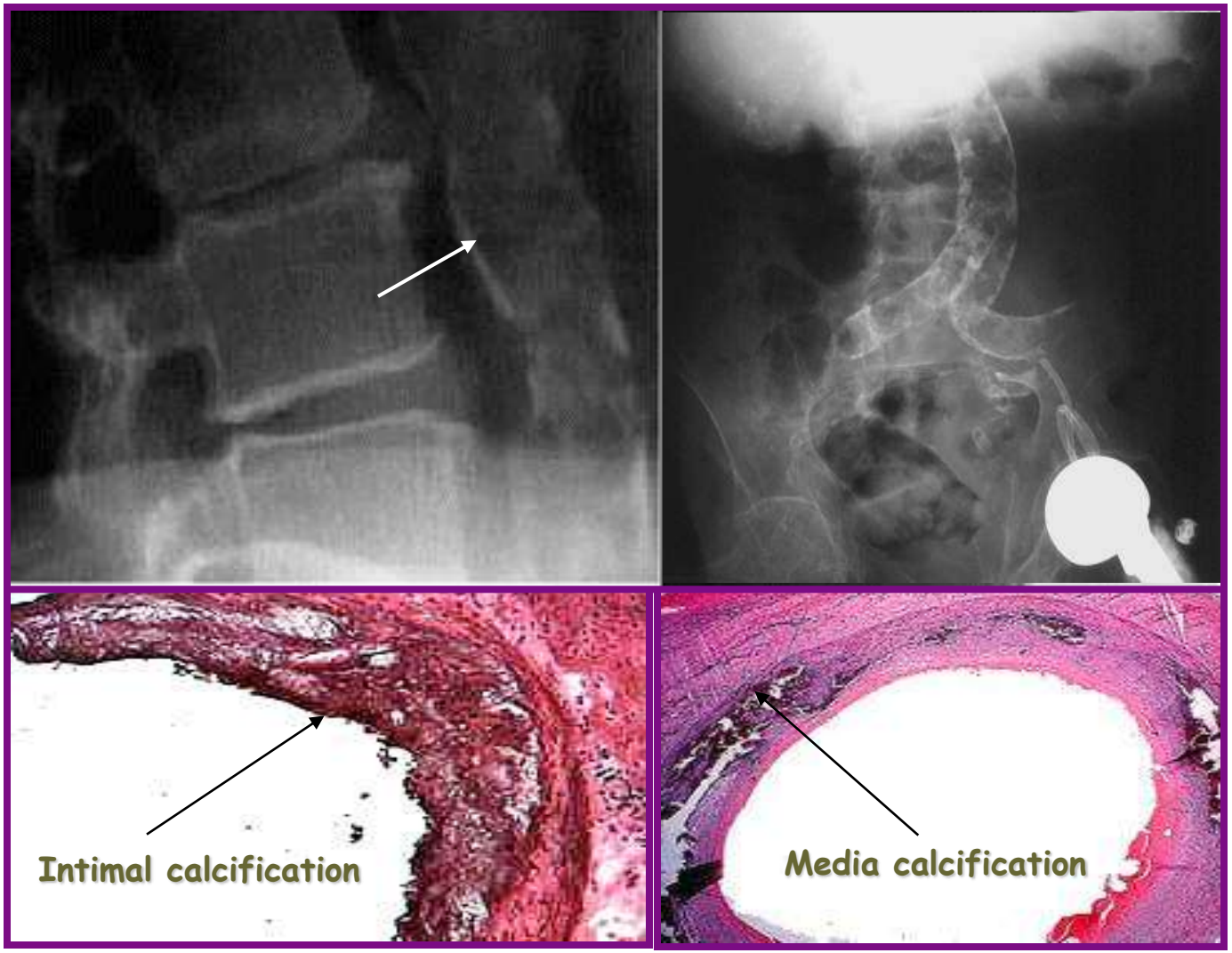
London GM, J Am Soc Neph 15: 1943-1951, 2004

VSMCs can Transdifferentiate into Osteoblasts



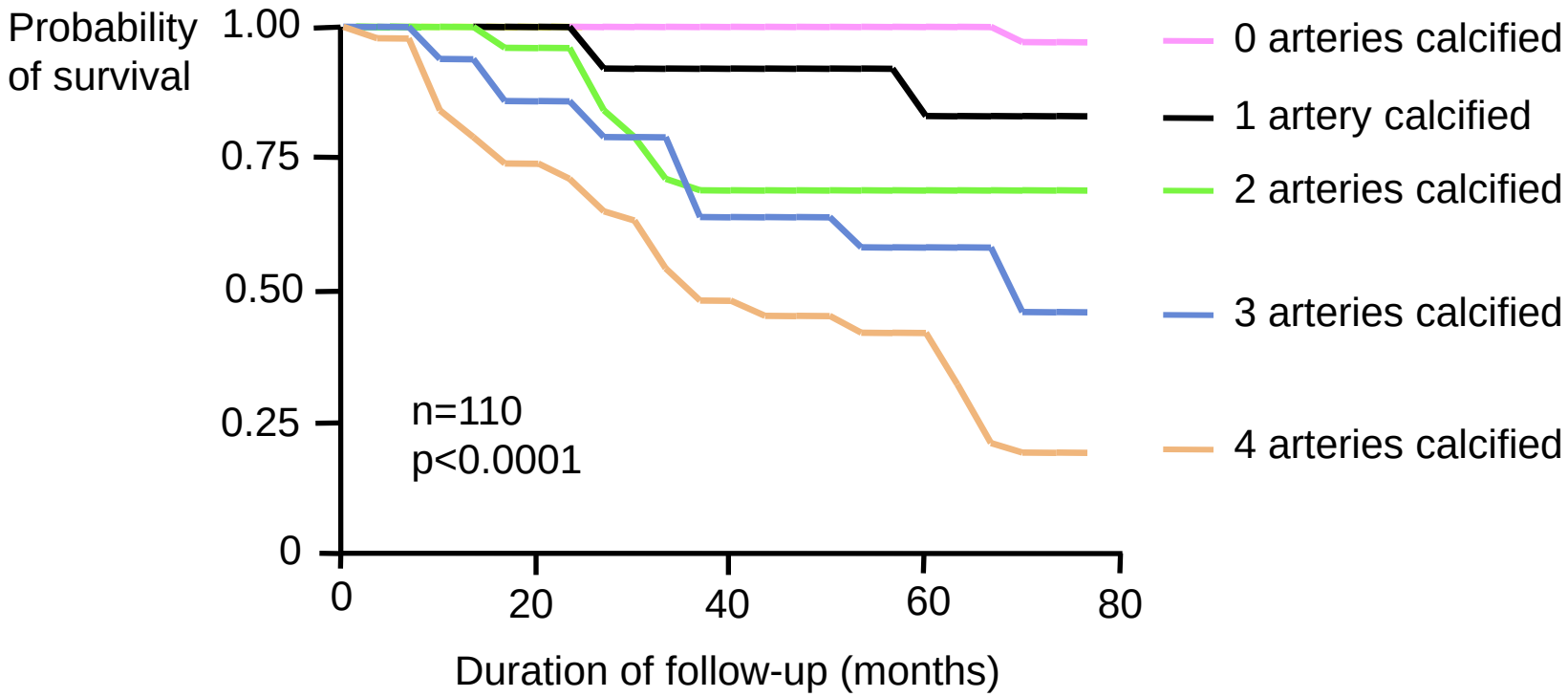
Modified from: Shanahan CM. Curr Opin Nephrol Hypertens 2005; 14(4):361-7

CKD - MBD: Vascular calcifications



More frequent & early occurrence vs. general population (London G et al. JASN, 2000, 11:778-8)
More rapid rate of progression (Tamashiro M et al., AJKD, 2001, 38:64-9)

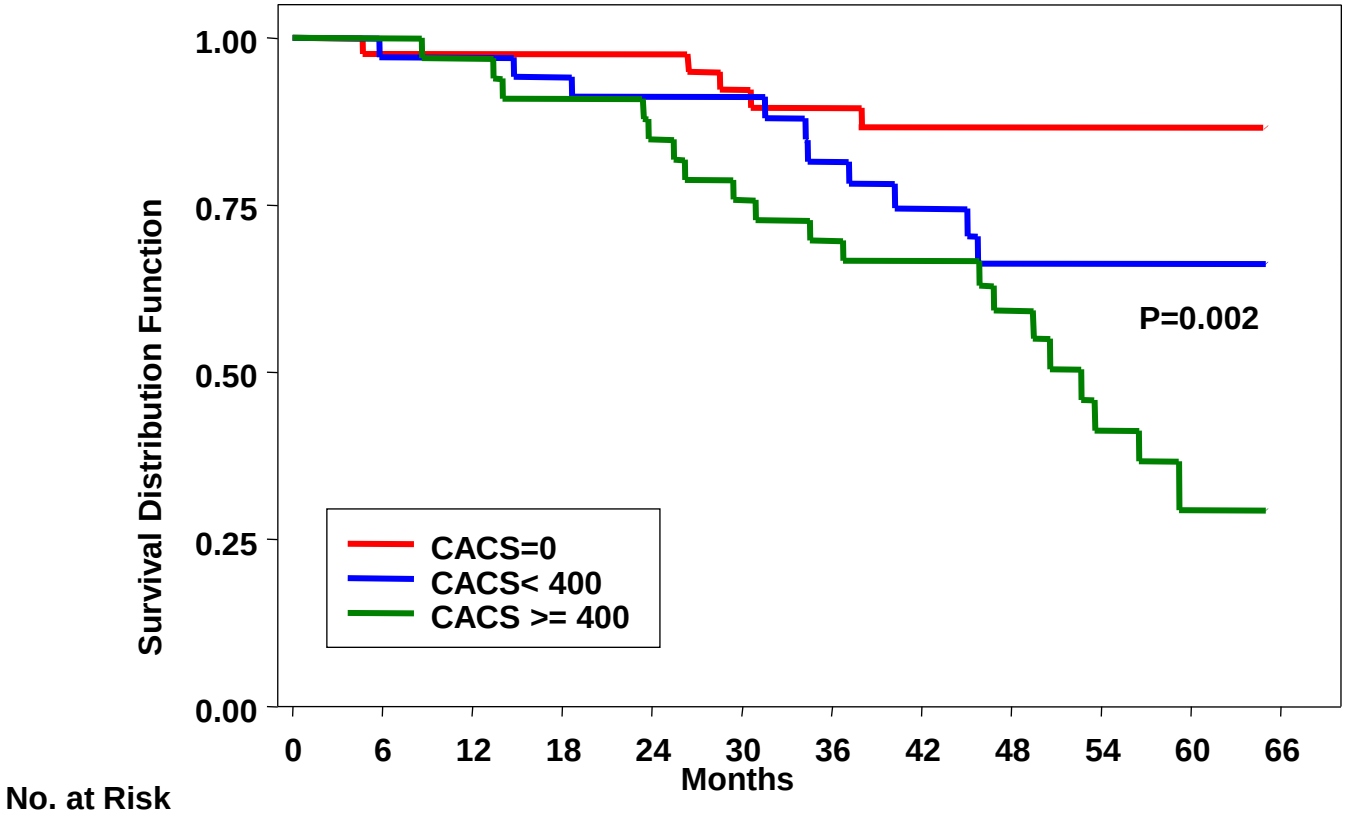
Arterial calcification increases mortality risk



Presence and extent of vascular calcifications predict cardiovascular and all-cause mortality in dialysis patients.

Prospective trial in 110 dialysis patients assessing cardiovascular (CV) calcifications , mean follow up 53 months. Endpoints: All cause and CV mortality using univariate and multivariate survival analysis. Blacher et al. Hypertension 2001;38:938–942

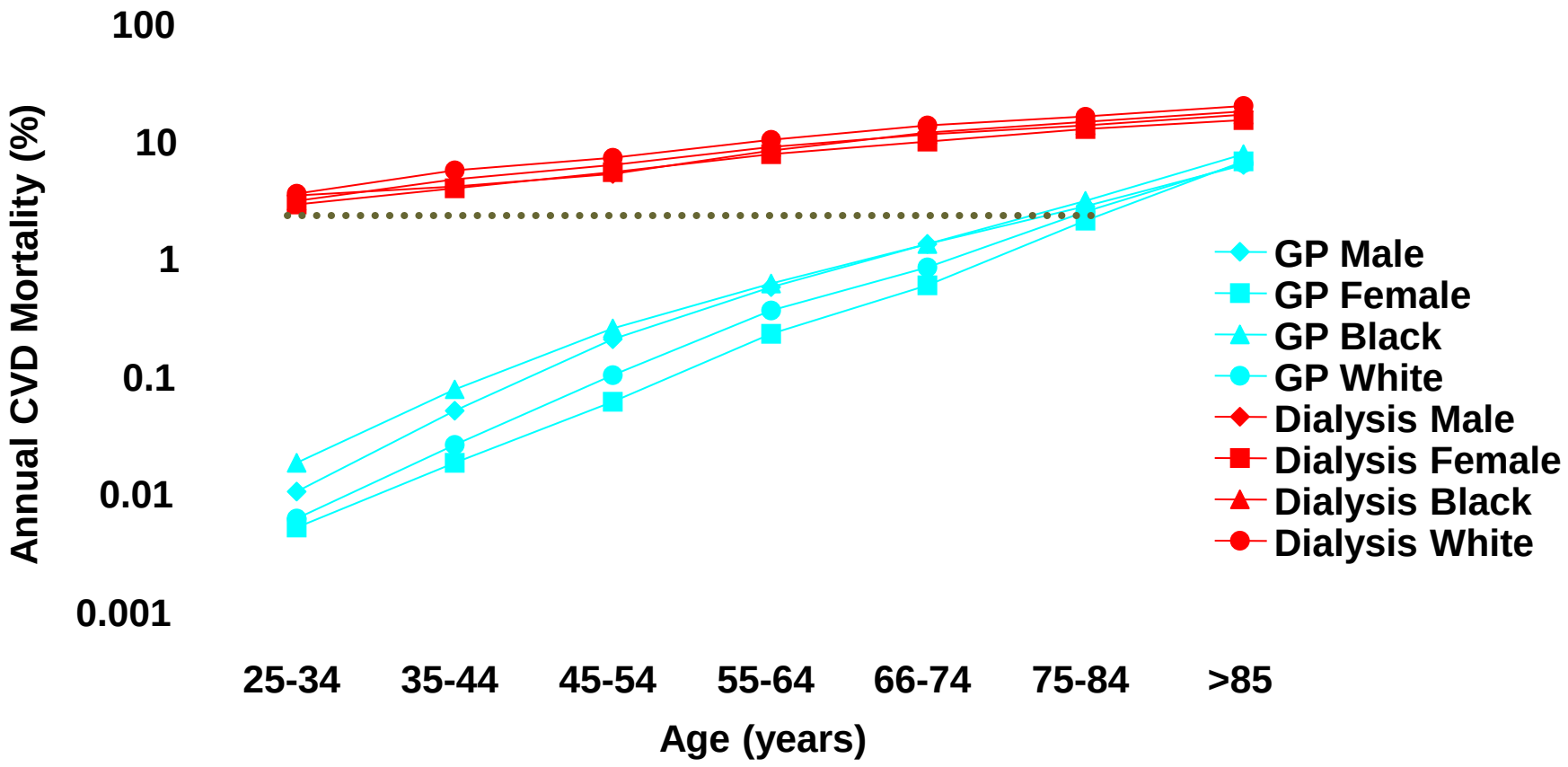
Survival by baseline CACS



Patients with cardiovascular calcifications had a higher mortality risk than non-calcified patients.

Follow up of a randomized, prospective, open label, multicenter study over a median of 44 months (RIND). 127 patients randomized to either sevelamer or Ca. Prespecified secondary endpoint. Block GA et al. *Kidney Int* 2007;71:438-441

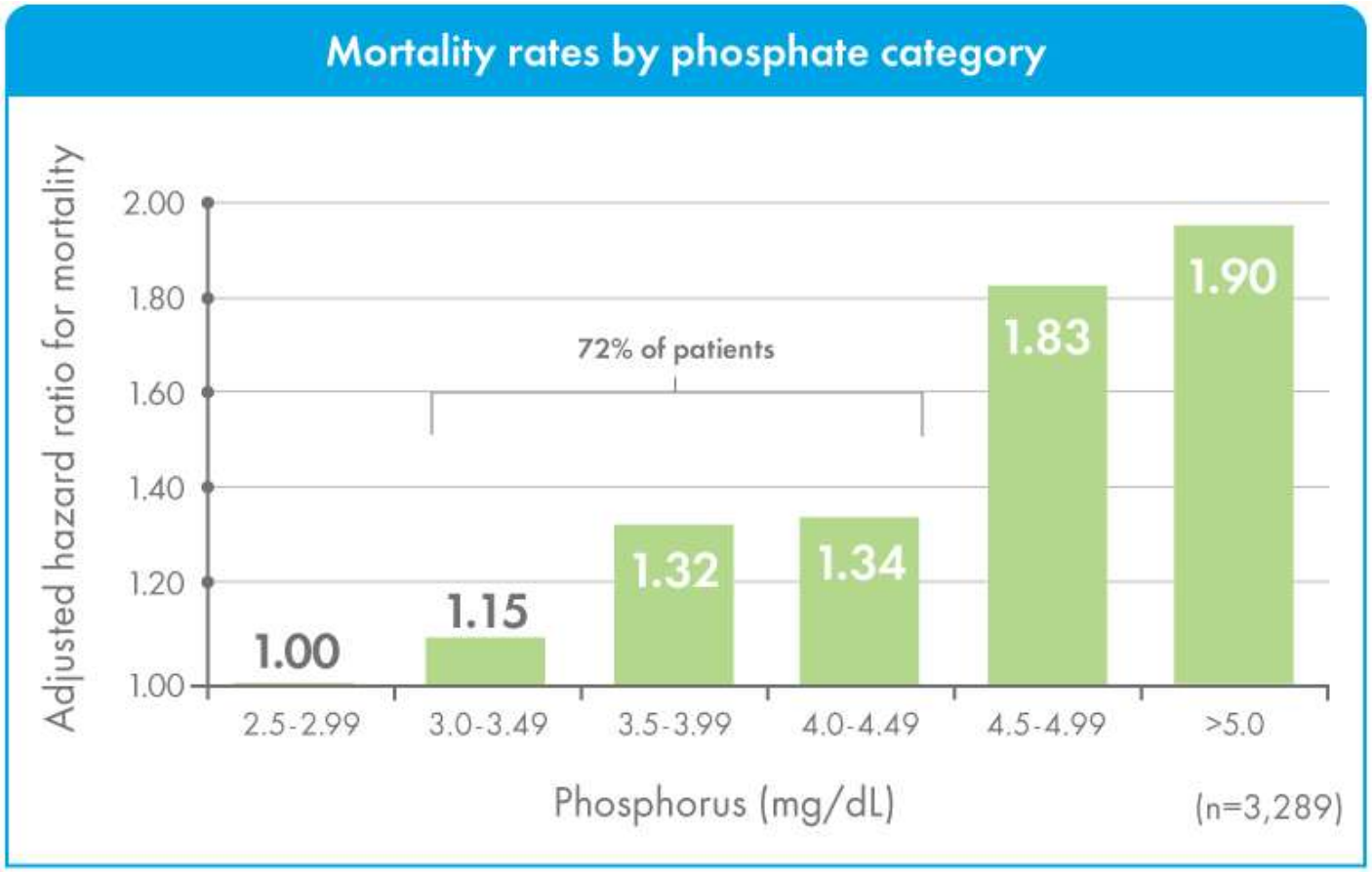
Increased CVD Morbidity & Mortality



CVD = cardiovascular disease
GP = general population

Foley FN et al. *AJKD* 1998;32:S112-S119

Increased serum phosphorus negatively impacts the mortality of CKD patients not on dialysis.



The association between higher phosphate levels and mortality risk was present among patients with absolute serum phosphate levels in the high-normal range.

Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol.* 2005;16:520-528.

Management of Hyperphosphatemia

1.

Dietary phosphorus restriction

2.

Dialysis

3.

Phosphate binders

Serum phosphorus not sufficiently controlled through dialysis and diet

Almost all dialysis patients need phosphate binders

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Spasovski G, *Recent Patents on Cardiovascular Drug Discovery*, 2008; 3(3):222-8.
NKF - K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.
***Am J Kidney Dis* 2003;42(Suppl 3):S1-S202.**

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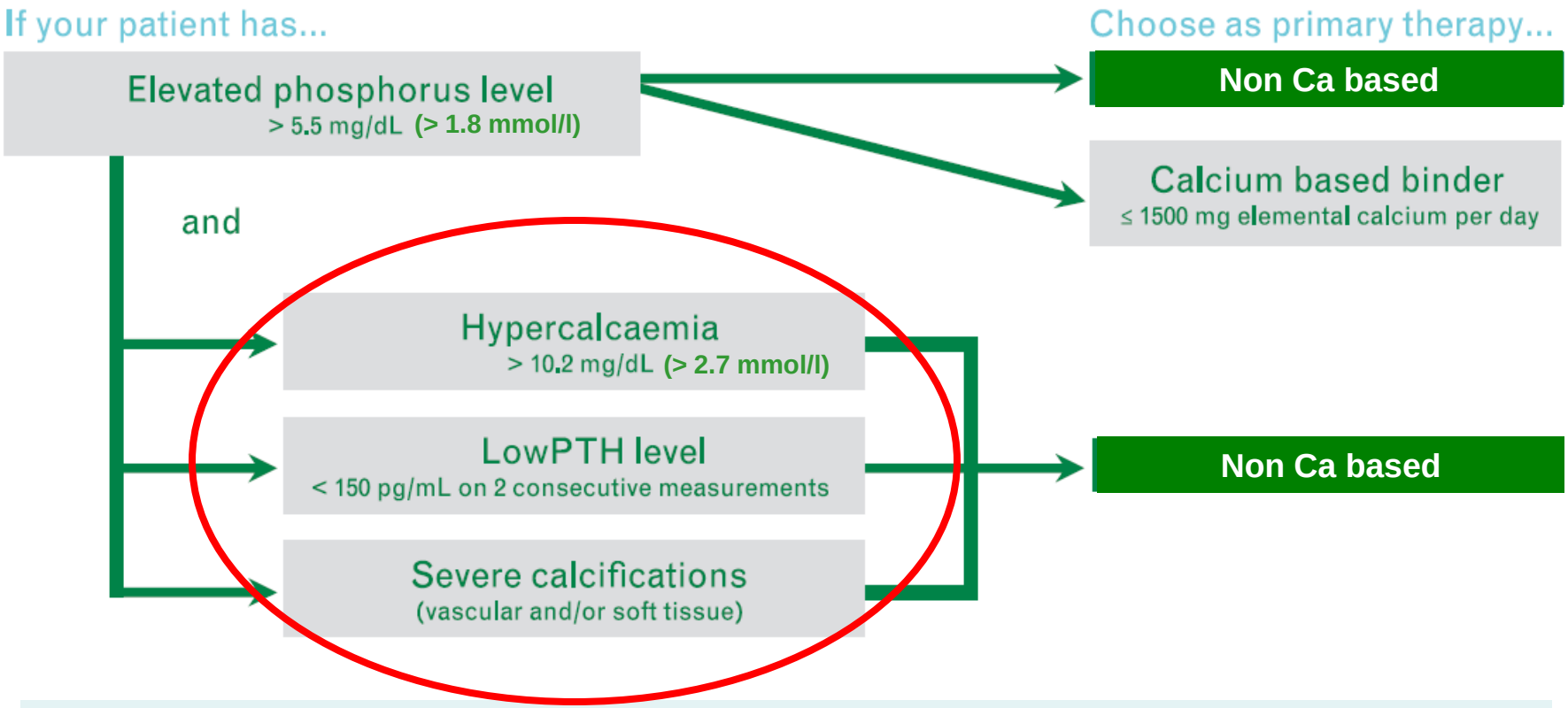

Sevelamer remains first line treatment option (Lanthanum, MCI 196)

Ca based binders contraindicated in low PTH, high Ca, severe calcifications

National Kidney Foundation K/DOQI Clinical Practic Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 2003;42(Suppl 3):S1-S202.

Calcium restriction in KDIGO

Calcification

51% - 83%[1,2,3]

Persistently Low PTH

57%[2]

Hypercalcemia

16% - 54%[2,3,4]

ABD

5 – 40% CKD 3/4[6]
20 – 50 % HD[6]
40 – 70% PD[5]

Recommended for Calcium Restriction

[1]Russo D, Corrao S, Miranda I, et al. *Am J Neph* 2007;27:152-8
[2]Chertow GM, Burke SK, Raggi P, et al. *Kidney Int*. 2002;62:245-52
[3]Block GA, Spiegel DM, Ehrlich J,et al. *Kidney Int*. 2005;68:1815-24
[4]Qunibi W, Moustafa M, Muenz LR, et al. *AJKD*. 2008
[5]Andress D. *Kidney Int.* 2008*;73:1345-1354*
[6]KDIGO. *Kidney Int.* 2009; 76 (Suppl 113):S1-S130

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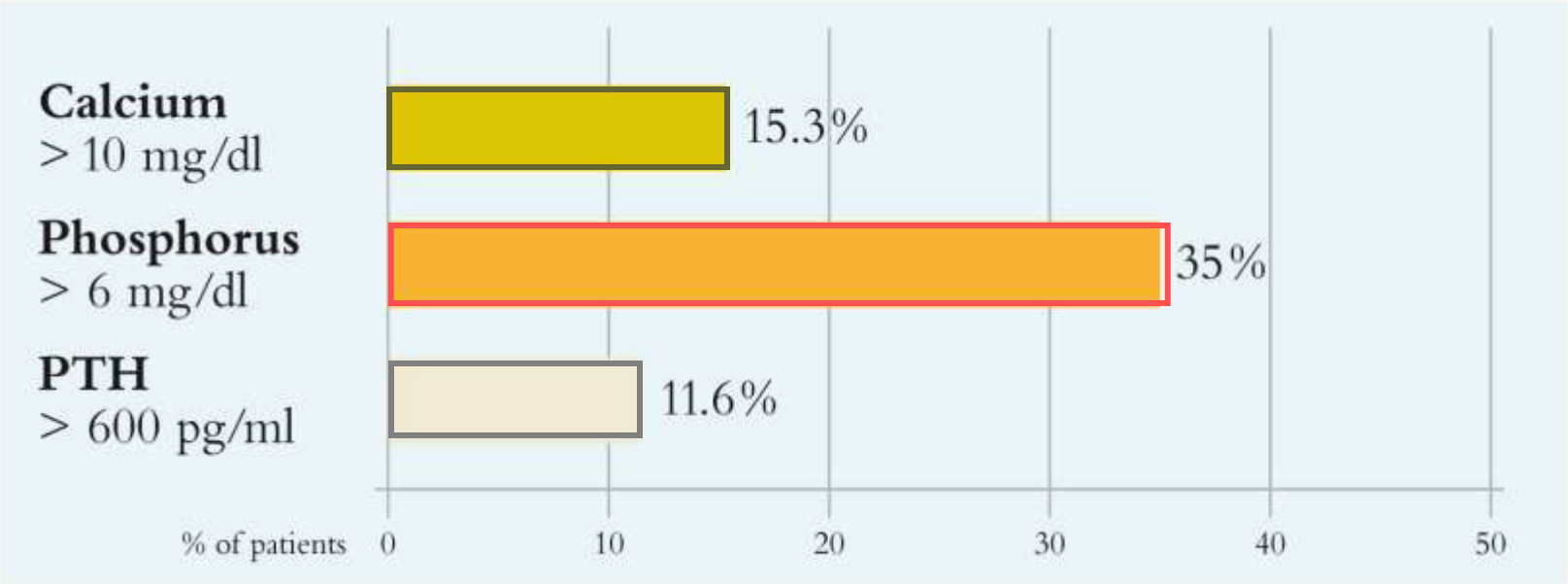

Hyperphosphatemia is the most frequent abnormality.

Around 90% of dialysis patients on phosphate binders, still 35% out of KDOQI targets.

Prospective observational cohort study. 25.588 patients with ESRD on hemodialysis. Outcomes: Adjusted hazard ratios (HR) for all-cause and cardiovascular mortality using Cox models. Tentori F et al. *Am J Kidney Dis*. 2008;52:519-530

Types of Phosphate Binders

- **Calcium-based**
  - **Calcium carbonate and acetate (Mg)**–effective at binding dietary phosphate, but associated with vascular-soft tissue calcification
- **Metal-based -** *(non-calcium)*
  - **Aluminium**–effective at binding dietary phosphate, but long-term toxicity shown
  - **Lanthanum** – systemically absorbed; bone deposition (no toxicity) has been demonstrated
- **Renagel® (sevelamer) –** *(non-calcium)*
  - Calcium-free, metal-free phosphate binder. The only non-absorbed phosphate binder. Does not expose patients to increased risk of vascular and soft tissue calcification
- ***MCI-196 –** *(non-calcium)*
  - Calcium & metal-free non-absorbed phosphate binder. Efficient and safe treatment, no risk of soft and VC

Goodman WG et al. *NEJM* 2000;342:1478-83. London GM et al. *JASN* 2004;15:1943-51. Malluche HH and Mawad H. *NDT* 2002;17:1170-75. Locatelli F et al. *Drugs* 2003;6:688-95. Chertow GM et al. *KI* 2002;62:245-52. Block GA et al. *KI* 2005;68:1815-24. Spasovski G et al. *NDT* 2006;21:2217-24. ***Locatelli F et al. *NDT* 2010;25:574-81.**

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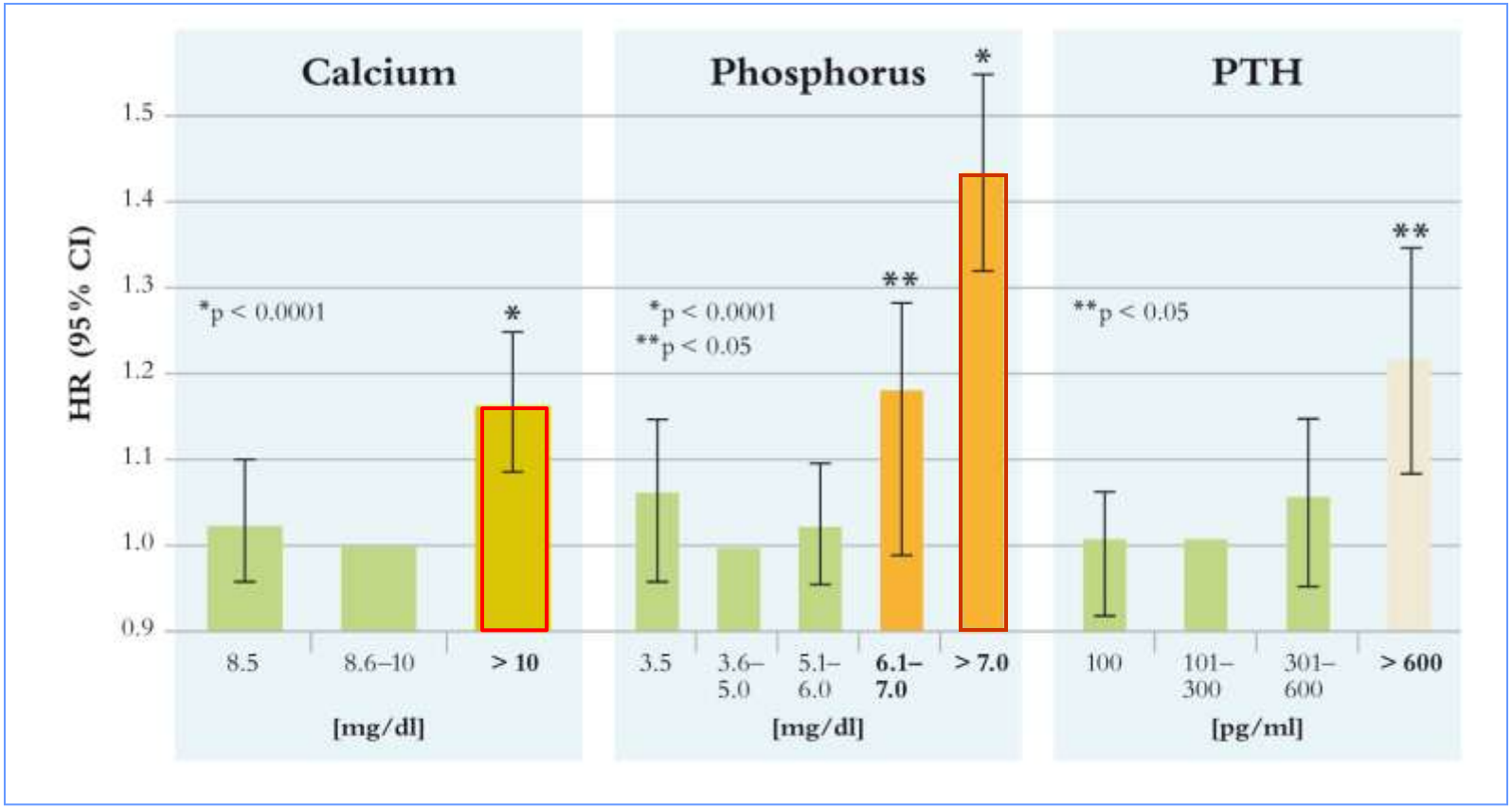
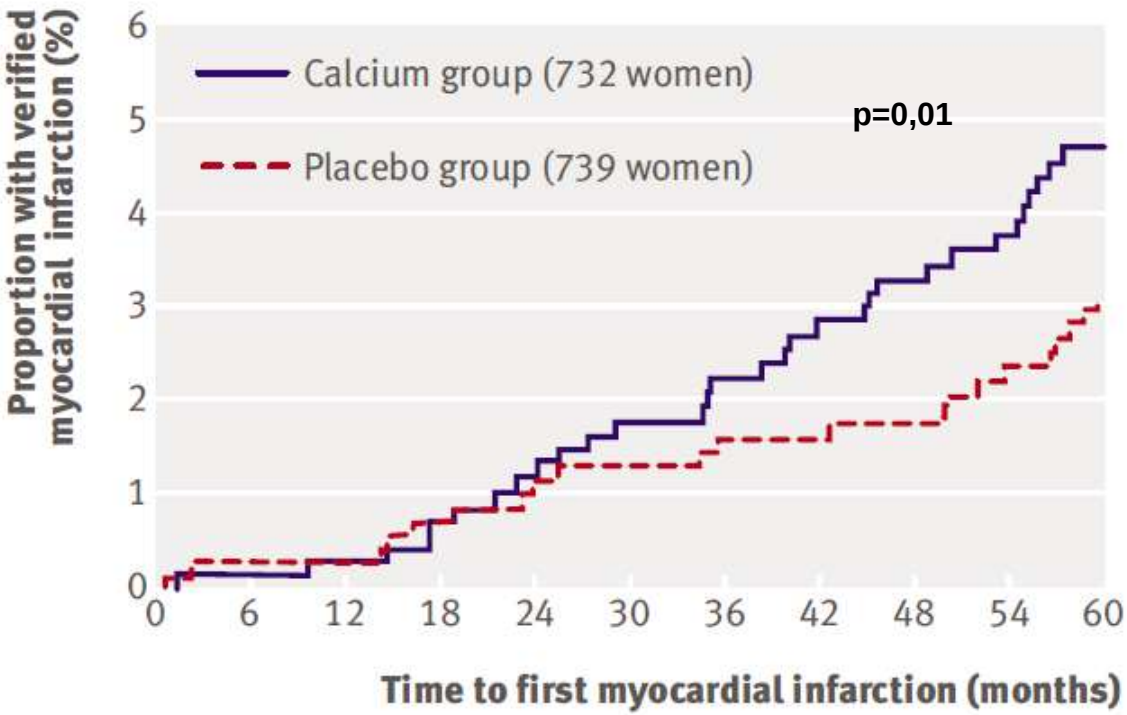


Disorders of mineral metabolism are associated with increased mortality

Prospective observational cohort study. 25.588 patients with ESRD on hemodialysis. Outcomes: Adjusted hazard ratios (HR) for all-cause and cardiovascular mortality using Cox models. Tentori F et al. *Am J Kidney Dis* 2008;52:519-530.

Vascular events in healthy older women on calcium supplementation



Myocardial infarction and the composite endpoint occurred more frequently in the calcium group

Randomized, placebo controlled trial in **1471 healthy postmenopausal women** to determine the effect of calcium supplementation on myocardial infarction, stroke, and sudden death in healthy postmenopausal women. Bolland MJ et al. BMJ 2008;336:262-6

Risk Factors Associated With Cardiac Calcification in Young Dialysis Patients

Factor	Coronary Calcification (n=14)	No Calcification (n=25)	*P* - value
Ca from calcium binders (mg/day)	6456 ± 4278	3325 ± 1490	**0.02**
Serum Ca (mmol/L)	2.4 ± 0.2	2.28 ± 0.23	0.25
Serum P (mmol/L)	2.2 ± 0.3	2.0 ± 0.4	0.06
Ca × P ($mmol^2/L^2$)	5.2 ± 0.9	4.5 ± 1.0	**0.04**
Age (years)	26 ± 3	15 ± 5	<0.001
Mean duration of dialysis (years)	14 ± 5	4 ± 4	<0.001

- **39 HD patients 7 – 30 years**
- **60 controls 20-30 years**
- **EBT scans at baseline and after 18-24 months**

Goodman WG et al. *N Engl J Med*. 2000; 342:1478-1483

NEW THERAPEUTIC APPROACH

PREVENTION OF

COMPLICATIONS OF THERAPY

. . .

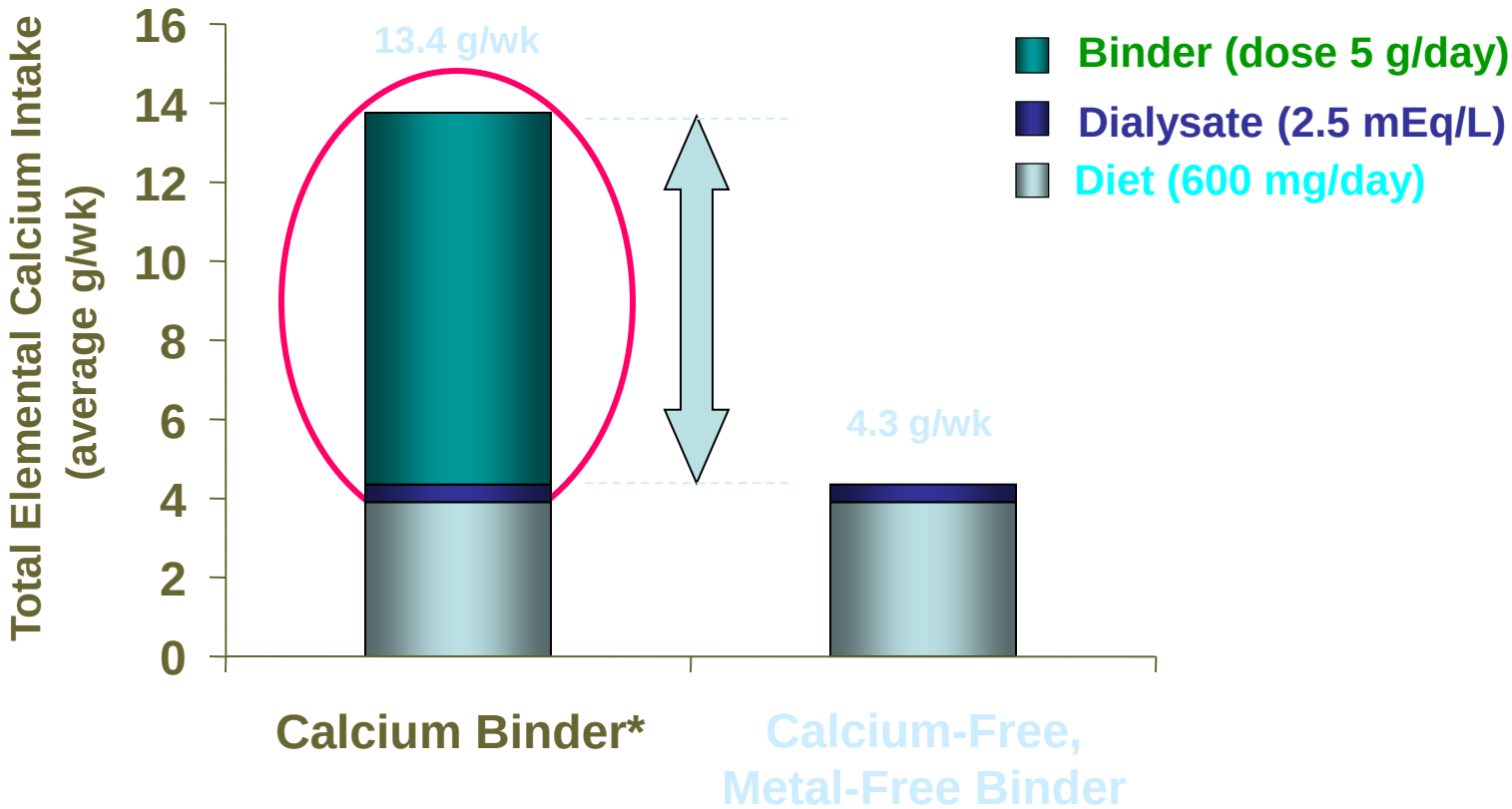
OF HYPERPHOSPHATEMIA

&

MBD & ROD & VC

IN CKD PATIENTS

Reducing Calcium Load With a Calcium-free Phosphate Binder



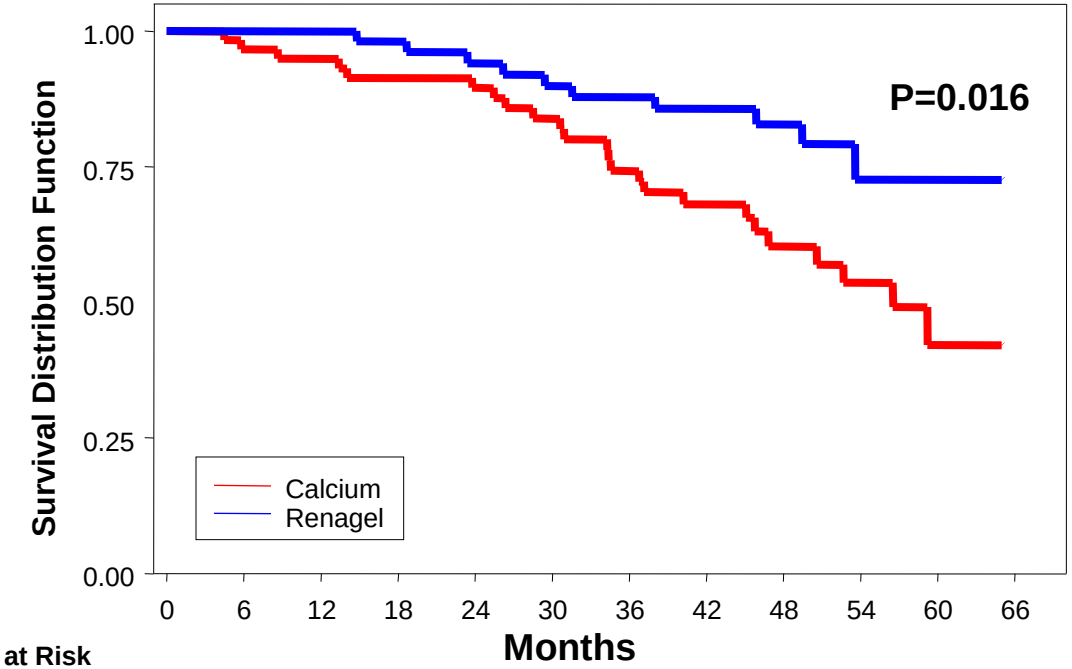
Phosphate binder: 3-5 g/day (20-30% resorption) ≈ 1300 mg/day

Dialysate: 1.25 moll/L - net influx ≈ 100-150 mg calcium / HD

Diet: intake ≈ 600 mg calcium per day

Bleyer AJ et al. *Am J Kidney Dis*. 1999;33:694-701
Data on file, Genzyme Corporation
Hsu CH. *Am J Kidney Dis*. 1997;29:641-649

Mortality effect of coronary calcification and phosphate binder choice

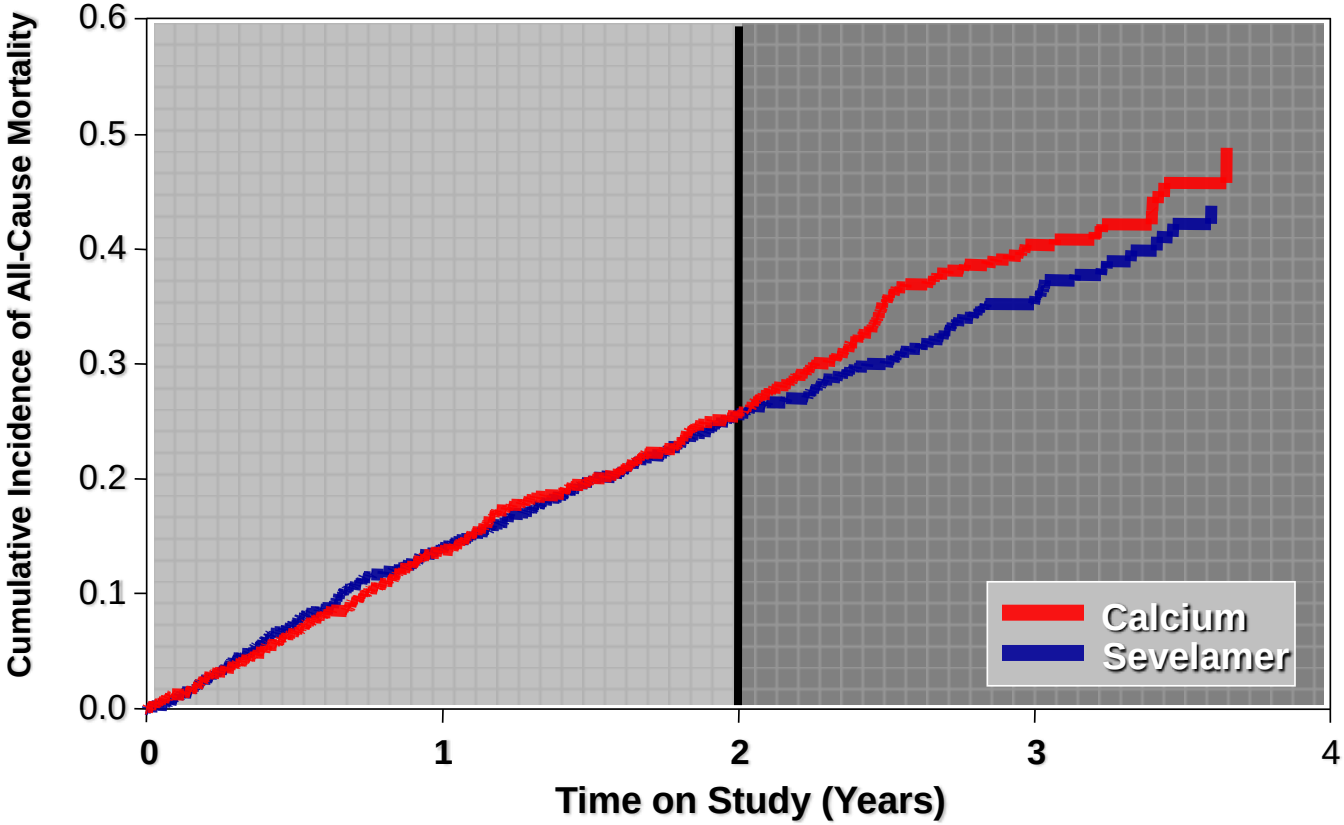


No. at Risk							
Calcium	**67**	**63**	**60**	**55**	**45**	**22**	**5**
Renagel	**60**	**57**	**57**	**51**	**47**	**25**	**4**

Treatment with sevelamer was associated with a significant survival benefit. There were 11 deaths in the sevelamer and 23 in the Calcium group.

Follow up of a randomized, prospective, open label, multicenter study over a median of 44 months (RIND). 127 patients randomized to either sevelamer or Ca. Prespecified secondary endpoint. Block GA et al. *Kidney Int* 2007;71:438-441

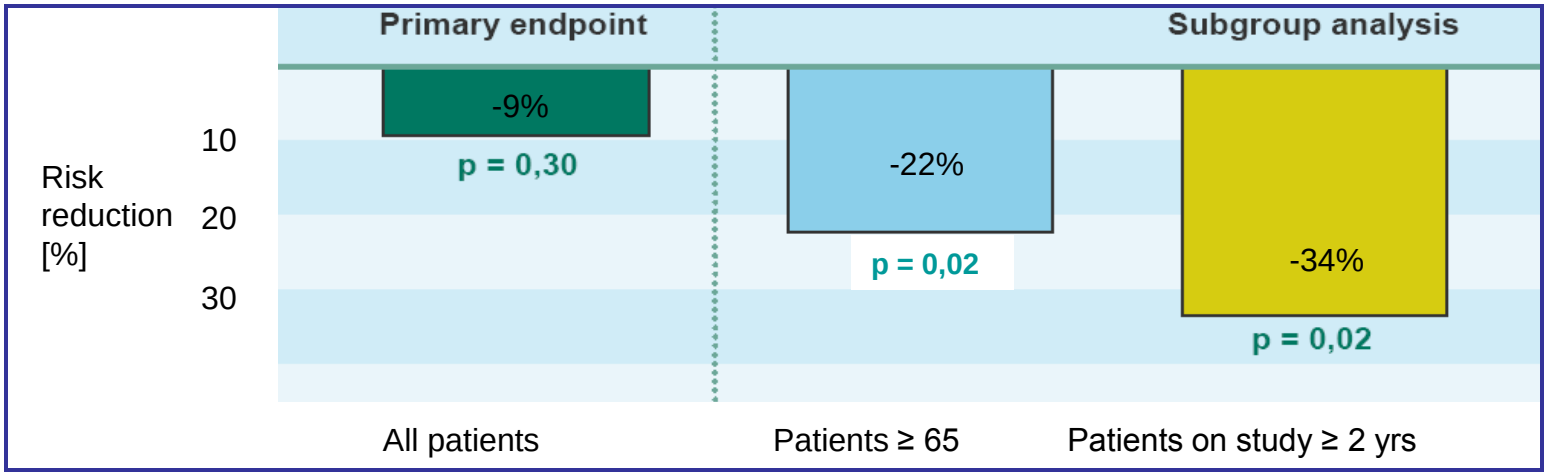
DCOR: All-Cause Mortality



Results of the DCOR trial were inconclusive for the primary end-point of all-cause mortality across the entire patient cohort (RR 0.91; p = 0.3)

Prospective, randomized trial in 2103 prevalent dialysis patients receiving either sevelamer or Ca-containing phosphate binders. Max. follow up 45 months. Primary endpoint: All cause survival. Secondary endpoints: Cause-specific mortality, all-cause and cause-specific hospitalization, medicare expenditures. Suki W et al. *Kidney Int 2007;*72:1130-1137.

DCOR: Mortality risk reduction with Renagel®



A mortality benefit for patients treated with Renagel® was shown in subgroups: Patients older than 65 (predefined) and patients on study for more than 2 years

Prospective, randomized trial in 2103 prevalent dialysis patients receiving either sevelamer or Ca-containing phosphate binders. Max. follow up 45 months. Primary endpoint: All cause survival. Secondary endpoints: Cause-specific mortality, all-cause and cause-specific hospitalization, medicare expenditures. Suki W et al. *Kidney Int 2007;* 72: 1130 - 1137

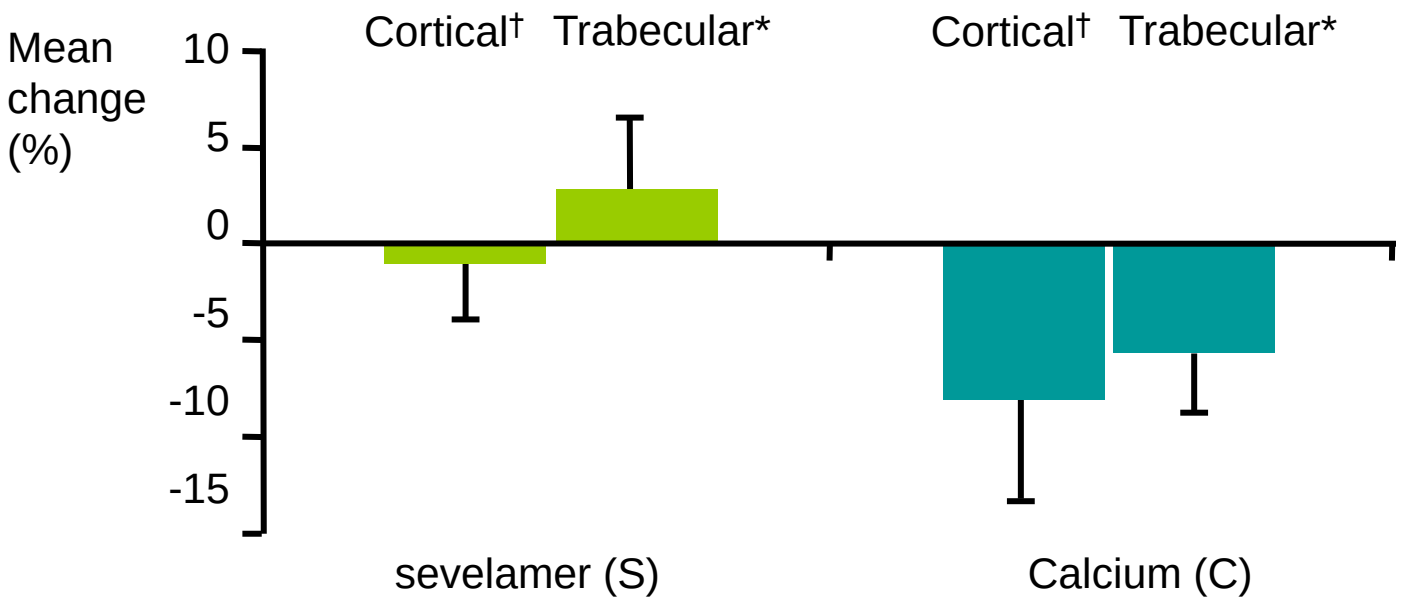
Hospitalisation rate by binder choice

Rate per patient-year	Sevelamer	Calcium	HR*	p*
First hospitalisations	0,96	0,97		ns
Multiple hospitalisations	1,70	1,91	0,89	0,02
Days in hospital	12,3	13,9	0,88	0,03

Almost every patient was hospitalised once per year. Renagel® treated patients were hospitalized less frequently and spent less time in the hospital.

Preplanned secondary analysis of DCOR for mortality, morbidity, and hospitalization end points, using Centers for Medicare & Medicaid Services data. St. Peter WL et al. *Am J Kidney Dis* 2008;51:445-454
*Adjusted for demographic variables and prestudy cardiovascular comorbidity

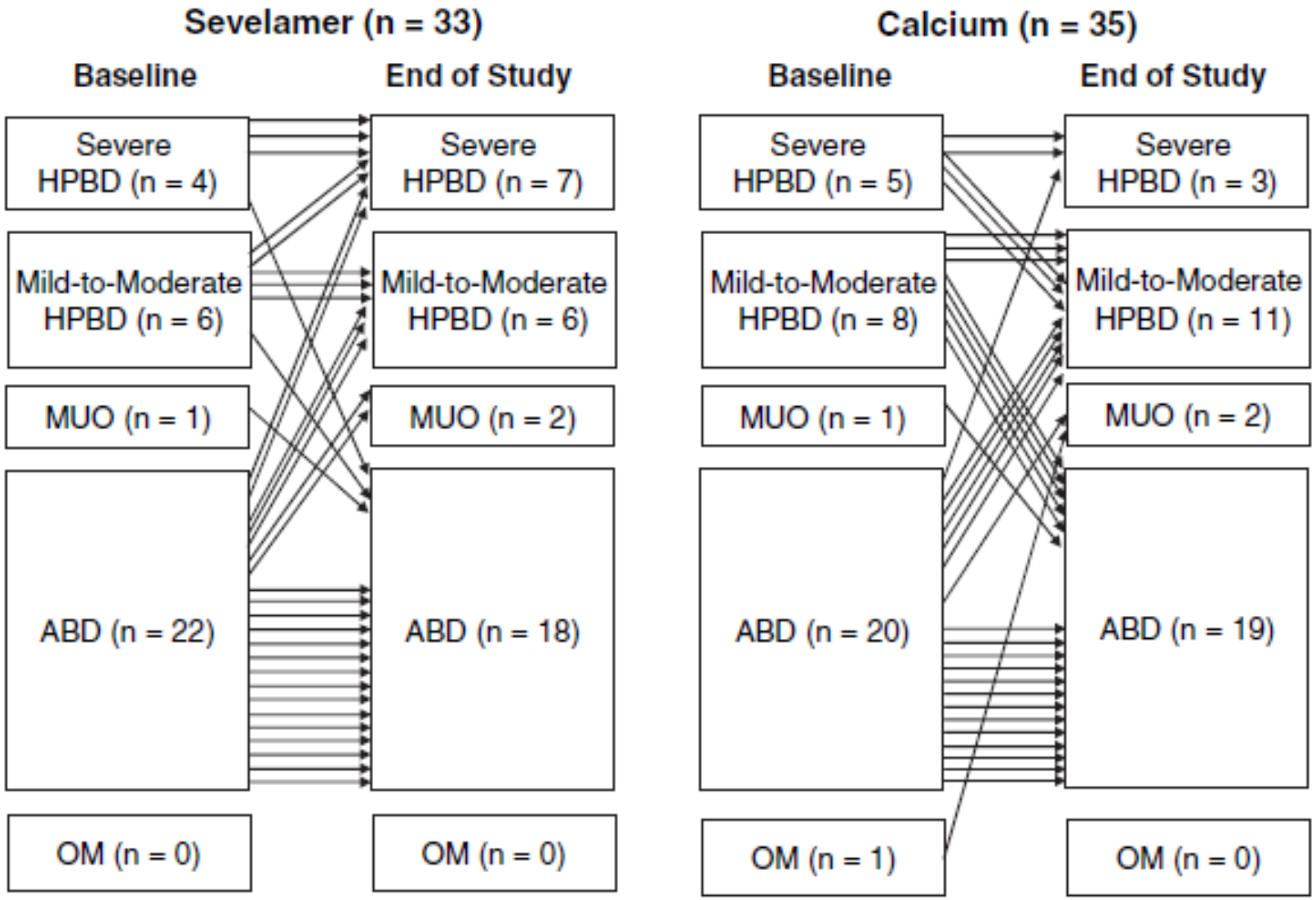
Calcium-treated subjects had decreased bone density



The lower time averaged PTH achieved in calcium-treated subjects is a likely explanation for the changes observed in bone attenuation.

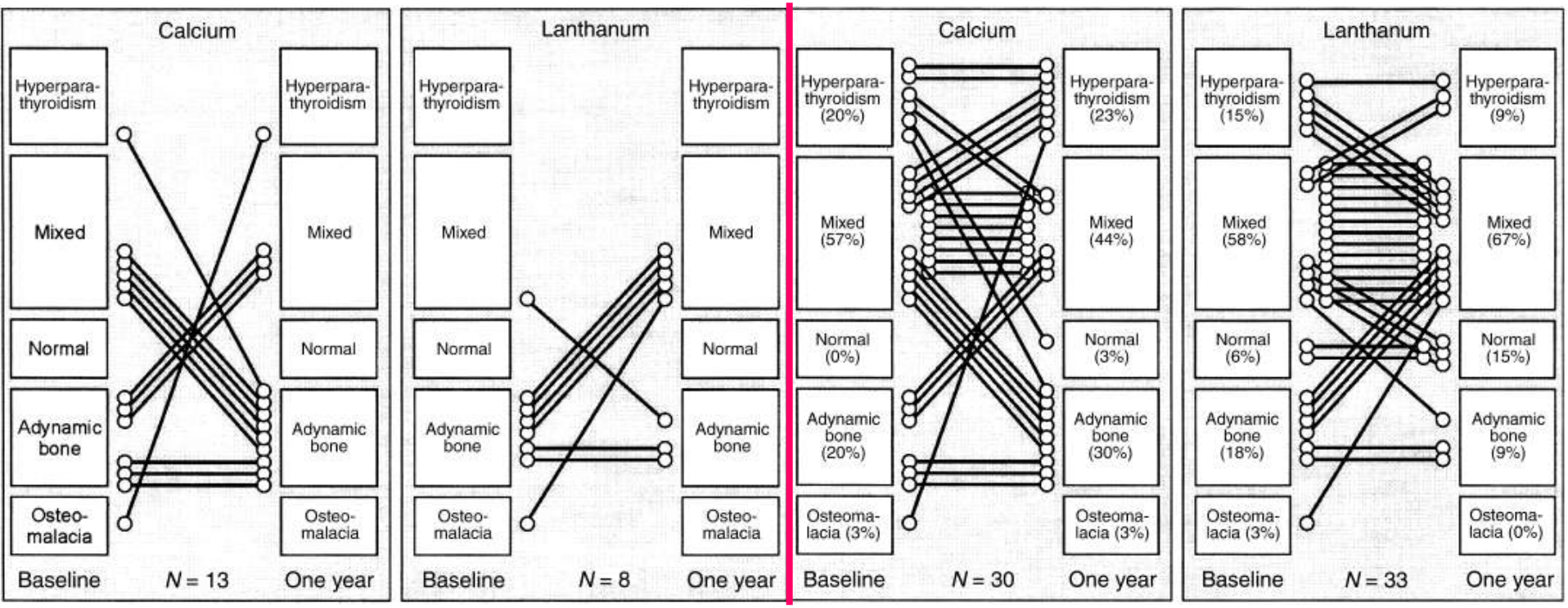
Post- hoc analysis of a randomized, prospective, open label, multicenter study over one year (Treat to Goal) evaluating EBCT scans of vertebrae. Raggi P et al. *J Bone Miner Res*. 2005;20:764-72. *p=0.01 Sevelamer vs. Calcium, *†ns*

Effects of Sevelamer Hydrochloride and Calcium Carbonate on ROD in HD Patients



Ferreira A, Frazao J et al. *J Am Soc Nephrol* 2008; 19: 405–12

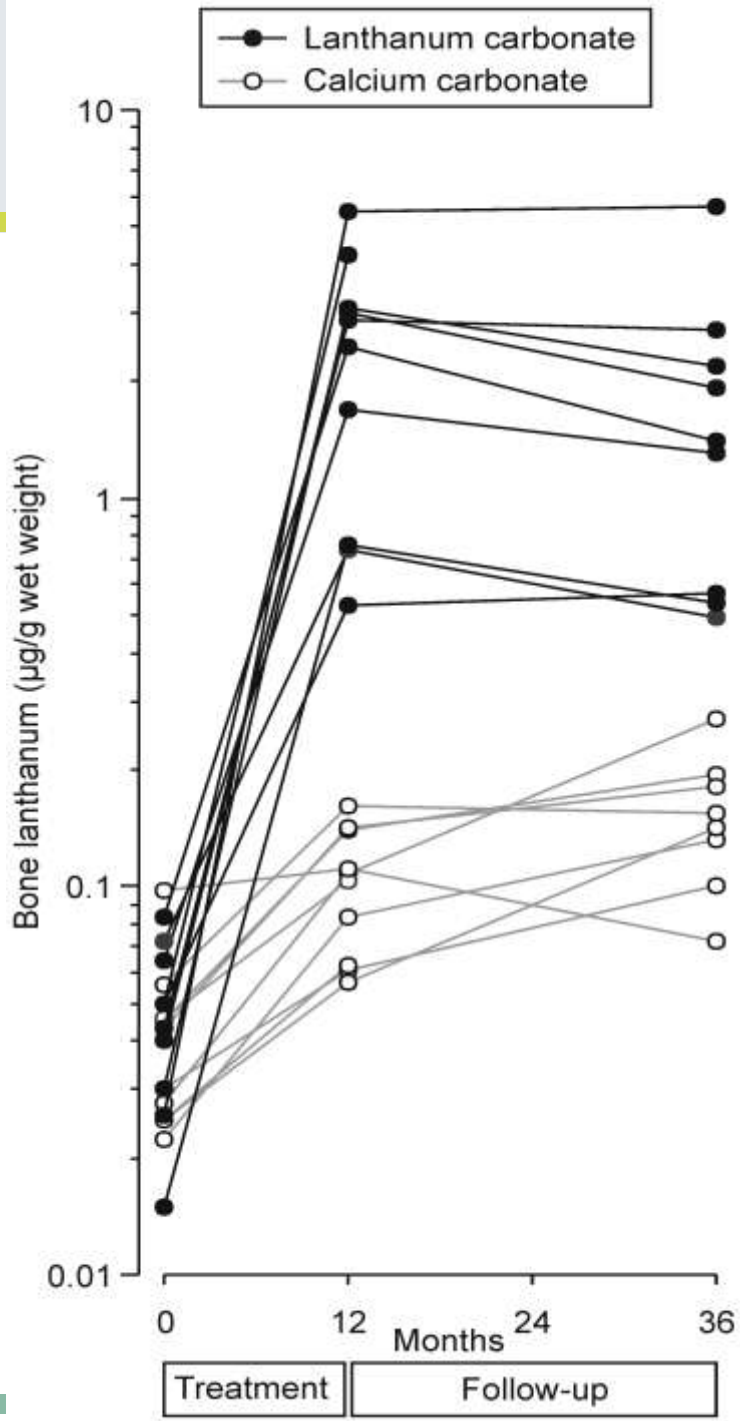
Classification of ROD in LC and CC group



Patients with either low bone turnover at baseline and those evolving toward low bone turnover at follow-up in both study groups

Evolution of renal bone disease of all patients after one year of treatment with either lanthanum or calcium carbonate

D'Haese PC, Spasovski GB et al. *Kidney Int* 2003; 63: Suppl 85:73-78



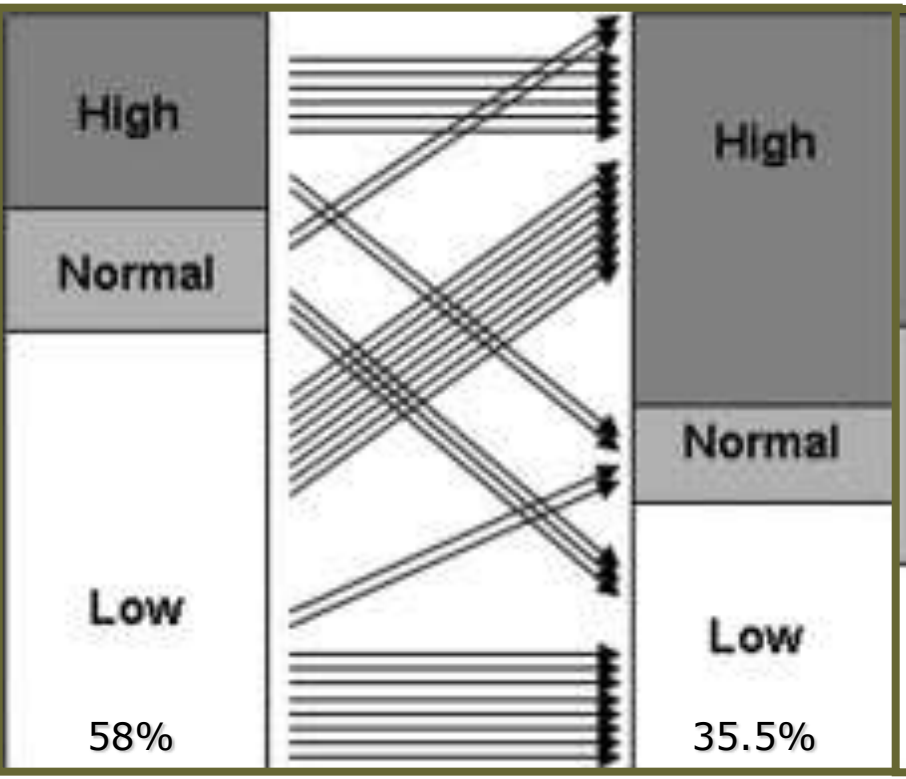
Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year treatment with lanthanum carbonate and after two years of follow up.

Bone lanthanum concentrations of patients receiving lanthanum carbonate (solid circle) and calcium carbonate treatment (open circle) for 12 months, followed by 2 years of treatment with calcium carbonate.

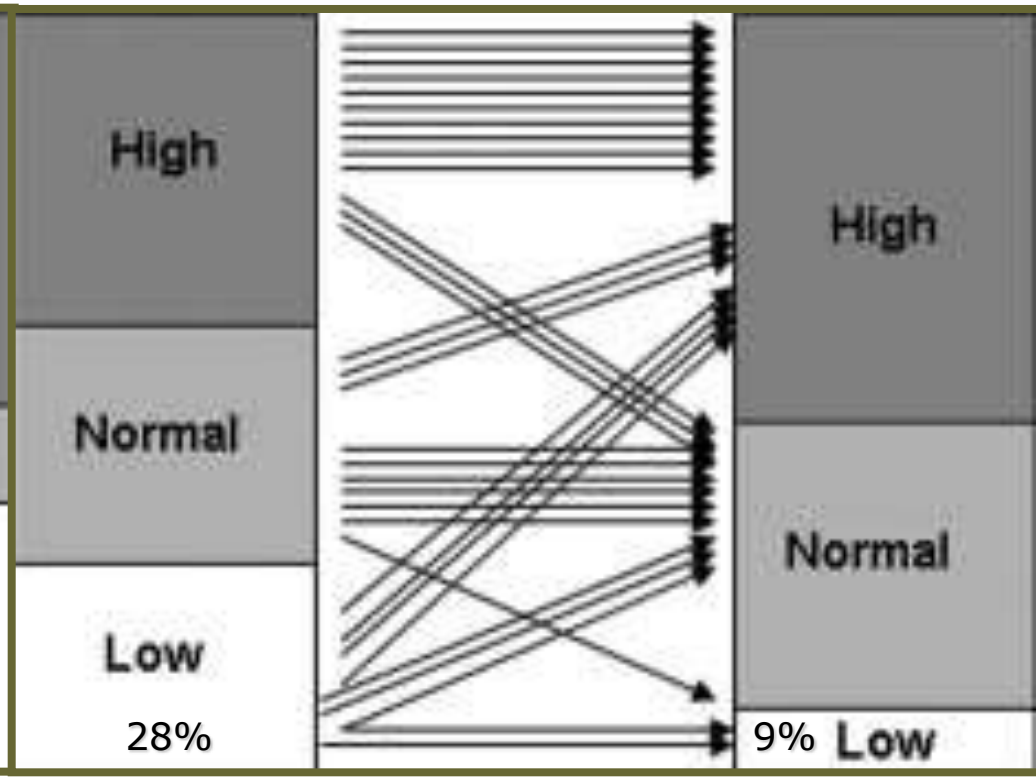
There is a slow release of lanthanum from its bone deposits 2 years after the discontinuation of the treatment and no association with aluminium-like bone toxicity.

Spasovski G et al. *Nephrol Dial Transpl* 2006; 21(8):2217-24

Effects of Treatment of Renal Osteodystrophy on Bone Histology



Baseline 1 year



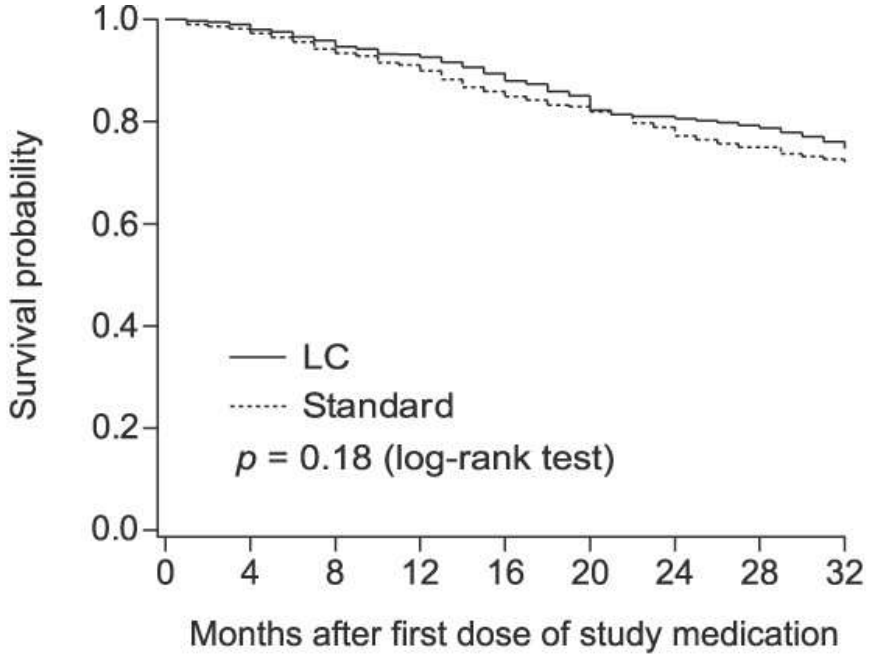
Baseline 2 years

Higher **activation frequency (bone turnover)** in patients who were treated with lanthanum carbonate after 1 year

Higher bone volume (tissue volume) in patients who were treated with lanthanum carbonate after 2 years

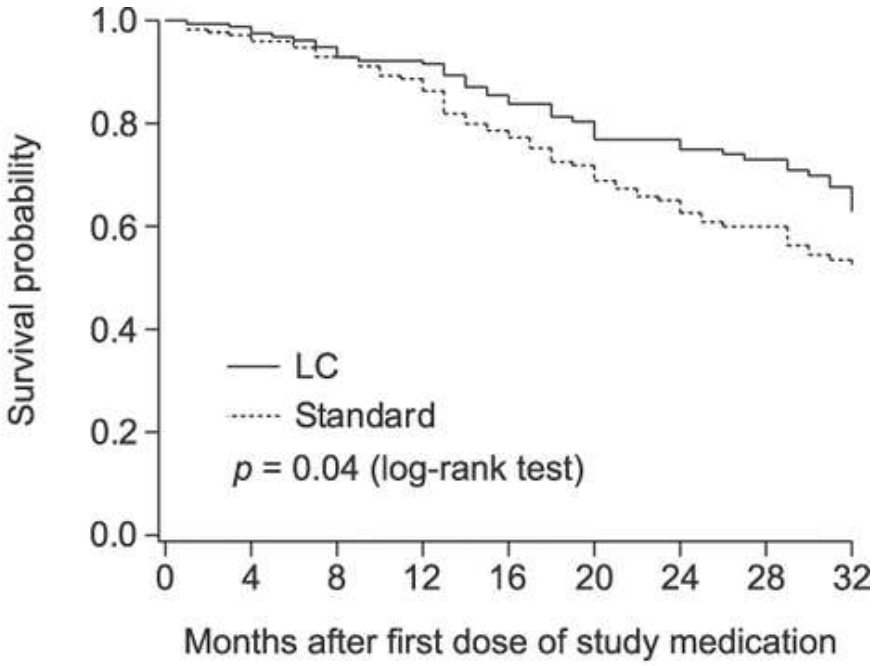
Malluche H et al. Clin Nephrol 2008; 70(4): 284-95
Malluche H et al. Clin J Am Soc Nephrol 2008; 3: S157–S163

Analysis of survival in a 2-year comparative study of lanthanum carbonate vs. standard therapy



At risk (*n*)									
LC	680	650	602	563	482	426	386	336	287
Standard	674	655	607	570	473	423	387	324	270

Figure 1. Survival probability: lanthanum carbonate versus standard therapy. LC, lanthanum carbonate; Standard, standard therapy.



At risk (*n*)									
LC	163	155	143	136	104	91	82	71	57
Standard	173	166	155	145	118	96	82	65	53

Figure 2. Survival probability in patients aged >65 years: lanthanum carbonate versus standard therapy. LC, lanthanum carbonate; Standard, standard therapy.

Wilson R, Zhang P, Smyth M, Pratt R. Curr Med Res Opin. 2009; 25(12):3021-8.

New Strategies in Treatment of MBD and Associated CVD in Patients with CKD

Spasovski G, *Recent Patents on Cardiovascular Drug Discovery,* 2008; 3(3):222-8

- **Cost-effectiveness** - **Good value for money!?**

- **Huybrechts KF, Caro JJ, Wilson DA, O'Brien JA. Health and economic consequences of sevelamer use for hyperphosphatemia in patients on hemodialysis. Value Health 2005; 8:549–561**

Lack of outcome data favorable enough to justify widespread utilisation

- **CA White, J Jaffey, P Magner. Cost of applying the K/DOQI guidelines for bone metabolism and disease to a cohort of chronic hemodialysis patients. Kidney International (2007) 71, 312–317**

The yearly cost of implementation of the K/DOQI guidelines for 416 pts. at this center (University of Ottawa) was estimated at $ 500 605 (American dollars). Given the significant cost, widespread adoption of the K/DOQI CPGs for Bone Metabolism and Disease should await the publication of compelling data demonstrating significant improved outcomes in patients treated with sevelamer.

Type of treatment for hyperphosphataemia and related outcomes

Nephrol Dial Transplant (2007) 22: 2867–2878
doi:10.1093/ndt/gfm367
Advance Access publication 25 June 2007

NDT
Nephrology Dialysis Transplantation

Original Article

Economic evaluation of sevelamer in patients with end-stage renal disease

Braden Manns[1,2,3], Scott Klarenbach[3,4], Helen Lee[1], Bruce Culleton[2], Fiona Shrive[1] and Marcello Tonelli[3,4,5,6]

Conclusions. The cost per QALY gained for treating all dialysis patients with sevelamer exceeds what would usually be considered good value for the money. While the high cost per QALY was in part due to the inclusion of the costs of dialysis and transplant in the analysis, the cost per QALY gained remained relatively unattractive even when these costs were excluded. Although a lower cost per QALY gained is realized when only patients older than 65 years are treated, this strategy remains economically unattractive, particularly given the uncertainty of clinical benefit in this group.

Type of treatment for hyperphosphataemia and related outcomes

Nephrol Dial Transplant (2009) 24: 3168–3174
doi: 10.1093/ndt/gfp350
Advance Access publication 21 July 2009

The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis

Sophie A. Jamal[1], David Fitchett[2], Charmaine E. Lok[3], David C. Mendelssohn[4] and Ross T. Tsuyuki[5]

Background. The effects of calcium compared with non-calcium-based phosphate binders on mortality, cardiovascular events and vascular calcification in patients with chronic kidney disease (CKD) are unknown.
Methods. To address this question, we conducted a systematic review. We electronically searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL. We identified 160 potential studies and included 8 randomized trials. Eligible studies, determined by consensus using predefined criteria, were reviewed, and data were extracted onto a standard from.

Conclusion. Despite the trends observed, we did not find a statistically significant difference in cardiovascular mortality and coronary artery calcification in patients receiving calcium-based phosphate binders compared to non-calcium-based phosphate binders. However, the data are limited by the small number of studies and the confidence intervals do not exclude a potentially important beneficial effect. Therefore, further randomized trials are required.

Clinical Medicine Insights: Therapeutics

Clinical Medicine Insights: Therapeutics 2011:3 51–55

REVIEW

A Review of Sevelamer Hydrochloride in End-Stage Renal Disease Patients on Dialysis

Goce Spasovski

Department of Nephrology, University of Skopje, Skopje, R. Macedonia. Corresponding author email: gspas@sonet.com.mk

Although KDOQI and KDIGO published CKD—MBD guidelines has clearly stated where calcium-based phosphate binders should not be used in D patients (hypercalcemia and low PTH) and where non calcium-containing phosphate binders are preferred (patients with severe vascular and/or other soft tissue calcifications), the greatest controversy and disagreements within the nephrological community still exists upon the cost-effectiveness of non calcium binder (sevelamer) use. Indeed, despite the evidence and recognised trend towards both a decrease in VC and CVD associated with sevelamer use, it is still an ongoing matter of debate. The magnitude of this controversy is increased when the issue of advanced medical and/or budgetary evaluation related to the implementation of clinical guidelines for CKD—MBD treatment is considered. Despite advocated use of sevelamer across a range of common clinical scenarios in CKD, its widespread utilization is challenged as exceeding what would usually be considered good value for money. If so, it is questionable whether the recommendations and suggestions from the guidelines should be followed, and further, do we need guidelines and innovative drugs for treatment of hyperphosphatemia? While awaiting the answer, as clinicians we should proceed with a treatment to "do no harm", trying to at least limit the calcium exposure of our dialysis patients.

Cost-effective Reduction of Calcium Load and possible treatment of ABD as most prevalent ROD type

"Individualized program"

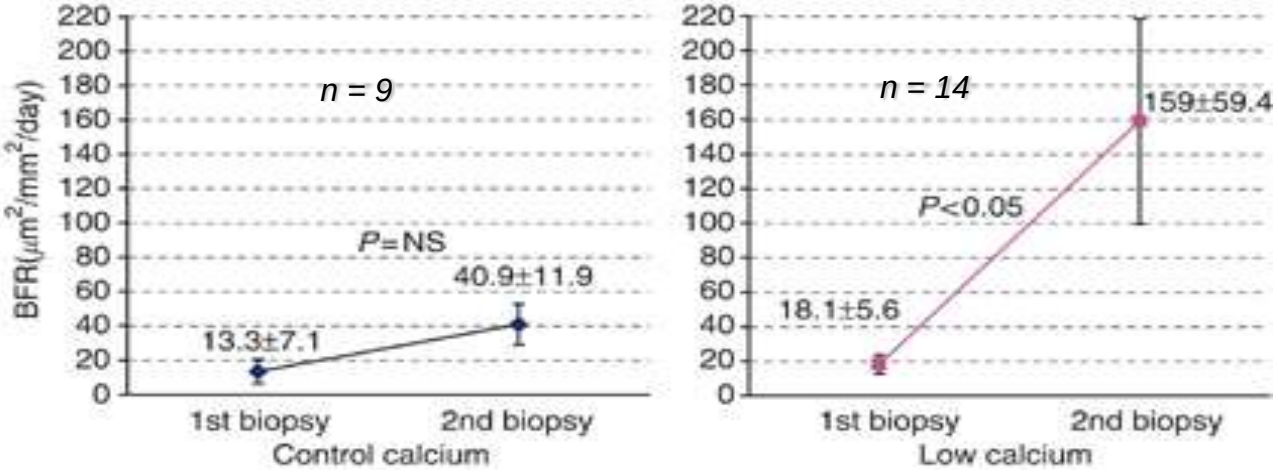
Dose reduction of the calcium phosphate binders 1-2 gr/day

Low-calcium dialysis bath 1.25 mmol/l

Lowered Dialysate Calcium in PD: Increased PTH and Bone Formation.

Haris A *et al. Kidney Int 2006; 70(5):931-7*

	Control Ca			Low Ca		
	Before	***After***	***P-value***	***Before***	***After***	***P-value***
tCa (mM)	2.19 ±0.08	2.18 ±0.03	NS	2.43 ±0.06	2.13 ±0.03	*P<0.001*
iCa (mM)	1.18 ±0.01	1.15 ±0.02	NS	1.25 ±0.02	1.09 ±0.02	*P<0.0001*
PO_4 (mM)	1.70 ±0.12	1.72 ±0.13	NS	1.89 ±0.13	1.92 ±0.14	NS
Mg (mM)	1.24 ±0.06	1.22 ±0.03	NS	1.21 ±0.05	1.20 ±0.05	NS
ALP (U/l)	87.3 ±11.4	76.5 ±8.9	NS	79.0 ±6.9	84.9 ±5.9	NS
PTH (pM)	7.3 ±1.6	9.4 ±1.5	NS	6.0 ±1.6	24.9 ±3.6	*P<0.0001*



Improvement of Bone and Mineral Parameters Related to ABD by Diminishing Dialysate Calcium

Pre HD param. unit	LCD			HCD		
	Baseline	3 months	6 months	Baseline	3 months	6 months
tCa Pre HD	2.44 ± 0.20	2.32 ± 0.19[a]	2.39 ± 0.19	2.46 ± 0.27	2.31 ± 0.19[a]	2.39 ± 0.17[b]
tCa Post HD	2.41 ± 0.19	2.34 ± 0.17	2.48 ± 0.20[b]	2.65 ± 0.18[c]	2.50 ± 0.17[a,c]	2.63 ± 0.19[b,c]
iCa Pre HD	1.10 ± 0.09	0.97 ± 0.12[a]	1.07 ± 0.09[b]	1.11 ± 0.12	1.08 ± 0.08[c]	1.07 ± 0.08
iCa Post HD	1.09 ± 0.08	0.91 ± 0.14[a]	1.12 ± 0.09[b]	1.20 ± 0.08[c]	1.16 ± 0.22[c]	1.18 ± 0.08[c]
P	1.50 ± 0.51	1.58 ± 0.46	1.48 ± 0.46	1.30 ± 0.41	1.51 ± 0.46[a]	1.58 ± 0.45[a]
Ca x P	3.68 ± 1.35	3.52 ± 1.21	3.36 ±1.23	3.05 ± 1.19	3.50 ± 1.09	3.44 ± 1.43
iPTH pg/ml*	38.6 ± 22.9	61.4 ± 43.4[a]	78.6 ± 44.7[a]	43.5 ± 27.1	48.6 ± 23.9	53.8 ± 29.6[c]
TAP U/L*	59.5 ± 18.7	75.9 ± 26.7[a]	84.0 ± 35.4[a]	58.0 ± 19.1	65.8 ± 28.1	65.6 ± 25.9[c]
BAP U/L*	23.4 ± 7.3	24.1 ± 15.9	35.6 ± 22.3[a]	25.4 ± 6.1	29.5 ± 21.9	22.5 ± 9.7[c]

Spasovski G et al. Bone 2007; 41: 698–703

Vitamin K_2 Improves Bone Metabolism in HD pts. with a Low PTH

	Group	Baseline	1 month	3months	12months
B-ALP(U/l)	Vitamin K_2	18.3±5.5	17.9±6.0	22.1±10.9	25.9±14.1*
	Control	19.3±7.6	20.5±10.3	20.4±8.8	20.6±8.6
intact-Osteocalcin(ng/ml)	Vitamin K_2	19.1±14.1	23.6±14.2*	25.5±13.2*	27.2±15.3*
	Control	22.5±15.8	21.3±15.5	22.6±15.1	22.1±11.8
NTX(nmol BCE/l)	Vitamin K_2	47.2±31.8	42.8±27.6	52.1±32.7	55.2±31.5*
	Control	51.3±52.0	47.5±43.9	54.8±43.9	51.1±25.7
intact-PTH (pg/ml)	Vitamin K_2	50.3±28.0	48.7±30.4	56.9±56.0	91.1±64.8*
	Control	46.7±29.6	44.5±27.6	43.8±24.1	47.4±28.4

40 HD pts with low intact PTH levels (<100 pg/ml) randomised into a vitamin K_2 group receiving oral menatetrenone (45 mg/day) for 1 year and a control group without vitamin K_2.

Ochiai M, et al. Nephron Clin Pract. 2011; 117(1):c15-9.

K/DOQI* guidelines for Bone Metabolism and Disease / Dislipidemia in Chronic Kidney Disease

	K/DOQI Guidelines
P	3.5 – 5.5 mg/dL **(1.1 – 1.8 mmol/l)**
Ca x P	< 55 mg^2/dL^2 **(< 4.4 $mmol^2/l^2$)**
PTH	150 – 300 pg/mL
LDL cholesterol	< 100 mg/dL **(< 2.56 mmol/l)**
Total cholesterol	< 200 mg/dL **(< 5.12 mmol/l)**

*National Kidney Foundation K/DOQI (Kidney Disease Outcome Initiative)

The K/DOQI guidelines have become widely accepted and are basis of many national treatment guidelines in Eastern Europe

National Kidney Foundation K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am J Kidney Dis* 2003;42(Suppl 3):S1-S202. National Kidney Foundation K/DOQI Clinical Practice Guidelines for managing Dyslipidemias in Chronic Kidney Disease. *Am J Kidney Dis.* 2003;41(suppl 3):S1-91.

Impact of the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in a Large Dialysis Network

Ron Wald, MDCM, Francesca Tentori, MD, Hocine Tighiouart, MS, Philip G. Zager, MD, and Dana C. Miskulin, MD

Am J Kidney Dis 49:257-266. © 2007

Application of NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease: changes of clinical practices and their effects on outcomes and quality standards in three haemodialysis units

M. Dolores Arenas[1], Fernando Alvarez-Ude[2], M. Teresa Gil[1], Antonio Soriano[1], Juan José Egea[1], Isabel Millán[1], M. Luisa Amoedo[1], Salomé Muray[1] and M. Antonia Carretón[1]

Nephrol Dial Transplant (2006) 21: 1663–1668

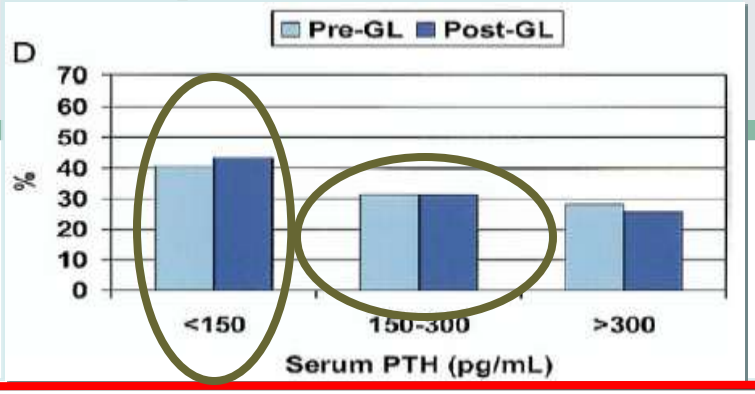
ACHIEVEMENTS IN CKD-MBD GUIDELINES TARGETS - IS THERE A PROGRESS IN THE IMPLEMENTATION PRACTICE

Spasovski G[1], Zdravkovska V[2], Zabzun M[3], Antarorov R[4], Ivanovski K[5], Janakievska P[6], Neskovski J[7], Karceva-Sarajlia E[8], Panova B[9], Petrovska T[10], Zulbeari L[11], Masin-Spasovska J[1], Taleska-Matovska N[3], Gelev S[1]

Implementation of CKD-MBD guidelines - IUN 2011.doc

K/DOQI guidelines achieved parameters

Parameter	Before Guidelines	After Guidelines
Calcium (mg/dL)	9.40 ± 0.66	9.33 ± 0.64
Phosphate (mg/dL)	5.49 ± 1.35	5.34 ± 1.28
Ca × P product (mg^2/dL^2)	51.51 ± 12.73	49.74 ± 12.12
PTH (pg/mL)	259.41 ± 248.31	241.48 ± 214.95



	Pre-K/DOQI (2003)	Post-K/DOQI (2004)	*P*
Serum PTH (pg/ml)			
Mean ± SD	201.4 ± 43.1	311.8 ± 64.5	<0.001
% of patients between 150 and 300	25.6	18.7	NS
Serum calcium (mg/dl)			
Mean ± SD	9.7 ± 0.3	9.4 ± 0.2	<0.01
% of patients between 8.4 and 9.5	38.7	46.6	<0.01
Serum phosphate (mg/dl)			
Mean ± SD	4.8 ± 0.2	4.9 ± 0.3	NS
% of patients between 3.5 and 5.5	56.9	56.2	NS

Parameters	**2009**	**2005**	**P**
Ca (mM/L)	2.30±0.24	2.36±0.33	<0.01
Ca (2.1 – 2.6)	79.0	67.4	<0.05
P (mM/L)	1.49±0.41	1.64±0.61	<0.01
P (1.1 - 1.8)	64.9	59	n.s.
Ca x P	3.44±1.05	3.79±1.62	<0.01
Ca x P (<4.4 mM^2/L^2)	80.6	71.1	n.s.
PTH	323.3±363.8	437.3±611.2	<0.01
PTH (150 - 300 pg/ml)	35.1	17.3	n.s.

Treatment options

Intravenous vitamin D preparations (%)		
Calcitriol	12.5	5.1
Doxercalciferol	44.1	48.2
Paricalcitol	35.8	10.3
Never used	36.8	40.1
Phosphate binders (%)		
Calcium carbonate	30.2	27.6
Calcium acetate	51.9	50.7
Aluminum based	7.0	5.7
Sevelamer	38.6	43.5
Cinacalcet (%)	0	6.3
Dialysate calcium (mEq/L)	2.57 ± 0.28	2.53 ± 0.28

	Pre-K/DOQI (2003)	Post-K/DOQI (2004)	*P*
Phosphate binders			
Calcium-containing (mg Ca/day)	891.9 ± 665.5	565.5 ± 550.0	<0.001
Sevelamer (800 mg tablets/day)	4.8 ± 4.4	7.5 ± 4.6	<0.001
Calcium in dialysate (mEq/l)			
% of patients with Ca 2.5	27.2	50.9	<0.001

Parameters	**2009**	**2005**	**P**
Ca dialysate (mM/L)	1.64±0.14	1.72±0.12	<0.01
Ca dialysate 1.25	3.7	6.1	n.s.
Ca dialysate 1.5	38.6	29.7	n.s.
Ca dialysate 1.75	57.7	64.2	n.s.
Calcium carbonate (g/day)	2.77±1.71	3.06±1.54	<0.01
Calcium carbonate	90.3	95.6	n.s.
Vitamin D (mcg/week)	0.63±0.85	0.98±0.94	<0.01

Conclusion from the KDOQI based studies

- The individualisation of the CKD-MBD management may be successful even in the absence of modern new treatment possibilities.
- Nephrologists should ask for advanced treatment options in accordance with the guidelines at least for a small subset of patients where current standard therapy does not work.
- Implementation process should be continuous and self-monitored at least through surveys.
- Judicious treatment could be a better option than overzealous treatment in order to “do no harm” for the patients’ health.

Modification of current therapeutic options in pts. with low PTH - ABD

- **Avoid hypoparathyroidism** ☯
- **Avoid high-dose vitamin D**
- **Avoid high-dose oral calcium**
- **Avoid high-Calcium dialysate**
- **Use low-Ca dialysate !**
- **Use Vit. K_2 !**

Summary: Treatment of MBD in CKD

- An **aggressive treatment** of hyperphosphatemia with Ca based P-binders might **lead towards** an opposite effect:
  - **hypoparathyroidism, hypercalcemia, calcifications**

- **An individualised treatment** and **prevention of complications of therapy** preserving bone and vascular health :
  - **Calcium phosphate binders (as less as possible / 1-2 g/day)**
  - **Low-calcium dialysis bath (1.25 mmol/l)**
  - **Vitamin K_2**
  - **Non Ca-based P binders in pts at risk for fractures&VC&CVD**
  - **Calcimimetics & Vit.D analogs - no other armamentarium is available**

Treat the Hyperphosphatemia & Bones in order to save blood vessels & the Heart!