Disturbed mineral metabolism in uremia – management

Eberhard Ritz
Heidelberg (Germany)

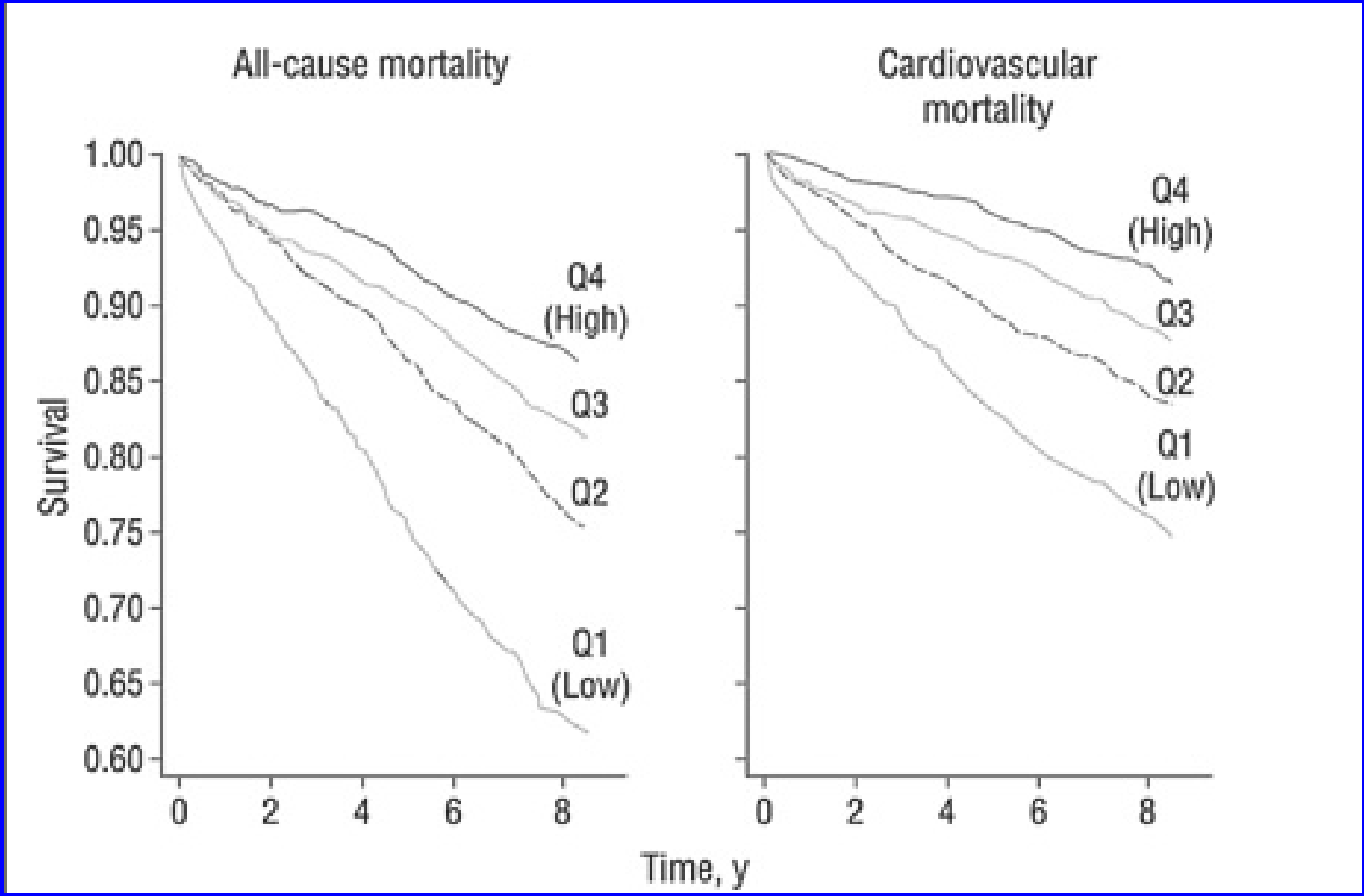
Proportion of patients outside target range – *DOPPS study*

country	% PTH <150 pg/ml	% PTH > 300 pg/ml	% Ca x P > 55 mg^2/dl^2	% phosphate > 5,5 mg/dl
France	55,6	21,4	38,0	45,1
Germany	50,5	25,5	56,5	69,6
Italy	52,6	25,5	35,1	37,8
Japan	58,5	19,1	43,1	53,6
Spain	50,8	27,5	43,2	46,4
England	47,8	31,2	44,9	50,8
USA	48,8	29,3	43,8	52,0

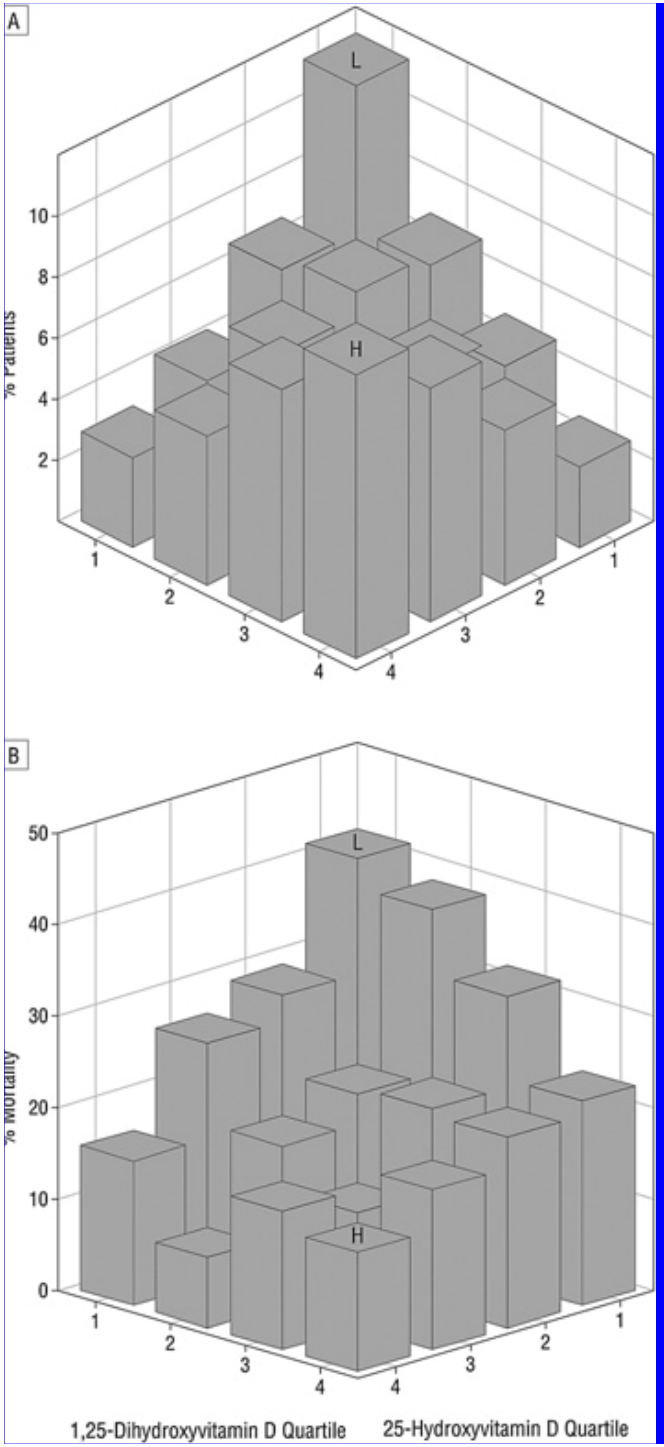
Locatelli, Nephrol.Dial.Transpant.(2004) Suppl. 19; v15-v19

Vitamin D and active vitamin D

Mortality according to 25(OH)D quartiles – *Ludwigshafen (LURIC) study*



Dobnig, Arch.Int.Med.(2008) 168: 1340



Frequency distribution

L= both 25(OH)D and $1,25(OH)_2D$ low

H= both 25(OH)D and $1,25(OH)_2D$ high

Mortality

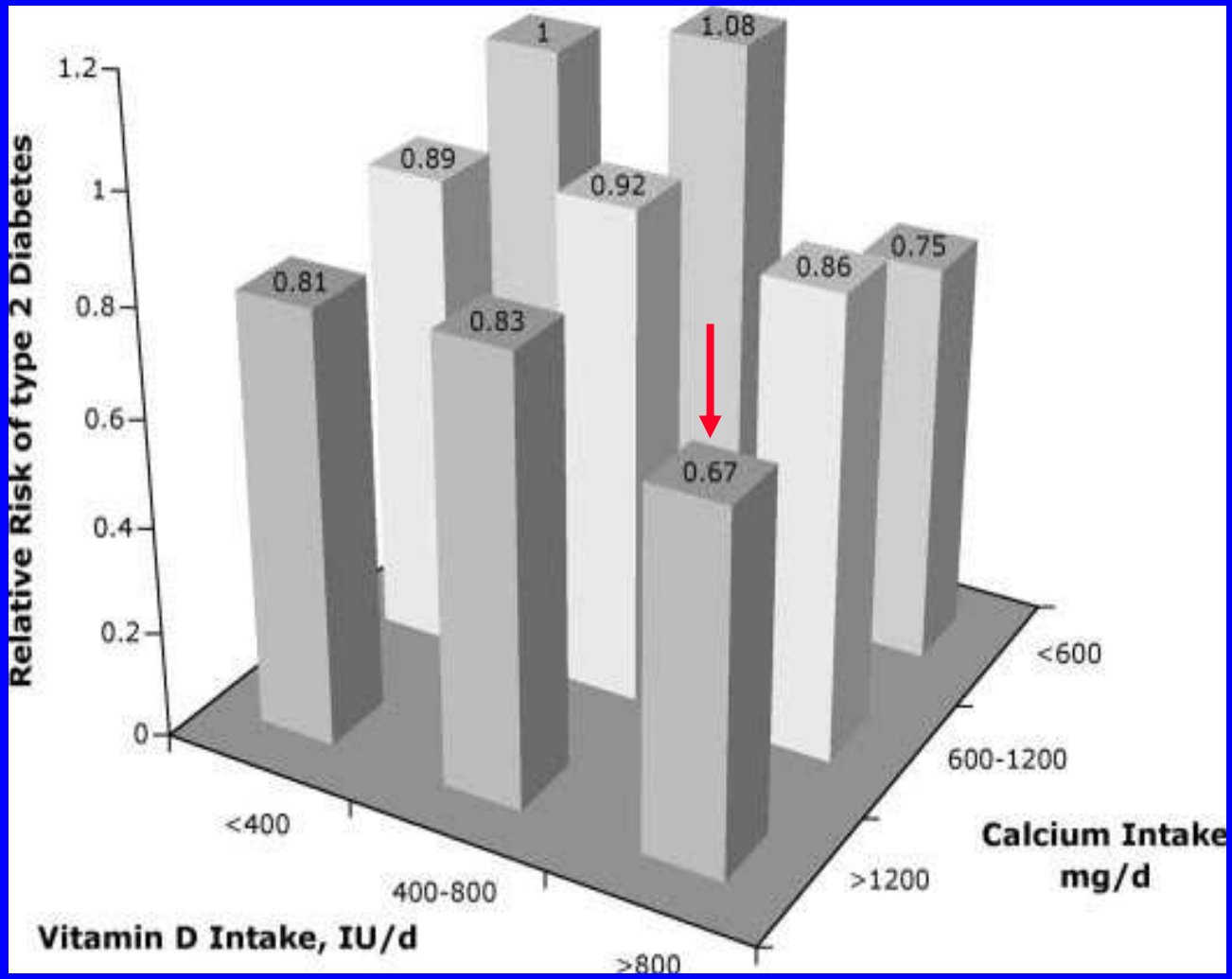
L= both 25(OH)D and $1,25(OH)_2D$ low

H= both 25(OH)D and $1,25(OH)_2D$ high

Dobnig, Arch.Int.Med.(2008) 168: 1340

Vitamin D intake and risk of type 2 diabetes

(Nurses Health Study)



Pittas, J.Clin.Endocrinol.Metab.(2007) 92:2017

Solanum malacoxylon

"entque secco"

Hypercalcemia of cattle in Argentina

Francois Lignière, 1898

Iberian rock lizard *(Lacerta monticola)*

Martín J. and López P.,

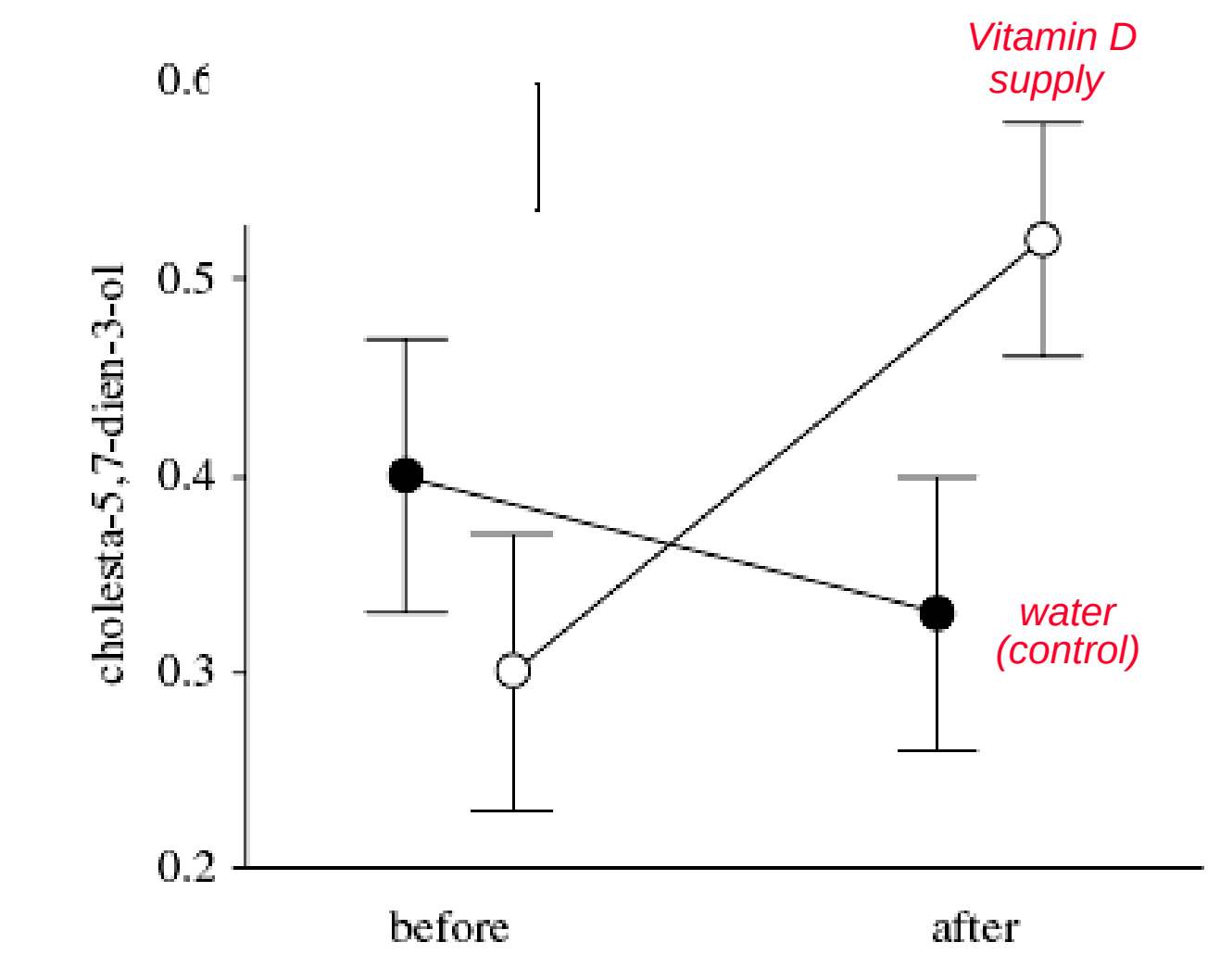
Vitamin D supplementation increases the attractiveness of males' scent for female Iberian rock lizards

Proc.R.Soc.B. (2006) 273: 2619

Vitamin D in the diet increases Cholest-5,7-dien-3-ol in apocrine femoral glands of male lizards and increases their sexual attractiveness for females

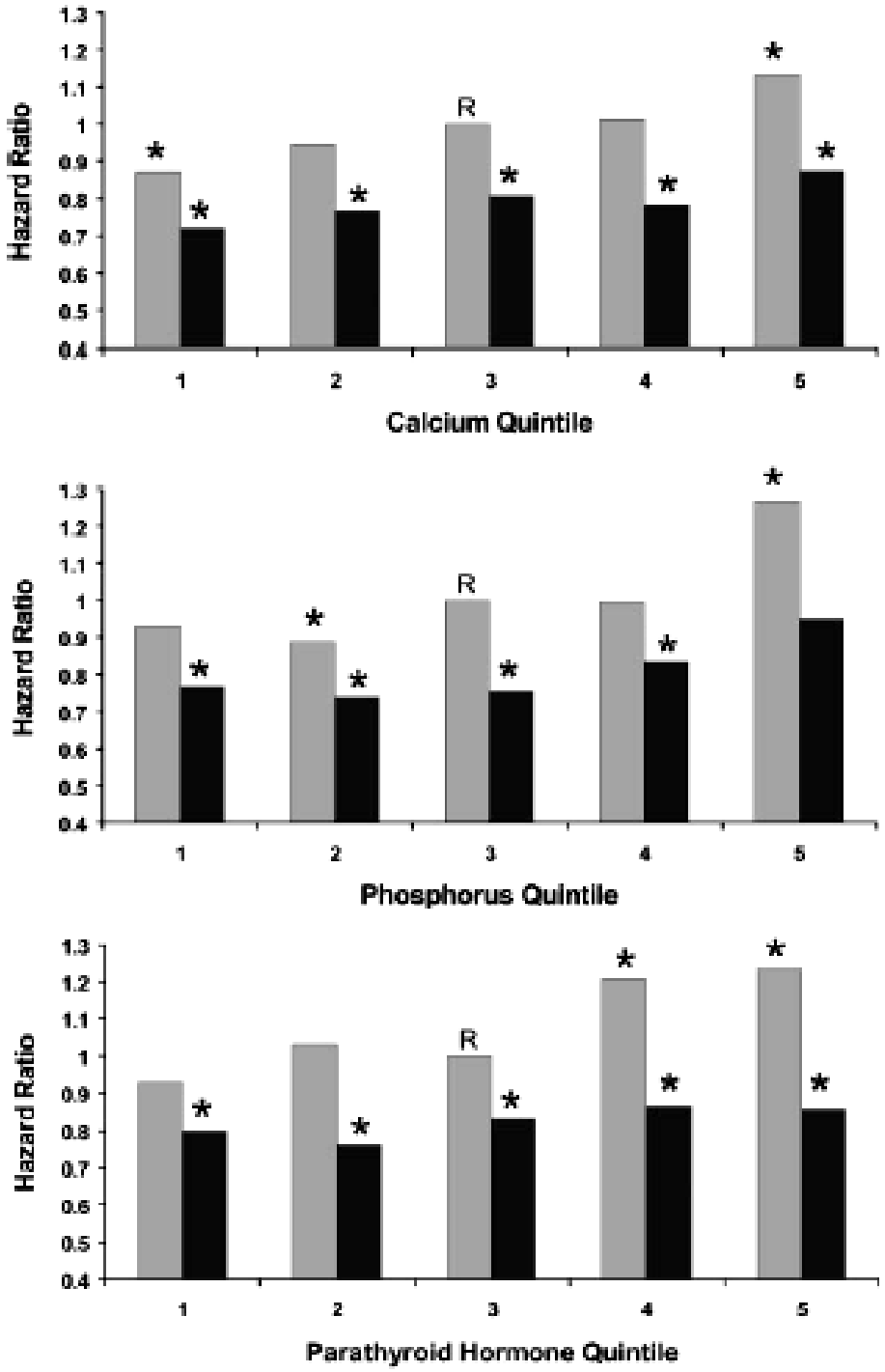
tongue flick test :

(effect of male sexual gland-secretion upon females)



Martín, Proc.R.Soc.B. (2006) 273: 2619

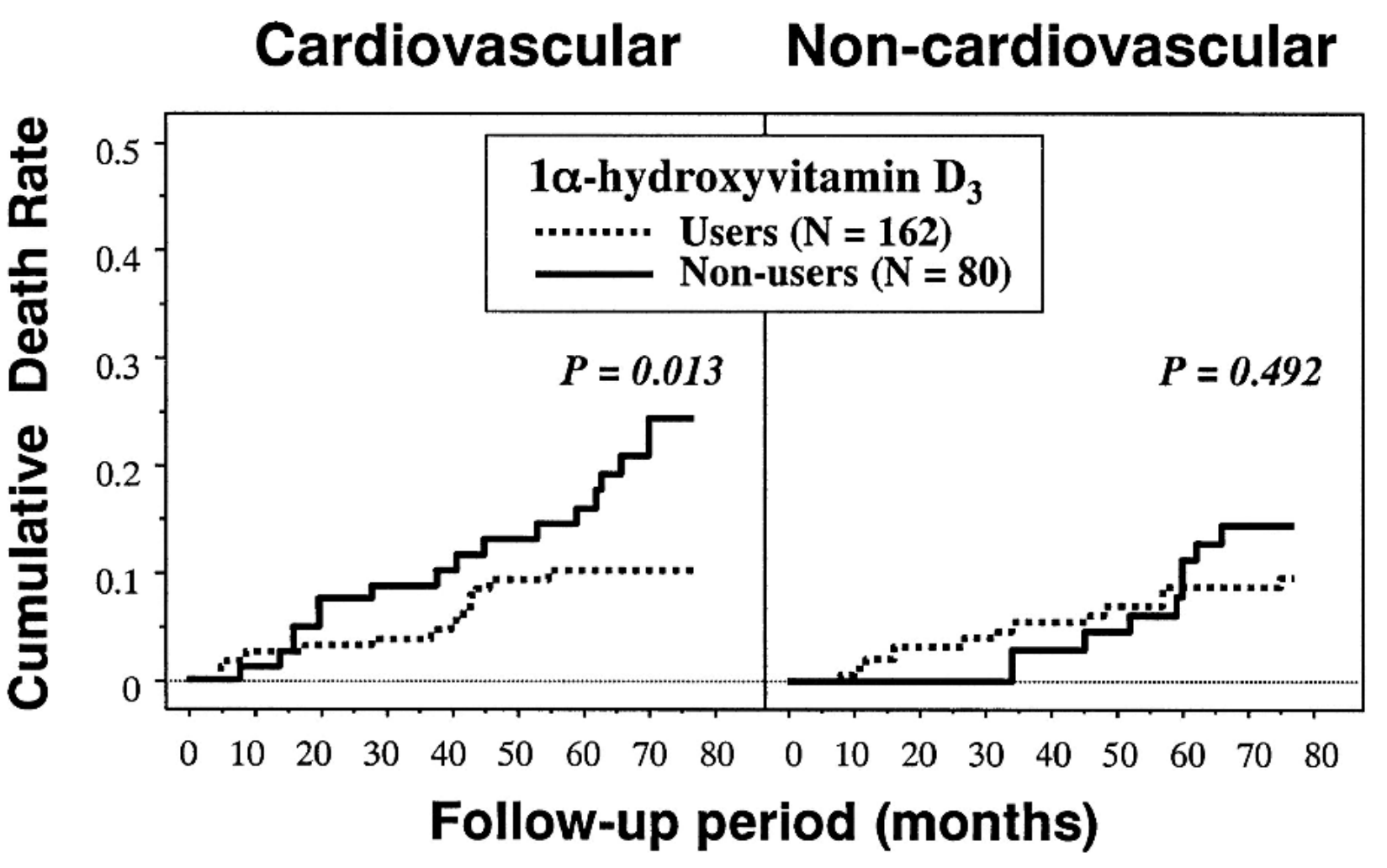
Treatment with (active) vitamin D – effects beyond mineral metabolism and bone



Injectable vitamin D and mortality according to Ca, P and PTH

Teng, J.Am.Soc.Nephrol (2005)16:1115

Lower cardiovascular mortality in HD patients on active vitamin D therapy



Nishizawa, Nephrol.Dial.Transplant.(2004) 19:179

Prospective observational study – inception cohort

at baseline

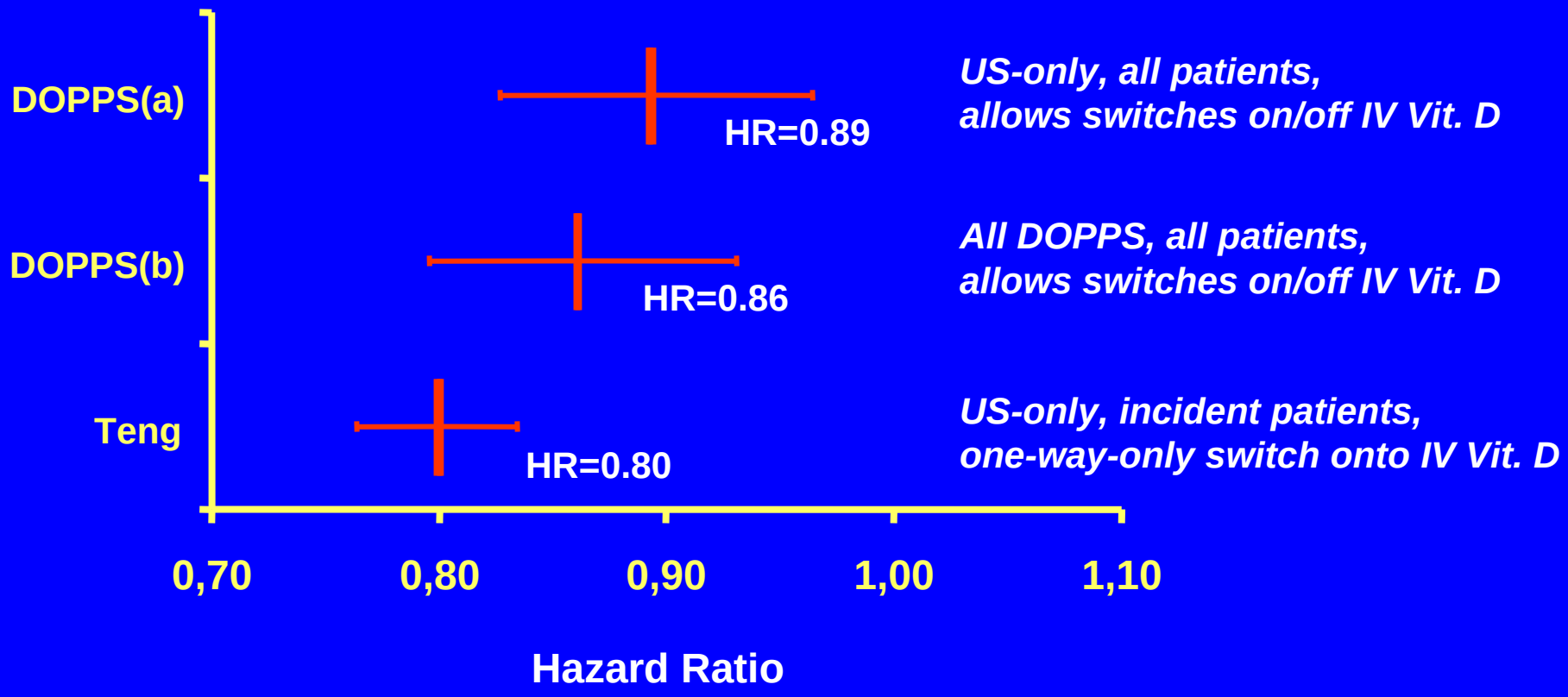
- **low $25(OH)D_3$**
- **low $1,25(OH)_2D_3$**

higher 1 year mortality

Thadhani R., Boston, 2006

DOPPS results –

iv vitamin D vs. no vitamin D



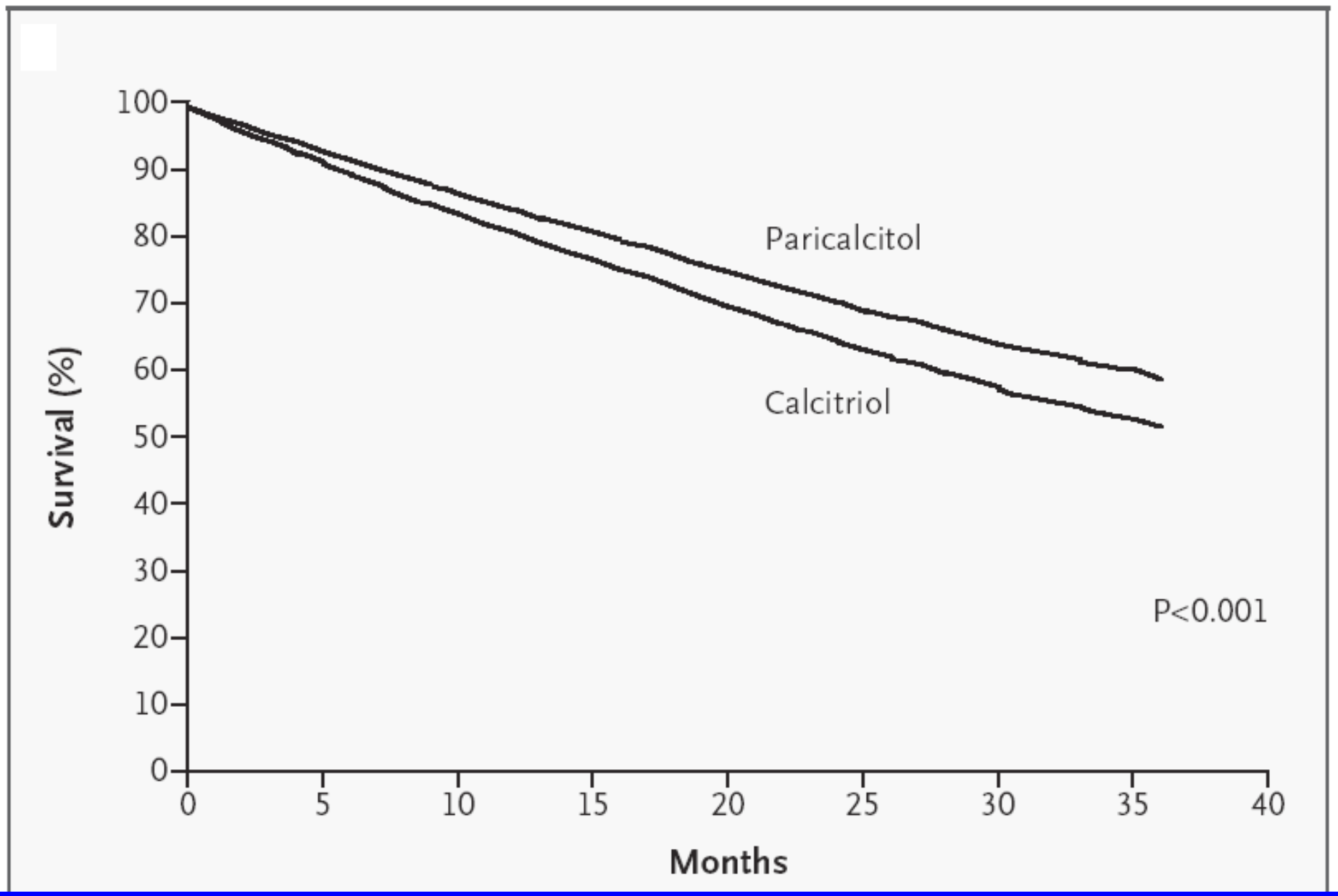
US-only, all patients, allows switches on/off IV Vit. D

All DOPPS, all patients, allows switches on/off IV Vit. D

US-only, incident patients, one-way-only switch onto IV Vit. D

Young, ASN TH-PO735 2005

Better survival of dialysis patients with Paricalcitol



Teng, New Engl J Med (2003) 349:446

The NEW ENGLAND JOURNAL of MEDICINE

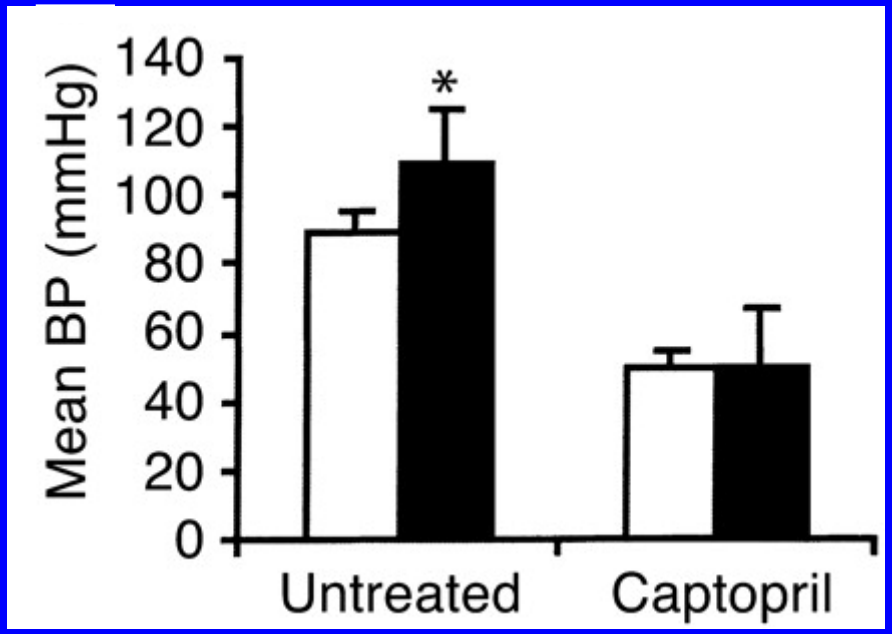
EDITORIAL

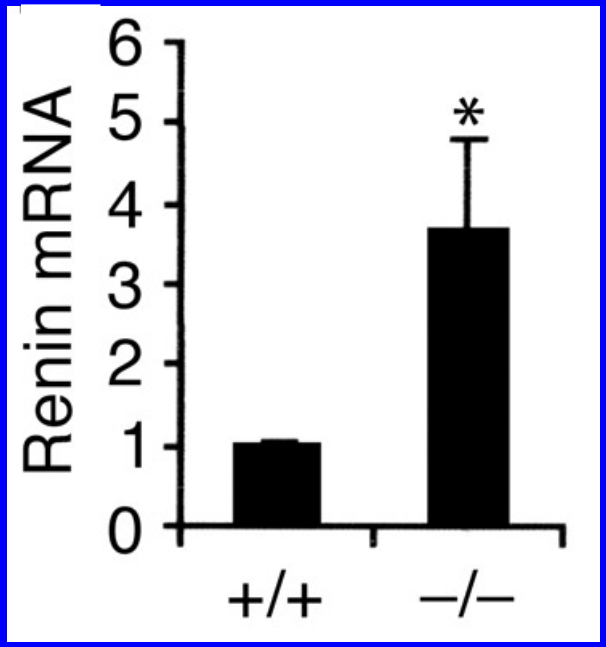
Paricalcitol as Compared with Calcitriol in Patients Undergoing Hemodialysis

Tilman B. Drüeke, M.D., and David A. McCarron, M.D.

Secondary hyperparathyroidism, a common consequence of chronic kidney disease, results from abnormal regulation of calcium and phosphate homeostasis. Three factors are central to its devel- of intact parathyroid hormone in patients undergoing hemodialysis who have severe forms of secondary hyperparathyroidism and also prevents its progression in patients who have less severe, earlier-

Hypertension and high renin expression in vitamin D receptor -/- mice

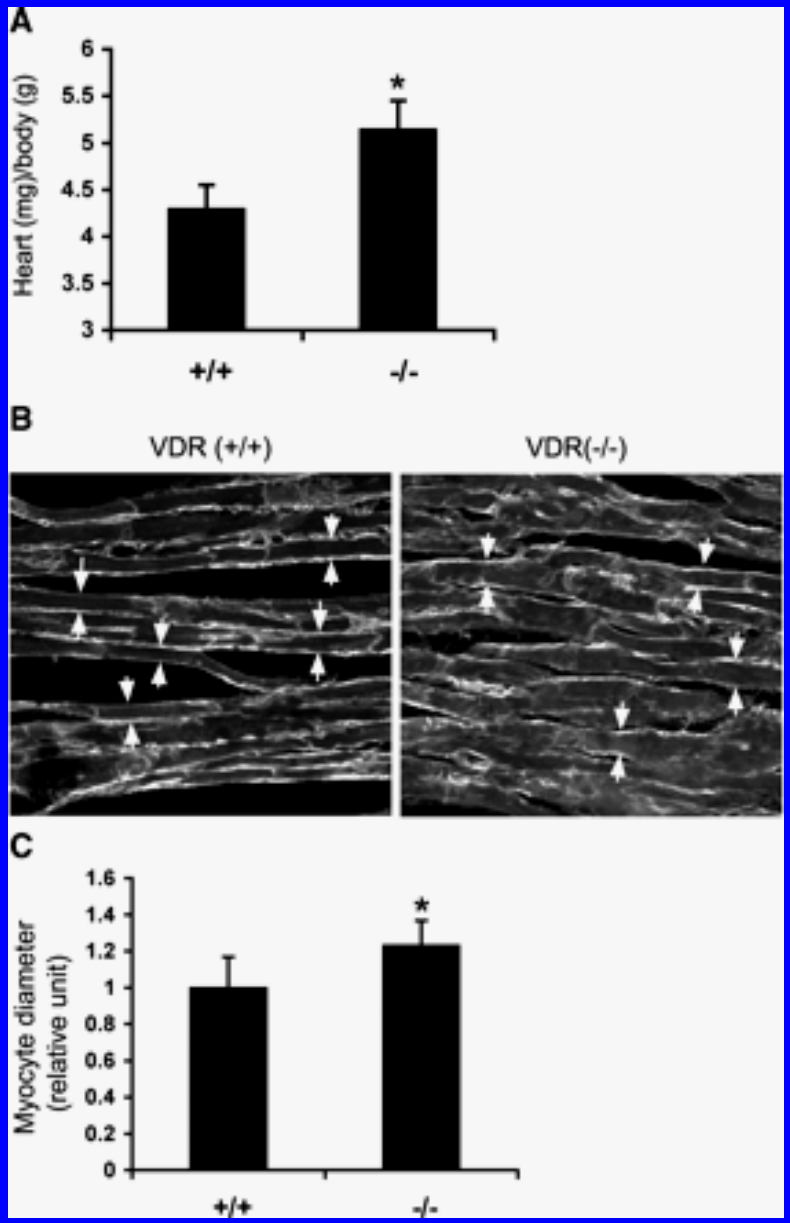




⇨ **active vitamin D suppresses renin expression and lowers blood pressure and LVH**

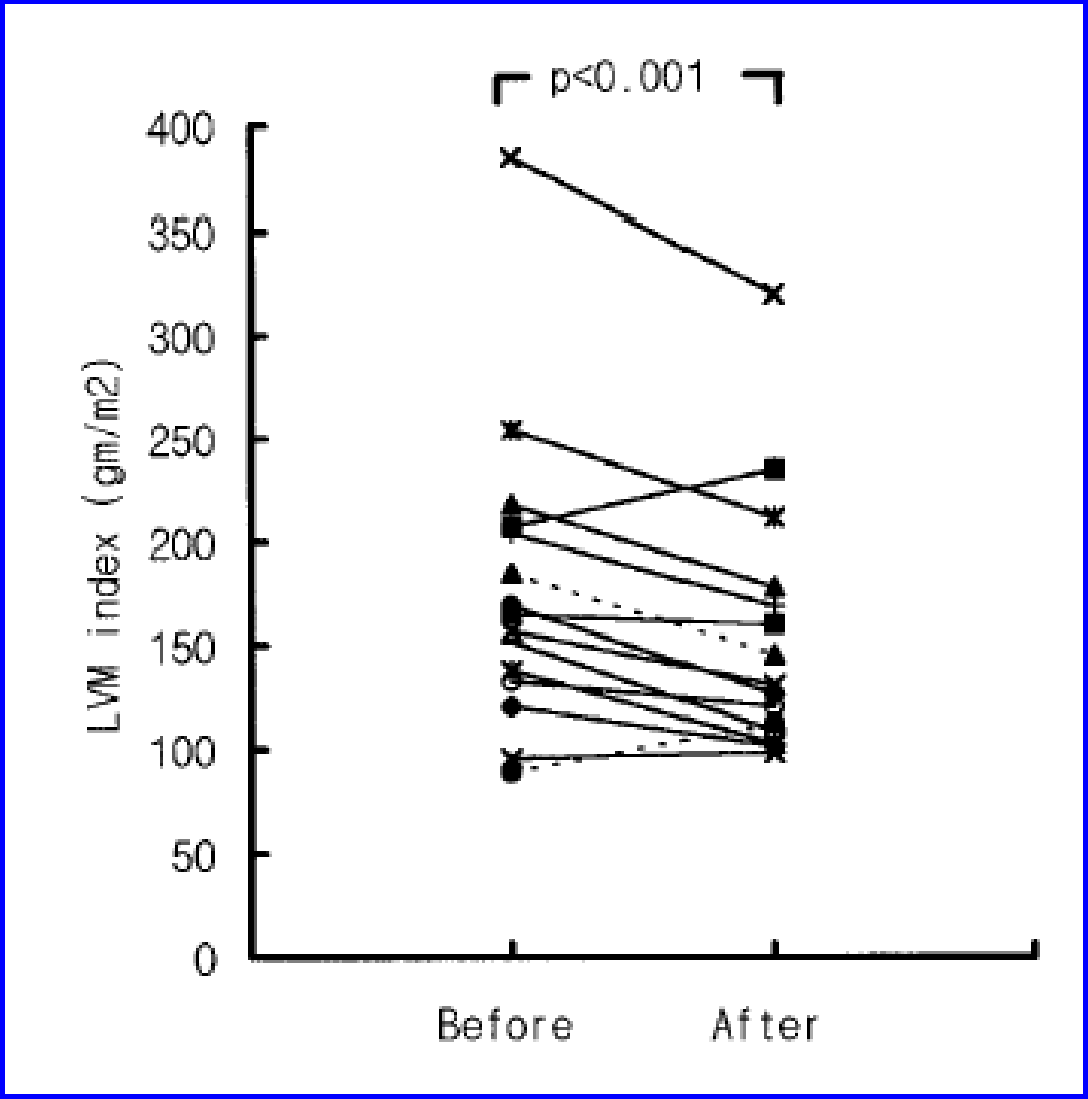
Li,J.Clin.Invest.(2002) 110: 229

Cardiac hypertrophy in VDR -/-mice



Xiang, Am.J.Physiol.(2005) 288:E125

Regression of LVH by 1αcalcidol iv in HD patients



Park, Am.J.Kid.Dis.(1999) 33:73

Is treatment with the precursor molecule vitamin also effective ?

25-HYDROXY-VITAMIN-D IN NEPHROTIC SYNDROME*

H. SCHMIDT-GAYK
CHRISTA GRAWUNDER
W. TSCHÖPE
W. SCHMITT
E. RITZ
V. PIETSCH
K. ANDRASSY

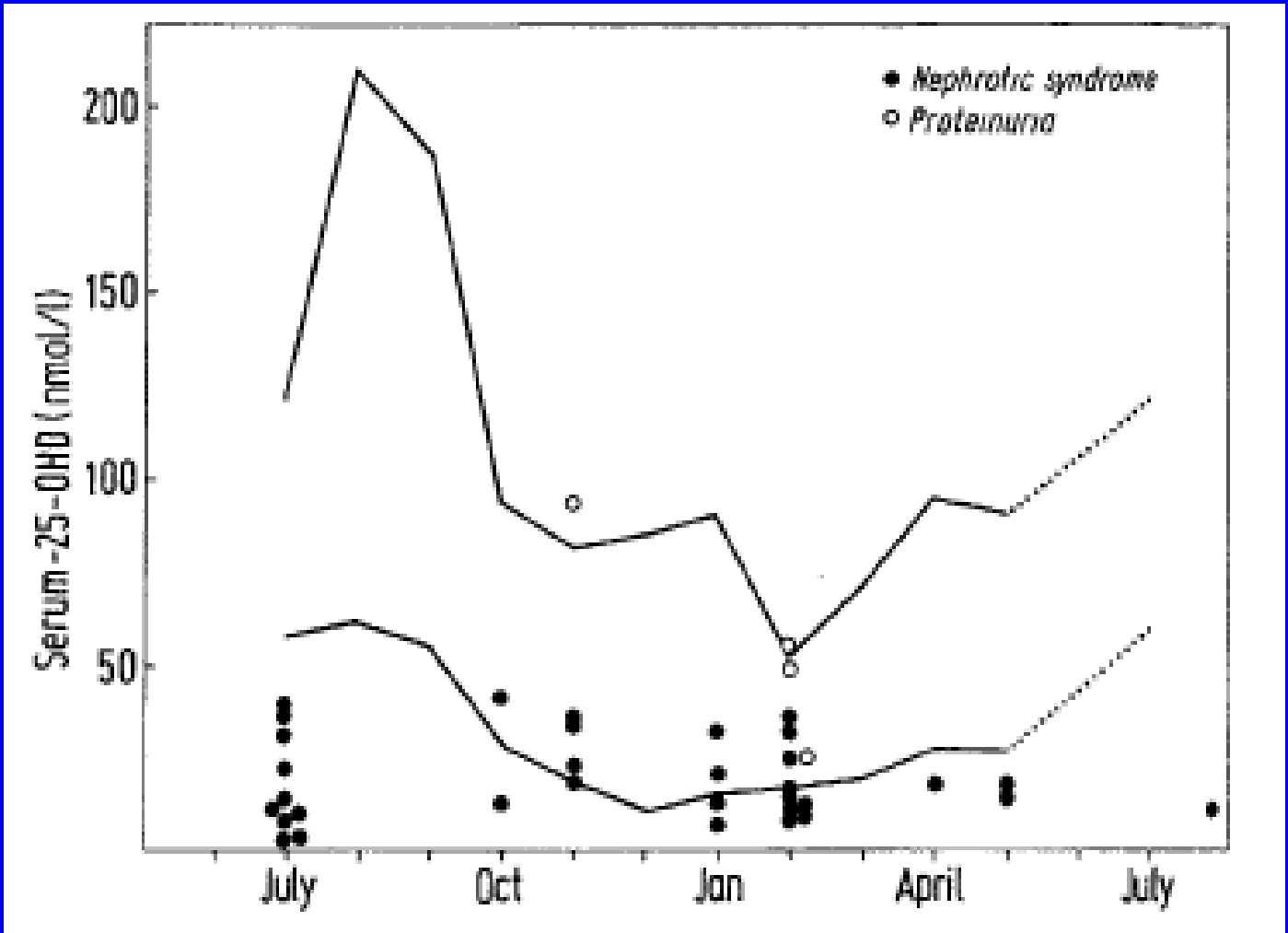
Medizinische Universitäts Klinik, Heidelberg, Federal Republic of Germany

R. BOUILLON

Katholieke Universiteit, Rega Instituut, Leuven, Belgium

Lancet (1977) ii:105

Low 25(OH)D concentrations irrespective of seasonal adjustment

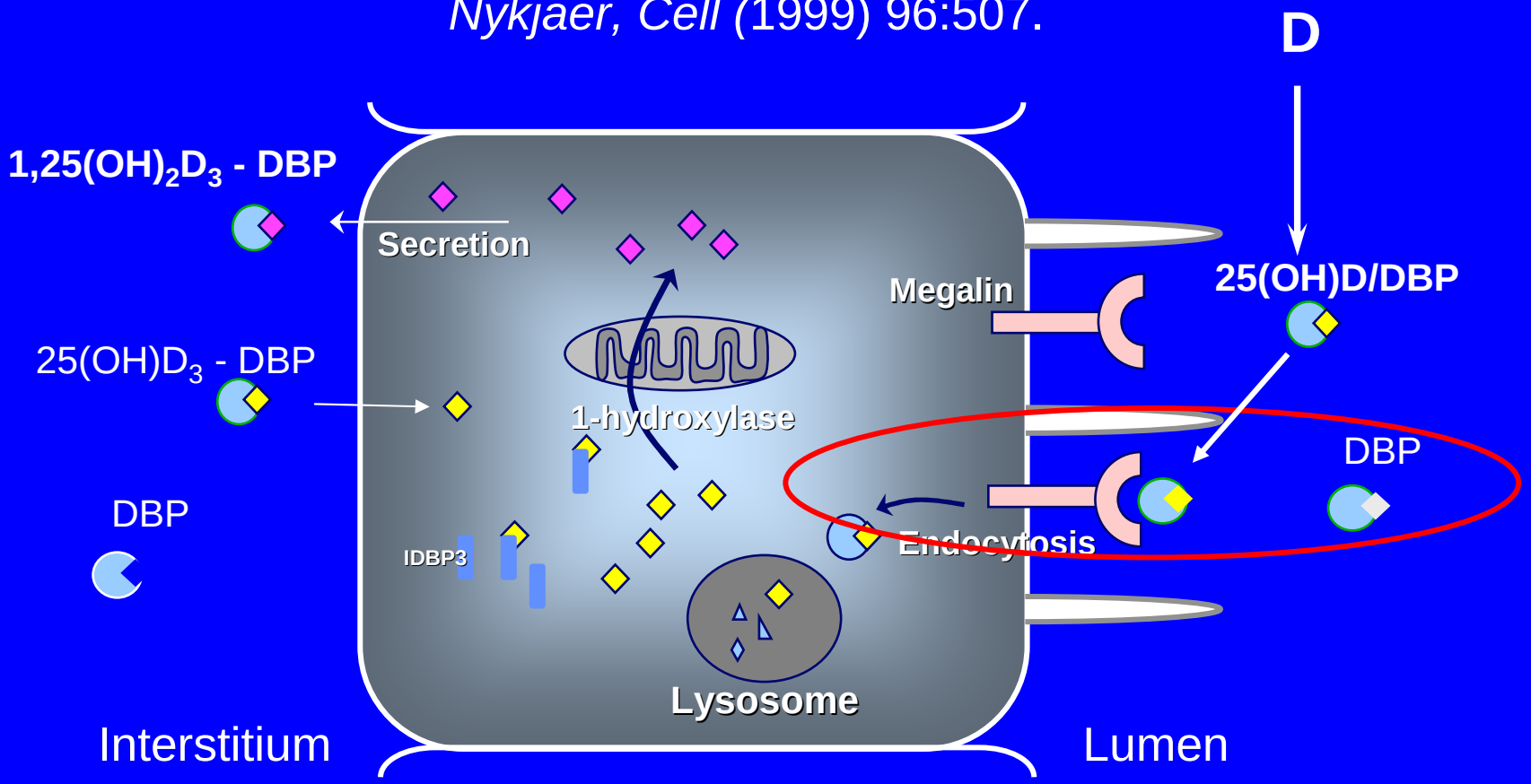


Schmitt-Gayk, Lancet (ii): 105

In proximal tubule :

uptake of complex D-binding protein/25(OH)D_3 via megalin

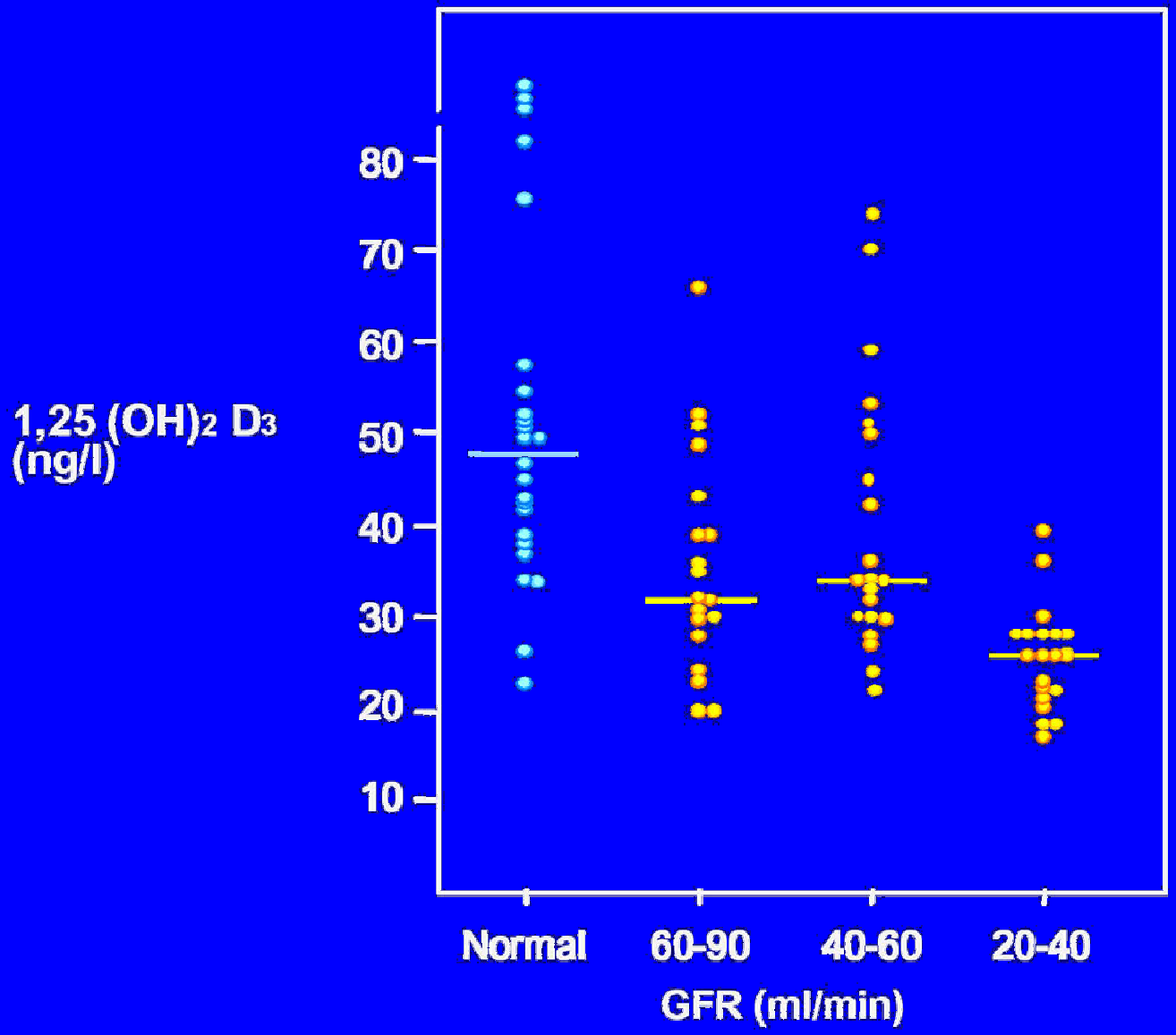
Nykjaer, Cell (1999) 96:507.



Megalin expression reduced in proteinuric conditions

megalin expression induced by 1,25(OH)$_2$D$_3$ treatment

$1,25(OH)_2D_3$ concentrations at different stages of CKD



Reichel, Nephrol.Dial.Transplant (1991) 6: 162

PTH –
survival risk must be interpreted in the context of other abnormalities of Ca,P metabolism

	risk
# normal PTH,Ca, P	1.0
# normal PTH, Ca↑,P↑	↑
# PTH↑, Ca↑, P↑	↑↑
# PTH↓, Ca↓, P↓	↑↑↑*

* *the group most likely to have not received active vitamin D ?*

Stevens, J.Am.Soc.Nephrol.(2004) 15:770

Why lack of active vitamin D ?

[1,25(OH)$_2$D$_3$]

- *reduced uptake of 25(OH)D$_3$ by proximal tubular epithelial cells (megalin defect)⇨ (substrate deficiency)*
- *not compensated by sufficient activation of 1- α- hydroxylase (inappropriate synthesis)*

Strategies for vitamin D-related interventions in CKD stages 3, 4 & 5

Strategy 1:

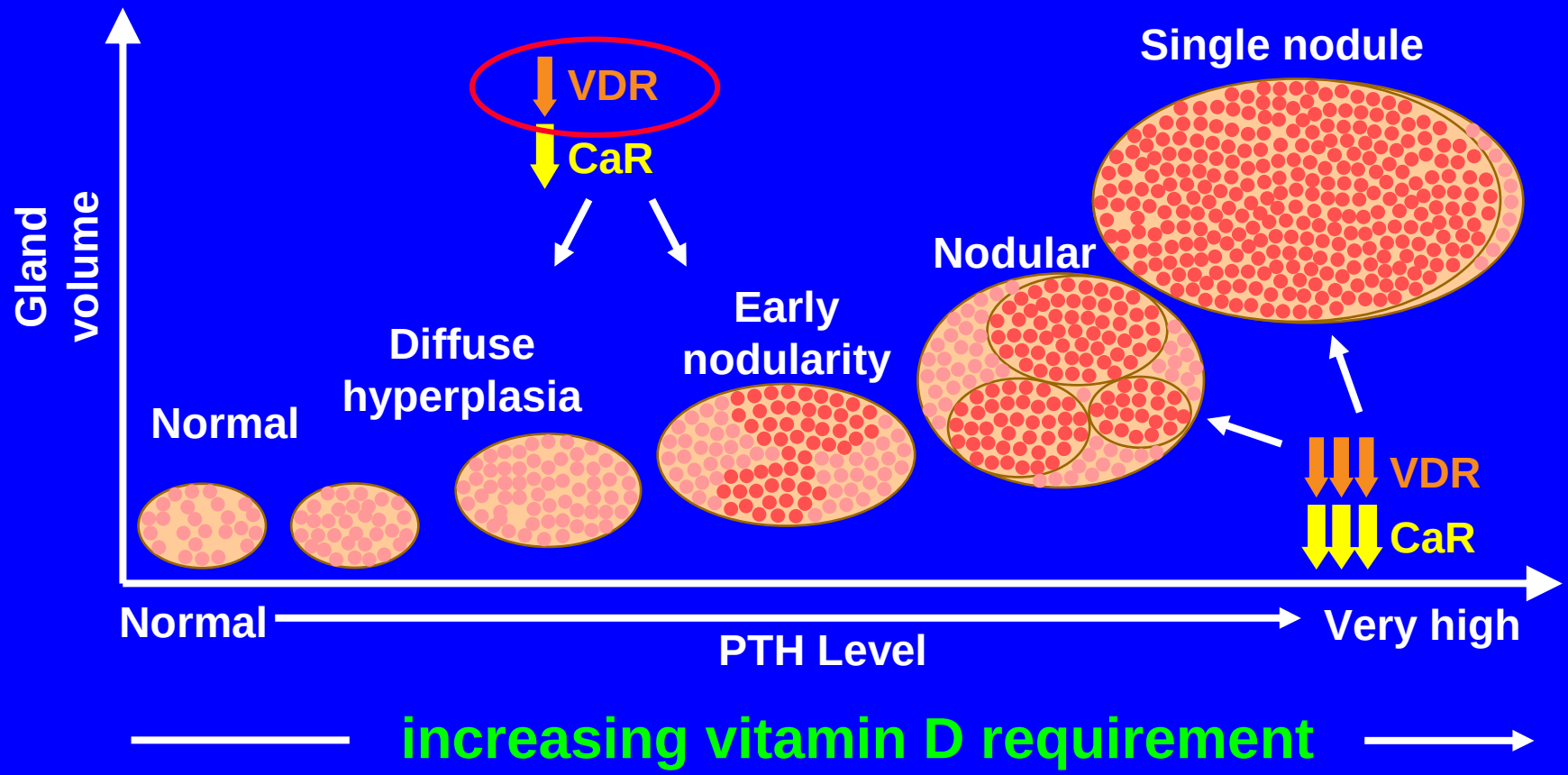
Provide vitamin D_3 to maintain plasma 25-OH-D until renal enzyme can no longer sustain blood calcitriol.

Strategy 2:

Replace calcitriol or a vitamin D analog to restore classical & non-classical functions of vitamin D.

Progression of secondary HPT -

⇨ *progressively higher doses of vitamin D required*



Tominaga, Curr Opin Nephrol Hypertens (1996)5:336

Treatment with vitamin D and/or active vitamin D

- *25(OH)D deficiency – strongly correlated to hyperparathyroidism (probably consequence of 1,25 synthesis in parathyroids)*

- *New role of active vitamin D ⇨ better patient survival ! pleiotropic effects ? (renin, cardiac mechanisms?)*

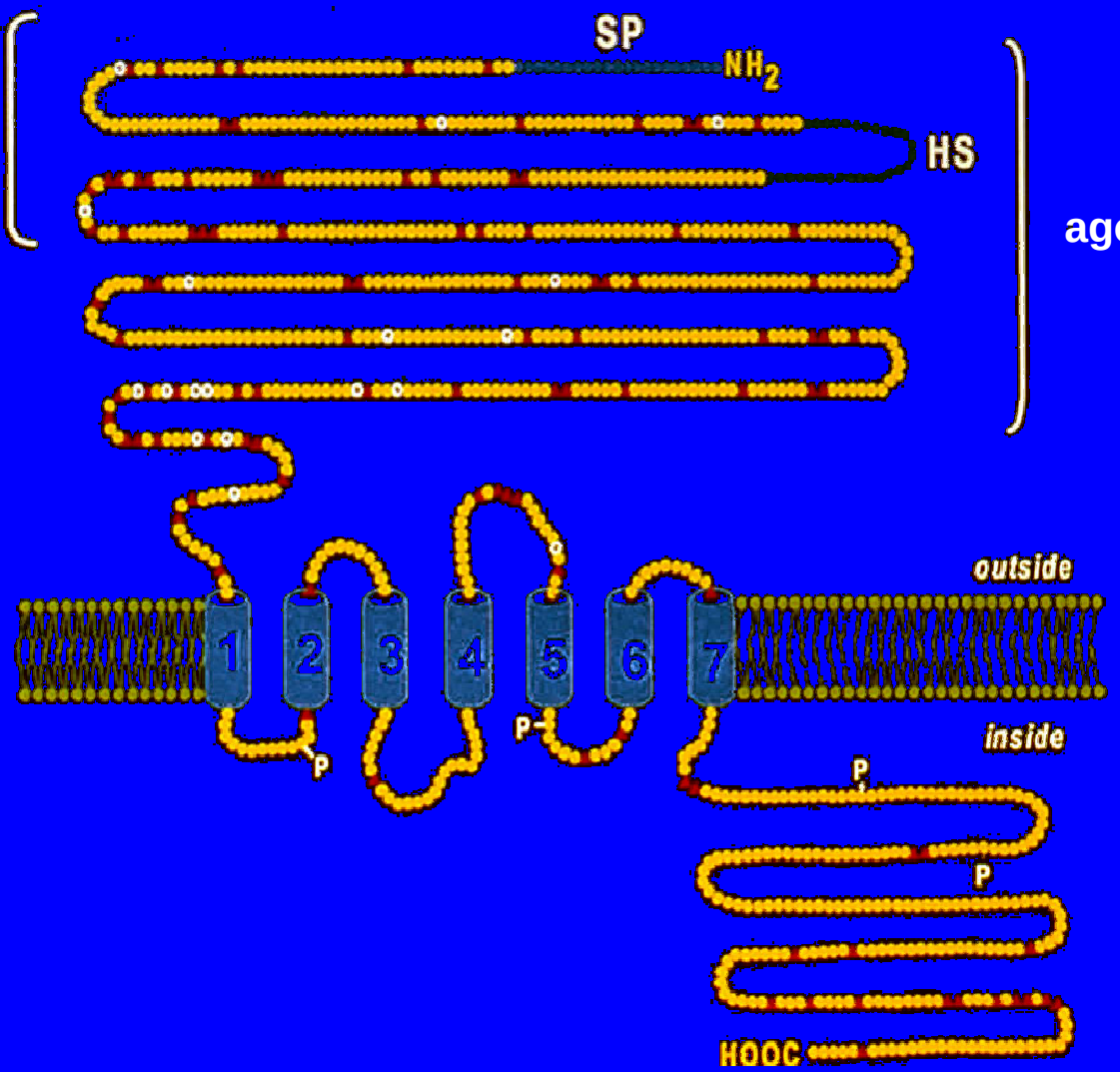
- *Disadvantages of vitamin D therapy (dose dependent. Kestenbaum):*
  - *positive Ca balance,*
  - *increase of S-phosphate concentration,*
  - *predisposition to vascular calcification ?*

- *diminished parathyroid repsonsiveness because of VDR receptor downregulation*

- Vitamin D and active vitamin D
- **PTH and calcium sensing**

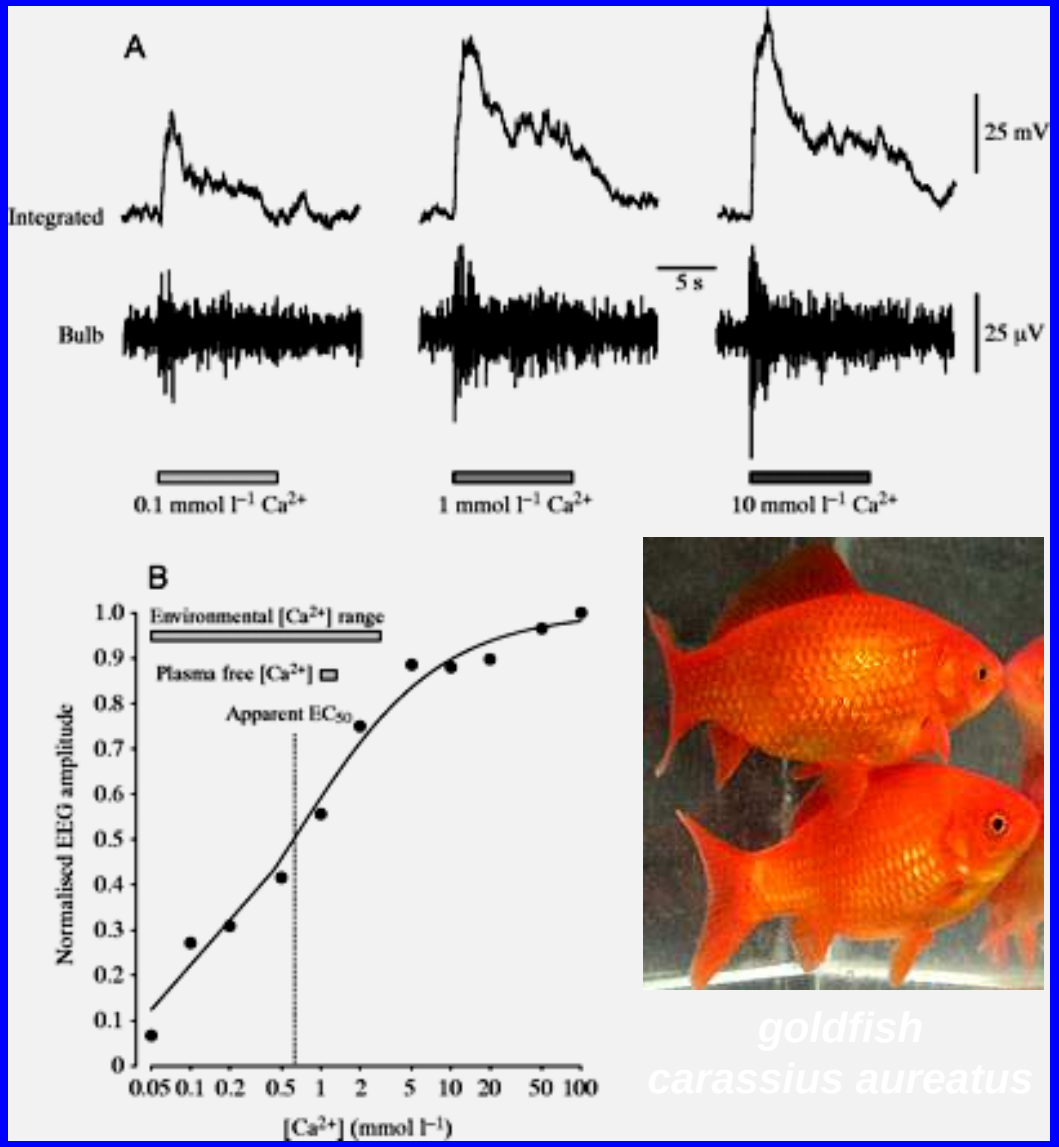
Calcium sensing receptor (CaR)

controls dimerization and normal receptor function



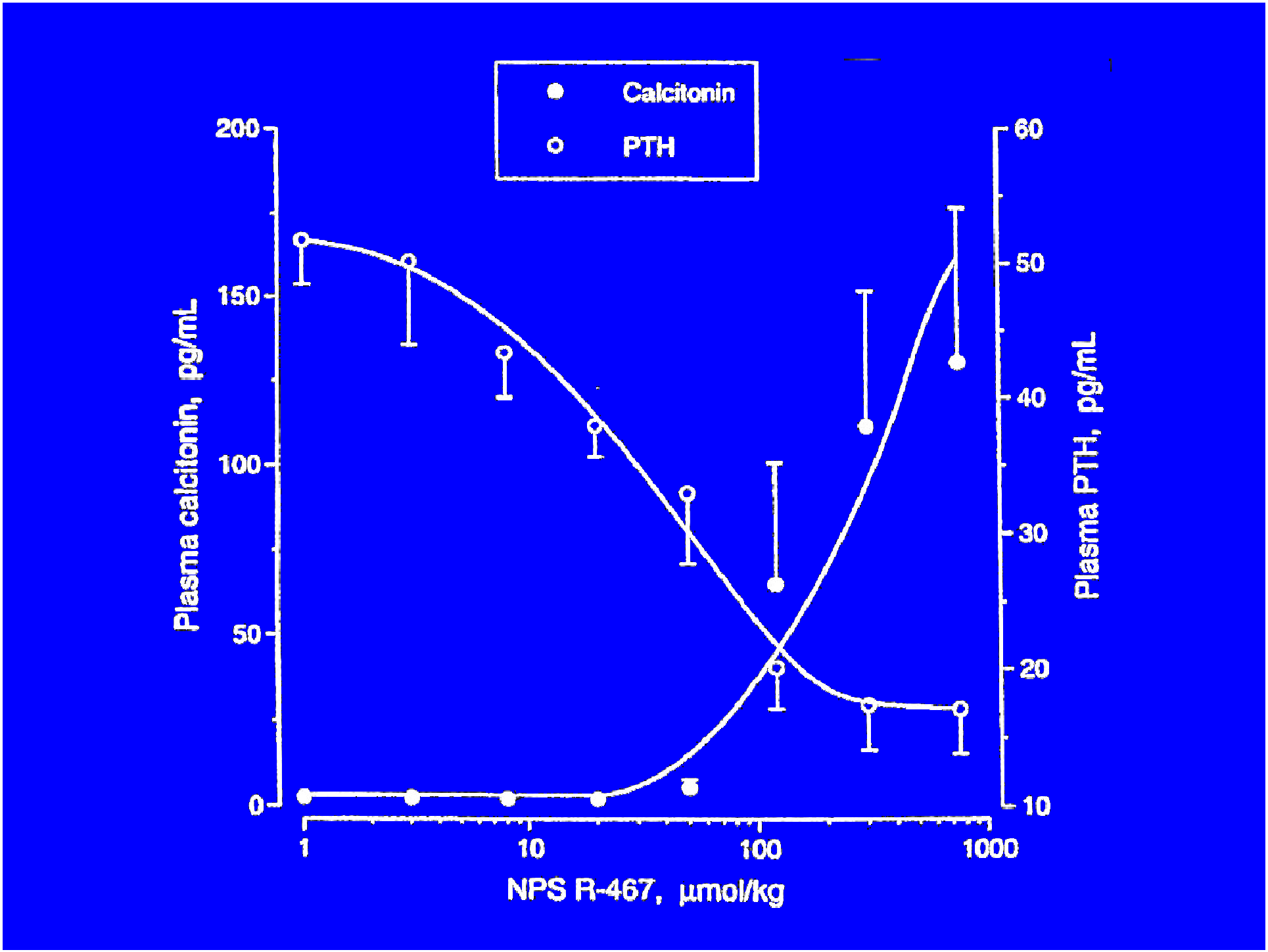
agonist binding

Olfactory sensing of Ca^{++} - by CaSr homologue

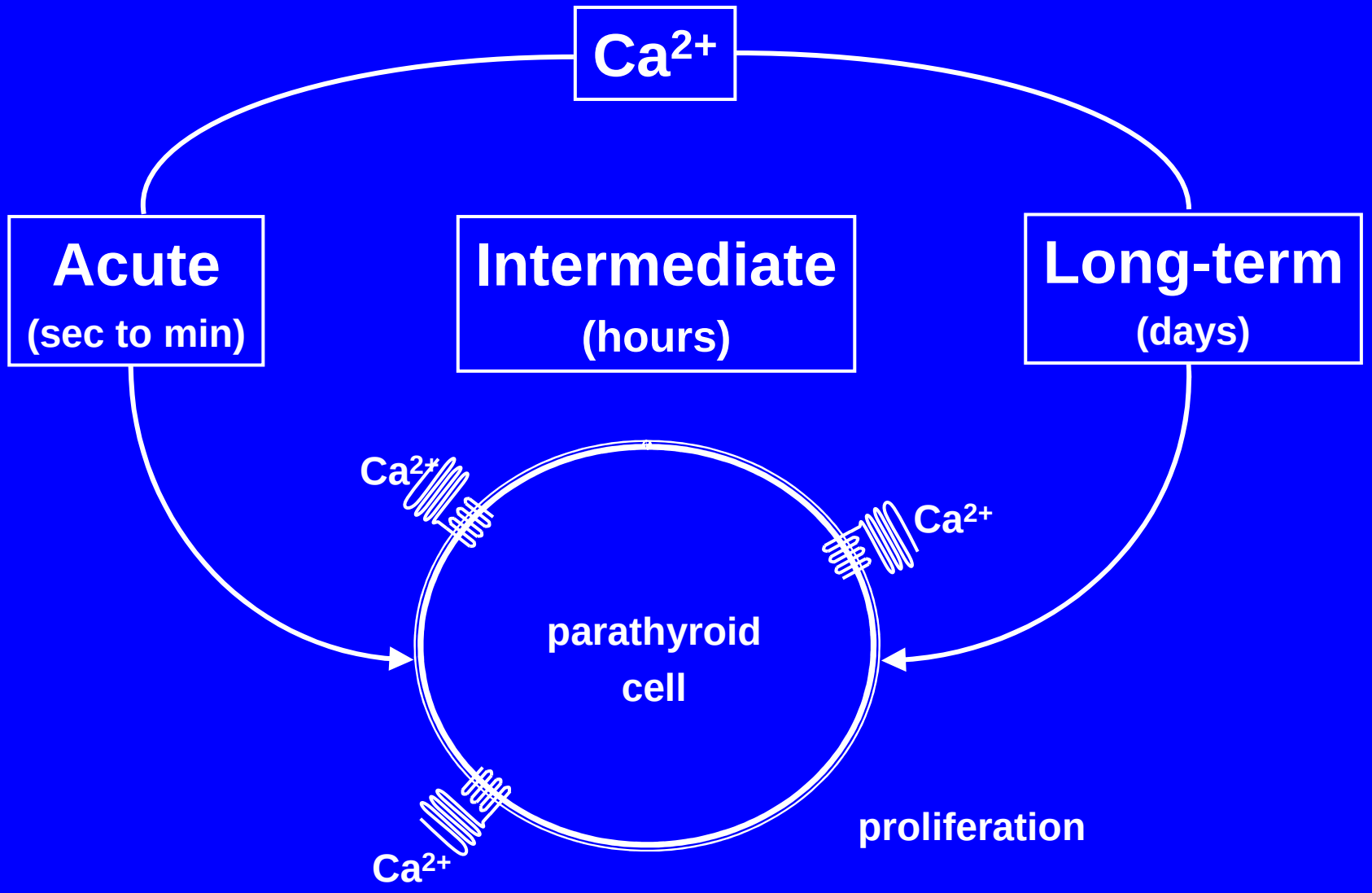


goldfish
carassius aureatus

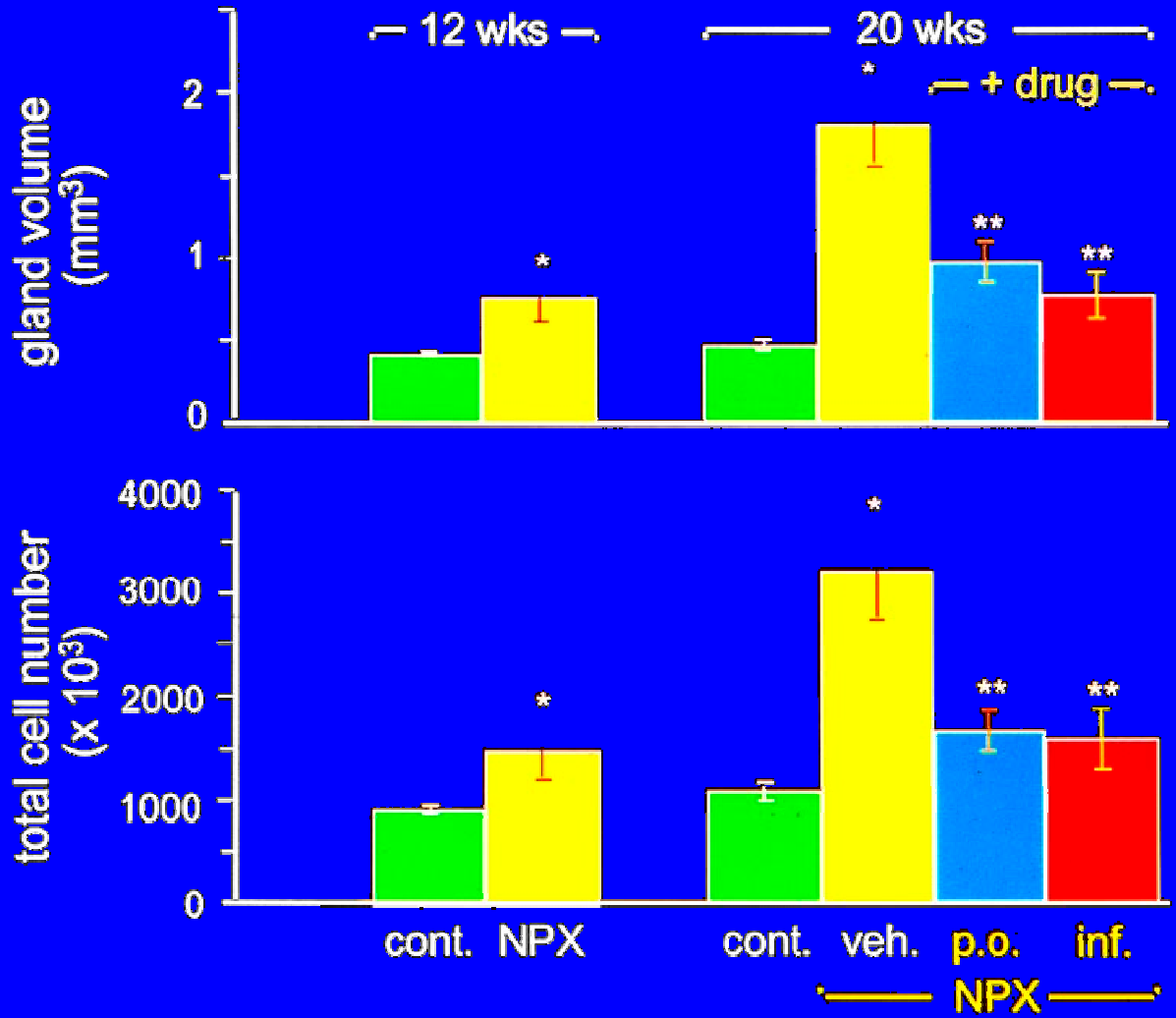
Hubbard, J.Experiment.Biol.(2002) 205:2755


Calcitonin
PTH
Plasma calcitonin, pg/mL
Plasma PTH, pg/mL
200
150
100
50
0
60
50
40
30
20
10
1
10
100
1000
NPS R-467, µmol/kg

Reaction of parathyroid to decrease of ionised Ca^{2+}

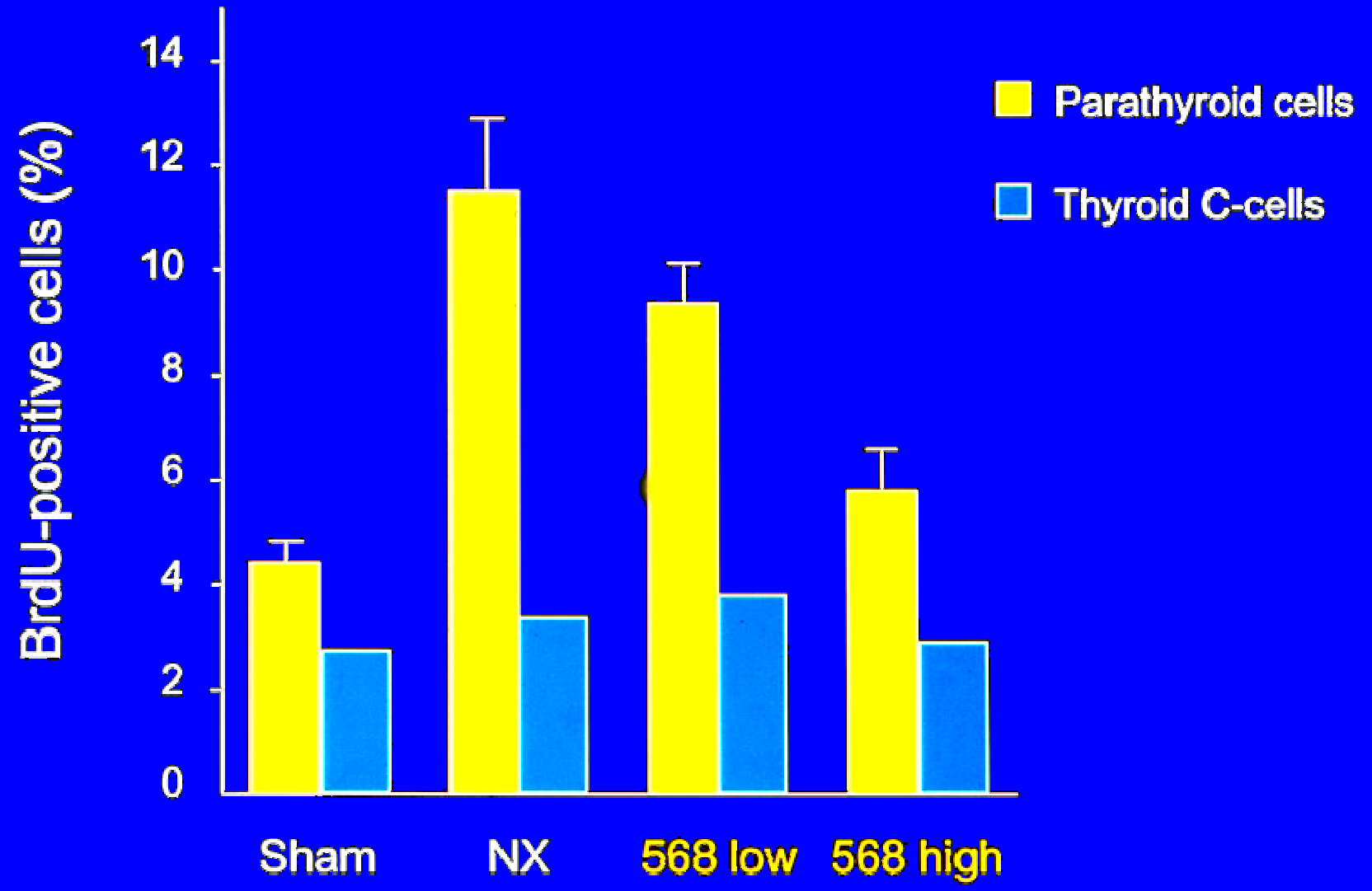


Prevention of parathyroid hyperplasia by calcimimetics



Wada, J.Clin.Invest.(1997) 100:2977

Tissue specific inhibition of proliferation of parathyroid cells



Calcium-receptor

- **expression decreased in uremia,**

  including uremic patients with nodular hyperplasia of parathyroids,

  <u>nevertheless</u>
- **dose response relationship of calcimimetics unchanged in uremia**

Goodman, J Am Soc Nephrol (2002) 13:1017

Calcium sensing receptor is upregulated by vitamin D, but not by calcium

Brown, Amer.J.Physiol.(1996) 270:F454

$1,25(OH)_2D_3$increases Ca^{++}sensitivity of PTH secretion in HD patients

Delmez, J.Clin.Invest.(1989) 83:1349

⇨ **- increased Ca^{++}sensitivity of parathyroid**
- reduced active intestinal Ca transport
argument for calcimimetic plus active vitamin D ?

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ORIGINAL ARTICLE

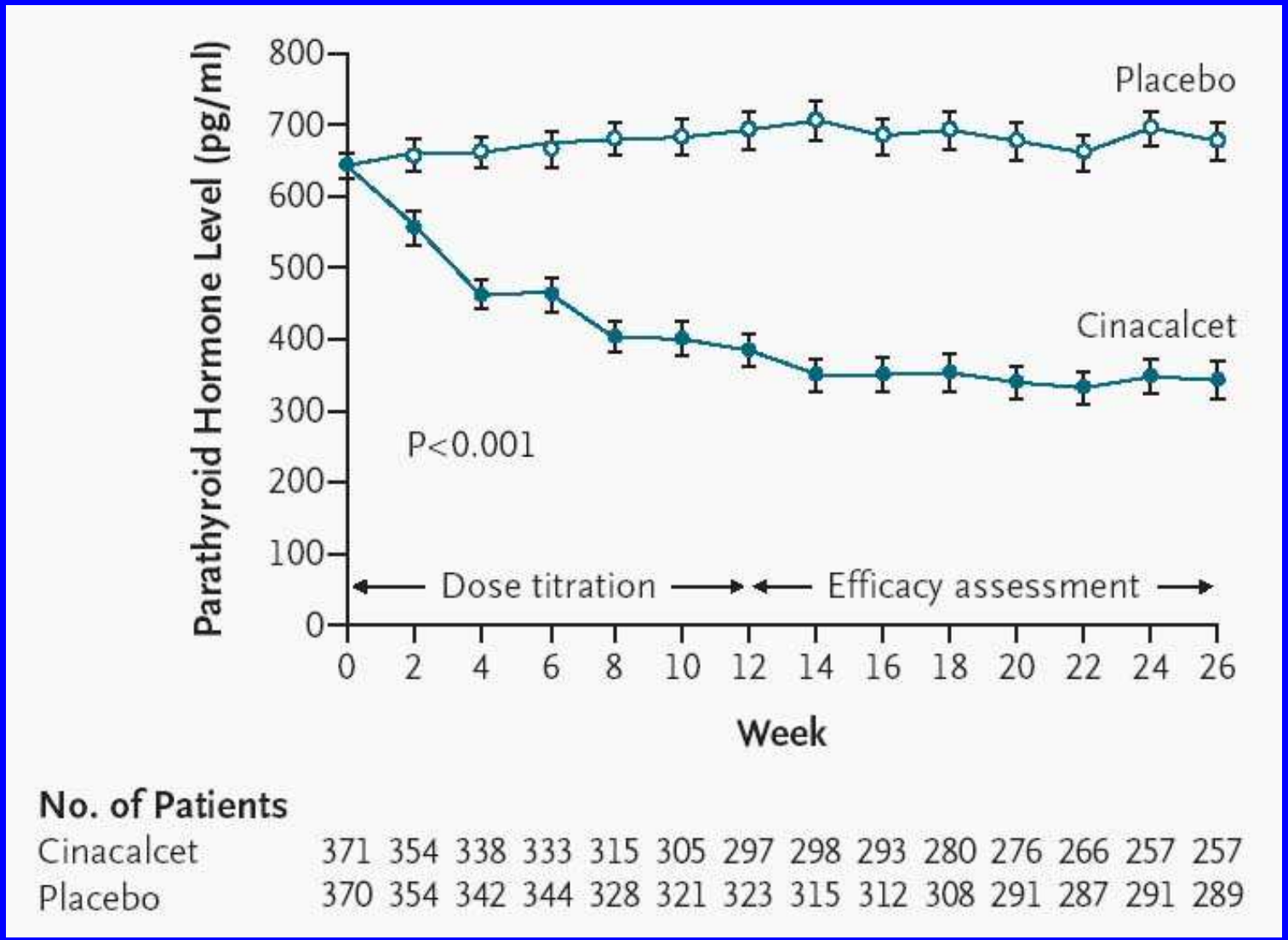
Volume 350:1516-1525 April 8, 2004 Number 15

Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis

Geoffrey A. Block, M.D., Kevin J. Martin, M.B., B.Ch., Angel L.M. de Francisco, M.D., Stewart A. Turner, Ph.D., Morrell M. Avram, M.D., Michael G. Suranyi, M.D., Gavril Hercz, M.D., John Cunningham, D.M., Ali K. Abu-Alfa, M.D., Piergiorgio Messa, M.D., Daniel W. Coyne, M.D., Francesco Locatelli, M.D., Raphael M. Cohen, M.D., Pieter Evenepoel, M.D., Sharon M. Moe, M.D., Albert Fournier, M.D., Johann Braun, M.D., Laura C. McCary, Ph.D., Valter J. Zani, Ph.D., Kurt A. Olson, M.S., Tilman B. Drüeke, M.D., and William G. Goodman, M.D.

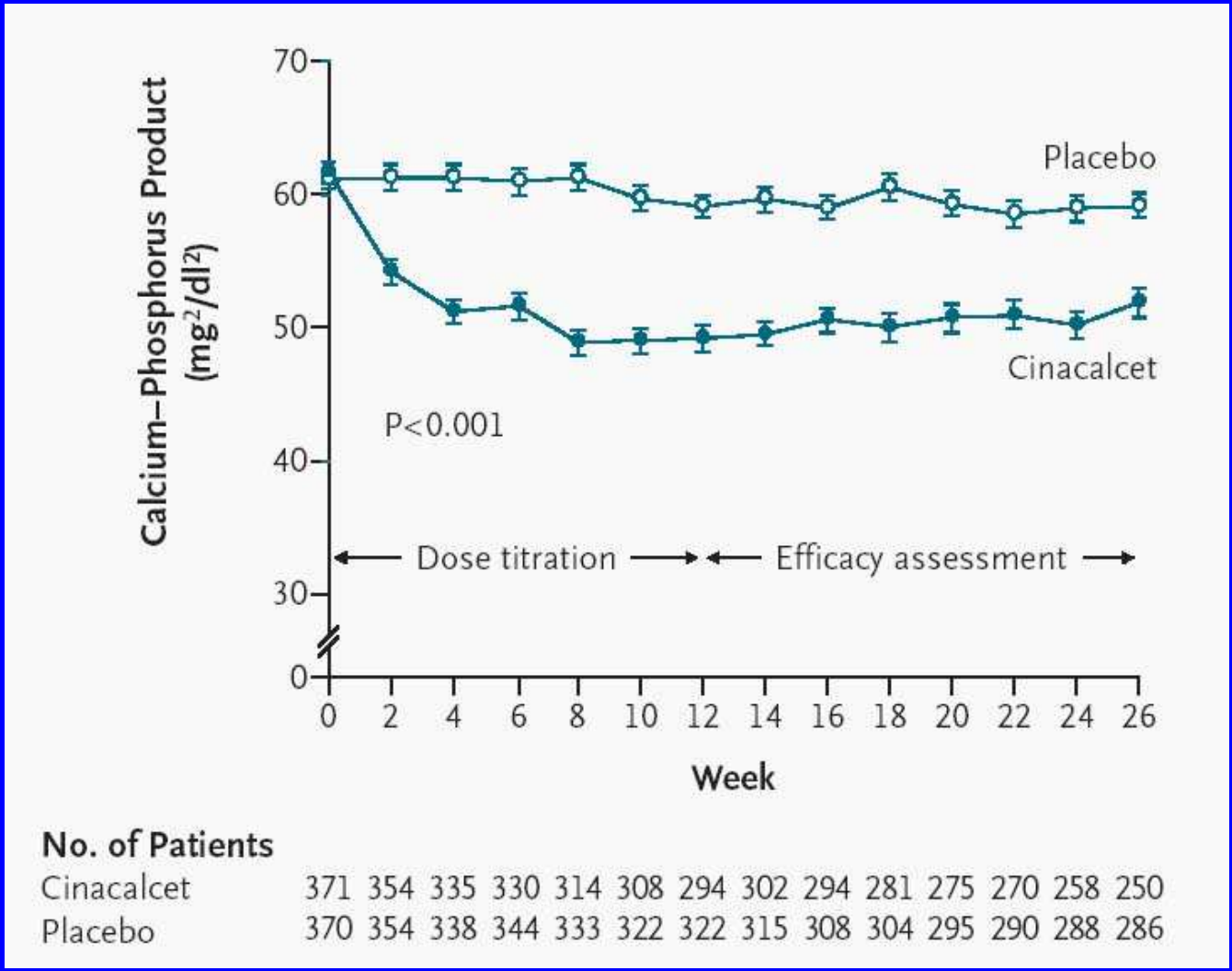
Block, New Engl J Med (2004) 350: 1516

Cinacalcet decreases PTH concentration



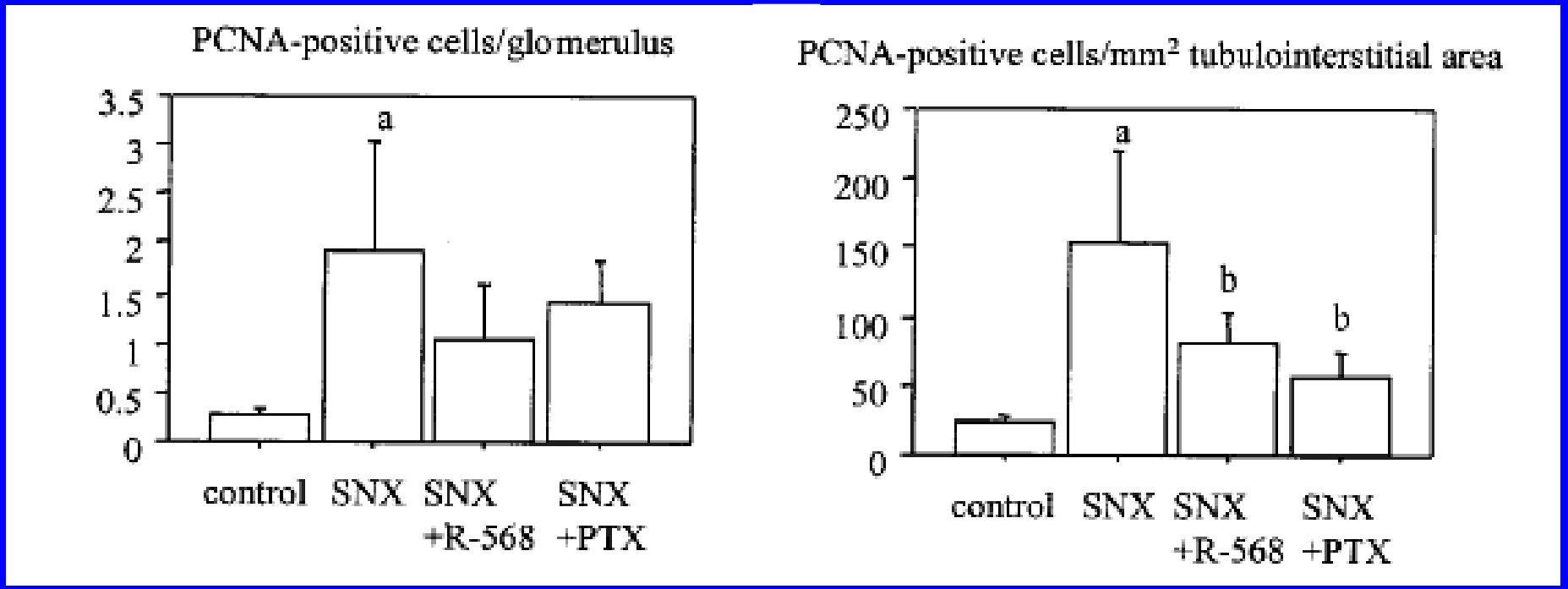
Block, New Engl J Med (2004) 350: 1516

Cinacalcet reduces Ca x P product



Block, New Engl J Med (2004) 350: 1516

SNX rats on calcimimetic or after PTX – *less glomerular and tubulointerstitial cell proliferation*

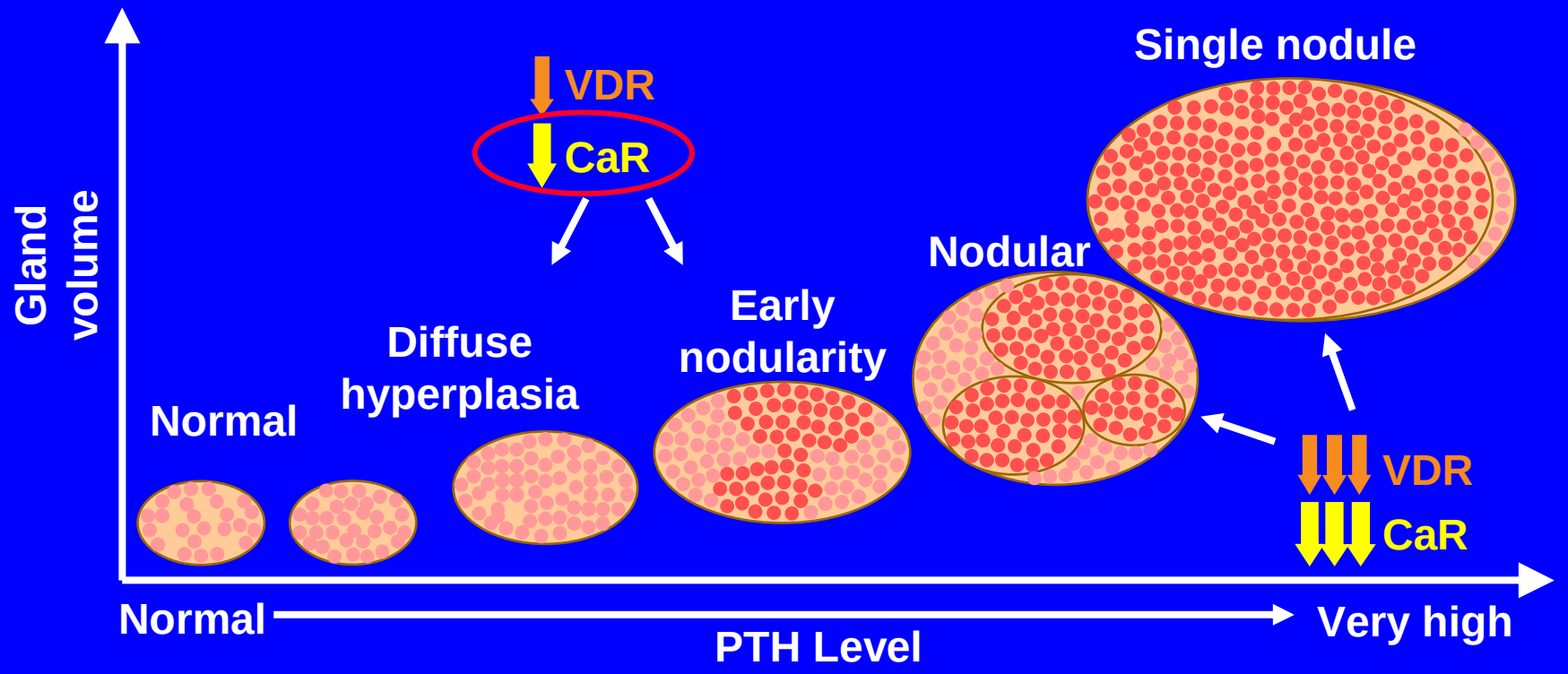


Ogata, J.Am.Soc.Nephrol.(2003) 14:959

Progression of secondary HPT -

⇨ *progressively higher doses of vitamin D required*

(decrease of vitamin D and calcium sensing receptors)



Tominaga, Curr Opin Nephrol Hypertens (1996)5:336

if PTH > 50 pmol/L (~ 500 pg/ml)
despite treatment with active vitamin D
or
if treatment contraindicated because of hypercalcemia / hyperphosphatemia

⇨ in the past: consider parathyroidectomy

⇨ new consideration : Cinacalcet ?

Rationale for parathyroidectomy

- nodular parathyroid hyperplasia,
- monoclonal growth and chromosomal abnormalities,
- loss of tumor suppressor genes,
- downregulation of vitamin D receptor,
- unresponsiveness to active vitamin D

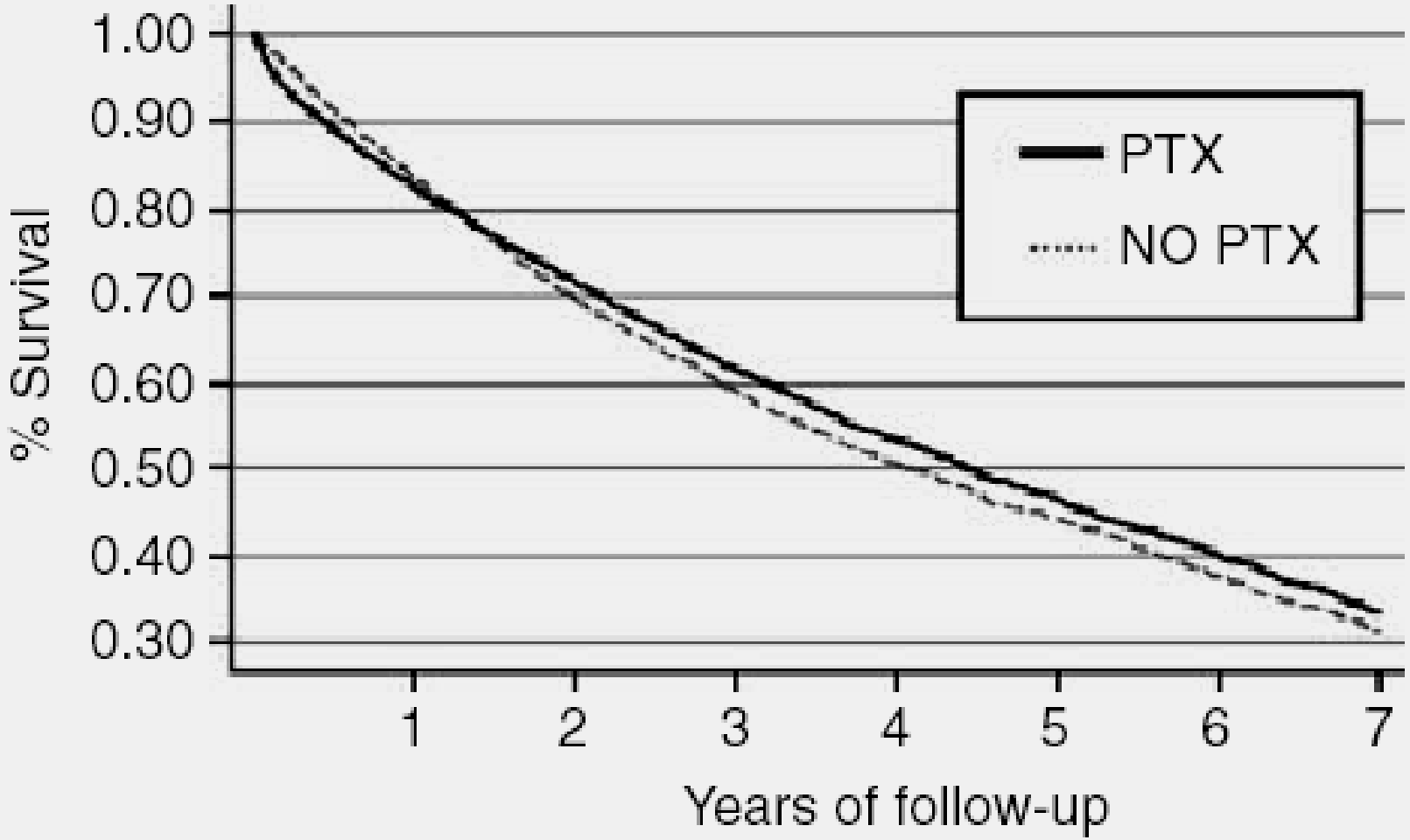
Less longterm mortality after PTX in hemodialysed patients

⇨ **Risk lower by 15% after PTX**

Kestenbaum, Kid.Intern (2004) 66: 2010

Foley, J.Am.Soc.Nephrol.(2005) 16:210

Survival of HD patients after PTX



Kestenbaum, Kidn.Intern.(2004) 66:2010

Guidance for Evaluating Elevated PTH Levels

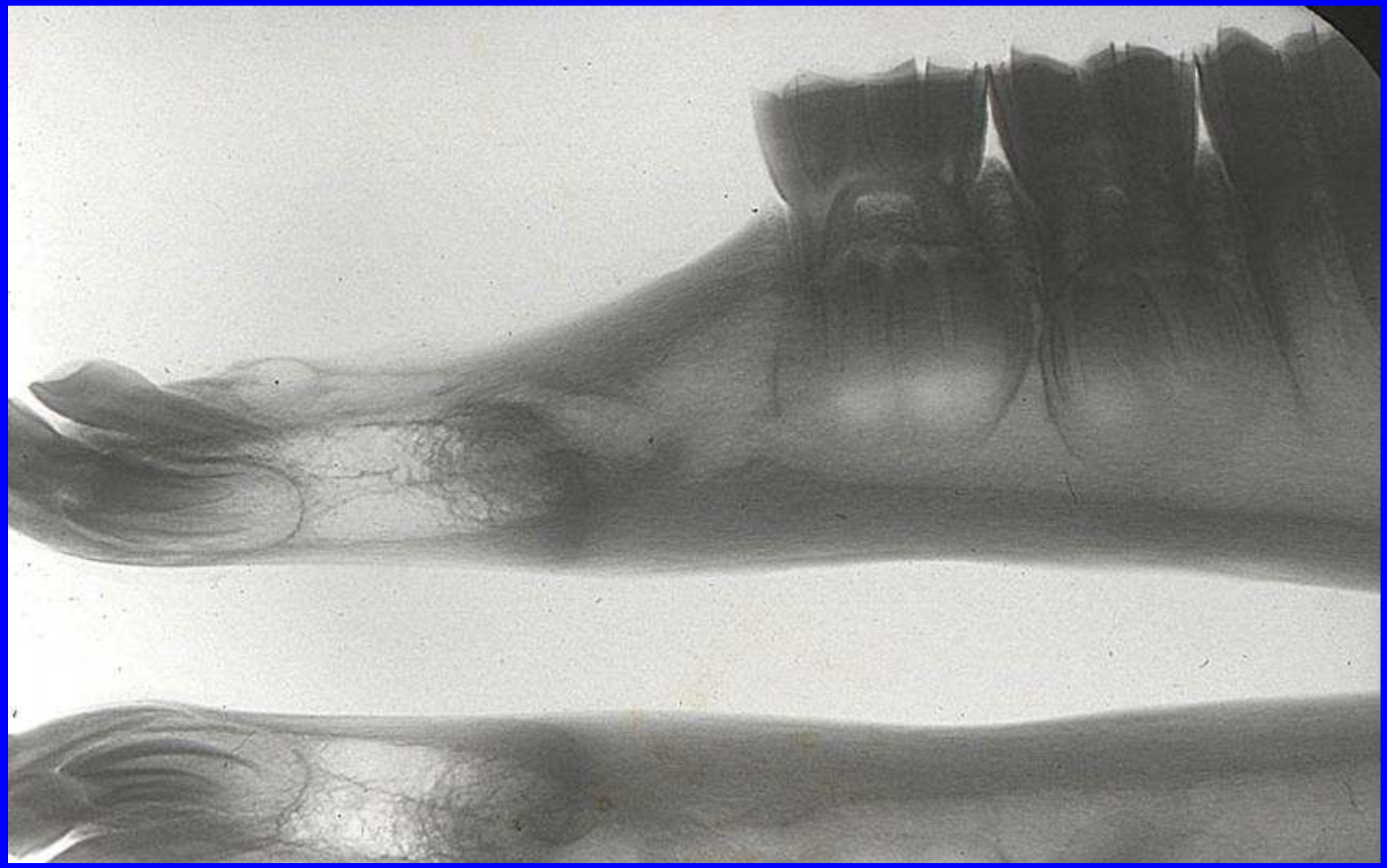
- **Is it due to excess PTH secretion ?**
  - *regulated by calcium via CaSR*
  - *hypocalcemia*
- **Is it due to excess PTH gene transcription ?**
  - *regulated by vitamin D*
  - *regulated by calcium*
  - *serum calcitriol ($1,25(OH)_2D$) levels*
  - *vitamin D nutrition (25(OH)D)*
  - *serum calcium concentration*

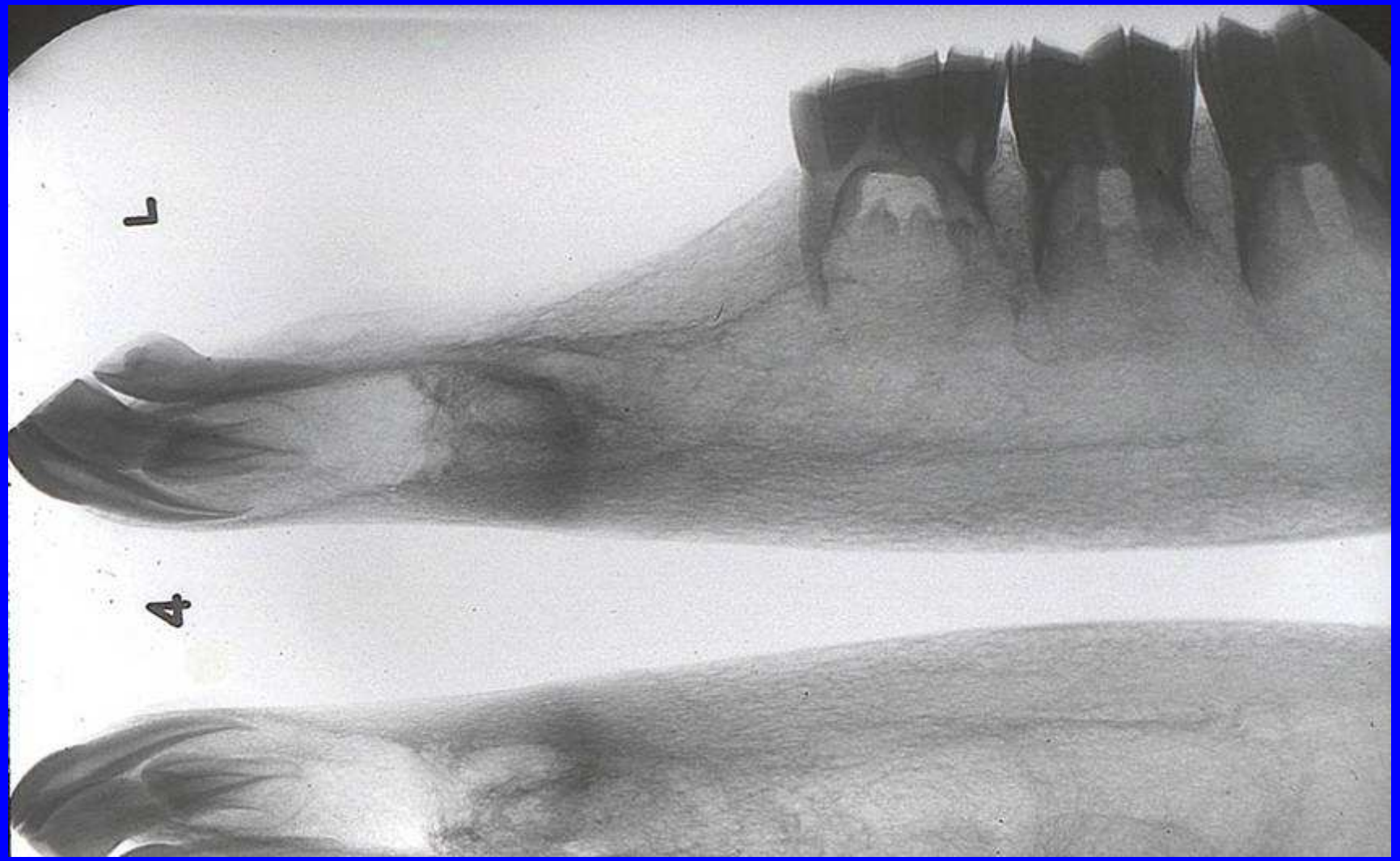
reversible

- **Is it due to refractory parathyroid gland enlargement from nodular hyperplasia ?**
  - *regulated by calcium via CaSR*
  - *triggered by phosphorus via TNFα and p21*

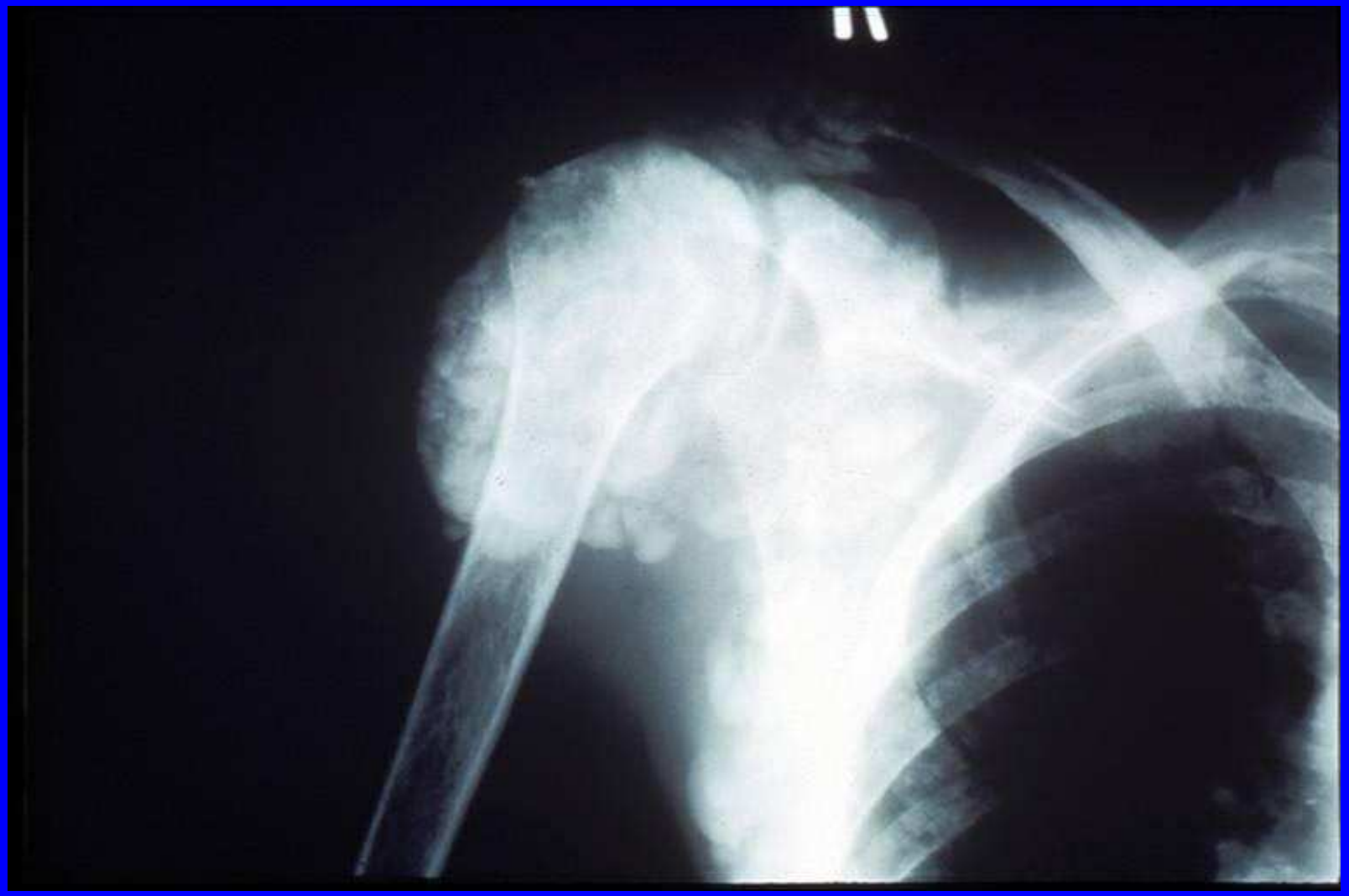
irreversible

- Vitamin D and active Vitamin D
- PTH and calcium sensing
- **Phosphate control**

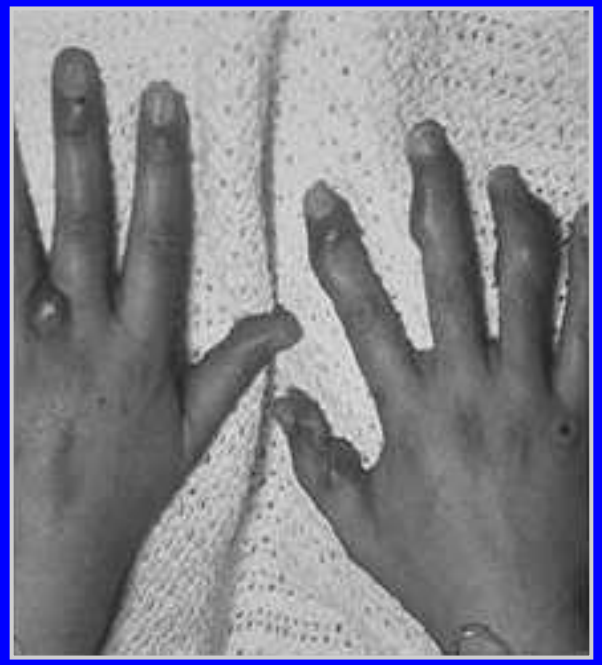



L
4

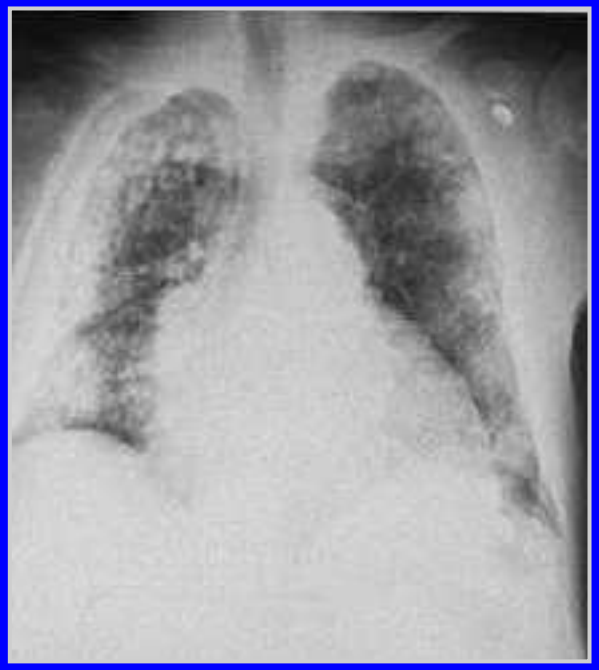
Periarticular calcification



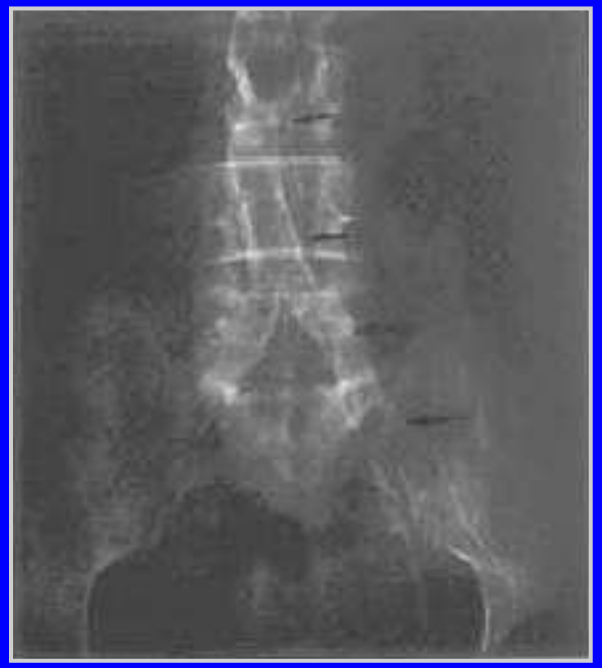
Types of calcification



Periarticular

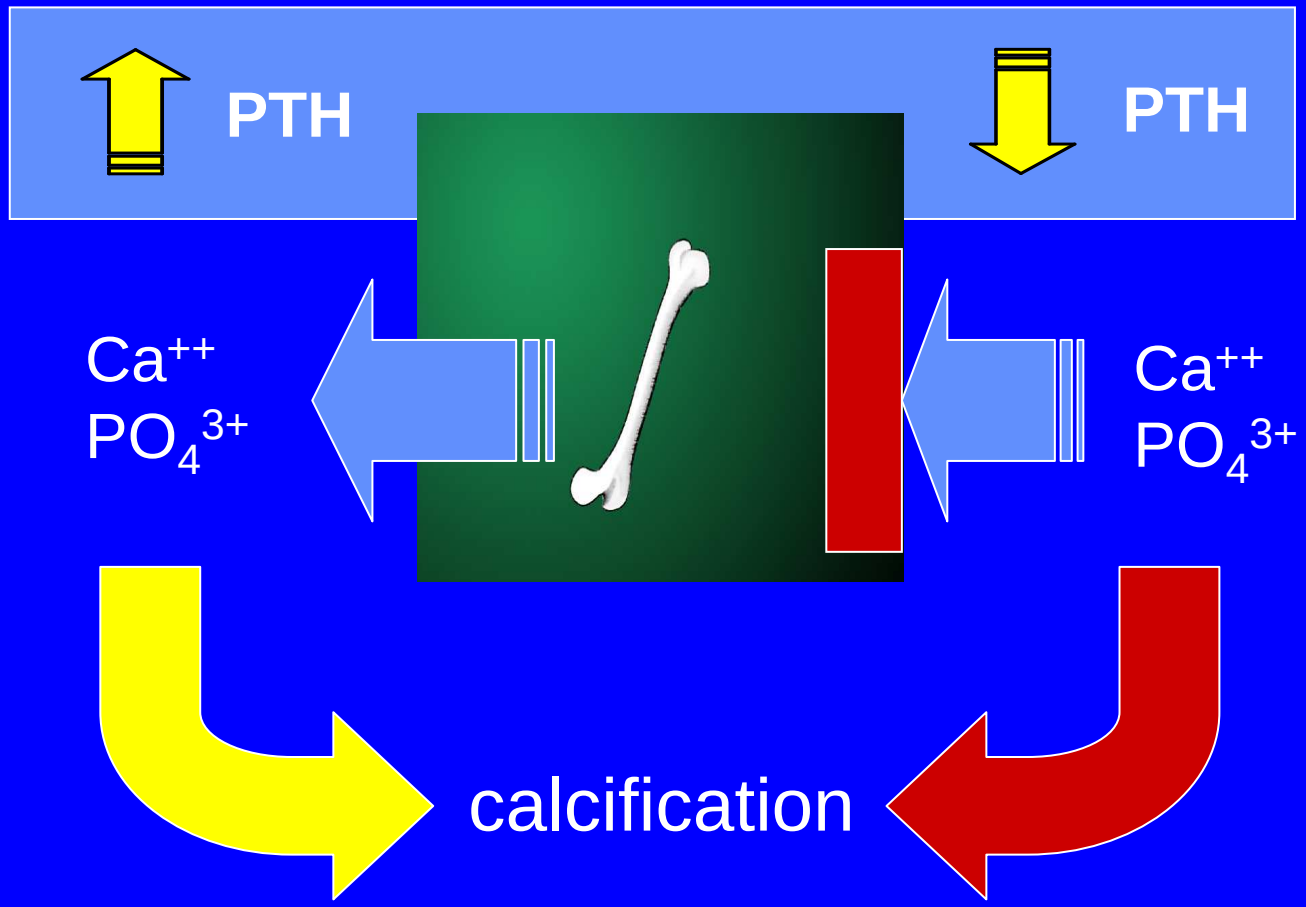


Visceral

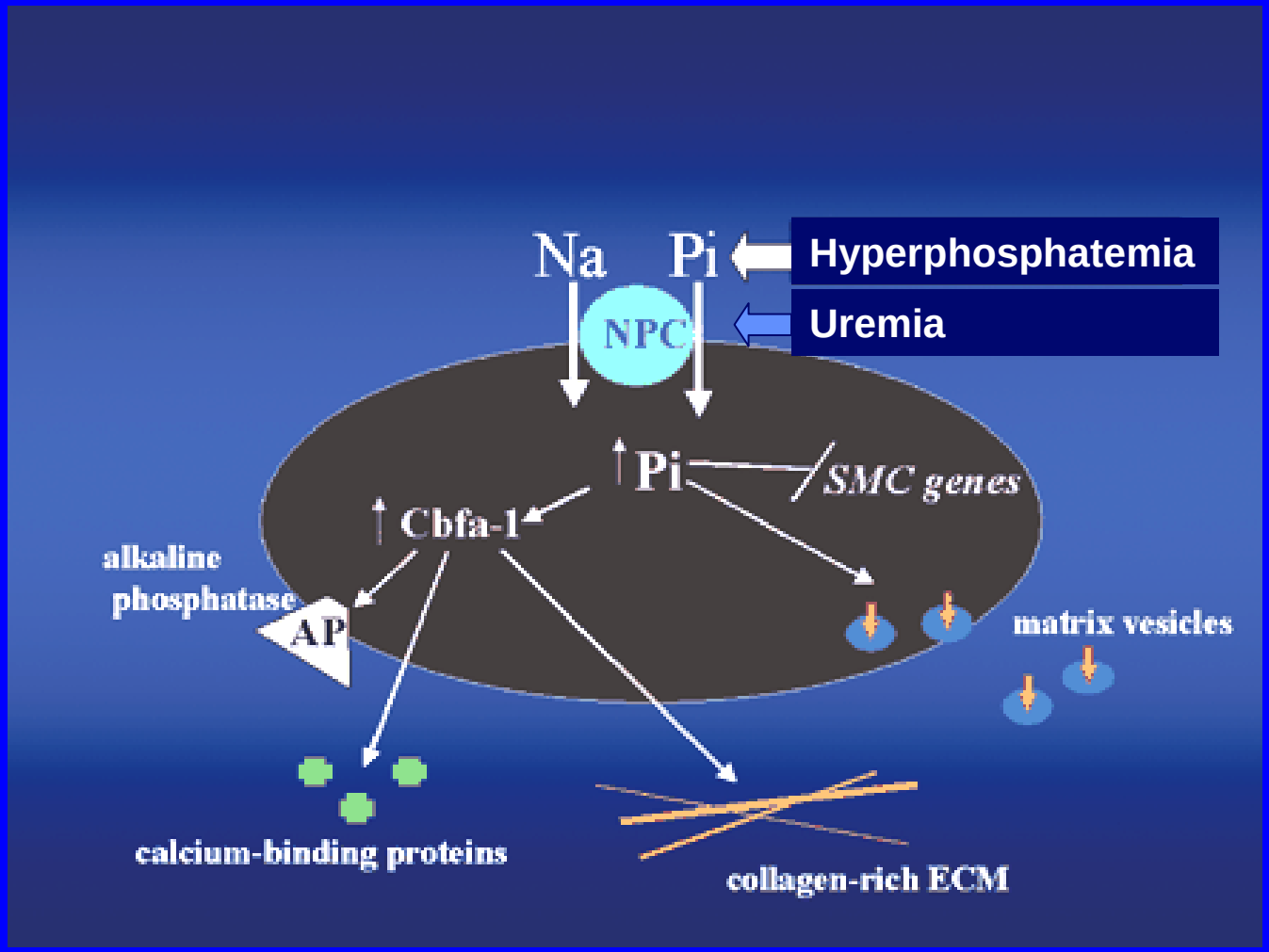


Vascular

Both high and low turnover bone disease favour calcification



Calcification active process: vascular smooth muscle cells into osteoblast-like cells



Giachelli, Am J Kidney Dis (2001);38: S34

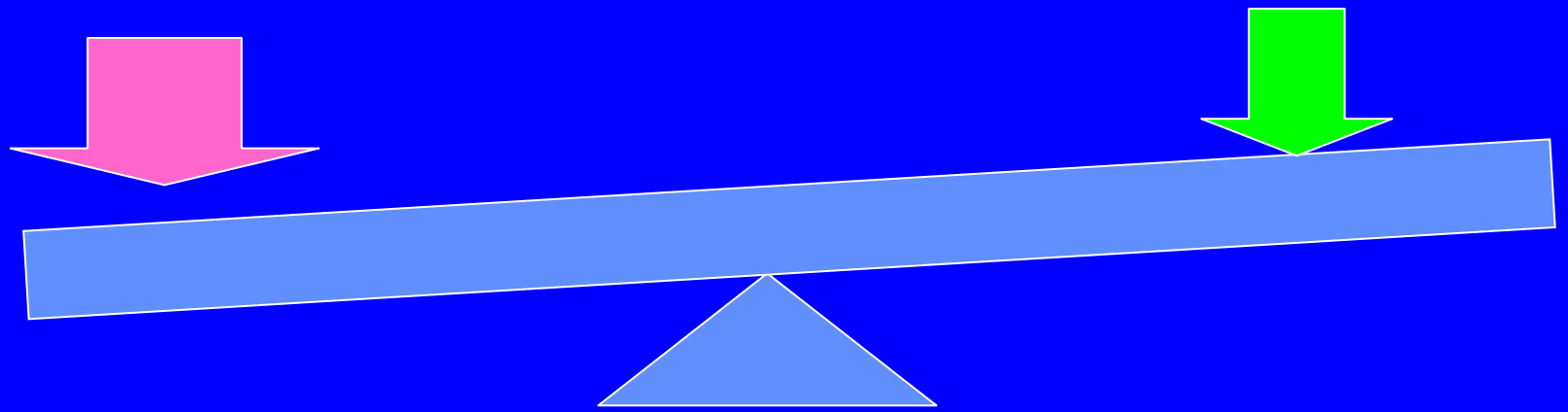
Calcification
Promotors ⇔ Inhibitors

Promotors

- ↑ phosphate, ↑ calcium
- ↑ Ca x P product
- ↑ vitamin D
- “uremic milieu”
- inflammation

Inhibitors

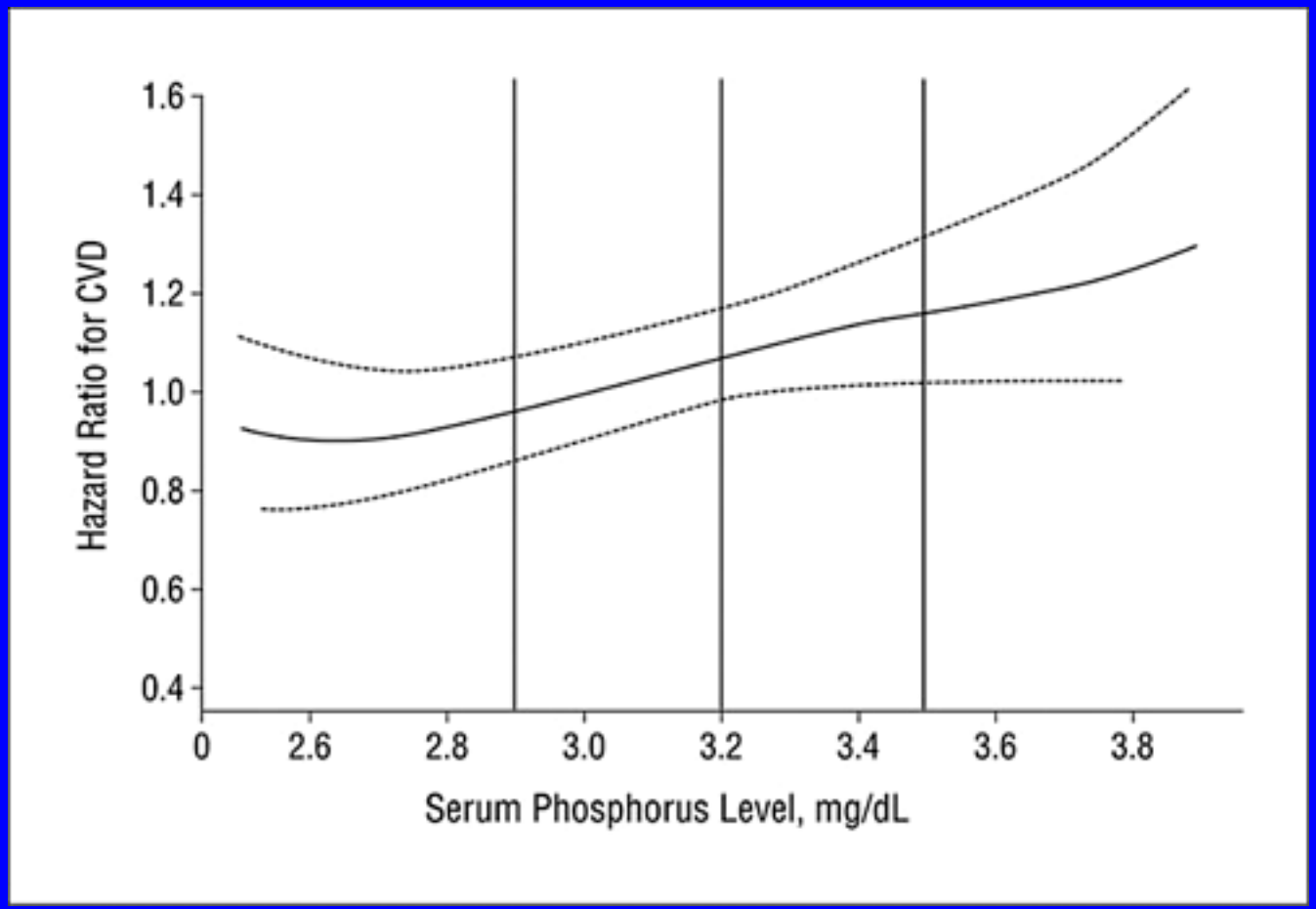
- systemic, e.g..
  - fetuin-A
- local, e.g..
  - matrix Gla protein
  - osteoprotegerin



Serum P increases concentration dependently cardiovascular risk in individuals without renal disease –

(Framingham study)

3368 offspring
mean age :
44 years
follow-up:
16 years



Dhingra, Arch.,Int.Med.(2007) 167:879

Relation between serum phosphate and all cause mortality in nonrenal patients

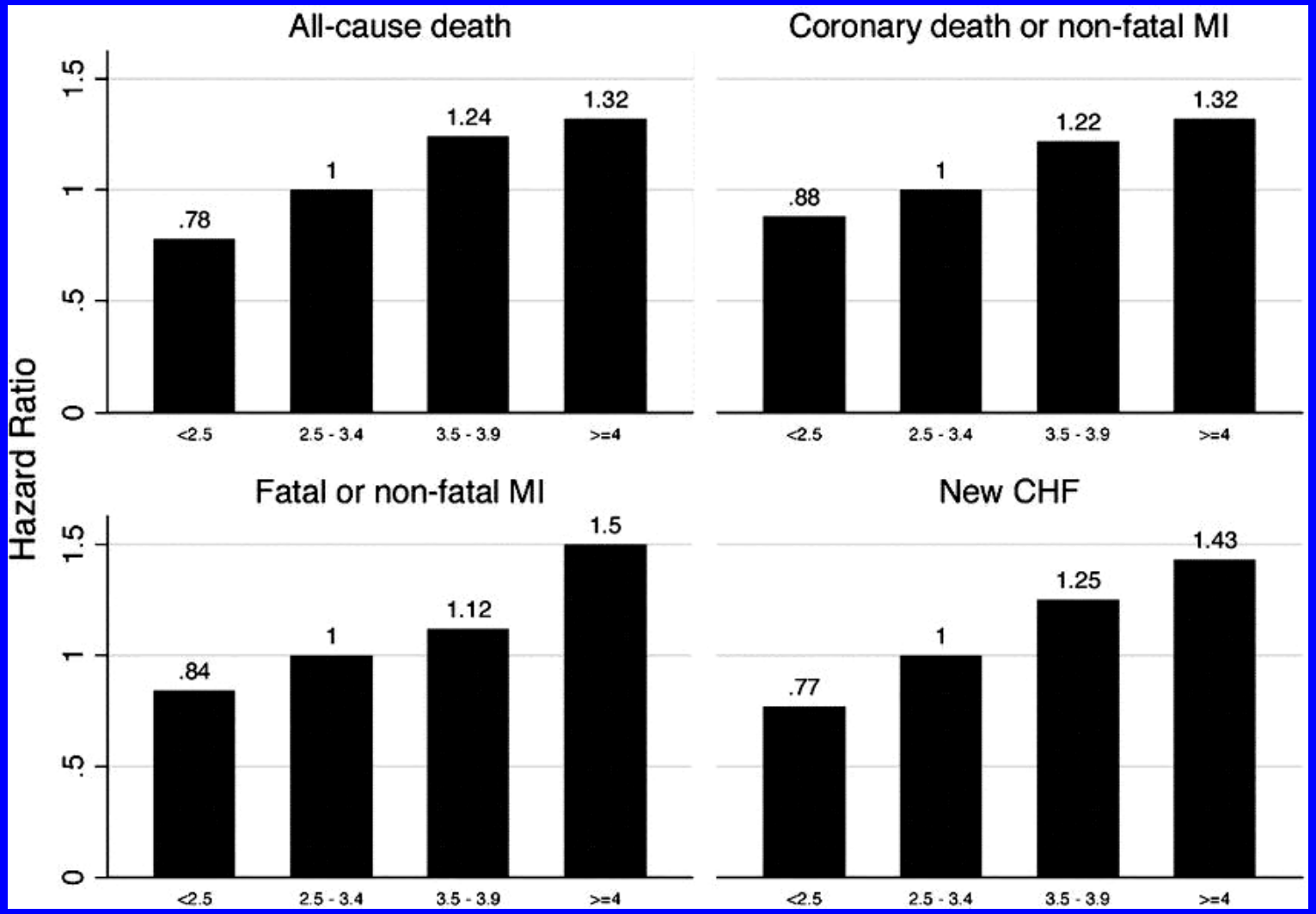
(CARE-study)

All-cause death				
<2.5 mg/dL	9 (6.9)	0.78	0.40–1.52	
2.5–3.4 mg/dL	229 (8.7)	1		0.01*
3.5–3.9 mg/dL	104 (10.0)	1.25	0.98–1.58	
≥4.0 mg/dL	33 (10.3)	1.42	0.97–2.07	
per 1 mg/dL		1.27	1.02–1.58	0.03

Tonelli, Circulation (2005)112:2627

Adjusted outcomes as a function of S-phosphate in nonrenal patients

causes of death



Tonelli, Circulation (2005)112:2627

Nephrol Dial Transplant (1999) 14: 2085–2087

Hyperphosphataemia—a silent killer of patients with renal failure?

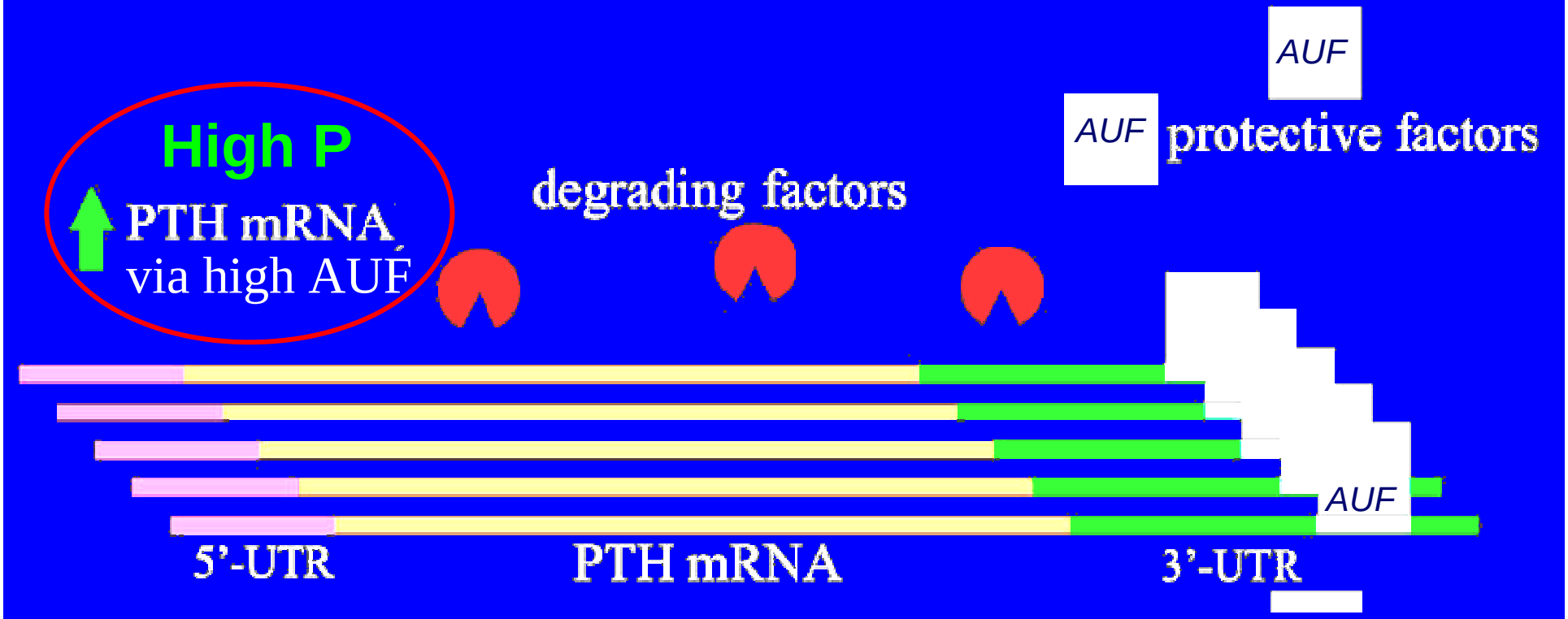
Kerstin Amann[1], Marie-Luise Gross[1], Gérard M. London[3] and Eberhard Ritz[2]

[1]Department of Pathology and [2]Department of Internal Medicine, Ruperto Carola University, Heidelberg, Germany and [3]Hôpital Manhes, Fleury Mérogis, France

Nephrol Dial Transplant (1999) 14: 2085

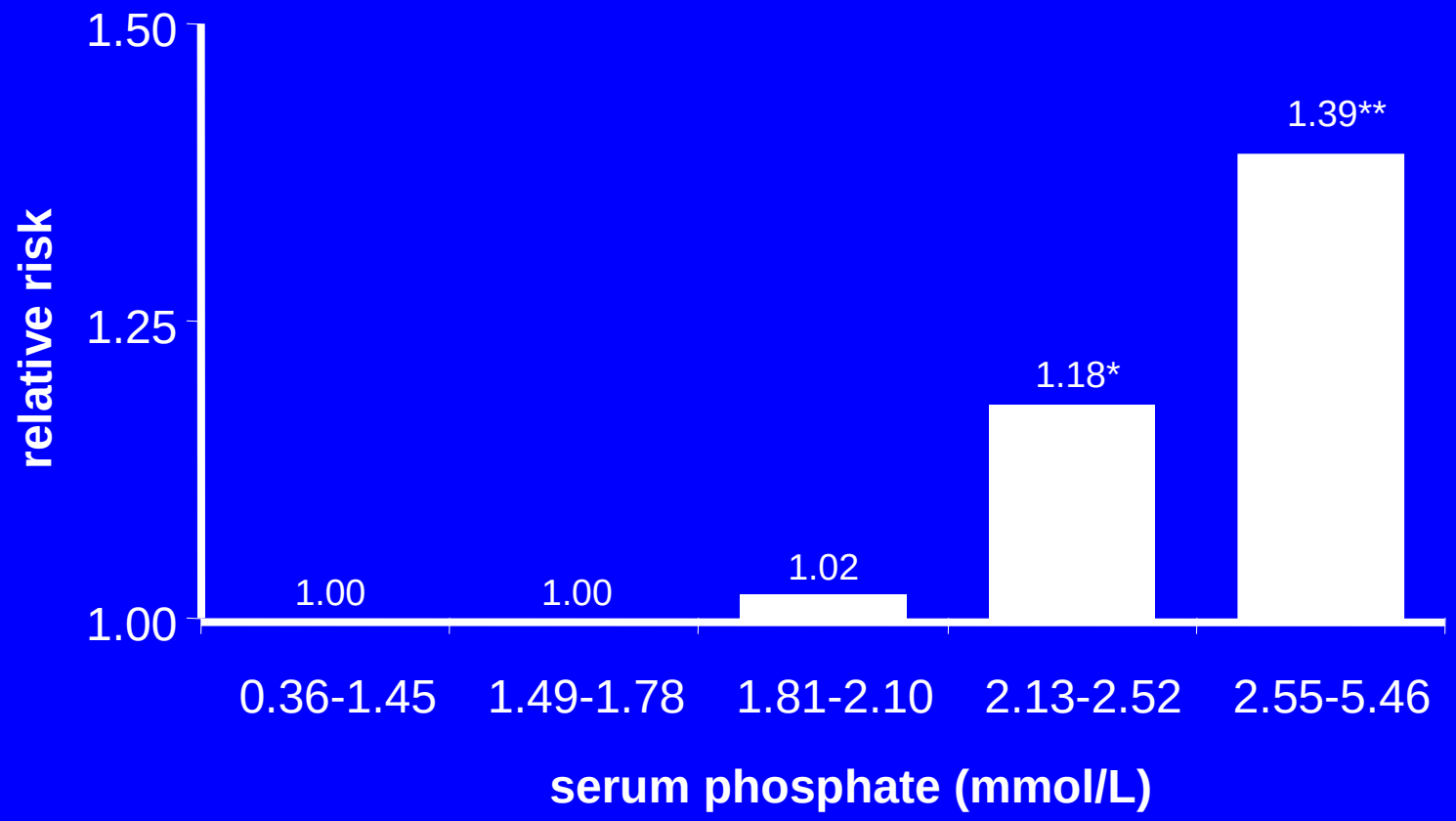
PTH mRNA –

stabilised by high P via greater availability of cytoplasmic protein AUF for binding to nontranslated 3'region



Yalcindag, JASN (1999) 10: 2562

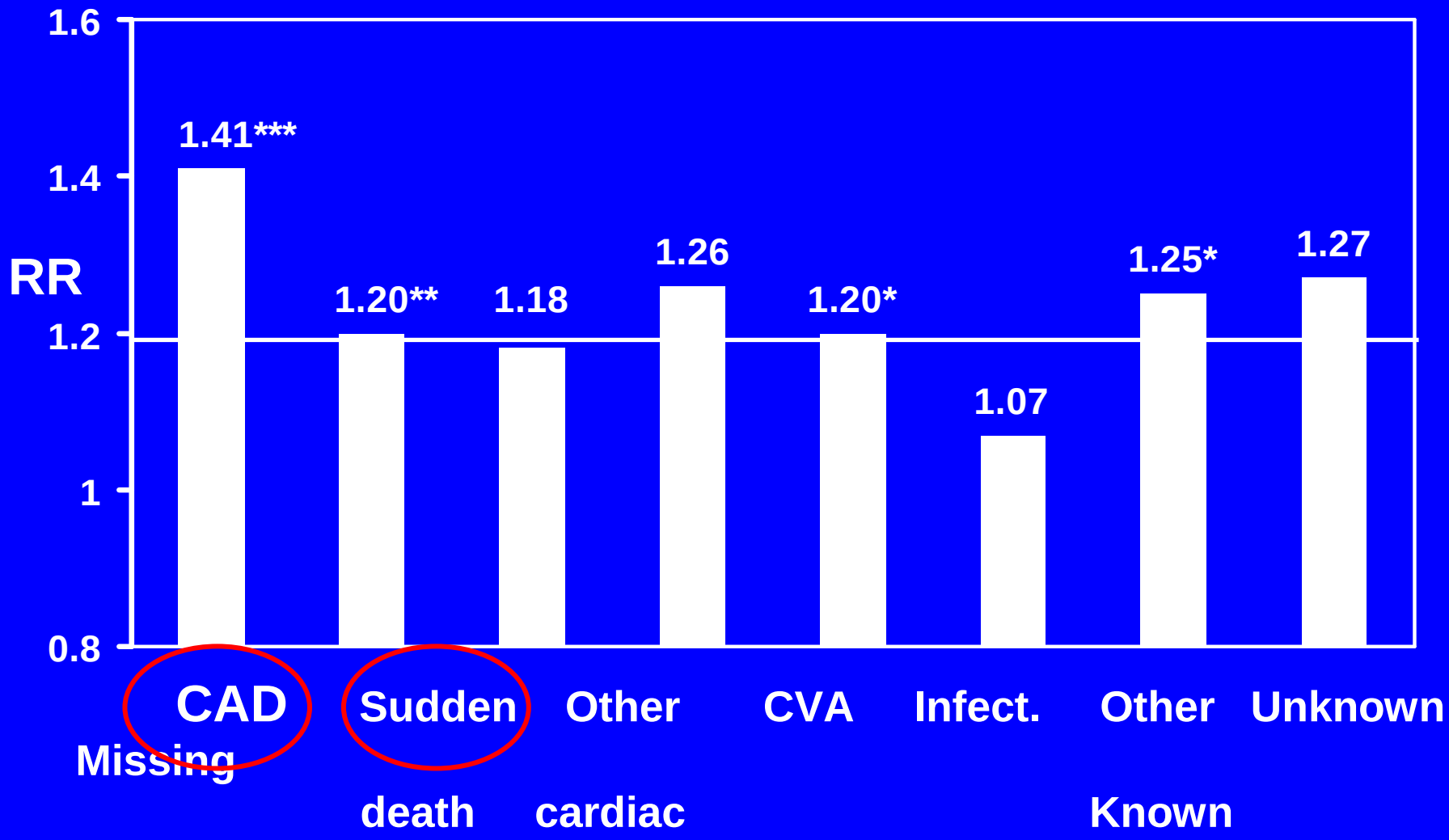
Serum phosphate and mortality in dialysed patients



Block . *Am J Kidney Dis.* 1998;31:607

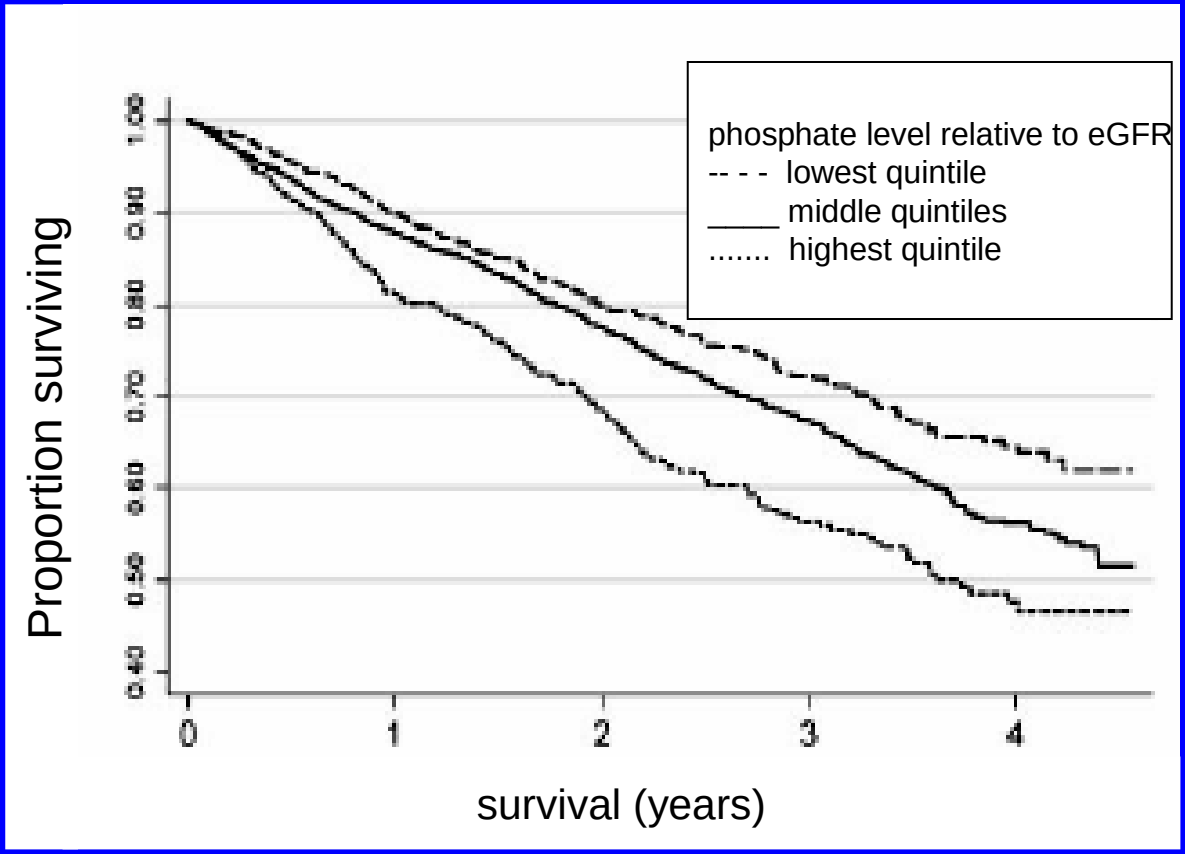
Causes of death in hemodialysed patients

PO_4 >6.5mg/dL vs 2.4-6.5mg/dL



Ganesh,J.Am.Soc.Nephrol. (2001) 12:2131

Serum phosphate and survival in predialysis patients with renal failure



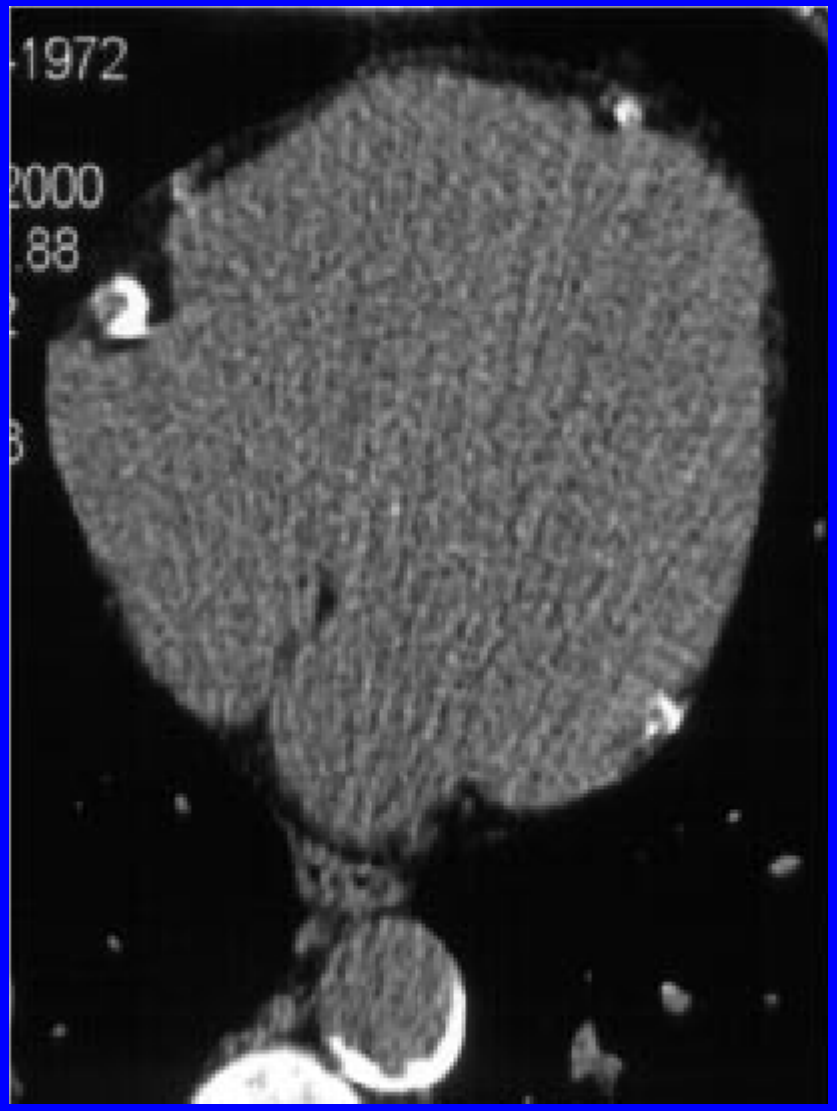
after adjustment;
serum phosphate > 3.5 mg/dl significantly increased risk of death

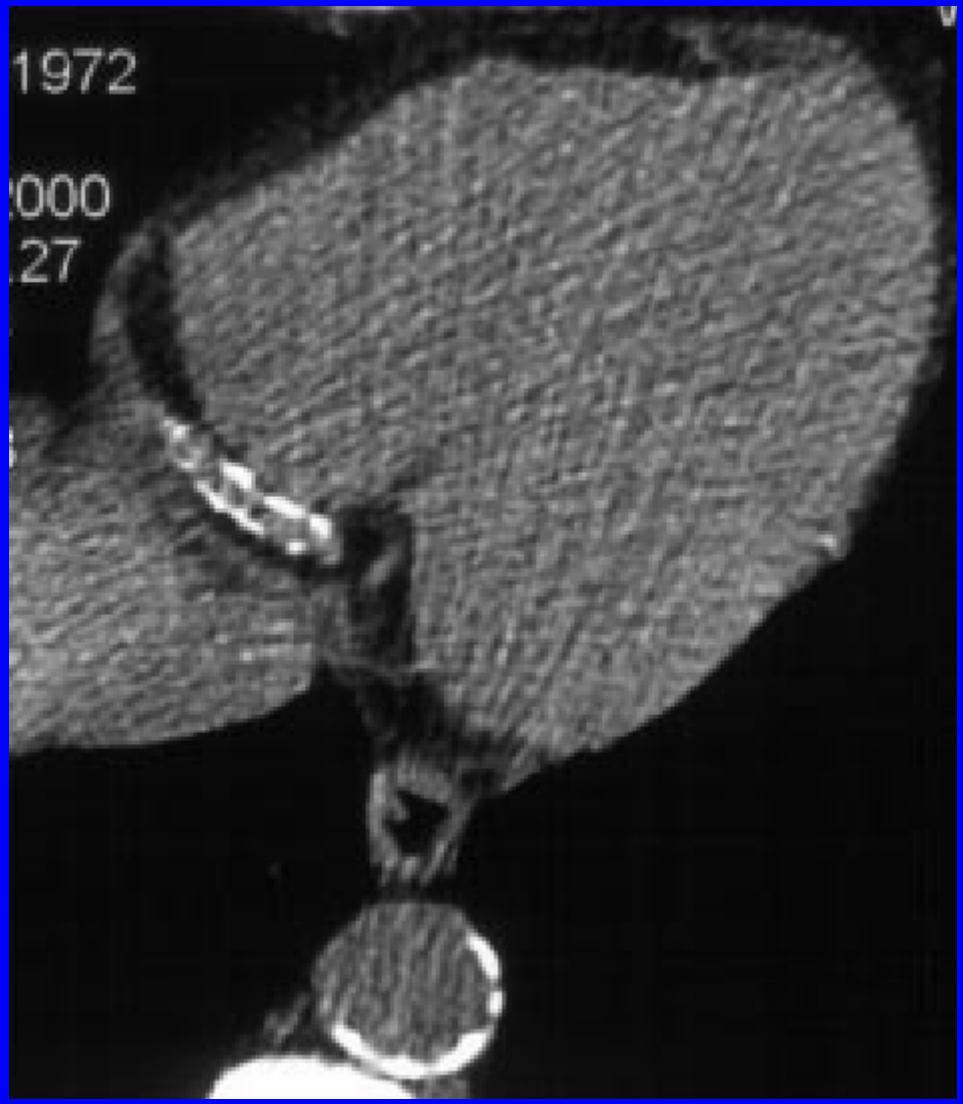
Kestenbaum, J.Am.Soc.Nephrol.(2005) 16:520

Coronary plaques in dialysed patients – more severe calcification

		no renal disease (n=27)	endstage renal disease (n=27)
type III	preatheroma	5	-
type IV	atheroma	9	2
type V	fibroatheroma	8	7
type VI	complicated plaque	-	-
type VII	calcified plaque	5	18

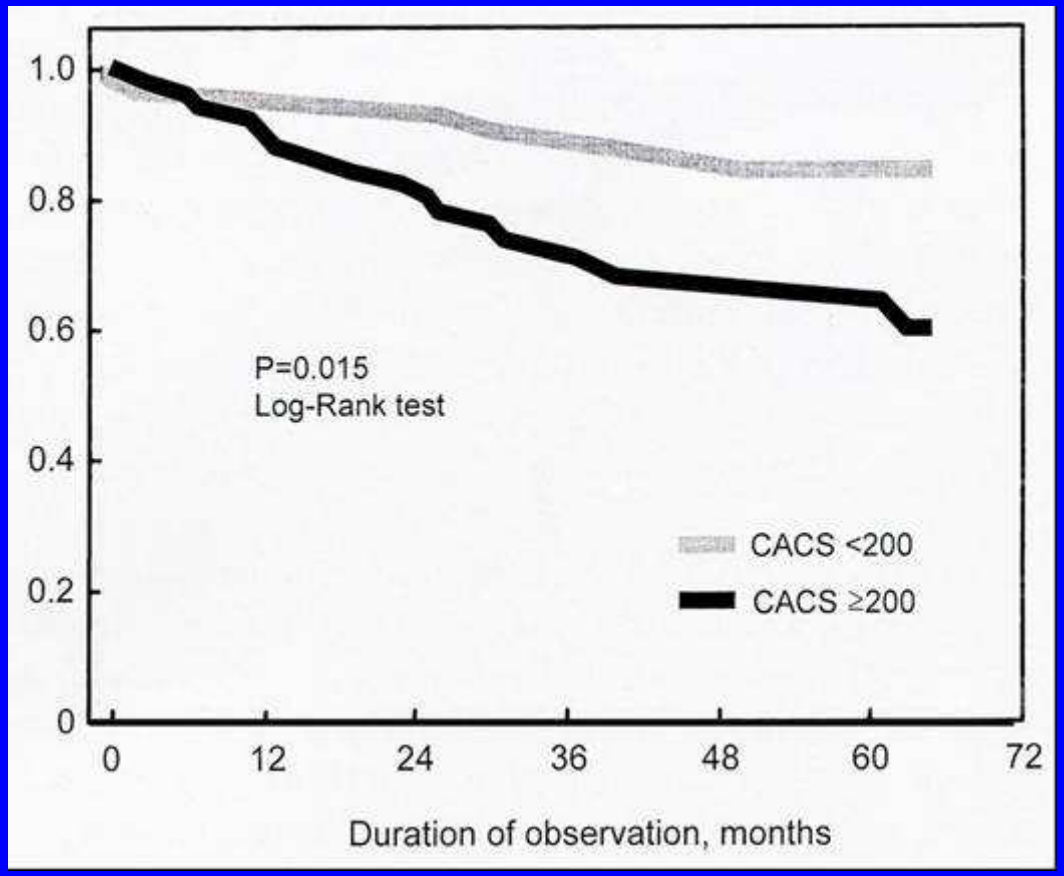
Schwarz, NDT (2000) 15: 218





Oh, Circulation (2002) 106: 100

Coronary calcium score (CACS) – predictor of survival in HD - patients

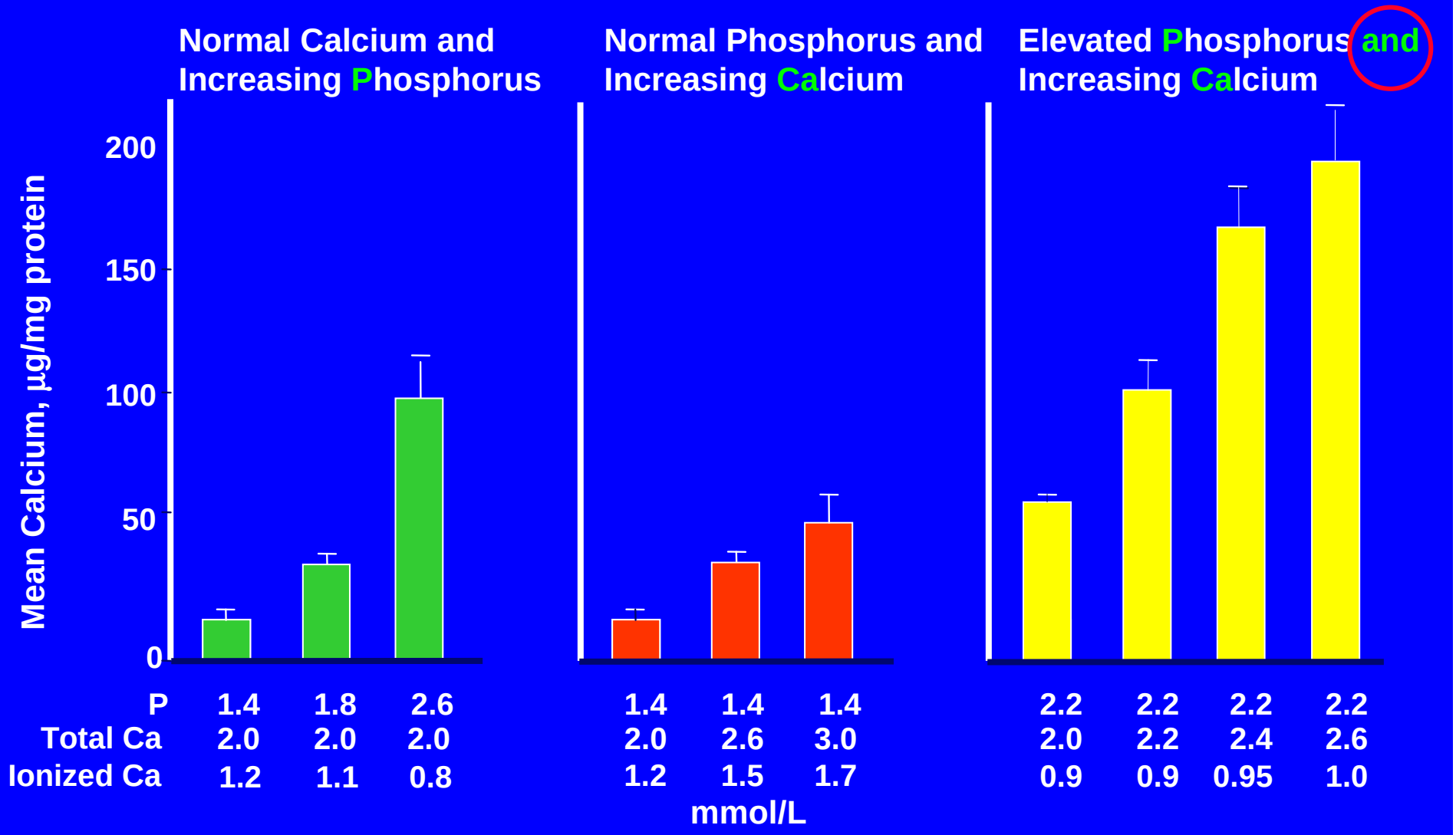


Matsuoka (2004), Clin Exp Nephrol 8: 54

"My bones are getting softer, but my arteries are getting harder so it balances out."

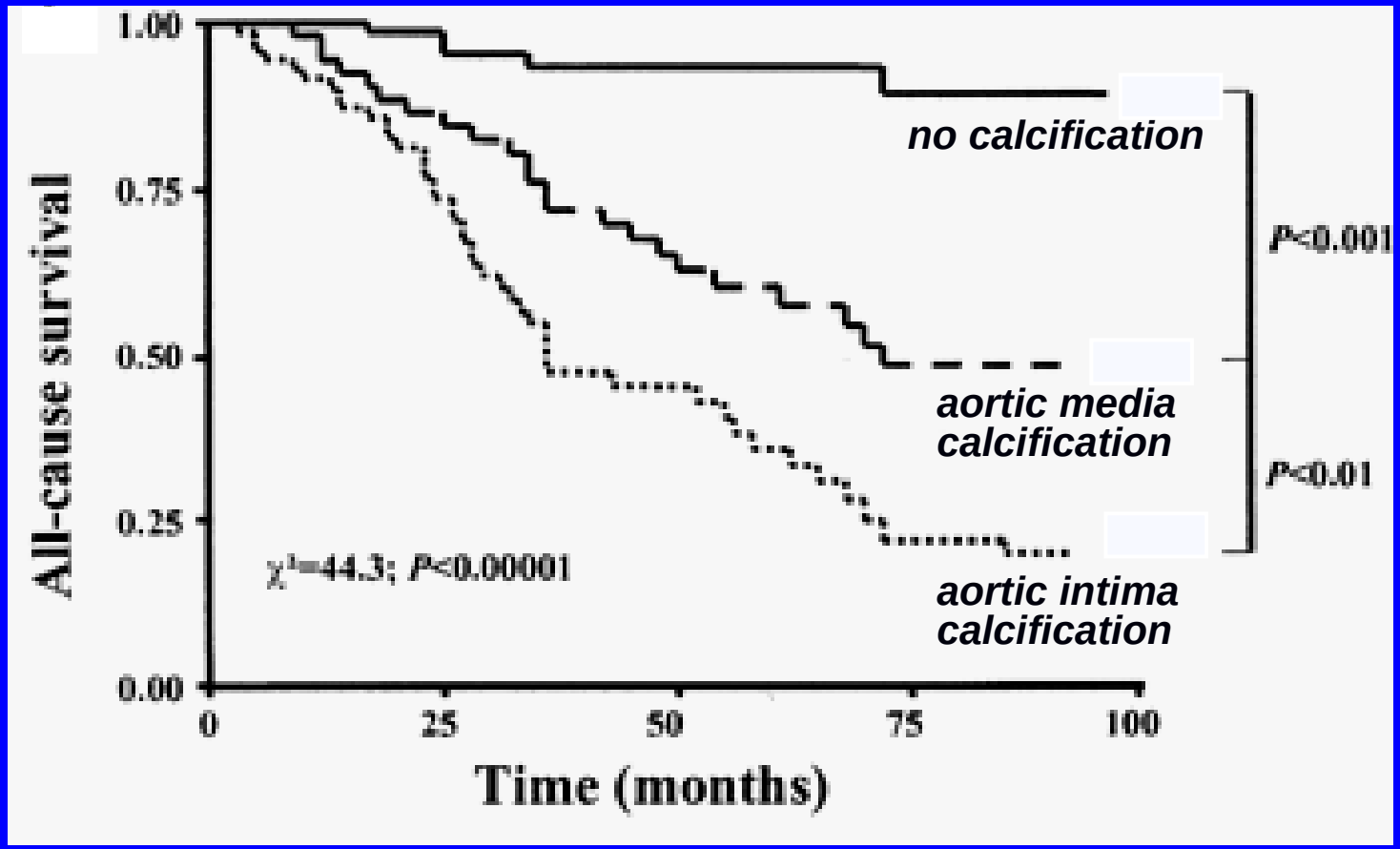
High serum calcium and/or phosphorus

⇨ *vascular calcification*



Yang H, Kidney Int. (2004)66:2293

Calcification of aortic media and intima increases mortality in dialysis patients



London, Nephrol Dial Transplant 2003;18:1731

Hyperphosphatemia control –

1. lowering of dietary phosphate intake

High phosphate of cow milk

- *growth velocity (and P requirement)*

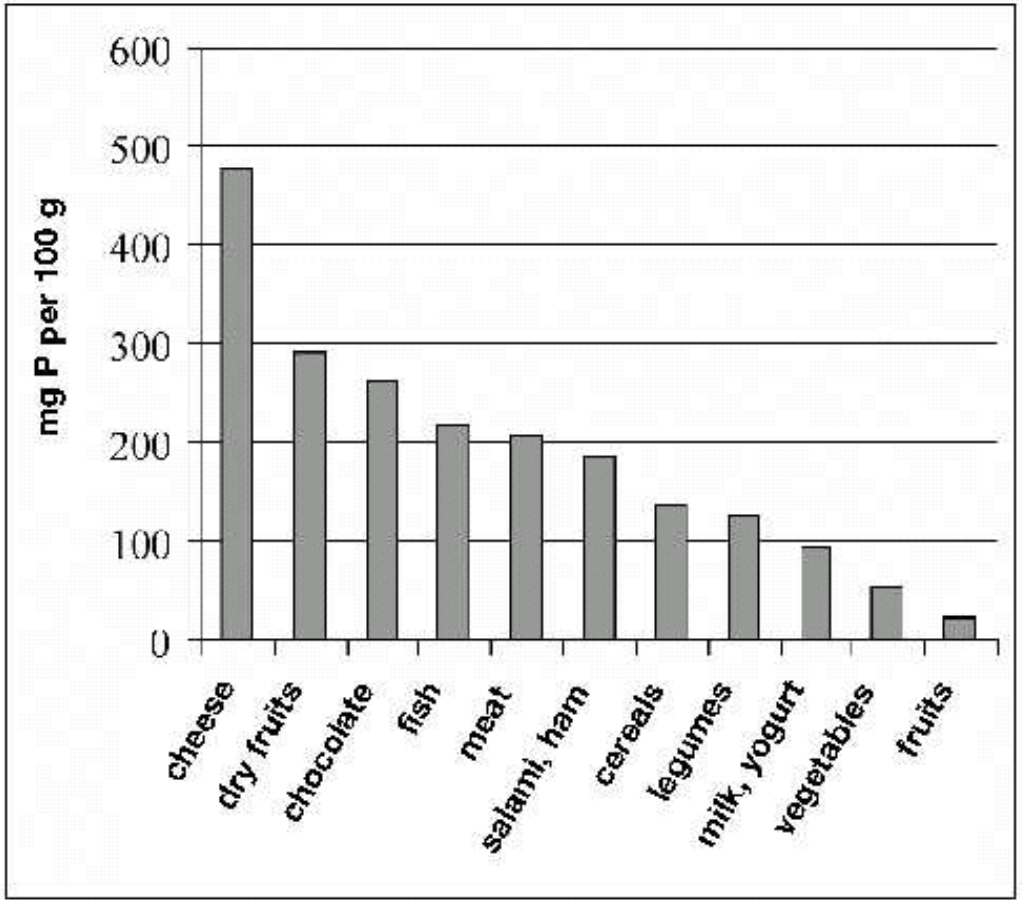
  calf > baby
- *in (premature) babies : unmodified cow milk*

  →

  hypocalcemia

Wharton, Lancet (2003) 362:1389

Phosphate content of common food items



(mg P per 100 g of food)

sausages →
addition of phosphate
(hygroscopic!)

Cupisti,
J NEPHROL 2003; 16: 29

Hyperphosphatemia control –

2. removal of P by dialysis

- *Increase the length of the dialysis session*

Charra,Kidney Int (1992) 41: 1286

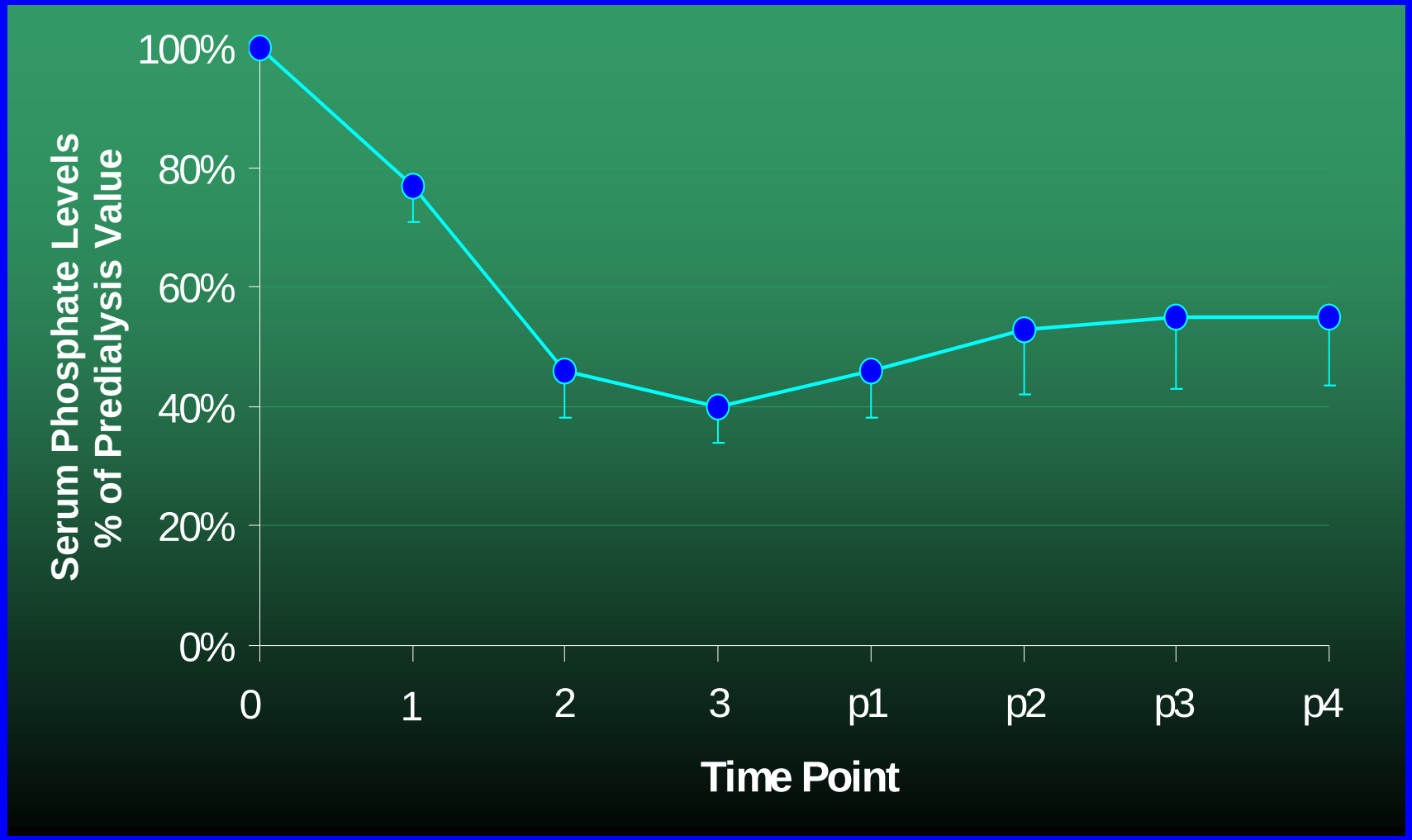
- *Increase the frequency of the dialysis sessions*
  – daily dialysis

Buoncristiani, Kidney Int 1988; 33 (Suppl 24): s137

- nocturnal haemodialysis (even hypophosphatemia !)

Mucsi, Kidney Int (1998) 53: 1399

Limitation –
Time course of serum phosphate concentration during and after one HD session



Zuchelli, Int J Art Org(1987) 10, 173

Why is removal of phosphate by conventional dialysis so unsatisfactory ?
What are alternative (or complementary) strategies?

- *P dialysable,*
  but slow equilibration between intra- / extra-cellular pool
- *relatively limited removal by high efficiency dialysis*
- *extremely effective removal by long, slow dialysis (hypophosphatemia !)*

Mucsi, Kidn.Intern.(1998) 53:1399

⇨ **removal by conventional dialysis not sufficient, P binders required**

Hyperphosphatemia control –

3. inhibition of intestinal binding or transport of P

- **Aluminium salts**
- **Ca carbonate**
- **Sevelamer (RenagelR)**
- **Lanthanum carbonate (FosrenolR)**

} *intestinal binding*

- **Nicotinamide**

} *inhlbition of active intestinal transport*

- **[Cinacalcet (MimparaR)]**

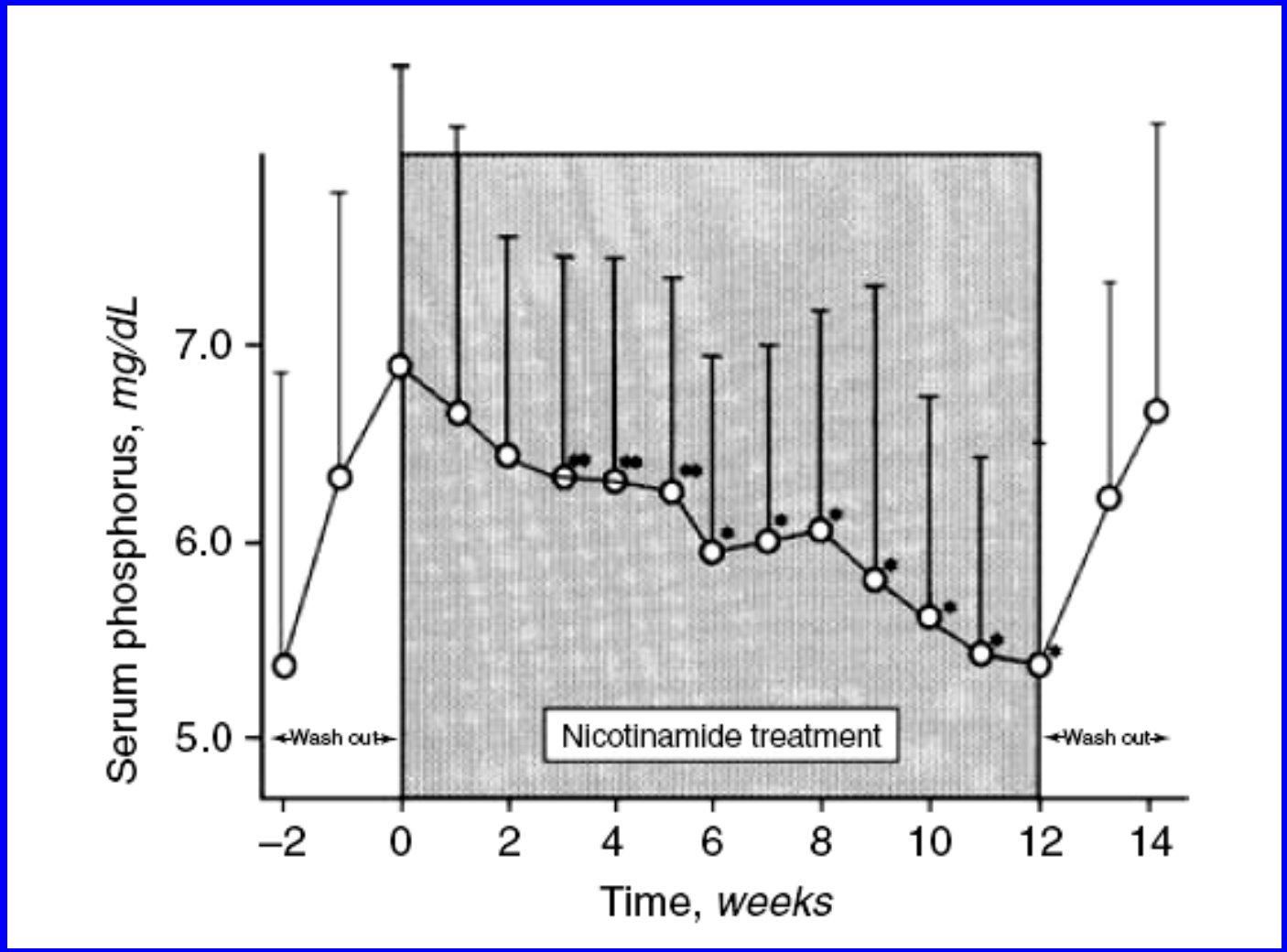
} *unknown*

“If a lot of cures are suggested for a disease it usually indicates that the disease is uncurable.”

Cherry Orchard, Tschechow

Changes of serum-P in hemodialysed patients ingesting nicotinamide

(inhibition of active intestinal transport)

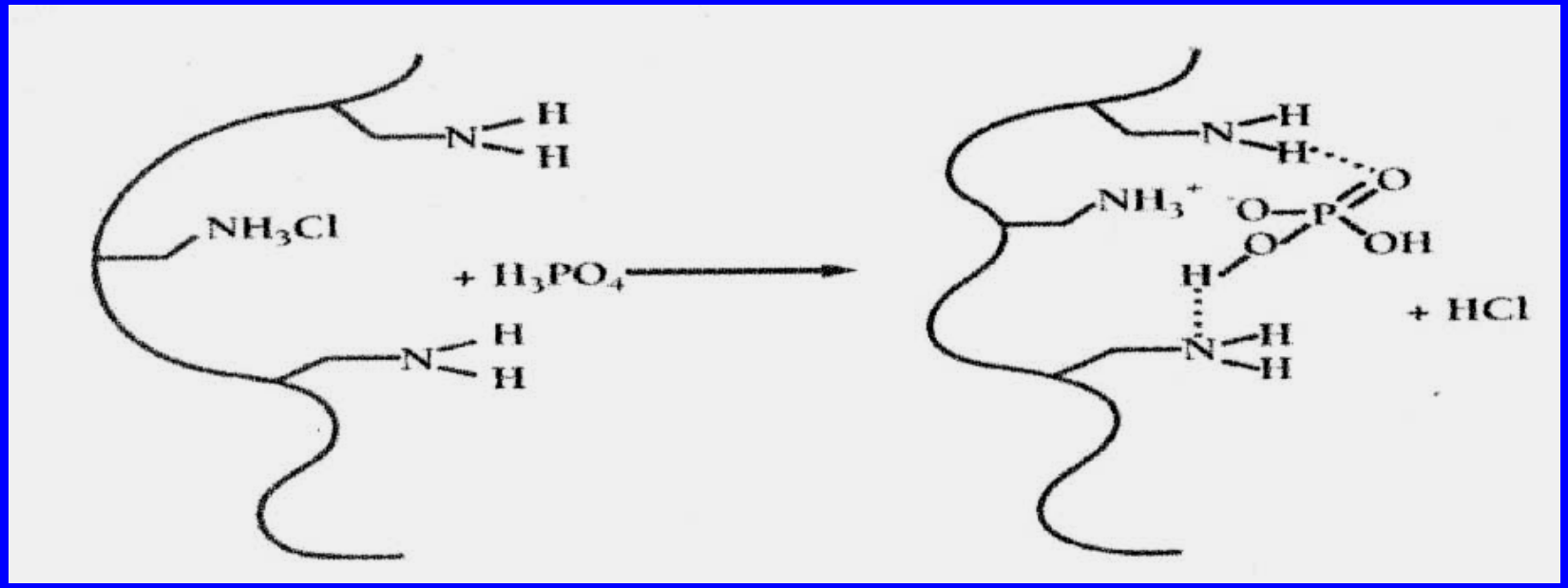


Takahashi,Kidn.Intern.(2004) 65:1099

Hyperphosphatemia control

Sevelamer

- Not absorbed in the GI tract



- Does not interfere with absorption of other drugs

Less increase of coronary calcification with Sevelamer than with Ca-carbonate

Sevelamer (n=23)	Calcium Carbonate (n=23)
Agatston score baseline	
1488 ± 1820	**1259 ± 1848**
increase within 2 years	
142 ± 829	**637 ± 898**
median + 20	***median + 83***

Asmus, Nephrol.Dial.Tranplant.(2005) 20:1653

Sevelamer and cardiac endpoints – is it phosphate lowering or lipid lowering ?

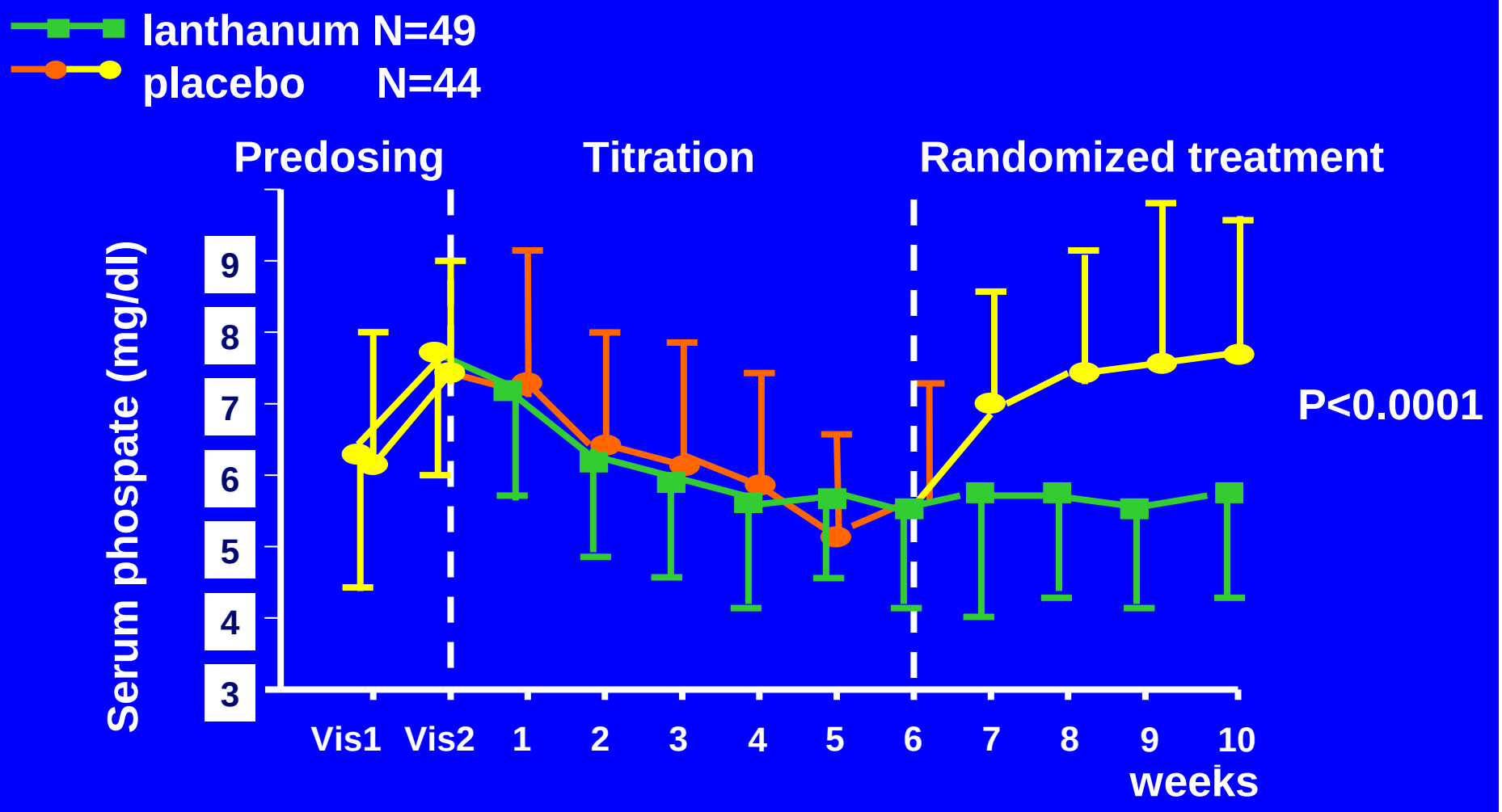
I don't care what colour the cat is –

so long as it catches mice

Deng Hsiao Ping
1904-1997

Lanthanum-based oral binders -

HD patients, randomized, double-blind placebo-controlled study



Joy, Am J Kid Dis (2003) 96

Lanthanum-based oral binders

Multicentre clinical study

- *98 patients*
  - *49 lanthanum carbonate up to 3750 mg/day (mean dose 1250)*
  - *49 calcium carbonate up to 9000 mg/day (mean dose 2000)*

- *well tolerated*
- *comparable side effects (53% vs 47%)*
- *lower incidence of hypercalcemia*
- *comparable phosphataemia control*
- *no aluminium-like toxic effects on the bone*

D'Haese, Kidney Int (2003) 63: 73

Hyperphosphatemia control -

Lanthanum-based oral binders

- *The long-term safety of lanthanum agents in humans needs to be accurately monitored in further phase III studies and throughout the post-marketing period*

Locatelli, Drugs (2003) 6: 688

- Vitamin D and active Vitamin D
- PTH and calcium sensing
- Phosphate control
- **Calcium balance and dialysate calcium**
- **Outlook**

Ca-carbonate vs Sevelamer –
more hypoparathyroidism, more bone loss

TREAT-TO-GOAL

6.5g Sevelamer vs 3.9g Ca carbonate

Ca carbonate : PTH ↓ 200→138 pg/ml

thoracic vertebral bone ↓

Raggi, J.Bone Miner.Res.(2005) 20:764

Ca carbonate : PTH ↓

more hypercalcemic episodes

loss of trabecular bone density

Asmus, Nephrol.Dial.Transplant. (2005) 20:1653

- **Dialysate Calcium concentration**

  avoid 1.75 mmol/L

  1.5 mmol/L

  1.25 mmol/L in adynamic bone disease

  - ionized Ca^{++} ↓

  - hypercalcemia episodes ↓

  - increase in PTH (4-fold)

  - bone specific AP ↑

  Fujimori, Clin.Nephrol.(2007) 67: 20

- **Calcium per os**

  K-DOQI guidelines

  dietary calcium and calcium containing P-binders

  < 2000 mg/day

Genesis of secondary hyperparathyroidism

the classical trio

- ***Ca^{++} ↓***
- ***P ↑***
- ***active vitamin D ↓***

now a quartet ?

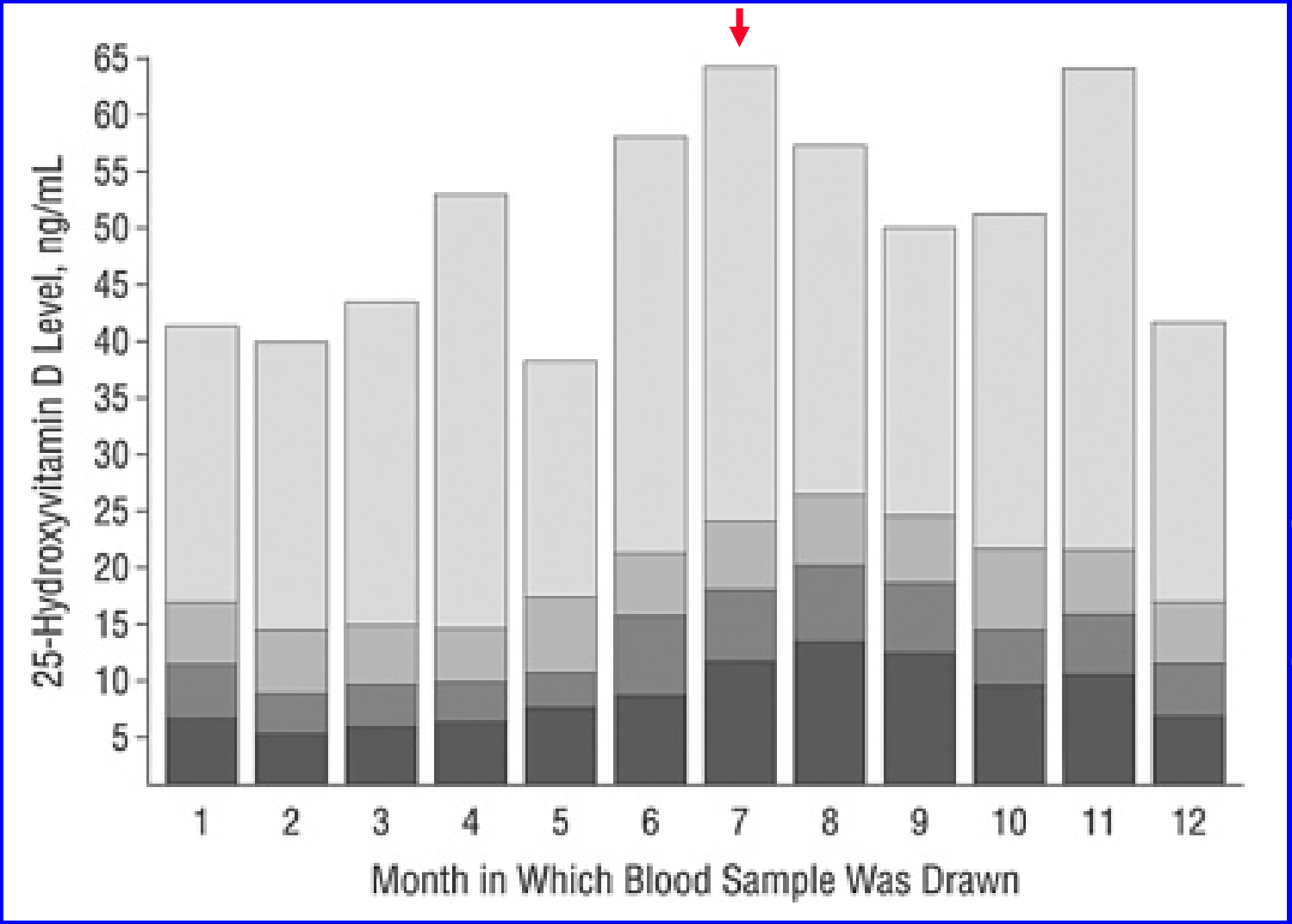
- ***Ca^{++} ↓***
- ***P ↑***
- ***active vitamin D ↓***
- ***FGF23 ↑***

⇨***we have to rewrite the textbooks and probably face new interventions***


Thank you for your attention

Changes of 25(OH)D concentrations throughout the year according to monthly quartiles

Ludwigshafen (LURIC) study, coronary patients



Dobnig, Arch.Int.Med.(2008) 168: 1340