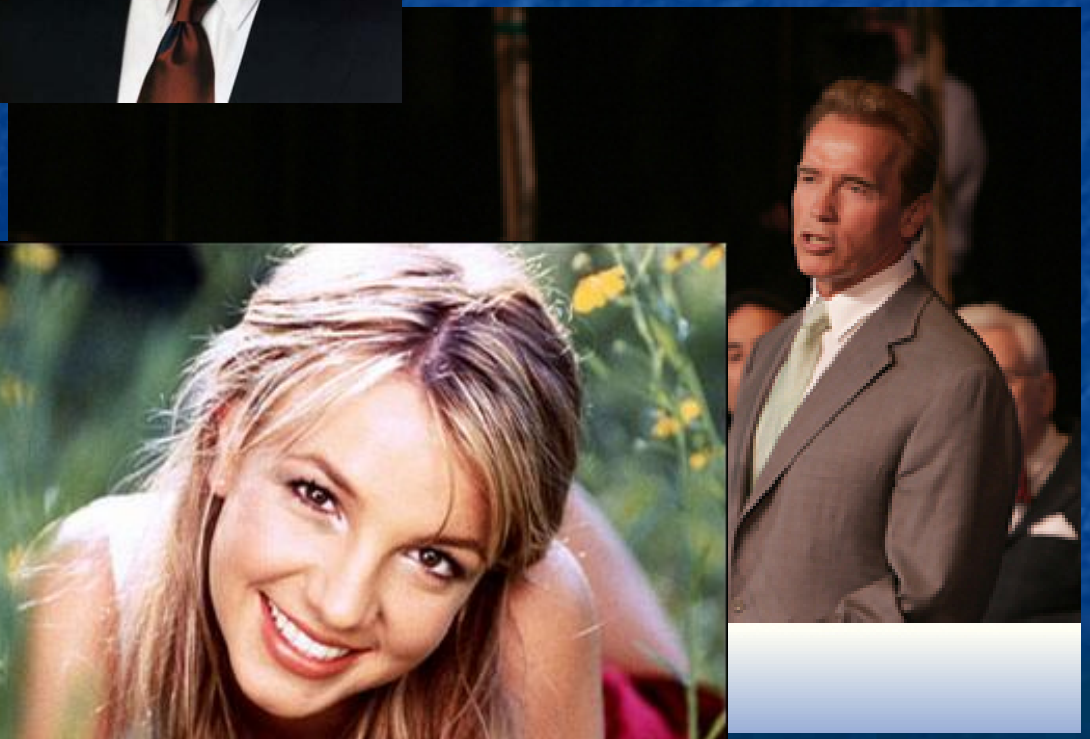
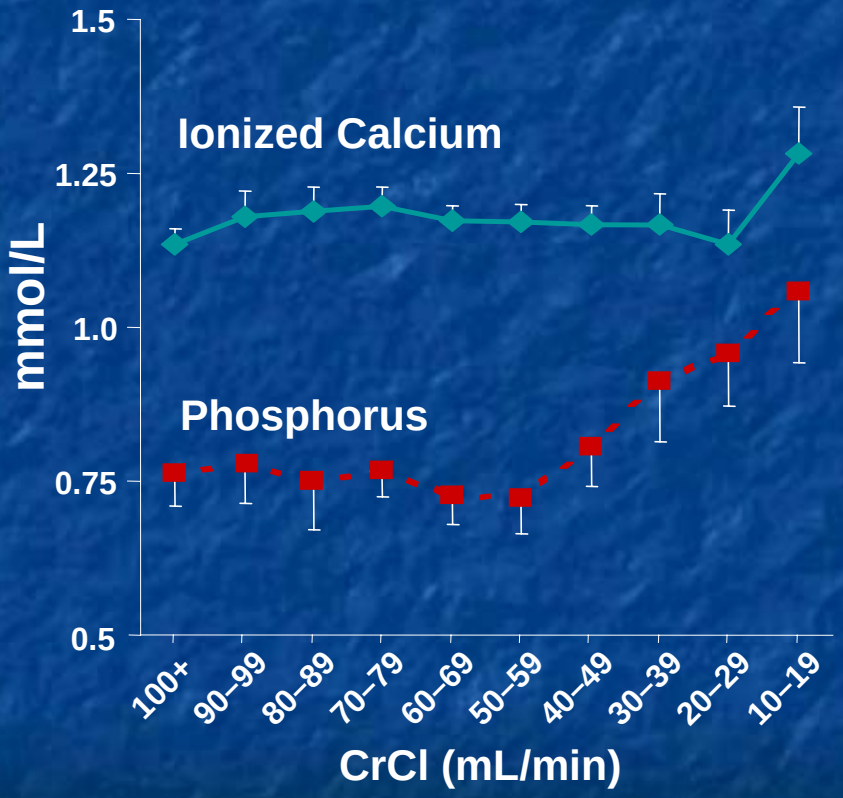
Mineral Metabolism in ESRD

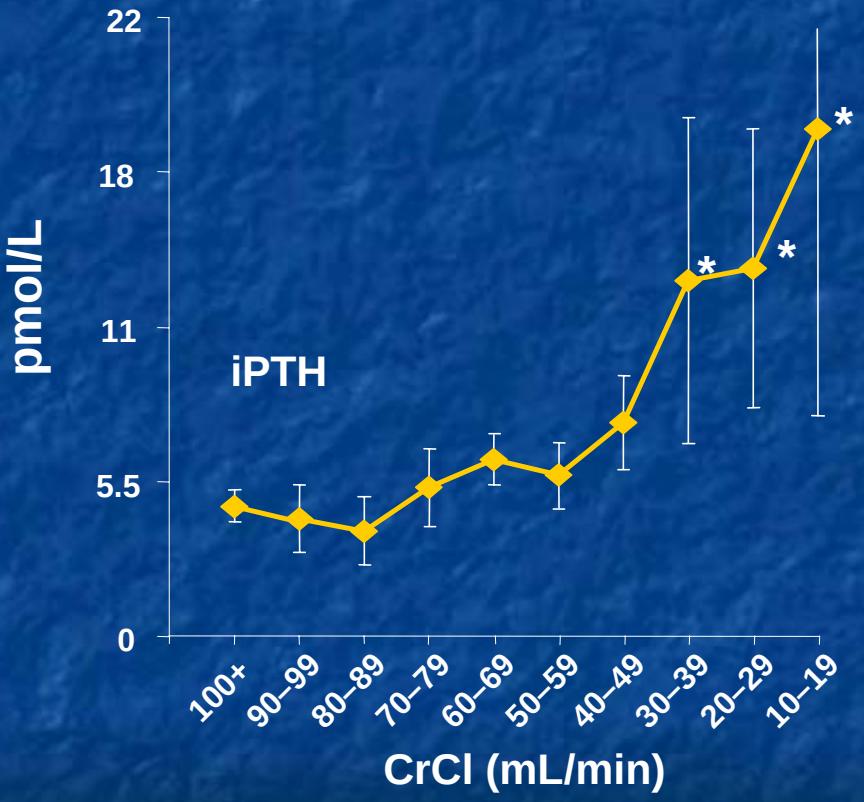
THE GOOD, THE BAD AND THE

Dr. Gordon Wong
The Credit Valley Hospital
May 12, 2007



As Kidney Function Declines, Secondary HPT Develops

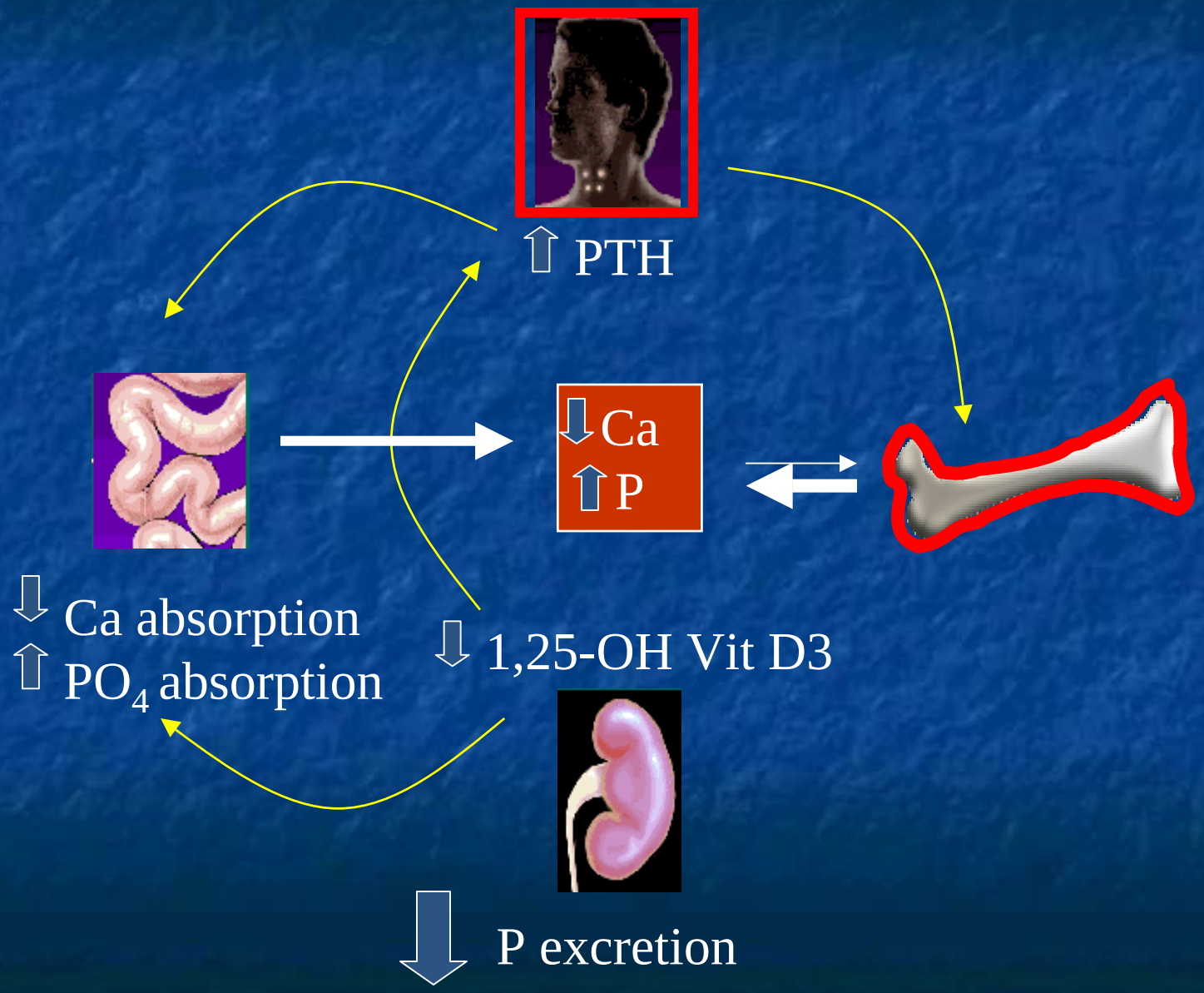




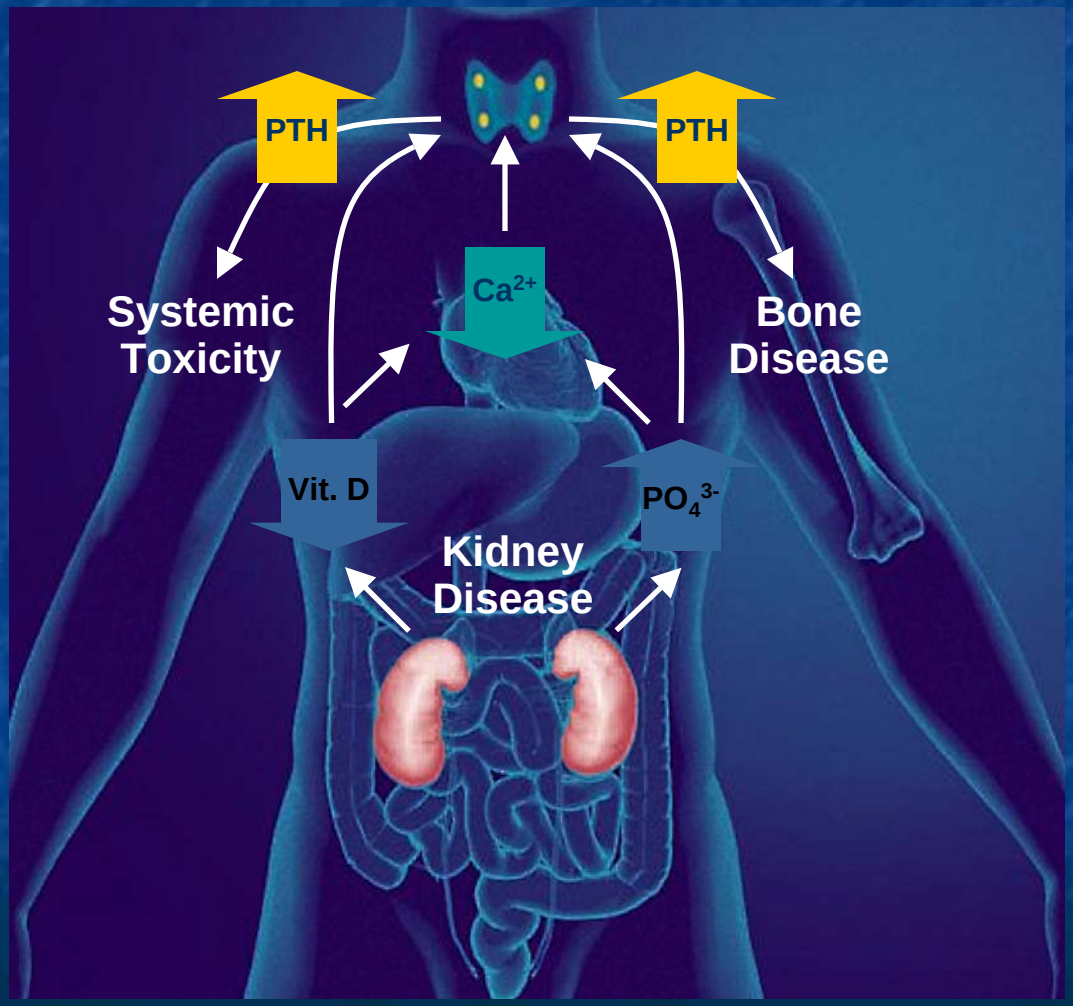
*p<0.05, compared to CrCl ≥ 50 mL/min

Martinez I et al. *Am J Kidney Dis* 1997;29:496-502.

Renal insufficiency:



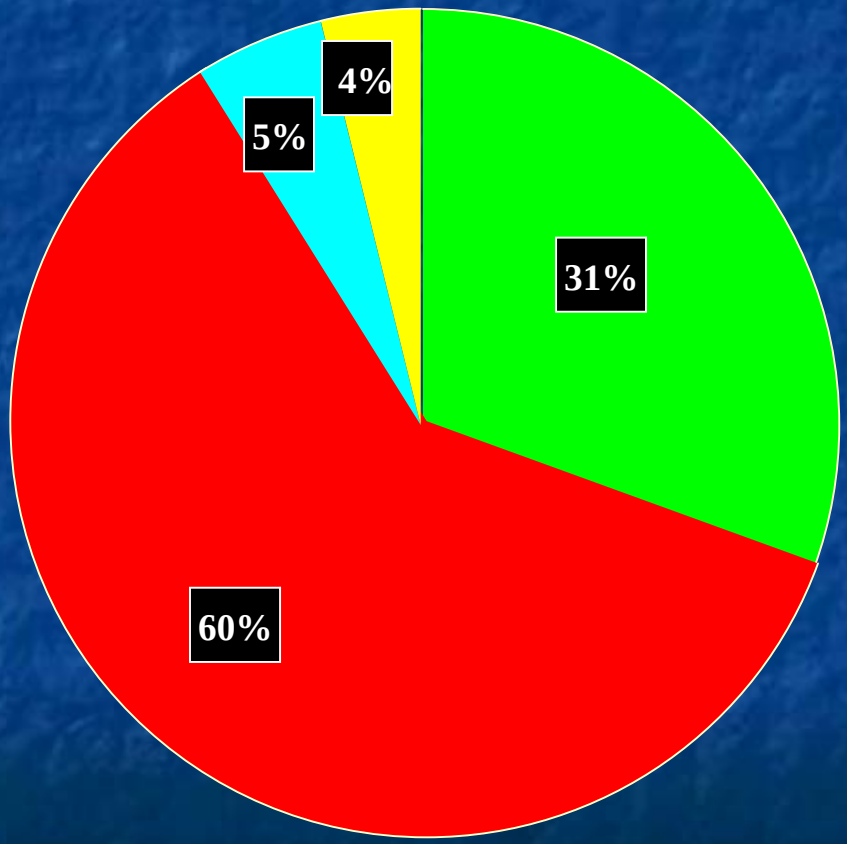
Pathophysiology of Secondary HPT in CKD



Adapted from Skorecki K et al. In: *Harrison's Principles of Internal Medicine*. 15th ed. 2002:1551-1562.

Renal Bone Disease: Histology Peritoneal Dialysis Patients (n=142: **Canada**)

- Hyperparathyroidism
  - HIGH TURNOVER
- Adynamic
  - LOW TURNOVER
- Osteomalacia
- Mixed
  - hyperparathyroidism
  - osteomalacia
- Normal



Sherrard DJ *et al*; Kidney Int 1993;43:436

Renal Bone Disease: Histology Hemodialysis Patients (n=117:**Canada**)

- Hyperparathyroidism
  - HIGH TURNOVER
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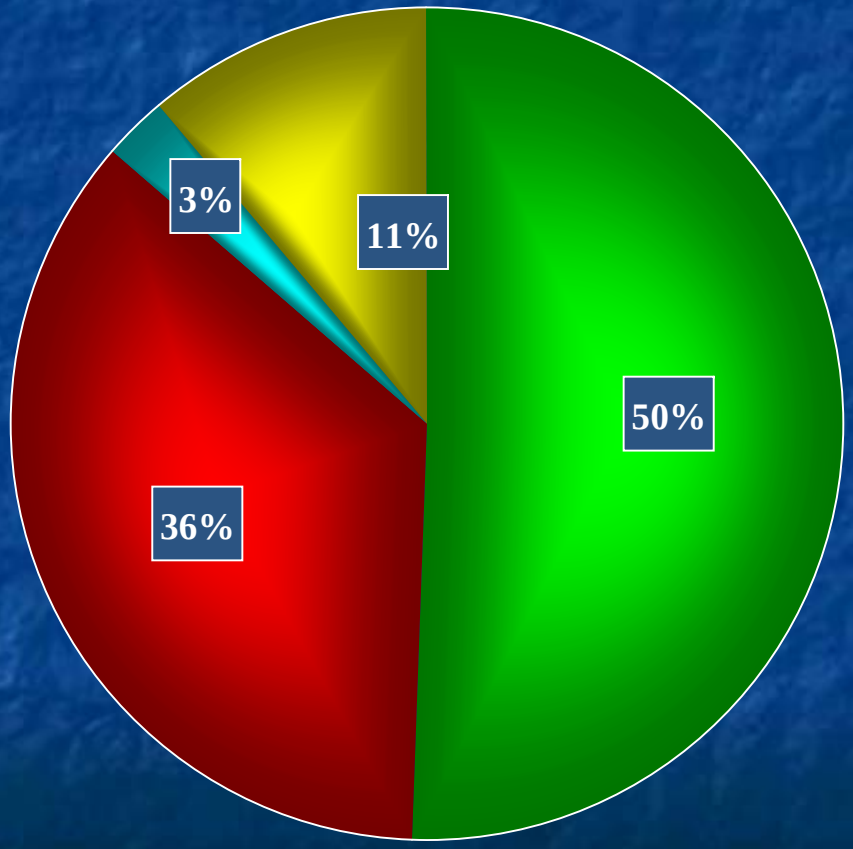
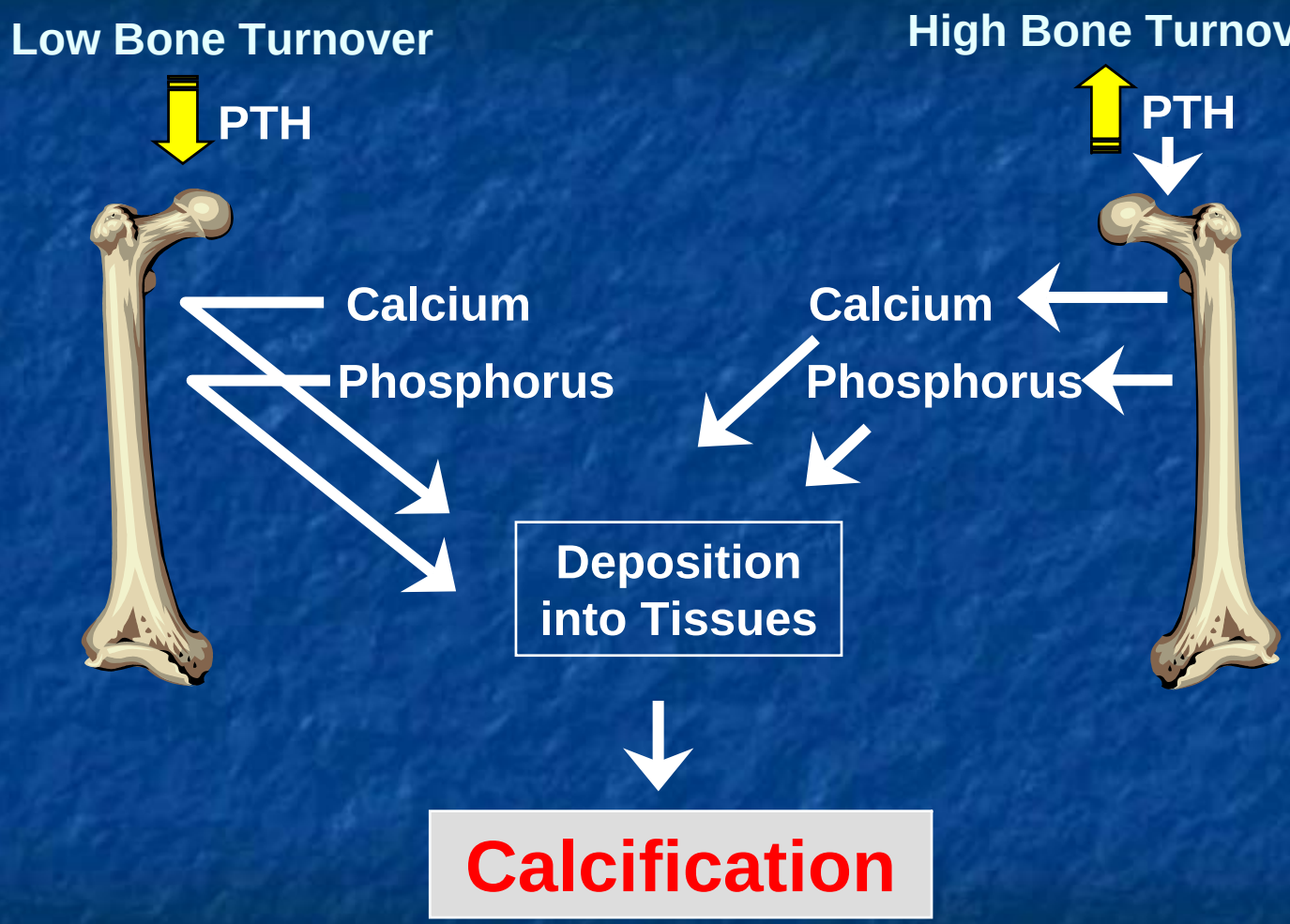


Sherrard DJ *et al*; Kidney Int 1993;43:436

Possible Effect of Bone Turnover on Extraskeletal Calcification



Slide courtesy of Dr. K. Martin

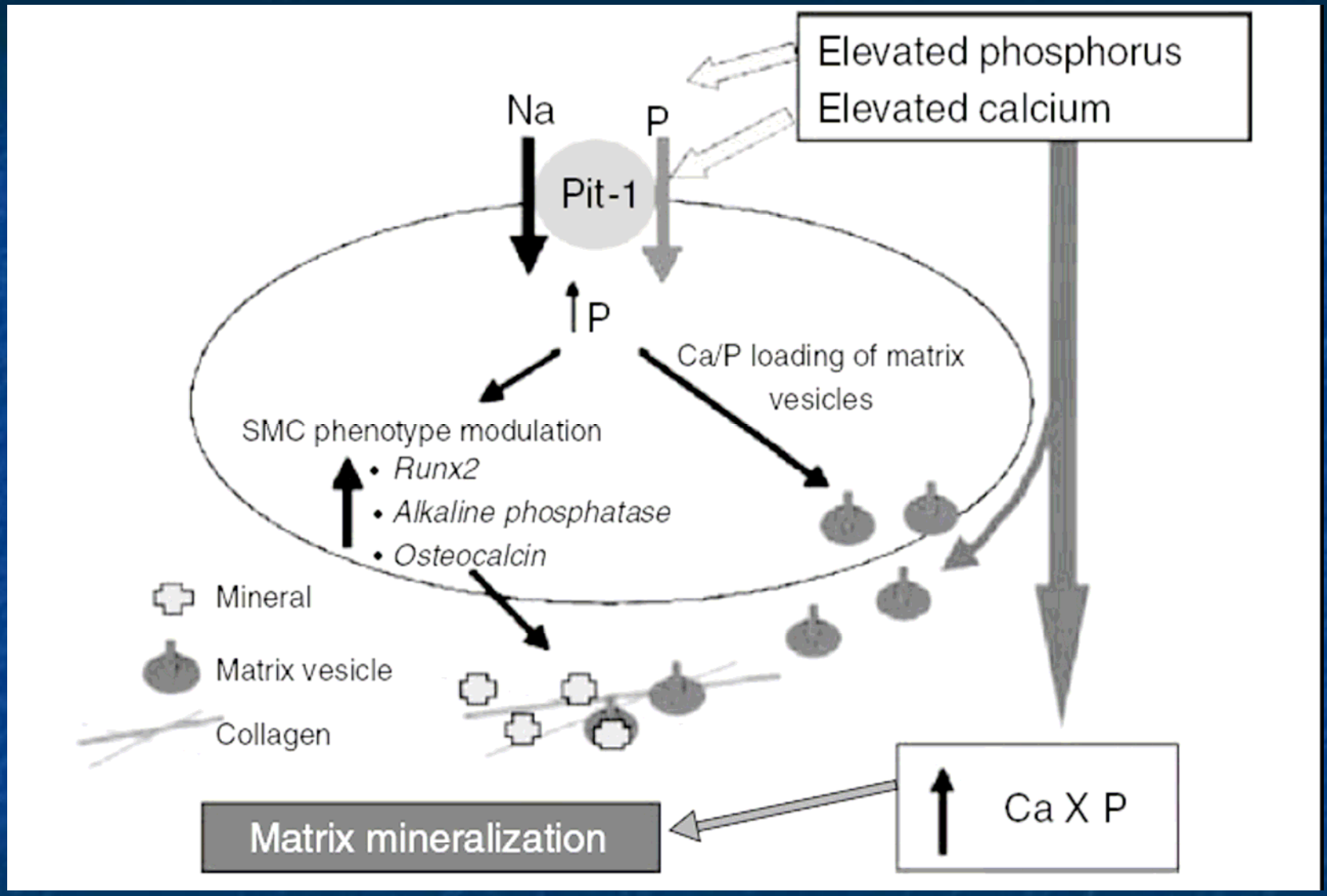
Vascular Calcification

Passive Process

- Altered mineral metabolism due to CRF
- A component of generalized soft tissue and visceral calcification
- Medial wall calcification
- Amorphous deposition of calcium and phosphorus
- Calcium oxalate

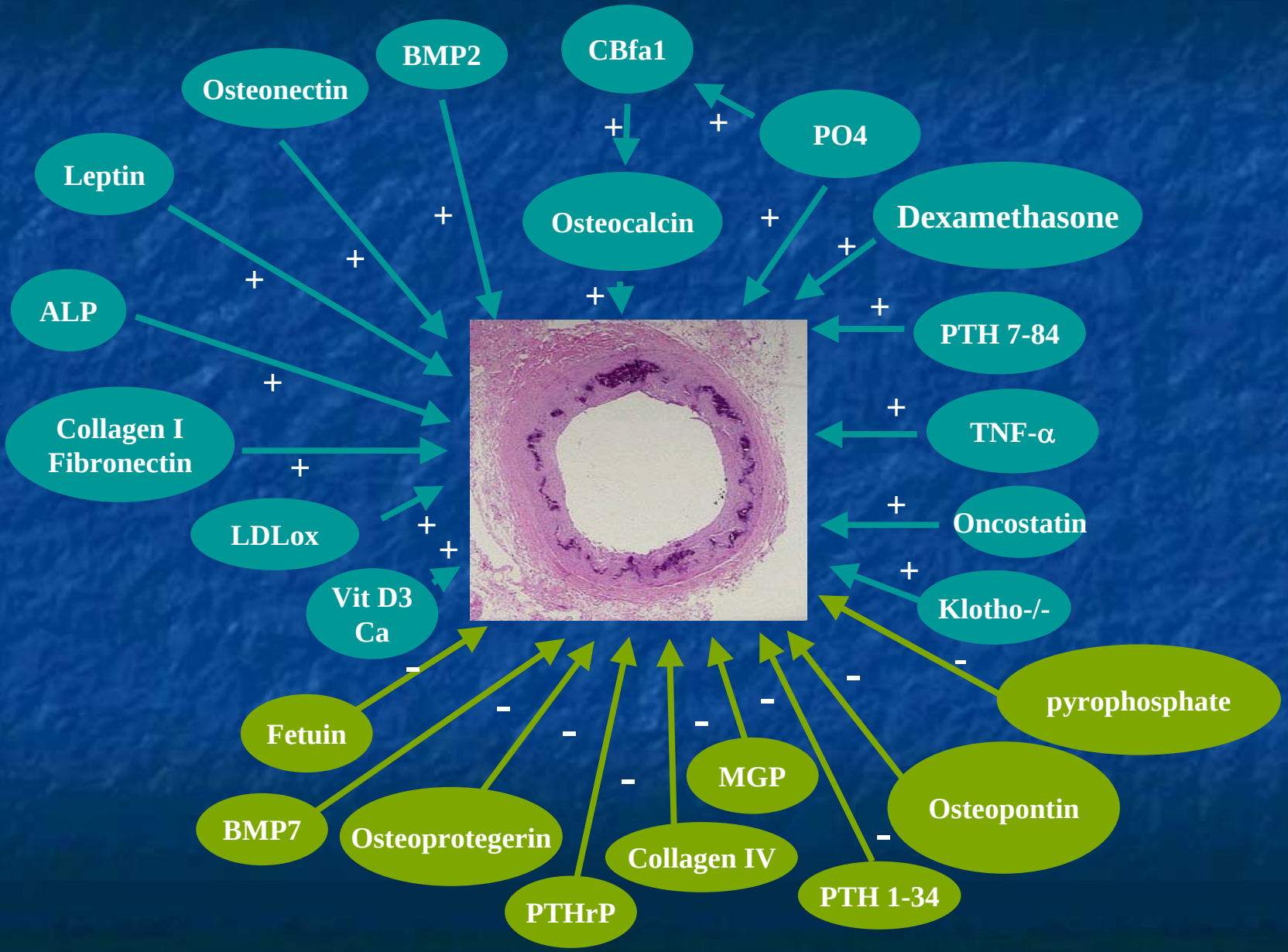
Active / Regulated Process

- Regulated or modulated by genetic factors
- Proteins involved in bone and mineral metabolism are expressed in calcified vascular lesions
- Both intimal and medial wall calcification
- Osteocalcin, matrix GLA protein, PTHrP
- Hydroxyapatite
- VSMC may assume characteristics of osteoblast-like cells *in vitro*

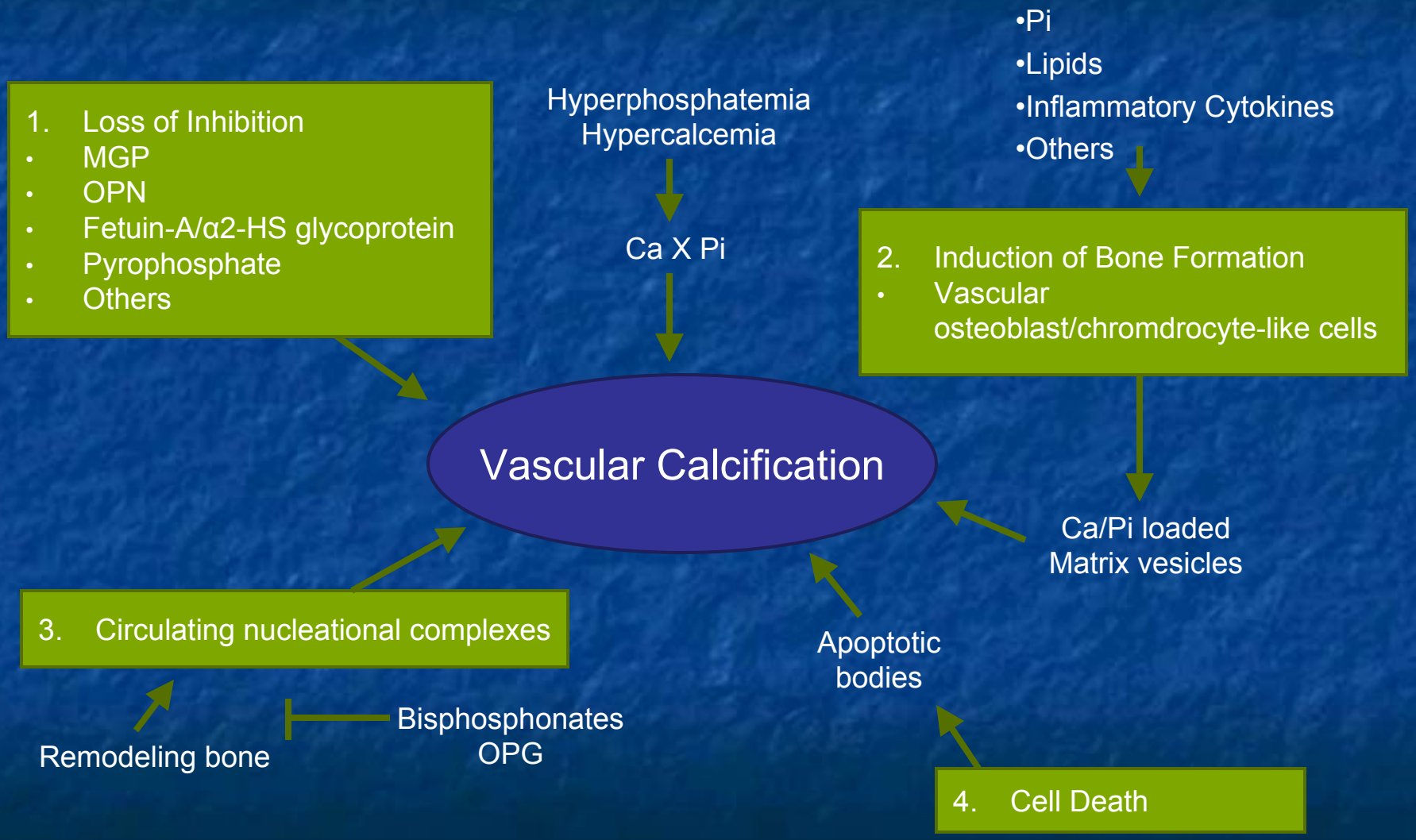


Ketteler, Kidney International (2006) 70, S5–S9.

Inductors (+) and Inhibitors (-) of Vascular Calcifications



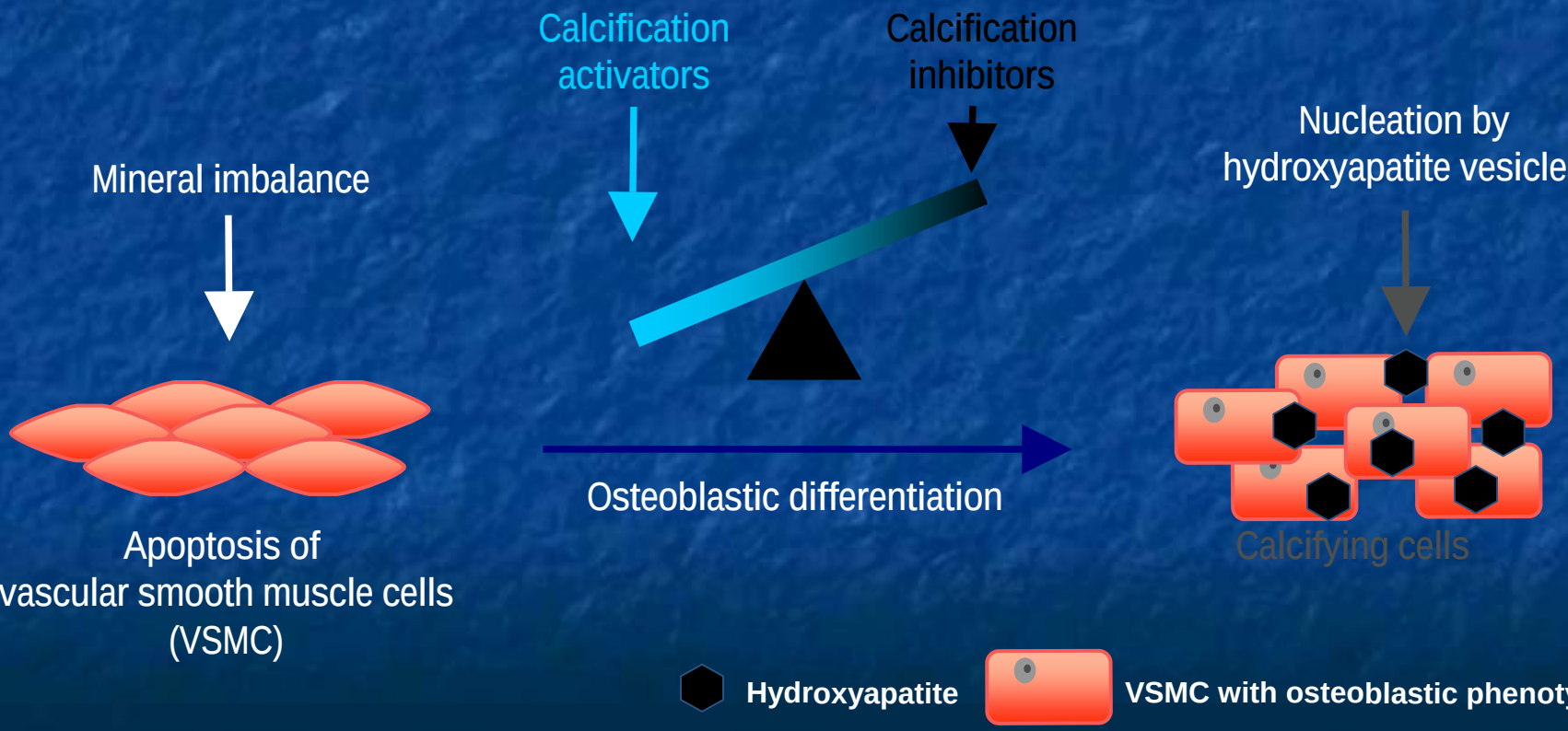
Molecular Mechanisms of Vascular Calcification
Four Theories



Speer MY & Giachelli M. *Cardiovascular Pathology* 2004;13:63-70.

Vascular Calcification is a Regulated Process

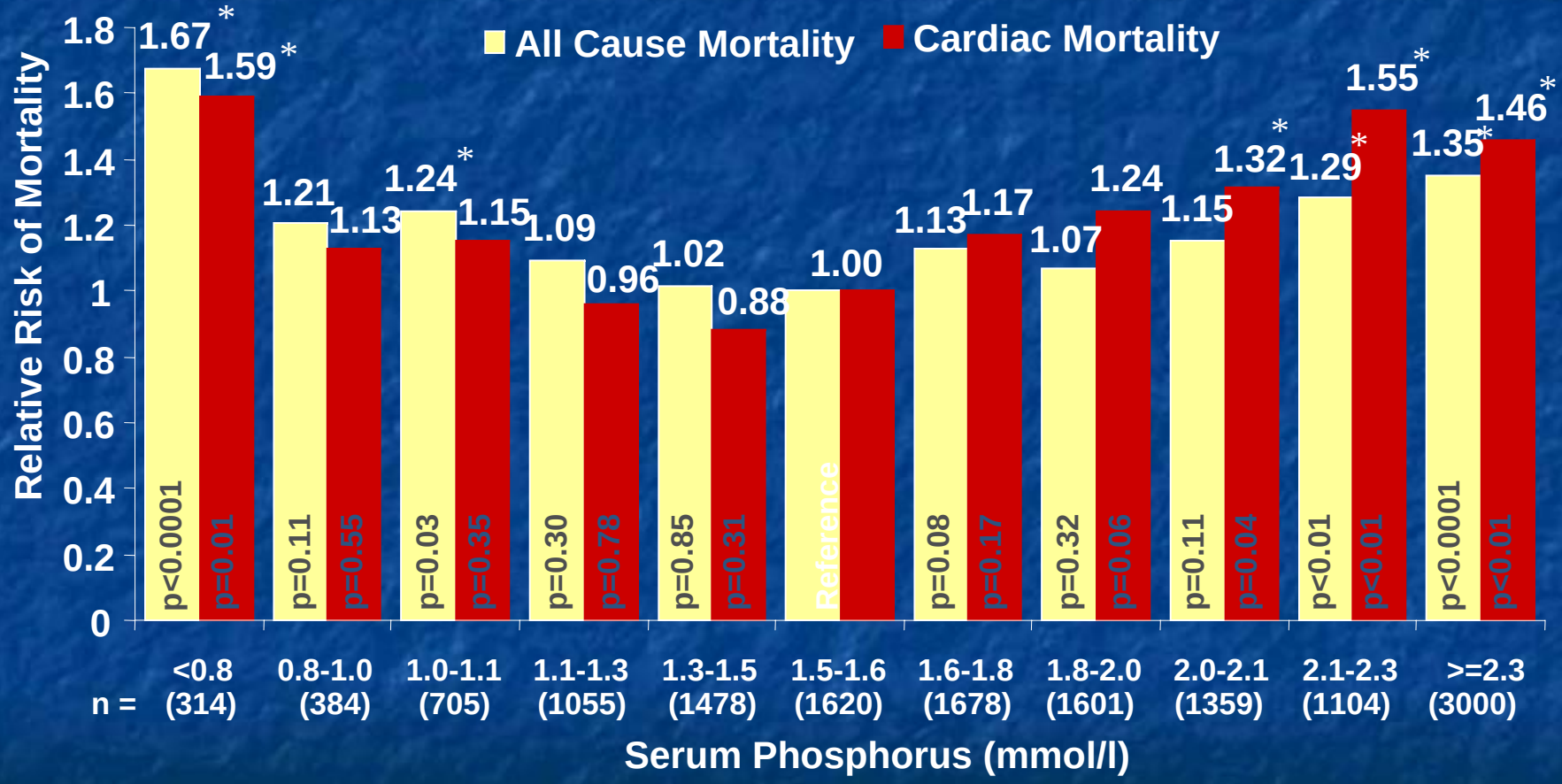
Mechanisms of transdifferentiation of vascular smooth muscle cells by uraemic conditions (*in vivo* and *in vitro*):



Adapted from Derici U et al. *Semin Dial* 2006;19:60–68

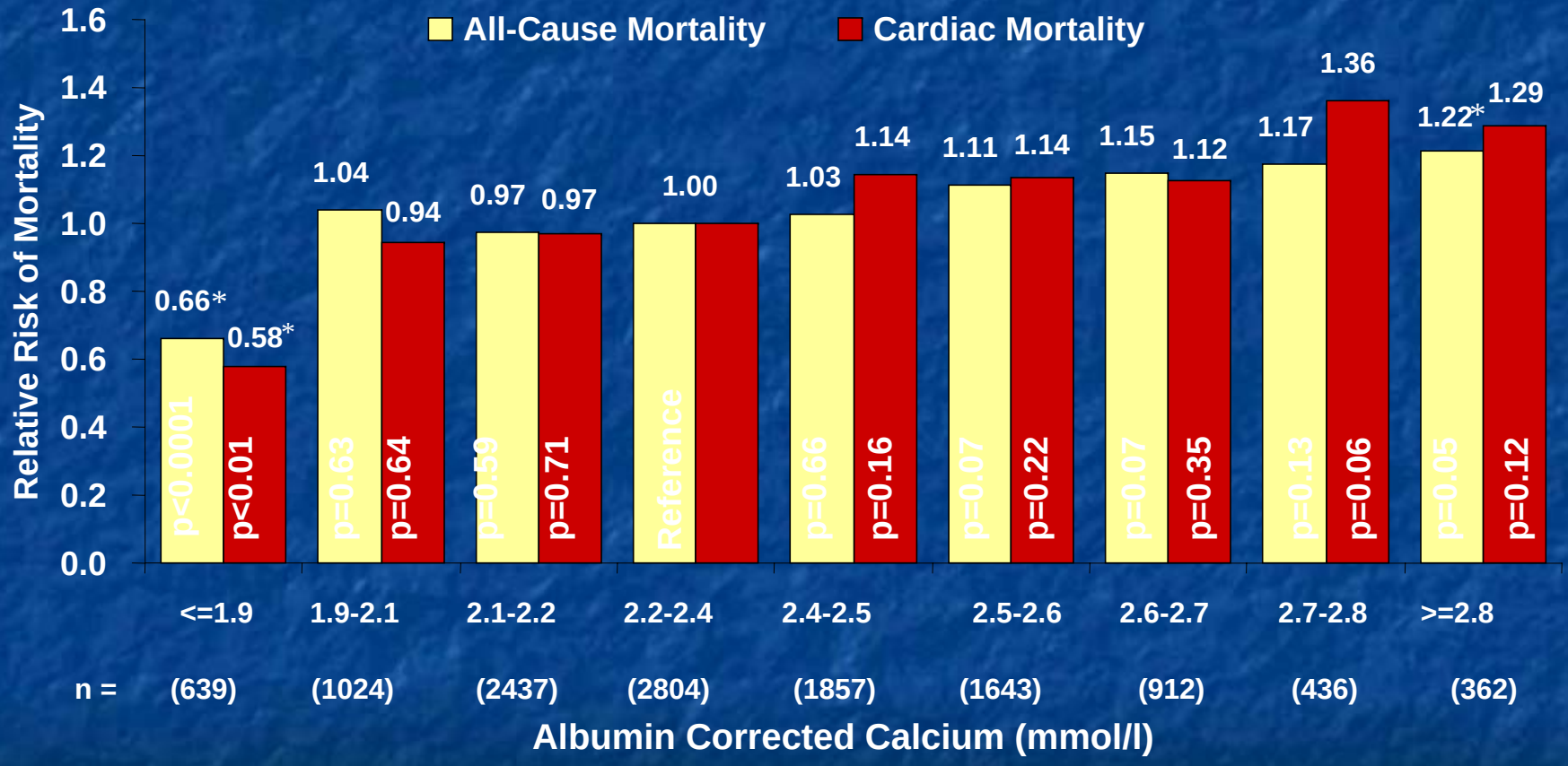
Identifying those at risk

Association Between Serum Phosphorus and All-Cause and Cardiac Mortality



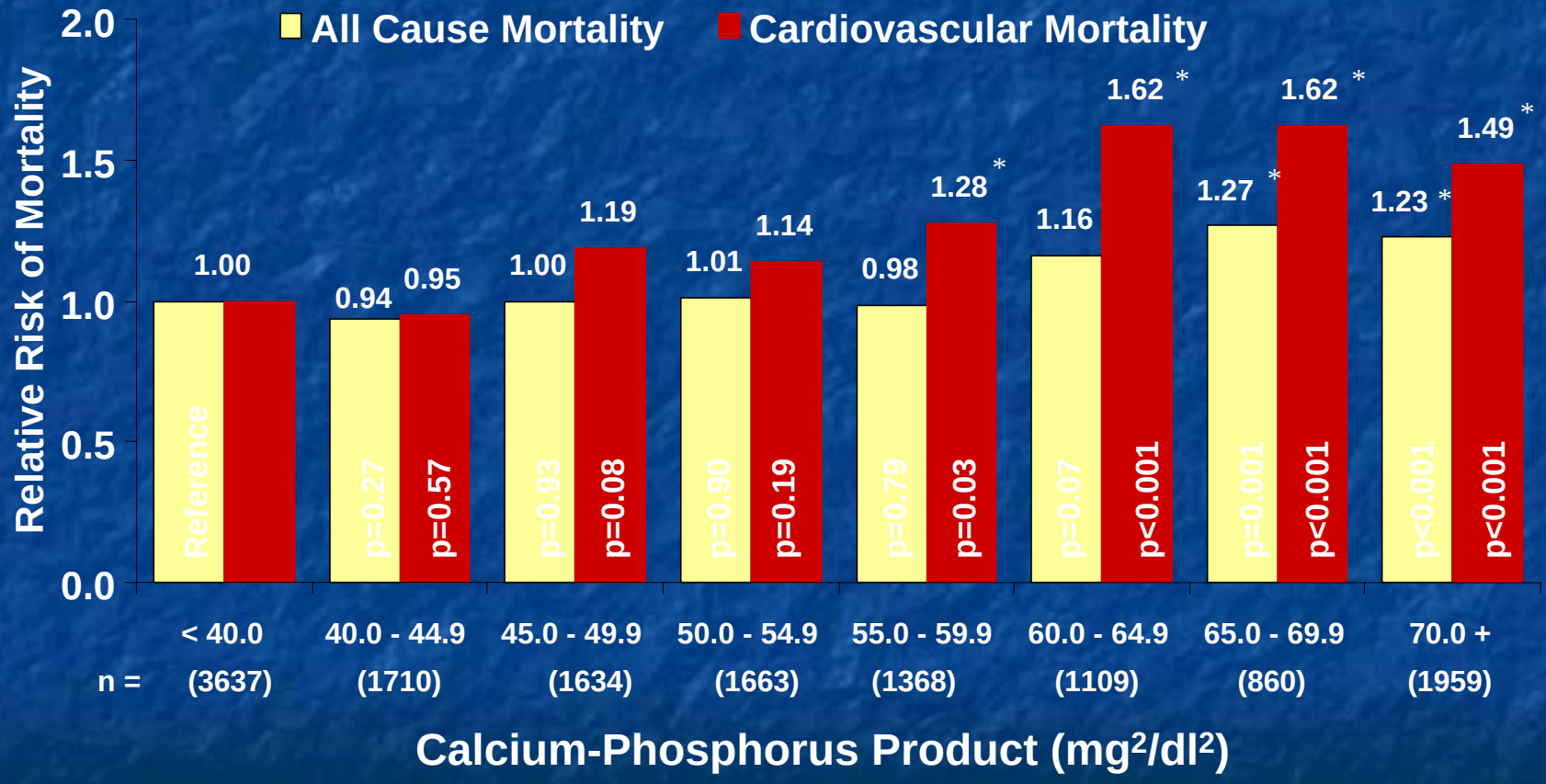
DOPPS I data (1996-2000). Model stratified by country, corrected for facility clustering, and adjusted for age, race, gender, years with ESRD, BMI, 14 summary comorbid conditions, dialysate calcium, serum albumin, iPTH, albumin-corrected calcium, vitamin D use, phosphate binder use, and prior parathyroidectomy. n= 14,298.

Association Between Albumin-Corrected Calcium and All-Cause and Cardiac Mortality



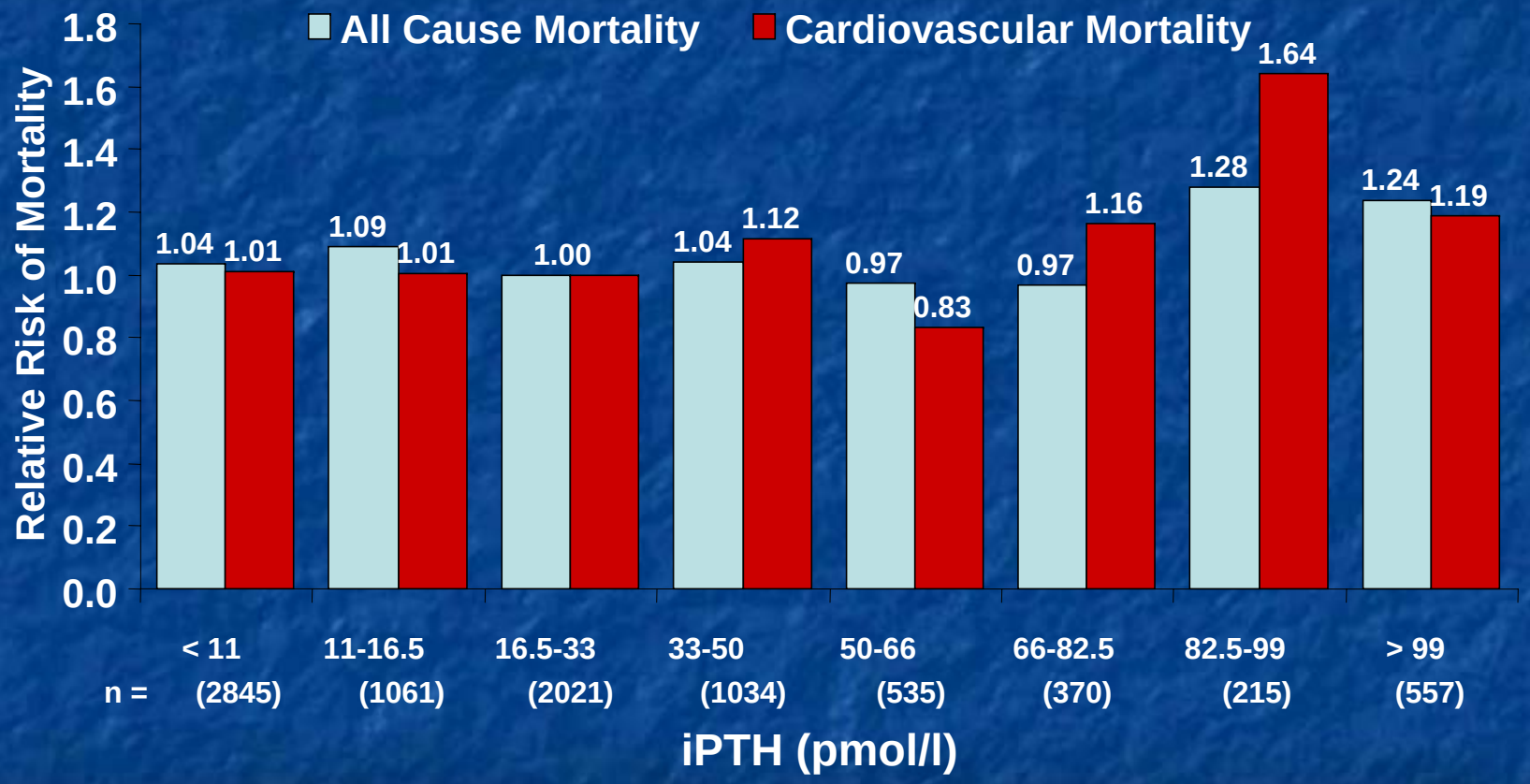
DOPPS I data (1996-2000). Model stratified by country, corrected for facility clustering, and adjusted for age, race, gender, years with ESRD, BMI, 14 summary comorbid conditions, dialysate calcium, serum iPTH, phosphorus, albumin, vitamin D use, phosphate binder use, and prior parathyroidectomy. n= 12,114.

Association Between Calcium- Phosphorus Product and All-Cause and Cardiac Mortality



DOPPS I data (1996-2000). Model stratified by country, corrected for facility clustering, and adjusted for age, race, gender, years with ESRD, BMI, 14 summary comorbid conditions, dialysate calcium, serum iPTH, albumin, vitamin D use, phosphate binder use, and prior parathyroidectomy. n=13,940.

Association Between Intact PTH (iPTH) and All-Cause and Cardiac Mortality



DOPPS I data (1996-2000). Model stratified by country, corrected for facility clustering, and adjusted for age, race, gender, years with ESRD, BMI, 14 summary comorbid conditions, dialysate calcium, serum albumin, phosphorus, albumin-corrected calcium, vitamin D use, phosphate binder use, and prior parathyroidectomy. n=8,638.

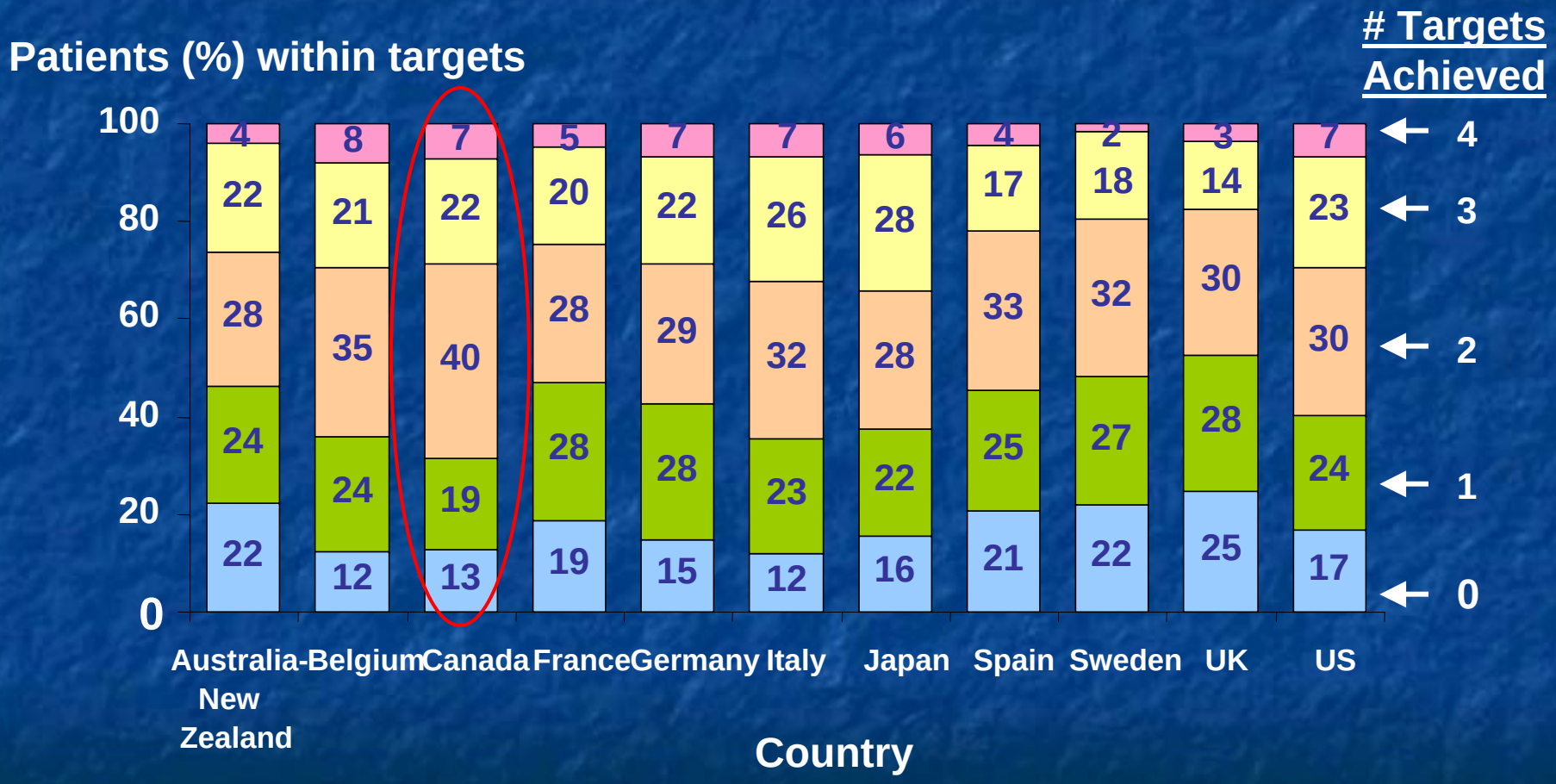
Young et al.; *Kidney Int;* In press

KDOQI vs CSN Target Ranges

	KDOQI		CSN 2006
	Conventional units (mg/dL)	SI units (mmol/L)	SI units (mmol/L)
Phosphate	3.5 – 5.5	1.13 – 1.78	0.81 – 1.42
Calcium	8.4 – 9.5	2.10 – 2.37	2.05 – 2.54
iPTH	150 – 300	16.5 – 33	10 – 50

CSN targets might lead to worse Canadian performance compared to KDOQI.

Number of Mineral Metabolism Target Levels Achieved, by Country



DOPPS II data (2002-04), among prevalent cross-section of patients with reported values for all four measures, n=4687

Projected Number of Patient-years Saved for all Hemodialysis Patients Who Attained the Best Targets According to the Guidelines Practiced in Canada: Projected for the Next 5 years (2006-2010)

Measure	Current statistics	1 Kt/V ≥1.2	2 Hb ≥110 g/L	3 PO_4 0.8-1.8 mmol/L	4 Calcium 2.2-2.6 mmol/L	5 Albumin ≥40 g/L	6 Facility catheter ≤10%	Total[1] (sum of 1-6)
Annual death rate (per patient year)	0.180	0.177	0.170	0.173	0.174	0.129	0.152	0.101
Patient years (total)	86,144	86,545	87,740	87,171	87,064	94,446	90,501	99,637
Patient years gained if 100% within targets (% of total years)[5]	-	401 (0.5%)	1,596 (1.9%)	1,026 (1.2%)	920 (1.1%)	8,302 (9.6%)	4,357 (5.1%)	13,492[3,4] (15.7%)

Nephrology News and Issues (NN&I) (21:5:69-85, 2007).

Treatment

Treatment overview:

- dietary PO_4 restriction
- PO_4 removal via dialysis
- PO_4 binders
- vitamin D supplementation
- calcimimetics

Treatment:

- dietary protein intake of 1 - 1.2 g/kg/day results in a P load of ~ 1 g/day or ~ 7 g/wk of which 60% is actually absorbed ~ 4 g/wk
- HD will remove ~ 3 g/wk
- PD will remove ~ 2 g/wk
- PO_4 binders are critical in management

Treatment: phosphate binders

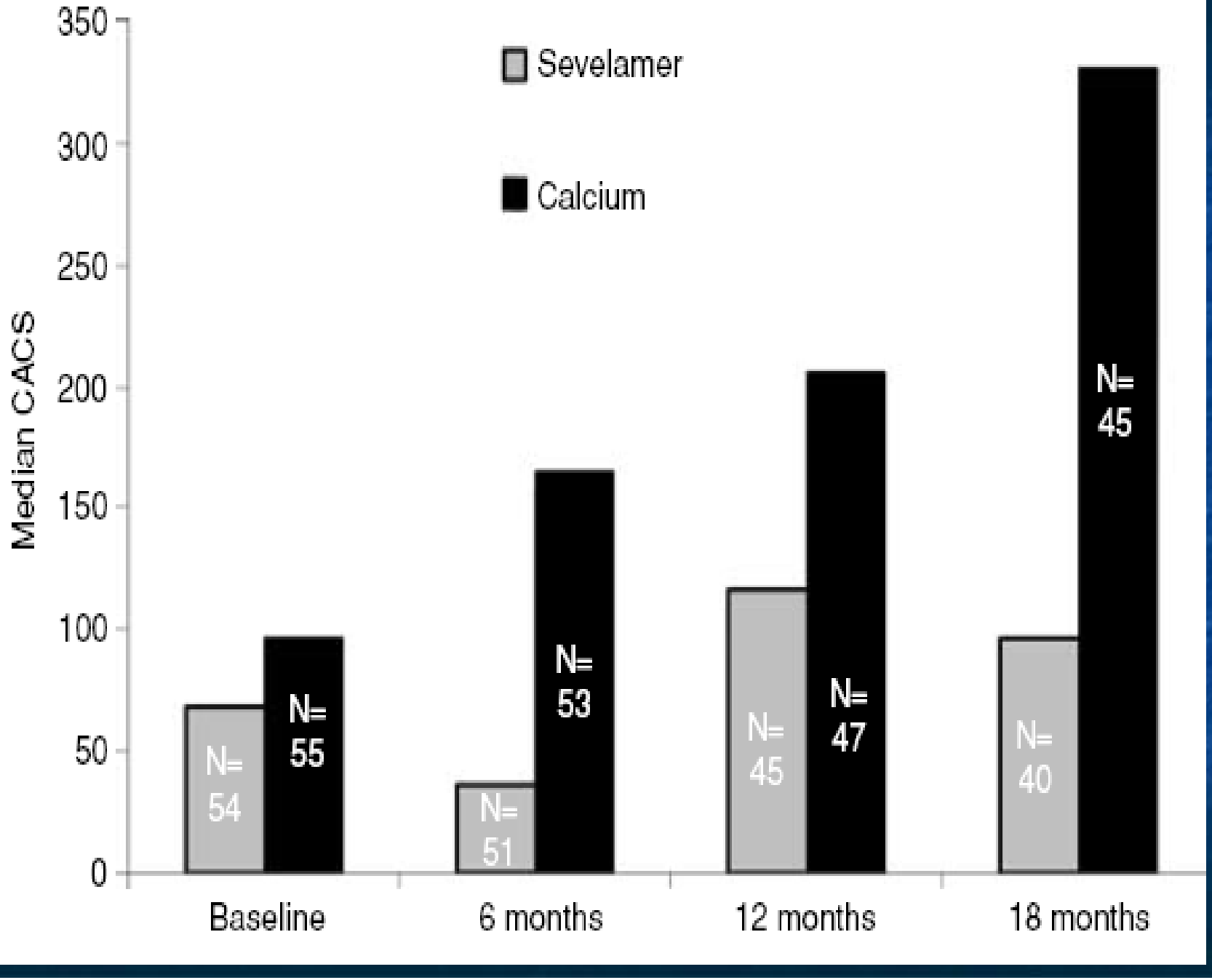
	Advantages	Disadvantages
$CaCO_3$	cost	hypercalcemia calcification risk
AlOH	efficacy	Al related toxicity
sevelamer (Renagel)	non-Ca, non-Al effect on dyslipidemia reduced vascular calcification	cost limited efficacy
lanthanum carbonate (Fosrenol)	non-Ca, non-Al potetncy	Build up ?significance

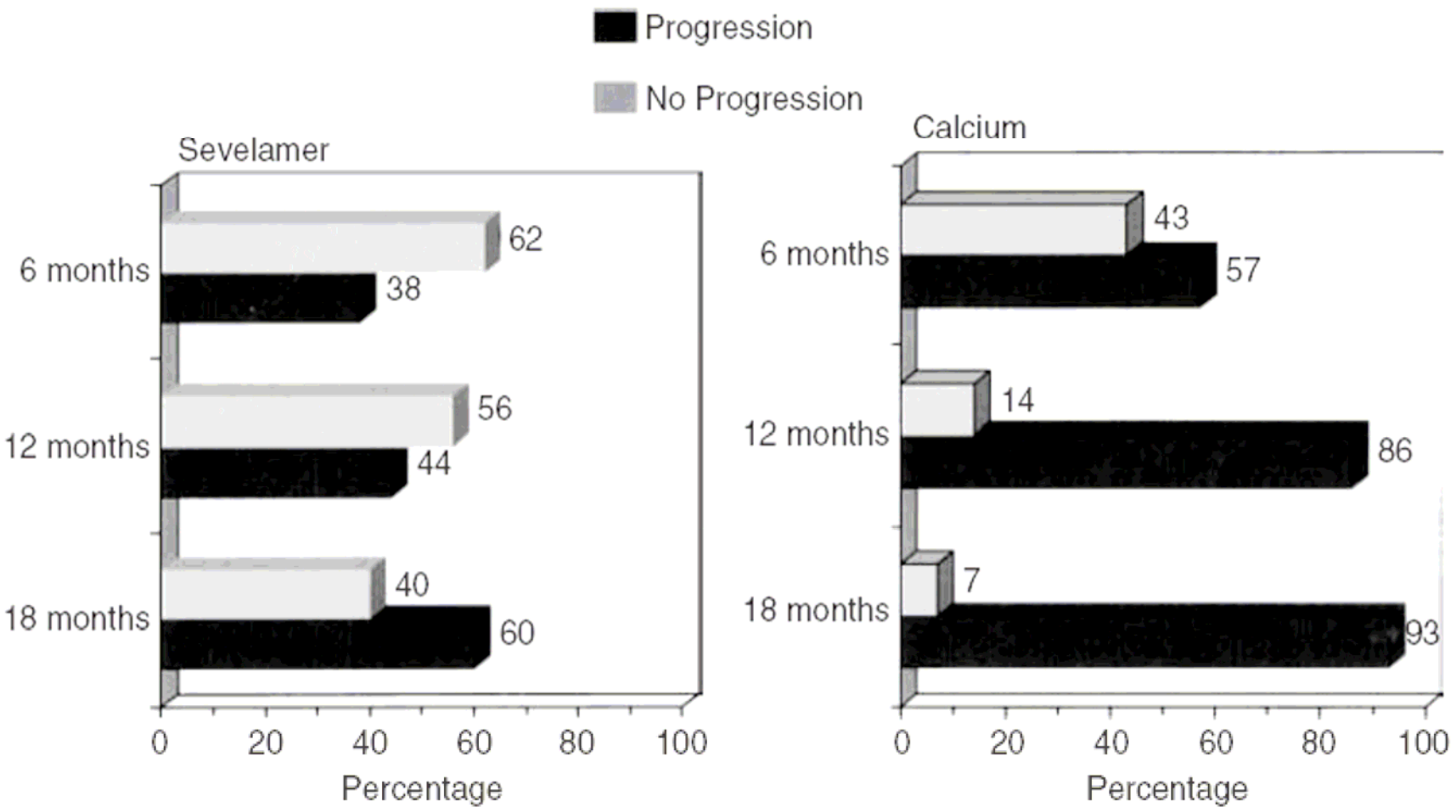
Sevelamer

Sevelamer: effect on coronary calcification

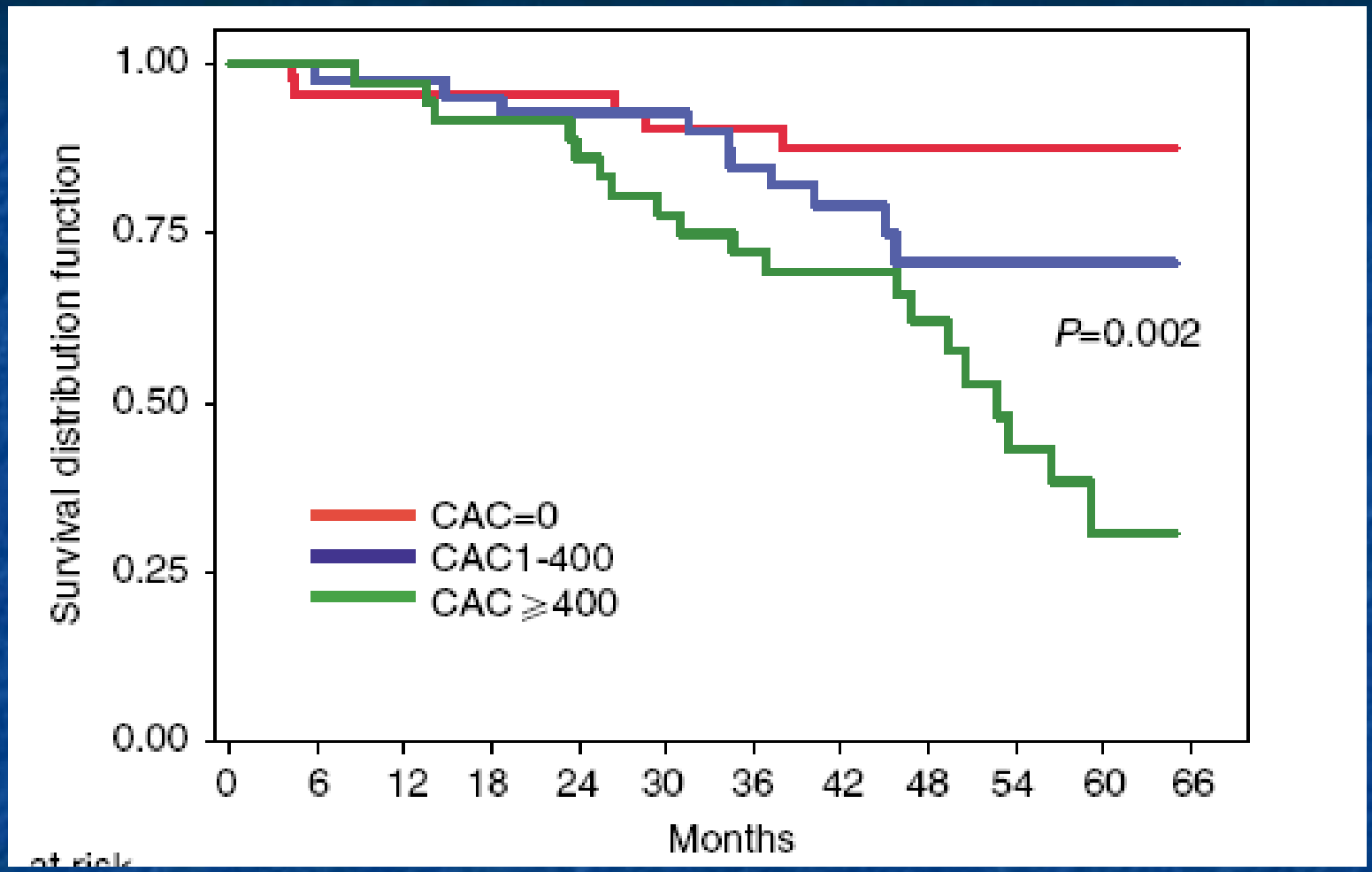
- 129 pts new to hemodialysis
- sevelamer vs Ca containing P binder
- EBCT baseline, 6 months, 12 months, 18 months
- *** at baseline 37% of sevelamer treated pts had no detectable coronary lesions vs 31% in Ca group (no comment as to statistical significance)

Block, *Kidney International, Vol. 68 (2005), pp. 1815–1824*

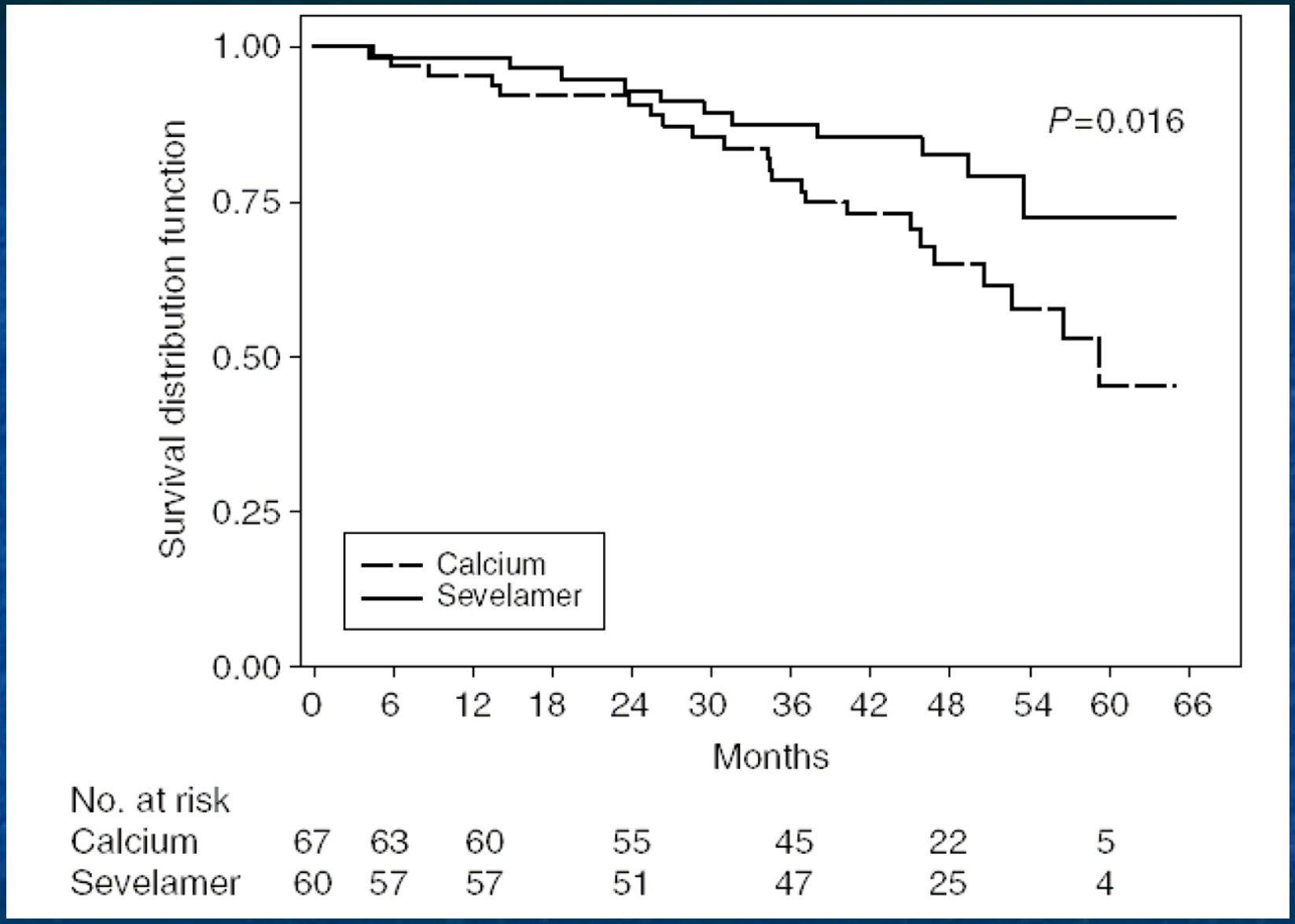

Median CACS
350
300
250
200
150
100
50
0
Sevelamer
Calcium
N= 54
N= 55
N= 51
N= 53
N= 45
N= 47
N= 40
N= 45
Baseline
6 months
12 months
18 months


Progression
No Progression
Sevelamer
6 months
62
38
12 months
56
44
18 months
40
60
0
20
40
60
80
100
Percentage
Calcium
6 months
43
57
12 months
14
86
18 months
7
93
0
20
40
60
80
100
Percentage

Variable (mean ± SD)	Sevelamer ($N = 54$)		Calcium ($N = 55$)	
	Baseline	On treatment average	Baseline	On treatment average
Albumin *g/dL*	3.5 ± 0.6	3.8 ± 0.3	3.7 ± 0.5	3.8 ± 0.4
Calcium corrected *mg/dL*	9.3 ± 1.0	9.1 ± 0.5[a]	9.3 ± 0.8	9.6 ± 0.5[a]
Phosphorus *mg/dL*	5.2 ± 1.6	5.2 ± .9	5.4 ± 1.4	5.1 ± 0.8
Ca × P mg^2/dL^2	48 ± 14	47 ± 7	49 ± 13	49 ± 8
Intact PTH *pg/dL*	293 ± 323	298 ± 152[a]	319 ± 383	243 ± 136[a]
Total cholesterol	157 ± 49	134 ± 52[a]	153 ± 39	160 ± 32[a]
LDL cholesterol *mg/dL*	72 ± 36	60 ± 34[a]	72 ± 30	81 ± 26[a]
Triglycerides *mg/dL*	183 ± 108	171 ± 108	188 ± 108	191 ± 106
C-reactive protein *mg/L*	6.7 ± 6.4	9.1 ± 9.7	7.6 ± 7.9	10.5 ± 10.3
HMG Co-A reductase use%	36%	42%	24%	35%
ACE inhibitor use%	49%	59%	54%	57%
Beta blocker use%	40%	45%	48%	59%
Vitamin D use%	55%	68%	52%	52%



Block G, Kidney International (2007) 71, 438–441.



Block G, Kidney International (2007) 71, 438–441.

DCOR(Dialysis Clinical OutcomesRevisited):

- 2100 HD pts
- open label sevelamer vs Ca based binders
- f/u 45 months
- primary endpoint: all cause mortality

Suki W, et al. Renal Week 2005; November 8-13, 2005; Philadelphia, PA. Abstract TH-PO745.

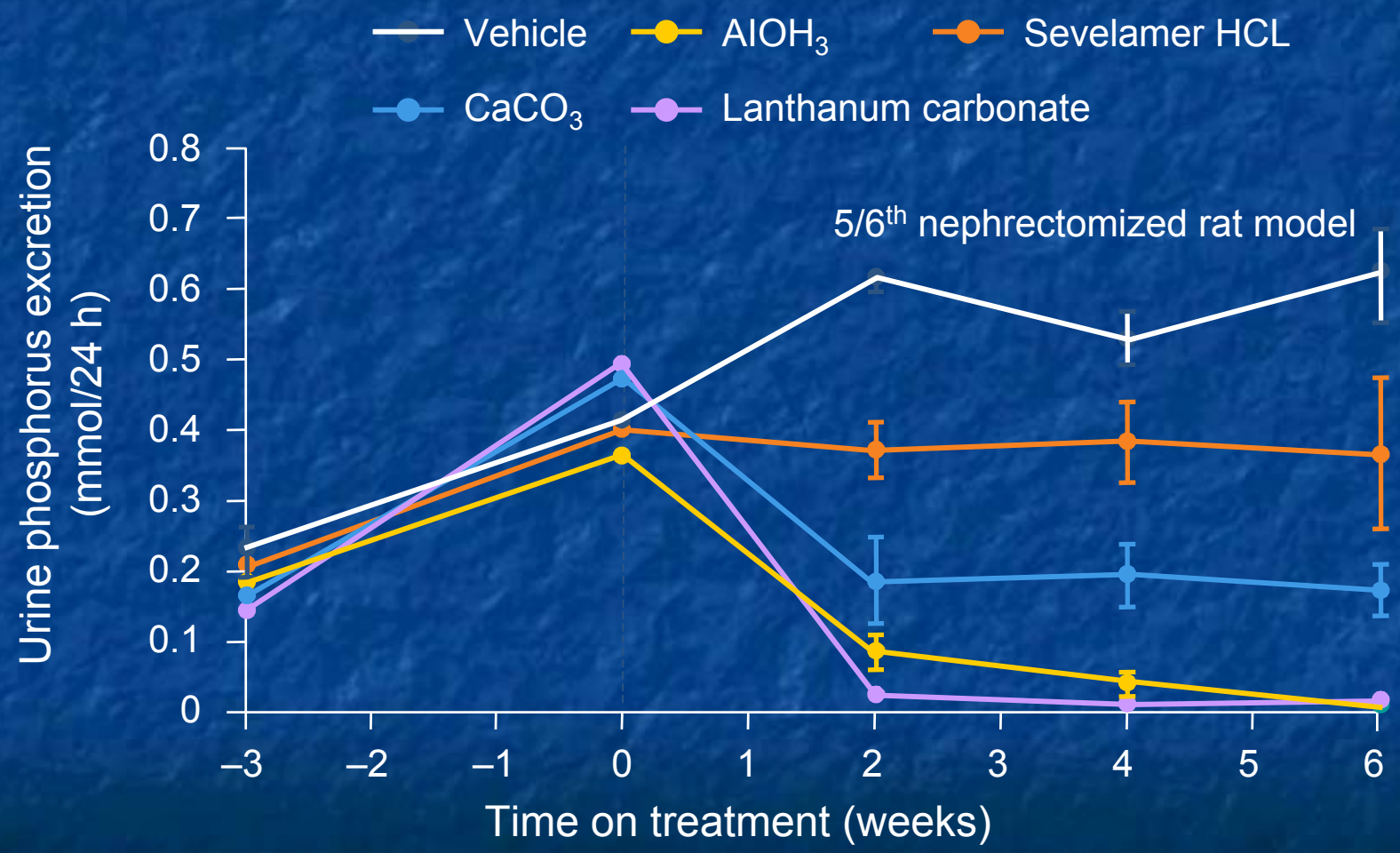
DCOR: Primary end point (all-cause mortality)

End point	Sevelamer	Calcium binders	Relative risk (95%)
Deaths, n (%)	265 (26)	274 (27)	0.91 (0.77–1.08)
Mortality incidence rate (per 100 patient-years)	15.02	16.15	

Suki W, et al. Renal Week 2005; November 8-13, 2005; Philadelphia, PA. Abstract TH-PO745.

Lanthanum Carbonate

Lanthanum carbonate is a high affinity phosphate binder *in vivo*



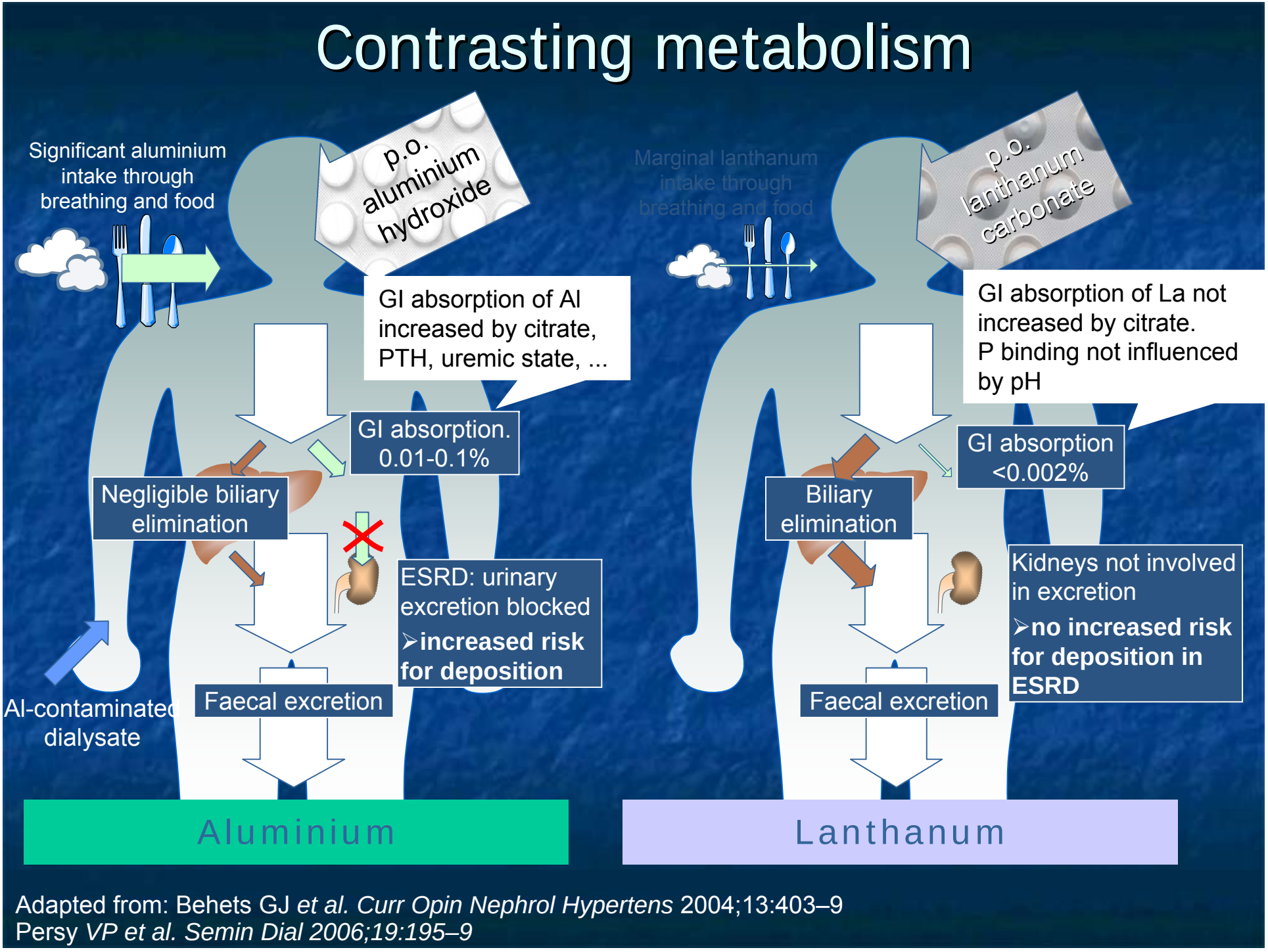
Adapted from: Damment SJP, Webster I. Poster presented at ASN 2003
Hutchison A. *Nephrol Dial Transplant* 2004;19 Suppl 1:i19–24

Adverse events versus standard therapy

Adverse event	Percentage of patients with adverse event	
	Fosrenol® (*n* = 682)	Standard therapy (adjusted rates) (*n* = 677)
Nausea	37	29
Vomiting	27	22
Dialysis graft complication	25	24
Diarrhoea	24	24
Dyspnoea	23	24
Headache	22	21
Dialysis graft occlusion	21	21
Dizziness	21	20
Myalgia	21	20
Chest pain	21	19
Coughing	20	20
Oedema, peripheral	16	20

Finn WF *et al. Clin Nephrol* 2006;65:191–202

Contrasting metabolism



Adapted from: Behets GJ *et al. Curr Opin Nephrol Hypertens* 2004;13:403–9
Persy *VP et al. Semin Dial 2006;19:195–9*

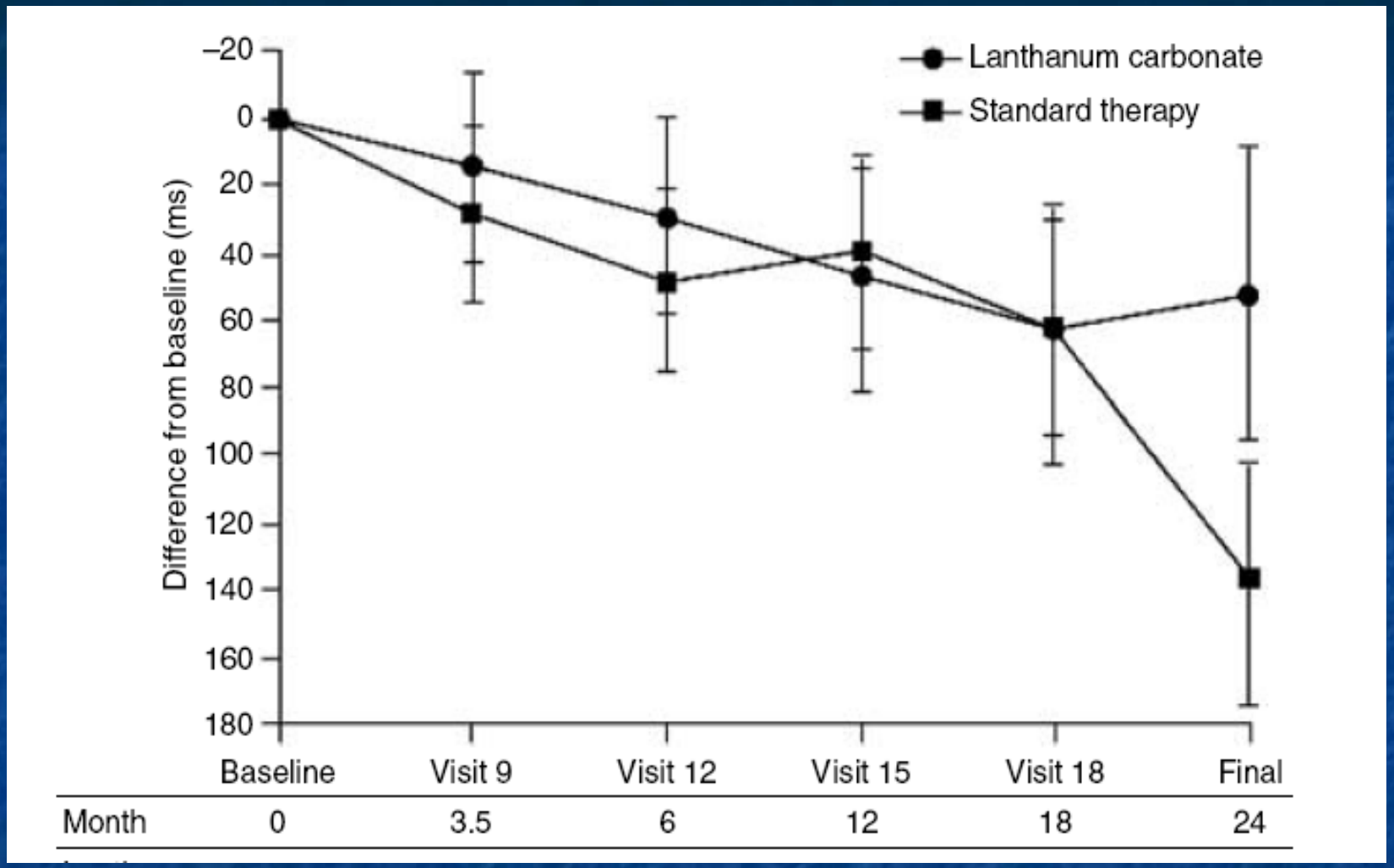
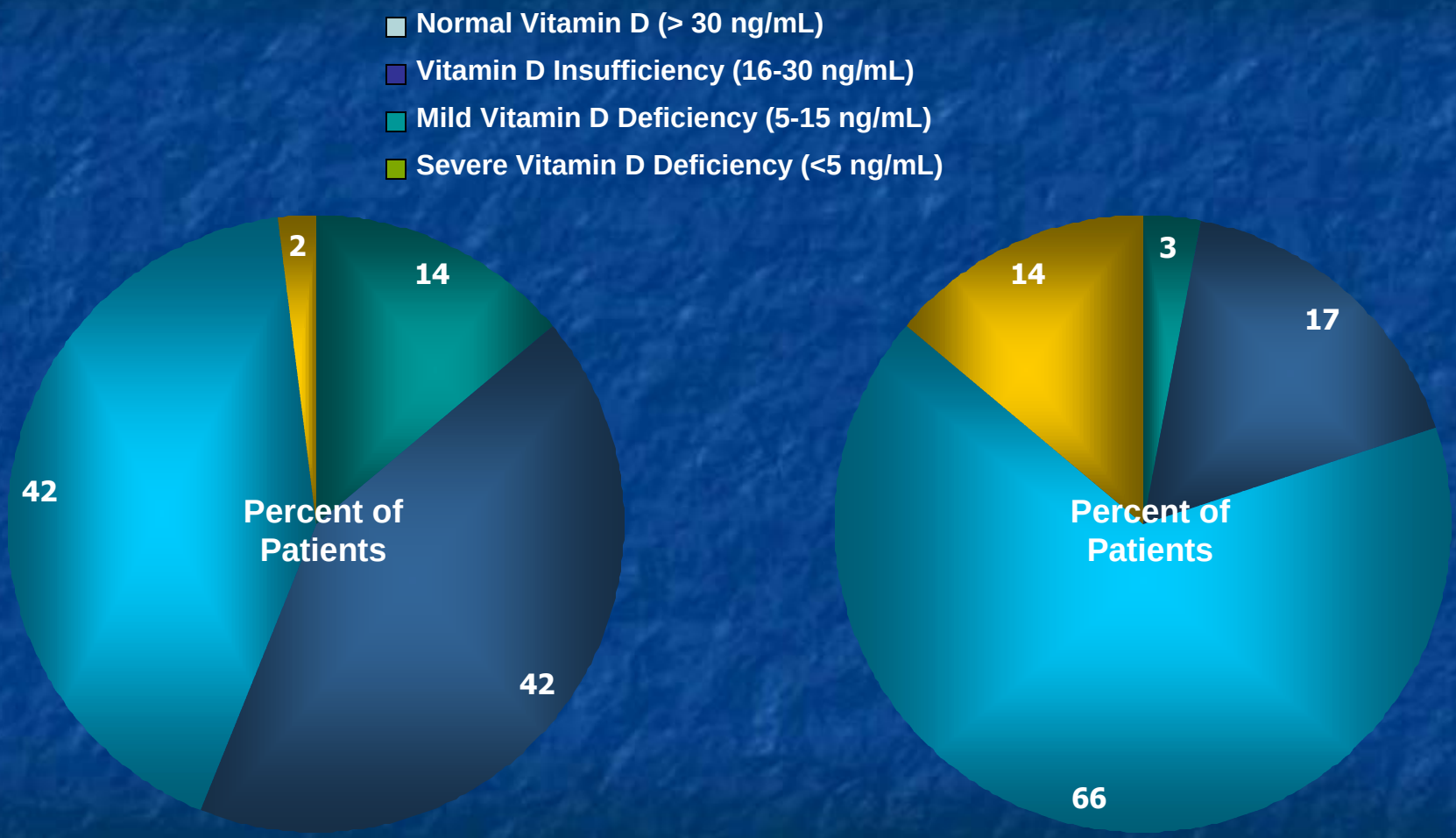


Figure 2 | Choice Reaction Time – response time (ms)

Altmann, Kidney International (2007) 71, 252–259.

Vitamin D

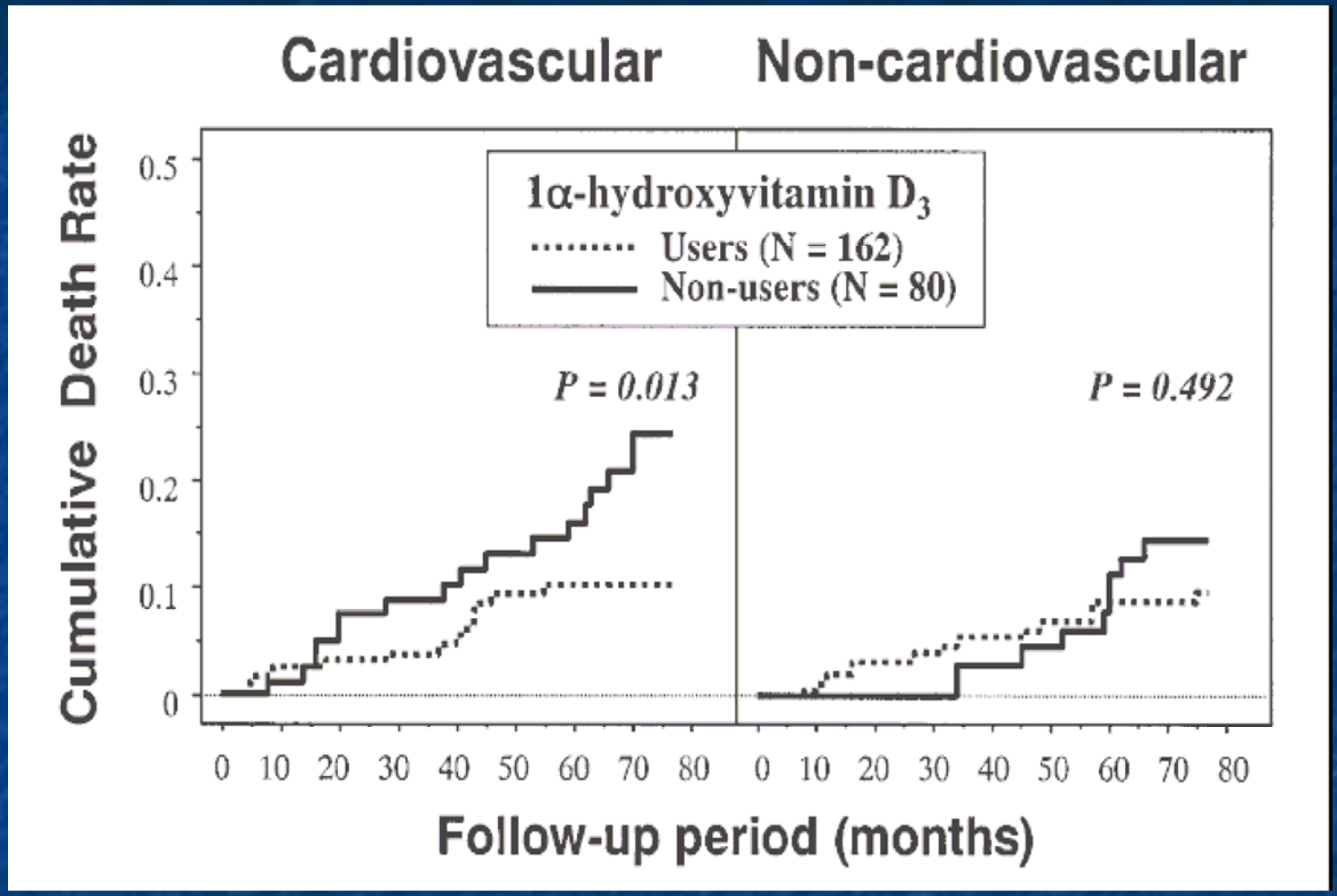
Vitamin D Deficiency is Prevalent in CKD Patients



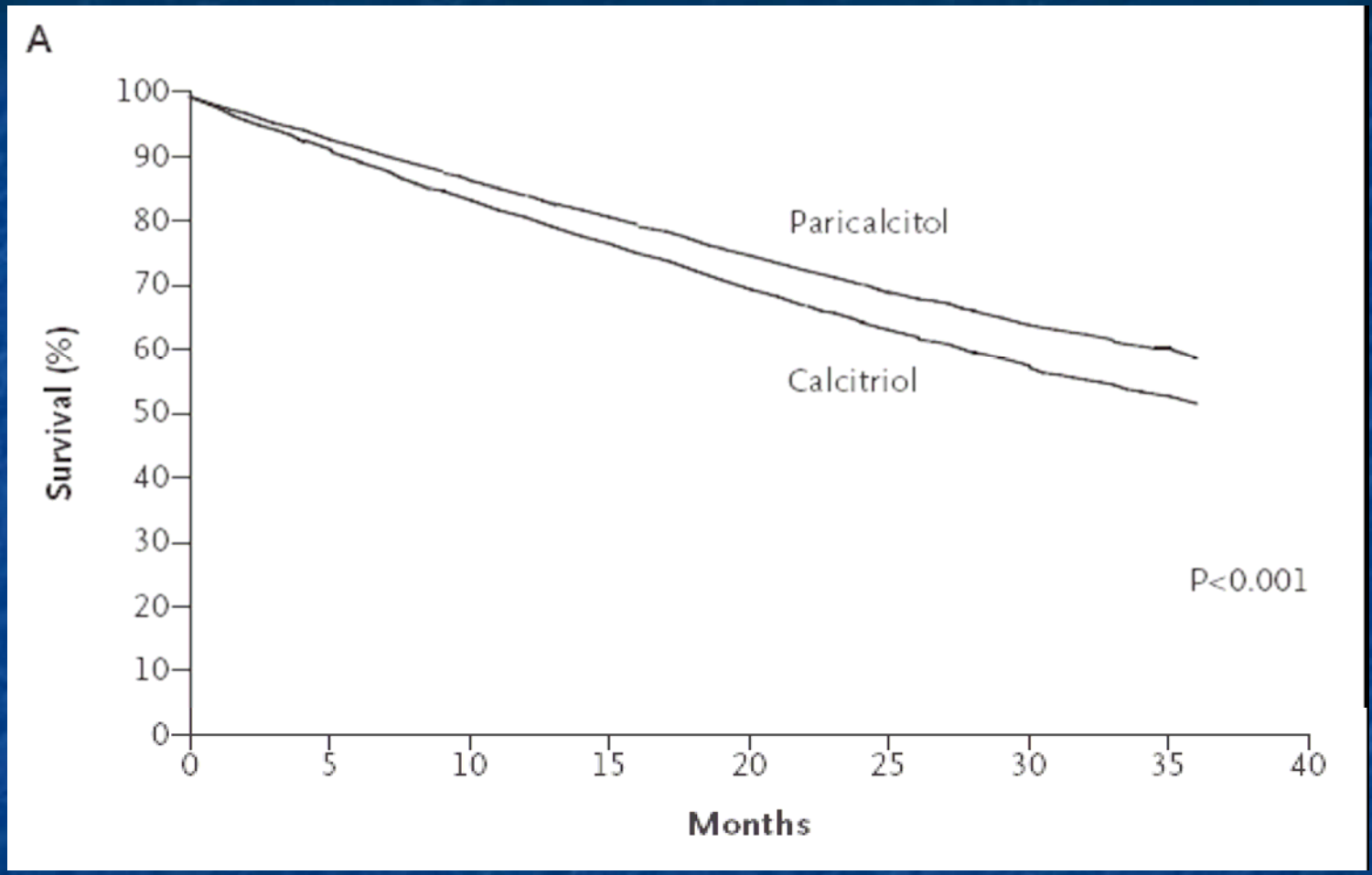
N=43 patients with SCr 1 and 5 mg/dL (calculated GFR 11-111 ml/min)

N=103 patients undergoing chronic HD

Gonzales EA et al. *Am J Nephrol 2004;24:503-510.*



Shoji, Nephrol Dial Transplant (2004) 19: 179–184



Teng, N Engl J Med 2003;349:446-56.

Model	No. of Patients	Hazard Ratio	95% Confidence Interval
Unadjusted	67,399	0.81	0.78–0.85
Adjusted			
Age, sex, race, diabetes status, and duration of dialysis	66,950	0.86	0.82–0.89
Age, sex, race, diabetes status, duration of dialysis, and study-entry period	66,950	0.90	0.86–0.95
Age, sex, race, diabetes status, duration of dialysis, study-entry period, and SMR†	66,950	0.89	0.85–0.94
Age, sex, race, diabetes status, duration of dialysis, study-entry period, SMR, and dialysis access	66,950	0.89	0.85–0.93
Age, sex, race, diabetes status, duration of dialysis, study-entry period, SMR, dialysis access, and base-line laboratory values‡	30,012	0.84	0.79–0.90

Teng, N Engl J Med 2003;349:446-56.

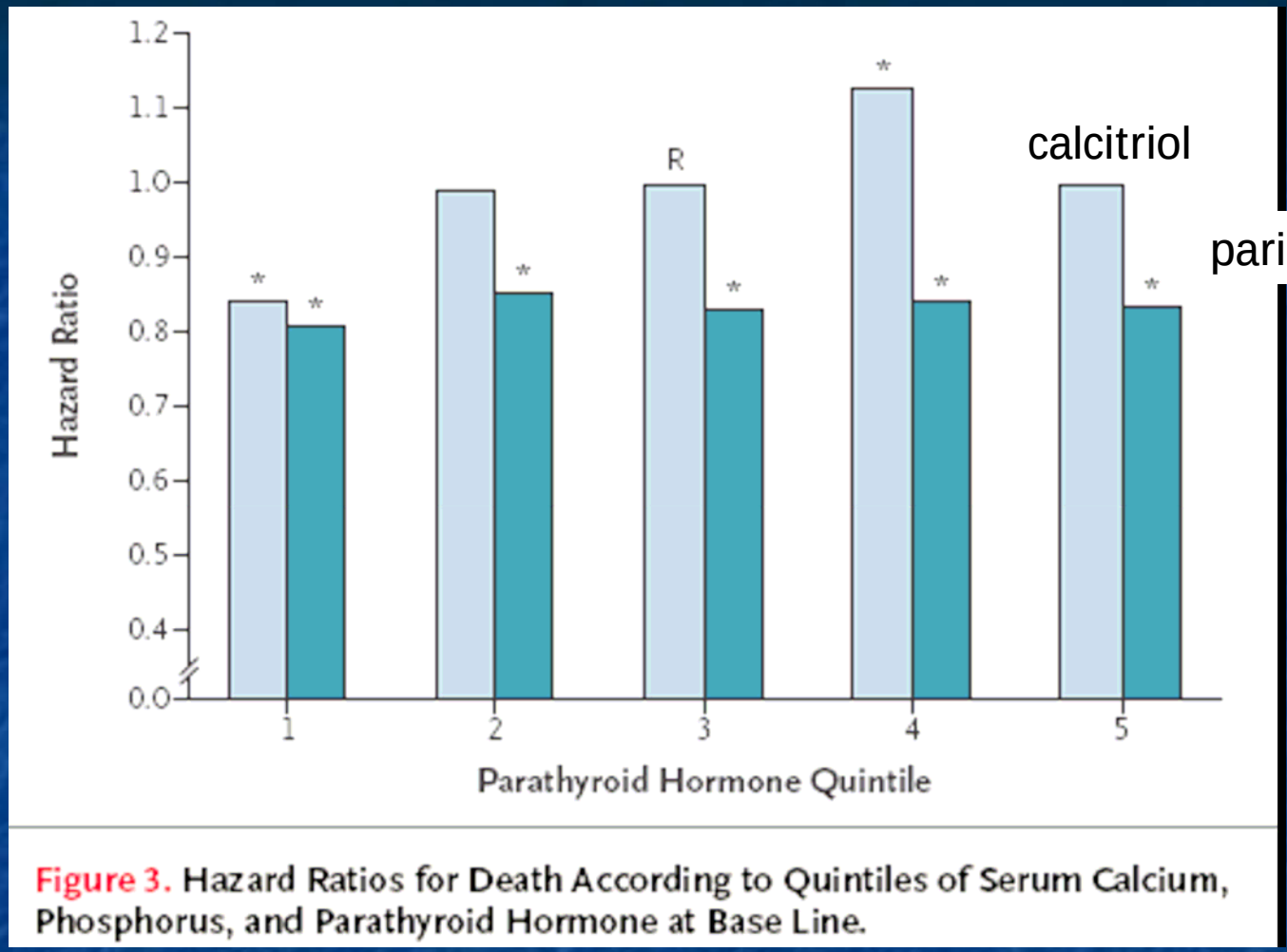
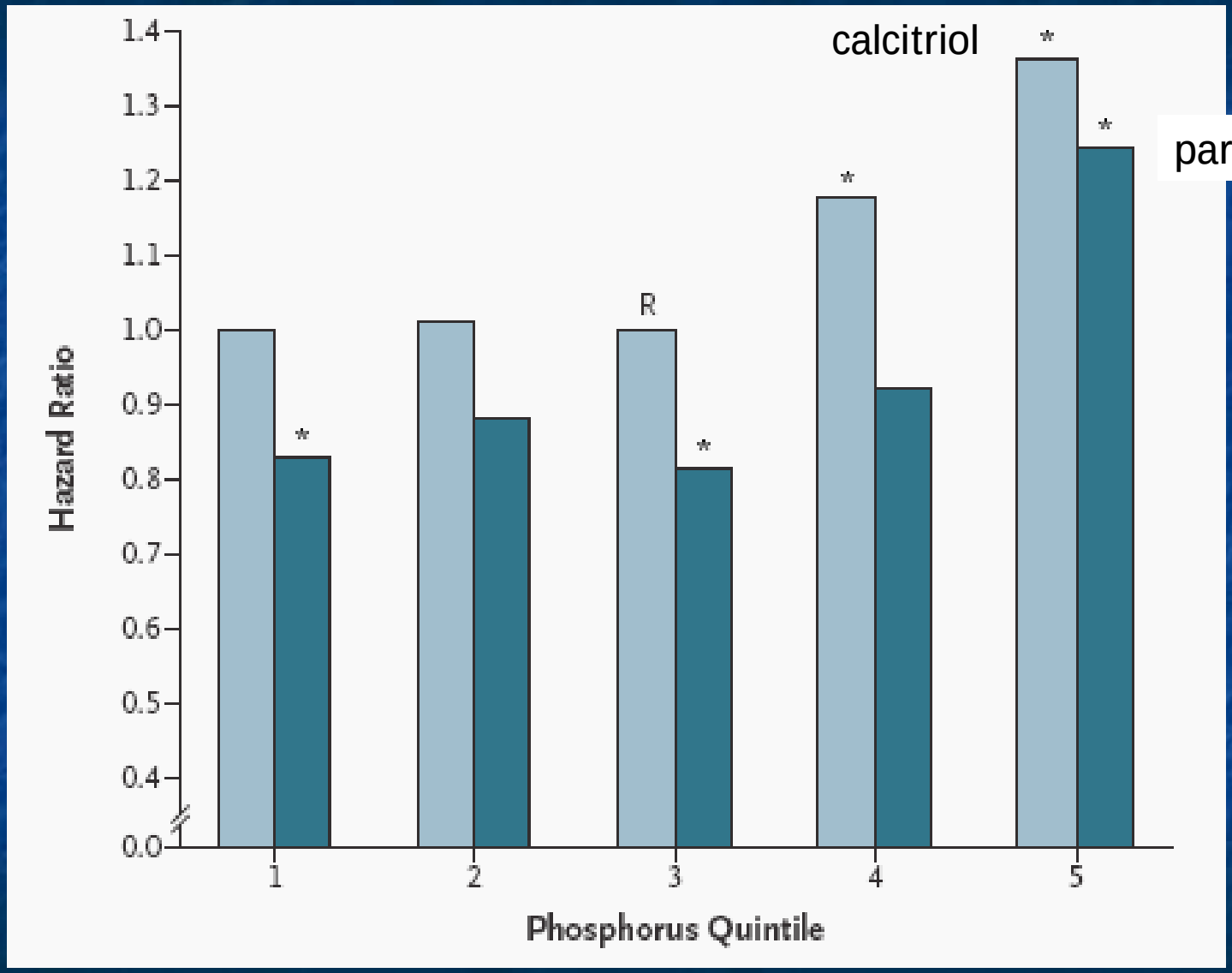
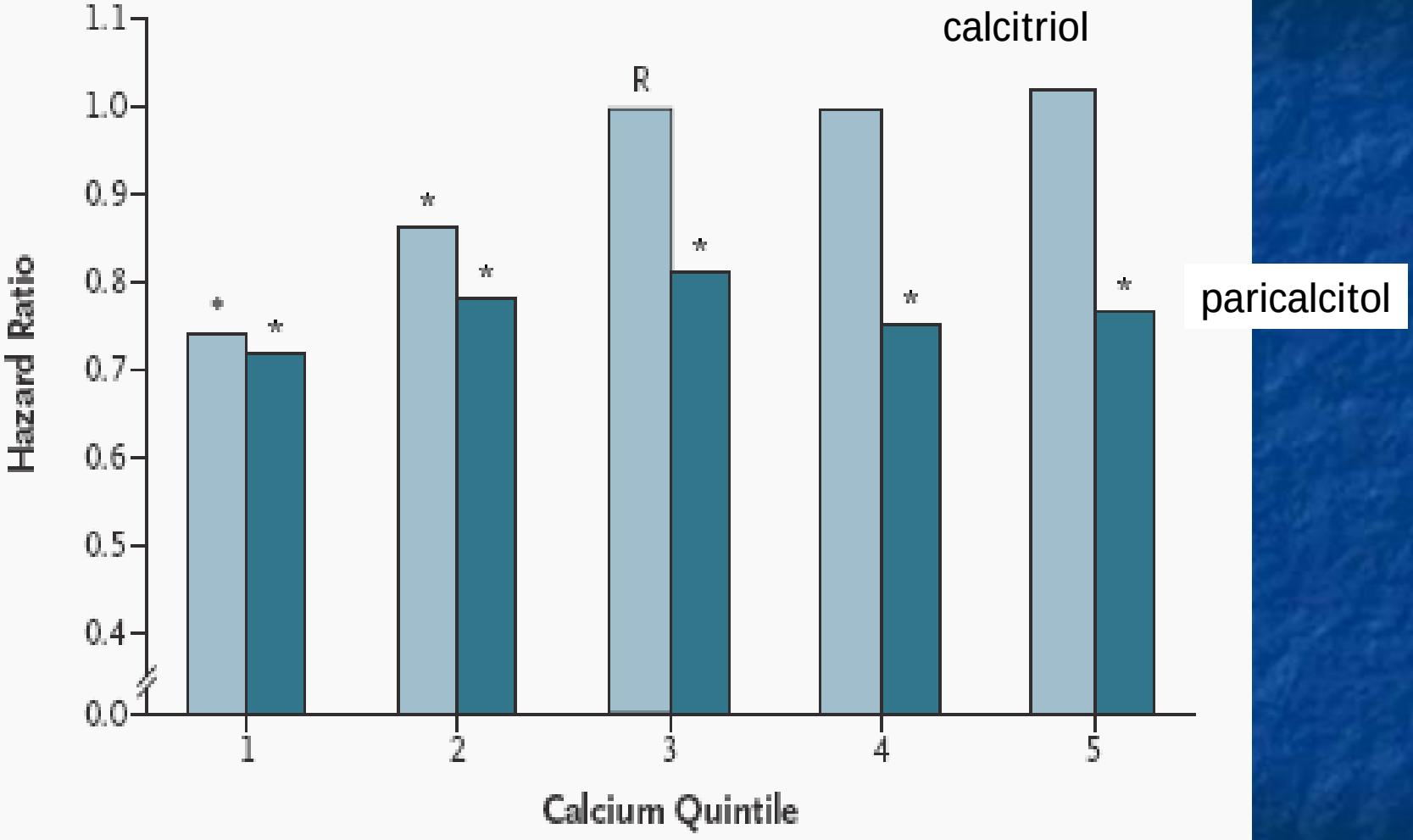


Figure 3. Hazard Ratios for Death According to Quintiles of Serum Calcium, Phosphorus, and Parathyroid Hormone at Base Line.

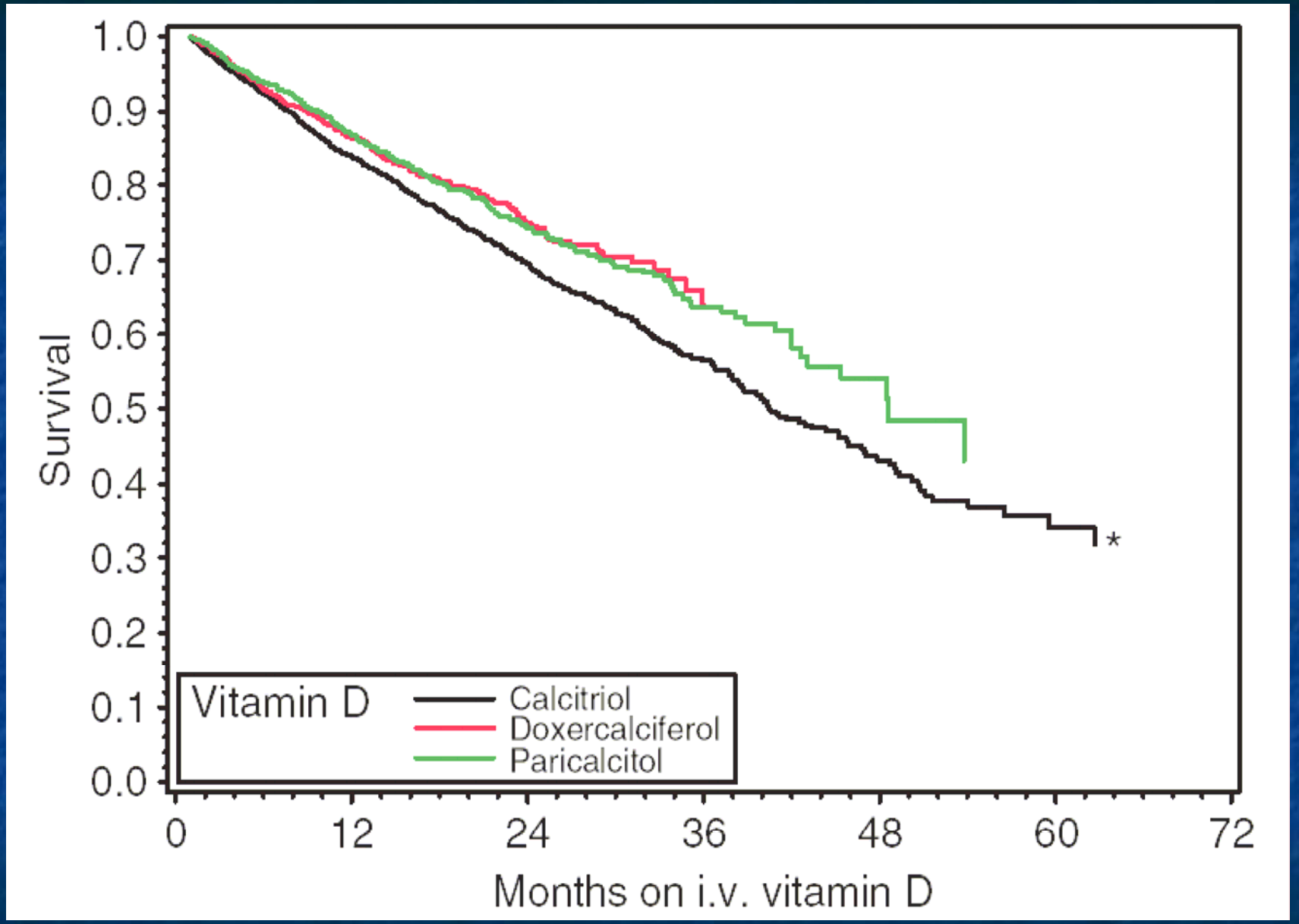
Teng, N Engl J Med 2003;349:446-56.



Teng, N Engl J Med 2003;349:446-56.



Teng, N Engl J Med 2003;349:446-56.



Tentori, KI 2006, 70, 1858–1865.

Model	Covariates	Doxercalciferol vs calcitriol	Paricalcitol vs calcitriol	Paricalcitol vs doxercalciferol
1	Unadjusted[a]	0.80 (0.69, 0.91)[b]	0.78 (0.69, 0.89)[b]	0.99 (0.84, 1.15)
2	Age, gender, race, cause of ESRD, year started HD, and time on HD before first vitamin D administration[a]	0.80 (0.66, 0.96)[b]	0.79 (0.68, 0.92)[b]	0.99 (0.83, 1.17)
3	Model 2 plus baseline serum calcium, phosphorus, PTH, albumin, *Kt/V*, creatinine, and Hct labs[c]	0.88 (0.71, 1.09)	0.93 (0.78, 1.11)	1.06 (0.88, 1.27)
4	Model 3 plus clinic SMR[c]	0.93 (0.75, 1.15)	0.94 (0.79, 1.13)	1.02 (0.84, 1.23)
5	Model 4 with time-varying labs[c]	0.95 (0.77, 1.18)	0.95 (0.79, 1.13)	1.00 (0.82, 1.21)

Tentori, KI 2006, 70, 1858–1865.

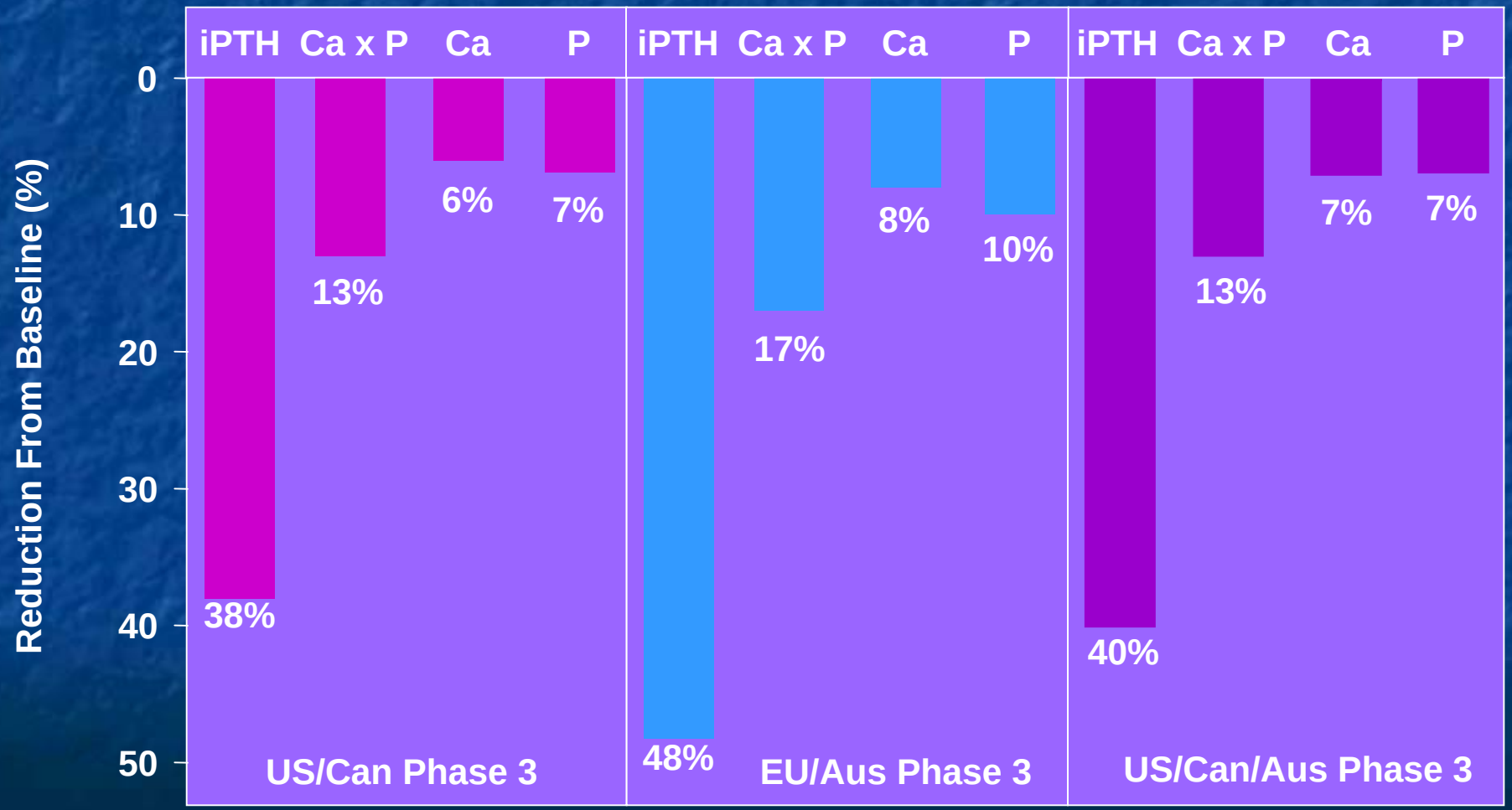
No vitamin D vs. Any vitamin D

Model	Covariates	Hazard ratios (95% CI)
1	Unadjusted[a]	1.53 (1.43, 1.63)[b]
2	Age, gender, race, cause of ESRD, and year started HD[a]	1.28 (1.20, 1.37)[b]
3	Model 2 plus baseline calcium, phosphorus, PTH, albumin, *Kt/V*, creatinine, and Hct[c,d]	1.21 (1.10, 1.33)[b]
4	Model 3 plus clinic SMR[e]	1.20 (1.10, 1.32)[b]

Tentori, KI 2006, 70, 1858–1865.

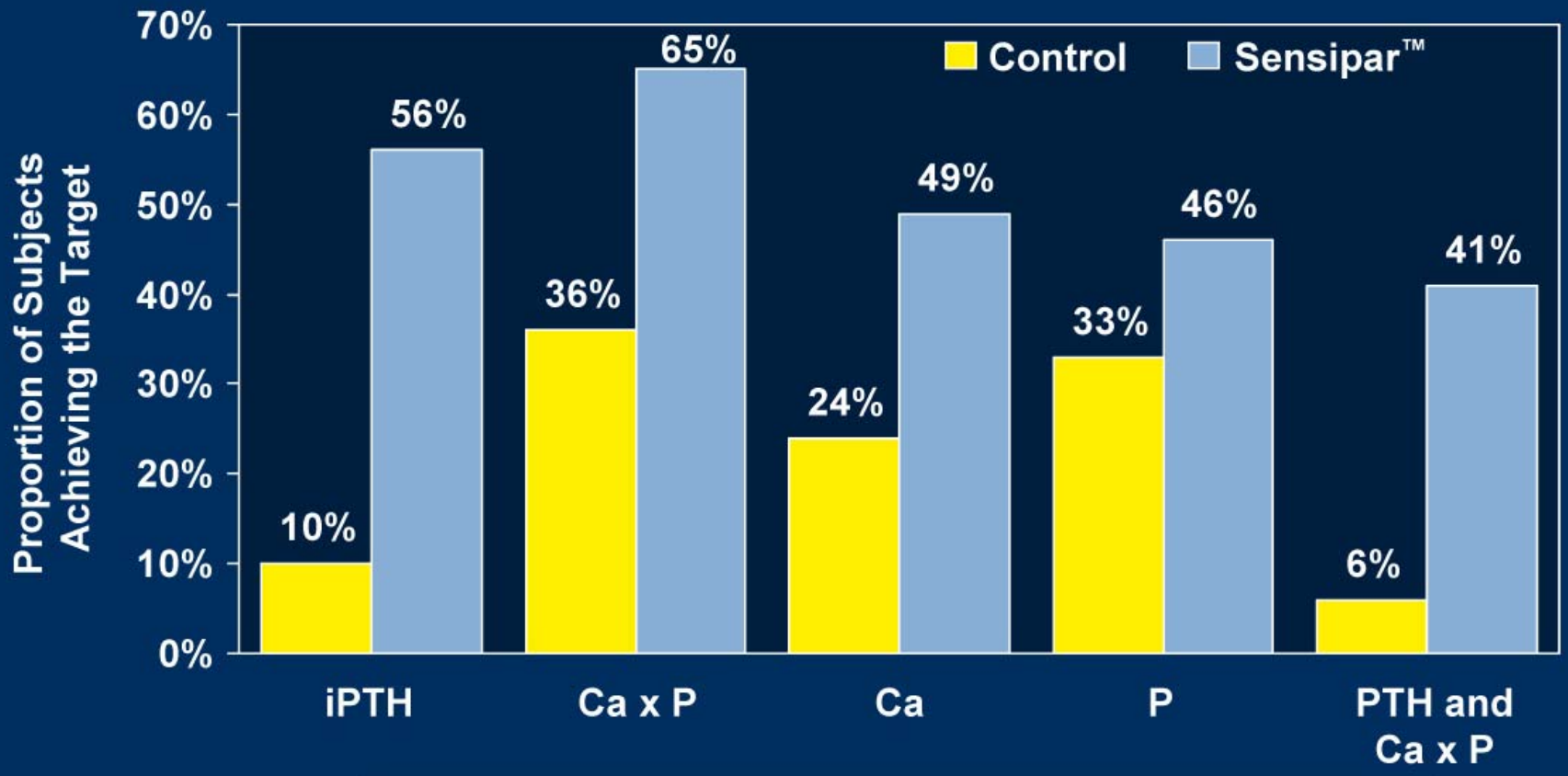
Cinacalcet

Sensipar™ Consistently Improved All Secondary HPT Endpoints in Phase III Trials



Sensipar™ Product Monograph

Sensipar™ (cinacalcet HCl) Facilitated Achievement of All Four Key K/DOQI™ Secondary HPT Targets



***TARGETS: iPTH 150 - 300 pg/mL (16.5 - 33 pmol/L), Ca x P < 55 mg^2/dL^2 (< 4.5 $mmol^2/L^2$), Ca 8.4–9.5 mg/dL (2.1-2.4 mmol/L), P 3.5–5.5 mg/dL (1.1-1.8 mmol/L)**

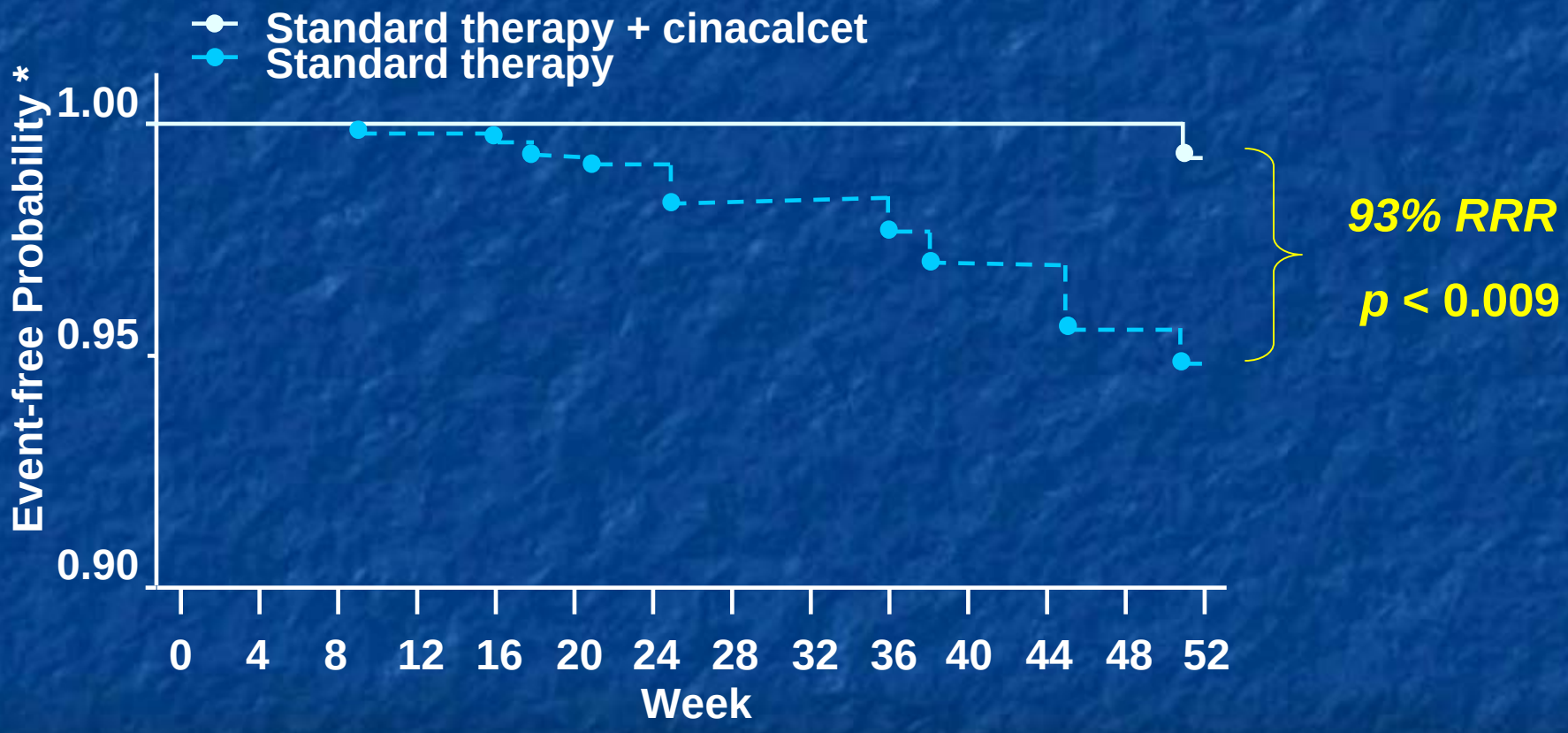
*The K/DOQI™ target range for iPTH is 150 to 300 pg/mL.
Data on file, Amgen.

Clinical Outcomes with Cinacalcet:

- Combined analysis of safety data
  - Parathyroidectomy, fracture, hospitalisations and mortality
- Methods:
  - Database: 1184 patients (697 cinacalcet, 487 control)
  - 4 similarly designed randomised, double-blind, placebo-controlled clinical trials
  - Cinacalcet or placebo administered to patients receiving standard care (phosphate binders and vitamin D) for SHPT
  - Relative risk assessment with follow-up times from 6 to 12 months

Adapted from Cunningham J *et al. Kidney Int* 2005

Reduction in the Risk of Parathyroidectomy with Cinacalcet

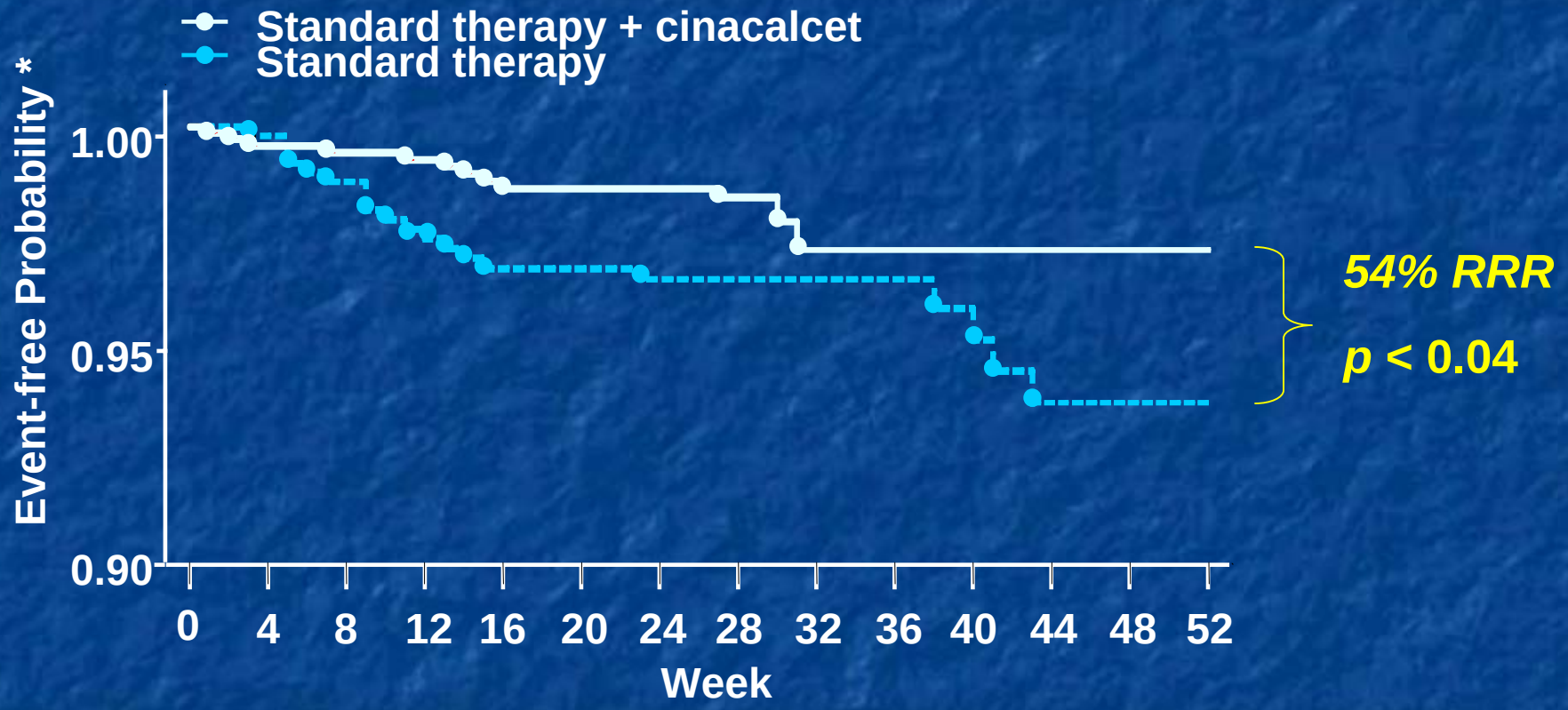


0.3 (cinacalcet) vs. 4.1 (control) parathyroidectomies per 100 patient years ($p < 0.01$)

* Refers to the risk that an event does not occur

Adapted from Cunningham J *et al. Kidney Int* 2005

Reduced Risk of Fracture with Cinacalcet

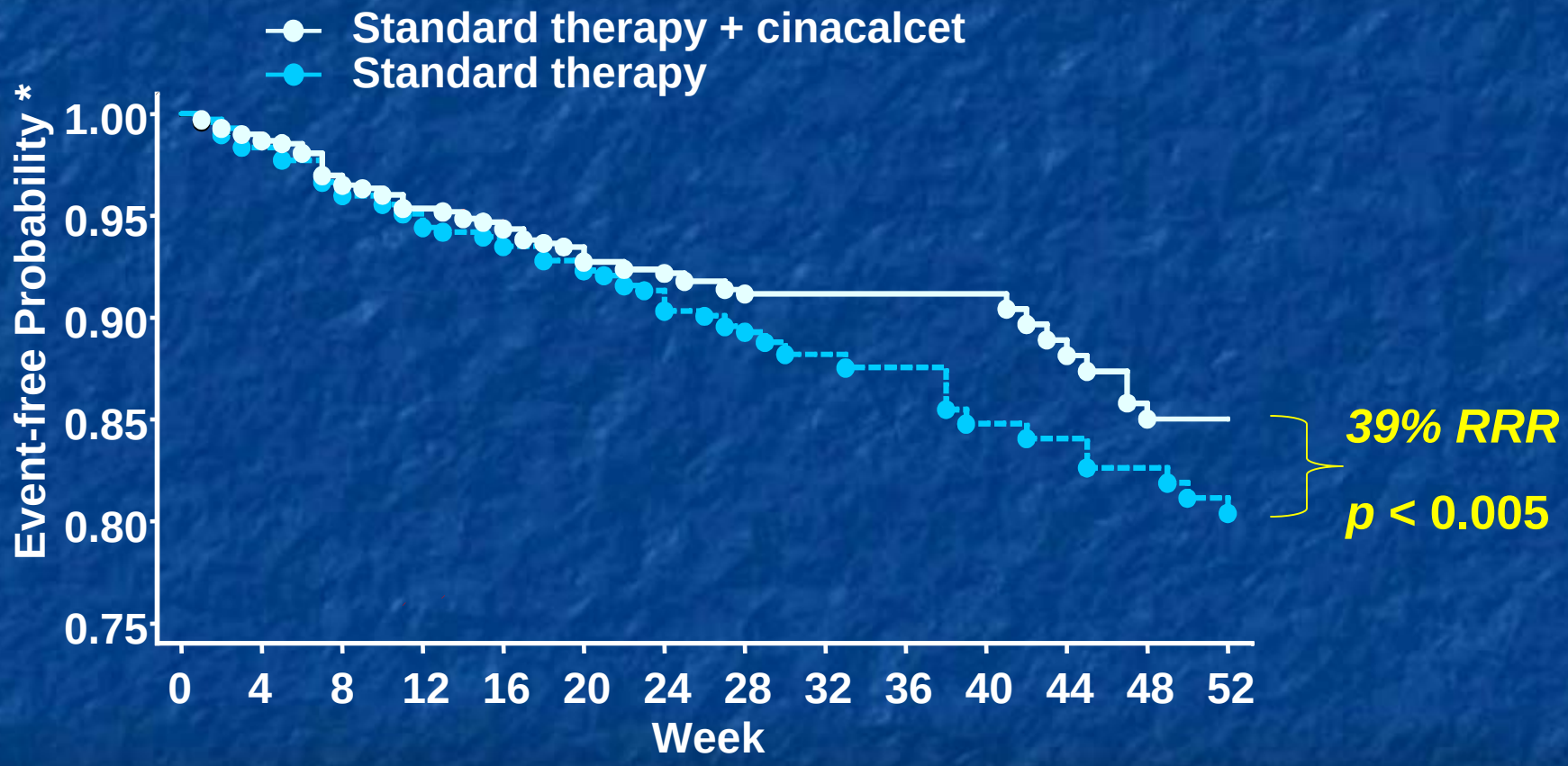


Patients treated with cinacalcet had a significant reduction in fracture rate compared to control **- 3.2 vs. 6.9 fractures per 100 patient years ($p < 0.05$)**

* Refers to the risk that an event does not occur

Adapted from Cunningham J *et al. Kidney Int* 2005

Reduced CV Hospitalization Rates with Cinacalcet



Patients treated with cinacalcet had a significant reduction in CV hospitalization rates compared to control **– 15.0 vs. 19.7 hospitalizations per 100 patient years (*p* < 0.01)**

* Refers to the risk that an event does not occur

Adapted from Cunningham J *et al. Kidney Int* 2005

Effects of Drug Therapies on Bone/Mineral Parameters

Agent	iPTH	P	Ca	Ca x P
Vitamin D	↓	↑	↑	↑
Ca-based PO_4 binders	↘	↓	↑	↘
Non Ca-based PO_4 binders	→	↓	→	↓
Cinacalcet HCl	↓	↓	↓	↓

Reduction
Slight Reduction
No effect
Increase

Summary:

- CVD is the major cause of mortality in ESRD
- vascular calcification is largely attributable to disordered mineral metabolism
- therapeutic strategies are evolving
- THE GOOD, THE BAD AND THE UGLY