Brigham and Women's Hospital
Founding Member, Mass General Brigham

Chronic Kidney Disease – Mineral and Bone Disorder

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John J. Kuiper Distinguished Professor of Medicine Emeritus
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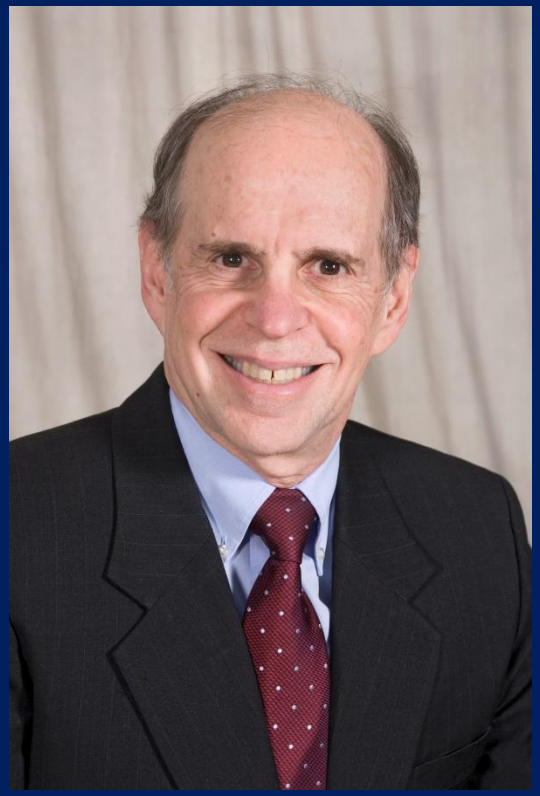
Rochester, New York

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

David Bushinsky, MD



MD at Tufts University School of Medicine
Residency at Tufts-New England Medical Center
Renal Fellowship at Tufts- New England Medical Center
Professor of Medicine and of Pharmacology and Physiology Emeritus at University of Rochester School of Medicine
John J. Kuiper Distinguished Professor Emeritus at University of Rochester School of Medicine
Academic Focus
- Effects of Acid on Bone
- Genetic Hypercalciuria & Kidney Stone Formation

David Bushinsky, MD
Disclosure Information

Employee of:	**University of Rochester, Rochester, NY**
Research support:	**National Institutes of Health**
Consultant:	**None**
Stockholder:	**Amgen**

66 yo obese Black male with DM and hypertension.

BMI = 31
DM – 20 years and moderately well controlled
Hypertension – 35 years – typical BP 142/86

On:
ARB (low dose secondary to hyperkalemia)
Loop diuretic
Insulin
MVI
Vitamin D_3

GFR = 9 ml/min
K = 4.8 meq/l
Ca = 9.2 mg/dl
P = 5.6 mg/dl
25 D = 25 ng/ml
PTH = 345 pg/ml

Over the course of the next 6 months GFR falls

GFR = 4 ml/min
K = 5.3 meq/l
Ca = 9.5 mg/dl
P = 6.1 mg/dl
25 D = 22 ng/ml
PTH = 469 pg/ml

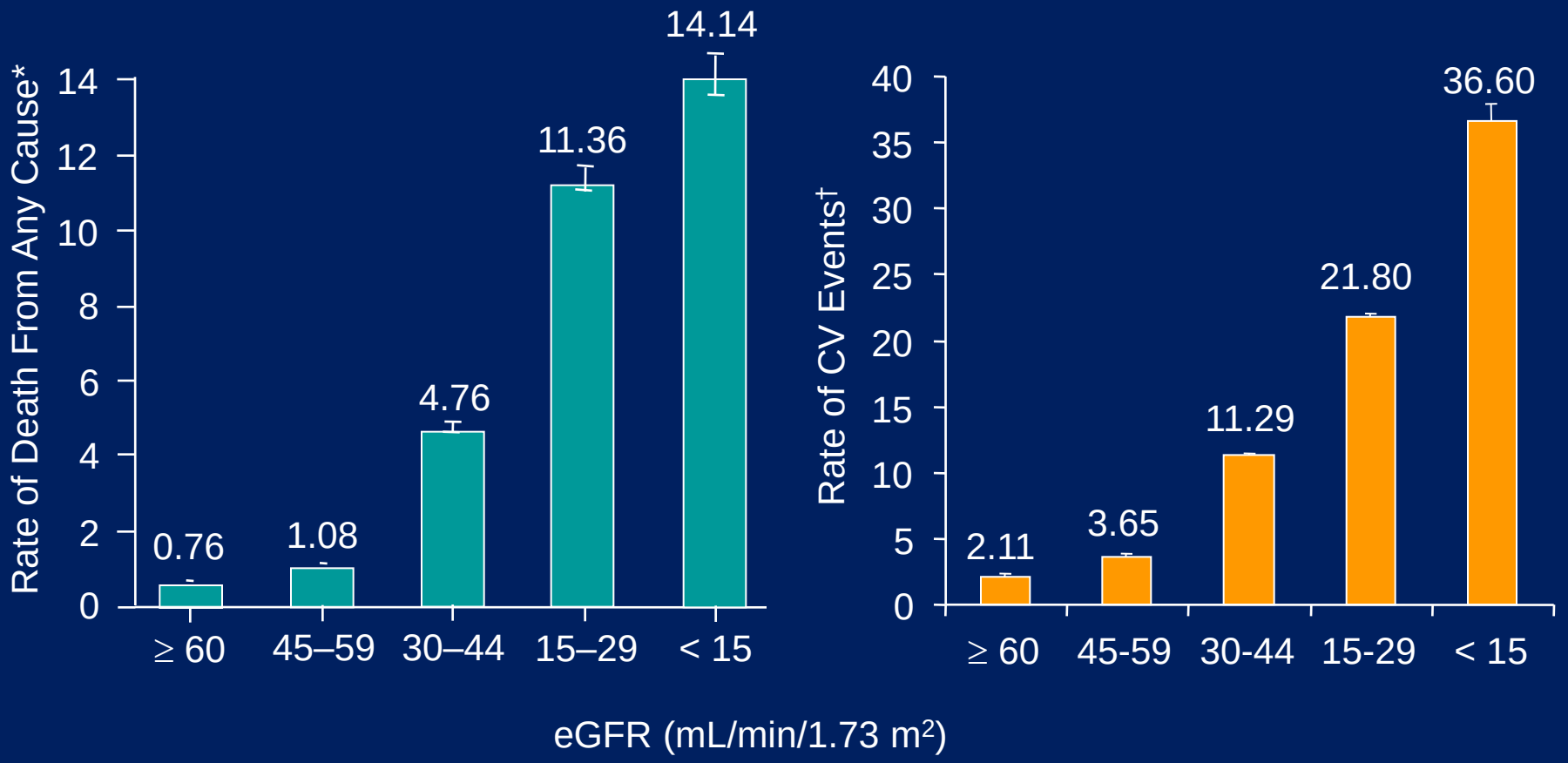
Patient has nausea, lethergy, wt loss and is started on 3X/wk HD

What do you do with respect to:

Phospahate Binders ?
Vitamin D – dietary and/or activated ?
Cinacalcet or Etelcalcetide ?

Is he at risk for vascular calcification?
can you prevent it?

Rate of Death and Cardiovascular Events According to Estimated GFR

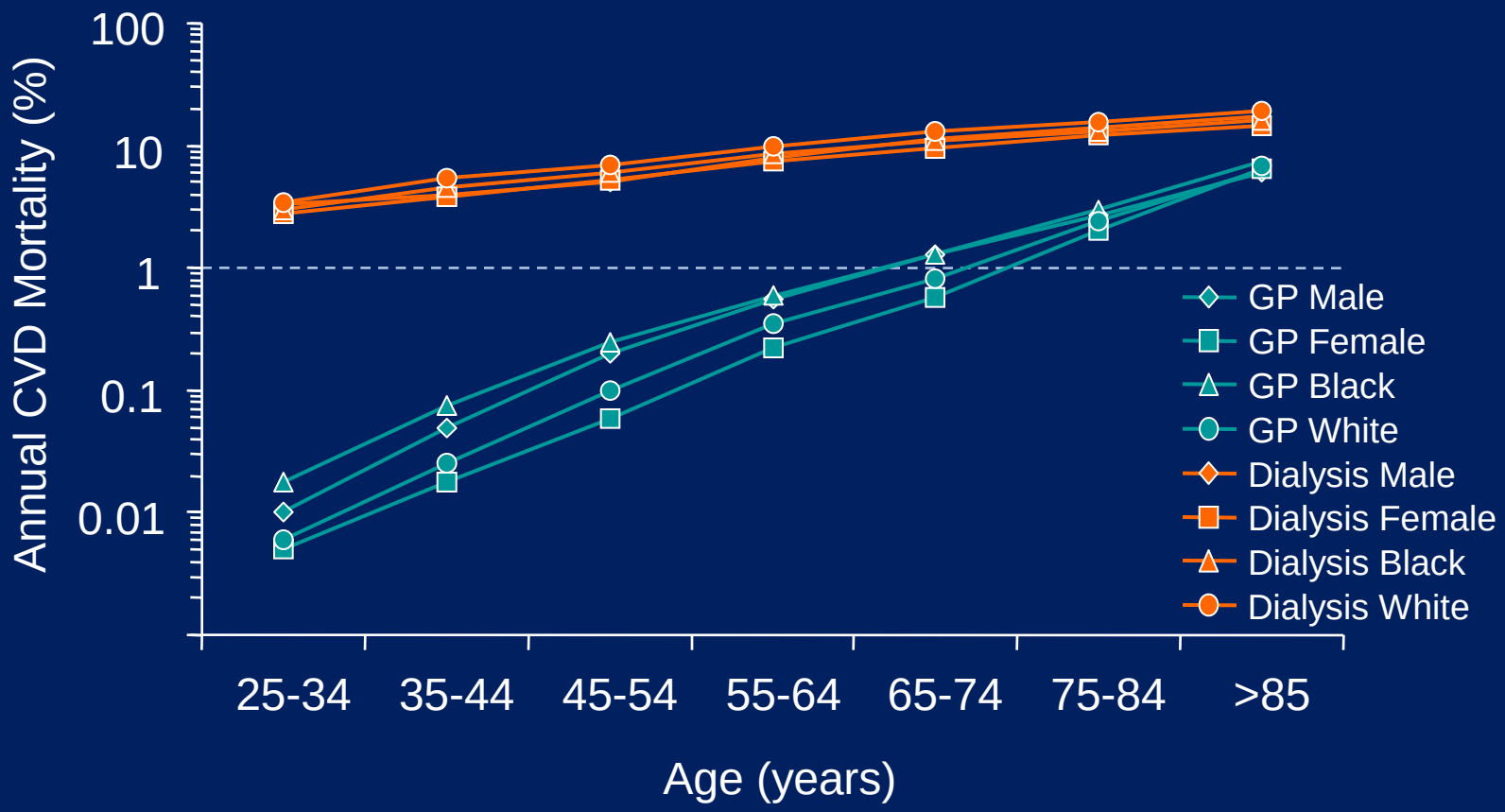


N = 1,120,295 adults.

*Age-standardized rates per 100 person-years; †CV event defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease per 100 person-years.

Go AS, et al. *N Engl J Med.* 2004,351:1296-1305.

Dialysis Patients Have Increased Cardiovascular Disease Mortality

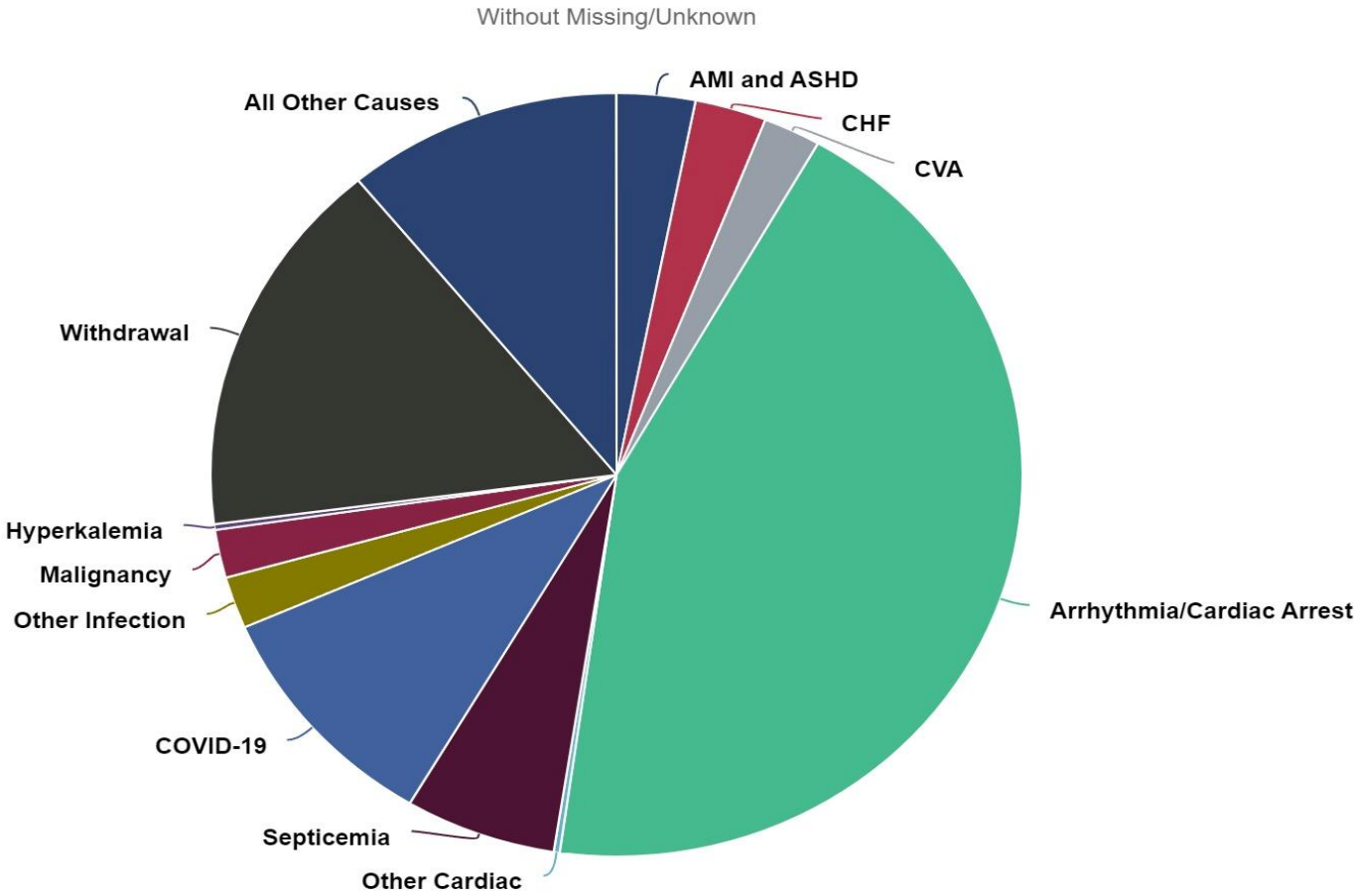


GP = general population.

Foley RN, et al. *Am J Kidney Dis*. 1998;32(suppl 3):S112-S119.

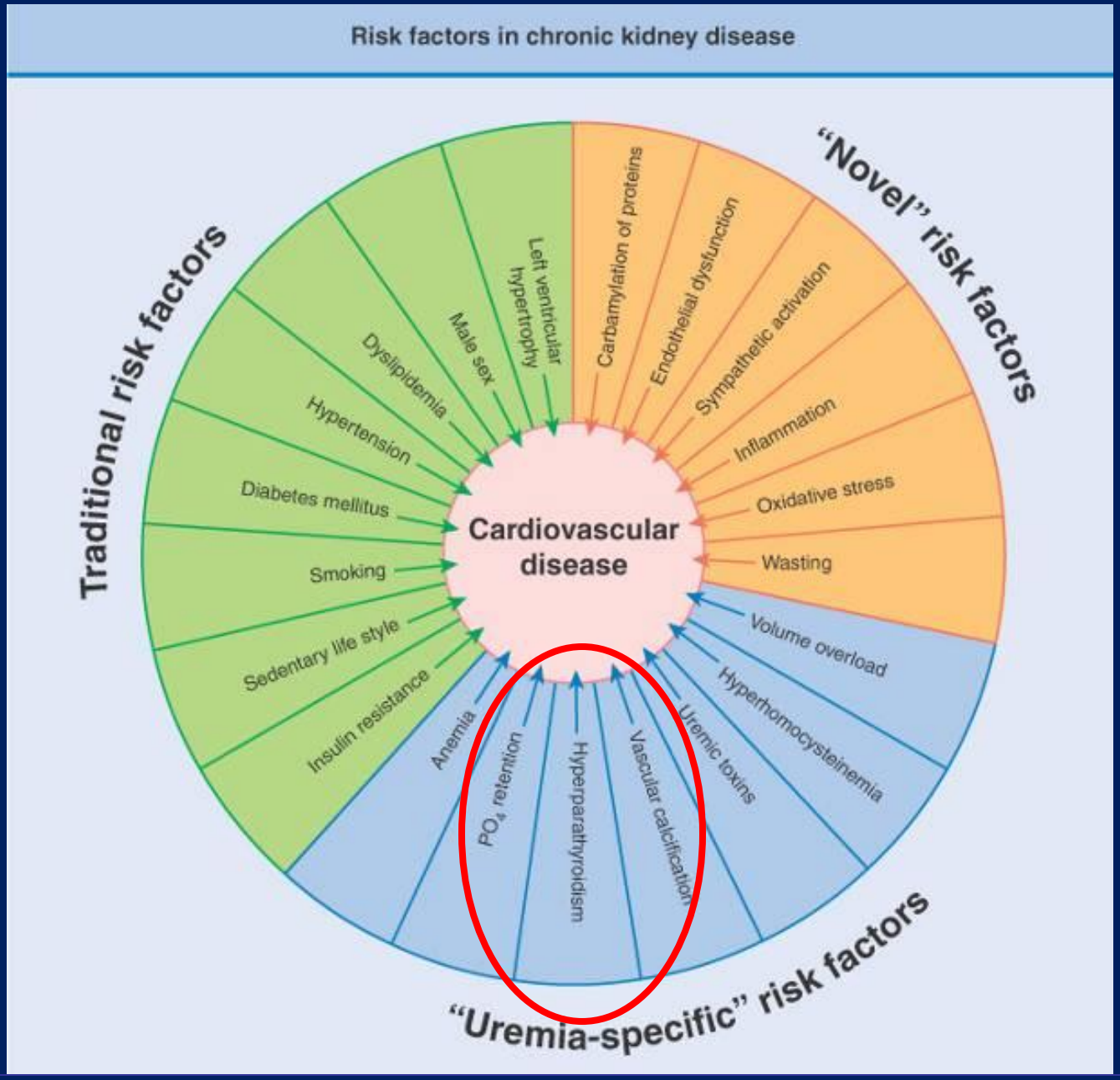
Dialysis patient mortality

Figure 6.6a Percentages of cause-specific mortality, with and without inclusion of missing and unknown causes of death, in patients with ESRD receiving hemodialysis, who died in 2021



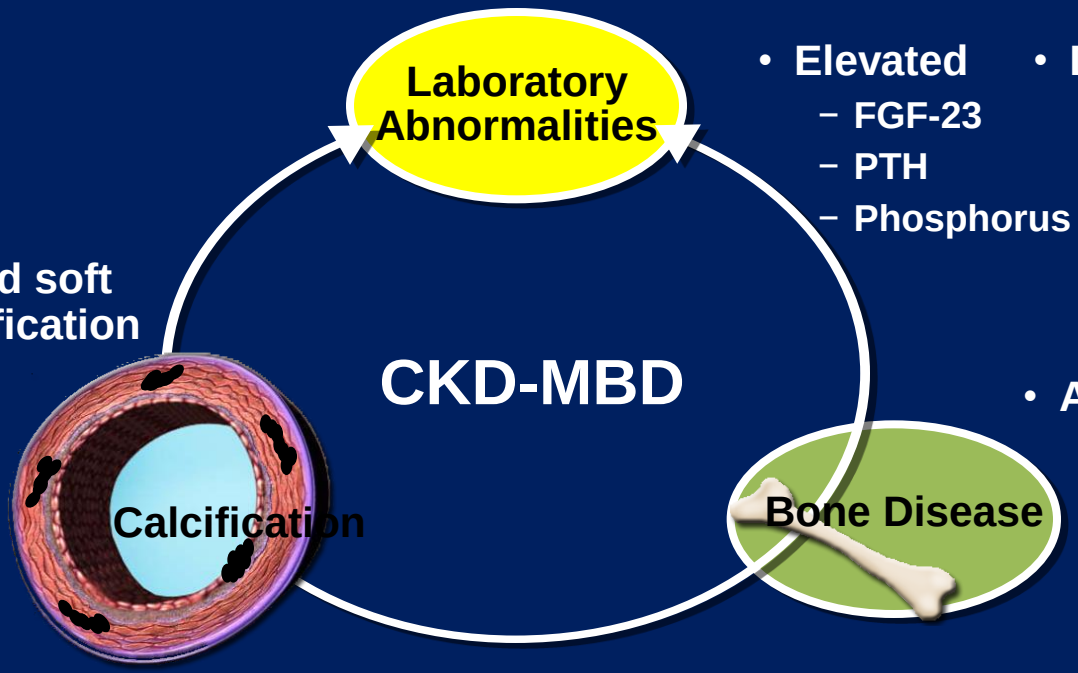
Data Source: 2023 United States Renal Data System Annual Data Report

52.5% of deaths were related to cardiovascular disease



Stenvinkel et al. Comprehensive Clin Neph 2007

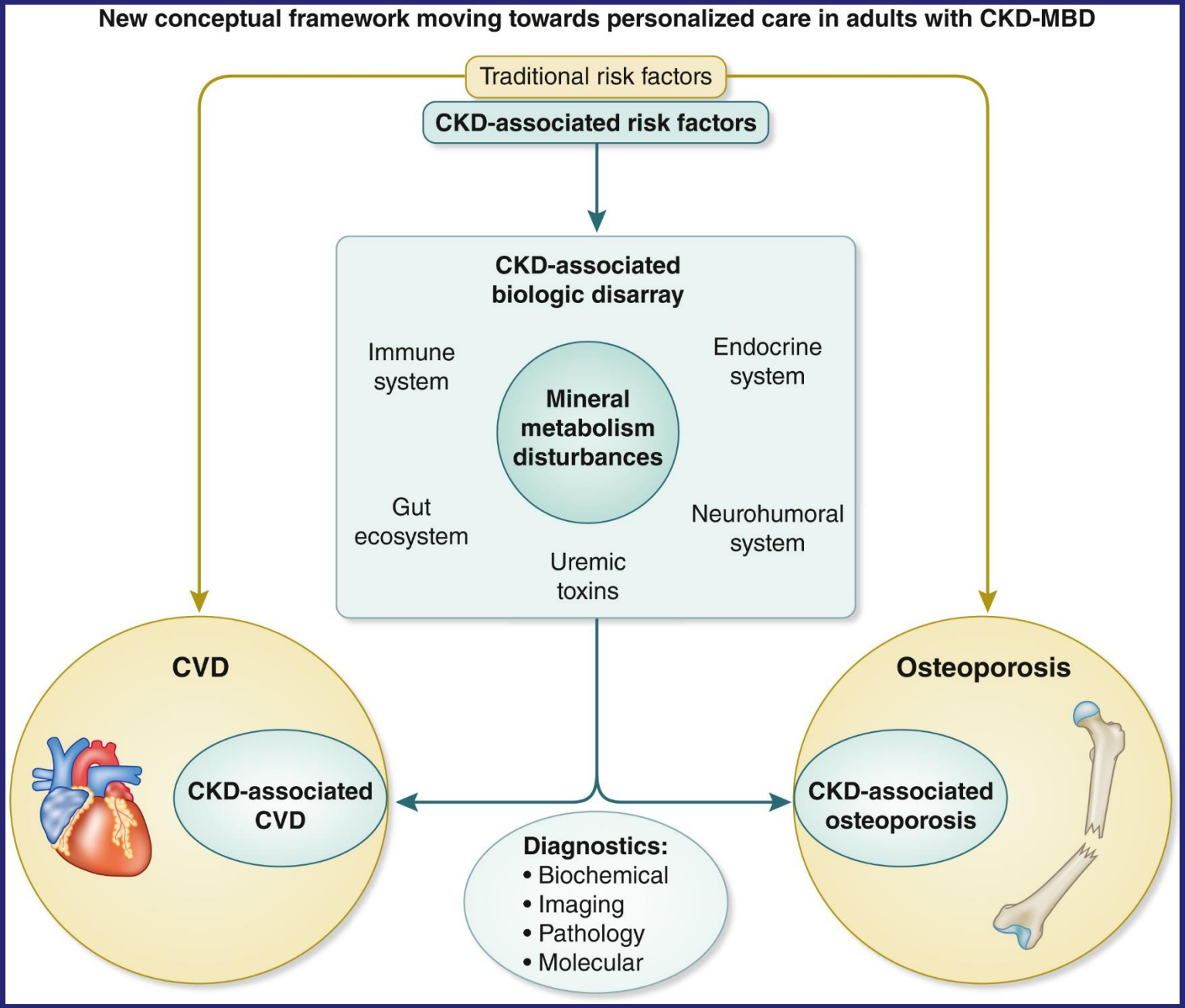
Chronic Kidney Disease-Mineral Bone Disorder



- Elevated
  - FGF-23
  - PTH
  - Phosphorus
- Decreased
  - $1,25(OH)_2D_3$
  - Calcium
- Vascular and soft tissue calcification
- Abnormal bone
  - Turnover
  - Mineralization
  - Volume
  - Linear growth
  - Strength

PTH = parathyroid hormone;
FGF-23 = fibroblast growth factor-23.

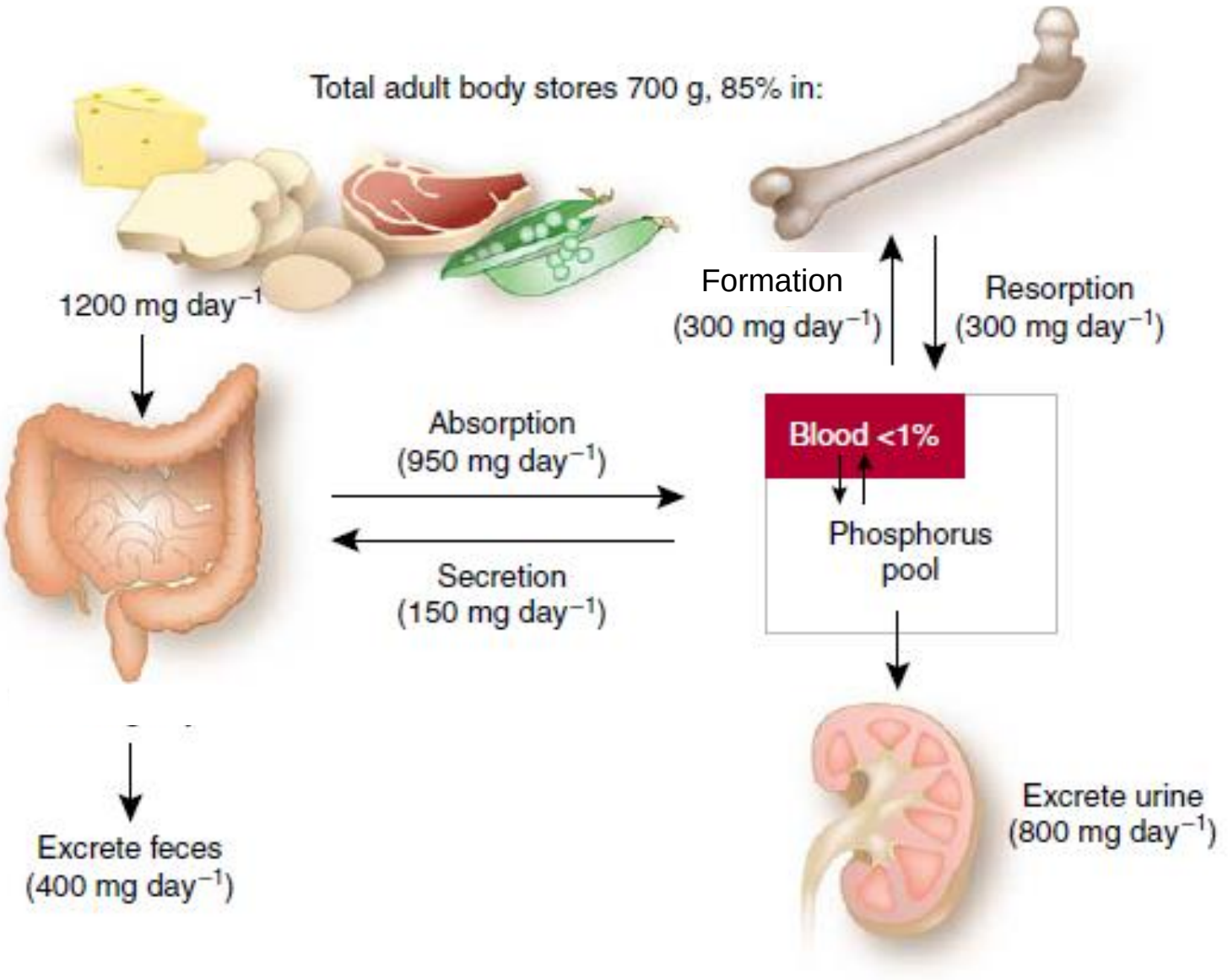
Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. *Kidney Int.* 2009;76



Kettler et al. Kid Intl. 2025:107,405

Pathophysiology of CKD-MBD

Phosphorus Balance in Health

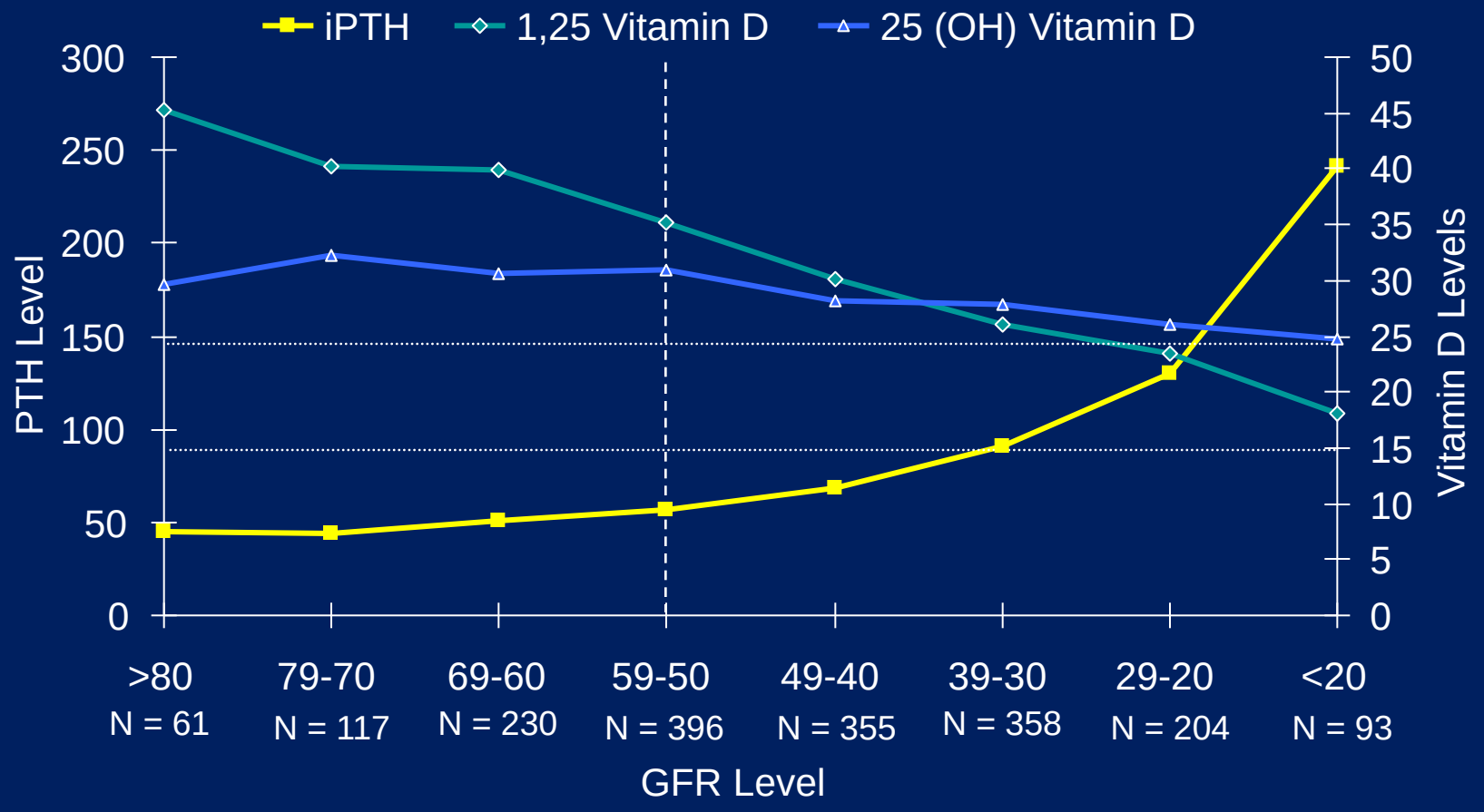


Hruska, KA et al. (2008). Kidney International, 74, 148–157.

1000 IU of oral vitamin D_3 per day will directly:

a. increase intestinal Ca absorption, increase intestinal P absorption, increase bone mineralization
b. increase intestinal Ca absorption, not alter intestinal P absorption, not alter bone mineralization
c. not alter intestinal Ca absorption, not alter intestinal P absorption, not alter bone mineralization
d. not alter intestinal Ca absorption, increase intestinal P absorption, not alter bone mineralization
e. increase intestinal Ca absorption, not alter intestinal P absorption, not alter bone mineralization
f. none of the above

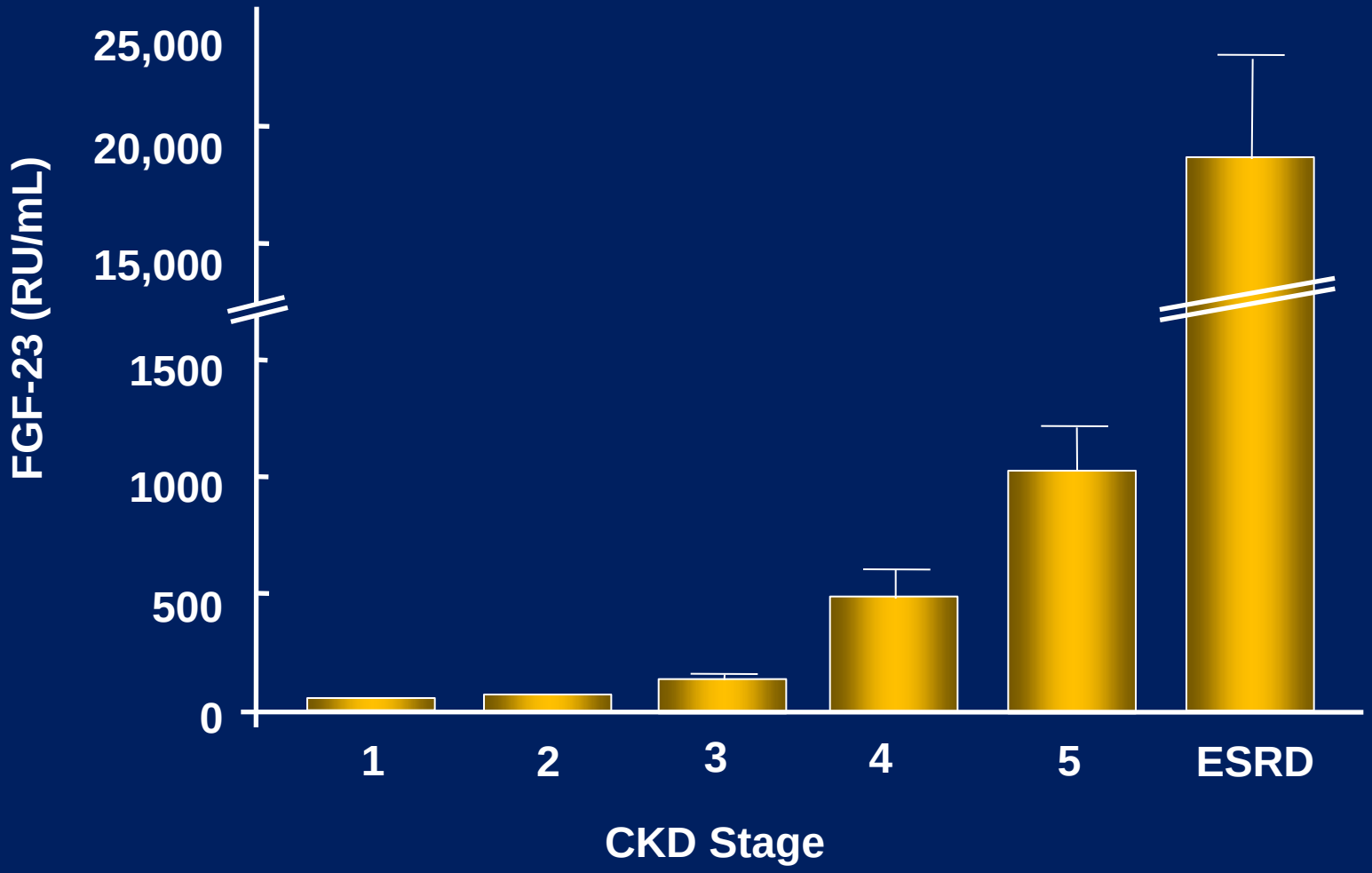
Progression of iPTH, Corrected Ca, and P Levels
Study for the Evaluation of Early Kidney Disease (SEEK)



N = 1814

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

Serum FGF-23 in Various Stages of CKD

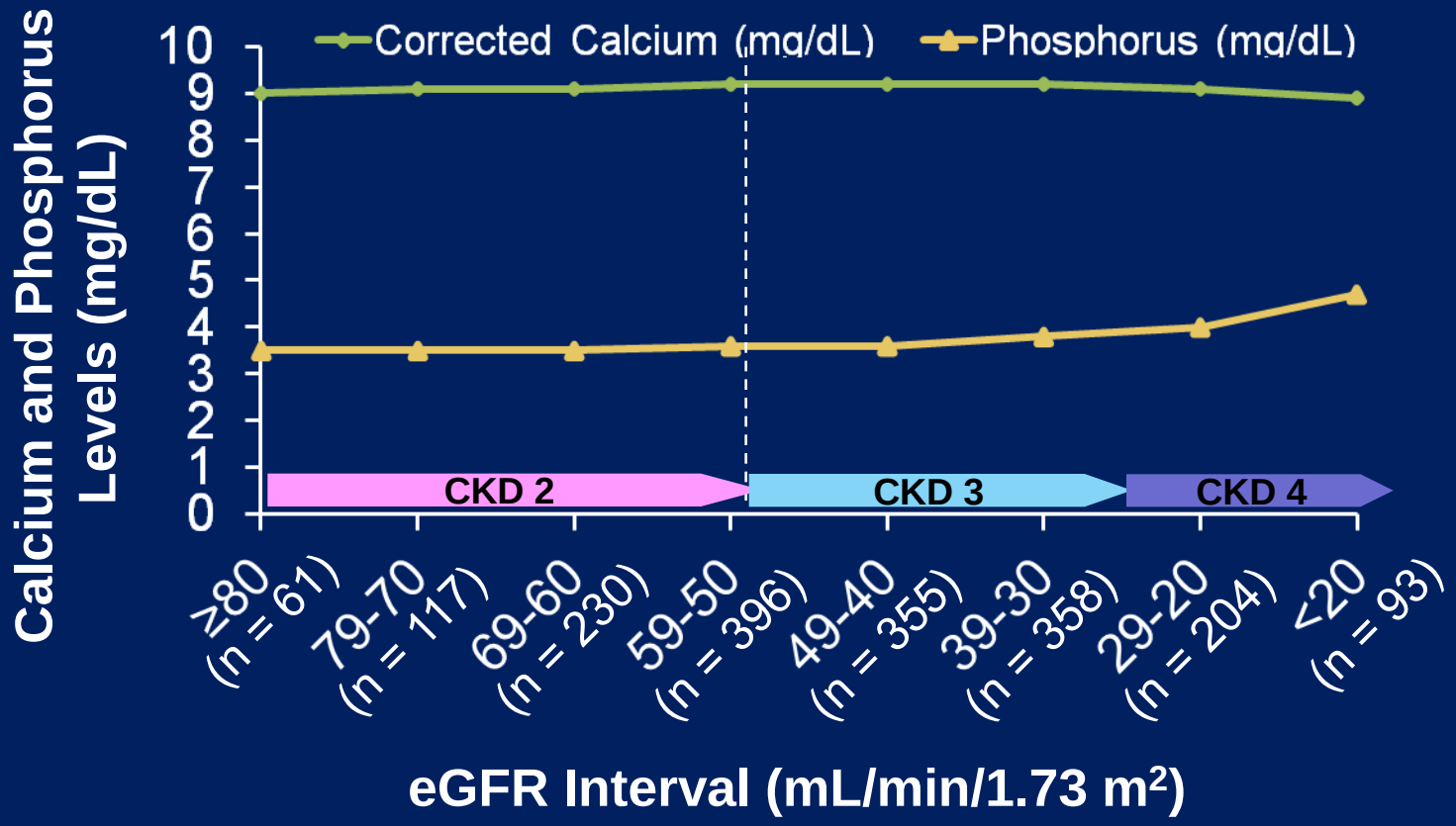


ESRD = end stage renal disease.

Pande S et al. *Nephron Physiol.* 2006;104:p23-p32.

Progression of iPTH, Corrected Ca, and P Levels Study for the Evaluation of Early Kidney Disease (SEEK)

Prospective, observational, multi-center study



N = 1814

Levin A et al. *Kidney Int*. 2007;71:31-38.

CKD-MBD

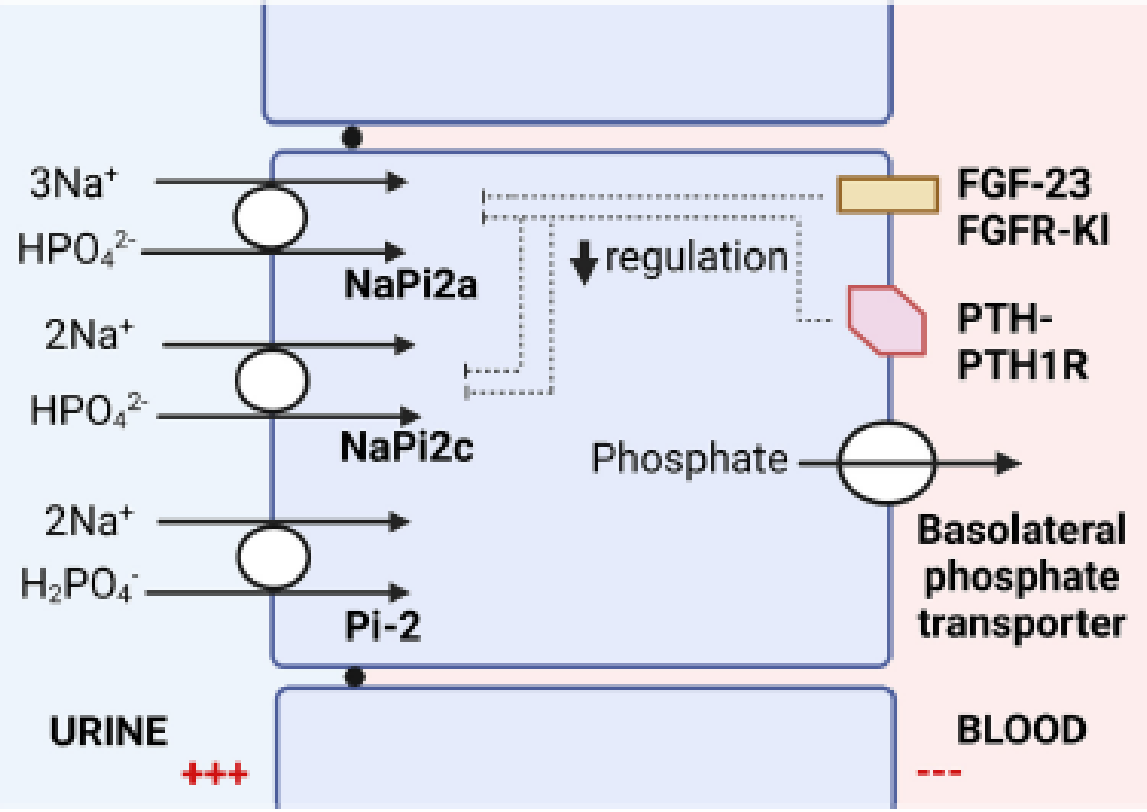


Figure 5. Phosphate transport in the proximal convoluted tubule. Phosphate is reabsorbed via transcellular transport in the proximal convoluted tubule. Three sodium-phosphate cotransporters, NaPi-2a, NaPi-2c, and PiT-2, transport phosphate from the tubular lumen into the cell. Phosphate is then transported out of the cell by an unknown basolateral phosphate transporter. Binding of FGF-23 to FGF receptor (FGFR)-klotho (Kl) complexes, and PTH to the PTH1R inhibits phosphate reabsorption by down-regulating apical expression of NaPi-2a and NaPi-2c. Created with Biorender. Abbreviations: FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; PTH1R, parathyroid hormone 1 receptor.

AJKD 83:2024

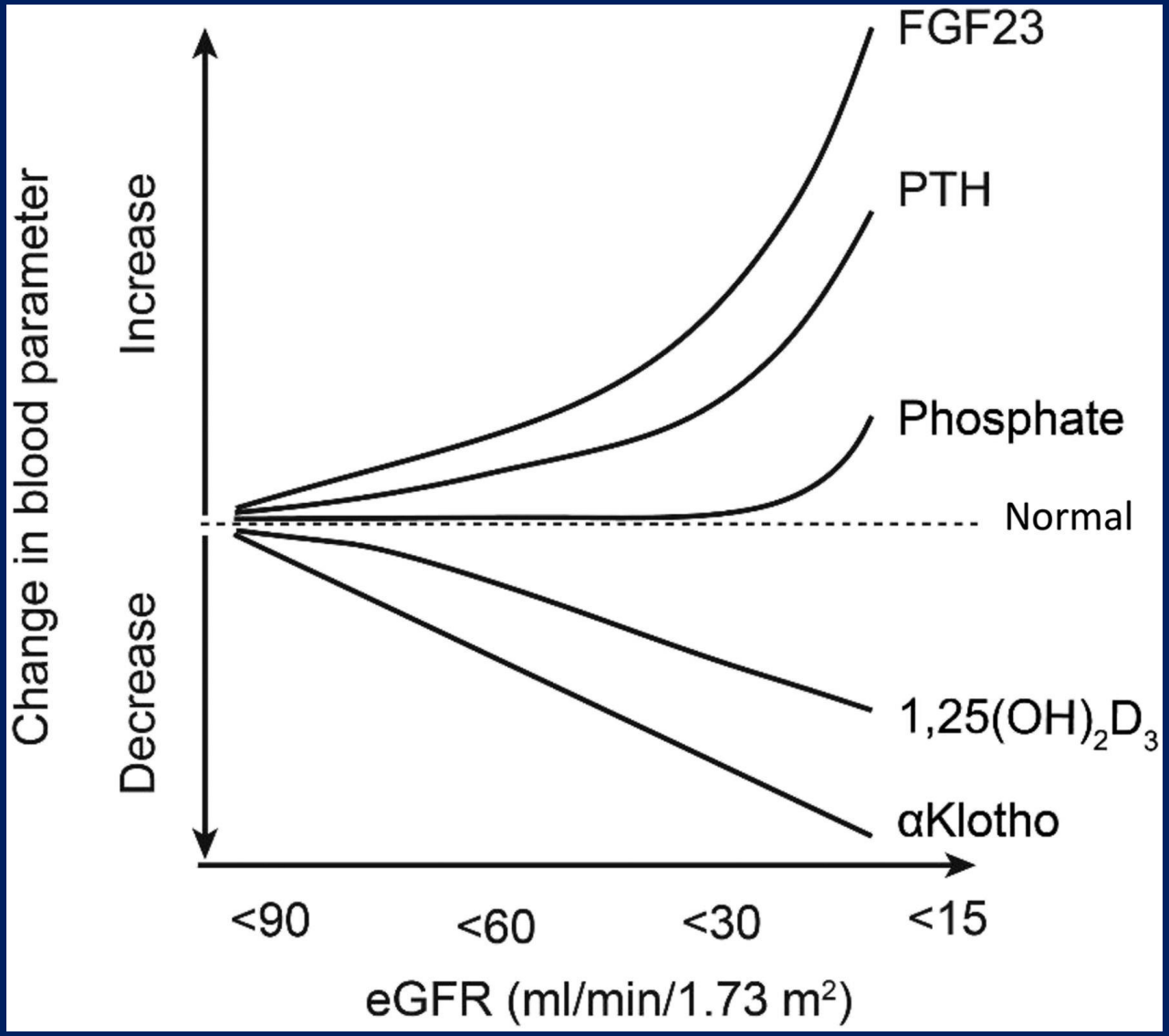
Comparison of FGF-23 and PTH

	FGF-23	**PTH**
Site of Production	Osteoblasts	Chief cells in parathyroid gland
Principal stimulus	Phosphorus load / hyperphosphatemia	Hypocalcemia
Principal regulator of	Phosphorus	Calcium Phosphorus
Effect on urinary phosphorus	Phosphaturic	Phosphaturic
Effect on 1,25 D production	Decreases	Increases

With respect to phosphorus, an acute infusion of FGF-23 will promptly:

a. not alter filtered load, increase tubular reabsorption, increase urine excretion
b. not alter filtered load, increase tubular reabsorption, stable urine excretion
c. not alter filtered load, increase tubular reabsorption, decrease urine excretion
d. decrease filtered load, decrease tubular reabsorption, increase urine excretion
e. increase filtered load, decrease tubular reabsorption, increase e urine excretion
f. decrease filtered load, decrease tubular reabsorption, decrease urine excretion

Changes in circulating soluble Klotho according to eGFR decline and its relationship to other mineral metabolism parameters. 1,25(OH)2D3, 1,25-dihydroxyvitamin D.



Javier A. Neyra et al. CJASN doi:10.2215/CJN.02840320

CKD-MBD

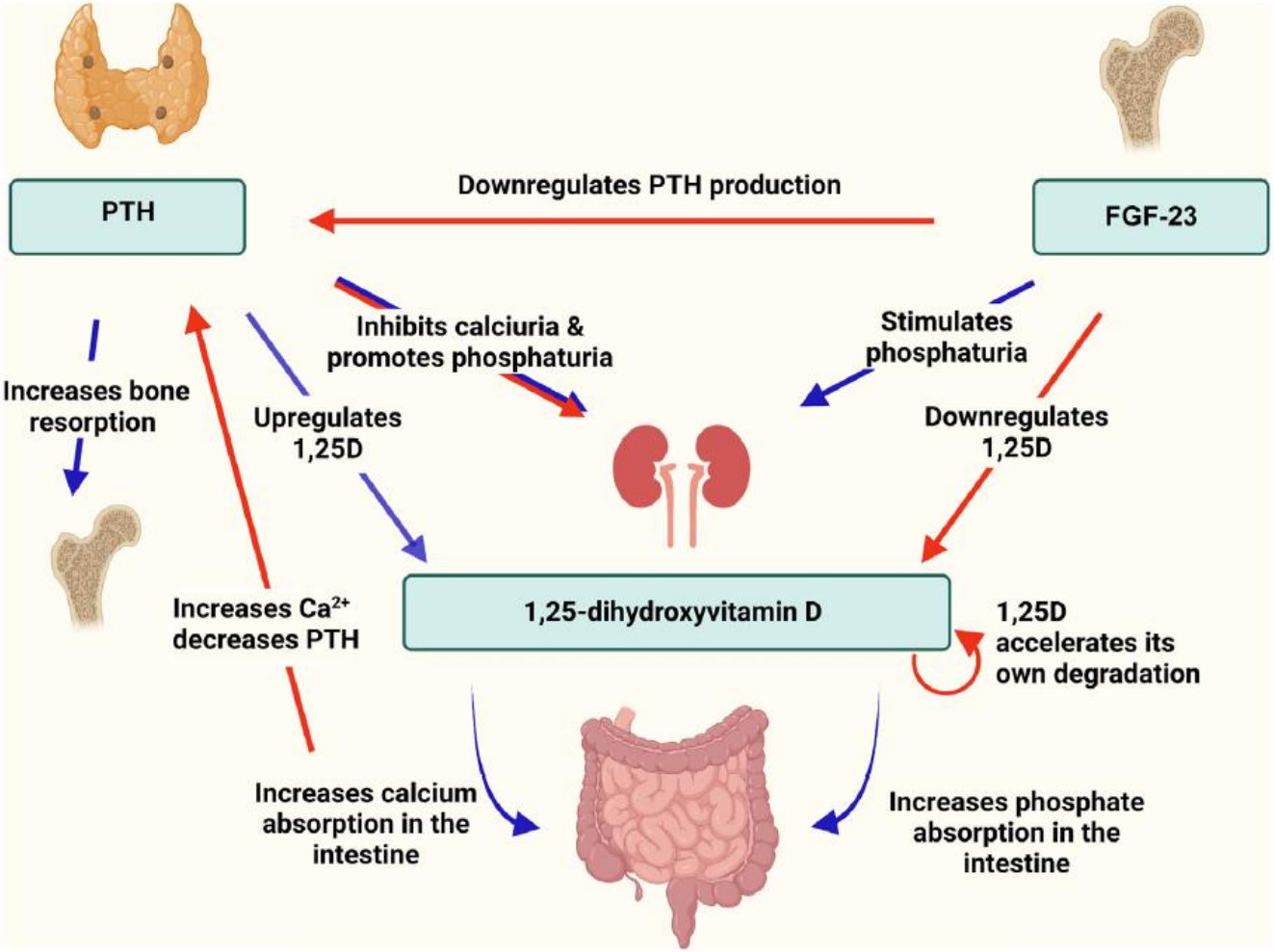
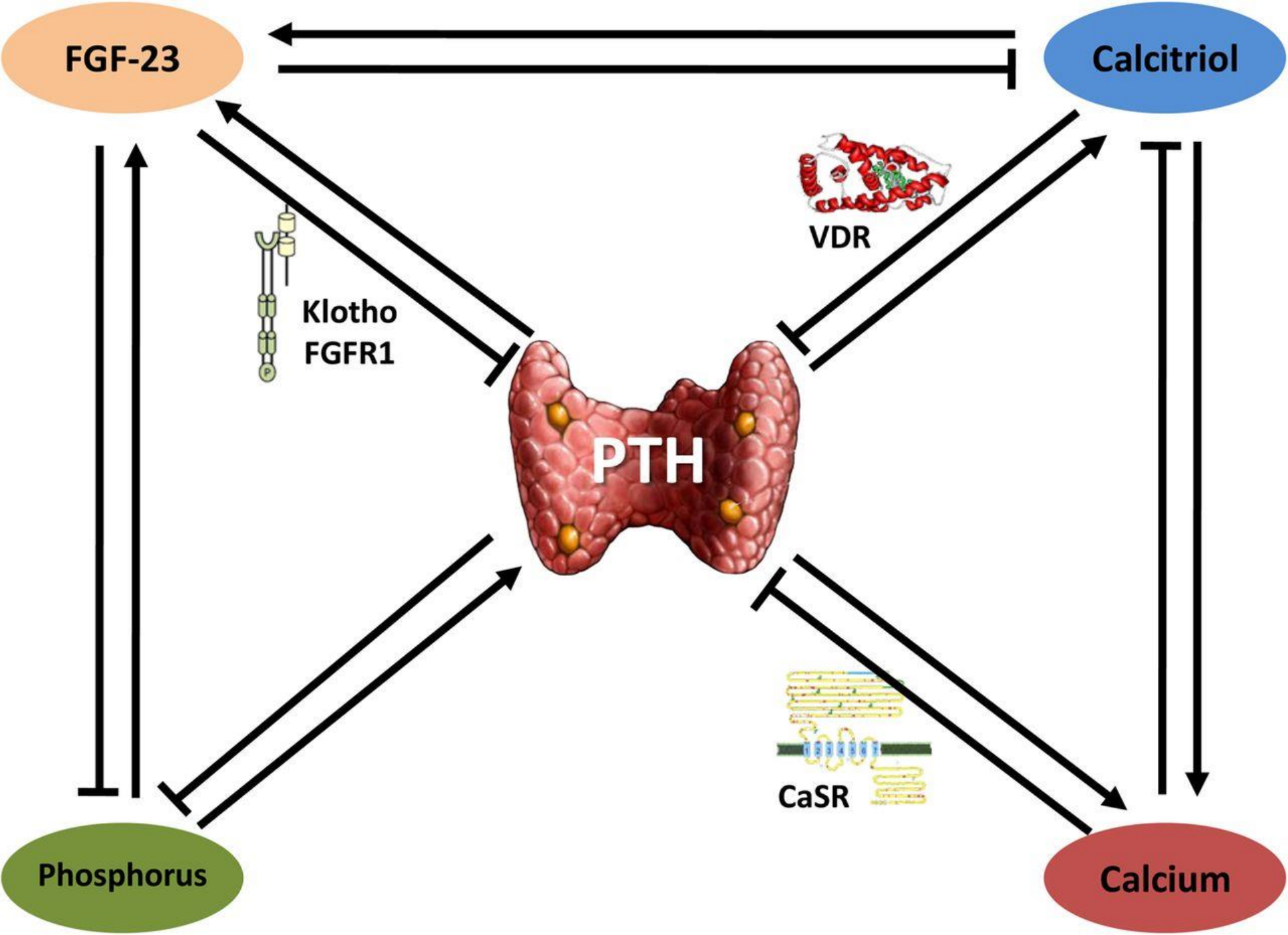


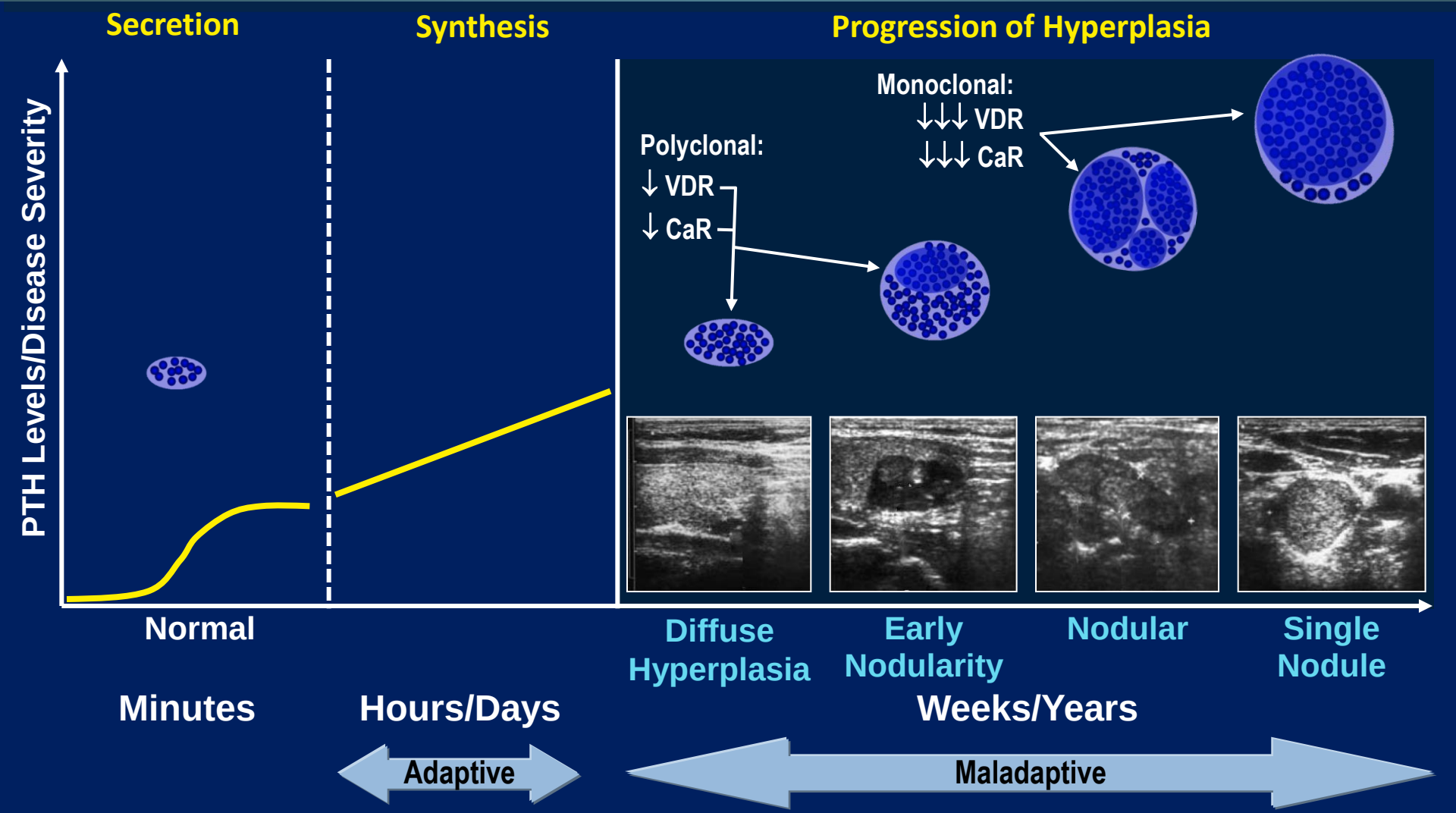
Figure 1. Axis of PTH, FGF-23, and 1,25-dihydroxyvitamin D. PTH, FGF-23, and 1,25$(OH)_2$D interact and regulate one another via classic negative endocrine feedback loops that affect calcium and phosphate transport in the kidney, bone, and intestine. Created with Biorender. Abbreviations: 1,25D, 1,25-diydroxyvitamin D; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.

AJKD 83:2024



Cannata-Andía, and Martin Nephrol. Dial. Transplant. 2015

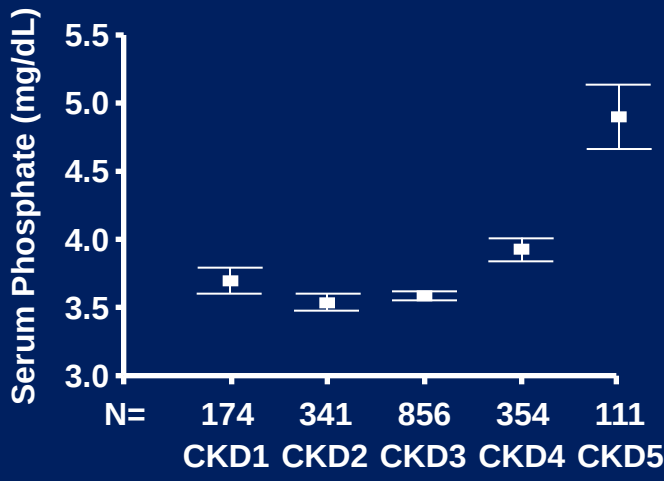
Progression of Parathyroid Gland Hyperplasia in Secondary HPT

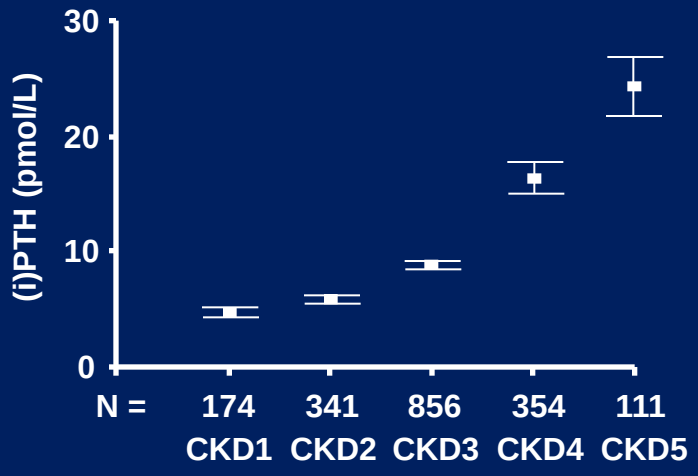


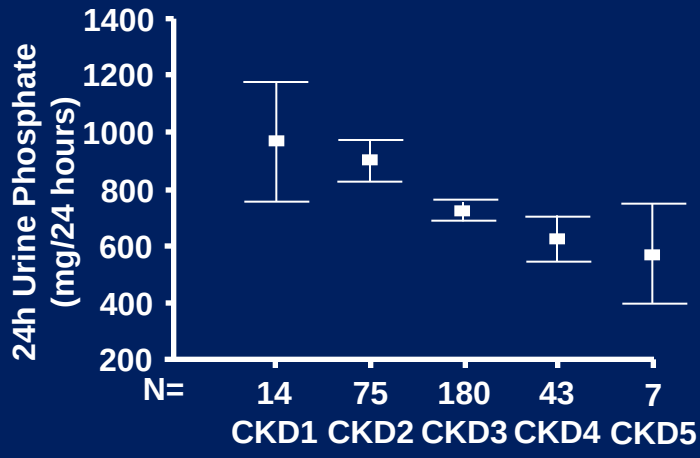
VDR = vitamin D receptor; CaR = calcium-sensing receptor.

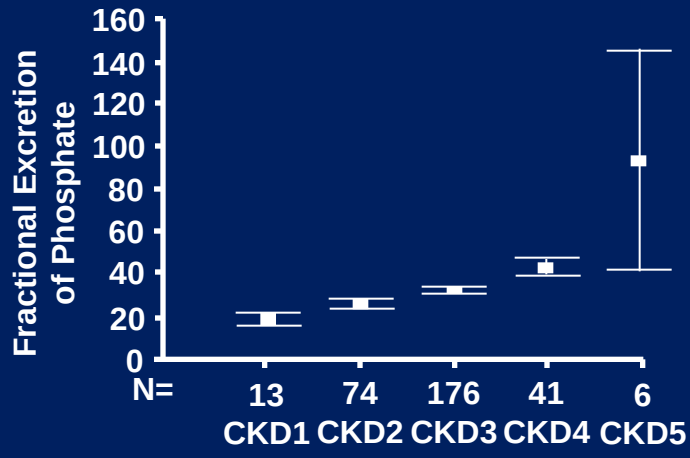
Adapted from Rodriguez M, et al. *Am J Physiol Renal Physiol*. 2005;288:F253-F264; Adapted from Tominaga Y, et al. *Semin Surg Oncol*. 1997;13:78-86; Adapted from Pavlovic D, et al. *Sci World J* 2006;6:1599-1608.

Phosphate Increases With Decreased Kidney Function



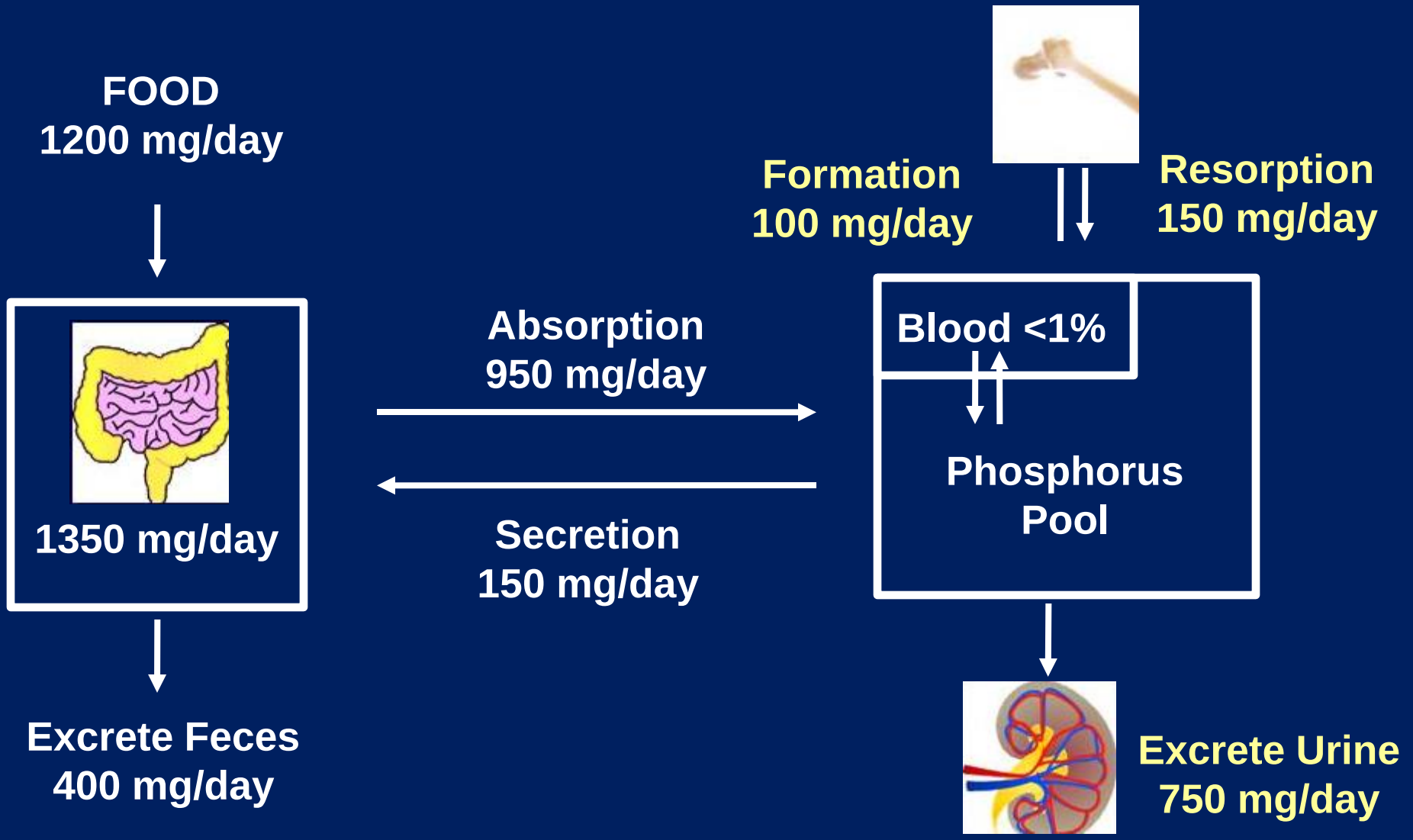




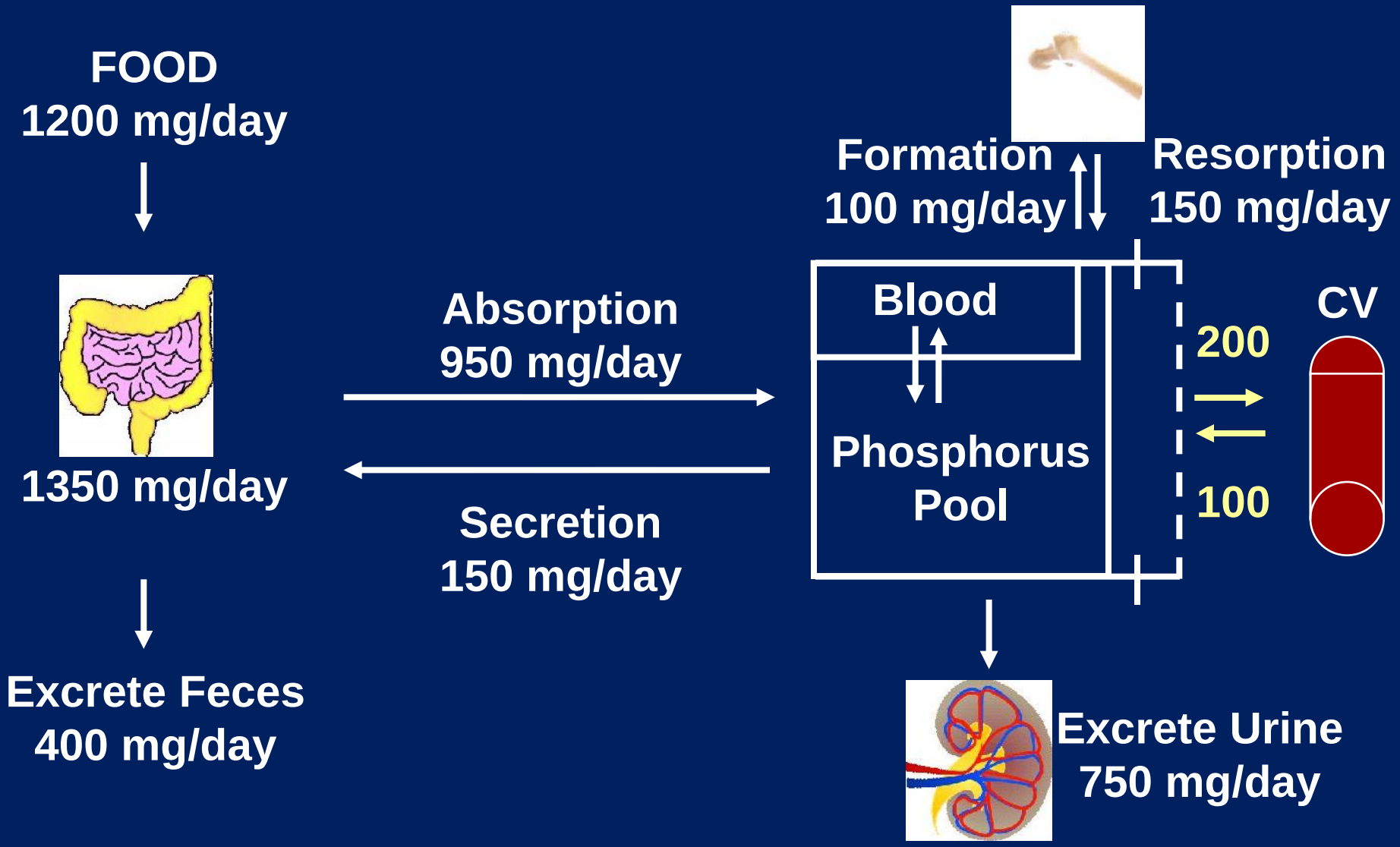


Craver L et al. *Nephrol Dial Transplant.* 2007;22:1171-1176.

Phosphorus Balance Is Lost in CKD

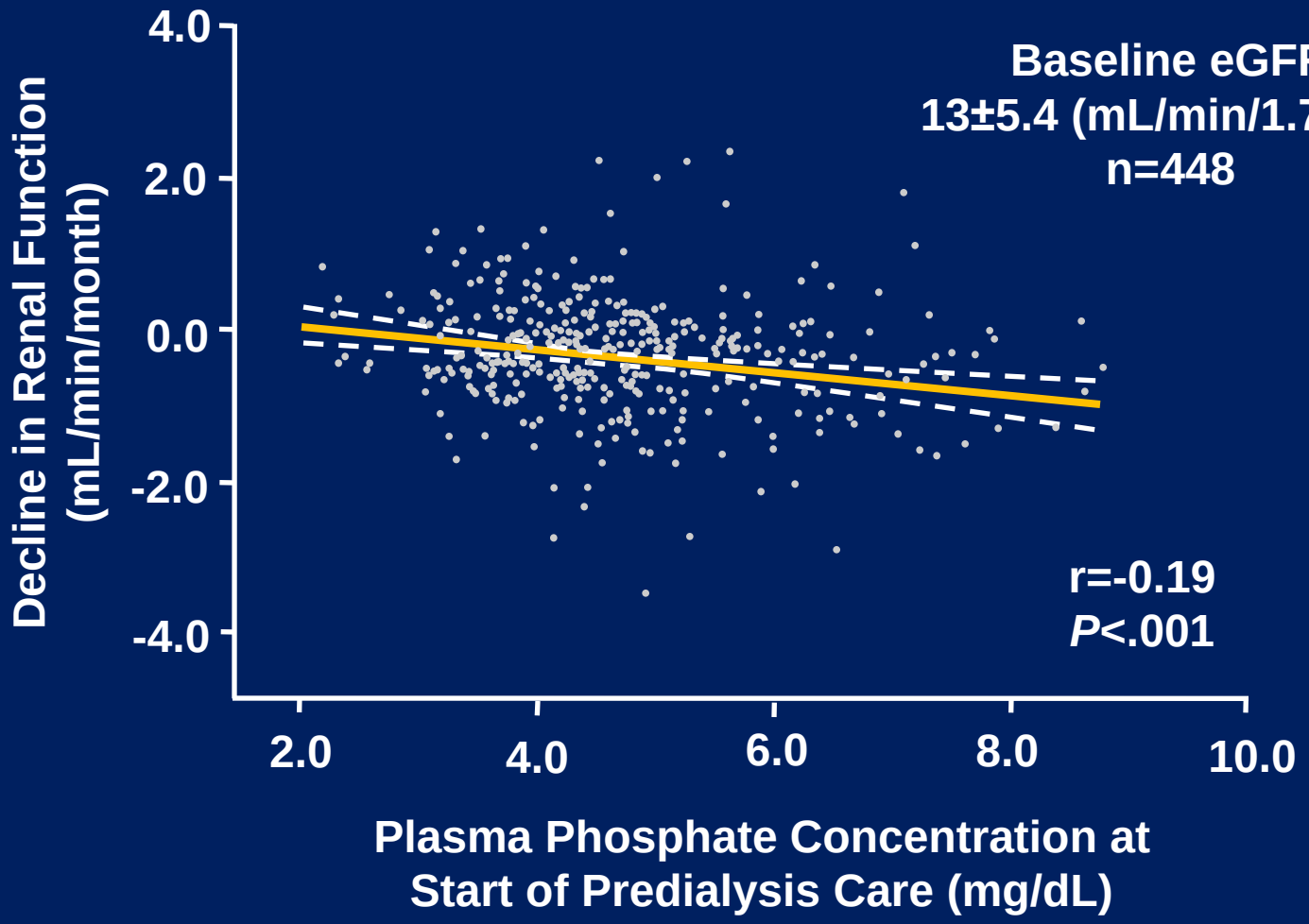


Phosphorus Balance Is Lost in CKD



Potential Deleterious Effects of Disorders of Mineral Metabolism

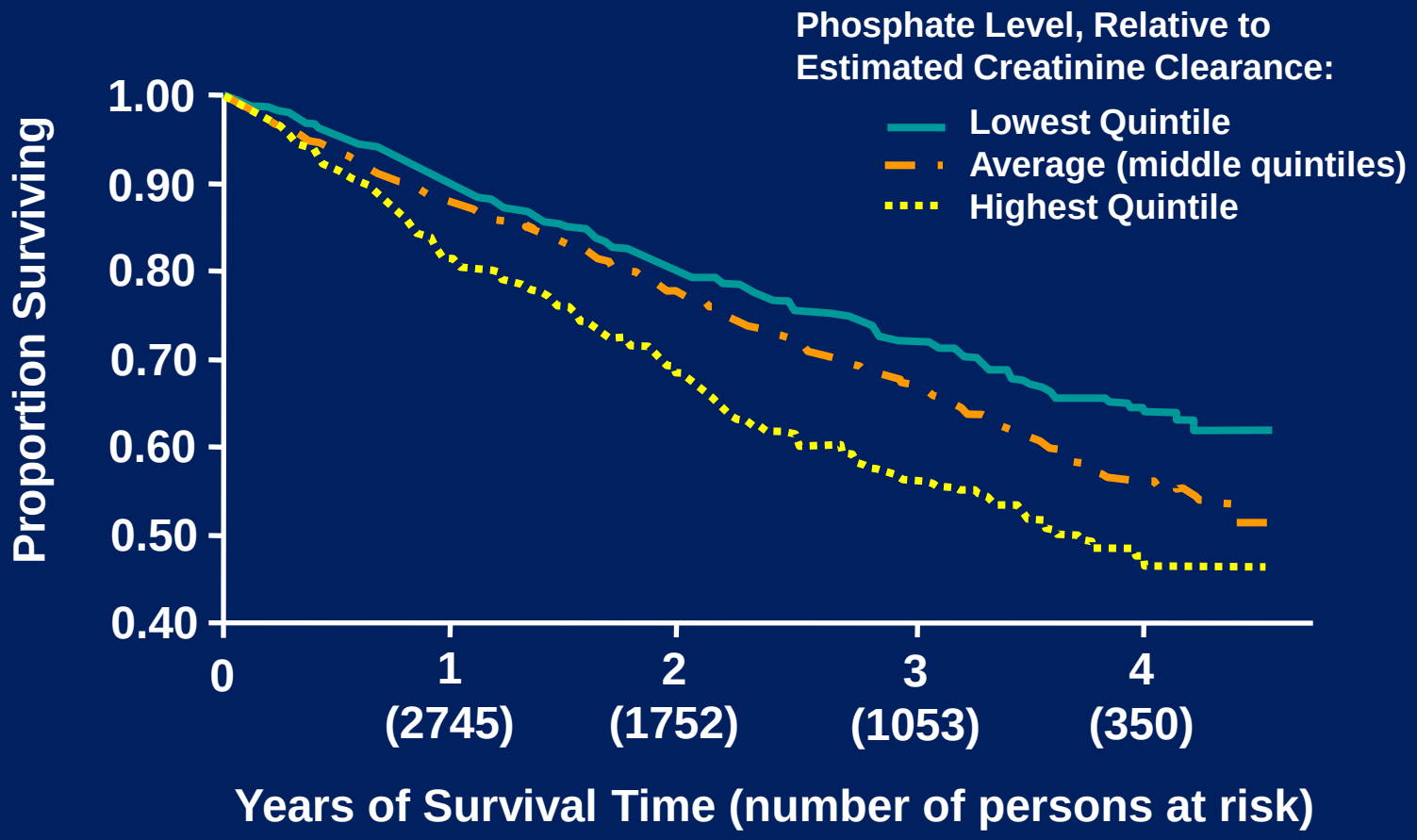
Higher Serum Phosphorus Is Associated With More Rapid Decline in Renal Function



Median follow-up = 337 days; range 31-1442 days.

Voormolen N et al. *Nephrol Dial Transplant.* 2007;22:2909-2916.

Serum Phosphorus and Mortality

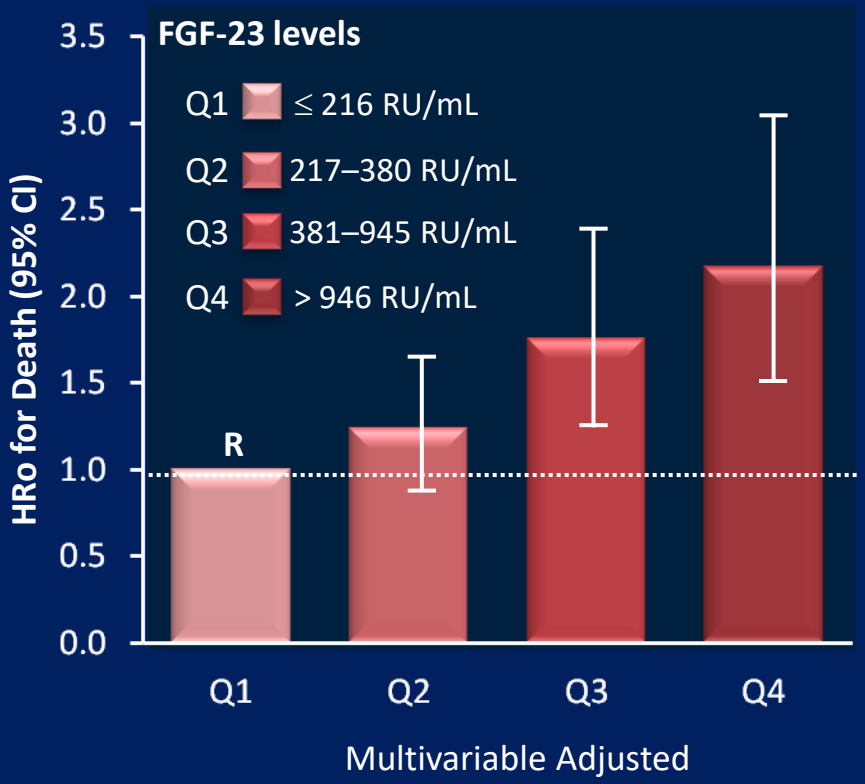


- Estimates of survival significantly different between patients with relative phosphorus levels in highest and lowest quintiles predicted by estimated creatinine clearance (P<.001)

Kestenbaum B et al. *J Am Soc Nephrol.* 2005;16:520-528.

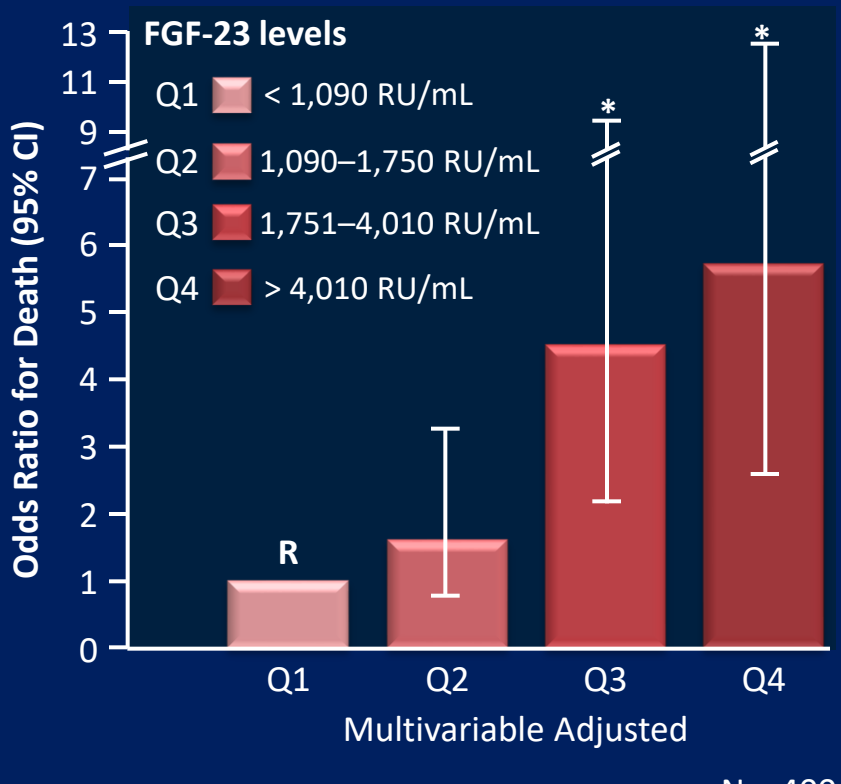
Across the Spectrum of CKD, Elevated FGF-23 Levels Were Associated With Higher Mortality Risk

Kendrick et al - Predialysis Population[1]



N = 1,099

Gutiérrez et al - Dialysis Population[2]



N = 400

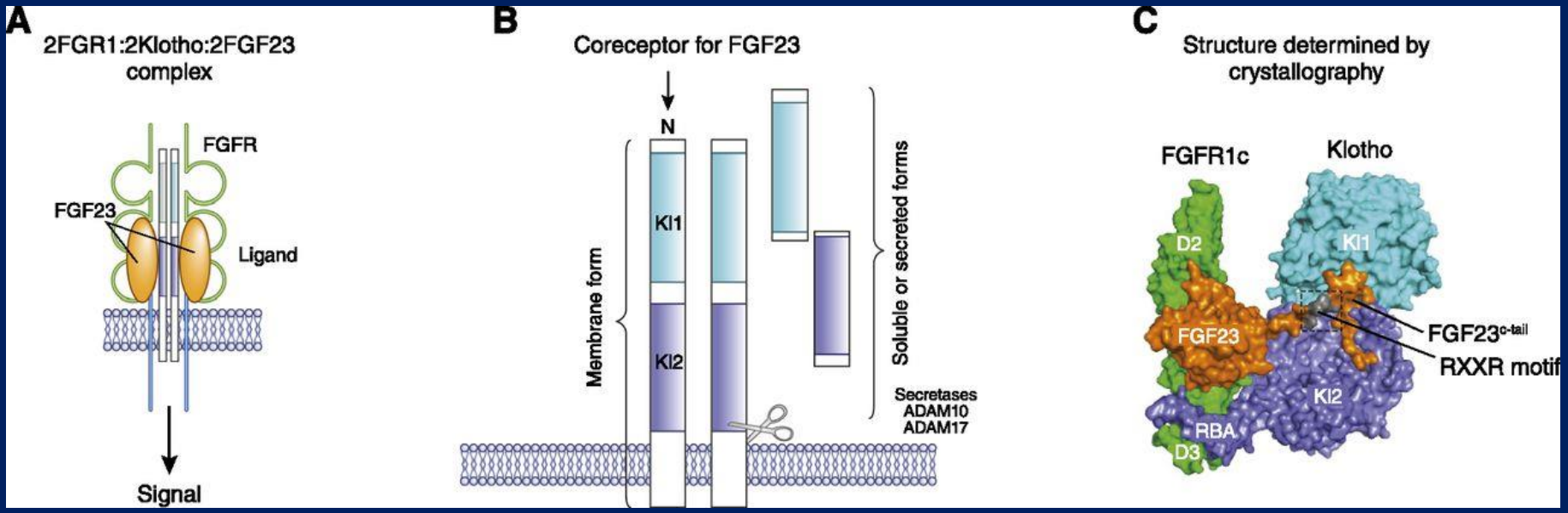
*$P < 0.05$

Patients in the highest quartiles of FGF-23 levels had the highest risk of mortality as compared with subjects in the lowest quartiles[1,2]

Q = quartile; R = reference.

1. Kendrick J, et al. *J Am Soc Nephrol*. 2011;22:1913-1922.
2. Gutiérrez OM, et al. *N Engl J Med*. 2008;359:584-592.

Overview of Klotho protein.

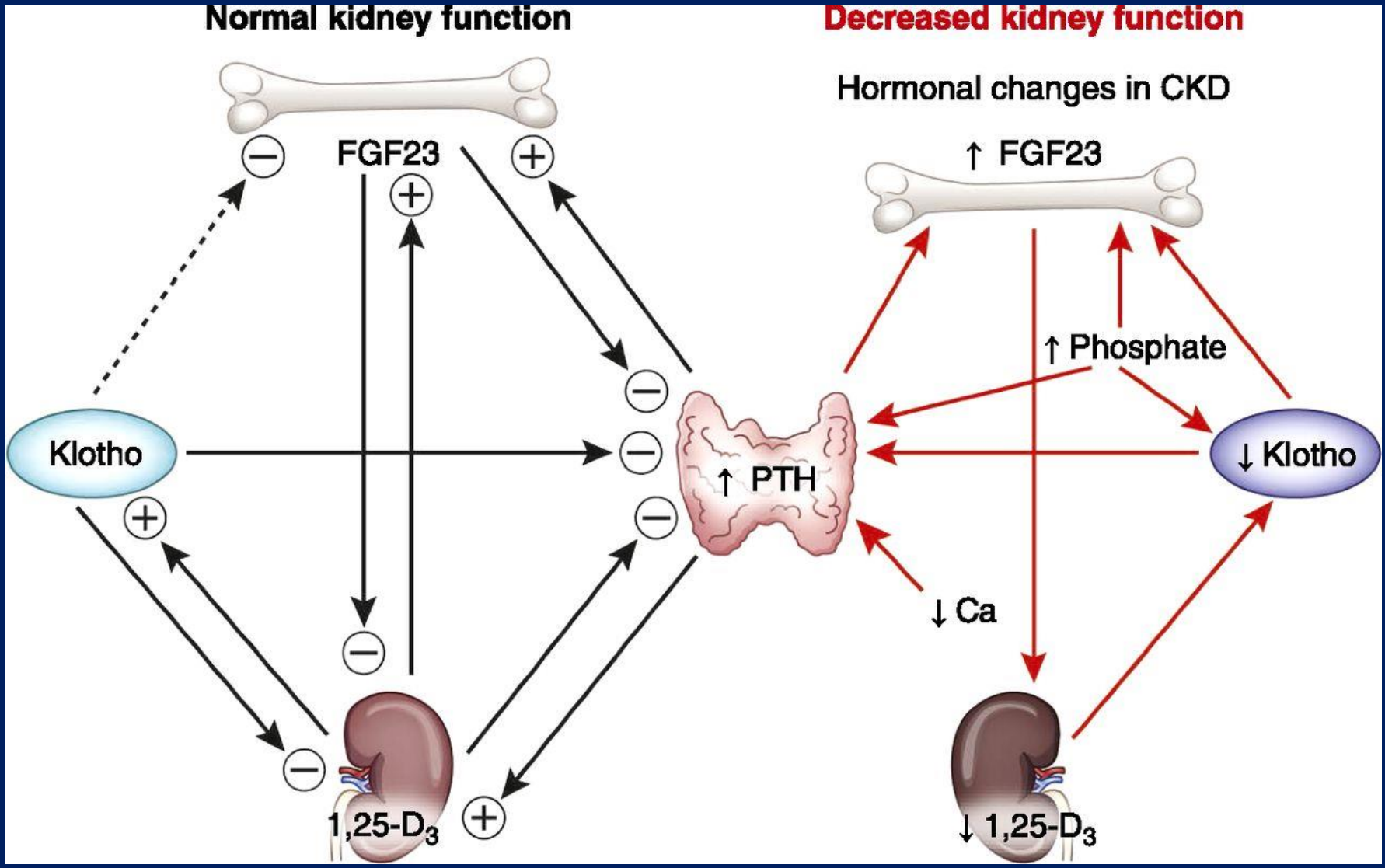


Javier A. Neyra et al. CJASN doi:10.2215/CJN.02840320

Klotho—the fountain of youth?

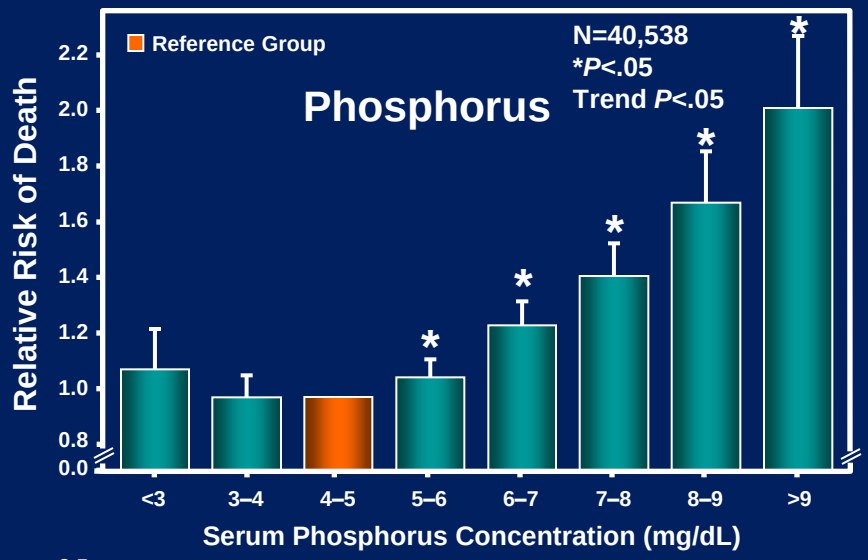
- Protects against renal fibrosis and promotes kidney regeneration after ischemic injury
- Inhibits vascular calcification.
- Reduces oxidative stress by inhibition of insulin and insulin-like growth factor-1 signaling pathways.
- Increases nitric oxide production /improves vasodilatation.
- Inhibits cell senescence and apoptosis
- Preserves stem cells

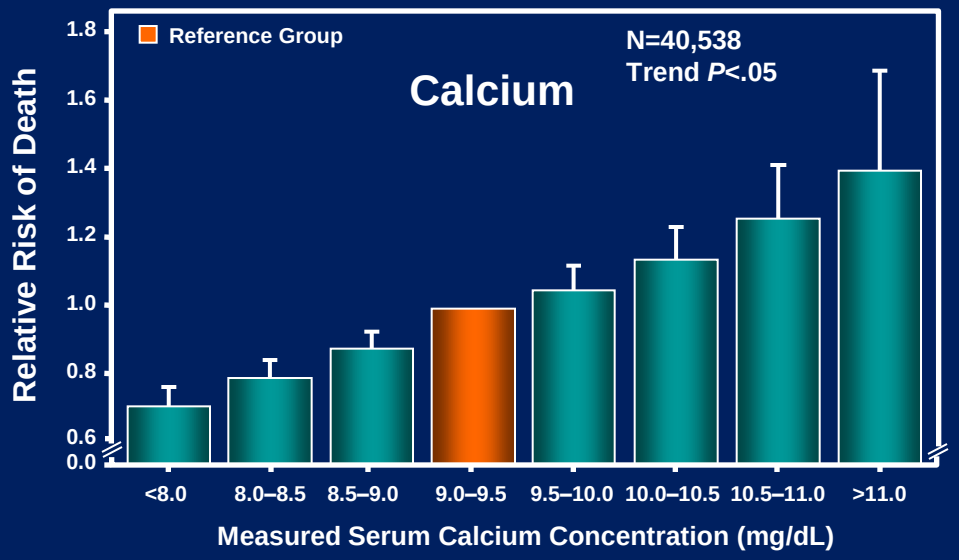
Physiologic and pathophysiologic role of Klotho in mineral metabolism with preserved and decreased kidney function.

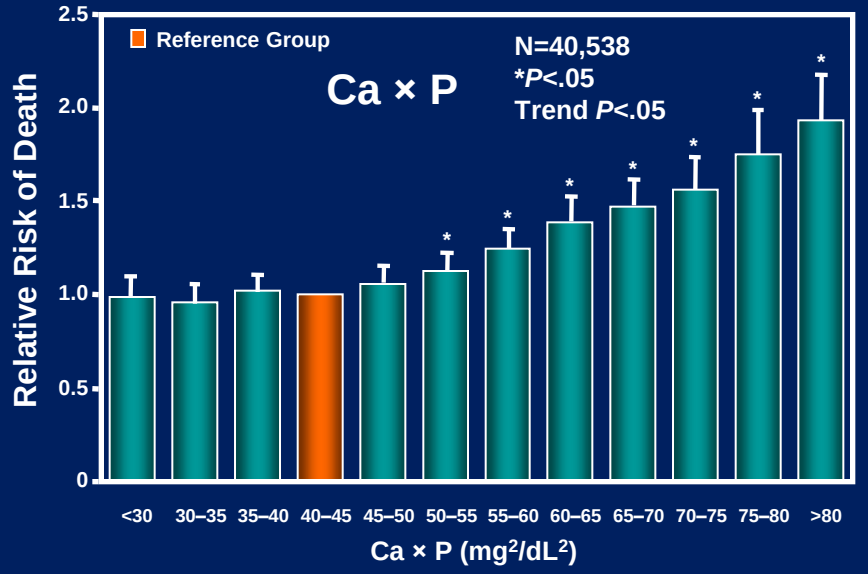


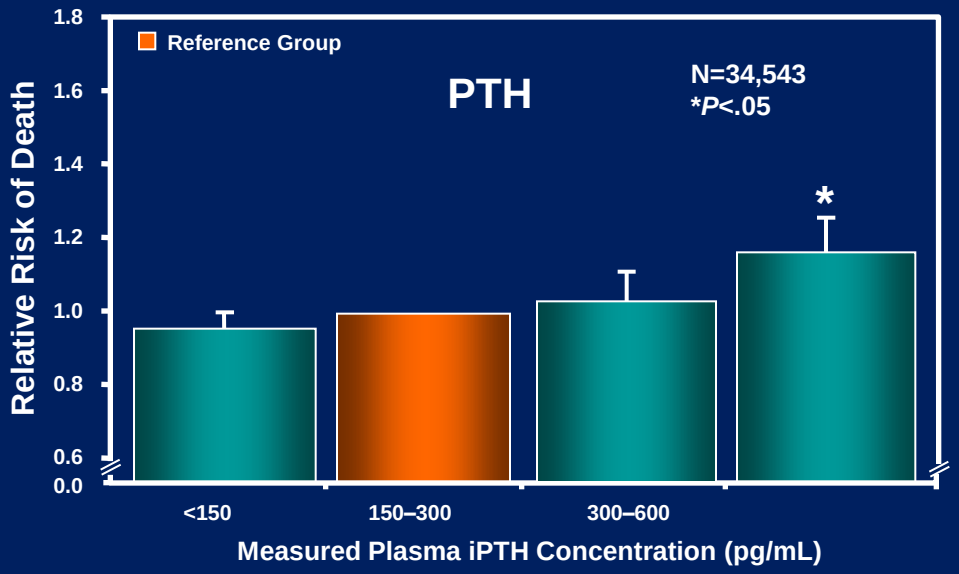
Javier A. Neyra et al. CJASN doi:10.2215/CJN.02840320

Observational Data Suggest a Link Between Laboratory Measures and Mortality



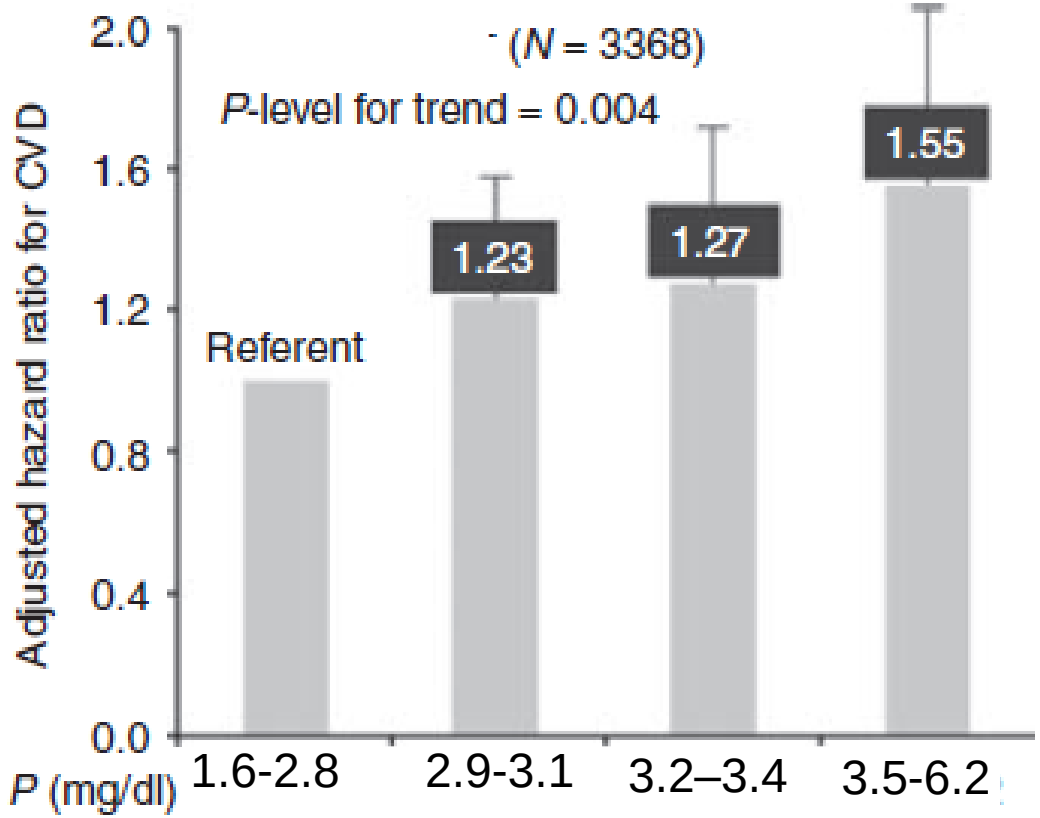






Adapted from Block GA et al. *J Am Soc Nephrol.* 2004;15:2208-2218.

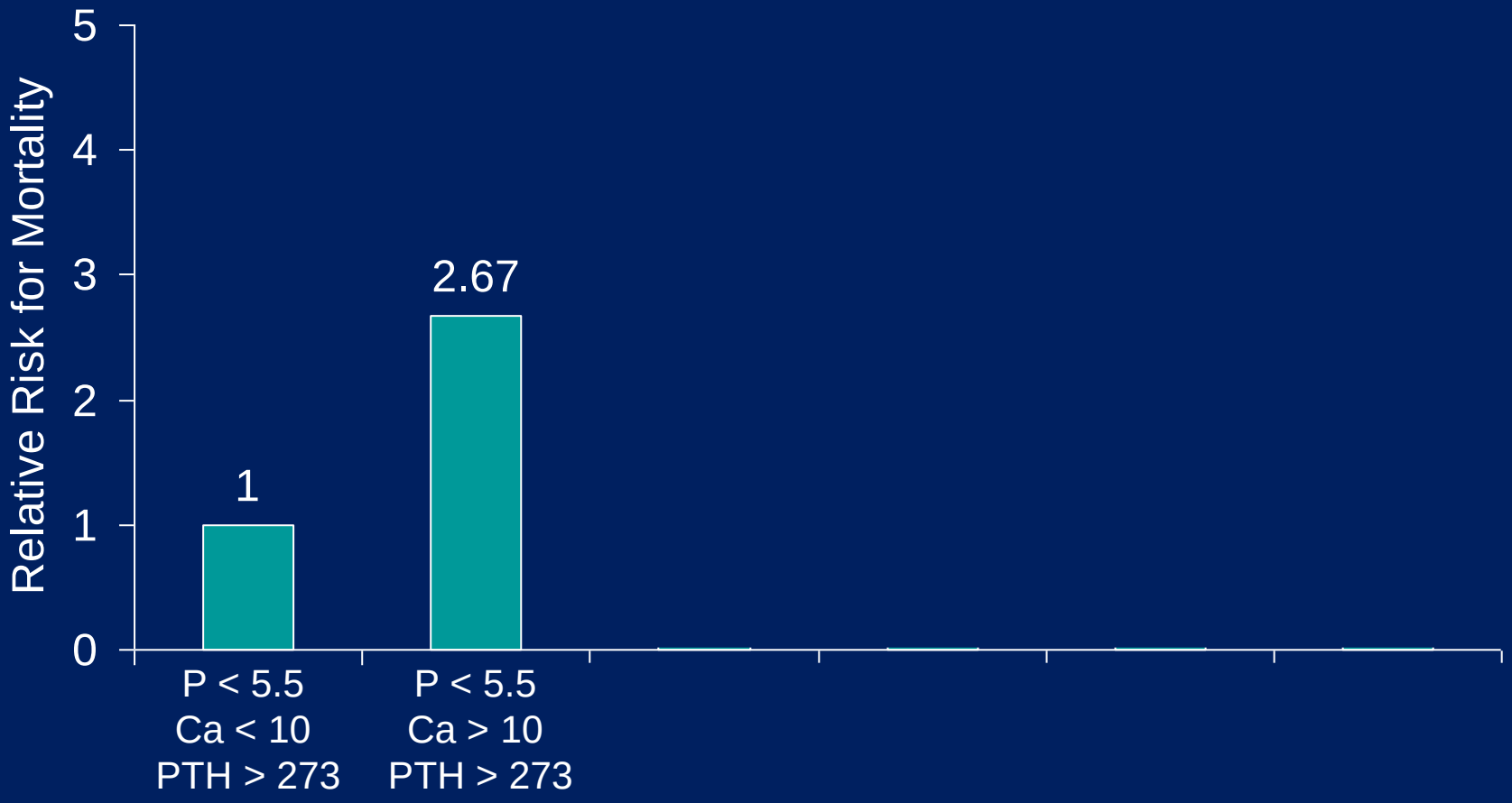
Rising phosphorus levels are associated with worse CVD outcomes in patients without CKD or CVD Framingham study data



Dhingra R et al, Arch Int Med 2007

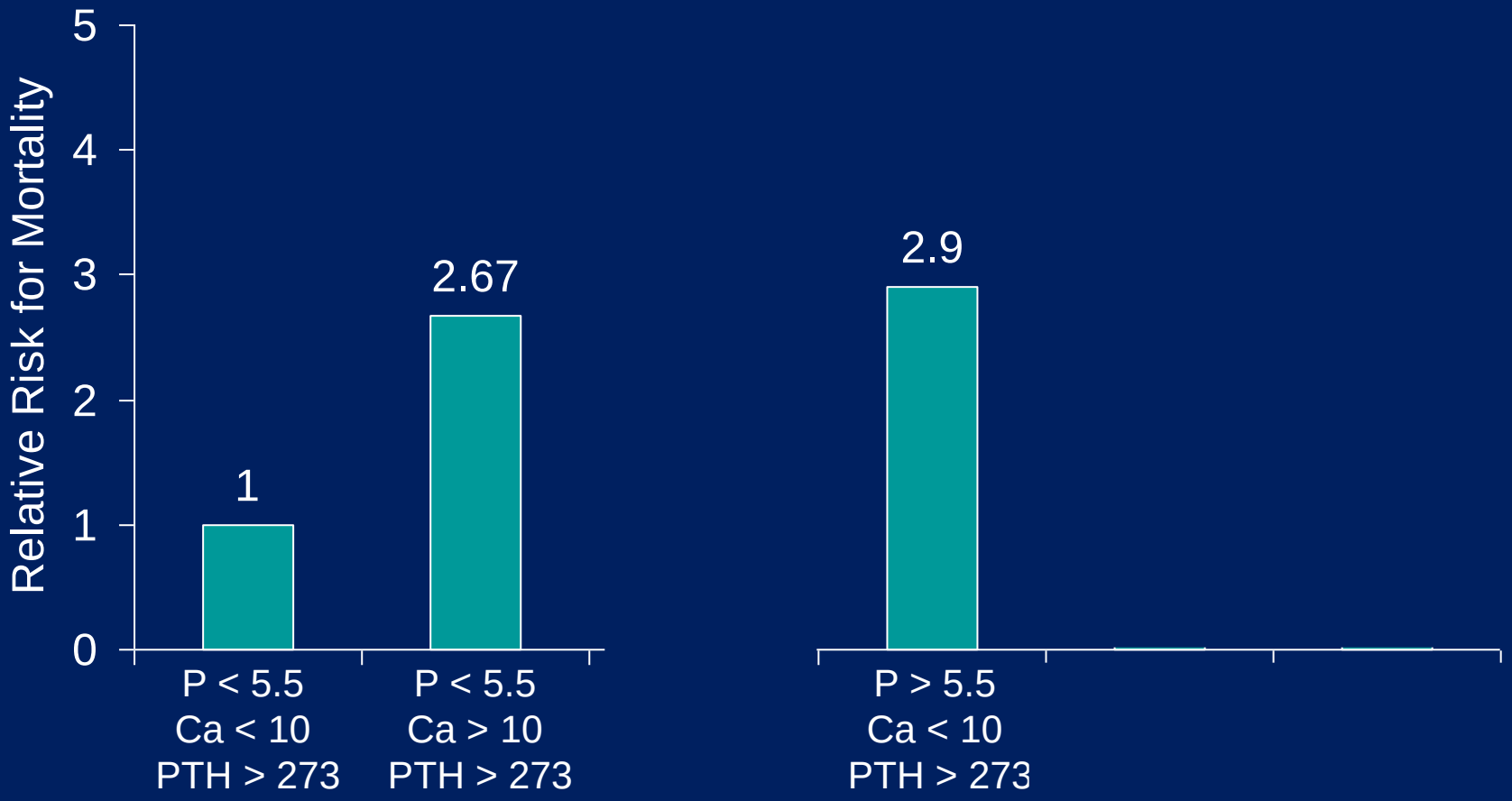
Calcification

Disordered Mineral Metabolism and Mortality: A Complex Relationship



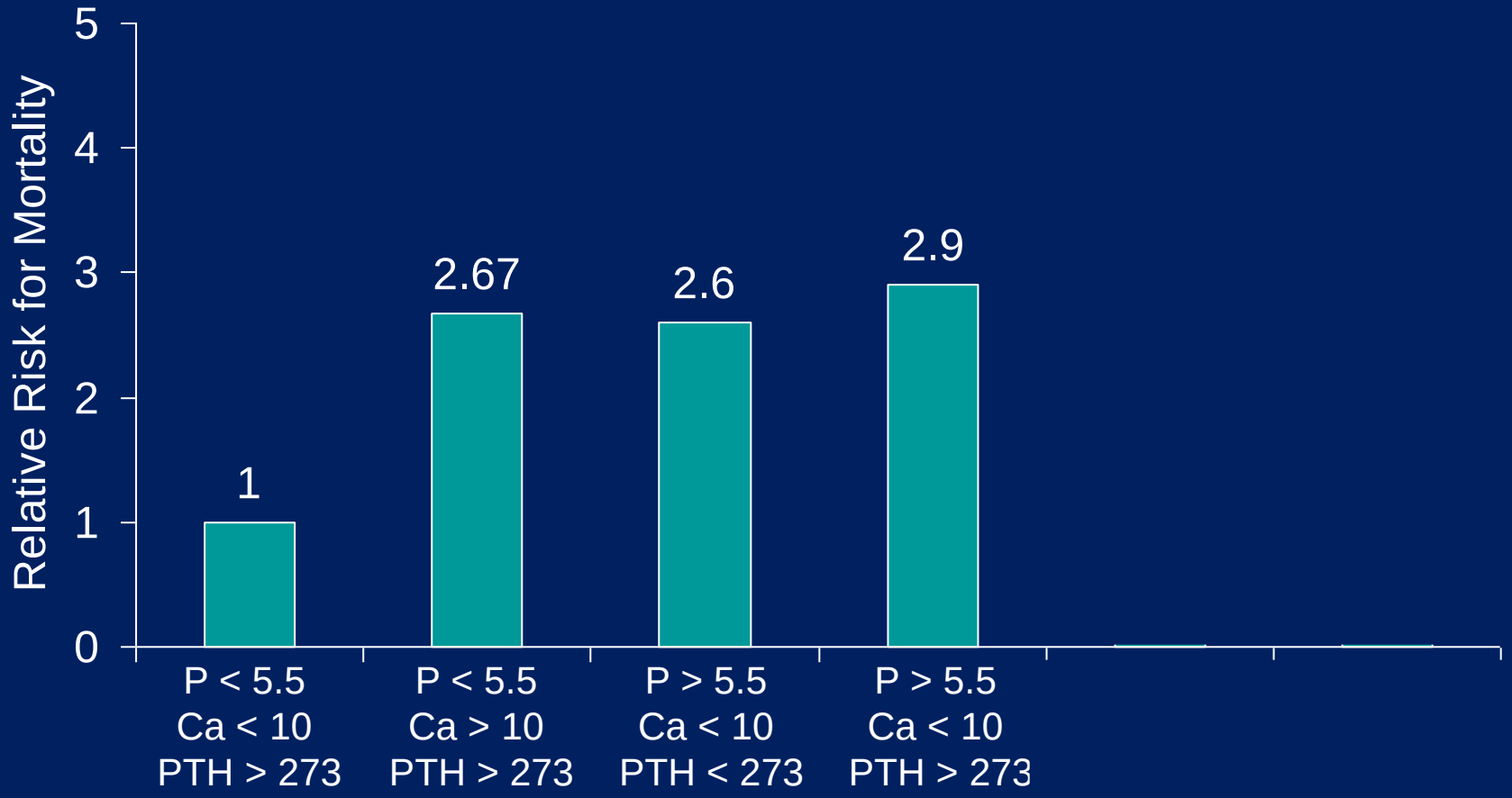
Stevens LA, et al. *J Am Soc Nephrol.* 2004;15:770-779.

Disordered Mineral Metabolism and Mortality: A Complex Relationship



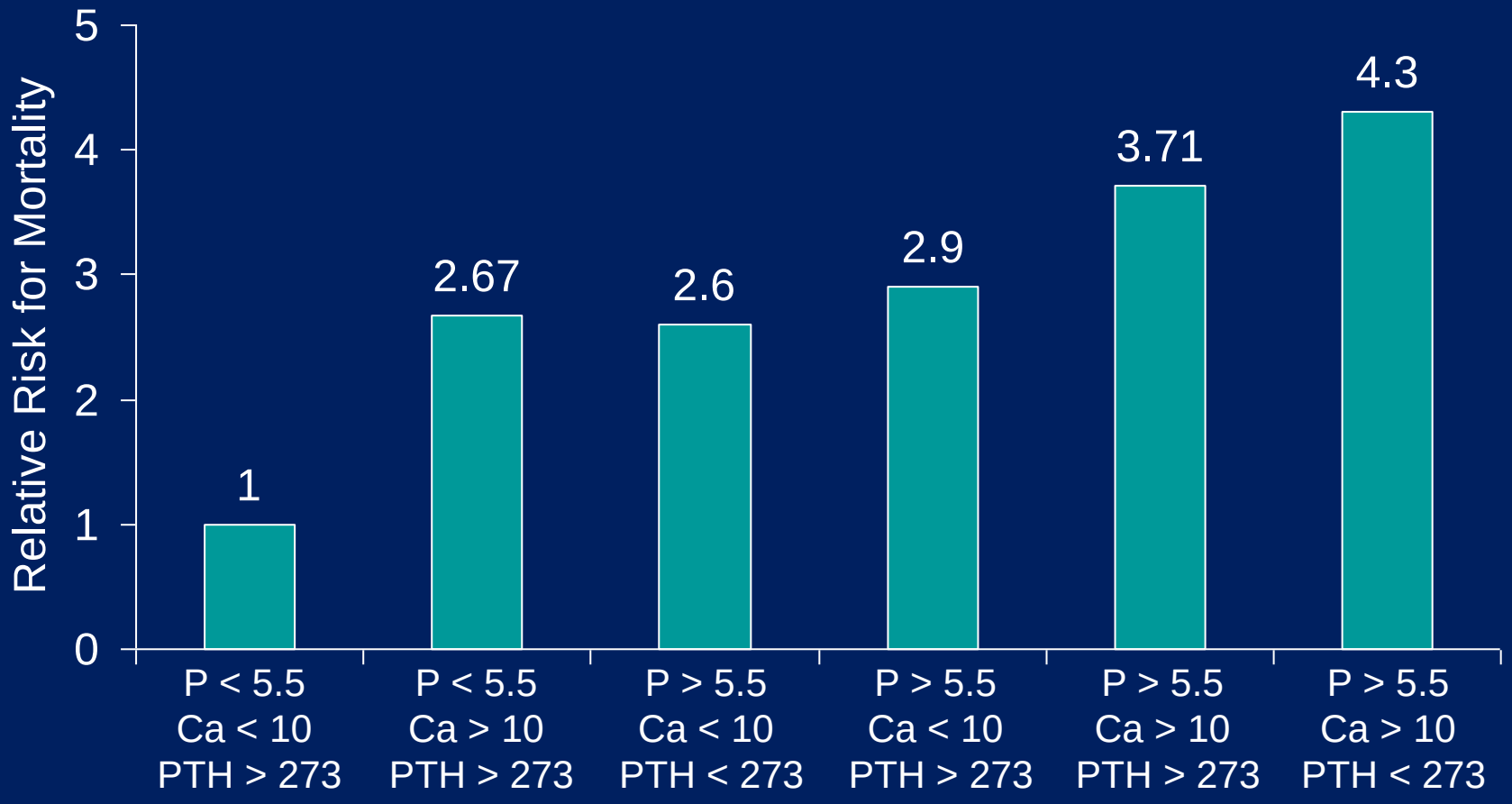
Stevens LA, et al. *J Am Soc Nephrol.* 2004;15:770-779.

Disordered Mineral Metabolism and Mortality: A Complex Relationship



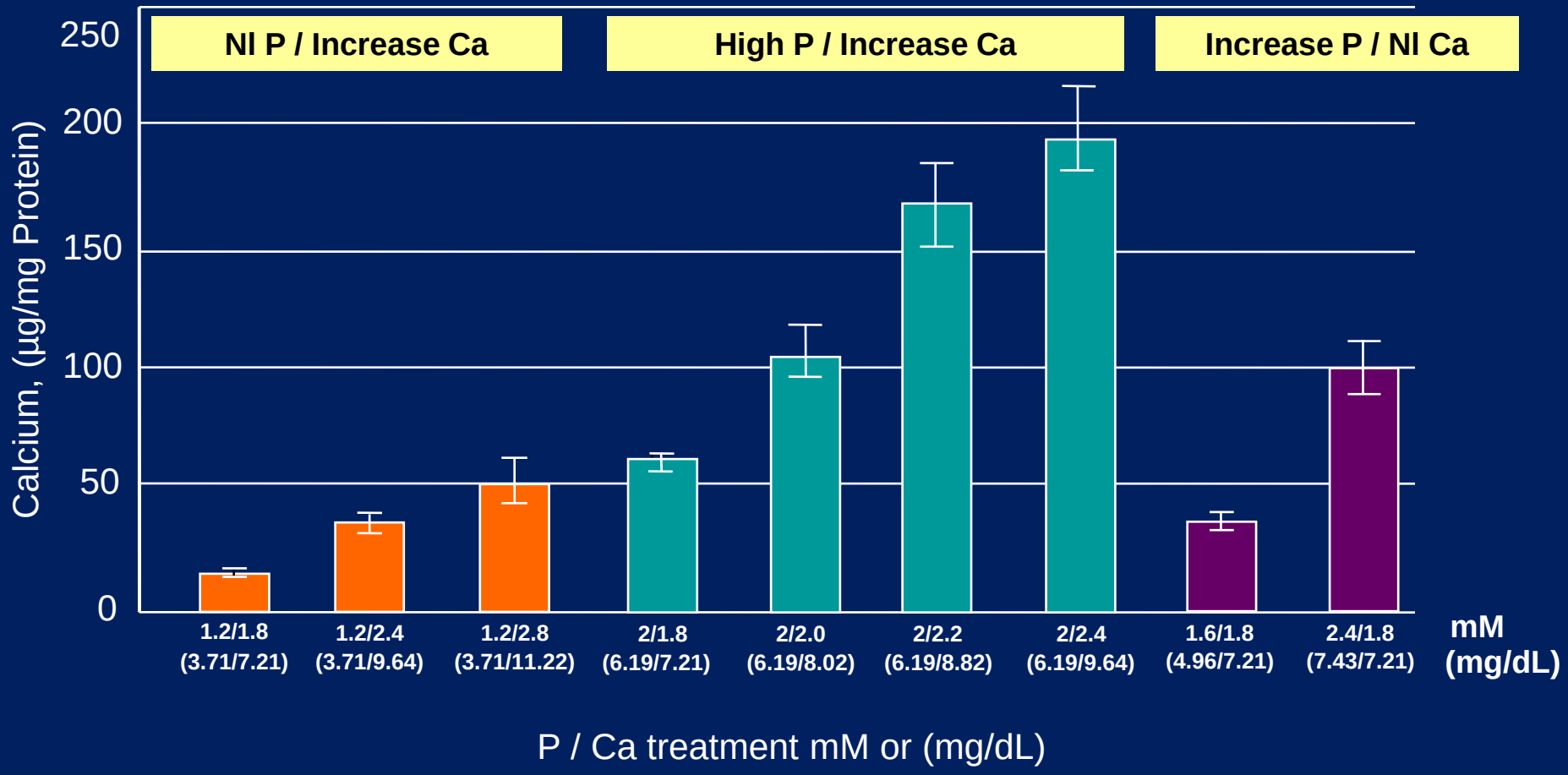
Stevens LA, et al. *J Am Soc Nephrol.* 2004;15:770-779.

Disordered Mineral Metabolism and Mortality: A Complex Relationship

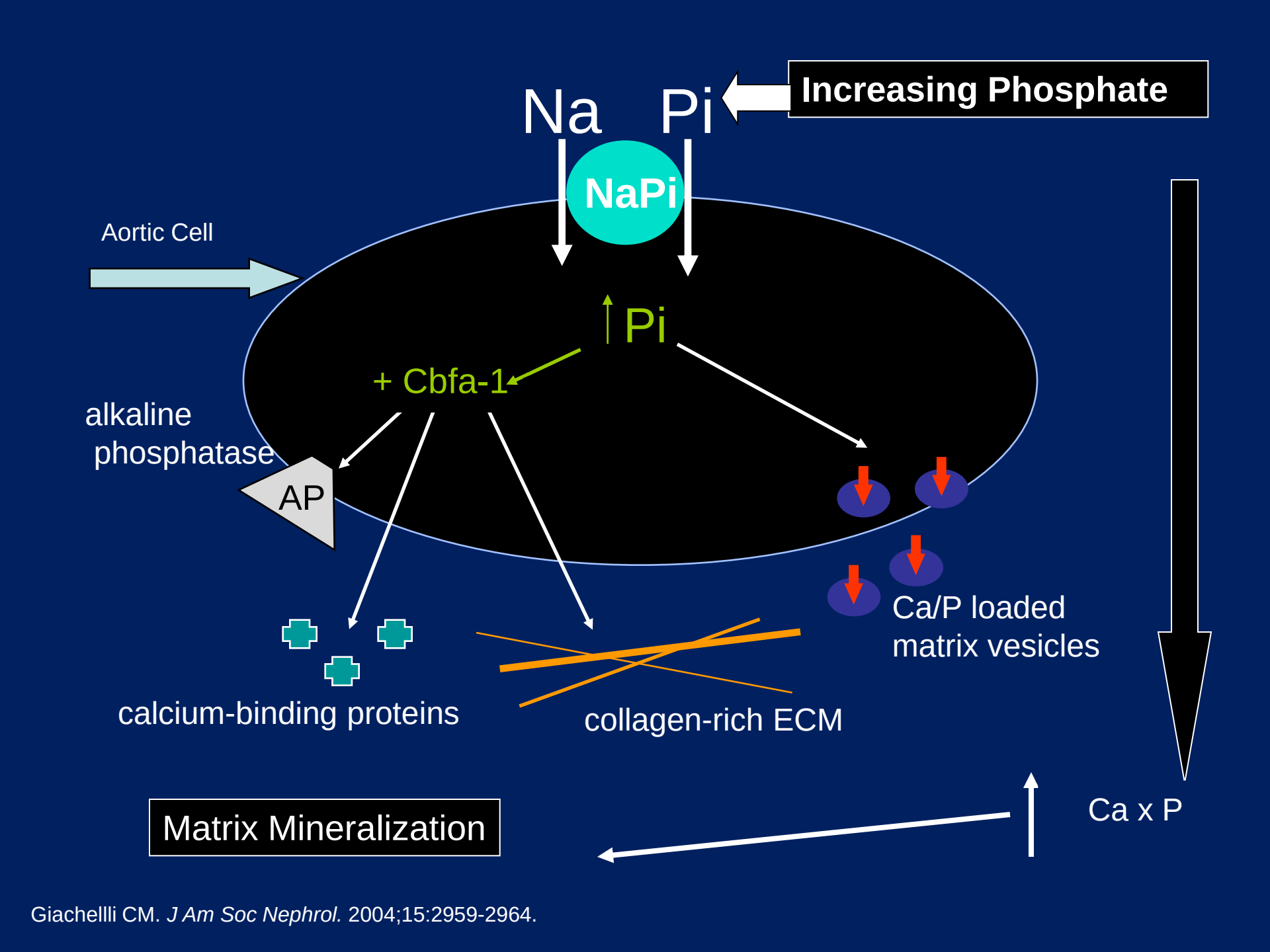


Stevens LA, et al. *J Am Soc Nephrol.* 2004;15:770-779.

Ca & P Induce Calcification in SMC

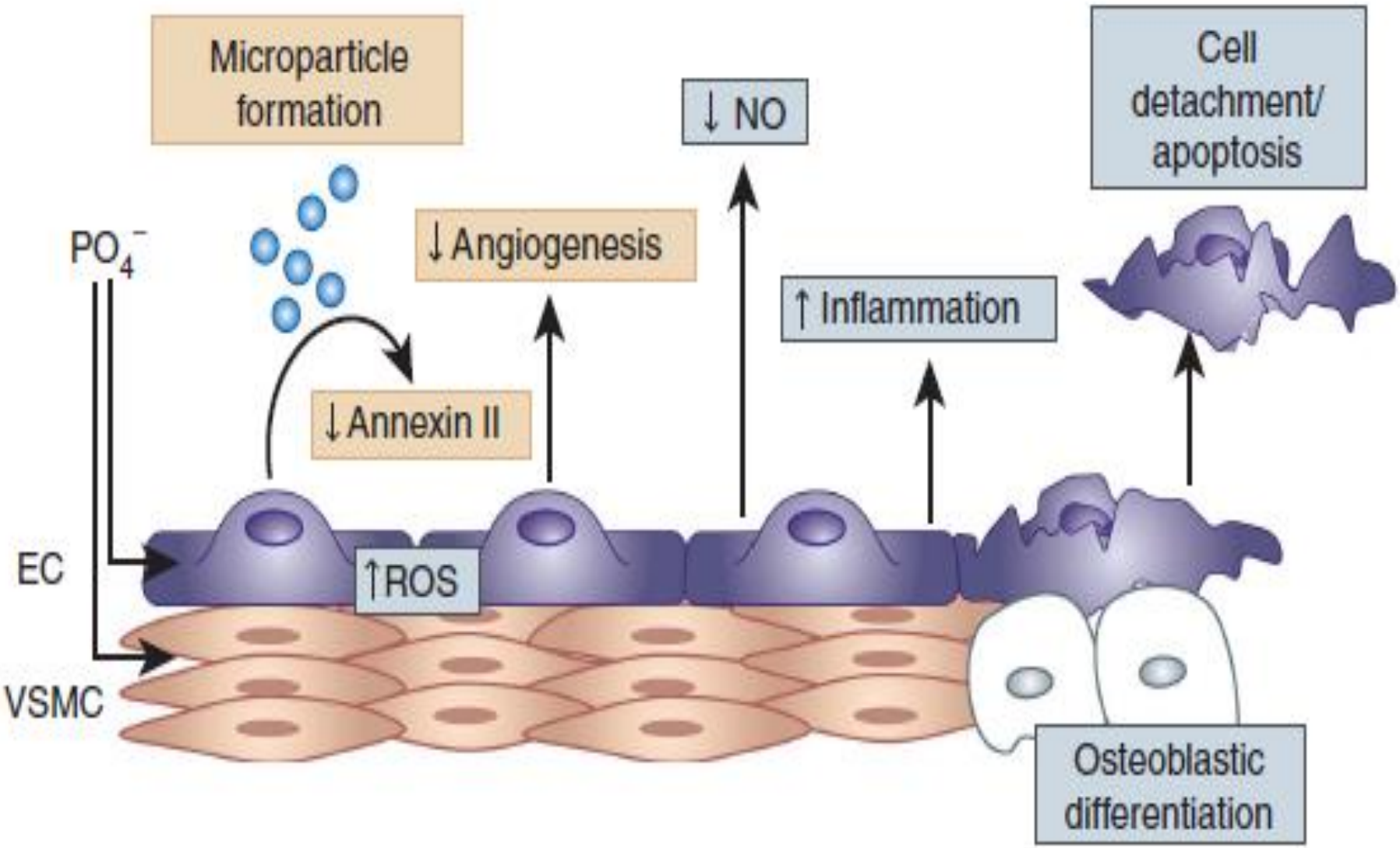


Yang H, et al. *Kidney Int*. 2004;66:2293-2299.

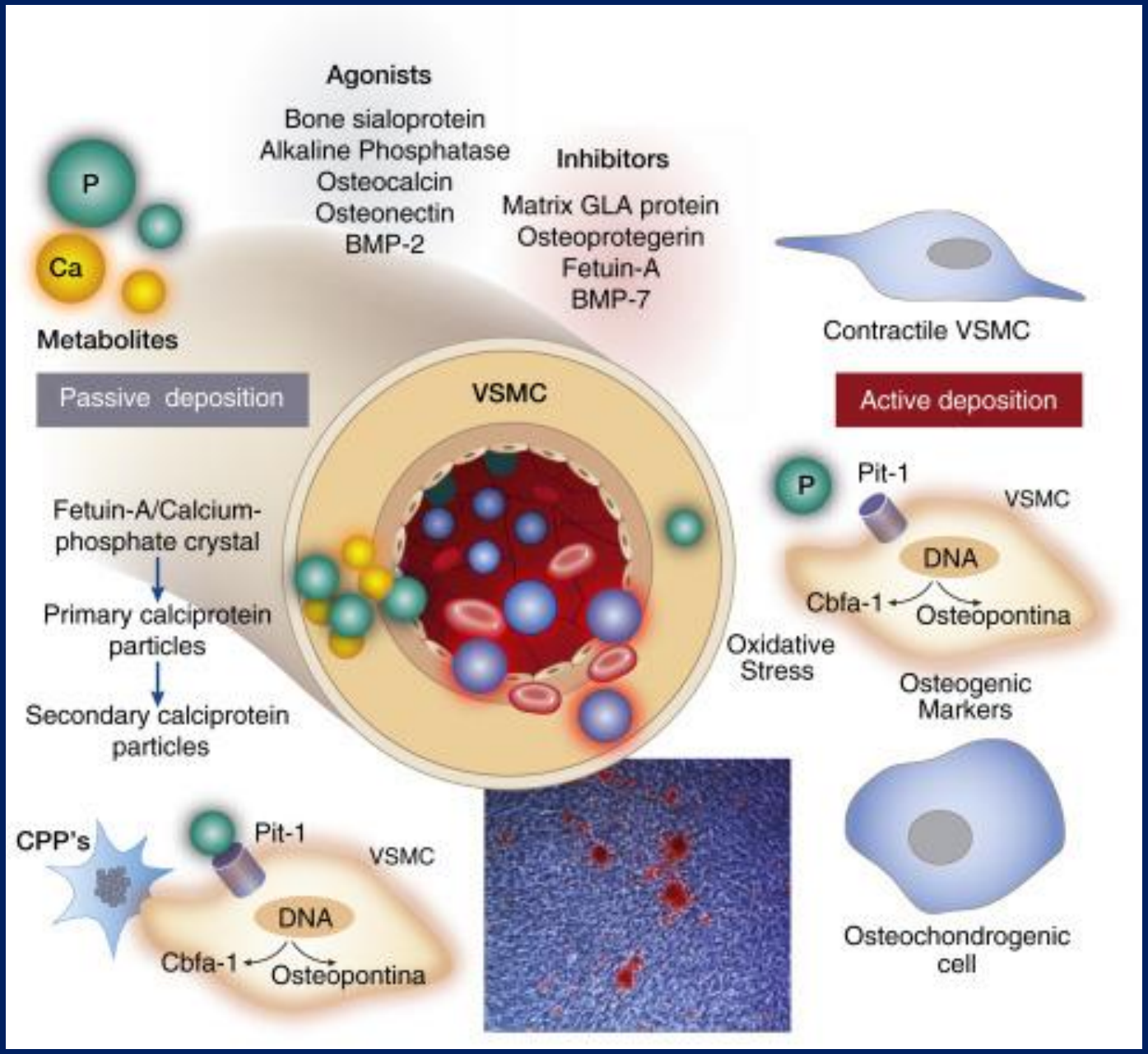


Giachellli CM. *J Am Soc Nephrol.* 2004;15:2959-2964.

Effects of Phosphate on Vascular Health



Burger, D. Kidney International (2013) 83, 187–189.

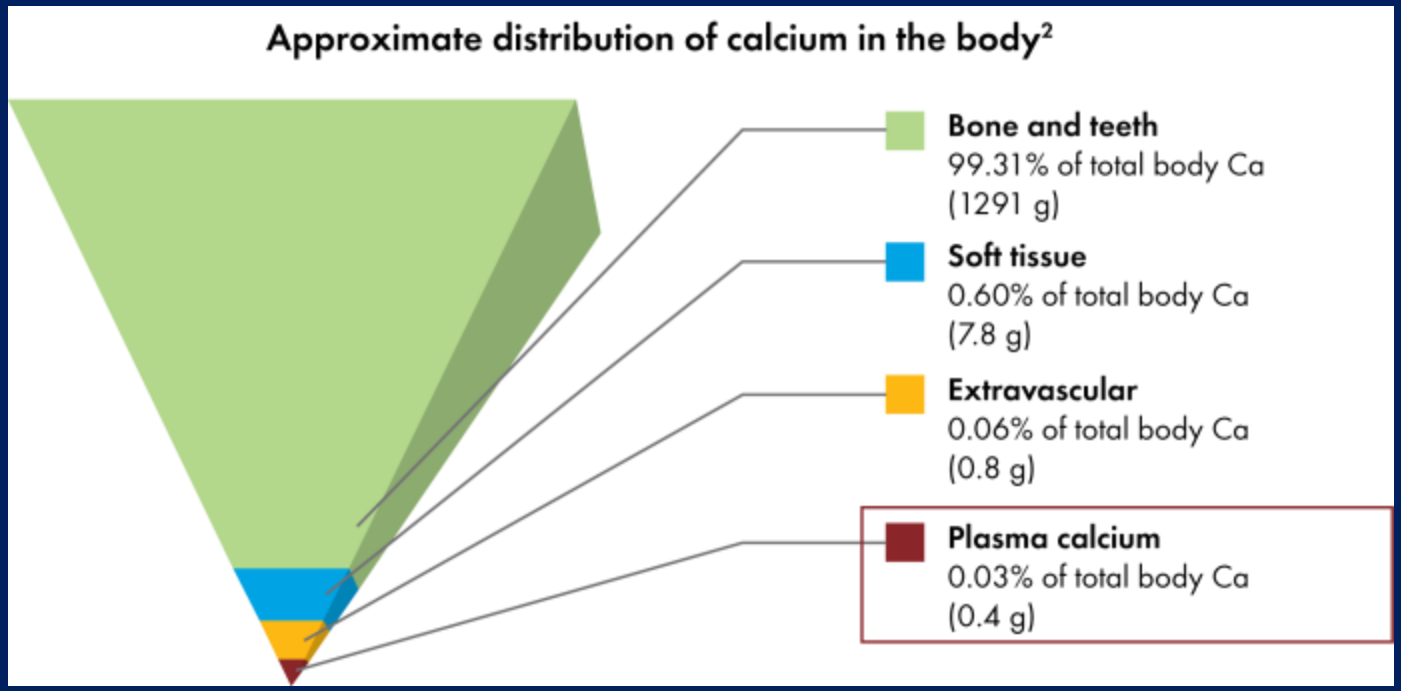


Vervloet et al. KI 2017; 91:808

Vascular and Valvular Calcification:

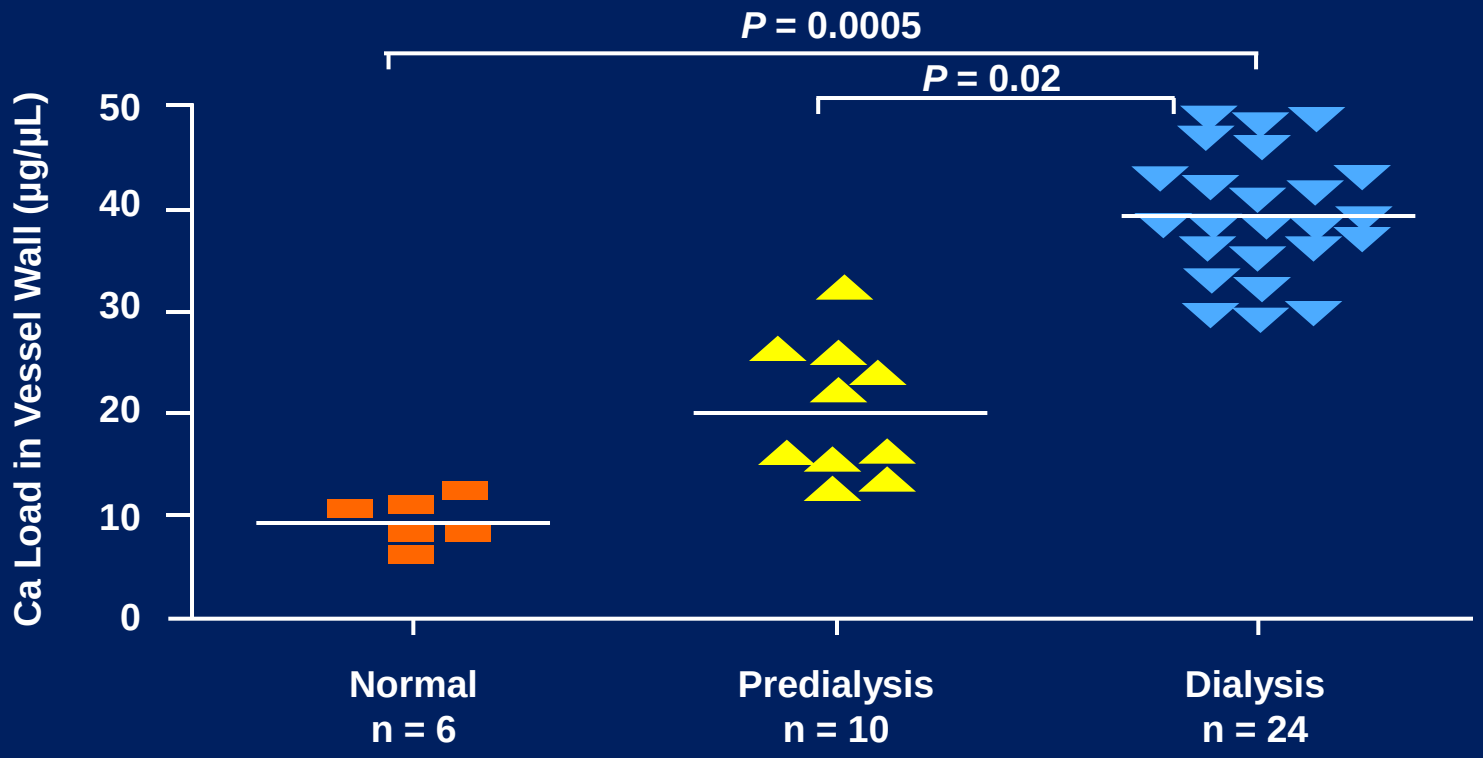
Potential Consequences of Disorders of Divalent Ion Metabolism

Calcium distribution in the body



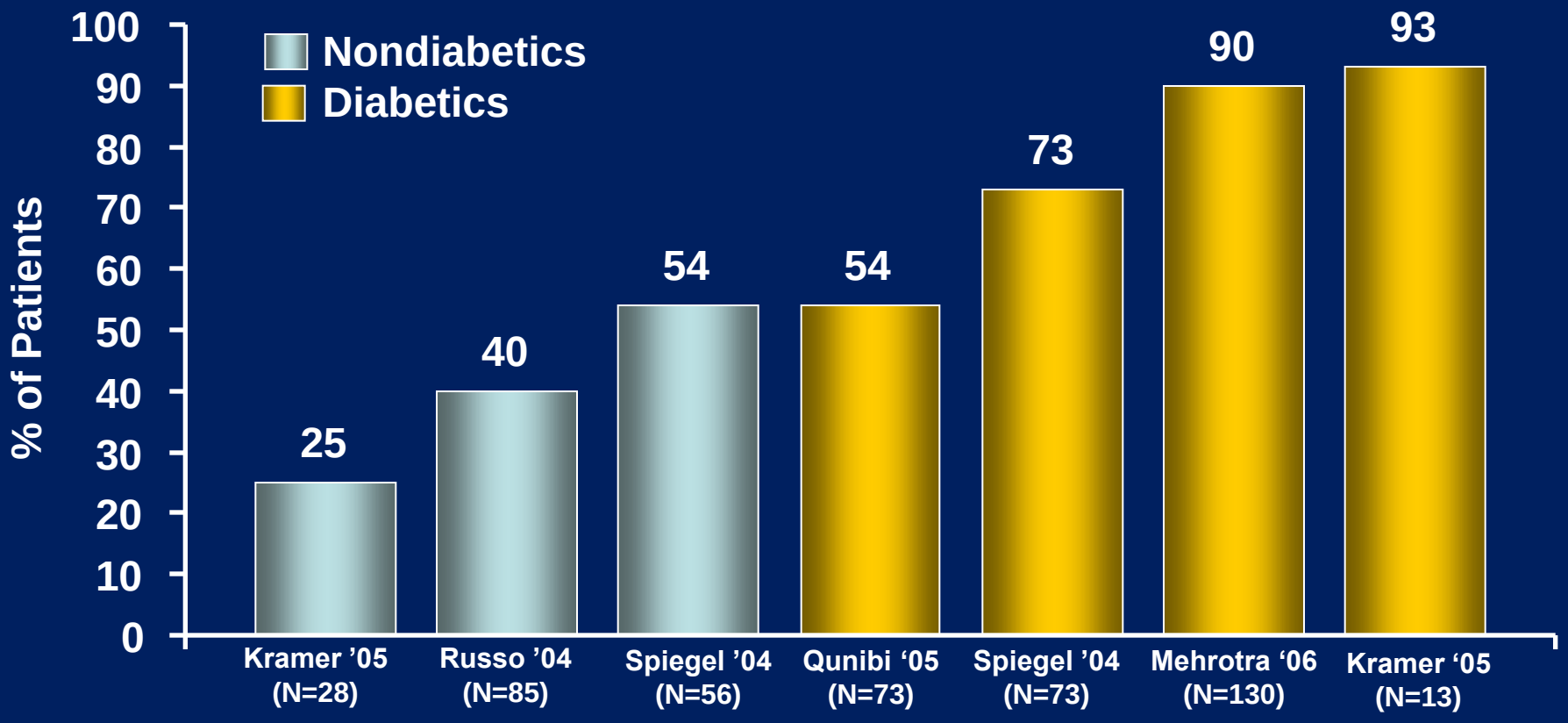
References: **1.** Houillier P, Froissart M, Maruani G, Blanchard A. What serum calcium can tell us and what it can't. *Nephrol Dial Transplantation*. 2006;21:29-32. **2.** Nordin BEC, ed. *Calcium, Phosphate and Magnesium Metabolism: Clinical Physiology and Diagnostic Procedures.* New York, NY: Churchill Livingstone; 1976. **3.** Hosking DJ, Chamberlain MJ. Calcium balance in chronic renal failure: a study using in vivo neutron activation analysis. *Q J Med*. 1973;42:467 479. **4.** Bushinsky DA. Contribution of intestine, bone, kidney, and dialysis to extracellular fluid calcium content. *Clin J Am Soc Nephrol*. 2010;5(suppl 1):S12-S22.

Vascular Calcium Loading in Children With CKD

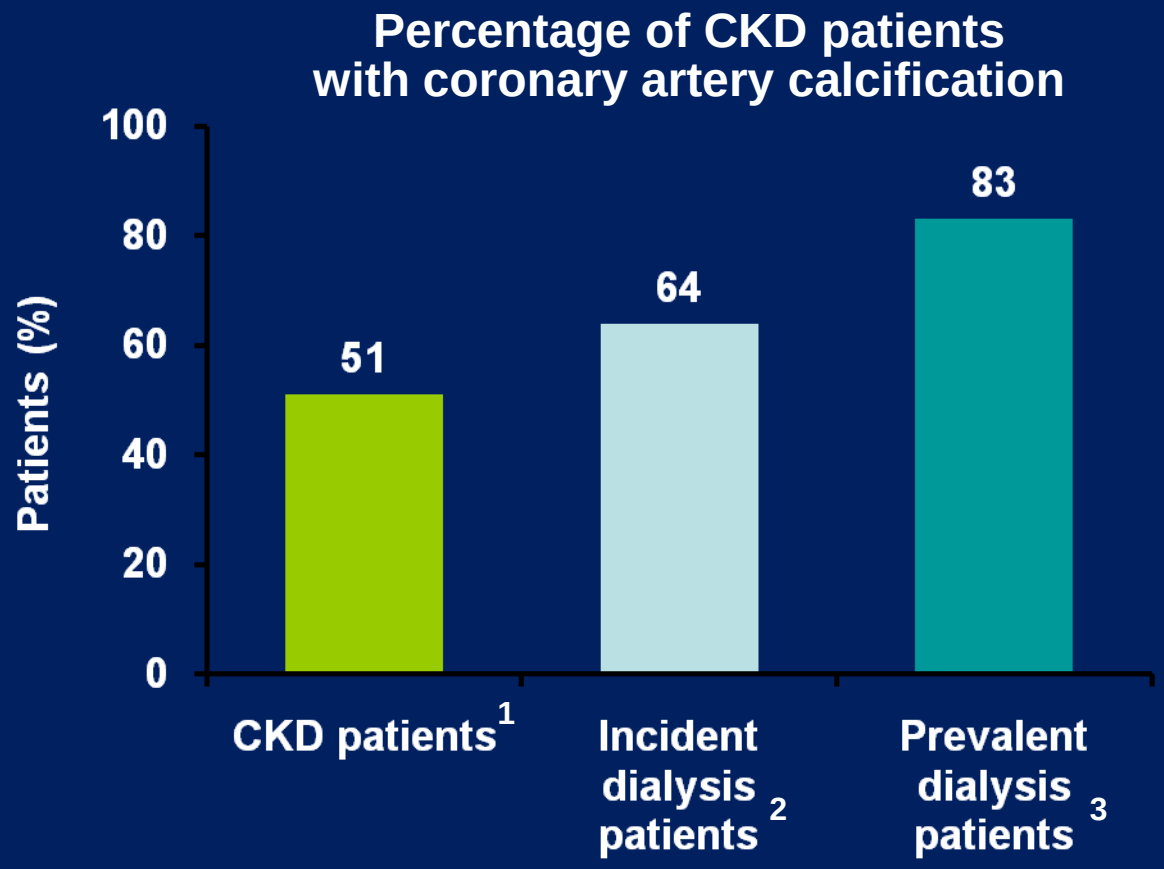


Shroff RC et al. *Circulation.* 2008;118:1748-1757.

Prevalence of Coronary Calcification in CKD Patients Not on Dialysis

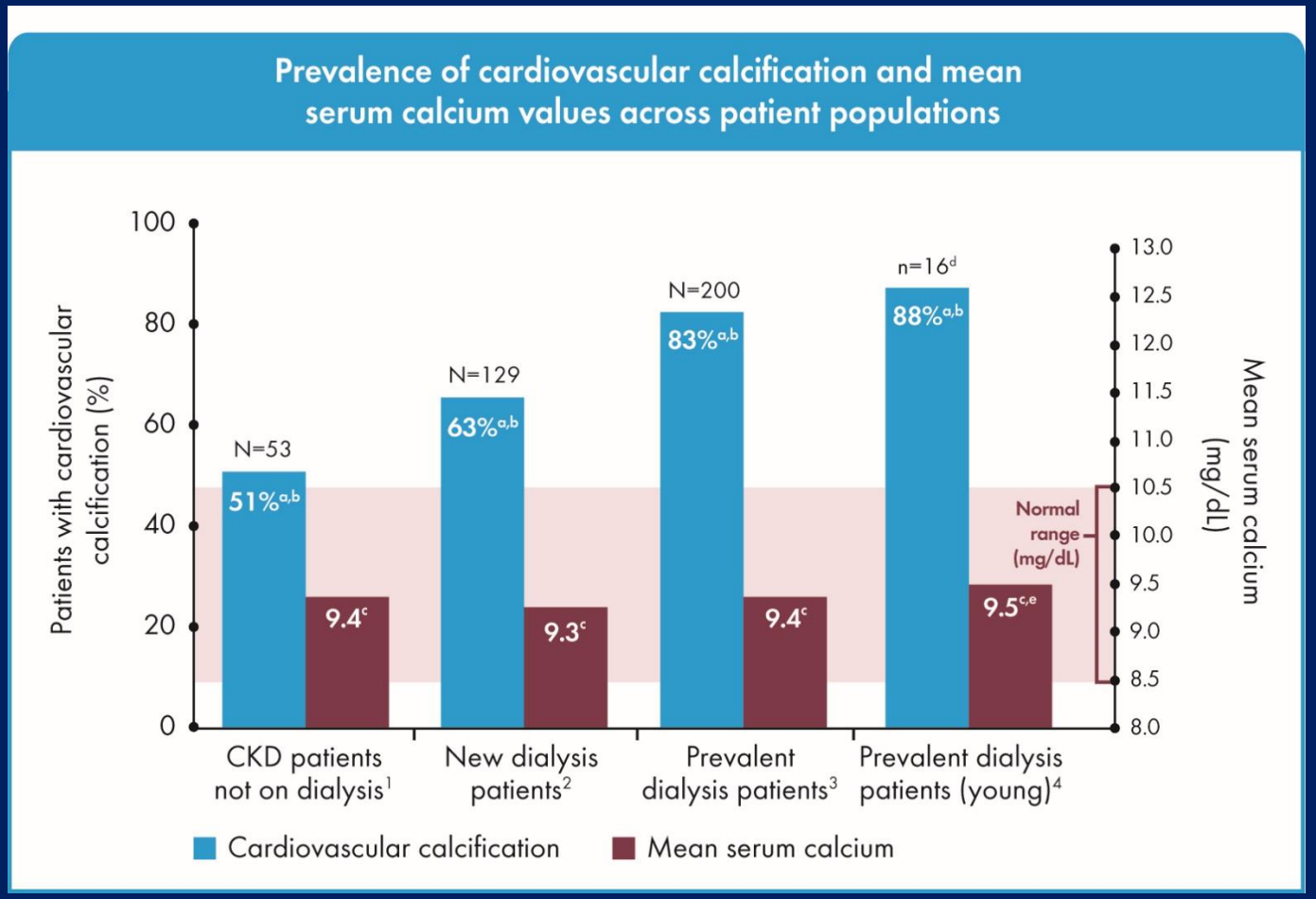


Across CKD Patient Populations, Calcification is a Common, Progressive Consequence of the Disease



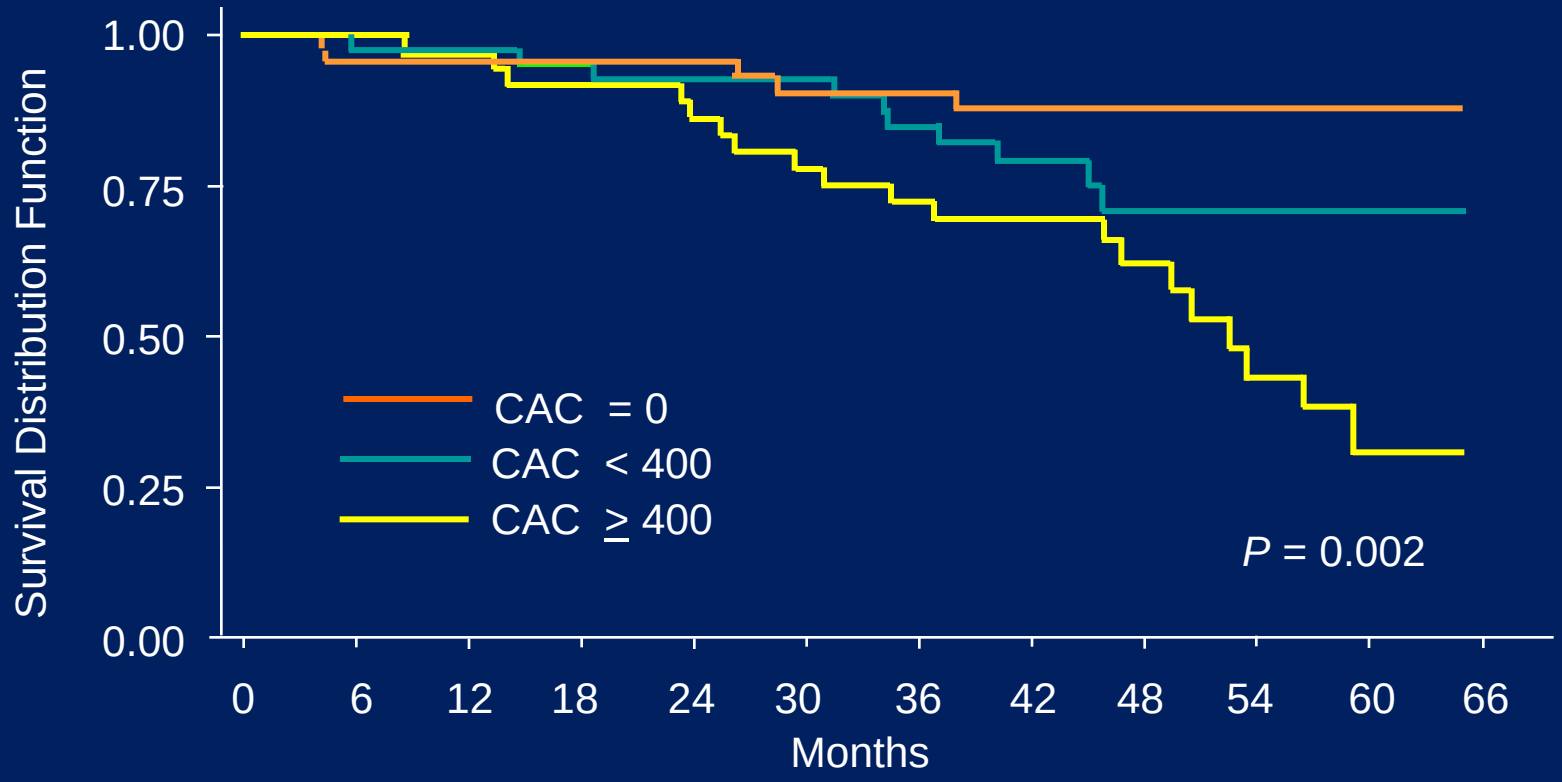
1. Russo D, Corrao S, Miranda I, et al. *Am J Nephrol*. 2007;27:152-158.
2. Spiegel DM, Raggi P, Mehta R, et al. *Hemodialysis Int*. 2004;8:265-272.
3. Chertow GM, Burke SK, Raggi P; *Kidney Int*. 2002;62:245-252.

Calcification is independent of serum calcium levels [1-5]



1. Russo D, et al. *Am J Nephrol.* 2007;27:152-158. **2.** Block GA, et al. *Kidney Int.* 2005;68:1815-1824. **3.** Chertow GM, et al *Kidney Int.* 2002;62:245-252. **4.** Goodman WG, et al. *N Engl J Med.* 2000;342:1478-1483. **5.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO *Kidney Int.* 2009;76(suppl 113):S1-S130.

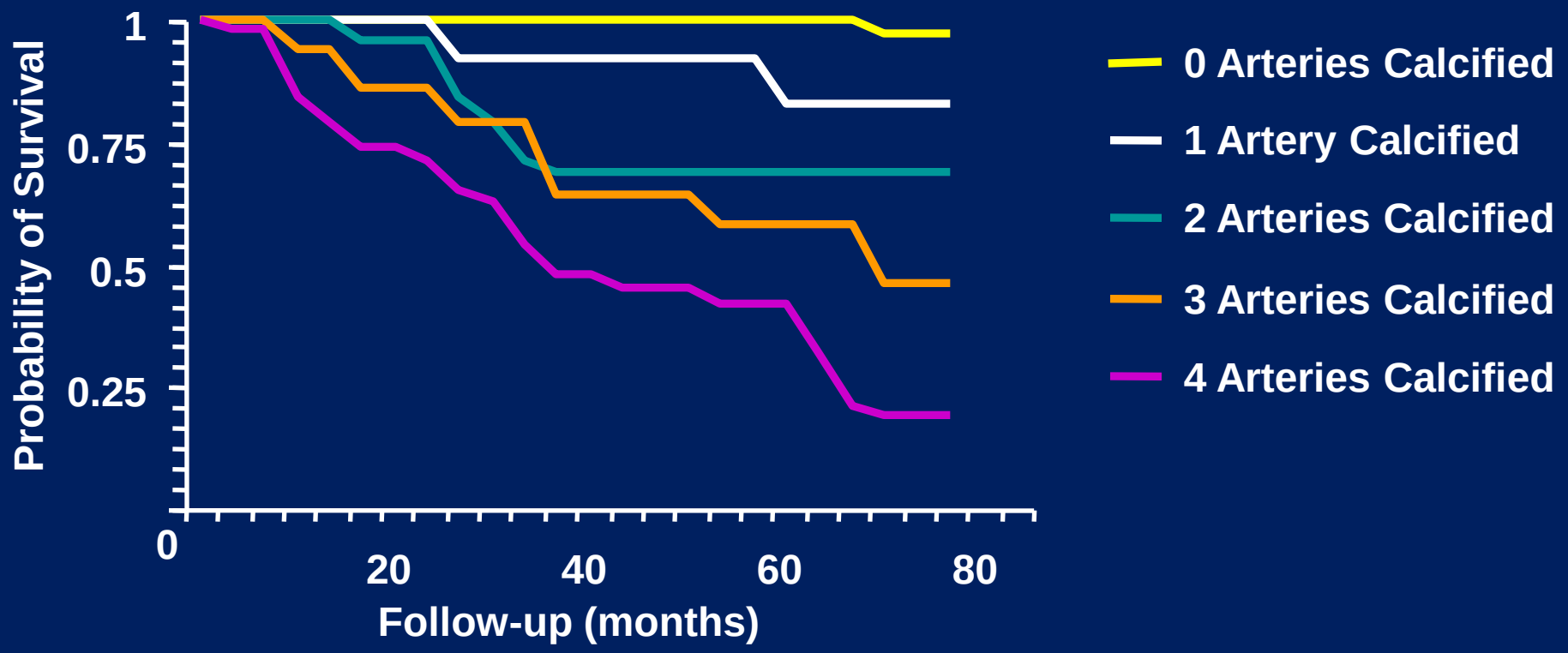
Coronary Artery Calcification Is Associated With Increased Mortality



No. at risk							
CCS = 0	46	42	42	39	34	18	4
CCS < 400	42	41	40	36	32	14	1
CCS ≥ 400	39	37	35	31	26	15	4

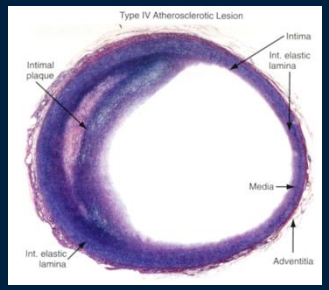
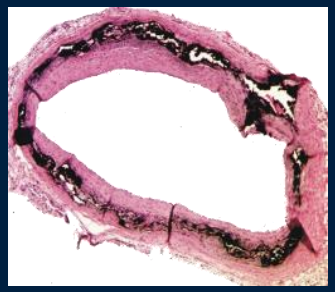
Block GA, et al. *Kidney Int*. 2007;71:438-441.

Probability of Survival Decreases With Increasing Arterial Calcification



N=110 stable dialysis patients with ESRD.
P<.0001 comparison among groups.
Adapted from Blacher J et al. *Hypertension*. 2001;38:938-942.

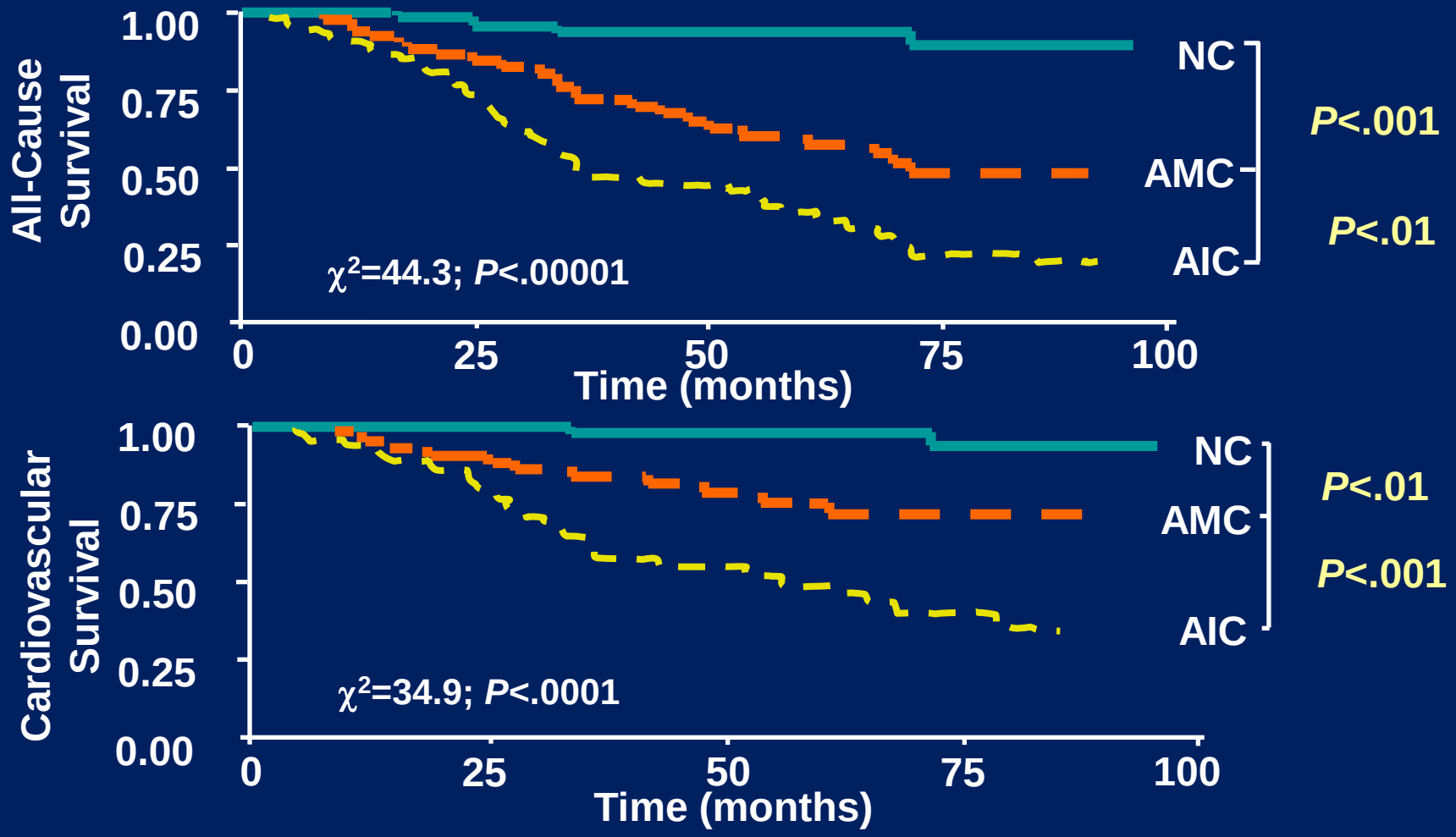
Arterial Calcification: Intima vs Media

	 **Intima**	 **Media**
Histology	**Atherosclerosis** Diffuse punctate morphology Aggregates of calcium crystals	**Arteriosclerosis** Linear deposits along elastic lamellae At most severe, a dense circumferential sheet of calcium deposition
Consequence	**Acute closure (occlusion)**	**Vascular stiffness (nonocclusive)**
Occurrence	Generalized CV disease	CKD, diabetes, aging (Monckeberg's sclerosis)
Factors	Lipid, macrophages, VSMC, inflammation	Elastin, VSMC

CKD Patients Often Exhibit Both Intimal and Medial Calcification

Proudfoot D, et al. *Herz.* 2001;26:245-251; Giachelli CM. *J Am Soc Nephrol.* 2004;15:2959-2964; London GM, et al. *Nephrol Dial Transplant*. 2003;18:1731-1740; Persy V, et al. *Ateriosclerosis Thromb Vasc Biol*. 2006;26:2110-2116; Moe SM, et al. In: Brenner BM, ed. *The Kidney*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2008:1784-1813.

Impact of Arterial Calcification in Stable Hemodialysis Patients With CKD Stage 5



Risk of calcification increased with hyperphosphatemia and dose of $CaCO_3$.

London GM et al. *Nephrol Dial Transplant.* 2003;18:1731-1740.

Bone Disease

Definition of Renal Osteodystrophy

- Alteration of bone morphology in patients with CKD characterized as abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
- It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by bone histomorphometry.

Role of PTH in Development and Progression of Renal Osteodystrophy

Low turnover

High turnover

Low

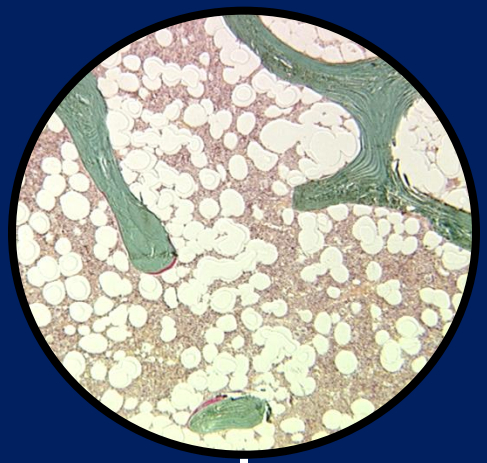
PTH

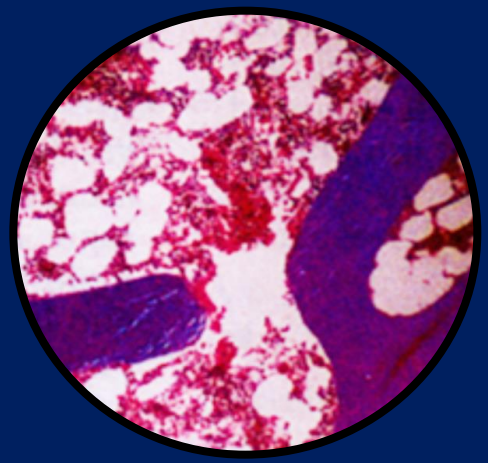
High

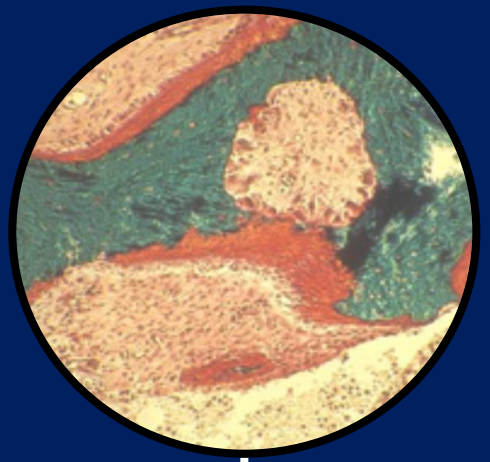
Adynamic Osteomalacia

Normal Bone Formation

Osteitis Fibrosa

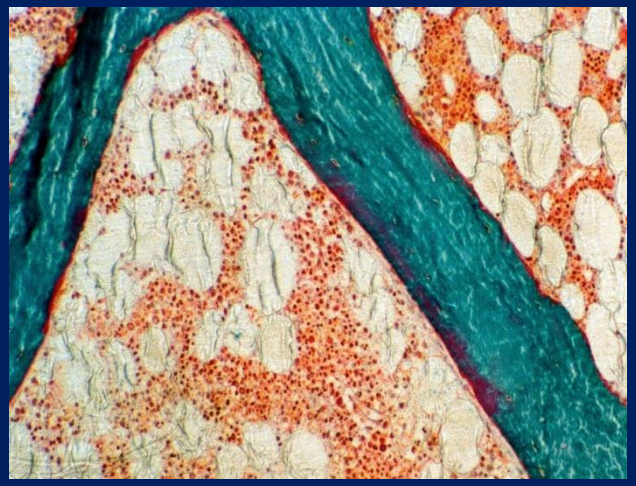




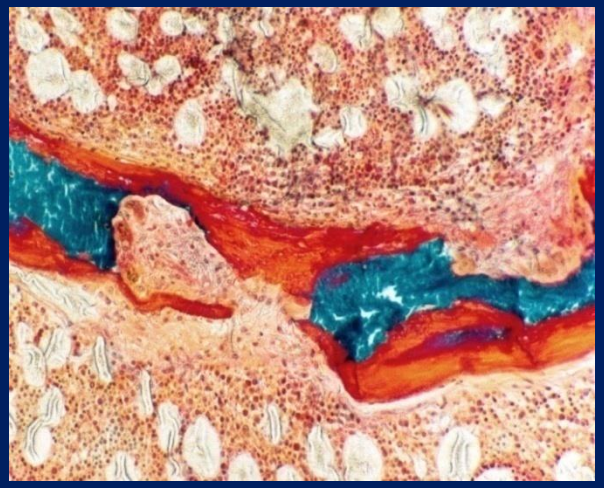


Mixed Lesion

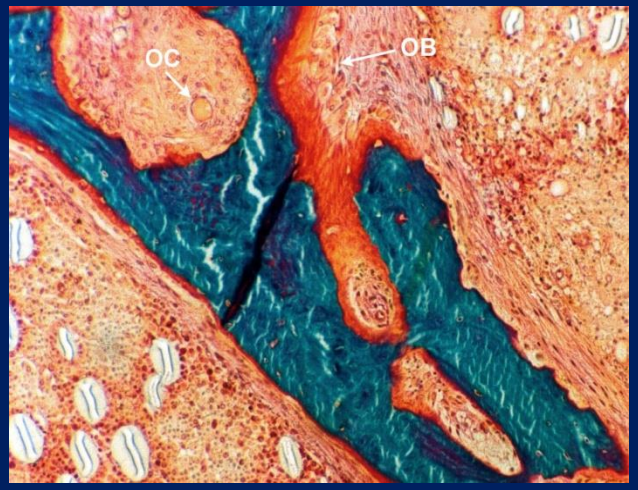
TMV Histologic Classification of ROD (KDIGO)



Adynamic bone



Mixed lesion



Osteitis fibrosa cystica

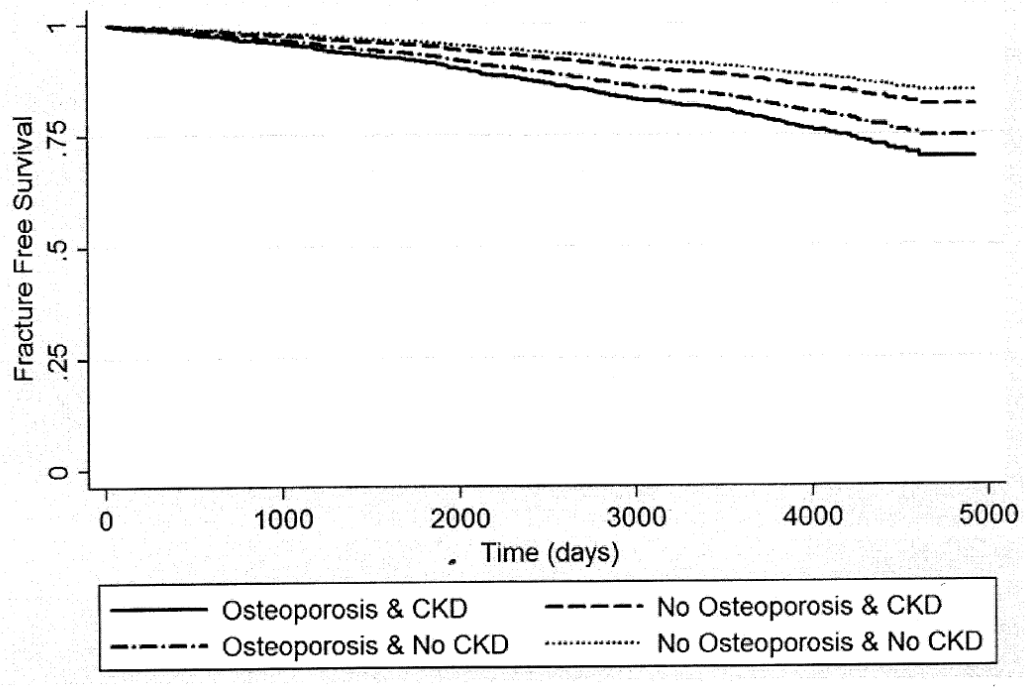
Turnover:	Low	High	High
Mineralization:	Abnormal	Abnormal	Abnormal
Volume:	Low	Low	Increased

TMV Distribution of Bone Lesions in CKD Stage 5

Mineralization (mlt_assm/Oth)	Turnover (bfrbs_assm)	Volume (bvtv_assm)	N (%)
Abnormal	1: Low	1: Low	166 (24.95)
		2: Normal	55 (11.25)
		3: High	46 (9.41)
	2: Normal	1: Low	35 (7.16)
		2: Normal	32 (6.54)
		3: High	16 (3.27)
	3: High	1: Low	25 (5.11)
		2: Normal	21 (4.29)
		3: High	10 (2.04)
Normal	1: Low	1: Low	8 (1.64)
		2: Normal	7 (1.43)
		3: High	5 (1.02)
	2: Normal	1: Low	17 (3.48)
		2: Normal	18 (3.68)
		3: High	2 (0.41)
	3: High	1: Low	4 (0.82)
		2: Normal	10 (2.04)
		3: High	74 (13.45)

Bone Mineral Density and Fracture Risk with CKD - Corrected

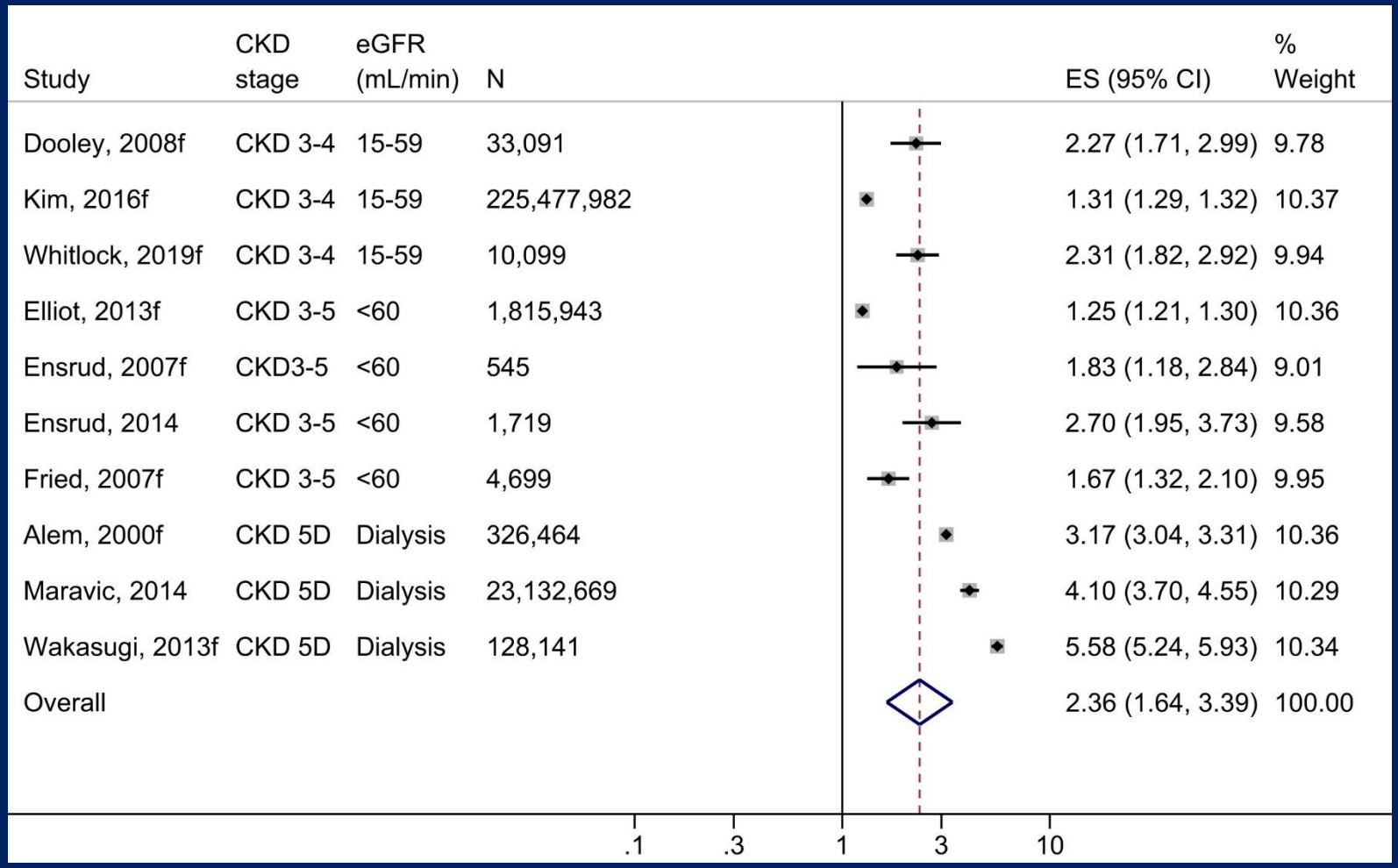
Figure 3.



Fracture-free survival curves adjusted for age, race, sex, body mass index, hyperparathyroidism, and vitamin D deficiency. The relationship with fracture risk is demonstrated between the CKD and osteoporosis groups.

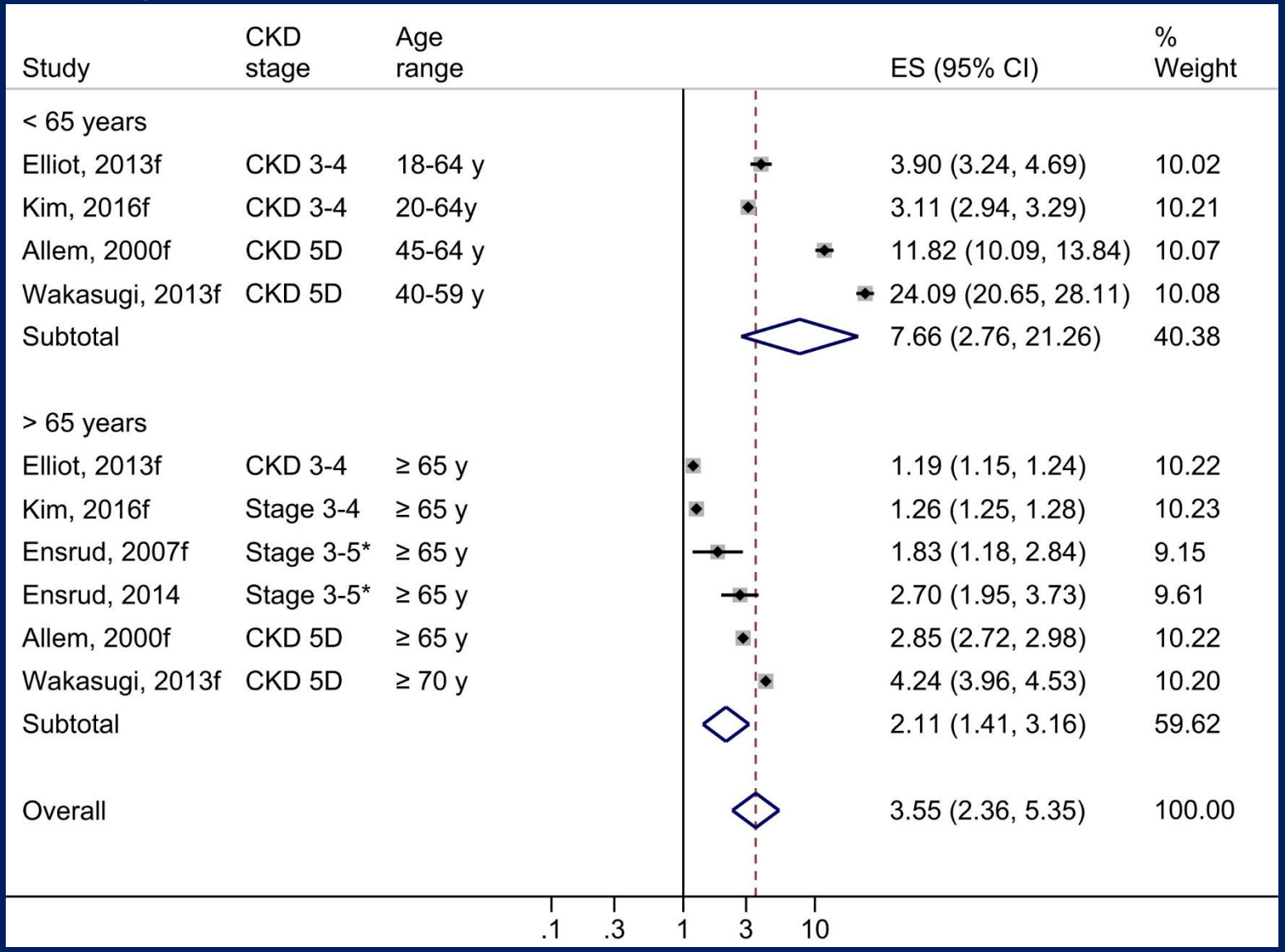
Yenchek et al. CJASN 7:1130, 2012

Overall Risk for Hip Fractures in CKD



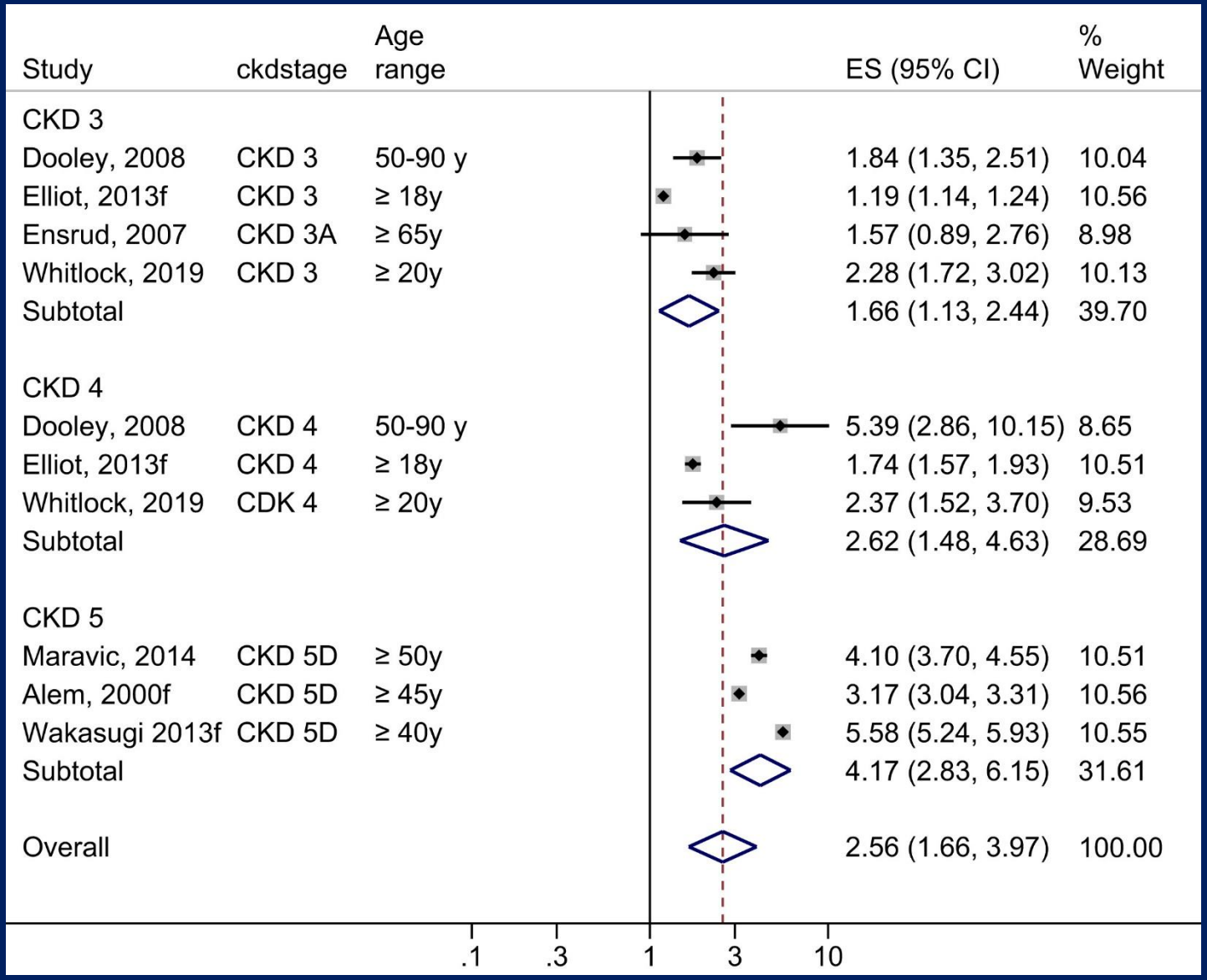
Tatiane V. et al. AJKD DOI: 10.1053/j.ajkd.2020.02.450

Hip Fracture Risk in CKD: Subgroup Analysis by Age Range



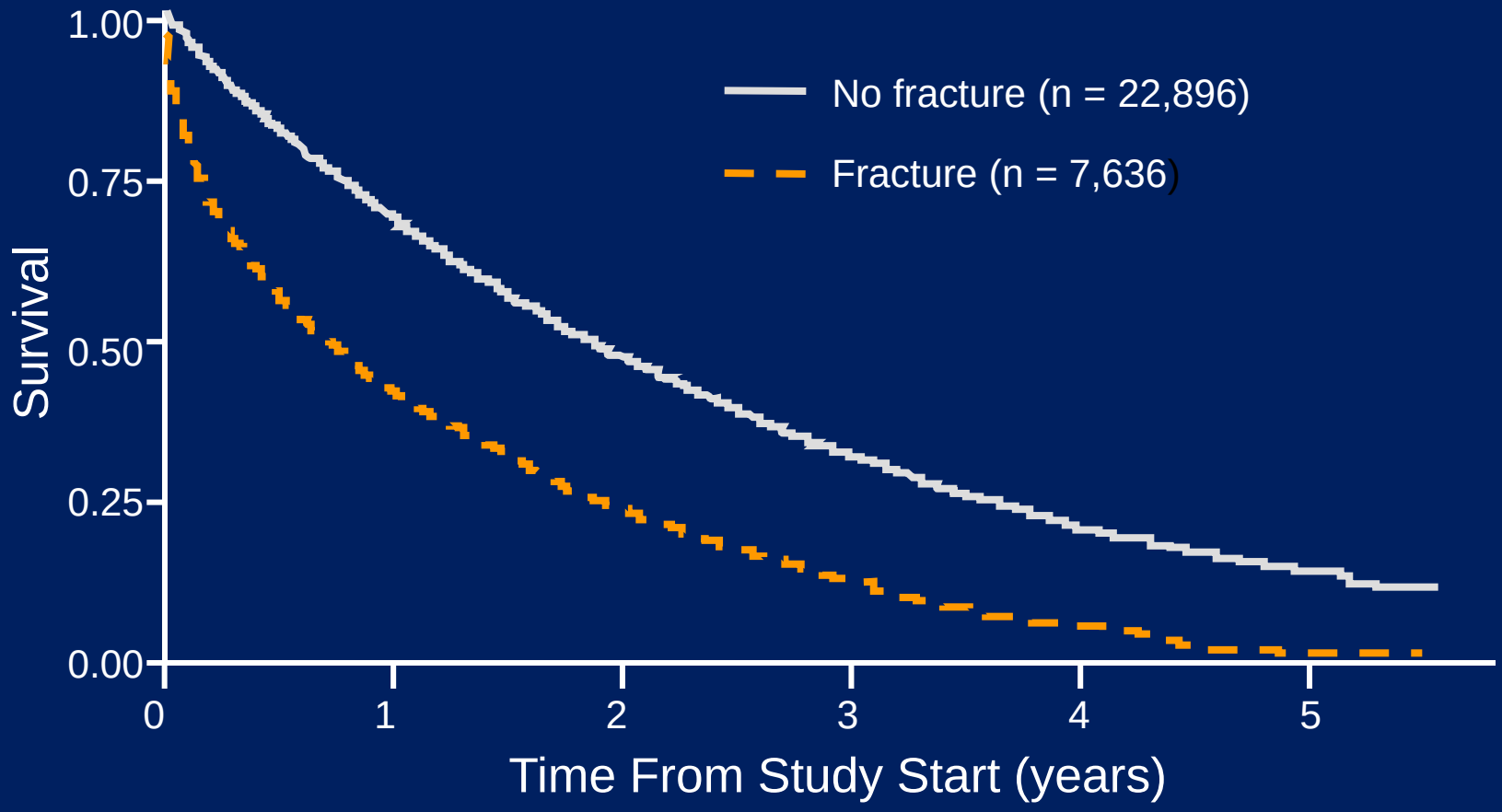
Tatiane V. et al. AJKD DOI: 10.1053/j.ajkd.2020.02.450

Hip Fracture Risk in CKD: Subgroup Analysis by Stage



Tatiane V. et al. AJKD DOI: 10.1053/j.ajkd.2020.02.450

Impact of Hip Fracture on All-Cause Mortality Risk in Dialysis Patients



CI = confidence interval.

Mittalhenkle A, et al. *Am J Kidney Dis.* 2004;44:672-679., Kaneko TM, et al. *Clin Orthop.* 2007;457:188-193.

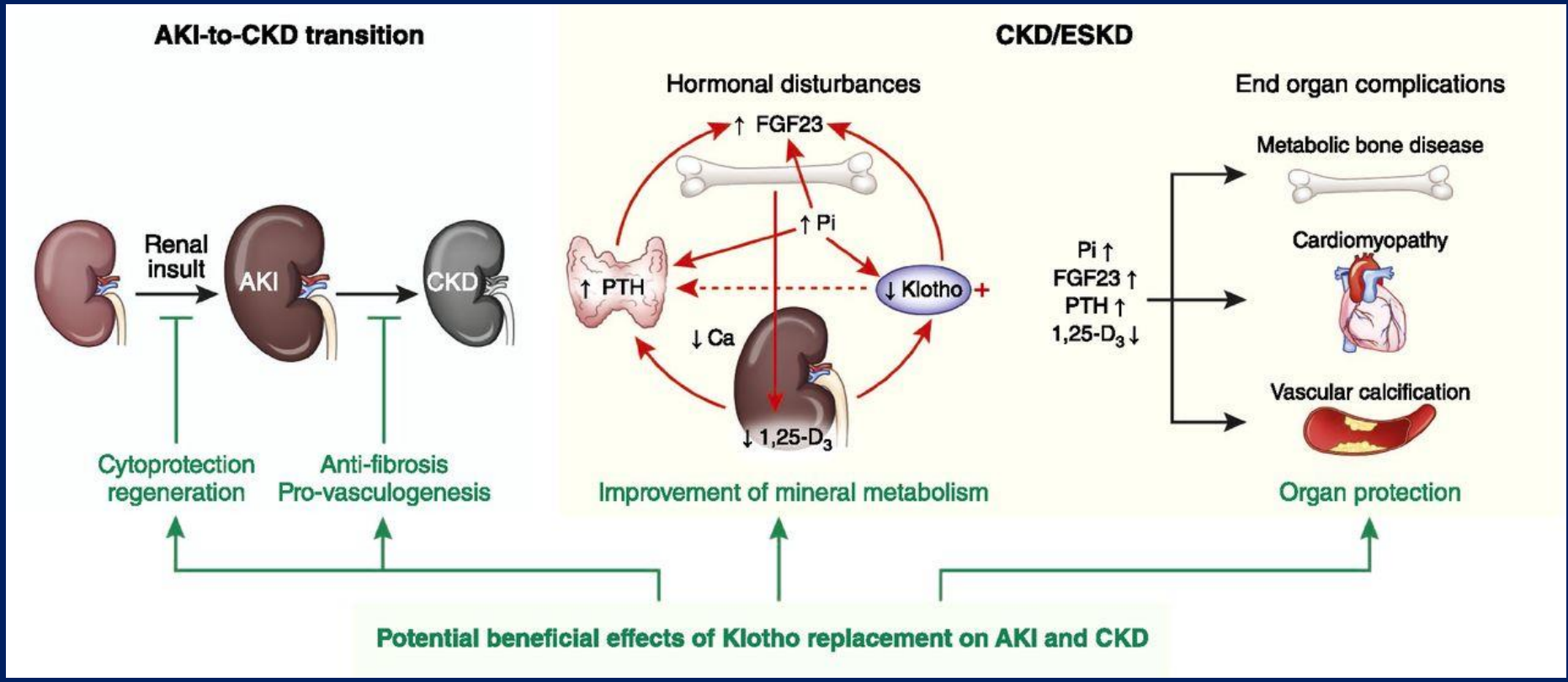
Bone Turnover Markers

	High Turnover	Low Turnover
PTH	High	Low
Formation		
Total ALP	High	Low
BALP	High	Low
Intact PINP	High	Low
Resorption		
TRACP5b	High	Low

PTH – parathyroid hormone
ALP – alkaline phosphatase
BALP – bone-specific alkaline phosphatase
PINP – intact procollagen type 1 N-propeptide
TRACP5b – tartrate-resistant acid phosphatase isoform 5b

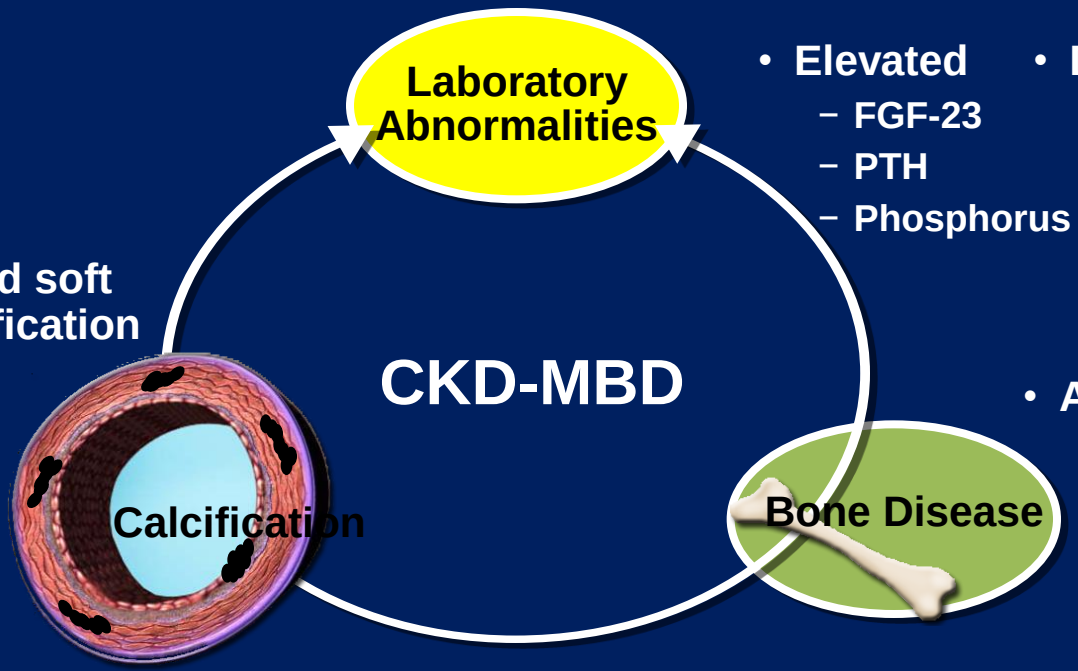
Kettler et al. Kid Intl. 2025:107,405

Role of Klotho in kidney and cardiovascular protection.



Javier A. Neyra et al. CJASN doi:10.2215/CJN.02840320

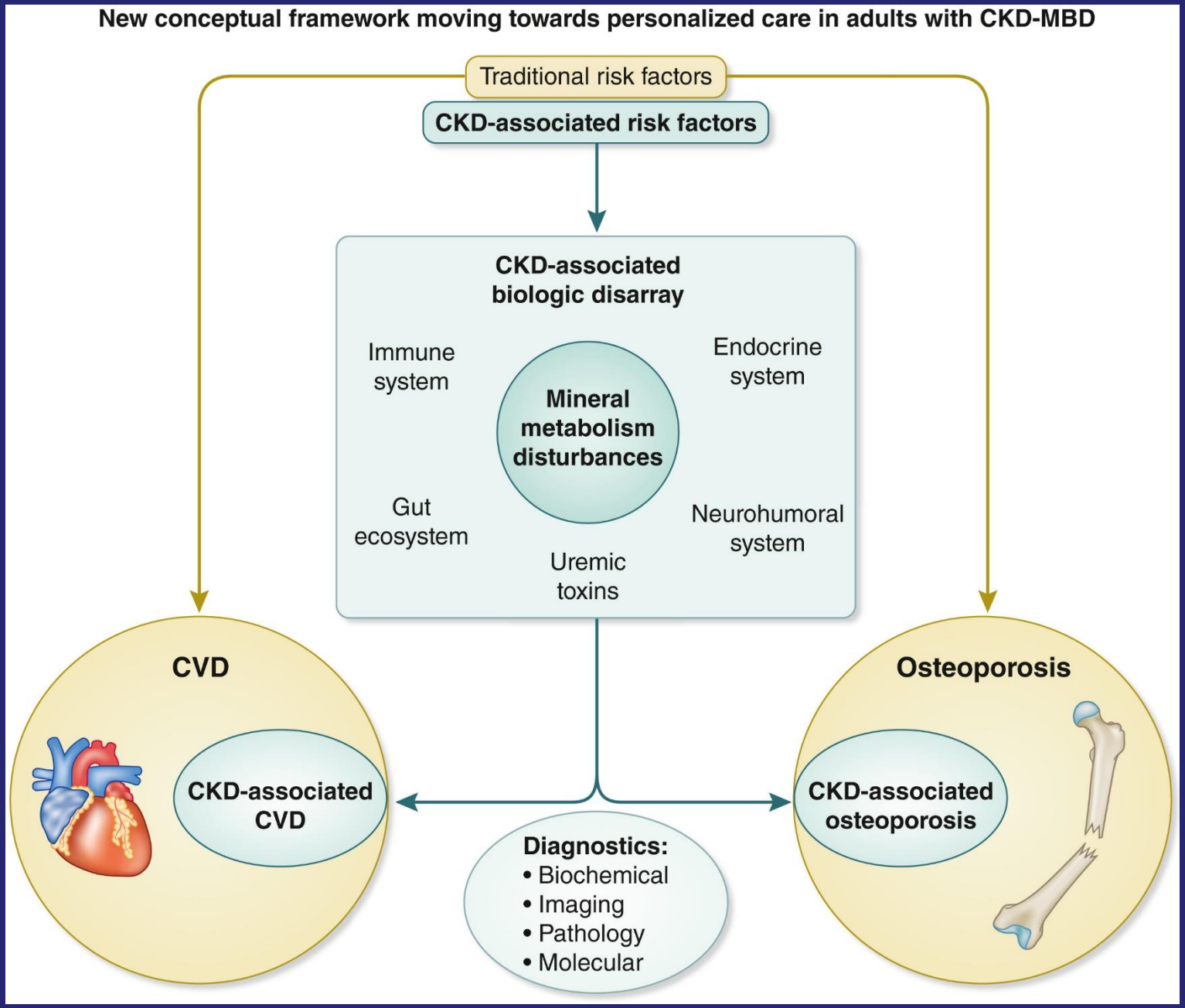
Chronic Kidney Disease-Mineral Bone Disorder



- Elevated
  - FGF-23
  - PTH
  - Phosphorus
- Decreased
  - $1,25(OH)_2D_3$
  - Calcium
- Vascular and soft tissue calcification
- Abnormal bone
  - Turnover
  - Mineralization
  - Volume
  - Linear growth
  - Strength

PTH = parathyroid hormone;
FGF-23 = fibroblast growth factor-23.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. *Kidney Int.* 2009;76



Kettler et al. Kid Intl. 2025:107,405

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Kettler et al. CKD-MBD: Conclusions from a KDIGO Controversies Conference. KI. 2025:107:405

Ketteler et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters KI 2017: 92, 26

Neyra et al. Klotho in Clinical Nephrology: Diagnostic and Therapeutic Implications. Published online: CJASN 2020 Jul 22;CJN.02840320. doi:10.2215.

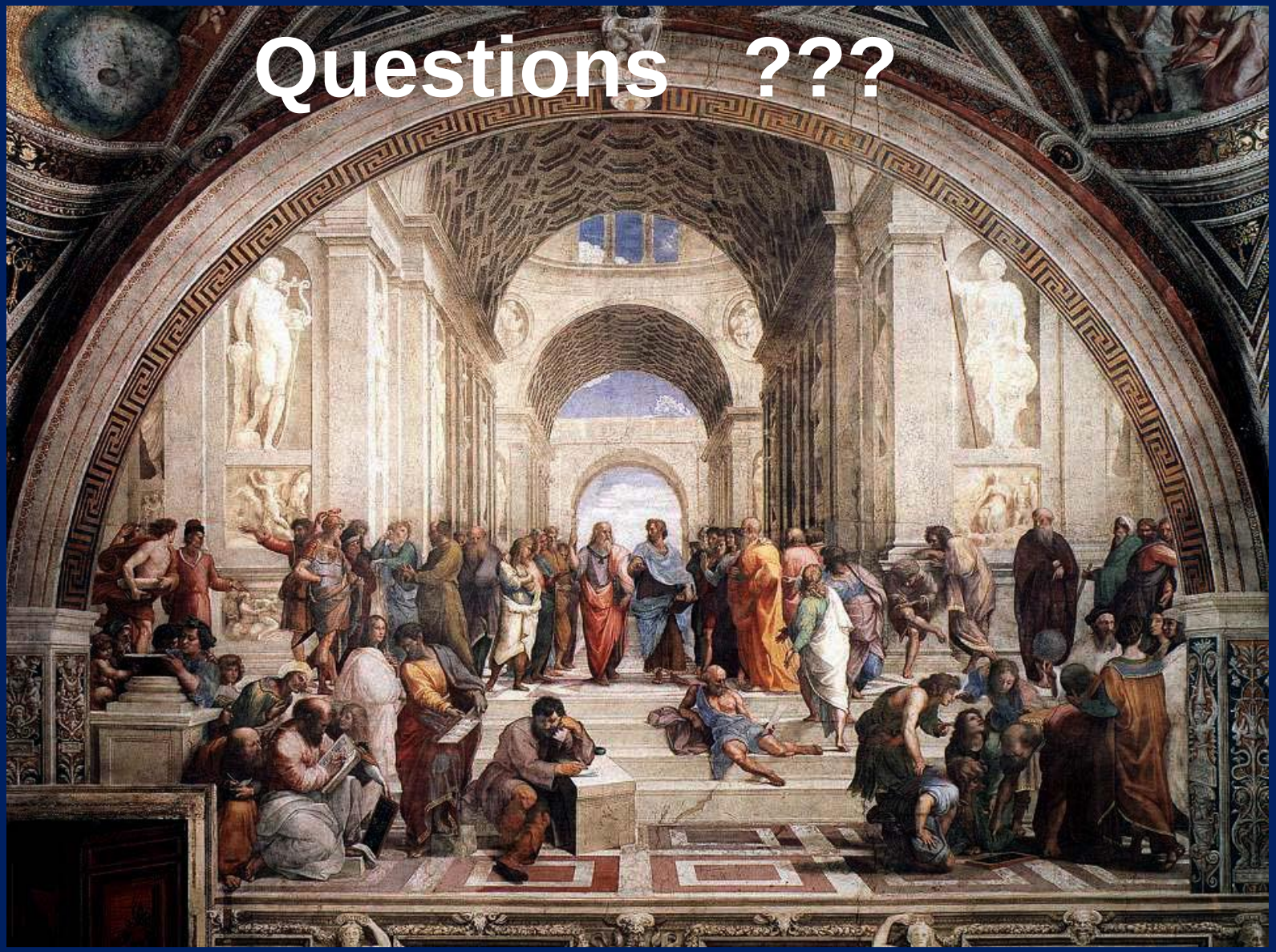
Tatiane et al. Risks of Hip and Nonvertebral Fractures in Patients With CKD G3a-G5D: A Systematic Review and Meta-analysis Published online: July 9, 2020 *AJKD* DOI: 0.1053/j.ajkd.2020.02.450

Vervloet et al. Vascular calcification in chronic kidney disease: different bricks in the wall? KI 2017; 91:808

Chen & Bushinsky, Mineral metabolism: The perils of a falling PTH due to high dialysate calcium *Nature Reviews Nephrology*, 2016; 12: 264

Chen & Bushinsky Chronic kidney disease: KDIGO CKD-MBD guideline update: evolution in the face of uncertainty. Nat Rev Nephrol. 2017;13:600

Questions ???



School of Athens / Scuola di Atene : Raphael / *Raffaello Sanzio* (1483-1520). Vatican. *The School of Athens* portrays Plato, Aristotle, and other ancient philosophers engaged in philosophic inquiry.