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

CKD-MBD
Case-Based Pearls

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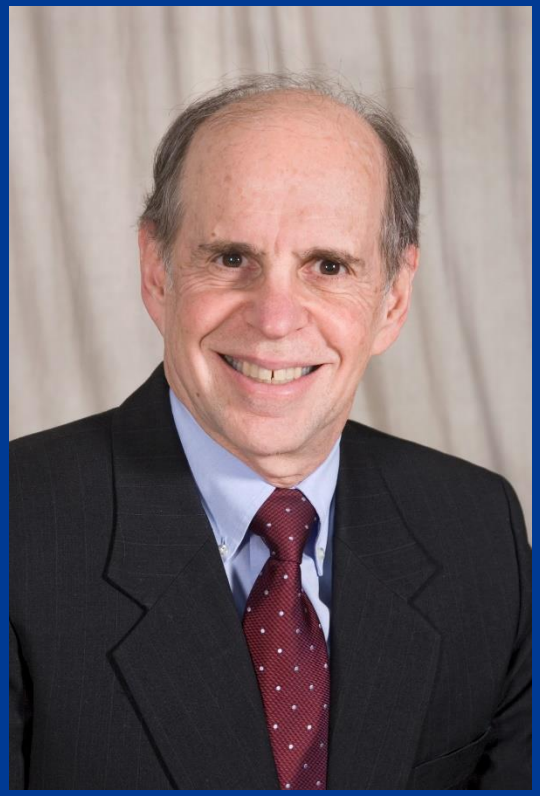
CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

David Bushinsky, MD



MD at Tufts University School of Medicine
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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**
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Consultant:	**None**
Stockholder:	**Amgen**

Case 1.

- This is a 46 year old female who presents with adult onset diabetes mellitus of 20 years duration.
- She has retinopathy and gastroenteropathy and her renal biopsy is compatible with diabetic nephropathy. Current meds include sevelamer (2 months) and calcium carbonate (3 months)
- She is begun on hemodialysis (SCa = 10.6 mg/dl) and 3 months later is found to be frankly hypercalcemic (SCa = 12.2 mg/dl).

What is the most probable cause of the hypercalcemia?

a) Hyperparathyroidism

b) Hypercalcemia of malignancy

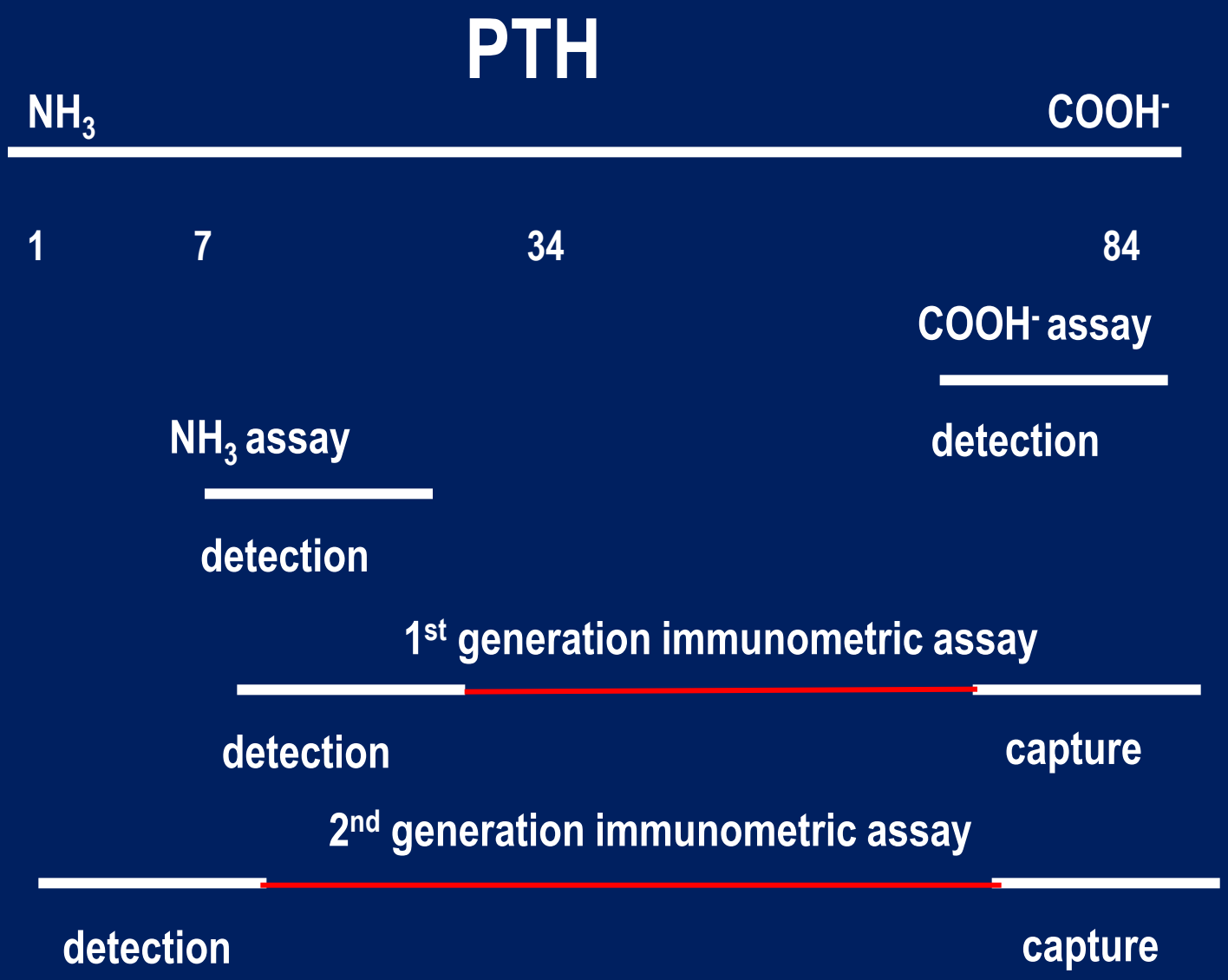
c) Immobilization

d) Vitamin D intoxication

e) Excess FGF-23

Case 2. Laboratory values

	Dialysis	+3 mos	+4 mos	+5 mos
SCa	10.6	12.2	12.4	11.4
SPO_4	7.8	6.4	6.9	6.7
Alk Phos		122		
25(OH)D		26 ng/ml		
PTH (nl 0-55)		200 ng/L		


PTH
NH3
COOH-
1
7
34
84
COOH- assay
detection
NH3 assay
detection
1st generation immunometric assay
detection
capture
2nd generation immunometric assay
detection
capture

Which of the following does she have?

a) Primary Hyperparathyroidism -
b) Secondary Hyperparathyroidism –
c) Refractory Secondary Hyperparathyroidism –
d) Tertiary Hyperparathyroidism –
e) Excess Vitamin D-

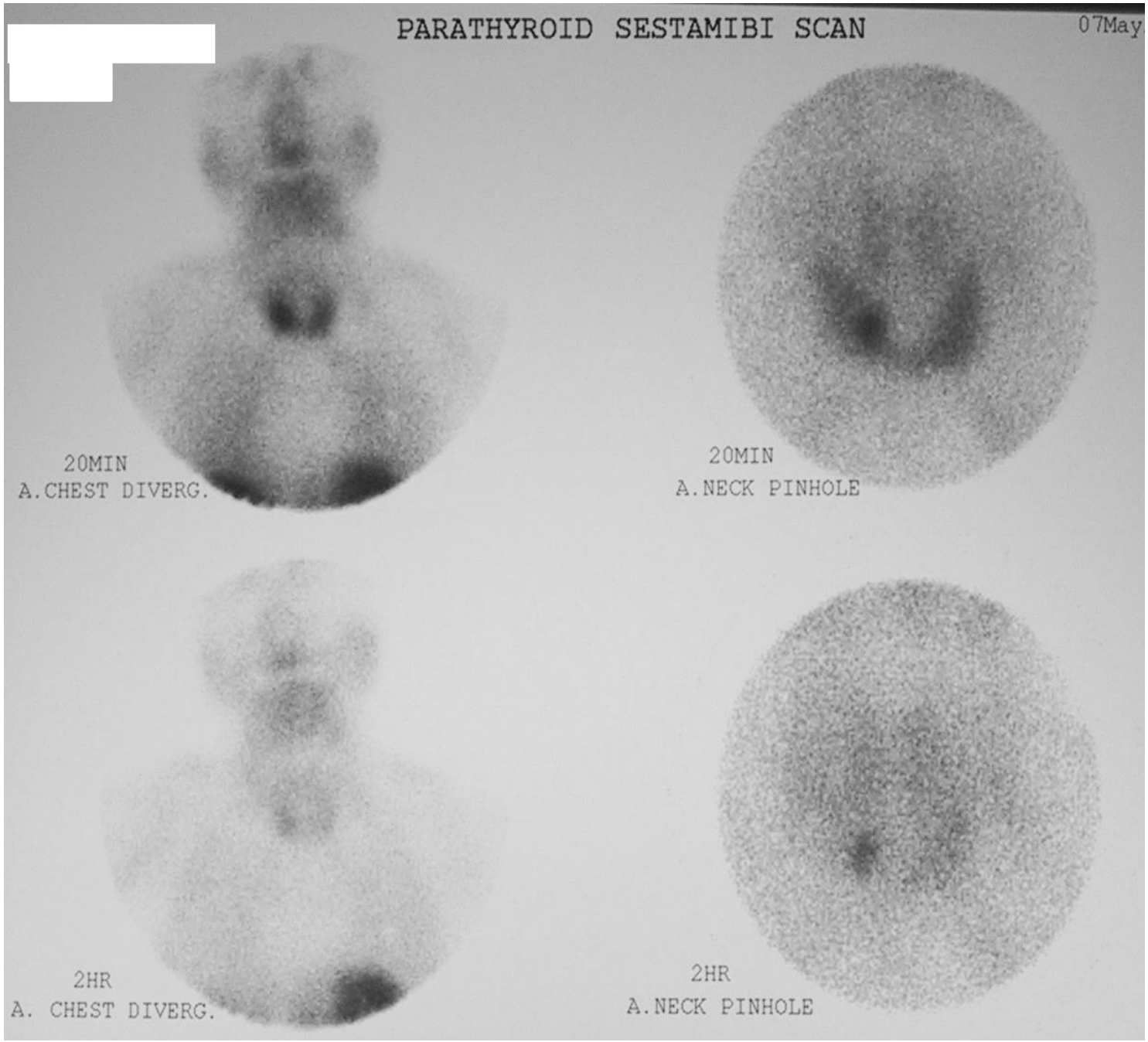
+ 8 months

Parathyroid scan

large nodule present below the left lobe of the thyroid

CXR - normal

Mammogram - normal


PARATHYROID SESTAMIBI SCAN
07May
20MIN
A.CHEST DIVERG.
20MIN
A.NECK PINHOLE
2HR
A. CHEST DIVERG.
2HR
A.NECK PINHOLE

+ 8 months

Surgery

LLP - 2 cm mass - adenoma

other three glands were “slightly hyperplastic”

mass and 2.5 of remaining 3 glands removed

Post op

[Ca] decreases to 7.9 mg/dl by the 3rd post op day

[Ca] = 9.1 mg/dl at discharge

Hyperparathyroidism

primary	autonomous secretion
secondary	response to normal regulatory stimuli
refractory secondary	nonsuppressible secretion after correction of metabolic abnormalities
tertiary	refractory secondary with hypercalcemia

Parathyroid Hormone (PTH)

Secretion:

Regulated principally by Ca^{++} via CaR
low Ca^{++} stimulates secretion
Also by $1,25(OH)_2D_3$
$1,25(OH)_2D_3$ inhibits secretion
Also by phosphate
phosphate stimulates secretion

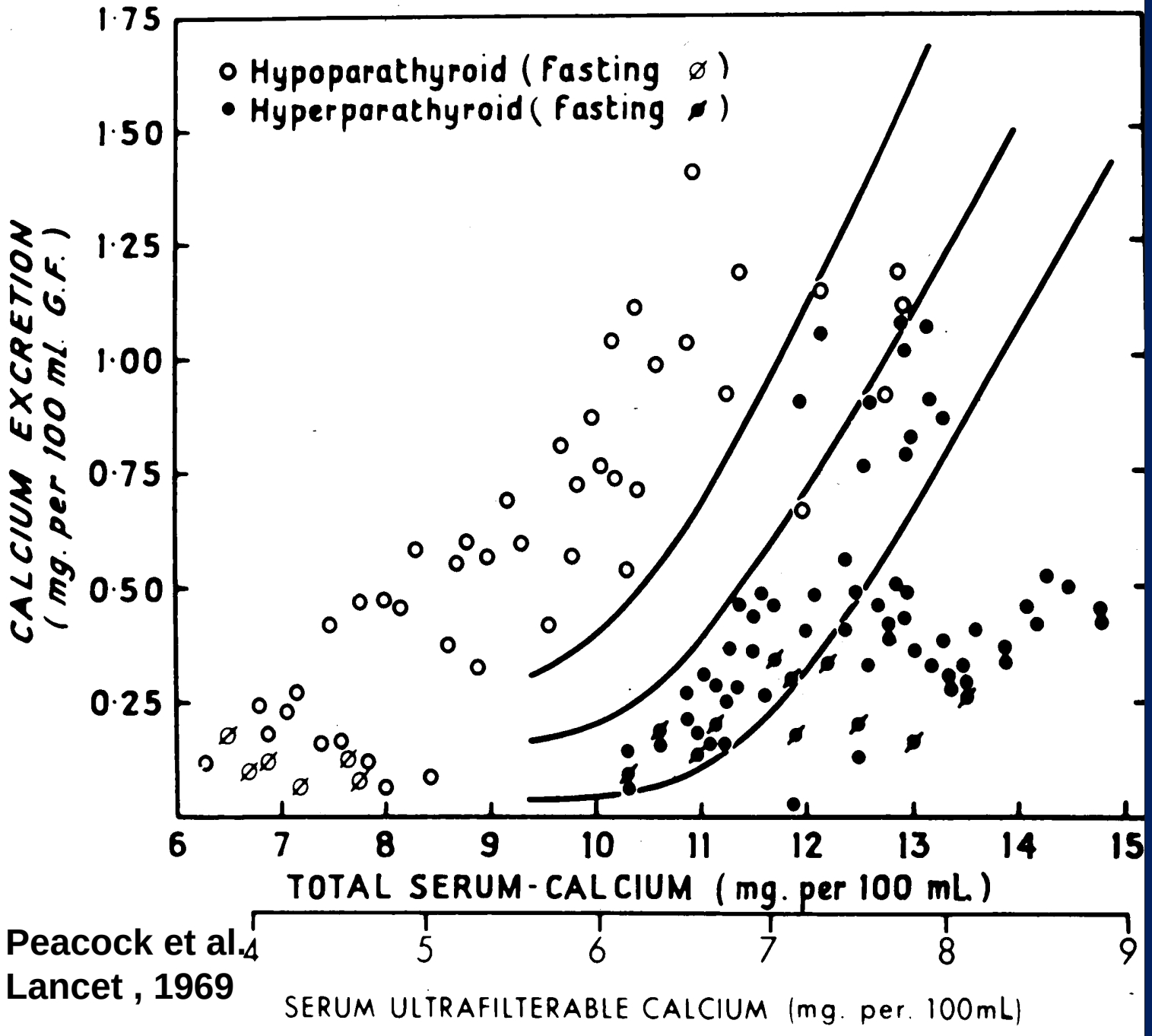
Parathyroid Hormone (PTH)

Actions

Kidney - stimulates reabsorption of calcium
inhibits reabsorption of phosphate
increases activity of 1α-hydroxylase
(enhances synthesis of $1,25(OH)_2D_3$)

Bone - stimulates resorption of calcium
stimulates resorption of phosphate
(intermittent doses can stimulate bone formation)

Intestine - no direct effect – only through increased $1,25(OH)_2D_3$



Peacock et al.
Lancet , 1969

Parathyroid Hormone (PTH)

Net effect on Ca homeostasis

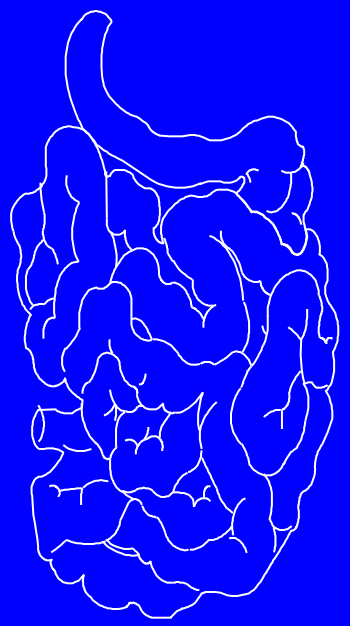
- Blood calcium increases
- Blood phosphorus decreases
- Urine calcium increases
  - Increase in filtered load exceeds increase in tubular reabsorption

Calcium

Continuous Excess PTH

↑ PTH

↑ $1,25(OH)_2D_3$



D_{Ca}

Intestine

↑ a_{Ca}

↑ ECF_{Ca}

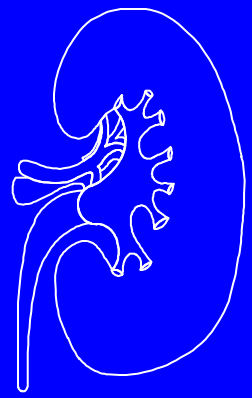
↑↑ Br_{Ca}

↑ Bf_{Ca}

Bone

↑ fr_{Ca}

↑↑ FL_{Ca}



Kidney

↑ U_{Ca}

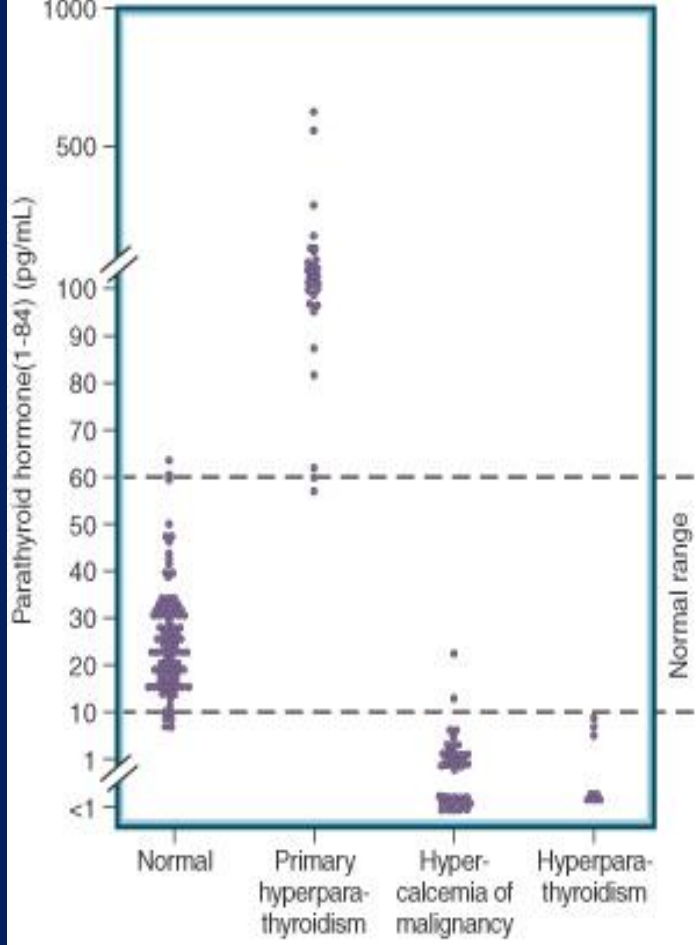


Figure 27–20. Intact immunoreactive parathyroid hormone (PTH) determined using a two-site immunoradiometric assay in normal and three different patient groups. Note there is some overlap between normal subjects and patients with primary hyperparathyroidism, but there is no overlap between hypercalcemic patients with primary hyperparathyroidism and those with hypercalcemia of malignancy.

(From Segre GV. Advances in techniques for measurement of parathyroid hormone: current applications in clinical medicine and directions for future research. Trends Endocrinol Metab 1990;1:243-247.)

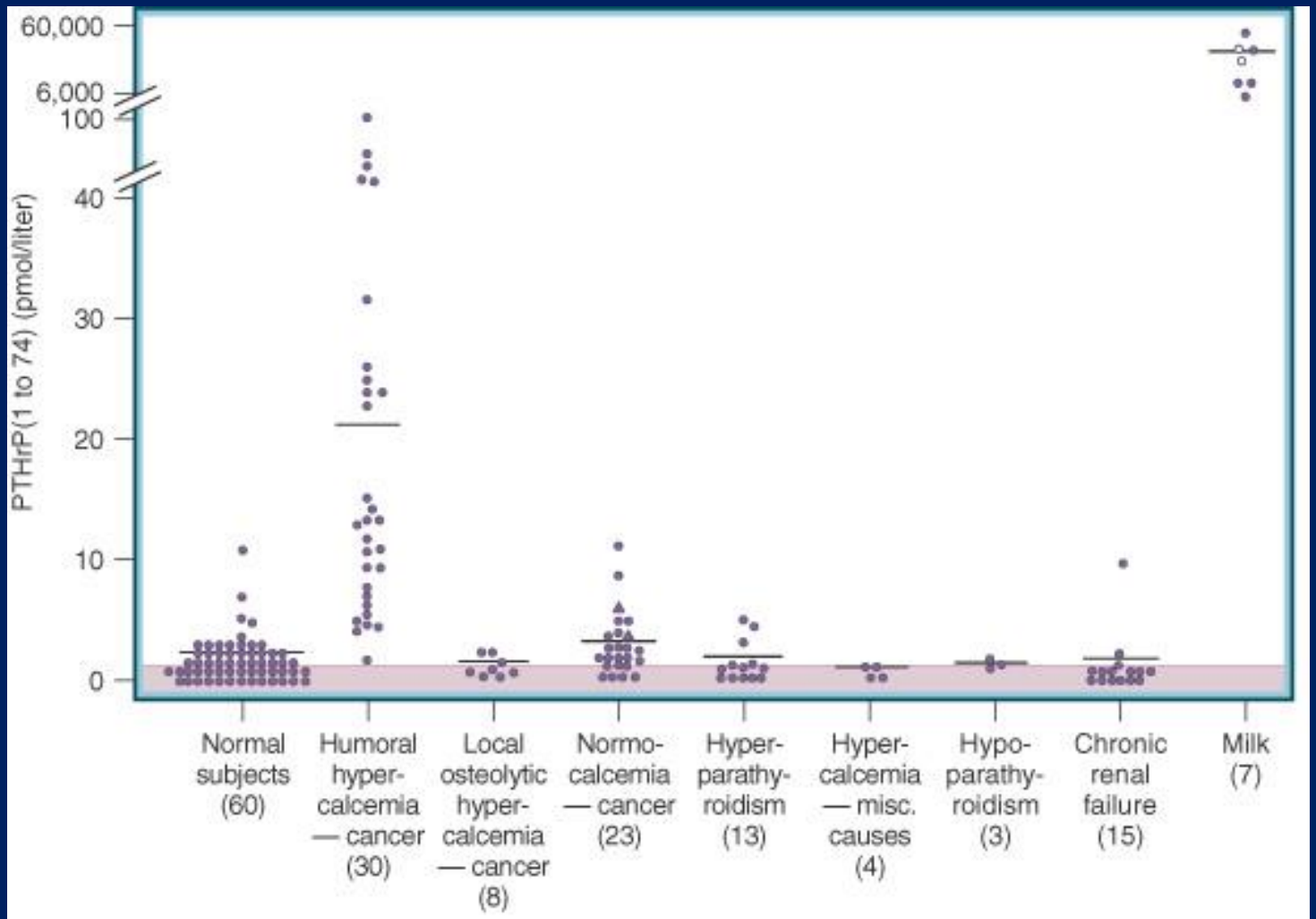


Figure 27–21. Plasma PTHrP(1-74) determined by two-site immunoradiometric assay in selected patient groups and normal subjects. Also shown are concentrations of PTHrP in human milk *(filled circles)* and in bovine milk *(open circles)*. Two normocalcemic patients with cancer *(filled triangles)* subsequently became hypercalcemic. *Hatched area* denotes levels too low to detect with this assay. PTHrP, parathyroid hormone–related protein.

(Adapted from Burtis WJ, Brady TG, Orloff JJ, et al. Immunochemical characterization of circulating parathyroid hormone related protein in patients with humoral hypercalcemia of cancer. N Engl J Med 1990;322:1106-1112.)

Primary Hyperparathyroidism – Indications for Surgery

Kidney Stones, Nephrocalcinosis

Fractures, ostitis fibrosa on x-ray

neuromuscular disease

symptomatic hypercalcemia

SCa > 1mg/dl over nl

UCa > 400 mg/dl

CrCl < 70% of predicted

BMD - T score < 2.5

Age < 50y

poor prospects for medical follow up

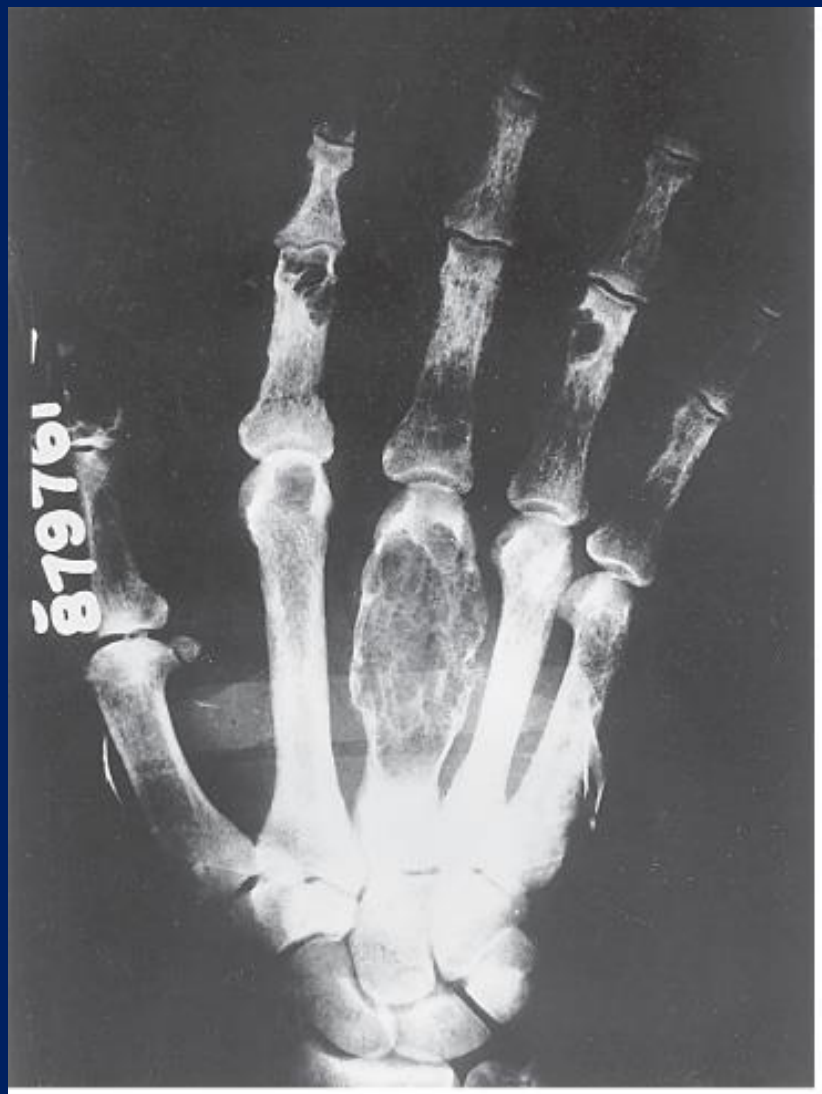


Figure 27–22. Radiograph of hand from a patient with severe primary hyperparathyroidism. Note the dramatic remodeling associated with the intense region of high bone turnover in the third metacarpal in addition to widespread evidence of subperiosteal, endosteal, and trabecular resorption.

(Courtesy of Fuller Albright Collection, Massachusetts General Hospital.)

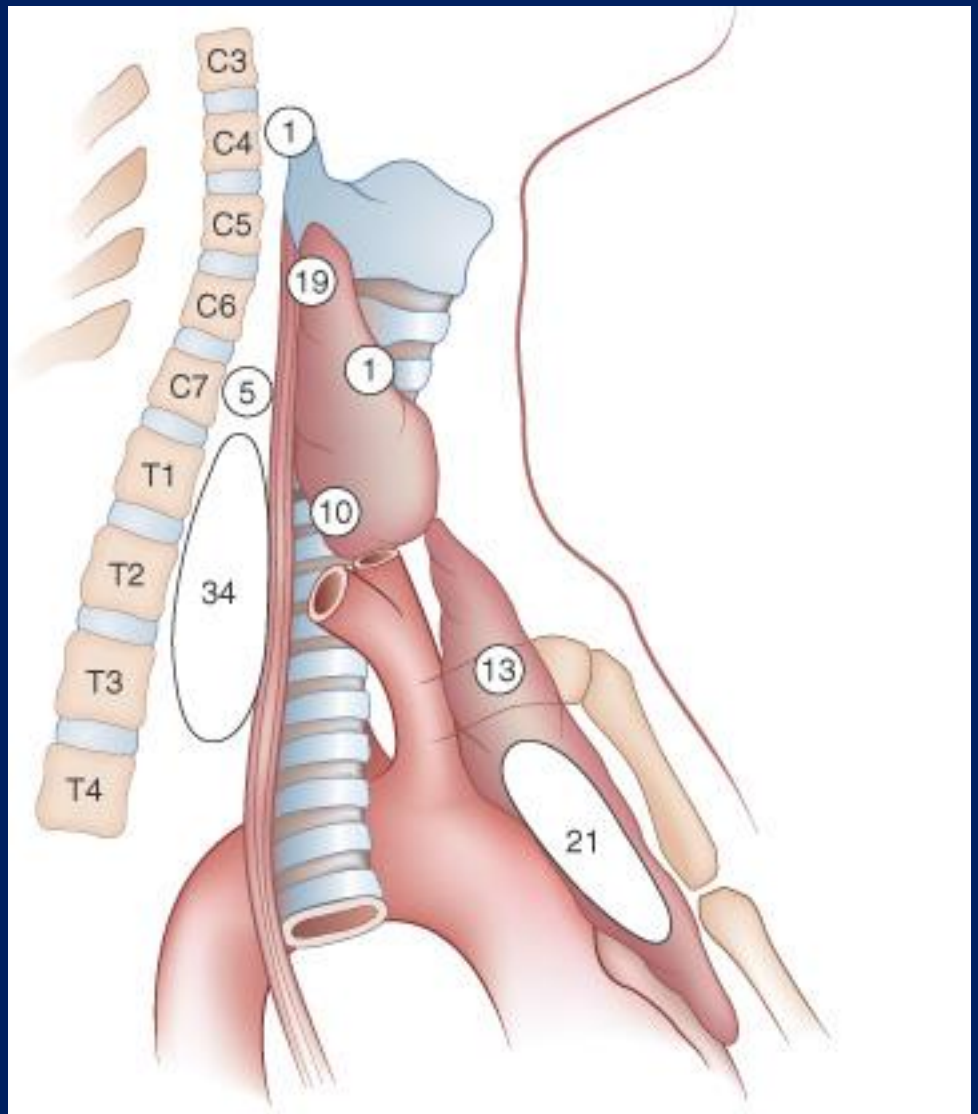


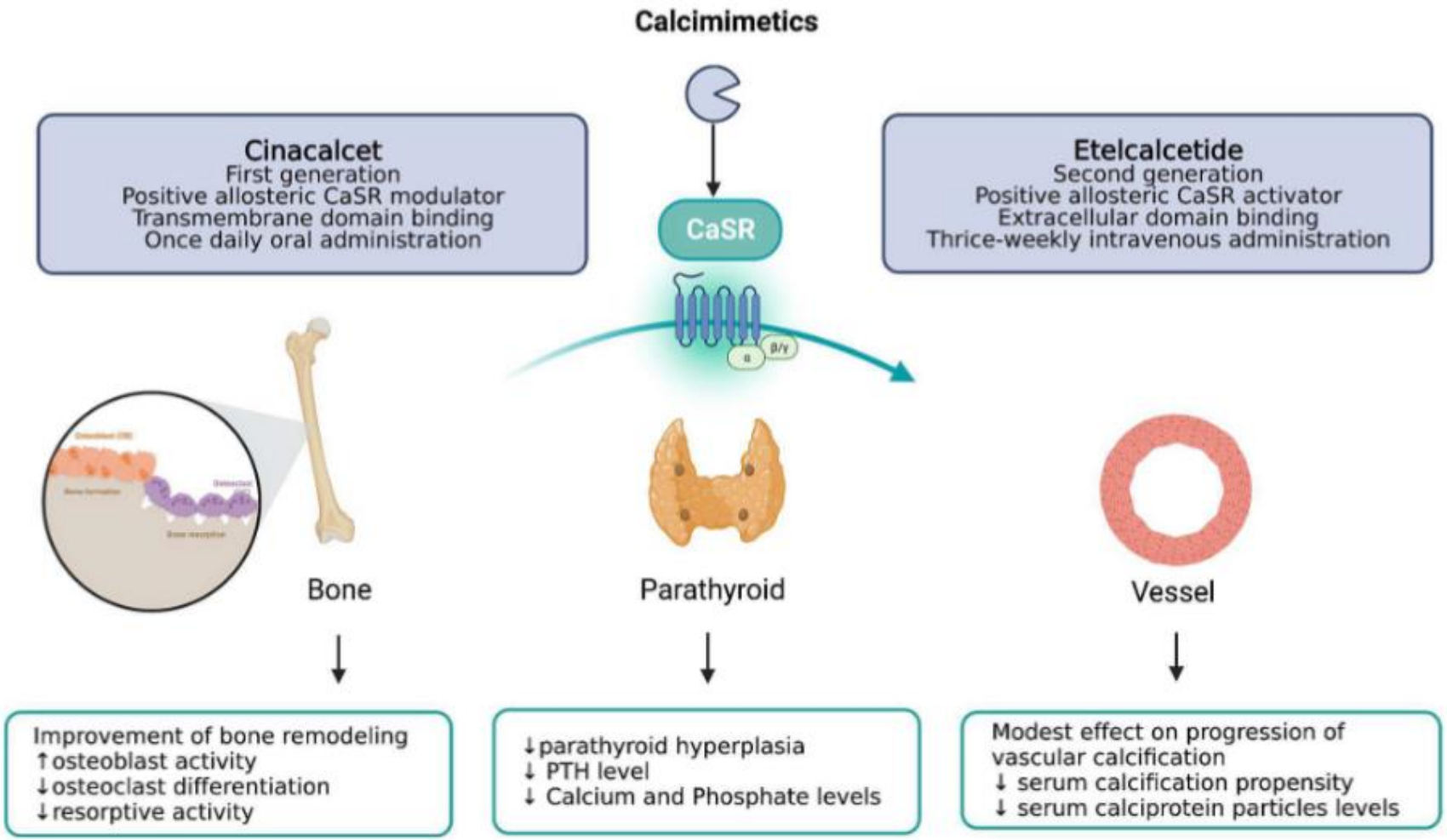
Figure 27–25. Sites of ectopic location of 104 parathyroid glands found at reoperation for primary hyperparathyroidism.

(From Wang C-A. A clinical and pathological study of 112 cases. Ann Surg 1977;186:140-145.)

Hyperparathyroidism – Rx

- Cinacalcet - po
  - approved
    - for secondary HPT in dialysis patients
    - parathyroid carcinoma
    - primary HPT who can not have surg
  - also
    - following kidney transplant with HPT
- Etelcalcetide – iv
  - approved
    - for secondary HPT in HD patients

Calcimimetics



Current Osteoporosis Reports (2023) 21:193–204

CALCIUM SENSING RECEPTOR

TALH

- increased peritubular Ca^{2+}
  - decreases tubular Ca^{2+} reabsorption
  - increased Ca^{2+}
    - reduces activity of K channel
    - decreasing positive potential gradient
    - decreasing Ca^{2+} reabsorption

IMCD

- elevated Ca^{2+} inhibits vasopressin-elicited
  - transepithelial water flow by 35-40%

Calcium Sensing Receptor

Inactivating Mutation – decreased Ca inhibition of PTH secretion

Hypercalcemia
Hypocalciuria
Elevation of PTH
Familial Hypocalciuric Hypercalcemia (FHH)
Neonatal severe primary hyperparathyroidism

Activating Mutation – increased Ca inhibition of PTH secretion

Hypocalcemia
Hypercalciuria
Inappropriately normal (or low) levels of PTH
Autosomal Dominant Hypocalcemia (ADH)

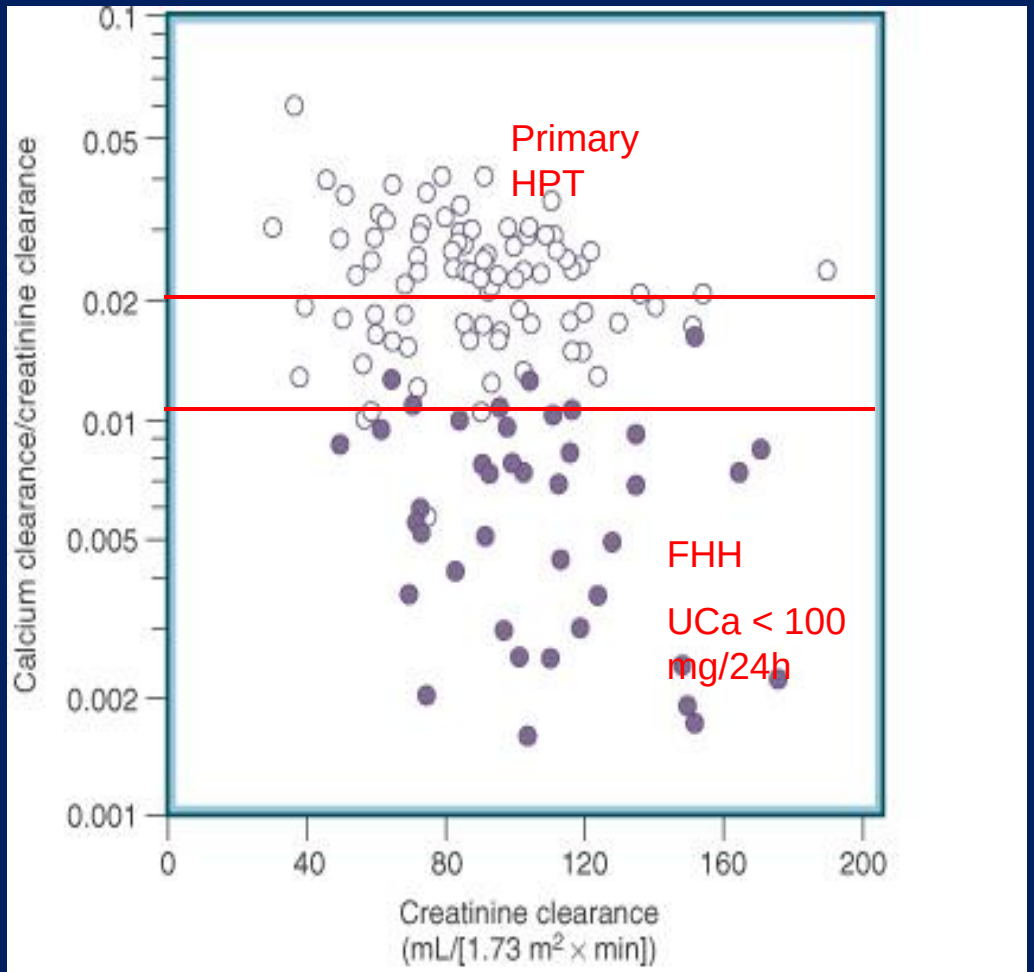


Figure 27–27. Index of urinary excretion rate for calcium as a function of creatinine clearance. Each point represents the mean of multiple determinations for a hypercalcemic patient with familial hypocalciuric hypercalcemia *(filled circles)* or with typical primary hyperparathyroidism *(open circles)*. The data are based on average 24-hour urinary excretion values and average fasting serum samples.

(From Marx SJ, Attie MF, Levine MA, et al. The hypocalciuric or benign variant of familial hypercalcemia: clinical and biochemical features in fifteen kindreds. Medicine (Baltimore) 1981;60(6):397-412.)

Case 2

- The patient is a 35 yo wm with adult onset PKD. The dx was made at age 27 while he was in the Army. He has had no medical follow-up following discharge. The patient is adopted and no family history is available.

- He has limited education and poor understanding of his disease.

- His main complaints are back pain and polyuria.

Case 2. Laboratory studies

BUN 111 mg/dL	Cr 9.3 mg/dL	CO_2 15 meq/L	
Ca 11.0 mg/dL	PO_4 9.1mg/dL	Alk Phos 163 IU/L	Mg1.3 meq/L

He refused phosphate binders and delayed getting access.

+ 3 months - began hemodialysis

Creat	9.1 mg/dl
BUN	134 mg/dl
[Ca]	11.2 mg/dl
[PO_4]	9.9 mg/dl

many missed treatments

many abbreviated treatments

diagnosed "attention-deficit hyperactivity disorder"

borderline intelligence on formal testing

Which condition does he have ?

a) Primary Hyperparathyroidism
b) Secondary Hyperparathyroidism
c) Refractory Secondary
d) Tertiary Hyperparathyroidism
e) Excess Vitamin D

+ 4 months - admitted

Infected renal cyst
Klebsiella bacteremia

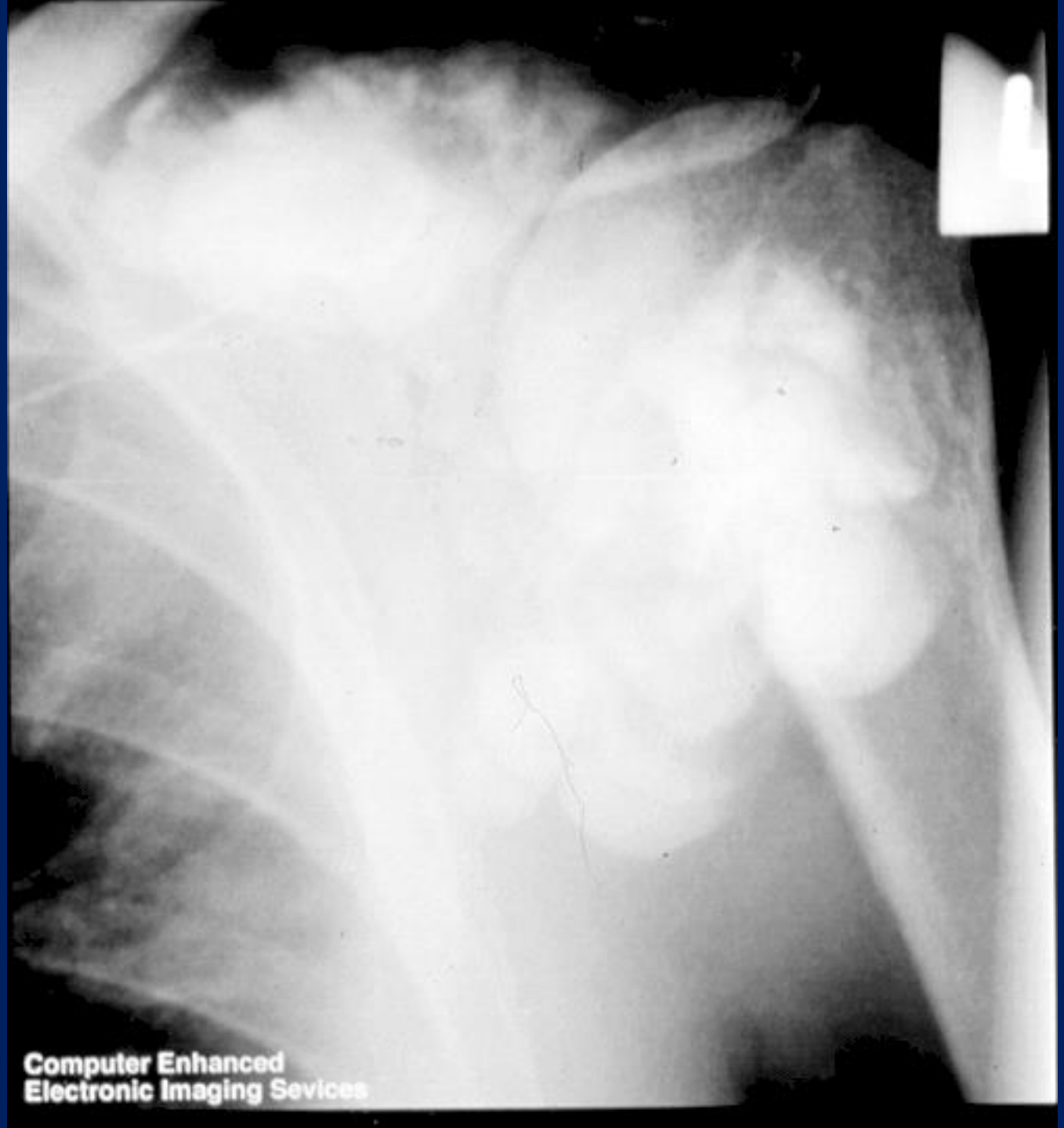
[Ca]	10.7 - 11.3 mg/dl
$[PO_4]$	5.8 - 8.1 mg/dl
PTH	1019 - 1311 pg/ml
$1,25(OH)_2D_3$	16 pg/ml

Parathyroid ultrasound

RUP 1.8 x 0.8 x 0.7 cm
LUP 1.4 x 1.3 x 1.4 cm

CXR right shoulder
extensive soft tissue calcification

Refused parathyroidectomy - judged competent


Computer Enhanced
Electronic Imaging Sevices

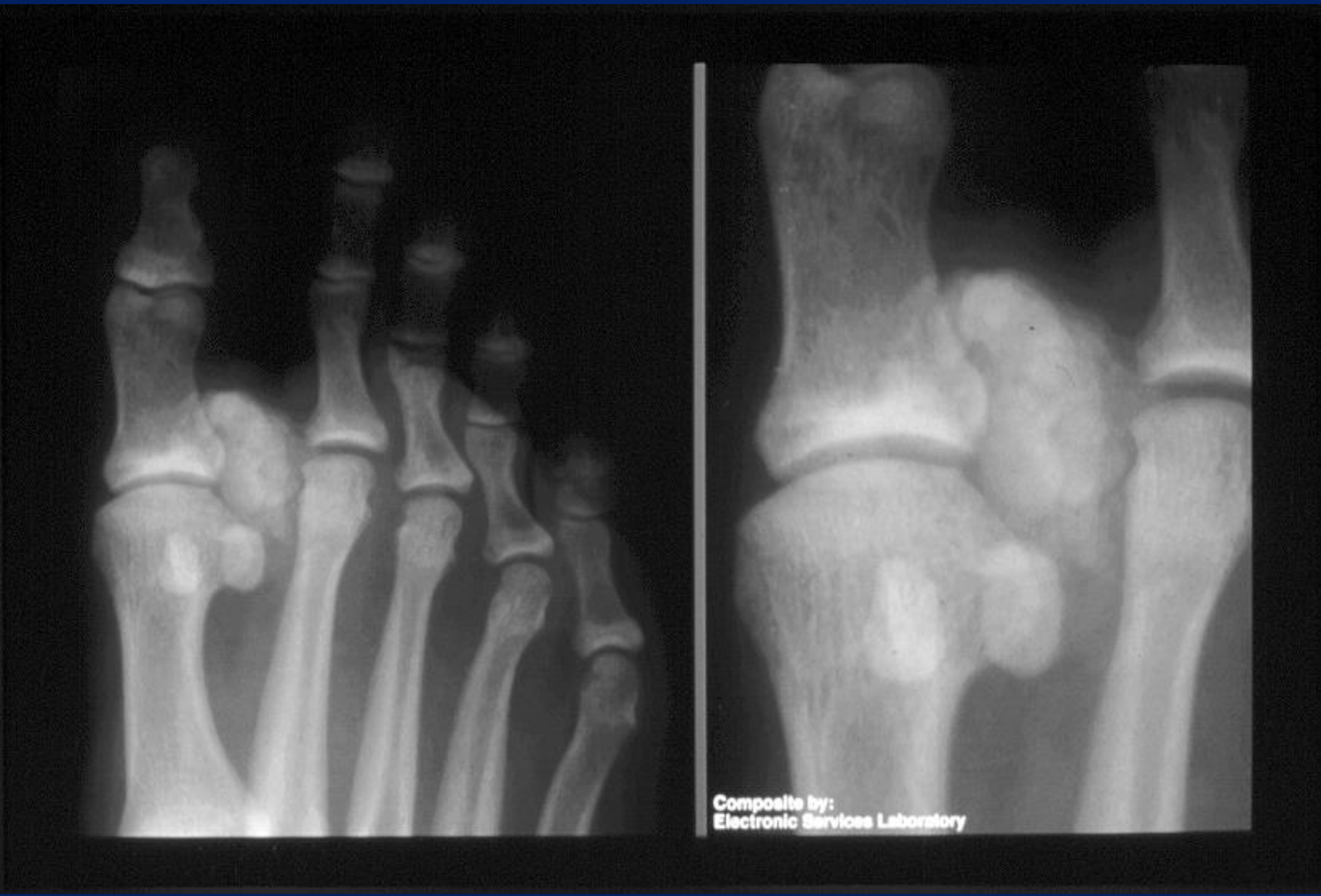
+ 8 months

Refused all meds

Intermittently shows up for dialysis

Agrees to parathyroidectomy

- multiple soft tissue calcifications
- ulcerations
- calciphylaxis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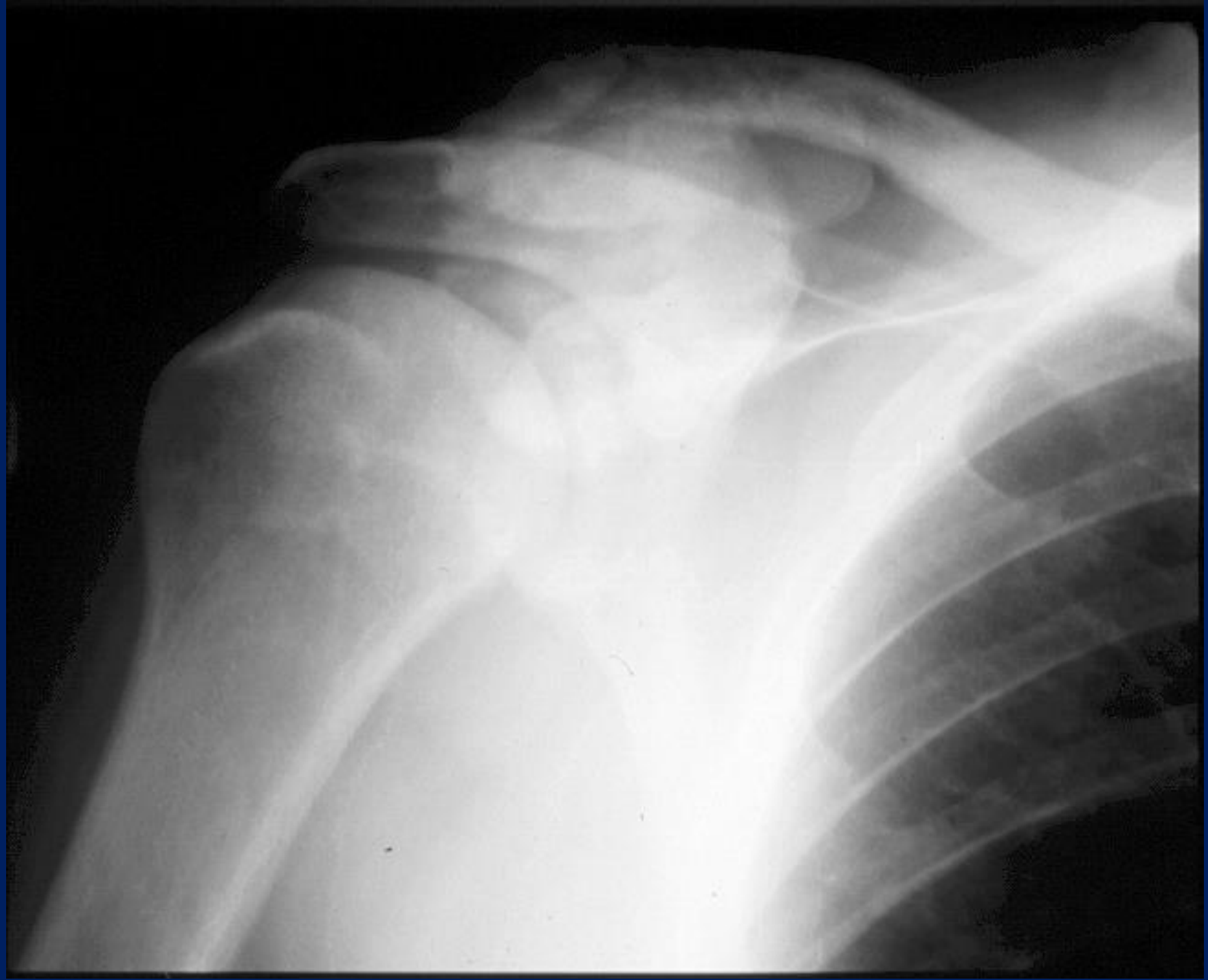
Electronic Services Laboratory



Surgery

- L side - two glands 1 cm and 2 cm
- R upper 1.5 cm
- R lower could not be identified
- Entire R lobe of thyroid resected -- no parathyroid tissue
- Reimplantation of parathyroid tissue into R forearm

Post Op - day 6

[Ca] 7.6 - 9.2 mg/dl

PTH 972 pg/ml (nl 0-55)

What would you do next ?

a) Parathyroid Scan
b) Scan for ectopic parathyroid tissue
c) Bone Scan
d) DEXA for bone mineral density
e) $1,25(OH)_2D_3$ level

MR scan of the neck

no evidence of an ectopic parathyroid gland

Parathyroid Scan

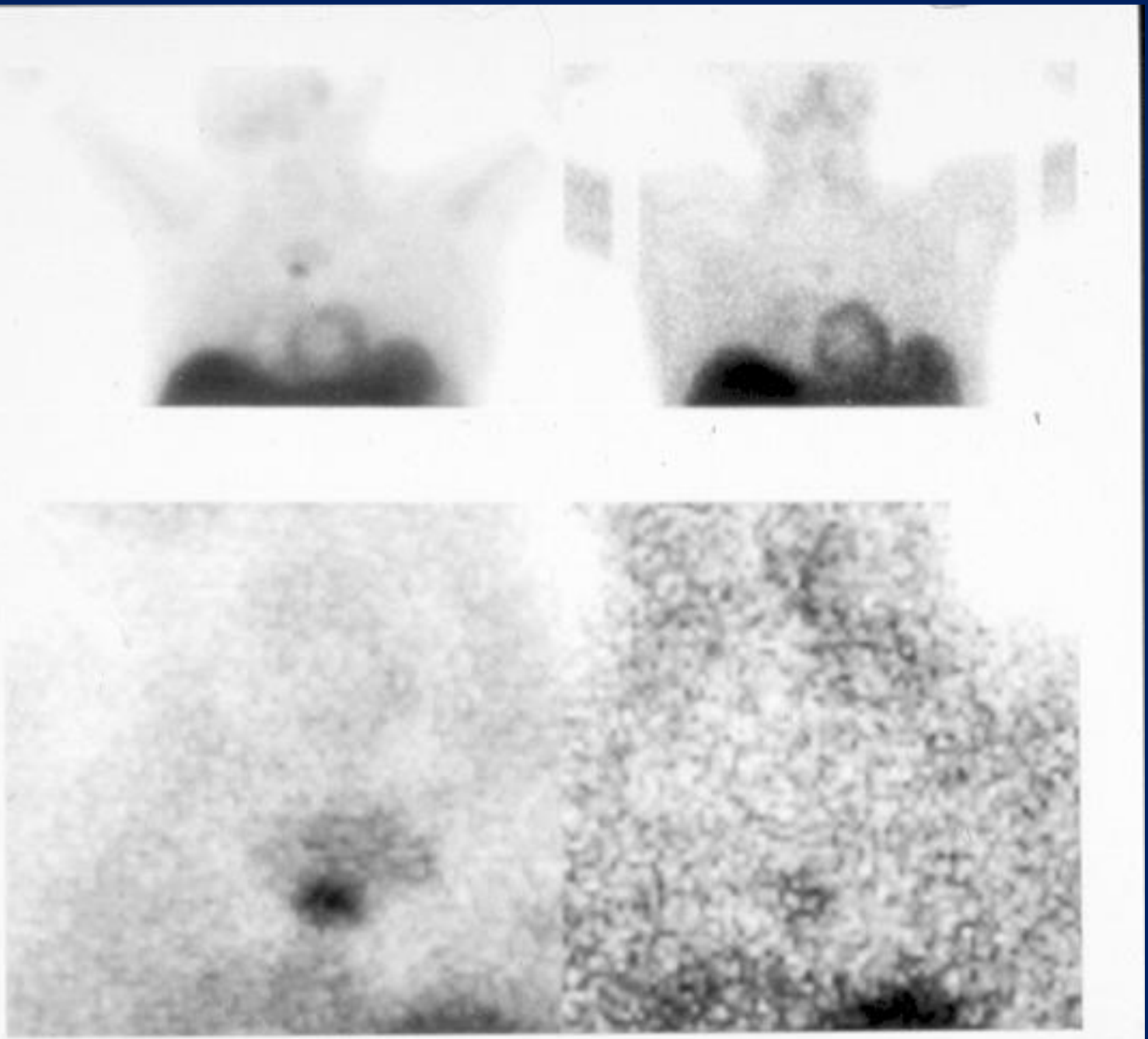
intense activity - inferior and to the R of the manubriosternal joint

Continued to be noncompliant

Psychiatry

Patient understands his disease and the consequences of non compliance.

Judged competent to make decisions.



20 Minutes

4hr Delay

- Would drink large amounts of milk brought in by the family
- Would take milk off other patients' trays
- Refused all phosphate binders
- Patient made himself DNR - family agreed
- Refused dialysis

[Ca] 11.3 mg/dl

[PO_4] 11.0 mg/dl

PTH 1303 pg/ml

Developed calciphylaxis

Became septic, hypotensive and died

Postmortem

Fourth parathyroid gland was found in the anterior, superior mediastinum within the loose connective tissue in front of the great vessels.

size 2.0 x 1.5 x 1.2 cm

weight 2.6 gm

Managing Hyperphosphatemia

- Dietary
- Dialysis
  - Conventional
  - Nocturnal
- Restrict vitamin D
- Correct Hyperparathryoidism
  - Calcimimetics
  - Parathyroidectomy

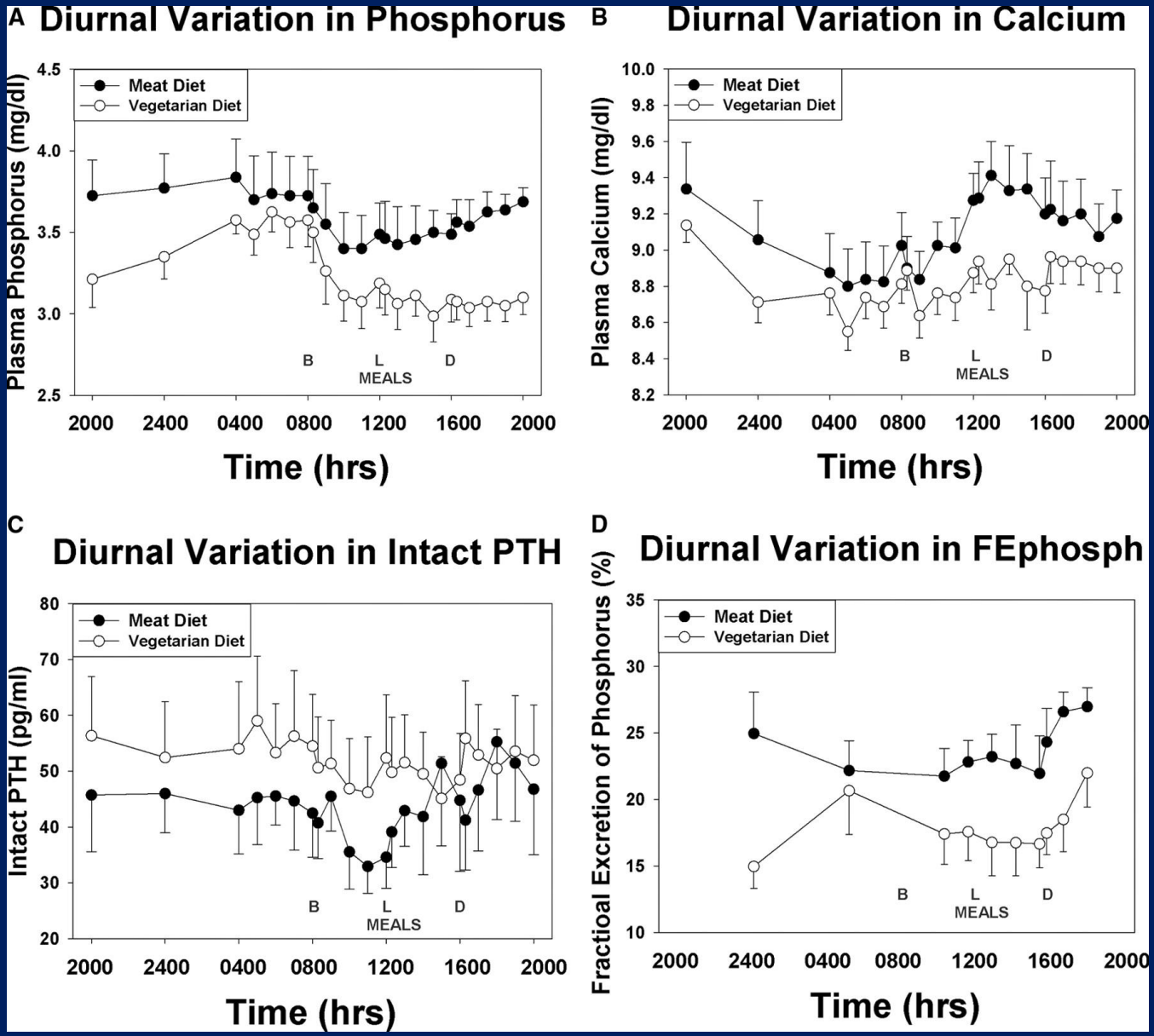
- Binders
  - Aluminum
  - Calcium salts
    - carbonate
    - acetate
  - Sevelamer
    - carbonate
  - Iron
    - ferric citrate
    - sucroferric oxyhydroxide
  - Lanthanum
- Other Agents

Phosphorus in Dietary Protein

Protein Intake (g/kg/d)	Dietary Phosphorus (mg)
>1.2	1353 ± 253
1.0-1.2	1052 ± 219
0.8-1.0	936 ± 217
0.6-0.8	831 ± 142
<0.6	599 ± 105

Rufino et al. *Nephrol Dial Transplant*.;13:65-67, 1998.

Vegetarian compared with Meat Diet: CRC for 24 hrs at end of 7-day diet



Moe et al. CJASN 2011;6:257-264

Dialysis Phosphorus Removal:
3 times per week

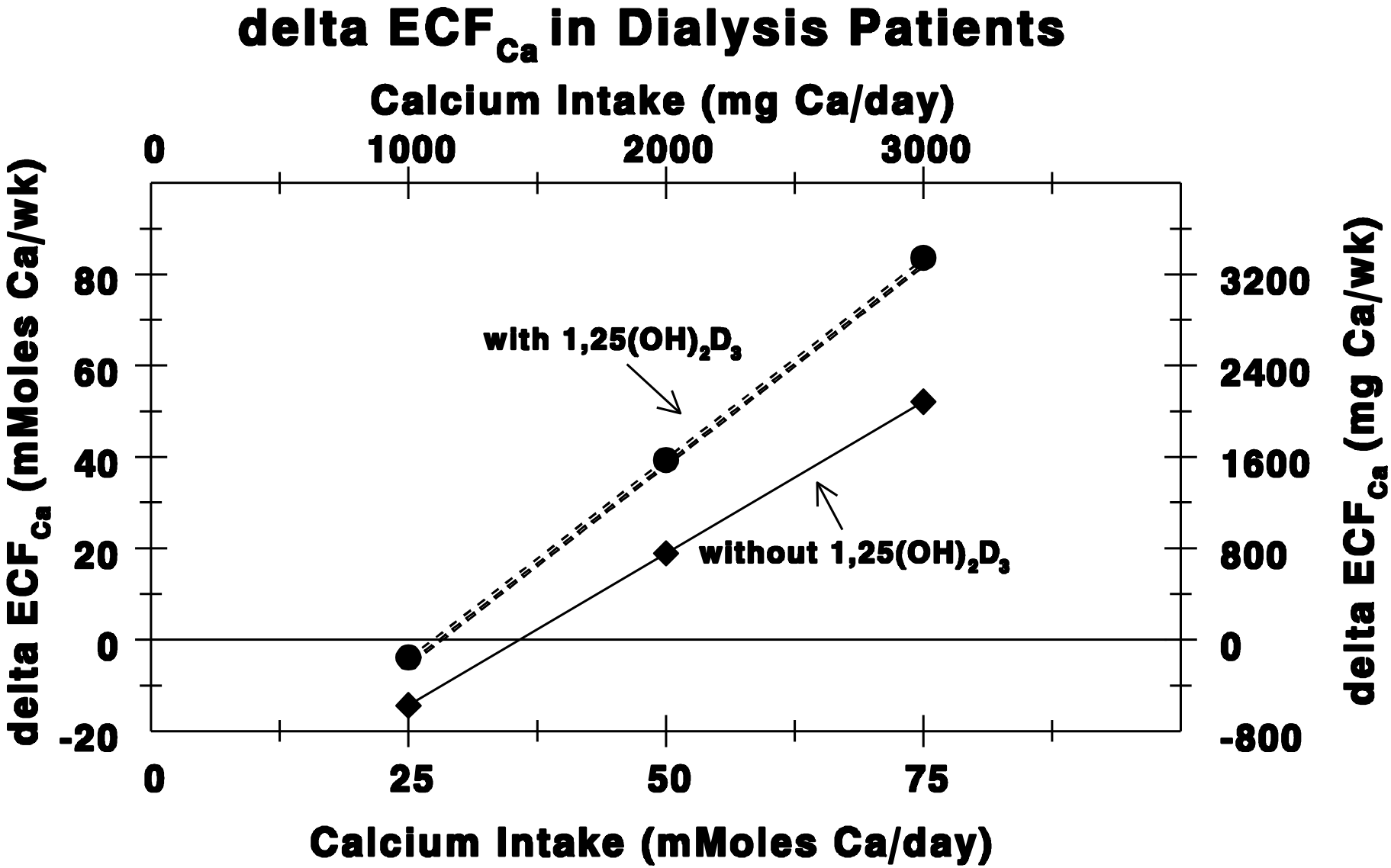
Diet	**1000 mg/day** **7 x 1000 (per week) =**	**7000 mg**
Absorption	**60%** **7000 x 60% =**	**4200 mg**
Dialysis	**800 mg** **3 x 800 (per week) =**	**2400 mg**
Balance	**4200 – 2400 =**	**1800 mg**

Dialysis Phosphorus Removal:
6 times per week

Diet	**1000 mg/day** **7 x 1000 (per week) =**	**7000 mg**
Absorption	**60%** **7000 x 60% =**	**4200 mg**
Dialysis	**800 mg** **6 x 800 (per week) =**	**4800 mg**
Balance	**4200 – 4800 =**	**- 600 mg**

Phosphate Binders

Aluminum-based	Magnesium-based
•Aluminum hydroxide •Aluminum carbonate	•Rarely used, limitations
Calcium-based	**Aluminum & Calcium-free**
•Calcium carbonate –many OTC brands available – frequently used •Calcium acetate	• Ferric Citrate • Sucroferric Oxyhydroxide • Sevelamer • Lanthanum carbonate • Tenapanor

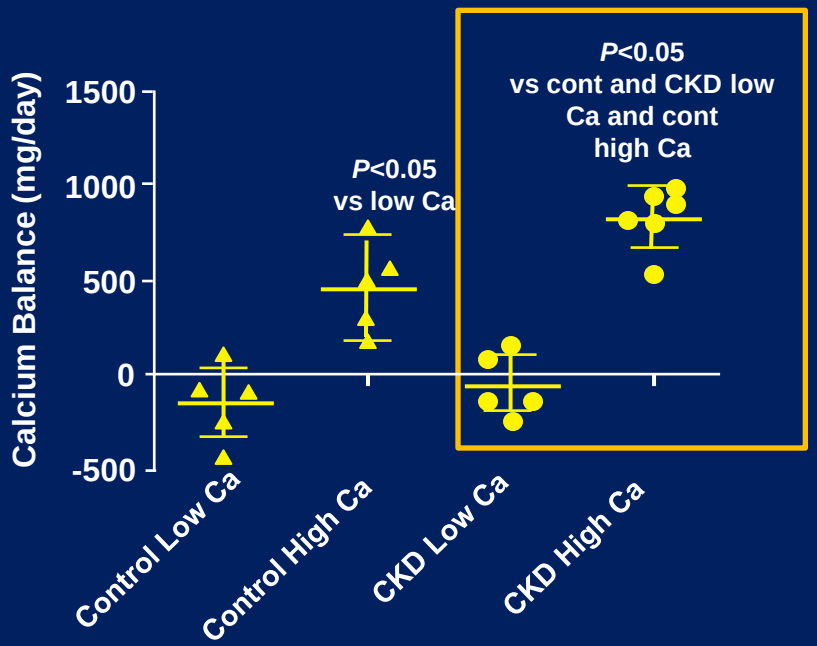


Bushinsky, D.A.. CJASN, 2010; Bushinsky, D.A. NDT 2012

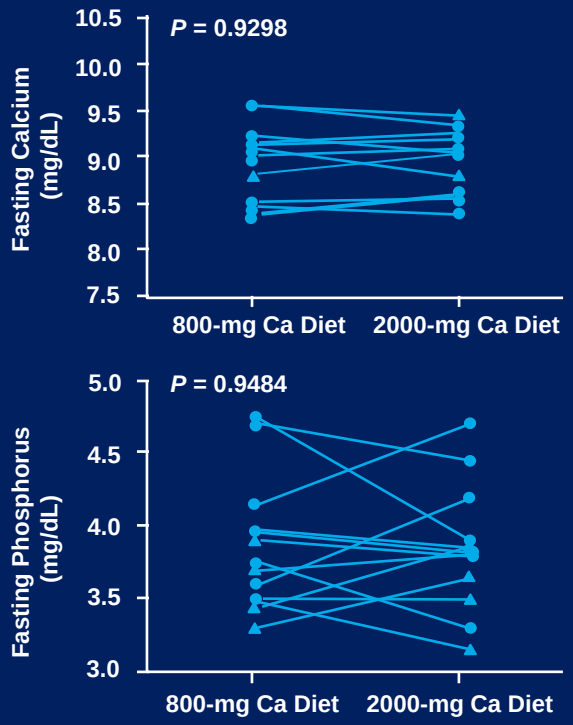
Calcium Balance in Patients With Stage 3/4 CKD on Low and High Calcium Diets

- N = 6 Patients with CKD and N = 6 healthy controls
- Cross-over study of low (800 mg/d) and high (2000 mg/d) calcium intakes
- Controlled diet for 2 weeks
  - Calcium balance performed during 48h inpatient stay

Neutral calcium balance with low calcium diet…
Positive calcium balance with high calcium diet



No effect on serum calcium or phosphate

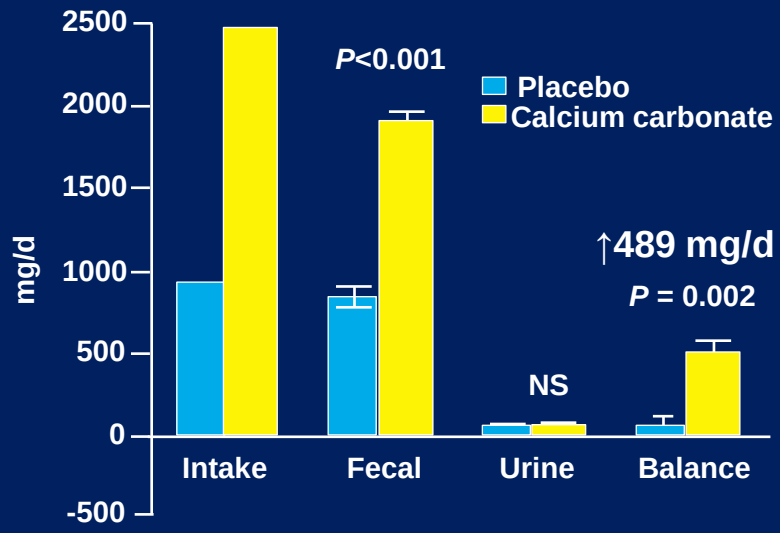


Spiegel DM, Brady K. *Kidney Int*. 2012;81:1116-1122.

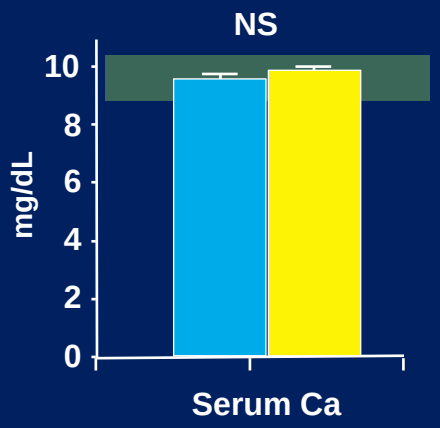
Calcium and Phosphorus Balance Study With Calcium Kinetics in Stage 3-4 CKD

- N = 8 patients with CKD
- Cross-over study of placebo and calcium carbonate (1500 mg/d Ca) while on controlled diet of 957 mg/d calcium
- Controlled diet for 3 weeks
  - Balance and kinetics for 2 weeks as inpatient at Indiana CRC

Neutral calcium balance on placebo…
Positive calcium balance with supplement



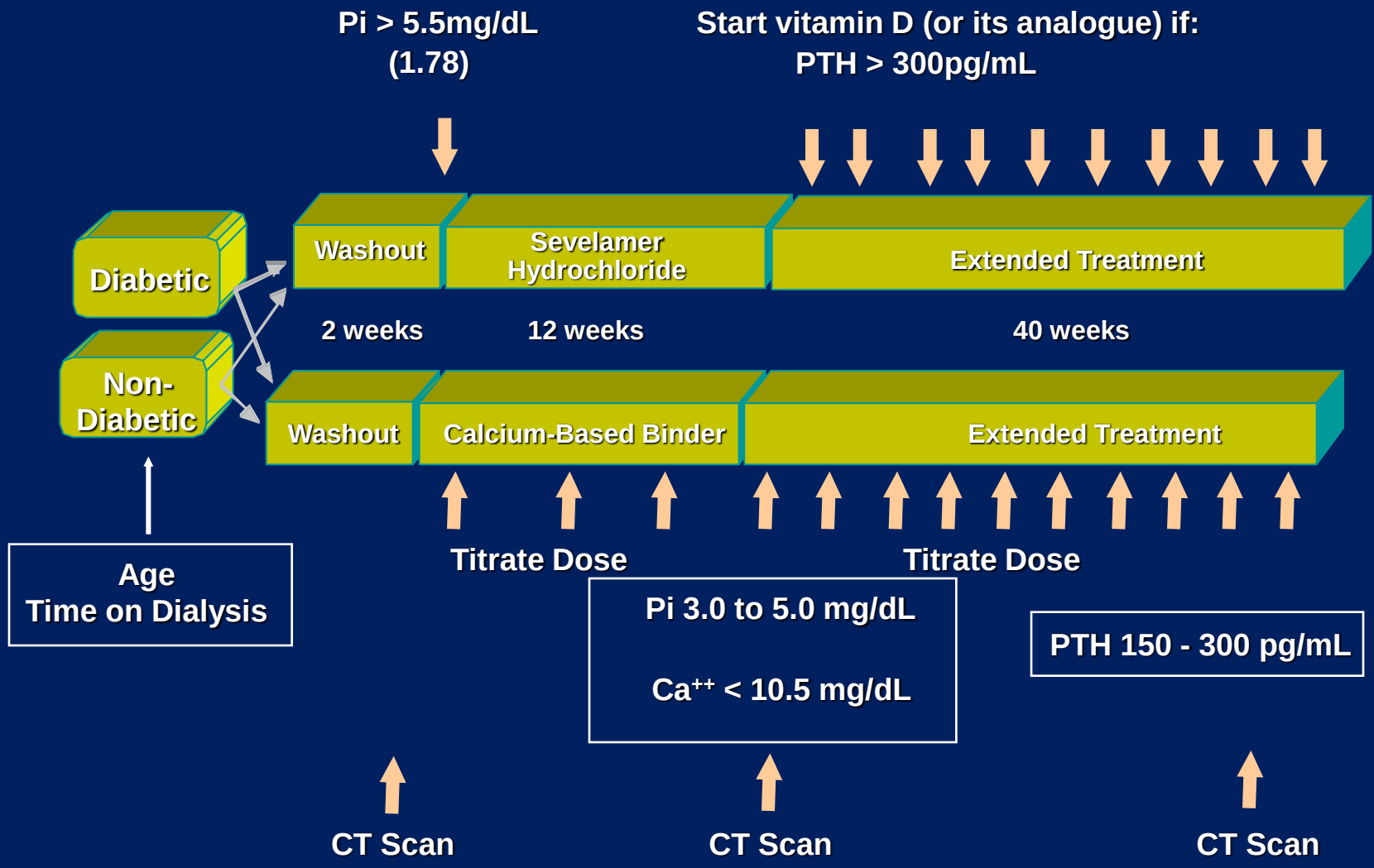
No effect on serum calcium



Lower urine calcium compared with healthy post-menopausal women

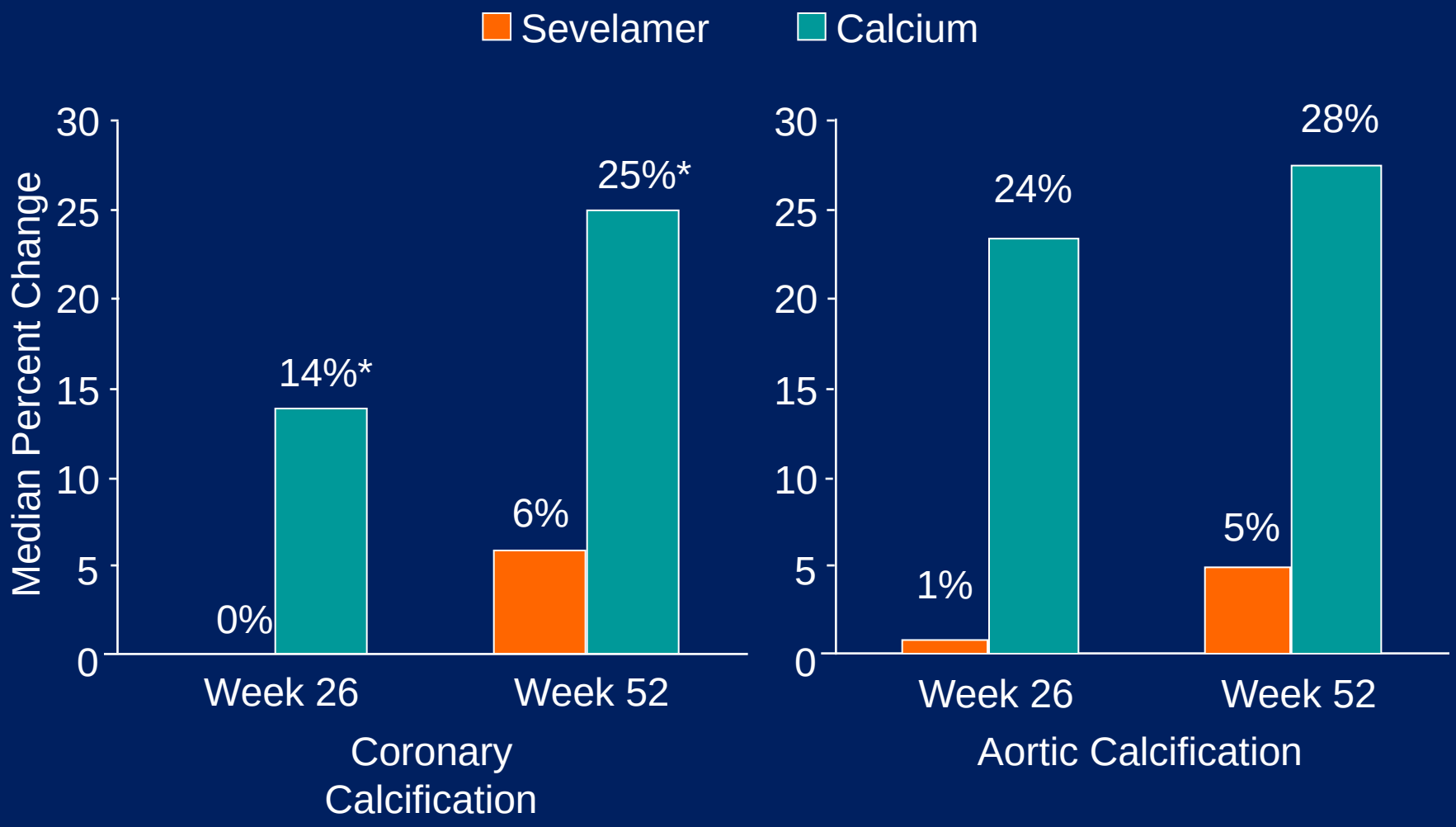
NS = not significant.
Hill KM et al. *Kidney Int.* 2012 Dec 19

Coronary Artery Calcification "Treat to Goal" Study



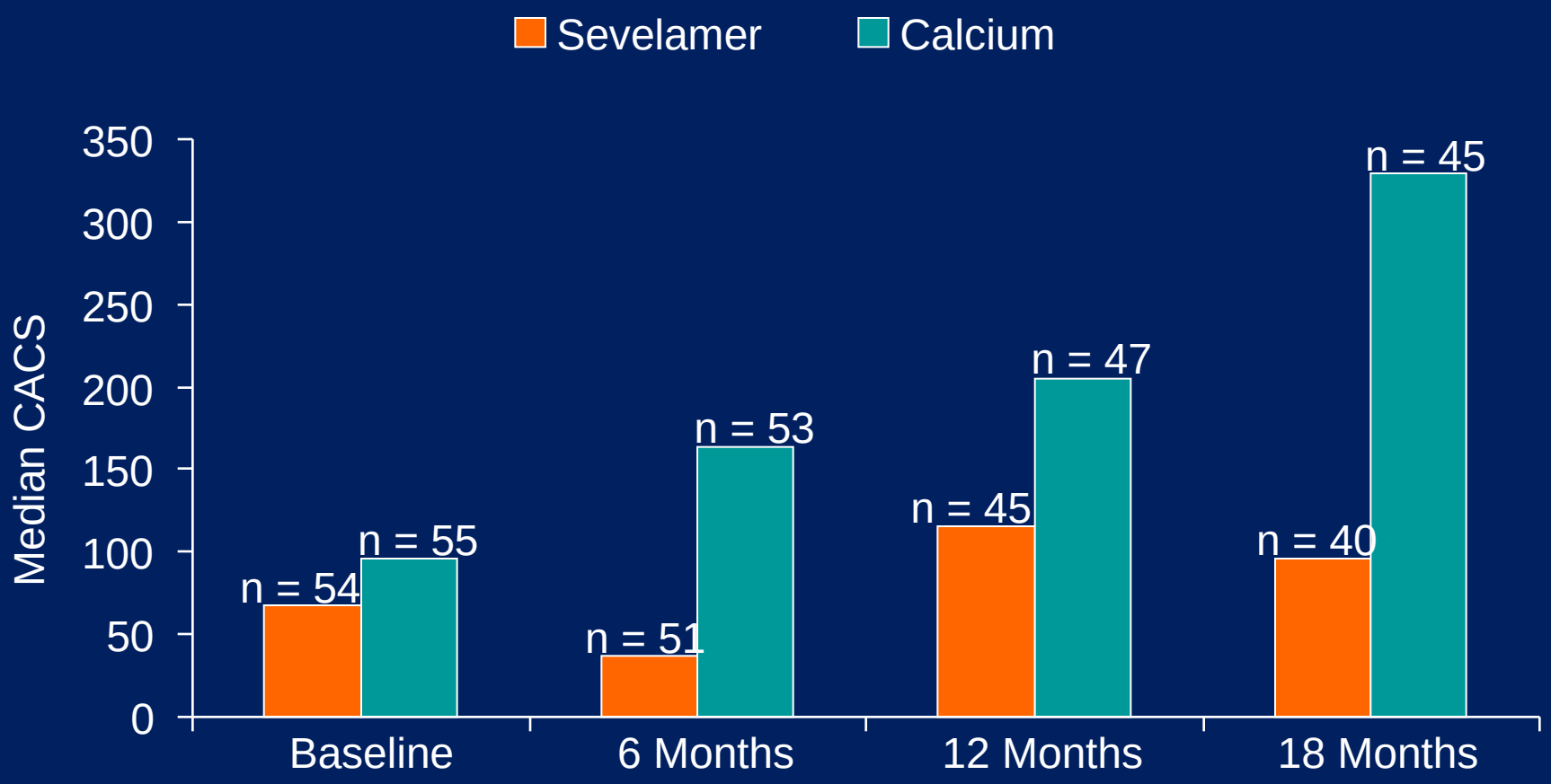
Chertow GM, Raggi P, and the Treat to Goal Working Group, *Kidney Int* Vol 62; 2002

Phosphate Binders and Calcification



Chertow GM, et al. *Kidney Int.* 2002;62:245-252.

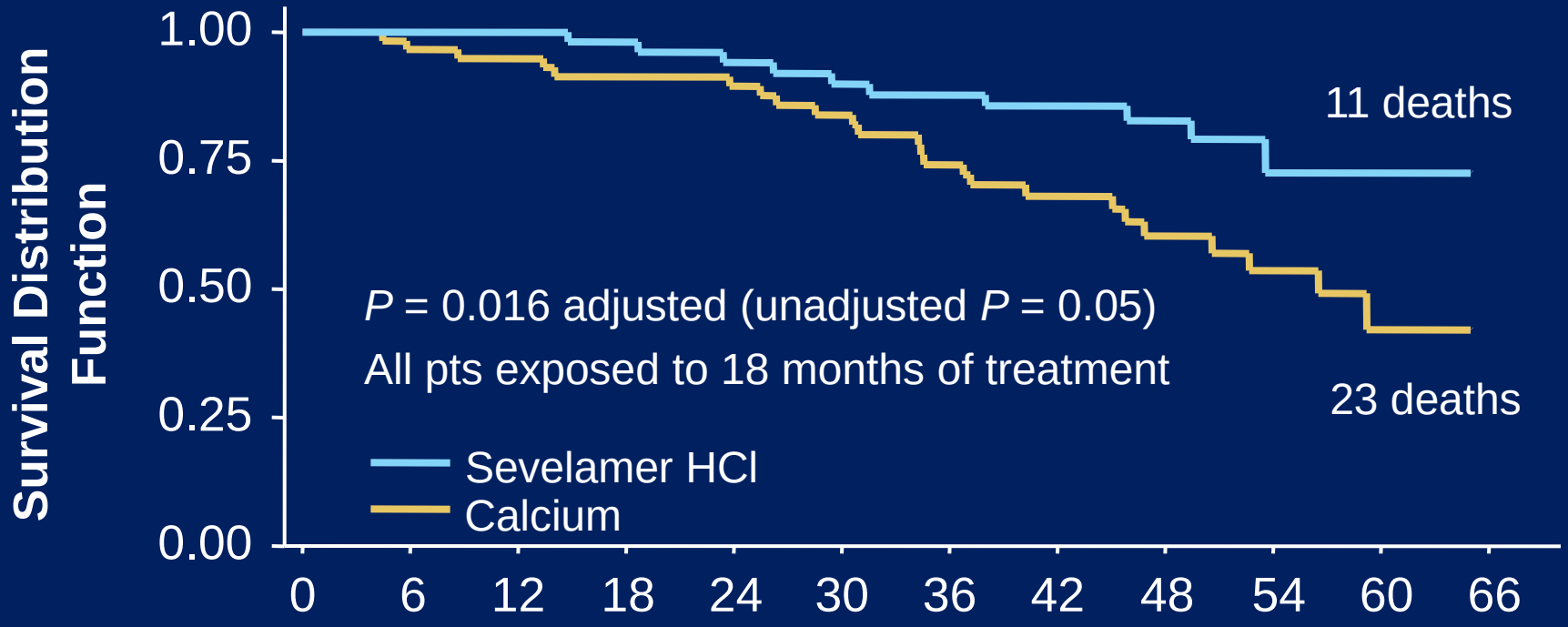
Phosphate Binders and Calcification



Block GA, et al. *Kidney Int*. 2005;68:1815-1824.

Sevelamer vs Calcium-Containing Phosphate Binders: RIND Study Outcomes

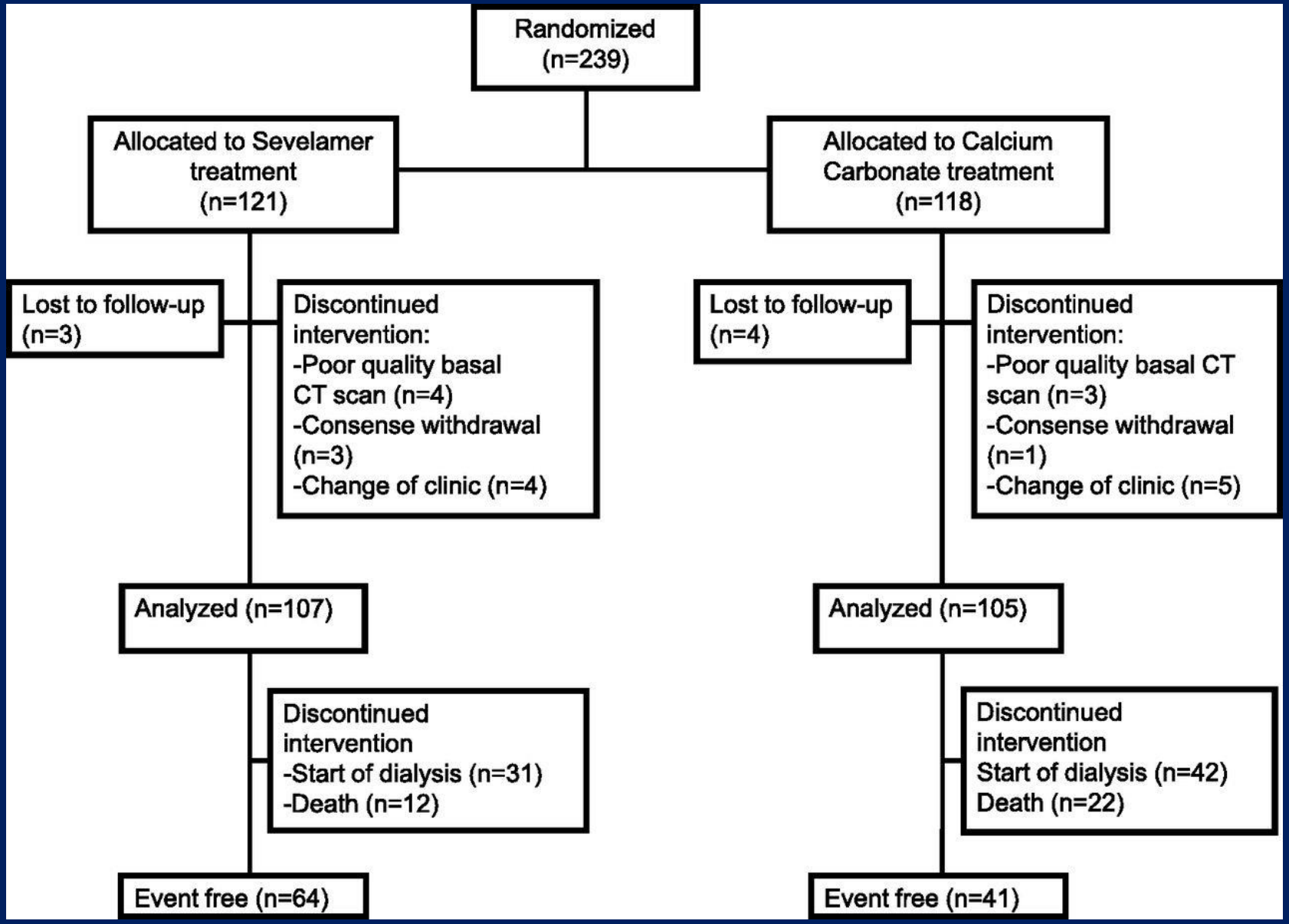
Increased Mortality in Patients Randomized to Calcium vs Sevelamer HCl



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

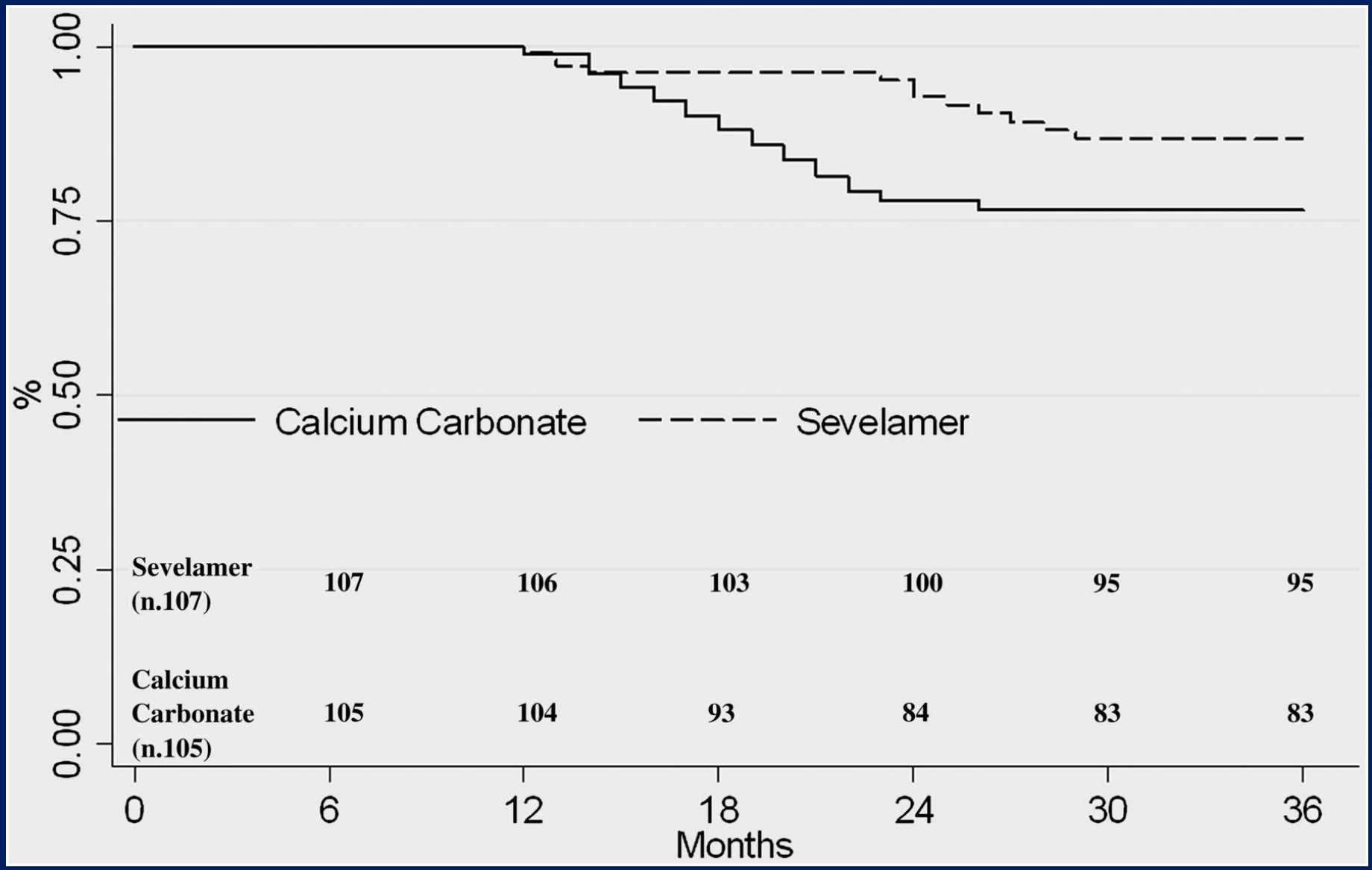
Block GA et al. *Kidney Int*. 2007;71:438-441

Patient flow chart indicating selection and discontinuation



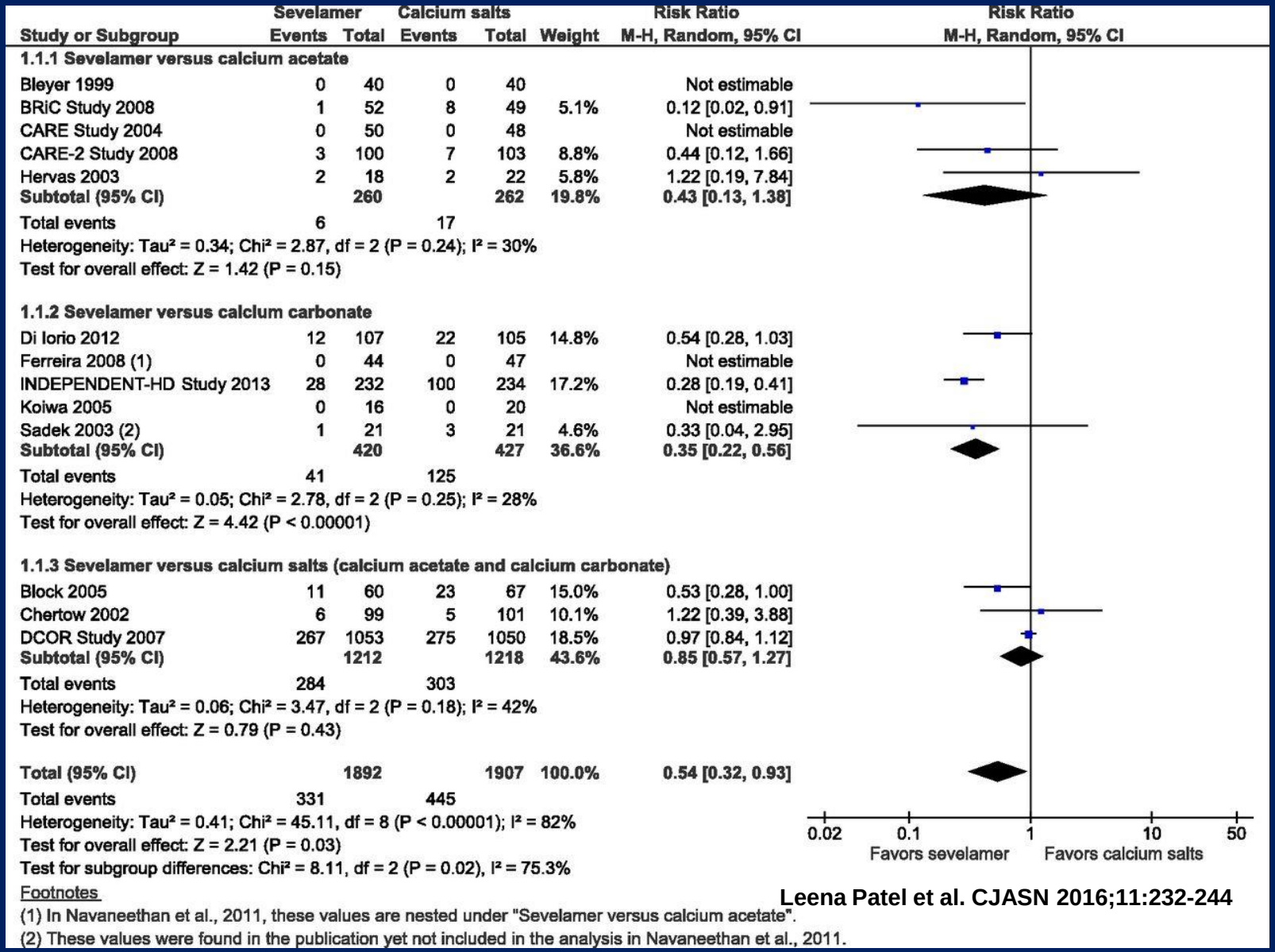
Biagio Di Iorio et al. CJASN 2012;7:487-493

All-cause mortality in patients randomized either to sevelamer (dotted line) or calcium carbonate (continuous line)



Biagio Di Iorio et al. CJASN 2012;7:487-493

Effect of sevelamer versus calcium-based binders on all-cause mortality in patients with CKD. Compared with calcium-based binders (CBBs), sevelamer significantly lowered all-cause mortality in patients with CKD stages 3–5 and on dialysis.



Footnotes

(1) In Navaneethan et al., 2011, these values are nested under "Sevelamer versus calcium acetate".

(2) These values were found in the publication yet not included in the analysis in Navaneethan et al., 2011.

Leena Patel et al. CJASN 2016;11:232-244

Landmark Trial

Compared lanthanum carbonate to calcium carbonate

Patients on hemodialysis
- 2374 subjects
- all with hyperphosphatemia (mean P = 5.3 mg/dl)
- mean BMI = 22
- mean PTH ~ 110 pg/dL
- with at least 1 vascular calcification risk factor
- open label

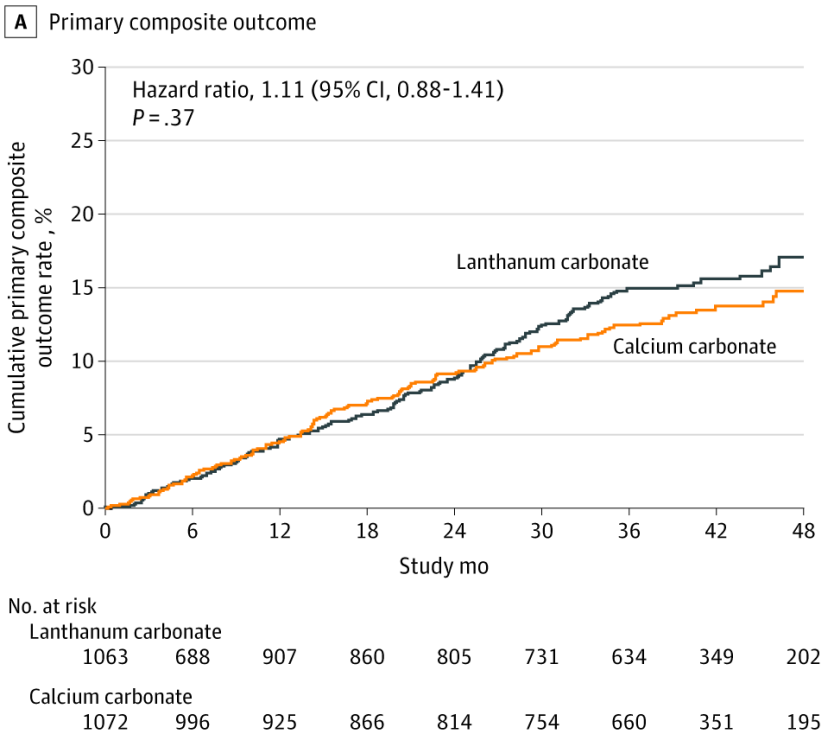
Based in Japan
- dietary calcium intake is low

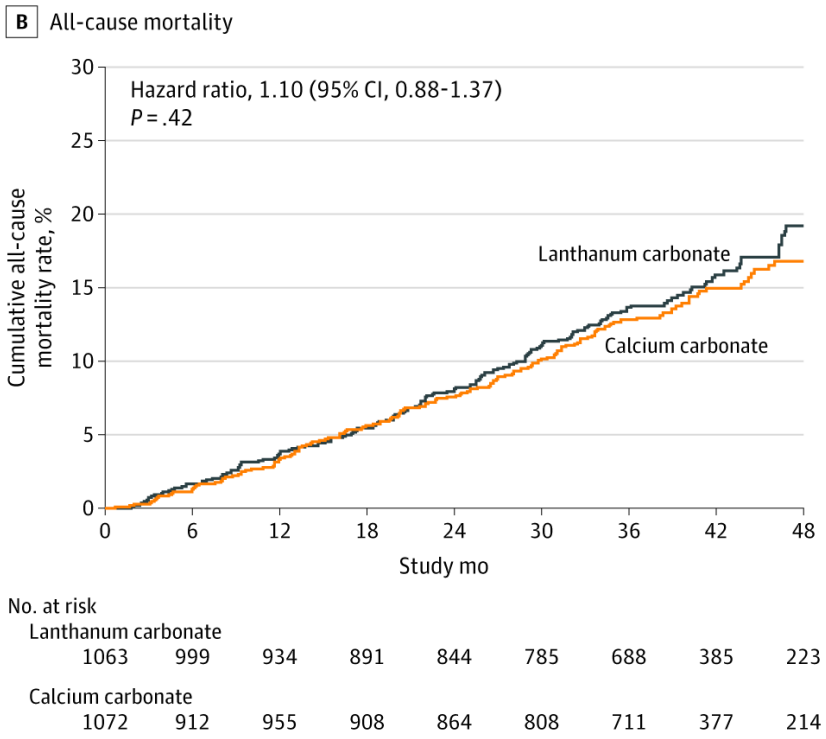
Calcium dose from the binder low at 600-1200 mg Ca/day

Excluded those with intact PTH > 240 pg/ml

Ogata et al. JAMA. 2021;325:1946

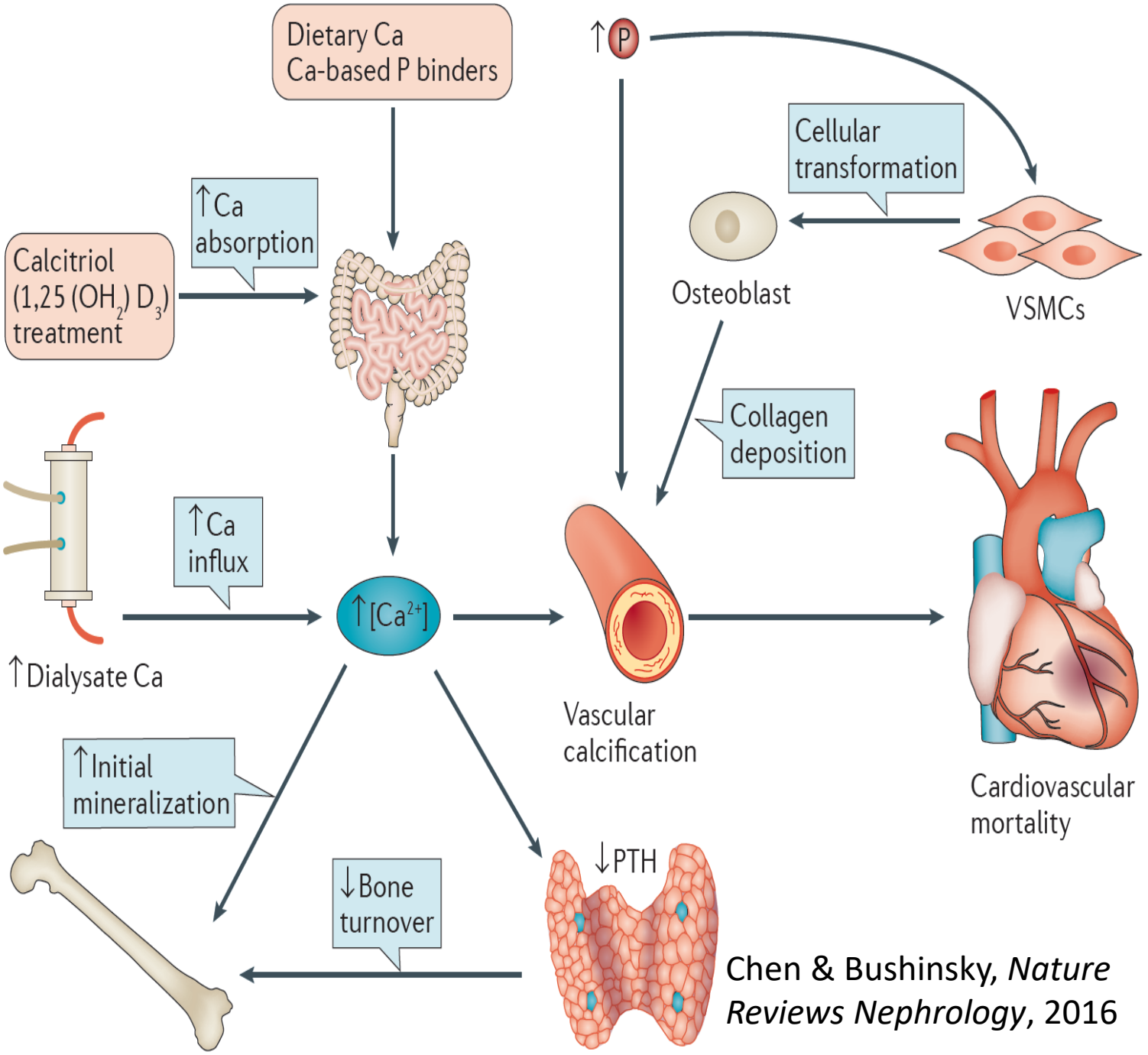
Effect of Treating Hyperphosphatemia With Lanthanum Carbonate vs Calcium Carbonate on Cardiovascular Events in Patients With Chronic Kidney Disease Undergoing Hemodialysis: The LANDMARK Randomized Clinical Trial





primary outcome was a composite: cardiovascular death, nonfatal myocardial infarction or stroke, unstable angina, and hospitalization for heart failure or ventricular arrhythmia.

Ogata et al. JAMA. 2021;325:1946



Chen & Bushinsky, *Nature Reviews Nephrology*, 2016

Iron

Ferric Citrate

- reduces serum phosphate
- raises hemoglobin, serum ion, transferrin saturation and ferritin
- citrate increases aluminum absorption
- no evidence of aluminum toxicity

Sucroferric oxyhydroxide

- reduces serum phosphate
- chewable
- some GI adverse events

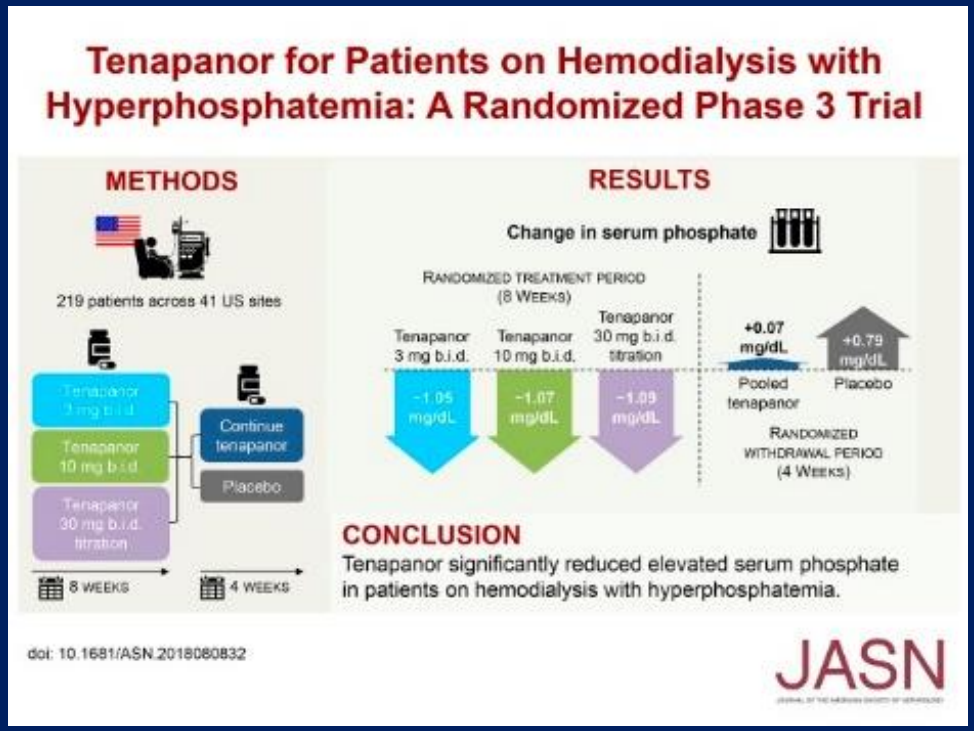
Other Phosphate Lowering Agents

Nicotinamide

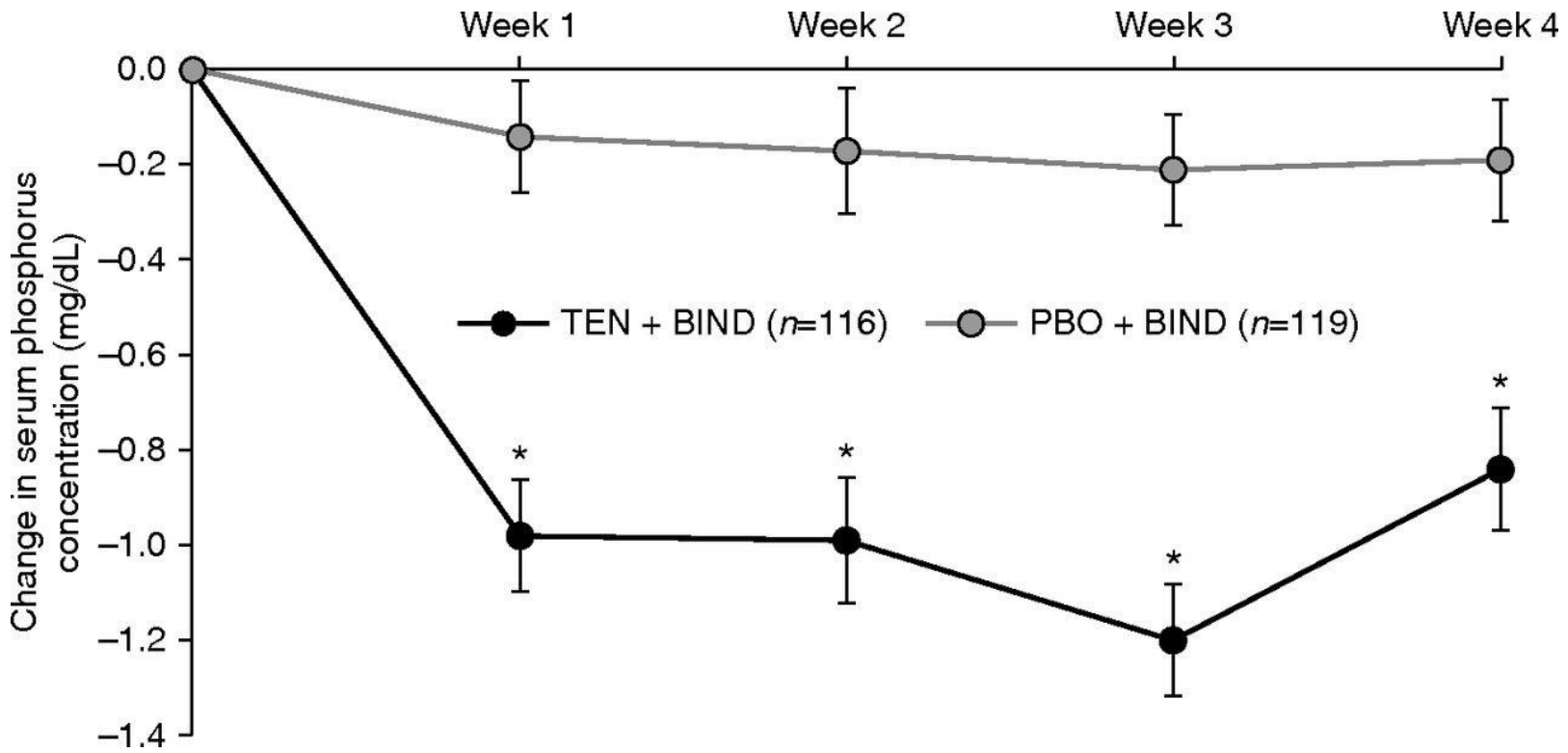
metabolite of nicotinic acid (vitamin B_3)
reduces GI phosphate adsorption
lowers phosphate in 2 published studies
however, less than 100 patients studied

Tanapanor

used for irritable bowel syndrome
inhibits intestinal Na/H exchanger 3
blocks paracellular P transport
increased bowel movement frequency



A Randomized Trial of Tenapanor and Phosphate Binders as a Dual-Mechanism Treatment for Hyperphosphatemia in Patients on Maintenance Dialysis (AMPLIFY)



Pergola et al. JASN 2021: 32):1465

Probably Reduce VC Progression	Possibly Reduce VC Progression[a]	Unlikely To Reduce VC Progression
Magnesium	Antiresorptive therapy	Vitamin D therapy
Sodium thiosulfate	Calcimimetics	Vitamin K2
Kidney transplantation	SNF472	HMG-CoA reductase inhibitors
Increased hours hemodialysis (nocturnal dialysis)	Low dialysate calcium concentration	Exercise
Noncalcium-based phosphate binders (when compared with calcium-based binders)	Strict control of phosphate balance	Phosphate binders (compared with placebo/standard of care)
	Sotatercept	Spironolactone
Xu et al. J Am Soc Nephrol. 2022;33:1011	Oral activated charcoal	Nicotinamide

Calciphylaxis

Skin biopsy
- not reliable for dx
- may lead to additional nonhealing ulcers

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

Prevention
- limit excess calcium and phosphate

Increased Risk
- use of vitamin K antagonists for anticoagulation is associated with up to 11-fold increased risk

Hayashi et al. NDT 2012:27,1580

- to treat a fib in dialysis patients
- consider apixaban (instead of warfarin) at lower dose

Garza-Mayers et al. Am J Neph. 2018:48,168

Treatment
- Sodium thiosulfate
- widely used but
  - no randomized trials
  - meta-analysis – Wen et al. JAMA Netw Open 2023:6
    - no association between use and wound improvement or survival

Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters

Ketteler et al. Kidney International (2017) 92, 26–36

Chapter 4.3: Treatment of bone with bisphosphonates, other osteoporosis medications, and growth hormone

4.3.1: In patients with CKD G1-G2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management as for the general population (1A).

4.3.2 In patients with CKD G3a-G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management as for the general population (2B).

4.3.3 In patients with CKD G3a-G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progress of CKD, with consideration of a bone biopsy (2D).

Kidney International Supplements 7:1-59, 2017

4.1.1. In patients with CKD G3a–G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (Not Graded).

4.1.2. In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).

4.1.3. In adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia (2C). In children with CKD G3a–G5D, we suggest maintaining serum calcium in the age appropriate normal range (2C).

4.1.4. In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2C).

Ketteler et al. Kidney International (2017) 92, 26–36

4.1.5. In patients with CKD G3a–G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (Not Graded).

4.1.6. In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders (2B).

4.1.8. In patients with CKD G3a–G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D). It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations (Not Graded).

4.3.2 In patients with predialysis CKD, calcitriol and vitamin D analogues should not be routinely used (2C).

Ketteler et al. Kidney International (2017) 92, 26–36

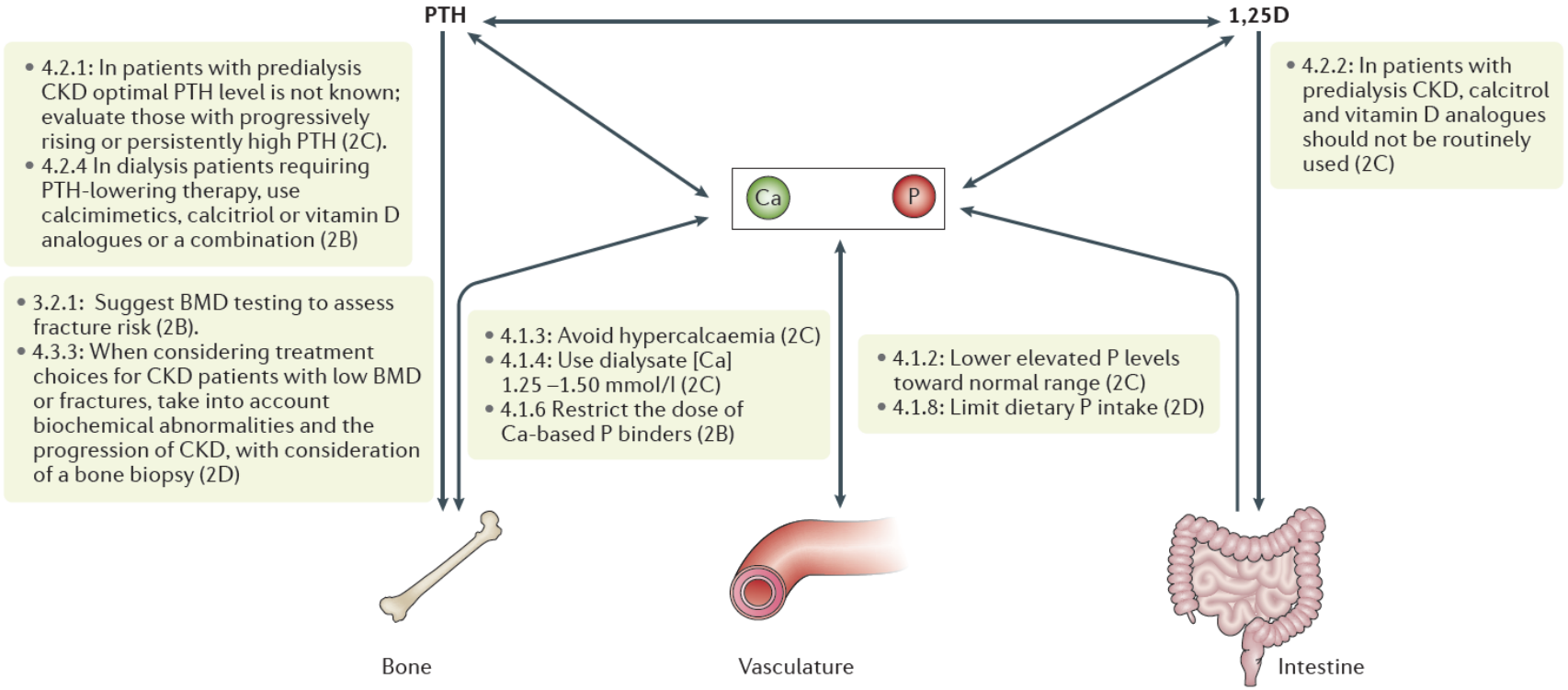


Figure 1 | **Revised recommendations from the 2017 KDIGO CKD–MBD guideline.** Only recommendations that are graded and apply to patients with chronic kidney disease and no history of kidney transplantation are shown, alongside the chapter from which the recommendation appears. Nomenclature for grading recommendations is as follows: level 2 (2, "we suggest") indicates that different choices will be appropriate for different patients; grade B (B) indicates moderate quality evidence; C, low-quality evidence; D, very low-quality evidence. 1,25D, 1,25-dihydroxyvitamin D; BMD, bone mineral density; Ca, calcium; [Ca], calcium concentration; CKD, chronic kidney disease; P, phosphorous; PTH, parathyroid hormone; MBD, mineral and bone disorder.

Chen and Bushinsky,
Nature Reviews Nephrology
5:264, 2017

Consensus points, clinical guideline–related commentary, key knowledge gaps, and research priorities in CKD-MBD

Type of statement	CKD-associated osteoporosis	CKD-associated cardiovascular disease
Important clinical concepts	In most cases**, bone formation and resorption markers are sufficient to assess bone turnover.** In some cases, bone biopsy may be needed to elucidate complex bone disease.	**Recommendations for calcium intake should be personalized**, considering the state of mineral metabolism, overall calcium balance, current medical therapy, and bone and vascular health.
	The concept of a "pleiotropic" effect for both nutritional and active vitamin D should be abandoned. However, for controlling PTH, low-dose active vitamin D could be a helpful supplement to nutritional vitamin D and dietary phosphate restriction.	**Risks of hypocalcemia should not be ignored**. It is reasonable to consider the cause of, and correct, hypocalcemia.
	PTH is not a bone turnover marker, and PTH values must be assessed in relation to values of calcium, phosphate, and 25(OH)-vitamin D.	
Commentary related to guideline recommendations	**Although the 2009 Guideline used the term "target" for PTH levels 2–9 times the ULN in CKD G5D,[1] there is uncertainty as to whether this is in fact the optimal range**.	**Guidance is needed on sufficient calcium intake in patients with CKD, including the safe upper limit to avoid the risk of vascular calcification progression**.
	Future guidelines should distinguish between persistent and secondary hyperparathyroidism after kidney transplantation, as these differ both in biochemical presentation and in pathophysiology.	Future Work Group could consider whether to recommend measuring ionized calcium in blood.
		There is a need for guidance on holistic management of calciphylaxis.

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

References

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.

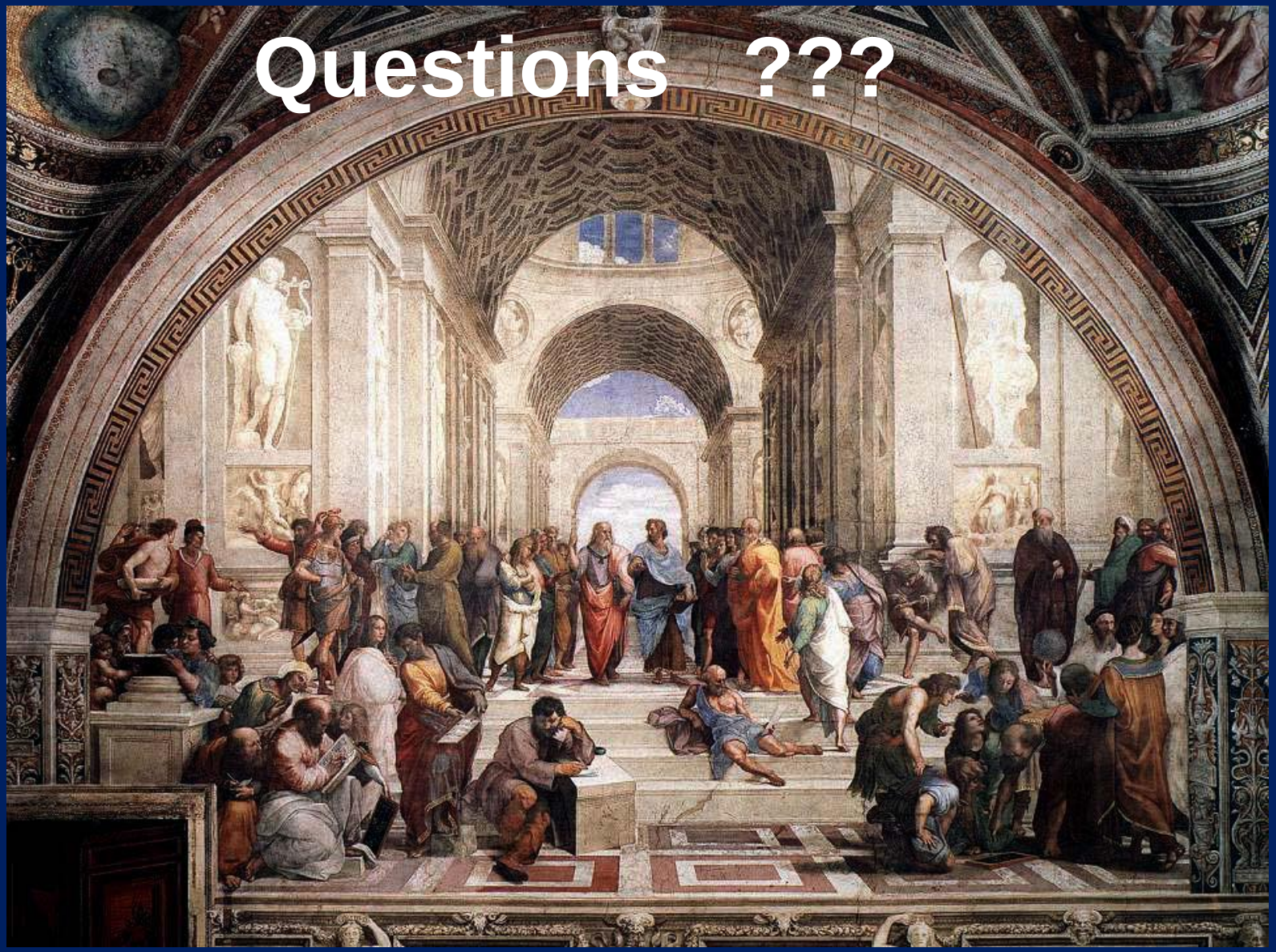
Tatiane et al. Risks of Hip and Nonvertebral Fractures in Patients With CKD G3a-G5D: A Systematic Review and Meta-analysis Published online: July 9, 2020 *AJKD* DOI: 0.1053/j.ajkd.2020.02.450

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.