

CKD-MBD

Case-Based Pearls

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL**

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Disclosure Information

Employee of:	University of Rochester, Rochester, NY
Research support:	National Institutes of Health
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		

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 $1,25(\text{OH})_2\text{D}_3$

$1,25(\text{OH})_2\text{D}_3$ inhibits secretion

Also by phosphate

phosphate stimulates secretion

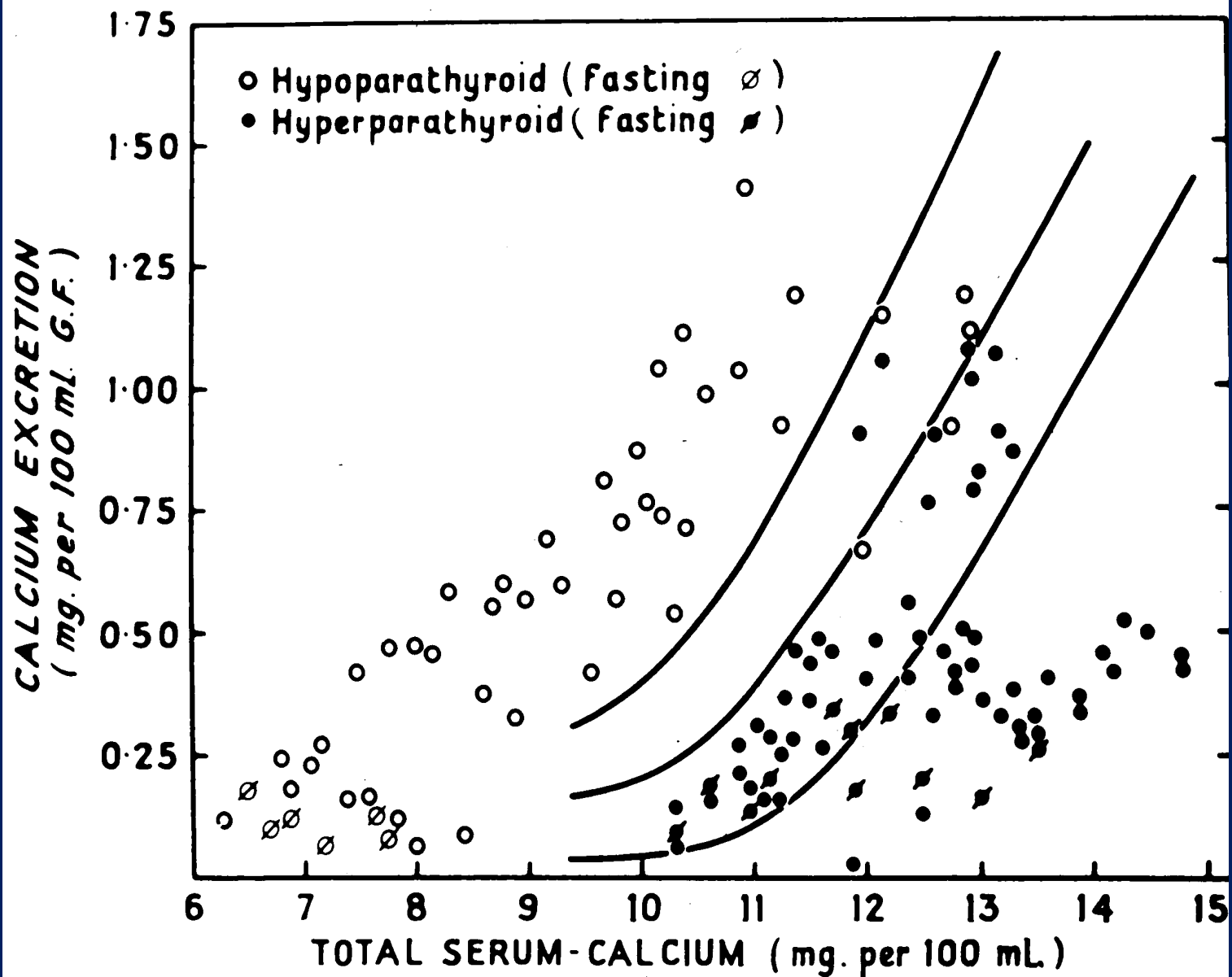
Parathyroid Hormone (PTH)

Actions

Kidney - stimulates reabsorption of calcium
inhibits reabsorption of phosphate
increases activity of 1α -hydroxylase
(enhances synthesis of $1,25(\text{OH})_2\text{D}_3$)

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

Intestine - no direct effect – only through increased $1,25(\text{OH})_2\text{D}_3$



Peacock et al.
Lancet, 1969

SERUM ULTRAFILTERABLE CALCIUM (mg. per 100mL)

Parathyroid Hormone (PTH)

Net effect on Ca homeostasis

- Blood calcium increases

- Blood phosphorus decreases

- Urine calcium increases

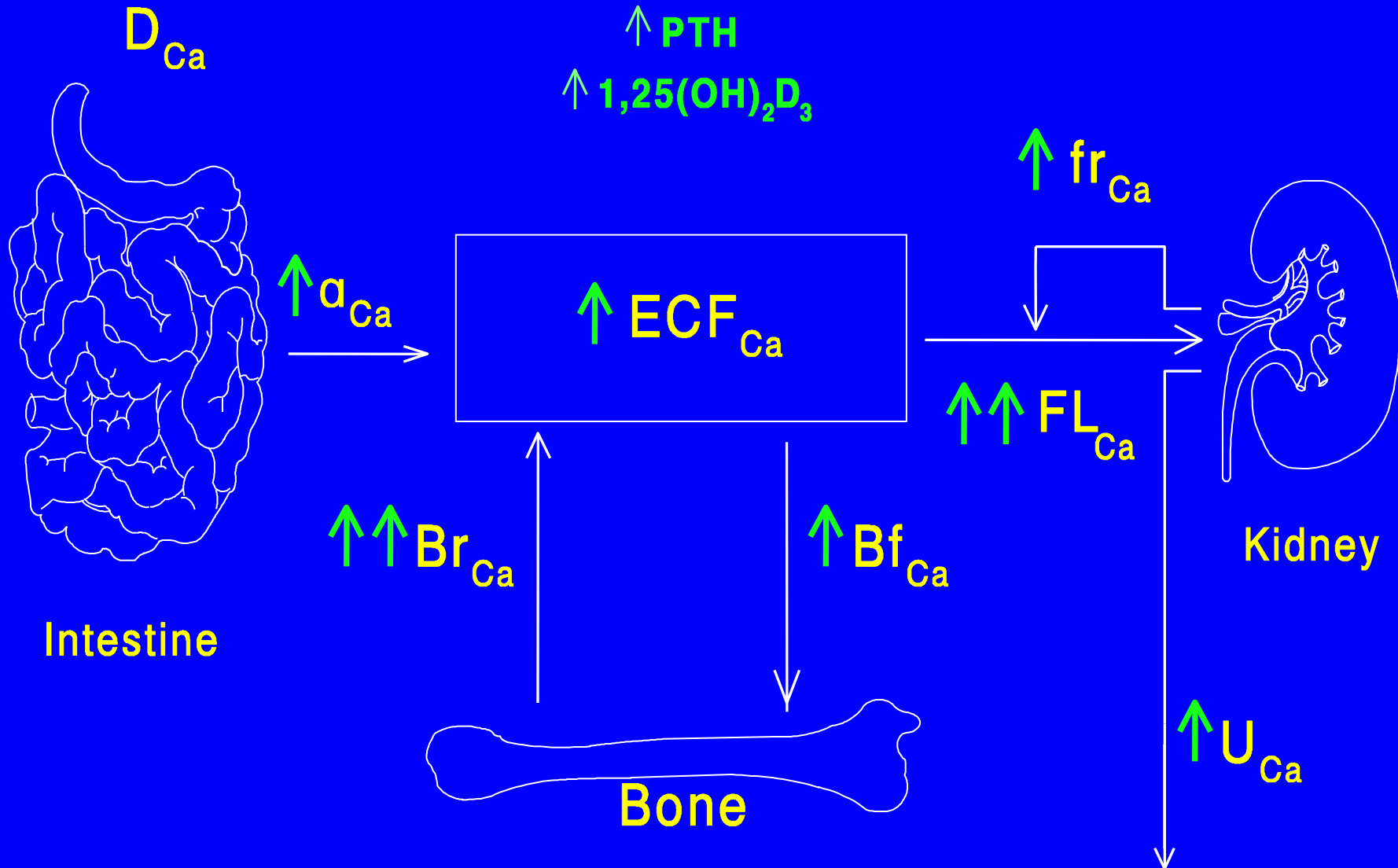
 - Increase in filtered load exceeds
increase in tubular reabsorption

Calcium

Continuous Excess PTH

$\uparrow$ PTH

$\uparrow$ $1,25(\text{OH})_2\text{D}_3$



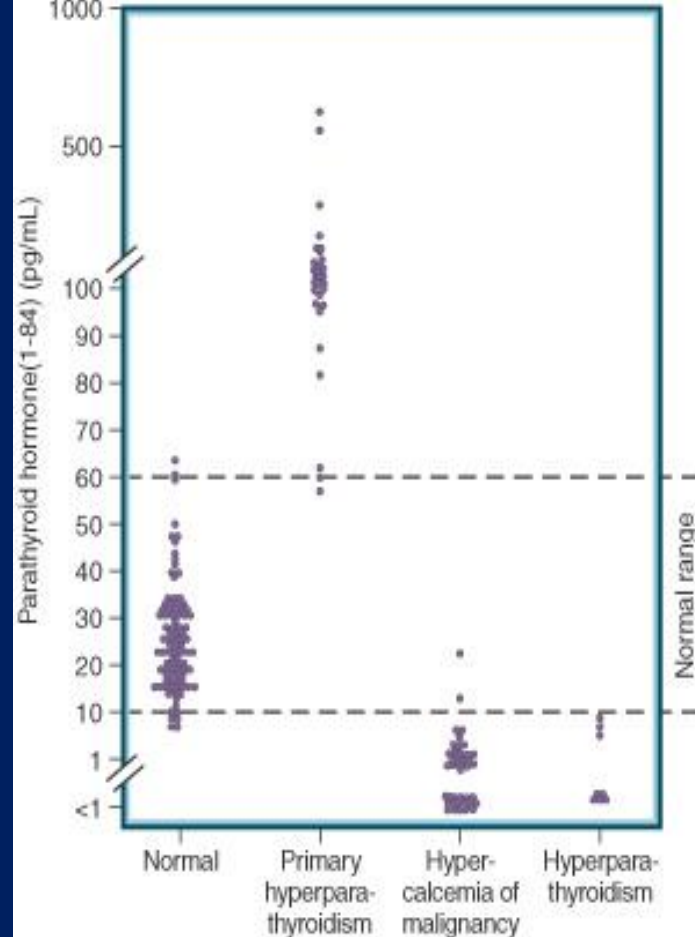


Figure 27–20. Intact immunoreactive parathyroid hormone (PTH) determined using a two-site immunoradiometric assay in normal and three different patient groups. Note there is some overlap between normal subjects and patients with primary hyperparathyroidism, but there is no overlap between hypercalcemic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

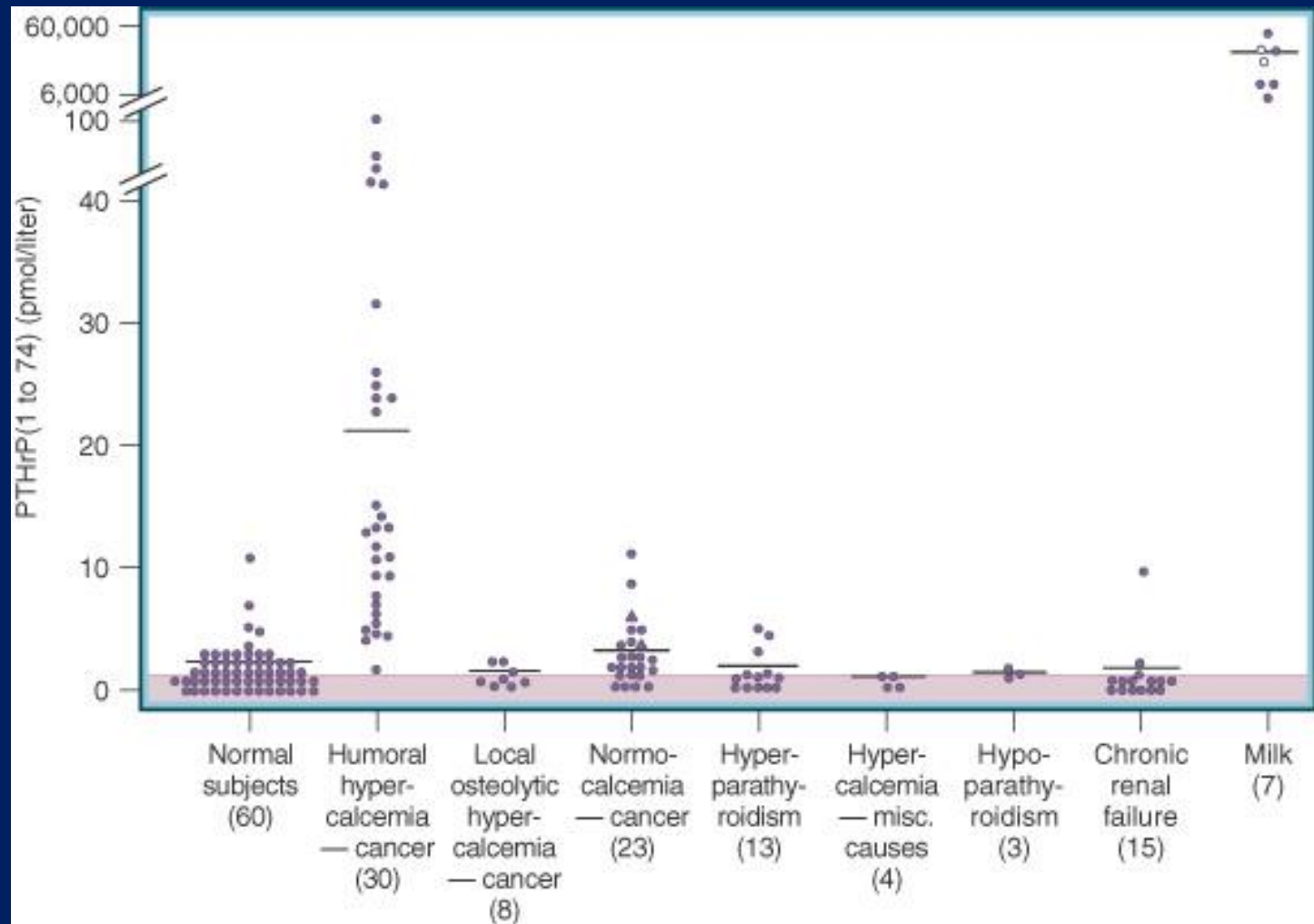


Figure 27–21. Plasma PTHrP(1-74) determined by two-site immunoradiometric assay in selected patient groups and normal subjects. Also shown are concentrations of PTHrP in human milk (*filled circles*) and in bovine milk (*open circles*). Two normocalcemic patients with cancer (*filled triangles*) subsequently 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, osteitis 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.)

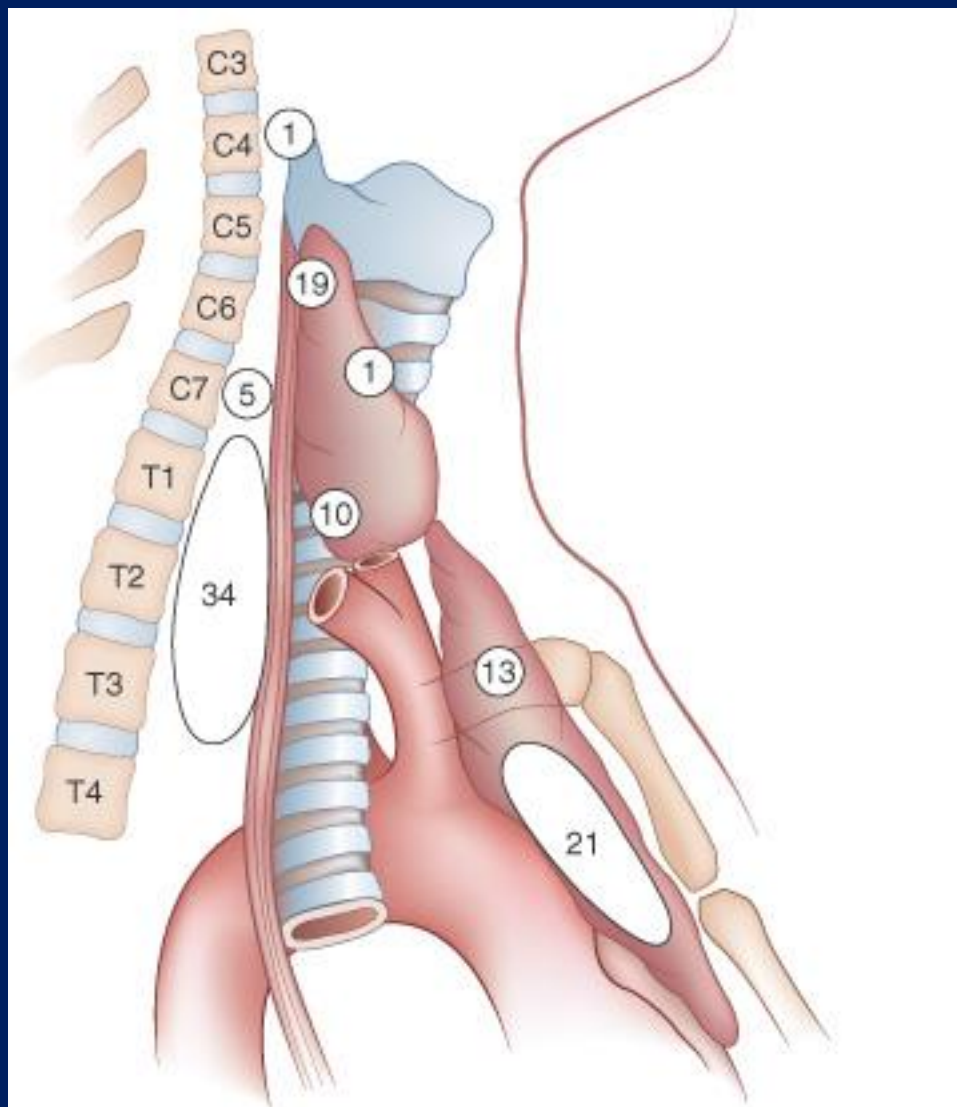


Figure 27–25. Sites of ectopic location of 104 parathyroid glands found at reoperation for primary hyperparathyroidism.

(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

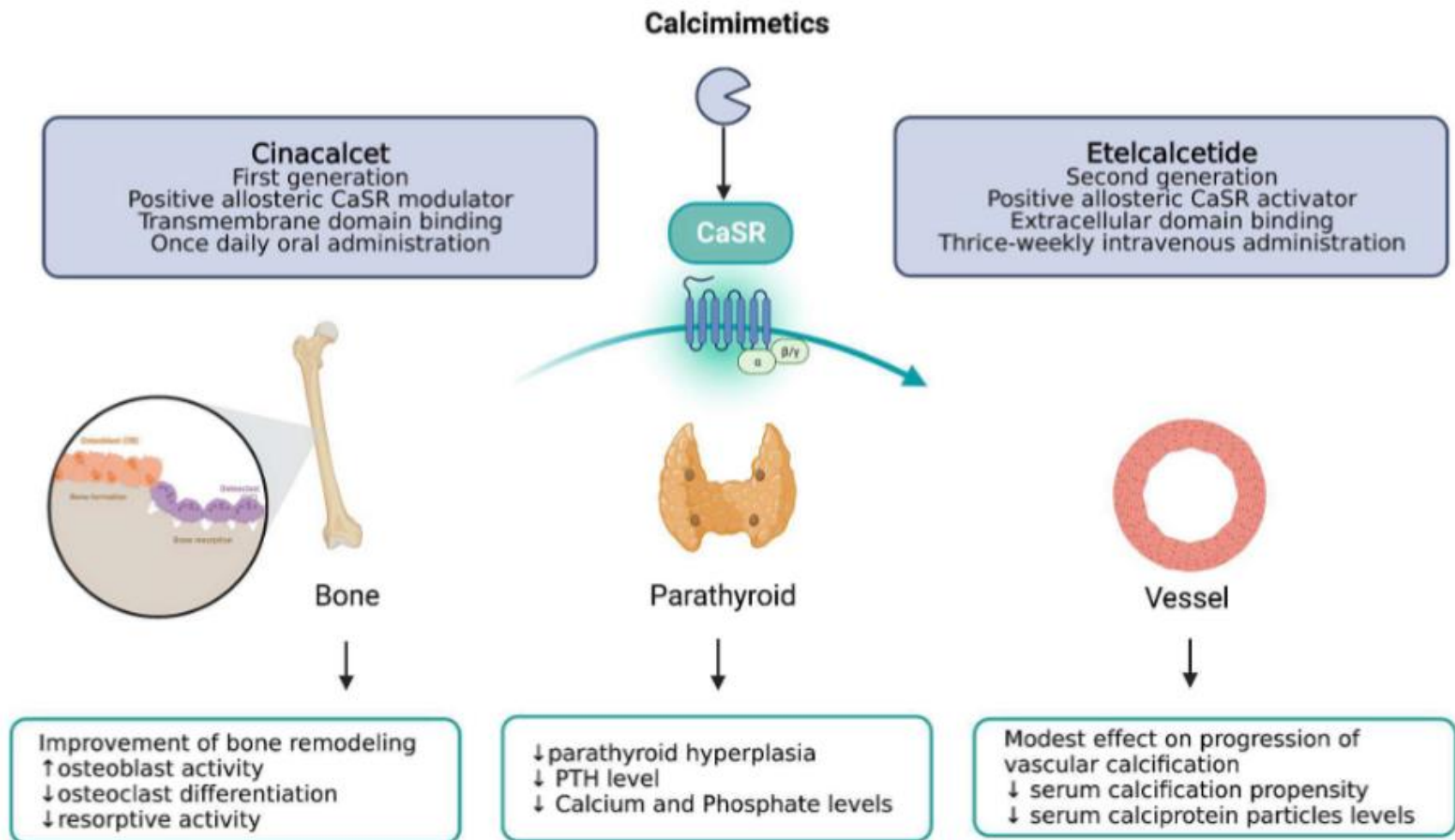
following kidney transplant with HPT

Etelcalcetide – iv

approved

for secondary HPT in HD patients

Calcimimetics



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)

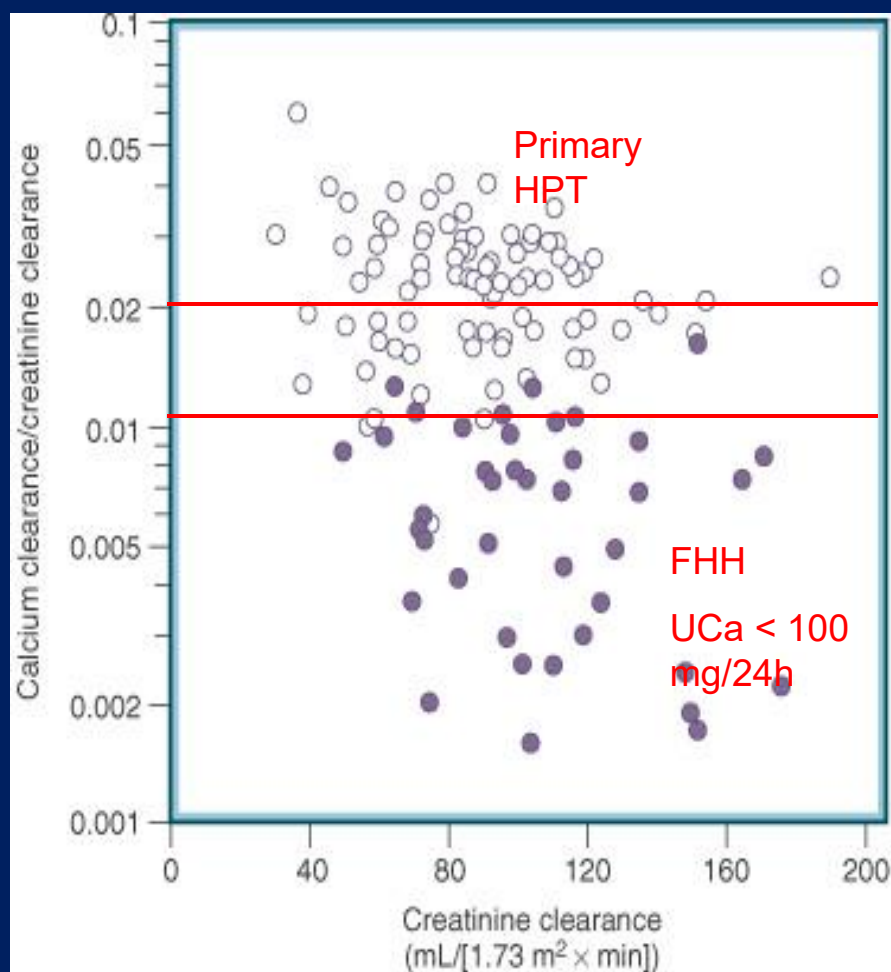


Figure 27-27. Index of urinary excretion rate for calcium as a function of creatinine clearance. Each point represents the mean of multiple determinations for a hypercalcemic patient with familial hypocalciuric hypercalcemia (*filled circles*) or with typical primary hyperparathyroidism (*open circles*). 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

[PO₄] 5.8 - 8.1 mg/dl

PTH 1019 - 1311 pg/ml

1,25(OH)₂D₃ 16 pg/ml

Parathyroid ultrasound

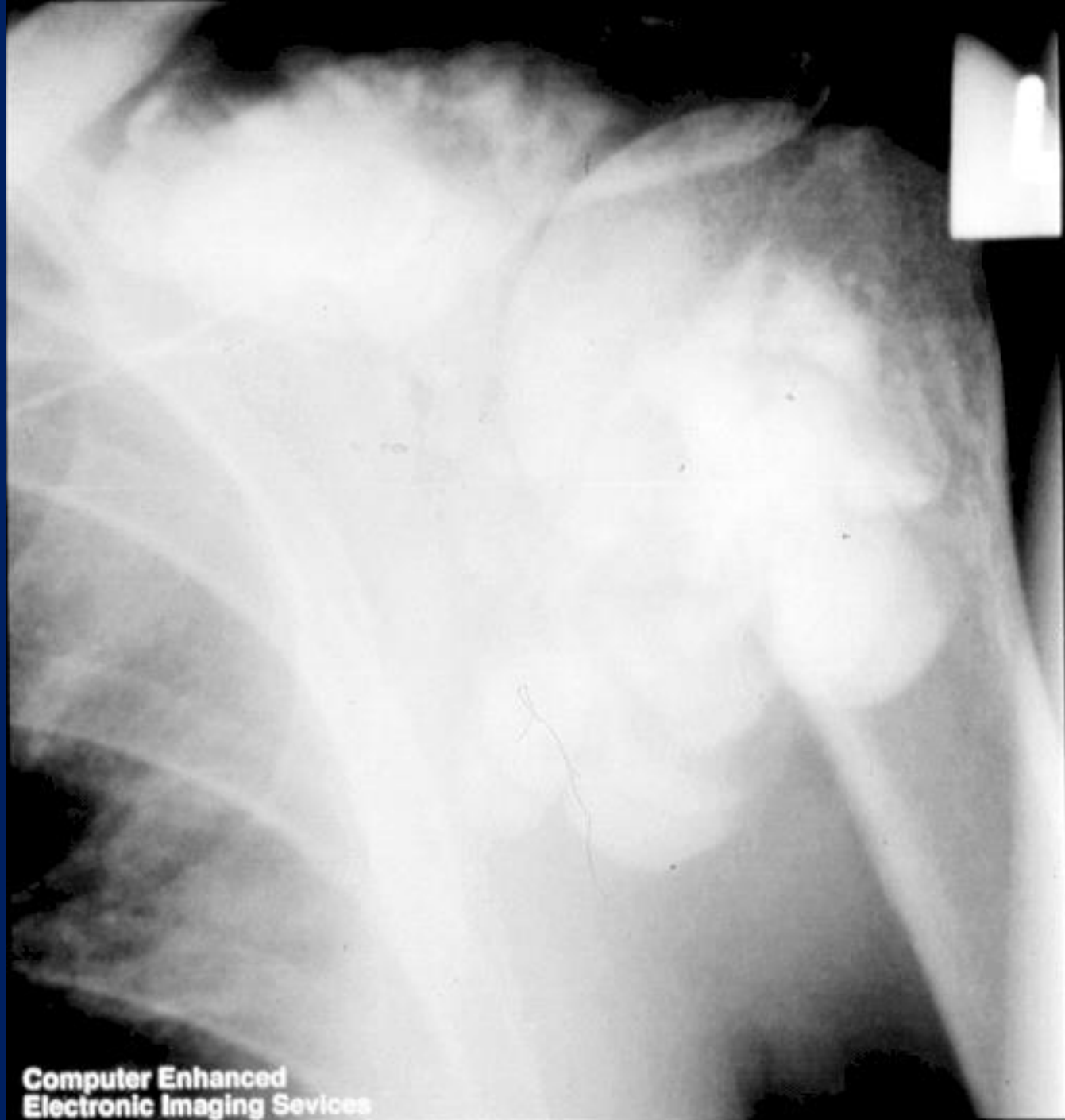
RUP 1.8 x 0.8 x 0.7 cm

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 Services**

+ 8 months

Refused all meds

Intermittently shows up for dialysis

Agrees to parathyroidectomy

- multiple soft tissue calcifications
- ulcerations
- calciphylaxis



Composite by:
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) $1,25(\text{OH})_2\text{D}_3$ level

MR scan of the neck

no evidence of an ectopic parathyroid gland

Parathyroid Scan

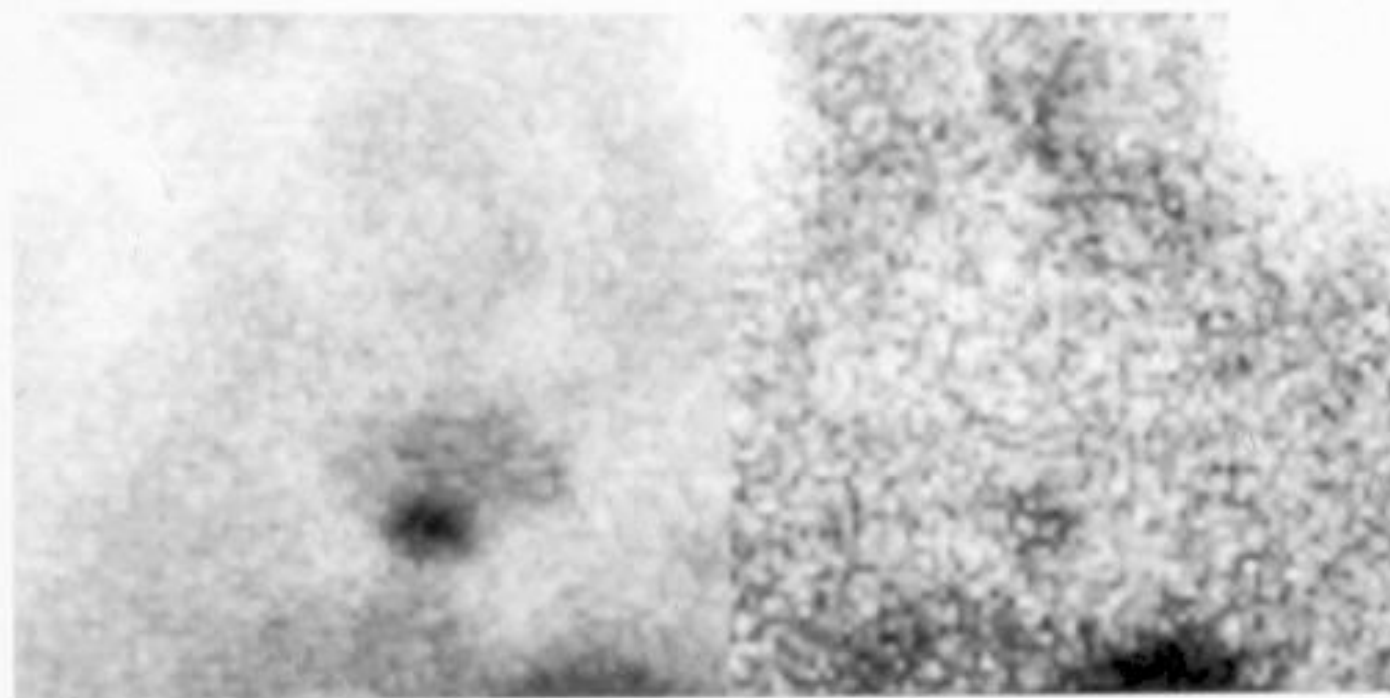
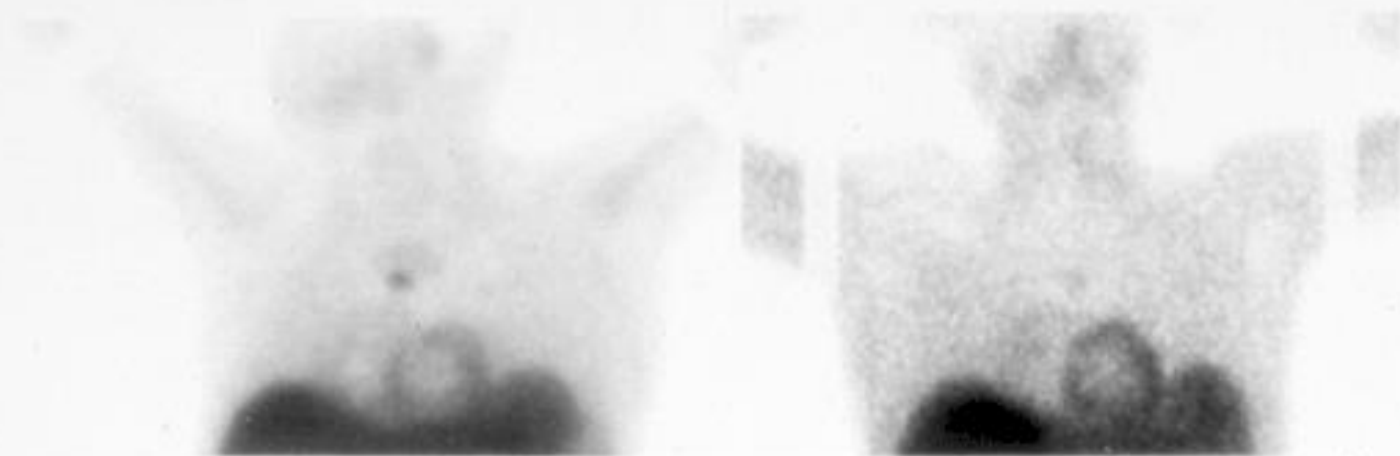
intense activity - inferior and to the R of the
manubriosternal joint

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

[PO₄] 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 Hyperparathyroidism

Calcimimetics

Parathyroidectomy

Binders

Aluminum

Calcium salts

carbonate

acetate

Sevelamer

carbonate

Iron

ferric citrate

sucroferric

oxyhydroxide

Lanthanum

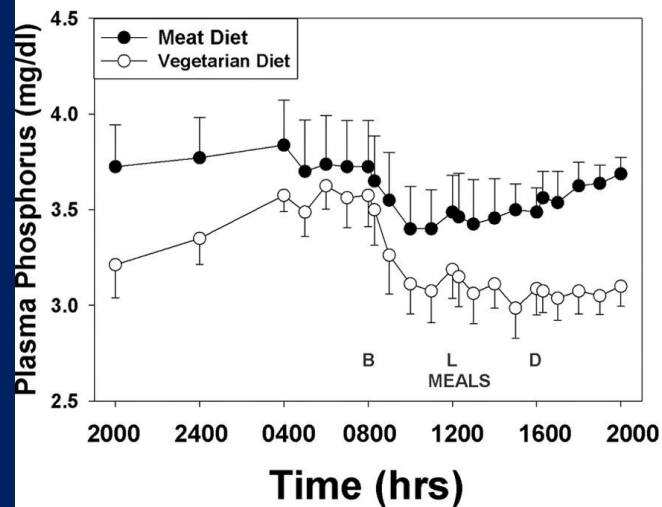
Other Agents

Phosphorus in Dietary Protein

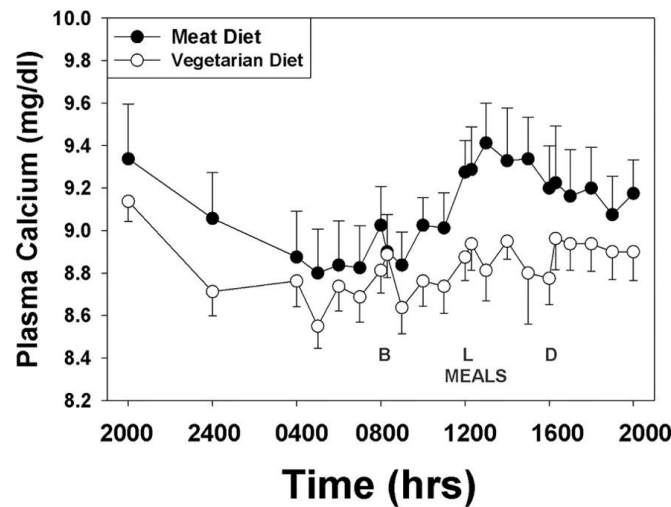
Protein Intake (g/kg/d)	Dietary Phosphorus (mg)
>1.2	1353 $\pm$ 253
1.0-1.2	1052 $\pm$ 219
0.8-1.0	936 $\pm$ 217
0.6-0.8	831 $\pm$ 142
<0.6	599 $\pm$ 105

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

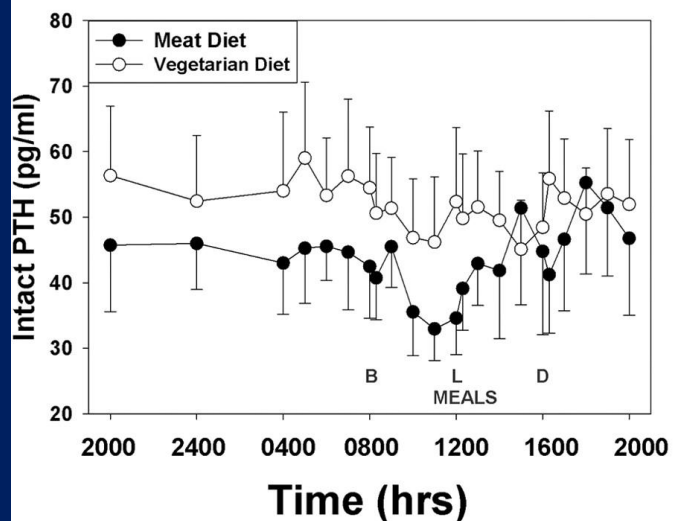
A Diurnal Variation in Phosphorus



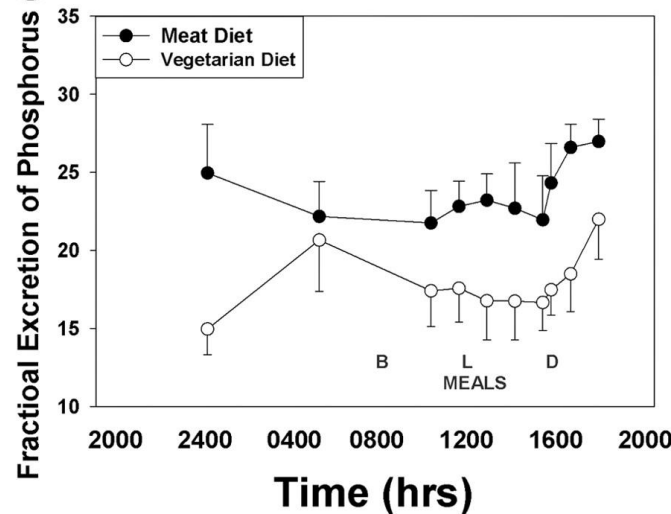
B Diurnal Variation in Calcium



C Diurnal Variation in Intact PTH



D Diurnal Variation in FEphosph



Dialysis Phosphorus Removal: 3 times per week

Diet	1000 mg/day 7×1000 (per week) =	7000 mg
Absorption	60% $7000 \times 60\% =$	4200 mg
Dialysis	800 mg 3×800 (per week) =	2400 mg
Balance	$4200 - 2400 =$	1800 mg

Dialysis Phosphorus Removal:

6 times per week

Diet	1000 mg/day $7 \times 1000 \text{ (per week)} =$	7000 mg
Absorption	60% $7000 \times 60\% =$	4200 mg
Dialysis	800 mg $6 \times 800 \text{ (per week)} =$	4800 mg
Balance	$4200 - 4800 =$	- 600 mg

Phosphate Binders

Aluminum-based

- Aluminum hydroxide
- Aluminum carbonate

Magnesium-based

- Rarely used, limitations

Calcium-based

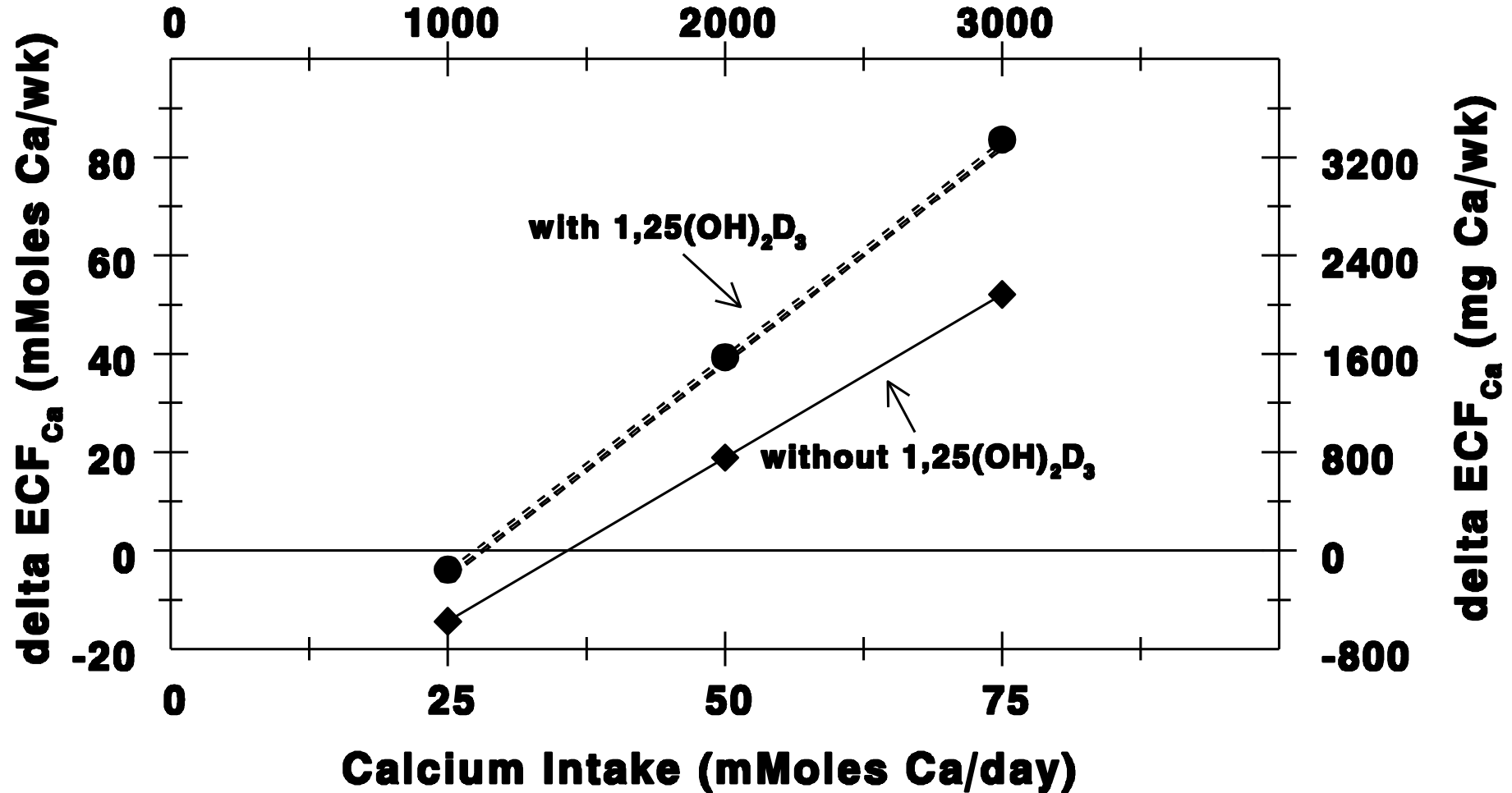
- Calcium carbonate
 - many OTC brands available
 - frequently used
- Calcium acetate

Aluminum & Calcium-free

- Ferric Citrate
- Sucroferric Oxyhydroxide
- Sevelamer
- Lanthanum carbonate
- Tenapanor

$\Delta \text{ECF}_{\text{Ca}}$ in Dialysis Patients

Calcium Intake (mg Ca/day)

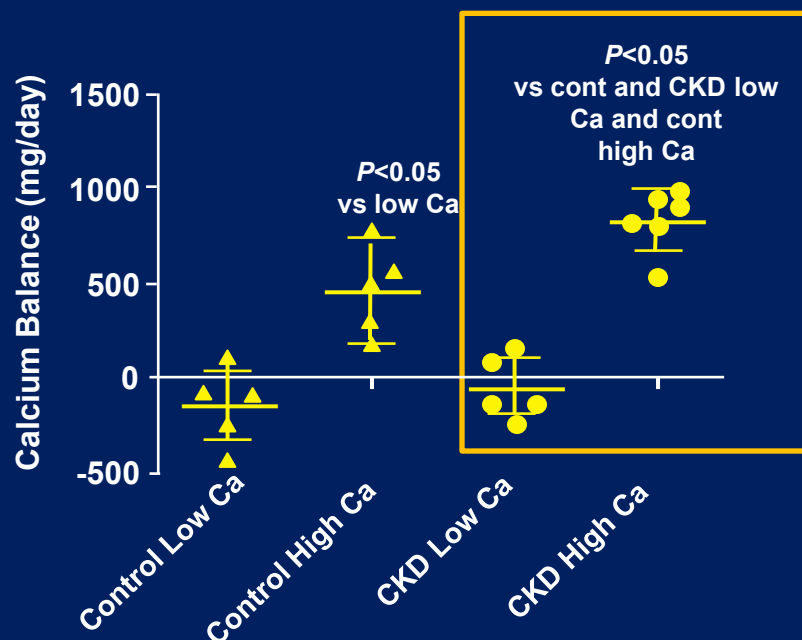


Bushinsky, D.A.. CJASN, 2010; Bushinsky, D.A. NDT 2012

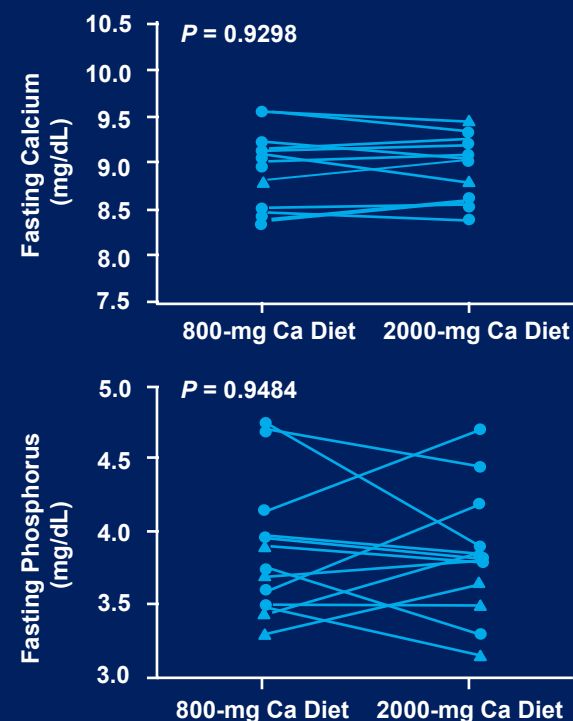
Calcium Balance in Patients With Stage 3/4 CKD on Low and High Calcium Diets

- 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*



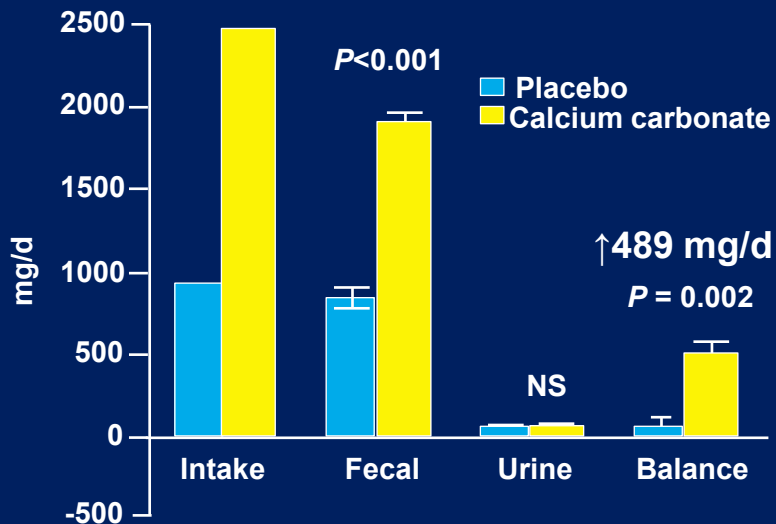
No effect on serum calcium or phosphate



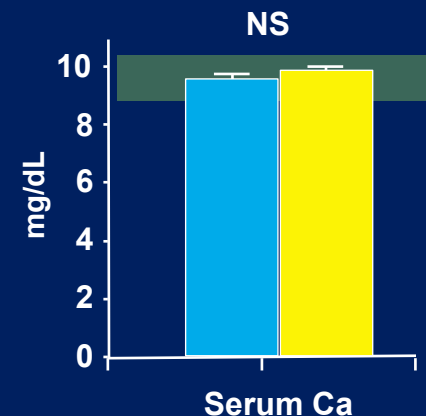
Calcium and Phosphorus Balance Study With Calcium Kinetics in Stage 3-4 CKD

- 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



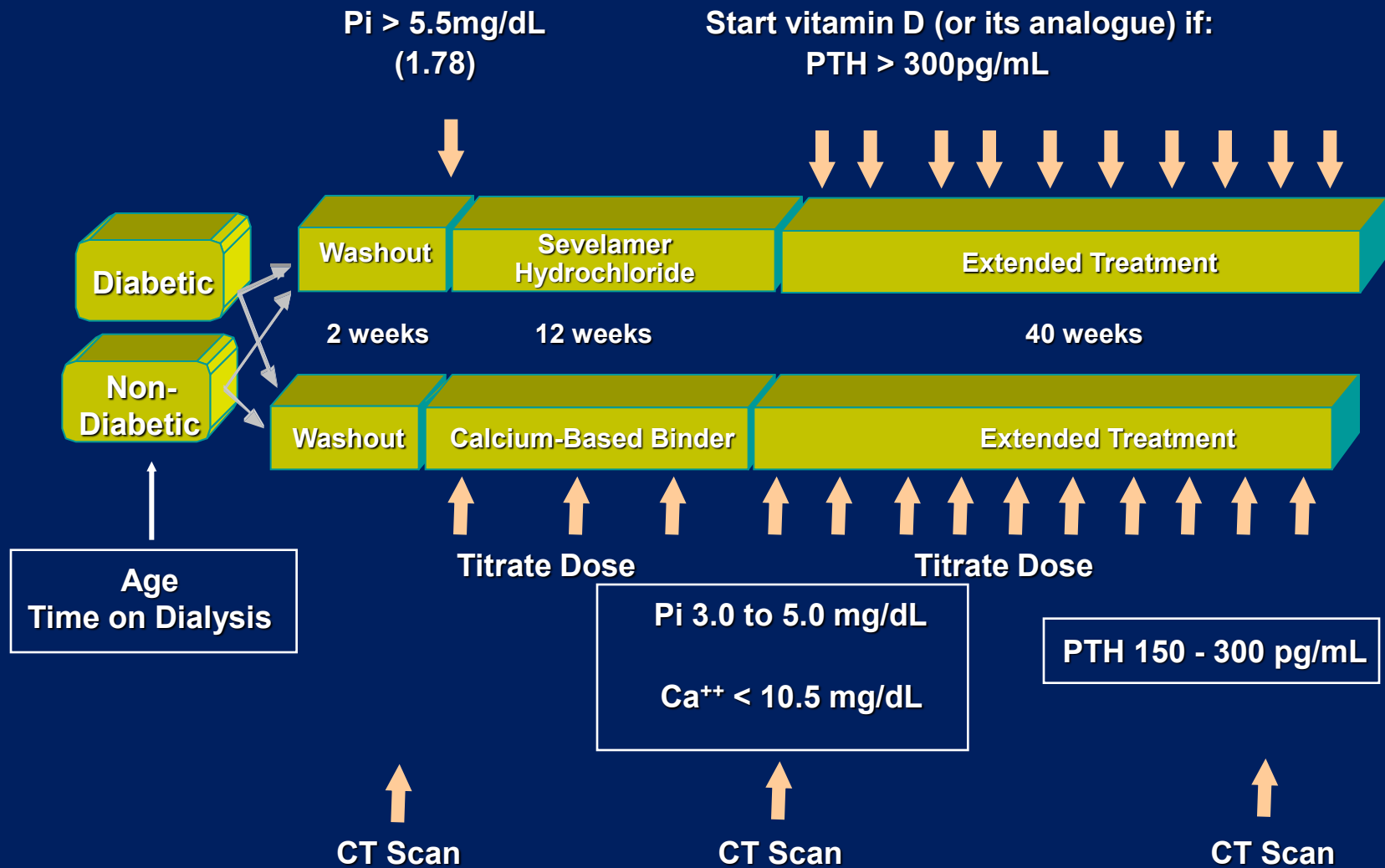
Lower urine calcium compared with healthy post-menopausal women

NS = not significant.

Hill KM et al. *Kidney Int.* 2012 Dec 19

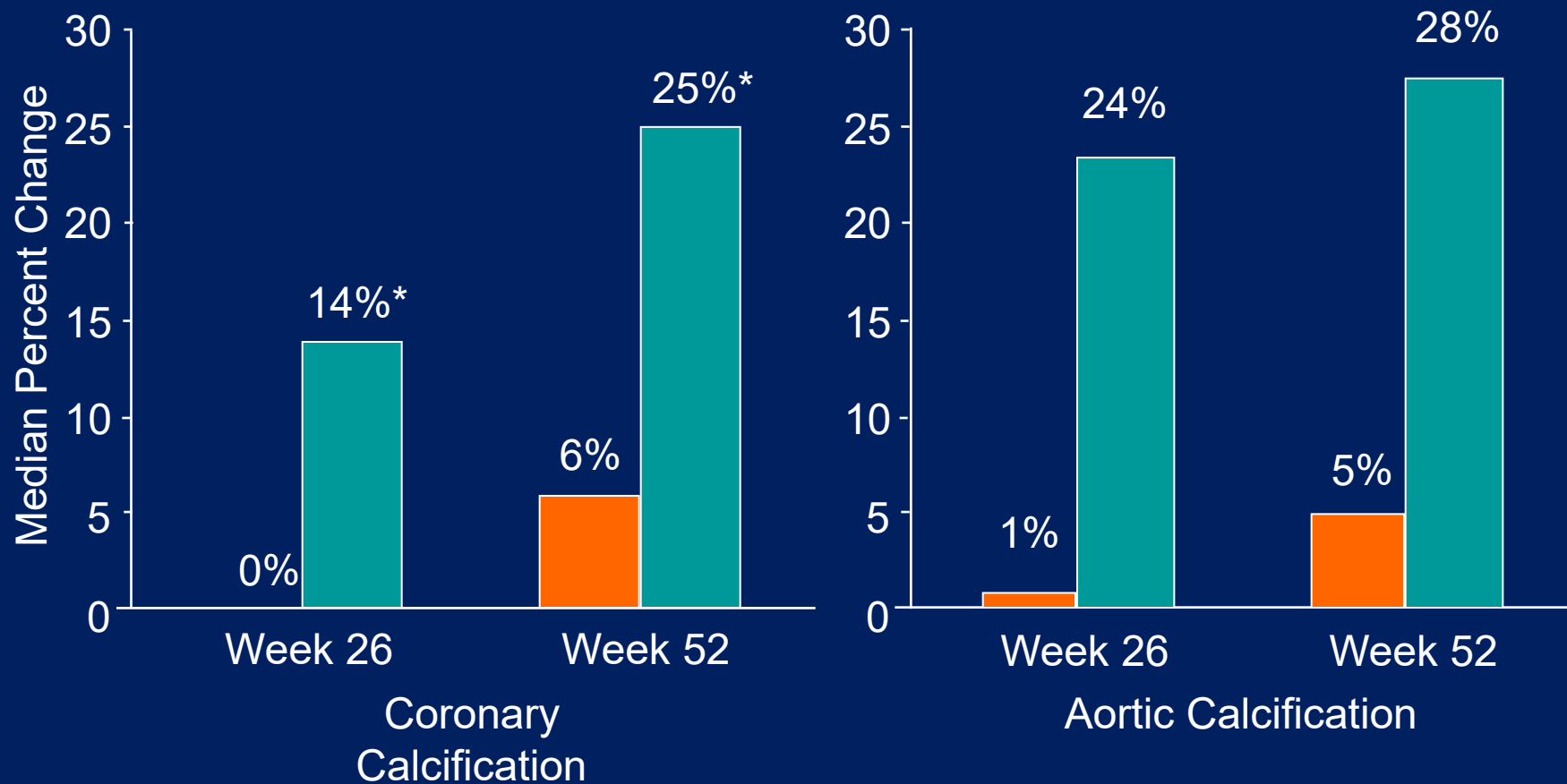
Coronary Artery Calcification

“Treat to Goal” Study

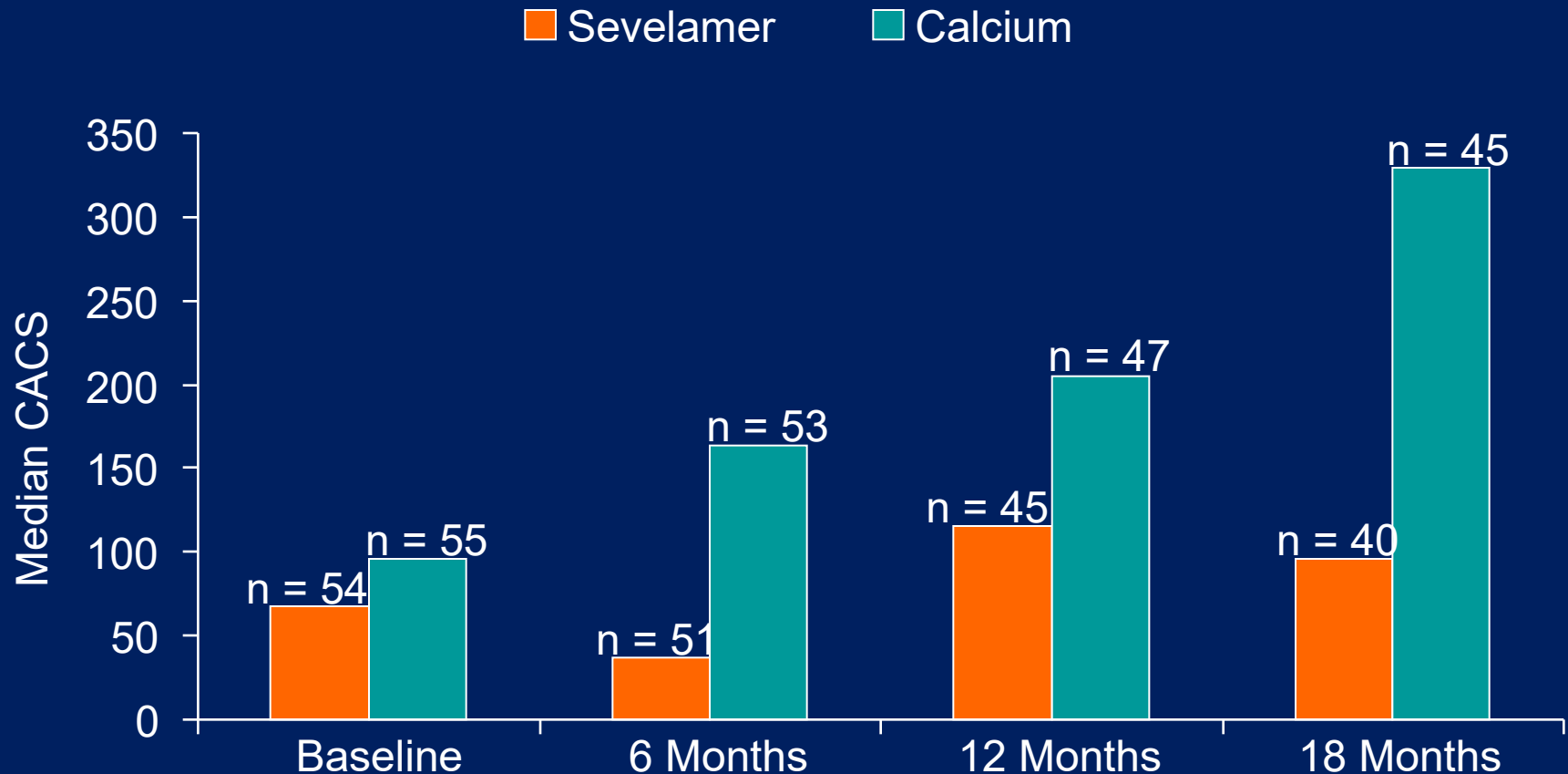


Phosphate Binders and Calcification

Sevelamer Calcium

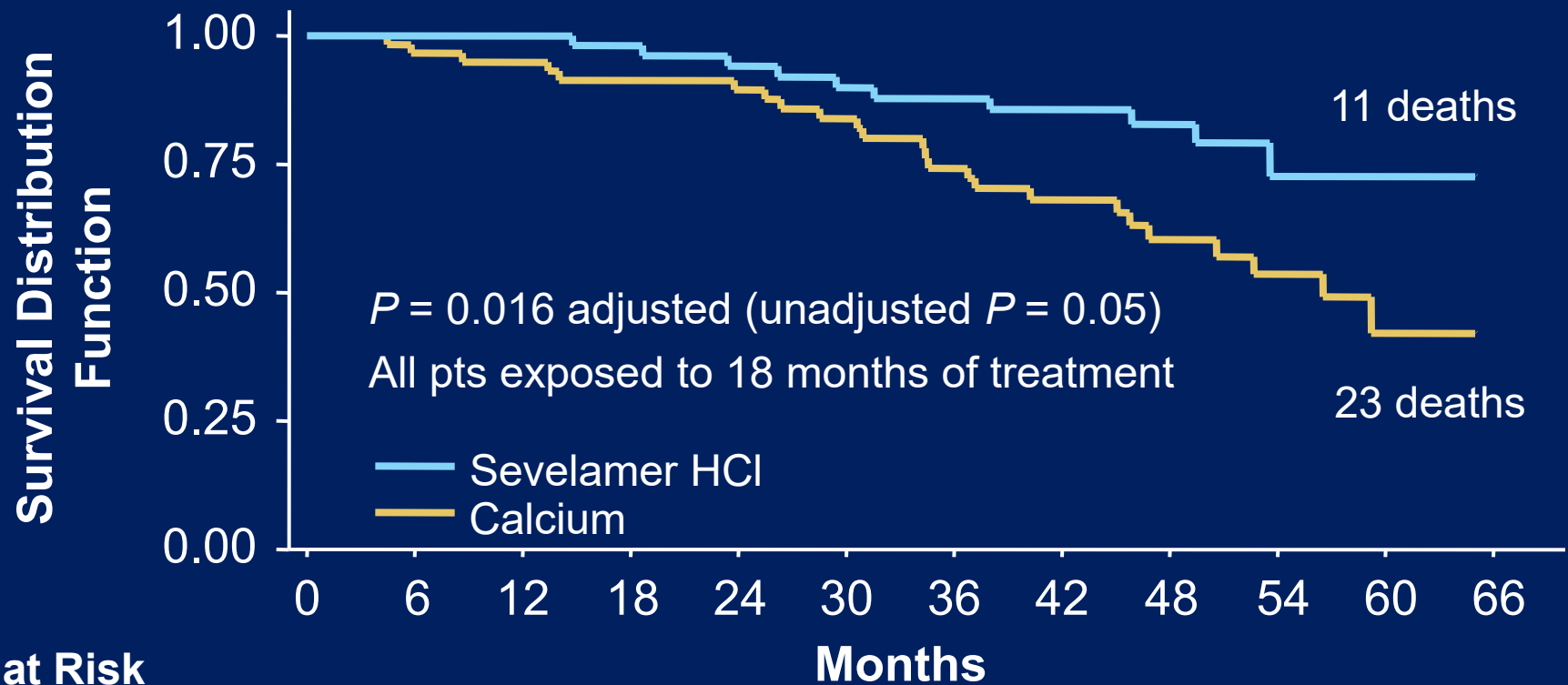


Phosphate Binders and Calcification



Sevelamer vs Calcium-Containing Phosphate Binders: RIND Study Outcomes

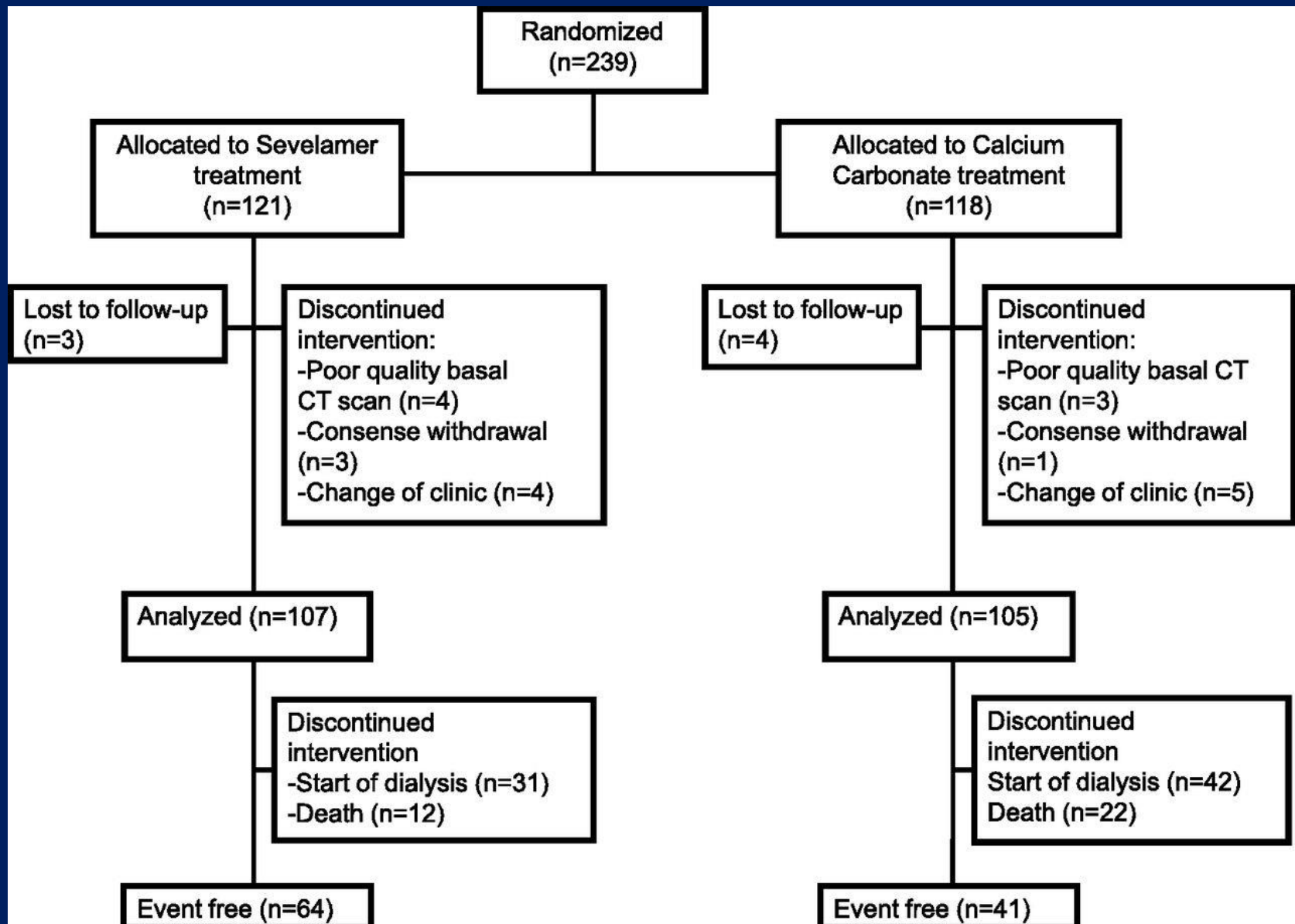
Increased Mortality in Patients Randomized to Calcium vs Sevelamer HCl



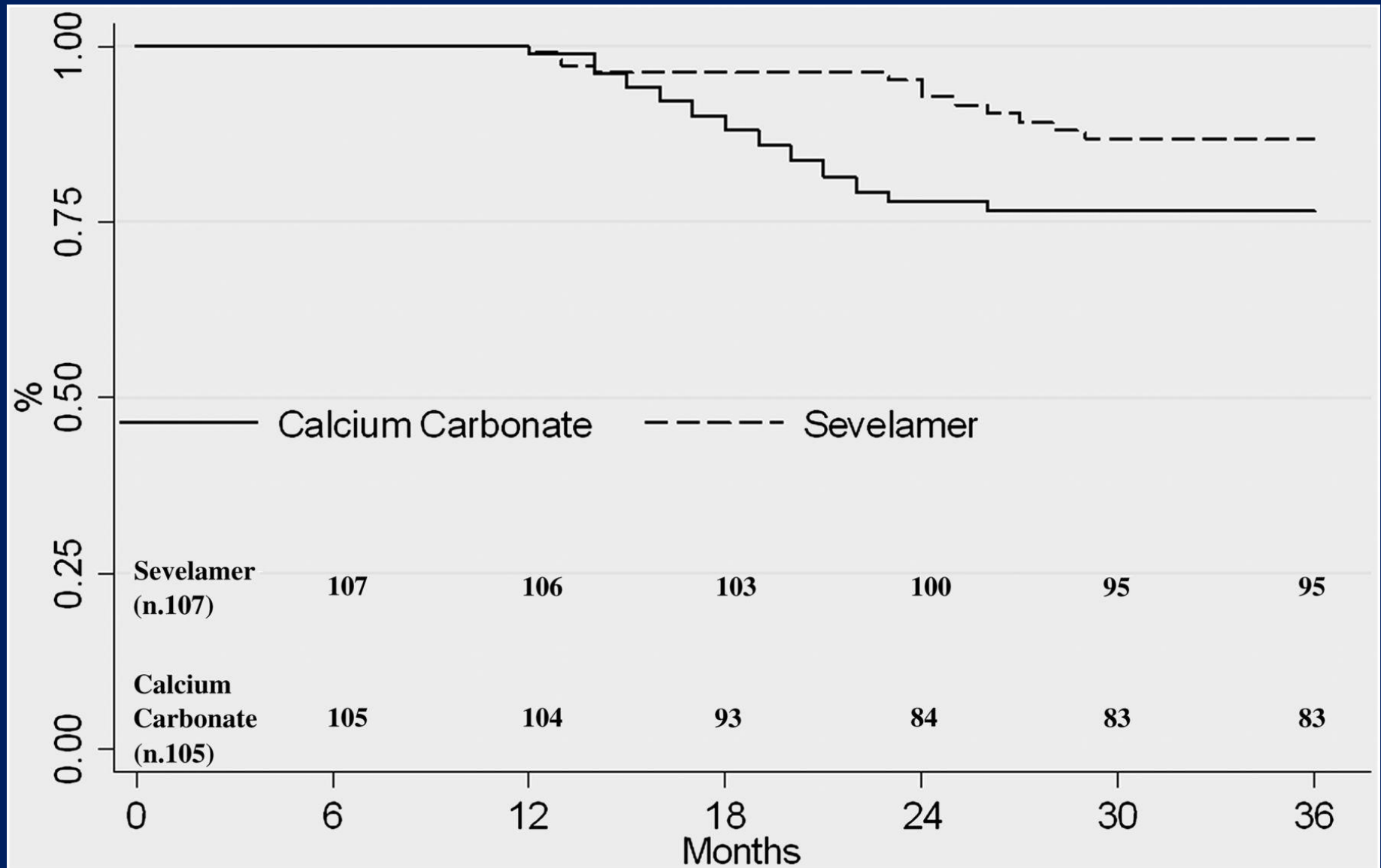
No. at Risk

Calcium	67	63	60	55	45	22	5
Sevelamer HCl	60	57	57	51	47	25	4

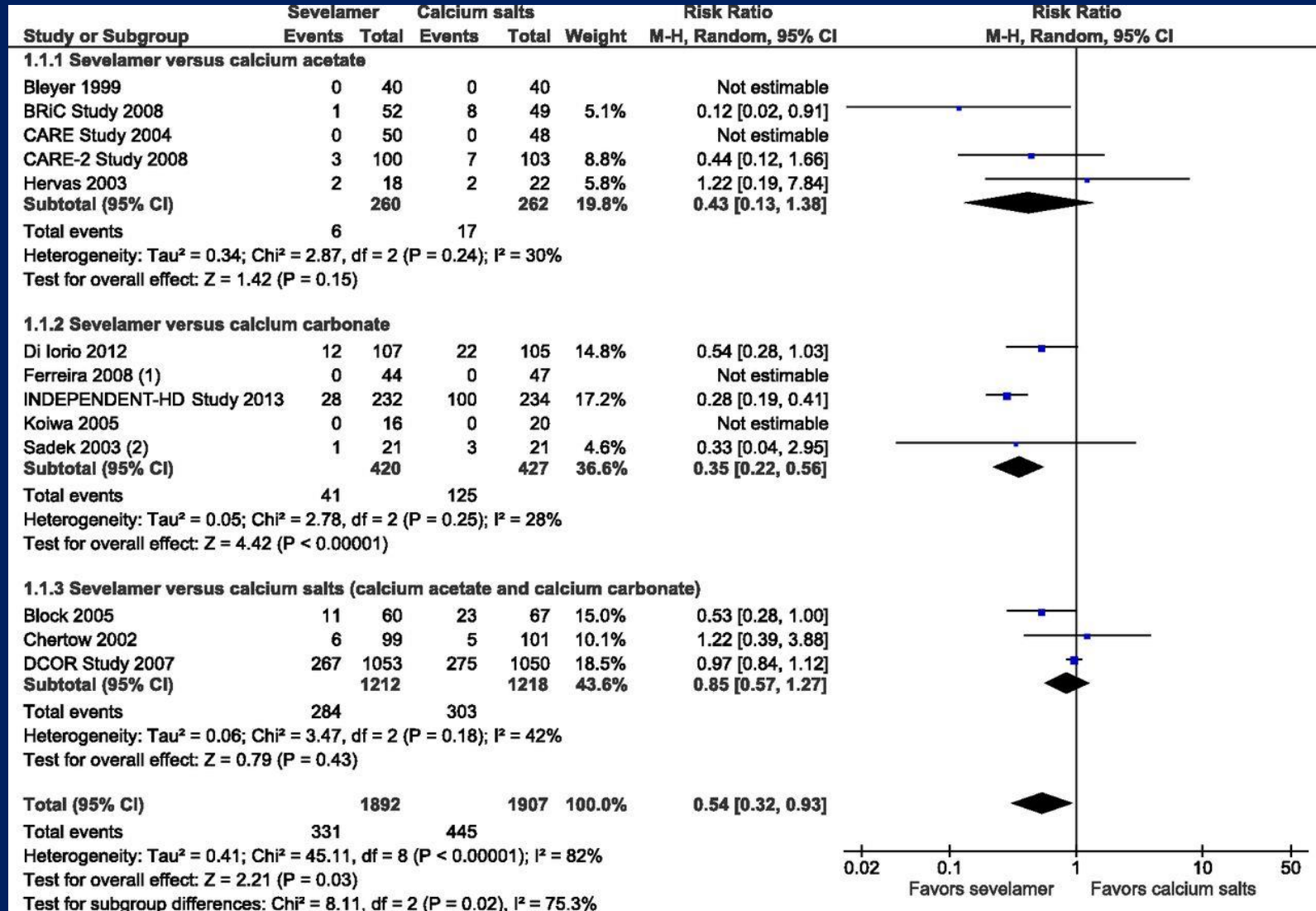
Patient flow chart indicating selection and discontinuation



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



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.



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

(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.

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

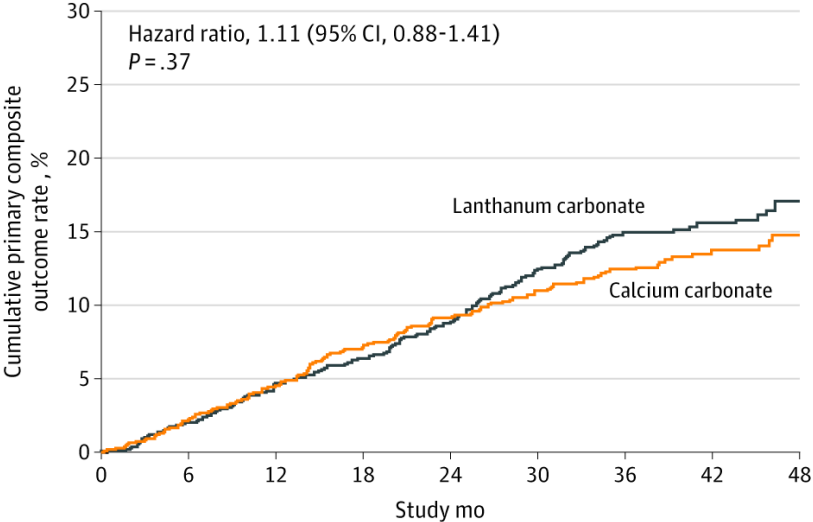
- dietary calcium intake is low

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

Excluded those with intact PTH > 240 pg/ml

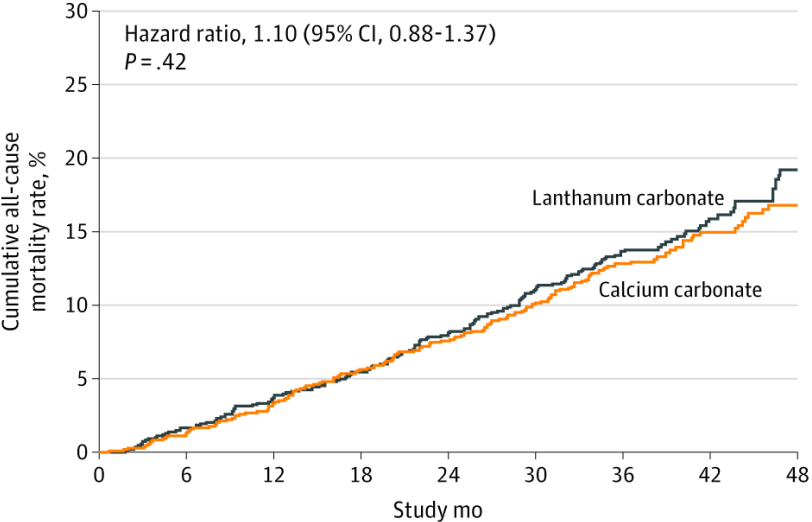
Effect of Treating Hyperphosphatemia With Lanthanum Carbonate vs Calcium Carbonate on Cardiovascular Events in Patients With Chronic Kidney Disease Undergoing Hemodialysis: The LANDMARK Randomized Clinical Trial

A Primary composite outcome



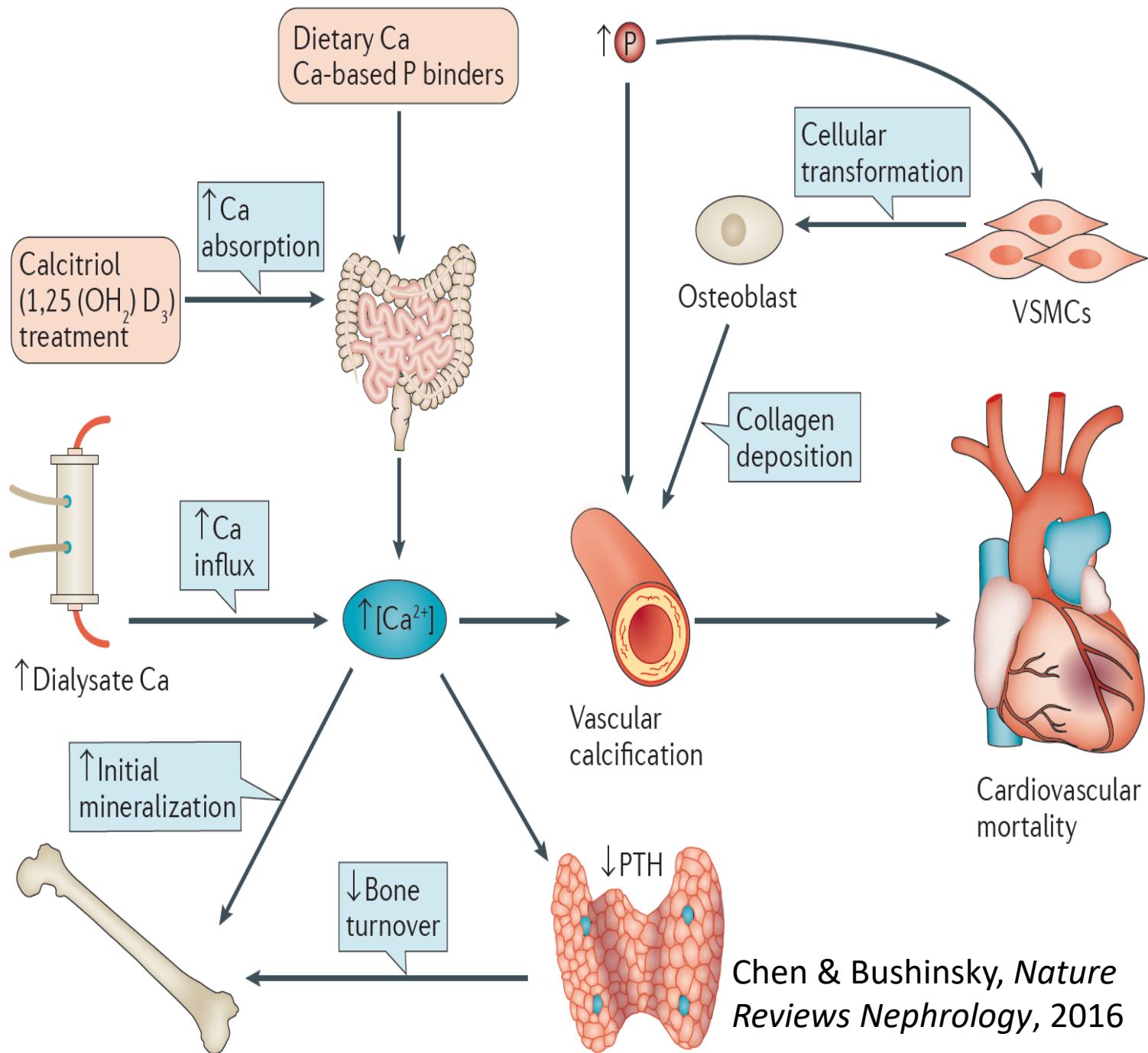
No. at risk										
Lanthanum carbonate		1063	688	907	860	805	731	634	349	202
Calcium carbonate		1072	996	925	866	814	754	660	351	195

B All-cause mortality



No. at risk										
Lanthanum carbonate		1063	999	934	891	844	785	688	385	223
Calcium carbonate		1072	912	955	908	864	808	711	377	214

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



Chen & Bushinsky, *Nature Reviews Nephrology*, 2016

Iron

Ferric Citrate

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

Sucroferric oxyhydroxide

reduces serum phosphate
chewable
some GI adverse events

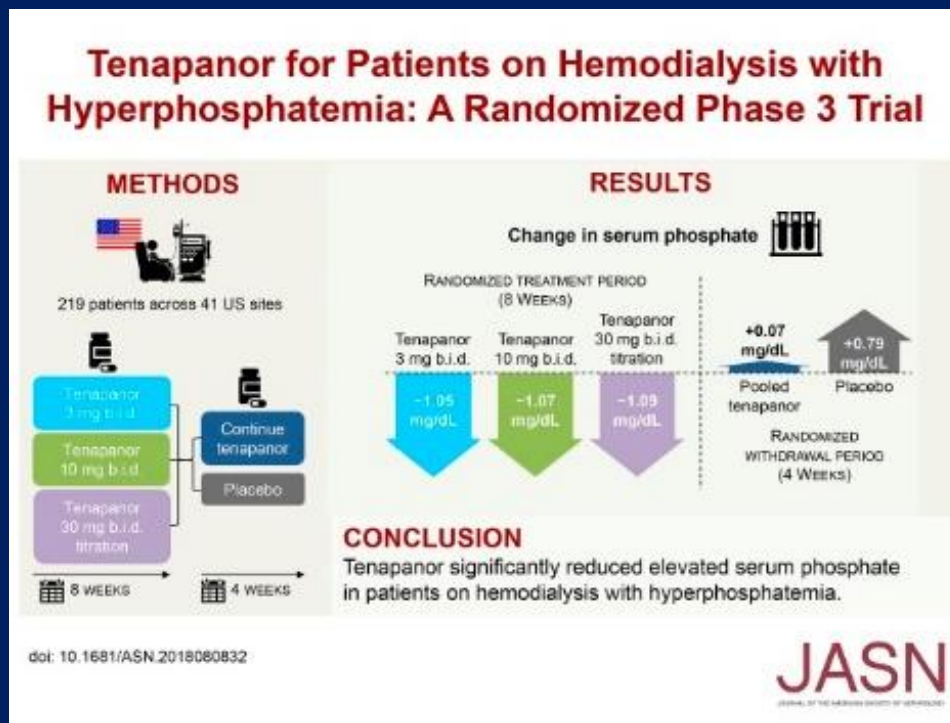
Other Phosphate Lowering Agents

Nicotinamide

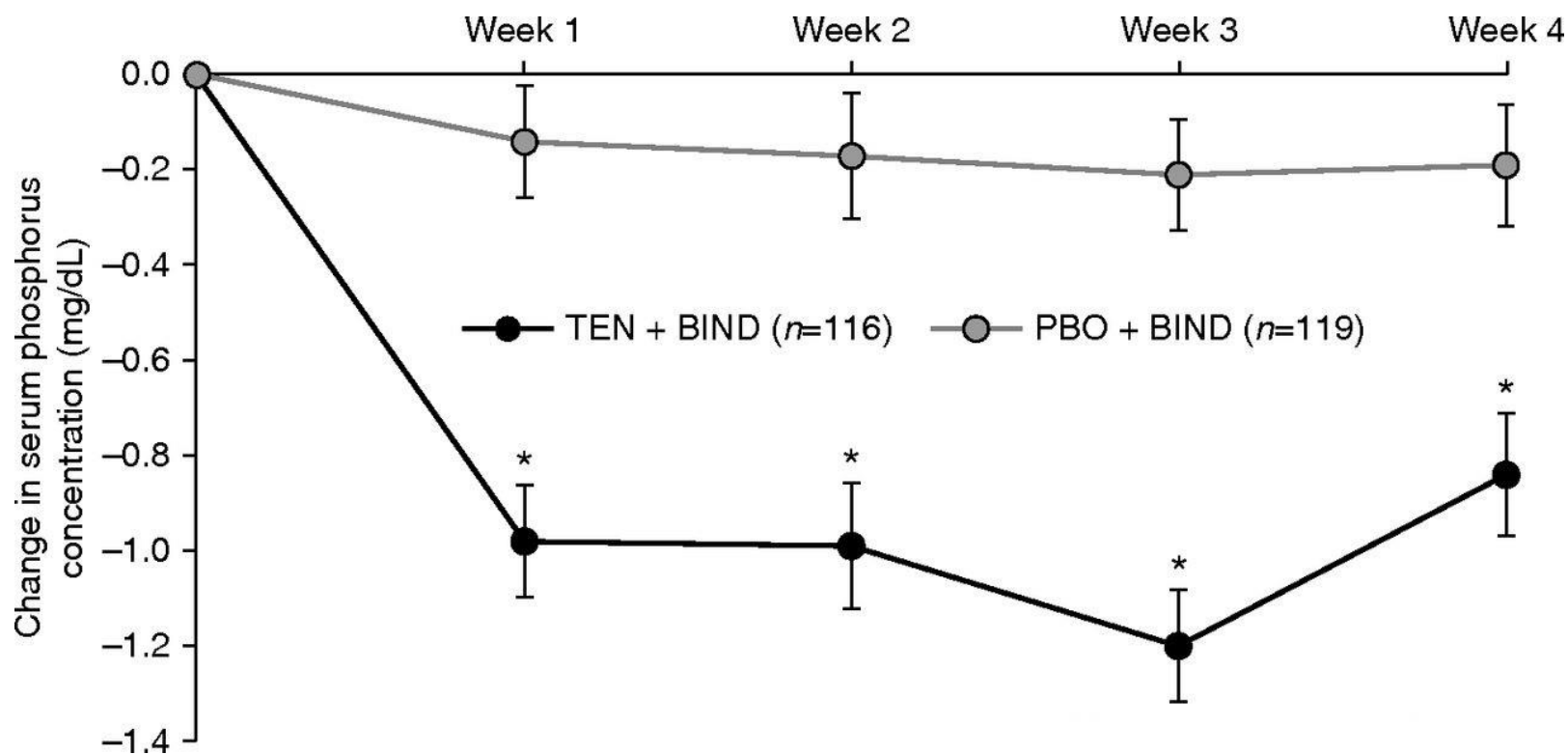
metabolite of nicotinic acid (vitamin B₃)
reduces GI phosphate adsorption
lowers phosphate in 2 published studies
however, less than 100 patients studied

Tenapanor

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)



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

Calciophylaxis

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).

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).

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

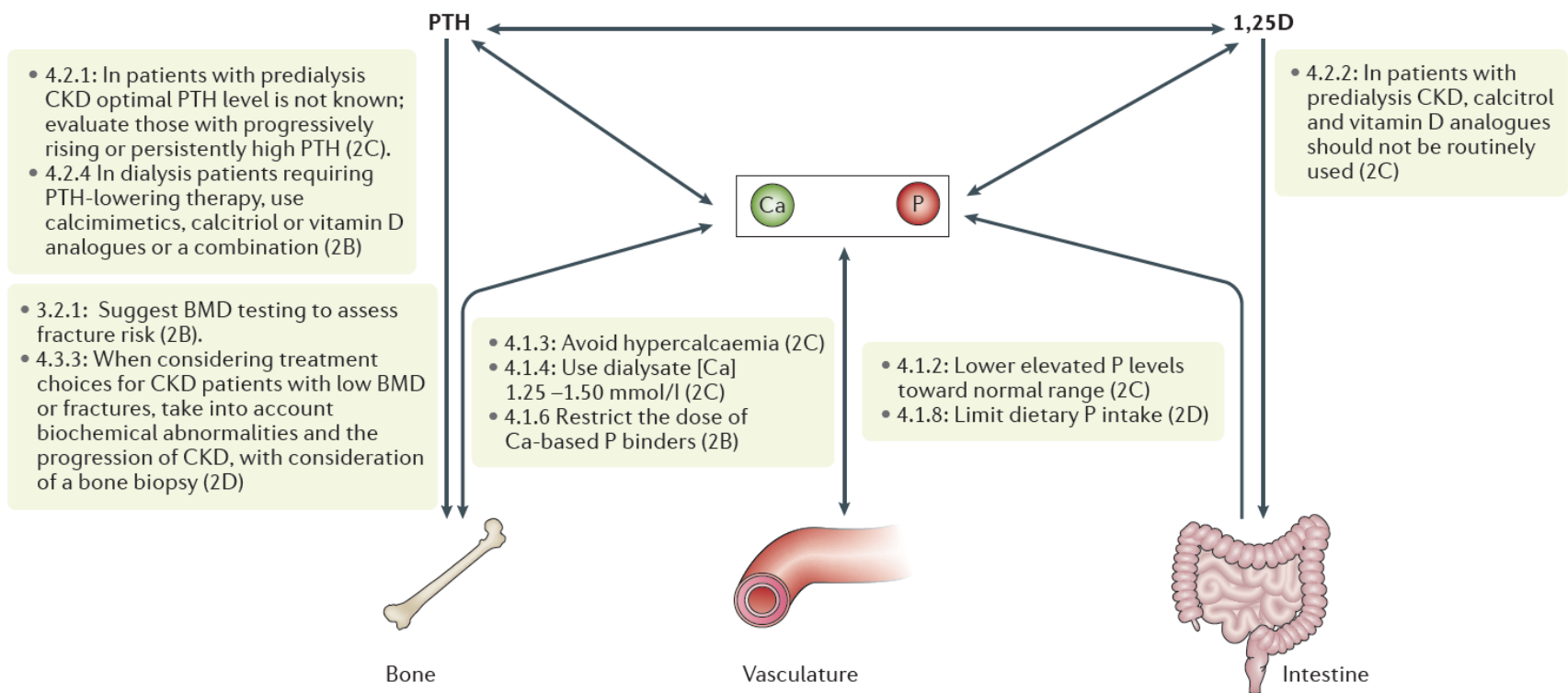


Figure 1 | Revised recommendations from the 2017 KDIGO CKD-MBD guideline. Only recommendations that are graded and apply to patients with chronic kidney disease and no history of kidney transplantation are shown, alongside the chapter from which the recommendation appears. Nomenclature for grading recommendations 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.

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.

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Questions ???



School of Athens / Scuola di Atene : Raphael / Raffaello Sanzio (1483-1520). Vatican. *The School of Athens* portrays Plato, Aristotle, and other ancient² philosophers engaged in philosophic inquiry.