

Management and markers of renal bone disease

3rd GCC Organ transplantation and Nephrology Congress

Kuwait 18th to 21st Jan 2017



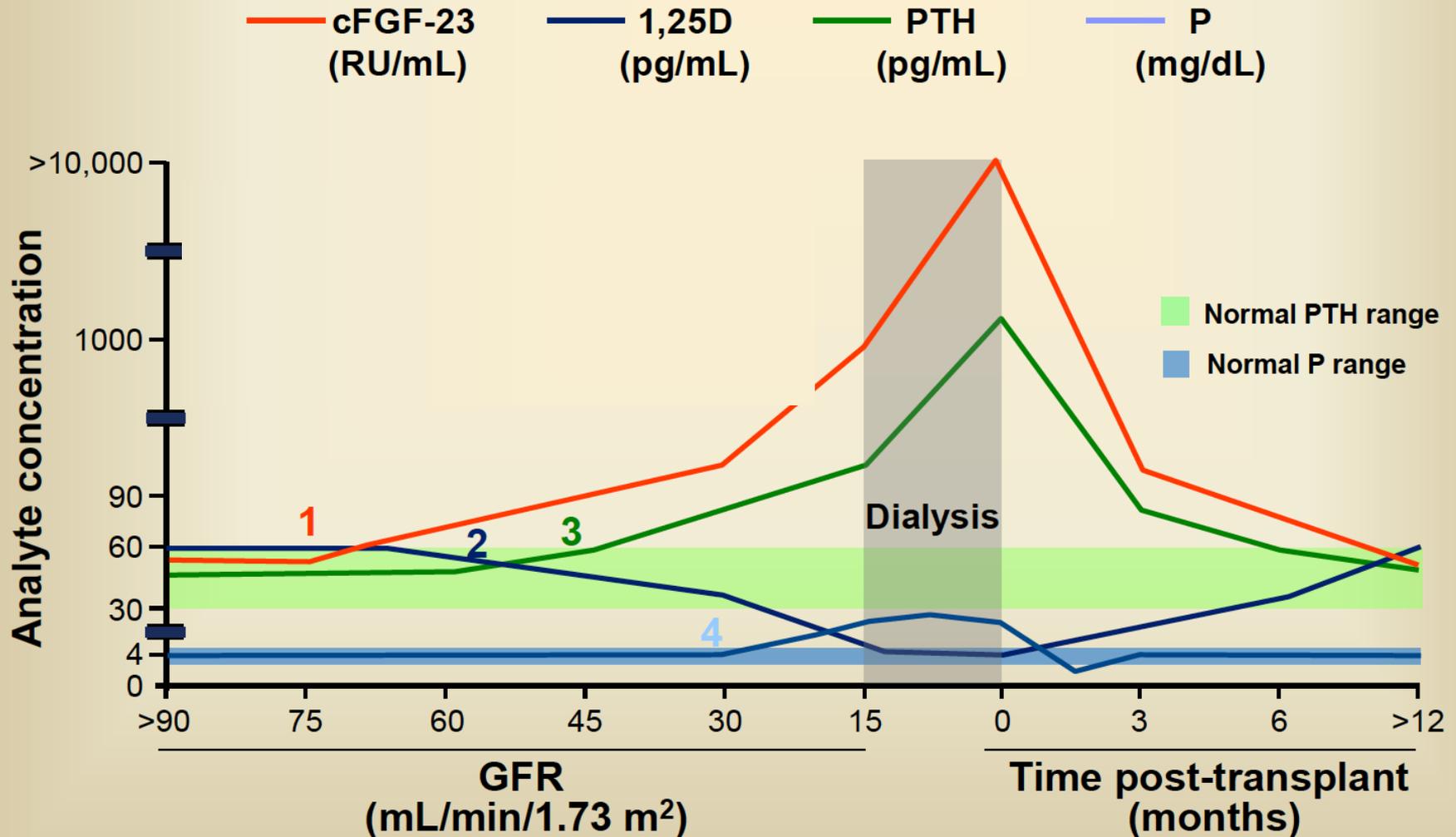
John Cunningham
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The Royal Free Hospital and UCL Medical School

CKD leads to

- Phosphate retention
 - Failure to make calcitriol
- } 2^o hyperparathyroidism
-

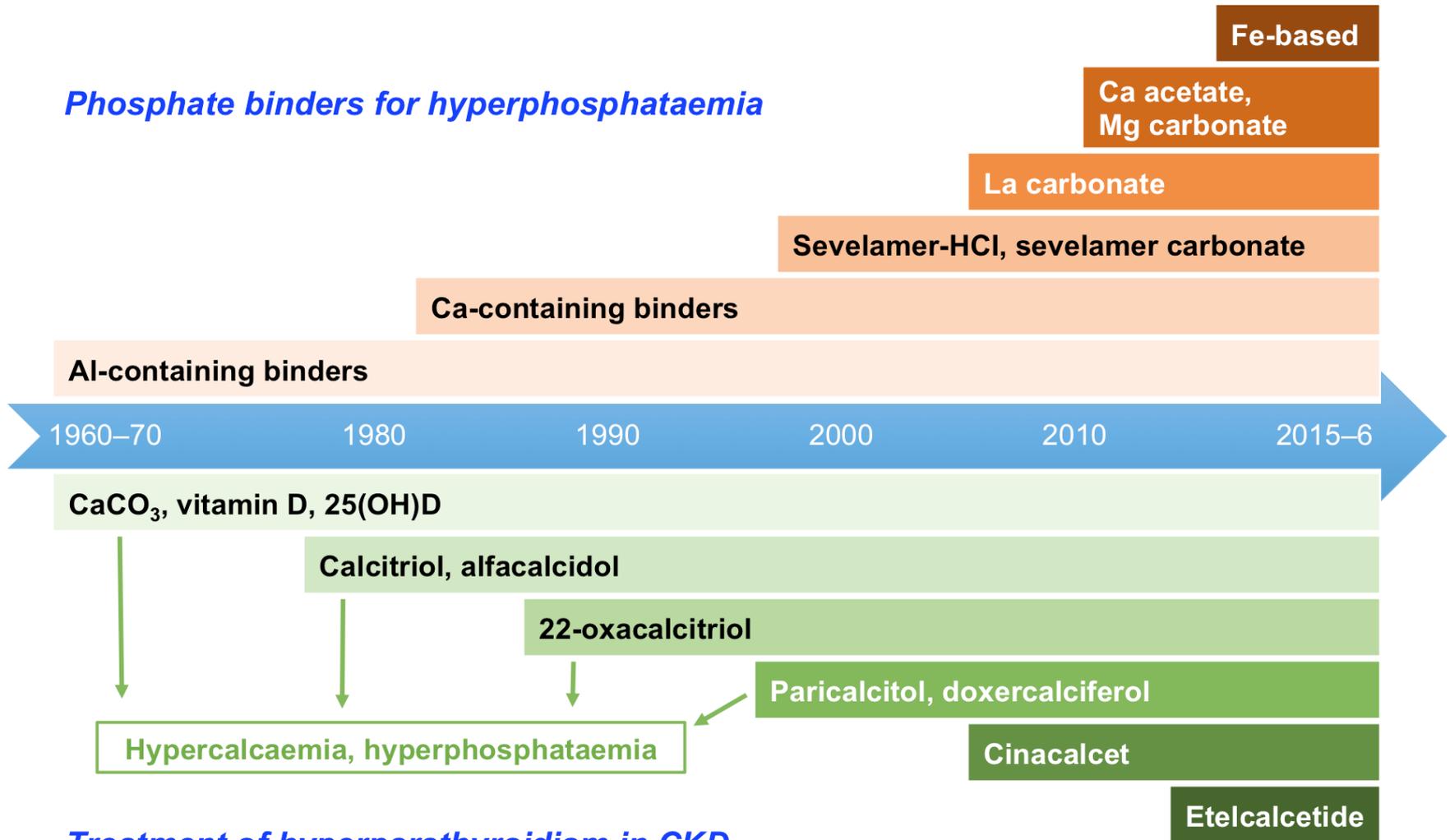
- An internal milieu that:
 - compromises bone cell functions
 - favours soft tissue calcification
 - stiffens arteries
- A patient with:
 - a poor quality skeleton
 - a propensity to early demise (mainly CV)

Temporal aspects of disordered mineral metabolism in CKD



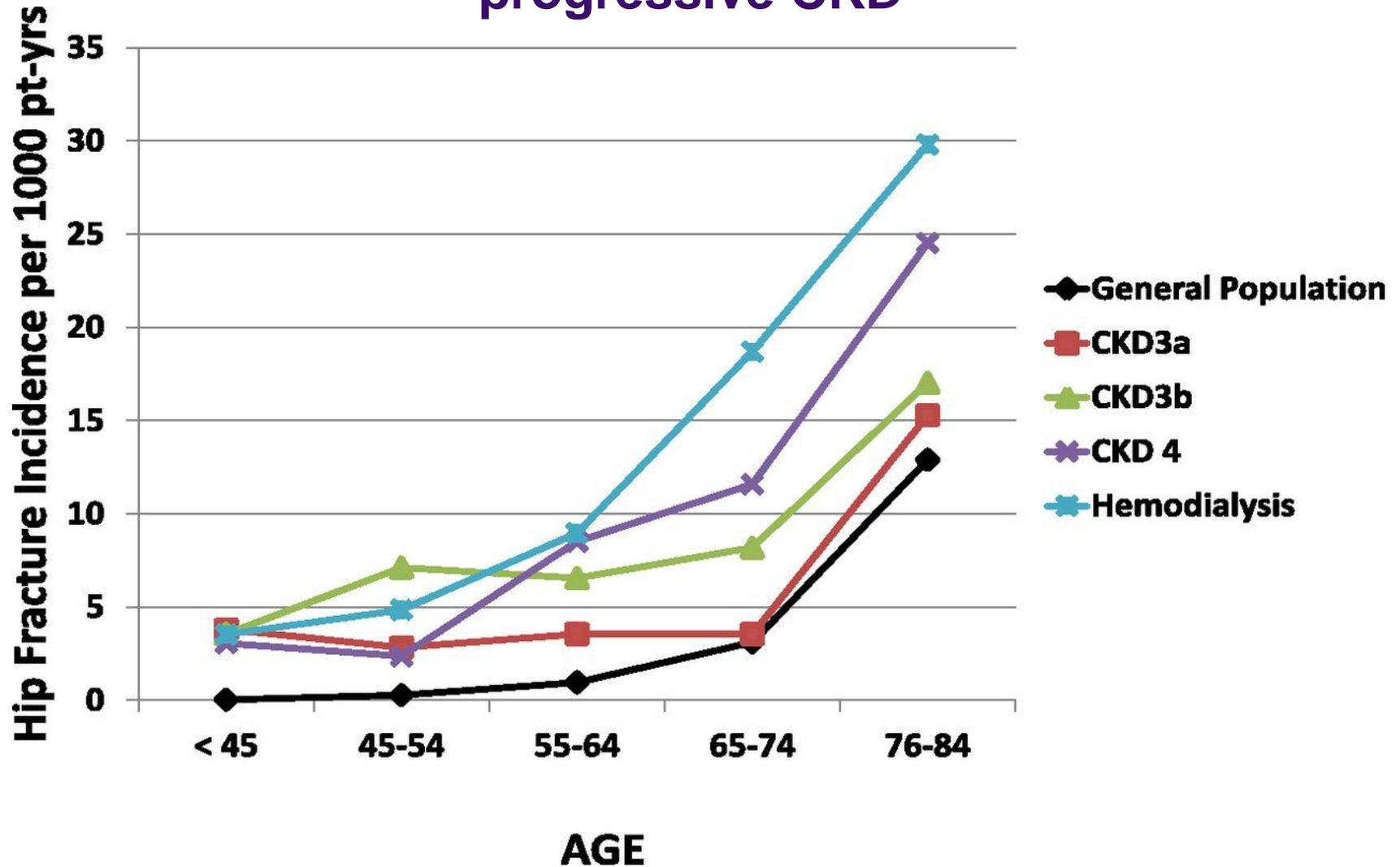
Evolution of Treatment Options for CKD-MBD

Phosphate binders for hyperphosphataemia



Treatment of hyperparathyroidism in CKD

Hip fracture incidence increases with progressive CKD

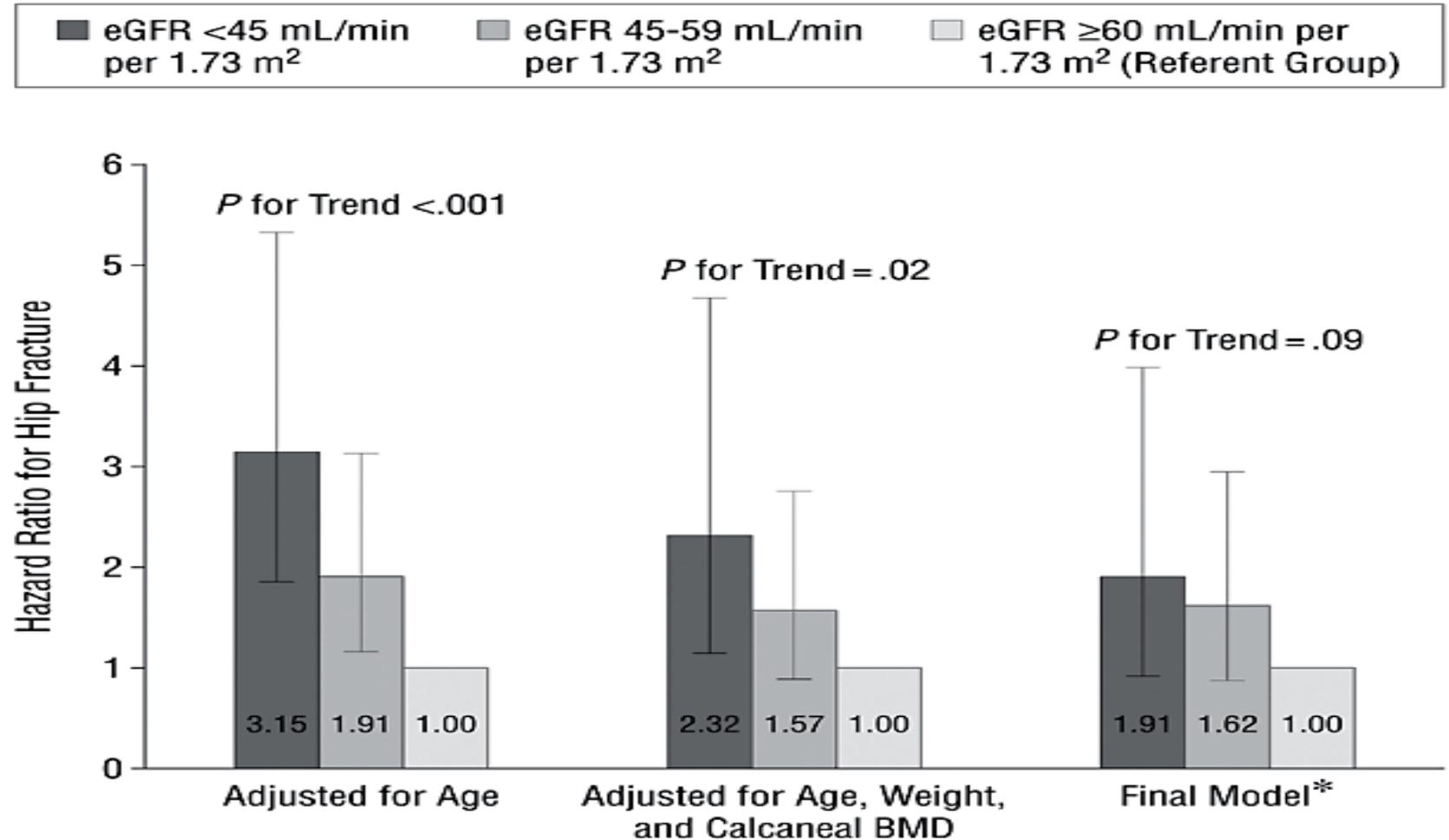


Early Observations

Amongst the first 22 patients to receive long-term HD:

- Fractures occurred in 47%

Renal function at baseline and risk of subsequent first hip fracture



BMD as a predictor of fracture risk

Non renal population	good
CKD 2 and 3	good
CKD 4 and 5	marginal
CKD 5D	poor
Transplanted	variable

Among men and women with CKD, FRAX is able to discriminate fracture status but performs no better than BMD alone

Quality

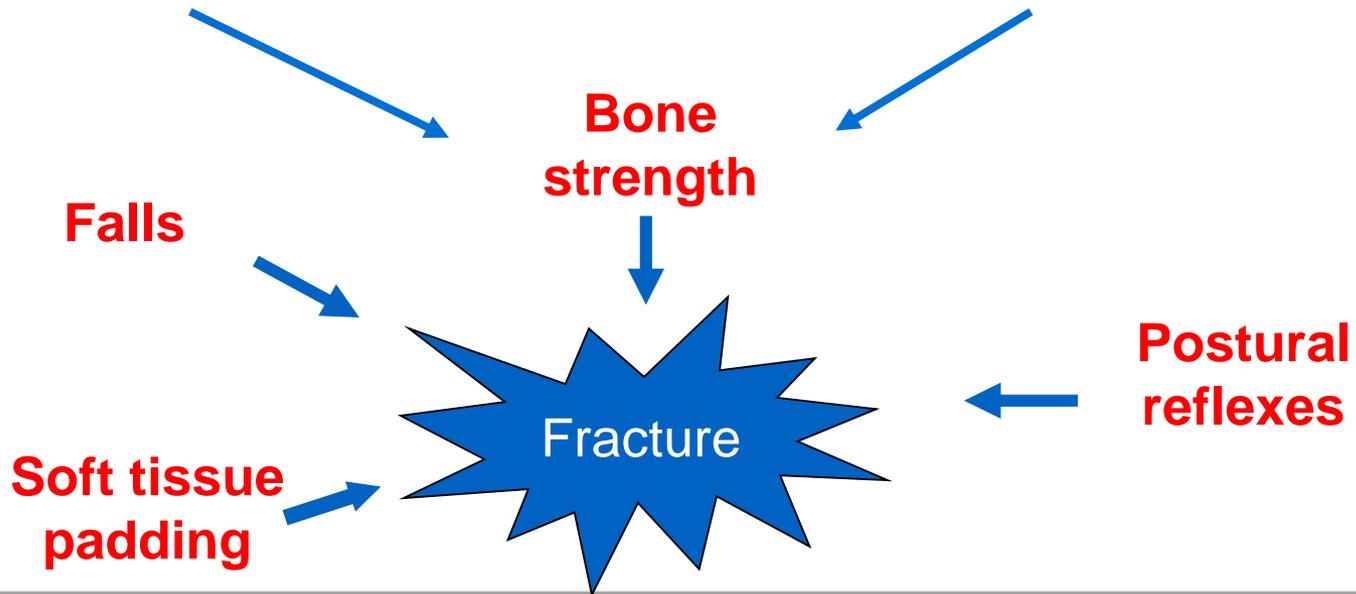


Physical composition,
architecture, turnover, damage
accumulation, mineralisation

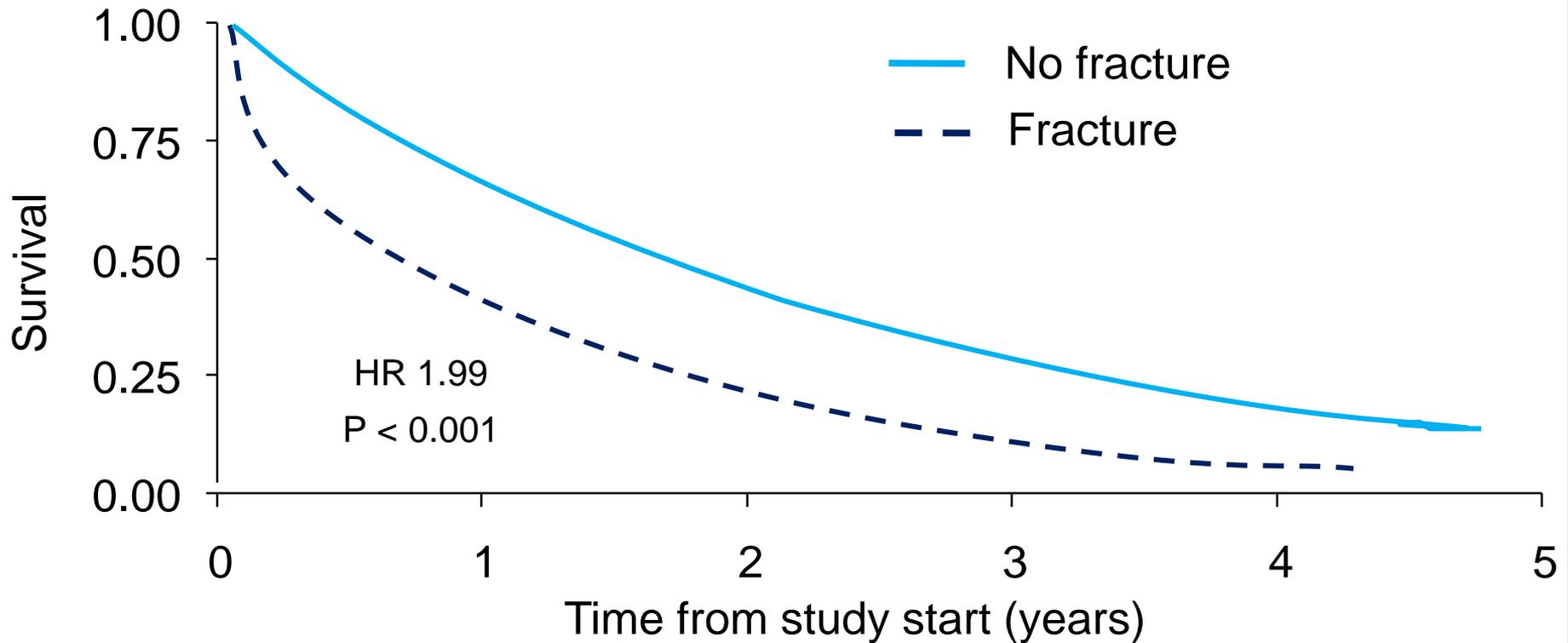
Density



Determined by peak
bone mass and amount
of bone loss

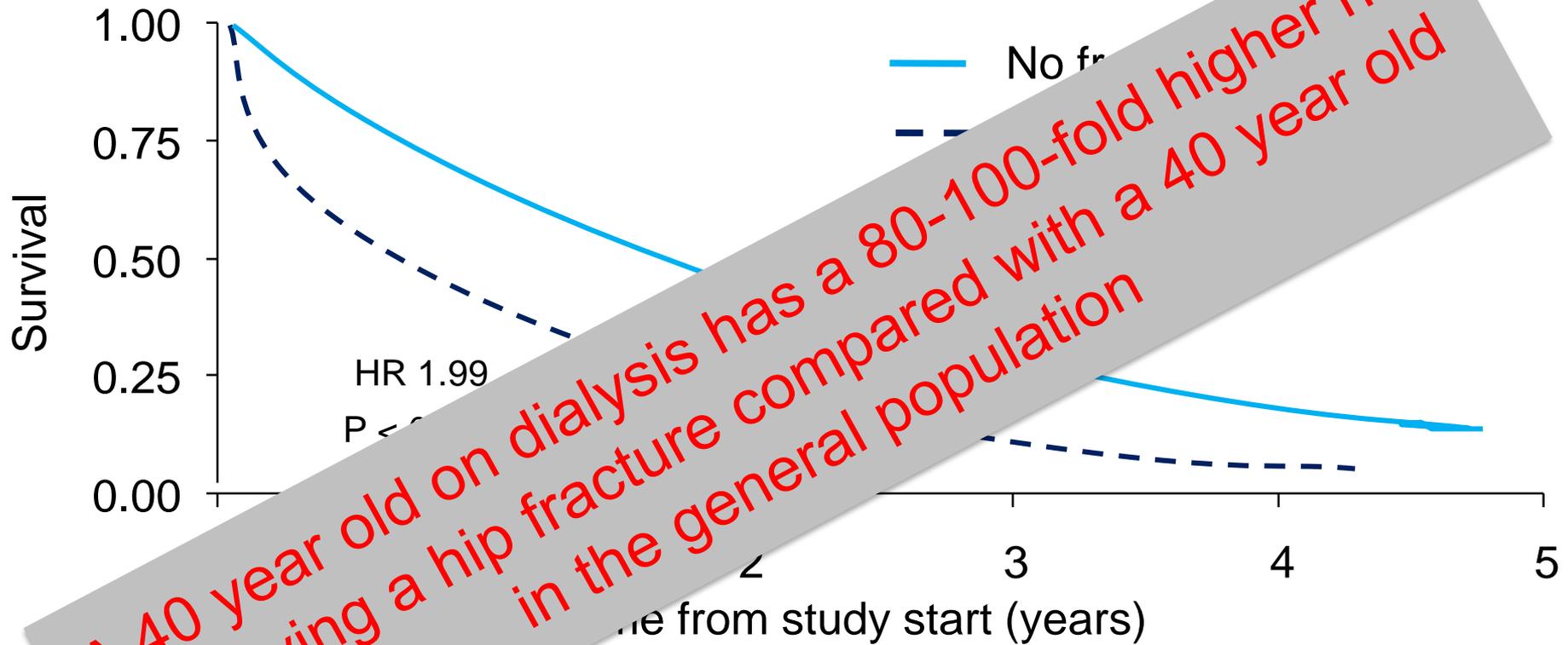


Increased risk of mortality associated with hip fracture in the dialysis population



Kaplan-Meier survival stratified by fracture status

Increased risk of mortality associated with hip fracture in the dialysis population



A 40 year old on dialysis has a 80-100-fold higher risk of having a hip fracture compared with a 40 year old in the general population

Kaplan-Meier survival stratified by fracture status

In populations with advanced CKD, fractures are:

- Not predicted by the usual tools
- More frequent
- More dangerous

The Spectrum of Renal Osteodystrophy

calcium, vitamin D, calcimimetics



PTH



< 16 pM

16-32 pM

> 32 pM

Normal bone turnover

low turnover

high turnover

adynamic/osteomalacia

osteitis fibrosa

Relationship between fractures and PTH in patients with CKD–MBD

Author, year	N	Relationship between fractures and PTH
Coco (2000) ⁹⁰	1272	High risk with low PTH
Stehman-Breen (2003) ²⁰⁴	4952	No relation
Block (2004) ²⁰⁵	40,538	Weak direct association, $P=0.035$
Danese (2006) ⁸⁹	9007	Higher risk with low or high PTH
Jadoul (2006) ²⁰⁶	12,782	RR=1.7 if PTH > 900
Mitterbauer (2007) ²⁰⁷	1774	No relation

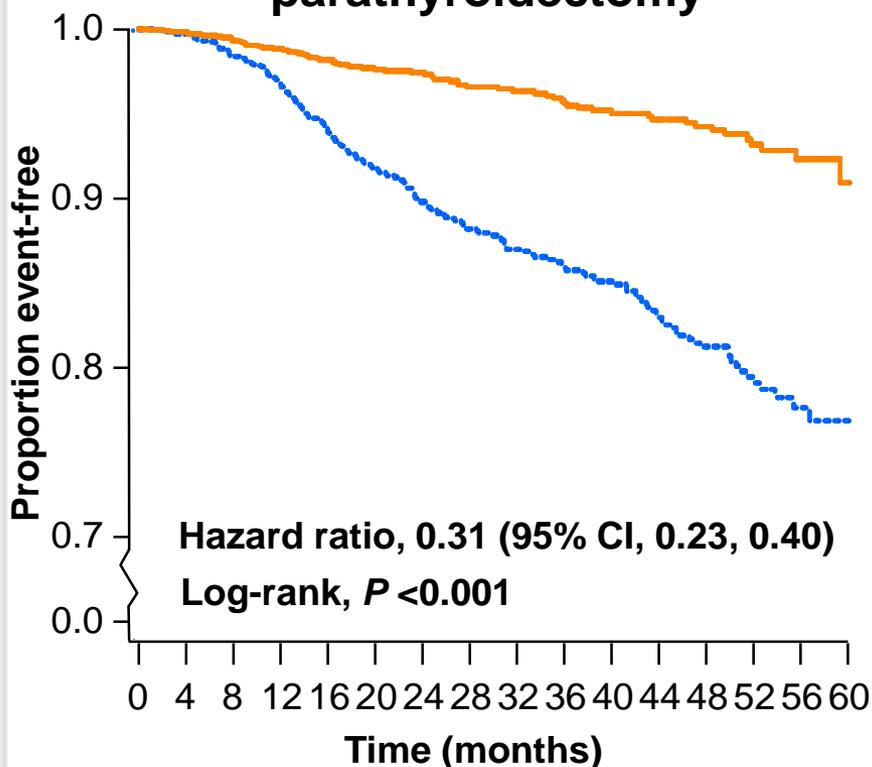
From: KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int 2009

EVOLVE

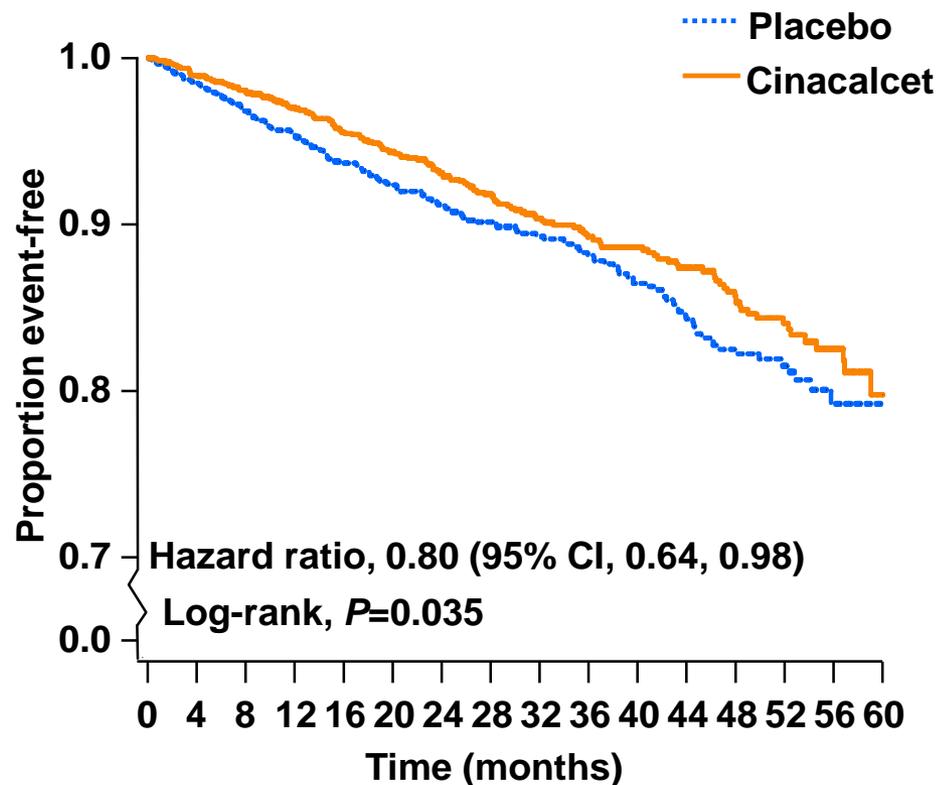
parathyroidectomy and fracture

secondary endpoints (lag censoring analysis)

Time to first parathyroidectomy



Time to first fracture



Biochemical markers of bone metabolism

Formation

Excreted by kidneys

Serum osteocalcin	yes
Propeptide type 1 collagen (P1NP)	yes
PTH	depends on assay
Total ALP	no
Bone ALP	no

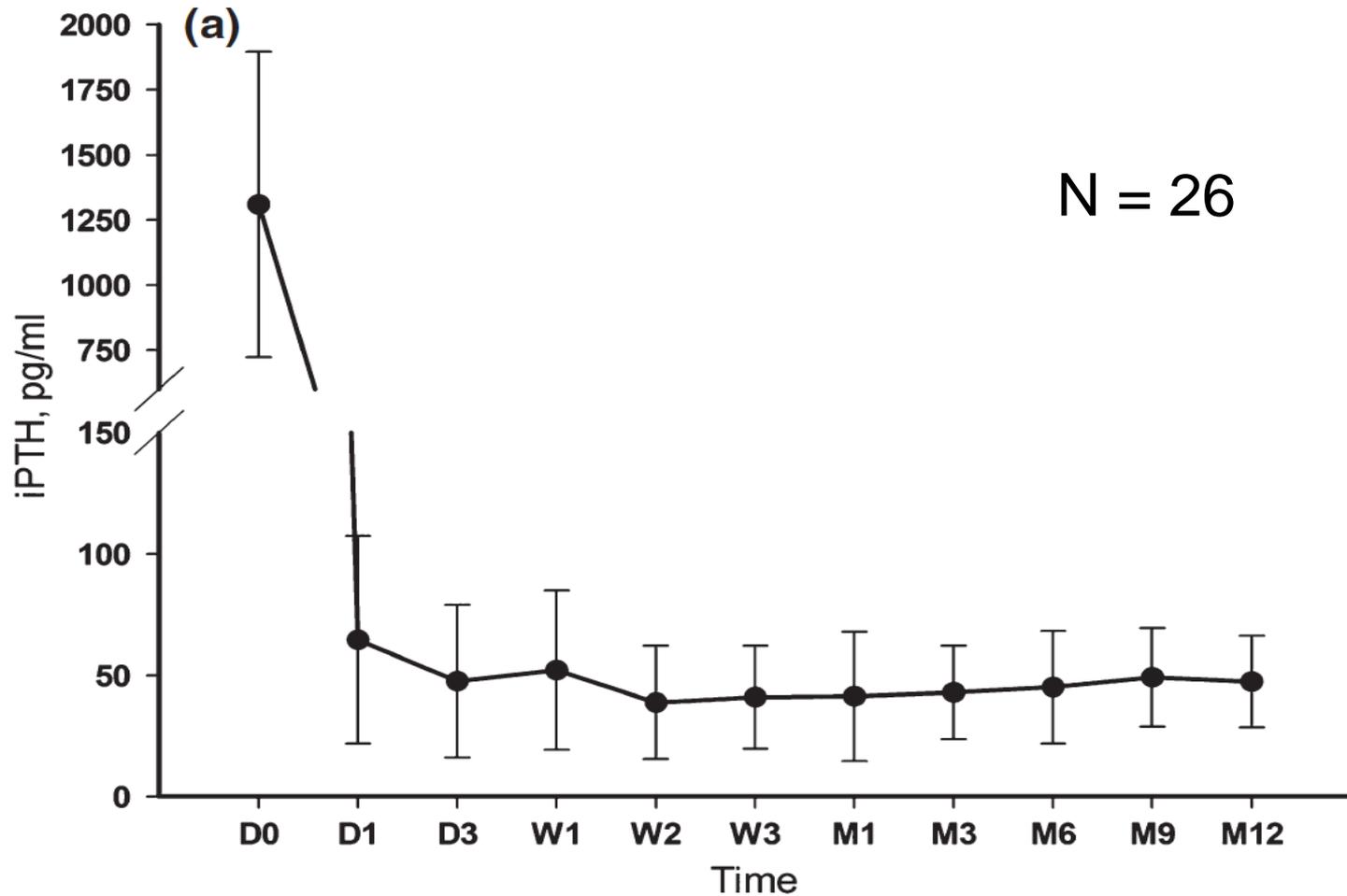
Resorption

N-telopeptide (NTx)	yes
C-telopeptide (CTx)	yes

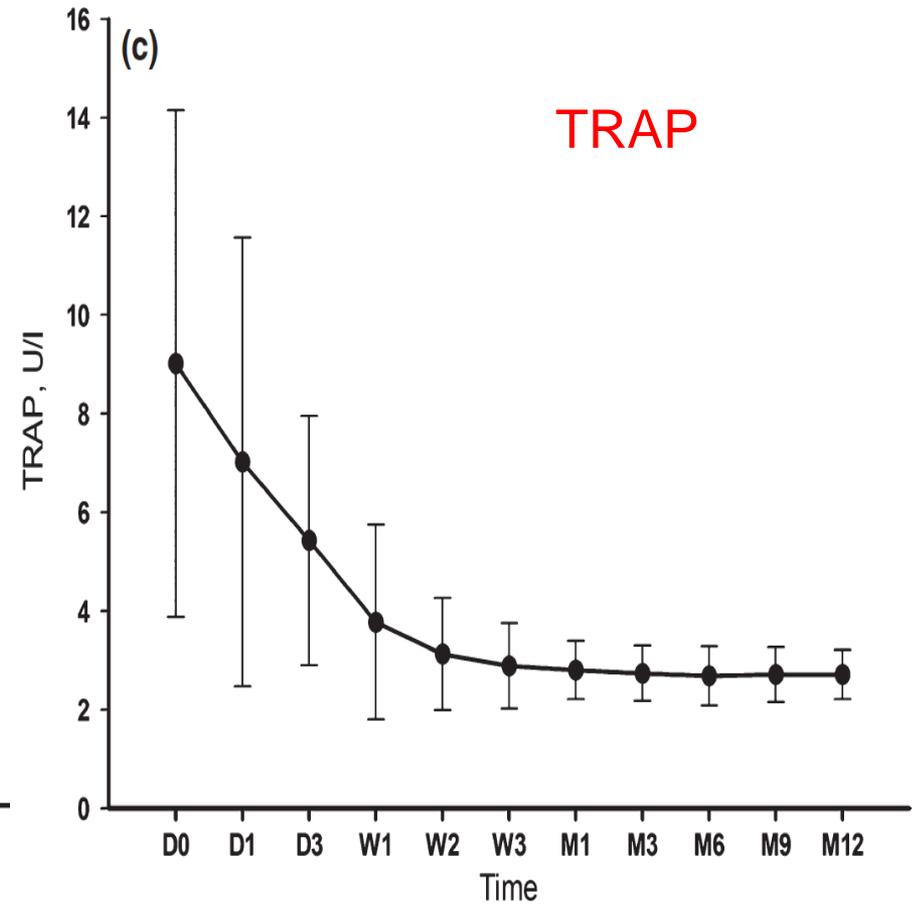
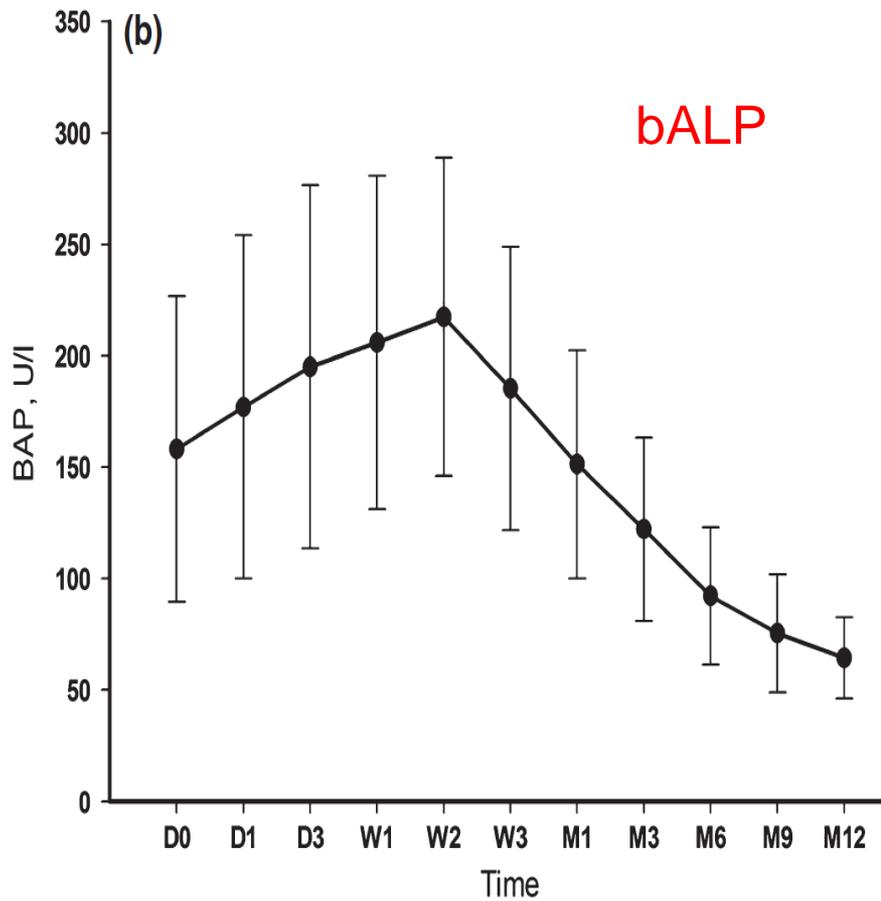
Parathyroid hormone and bone-specific alkaline phosphatase levels in specific forms of renal osteodystrophy

DISORDER	PTH	bALP
Hyperparathyroidism		
Mild	20–40 pM	Normal
Moderate	35–80 pM	Normal/elevated
Severe	> 80 pM	Elevated
Aluminium bone disease	< 50 pM (mostly < 10)	Normal
Adynamic bone disease	< 10–15 pM	Normal to low
Osteomalacia	Normal or mildly elevated	Mildly elevated

Bone turnover markers after PTX



Bone turnover markers after PTX



N = 26

Biomarkers of bone remodelling

Less well established in CKD than in normals

Added potential if the marker is itself a “player”

- PTH
- Sclerostin

Some marker data confounded by renal excretion

No studies with patient level endpoints

Stimulating formation or inhibiting resorption?

- stimulating formation
 - PTH (teriparatide)
 - sclerostin antagonist (romosozumab)
 - sodium fluoride
- antiresorptives
 - bisphosphonates *
 - RANK ligand inhibitors (denosumab) *

** fracture reduction in CKD 1-3/4*

none of above licensed in CKD

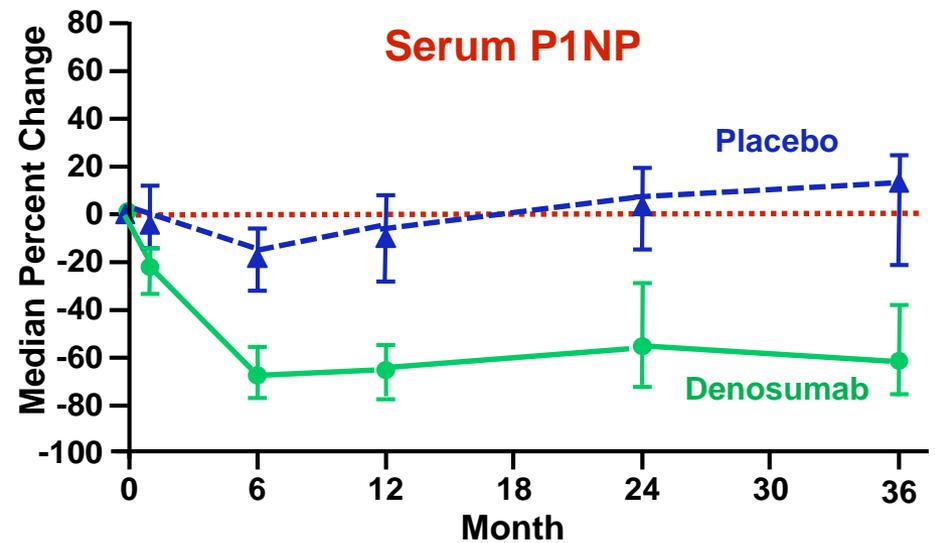
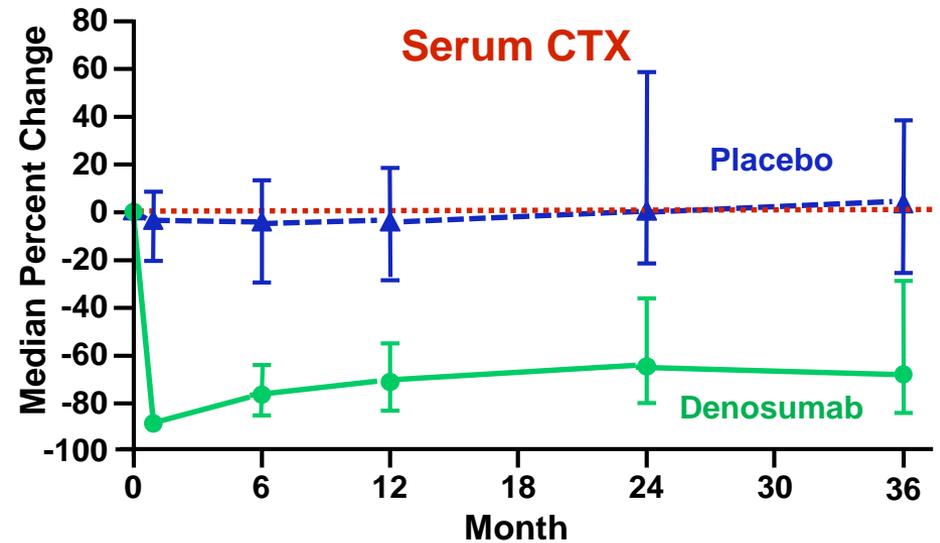
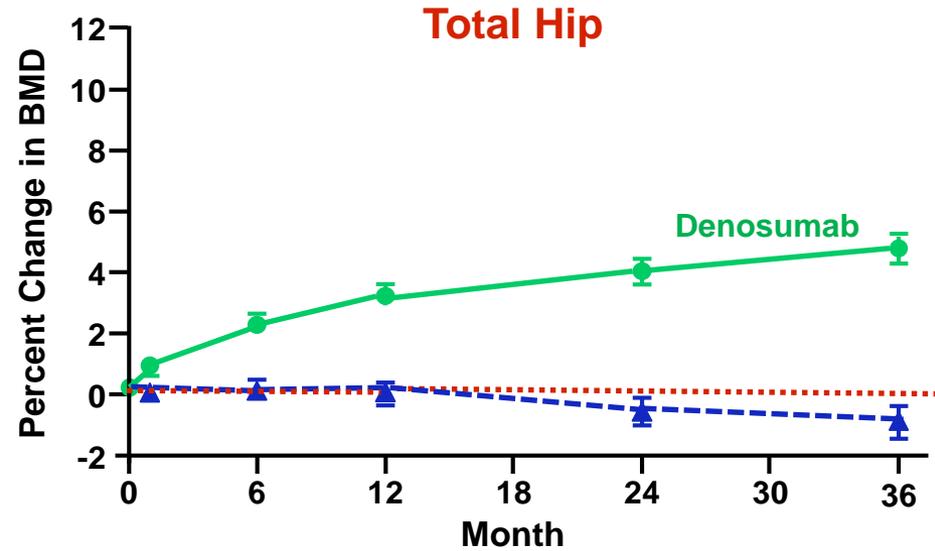
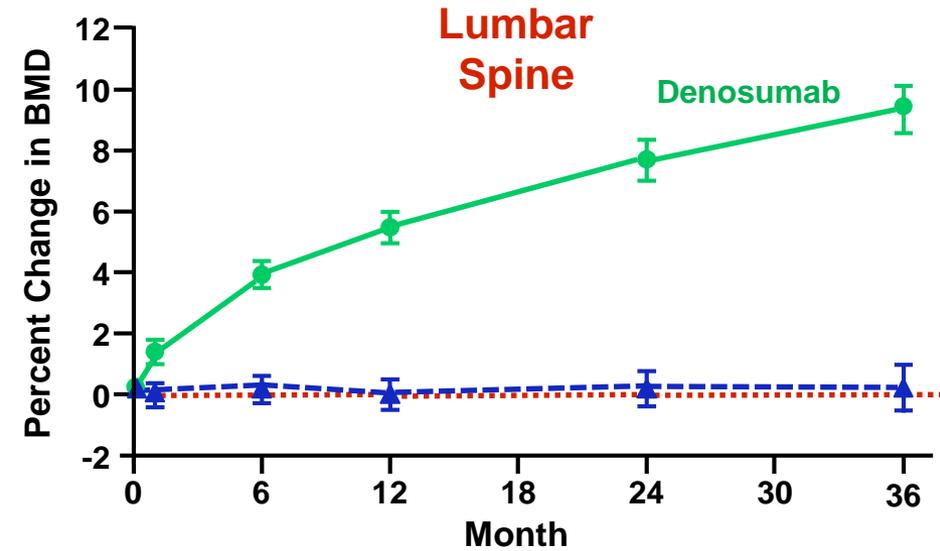
Pitfalls with bisphosphonates

- good for BMD but perhaps not for strength
- possibility of long-term bone toxicity
- nephrotoxicity
- low bioavailability
- unlicensed use

Bisphosphonates in the CKD patient

- Alendronate
 - creatinine cutoffs >130 μM (>1.5 mg/dl) and >144 μM (>1.6 mg/dl)
 - safe and effective in CKD 1-3 up to 4 yrs
 - limited data for CKD 4
- Risedronate
 - pooled data from nine randomized controlled trials. 45% in this analysis had CrCl between 30 and 50 ml/min and 7% had CrCl <30 ml/min
 - safe and effective in CKD 1-3 up to 3 yrs
- Ibandronate
 - limited data in CKD
- Zoledronate
 - Cr Cl cutoff <30 ml/min
 - effective in CKD 1-3. No data for CKD 4

Bone Mineral Density and Bone Turnover Markers RANKL Inhibition with Denosumab



Effects of Denosumab on Fracture and Bone Density by Level of Kidney Function

Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) Study

- Subgroup interaction term to determine if there were differences in treatment effect by eGFR (stage 1-4)
- Fracture risk reduction and changes in BMD at all sites
- Treatment efficacy did not differ by level of kidney function
- A similar picture exists with bisphosphonates

Differences between postmenopausal osteoporosis and CKD-MBD

CKD-MBD

High prevalence of adynamic bone or very high bone turnover

Abnormal calcium, phosphate, FGF23, BMP7, Klotho, 1,25-D, iron, bicarbonate, sclerostin, and cytokines

Bone density weakly related to fractures

Bone loss mostly cortical

Vascular calcification common

Ordinary Osteoporosis

Bone formation normal to slightly high

Normal or mildly abnormal

Bone density predicts fractures

Bone loss trabecular and cortical

Vascular calcification rare

What should we do now.....

- Is this CKD-MBD, osteoporosis, or both?
- Many osteoporosis drugs are different in the CKD pt.
- **First** identify and manage the CKD-MBD issues first
 - PTH – active vitamin D sterol/calcimimetic
 - Hyperphosphataemia – dietary restriction/phosphate binder
 - Vitamin D deficiency - cholecalciferol
- **Then** consider the osteoporosis
 - CKD stage 1-3; generally treat as with 'normals'.
 - CKD stage 4-5; limited applicability of standard therapies
 - CKD stage 5D; usually no role for standard therapies

Looking Ahead....

Sclerostin

Sclerostin is an endogenous soluble product of the SOST gene predominately expressed by osteocytes.

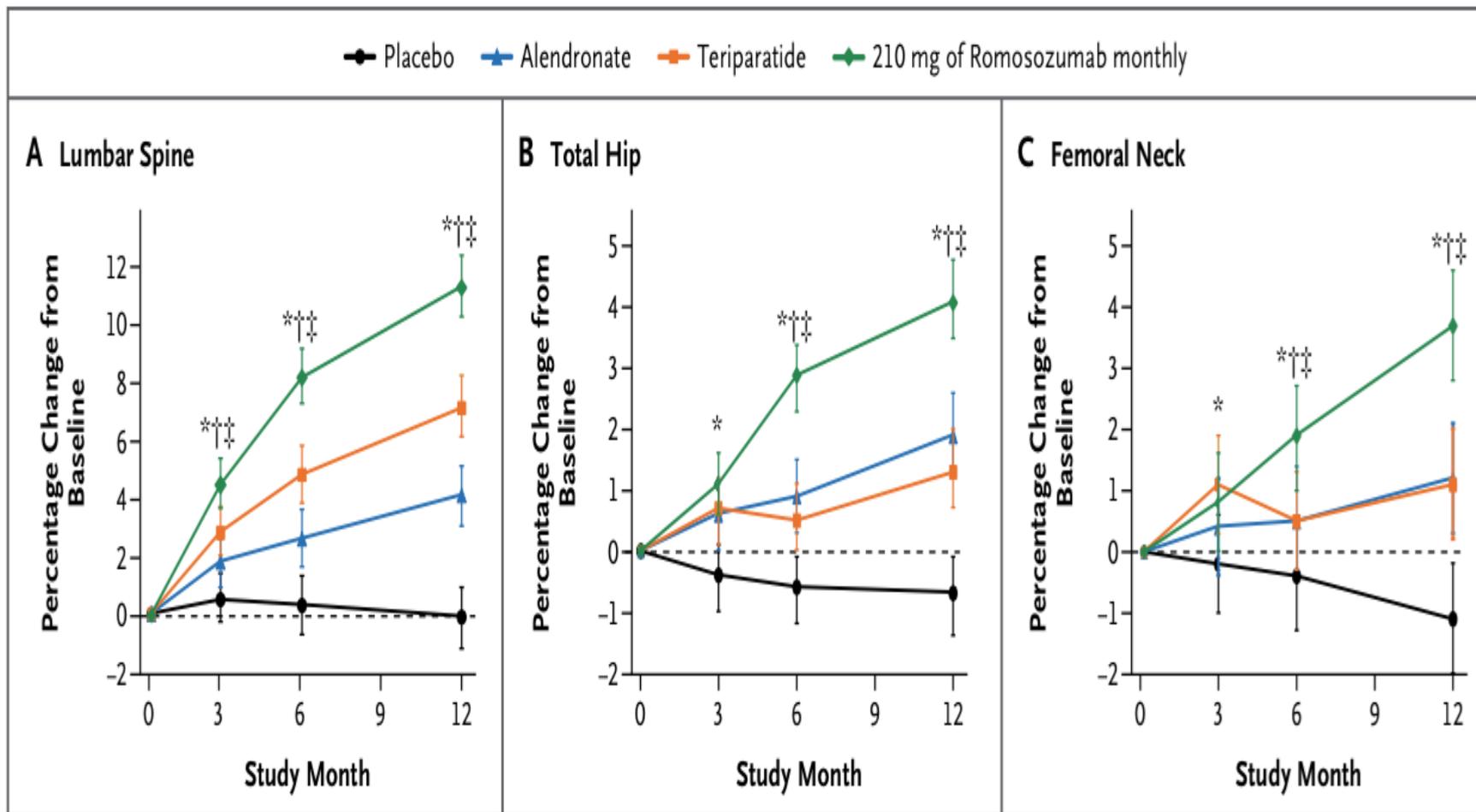
Sclerostin inhibits Wnt signaling and reduces osteoblastic bone formation

Elevated sclerostin in patients with CKD may be associated with better survival

Sclerostin

- animal models of low bone turnover CKD show that Scl-Ab improves trabecular bone volume and mineralization without affecting biochemical indices
- Modulation of sclerostin levels in CKD patients may have beneficial skeletal and vascular effects
- Antibodies to sclerostin (romosozumab) increase bone formation, decrease resorption and increase bone mass in women without CKD
- No published studies with romosozumab or blosozumab have yet been powered to evaluate fracture prevention efficacy

Romosozumab humanized anti-sclerostin monoclonal antibody active in osteoporosis



odanacatib

- is a cathepsin K inhibitor investigated for the treatment of postmenopausal osteoporosis
- A phase 3 study was terminated early because of a strongly positive signal on fracture reduction

‘Renal - Osteoporosis Interface’

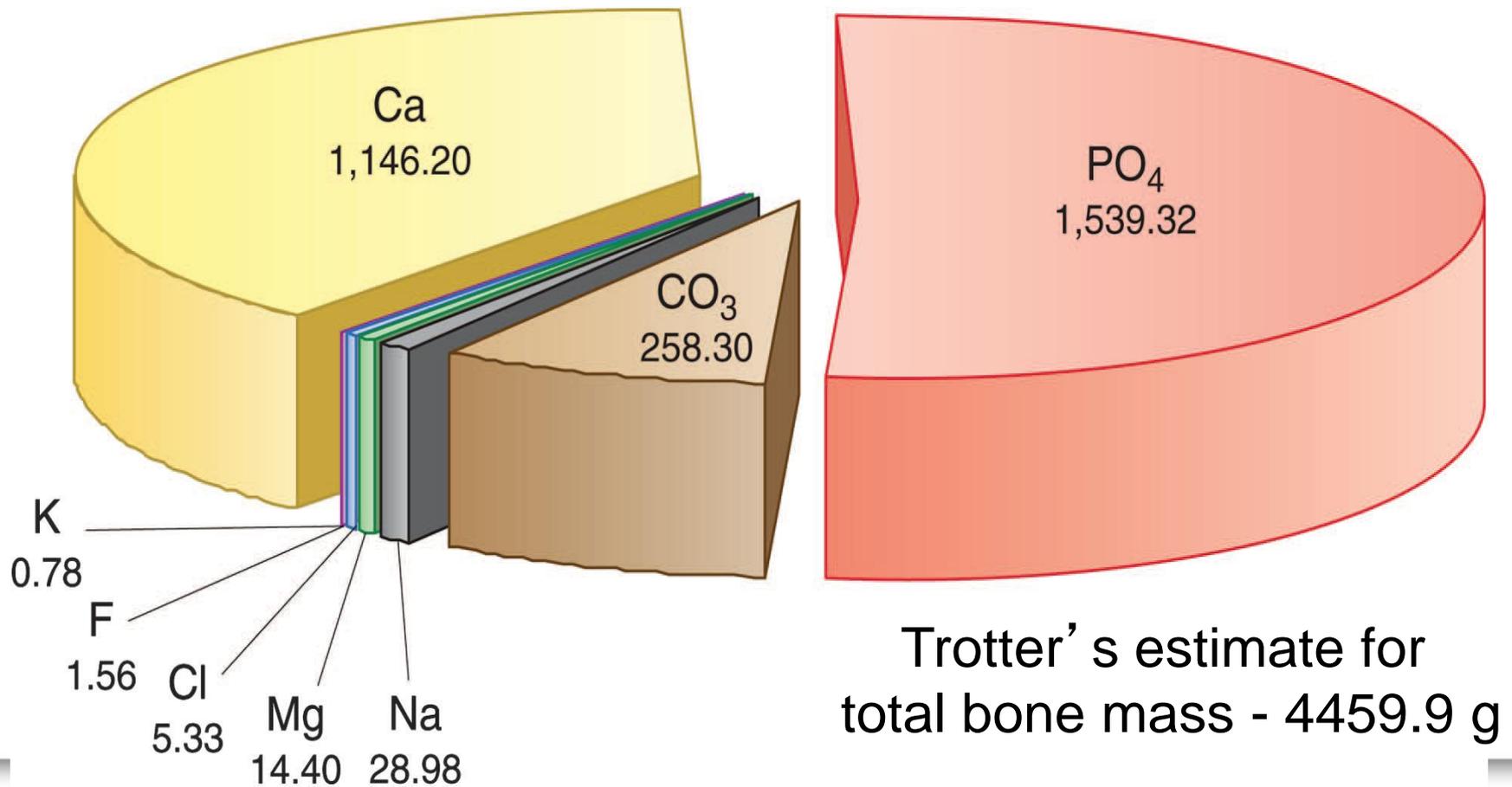
bone doctors and rheumatologists mess up renal patients

and

nephrologists mess up bone patients

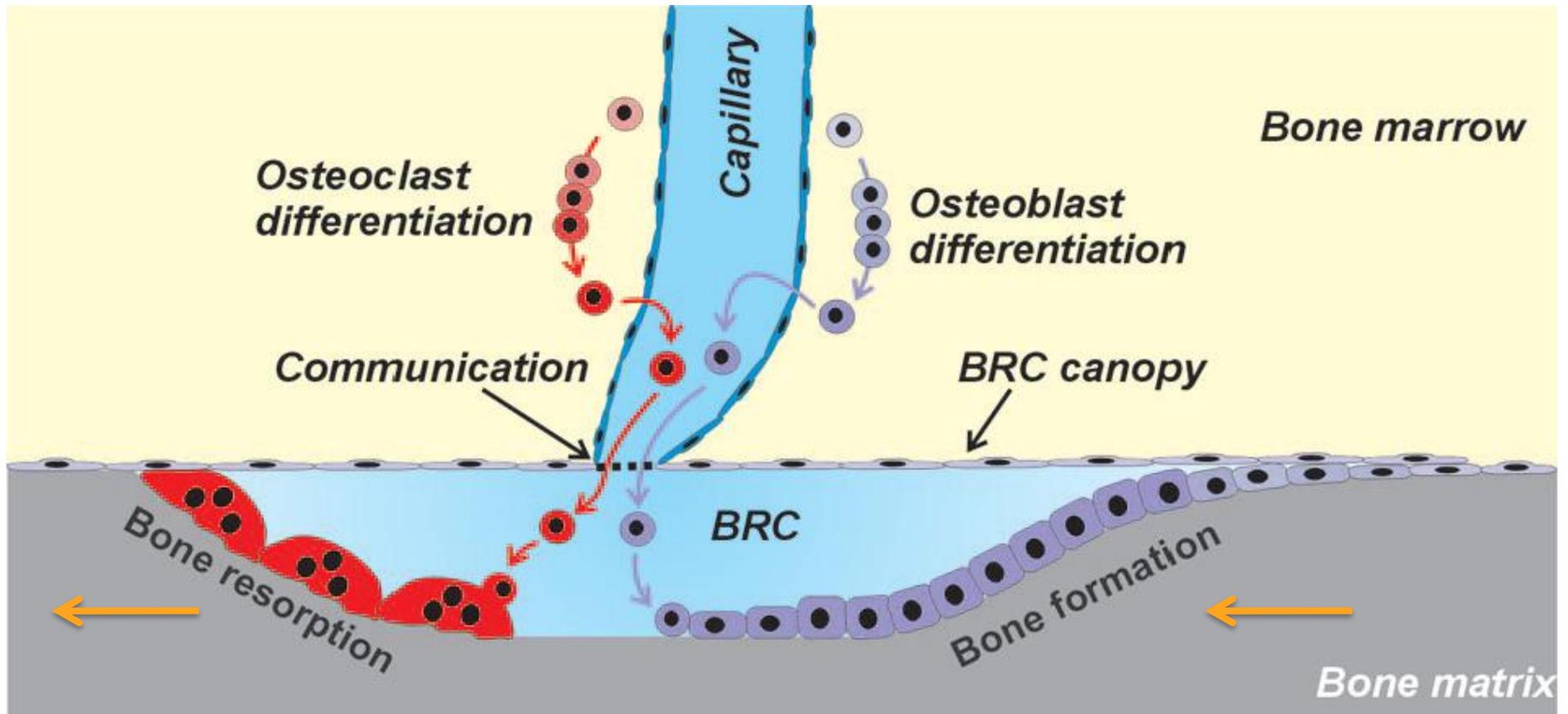
Bone composition in normal individuals (g)

mean values from 109 human bone specimens



Pellegrino ED, Biltz RM Medicine (Baltimore) 1965

Bone remodelling compartment - BRC

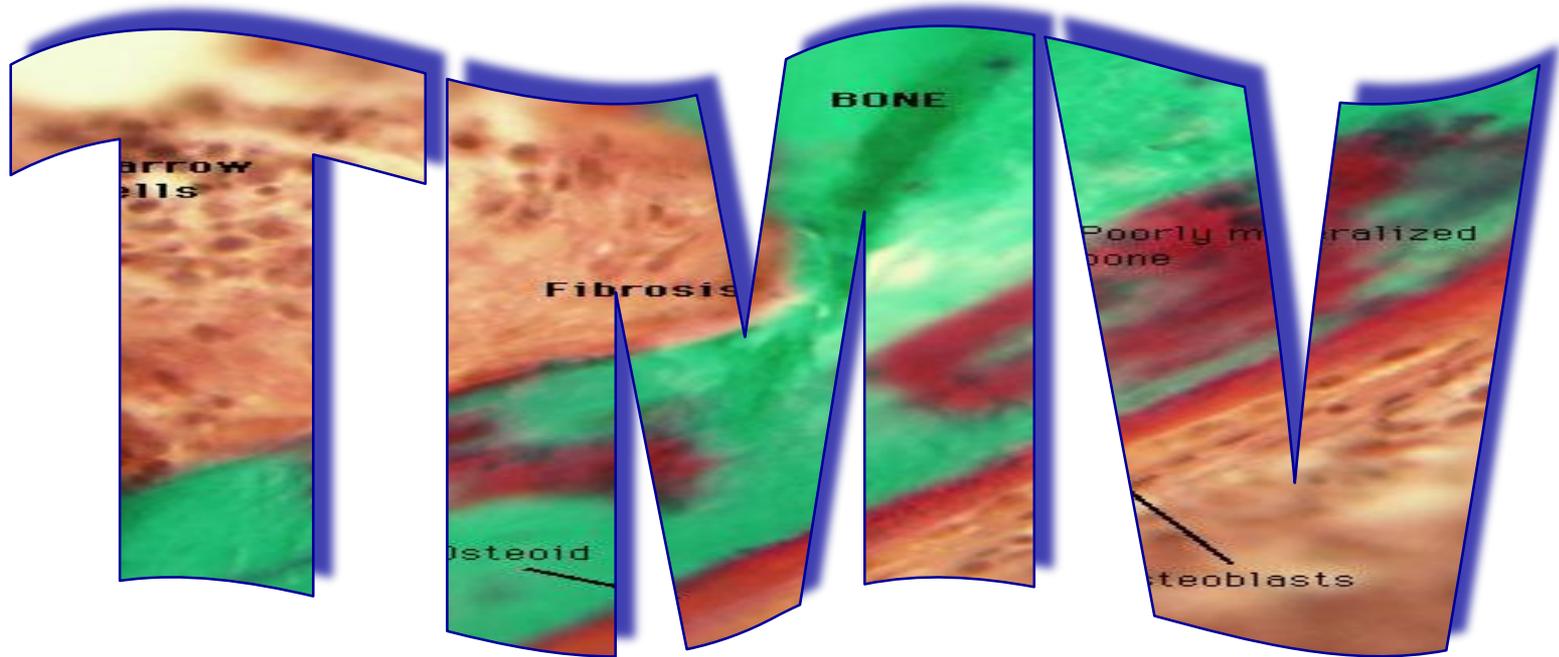


Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)

S Moe¹, T Drüeke², J Cunningham³, W Goodman⁴, K Martin⁵, K Olgaard⁶, S Ott⁷, S Sprague⁸, N Lameire⁹ and G Eknoyan¹⁰

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Renal Osteodystrophy (Histology) Classification



Turnover

High
Normal
Low

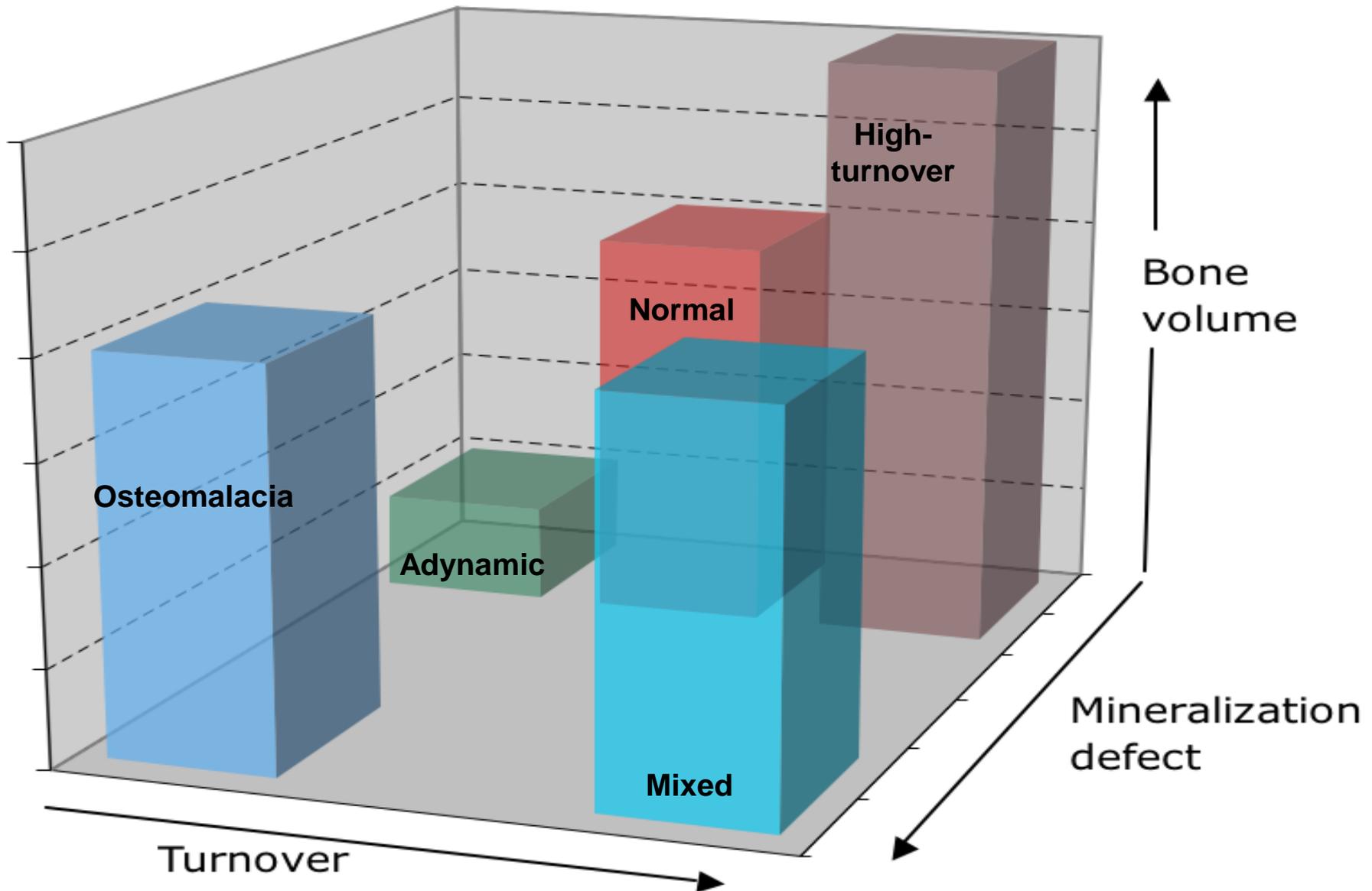
Mineralisation

Normal
Defective

Volume

High
Normal
Low

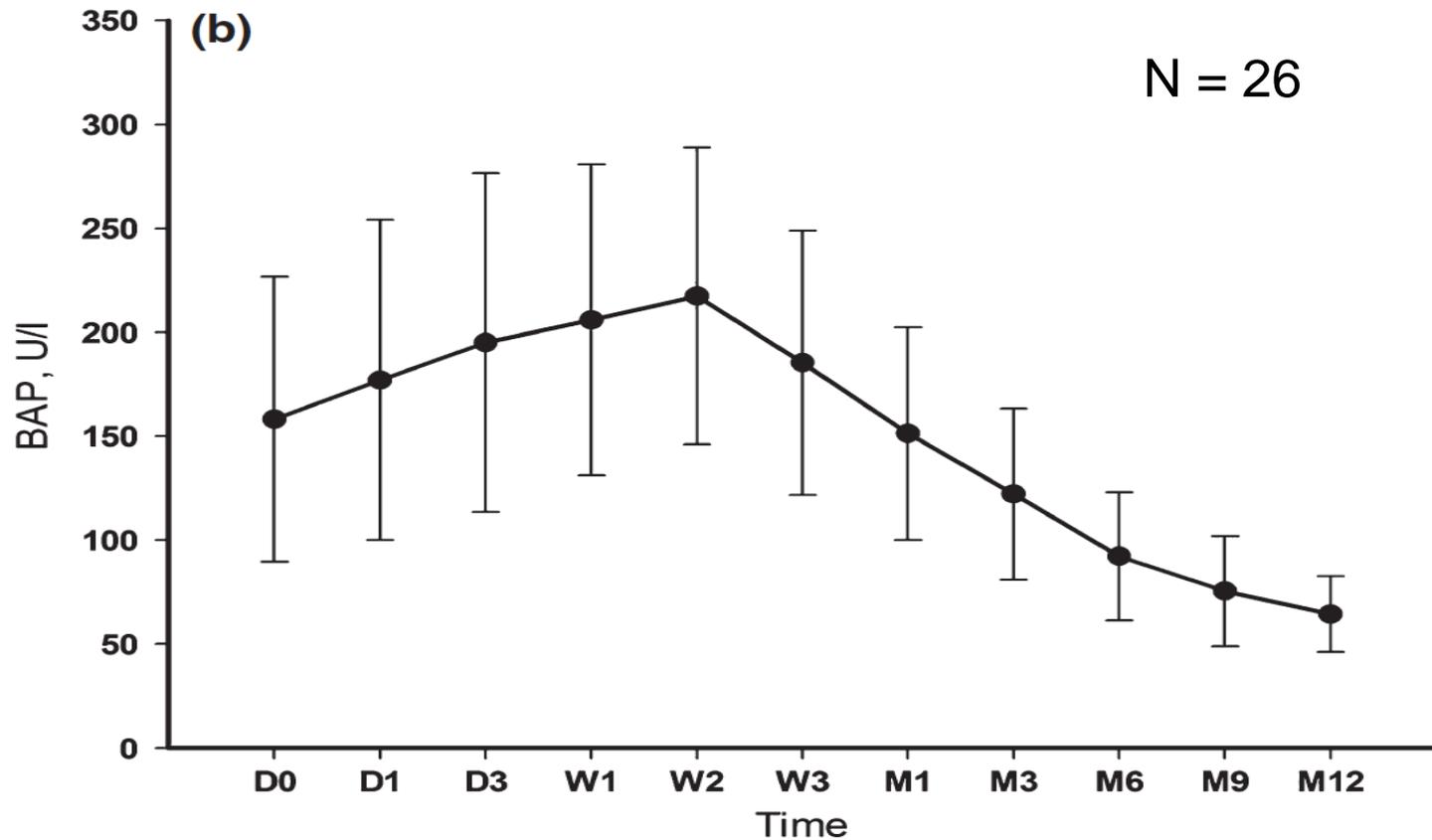
Evaluation of ROD: the TMV system



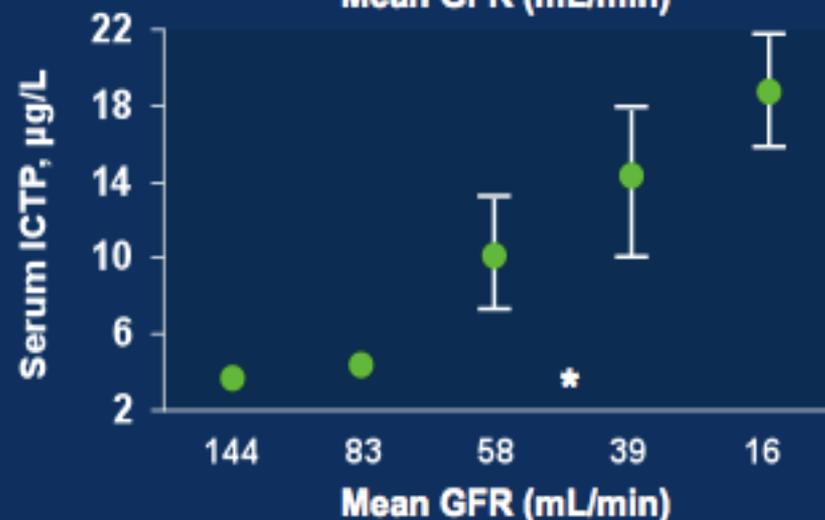
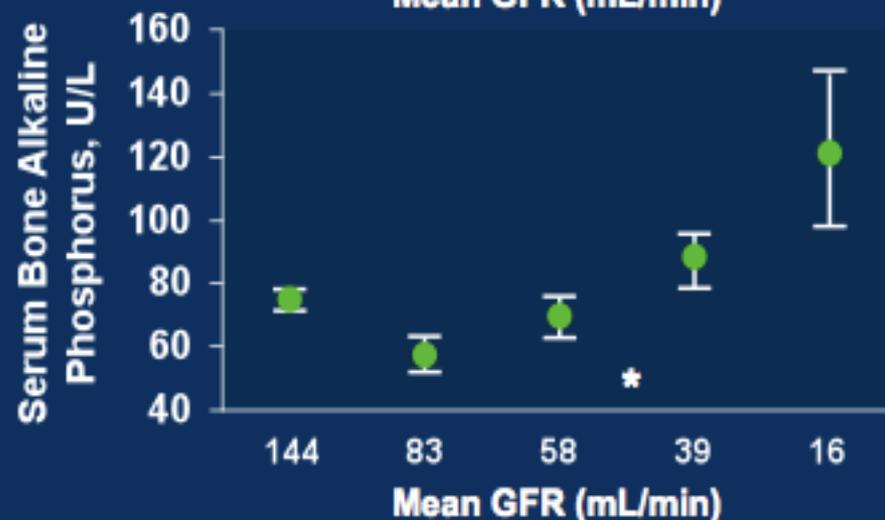
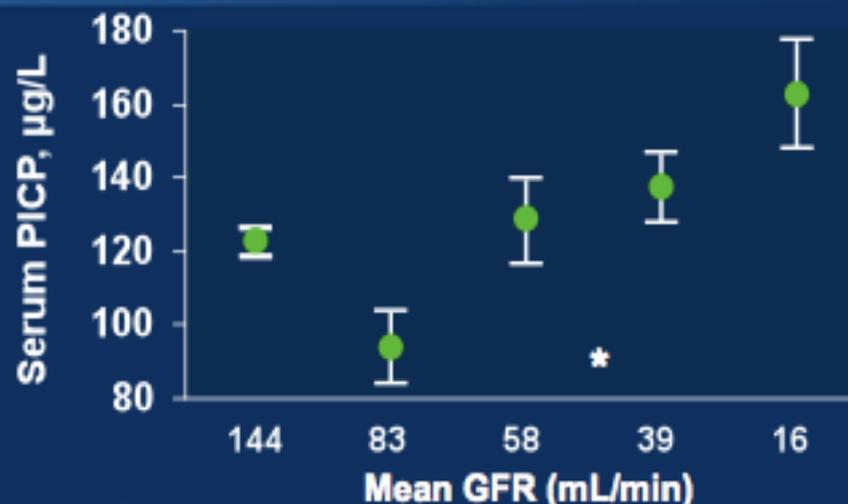
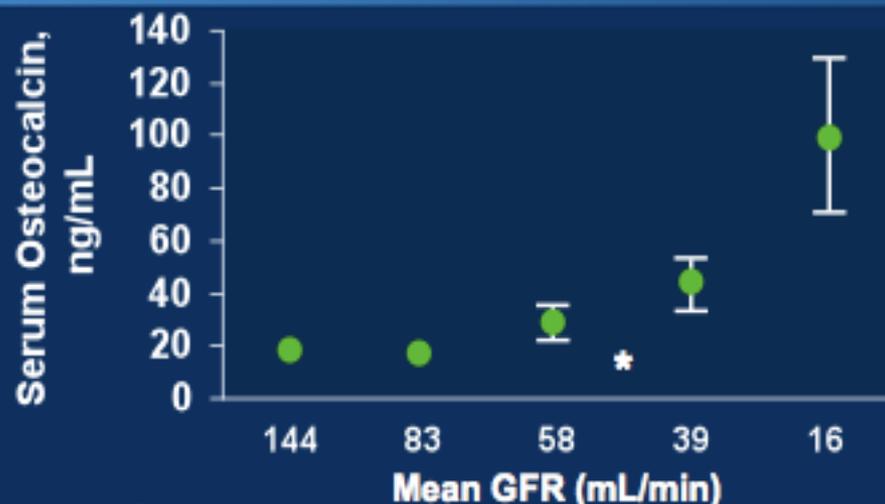
Biochemical Markers of Bone

- An attempt to diagnose specific bone pathologies without recourse to a biopsy
- A tool for monitoring the progression of a disease and/or its response to treatment

Bone turnover markers after PTX



Biochemical Markers of Bone Turnover in Patients With Predialysis Chronic Kidney Disease



* $P < 0.05$, Kruskal-Wallis

ICTP = serum carboxy-terminal telopeptide of type I collagen.
PICP = serum carboxy-terminal propeptide of type I collagen.
Adapted from Rix M, et al. *Kidney Int.* 1999;56:1084-1093.

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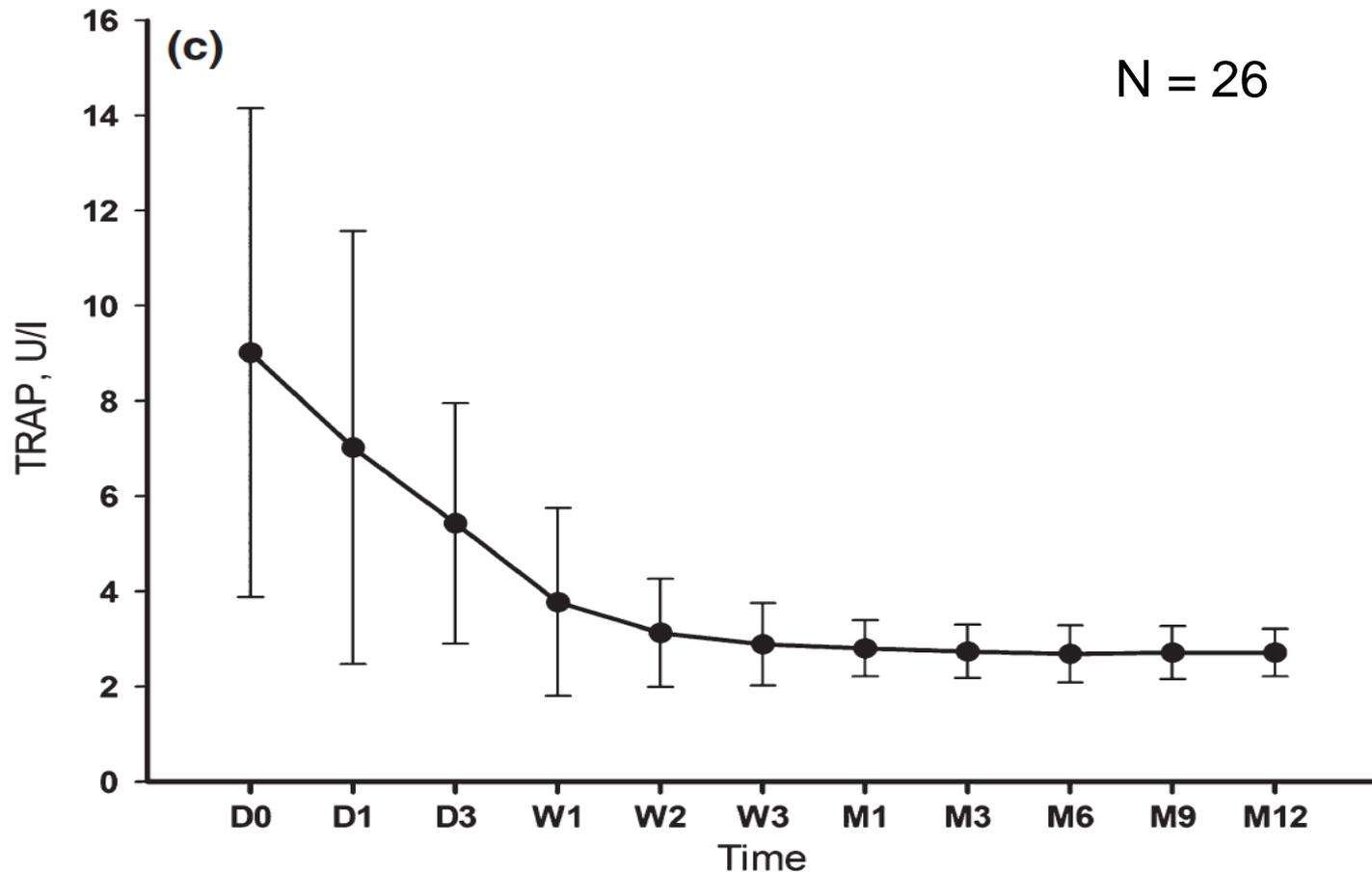
N = 113 CKD

N = 89 control (mean GFR 144 mL/min)

Please note suppressed zeros used in this graph

Bone turnover markers after PTX

predict changes in bone mineral density



Bone histology in CKD

traditional view

- High turnover lesions:
 - hyperparathyroid bone disease
- Low turnover lesions:
 - osteomalacia
 - adynamic (AI -ve)
 - adynamic (AI +ve)
- Mixed uraemic osteodystrophy

Manufacturer's Recommendations for Osteoporosis Therapies in Renal Impairment

Osteoporosis therapy	Cr (uM)	CrCL (mL/min)
Alendronate		>35
Risedronate		>30
Zoledronic acid		>35
Ibandronate		>50
Raloxifene		no dose adjustment
Strontium ranelate		>30
Denosumab		>30
Teriparatide	<177	
Calcitonin		"mild" dose adjustment

