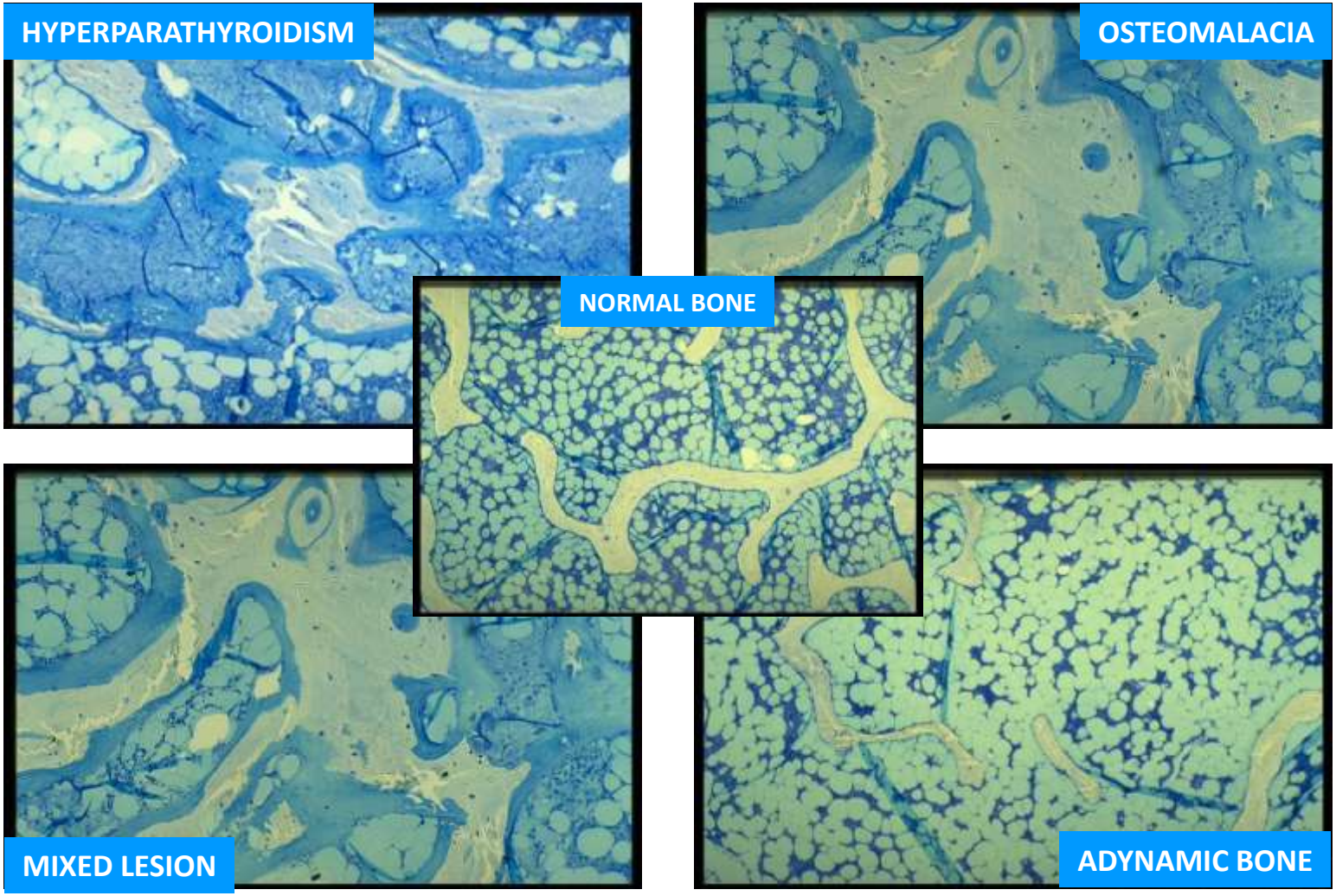
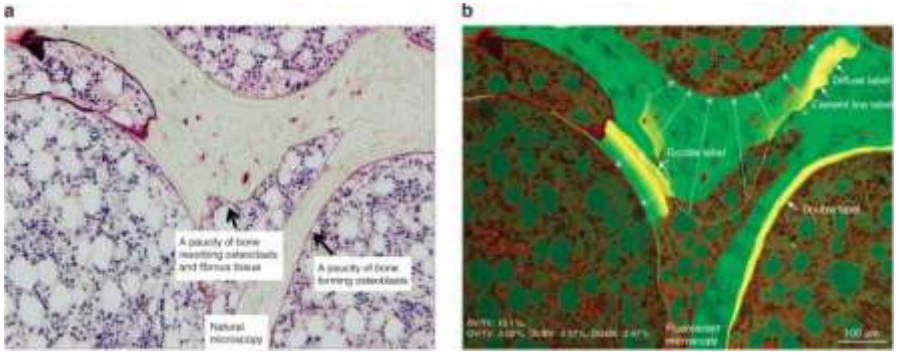
Farmaci “vecchi e nuovi” disponibili per il controllo della malattia metabolica dell’osso

Dott. G Cianciolo , Dott.ssa V Aiello

Histology of Renal Osteodystrophy

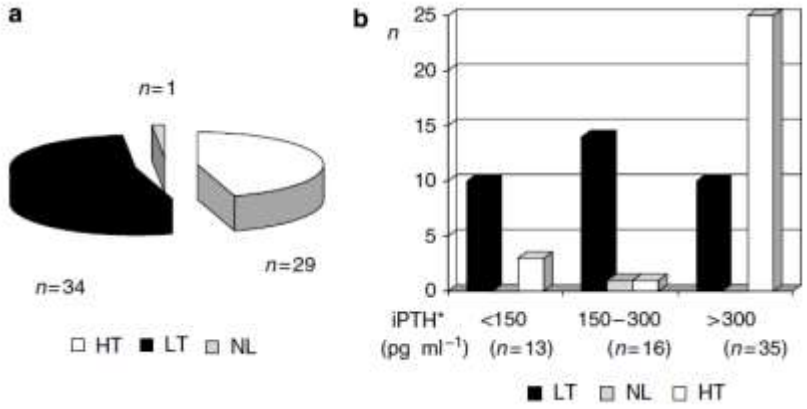


Bone Biopsy in Adynamic Bone disease



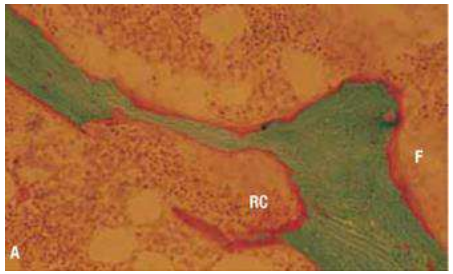
K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients

FC Barreto[1], DV Barreto[1], RMA Moysés[2], KR Neves[2], MEF Canziani[1], SA Draibe[1], V Jorgetti[2] and AB Carvalho[1]

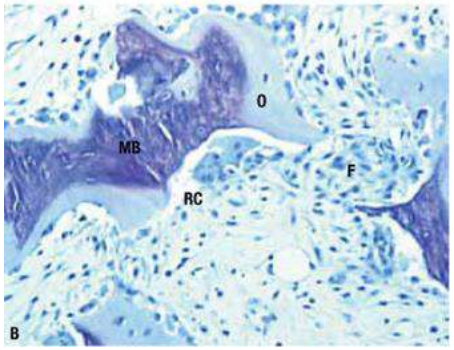


Kidney International 2008

Bone Biopsy in patient with CKD

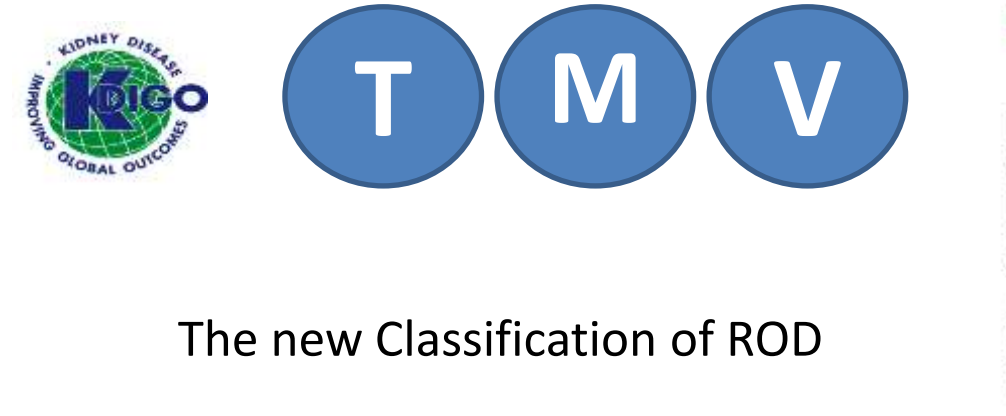


A) Biopsy from a patient with secondary hyperparatiroidism demonstrating a large resorption cavity and peritrabecular fibrosis



B) Mixed uremic disease with an increased number and extent of osteoid seams (osteomalacia), resorption cavities and fibrosis (hyperparatiroidism

T M V


http://www.kidney-international.org review
© 2006 International Society of Nephrology

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

S Moe[1], T Drüeke[2], J Cunningham[3], W Goodman[4], K Martin[5], K Olgaard[6], S Ott[7], S Sprague[8], N Lameire[9] and G Eknoyan[10]

[1]Indiana University School of Medicine and Roudebush VAMC, Indianapolis, Indiana, USA; [2]Inserm Unit 507 and Division of Nephrology, Hôpital Necker, Université René Descartes, Paris, France; [3]The Royal Free Hospital and University College London, London, UK; [4]Division of Nephrology, UCLA Medical Center, Los Angeles, California, USA; [5]Division of Nephrology, St Louis University, St Louis, Missouri, USA; [6]Department of Nephrology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [7]University of Washington Medical Center, Seattle, Washington, USA; [8]Evanston Northwestern Healthcare, Feinberg School of Medicine, Northwestern University, Evanston, Illinois, USA; [9]Ghent University Hospital, Ghent, Belgium and [10]Baylor College of Medicine, Houston, Texas, USA

The new Classification of ROD

Bone Strength = **Bone Density** + **Bone Quality**

Bone Density → **BMD**

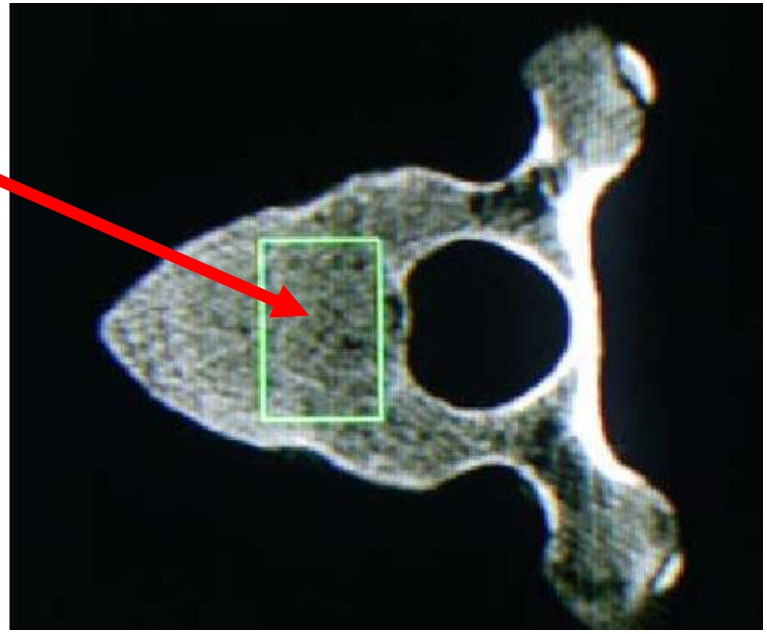
Bone Quality → **Turn over**
Mineralization
Architetture (T and C Volume)
Material properties

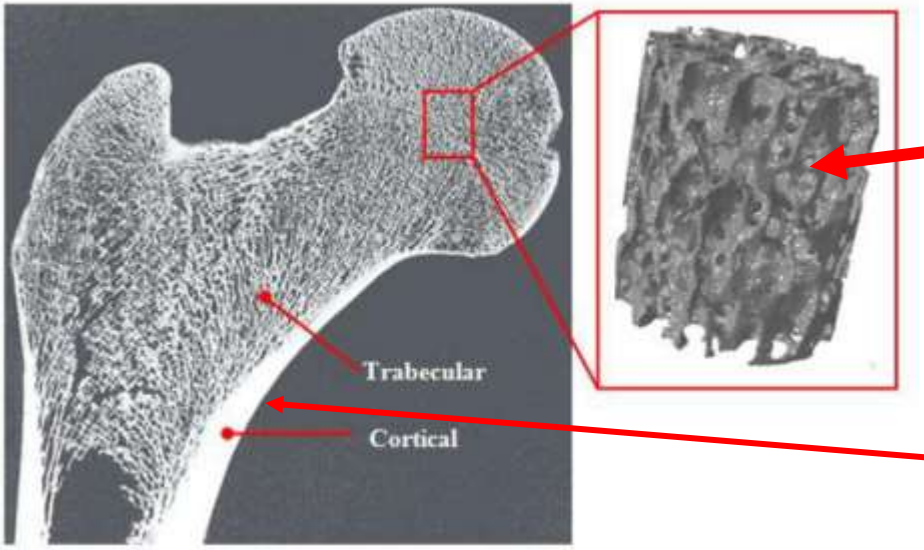
Turnover	Mineralization	Volume
Low bone turnover	Abnormal mineralization	Low bone volume
Normal bone turnover	Normal mineralization	Normal bone volume
Normal bone turnover		High bone volume

Effect of PTH on cortical and trabecular bone

Anabolic effect

Catabolic effect

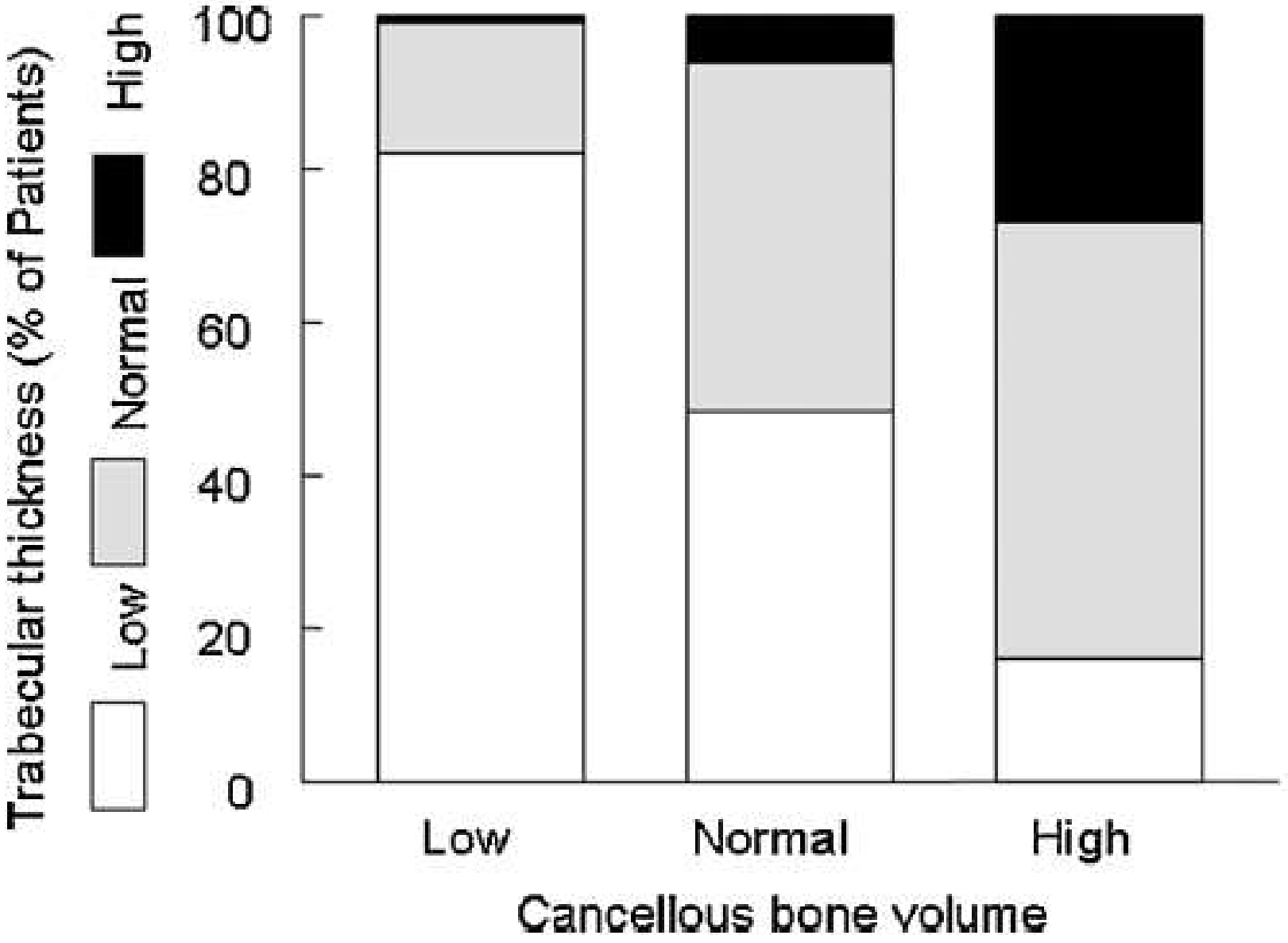




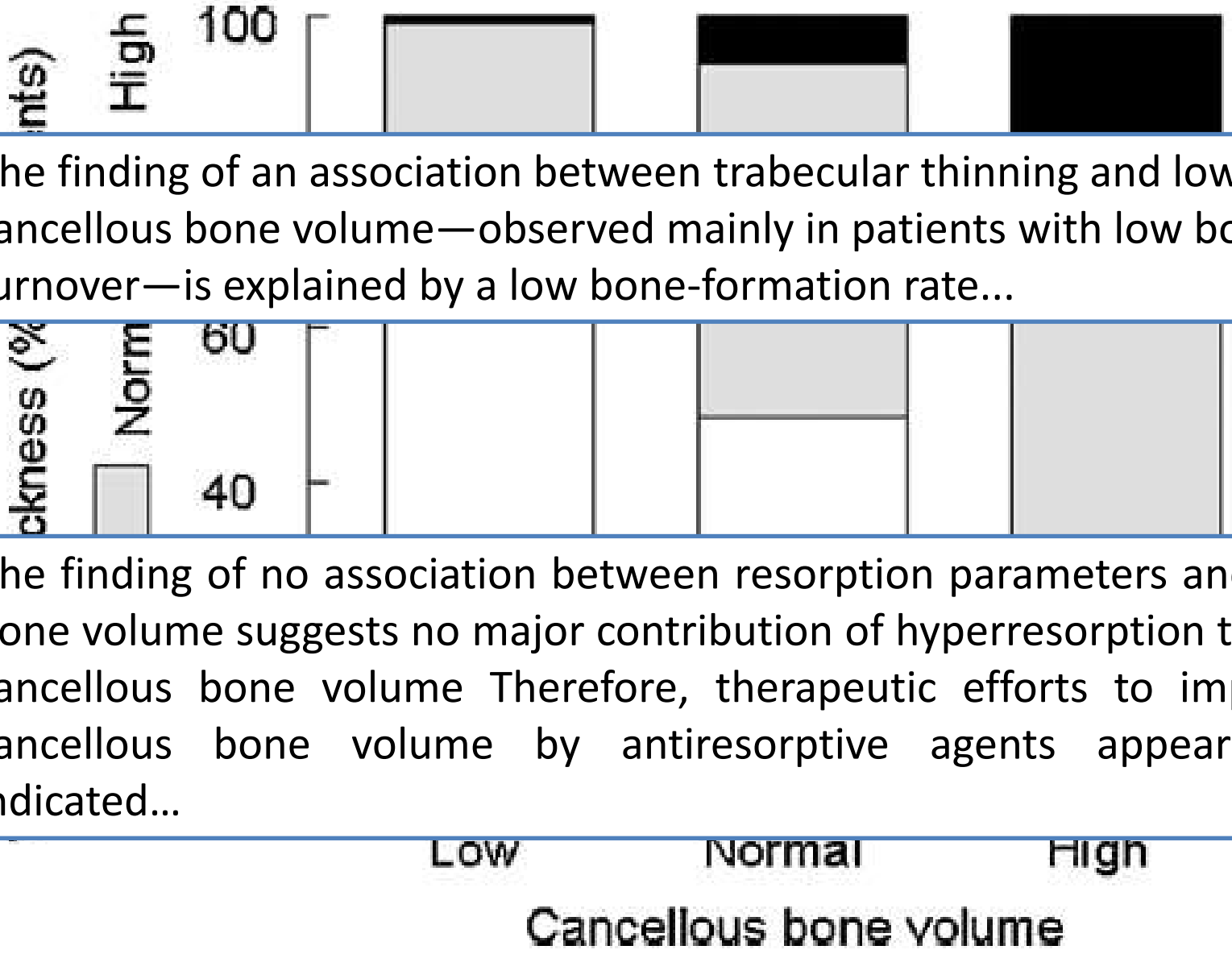
Anabolic effect

PTH

Catabolic effect



Malluche et al., JBMR 2011

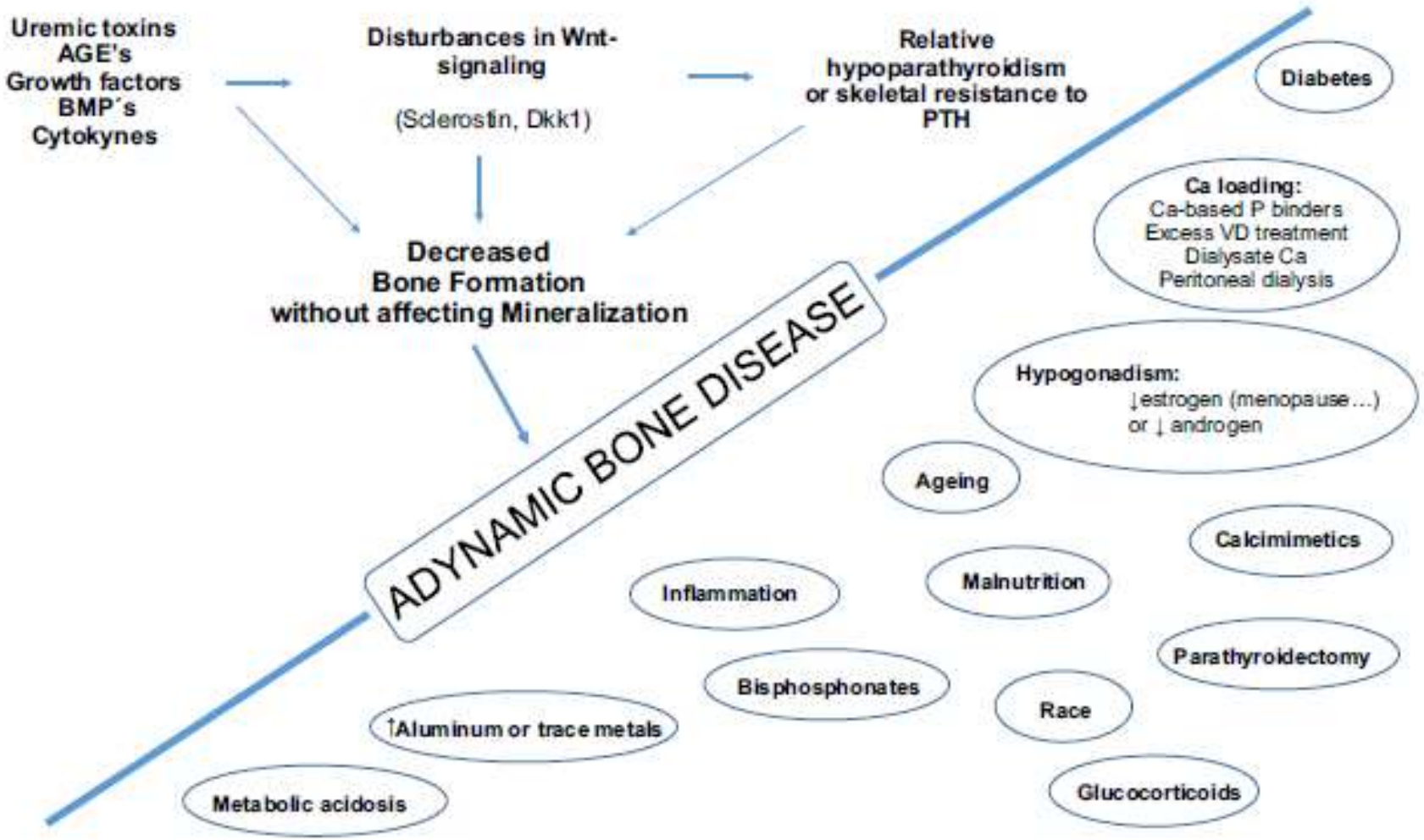


...The finding of an association between trabecular thinning and low cancellous bone volume—observed mainly in patients with low bone turnover—is explained by a low bone-formation rate...

...The finding of no association between resorption parameters and low bone volume suggests no major contribution of hyperresorption to low cancellous bone volume Therefore, therapeutic efforts to improve cancellous bone volume by antiresorptive agents appear not indicated…

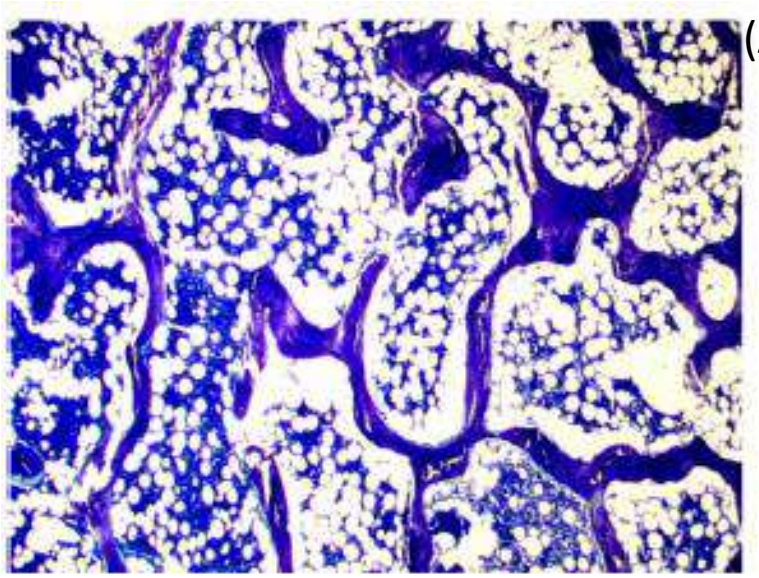
Malluche et al., JBMR 2011

Adynamic Bone Disease: From Bone to Vessels in Chronic Kidney Disease

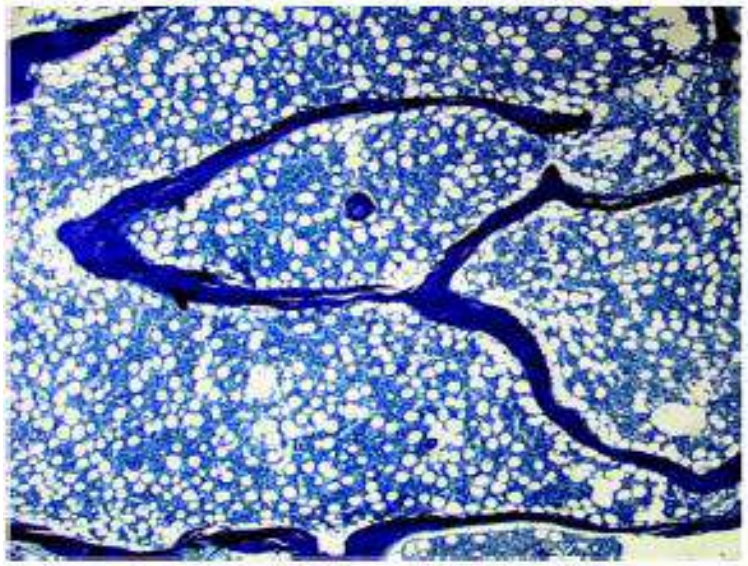


Bover et al Seminars in Nephrology 2014

Adynamic Bone Disease: From Bone to Vessels in Chronic Kidney Disease



(**A**) Normal bone histology is made of a connected trabecular network.



(**B**) ABD is characterized by low or normal bone volume and the trabecular network might be diminished and trabeculae are thin. In addition, the number of osteoblasts and osteoclasts are diminished markedly and marrow fibrosis is mini mal or absent. Normal mineralization is represented by an absence of osteoid accumulation.

Bover et al Seminars in Nephrology 2014

Role of PTH on bone fractures

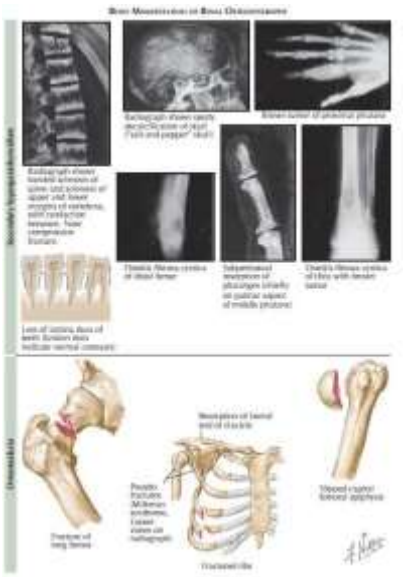
PTH

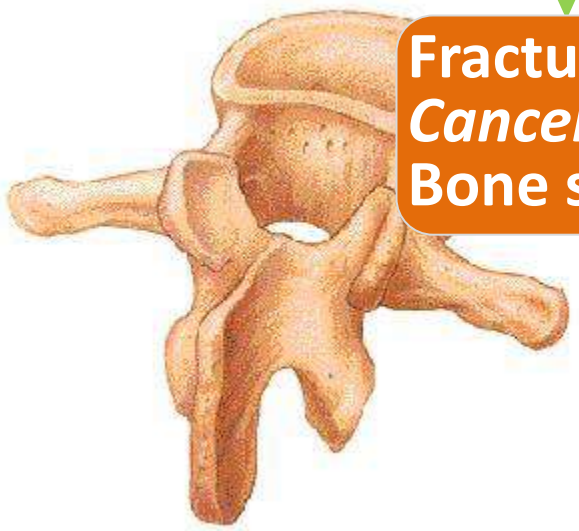
Low PTH

-Adinamic Bone Disease
-Osteomalacia

High PTH

-Osteitis fibrosa cystica
-Mixed Uremic Osteodystrophy

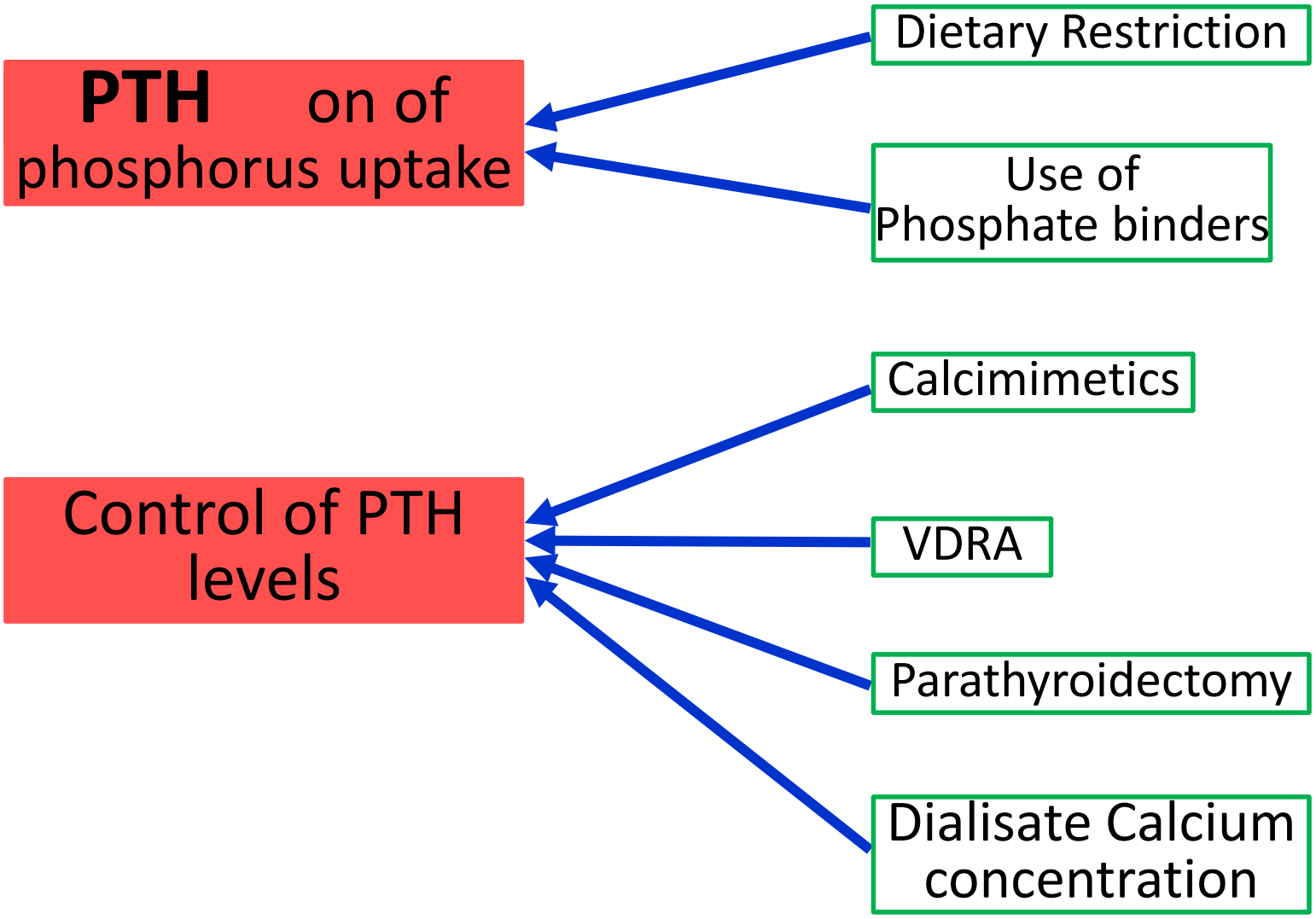




Fracture on *Cancellous* Bone side

Fracture on *Cortical* Bone side

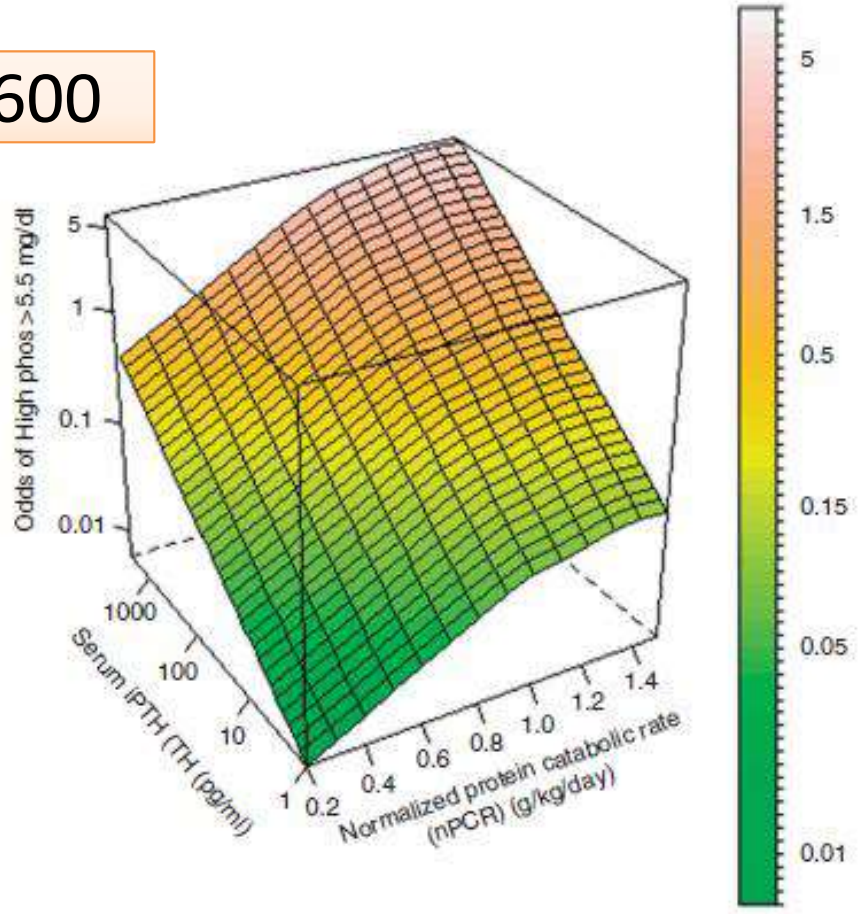
Current treatment of secondary Hyperparathyroidism



Hyperphosphatemia is a combined function of high serum PTH and high dietary protein intake in dialysis patients

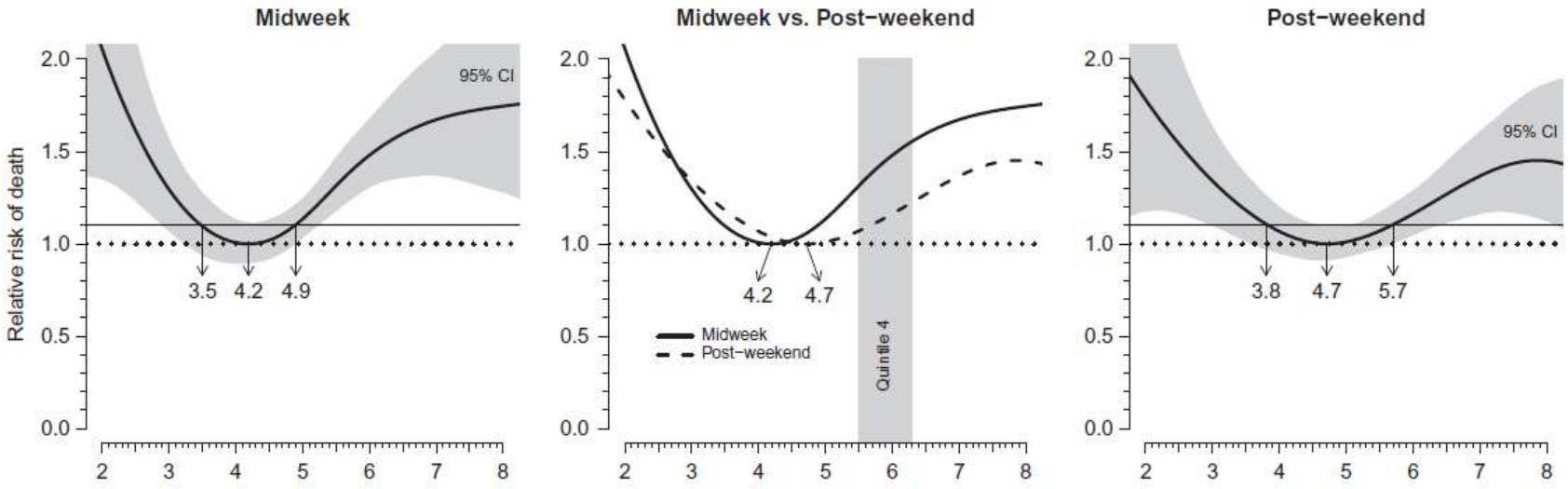
Elani Streja[1,8], Wei Ling Lau[1,8], Leanne Goldstein[1], John J. Sim[2], Miklos Z. Molnar[1], Allen R. Nissenson[3,4], Csaba P. Kovesdy[5,6] and Kamyar Kalantar-Zadeh[1,7]

> 600

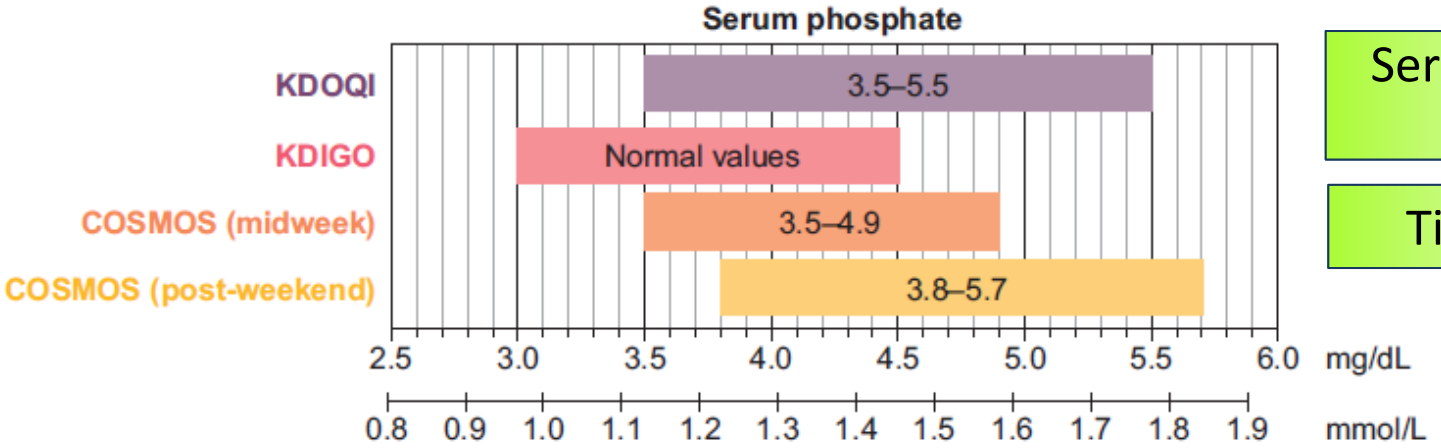


**Relationship between the dependent variable, log odds ratio of serum phosphorus >5.5 mg/dl and independent variables, serum intact parathyroid hormone (iPTH), and normalized protein catabolic rate (nPCR)

Association with all cause mortality and serum phosphate in midweek and post weekend patients



Comparison of KDOQI and KDIGO recommended targets and COSMOS lowest mortality ranges (midweek and post weekend)



Serum Phosphorus Targets ?

Timing to dose?

COSMOS Study, NDT 2018

KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

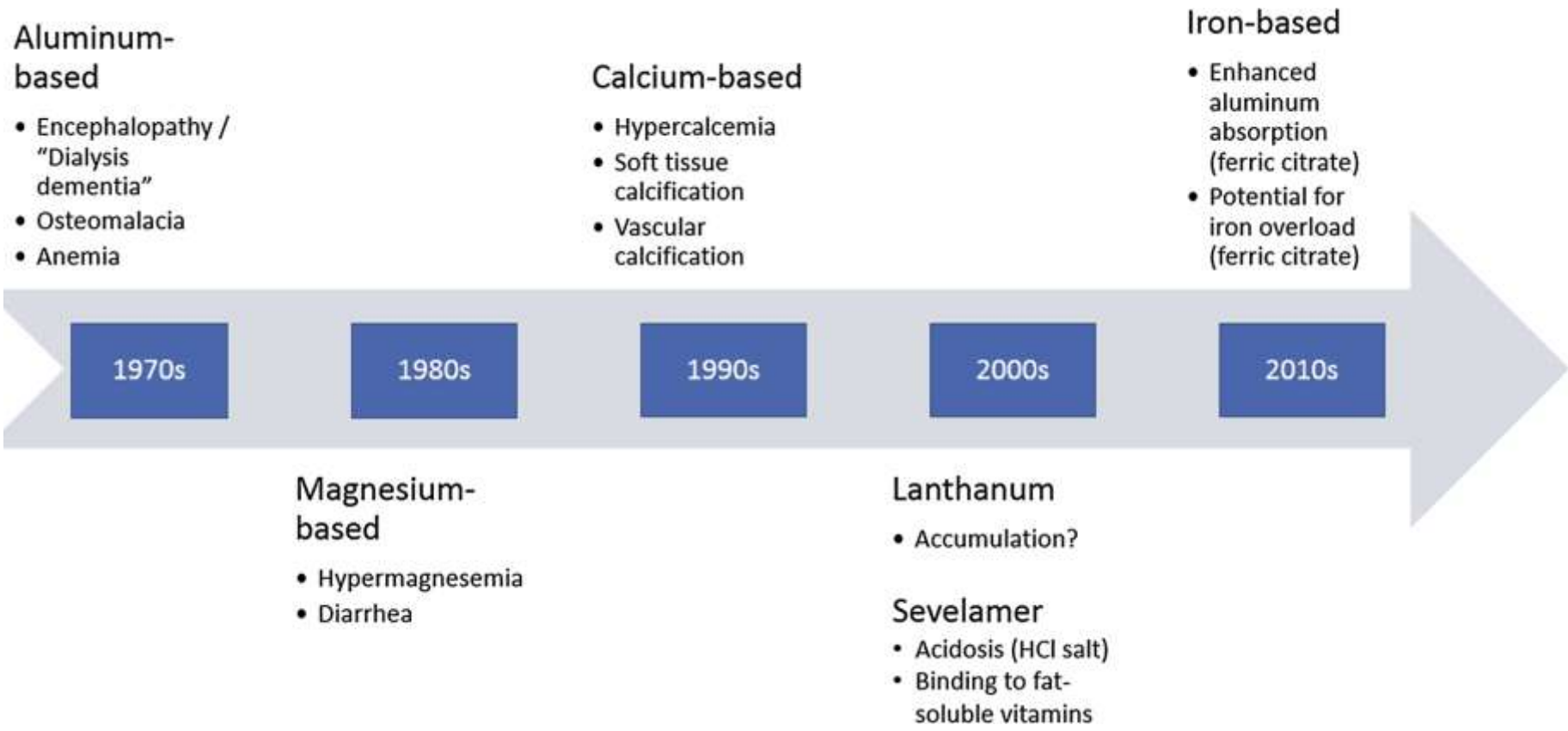
Tamara Isakova, MD, MMSc,[1] Thomas L. Nickolas, MD, MS,[2] Michelle Denburg, MD, MSCE,[3,4] Sri Yarlagadda, MD,[5] Daniel E. Weiner, MD, MS,[6] Orlando M. Gutiérrez, MD, MMSc,[7,8] Vinod Bansal, MD,[9] Sylvia E. Rosas, MD,[10] Sagar Nigwekar, MD, MMSc,[11] Jerry Yee, MD,[12] and Holly Kramer, MD, MPH[9,]*

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*).

work group has concern that there may be an unintended consequence of discouraging clinicians from recommending reductions in dietary phosphate intake (in a way that does not impede adequate protein intake) in a patient with gradually increasing serum phosphate levels within the normal range. Such dietary interventions might prevent or delay the onset of secondary hyperparathyroidism, and their reduced use may result in greater incidence of severe secondary hyperparathyroidism later in the course of CKD, which may lead to greater use of expensive PTH-lowering therapies. It is important to emphasize that

Low phosphorus diet?

Phosphate Binders: timeline for entry and principles side effects



Modified from St Peter et al, Drugs 2017

Which phosphate binders???

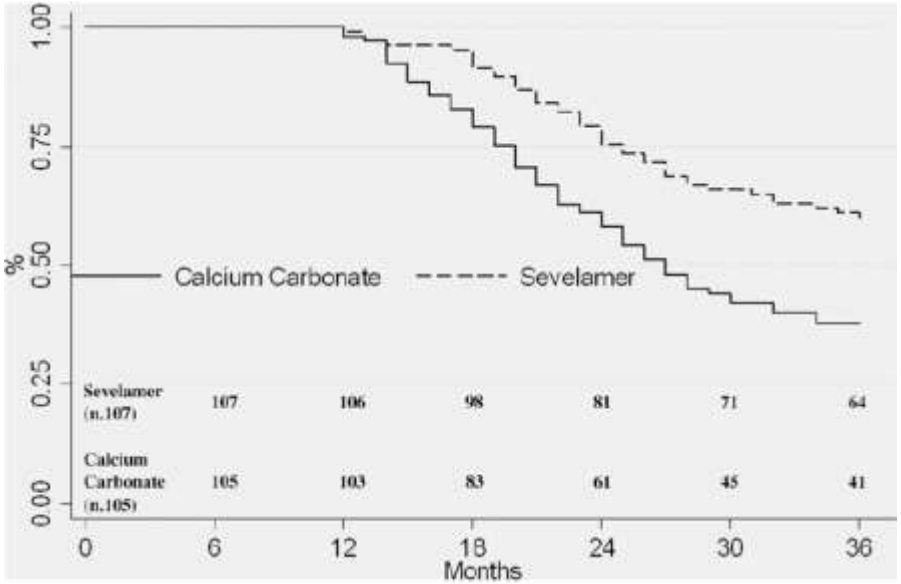
4.1.6: In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders (*2B*). In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (*Not Graded*).

In studies of adults with CKD G5D treated with dialysis, SEVELAMER may lower death (all causes) compared to calcium-based binders and incur less treatment-related hypercalcaemia, while we found no clinically important benefits of any phosphate binder on cardiovascular death, my o cardial infarction, stroke, fracture or coronary artery calcification…

The effects of binders on patient important outcomes compared to placebo are uncertain In patients with CKD G 2 to G 5 the effects of sevelamer, lanthanum and iron based phosphate binders on cardiovascular, vascular calcification, and bone outcomes compared to placebo or usual care, are also uncertain

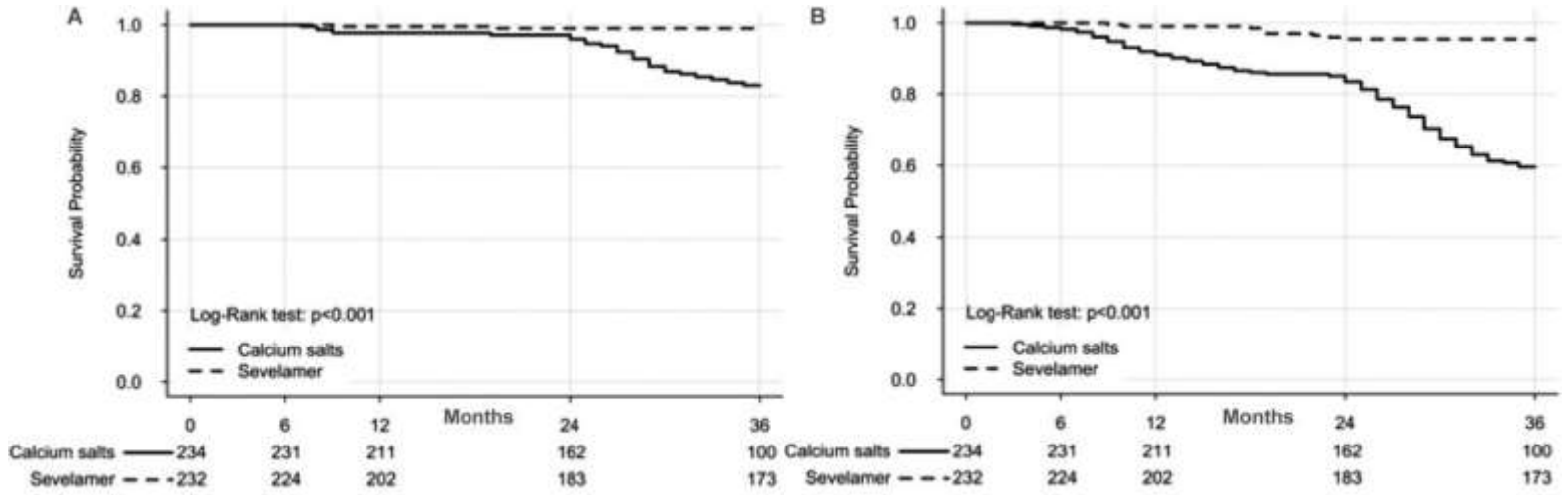
Cochrane Database 2018

Which phosphate binders?



Event-free survival from the composite end point among patients treated either with sevelamer or calcium carbonate

B. Di Iorio et al, CJASN 2012



B. Di Iorio et al, AJKD 2013

Which phosphate binders?

AN UNSOLVED PROBLEM

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

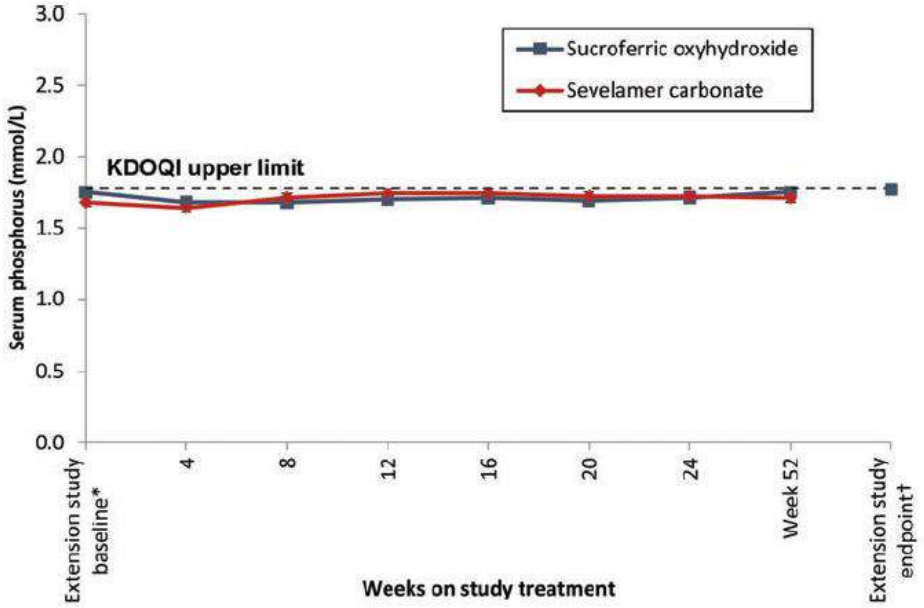
Markus Ketteler[1], Geoffrey A. Block[2], Pieter Evenepoel[3], Masafumi Fukagawa[4], Charles A. Herzog[5], Linda McCann[6], Sharon M. Moe[7,8], Rukshana Shroff[9], Marcello A. Tonelli[10], Nigel D. Toussaint[11], Marc G. Vervloet[12] and Mary B. Leonard[13]

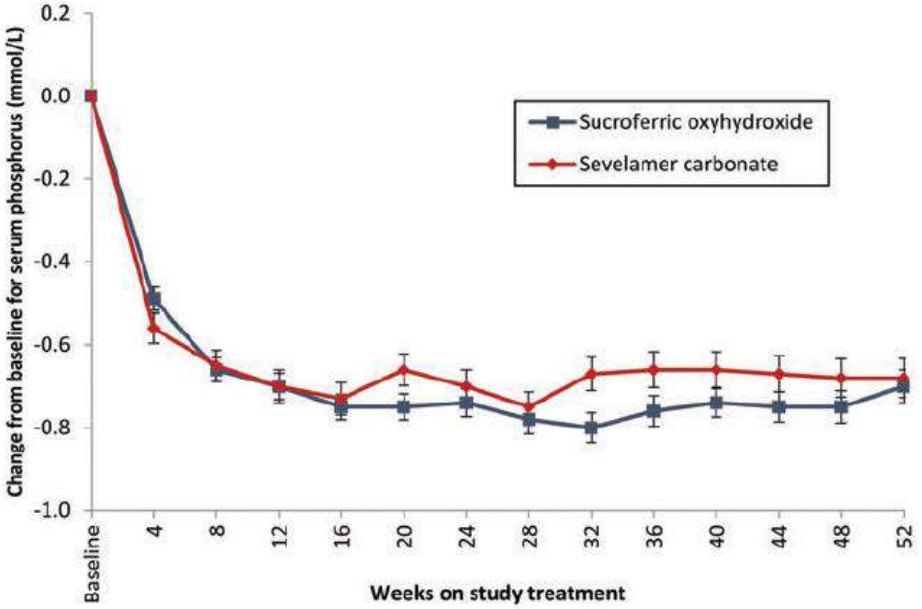
Finally, because KDIGO guidelines are intended for a global audience and calcium Free agents are not available or affordable in all jurisdictions, recommending against the use of calcium based binders would imply that no treatment is preferable to using calcium based agents

Despite the understandable clinical desire to have numeric targets and limits, the Work Group could not make an explicit recommendation about a maximum dose of calcium based binders , preferring to leave this to the judgment of individual physicians while acknowledging the potential existence of a safe upper limit of calcium dose .

Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients

Jürgen Floege[1], Adrian C. Covic[2], Markus Ketteler[3], Johannes F.E. Mann[4], Anjay Rastogi[5], Bruce Spinowitz[6], Edward M.F. Chong[7], Sylvain Gaillard[7], Laura J. Lisk[7] and Stuart M. Sprague[8], on behalf of the Sucroferric Oxyhydroxide Study Group



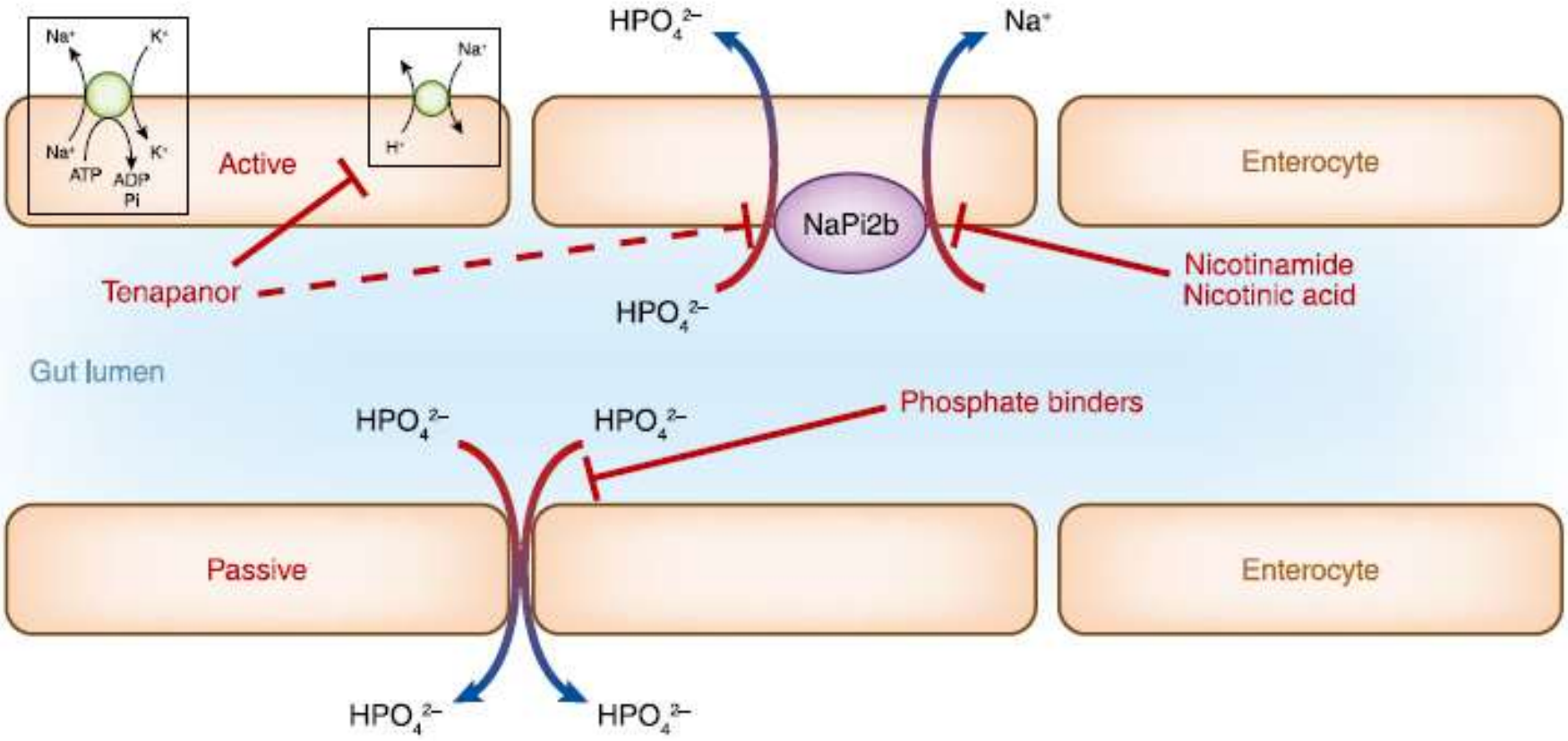


Serum Phosphorus and its change from baseline

SUCROFERRIC OXYHYDROXIDE vs SEVELAMER CARBONATE

Floege et al. NDT 2015

Schematic view of the action of oral inhibitors of active intestinal phosphate absorption compared with the chelation of phosphate in the gut lumen by oral phosphate binders



T. B. Drueke et al, Clin J Am Soc Nephrol 2018

Patient parathyroid hormone (PTH) levels from August 2010 to August 2014

COSMOS: the dialysis scenario of CKD MBD in Europe

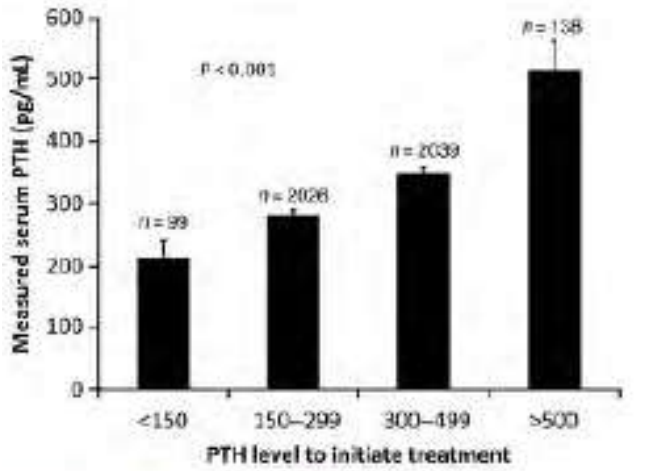
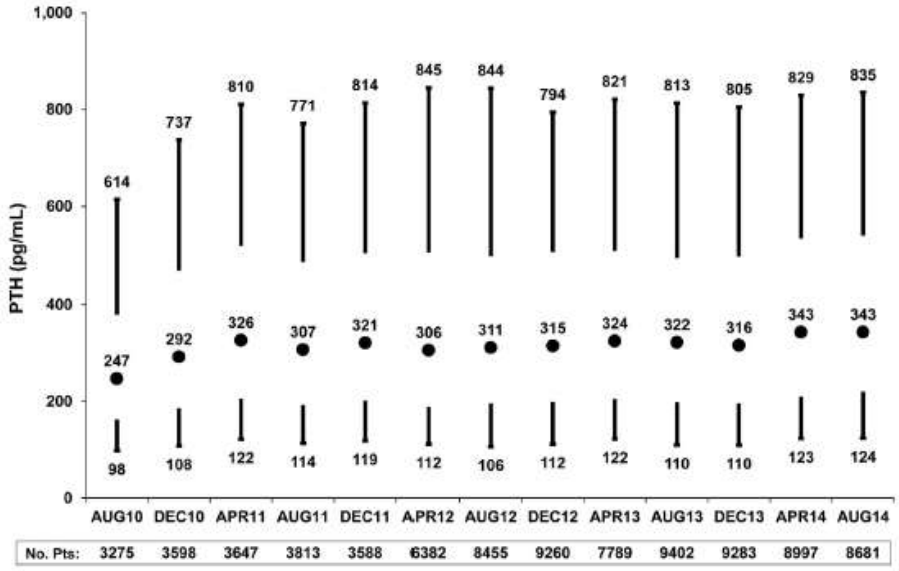


FIGURE 2: Measured serum PTH in patients (patient form) and serum PTH levels a patient is considered to require active treatment to lower PTH (centre-specific form) (mean ± standard error of the mean). ANOVA test was used to analyse statistical differences.

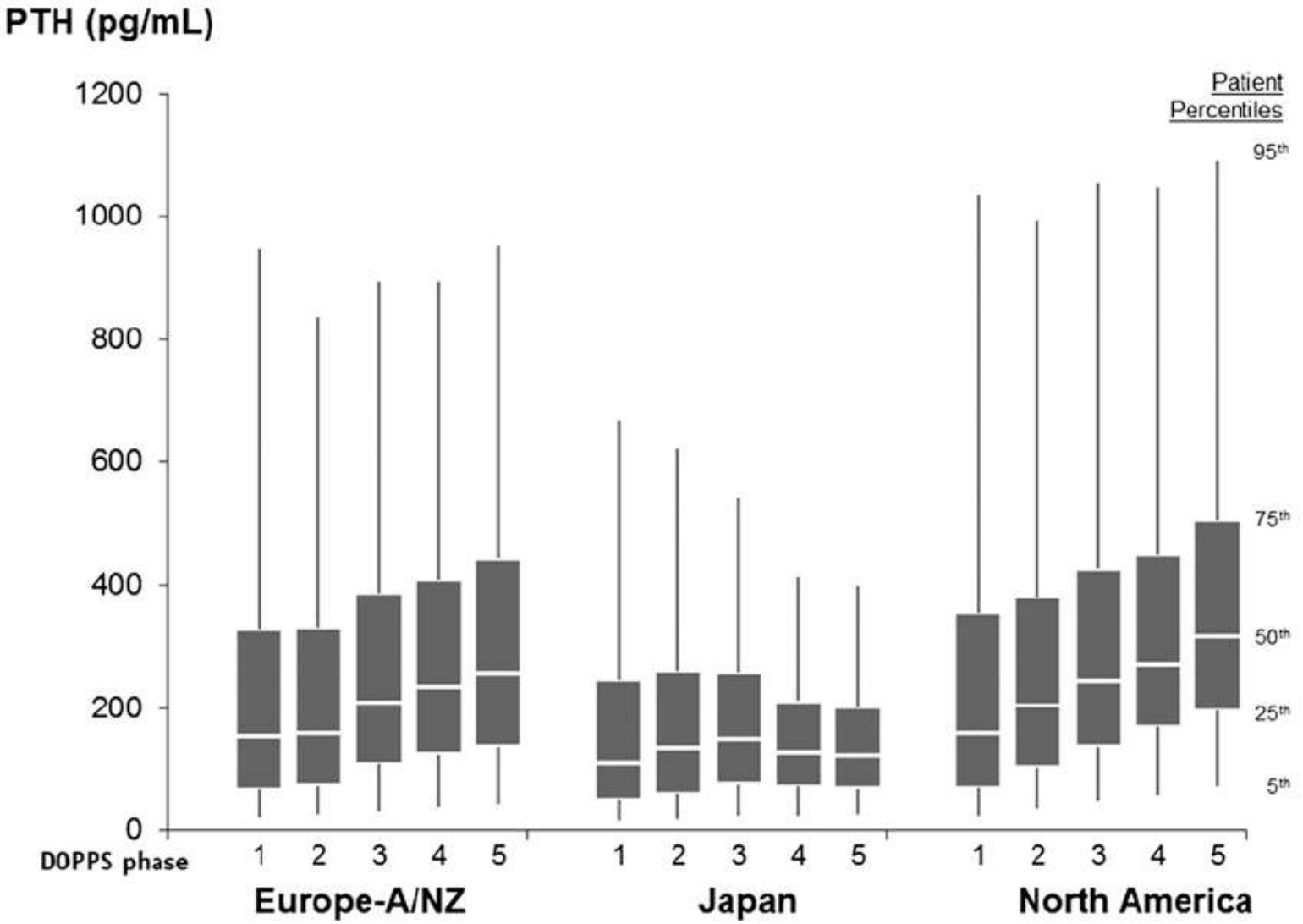
Fernandez Martin Nephrol Dial Transplant (2013)

DOPPS Practice Monitor Update*



F. Tentori et al, Am J Kidney Dis. 2015

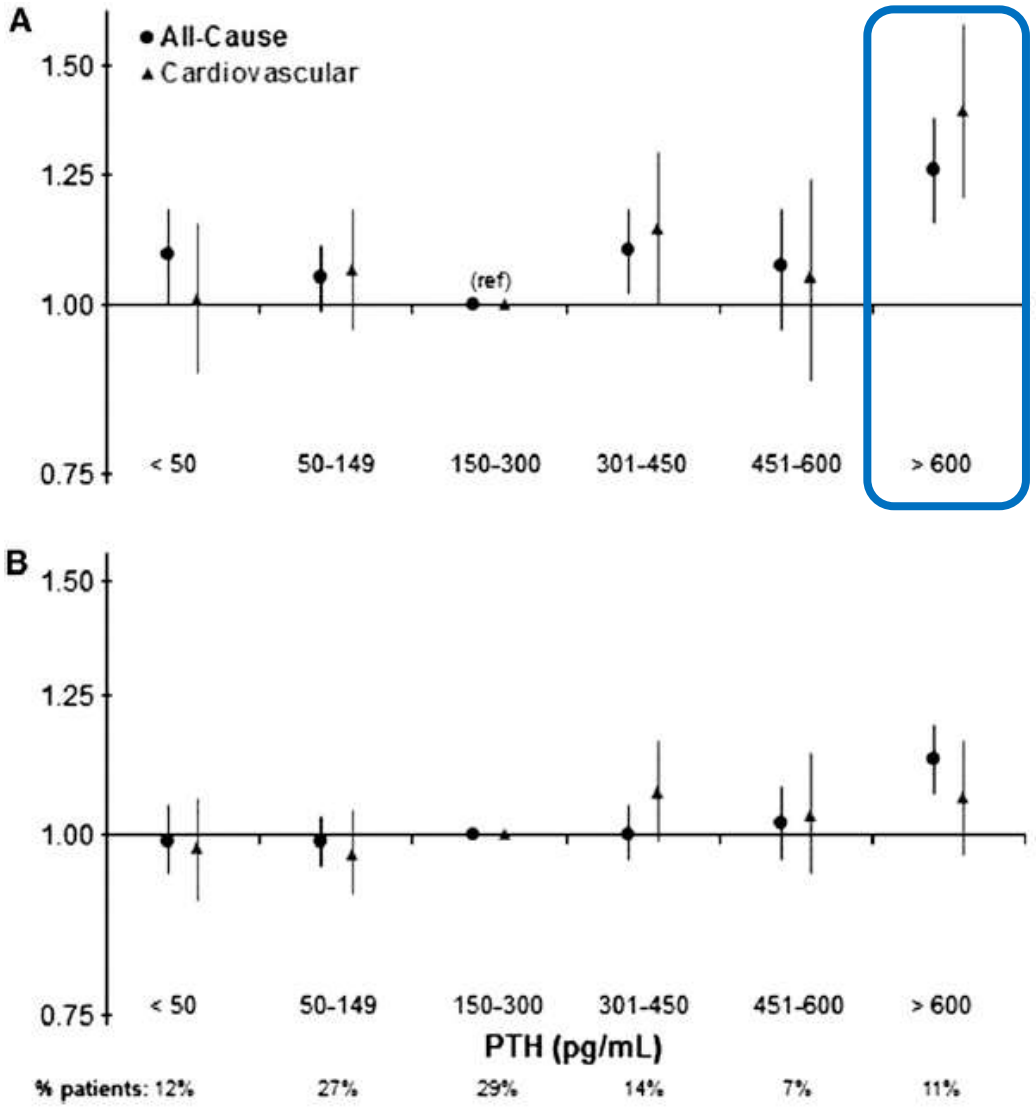
PTH levels by Dialysis Outcomes and Practice Patterns Study region and phase.



F. Tentori et al, Clin J Am Soc Nephrol 2015

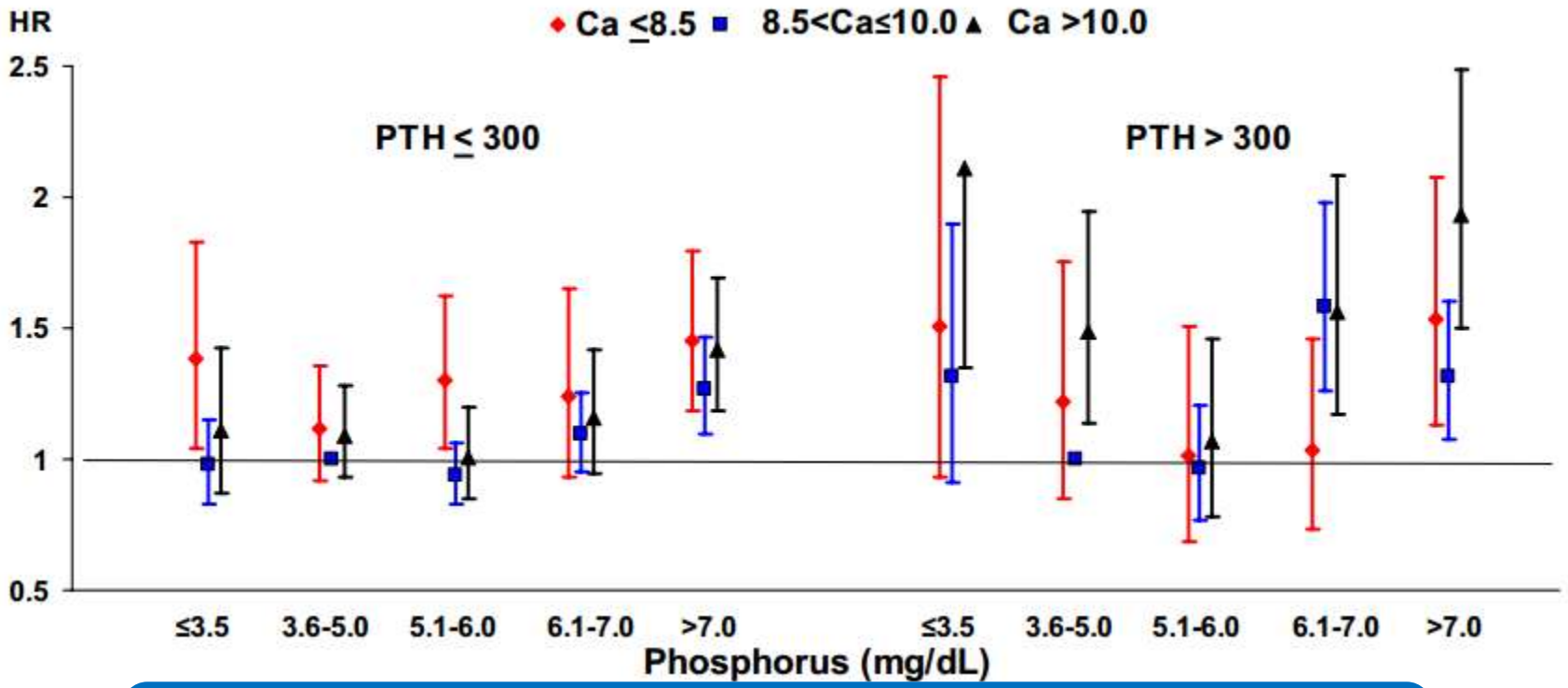
Associations of PTH levels with mortality and hospitalizations among all Dialysis Outcomes and Practice Patterns Study participants

DOPPS 1-2-3-4



F. Tentori et al, Clin J Am Soc Nephrol 2015

Risk of all cause mortality associated with combinations of baseline serum P and Ca categories by parathyroid hormone (PTH) level



.... In patients with PTH levels of 300 pg/mL or less, patients with calcium levels of 8 5 mg/dL or less appeared to be at greatest risk at all phosphorus levels ....

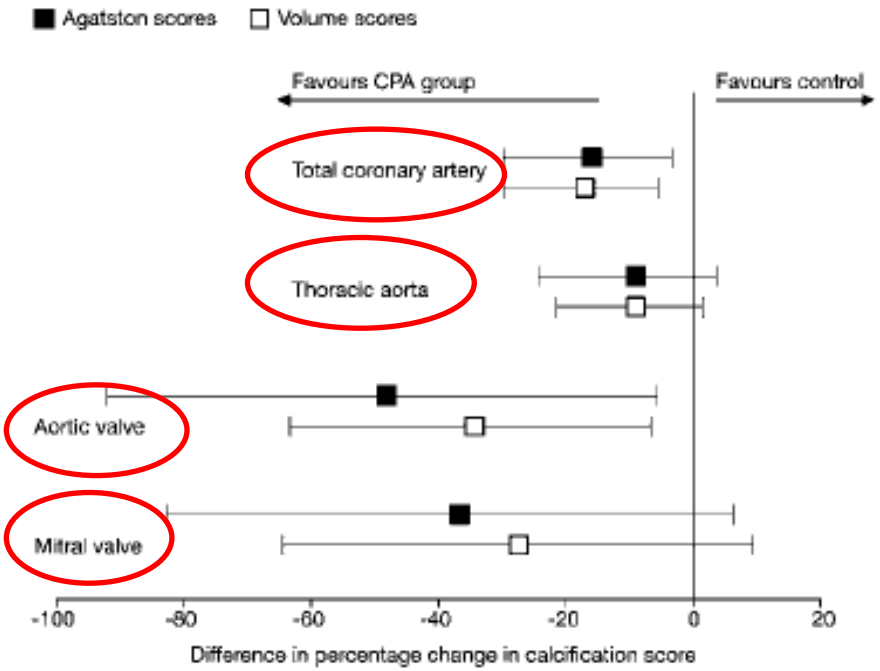
... In patients with PTH levels greater than 300 pg/mL (ng/ patients with calcium levels greater than 10 0 mg/dL appeared to be at greatest risk ...

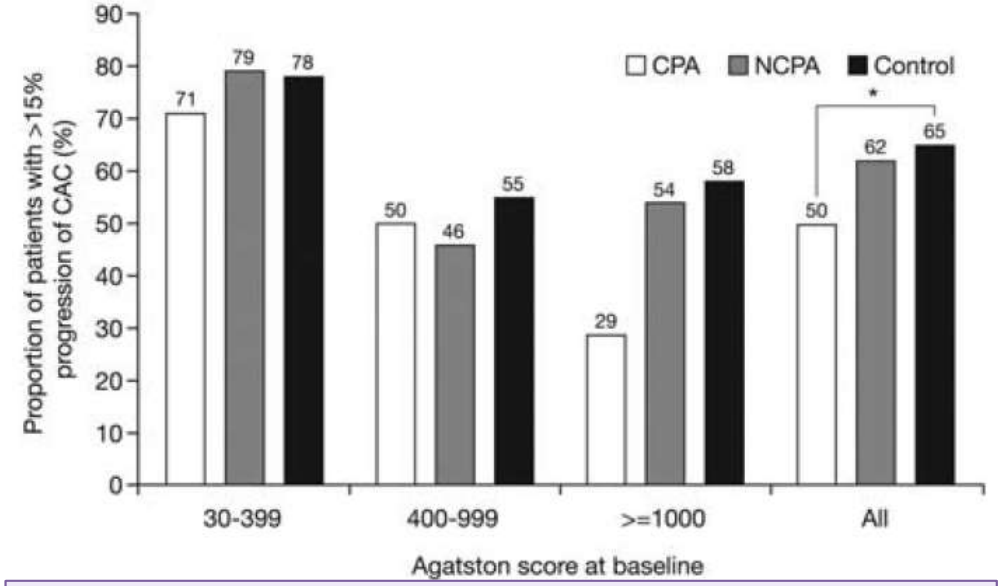
F. Tentori et al, Am. J. Kidney Dis. 2008

Nephrol Dial Transplant (2013) 28: 146–152
doi: 10.1093/ndt/gfs356
Advance Access publication 30 September 2012

Protocol adherence and the progression of cardiovascular calcification in the ADVANCE study

Pablo A. Ureña-Torres[1], Jürgen Floege[2], Carmel M. Hawley[3], Eugenie Pedagogos[4], William G. Goodman[5], Frank Pétavy[6], Maureen Reiner[5] and Paolo Raggi[7]

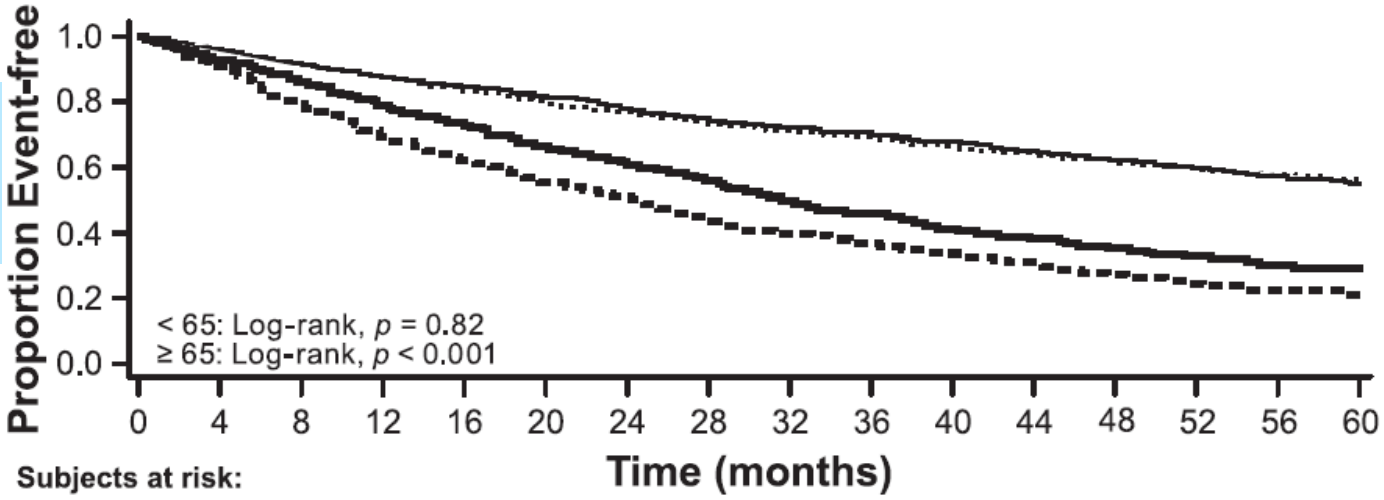




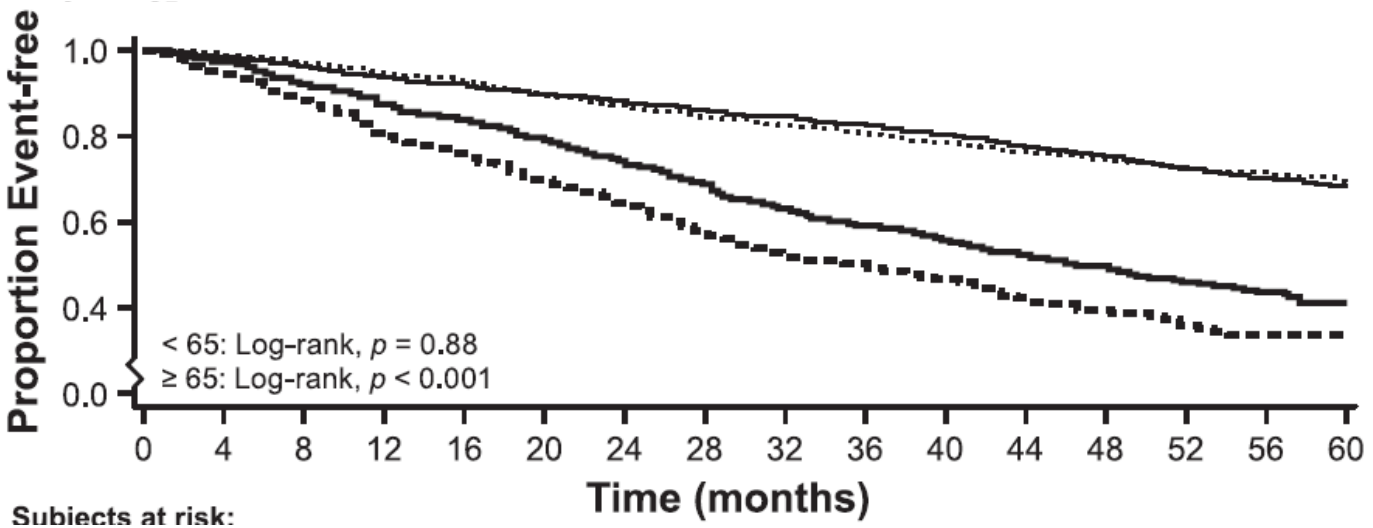
Percentages of patients with 15% progression of CAC categorized by Agatston score at baseline

The Effects of Cinacalcet in Older and Younger Patients on Hemodialysis: The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial

Primary composite cardiovascular end point



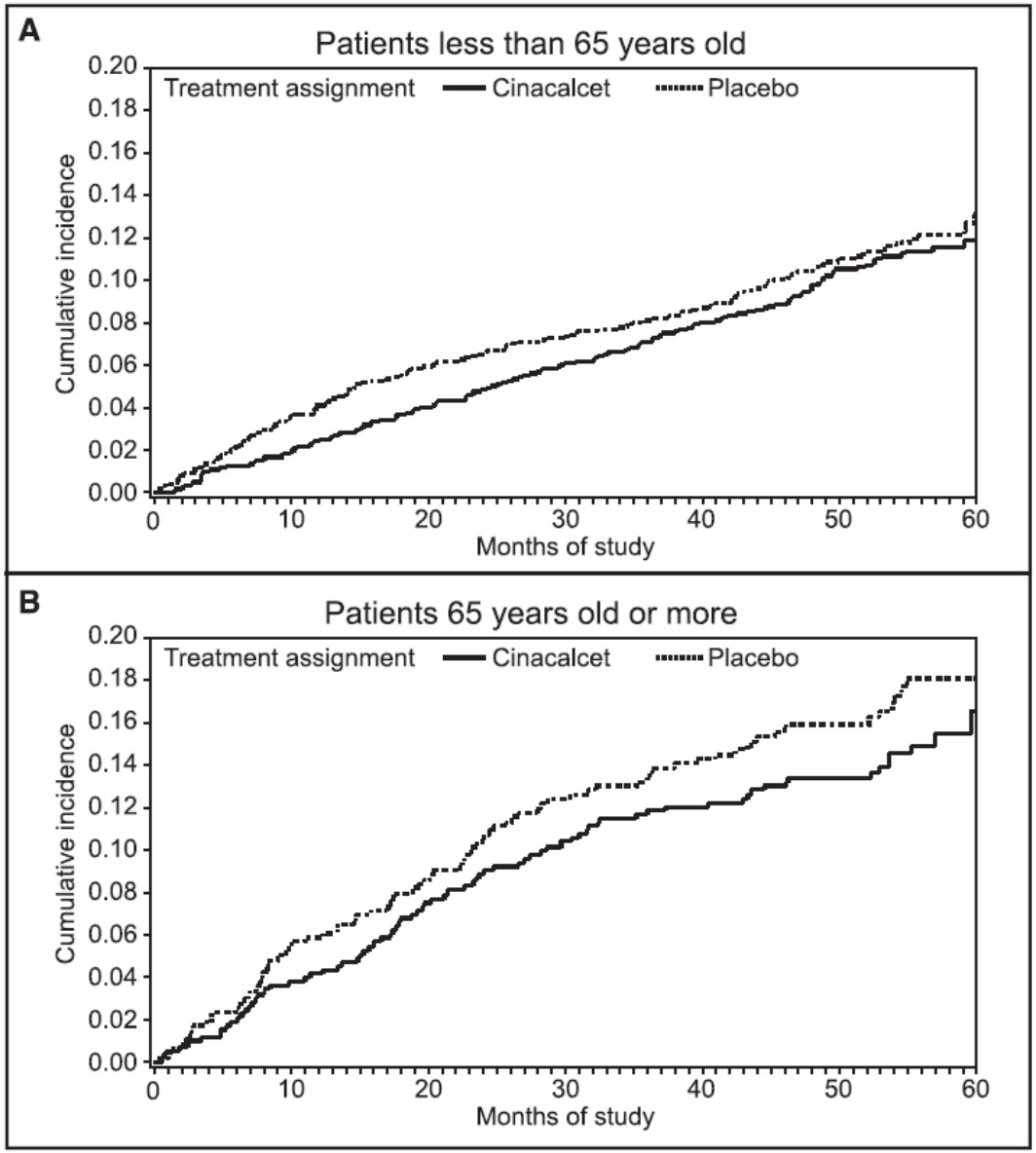
death



dotted line: placebo
solid line: Cinacalcet

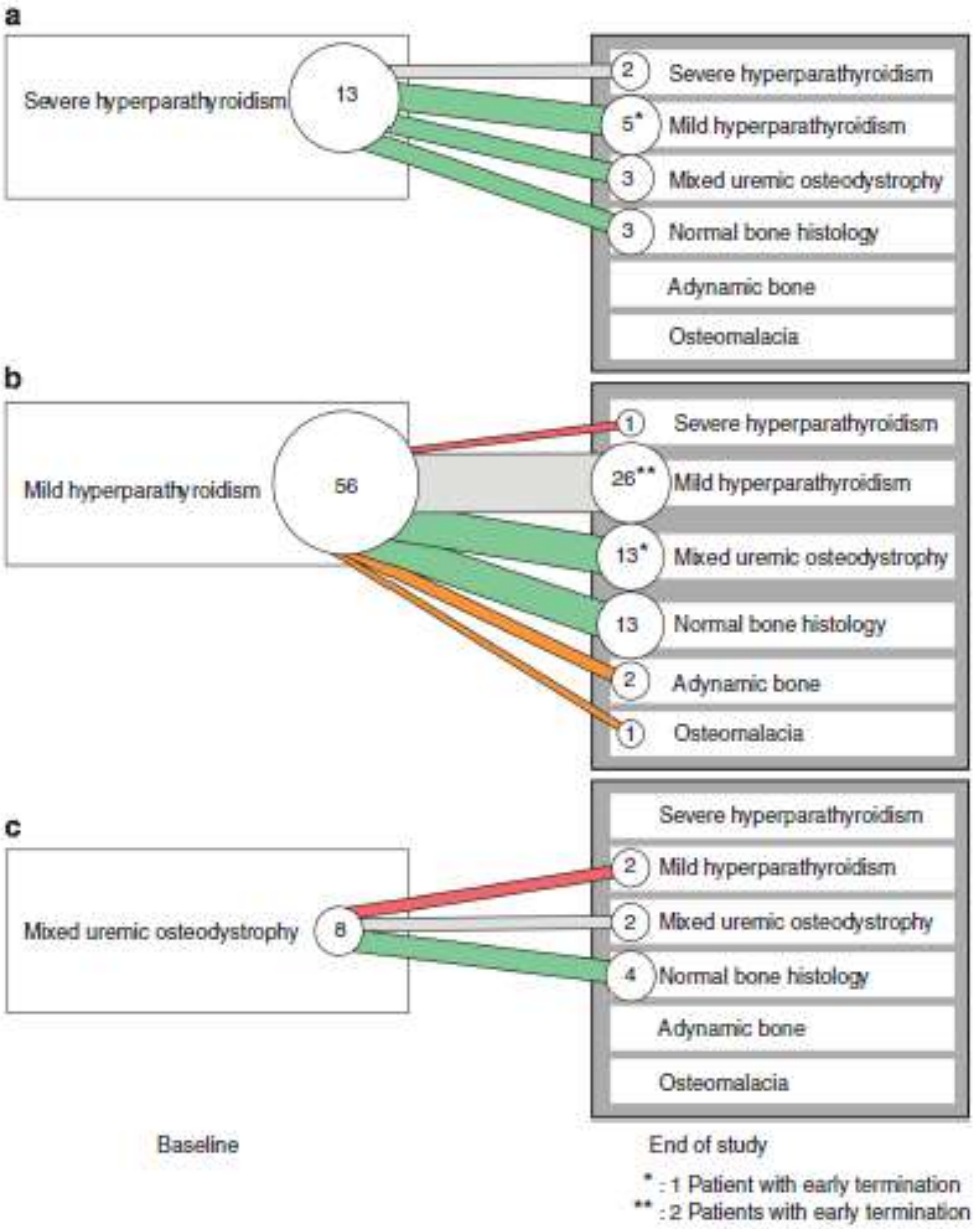
Parfrey et al, Clin J Am Soc Nephrol, 2015

EVOLVE: Cumulative Incidence of Fractures



Sharon M. Moe et al, J Am Soc Nephrol 2015

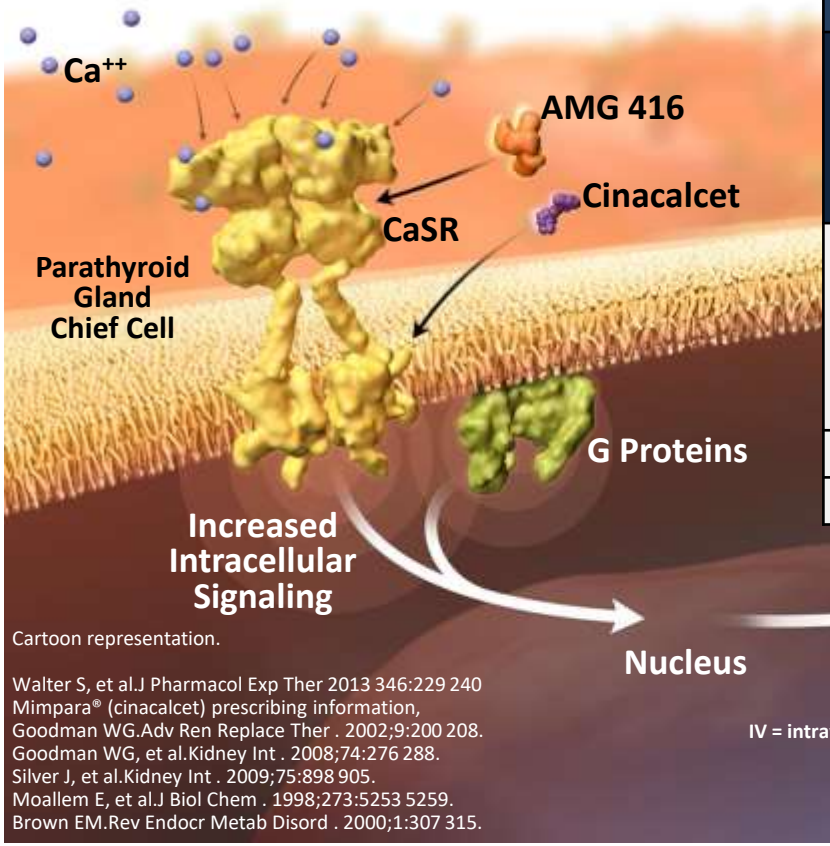
Evolution of type of renal osteodystrophy after cinacalcet treatment



B. Di Iorio et al, AJKD 2013

Structure and Characteristics of AMG 416 Compared to Cinacalcet

AMG 416 and Cinacalcet: Calcimimetic Agents With Similar Characteristics but Different Structures and Routes of Administration



AMG 416[1,2,3]	Cinacalcet[4,5]
Calcimimetic *Synthetic 8-amino acid peptide compound*	*Calcimimetic* *Small organic molecule; molecular weight = 393.9 g/mol*
Interacts with the extracellular domain of CaSR to enhance signal transduction, thereby reducing PTH secretion	*Interacts with membrane-spanning segments of CaSR and enhances signal transduction, thereby reducing PTH secretion*
Long-acting	*Short-acting*
IV form	*Oral form*

Cartoon representation.

Walter S, et al.J Pharmacol Exp Ther 2013 346:229 240
Mimpara® (cinacalcet) prescribing information,
Goodman WG.Adv Ren Replace Ther . 2002;9:200 208.
Goodman WG, et al.Kidney Int . 2008;74:276 288.
Silver J, et al.Kidney Int . 2009;75:898 905.
Moallem E, et al.J Biol Chem . 1998;273:5253 5259.
Brown EM.Rev Endocr Metab Disord . 2000;1:307 315.

IV = intravenous ; CaSR = calcium sensing receptor; PTH = parathyroid hormone

JAMA | Original Investigation

Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

A Randomized Clinical Trial

Geoffrey A. Block, MD; David A. Bushinsky, MD; Sunfa Cheng, MD; John Cunningham, MD; Bastian Dehmel, MD; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; Yan Sun, MS; Hao Wang, PhD; Glenn M. Chertow, MD, MPH

Research

JA

E

Hormone in Patients Receiving Hemodialysis

With Secondary Hyperparathyroidism

A Randomized Clinical Trial

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- The primary efficacy end point was the proportion of patients with greater than 30% reduction from baseline in mean PTH during the efficacy assessment phase (weeks 20-27).

- Secondary end points included the proportion of patients with mean PTH levels of 300 pg/mL or lower and percentage reductions in PTH, calcium, calcium × phosphate, and phosphate.

1006 Patients undergoing hemodialysis with PTH concentrations ≥500 pg/mL screened

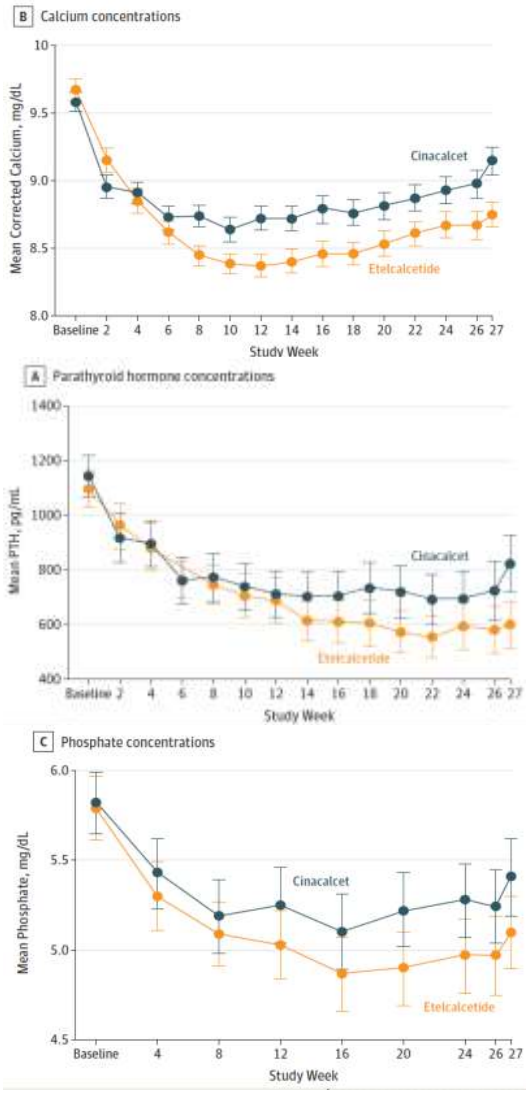
- Exploratory end points included change in FGF 23 and the bone turnover markers of bone-specific alkaline phosphatase and collagen type 1 cross- linked C-telopeptide

- The primary efficacy (noninferiority) end point was the proportion of patients with more than 30 reduction from baseline in mean PTH concentrations during the efficacy assessment phase (weeks 20 27

- Key secondary end points included the proportion of patients with more than a 30% and more than a 50% reduction in PTH concentrations (superiority), and the mean weekly days of self reported nausea and vomiting over the first 8 weeks

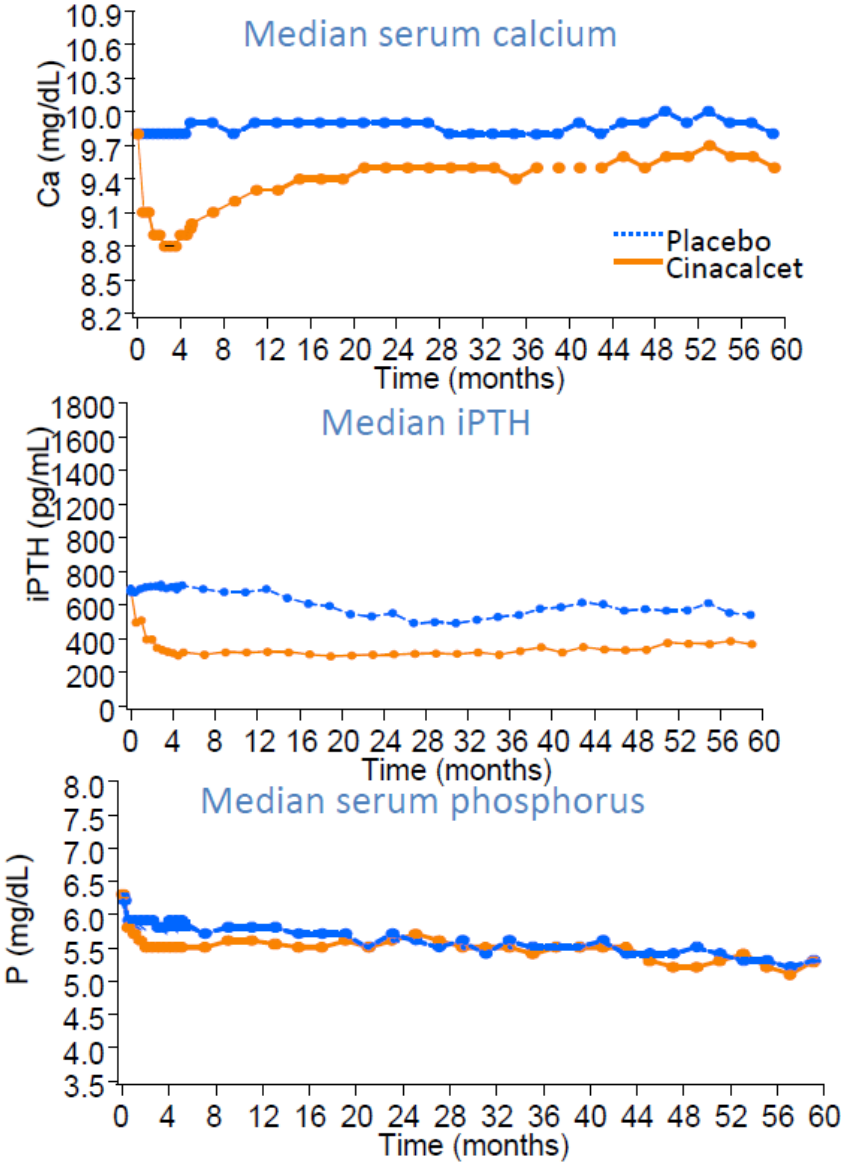
- Relative effects on FGF 23 bone specific alkaline phosphatase, and collagen type 1 cross linked C-telopeptide were considered exploratory end points

Parathyroid Hormone, Calcium, and Phosphate Concentrations in Patients Receiving Cinacalcet or Etelcalcetide by Study Week



Geoffrey A. Block et al JAMA, 2017

Biochemical parameters (ITT): Substantial reductions in PTH and Ca



Chertow GM, et al. N Engl J Med. 2012

Incidence (%) of most frequent adverse drug reactions

Most frequent adverse events	Placebo-controlled studies		Cinacalcet-controlled studies	
	Placebo n=513	Etelcalcetide n=503	Cinacalcet n=341	Etelcalcetide n=338
Diarrhea	8.6	10.7	10.3	6.2
Nausea	6.2	10.7	22.6	18.3
Vomiting	5.1	8.9	13.8	13.3
Calcium reduction	10.1	63.8	59.8	68.9
Hypocalcemia[a]	0.2	7.0	2.3	5.0
Hyperkalemia	3.1	4.4	5.3	3.8
Muscle spasms	6.6	11.5	5.9	6.5
Paraesthesia	1.2	6.2	2.6	3.3
Hypotension	–	–	2.9	6.8

Note: [a]Hypocalcemia definition: symptomatic reduction in serum corrected calcium <8.3 mg/dL.

Cozzolino et al Therapeutics and Clinical Risk Management 2017

Patient characteristics affecting adverse events and calcemic reduction

PTH
< 600 pg/ml

With regard to the incidence of serious AEs, these were less frequent 21 4 in patients with a PTH value of 1 000 pg/mL at the screening compared with subjects with PTH 600 1 000 pg/mL 26 2 or 600 pg/mL 28 2

PTH
>1000 pg/ml

Age < 65 years

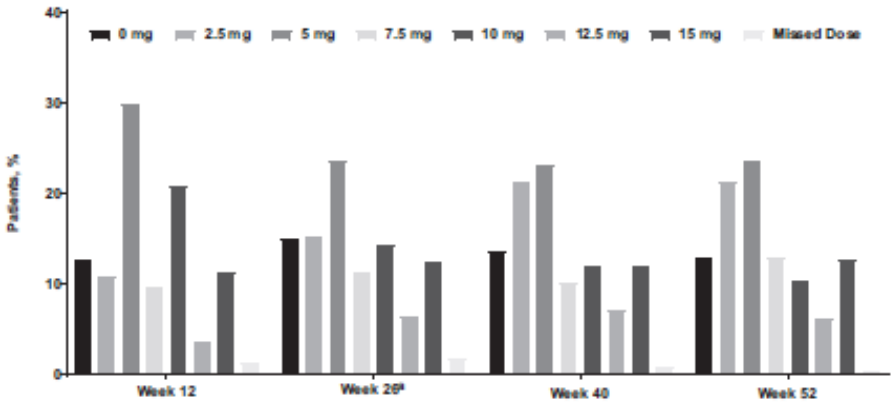
-Blood calcium decreased 69.6%

-Hypocalcemia (symptomatic) 7.1%

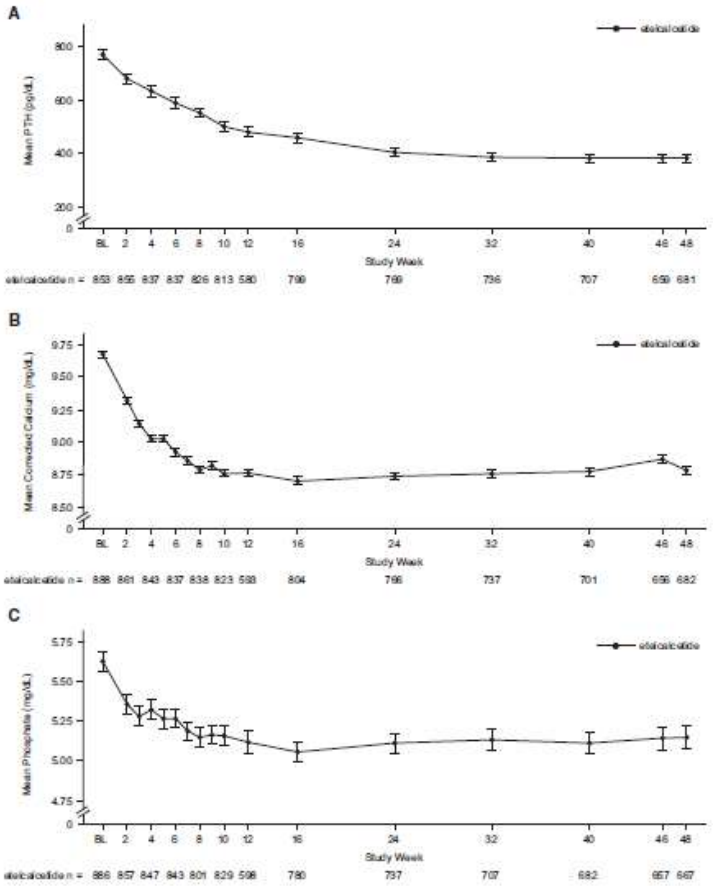
EMA Assessment Report 15 September 2016

One year safety and efficacy of intravenous Etelcalcetide in patients on hemodialysis with secondary hyperparathyroidism

Proportion of patients receiving each dose level of etelcalcetide (mg/session) at selected visits. [a]One patient received 17.5 mg of etelcalcetide in Week 26, although the maximum dose per protocol was 15 mg.



Mean (SE) predialysis PTH (A), Ca (B) and P (C) concentrations over time. BL, baseline; Ca, albumin corrected calcium; P, phosphate.



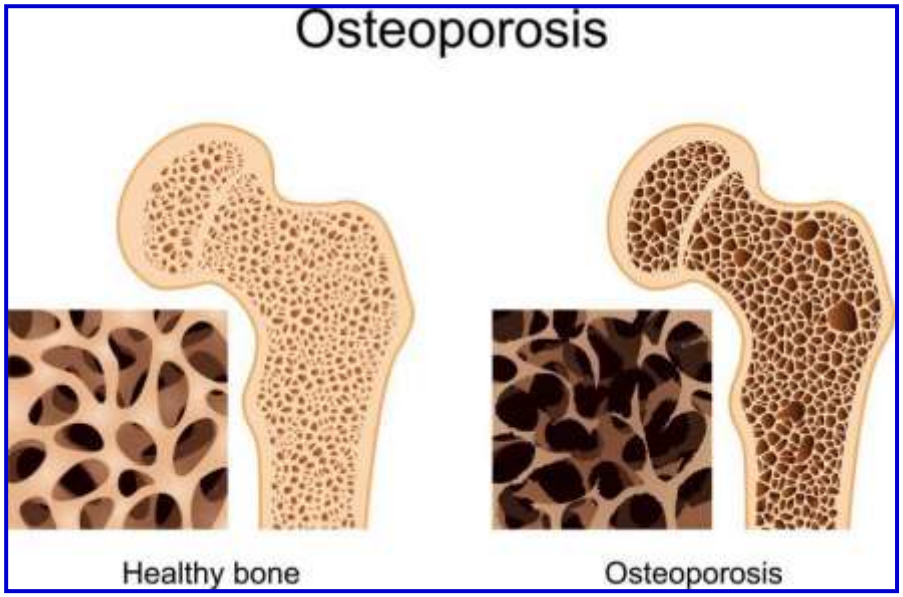
Bushinsky et al Nephrol Dial Transplant (2019) 1-10

What's new

Osteporosis

Disease where decreased bone strength due to low bone mineral density and poor bone quality increases the risk of a broken bone

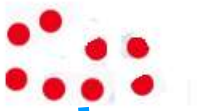
Screening test for OP = BMD



- **Normal= T-score of -1.0 or higher**
- **Osteopenia= between -1.0 and -2.5**
- **Osteoporosis= -2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.**

Osteporosis

Proinflammatory cytokines



↓RANKL ↓OPG
- Stromal cells
- Osteoblasts
- Osteoblast precursor

CNI

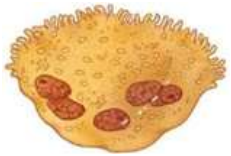
↓Testosteron

↓Estrogens

Steroids

Diabetes

Osteoclast



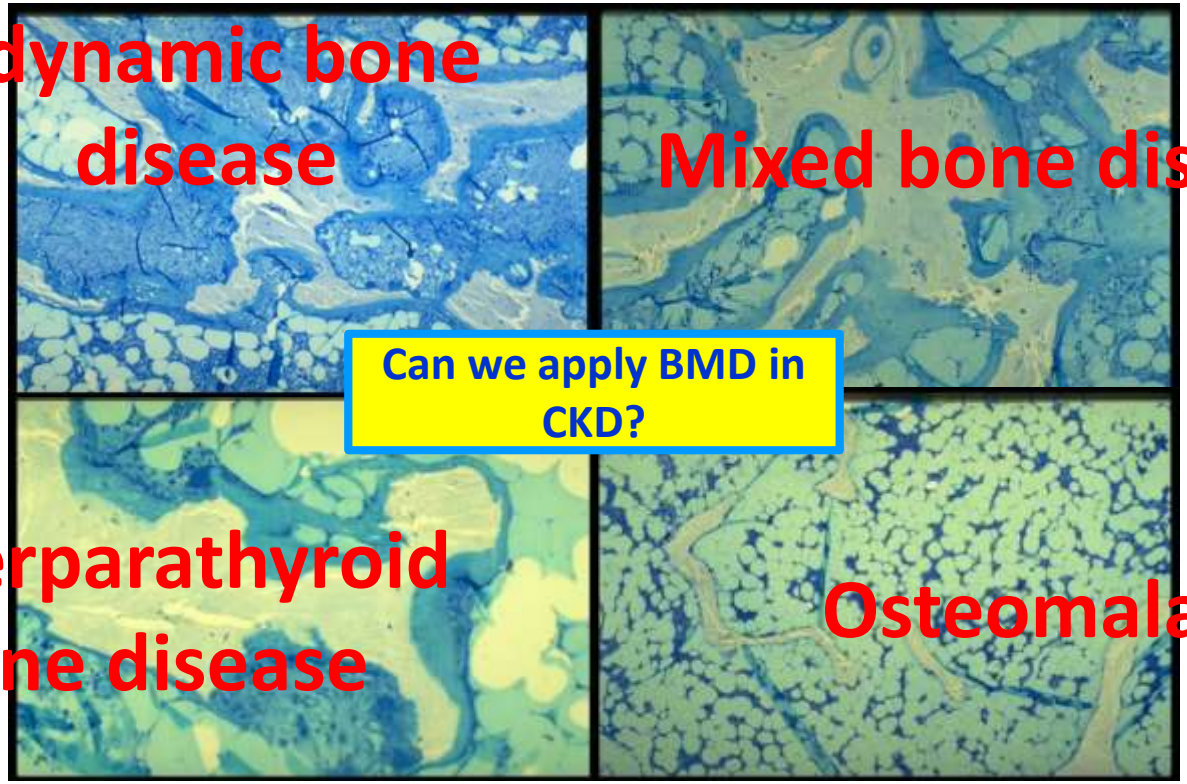
Bone Resorption

Bone Formation

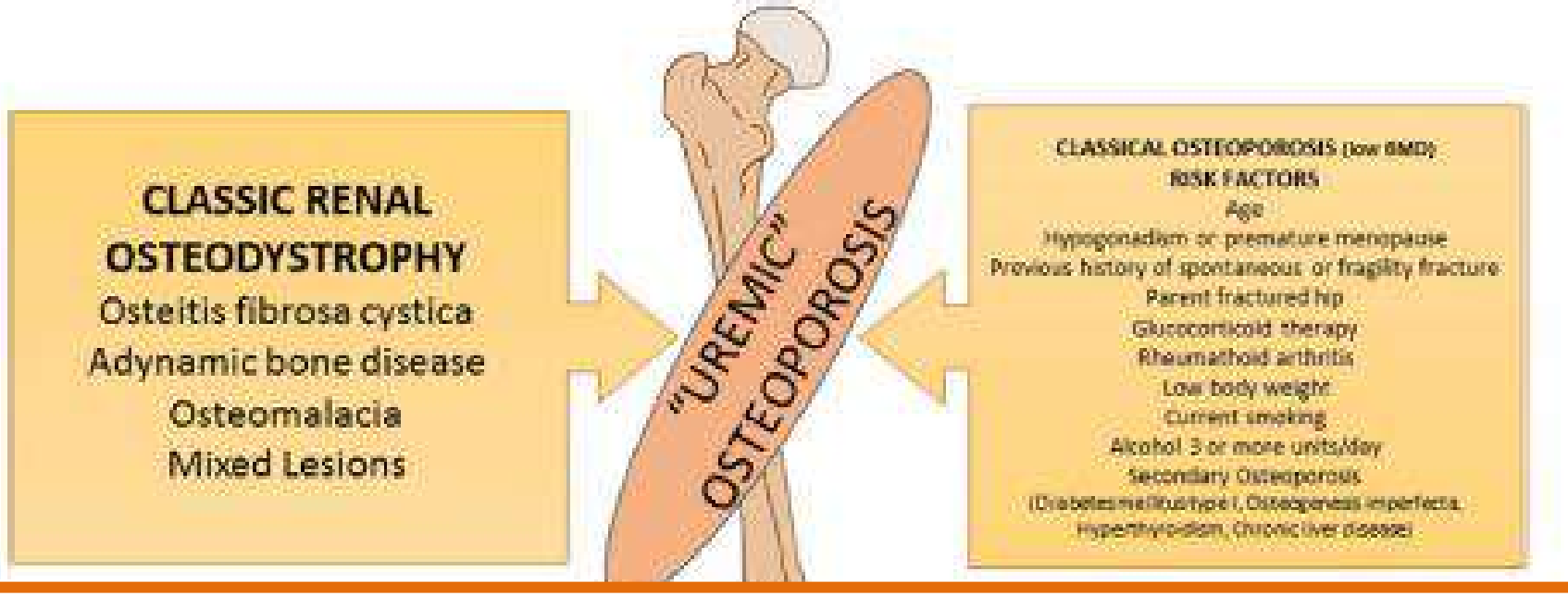
Hyperthyroidism

Osteoporosis

Aging


Adynamic bone disease
Mixed bone disease
Can we apply BMD in CKD?
Hyperparathyroid bone disease
Osteomalacia

Osteporosis



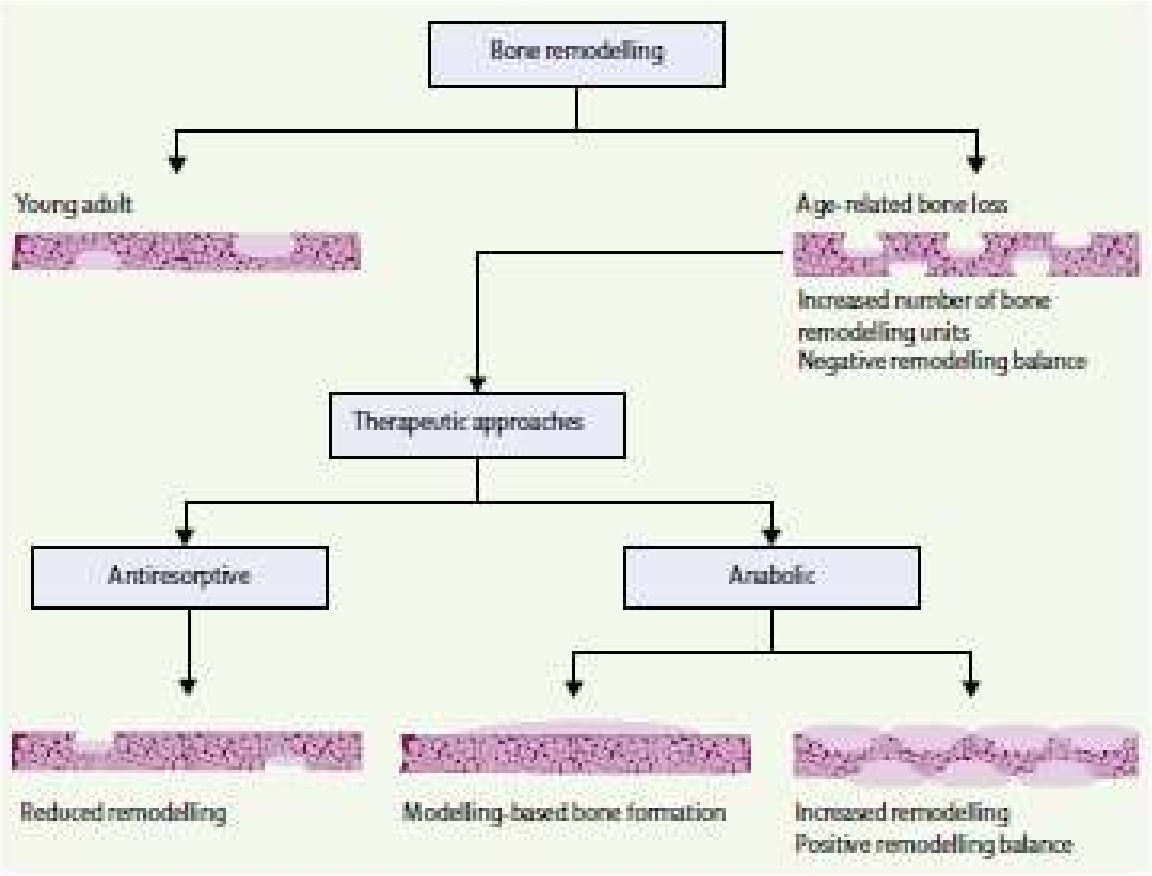
....the operational clinical differentiation among the diseases accompanying CKD lies in distinguishing between adynamic bone disease, hyperparathyroid bone disease, mixed renal bone disease, osteomalacia, and osteoporosis, all of which may have low BMD and/or be associated with fragility (including hip) fractures...

...The challenge for physicians managing fragility fractures in patients with CKD is discriminating fractures due to osteoporosis from fractures due to the traditional bone diseases accompanying CKD...

Miller AJKD 2014

Bover et al, J Nephrol (2017)

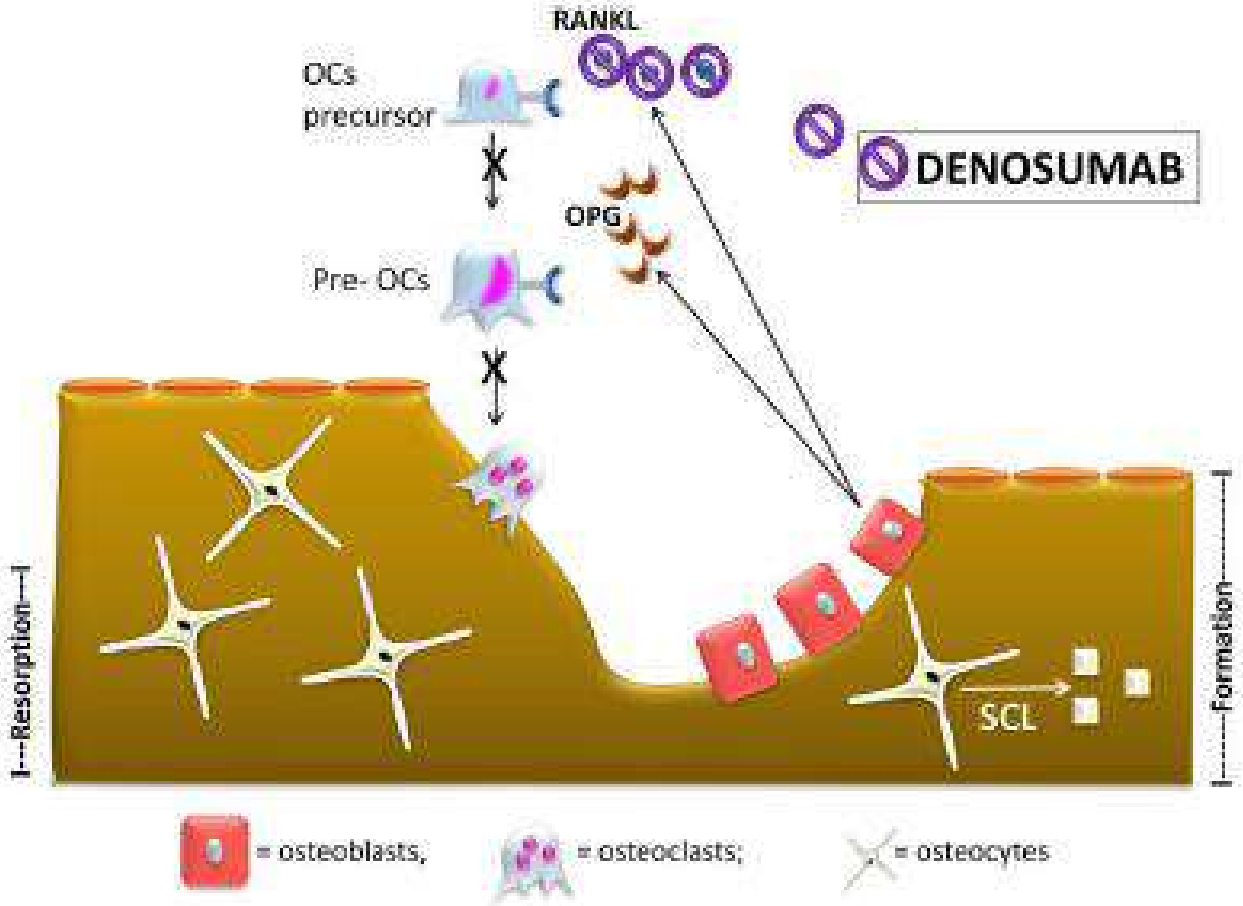
Effects of antiresorptive and anabolic drugs on bone remodelling and modelling



Age-related bone loss is associated with an increase in remodelling and a negative remodelling balance in individual bone remodelling units. Antiresorptive agents act predominantly by reducing remodelling rate. Anabolic agents produce their effects by increasing remodelling in combination with a positive remodelling balance, or stimulating bone modelling

Juliet E Compston et, Lancet 2019

Effects of denosumab on bone

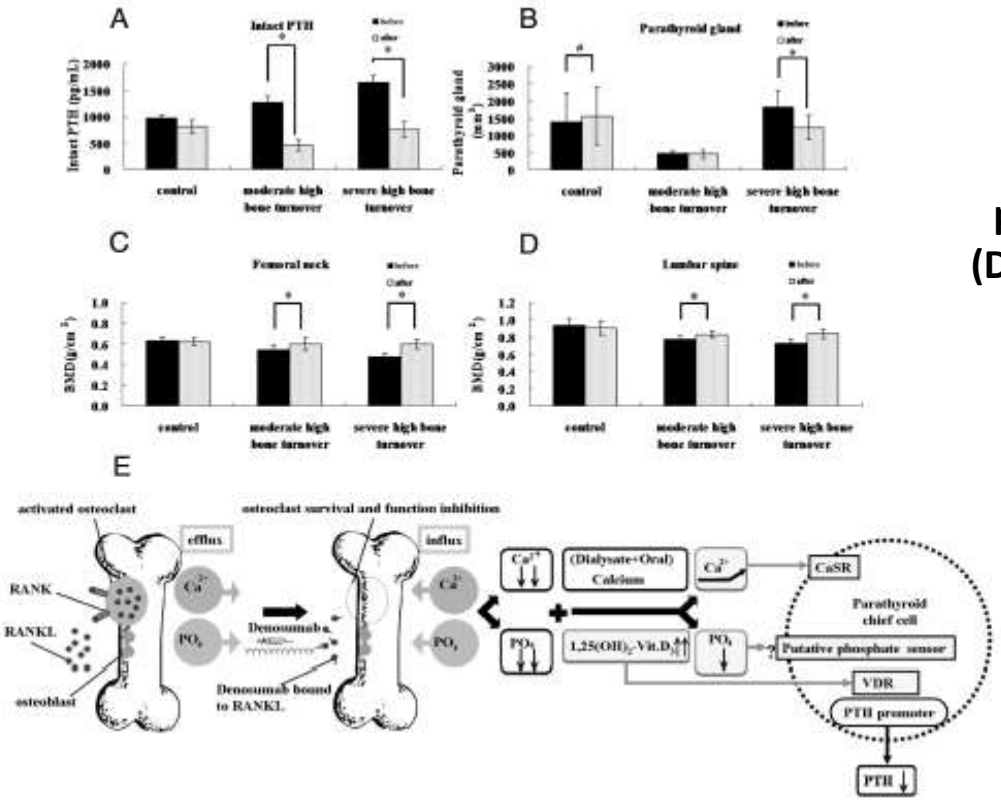


Denosumab targets and binds receptor activator of NF-κB ligand (**RANK-L**) with high affinity and specificity. RANK-L inhibition leads to **suppression of osteoclasts** differentiation, activity and survival.

The final effect is the **reduction of bone resorption** sites and increased bone volume.

Tartaglione et al, J of Nephrology 2017

Denosumab



Changes in (A) Serum intact PTH levels and (B) parathyroid gland volume, (C) femoral neck, and (D) vertebra BMD. (E), Schematic representation of Denosumab action

Chen CL, Chen NC, Hsu CY et al J Clin Endocrinol Metab, July 2015

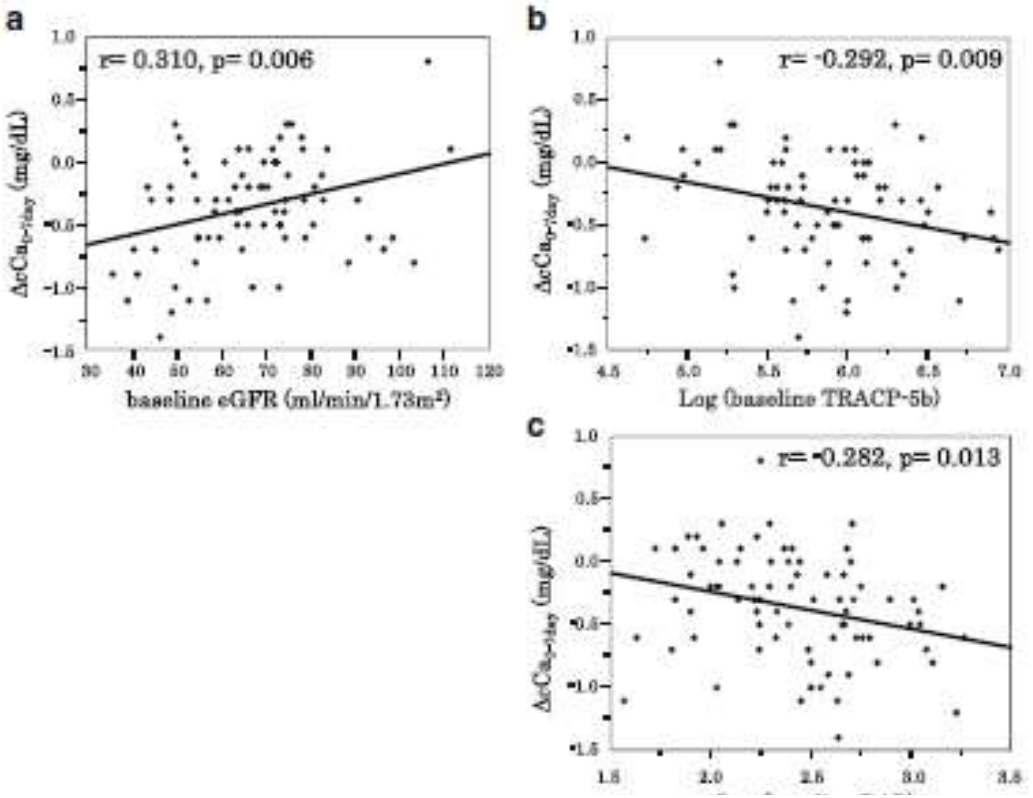
Effect of Denosumab, Compared with Placebo, on BMD Over 36 Months, by Stage of Kidney Function Estimated by CG

Outcome	Stage 4 CKD eGFR 15 to 29 mL/min ($N = 73$)	Stage 3 CKD eGFR 30 to 59 mL/min ($N = 2817$)	Stage 2 CKD eGFR 60 to 89 mL/min ($N = 4069$)	Stage 1 CKD/normal eGFR $\geq$ 90 mL/min ($N = 842$)
Lumbar spine BMD, % change	5.0 (−0.8–10.8)	8.9 (8.4–9.3)*	9.0 (8.6–9.4)*	8.1 (7.2–8.9)*
Femoral neck BMD, % change	5.9 (3.3–8.5)*	5.1 (4.7–5.5)*	5.2 (4.9–5.5)*	5.6 (4.9–6.3)*
Total-hip BMD, % change	5.9 (3.0–8.7)*	6.4 (6.1–6.7)*	6.4 (6.2–6.7)*	5.8 (5.2–6.3)*

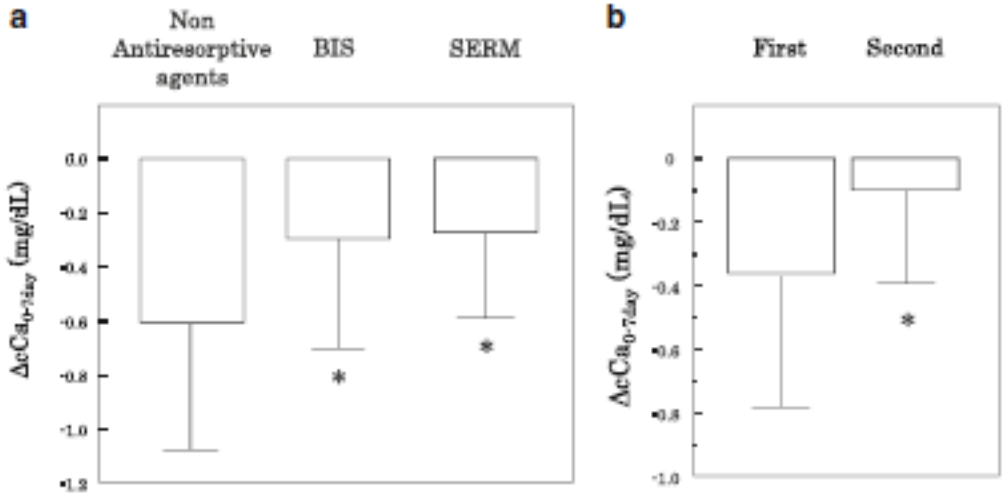
N = number of randomized subjects. A difference in BMD% change > 0 in favor of denosumab.
*$p \leq .0002$.

S.A.Jamal et al Journal of Bone and Mineral Research

Denosumab



Correlations between the absolute reduction in cCa concentration from baseline to day 7 (ΔcCa0-7 days) and clinical parameters following denosumab administration

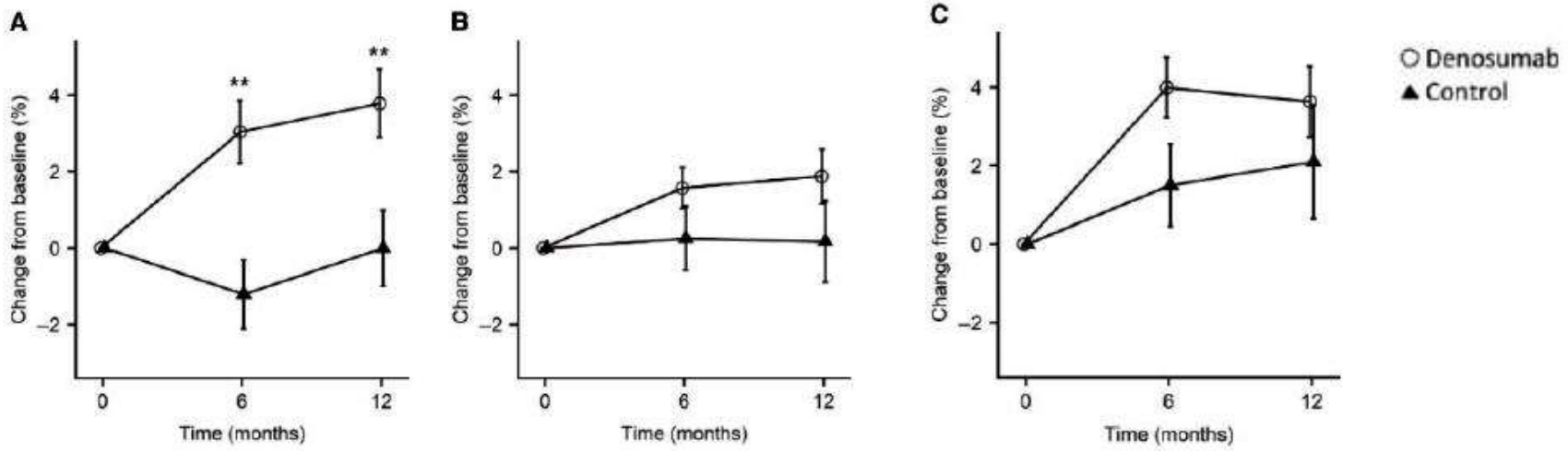


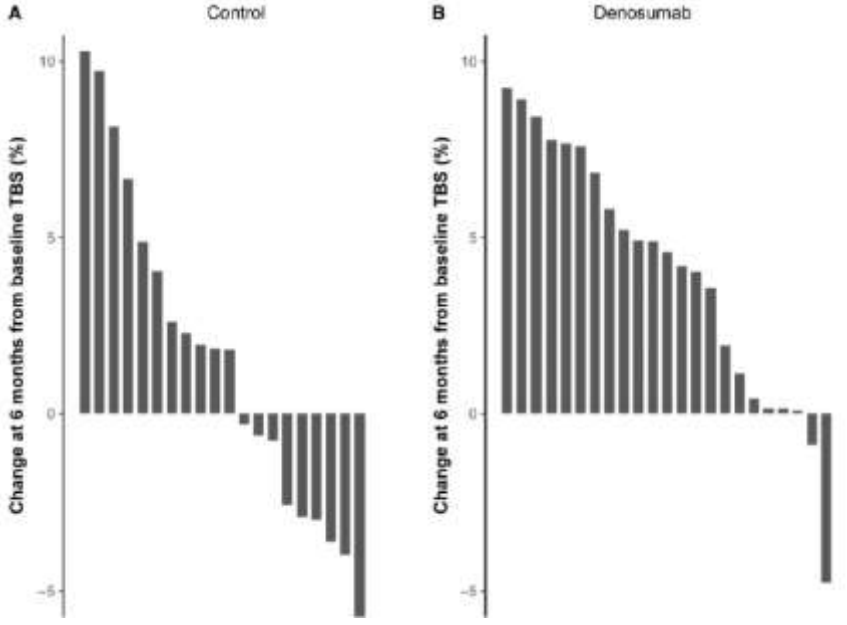
Effects of previous treatment, including denosumab, on $\Delta cCa_{0\text{-}7\ day}$

D. Miyaoka et al Osteoporosis int 2019

Effect of denosumab on trabecular bone score in de novo kidney transplant recipients

Percentage change from baseline to 6 and 12 months for lumbar spine aBMD (A), total hip aBMD (B) and TBS C

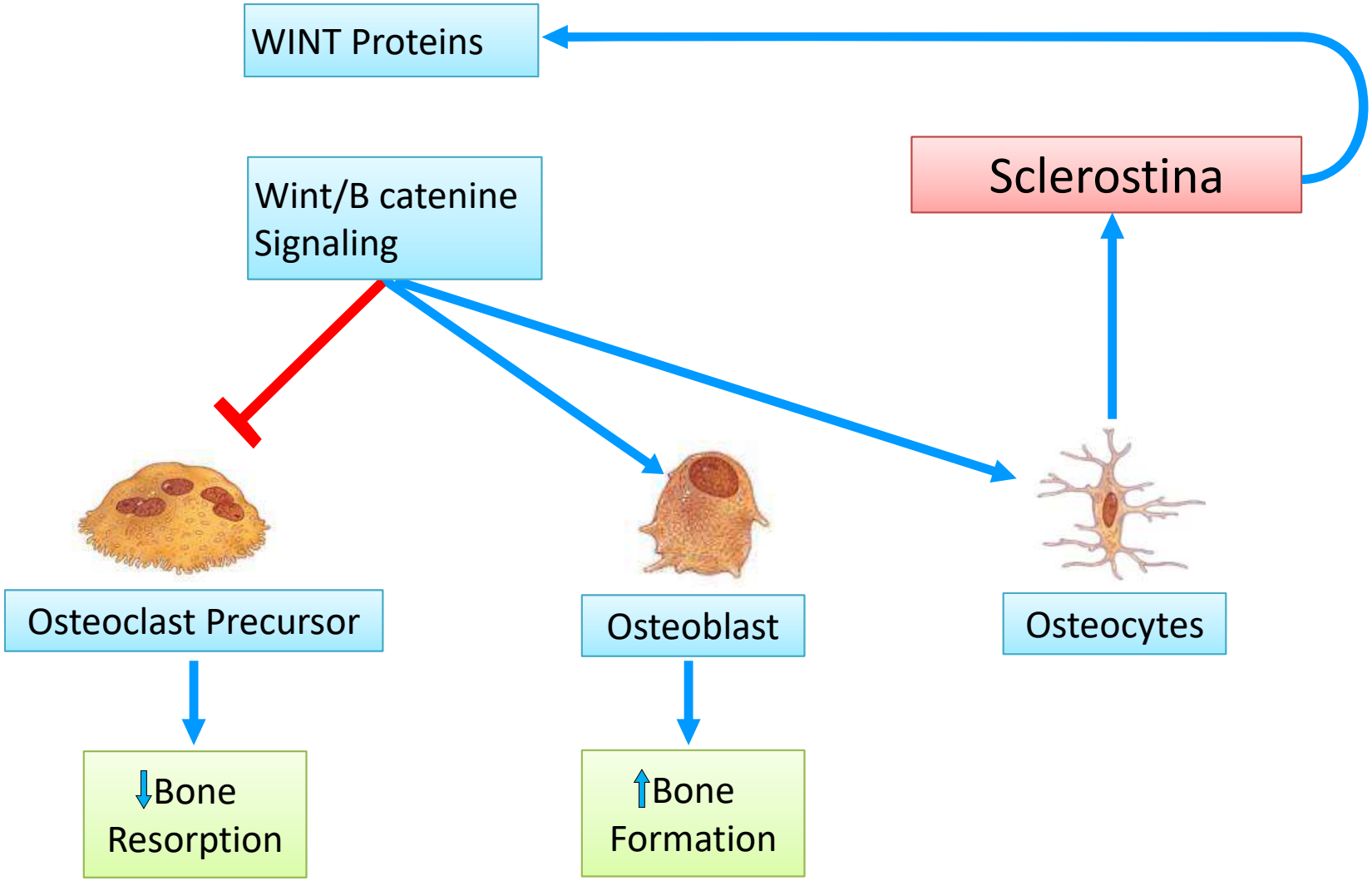




Waterfall plot of TBS changes in percentage from baseline to 6 months in control KTR (n¼20) (A) and denosumab-treated KTR (n¼23) (B). P¼0.007 for group difference by Chi-square test.

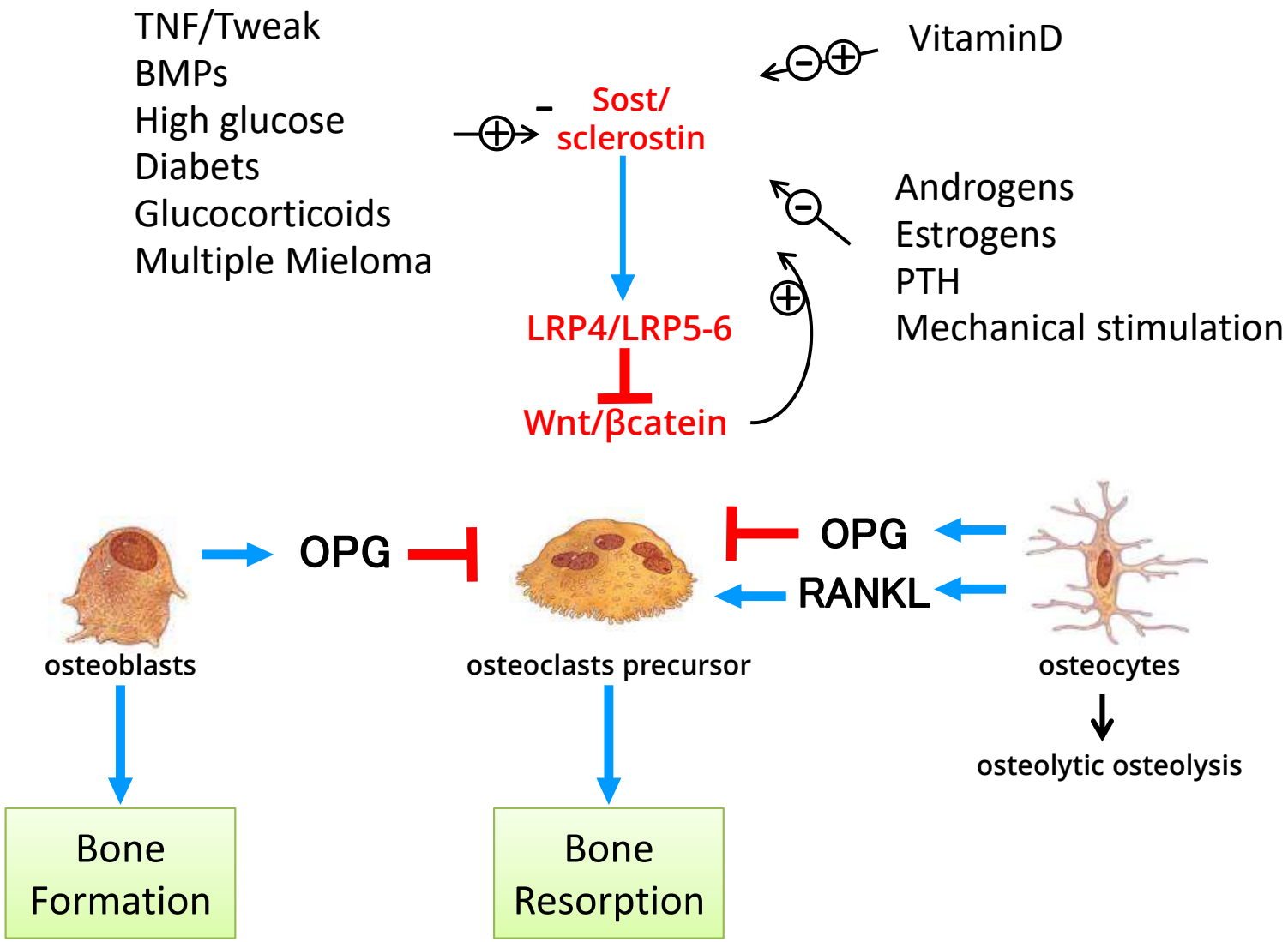
D. Miyaoka et al Osteoporosis int 2019

Role and mecchanism of action of Wint /B eta Catenine



J D Delgado Colle e al Bone 2016

Role and mechanism of action of Sost /sclerostin in bone

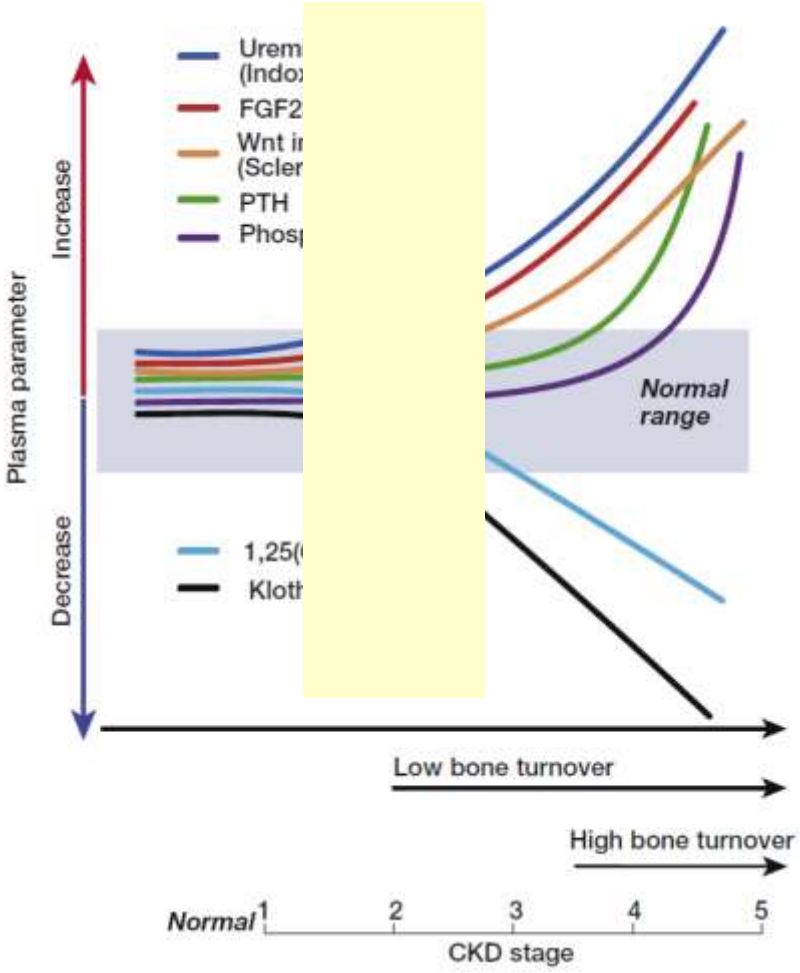


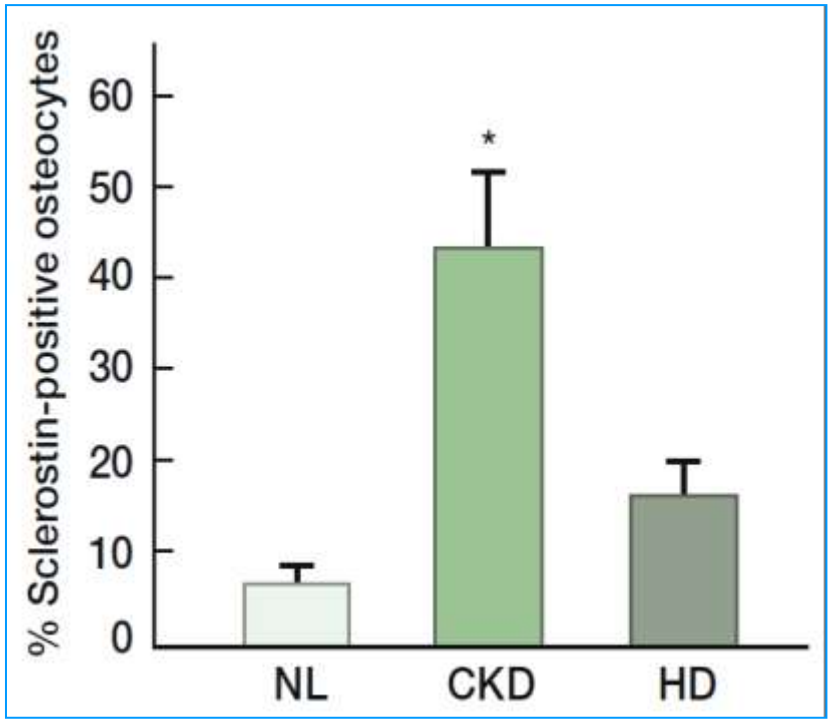
Modified from J D Delgado Colle e al Bone 2016

Changing bone patterns with progression of chronic kidney disease

Tilman B. Drüeke[1] and Ziad A. Massy[1,2]

[1]Institut National de la Santé et de la Recherche Médicale (Inserm) Unité 1018, Centre de recherche en épidémiologie et santé des populations, Equipe 5, Villejuif; Paris-Sud University and University of Paris–Ouest, Versailles-Saint-Quentin-en-Yvelines; Paris, France; and [2]Division of Nephrology, Ambroise Paré Hospital, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt/Paris; University of Paris–Ouest, Versailles-Saint-Quentin-en-Yvelines; Paris, France

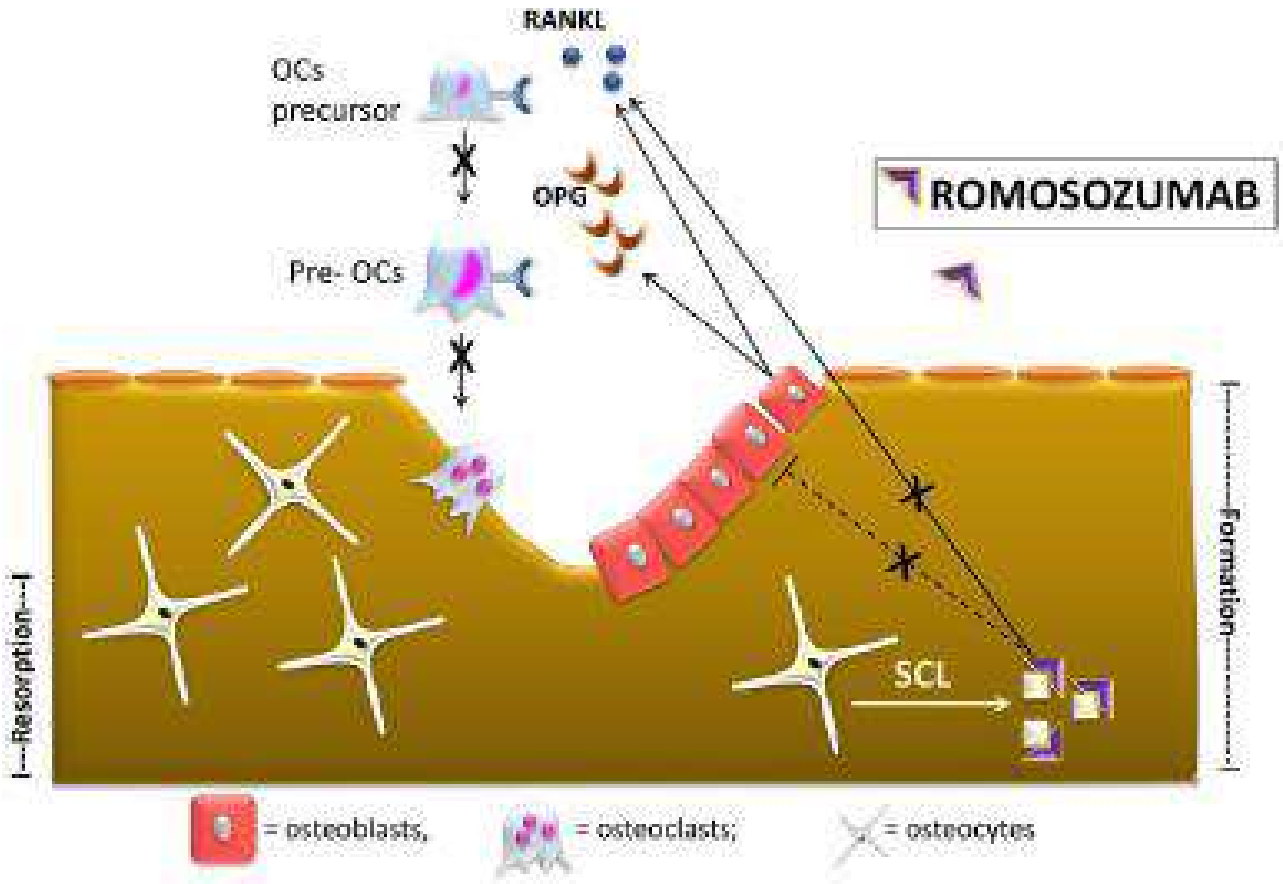




Sabbagh J Bone Min Res 2016. Bone biopsy from NL or CKD patients, showing highest Sclerostin expression in non-dialysis CKD

Kidney International (2016) 89, 289-302

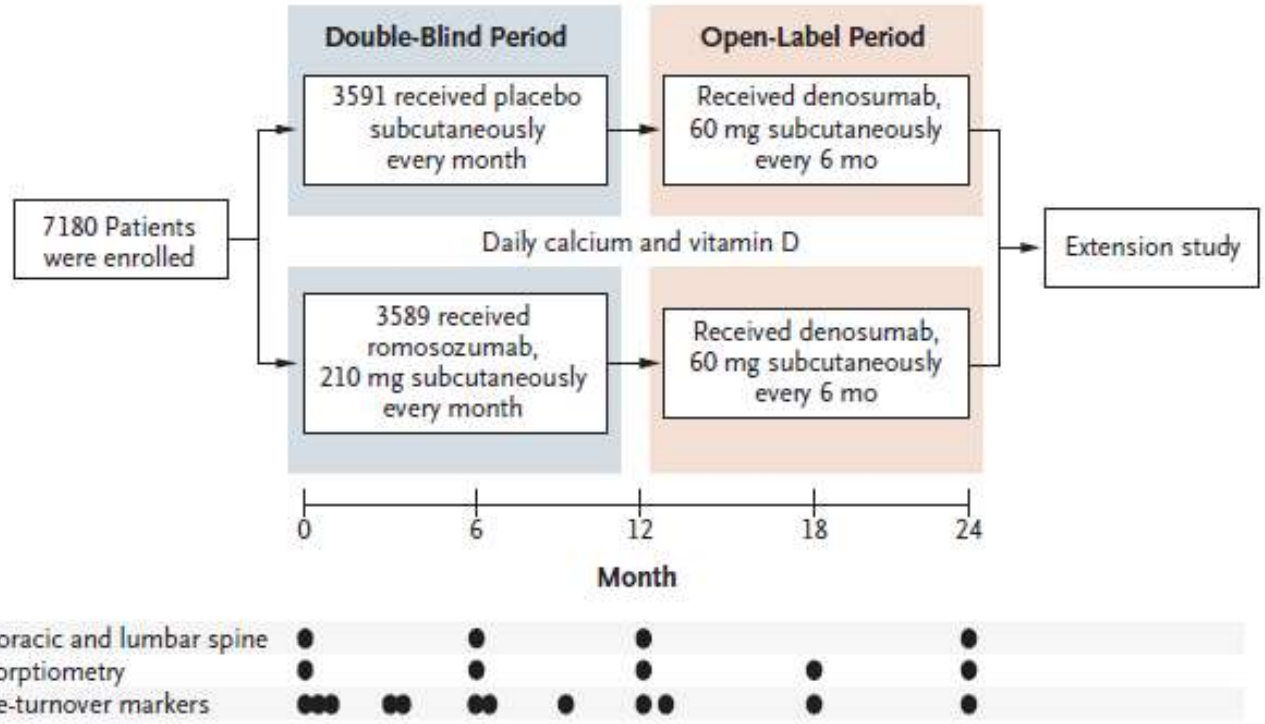
Effects of Romosozumab on bone.



Romosozumab targets and binds sclerostin (Scl). Physiologically, Scl reduces osteoblastogenesis and promotes osteoclastogenesis. Thus, Scl inhibition leads to both anabolic (increased osteoblast activation) and anti-resorptive (reduced osteoclastogenesis) effects

Tartaglione et al J of Nephrology 2017

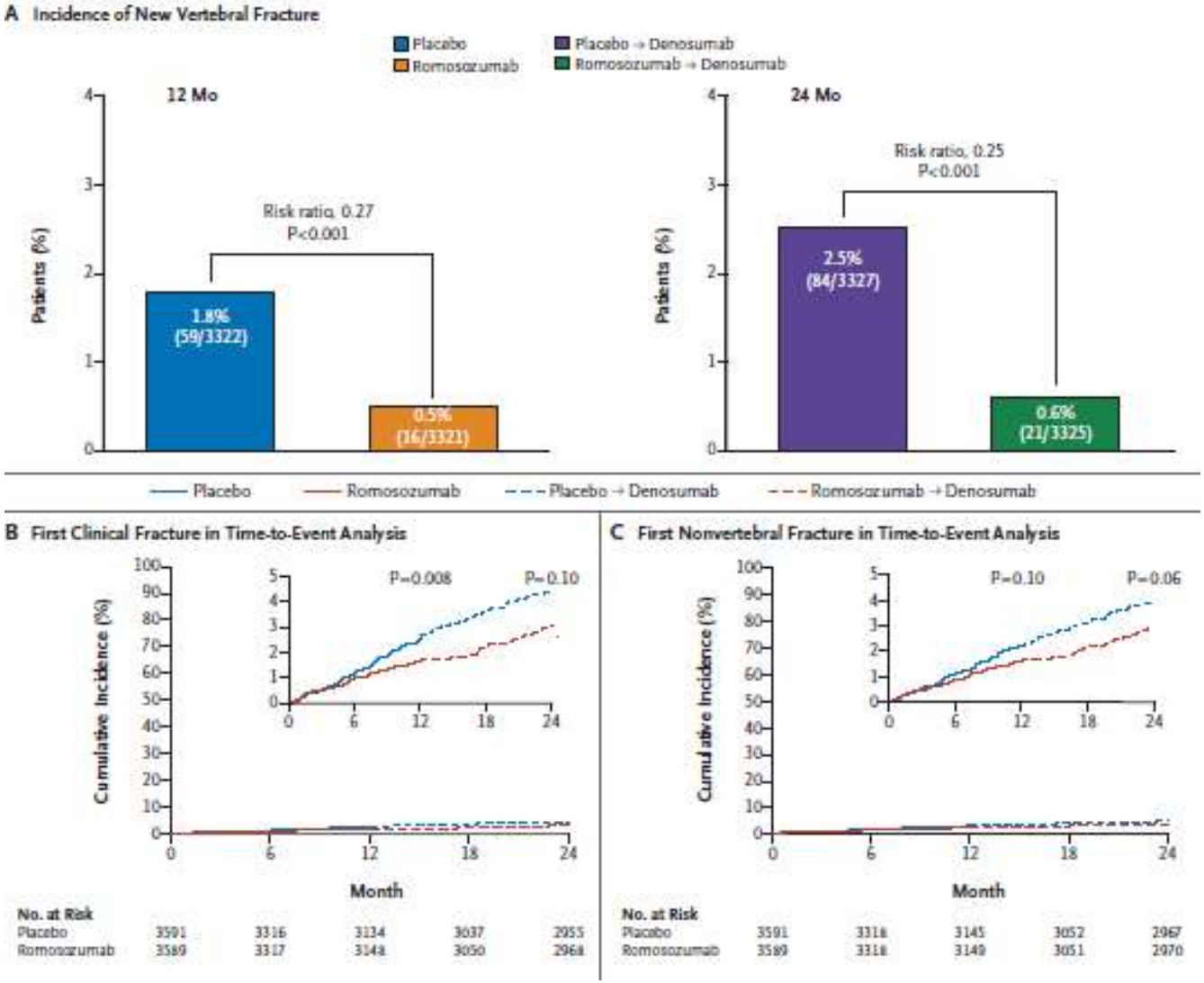
Trial Regimens and Assessments.****



Women were randomly assigned, in a 1:1 ratio, to receive subcutaneous injections of 210 mg of romosozumab or placebo once monthly for 12 months during the double blind phase of the trial. Patients then received open label denosumab, administered subcutaneously at a dose of 60 mg every 6 months for an additional 12 months; the initial group assignment was still blinded. Patients were stratified according to age (<75 years vs. ≥75 years) and prevalent vertebral fracture (yes vs. no). In a subst udy of the overall population that involved 128 patients, bone mineral density was assessed at baseline and every 6 months. In a substud y o f the overall population that involved 129 patients, the levels of bone turnover markers were assessed at baseline, at day 14, and at months 1, 3, 3+14 days, 6, 6+14 days, 9, 12, 13, 18, and 24. After the 24 month trial period, patients continue to receive open label denosumabi n a 1 year extension study (data not shown).

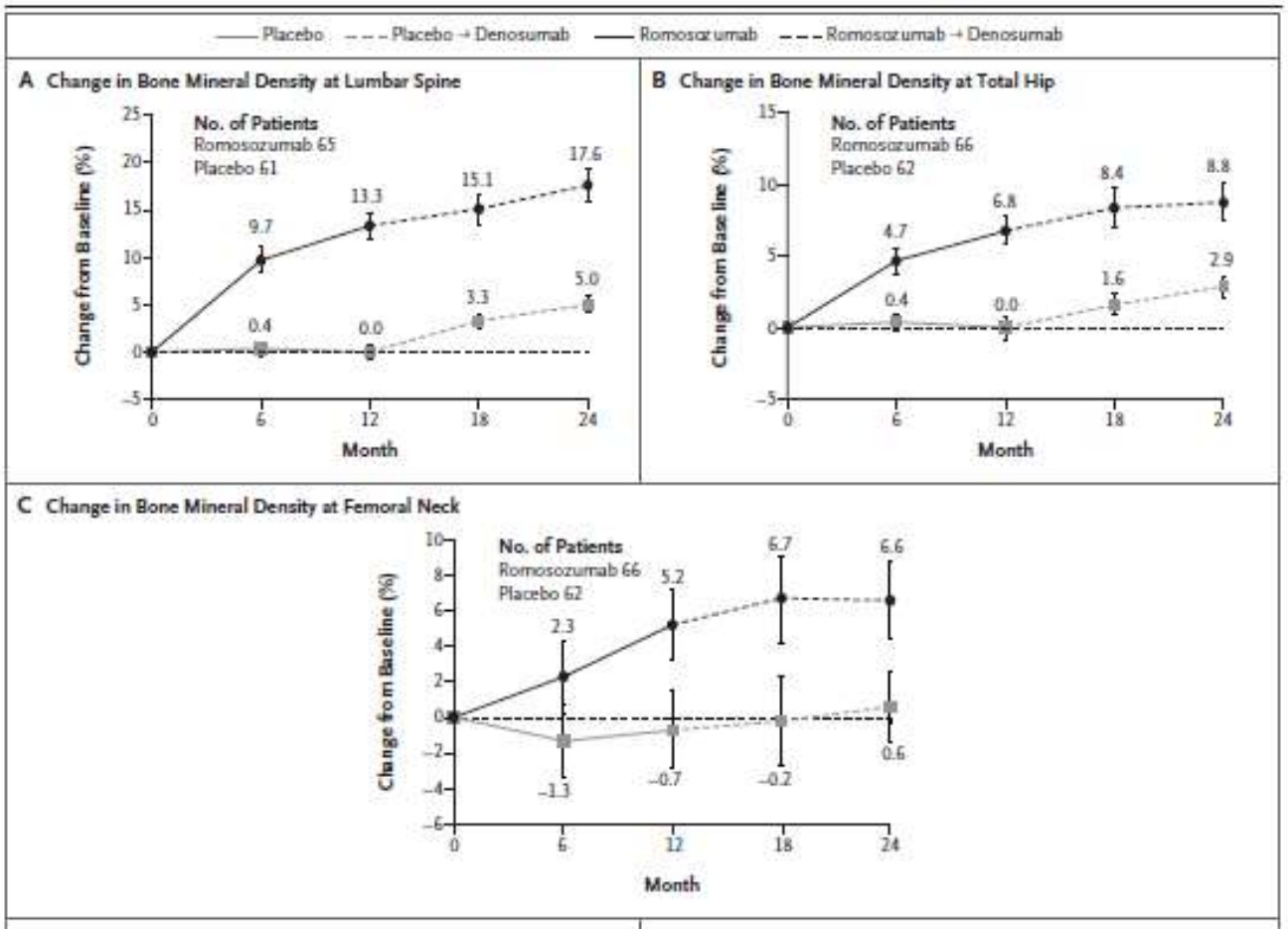
F. Cosman Et al NEJM

Incidence of New Vertebral, Clinical, and Nonvertebral Fractures.



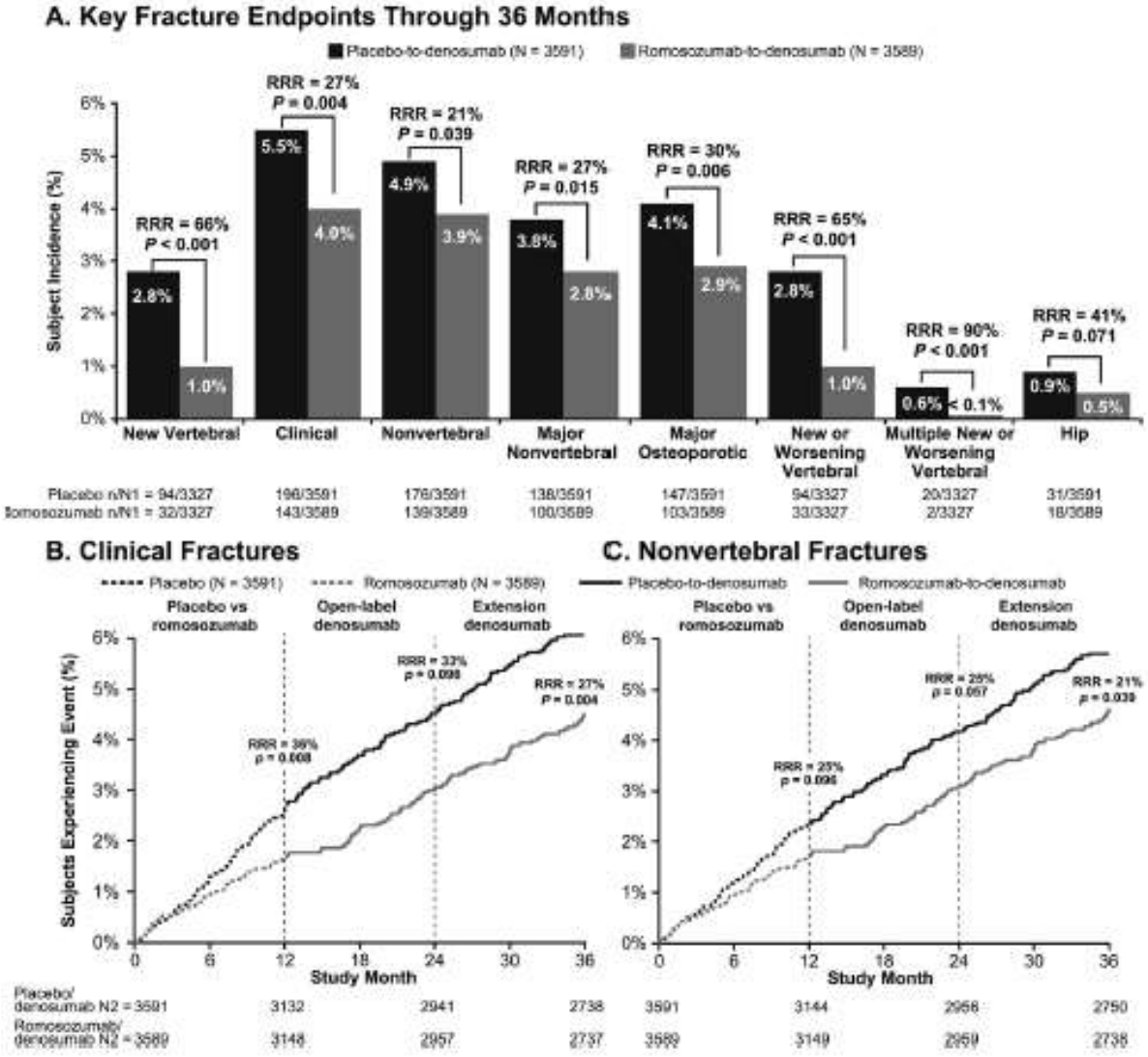
F. Cosman Et al NEJM

Percentage Change from Baseline in Bone Mineral Density and Levels of Bone Turnover Markers.



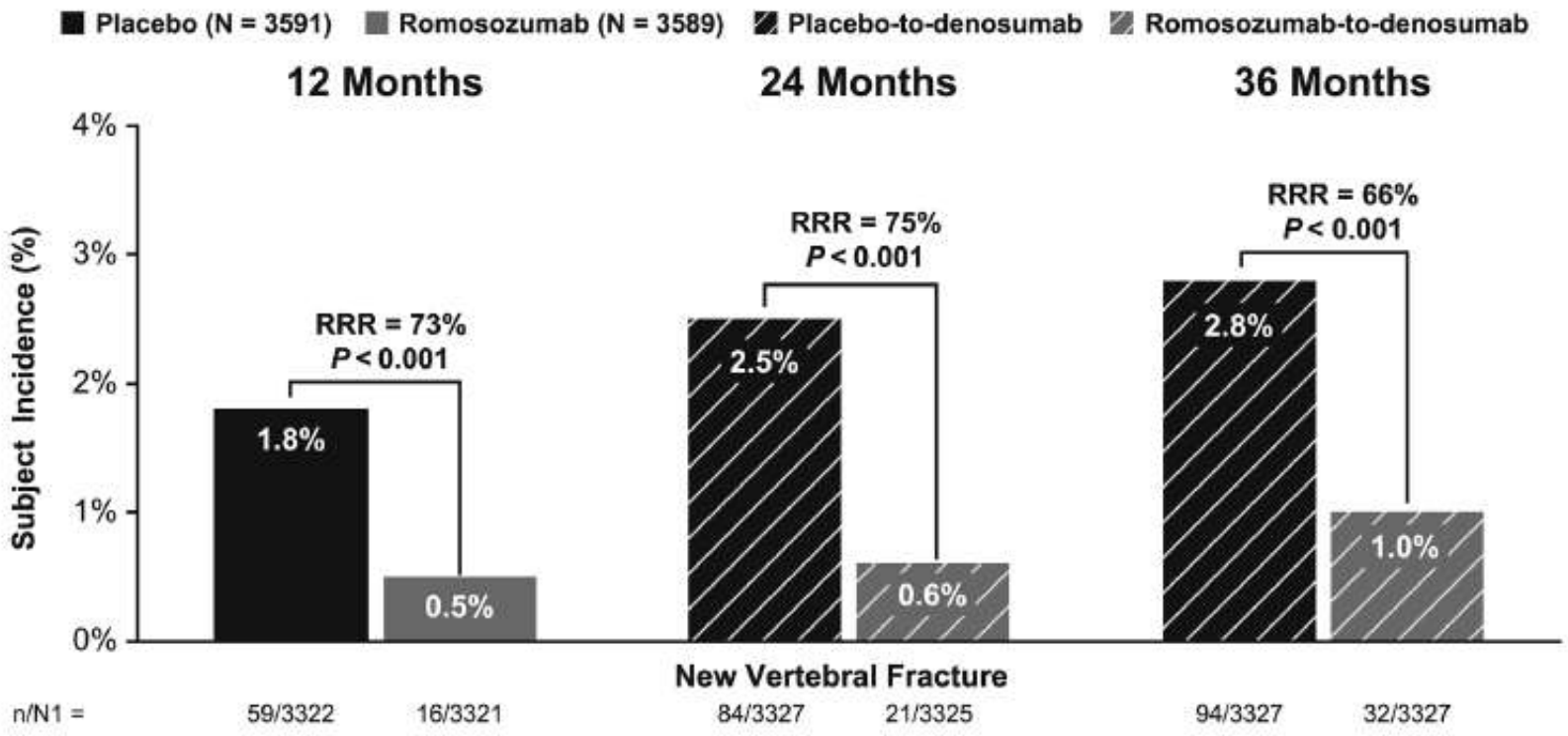
F. Cosman Et al NEJM

Effect of Romosozumab treatment for 12 months followed by Denosumab for 24 months on fracture.



E Michael Lewiecki Et al JBMR

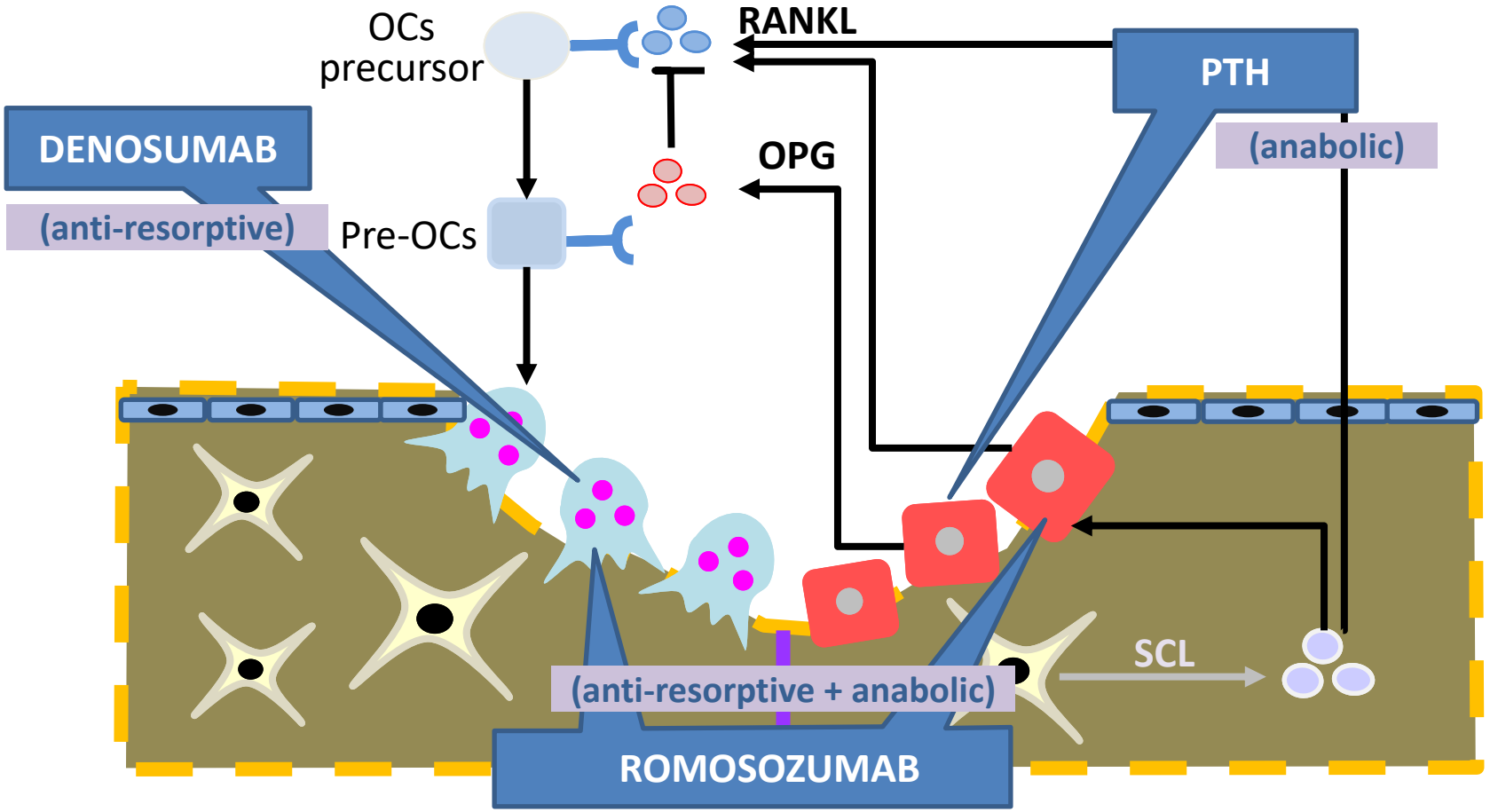
Subject incidence of new vertebral facture through 12, 24, and 36 months for the overall population



The RRR was assessed among
subjects in the romosozumabgroup as compared with those in the placebo group at 12, 24 and 36 months. N=number of subjects randomized; n=number of subjects with fractures; N1=number of subjects in the analysis set; RRR = relative risk reduction

E Michael Lewiecki Et al JBMR

New drugs allow to modulate bone cells activity!



= osteoblasts, = osteoclasts; = osteocytes

We need to know how employ best these drugs in CKD!

Sclerostin levels in CKD patients: an important, but not definitive, step on the way to clinical use

Pierre Delanaye[1], Etienne Cavalier[2], Antoine Bouquegneau[1] and Arif Khwaja[3]

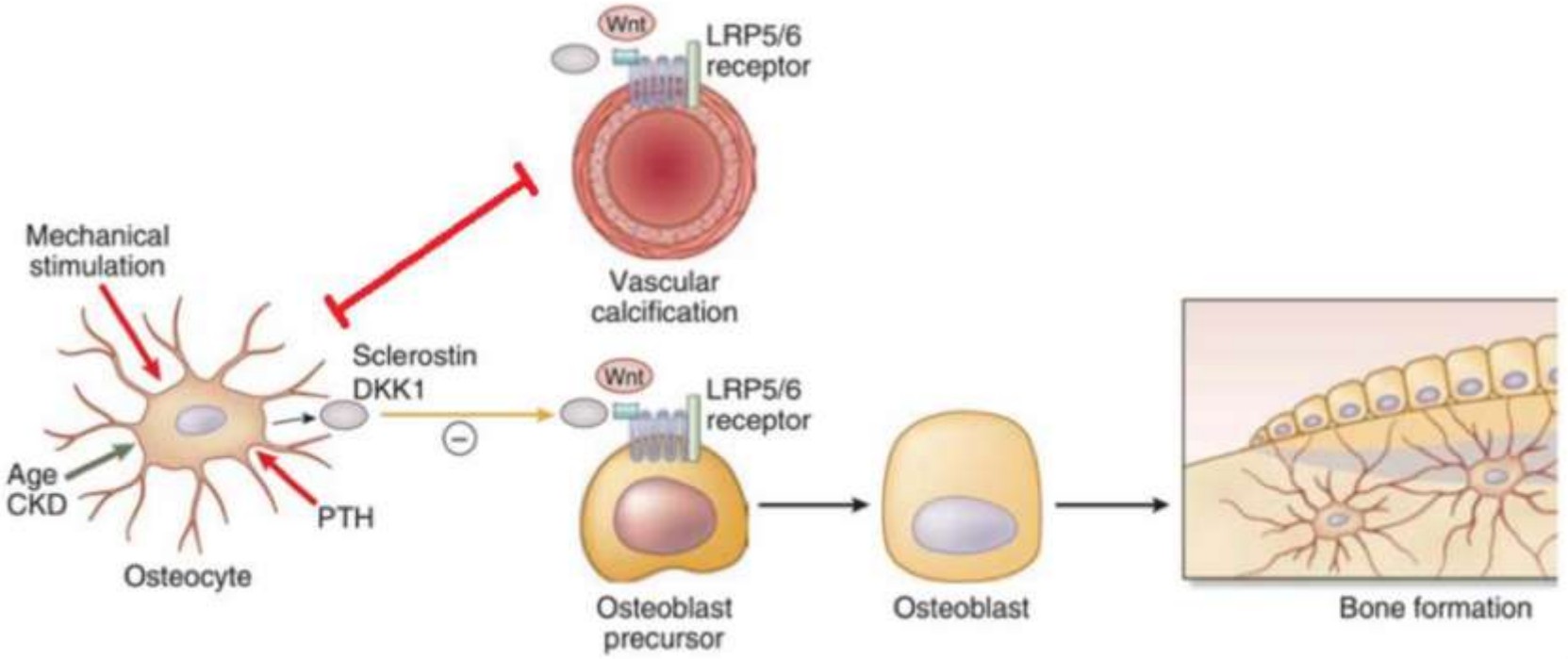


Figure 1 | Sclerostin: regulation, bone effect, and (hypothetical) link with vascular calcifications. The absence of mechanical stimulation induces sclerostin secretion by osteocytes. Sclerostin inhibits the Wnt receptor (LRP5/6), inducing inhibition of differentiation and proliferation of osteoblast precursors into mature osteoblasts. Age and CKD increase sclerostin secretion. Parathyroid hormone (PTH) decreases sclerostin production. Green arrow: Promotion of sclerostin production by osteocytes. Red solid line: Inhibition of sclerostin secretion by osteocytes. Yellow line: Inhibition of the Wnt pathway by sclerostin in bones through the LRP5/6 receptor. Black arrow: Regular way of bone formation. The link between sclerostin and vascular calcifications remains hypothetical (red dotted line). Red solid line: Inhibition of sclerostin secretion by osteocytes. Grey solid line: Stimulation of sclerostin secretion by osteocytes. Yellow line: Inhibition of the Wnt pathway by sclerostin in bones through the LRP5/6 receptor. Black arrow: Regular way of bone formation. The link between sclerostin and vascular calcifications remains hypothetical (red dotted line).

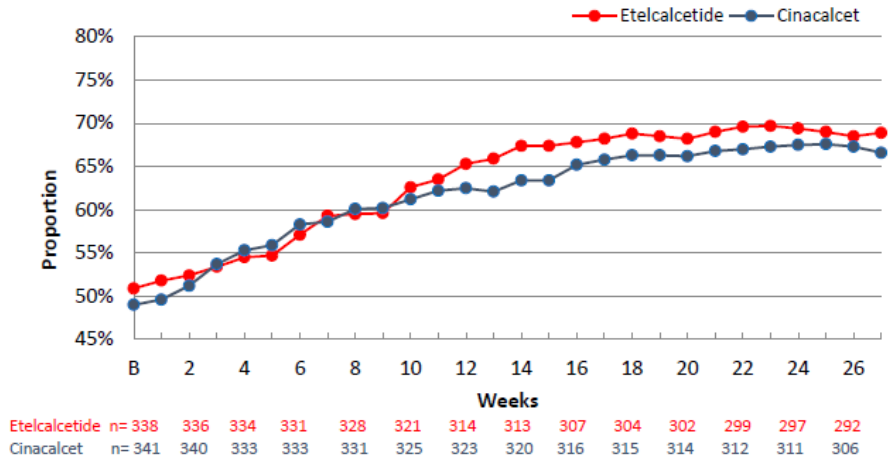
Modified from Kidney International 2015

Administration of etelcalcetide may be associated with QT prolongation secondary to hypocalcaemia

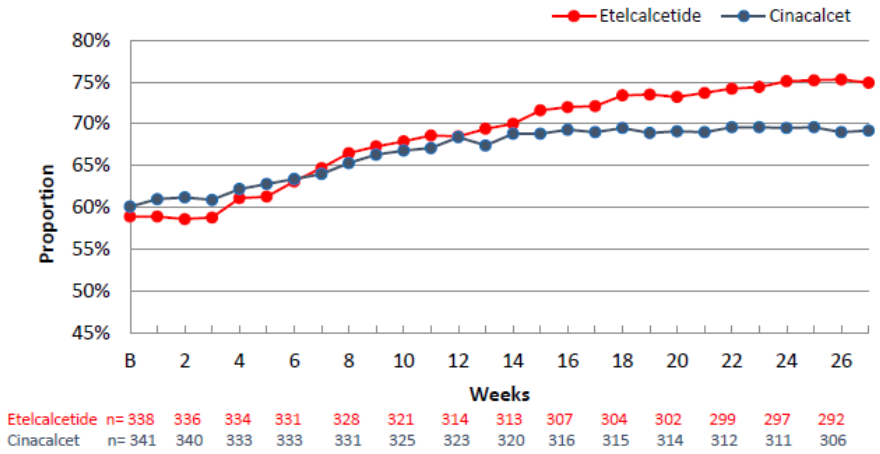
	Placebo-controlled pivotal studies	
	Placebo (N = 513) n (%)	Etelcalcetide (N = 503) n (%)
Maximum QTc increased from baseline (msec)		
> 30 to 60	29 (5.7)	99 (19.7)
> 60	0 (0.0)	6 (1.2)
Maximum QTc post-baseline (msec)		
>480-500	5.5	7.2
>500	1.9	4.8

- Decreases in serum calcium can prolong the QT interval, potentially resulting in ventricular arrhythmia.
- Significant, but clinically silent, QT prolongation was observed in some etelcalcetide-treated patients, which may be related to changes in calcium.
- ECG categorical analyses indicated that the subject incidence of post-baseline increases in QTc was higher in the etelcalcetide group than the placebo group.

Cunningham J et al-ERA EDTA Congress 2015



Use of calcium supplements or calcium-containing binders over time



Use of calcitriol or active vitamin D analogs over time

Block GA, Bushinsky DA, Cheng S, et al. *Supplement 9 JAMA 2017*

Bone: a new endocrine organ at the heart of chronic kidney disease and mineral and bone disorders

*Marc G Vervloet, Ziad A Massy, Vincent M Brandenburg, Sandro Mazzaferro, Mario A Cozzolino, Pablo Ureña-Torres, Jordi Bover, David Goldsmith, on behalf of the CKD-MBD Working Group of ERA-EDTA**

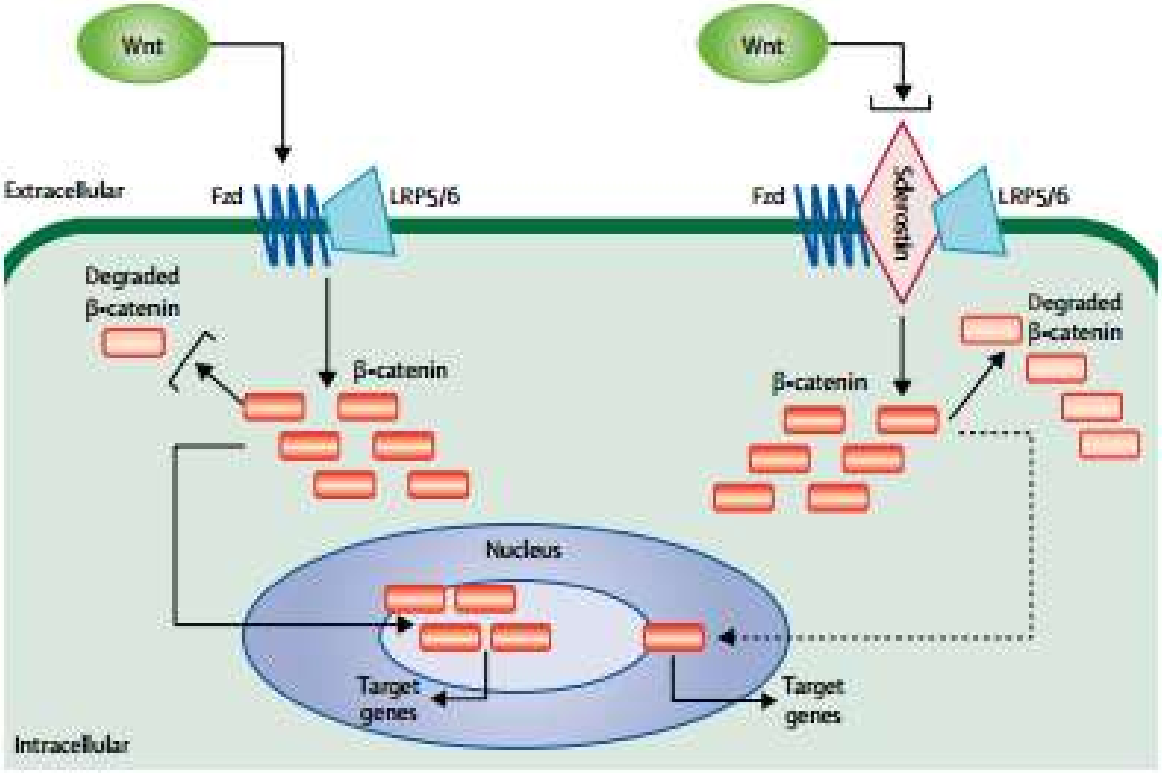


Figure 2: Inhibition of Wnt signalling
Within the canonical pathway, Wnt ligands interact with a transmembrane receptor complex including frizzled (Fzd) and LRP5/6. Activation of the receptor complex stabilises cytosolic β-catenin by blocking degradation processes. Hence, more β-catenin can enter the nucleus and assist activation of target genes. Wnt inhibitors such as sclerostin interfere with Wnt-receptor complex activation and finally reduce intranuclear β-catenin activity by stimulating phosphorylation degradation.

The Lancet 2014

Turning over renal osteodystrophy dogma: direct actions of FGF23 on osteoblast β-catenin pathway

Susan C. Schiavi[1] and Rosa M.A. Moysés[2,3]

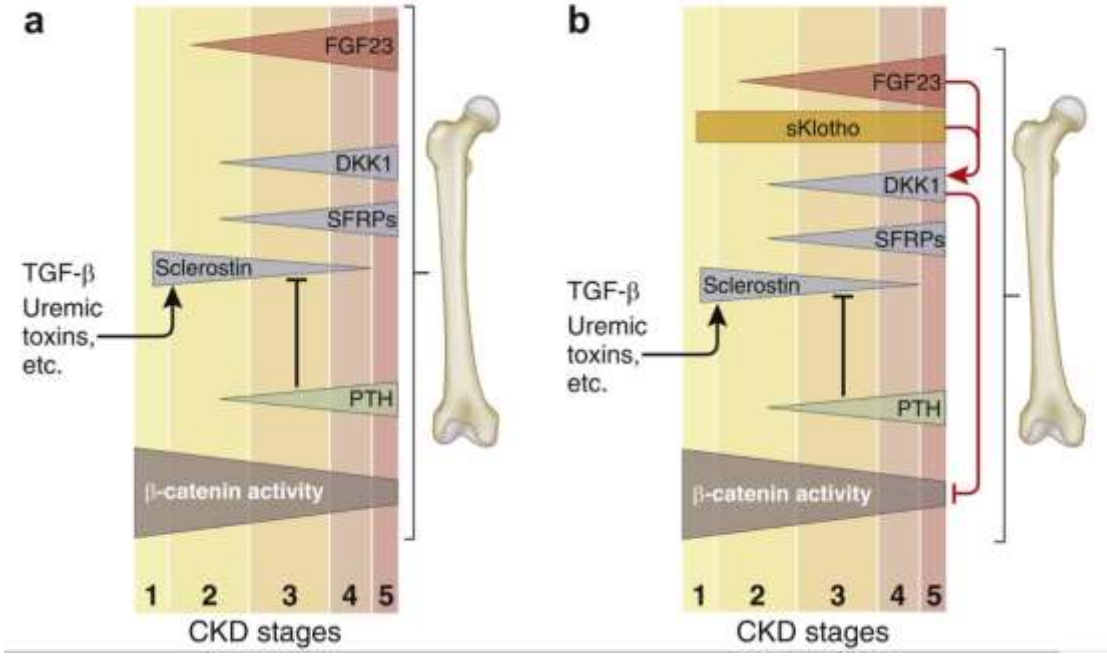
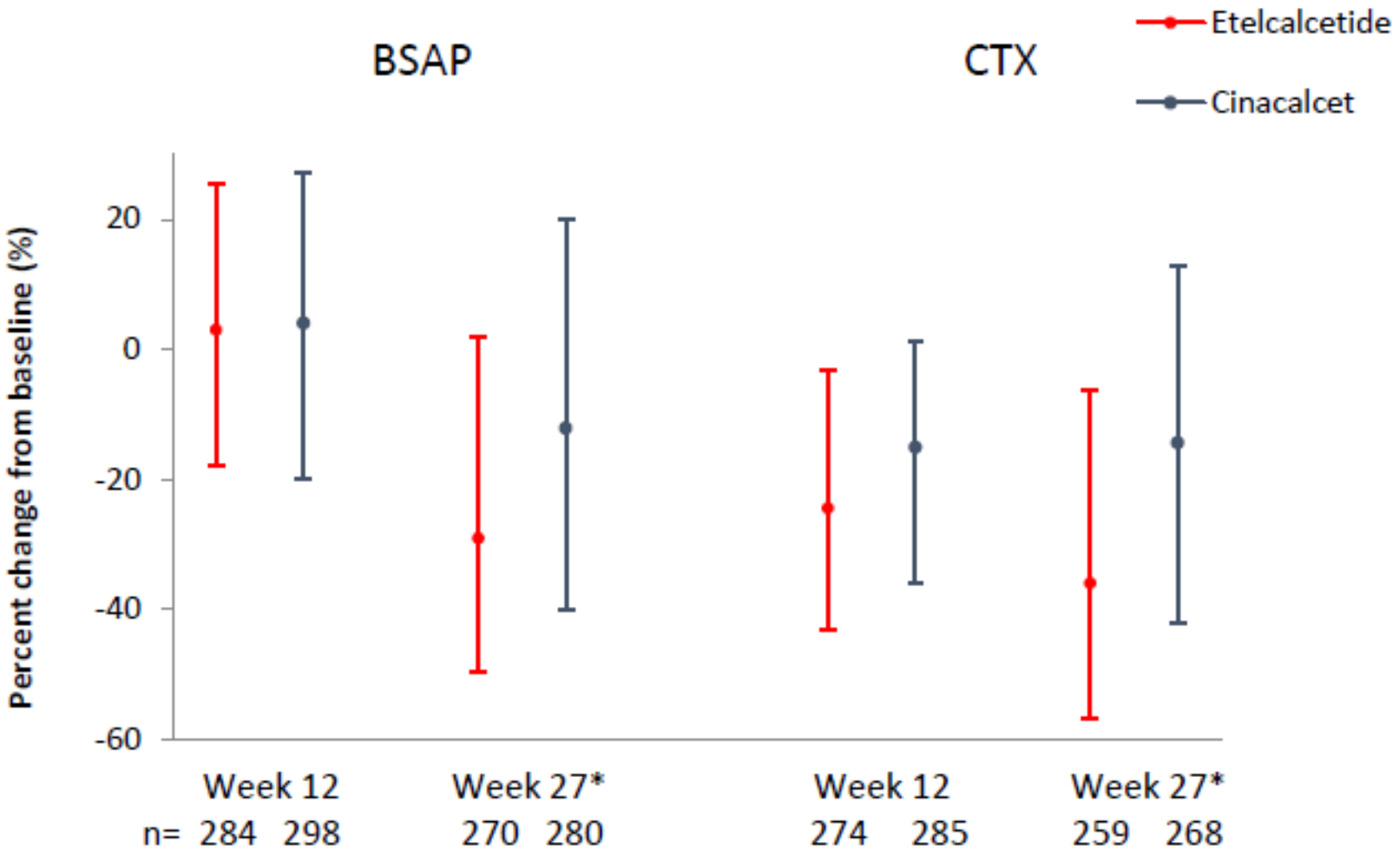


Figure 1 | Current concept of the natural history of CKD-MBD updated with the hypothesis provided by Carrilo-Lopez *et al.*[6] (**a**) Natural history of chronic kidney disease–mineral and bone disorder (CKD-MBD). In early stages of CKD, sclerostin expression is increased, leading to Wnt pathway inhibition and β-catenin phosphorylation. As CKD progresses, parathyroid hormone (PTH) rises and inhibits sclerostin. However, late in the disease, other Wnt pathway inhibitors, such as SFRPs and DKK1 are elevated. (**b**) According to Carrilo-Lopez *et al.*,[6] the combined action of high fibroblast growth factor 23 (FGF23) and maintained soluble Klotho (sKlotho) increase levels of the inactive form of β-catenin through upregulation of DKK1. TGF-β, transforming growth factor β.

Kidney International 2016

Median (IQR) percent change in BSAP and CTX



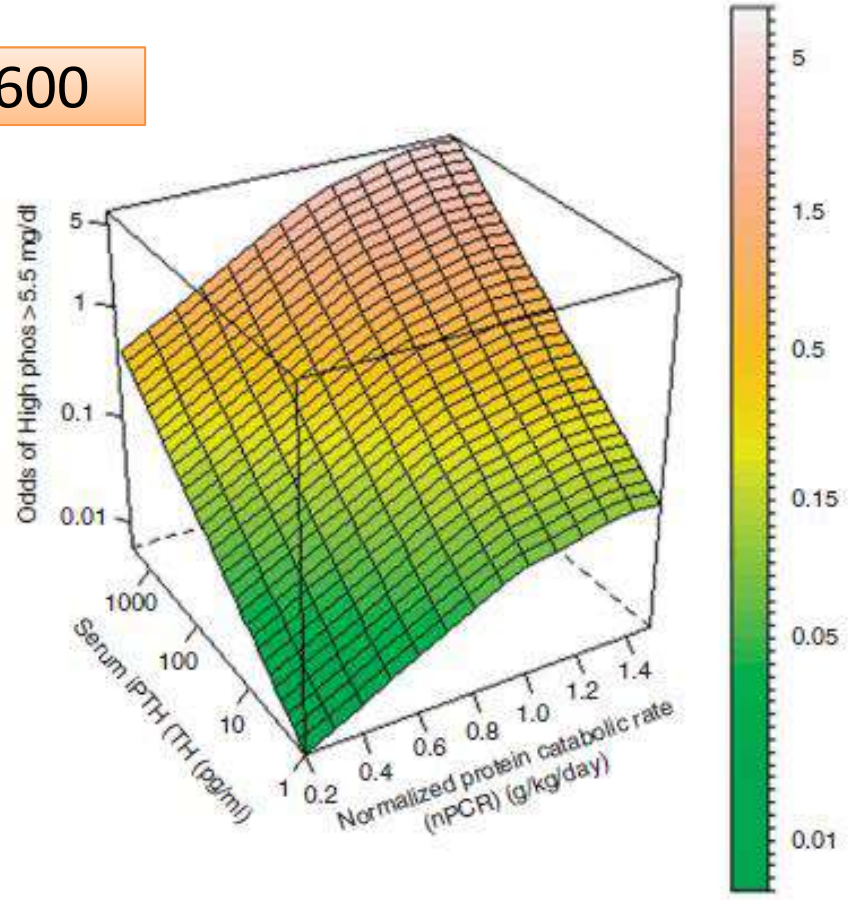
*p-value < 0.0001 for both BSAP and CTX by Wilcoxon rank-sum test

Block GA, Bushinsky DA, Cheng S, et al. Supplement 9 JAMA 2017

Hyperphosphatemia is a combined function of high serum PTH and high dietary protein intake in dialysis patients

Elani Streja[1,8], Wei Ling Lau[1,8], Leanne Goldstein[1], John J. Sim[2], Miklos Z. Molnar[1], Allen R. Nissenson[3,4], Csaba P. Kovesdy[5,6] and Kamyar Kalantar-Zadeh[1,7]

> 600



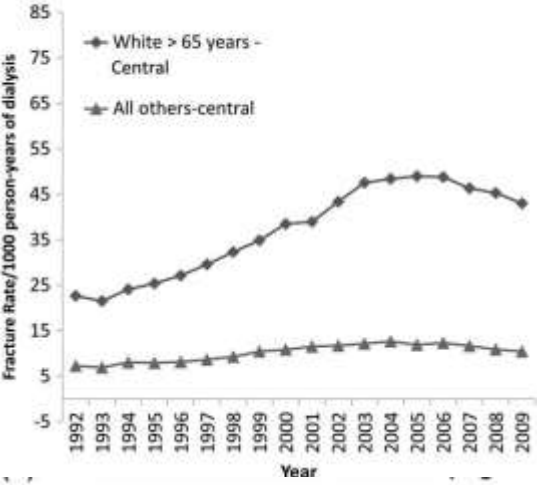
**Relationship between the dependent variable, log odds ratio of serum phosphorus >5.5 mg/dl and independent variables, serum intact parathyroid hormone (iPTH), and normalized protein catabolic rate (nPCR)

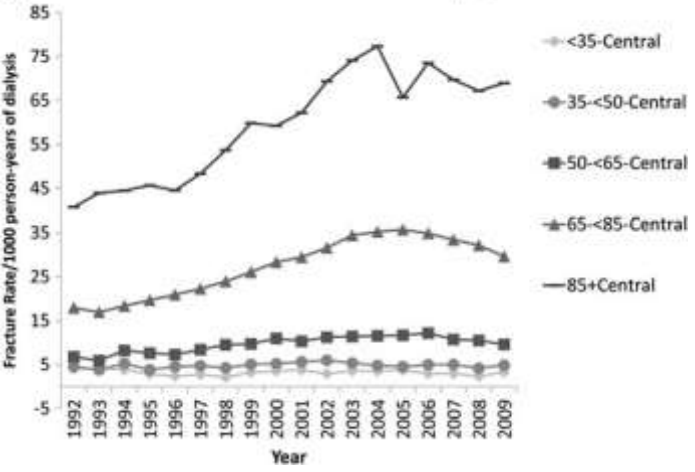
Increased bone fractures among elderly United States hemodialysis patients

John Wagner,
Kenar D. Jhaveri,
Lisa Rosen,
Suzanne Sunday,
Anna T. Mathew
and Steven Fishbane

Division of Kidney Disease and Hypertension, Department of Medicine and Department of Biostatistics, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, Great Neck, NY, USA

Rates of central bone breaks:
By White ≥ 65 years





Renal Osteodystrophy in the First Decade of the New Millennium: Analysis of 630 Bone Biopsies in Black and White Patients

Hartmut H Malluche, Hanna W Mawad, and Marie-Claude Monier-Faugere

T

Bone Turnover (T)

Most frequently LOW, especially in Whites

M

Mineralization (M)

Rarely defective

V

LOW in Whites; HIGH/NOR in Blacks

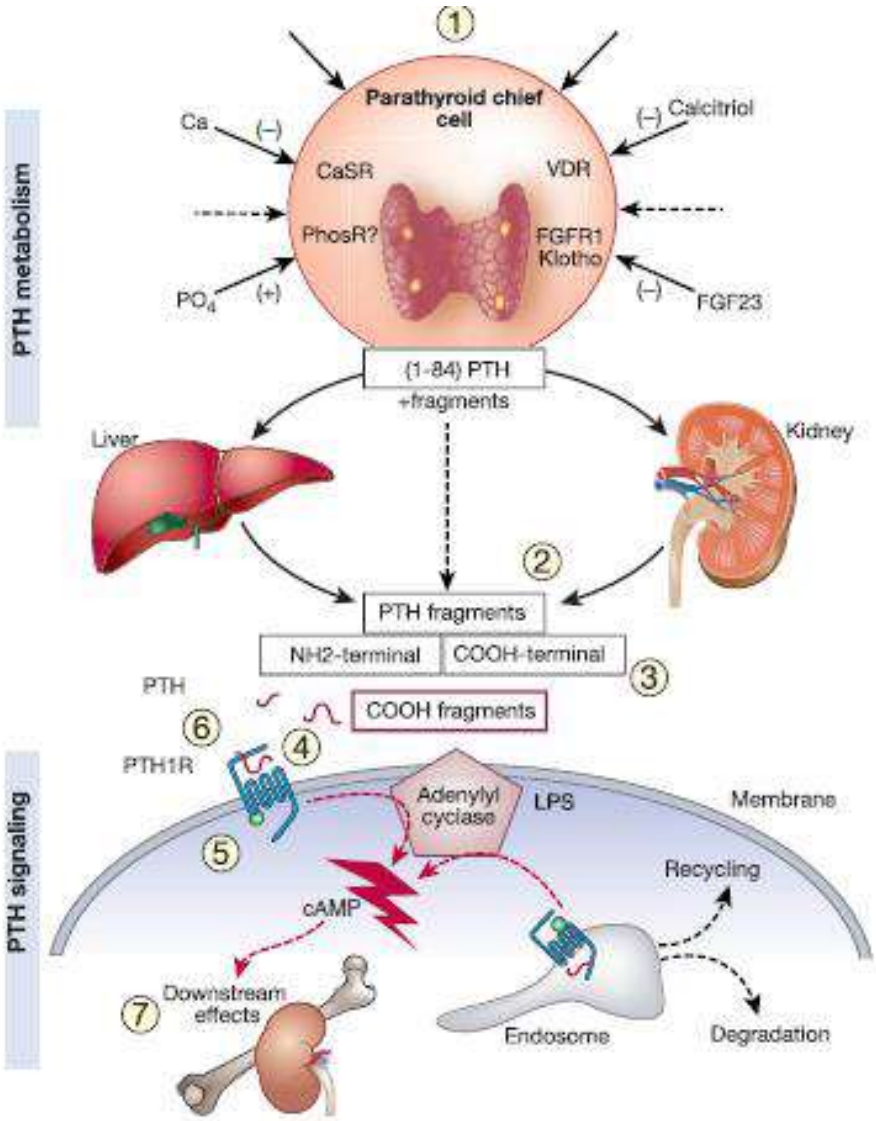
Cortical Porosity

LOW in Whites; HIGH/NOR in Blacks

Architecture

JBMR 2011

Impact of chronic kidney disease on parathyroid hormone metabolism and signaling



P Evenepoel et al, Kidney International (2016)

Renal Osteodystrophy in the First Decade of the New Millennium: Analysis of 630 Bone Biopsies in Black and White Patients

Hartmut H Malluche, Hanna W Mawad, and Marie-Claude Monier-Faugere

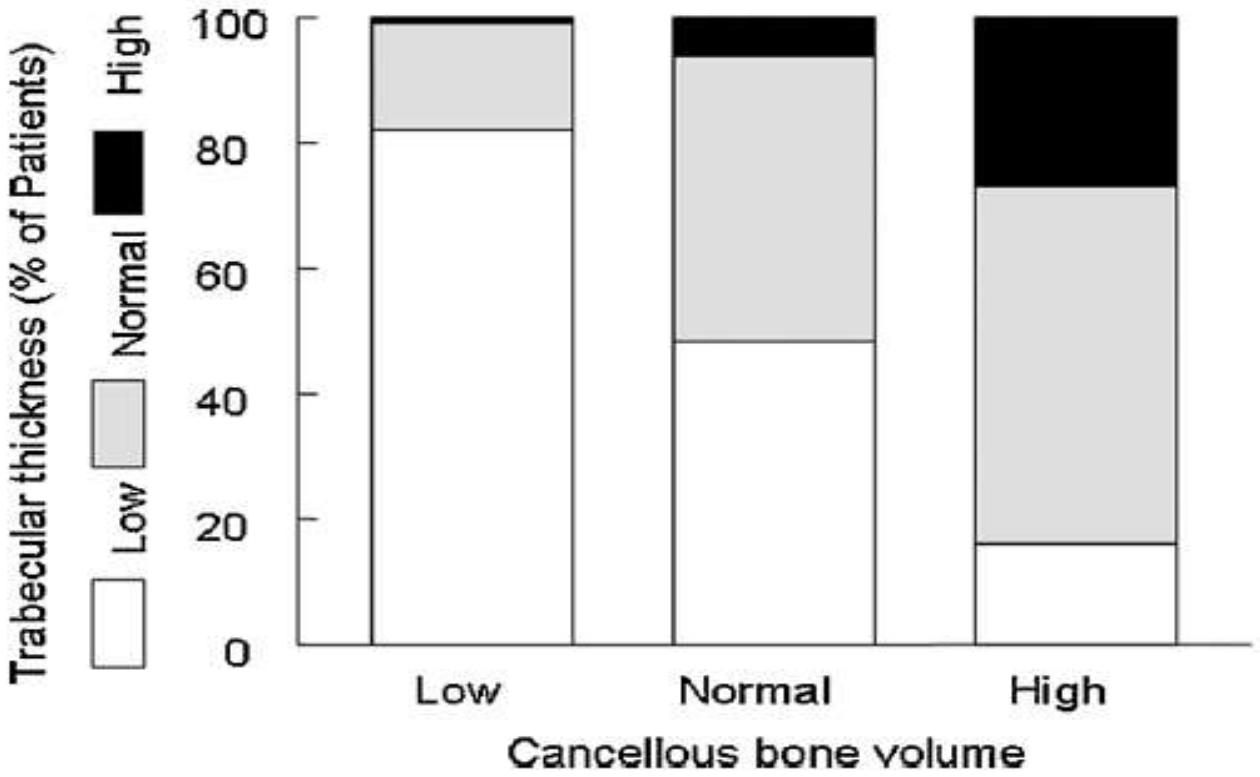


Fig. 5. Prevalence of low, normal, and high trabecular thickness in CKD stage 5 patients on maintenance dialysis with low, normal, or high cancellous bone volume/tissue volume. Significant difference in distribution (chi-square, $p < .001$).

JBMR 2011

The pitfall of treating low bone turnover: Effects on cortical porosity

Maria Julia C.L.N. Araujo [a], Cristina Karohl [b], Rosilene M. Elias [a], Fellype C. Barreto [c,f], Daniela Veit Barreto [c], Maria Eugenia F. Canziani [d], Aluizio B. Carvalho [d], Vanda Jorgetti [a], Rosa M.A. Moyses [a,e,*]

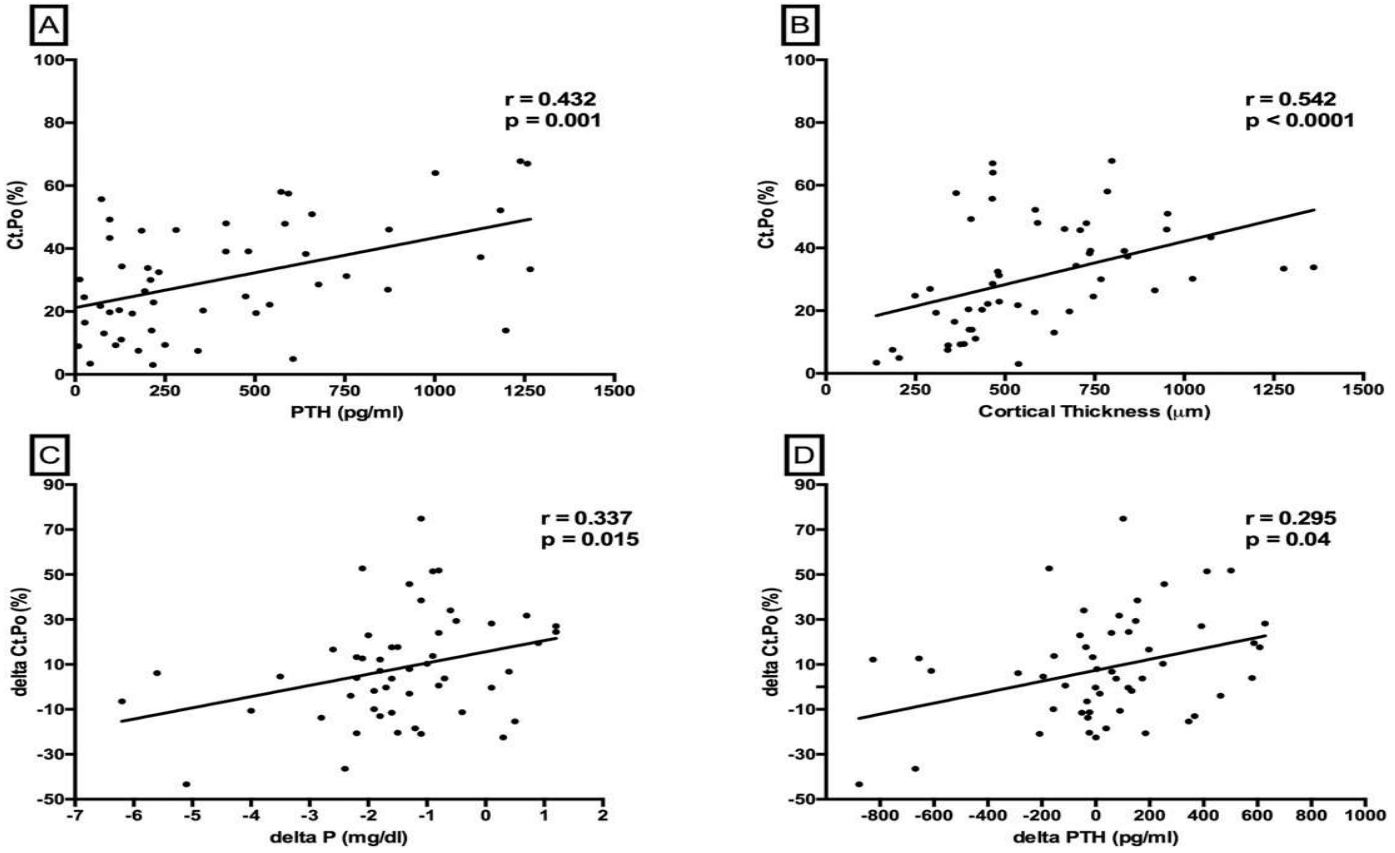


Fig. 3. Correlations between Cortical Porosity at Baseline and after one-year treatment. A. Relationship between cortical porosity (Ct.Po) and parathyroid hormone (PTH), both measured at baseline. B. Relationship between cortical porosity (Ct.Po) and cortical thickness, both measured at baseline. C. Relationship between the delta of cortical porosity (Ct.Po) and the delta of phosphate (P). D. Relationship between the delta of cortical porosity (Ct.Po) and the delta of parathyroid hormone (PTH). Delta: change from baseline to one year later.

Araujo et al., Bone 2016

Management of ventricular arrhythmia and QT prolongation secondary to hypocalcaemia:

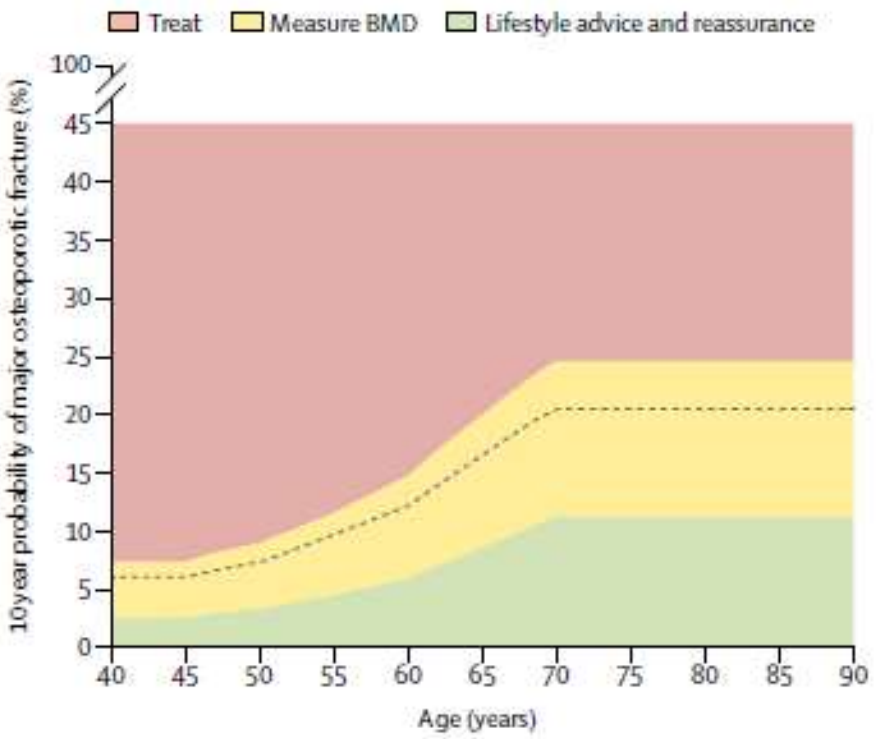
- Decreased in serum calcium can prolong the QT interval, potentially resulting in ventricular arrhythmia
- Serum calcium levels should be closely monitored on patients with
  - congenital long QT syndrome
  - previous history of QT prolongation
  - family history of long QT syndrome or sudden cardiac death
  - other conditions that predispose to QT prolongation and ventricular arrhythmia

Proportion of patients treated with dialysate calcium concentrations of 2.5, >2.5 and <3.5 and 3.5 mEq/L at baseline and end-of-study

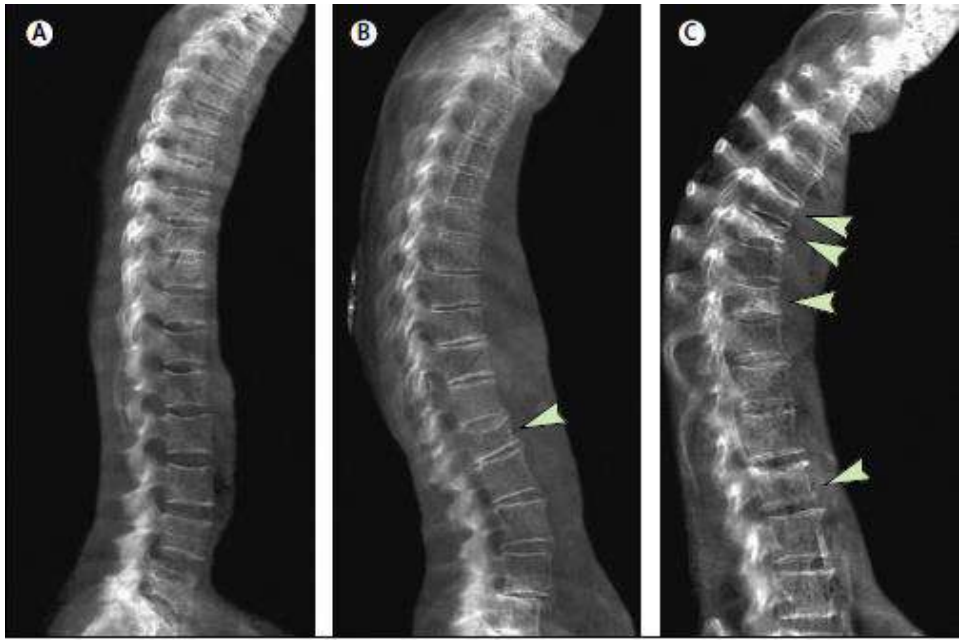
Dialysate Calcium Concentration	Etelcalcetide (N = 337) n (%)	Cinacalcet (N = 342) n (%)
Baseline (mEq/L)		
2.5	185 (54.9)	185 (54.1)
> 2.5 - < 3.5	144 (42.7)	143 (41.8)
3.5	8 (2.4)	14 (4.1)
End of Study (mEq/L)		
2.5	139 (41.2)	137 (40.1)
> 2.5 - < 3.5	155 (46.0)	162 (47.4)
3.5	43 (12.8)	43 (12.6)

Block GA, Bushinsky DA, Cheng S, et al. Supplement 9 JAMA 2017

**UK National Osteoporosis Guidelines Group assessment and treatment thresholds: sbagliate le fig: ci vogliono la 2 e la 3

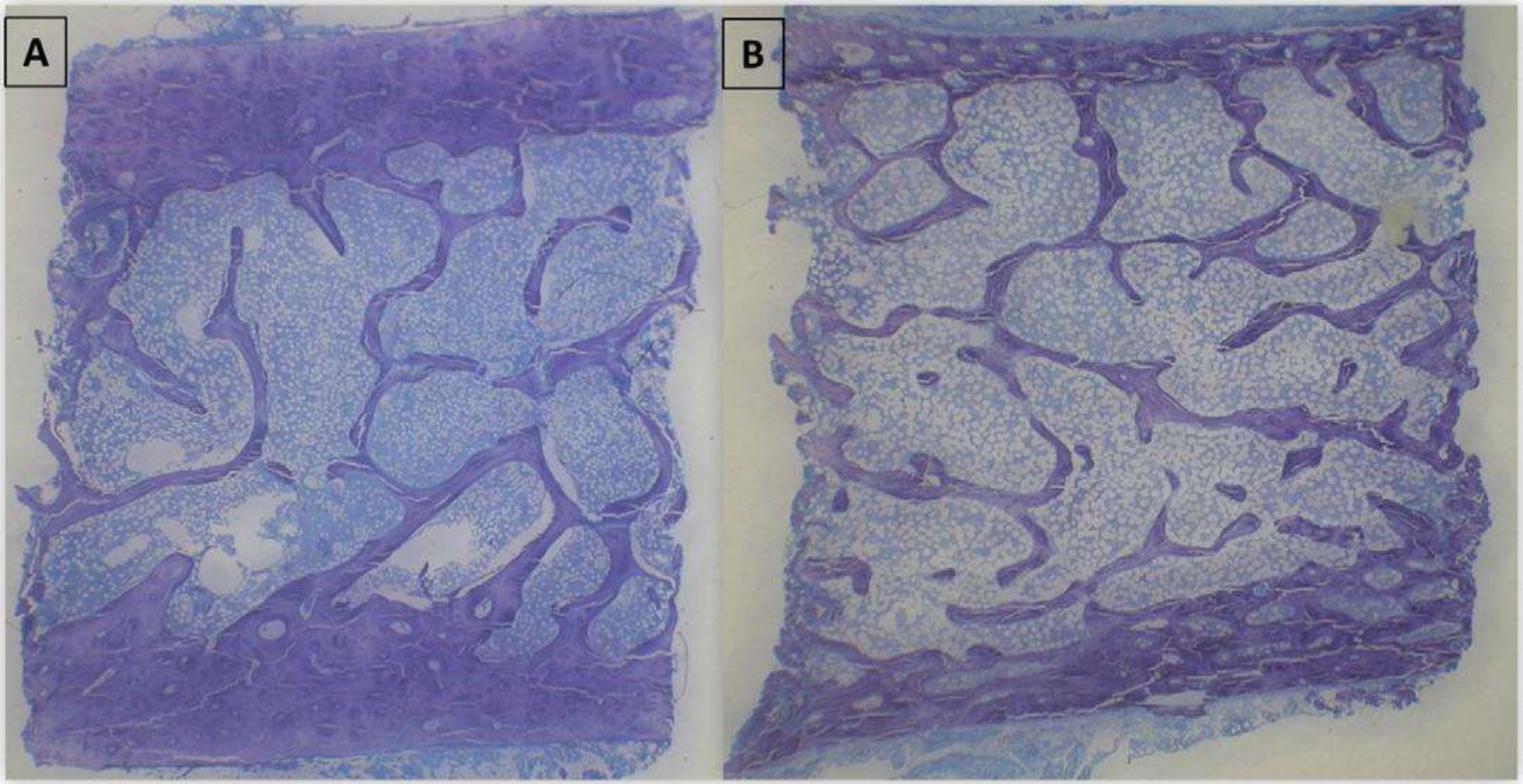


Previously unrecognised vertebral fractures



D. Miyaoka et al Osteoporosis int 2019

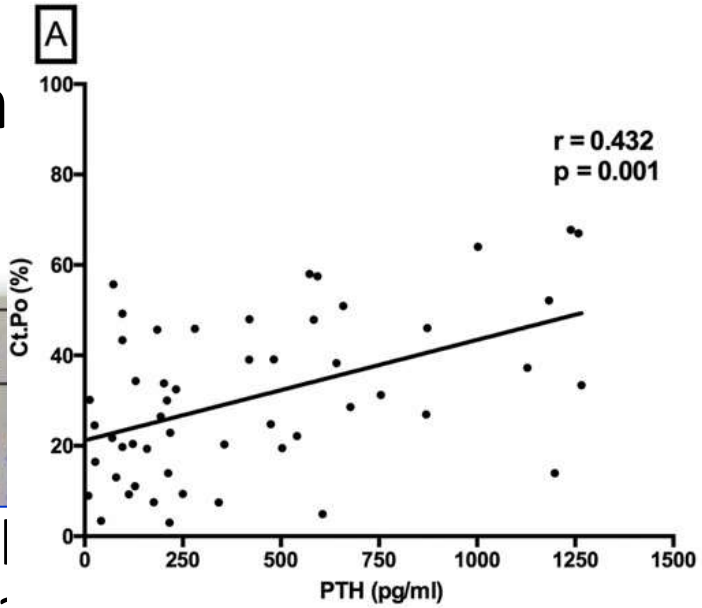
Comparison of cortical compartments in bone biopsies

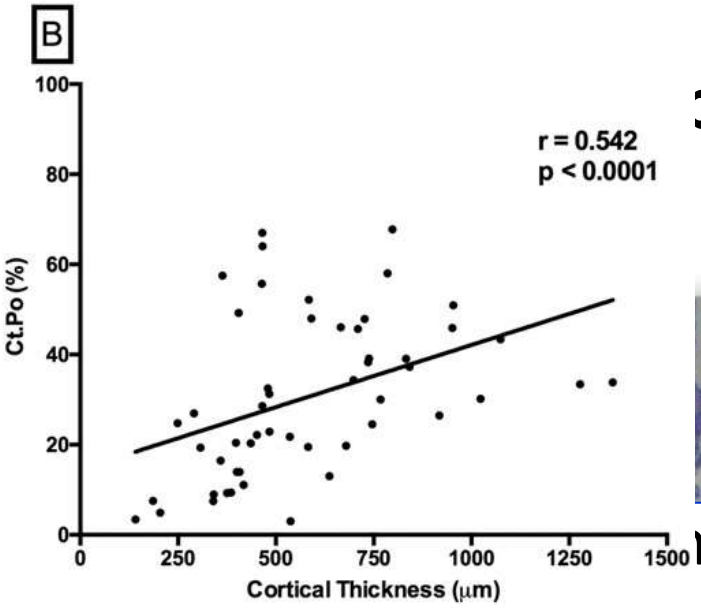


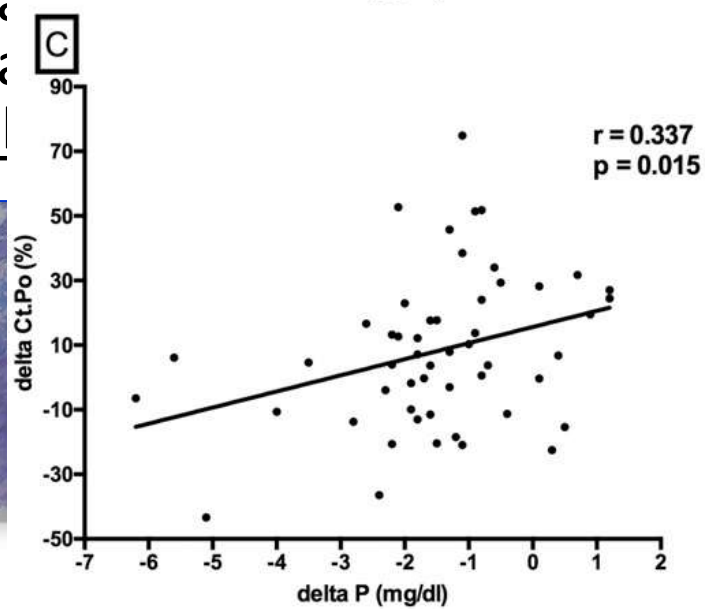
Bone biopsy with normal cortical thickness and cortical porosity from a <u>non CKD patient</u>

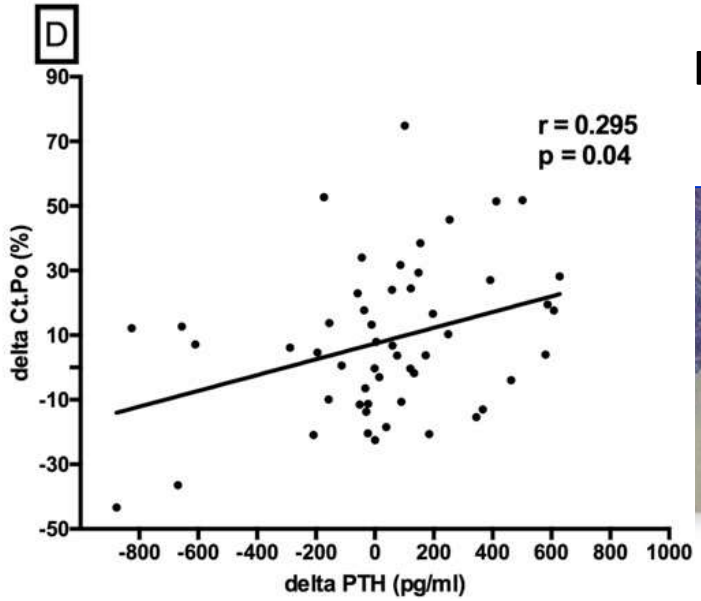
Bone biopsy with high porosity and low cortical thickness from a dialysis patient

Com



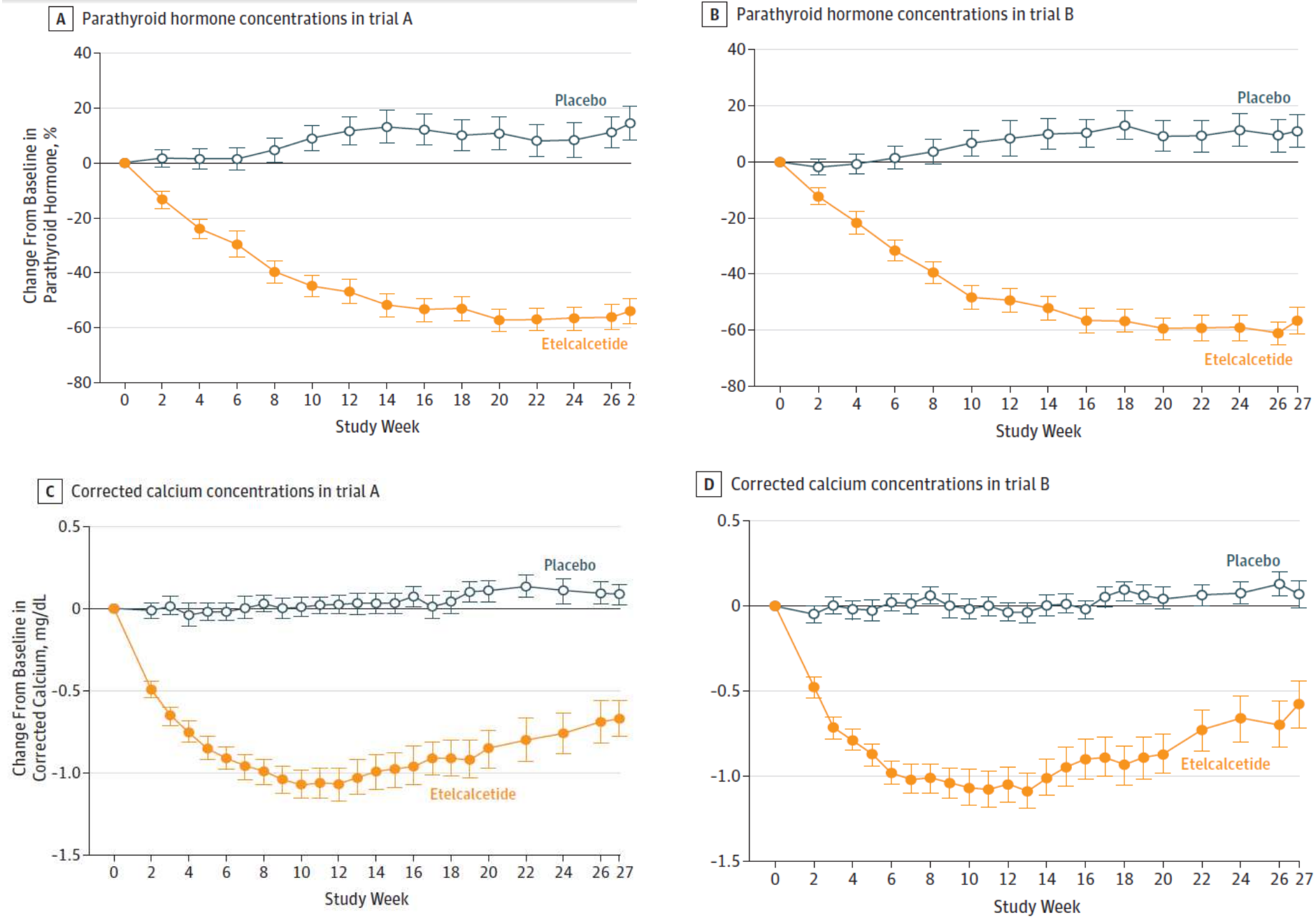


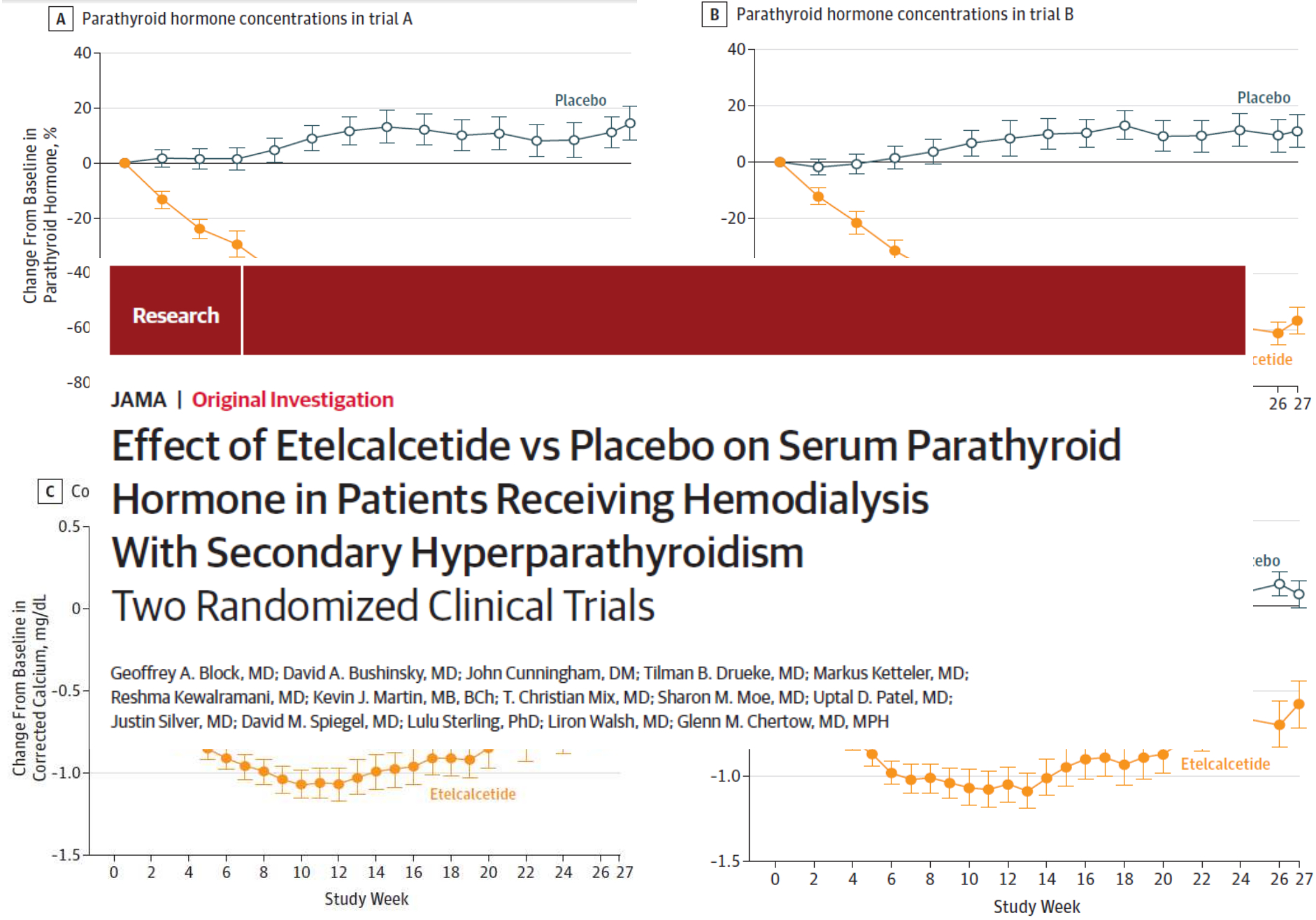




Correlations between Cortical Porosity at Baseline and after one-year treatment.

Araujo et al., Bone 2016


A Parathyroid hormone concentrations in trial A
Change From Baseline in Parathyroid Hormone, %
40
20
0
-20
-40
-60
-80
Placebo
Etelcalcetide
0 2 4 6 8 10 12 14 16 18 20 22 24 26 2
Study Week
B Parathyroid hormone concentrations in trial B
40
20
0
-20
-40
-60
-80
Placebo
Etelcalcetide
0 2 4 6 8 10 12 14 16 18 20 22 24 26 27
Study Week
C Corrected calcium concentrations in trial A
Change From Baseline in Corrected Calcium, mg/dL
0.5
0
-0.5
-1.0
-1.5
Placebo
Etelcalcetide
0 2 4 6 8 10 12 14 16 18 20 22 24 26 27
Study Week
D Corrected calcium concentrations in trial B
0.5
0
-0.5
-1.0
-1.5
Placebo
Etelcalcetide
0 2 4 6 8 10 12 14 16 18 20 22 24 26 27
Study Week


A Parathyroid hormone concentrations in trial A
B Parathyroid hormone concentrations in trial B
Change From Baseline in Parathyroid Hormone, %
Placebo
Etelcalcetide
Research
JAMA | Original Investigation
Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism
Two Randomized Clinical Trials
Geoffrey A. Block, MD; David A. Bushinsky, MD; John Cunningham, DM; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; T. Christian Mix, MD; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; David M. Spiegel, MD; Lulu Sterling, PhD; Liron Walsh, MD; Glenn M. Chertow, MD, MPH
C
Change From Baseline in Corrected Calcium, mg/dL
Study Week

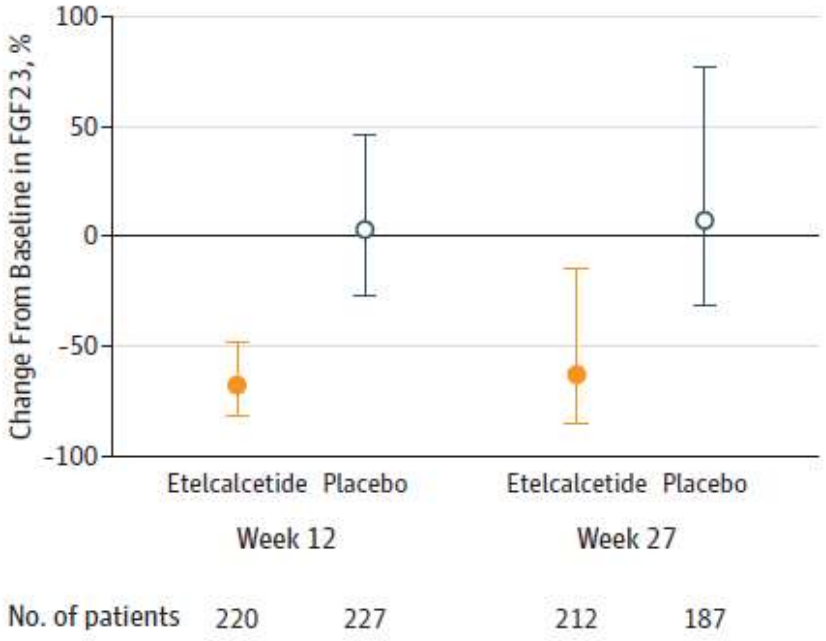
JAMA | Original Investigation

Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

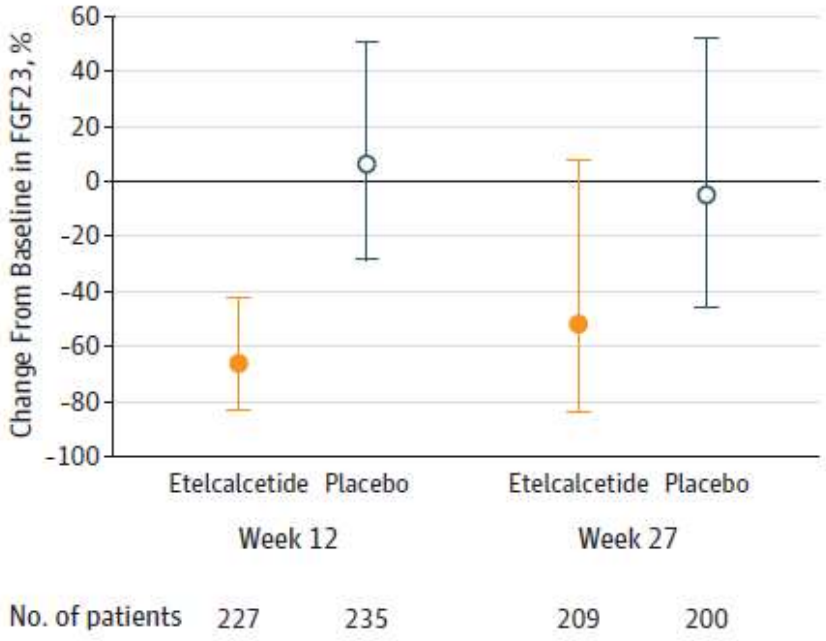
Two Randomized Clinical Trials

Geoffrey A. Block, MD; David A. Bushinsky, MD; John Cunningham, DM; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; T. Christian Mix, MD; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; David M. Spiegel, MD; Lulu Sterling, PhD; Liron Walsh, MD; Glenn M. Chertow, MD, MPH

A FGF23 concentrations in trial A

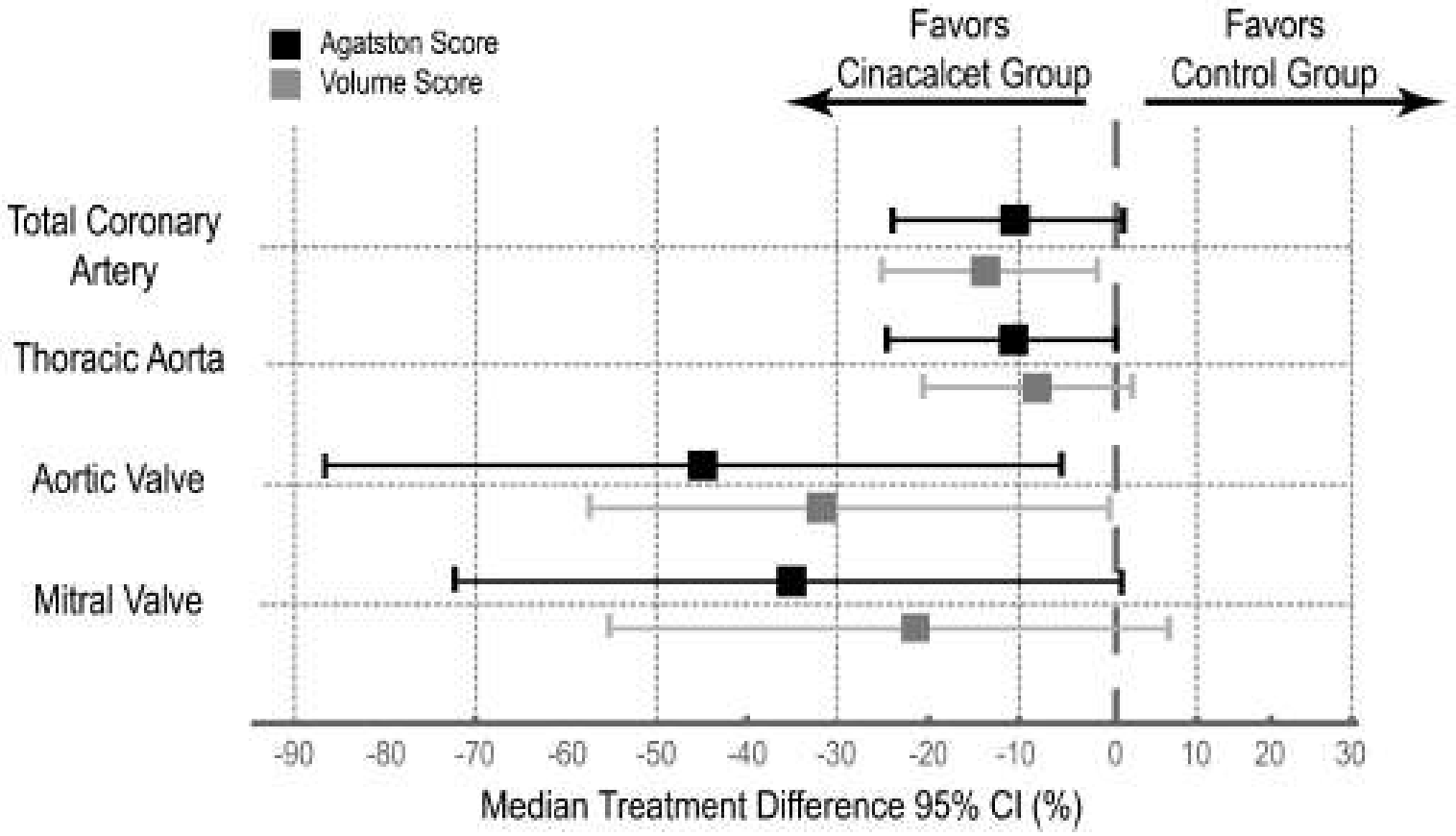


B FGF23 concentrations in trial B

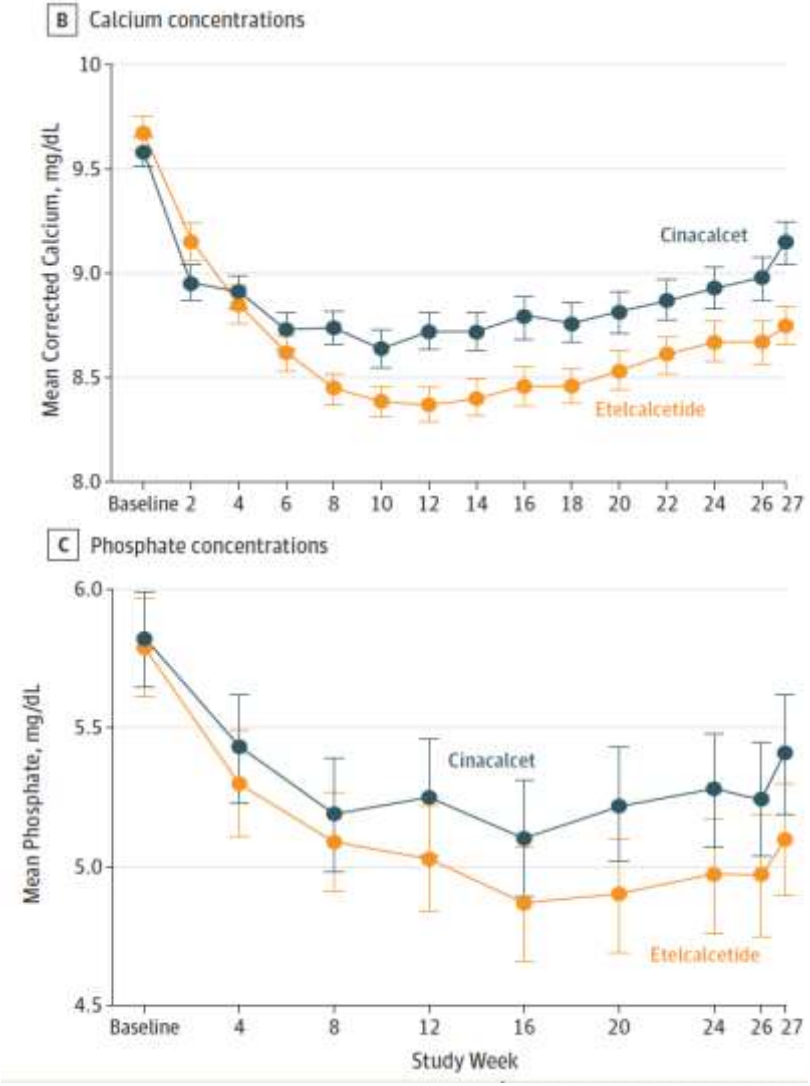


The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis

Paolo Raggi[1], Glenn M. Chertow[2], Pablo Urena Torres[3], Botond Csiky[4], Agostino Naso[5], Kaldun Nossuli[6], Moustafa Moustafa[7], William G. Goodman[8], Nicole Lopez[8], Gerry Downey[9], Bastian Dehmel[10], Jürgen Floege[11] and on behalf of the ADVANCE Study Group

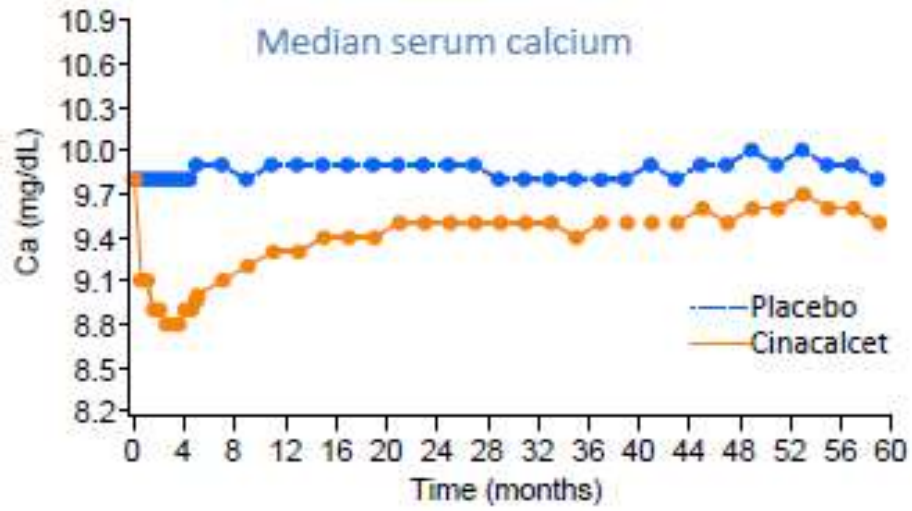


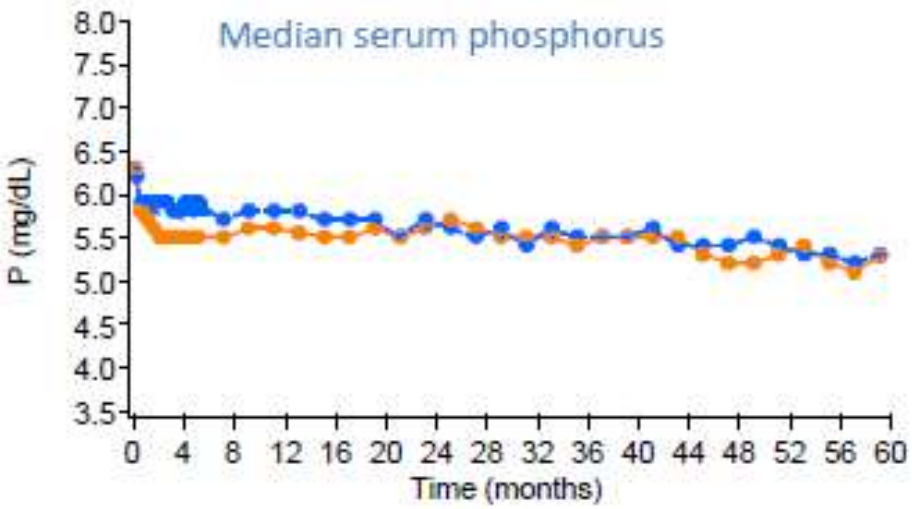
Parathyroid Hormone, Calcium, and Phosphate Concentrations in Patients Receiving Cinacalcet or Etelcalcetide by Study Week



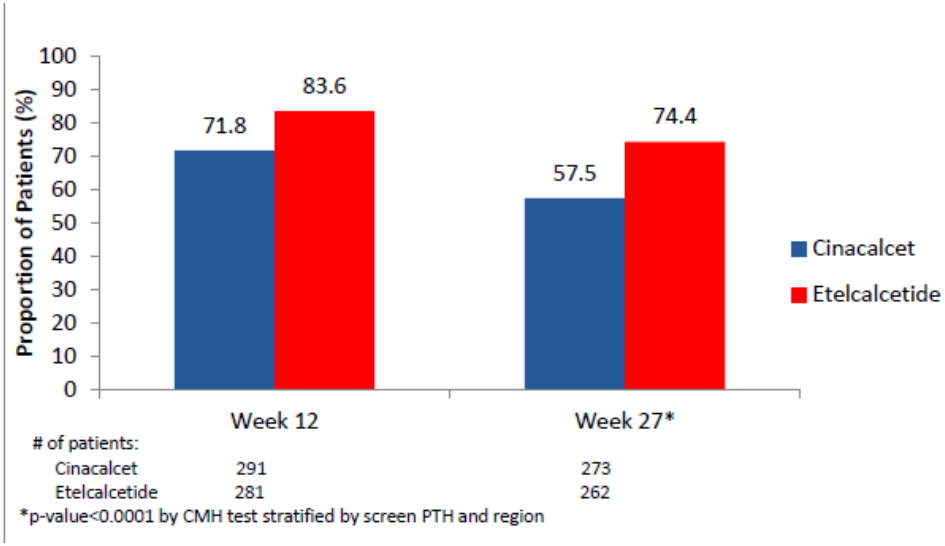
Geoffrey A. Block et al JAMA, 2017

Biochemical parameters (ITT): Substantial reductions in PTH and Ca

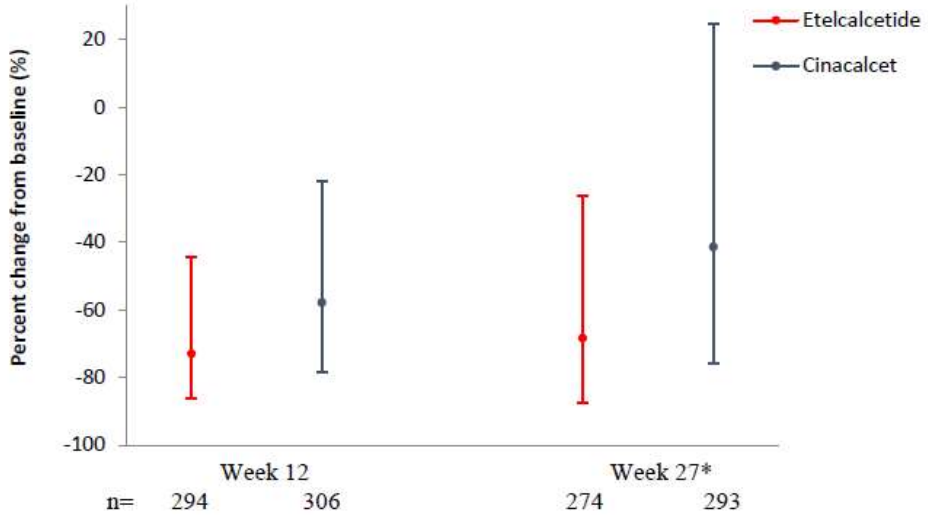




Chertow GM, et al. N Engl J Med. 2012



Proportion of patients with >30% reduction in FGF 23



Median (IQR) percent change in FGF 23

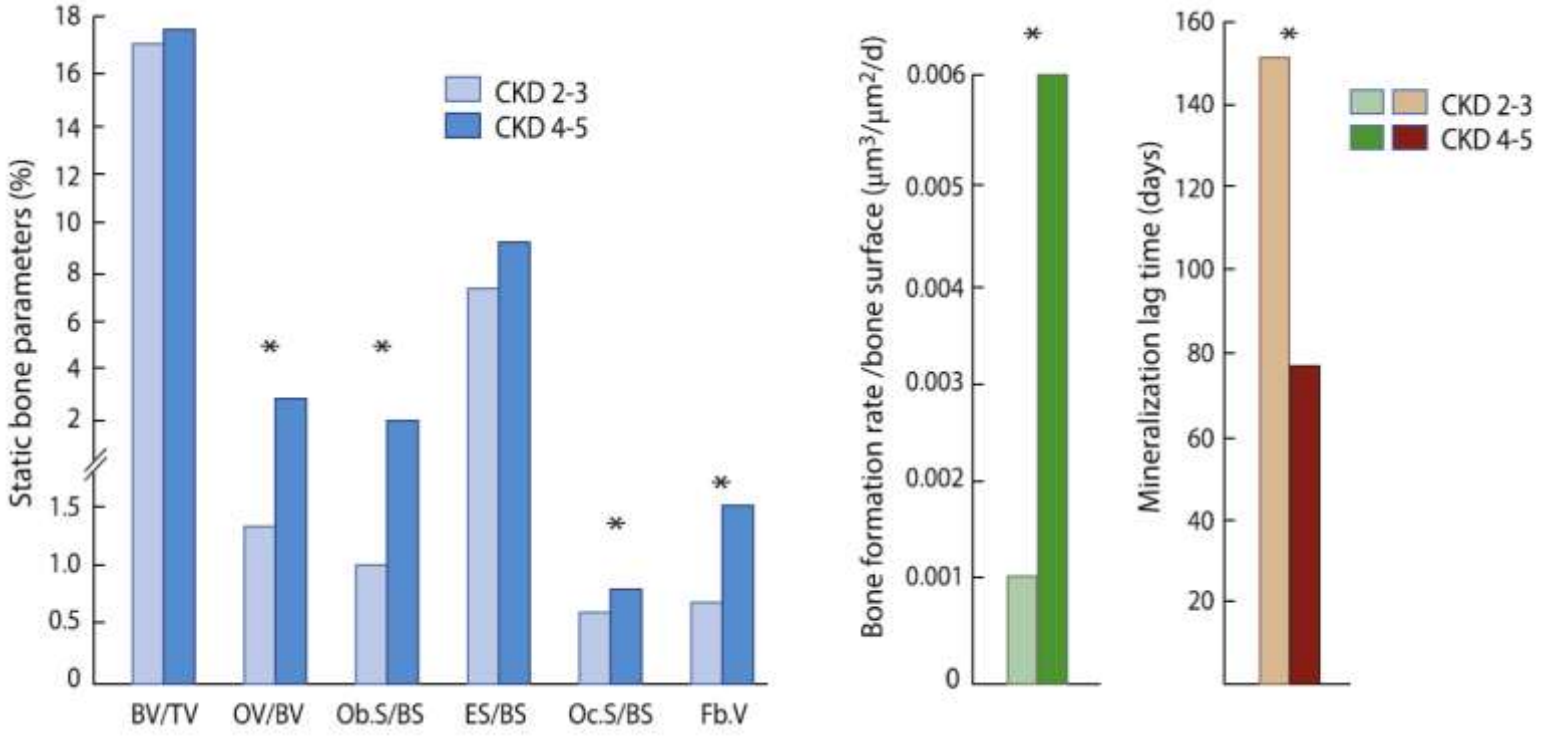
Block GA, Bushinsky DA, Cheng S, et al. Supplement 9 JAMA 2017

Changing bone patterns with progression of chronic kidney disease

Tilman B. Drüeke[1] and Ziad A. Massy[1,2]

[1]Institut National de la Santé et de la Recherche Médicale (Inserm) Unité 1018, Centre de recherche en épidémiologie et santé des populations, Equipe 5, Villejuif; Paris-Sud University and University of Paris–Ouest, Versailles-Saint-Quentin-en-Yvelines; Paris, France; and [2]Division of Nephrology, Ambroise Paré Hospital, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt/Paris; University of Paris–Ouest, Versailles-Saint-Quentin-en-Yvelines; Paris, France

… … available clinical studies indicate higher prevalence of low turnover early and of increased turnover later in CKD



Kidney International (2016) 89, 289

Repression of Osteocyte Wnt/β-Catenin Signaling Is an Early Event in the Progression of Renal Osteodystrophy

Yves Sabbagh,[1]* Fabiana Giorgeti Graciolli,[2]* Stephen O'Brien,[1] Wen Tang,[1] Luciene Machado dos Reis,[2] Susan Ryan,[1] Lucy Phillips,[1] Joseph Boulanger,[1] Wenping Song,[1] Christina Bracken,[1] Shiguang Liu,[1] Steven Ledbetter,[1] Paul Dechow,[3] Maria Eugenia F Canziani,[4] Aluizio B Carvalho,[4] Vanda Jorgetti,[2] Rosa MA Moyses,[2] and Susan C Schiavi[1]

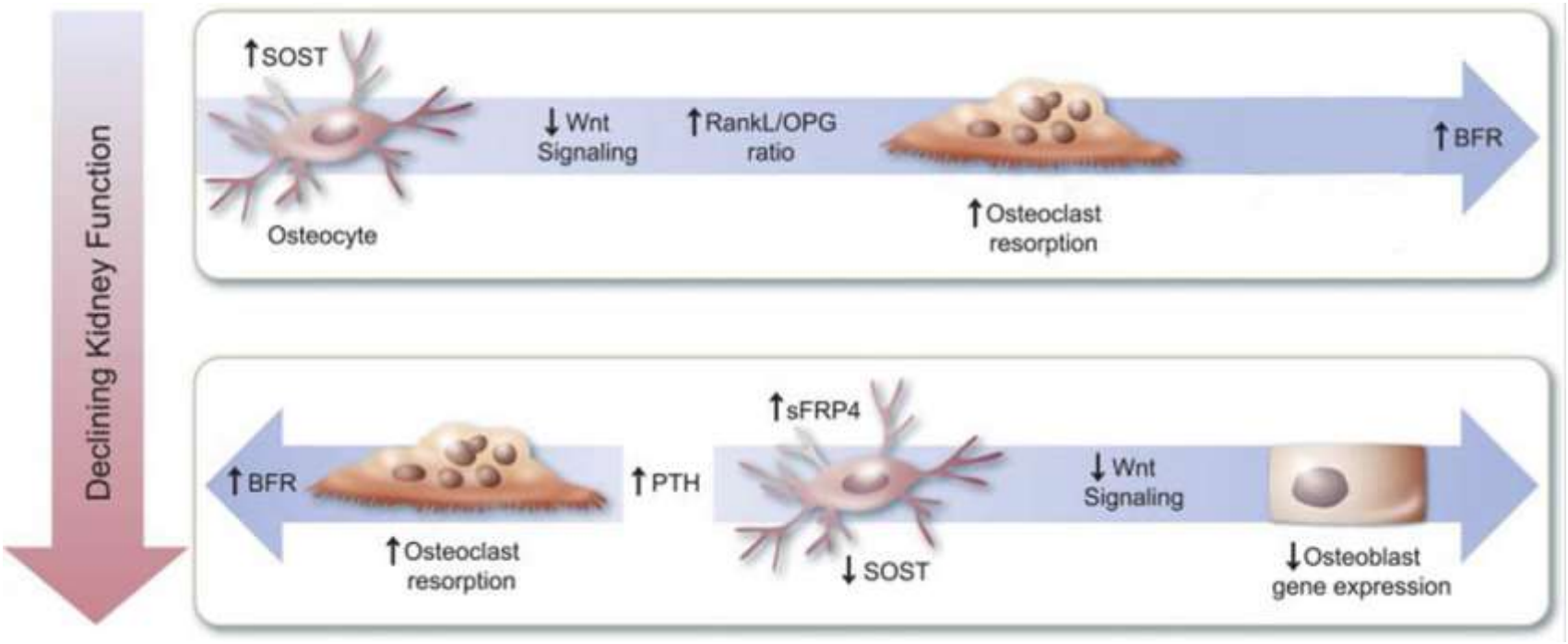
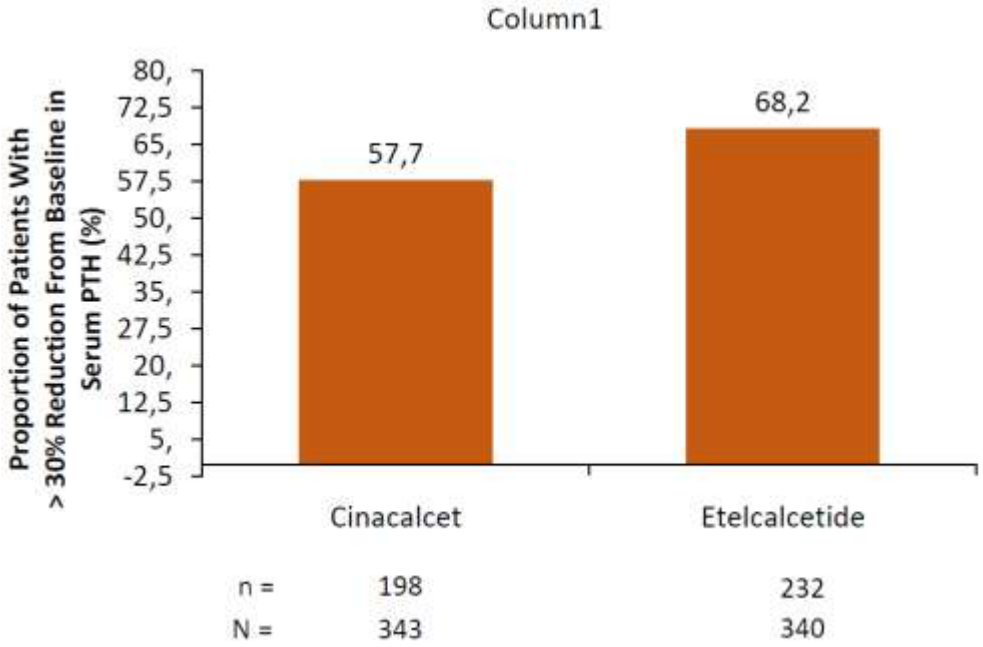


Fig. 10. Unified model demonstrating that early in disease, sclerostin inhibits β-catenin pathway and increases osteoclast activity. Late in disease, elevated PTH levels contribute to the high turnover and the decrease in sclerostin levels. However, sFRP4 levels rise with disease progression leading to continuous β-catenin repression and possibly affecting osteoblast function.

Modified from Journal of Bone and Mineral Research, 2012

Head-to-Head Study: Etelcalcetide vs Cinacalcet

Proportion of Patients Achieving > 30% Reduction in Serum PTH During the EAP



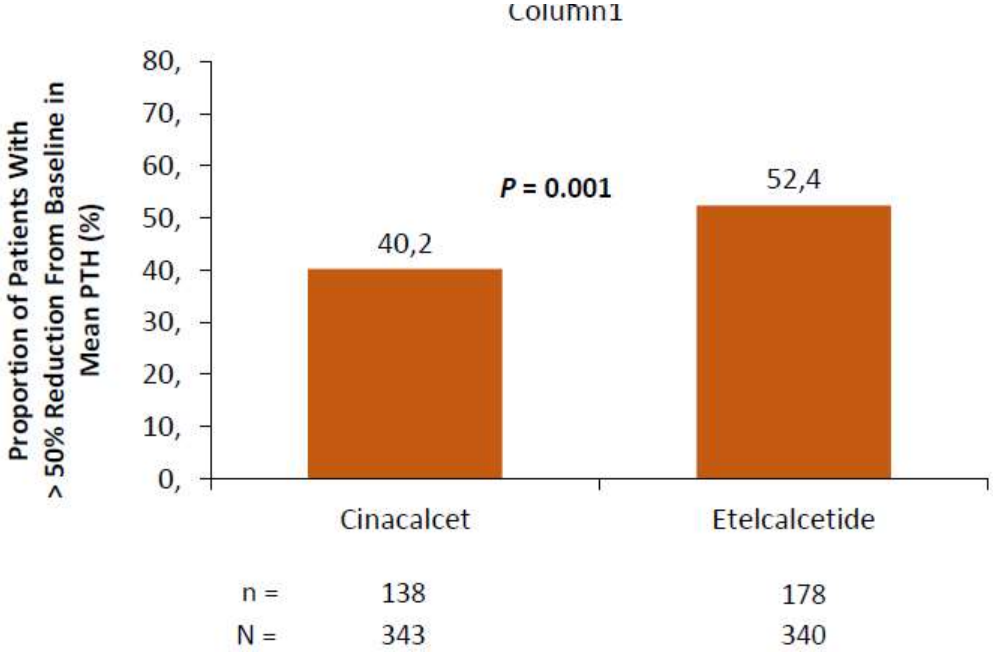
- The proportion of patients achieving > 30% reduction from baseline in serum PTH was greater with etelcalcetide vs cinacalcet (68.2% vs 57.7%)
- The estimated treatment difference (cinacalcet –etelcalcetide) was –10.5% (95% CI –17.5%, –3.5%; noninferiority was met; *P*= 0.004 for superiority)

EAP was defined as weeks 20–27. CI = confidence interval; EAP = efficacy assessment phase; PTH = parathyroid hormone.

Block GA, et al. JAMA.2017;317:156-164.

Head-to-Head Study: Etelcalcetide vs Cinacalcet

Secondary Endpoint: Proportion of Patients Achieving > 50% Reduction in Serum PTH During the EAP



The proportion of patients achieving > 50% reduction from baseline in serum PTH was greater with etelcalcetide vs cinacalcet (52.4% vs 40.2%; P =

EAP was defined as weeks 20-27.
EAP = efficacy assessment phase; PTH = parathyroid hormone.

Block GA, et al. JAMA. 2017;317:156 164.