A scenic landscape at sunset over a large body of water, with a large tree in the foreground and mountains in the distance. The sun is low on the horizon, casting a warm orange glow across the sky and water. The foreground features a grassy area with a large, leafless tree on the left. In the middle ground, a sandy beach is visible with several people walking along the shoreline. The background shows a range of mountains under a clear sky.

Osteoporosis medications in CKD patients

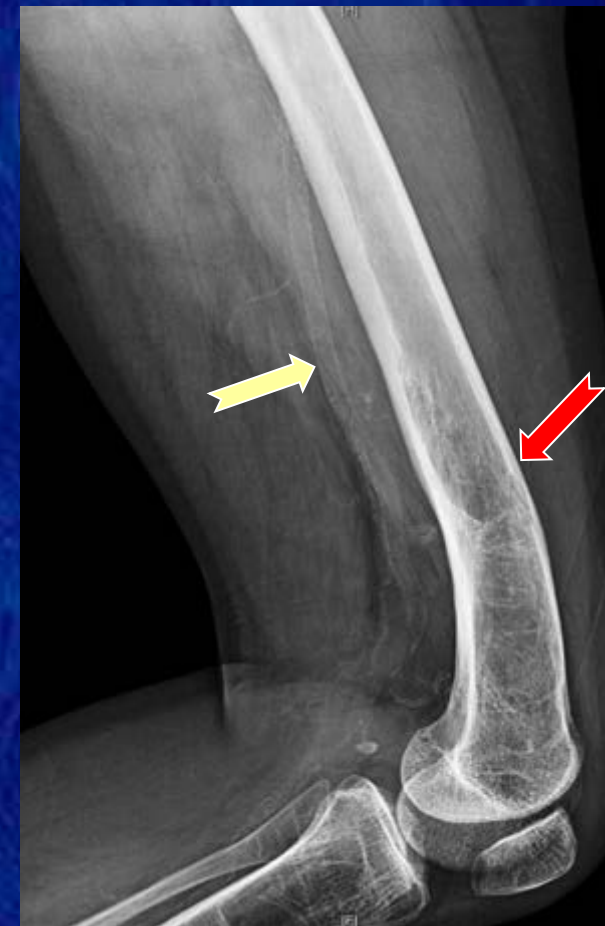
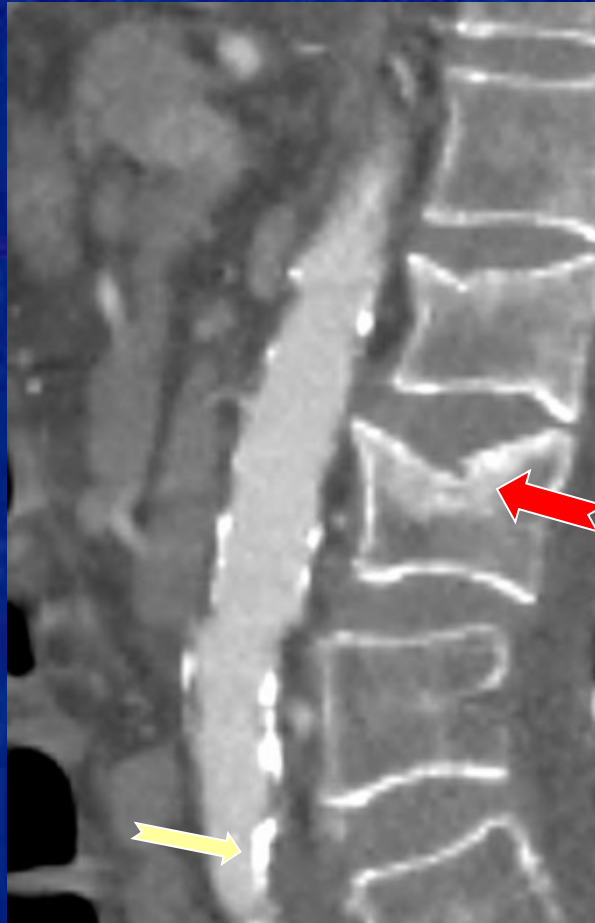
Susan Ott
March 2021



No conflicts of interest

Patients with CKD have high fracture risk

and they die of heart failure



CKD-MBD

Ordinary Osteoporosis

Increased PTH and alkaline phosphatase	Normal PTH and alkaline phosphatase
Bone density weakly related to fractures	Bone density predicts fractures
Bone loss mostly in cortical bone	Bone loss in trabecular and cortical bone
High prevalence of adynamic bone or very high bone formation	Bone formation generally normal to slightly high
Associated with vascular calcifications	Weakly associated with vascular calcifications
Abnormal calcium, phosphate, FGF23, BMP7, Klotho, 1,25-vitamin D, iron, bicarbonate, sclerostin, and cytokines	Normal or mildly abnormal

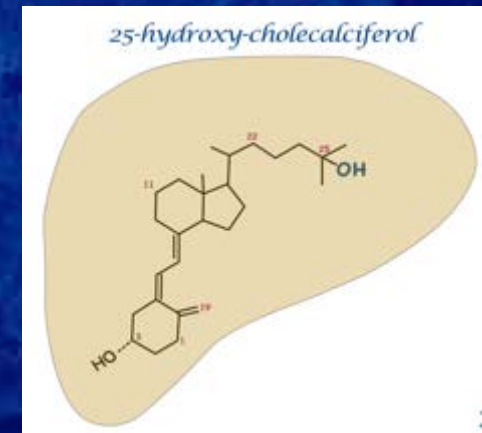
Vitamin D

600 IU/day younger than 70

800 IU/day older than 70

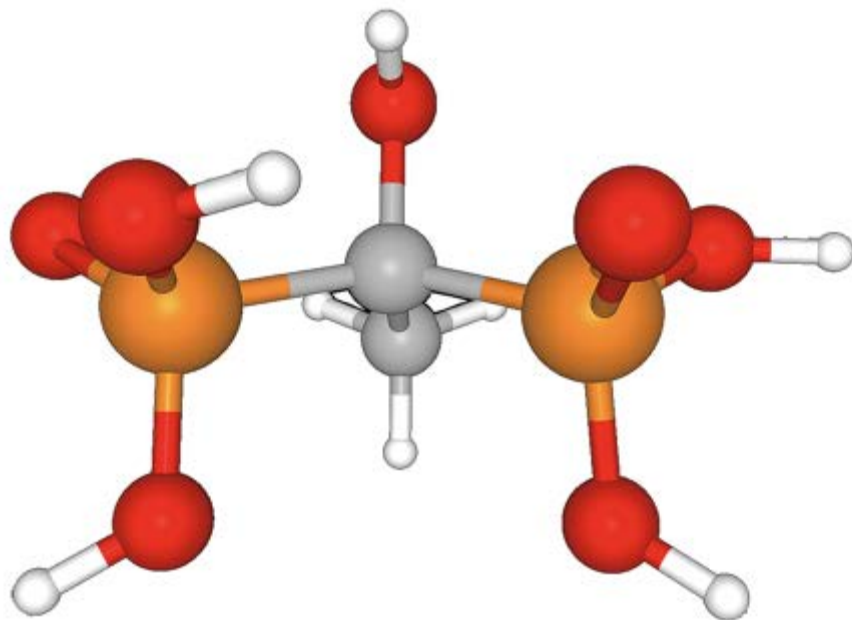
Blood levels of vitamin D should be
between 20 and 50 ng/dl
(= 50 to 125 nmol/l)

No convincing evidence that these levels
should be different in CKD patients

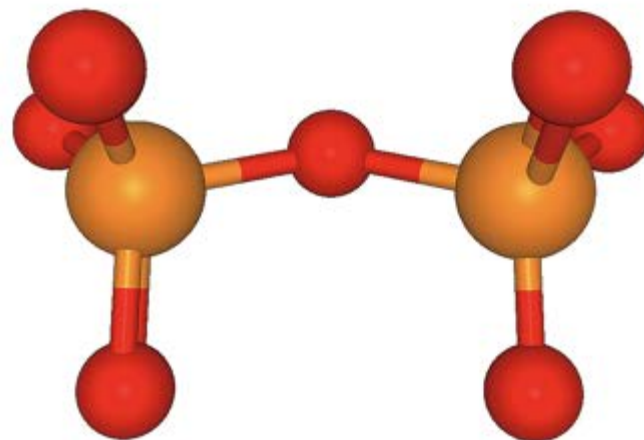


Bisphosphonates

Etidronate



Pyrophosphate



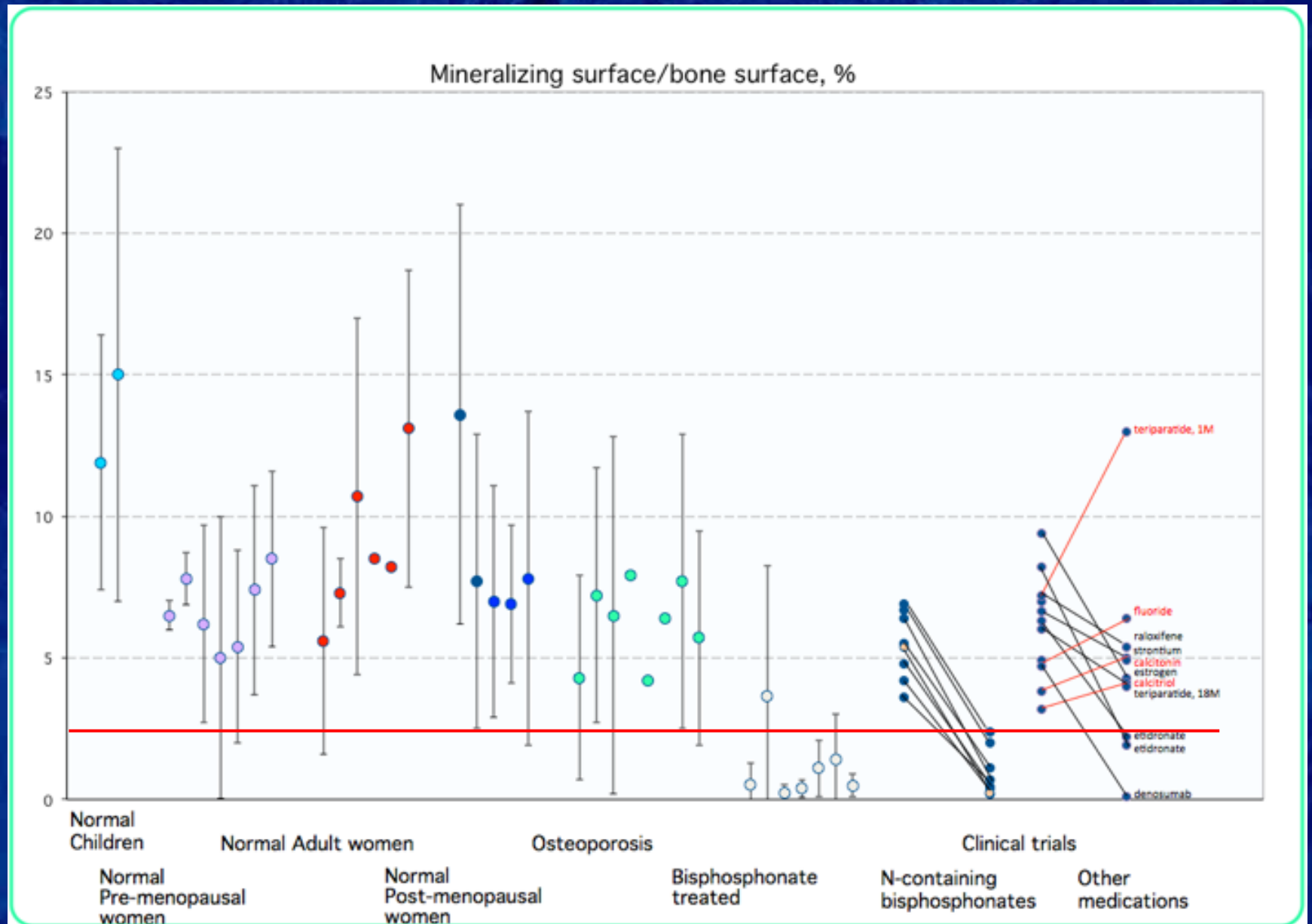
Bisphosphonates in ordinary osteoporosis

Large randomized trials, including about 35,000 subjects, have shown that 2nd generation bisphosphonates reduce fractures during the first 3-4 years of treatment.

They work by blocking bone resorption, which prevents deterioration of the bone architecture.

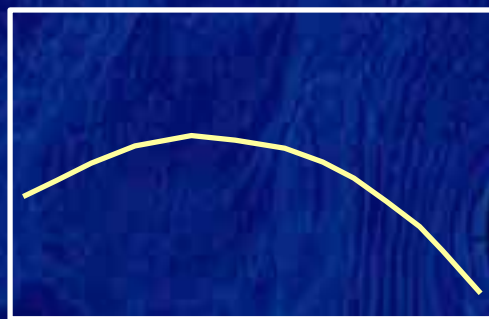
They secondarily inhibit bone formation to very low levels (adynamic).

Bone formation Rates

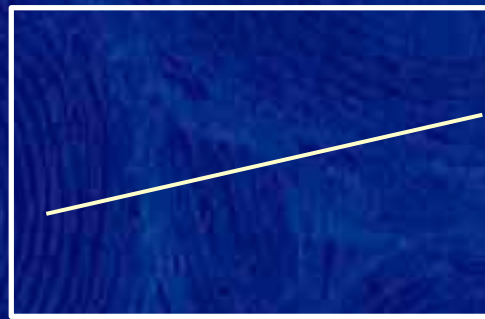


Bone strength with long-term bisphosphonates

Bone biopsies from ordinary osteoporotic patients on bisphosphonates from 1 to 17 years showed that strength peaked at 7 years and then declined to levels below baseline. Crack density increased progressively.

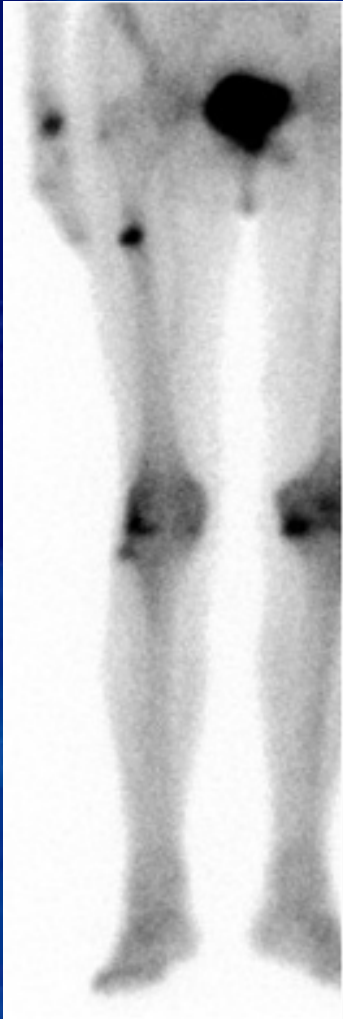


STRENGTH

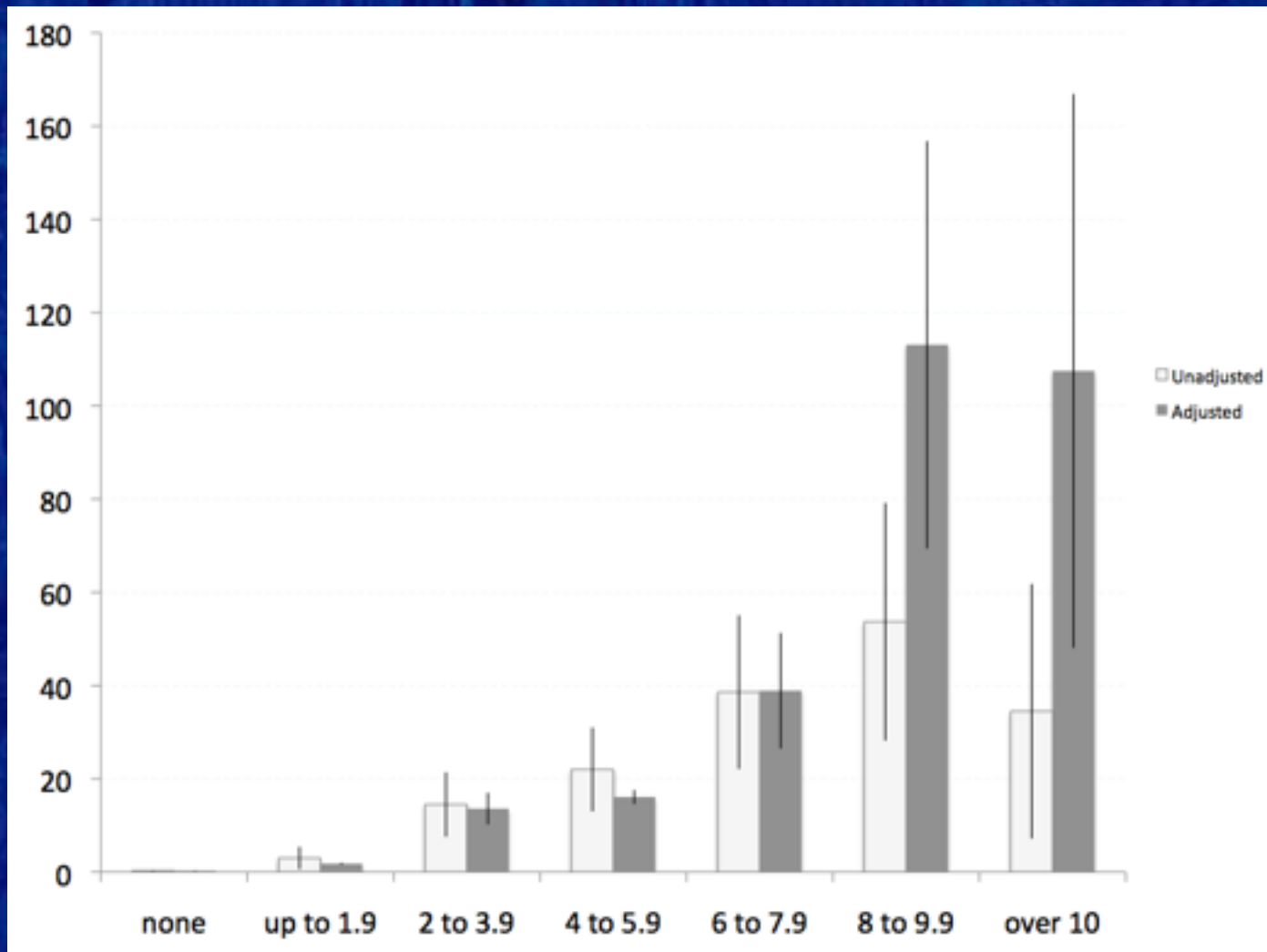


CRACKS

Atypical femur fracture



Incidence of atypical femur fracture



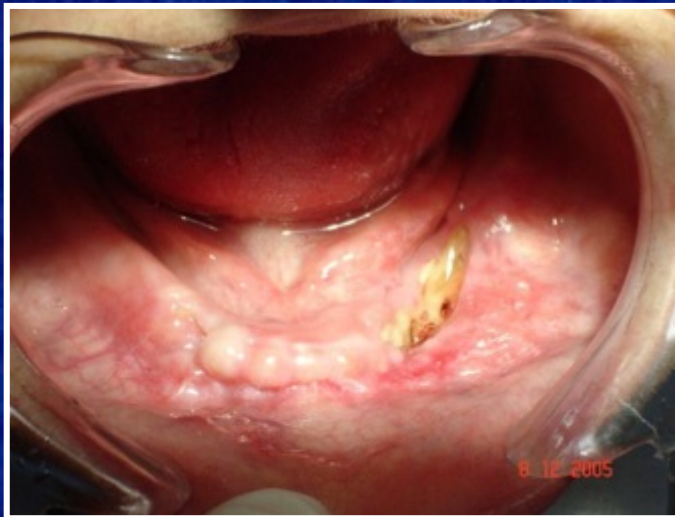
Duration bisphosphonate use, years



Schubert 2004



Schubert 2007



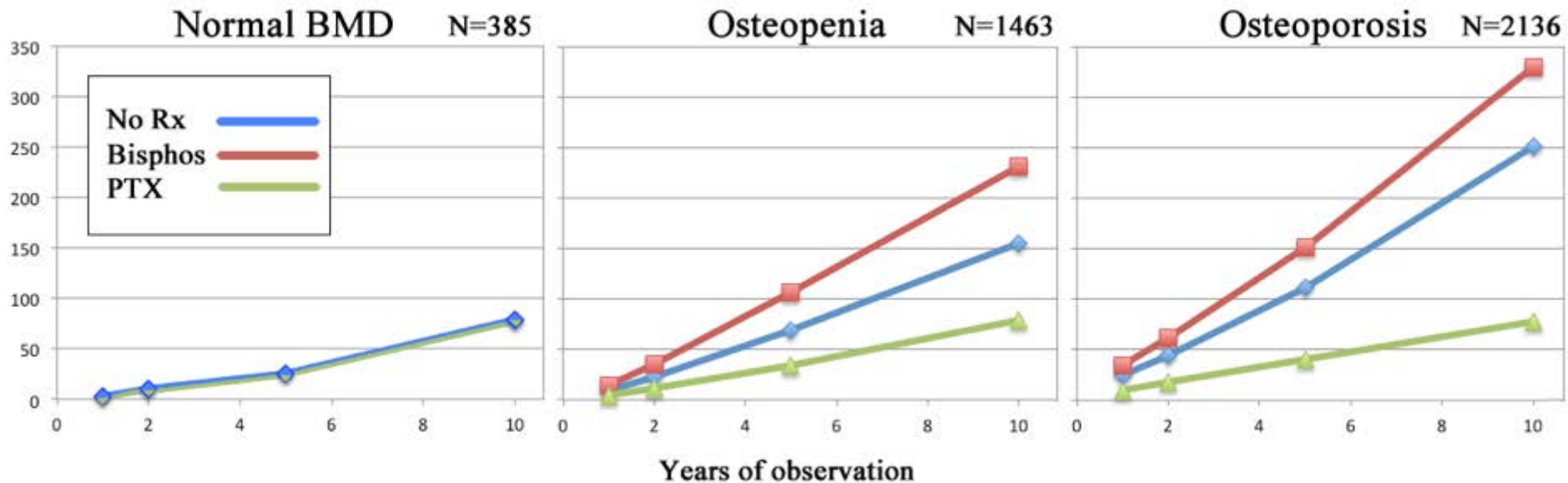
8 12 2005



Correa 2006

Fractures in primary hyperparathyroid patients without CKD

Bisphosphonate use significantly increased the bone density, but there were more fractures



Graph shows risk of any fracture per 1,000 patients according to baseline BMD

CKD grade 3

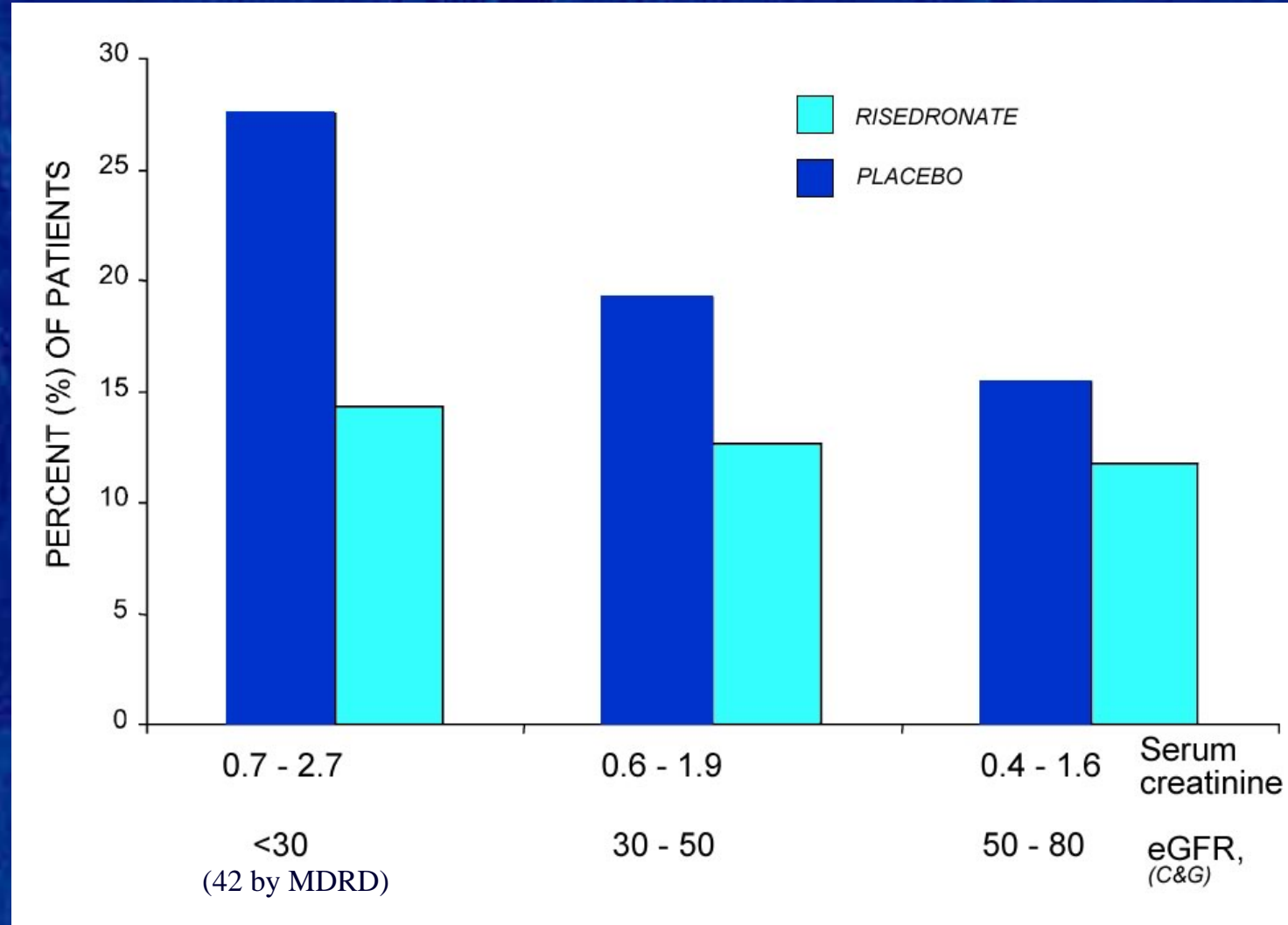
In the studies of bisphosphonates, raloxifene, teriparatide and denosumab, the subjects with age-related CKD grade 3 had fracture benefit, similar to patients with normal eGFR



CAUTION

These studies excluded sick patients. The subjects had normal calcium, PTH, and alkaline phosphatase.

Risedronate in early CKD: Fractures



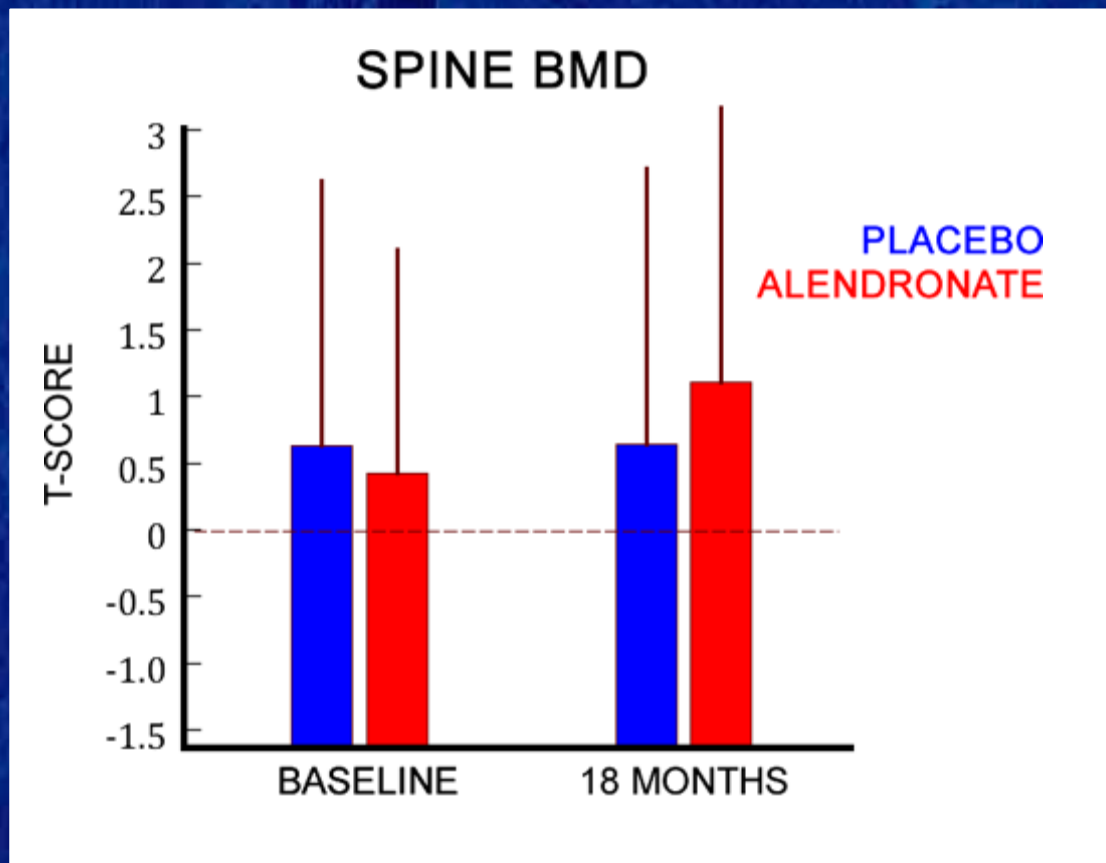
mean age 75, normal PTH and alk phos

Miller, JBMR '05

Randomized clinical trials of bisphosphonates in CKD stage 4-5

(minimum criteria: $N > 49$, duration > 5 mo)

Alendronate in CKD stage 4-5



N=51
48 completed

Fem neck T scores were -1.26 and -1.28 at baseline.

At 18 mo. the difference between groups was not significant at the hip ($\Delta = 0.03$ T-score units).

Vascular calcification progression was not different.

Be wary about bisphosphonates in patients with CKD stages 4-5

- 1) Inadequate studies in this population.
- 2) Data from patients with early stages of CKD may not reliably be extrapolated to later stages.
- 3) Bisphosphonates can increase PTH.
- 4) Bisphosphonates markedly reduce the bone formation rates.
- 5) In osteoporotic patients prolonged use increases incidence of atypical femur fractures.
- 6) In primary hyperparathyroidism patients treated with bisphosphonates had higher fracture rate than untreated patients despite increase in bone density.
- 7) Long-term effects on vascular calcifications uncertain.

Denosumab: From the frying pan into the fire



Denosumab inhibits bone formation more than bisphosphonates.

It is not cleared by the kidney, but this does not mean it is effective in CKD.



Denosumab

Increases bone density

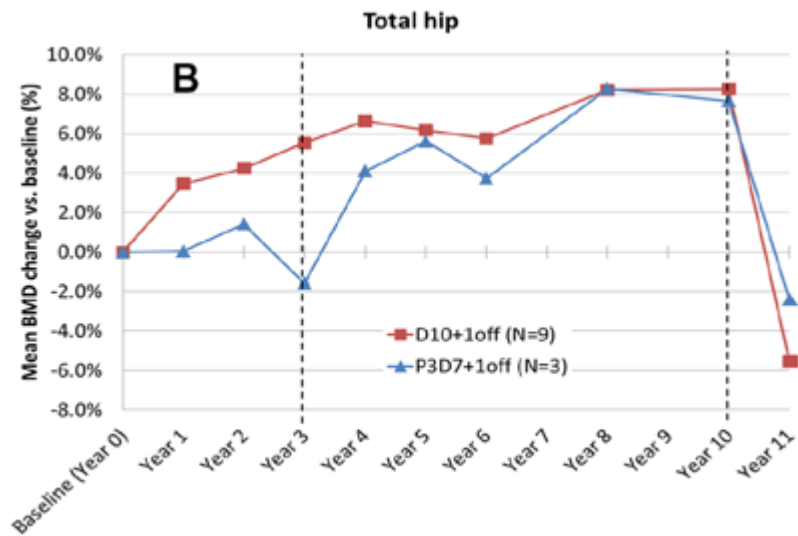
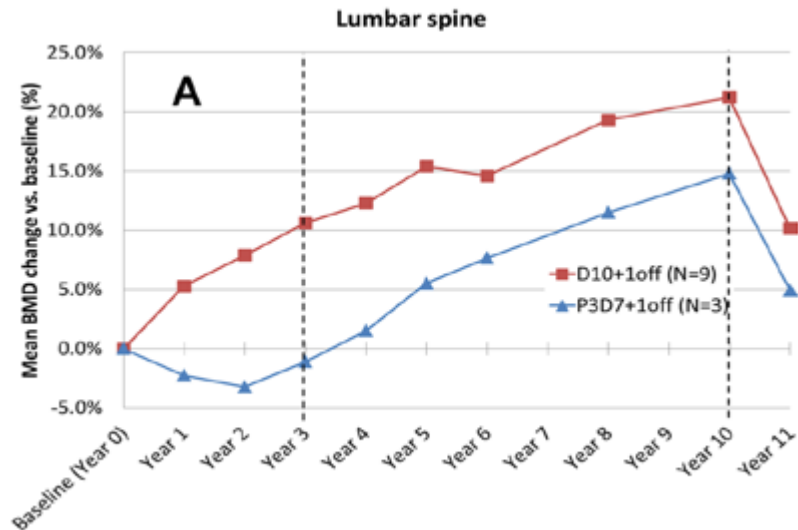
Reduces clinical fractures

Stops bone resorption and also completely stops bone formation

Some cases of atypical fractures and jaw osteonecrosis

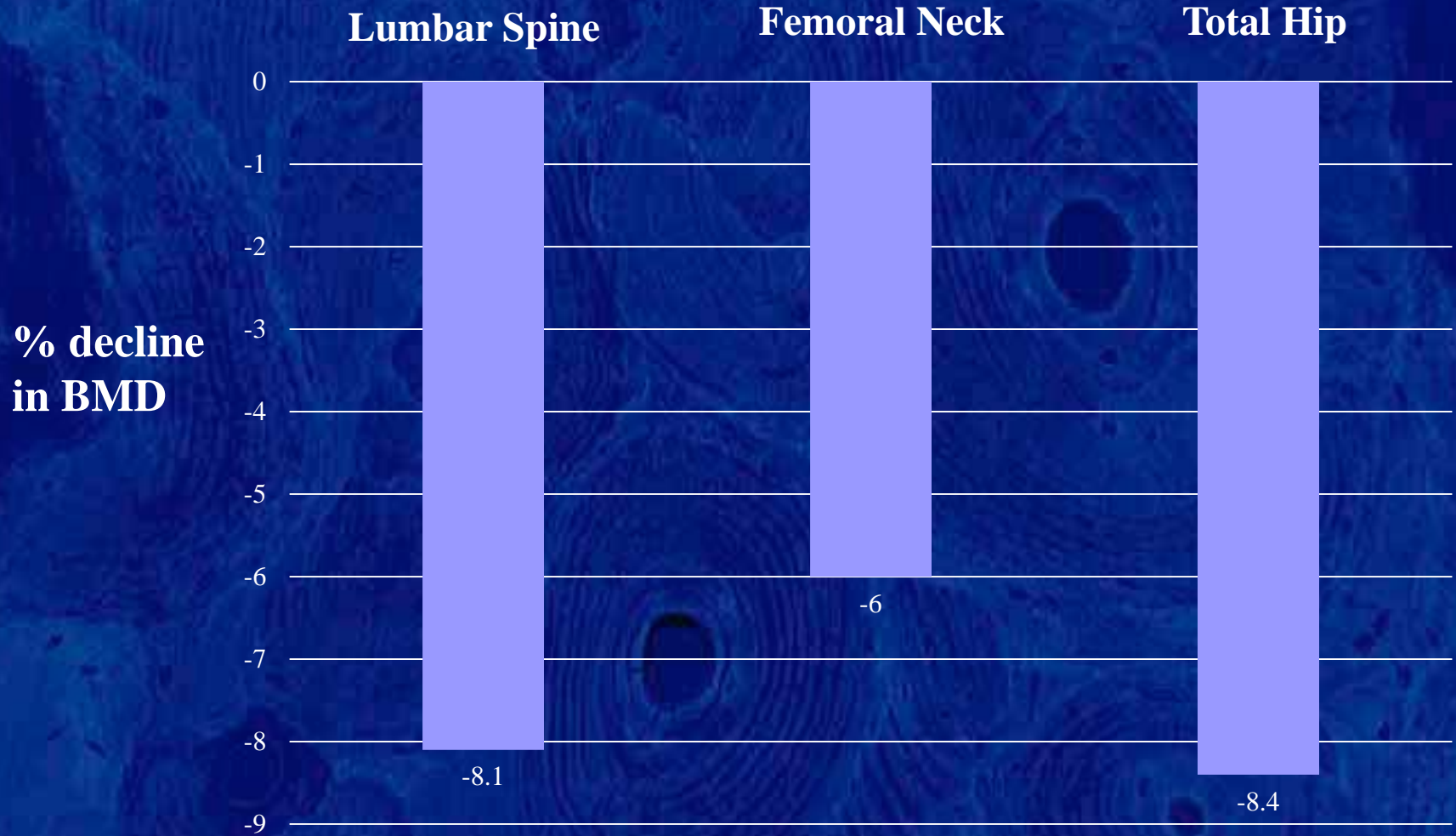
Rebound loss after it wears off in 6 mo.

Bone density after long-term denosumab



N=12
Subjects from FREEDOM
trial

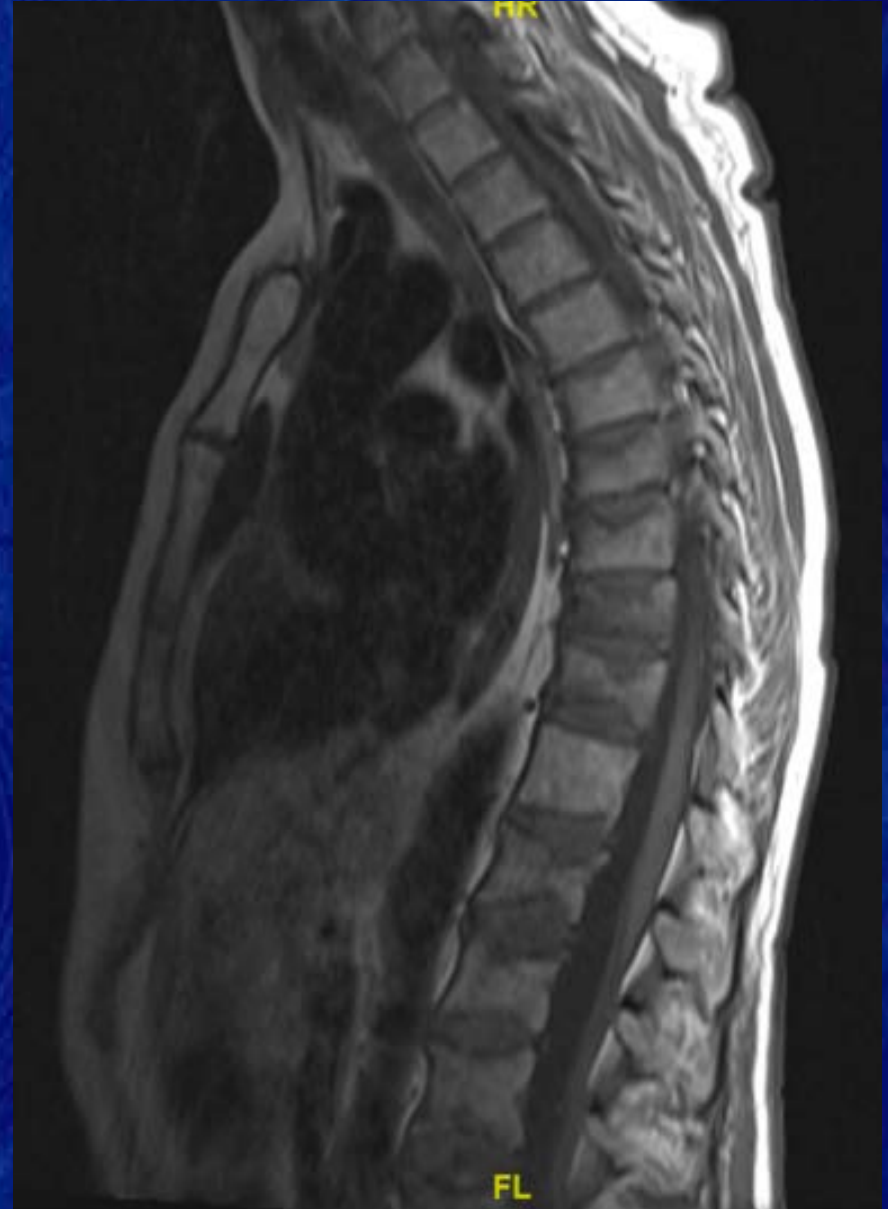
Bone Loss after Denosumab Stop



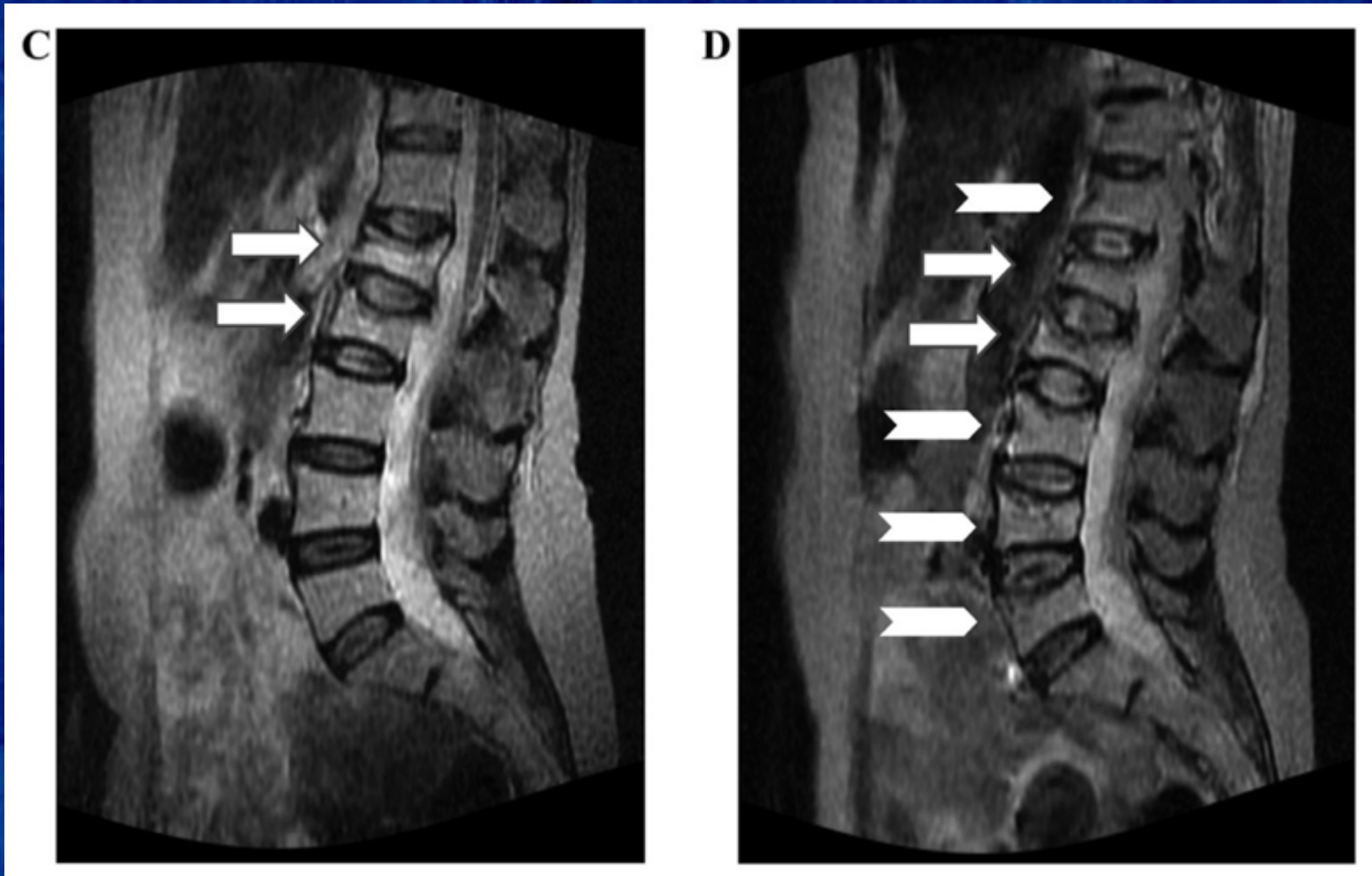
Clinical features of 35 patients with 172 spontaneous vertebral fractures after denosumab discontinuation

- 66.3 ± 9.6 years
- 11.6 ± 2.8 months (median 11; min 7, max 20) following the last denosumab injection
- 12 women had vertebroplasties with 58 new VF in the following days.

Before and after skipping a denosumab dose



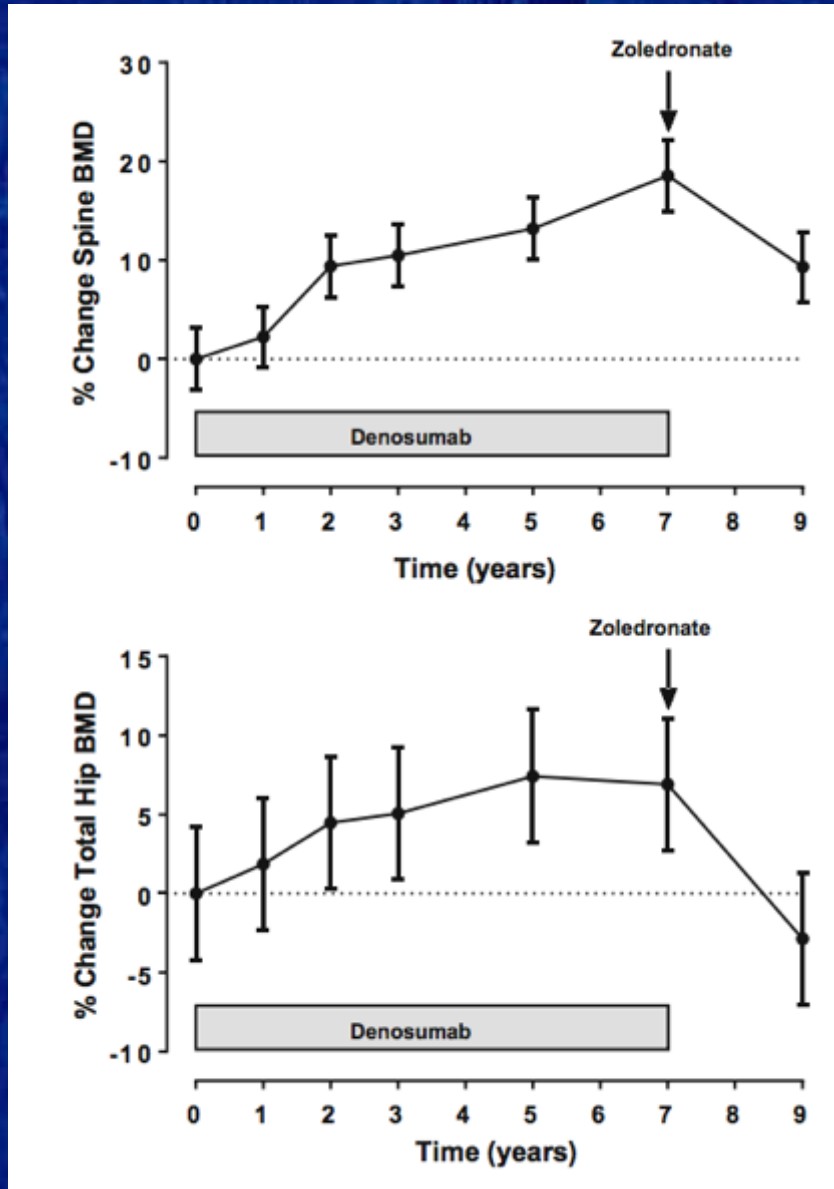
14th dose of denosumab given May 2019



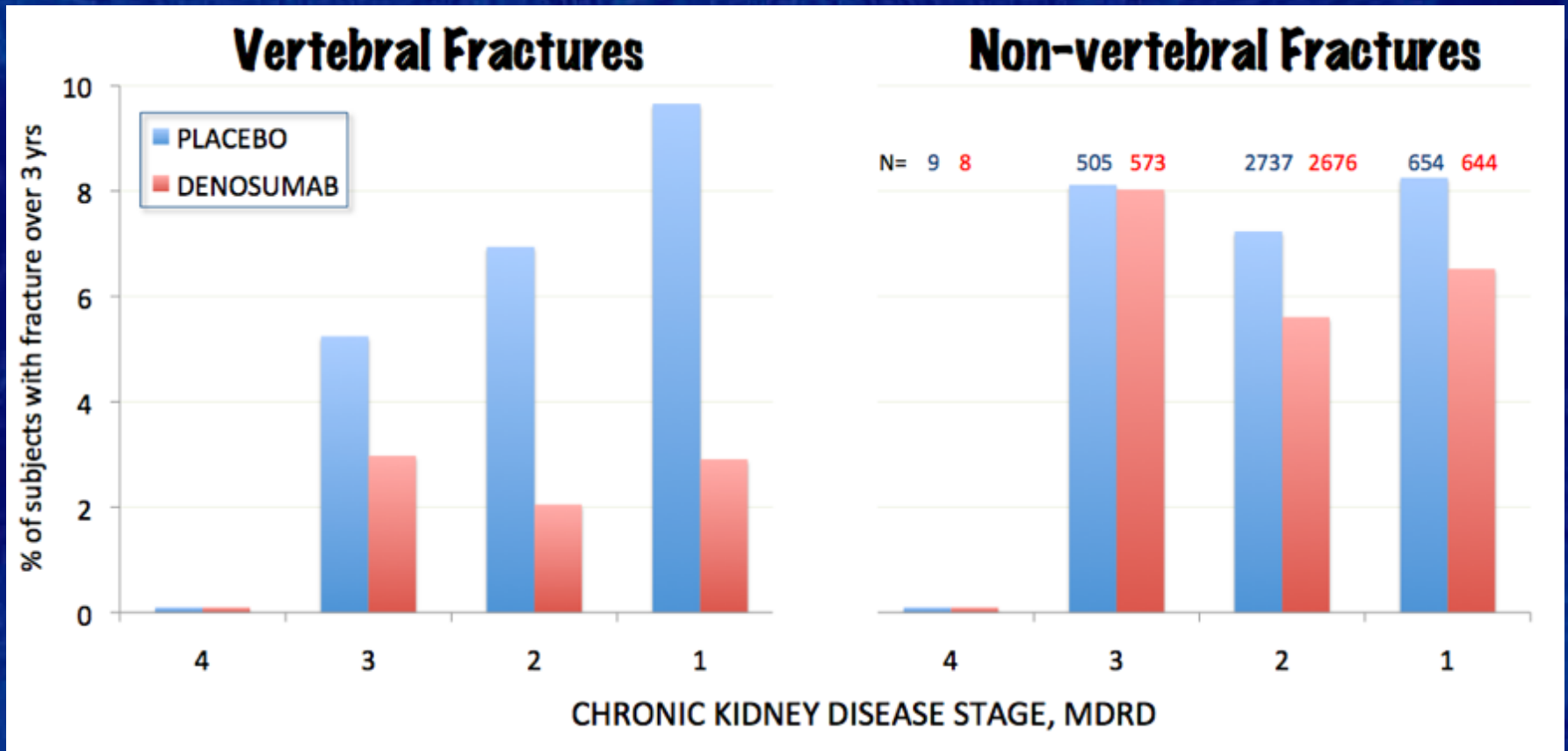
January 2020, new fractures
Given 15th dose

March 2020

Zoledronate May not Attenuate BMD Loss with denosumab



Denosumab in early CKD

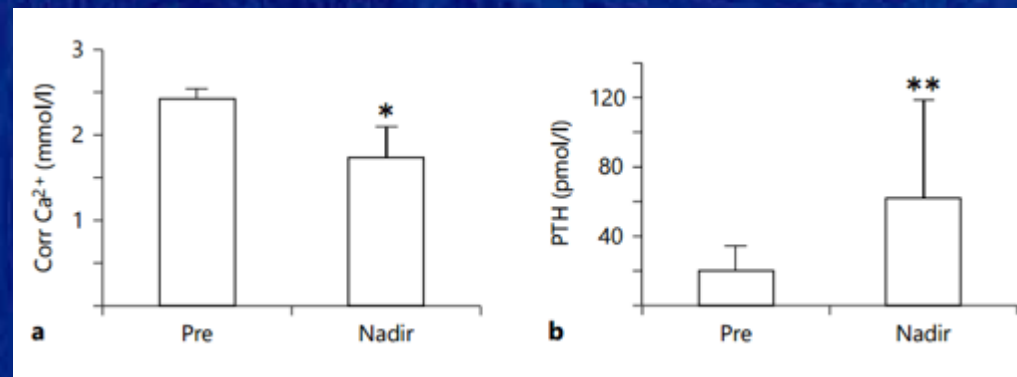


Hypocalcemia Post Denosumab in Patients with Chronic Kidney Disease Stage 4-5

Vatsa Dave^a Cherie Y. Chiang^b Jane Booth^c Peter F. Mount^a

Departments of ^aNephrology, ^bEndocrinology, and ^cPharmacy, Austin Health, Heidelberg, Melbourne, Vic.,

After denosumab treatment, 6/8 patients with CKD-5/5D, and 2/5 patients with CKD-4 developed severe hypocalcemia.

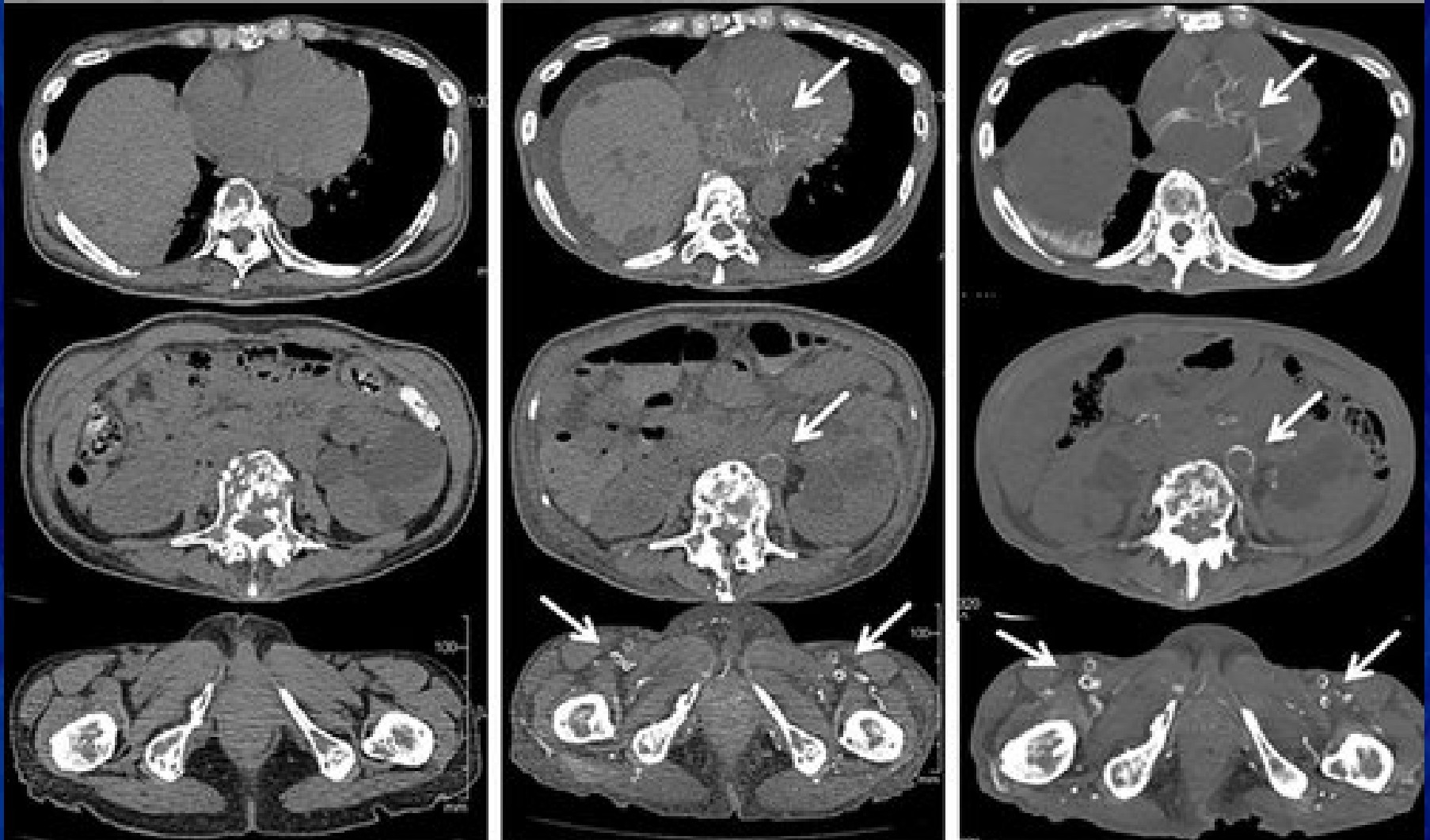


Denosumab lowers serum calcium in CKD

In CKD 4 – 5, calcium <7.5 mg/dl
in 25 -70% of patients.

Can be severe, with muscle cramping,
seizures, tetany, laryngospasm or cardiac
arrhythmias.

Rapid progression of calcifications with denosumab

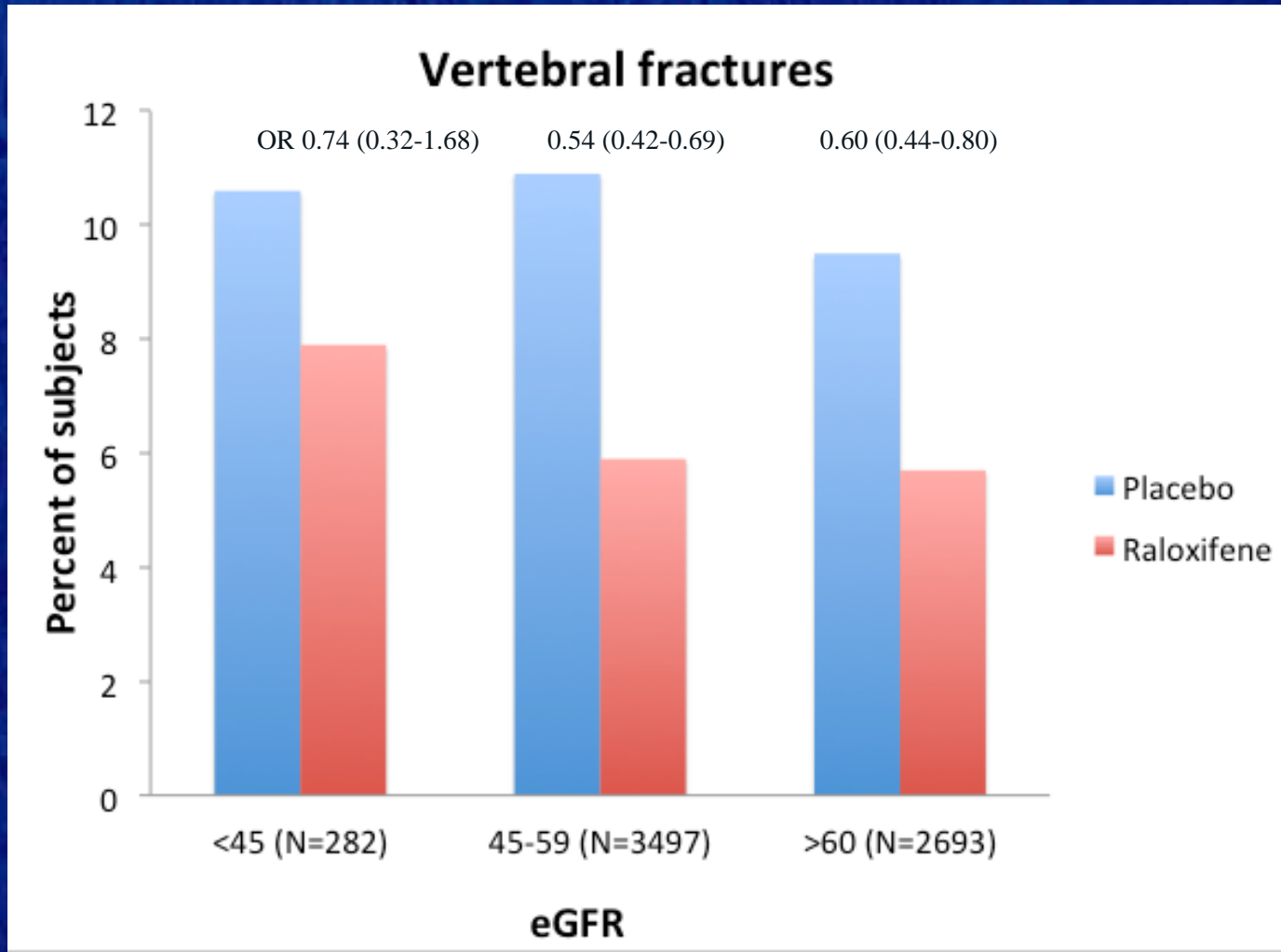


Over ten months

Summary: Denosumab

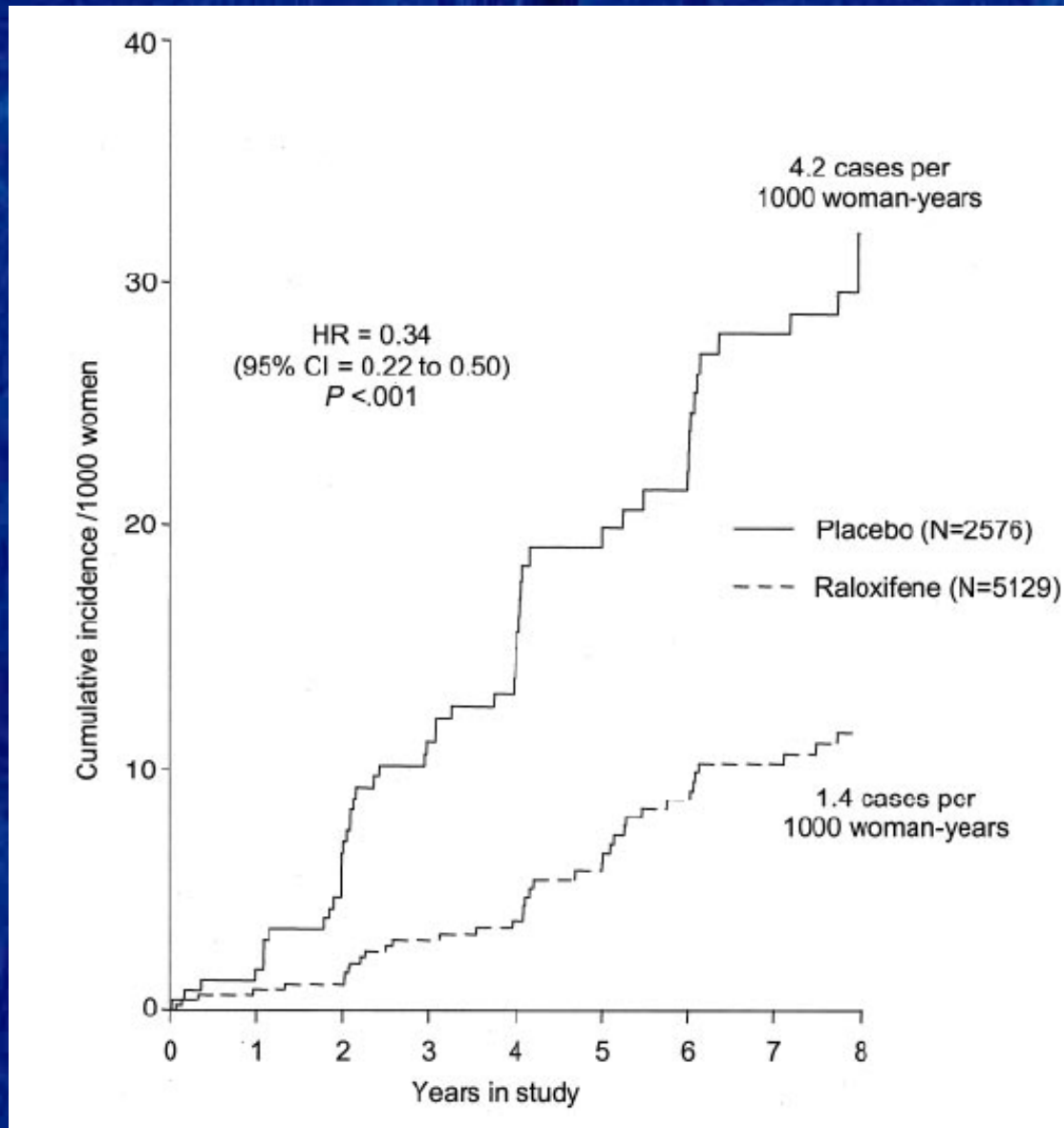
- 1) Uncontrolled studies report increased BMD with denosumab in CKD 4-5 patients.
- 2) Hypocalcemia is common and can be severe.
- 3) Giving calcitriol to prevent hypocalcemia can result in serious vascular calcifications.
- 4) Osteoporosis patients may develop atypical femur fractures or jaw osteonecrosis.
- 5) After stopping there is rapid rebound bone loss that may result in multiple vertebral compression fractures.

Raloxifene in early CKD



No significant benefit to non-vertebral fractures

Raloxifene and breast cancer



Raloxifene in CKD 4-5

Acts like estrogen on the bone. For use in postmenopausal women.

In women without CKD, reduces breast cancer and vertebral fractures. No studies large enough in CKD 4-5.

Increased risk of thrombophlebitis

In ordinary osteoporosis, no increase in strokes. Women with coronary artery disease had the same number of strokes as placebo, but a higher percentage were fatal.

Raloxifene in women on dialysis

One year BMD results	Placebo N = 25	Raloxifene N = 25
Spine	.952 - .949	.942 - .973*
Hip	.745 - .753	.722 - .727

Raloxifene : Cross-links

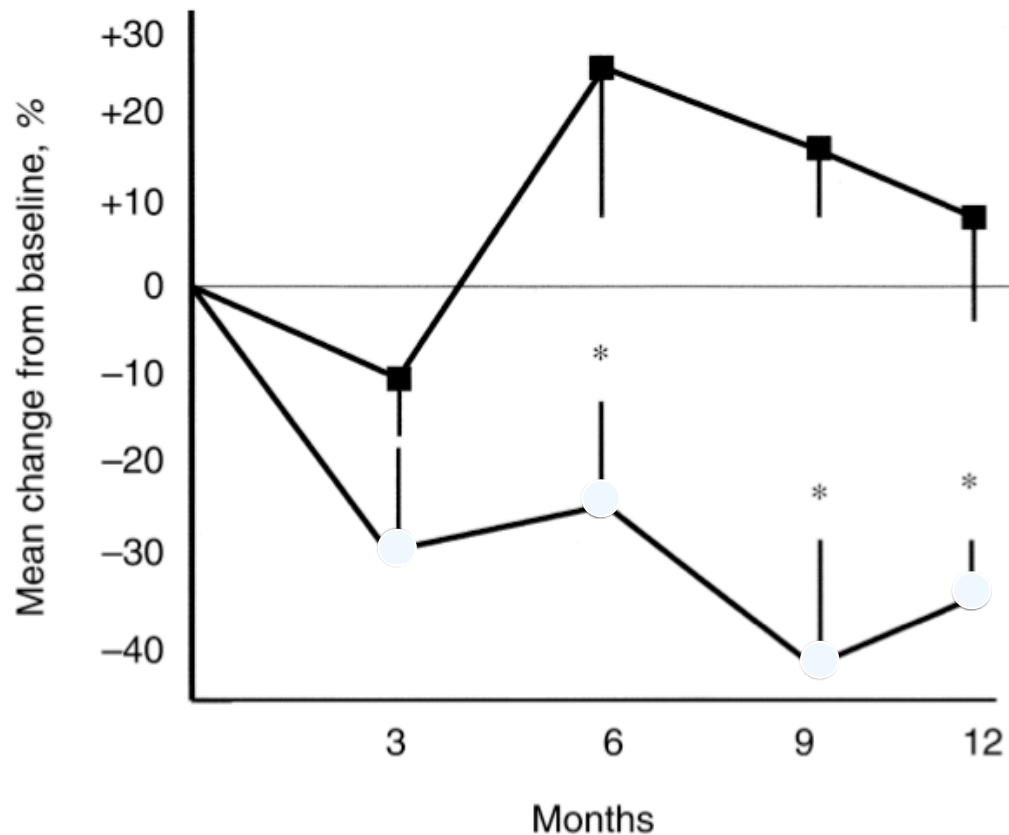
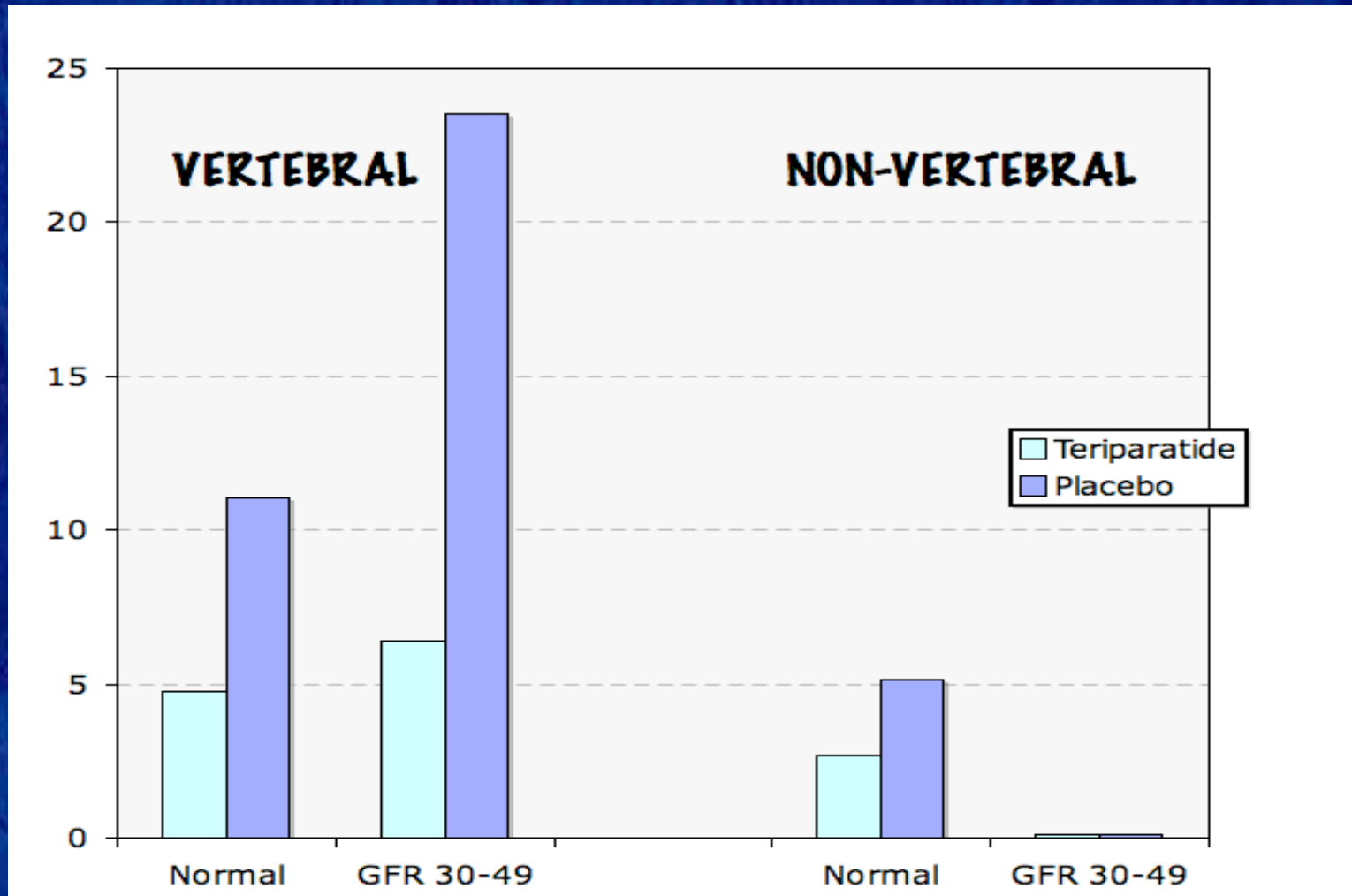
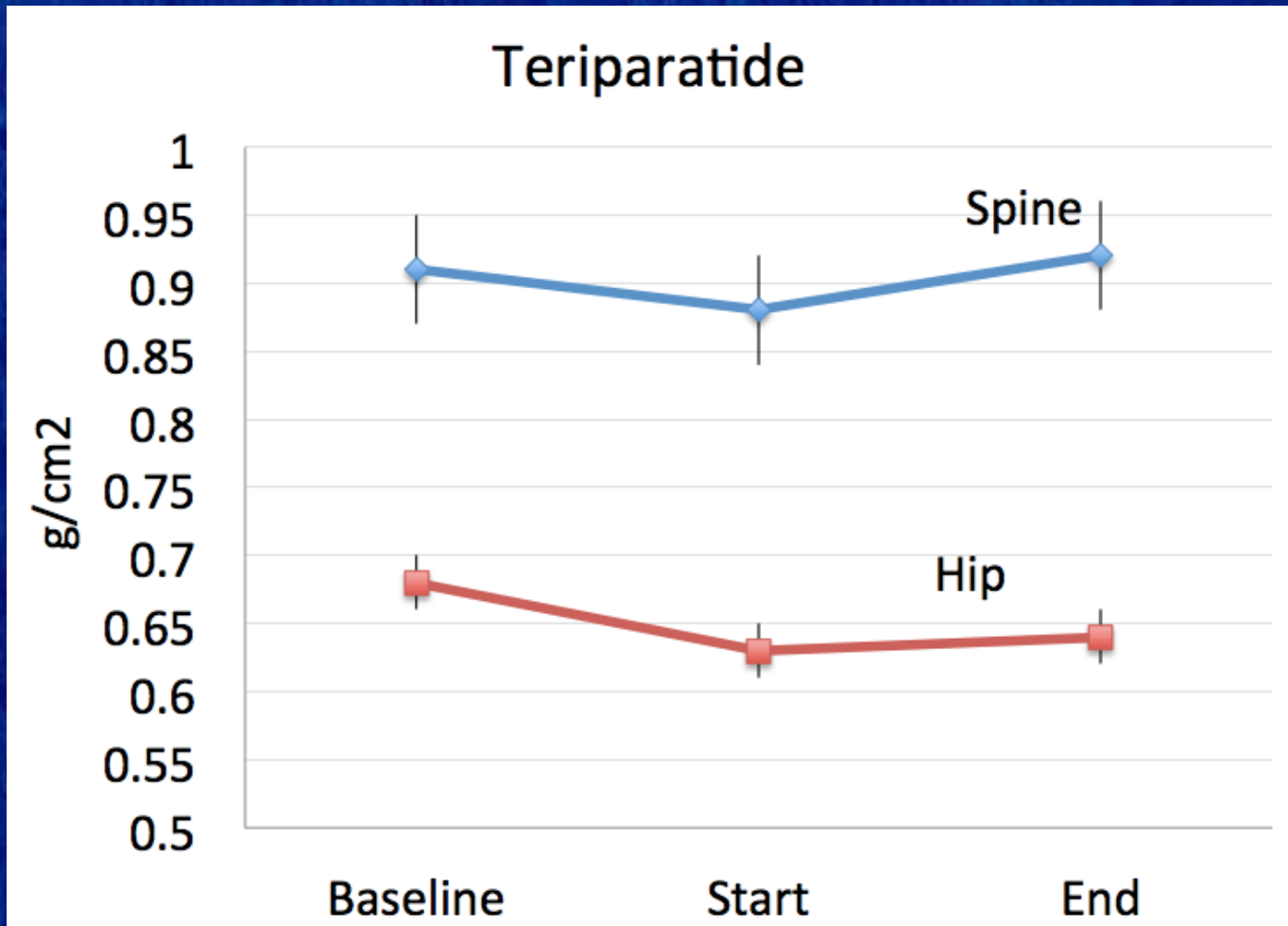


Fig. 1. Mean (SD) percentage changes from baseline in serum pyridinoline crosslinks levels in postmenopausal hemodialyzed women given raloxifene (60 mg/day) (●) or placebo (■) for 1 year. * $P < 0.01$ vs. placebo.

Teriparatide in early CKD



Teriparatide in CKD-MBD

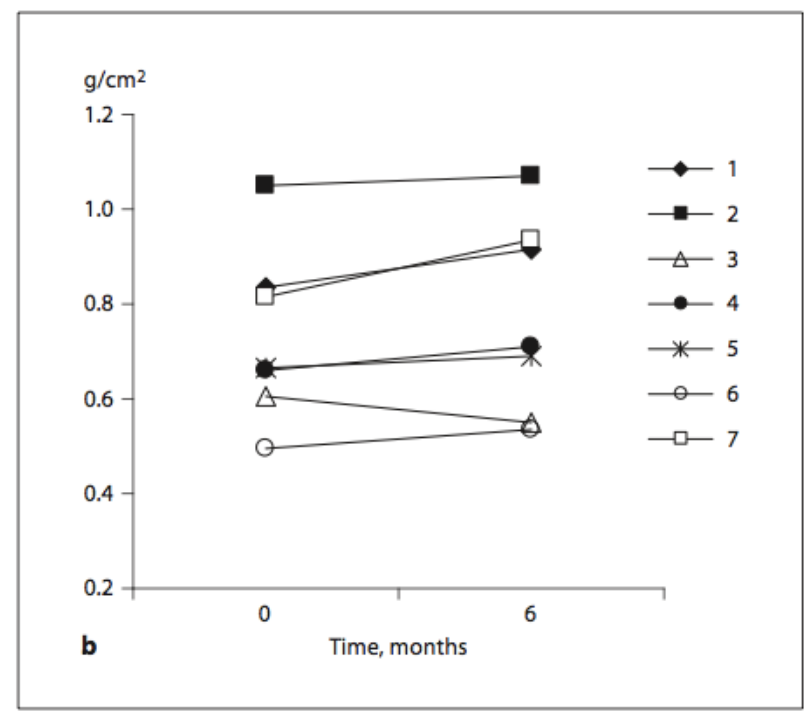
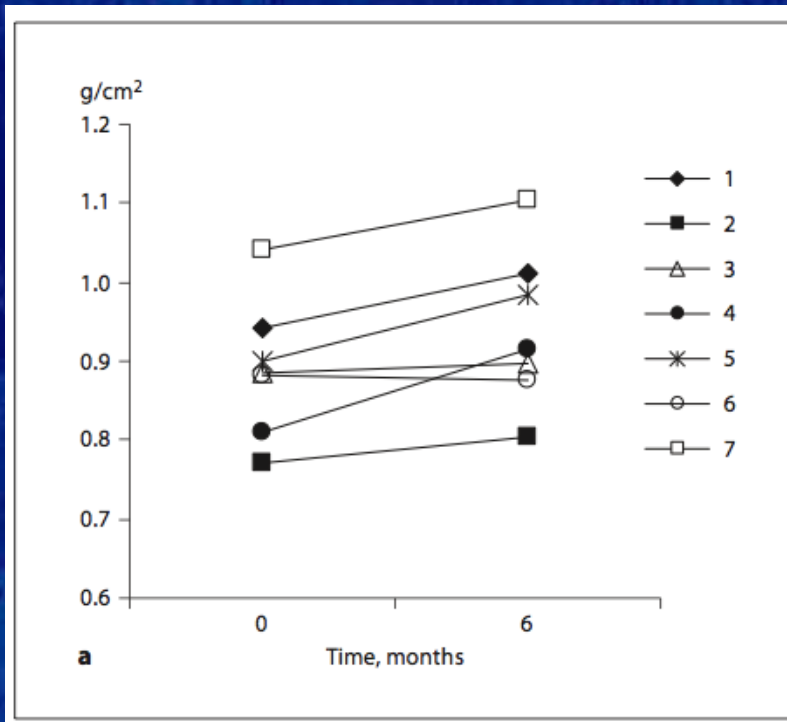


N = 8; mean PTH = 150 pg/ml

Teriparatide in CKD-MBD

SPINE

HIP



N = 7; hx PTX in 6

Teriparatide in CKD 4-5

- 1) Studies very small but have positive results on BMD.
- 2) Physiological rationale for giving to patients with low serum PTH and adynamic bone disease.
- 3) Must be given by intermittent injections on regular schedule.
- 4) Causes osteosarcoma in a rat model, avoid in patients with history of cancer or radiation.
- 5) Can increase serum calcium and uric acid.
- 6) Bone develops resistance after about 18 months.
- 7) Bone loss following discontinuation, need to plan for second medication but there's no data about choices.

Effects of Cinacalcet on Fracture Events in Patients Receiving Hemodialysis: The EVOLVE Trial

Sharon M. Moe,* Safa Abdalla,[†] Glenn M. Chertow,[†] Patrick S. Parfrey,[‡] Geoffrey A. Block,[§] Ricardo Correa-Rotter,^{||} Jürgen Floege,[¶] Charles A. Herzog,^{**} Gerard M. London,^{††} Kenneth W. Mahaffey,[‡] David C. Wheeler,^{‡‡} Bastian Dehmel,^{§§} William G. Goodman,^{§§} and Tilman B. Drüeke,^{||} for the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial Investigators

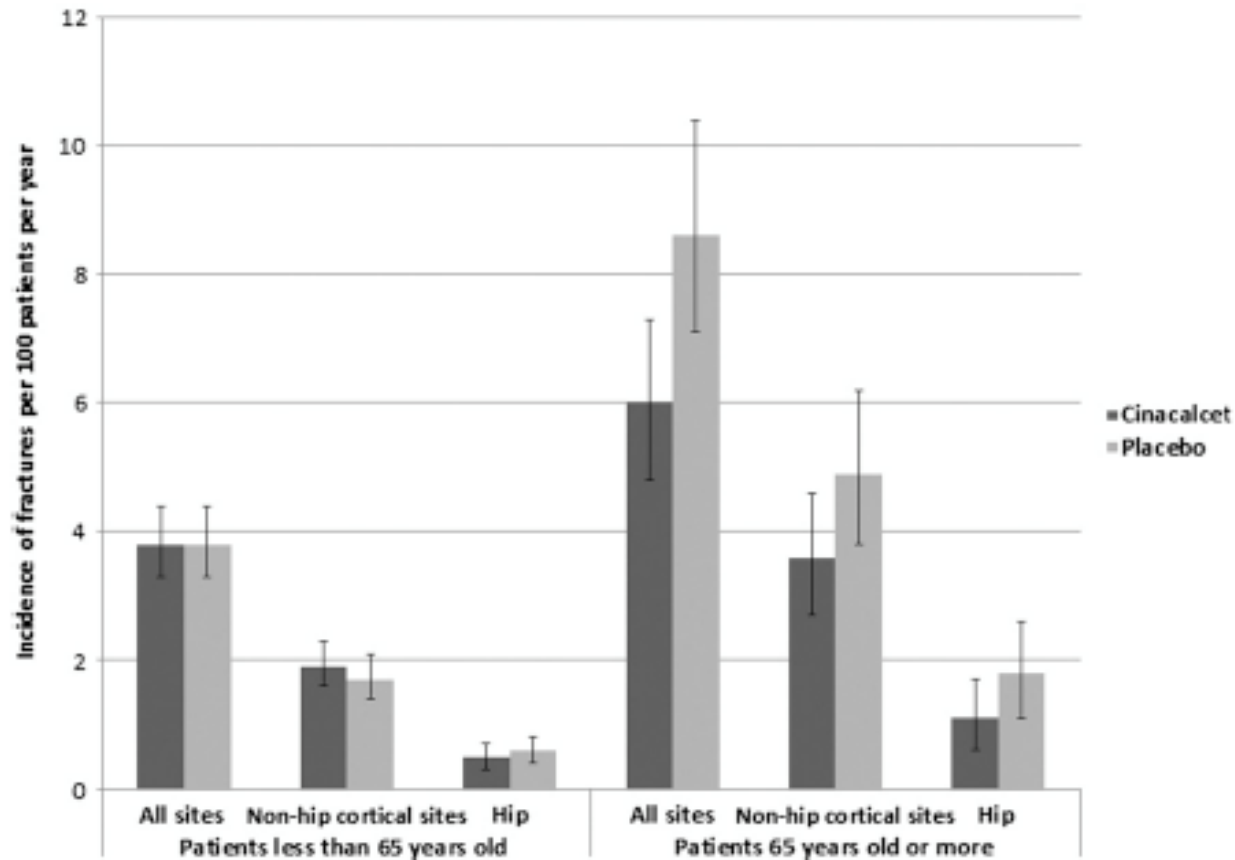


Figure 1. Unadjusted fracture rates by site, age, and treatment group. Fractures are more common at nonhip cortical sites compared with the hip, and are more common in patients aged ≥ 65 years. Bar graphs represent the mean \pm SD.

Romosozumab

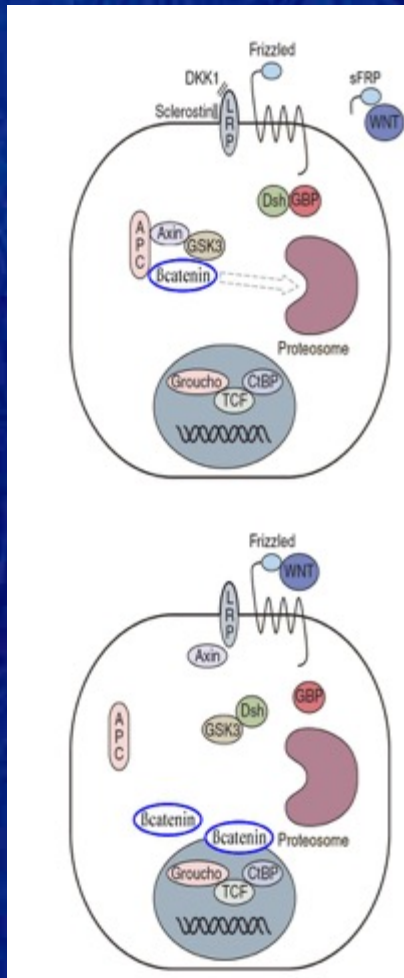
Very new and promising medicine.

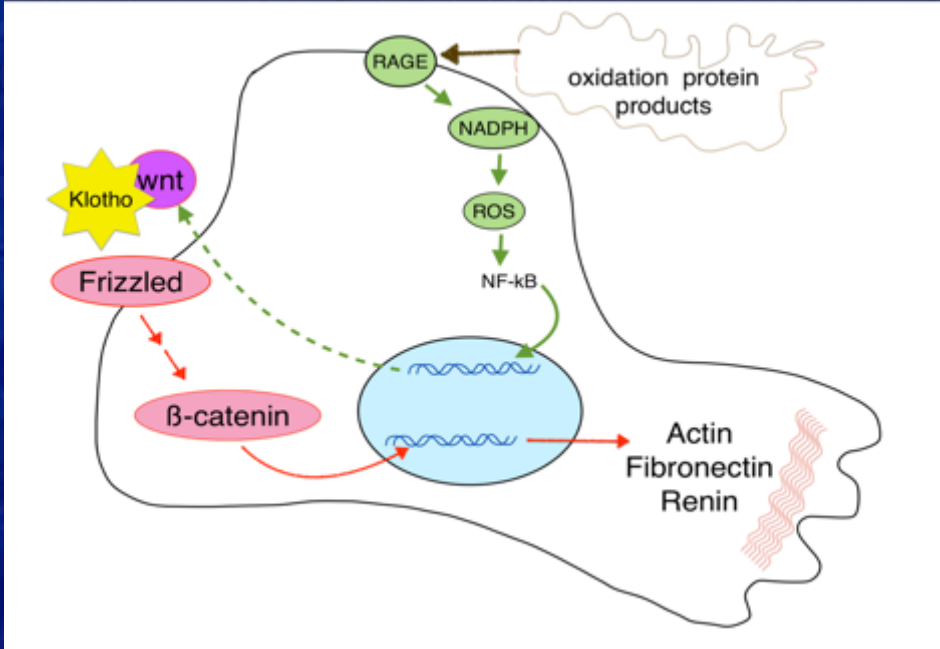
Antibody to sclerostin, which is an inhibitor of bone formation made by osteocytes.

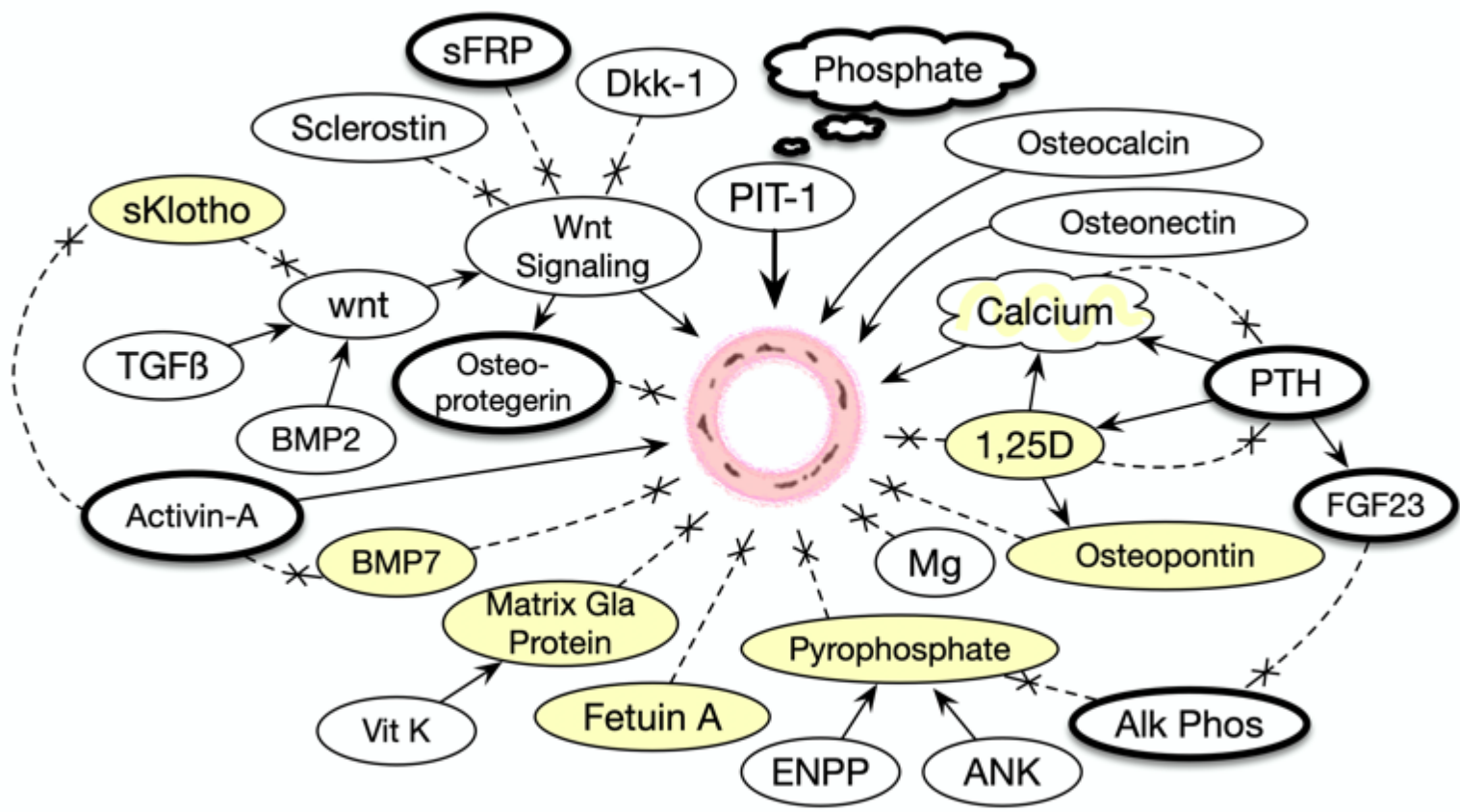
If sclerostin is not important to the vasculature, then it may be a treatment for CKD patients with fractures or low bone density.

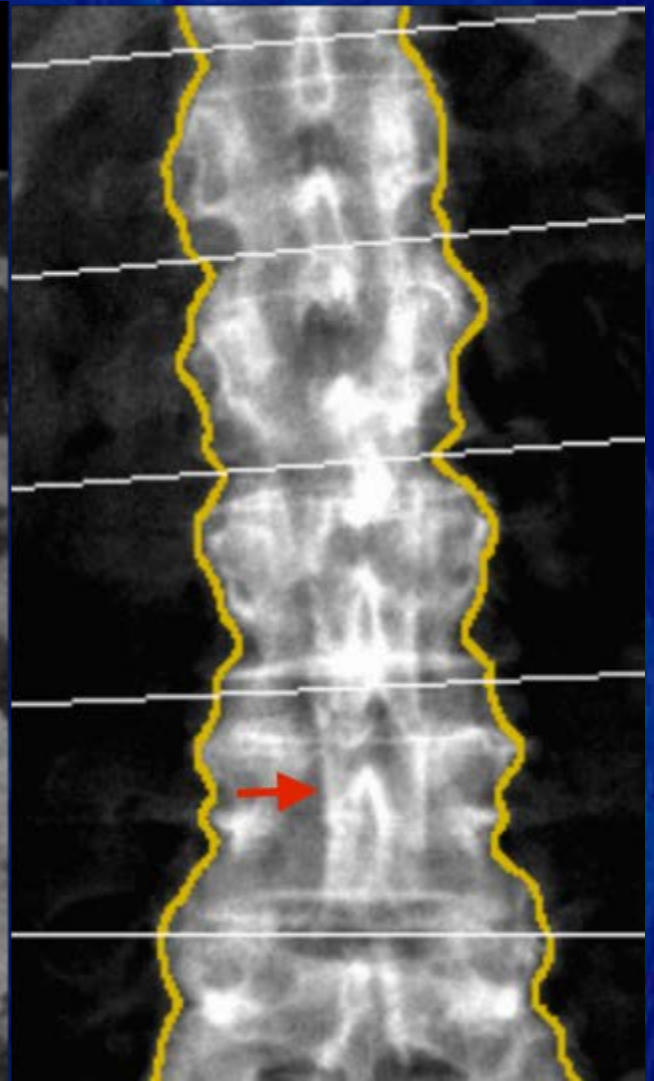
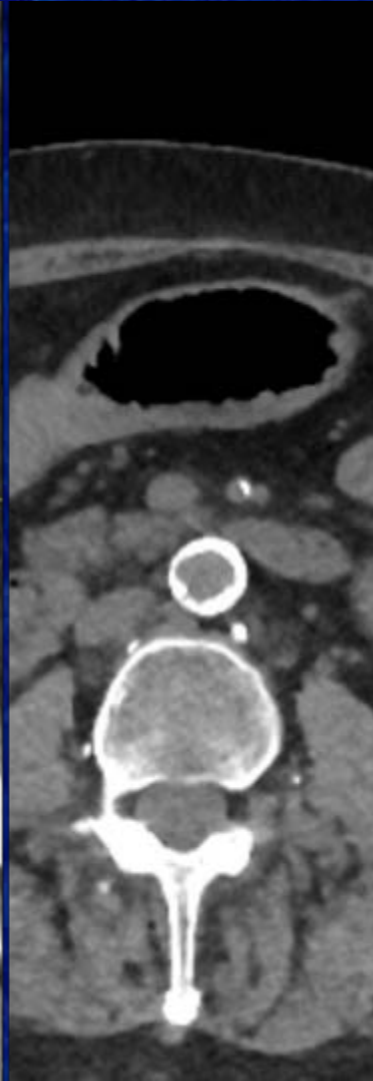
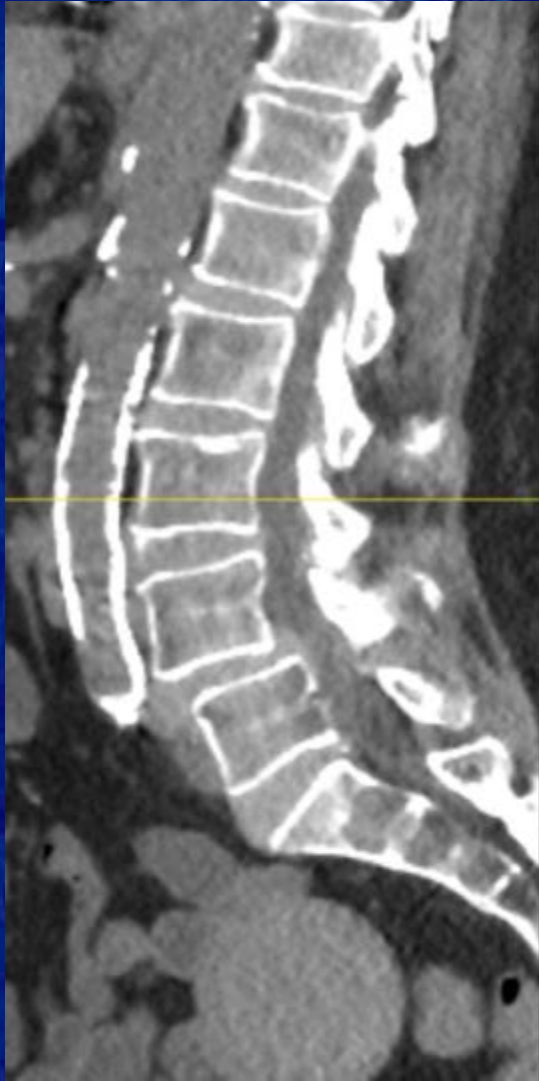
Wnt-signaling pathway

This pathway is necessary for differentiation of osteoblasts











Wnt-signaling

- Increases bone formation and decreases bone resorption
- Increases renal fibrosis
- Increases arterial wall calcification
- Is inhibited by klotho in the bone, kidney, and vasculature



