

Diagnosis and treatment of osteoporosis

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Disclosures

Lecture fee Abiogen

Chair 18th Vitamin D Workshop
Delft 2015



Anatomical lesson of Dr Sebastiaen Egbertsz De Vrij
painted by Thomas de Keyser 1619

Diagnosis and treatment of osteoporosis

- Diagnosis of osteoporosis, criteria, secondary osteoporosis
- Treatment: lifestyle, calcium vitamin D
- Specific treatment: inhibition of bone resorption
- Stimulation of bone formation: anabolic treatment
- Design of new drugs interfering with bone cells
- Summary and conclusion

Significance of the clinical problem

- Fractures are very common in patients above 50 years
about 45 % of women will experience a fracture
about 20 % of men will experience a fracture
- Hip fractures cause considerable morbidity and mortality
25 % dies within one year, 25 % goes to nursing home
- Vertebral fractures cause pain, loss of quality of life, and are associated with morbidity and mortality

Diagnosis of osteoporosis

- According to World Health Organization: T-score lower than -2.5 in femoral neck or lumbar spine measured by DXA
- About 50 % of patients with hip fracture or vertebral fracture have T-score between -1 and -2.5
- Treatment of patients with osteoporotic fractures decreases the risk of new fractures



Dual X-ray Absorptiometry and Instant Vertebral assessment

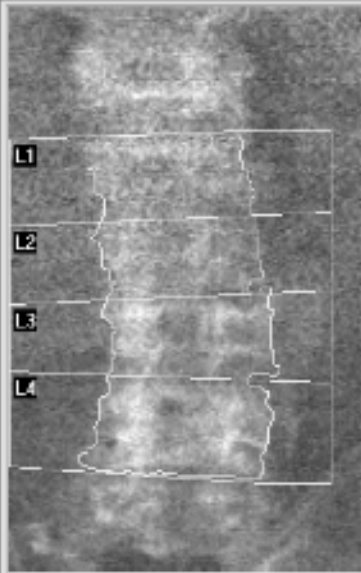
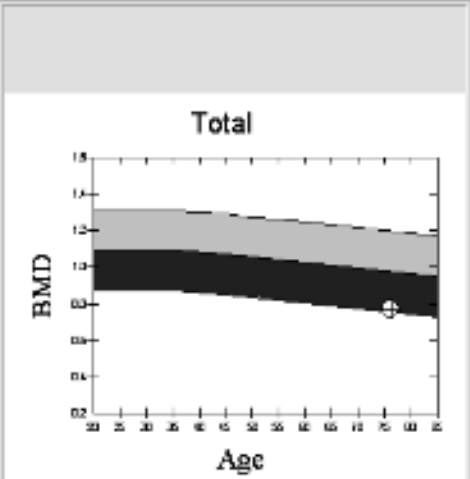


Image set for diagnostic use
L1 to L2



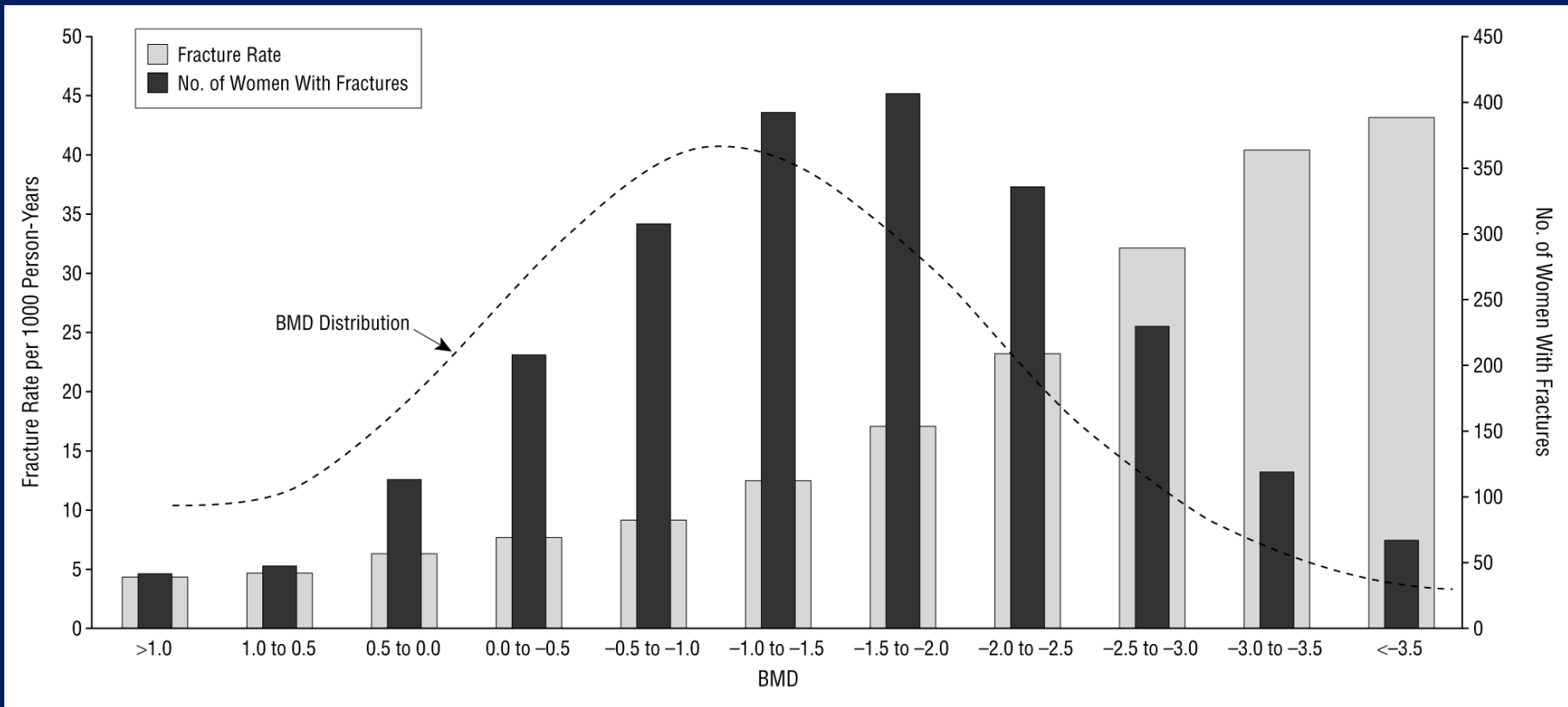
Reference curve and norm matched to 70-year Male

Results Summary:


Region	Area [cm²]	BMC [(g)]	BMD [g/cm²]	T-Score	PR (Peak Reference)	Z-Score	AM (Age Matched)
L1	16.36	12.08	0.738	-2.5	73	-1.5	82
L2	15.65	9.24	0.591	-4.6	54	-3.5	60
L3	16.81	10.71	0.637	-4.2	58	-3.2	65
L4	21.40	21.95	1.025	-1.1	90	0.0	100
Total	70.23	53.99	0.769	-2.9	70	-1.9	79

Total BMD CV 1.0%, ACF = 1.020, BCF = 0.995

The osteoporosis paradox: most fractures occur with T-score -1 to -2.5



Fracture Calculation Tool (FRAX)

Country: **Netherlands** Name/ID: [About the risk factors](#) 

Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age:

Date of birth:

Y:

M:

D:

2. Sex

☐

Male

☒

Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture

☐

No

☒

Yes

6. Parent fractured hip

☒

No

☐

Yes

7. Current smoking

☒

No

☐

Yes

8. Glucocorticoids

☒

No

☐

Yes

9. Rheumatoid arthritis

☒

No

☐

Yes

10. Secondary osteoporosis

☒

No

☐

Yes

11. Alcohol 3 or more units per day

☒

No

☐

Yes

12. Femoral neck BMD (g/cm²)

T-Score



Clear

Calculate

BMI 18.8

The ten year probability of fracture (%)



with BMD



Major osteoporotic

17

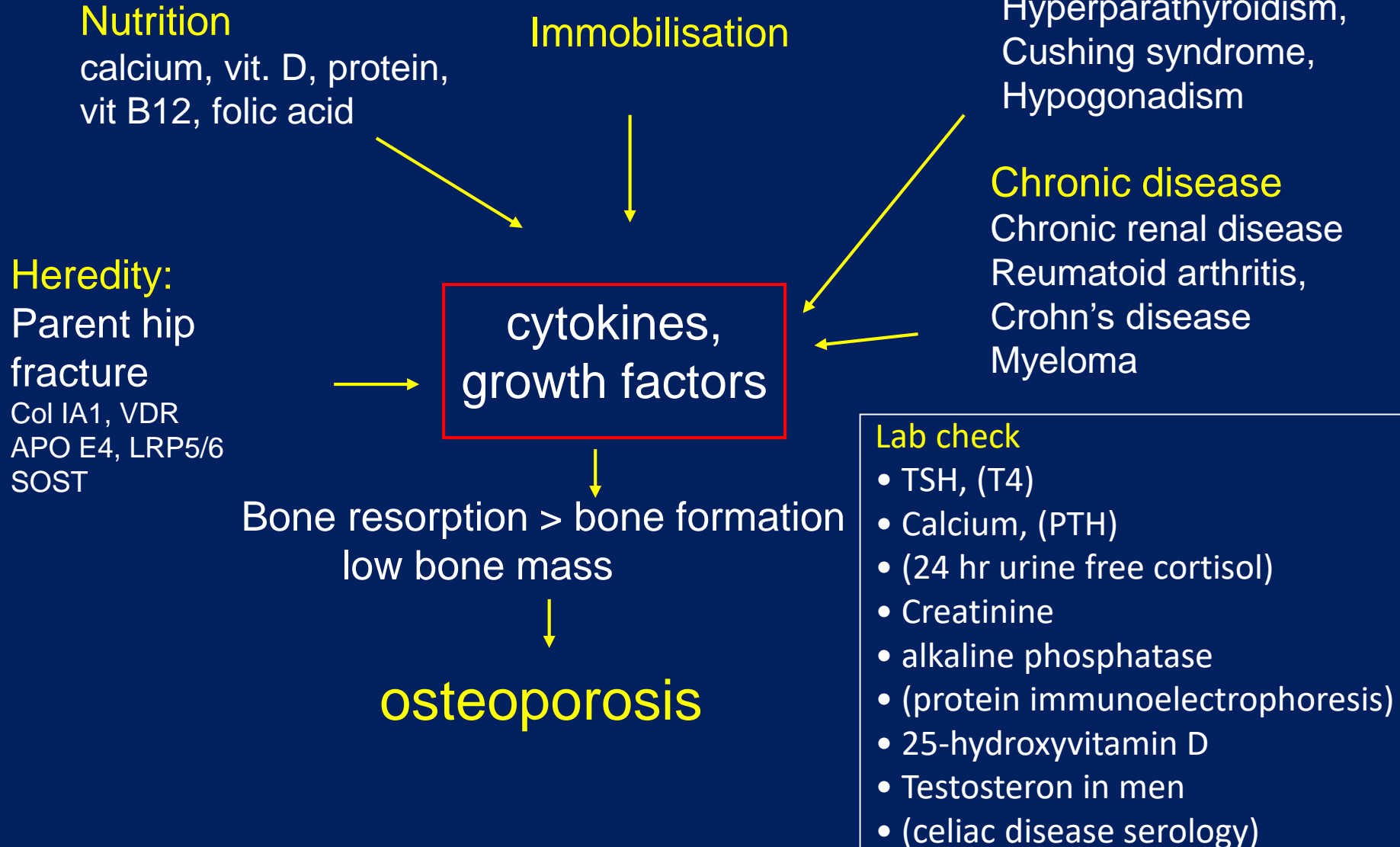


Hip fracture

8.5

Multifactorial etiology of osteoporosis

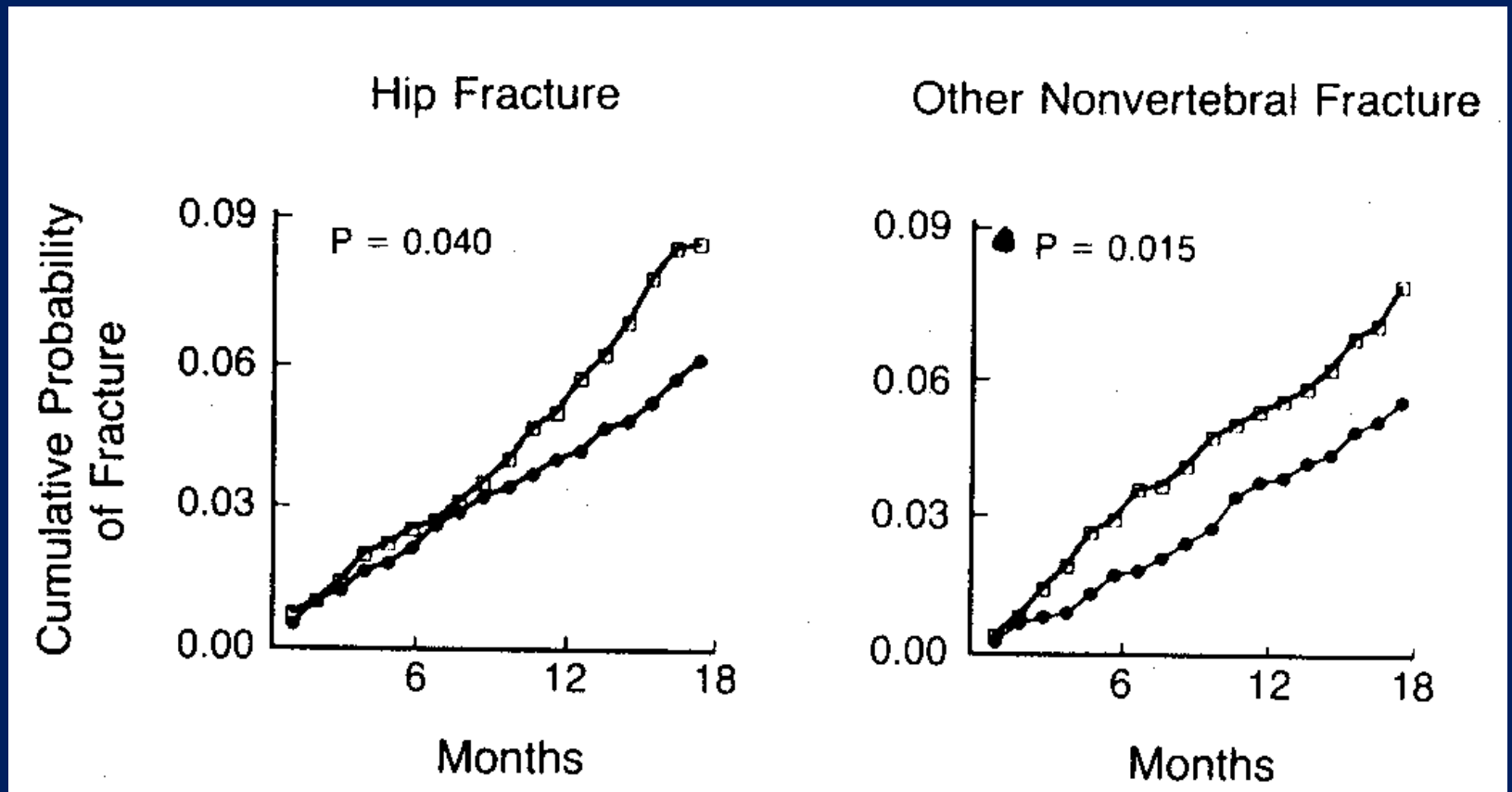
Causes of secondary osteoporosis



Lifestyle intervention

- Stop smoking, decrease alcohol consumption
- Increase weightbearing activity, such as walking, aerobics, TaiChi
- Moderate sun exposure
- Increase calcium intake
- Increase vitamin D intake, vitamin D supplement

Effect of vitamin D3 800 IU/d and calcium 1200 mg/d vs placebo on fracture incidence in 3270 French nursing home residents (mean age 84 yr)



MC Chapuy et al. N Engl J Med 1992; 327: 1637-42

Osteoporosis: Calcium and vitamin D

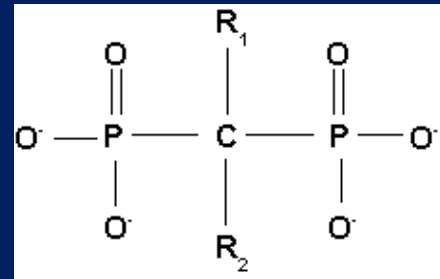
Calcium

- Increase dietary calcium intake to 1000 mg/d
1 glass of milk, yoghurt = 200-300 mg
50 gram cheese = 200-400 mg
- If not possible: one or two calcium tablets,
containing 500 mg of calcium

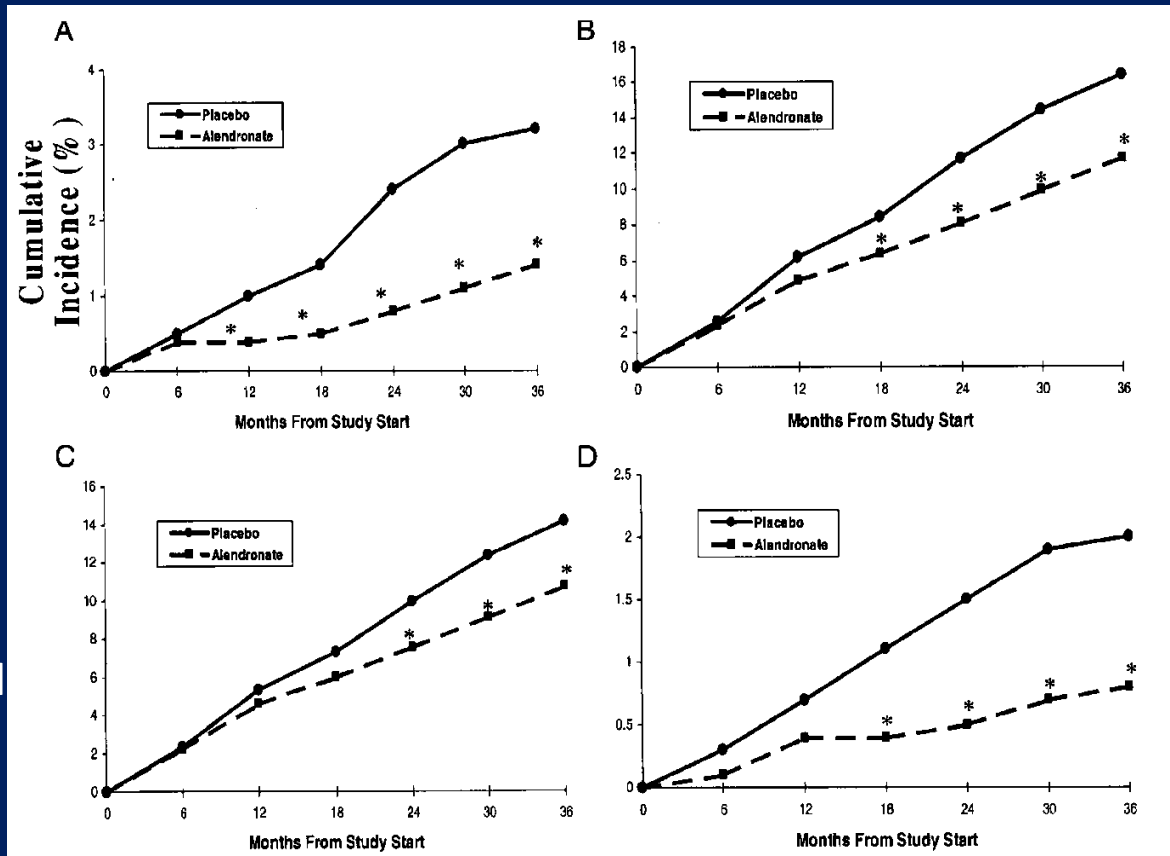
Vitamin D

- Vitamin D3 800 IU/d (20 µg/d)

Proportion of women with various fracture types during alendronate vs placebo treatment



Any fracture



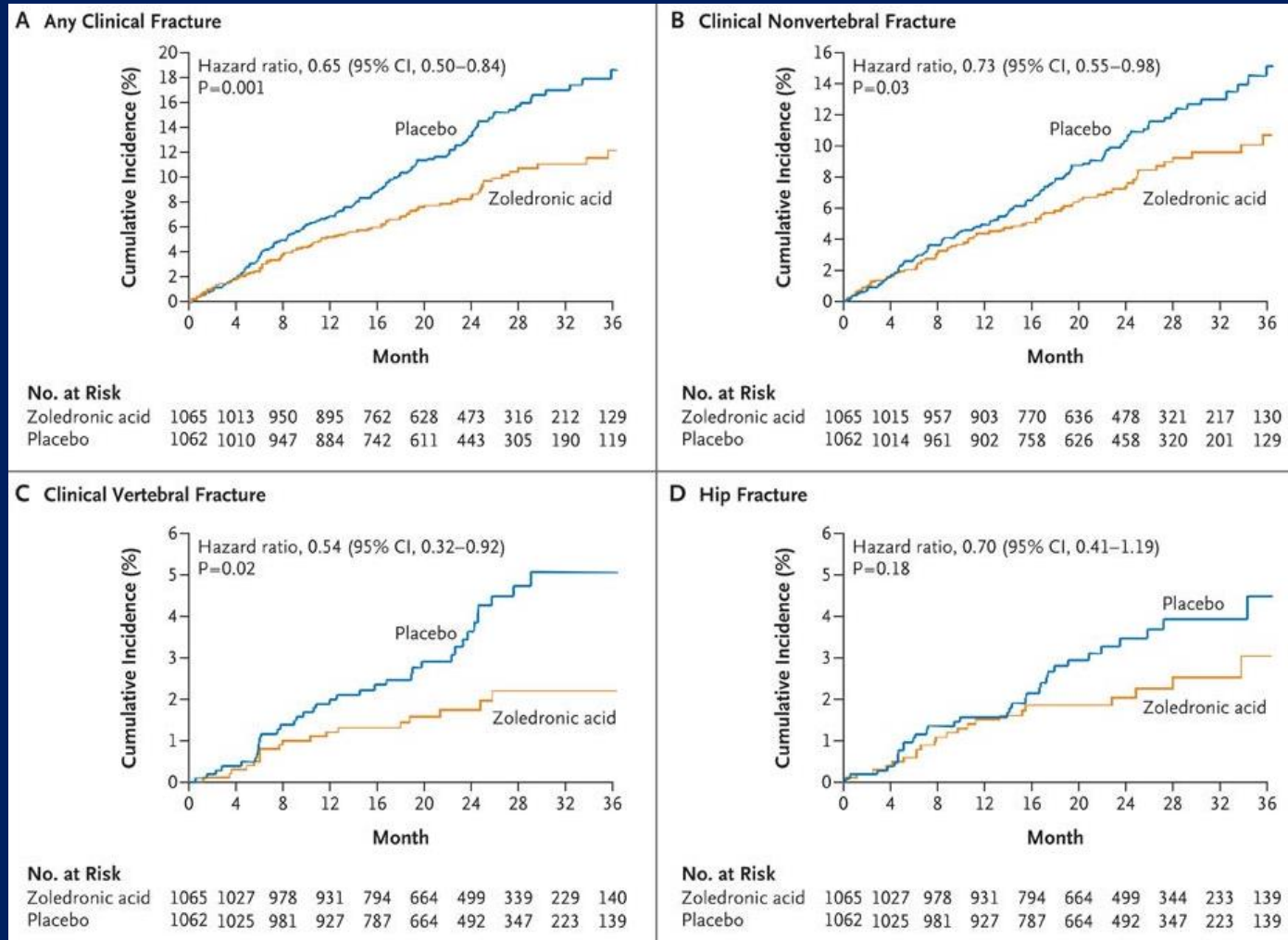
Hip fracture

Clinical
vertebral
fracture

Non-vertebral
fracture

Zoledronic acid 5 mg per year in patients with hip fracture; prevention of new clinical fractures

A study in 2127 men and women of 74.5 yr



Lyles et al NEJM 2007; 357: 1799-1809

Bisphosphonates: side effects

- Short term side effects

Oral: alendronate, risedronate may cause gastrointestinal problems (5-10%), bone, joint or muscle pain, headache

Intravenous: zoledronate causes acute phase reaction, i.e. fever, flu-like symptoms

- Long term side effects

Osteonecrosis of the jaw

Atypical femoral shaft fractures



Alternative antiresorptive treatment

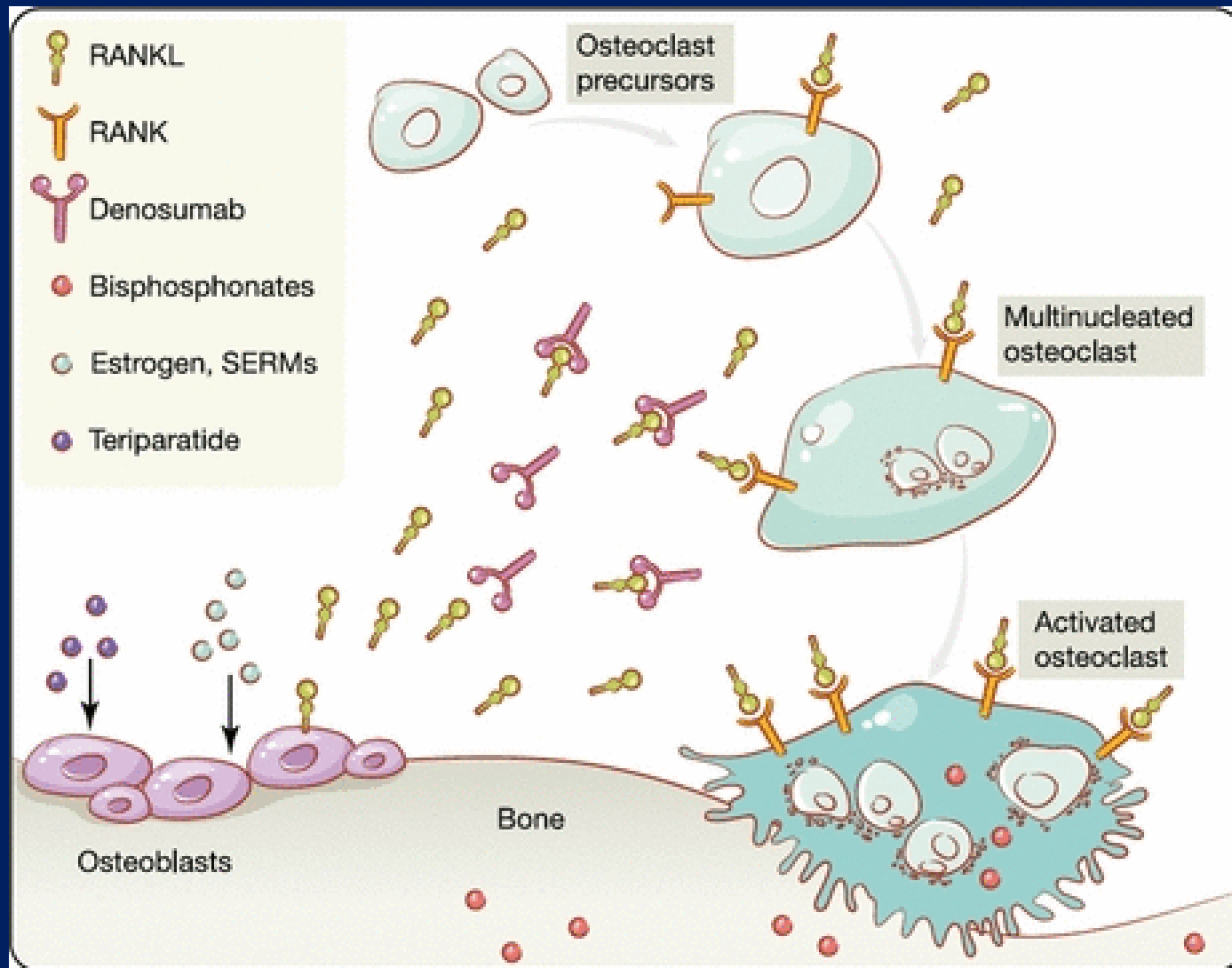
- Selective estrogen receptor modulator (SERM) raloxifene, bazedoxifene, prevent vertebral fractures, safe in women 50-60 years;

Side effects: menopausal symptoms, edema, leg cramps, thrombo-embolic events

- Strontium ranelate may prevent different fracture types, but safety profile is uncertain.

Side effects: nausea and diarrhea, mouth ulcers, thrombo-embolism, heart disease

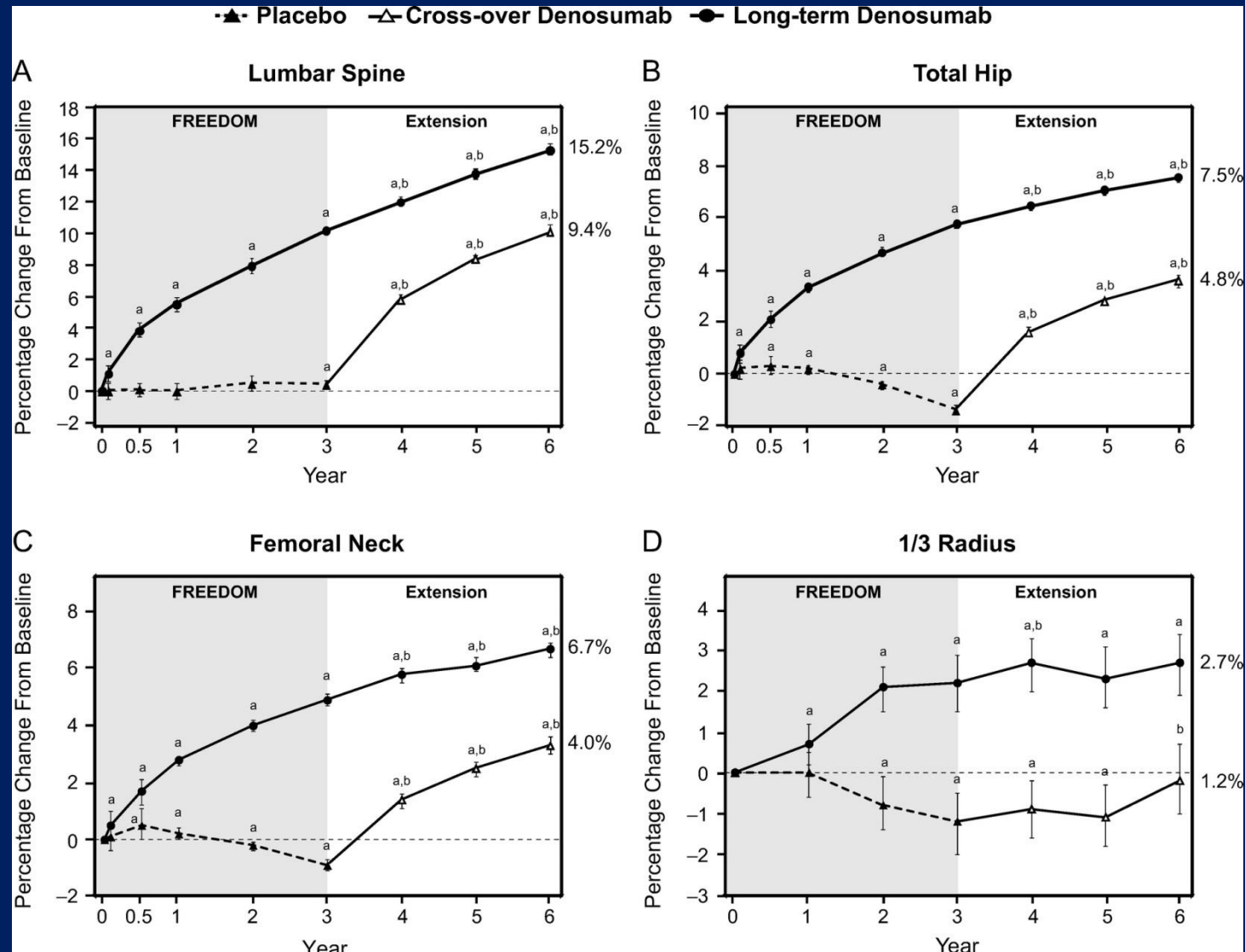
Denosumab: mechanism of action



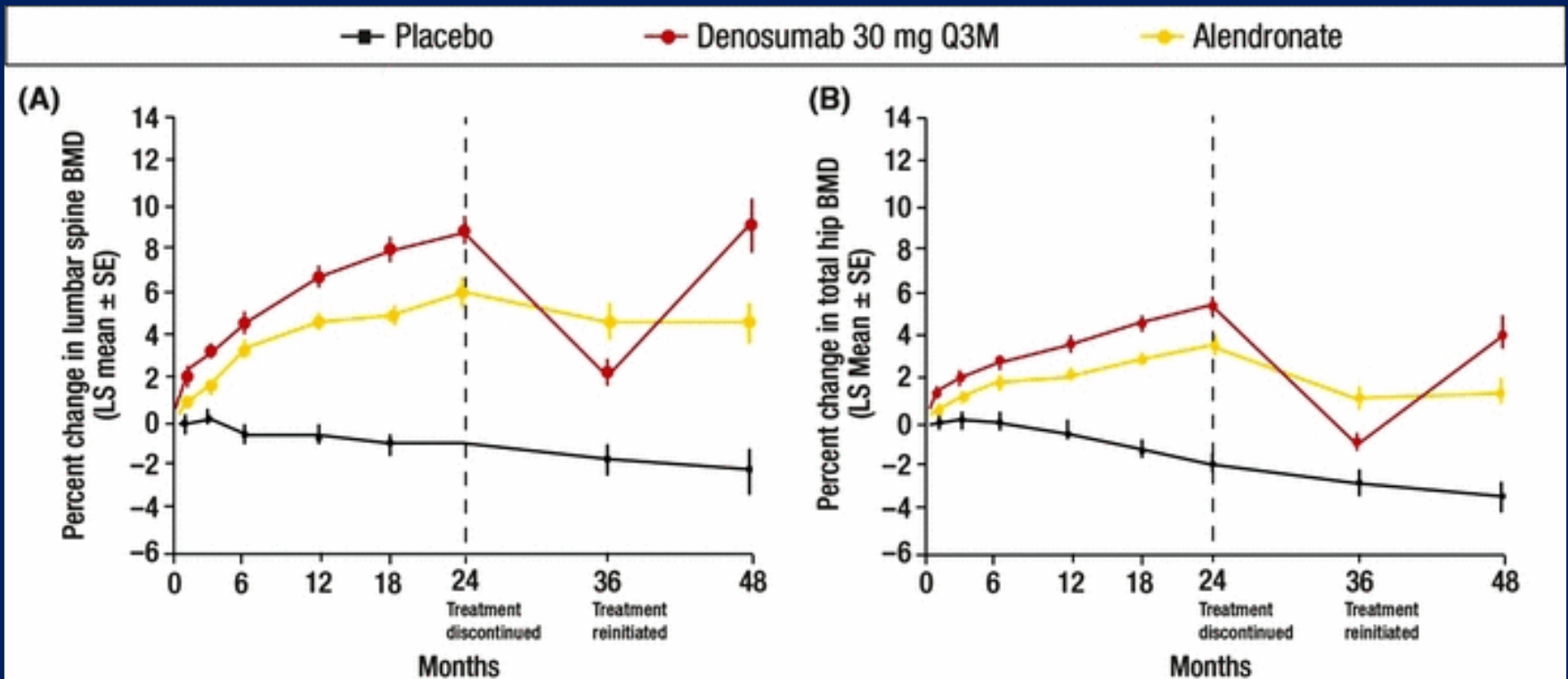
New antiresorptive drug: denosumab

- RANK-L antagonist: interferes with stimulation of osteoclast by osteoblast
- Denosumab is given by subcutaneous injection 60 mg once in 6 months
- Denosumab may be prescribed to patients with chronic renal failure.
- Side effects; infections (urinary, respiratory, skin), hypocalcemia, (limb pain)
- Long term side effects: osteonecrosis of the jaw, atypical femoral fractures

Effect of denosumab on BMD in 6 years: FREEDOM Trial

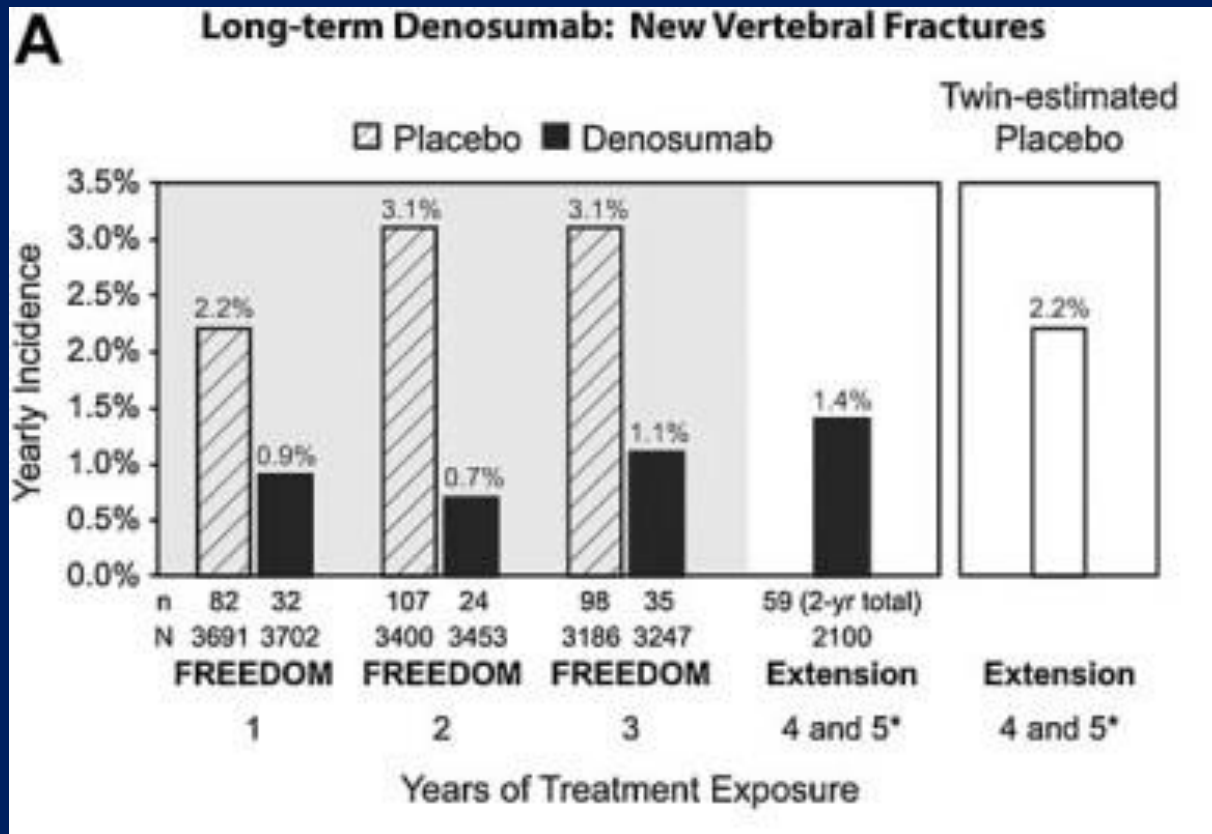


Bone loss after stopping denosumab: immediate fast bone loss



Hanley et al Int J Clin Pract 2012; 66: 1139-46

Denosumab: effect on vertebral fractures



Anabolic effect of teriparatide

Continuous PTH

- Stimulates RANK-L
- Suppresses OPG
- Activates osteoclasts
- Downregulation PTHR1, IGF-1
- Decreased bone formation

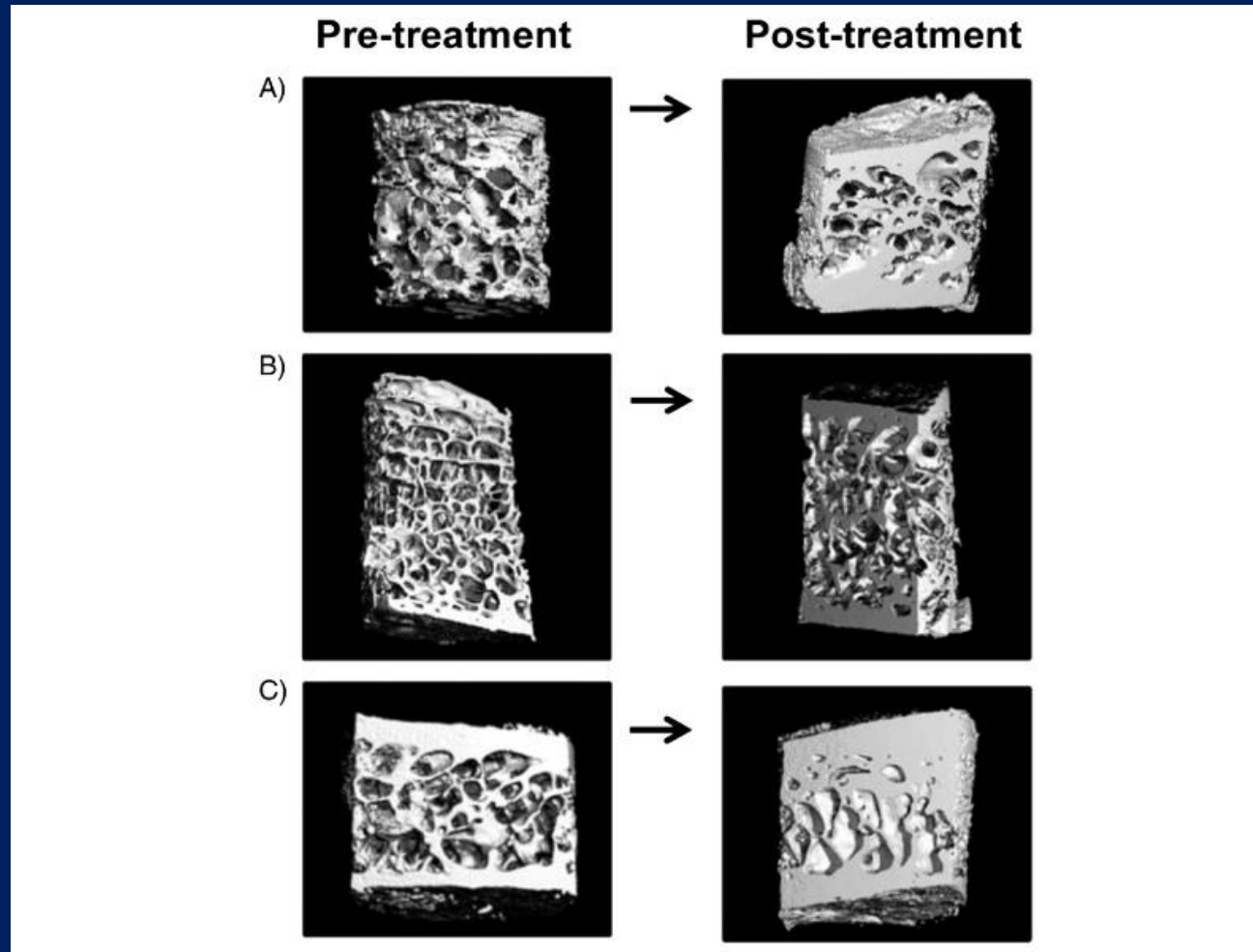
Catabolic action on bone

Intermittent PTH

- Stimulates adenylate cyclase and osteoblast proliferation
- Stimulates osteoblast function through IGF-1 and FGF-2
- Increased bone formation

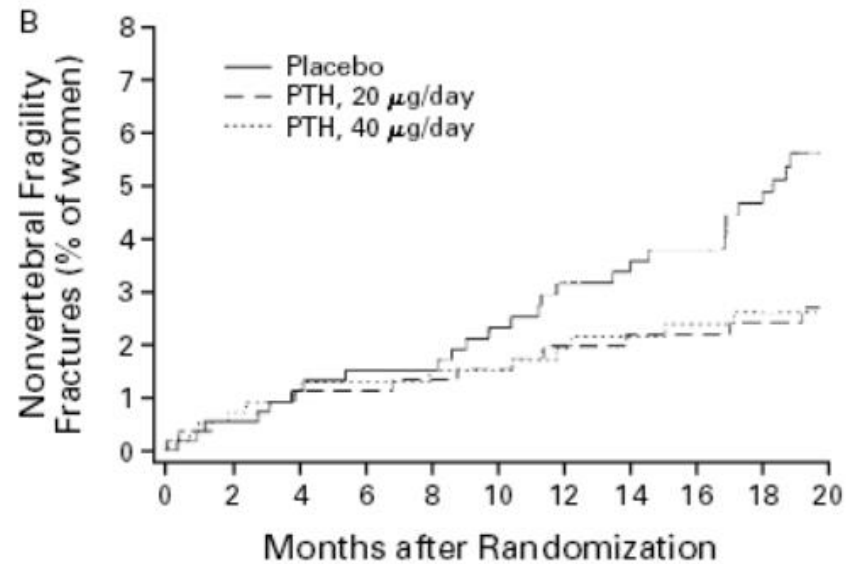
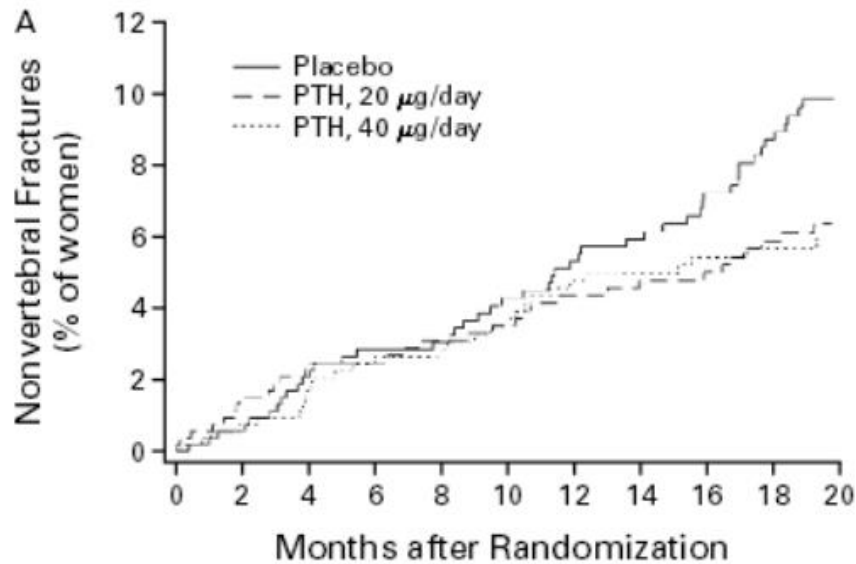
Anabolic action on bone

Effect of teriparatide on bone biopsies using micro CT



Eriksen EF et al . Bone 2014; 67: 246-56

Effect of teriparatide on fracture incidence



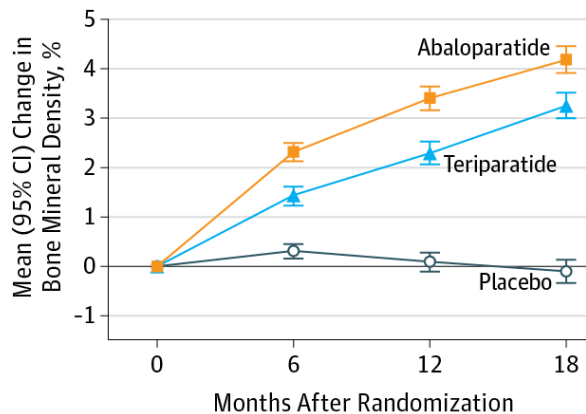
Neer et al N Engl J Med 2001; 344: 1434-41

Teriparatide: dose, contraindication, side effects

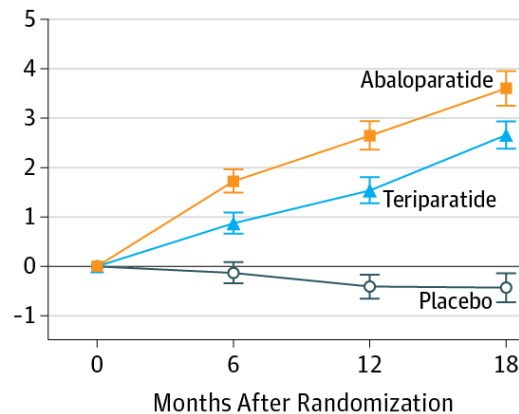
- Dose: 20 μg per day by subcutaneous injection
- Contraindication: hypercalcemia, renal disease, liver disease, Paget's disease, irradiation to the skeleton, cancer with risk for bone metastasis.
- Side effects: pain in arms or legs, nausea, headache, dizziness, local irritation on injection site.

PTHrP analogue Abaloparatide compared with Teriparatide and Placebo

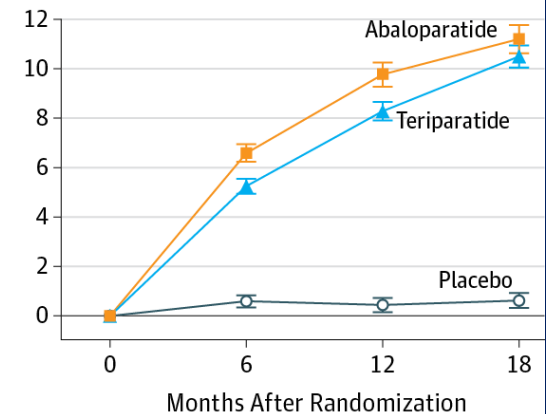
A Total hip



B Femoral neck



C Lumbar spine



No. of participants evaluated

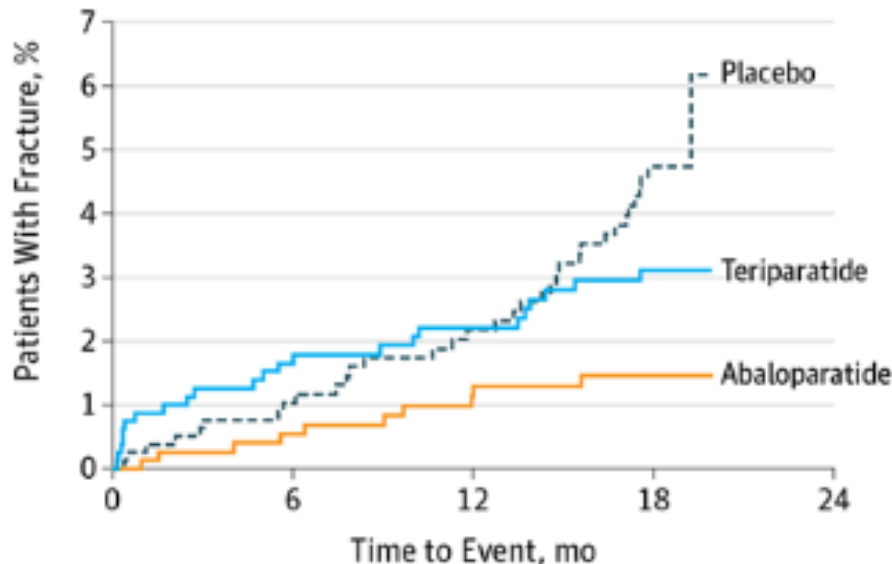
Abaloparatide	822	736	651	615
Placebo	820	762	693	651
Teriparatide	818	754	705	660

822	736	651	615
820	762	693	651
818	754	705	660

823	738	652	617
821	764	694	650
818	755	704	665

Abaloparatide: effect on fracture incidence

C Major osteoporotic fractures



Log-rank *P* value
 <.001 Abaloparatide vs placebo
 .14 Teriparatide vs placebo
 .03 Abaloparatide vs teriparatide

Median follow-up time, mo
 18.93 Abaloparatide
 18.93 Placebo
 18.90 Teriparatide

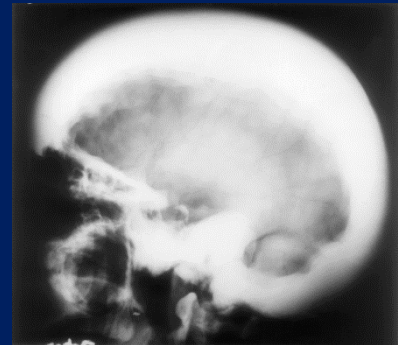
No. at risk				
Abaloparatide	824	693	640	606
Placebo	821	728	671	616
Teriparatide	818	729	678	637
Cumulative No. with event				
Abaloparatide		4	9	10
Placebo		8	16	33
Teriparatide		13	17	23

New drug design interfering with bone cell metabolism: from inborn error to new drug

- Pycnodysostosis: disease of osteoclast: lack of cathepsin K results in sclerotic bone disease and short stature. Cathepsin K antagonist is developed for osteoporosis
- Sclerosteosis: disease of osteocyte: lack of sclerostin results in severe sclerosis of all bones.
Antibody against sclerostin is developed for osteoporosis.



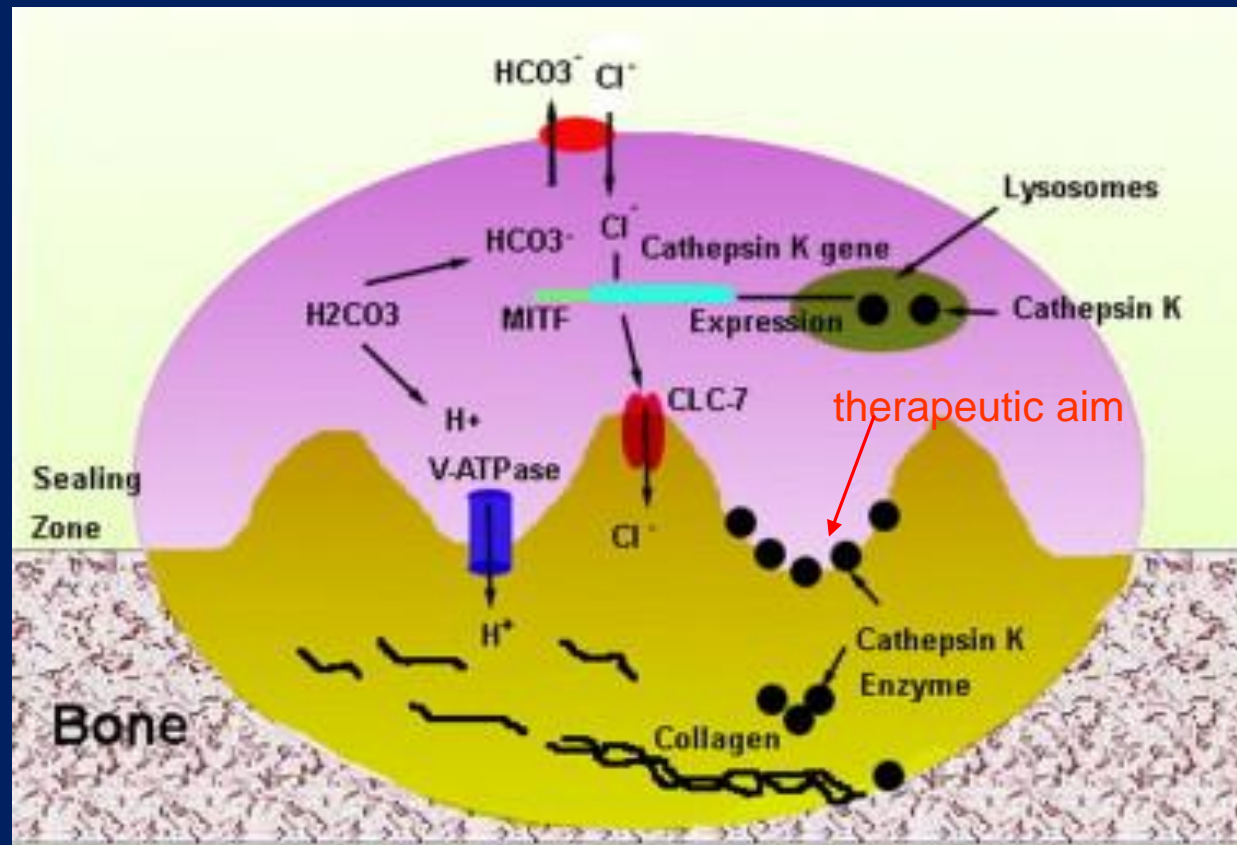
Toulousse-Lautrec



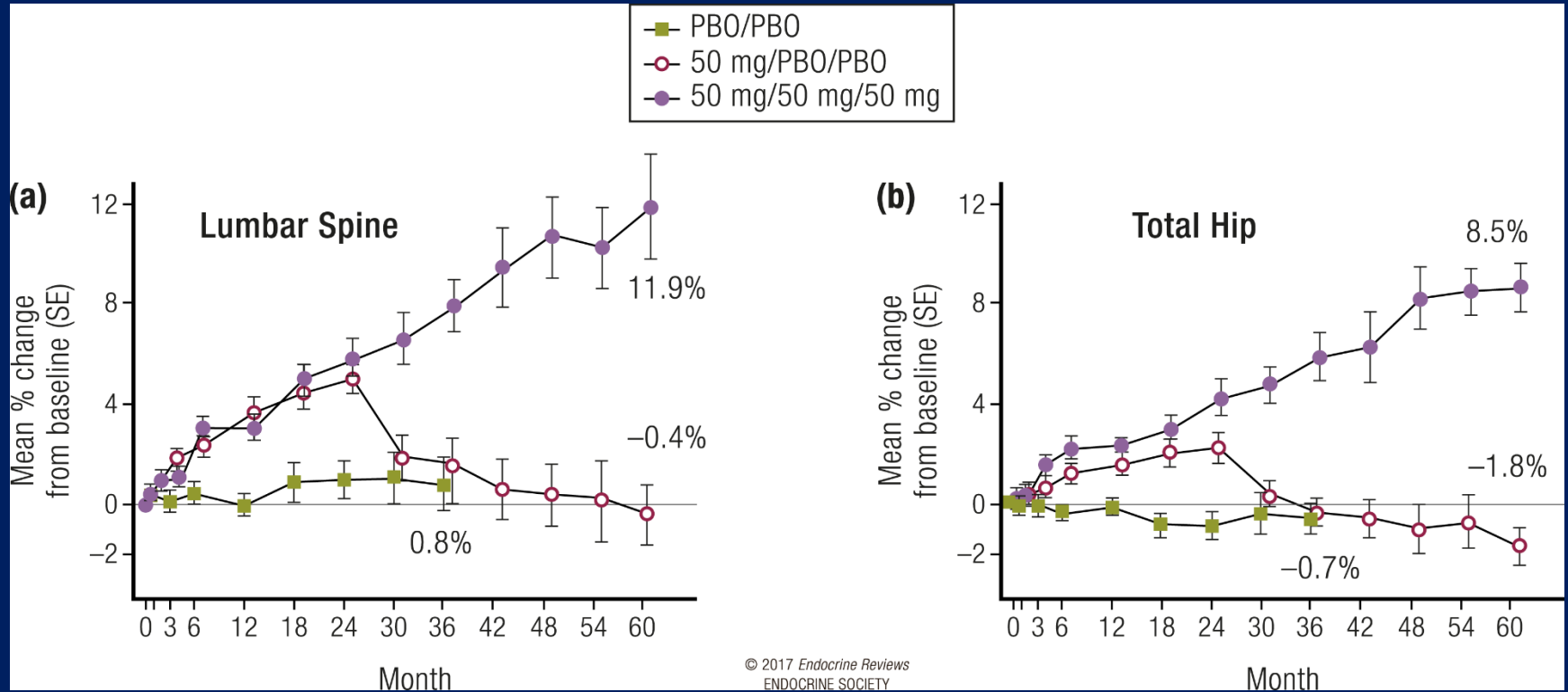
Sclerosteosis

Bone resorption by the osteoclast

therapeutic aim: cathepsin K antagonist



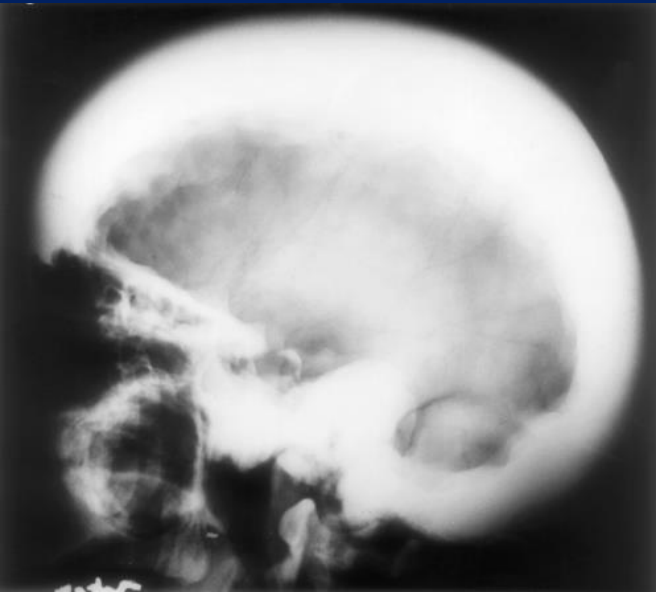
Effect of odanacatib 50 mg/week on BMD in postmenopausal women



Cerebrovascular side effects!

Langdahl et al J Bone Miner Res 2012; 27:2251-8

Sclerosteosis: mainly in South Africa
due to mutation in the SOST gene, recessive disease
leading to very low sclerostin levels and severe osteosclerosis



Hamersma et al. The natural history of sclerosteosis. Clin Genet 2003; 63: 192-7

Osteocytes stained for sclerostin

Sclerostin suppresses bone formation in osteon

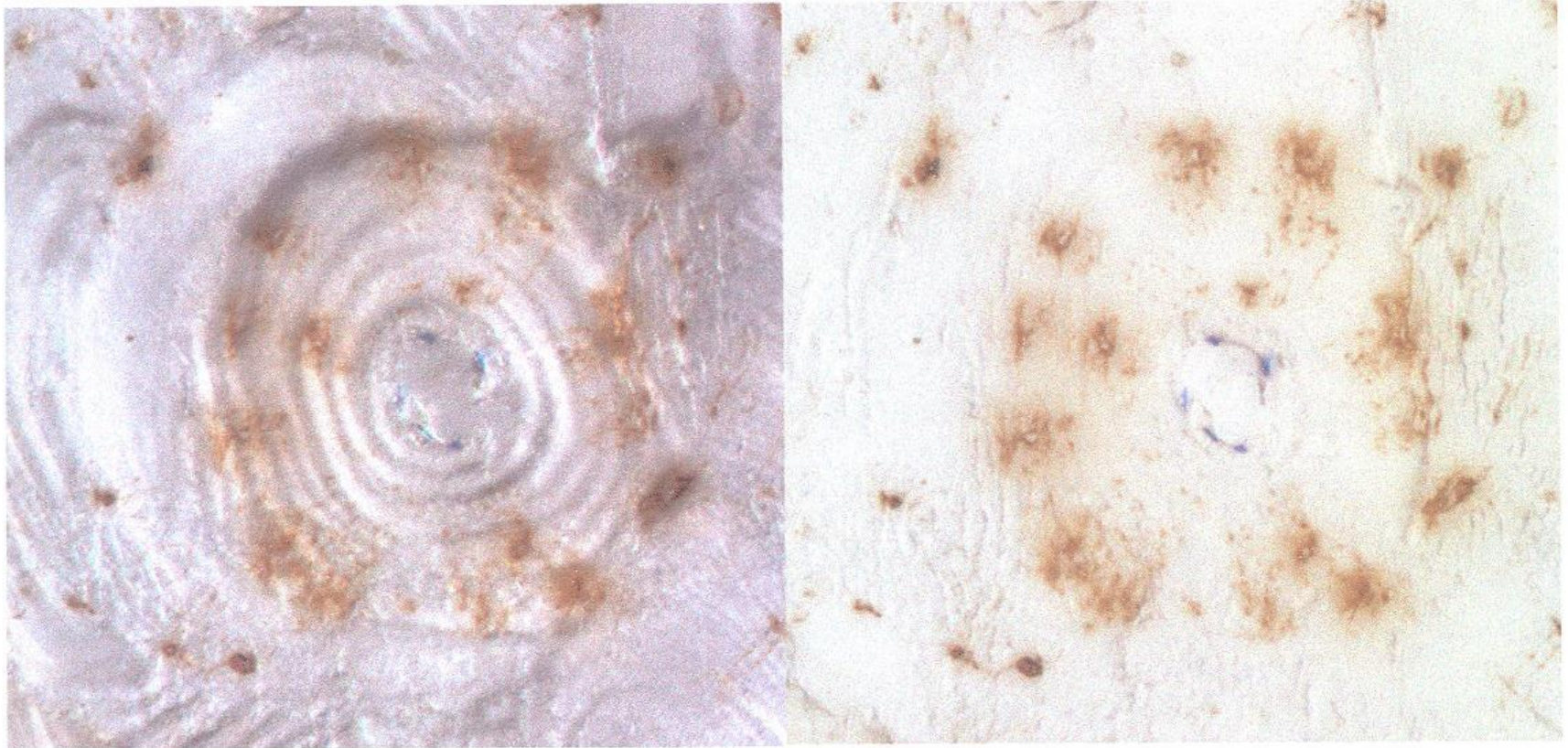
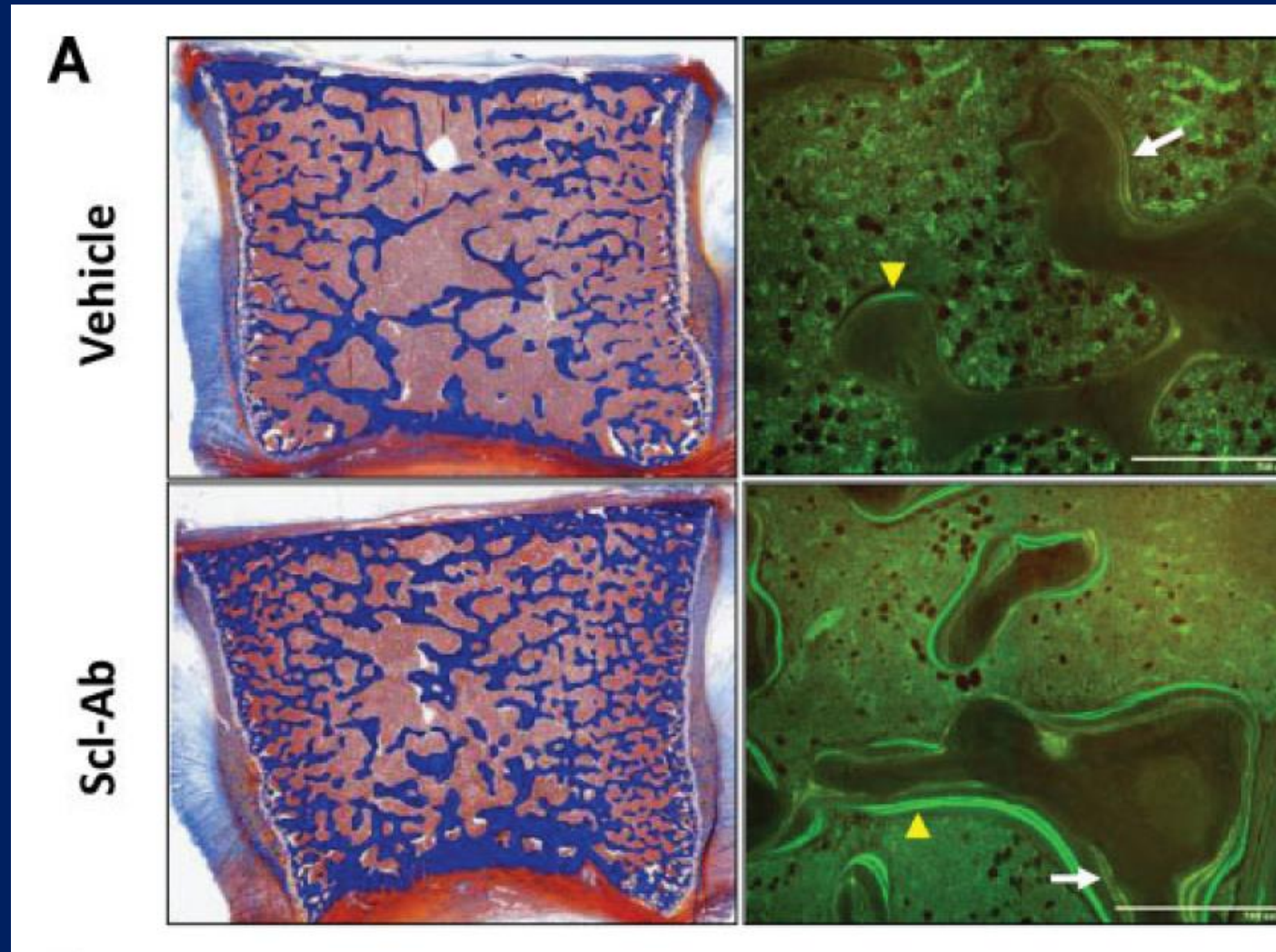


Figure 2.3 Osteocytes and their canaliculi in a newly formed cortical osteon seen using polarised light (left) and bright field microscopy (right). x126 magnification. Osteocytes are stained for the protein sclerostin.

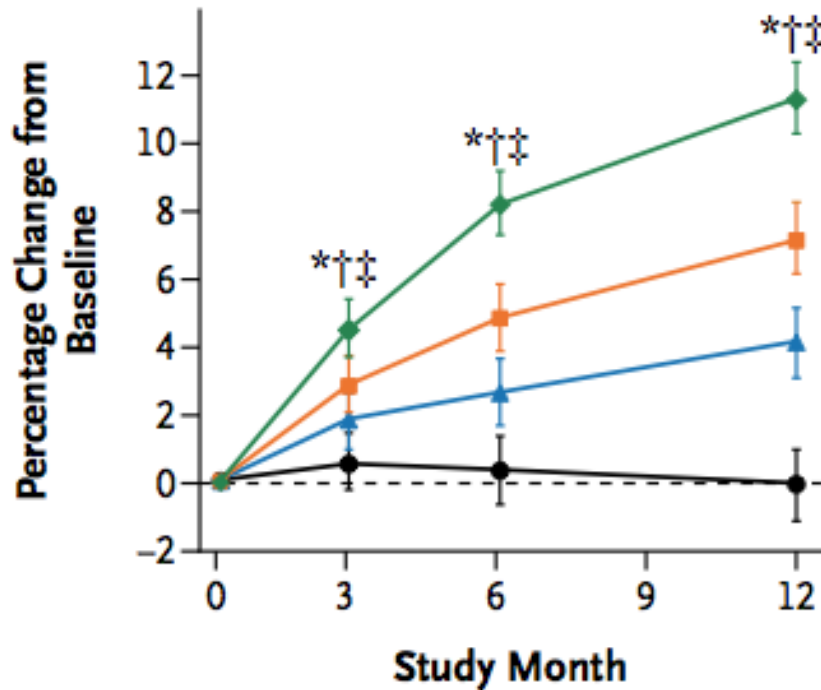
Sclerostin antibody in Cynomolgus monkeys: bone formation in vertebrae



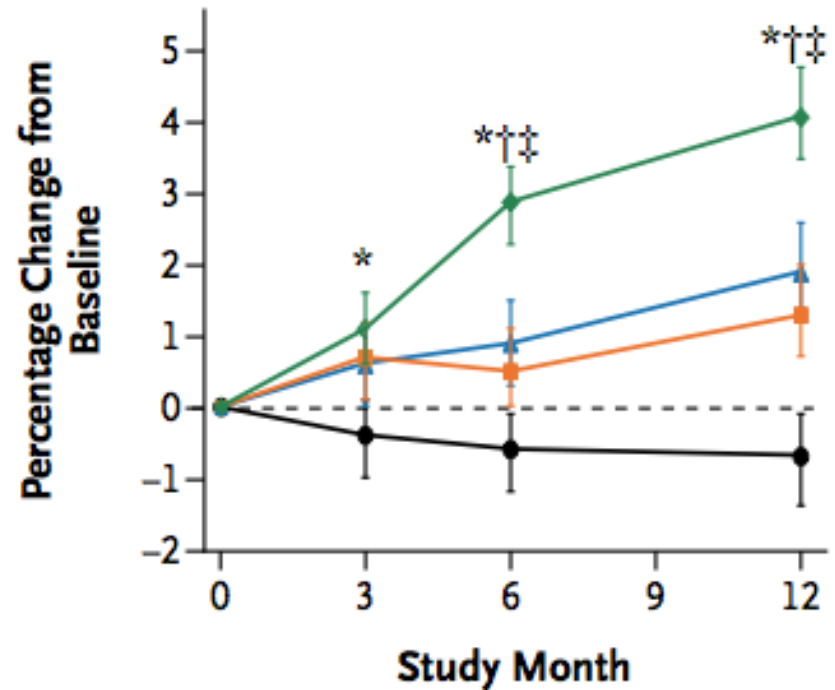
Effects of romosozumab on BMD compared with alendronate and teriparatide

—●— Placebo —▲— Alendronate —■— Teriparatide —◆— 210 mg of Romosozumab monthly

A Lumbar Spine

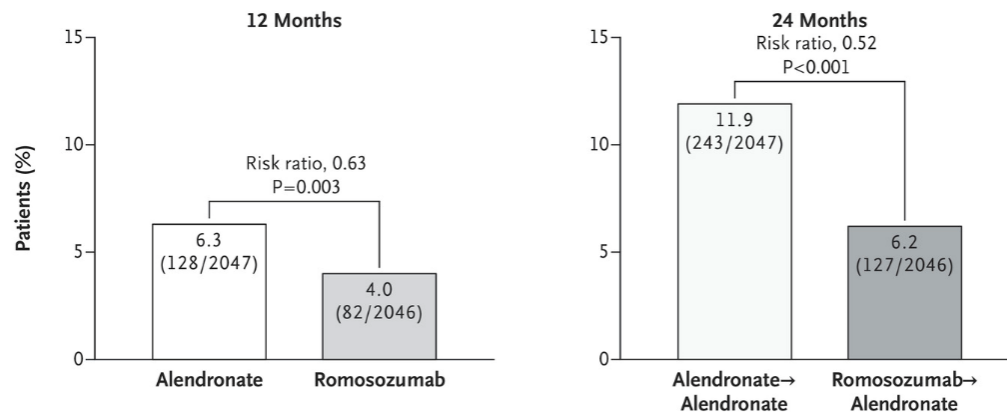


B Total Hip

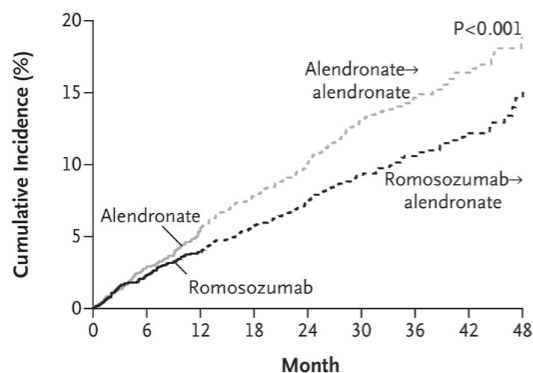


Romosozumab vs alendronate for fracture prevention

A Incidence of New Vertebral Fracture



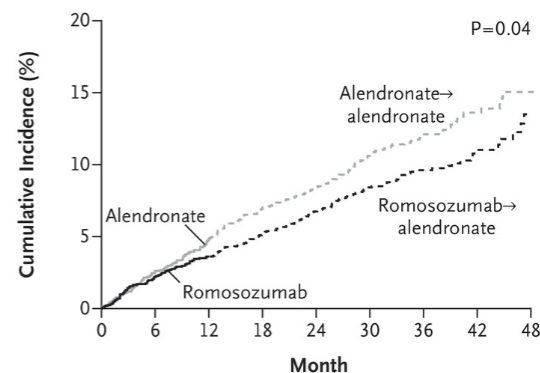
B First Clinical Fracture in Time-to-Event Analysis



No. at Risk

Alendronate	2047	1868	1743						
Romosozumab	2046	1865	1770						
Alendronate→alendronate				1645	1564	1066	680	325	108
Romosozumab→alendronate				1683	1615	1103	705	347	109

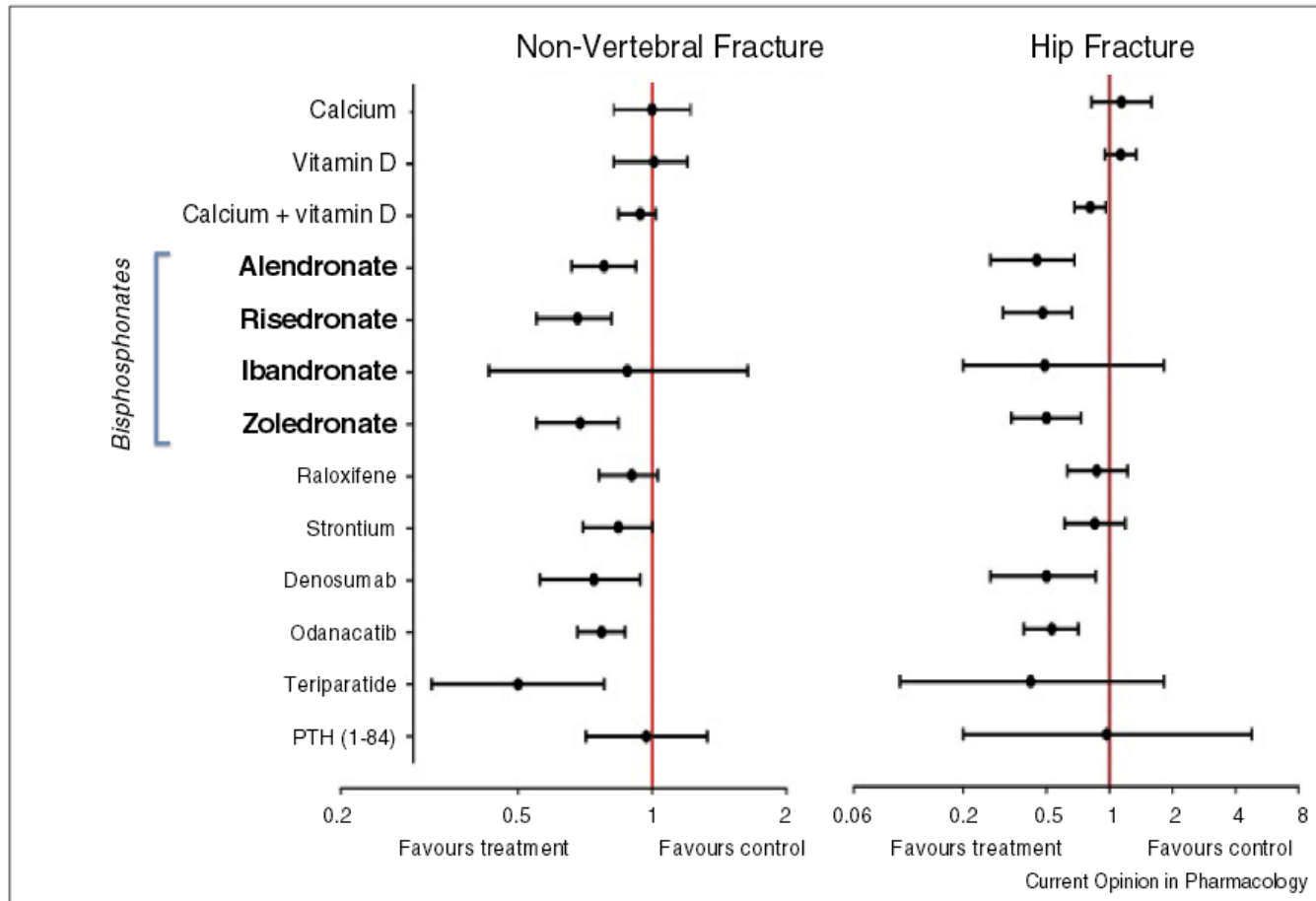
C First Nonvertebral Fracture in Time-to-Event Analysis



No. at Risk

Alendronate	2047	1873	1755						
Romosozumab	2046	1867	1776						
Alendronate→alendronate				1661	1590	1097	697	330	110
Romosozumab→alendronate				1693	1627	1114	714	350	109

Relative efficacy of drugs on non-vertebral fracture and hip fracture



Specific treatment flow diagram

- T-score < -2.5 or vertebral fracture or high risk (FRAX)
→ start bisphosphonate
- + Renal function impairment (GFR < 30 ml/min)
→ start denosumab
- Vertebral fractures during bisphosphonate treatment
→ start teriparatide
- Second choice in women < 60 yr: SERM (raloxifene),
- Future: sclerostin antibody (romosozumab)
PTH related peptide analog (abaloparatide)

Summary

- Diagnosis of osteoporosis (T-score < -2.5) or vertebral fracture(s) or high fracture risk.
- Exclude or treat secondary causes
- Lifestyle intervention, exercise, calcium, vitamin D
- Specific treatment in case of T-score lower than -2.5 and/or vertebral fracture(s) and/or high fracture risk (FRAX score)

Summary (2)

- The first choice treatment is an oral bisphosphonate. In case of gastro-intestinal side effects, intravenous bisphosphonates may be given.
- When renal function is impaired, the RANK-L antagonist denosumab can be prescribed.
- In postmenopausal women of 50-60 years a SERM can be considered.

Summary (3)

- In case of fractures during bisphosphonate treatment or multiple vertebral fractures, an anabolic e.g. teriparatide can be prescribed during 2 years followed by bisphosphonate treatment.
- Combination therapy with denosumab and teriparatide is very effective in severe osteoporosis.
- Promising future treatment is an anti-sclerostin antibody.