The recent trend for osteoporosis treatment : Anti-resorptive agent and Anabolic agent

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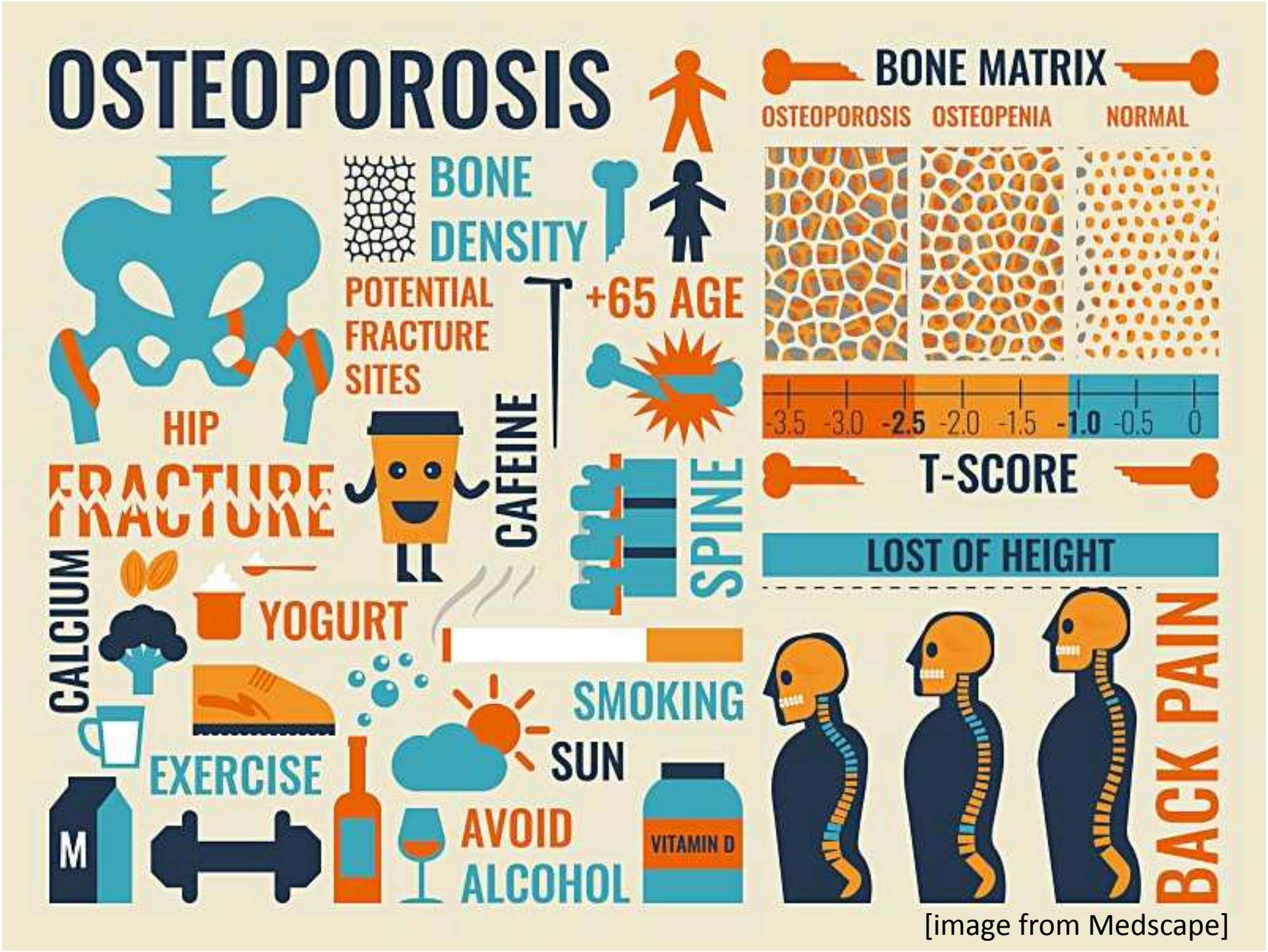
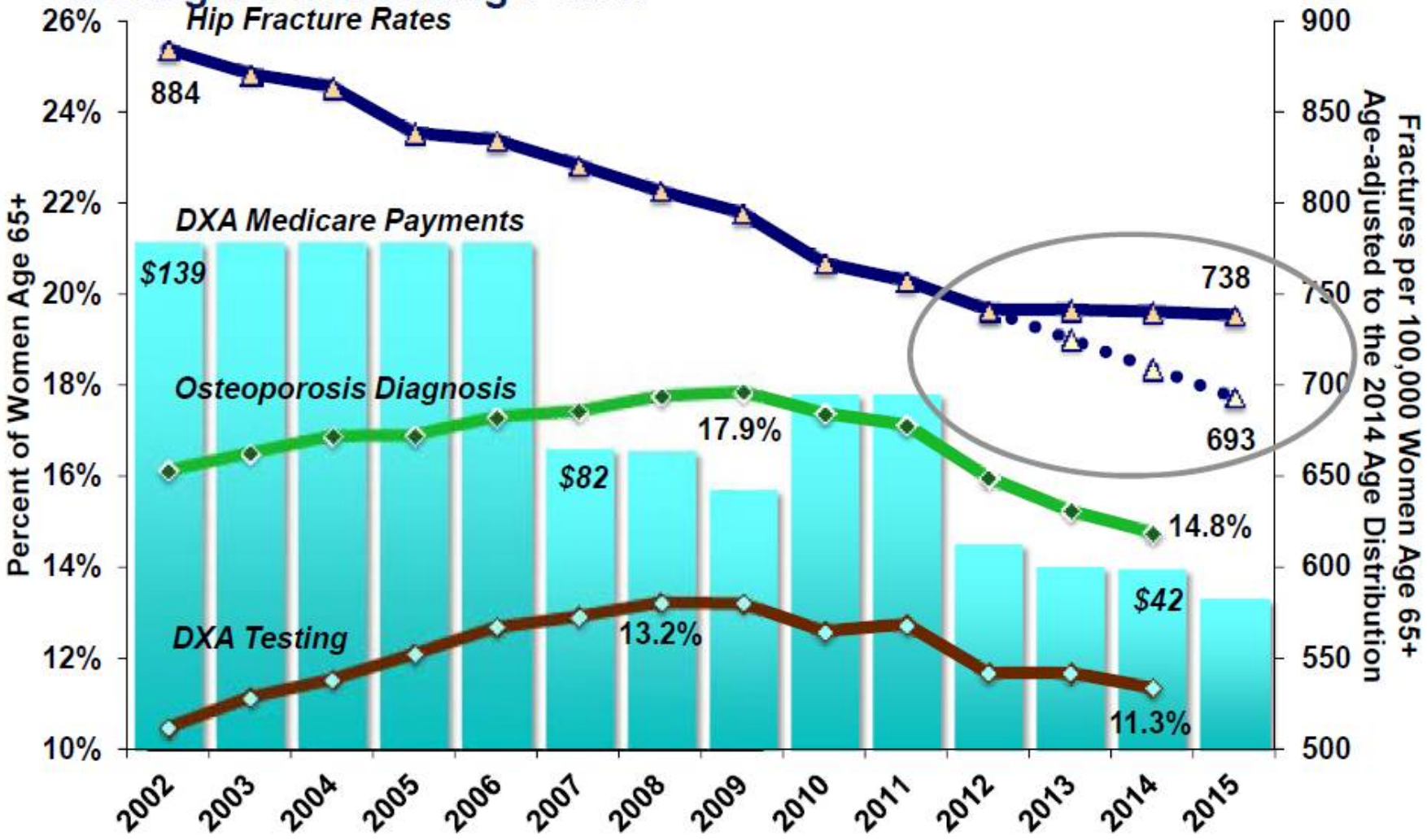
내과학교실 세브란스병원
이 유 미



[image from Medscape]

[image from Tinobusiness.com]

Abs #1077: Lewiecki et al. Hip Fractures and Declining DXA Testing: At a Breaking Point?



Direct Research LLC, Medicare PSPS Master Files and Medicare 5 Percent Sample LDS SAF, analysis by Peter M. Steven, PhD.

Therapeutic decisions, “Treat-to-Target”

Goals

- Free from fractures
- Low risk of fractures

Goal-Directed Treatment

1) a goal of treatment is established for a patient

2) the initial choice of treatment is based on the probability of reaching the goal

3) progress toward reaching the patient's goal is reassessed periodically, with decisions to stop, continue, or change treatment based on achievement of the goal or progress toward achievement of the goal.

Specific osteoporosis therapies

Maintain bone

Antiresorptive therapy

- Targets osteoclasts[1]
- Reduces bone turnover[1]
- Reduces cortical porosity[2]
- Increases BMD[1,3,4]
- Reduces fracture risk[3-5]

Build bone

Anabolic therapy

- Targets osteoblasts[6]
- Increases bone formation[6,7]
- Increases trabecular bone volume[7]
- Increases BMD[6,8]
- Improves cancellous microarchitecture[7]
- Increases cortical thickness and improves cortical bone geometry[7]
- Reduces fracture risk[6,8]

1. Fleisch H. *Endocr Rev* 1998;19:80–100; 2. Borah B, *et al. J Bone Miner Res* 2010;25:41–47; 3. Boivin G, Meunier PJ. *J Musculoskel Neuron Interac* 2002;2:538–43; 4. Eastell R, *et al. J Bone Miner Res* 2011;26:530–37
5. Bilezikian JP. *Am J Med* 2009;122:S14–S21; 6. Arlot M, *et al. J Bone Miner Res* 2005;20:1244–53; 7. Jiang Y, *et al. J Bone Miner Res* 2003;18:1932–41; 8. Neer RM, *et al. N Engl J Med* 2001;344:1434–41.

The strength of evidence among the medication for decreasing the risk of hip and other non-vertebral fractures

Summary of **AHRQ's Comparative Effectiveness Review** of Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of the 2007 Report

	Fracture Skeletal Sites			
Agent	Vertebral	Nonvertebral	Hip	Wrist
Alendronate	●●●	●●●	●●●	●
Ibandronate	●●●	●●	●	❙
Risedronate	●●●	●●●	●●●	●
Zoledronic acid	●●●	●●●	●●●	❙
Denosumab	●●●	●●●	●●●	❙
Teriparatide	●●●	●●	●	❙
Raloxifene	●●●	❙	❙	❙

Sources: Crandall CC, Newberry SJ, Gellad WG et al. Comparative effectiveness of treatment to prevent fractures in men and women with low bone density or osteoporosis - update of a 2007 report. AHRQ comparative effectiveness review no. 53. March 2012.

Strength of evidence symbol legend: ❙ = insufficient strength of evidence; ● = low strength of evidence; ● ● = moderate strength of evidence; ● ● ● = high strength of evidence.

Adapted from Levis S, et al. J Manag Care Pharm 18(4-b): S3-S15, 2012

Different effects against fracture

- Satisfactory
- Within 6 months
- By reducing the stress risers in trabecular bones
- Contribution of increase in spine BMD - < 50%

- Well…
- Longer than 1 year
- By targeting both trabecular & cortical bones
- Contribution of increase in hip BMD – 60~90%

The strength of evidence among the medication for decreasing the risk of hip and other non-vertebral fractures

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Ibandronate	●●●	●●	●	I
Risedronate	●●●	●●●	●●●	●
Zoledronic acid	●●●	●●●	●●●	I
Denosumab	●●●	●●●	●●●	I
Teriparatide	●●●	●●	●	I
Raloxifene	●●●	I	I	I

Sources: Crandall CC, Newberry SJ, Gellad WG et al. Comparative effectiveness of treatment to prevent fractures in men and women with low bone density or osteoporosis - update of a 2007 report. AHRQ comparative effectiveness review no. 53. March 2012.

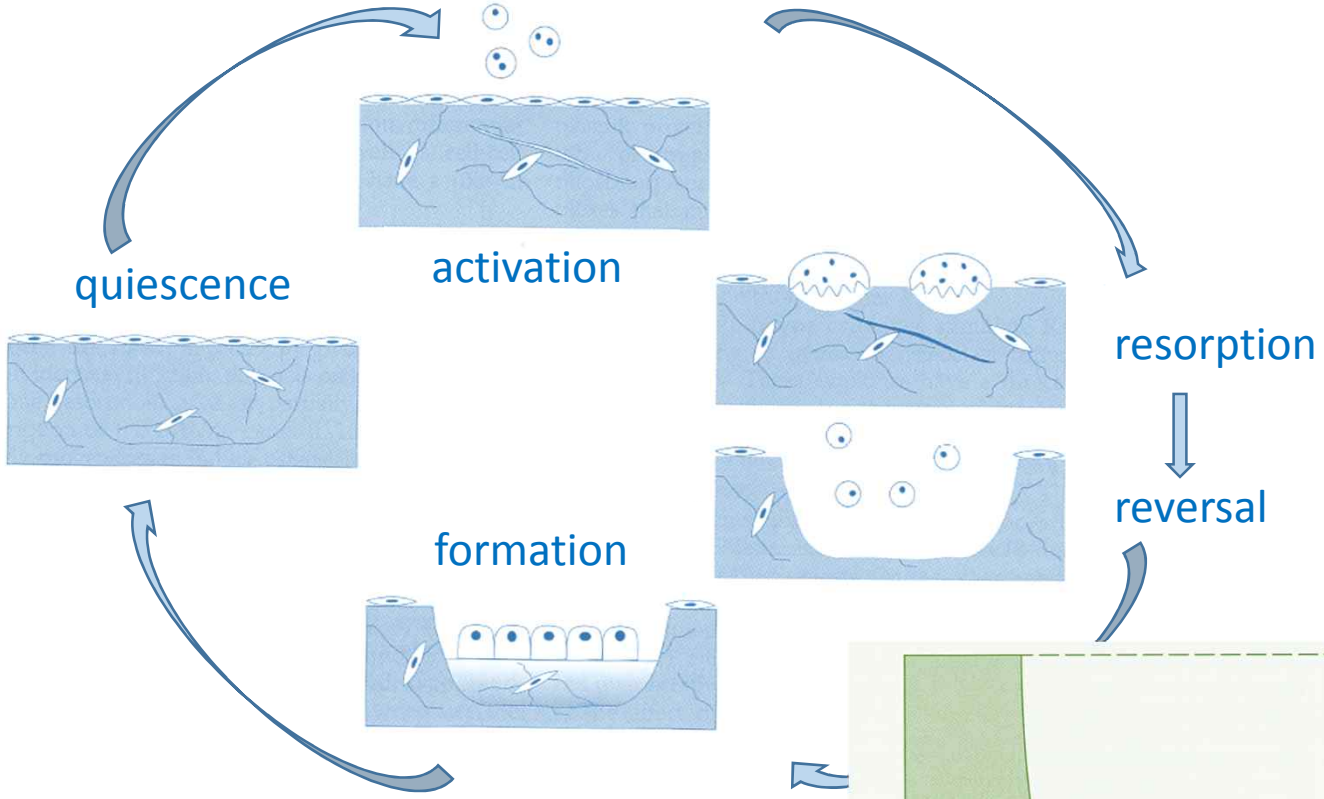
Strength of evidence symbol legend: I = insufficient strength of evidence; ● = low strength of evidence; ● ● = moderate strength of evidence; ● ● ● = high strength of evidence.

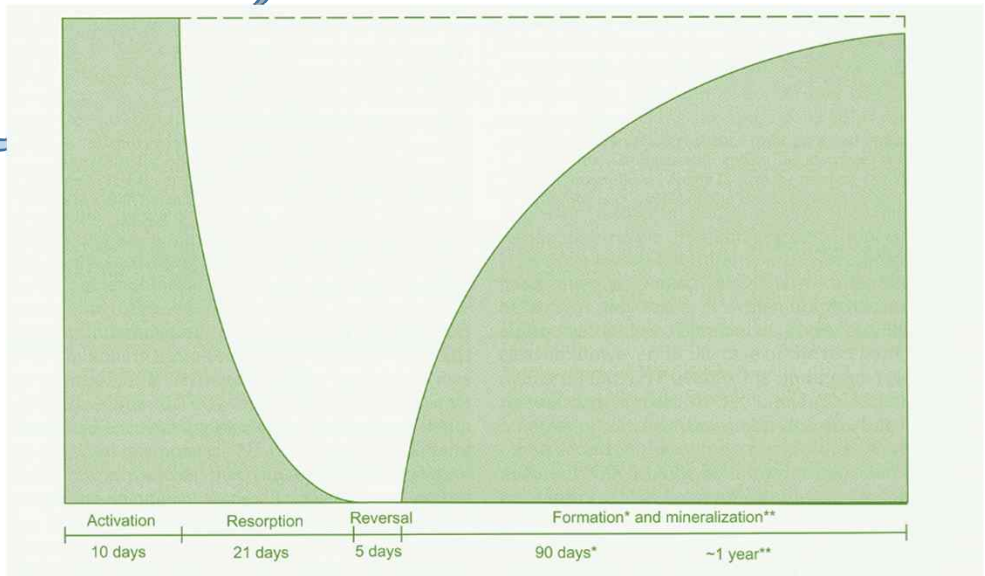
Adapted from Levis S, et al. J Manag Care Pharm 18(4-b): S3-S15, 2012

Bone remodeling

- Players – Osteoclast-Osteoblast coupled!
- Cycle – every 10 years
- BRU(basic remodeling units) – 4 million (1 million, active)
- Remodeling cycle

Remodeling cycle

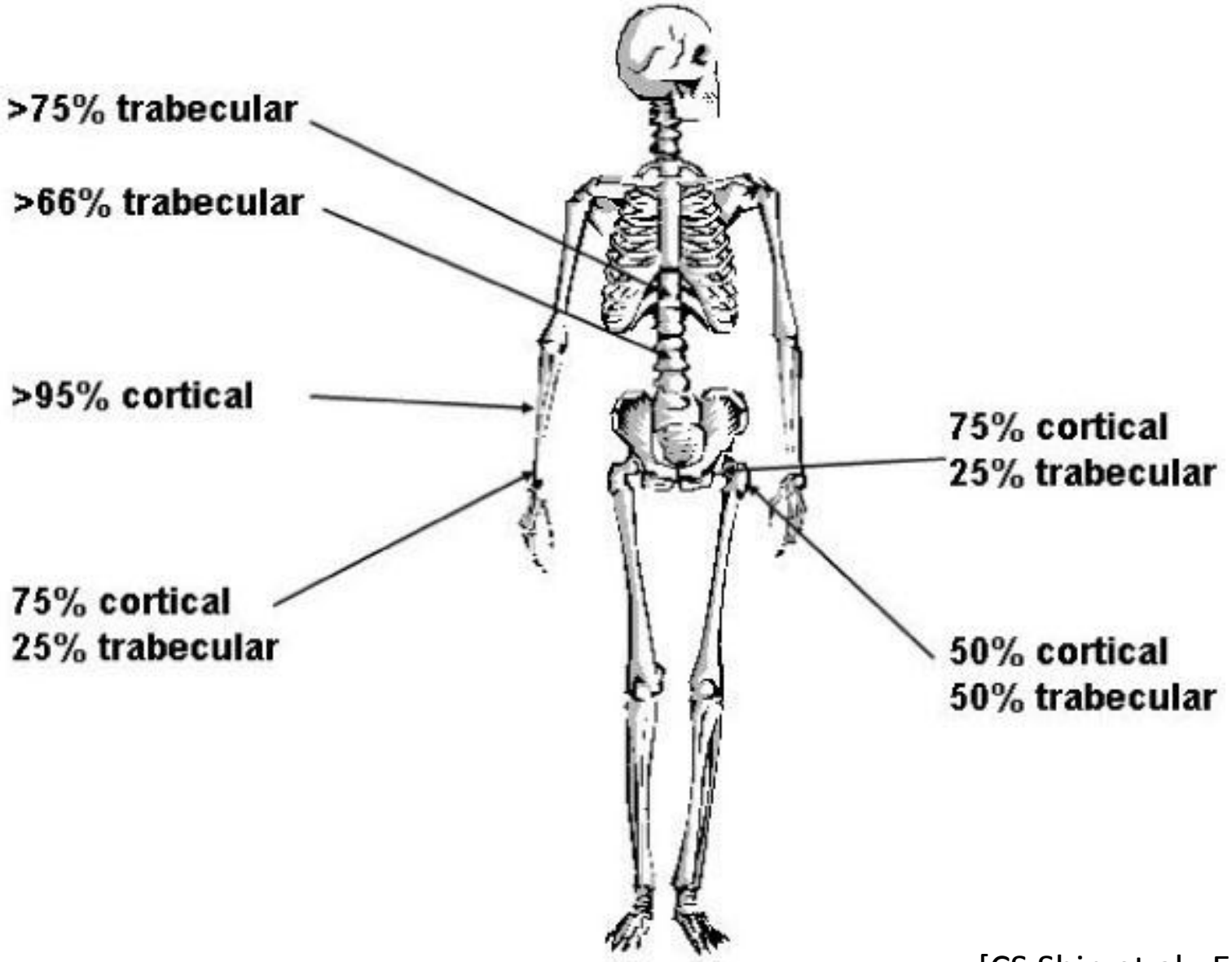




[Basic and Applied Bone Biology by D. Burr & M. Allen, 2014, Chapter 4, Fig 4.9-10]

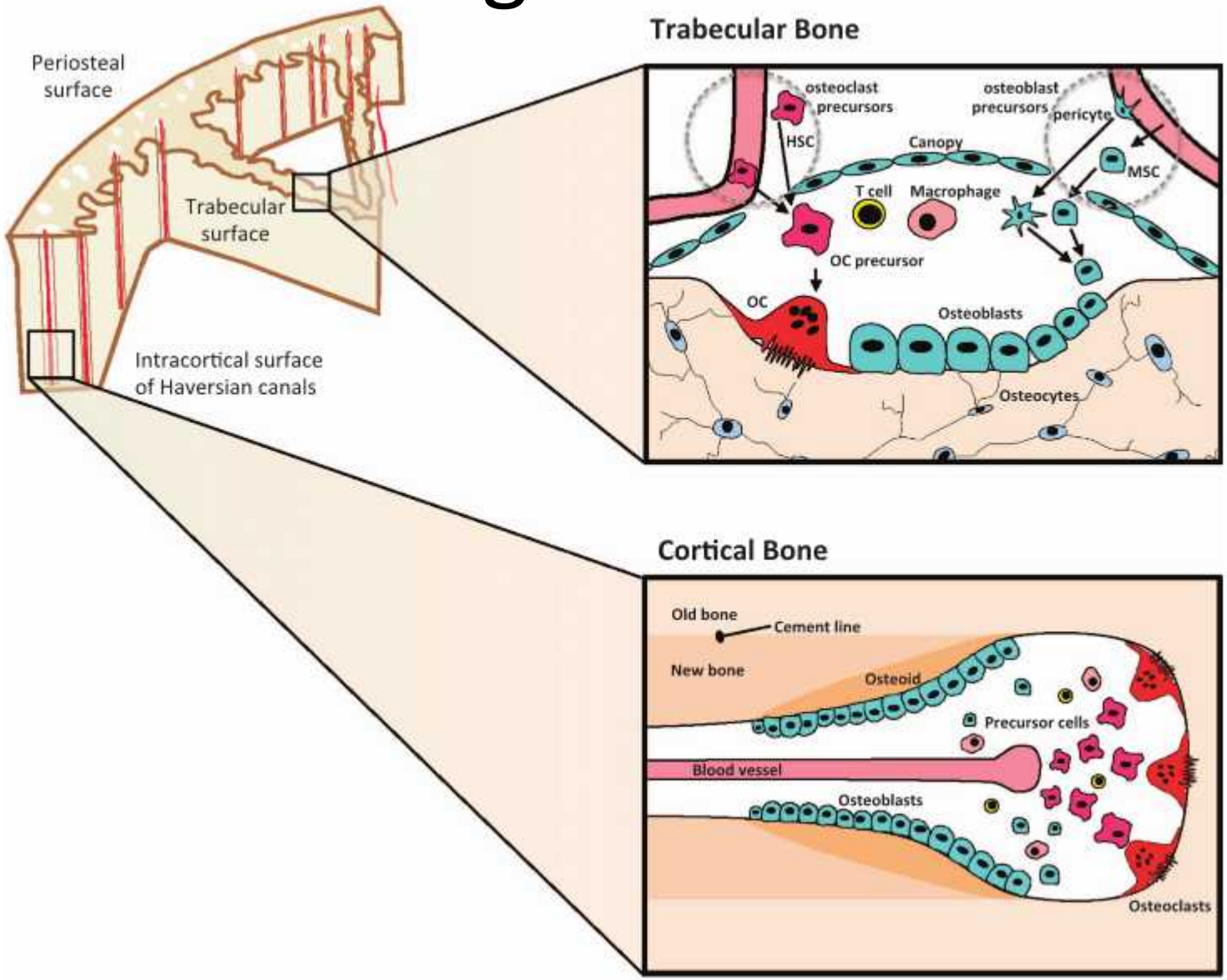
Bone remodeling

- Players – Osteoclast-Osteoblast coupled!
- Cycle – every 10 years
- BRU(basic remodeling units) – 4 million (1 millon, active)
- Remodeling cycle
- Site
  - 80% in cancellous bone (20% of the whole body)
  - Also in cortical bone with aging, endocortical/periosteal/intracortical(Haversian remodeling system)



[CS Shin et al., EnM 2005]

Bone remodeling



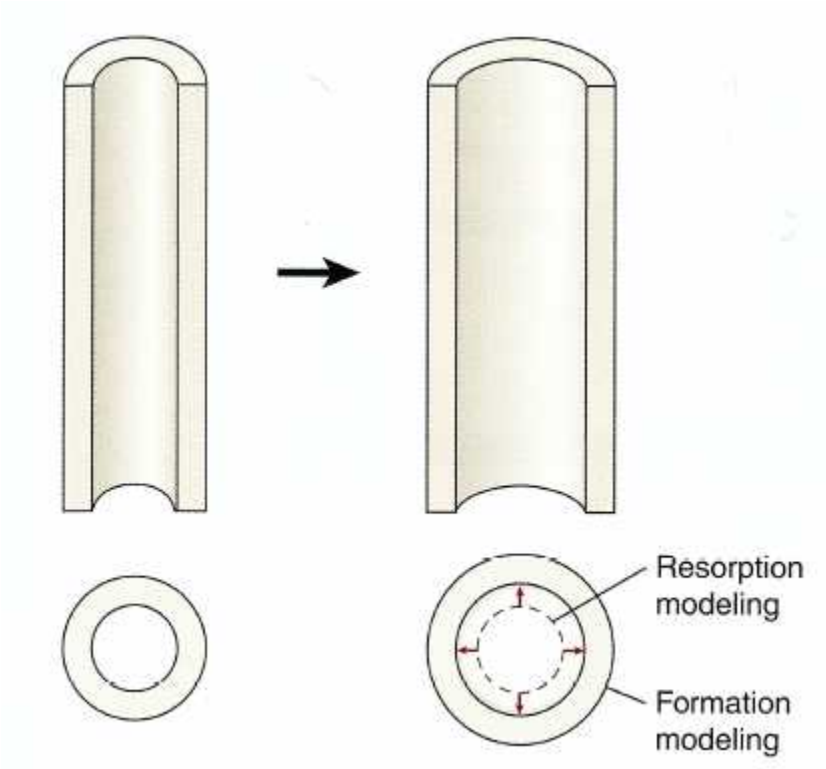
[Sims, NA et al., *Bonkey Reports* 2014]

Bone modeling

- Player – Osteoblast, not necessarily coupled, anatomically or temporally
- Role – skeletal development & growth
- MBF(modeling-based formation) ; periosteal expansion vs. RBF(remodeling-based formation) ; medullary expansion

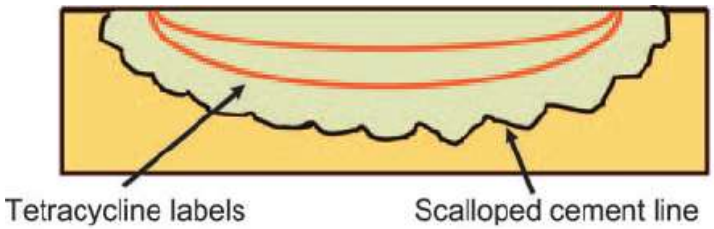
Radial bone growth

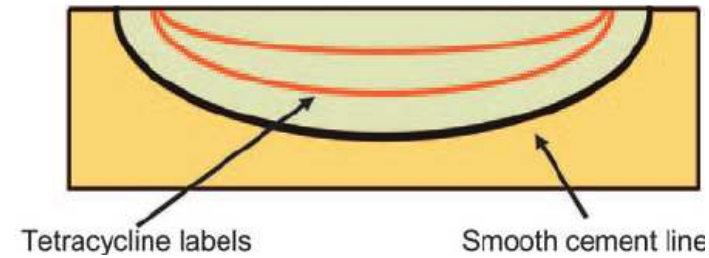
- Formation modeling on periosteal surfaces
- Resorption modeling on the endocortical surfaces

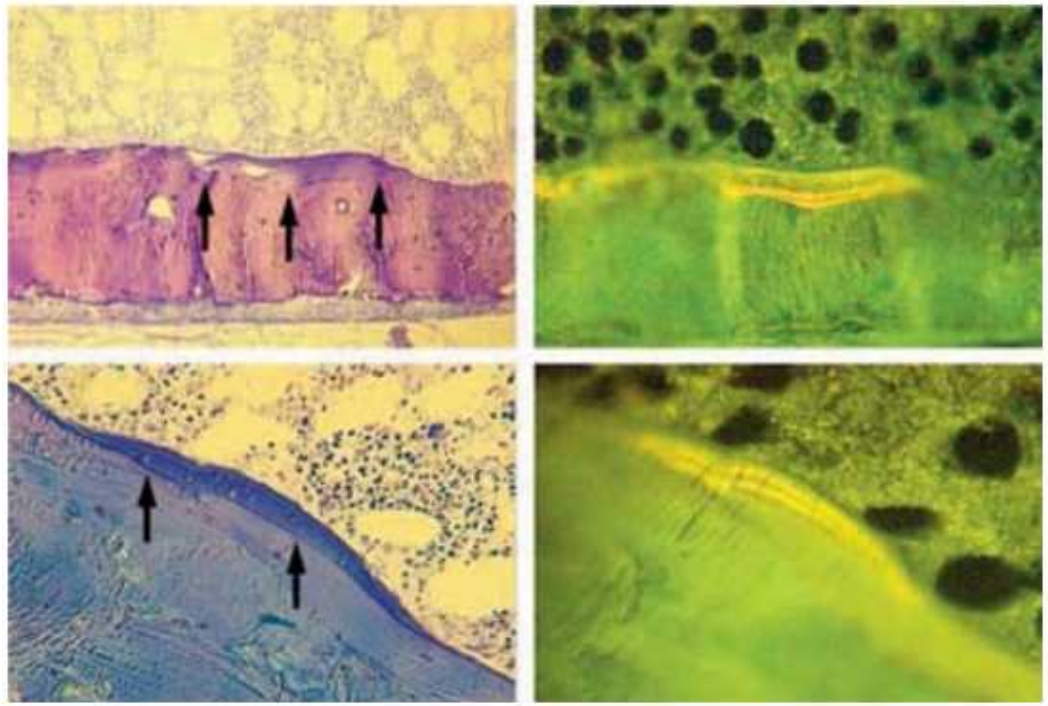


[Basic and Applied Bone Biology by D. Burr & M. Allen, 2014, Chapter 4, Fig 4.5]

MBF vs. RBF





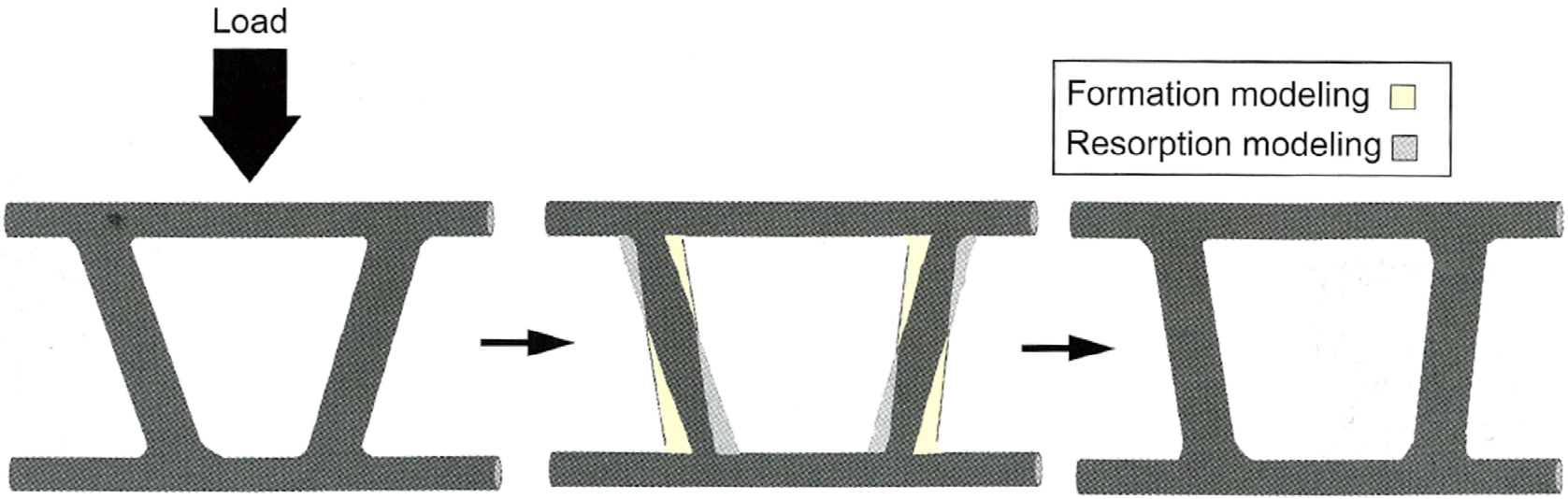


[Lindsay R et al, JBMR 21(3):366, 2004]

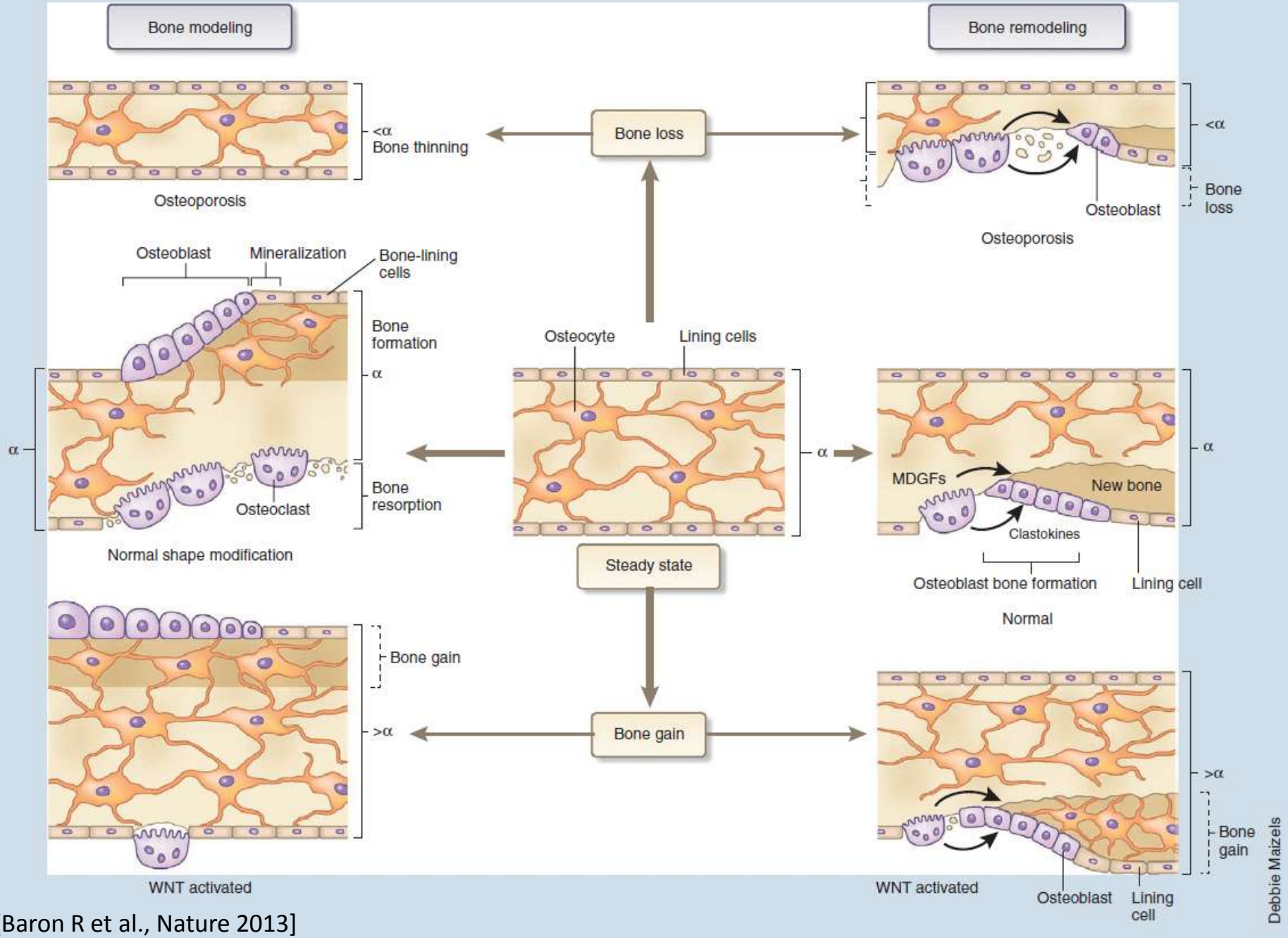
Bone modeling

- Player – Osteoblast, not necessarily coupled, anatomically or temporally
- Role – skeletal development & growth
- MBF(modeling-based formation) ; periosteal expansion vs. RBF(remodeling-based formation) ; medullary expansion
- Related factors
  - Genetic
  - Environmental (physical stress)
  - Hormonal factors (PTH, sclerostin) [다음 장]

Loading leading to modeling

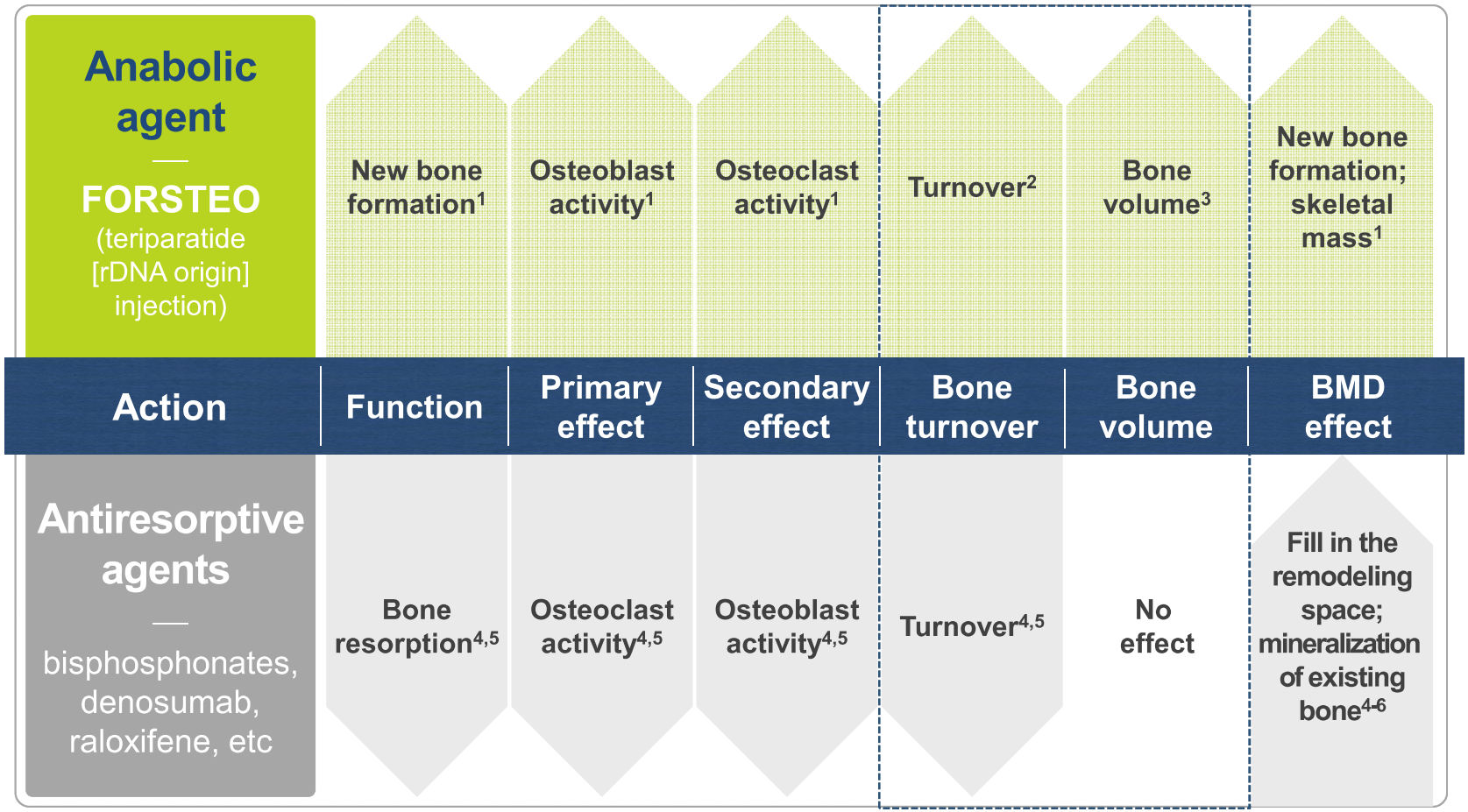


[Basic and Applied Bone Biology by D. Burr & M. Allen, 2014, Chapter 4, Fig 4.7]



[Baron R et al., Nature 2013]

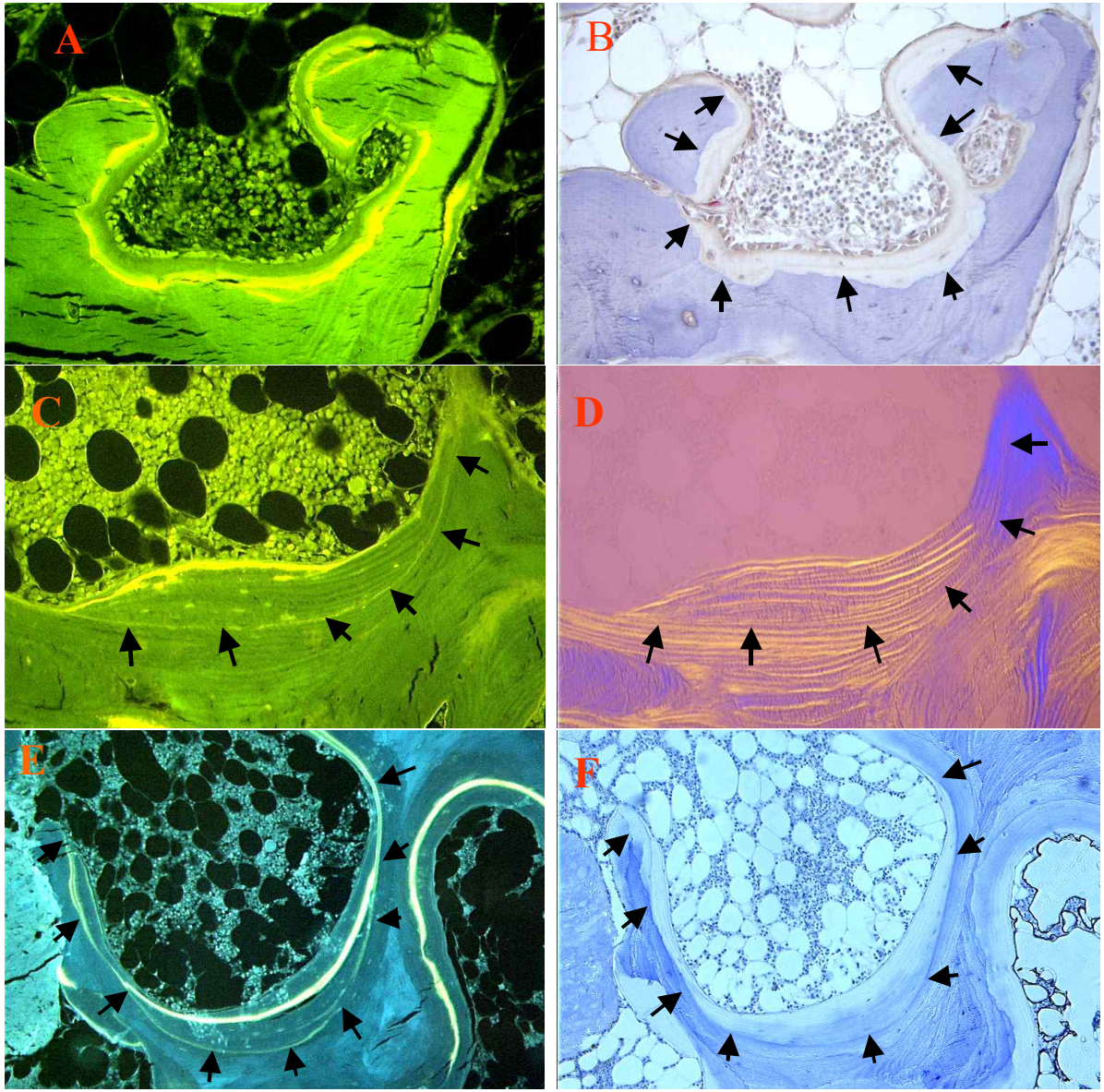
Osteoporosis treatments have different effects on the bone remodeling cycle



Information regarding mechanisms of action does not provide evidence of comparative fracture protection

1. FORTEO Prescribing Information. 2. Arlot M, *et al. J Bone Miner Res*. 2005;20:1244–1253. 3. Jiang Y, *et al. J Bone Miner Res*. 2003;18:1932–1941. 4. Fleisch H.. *Endocr Rev*. 1998;19:80-100.
5. Russell RG, *et al. Osteoporos Int* 1999;9:S66-S80. 6. Riggs BL, Parfitt AM. *J Bone Miner Res* 2005;20:177-184.

Teriparatide induces new bone formation (modeling) at quiescent surfaces



Remodeling osteon

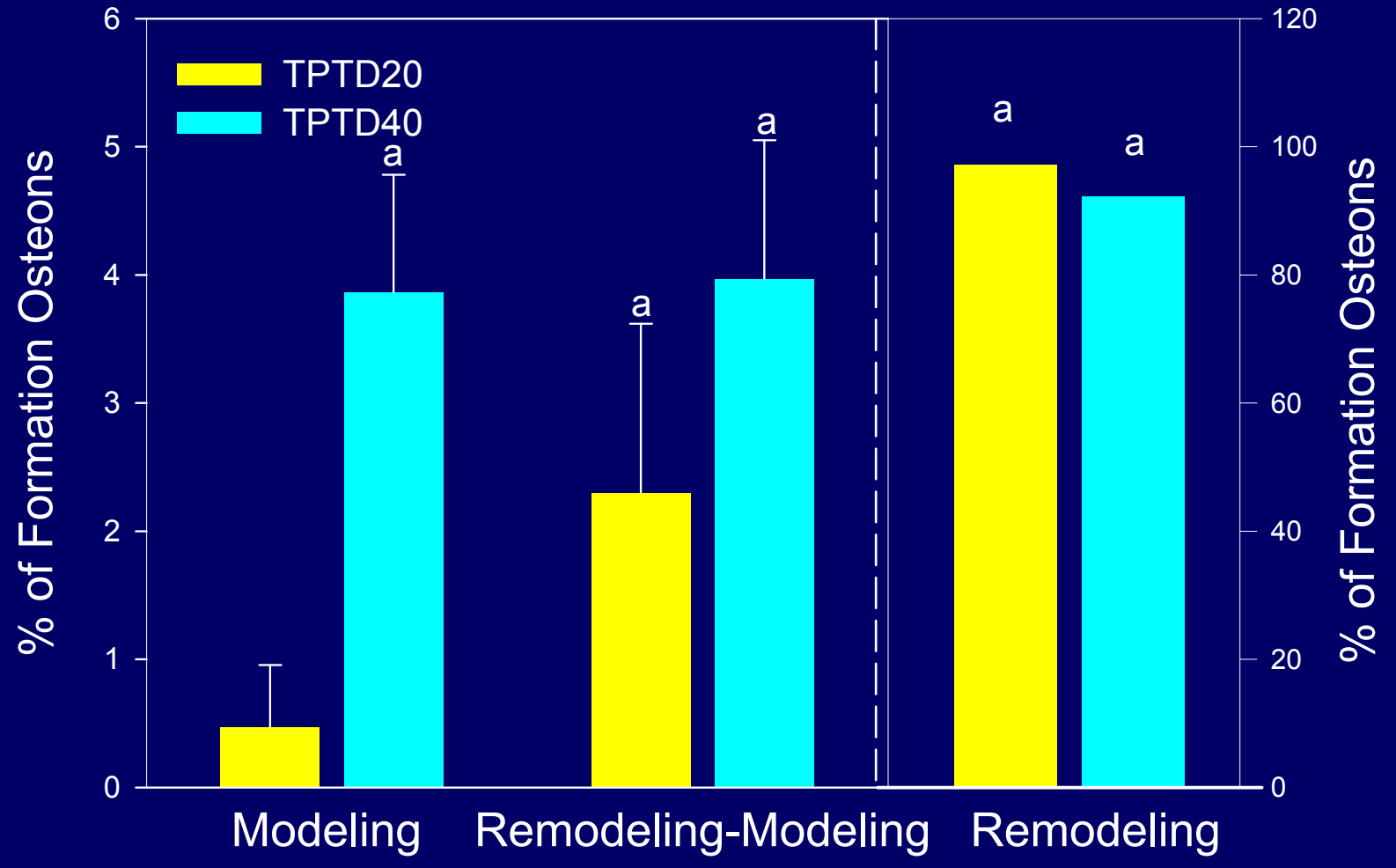
Modeling osteon –
New bone formation

Mixed remodeling-modeling osteon
Prolonged formation on remodeling osteon

[Ma, et al. *J Bone Miner Res* 2006;21:855]

Modeling during teriparatide treatment

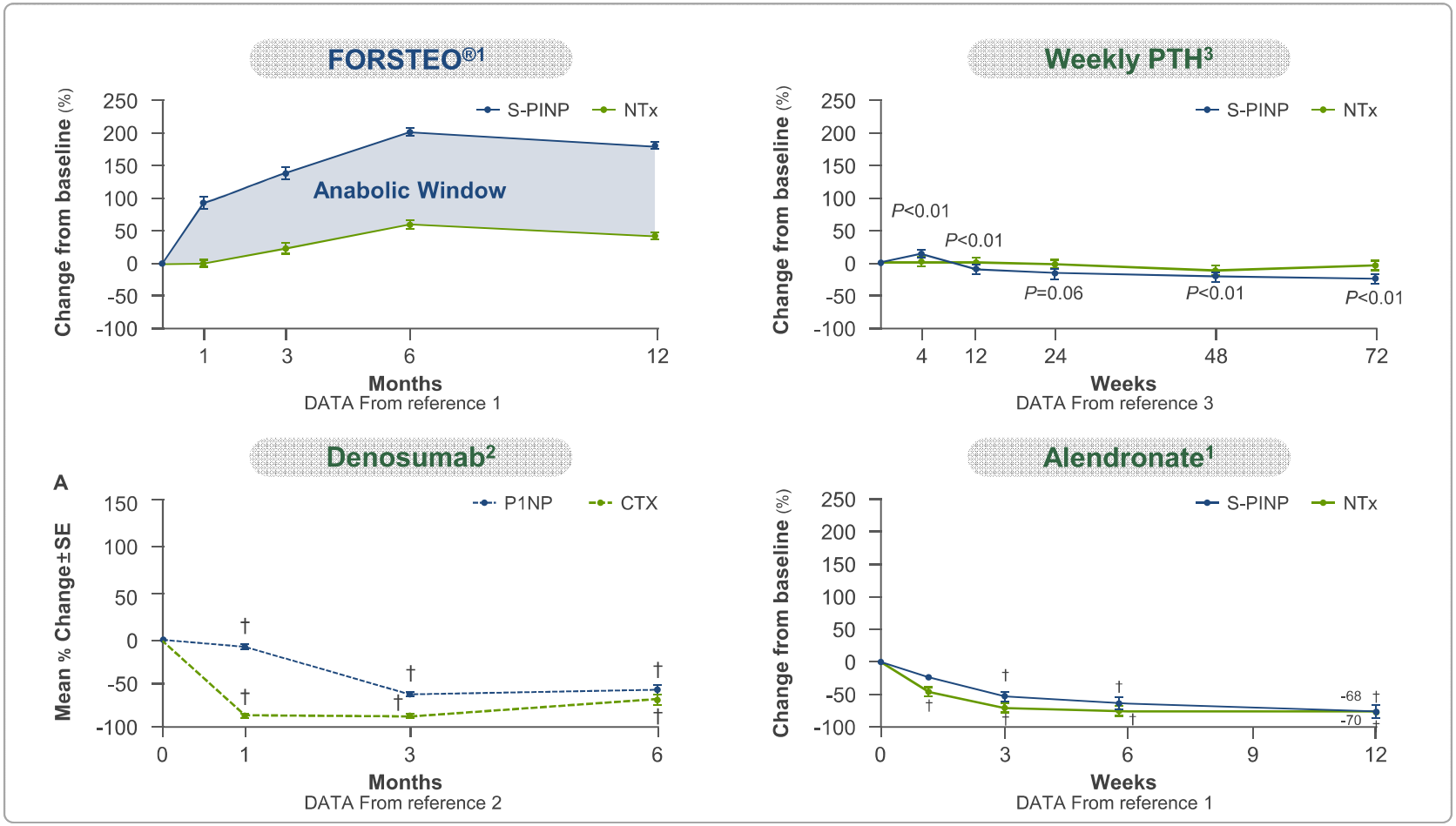
% of Patients Showing Modeling and Remodeling-Modeling



a: P < 0.001 vs placebo

[Ma, et al. *J Bone Miner Res* 2006;21:855]

Anabolic window of Teriparatide

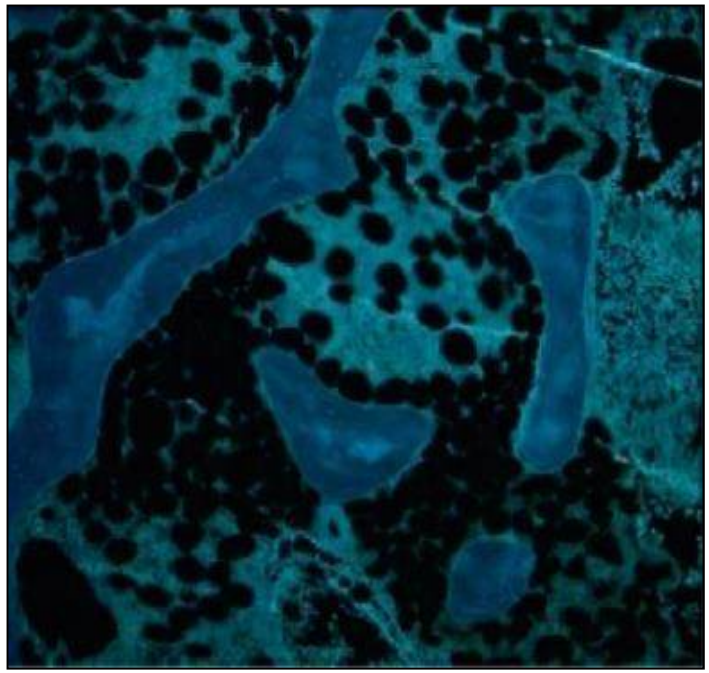


FORSTEO®와 alendronate (McClung, 2005), denosumab (Tsai,2013)은 직접비교, weekly teriparatide와는 직접비교는 아니며 논문에서 발췌

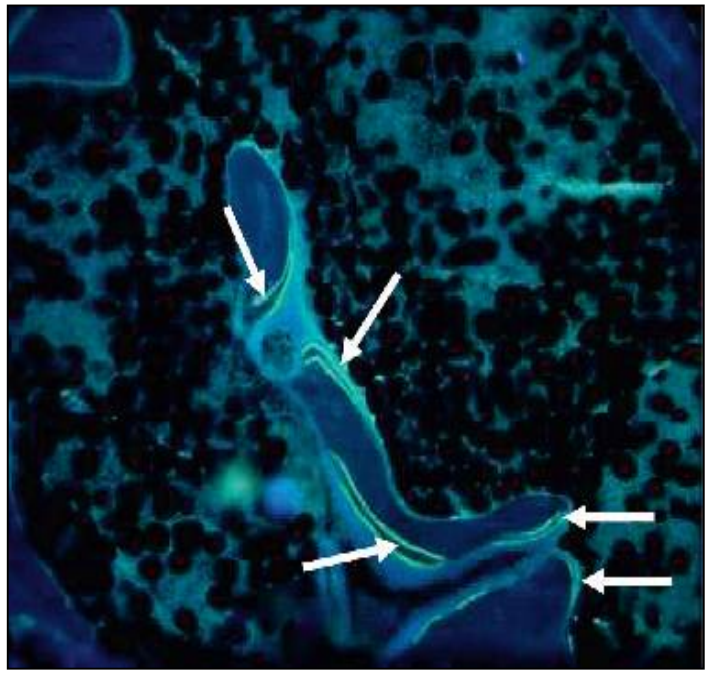
1. McClung MR, *et al. Arch Intern Med.* 2005;165(15):1762-1768. 2. Tsai JN, *et al. Lancet*. 2013 Jul 6;382(9886):50-6. 3. Nakamura T, *et al. J Clin Endocrinol Metab*. 2012 Sep;97(9):3097-106.

Teriparatide Increases New Bone Formation

Alendronate



Teriparatide



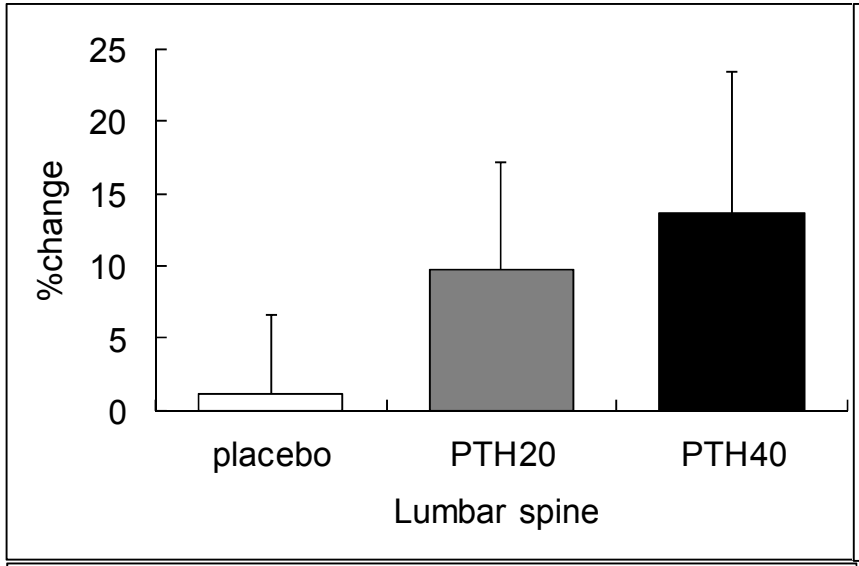
Individual patient results may vary.

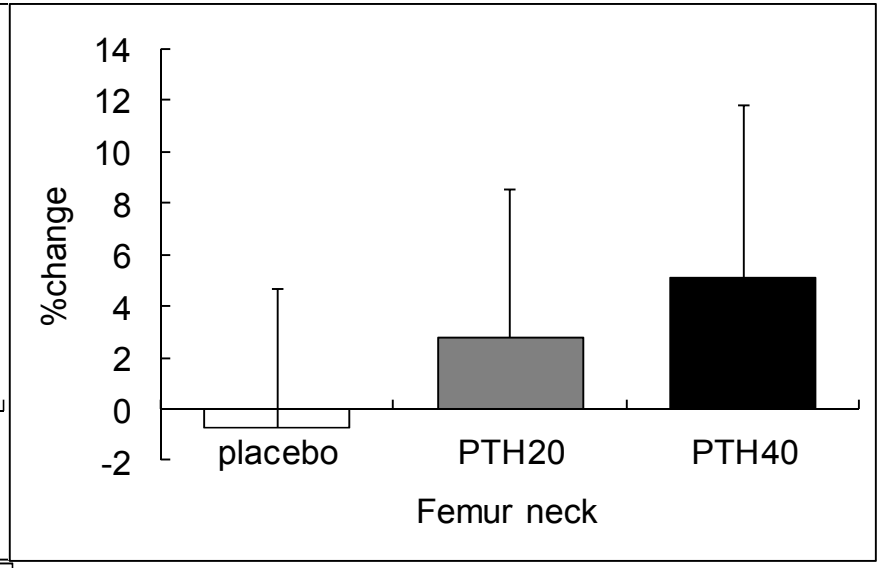
Arrows indicate tetracycline labels and sites of new bone formation after 6 months of treatment with alendronate or FORSTEO

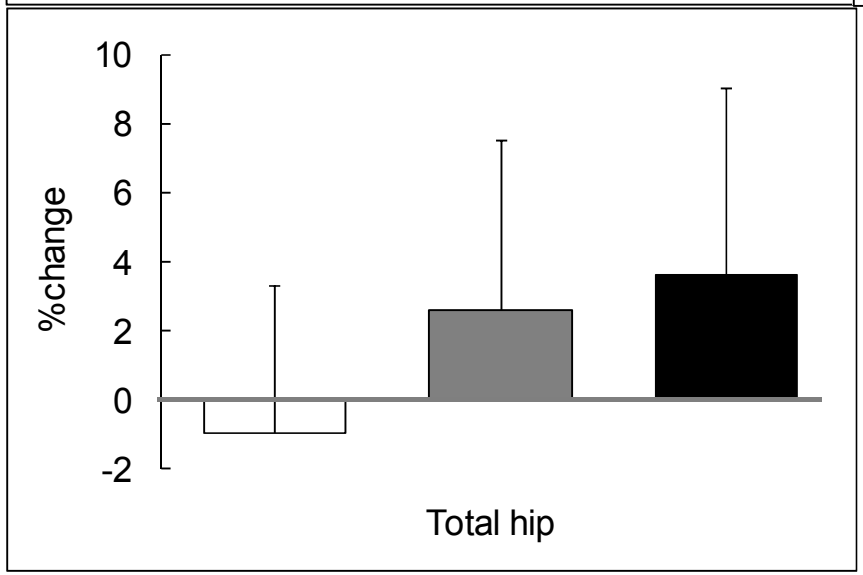
Information regarding mechanisms of action does not provide evidence of comparative fracture protection

1. Arlot *et al. J Bone Miner Res*. 2005;20(7):1244-53.

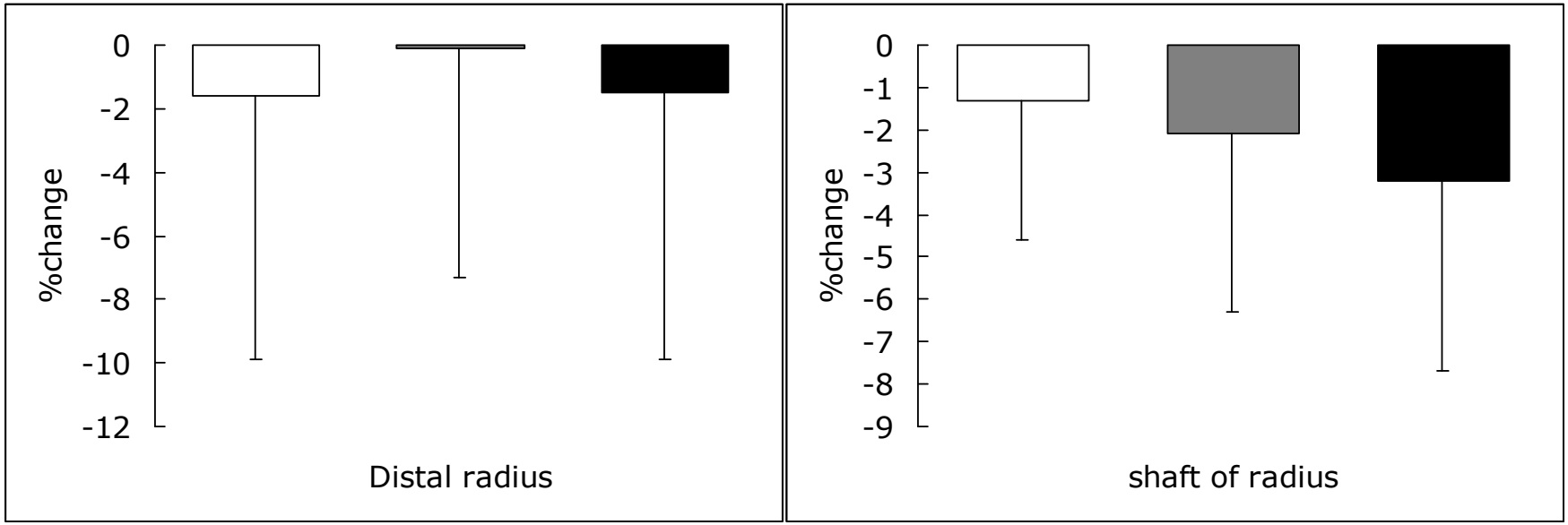
Fracture Prevention Trial-BMD







[Neer et al., NEJM 2001:344;1434]


0
-2
-4
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-8
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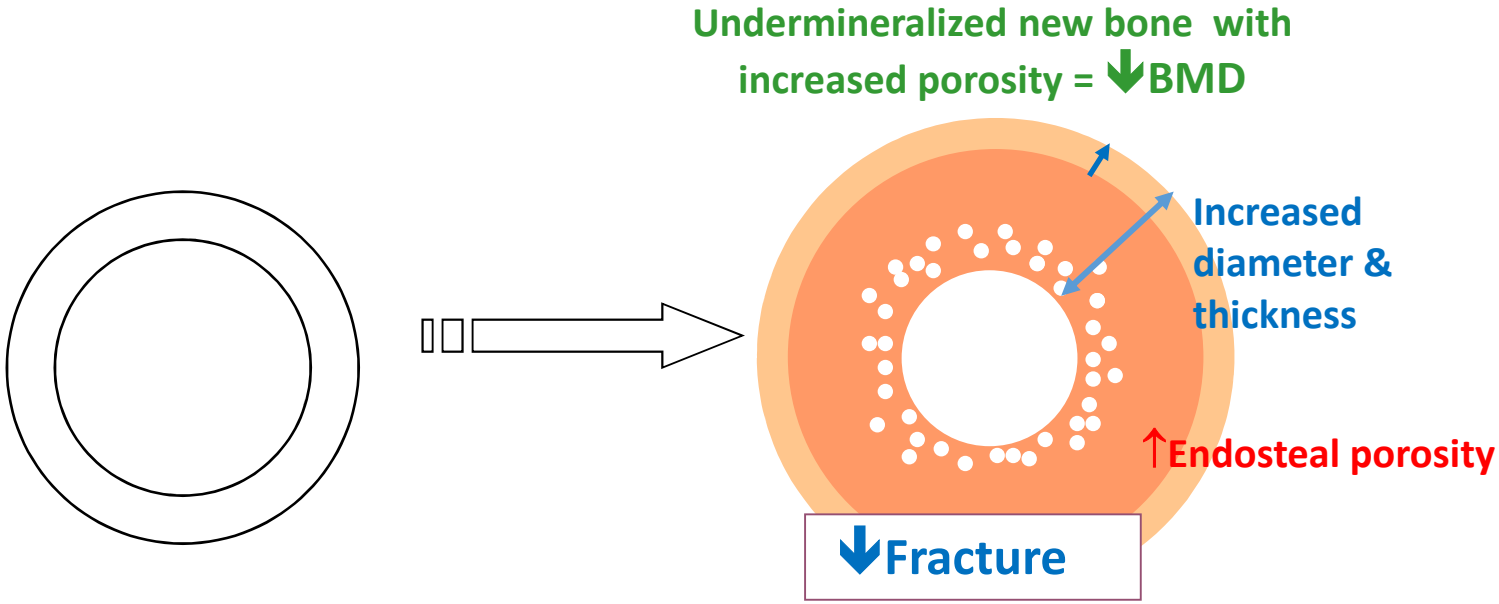
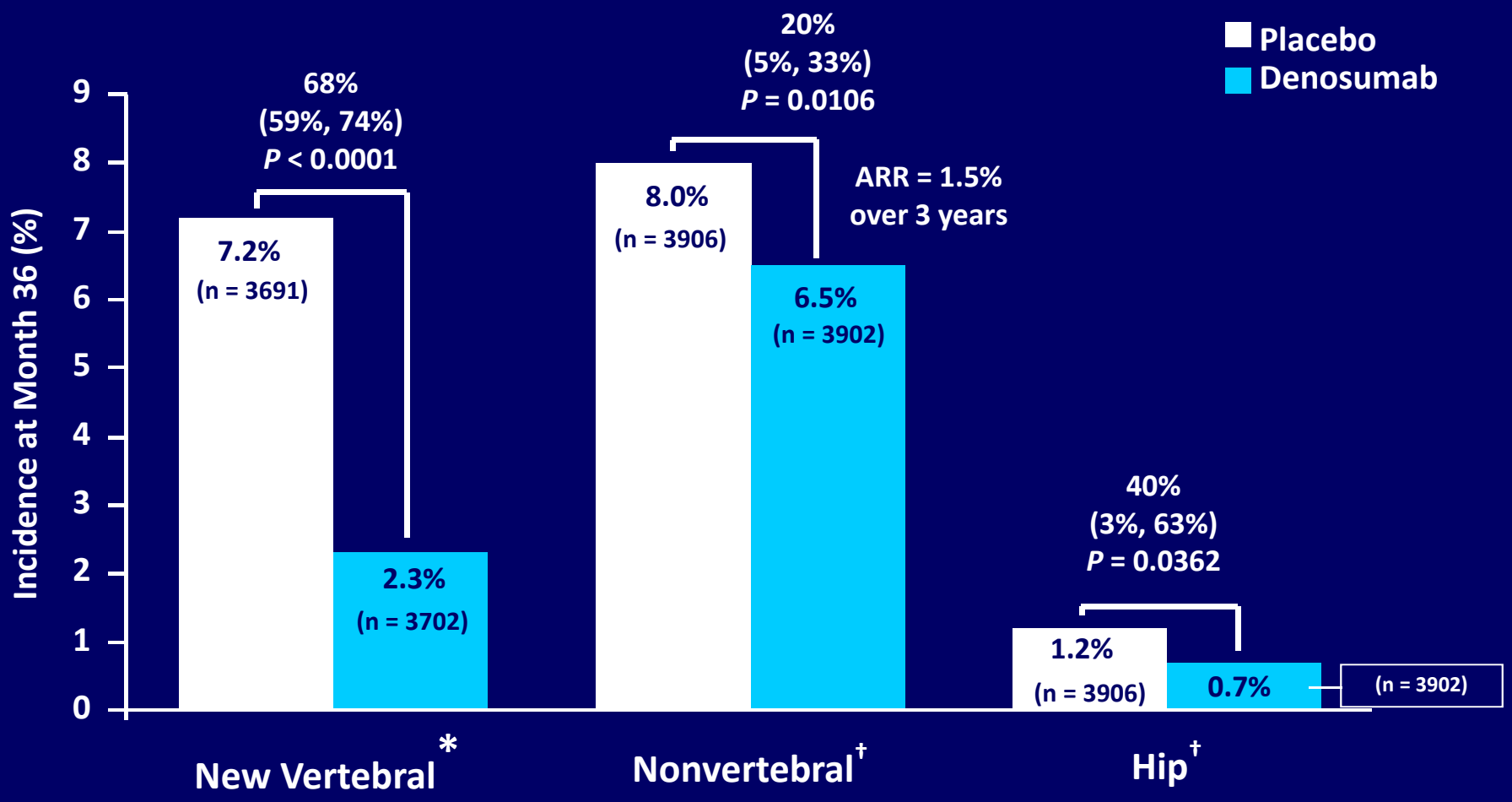
shaft of radius


Undermineralized new bone with
increased porosity = ↓BMD
Increased
diameter &
thickness
↑Endosteal porosity
↓Fracture

Denosumab Treatment Over 3 Years Reduced Fracture Risk *Phase 3: The FREEDOM Trial*

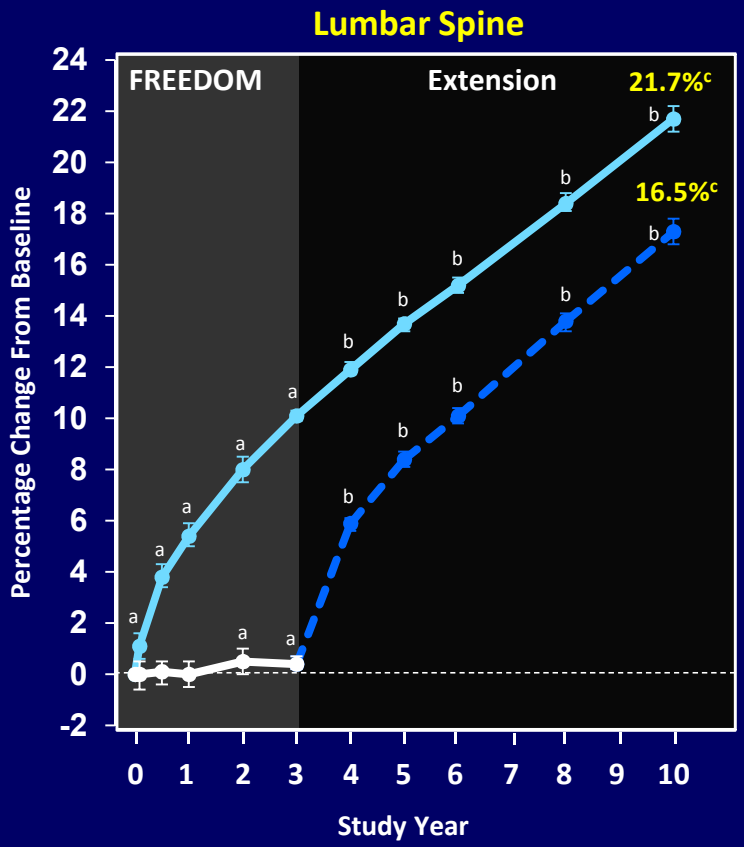


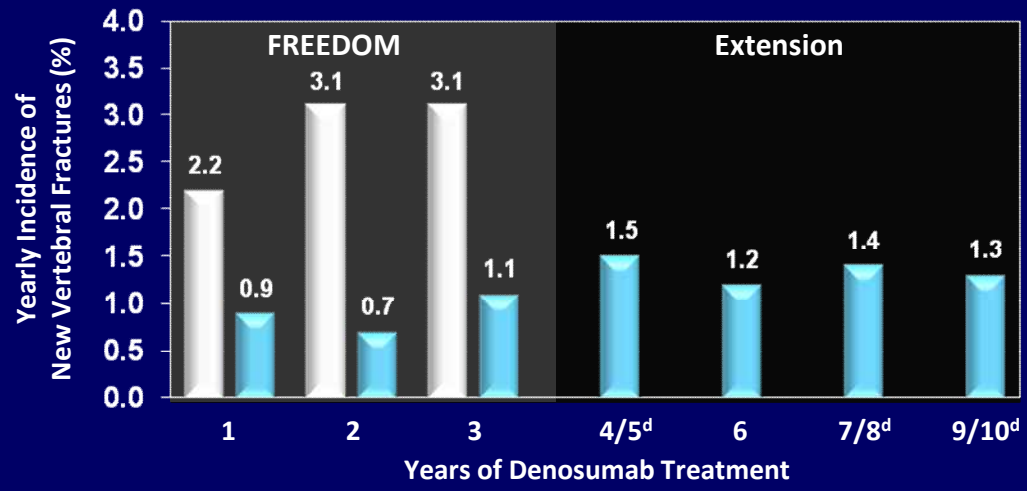
*Crude incidence
†Kaplan-Meier estimate of incidence

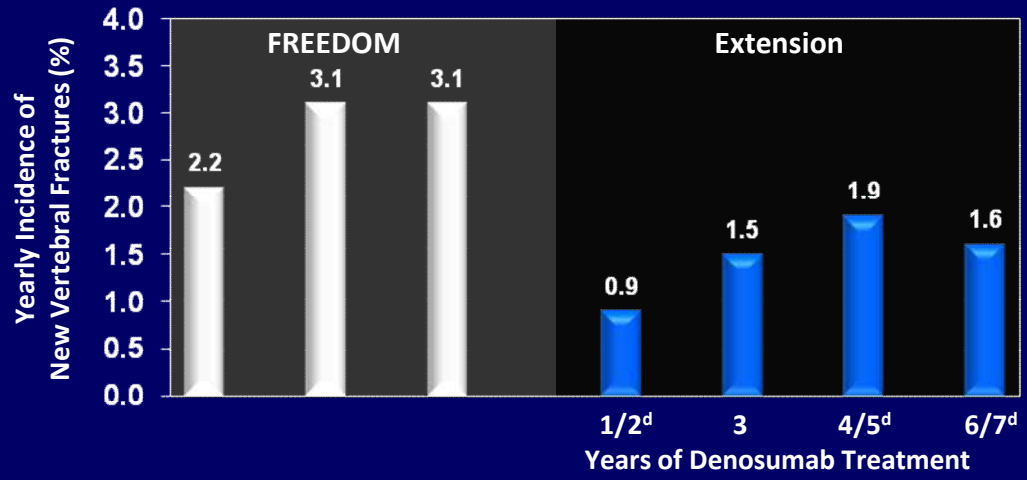
Cummings SR, McClung M et al. *New Engl J Med* 2009;361:756-65

Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years

Placebo Long-term Denosumab Cross-over Denosumab



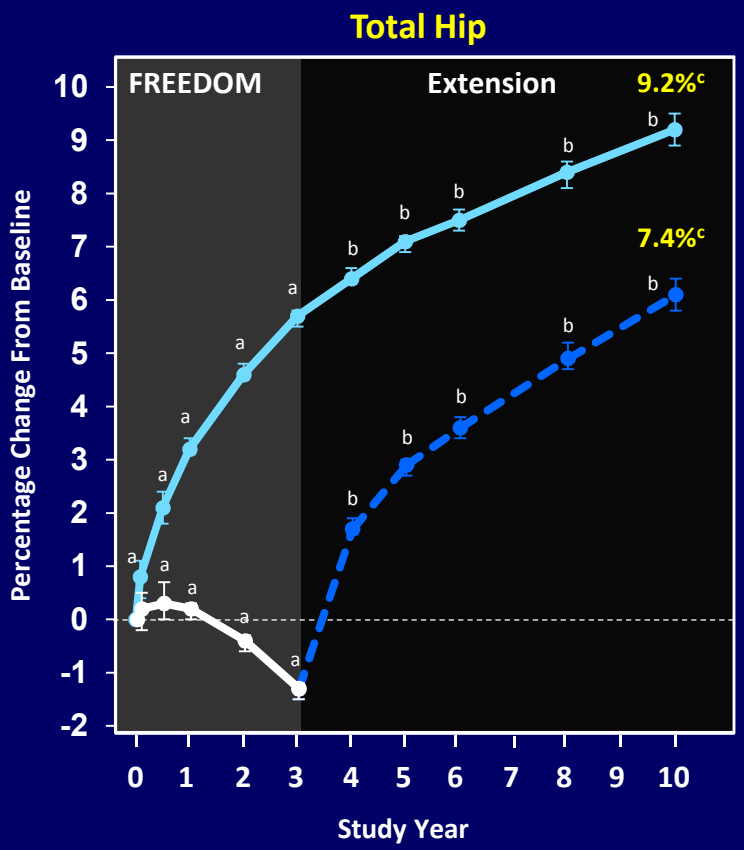


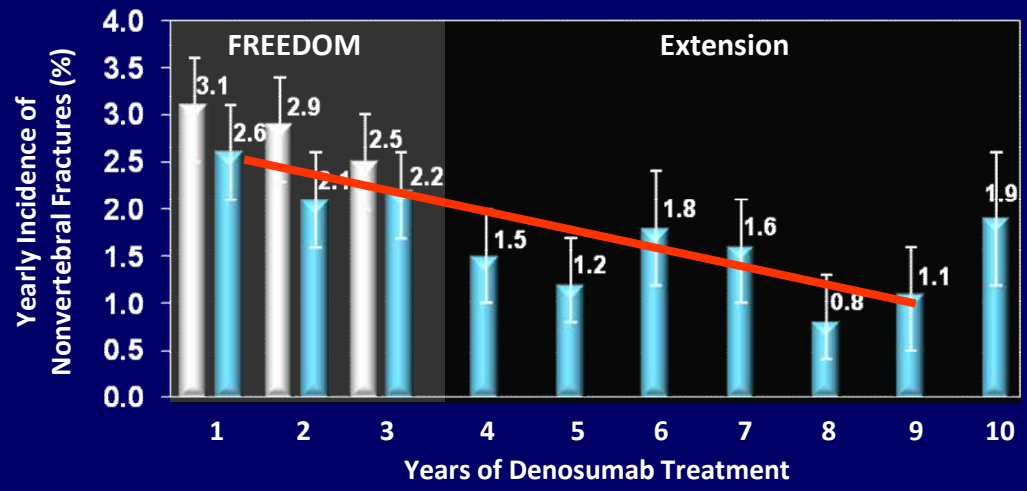


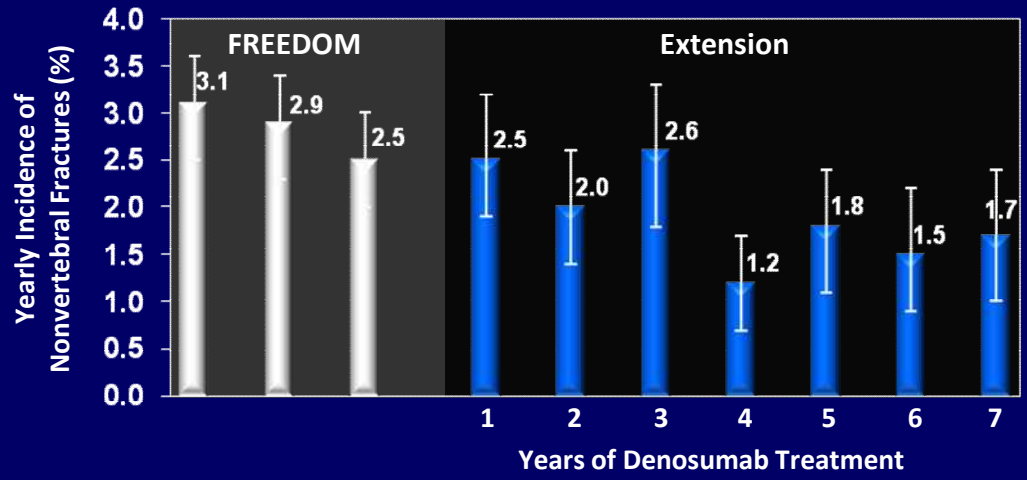
Bone HG et al. ASBMR; Seattle, WA; October 12, 2015; #LB-1157

Effects of Denosumab Treatment on Total Hip BMD and Nonvertebral Fractures Through 10 Years

Placebo Long-term Denosumab Cross-over Denosumab



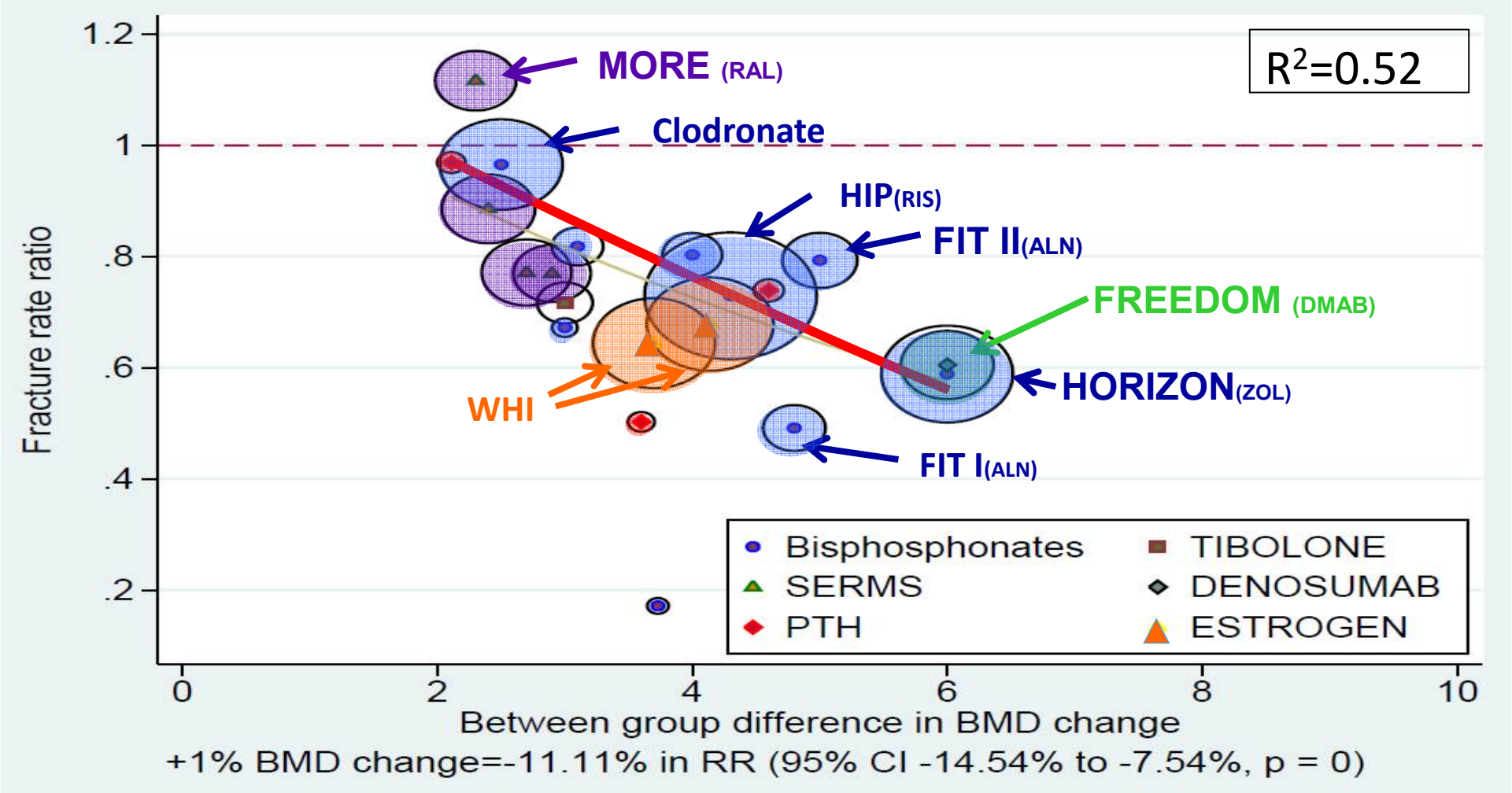




Bone HG et al. ASBMR; Seattle, WA; October 12, 2015; #LB-1157

FNIH Meta-regression

Change in Total Hip BMD vs Reduction in Hip Fracture

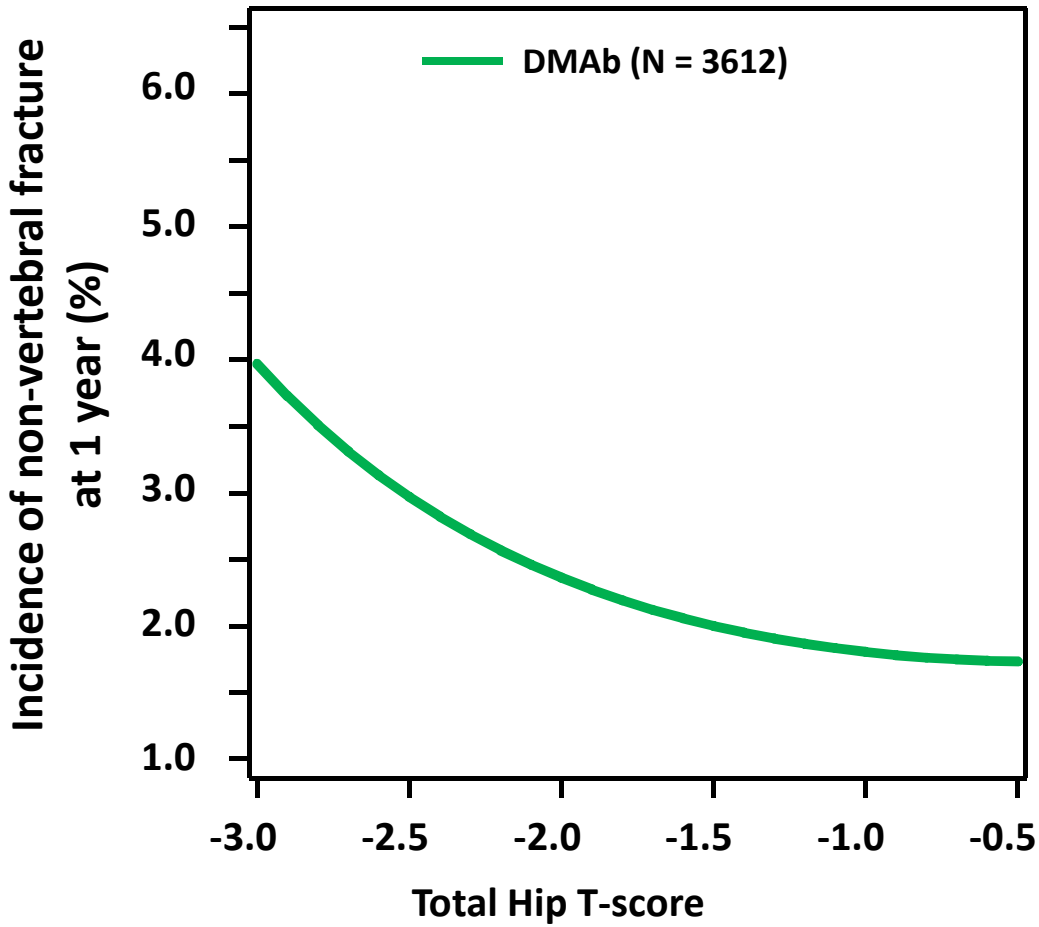


**Bubble size ~ to n fractures in study*

Courtesy of Dr D Black et al, ASBMR 2015

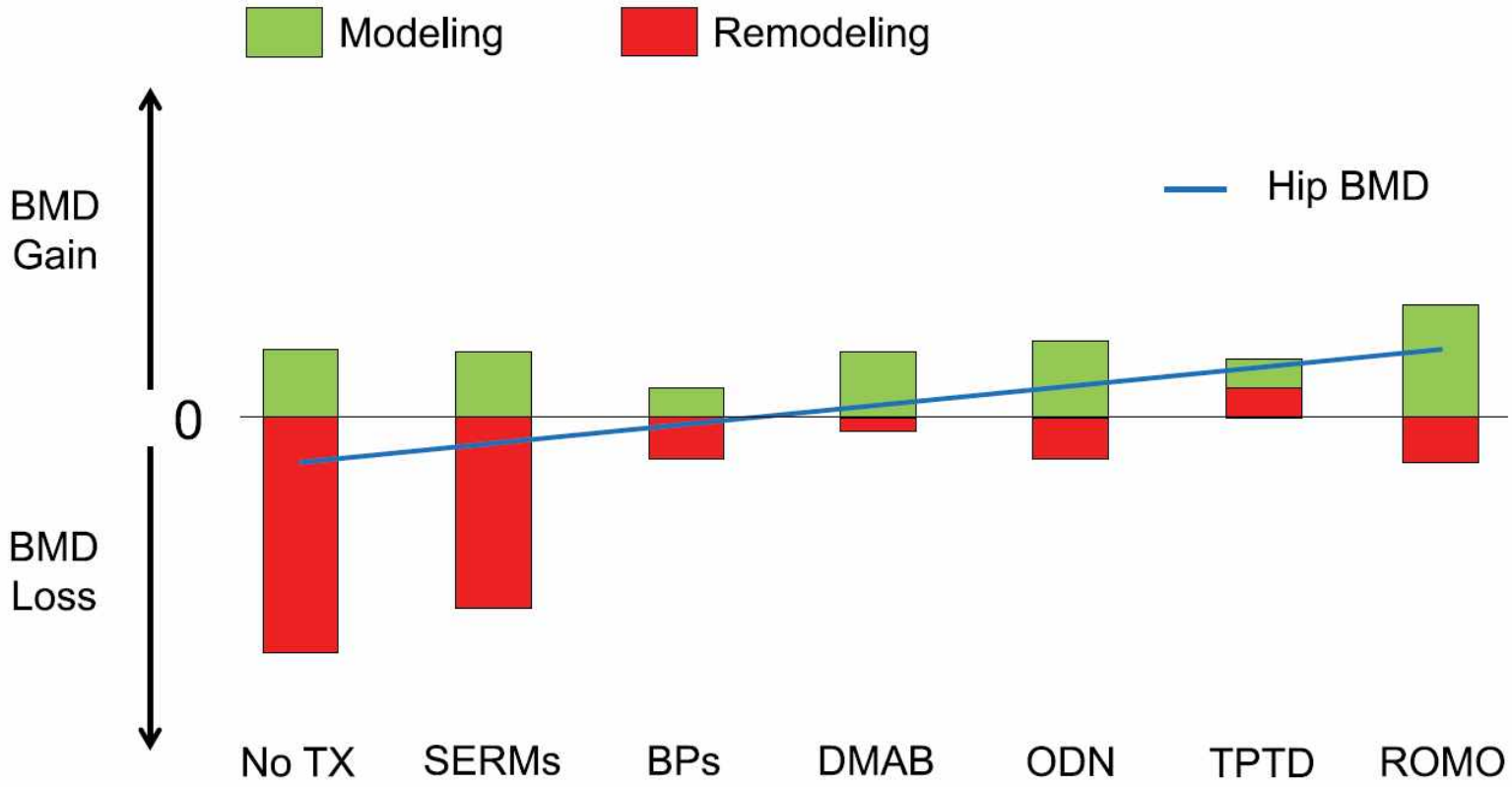
Relationship Between Total Hip T-score and Non-vertebral Fracture Risk

On therapy Total Hip BMD is predictive of current fracture risk



Ferrari S et al. ASBMR 2015

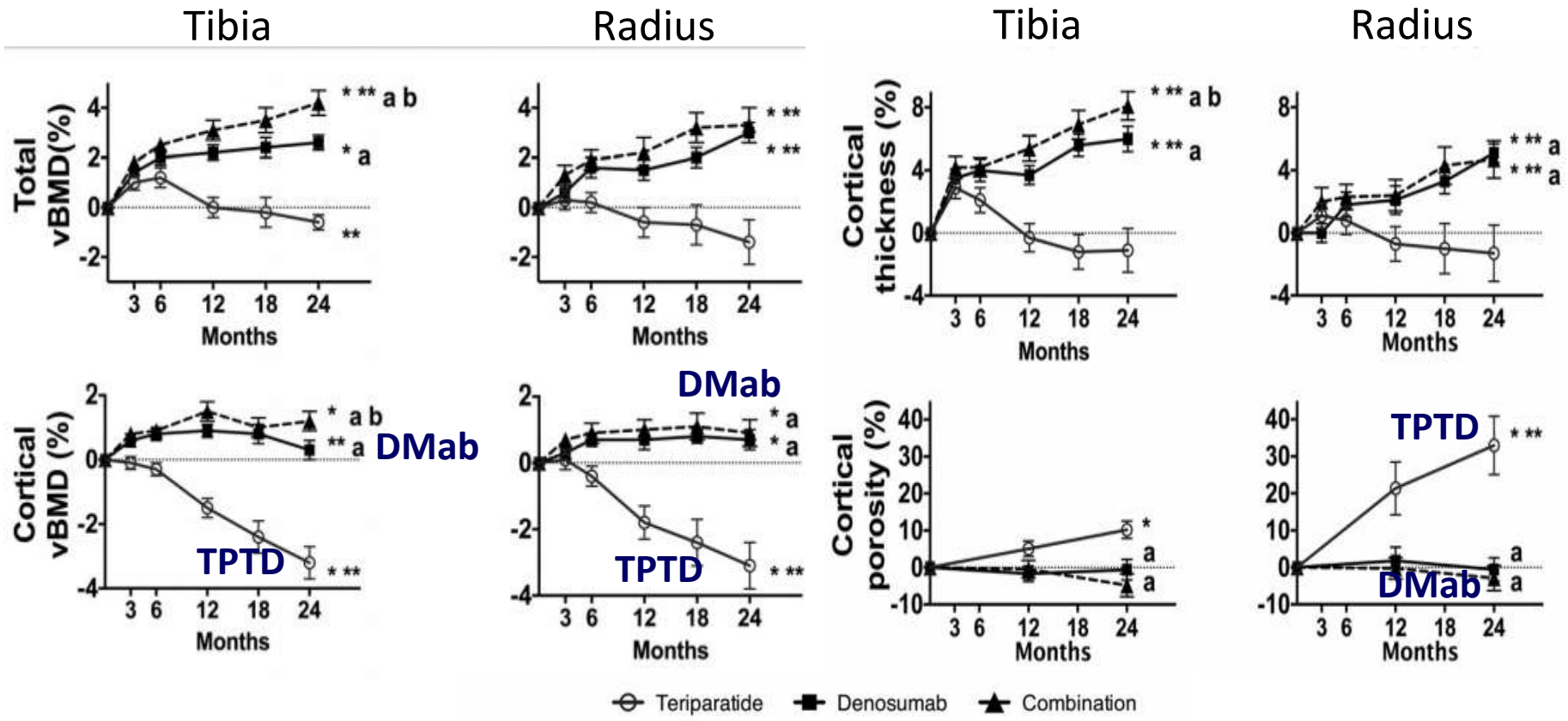
The theoretical contribution of bone remodeling and modeling



[B Langdahl et al., *Ther Adv Musculoskel Dis* 2016, Vol. 8(6) 225]

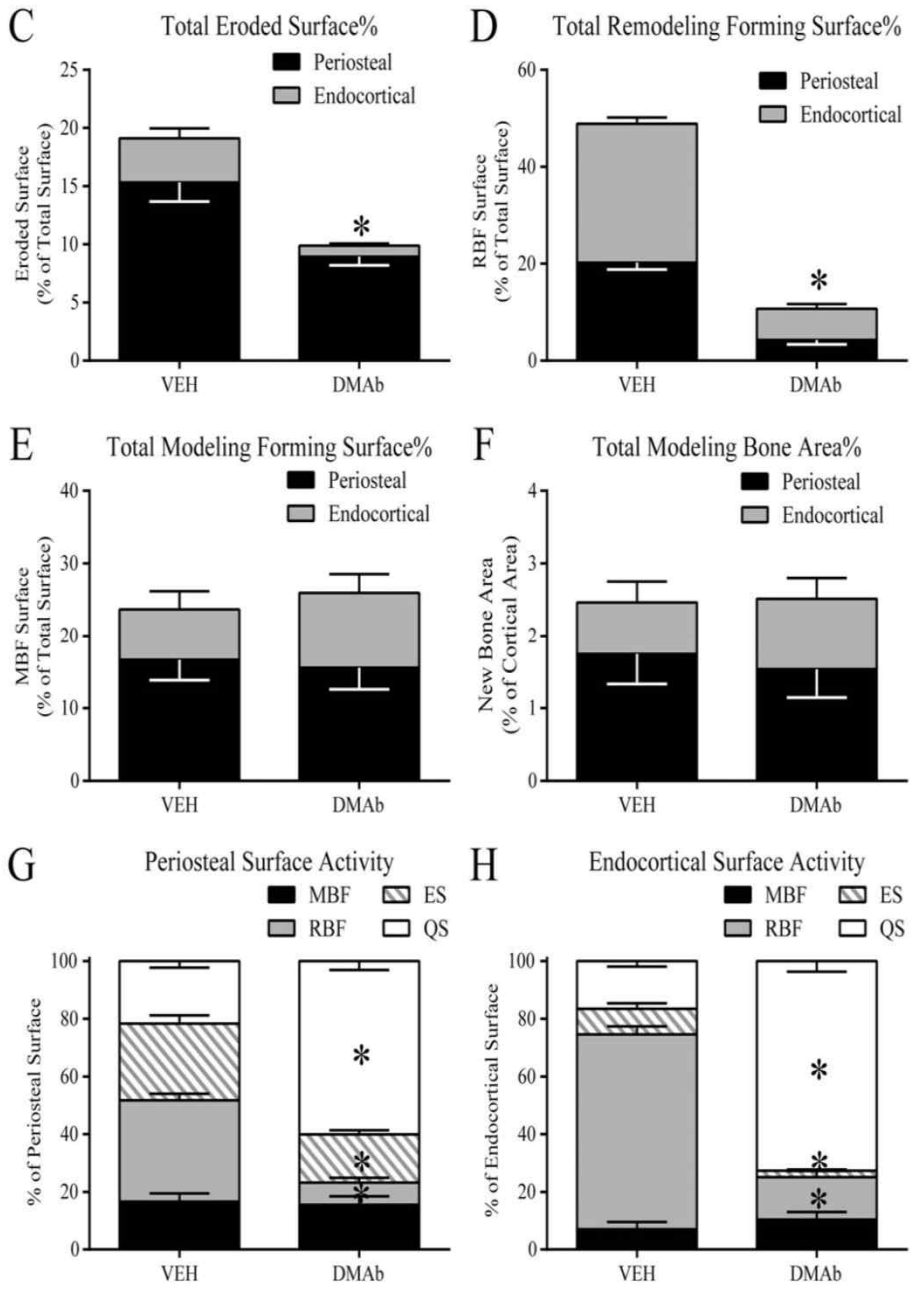
Effects of Denosumab and Teriparatide on Cortical Bone Mass and Porosity

DATA Trial: Denosumab increases cortical vBMD and decreases porosity while teriparatide does the opposite.



[Tsai J et al. *J Clin Endo Metab* 2016;101:2023]

Sustained MBF with Dmab

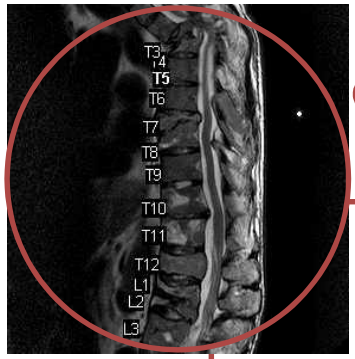


[Ominsky MS et al, JBMR, 2015]

Importance of fracture

Greater risk of Fx!!!

recent



severity

Clinical assessment of response to treatment

A. Response criteria*	B. Review	C. Switch options
1) BMD increased? 2) BTM decreased?	1) Adherence 2) Secondary causes of osteoporosis	**1) Same class:** Increase potency of anti-resorptive **2) Change route:** Oral to parenteral **3) Change MOA:** Strong anti-resorptive to anabolic agent
Met within 12 months?	**Switch treatment if:**	
YES – Maintain treatment NO – Review treatment	1) ≥ 2 fragility fractures 2) 1 fracture + ↑ BTM and/or ↓ BMD 3) Both ↑ BTM and ↓ BMD	

*Response criteria met (to the extent expected) within 12 months of commencing treatment.

BMD, bone mineral density; BTM, bone turnover markers.

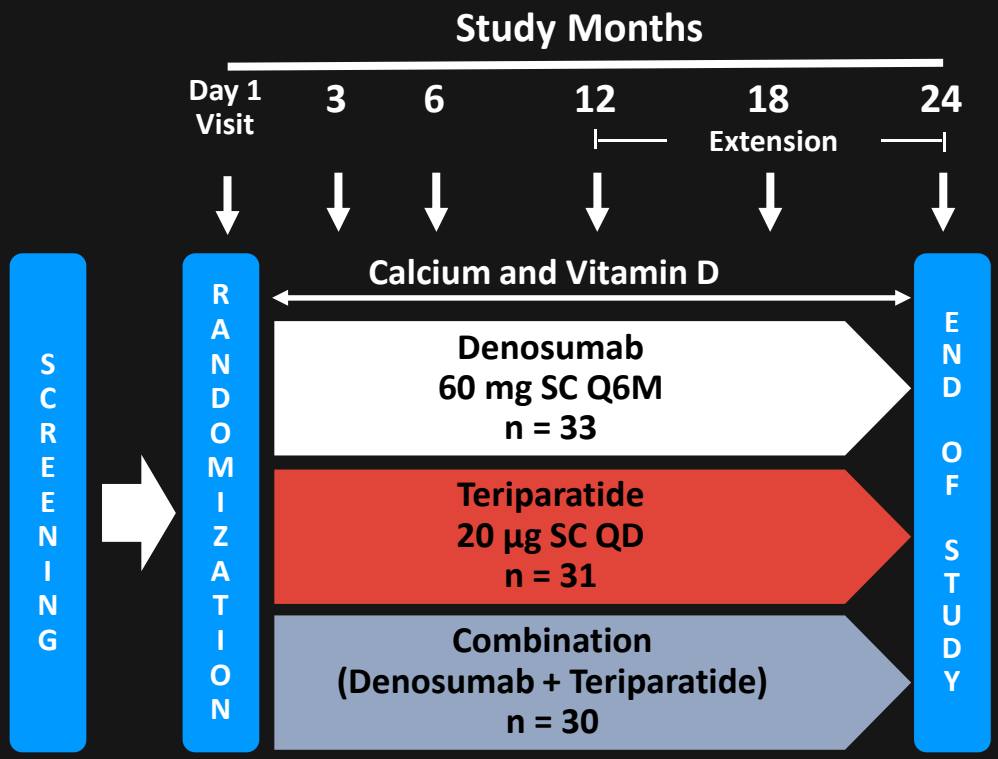
Diez-Perez A, et al. *Osteporos Int* 2012;23:2769–74.

Sequential or combinative therapy:

Using different MOA drugs

Study Design

DATA Extension Study – 24 Months



- **Open-label, randomized, single center study**

Study population

- Postmenopausal women ≥ 45 years old
- T-score ≤ –2.5 at the spine, hip, or femoral neck; T-score ≤ –2.0 with ≥ one BMD-independent risk factor; or T-score ≤ –1.0 with history of fragility fracture

Objective

- To evaluate the effects of combined therapy of teriparatide and denosumab on hip and spine BMD at 24 months compared to monotherapy of either agent

Primary endpoints

- Percentage change in PA spine BMD at 24 months

Secondary endpoints

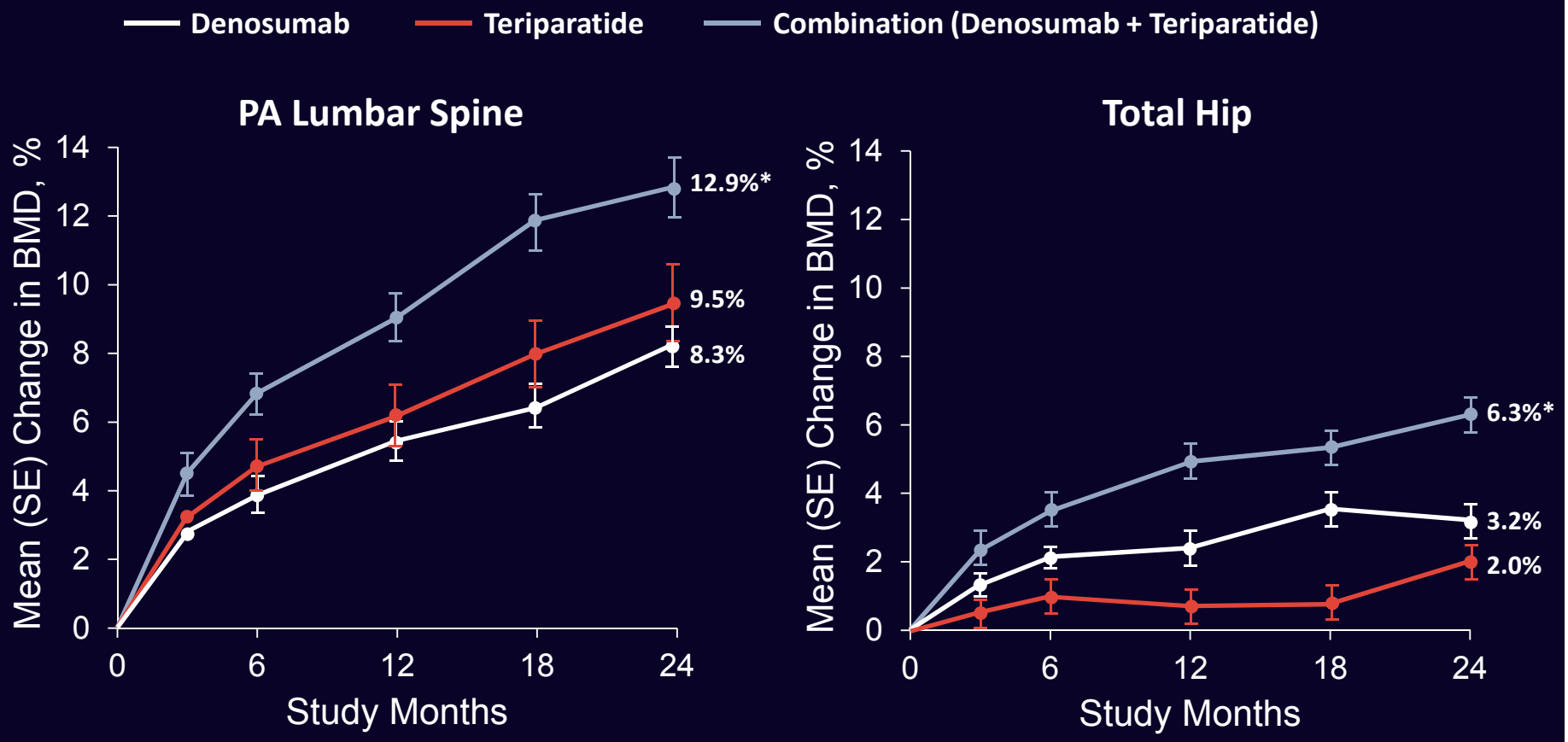
- Percentage change in BMD of total hip, femoral neck, and distal 1/3 of the radius shaft
- Changes in CTX, P1NP, and osteocalcin concentrations

SC = subcutaneous; Q6M = every 6 months; QD = once a day; BMD = bone mineral density; PA = posterior-anterior; CTX = serum C-telopeptide of type I collagen; P1NP = procollagen type 1 N-terminal propeptide

Leder BZ, et al. *J Clin Endocrinol Metab*. 2014;99:1694-1700.

Changes in BMD of Lumbar Spine and Total Hip

DATA Extension Study – 24 Months



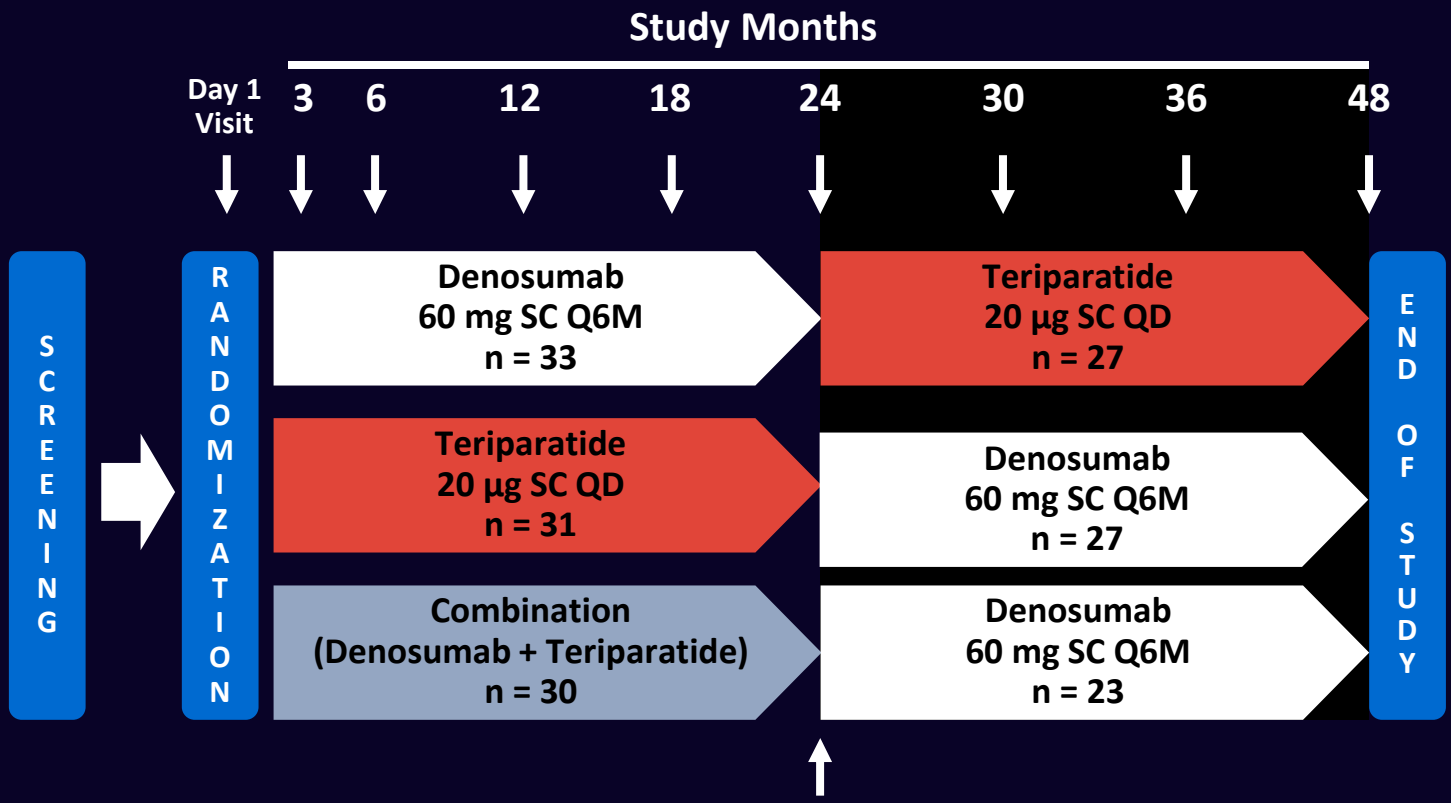
*$p < 0.05$ vs denosumab and vs teriparatide.

SE = standard error

Adapted from: Leder BZ, et al. *J Clin Endocrinol Metab*. 2014;99:1694-1700.

Study Design

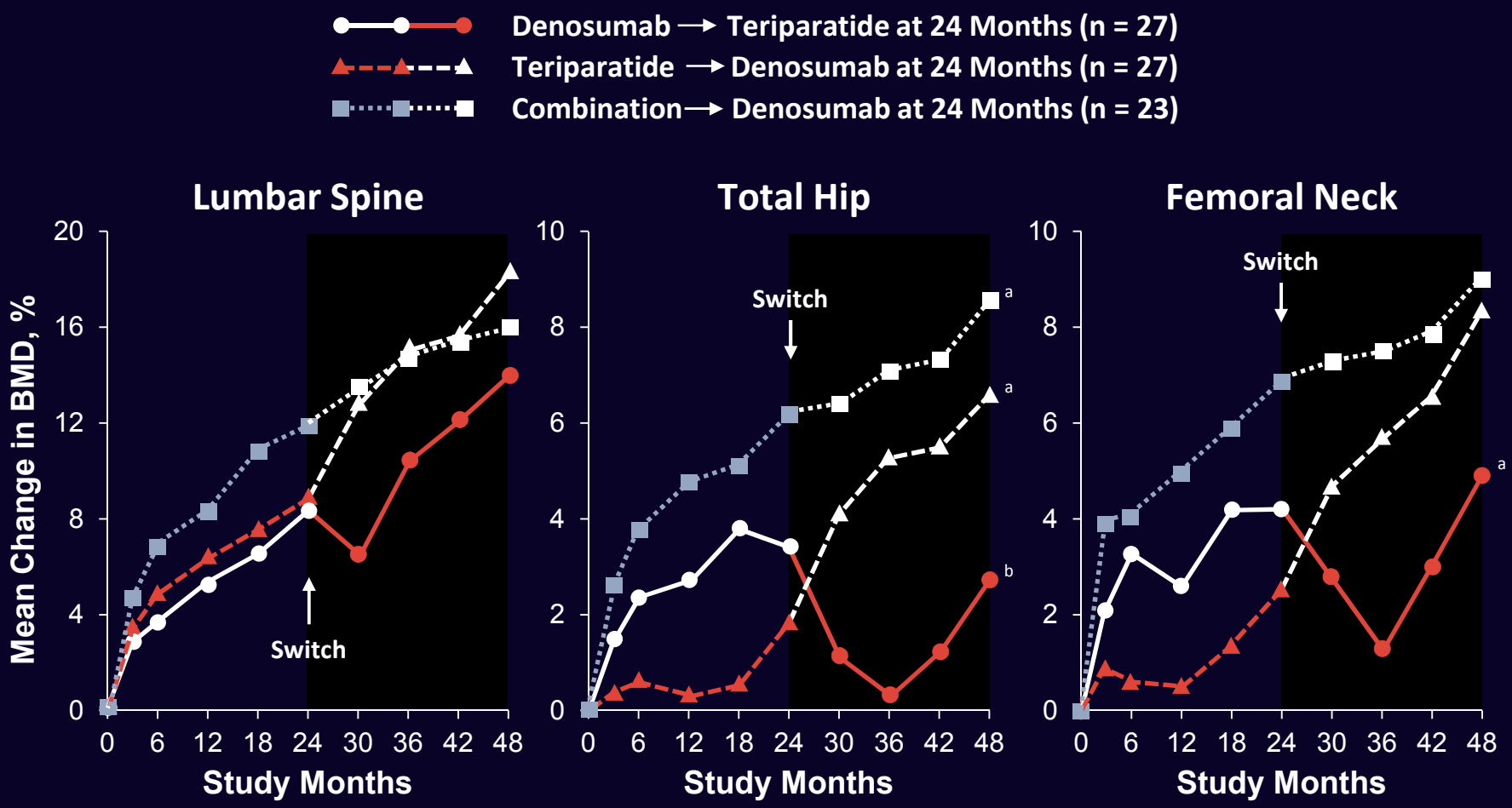
DATA Switch Study – 48 Months



Leder BZ, et al. *J Clin Endocrinol Metab*. 2014;99:1694-1700.
Leder BZ, et al. *Lancet*. 2015;386:1147-1155.

Changes in Spine, Total Hip, and Femoral Neck BMD

DATA Switch Study – 48 Months



[a]$p < 0.05$ vs both other groups.
[b]$p < 0.0005$ vs both other groups.

Adapted from: Leder BZ, et al. *Lancet*. 2015;386:1147-1155.

Summary of the Webinar

- Keep in mind the importance of “Goals”
  - FRACTURE(initial decision), FRACTURE(monitoring), FRACTURE(goal)!
- Understand the concept of bone remodeling & modeling
- Choose the medication that fits the need & goal of the patient with osteoporosis
- Improve the treatment with
  - newer, stronger drugs
  - modified way of administration ; sequential, combinative

고맙습니다

Q1. What is the most appropriate description regarding the goal of osteoporosis treatment?

① Normalization of one's spinal BMD
② Normalization of one's femoral BMD
③ Achievement of premenopausal range of bone turnover
④ Increasing spinal & femoral BMD more than least significant change(LSC) of DXA
⑤ Reducing the risk of fracture

Q2. According to “DATA switch study”, which was the best order of administration on total hip BMD?

① Denosumab then teriparatide
② Teriparatide then denosumab
③ Denosumab & teriparatide then denosumab
④ All the orders showed similar effects.
⑤ Every sequential order was ineffective.