



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Bone Health in 2024

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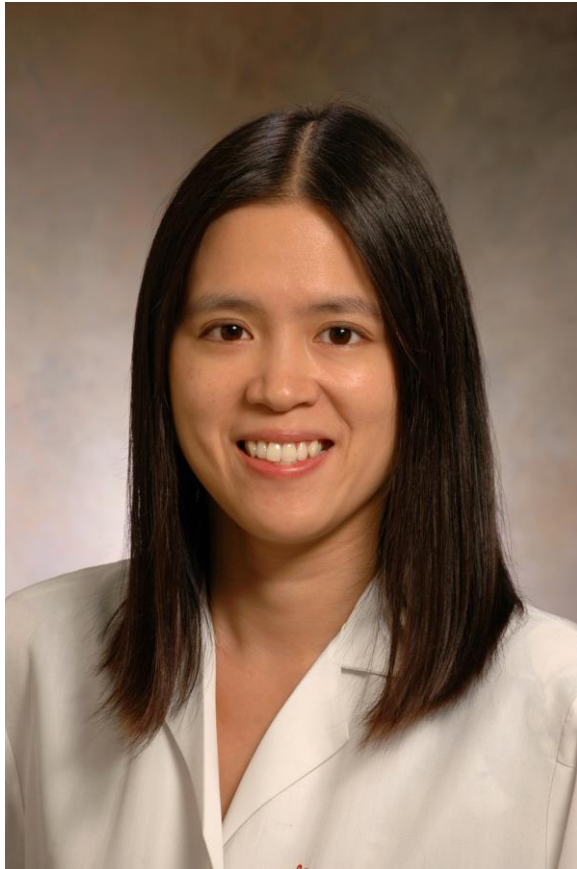
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- Associate Physician, Brigham and Women's Hospital
 - Clinical focus: osteoporosis



Disclosures

No relevant disclosures.



Learning Objectives

- Assess fracture risk beyond bone density
- Understand when and how to use non-bisphosphonate osteoporosis treatments



Case 1

Case 1: 62 yo postmenopausal woman

- 62-year-old postmenopausal woman with history of lupus, diagnosed at age 19 years old and treated with glucocorticoids for the first 10 years with concurrent irregular menses, and GERD on PPI
 - No history of fracture
 - Screening DXA:

Patient:

- **Major osteoporotic fracture: 13%**
- **Hip fracture: 1.5%**

	T-score	Z-score
L1-L4 spine	-1.6	0.0
L total hip	-1.2	-0.1
L femoral neck	-1.3	0.0



Case 1: 62-year-old postmenopausal woman

- 3 months later, she fell and sustained a R femoral neck fracture.



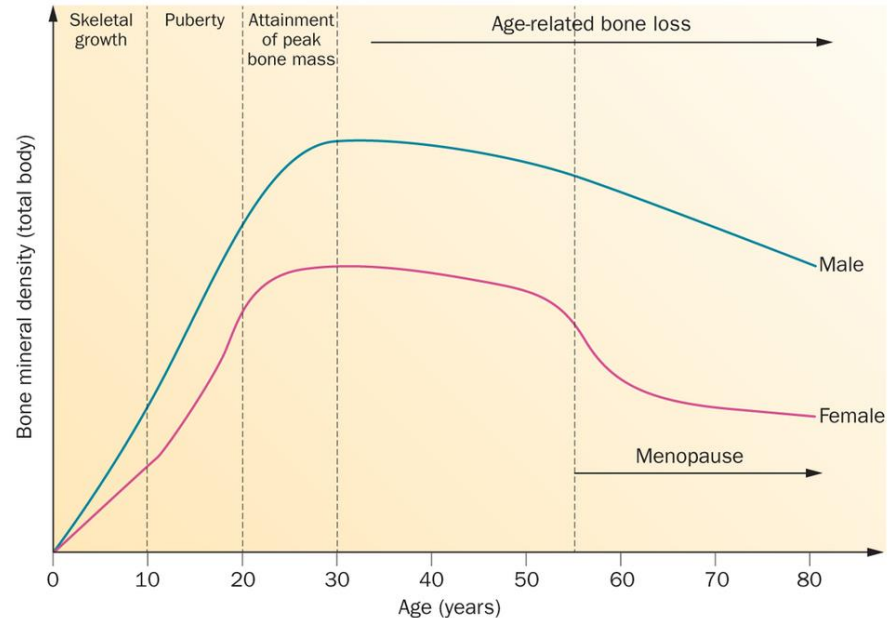
Osteoporosis is defined as a skeletal disorder characterized by *compromised bone strength* predisposing a person to an *increased risk of fracture*



Bone Strength is Determined by Bone Density AND Bone Quality

Bone Density

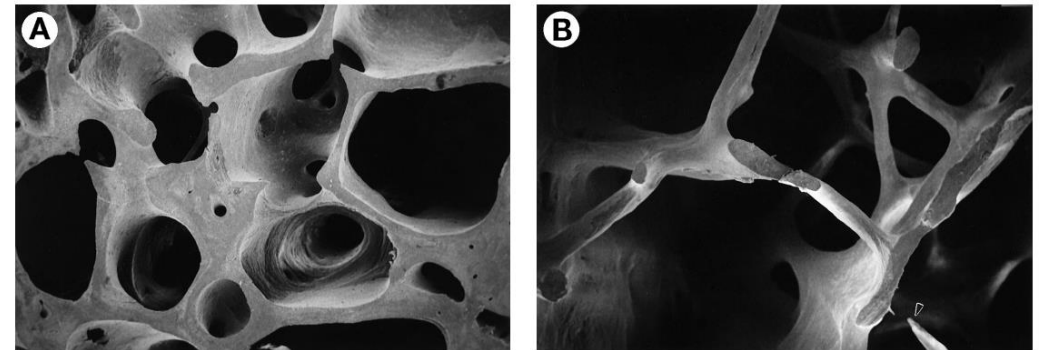
- Peak bone density
- Amount of bone loss



Hendrickx et al. *Nat Rev Rheumatol.* 2015;11(8).

Bone Quality

- Microarchitecture
- Turnover
- Accumulation of damage
- Mineralization
- Collagen



Dempster. *J Bone Miner Res.* 2000;15(1).
NIH Consensus Development Panel. *JAMA.* 2001;285(6).

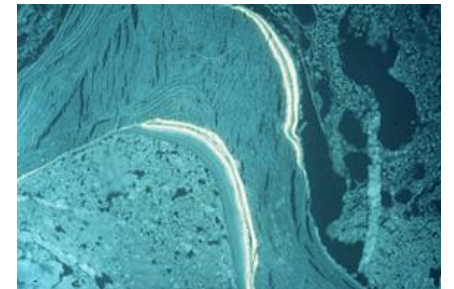
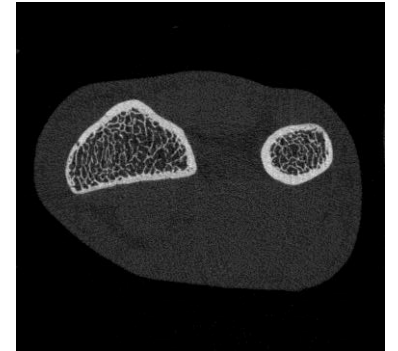
Bone Quality is More Difficult to Measure Clinically

Bone Density



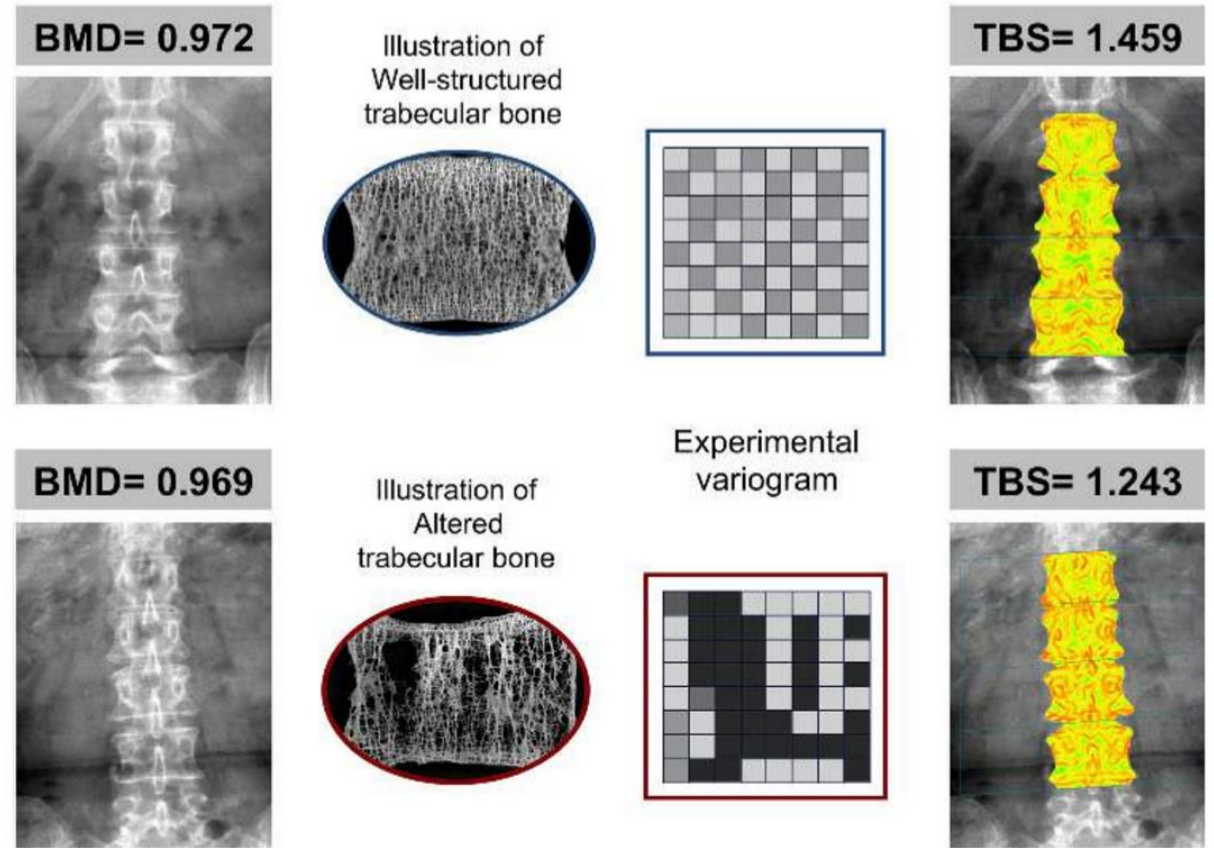
Bone Quality

- Microarchitecture
 - High resolution peripheral quantitative CT (hr-pQCT)
 - Trabecular bone score (TBS)
- Turnover:
 - Bone biopsy with double tetracycline labeling
 - Serum, urine markers
- Accumulation of damage: ?
- Mineralization:
 - Ca, phos, 25OHD, PTH
- Collagen:
 - Genetic testing (osteogenesis imperfecta)



Trabecular Bone Score Estimates Microarchitecture

- Analytical, non-invasive measure of grey-level variation in lumbar spine DXA images to estimate 3D textural characteristics of vertebrae
- Higher TBS associated with better bone *microarchitecture* and lower risk of fractures



Normal	≥ 1.350
Partially degraded	1.2-1.350
Degraded	≤ 1.200



TBS predicts fracture risk independent of BMD and FRAX

FRAX® Fracture Risk Assessment Tool

Home Calculation Tool Paper Charts FAQ References

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture

Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 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/day No Yes

12. Femoral neck BMD (g/cm²)
Hologic T-score: -2.0

BMI: 26.2
The ten year probability of fracture (%)
with BMD

Major osteoporotic	11
Hip Fracture	1.6

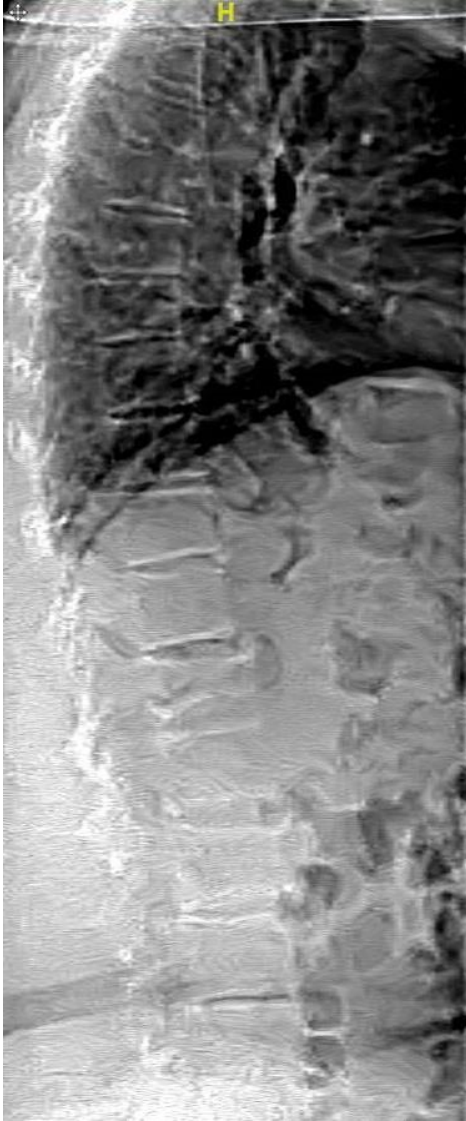
If you have a TBS value, click here:

If you have a TBS value, click here:

Particularly in patients with diabetes and long-term glucocorticoid use



Vertebral Fracture Assessment (VFA)



- Obtained by densitometer
- Importance of vertebral fractures:
 - Associated with increased morbidity and mortality
 - Predict future fractures *independent* of BMD
 - Meets criteria for diagnosis of osteoporosis and indication for treatment

Only 1/3 are clinically diagnosed!

Bliuc et al. *JAMA*. 2009;301(5).

Ross et al. *Ann Intern Med*. 1991;114(11).

Cooper et al. *Bone*. 1993;14 Suppl 1.



Indications for VFA

- T-score <-1.0 AND
 - Women age ≥ 70 years or men age ≥ 80 years
 - Historical height loss >1.5 inches
 - Self-reported but undocumented prior vertebral fracture
 - Glucocorticoid therapy equivalent to ≥ 5 mg of prednisone or equivalent per day for ≥ 3 months



Bone Turnover Markers

- Markers of bone resorption: urinary N-telopeptide (NTX), serum C-telopeptide (CTX)
- Markers of bone formation: serum bone specific alkaline phosphatase, procollagen type 1 N-terminal propeptide (P1NP), osteocalcin
- Epidemiologic studies show high levels predict fracture risk
- Limited clinical usefulness for fracture prediction
 - Large variability (20-70% least significant change)
 - No cut-off to help determine who should be treated



Diagnosis of Osteoporosis

- WHO criteria: BMD at spine, total hip, femoral neck, or 1/3rd radius
- Elevated FRAX:
 - 10-year probability of major osteoporotic fracture $\geq 20\%$
 - 10-year probability of hip fracture $\geq 3\%$
- History of fragility fracture
 - **Hip or spine regardless of BMD**
 - Proximal humerus, pelvis, (wrist) if BMD is in the osteopenia

	T-score criteria
Normal	≥ -1.0
Osteopenia	< -1.0 to > -2.5
Osteoporosis	≤ -2.5

LeBoff et al. *Osteoporos Int.* 2022;33(10).

Camacho et al. *Endocr Pract.* 2020;26(Suppl 1).

Siris et al. *Osteoporos Int.* 2014;25(5).

Wainwright SA et al. *J Clin Endocrinol Metab.* 2005;90.

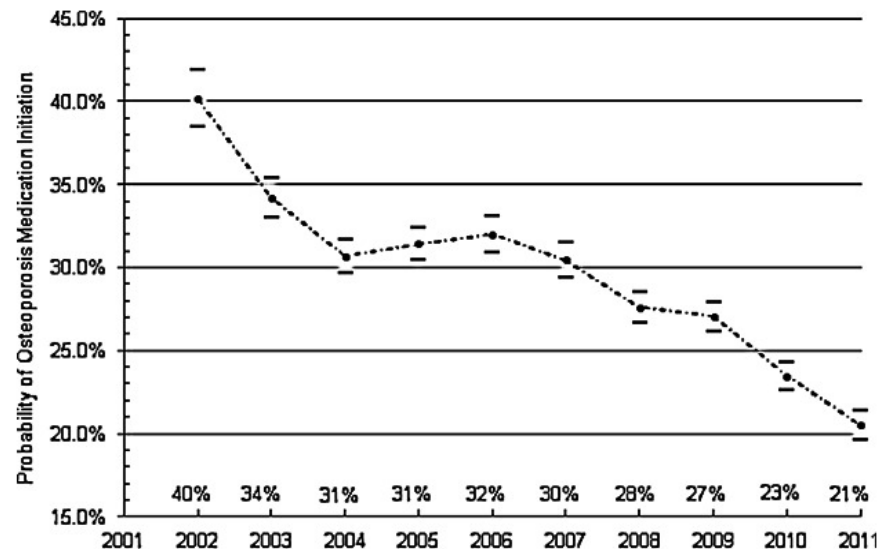


Sustaining a major osteoporotic fracture is highly predictive of having another fracture within 1 year

Subsequent Fracture Rates, within 1 year of Index Fracture

		Overall	Vertebral	Hip
Index fracture	Medicare, n (%)			
	Overall (N=45,603)	7,604 (16.7)	1,746 (3.8)	1,256 (2.8)
	Vertebral (n=9,465)	1,908 (20.2)	1,235 (13.1)	101 (1.1)
	Hip (n=5,024)	1,280 (25.5)	84 (1.7)	719 (14.3)

Yet, only 21% of hip fracture patients were treated for osteoporosis within 12 mo.



Weaver J, et al. *J Manag Care Spec Pharm.* 2017;23(4).
 Solomon DH, et al. *J Bone Miner Res.* 2014;29(9).



Case 1: 62-year-old postmenopausal woman

What do you now recommend?

- A) Hormone replacement therapy
- B) Raloxifene
- C) Alendronate
- D) Zoledronic acid
- E) Denosumab



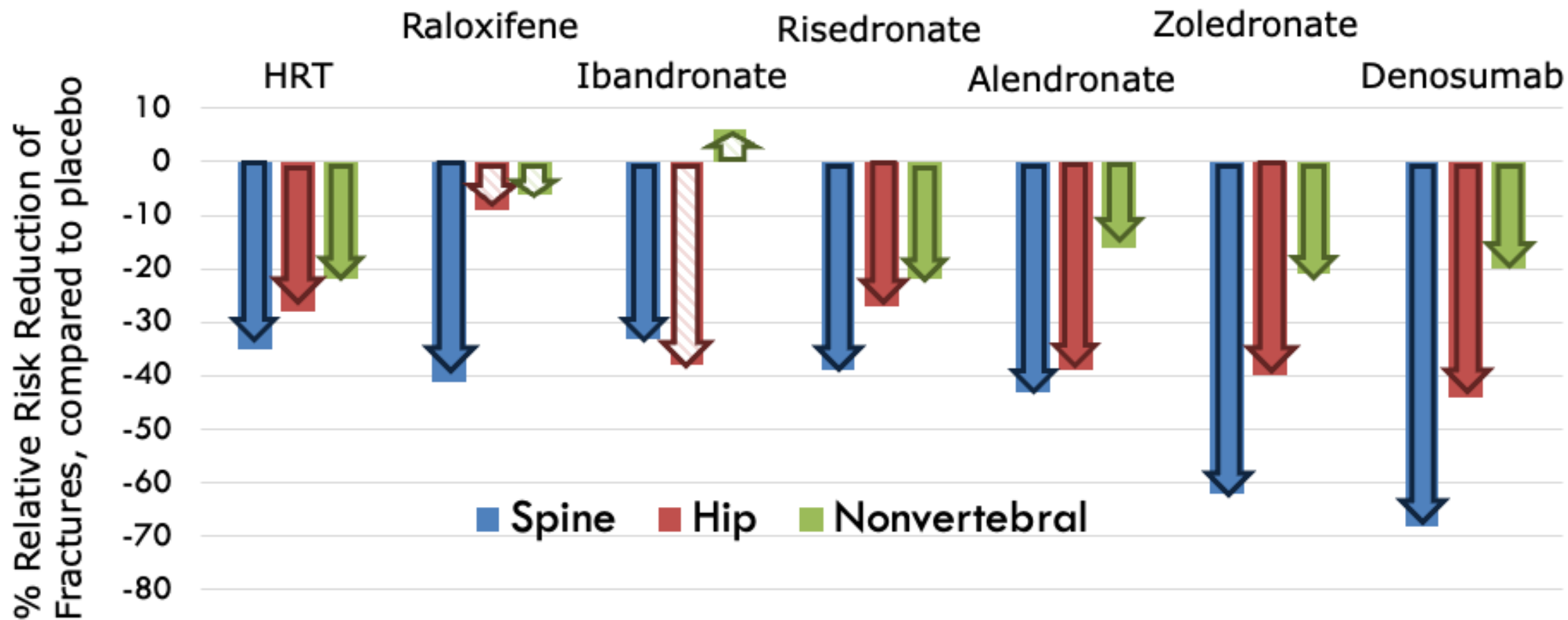
Case 1: 62-year-old postmenopausal woman

What do you now recommend?

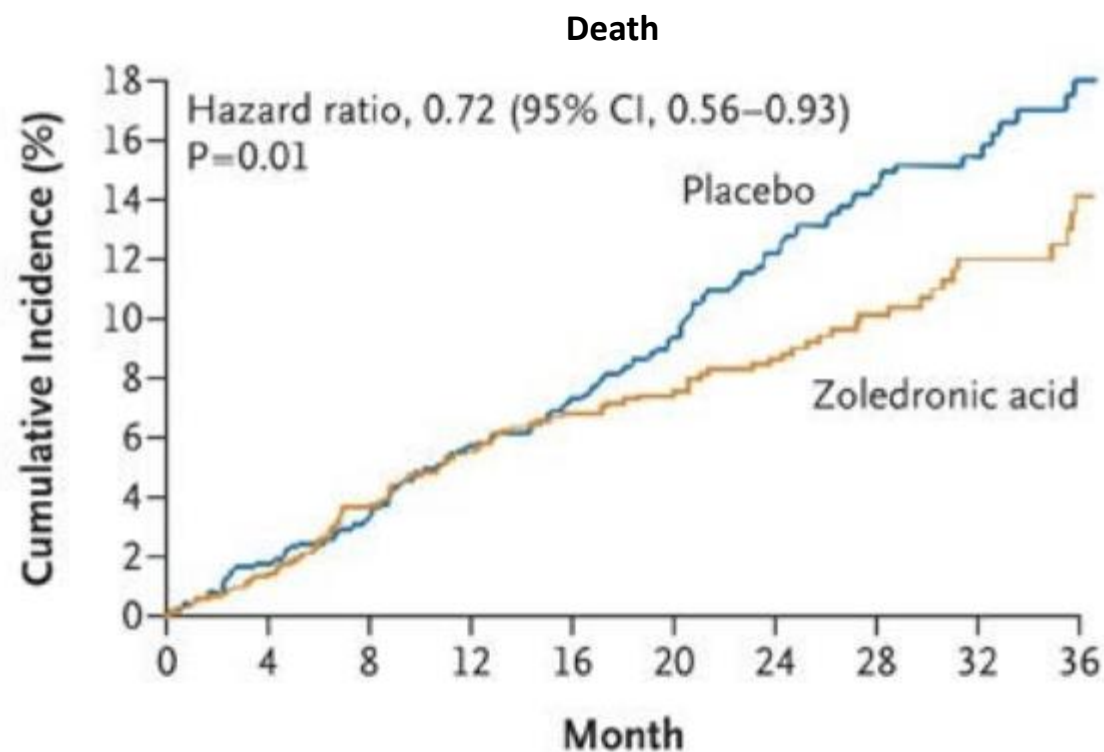
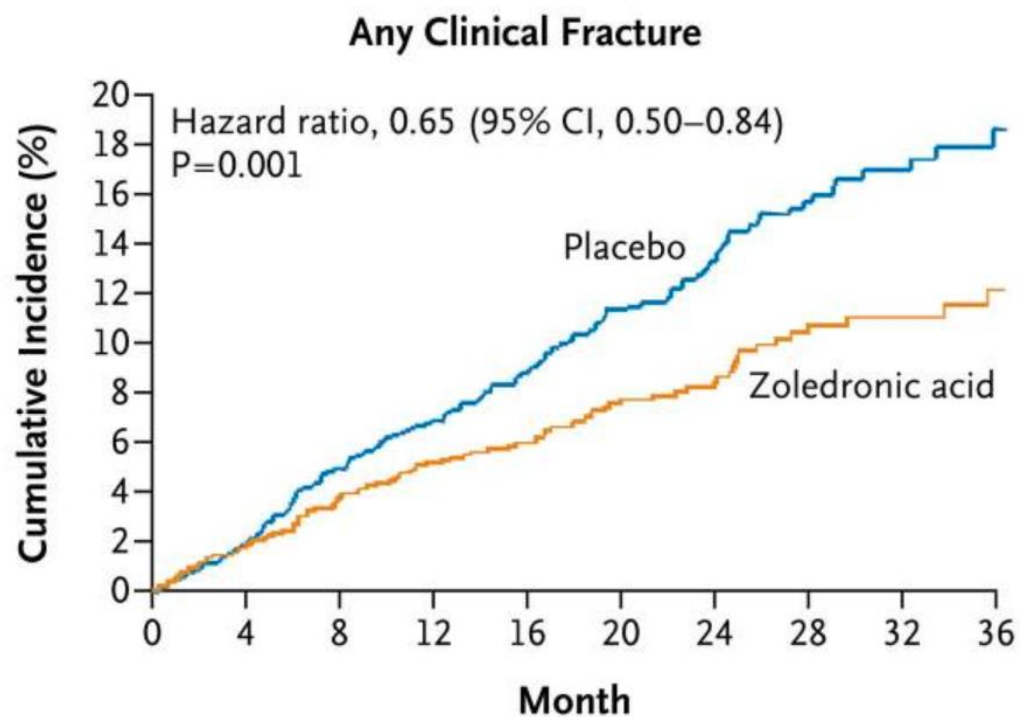
- A) Hormone replacement therapy—>10 years out from menopause
- B) Raloxifene—not potent enough to reduce hip fractures
- C) Alendronate—has a history of GERD
- D) Zoledronic acid**
- E) Denosumab—an option but discontinuation remains a problem



Osteoporosis Medications are Very Effective at Preventing Fractures



Zoledronic acid reduces fractures and mortality post-hip fracture: a randomized controlled trial



Reduced risks of:

- Fractures by 35%
- Vertebral fractures by 46%

Reduces mortality by 28%!



Osteonecrosis of the Jaw is Very Rare

- Presence of exposed bone in the maxillofacial region for >8 weeks
- Multifactorial pathogenesis, including bone remodeling inhibition, inflammation/infection, angiogenesis inhibition, immune dysfunction, genetic predisposition
- Rare in patients treated for osteoporosis:
 - Oral bisphosphonates: $\leq 0.05\%$ (≤ 5 per 10,000)
 - IV bisphosphonates: $\leq 0.02\%$ (≤ 2 per 10,000)
 - Denosumab: 0.04-0.3%
 - Placebo: 0-0.02%
 - Cancer patients: <5%
- Higher risk with invasive procedure (tooth extraction, dental implant)
- Vast majority of cases are mild and treated conservatively



Ruggiero et al. *J Oral Maxillofac Surg.* 2022;80.

Anastasilakis et al. *JCEM.* 2022;107.

Williams et al. *Oral Maxillofac Sug Clin North Am.* 2015;27(4).



Osteonecrosis of the Jaw is Very Rare

American Association of Oral and Maxillofacial Surgeons' Position Paper on ONJ, 2022:

- “Patients are *irrationally* denying themselves the tangible therapeutic benefit of antiresorptive therapy to minimize the risk of fragility fractures in order to prevent a *minuscule* risk of developing MRONJ.”
- Do NOT recommend routine discontinuation of osteoporosis treatment prior to dental procedures
 - Unable to reach a consensus—evenly split between offering drug holidays on a case-by-case recommendations vs never recommending drug holidays



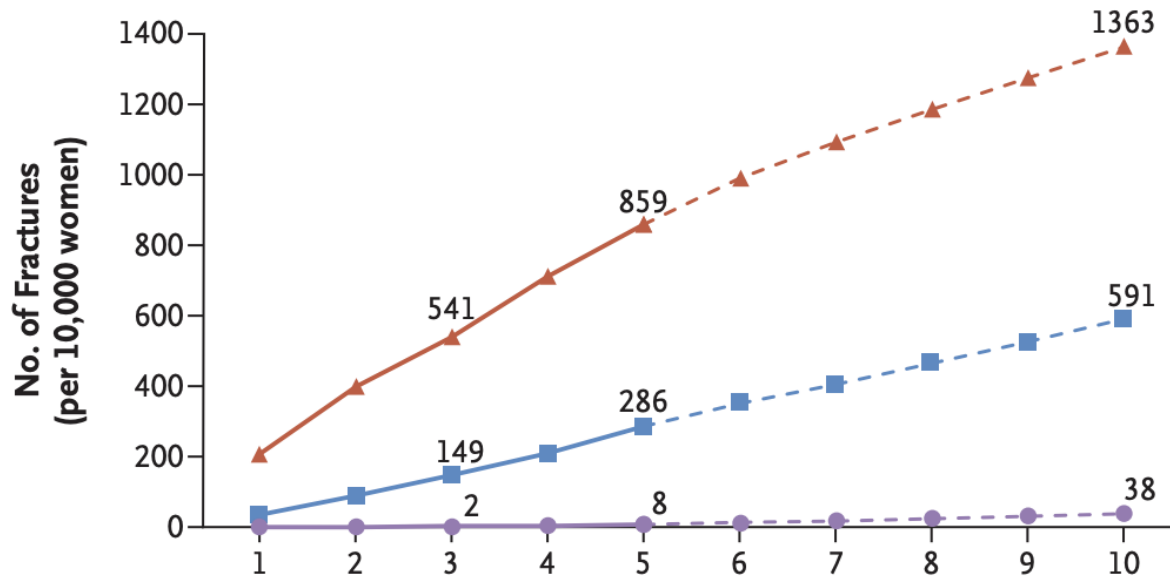
Atypical Femur Fractures are Also Very Rare

- Low-trauma fractures in the subtrochanteric region or femoral shaft
- May begin with stress reaction or stress fracture
 - Anti-resorptive agents may impair the repair process.
- 70% have prodrome of pain in thigh or groin
- 28% with bilateral fractures/radiographic abnormalities
- Absolute risk of 3.2 to 50 cases per 100,000 person-years
 - Decreases 70% per year after stopping BPs

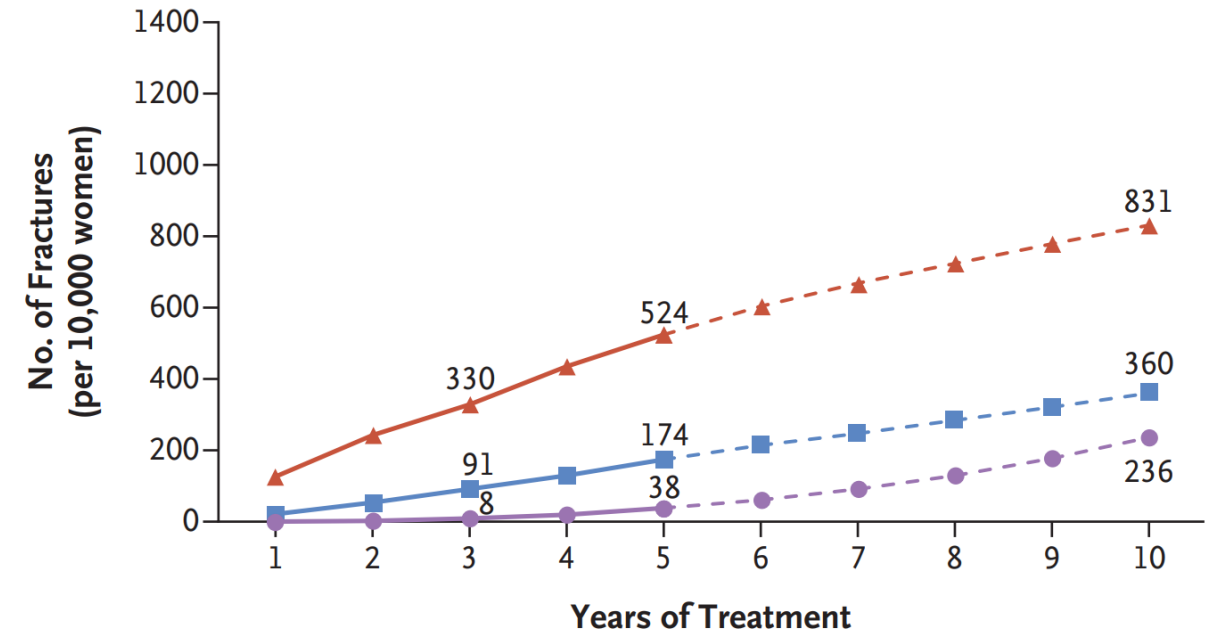


Bisphosphonates prevent many more fractures than cause AFFs, but there are racial differences

B White Women



A Asian Women

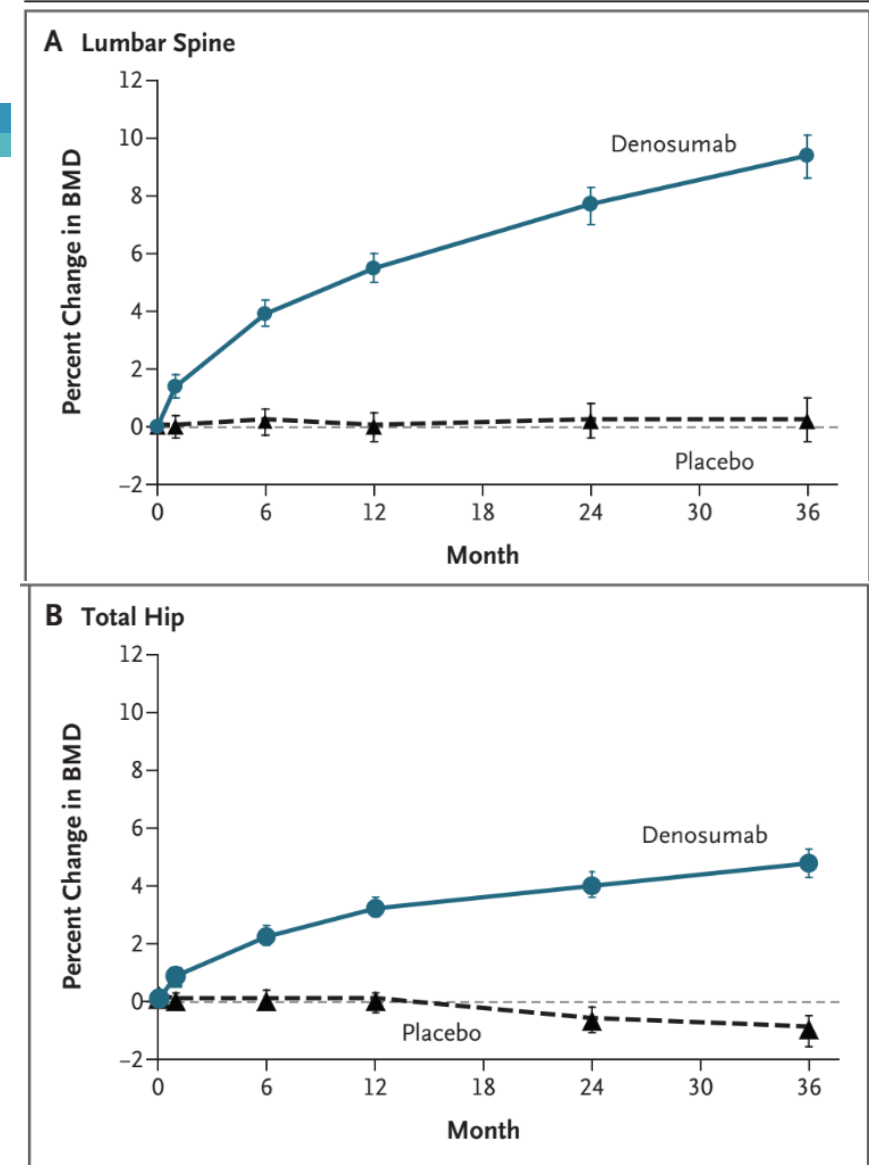


■ No. of hip fractures prevented ▲ No. of clinical fractures prevented ● No. of bisphosphonate-associated AFFs



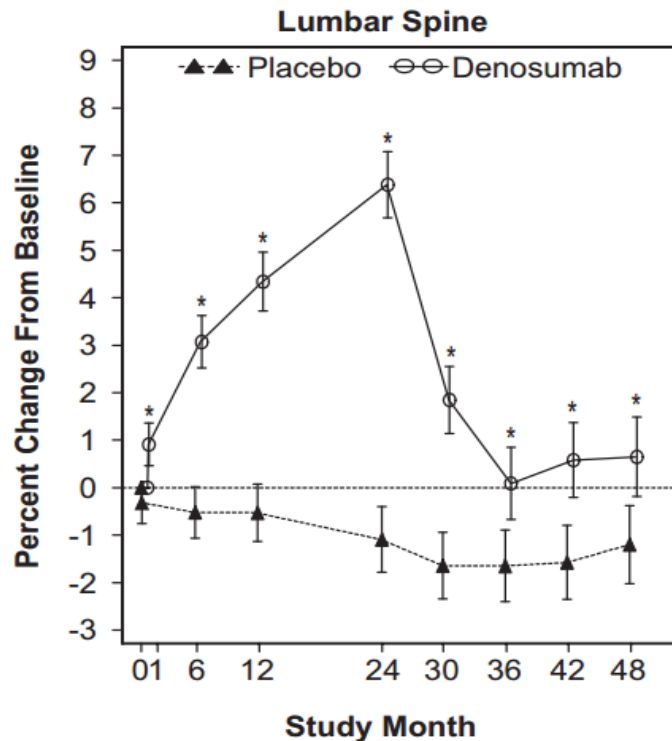
Denosumab

- Antibody that binds and inhibits RANKL, which regulates osteoclastic bone resorption
- Reduces risk of vertebral fractures by 68% and hip fractures by 40% over 3 years
- Okay to use in renal insufficiency
- Adverse events:
 - Hypocalcemia
 - Rashes
 - Cellulitis
 - ONJ, AFF



Denosumab vs. Bisphosphonates

- Similar fracture reduction compared to zoledronate
- Greater, continued increase in BMD
- NO DRUG HOLIDAYS



SHORT REPORT

JBMR®

Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases

Athanasios D Anastasilakis,¹ Stergios A Polyzos,² Polyzois Makras,³ Berengere Aubry-Rozier,⁴ Stella Kaouri,⁵ and Olivier Lamy⁴



Case 1: 62-year-old postmenopausal woman

- Started zoledronic acid 5 mg IV annually
- Repeat DXA, 1 year after 1st dose:

	T-score	Comparison to prior scan
L1-L4 spine	-1.3	+3.4%
L total hip	-1.3	No change
L femoral neck	-1.5	No change

Plan up to 6 years of IV zoledronic acid given history of hip fracture (high risk patient)

- No further fractures



Case 2

Case 2: 55 yo postmenopausal woman

- 55-yo woman with history of breast cancer diagnosed at the age of 50. She had regular menses until chemotherapy. She took tamoxifen for 3.5 years, followed by anastrozole for 1.5 years, stopped in 12/2014.
- No fracture history.
- Concurrently treated with alendronate
- Despite this, DXA from 11/2014:

	T-score	Comparison to 10/2012
L1-L3 spine	-3.1	-12.1%
L total hip	-1.6	-9.2%
L femoral neck	-2.4	



Case 2: 55 yo postmenopausal woman

- Reports adherence, took properly
- No other major illness, no weight loss
- Adequate calcium and vitamin D intake, exercise
- Secondary work up was unremarkable
- Switched to denosumab in 3/2015
- DXA scan, 10/2016:

	T-score	Comparison to 11/2014
L1-L3 spine	-2.7	+5.0%
L total hip	-1.3	+4.7%
L femoral neck	-2.1	



Case 2: 55 yo postmenopausal woman

- Received denosumab for 3 years
- DXA scan, 10/2017:

	T-score	Comparison to 10/2016
L1-L3 spine	-2.6	No change
L total hip	-1.3	No change
L femoral neck	-2.0	

- She'd like to stop denosumab.



Case 2: 55 yo postmenopausal woman

She'd like to stop denosumab. What's the next best step?

- A) Stop denosumab, monitor BMD in 1 year
- B) Start raloxifene
- C) Start alendronate, plan for 1 year
- D) Start zoledronic acid, plan for 1 year



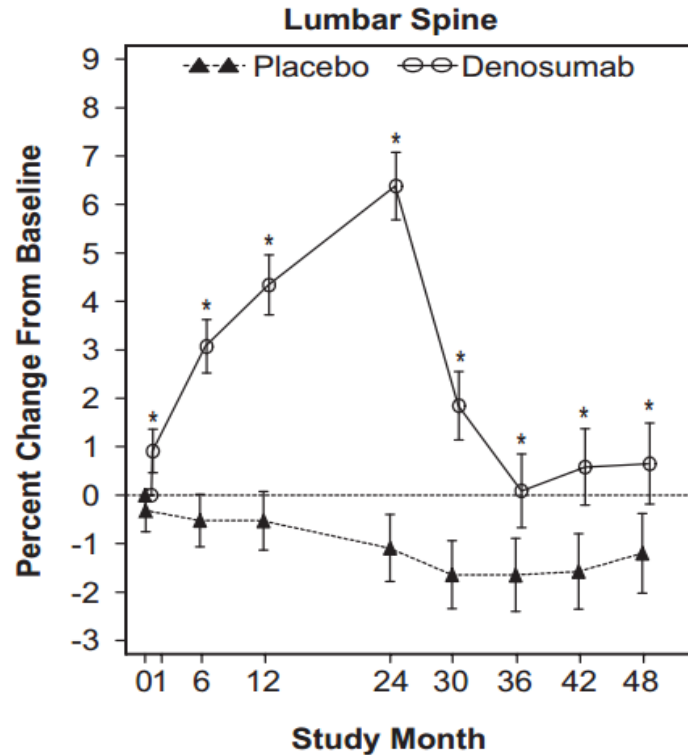
Case 2: 55 yo postmenopausal woman

She'd like to stop denosumab. What's the next best step?

- A) Stop denosumab, monitor BMD in 1 year—BMD is expected to decline without subsequent treatment
- B) Start raloxifene—not a strong anti-resorptive agent
- C) Start alendronate, plan for 1 year—denosumab treatment for ≥ 2.5 years seems to need IV vs. oral bisphosphonate
- D) Start zoledronic acid, plan for 1 year**



Denosumab Discontinuation Results in Rebound Bone Loss and May Increase Vertebral Fracture Risk



SHORT REPORT

JBMR®

Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases

Athanasios D Anastasilakis,¹ Stergios A Polyzos,² Polyzois Makras,³ Berengere Aubry-Rozier,⁴ Stella Kaouri,⁵ and Olivier Lamy⁴

Higher risk of multiple vertebral fractures, particularly in patients with history of *prior vertebral fracture* (3.9x).

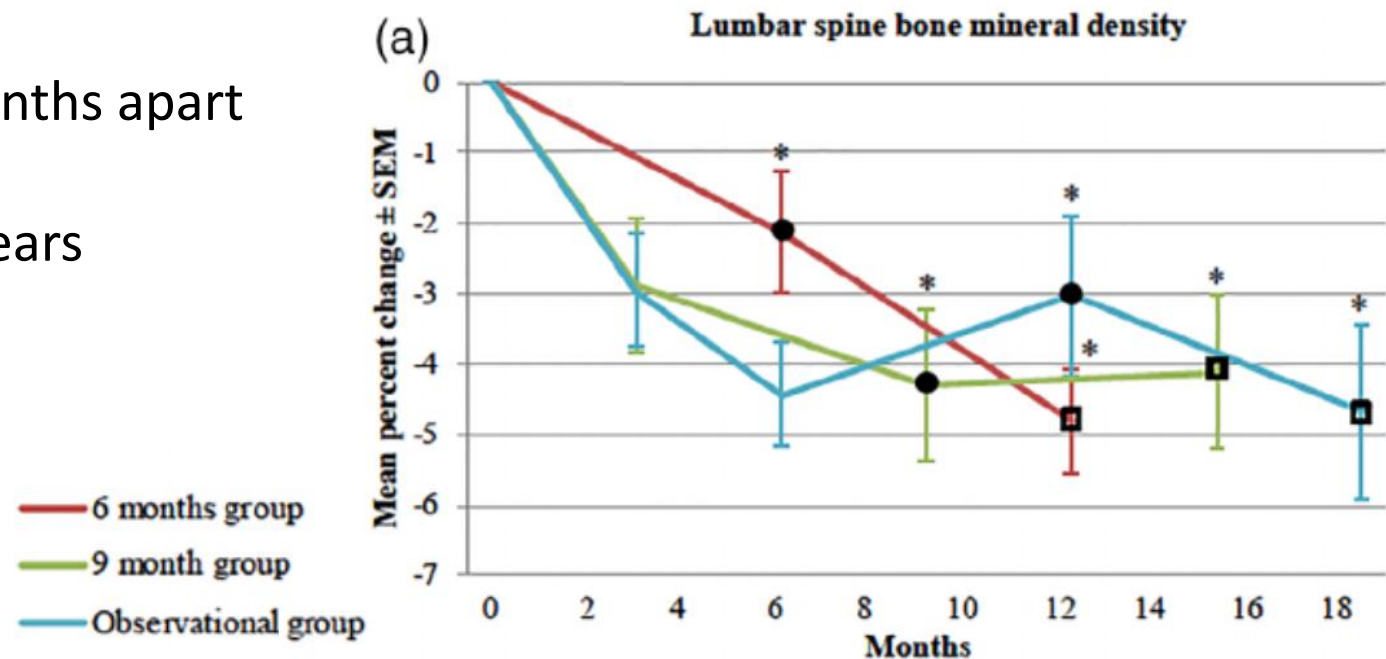
Brown et al. *J Bone Miner Res.* 2013;28(4).

Cummings et al. *J Bone Miner Res.* 2018;33(2).

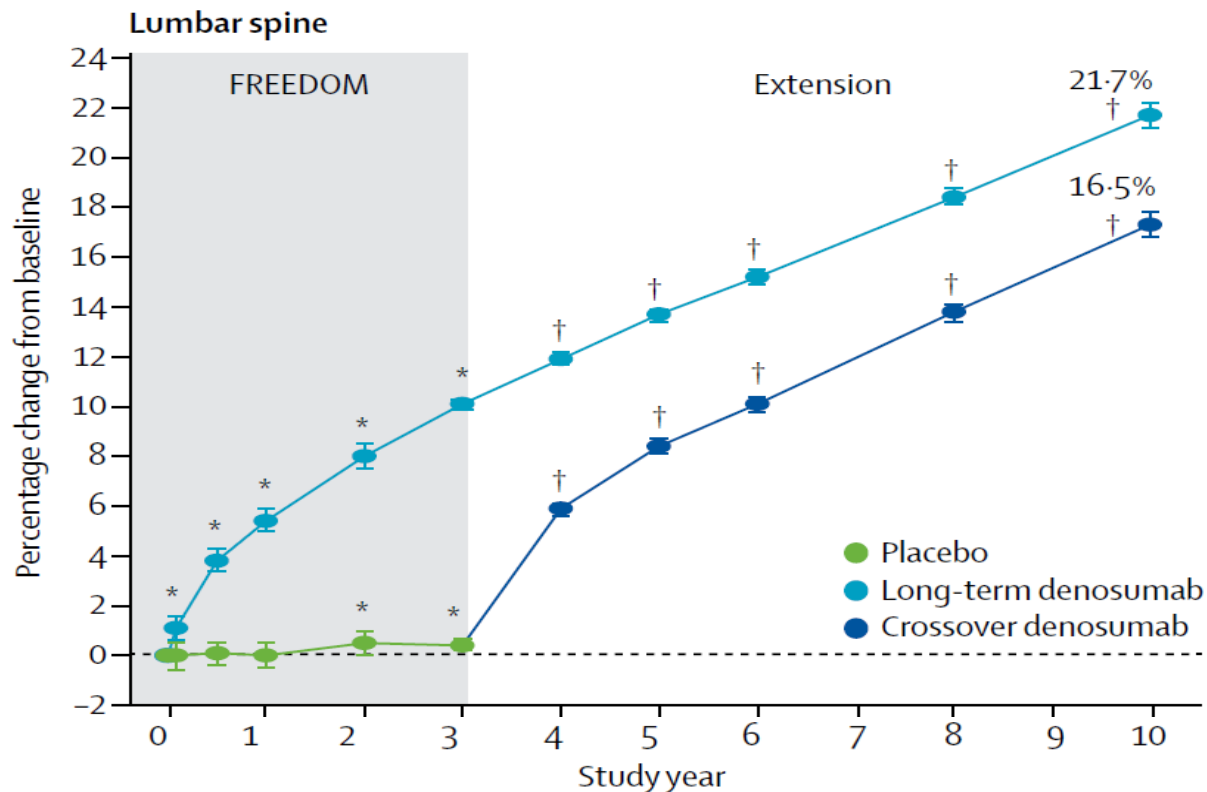
Bone et al. *J Clin Endocrinol Metab.* 2011;96(4).

How Can Denosumab be Safely Discontinued? (Can it be?)

- 2020 European Calcified Tissues Society position statement:
 - Short-term use of denosumab (≤ 2.5 years): oral/IV bisphosphonate for 1-2 years with monitoring of bone turnover markers (BTMs)
 - Long-term use of denosumab: zoledronic acid 6 months after last dose of denosumab, monitor BTMs after 3 and 6 months, and repeat zoledronic acid if BTMs persistently increase
 - 2 doses of zoledronic acid 6 months apart if unable to measure BTMs
 - Oral bisphosphonates for 1-2 years



Denosumab is Safe with 10-year Data



Fracture risk continues to decline as well.

Bone et al. *Lancet Diabetes Endocrinol.* 2017;5(7).

Ferrari et al. *J Clin Endocrinol Metab.* 2019;104.

Watts et al. ASBMR Annual Meeting. 2017, abstract 1016.

- Stable incidence of all adverse events
 - 2 cases of AFF (out of 4,074)
 - 12 cases of ONJ
 - 0.7% in women reporting an invasive oral procedure/event
 - 0.05% in women without

For older patients (~70+ yo) at high risk of fracture, plan to continue denosumab indefinitely.

Case 2: 55 yo postmenopausal woman

- Received zoledronic acid in 6/2018
- DXA scan, 6/2019:
- DXA scan, 8/2020:

	T-score	Comparison to 10/2017
L1-L3 spine	-2.9	-4.2%
L total hip	-1.6	-4.2%
L femoral neck	-2.3	

	T-score	Comparison to 6/2019
L1-L3 spine	-3.9	-14.8%
L total hip	-2.0	-7.2%
L femoral neck	-2.7	



Case 2: 55 yo postmenopausal woman

- Secondary work up was unremarkable
- Started romosozumab
- DXA scan, 12/2021

	T-score	Comparison to 8/2020
L1-L3 spine	-3.1	+13.9%
L total hip	-1.7	+5.6%
L femoral neck	-2.0	

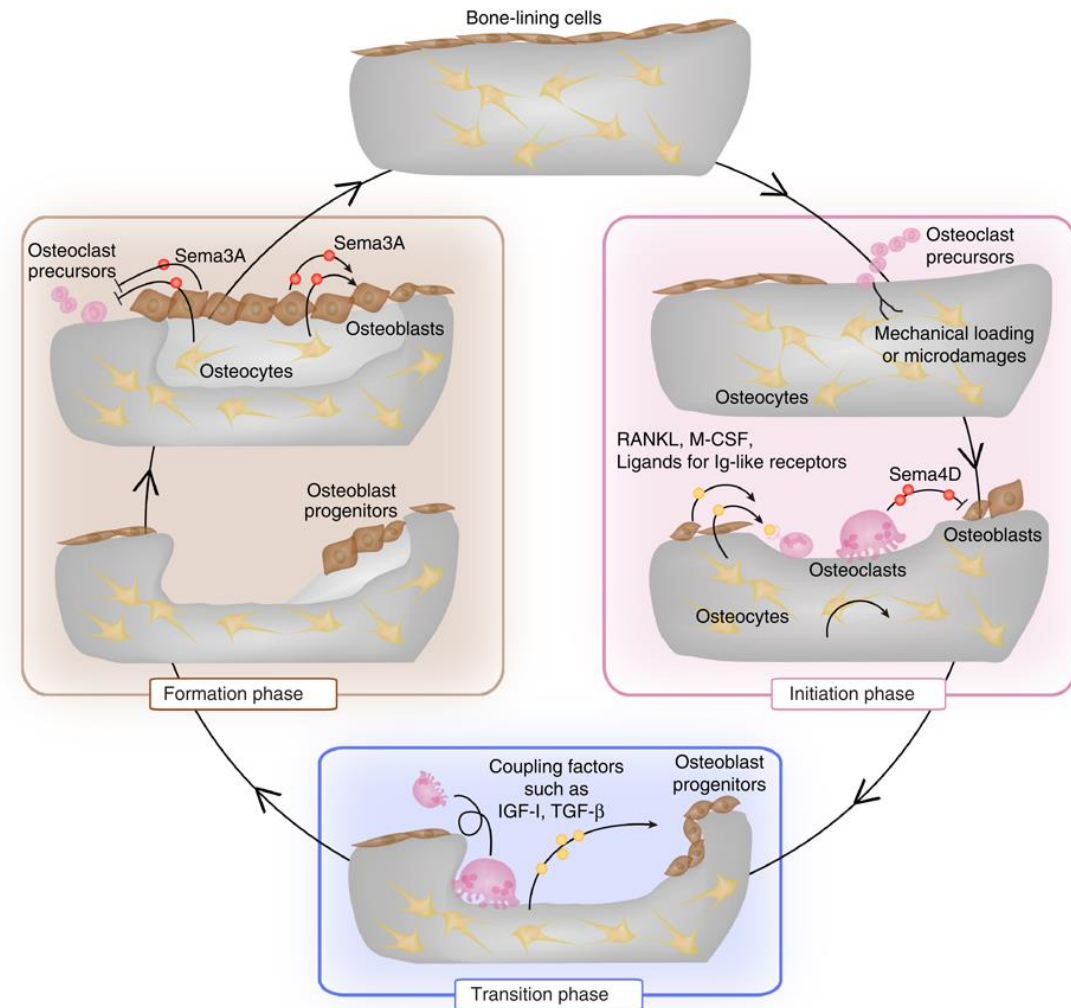


Categories of Pharmacologic Treatment

Antiresorptive therapies
block osteoclastic bone
resorption.

Anabolic therapies
promote osteoblastic bone
formation.

Dual action



The NEW Anabolic Agent (technically dual agent): Romosozumab

- FDA approved in 2019
- Monthly subcutaneous injection for 12 months
- Based on the disease sclerosteosis, a rare genetic disorder with high bone mass due to loss-of-function mutation in SOST
- Sclerostin is produced by osteocytes, inhibits bone formation and enhances bone resorption
- Monoclonal antibody that binds and inhibits sclerostin

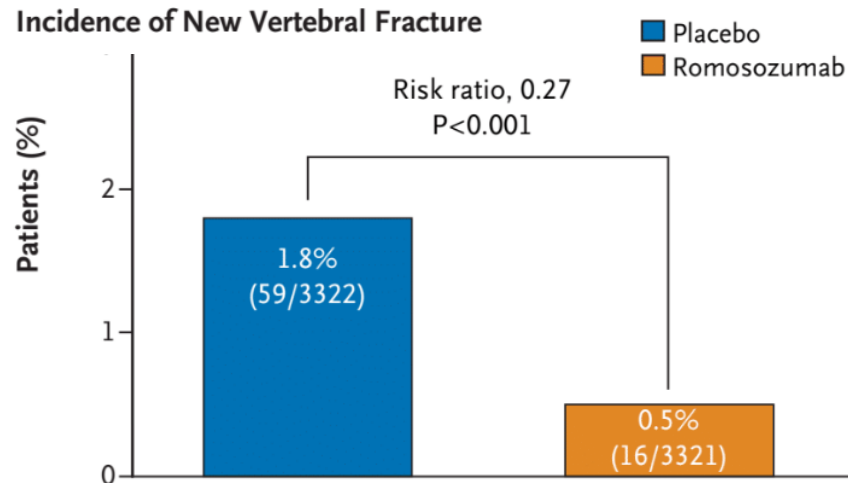
Romosozumab increases bone formation and bone resorption *at the same time*



Romosozumab Reduces Fractures Better than Alendronate

FRAME

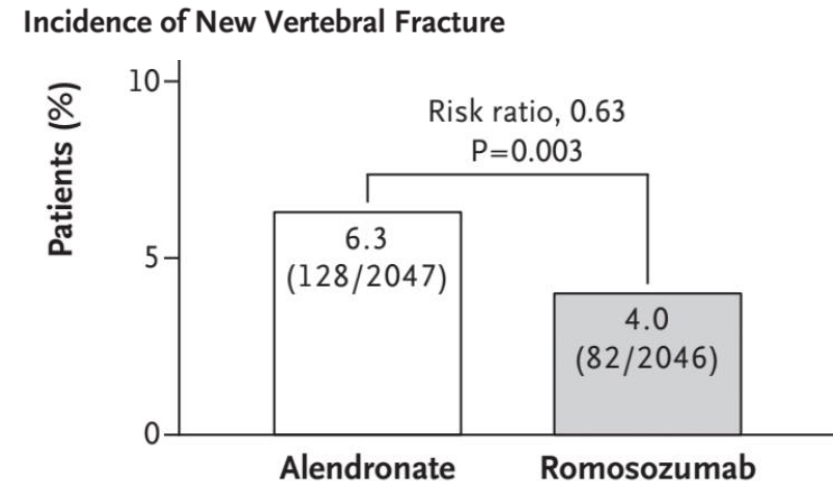
Vs. placebo for 12 mo, followed by denosumab for 12 mo



36% reduction in clinical fractures
(1.6 v. 2.5%)

ARCH

Vs. alendronate for 12 mo, followed by alendronate



19% reduction in nonvertebral fractures,
38% in hip fractures



Romosozumab May Increase Cardiovascular Risk

- Injection site reaction, mostly mild: 5.2% v. 2.9%
- Few cases of ONJ and AFF
- More adjudicated serious cardiovascular events with romosozumab (2.5%) than with alendronate (1.9%; OR 1.31 [0.85-2.00])
 - Not seen against placebo

Should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year.

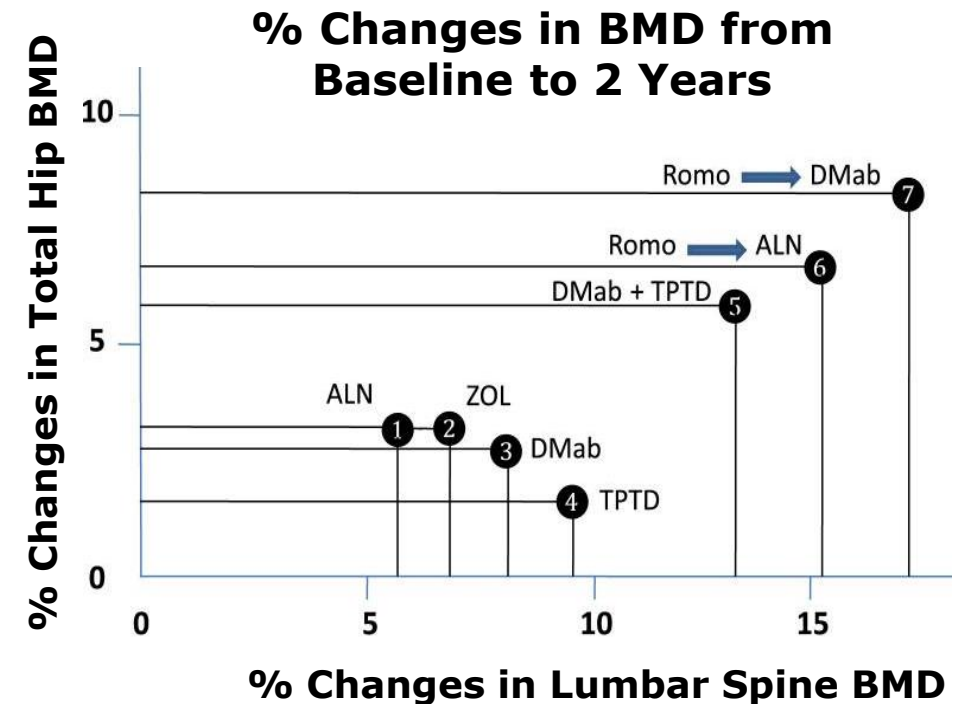


Case 2: 55 yo postmenopausal woman

- She completed 1 year of romosozumab. Now what?
- Returned to denosumab

	12/2021: T-score	12/2023: T-score
L1-L3 spine	-3.1	-2.6
L total hip	-1.7	-1.4
L femoral neck	-2.0	-2.0

...but plan to keep to ≤ 2 years.



Case 3

Case 3: 71 yo woman with vertebral fractures

- 71-year-old postmenopausal woman
 - T8 compression fracture from swinging a golf club in 5/2018
 - L1 compression fracture from hanging a mirror over her bathroom sink in 10/2018
 - DXA scan from 6/2018:
 - Never been treated previously

	T-score	Z-score	Comparison to 4/2001
L1-L4 spine	-3.8	-2.5	-24.0%
L total hip	-3.2	-2.1	-29.6%
L femoral neck	-3.0	-1.7	



Case 3: 71 yo woman with vertebral fractures

Her secondary work up was unremarkable. What is the best treatment option?

- A) Zoledronic acid
- B) Denosumab
- C) Teriparatide/abaloparatide
- D) Romosozumab
- E) C or D



Case 3: 71 yo woman with vertebral fractures

Her secondary work up was unremarkable. What is the best treatment option?

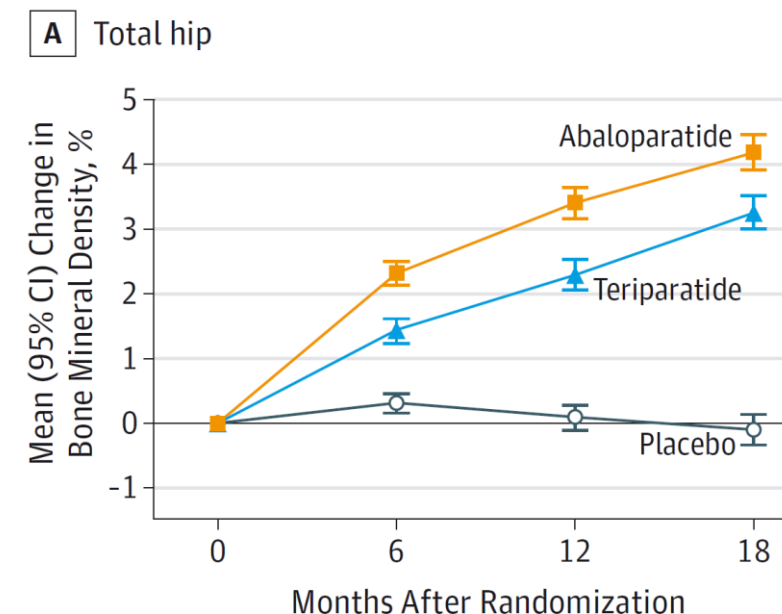
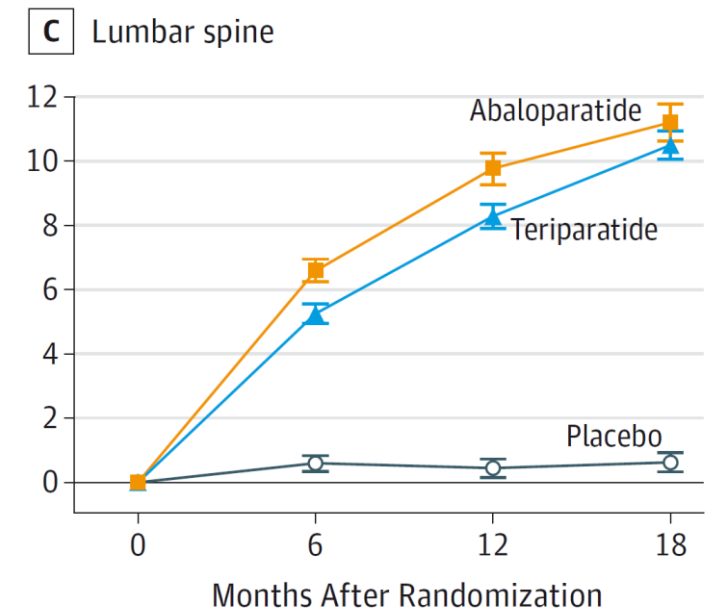
- A) Zoledronic acid
- B) Denosumab
- C) Teriparatide/abaloparatide
- D) Romosozumab
- E) **C or D:** anabolic agents are more effective than at reducing vertebral fractures than bisphosphonates (oral) and starting with anabolic agents before antiresorptive agents results in greater gains in BMD



Anabolic Agents: parathyroid hormone-based therapies

- Teriparatide (PTH) vs. Abaloparatide (PTHrP)
- Daily subcutaneous injections

	Abaloparatide vs. placebo	Teriparatide vs. placebo	Abaloparatide vs. teriparatide
Vertebral fracture	0.14 (0.05-0.39)	0.20 (0.08-0.47)	
Nonvertebral fracture	0.57 (0.32-1.00)	0.72 (0.42-1.22)	0.79 (0.43-1.45)
Major osteoporotic fracture	0.30 (0.15-0.61)	0.67 (0.39-1.14)	0.45 (0.21-0.95)

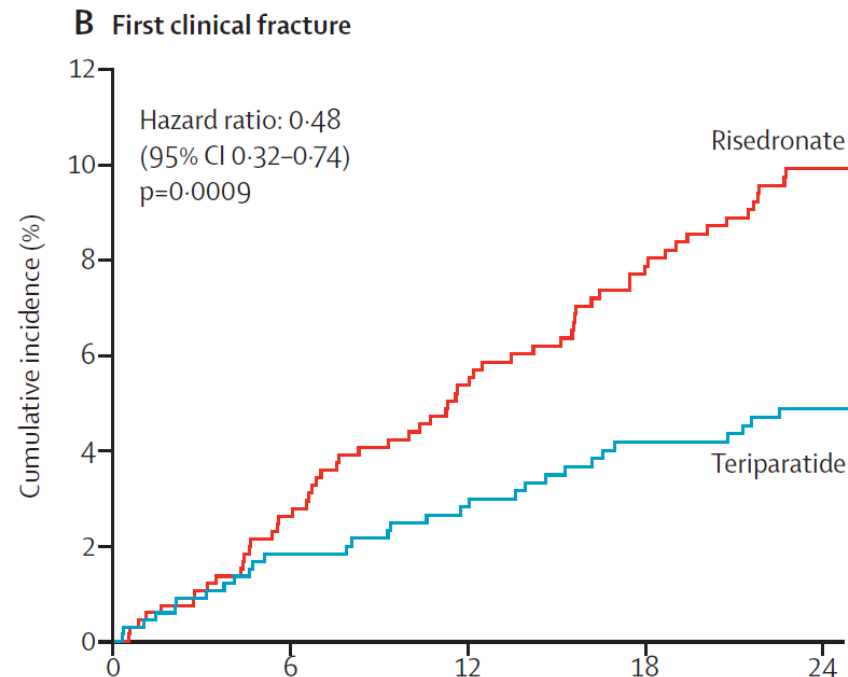
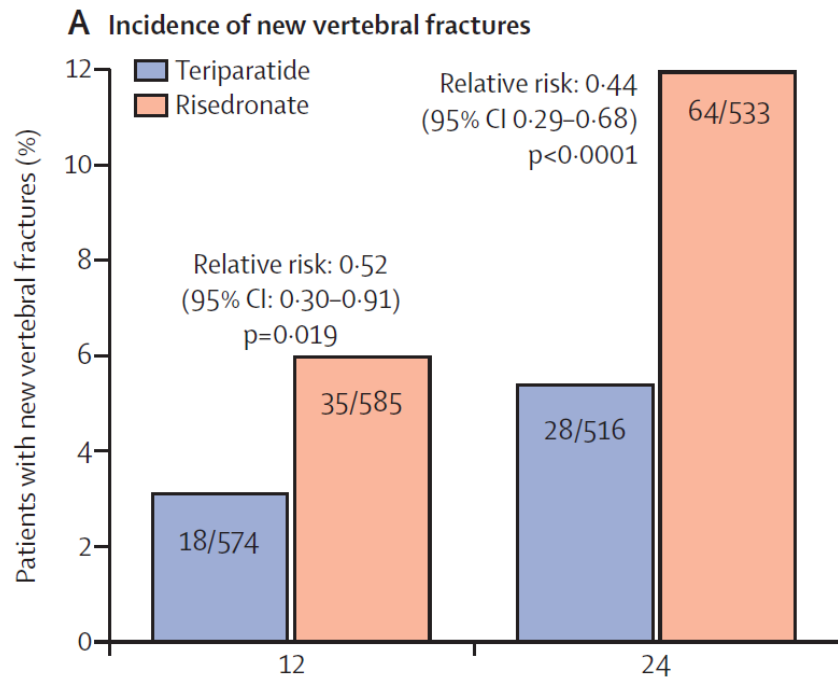


Parathyroid hormone-based therapies

- *Prior* black box warning: osteosarcoma noted in rats
 - *2-year lifetime limit removed from teriparatide!*
 - Still avoid in patients with Paget's disease, bone metastases or history of skeletal malignancies, prior radiation therapy involving the bone
- Other precautions: hypercalcemia, primary hyperparathyroidism, nephrolithiasis, hypercalciuria
- Adverse effects: dizziness, palpitations, headaches, nausea, and leg cramps



PTH-based Therapies are More Effective than Oral Bisphosphonates in Patients with Vertebral Fractures



Teriparatide vs. risedronate for 2 years in 1,360 postmenopausal women with history of vertebral fracture(s)



Sequence Matters

Use anabolic agents PRIOR to anti-resorptive agents
to get the most gains in BMD

Treatment paradigm	% Change in total hip BMD during TPTD/PTH treatment			
	6 mo	12 mo	18 mo	24 mo
Alendronate (mean 29.3 mo) → TPTD (18 mo)	-1.8%	-1.0%	+0.3%	-
Alendronate (median 29.2 mo) → TPTD (24 mo)	-1.2%	-0.6%	+0.6%	+2.1%
Risedronate (median 23.4 mo) → TPTD (24 mo)	-1.6%	-0.4%	+0.9%	+2.9%
Risedronate (mean 37.2 mo) → TPTD (12 mo)	-1.2%	-0.3%	-	-
Alendronate (mean 38.0 mo) → TPTD (12 mo)	-1.9%	-1.7%	-	-
Alendronate (mean 45.7 mo) → TPTD (18 mo)	-0.8%	-	+0.9%	-
Teriparatide (treatment naïve)		+2%	+3%	



Case 3: 71 yo woman with vertebral fractures

- Started abaloparatide in 12/2018, completed 2 years
- DXA scans:

	12/2019 T-score	11/2020 T-score
L1-L4 spine	-3.1 (+11.9%)	-2.8 (+4.5%)
L total hip	-2.7 (+10.3%)	-2.5 (+3.8%)
L femoral neck	-2.5	-2.2

Plan to follow with bisphosphonates, was reluctant but agreed on alendronate



Case 3: 71 yo woman with vertebral fractures

- DXA scan, 11/2021:

	11/2021 T-score
L1-L4 spine	-3.5 (-10.7%)
L total hip	-2.8 (-4.2%)
L femoral neck	-2.5

She never ended up starting the alendronate!

Started teriparatide in 1/2022.

Must be followed by an antiresorptive therapy!



When to Use Anabolic Agents

- Recommended for patients with very high risk of fracture
 - Very low bone density, esp. at the spine (before antiresorptive therapy)
 - History of fragility fracture, esp. vertebral fracture (VERO trial)
 - Failed other osteoporosis therapies
 - Prolonged antiresorptive therapy (no ONJ, AFF)



How to Choose Therapy

- For most patients, consider bisphosphonates (oral or IV) or denosumab
 - Ibandronate or raloxifene for patients with only spinal concerns
- For *very* high-risk patients, consider PTH analogs, romosozumab, denosumab, and zoledronate:
 - Recent fracture (within past 12 months)
 - Fracture while on osteoporosis therapy
 - Multiple fractures
 - Fractures while on drugs with skeletal harm (eg glucocorticoids)
 - Very low T-score (<-3.0)
 - High risk of falls or history of injurious falls
 - Very high FRAX (>30%, >4.5%)



Key Points

- A major osteoporotic fracture (spine, hip) should trigger osteoporosis treatment, regardless of BMD results.
- The benefits of osteoporosis treatments far outweigh the risks of ONJ and AFF.
- Denosumab should not be stopped without being followed by a different medication for osteoporosis.
- Consider anabolic agents in patients with very low bone density (prior to anti-resorptive treatments) or history of vertebral fractures.



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