Brigham and Women's Hospital
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# Bone Health in 2026

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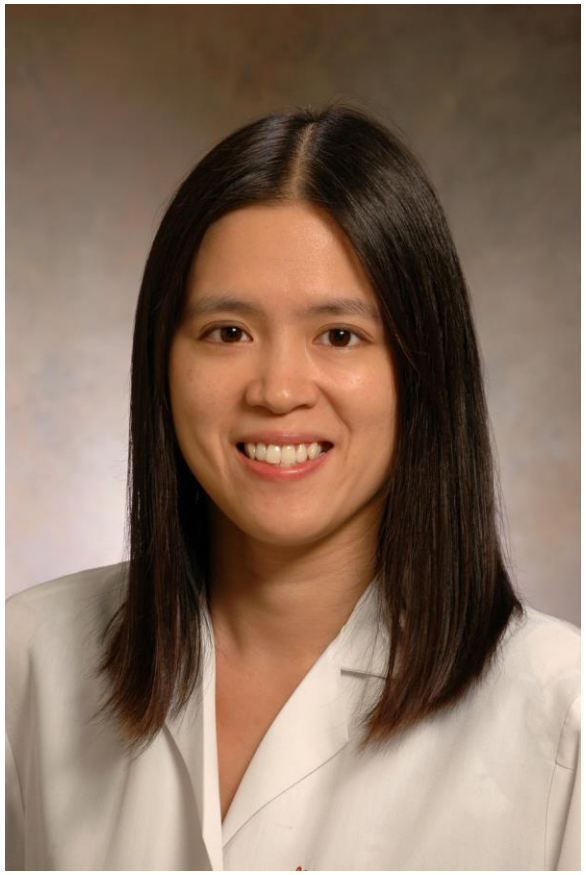
# Sharon H. Chou, MD



- University of Illinois College of Medicine at Rockford
- Internal Medicine Residency at Beth Israel Deaconess Medical Center in Boston
- Endocrinology Fellowship at University of Chicago
- Assistant Professor, Harvard Medical School
- Associate Physician, Brigham and Women's Hospital
  —Clinical focus:  osteoporosis

# Disclosures

Shire Pharmaceuticals (not relevant)

# 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

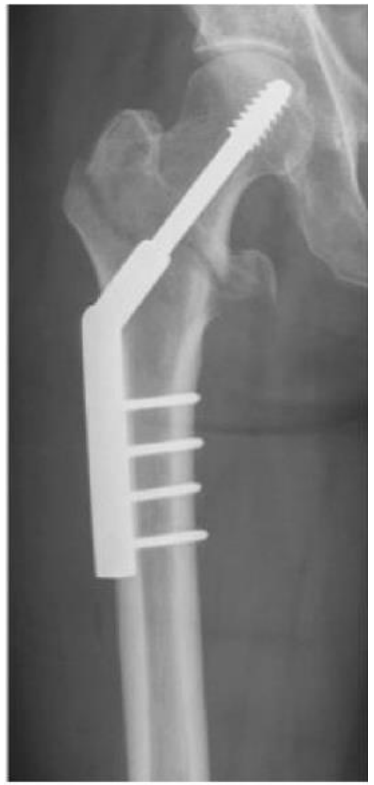
- 62-year-old postmenopausal woman with history of lupus, diagnosed at age 19 years old and treated with glucocorticoids for the first 10 years, and GERD on PPI
  - Gyn history: irregular menses while on glucocorticoids, menopause at 48 years old
  - No history of fracture
  - Screening DXA:

**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.



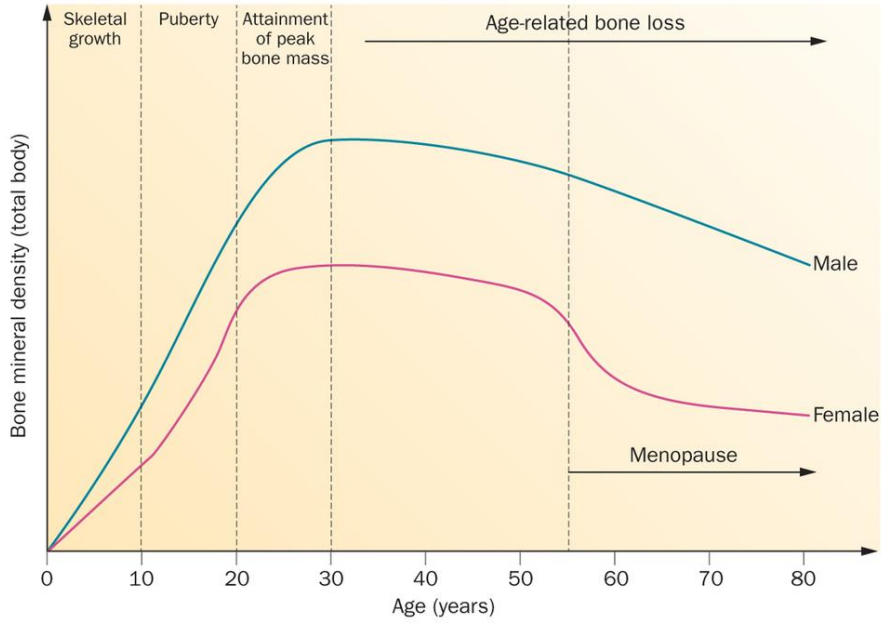
**Osteoporosis is a defined as a skeletal disorder characterized by *compromised bone strength* predisposing a person to an *increased risk of fracture***

NIH Consensus Development Panel. *JAMA.* 2001;285(6).

# Bone Strength is Determined by Bone Density AND Bone Quality

## Bone Density

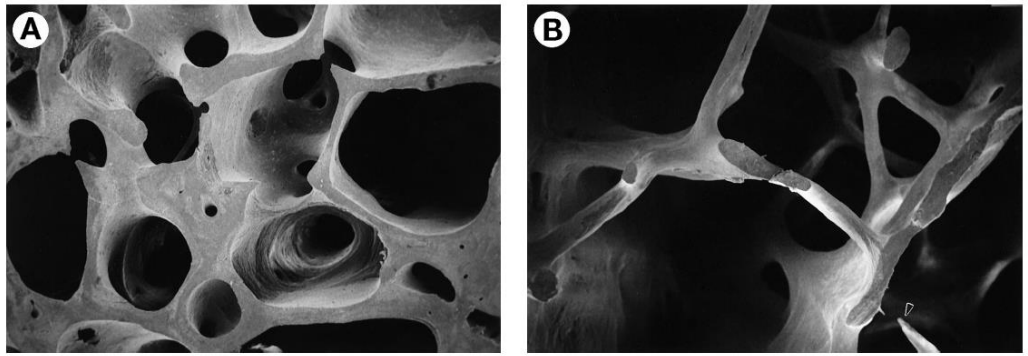
- Peak bone density
- Amount of bone loss




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

## Bone Quality

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

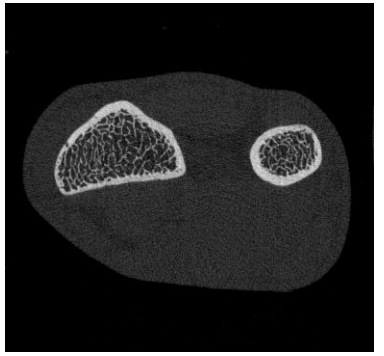



Dempster. *J Bone Miner Res.* 2000;15(1).
NIH Consensus Development Panel. *JAMA. 2001;285(6).*

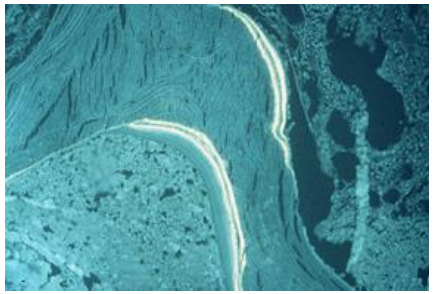
# Bone Quality is More Difficult to Measure Clinically

## Bone Density

## Bone Quality

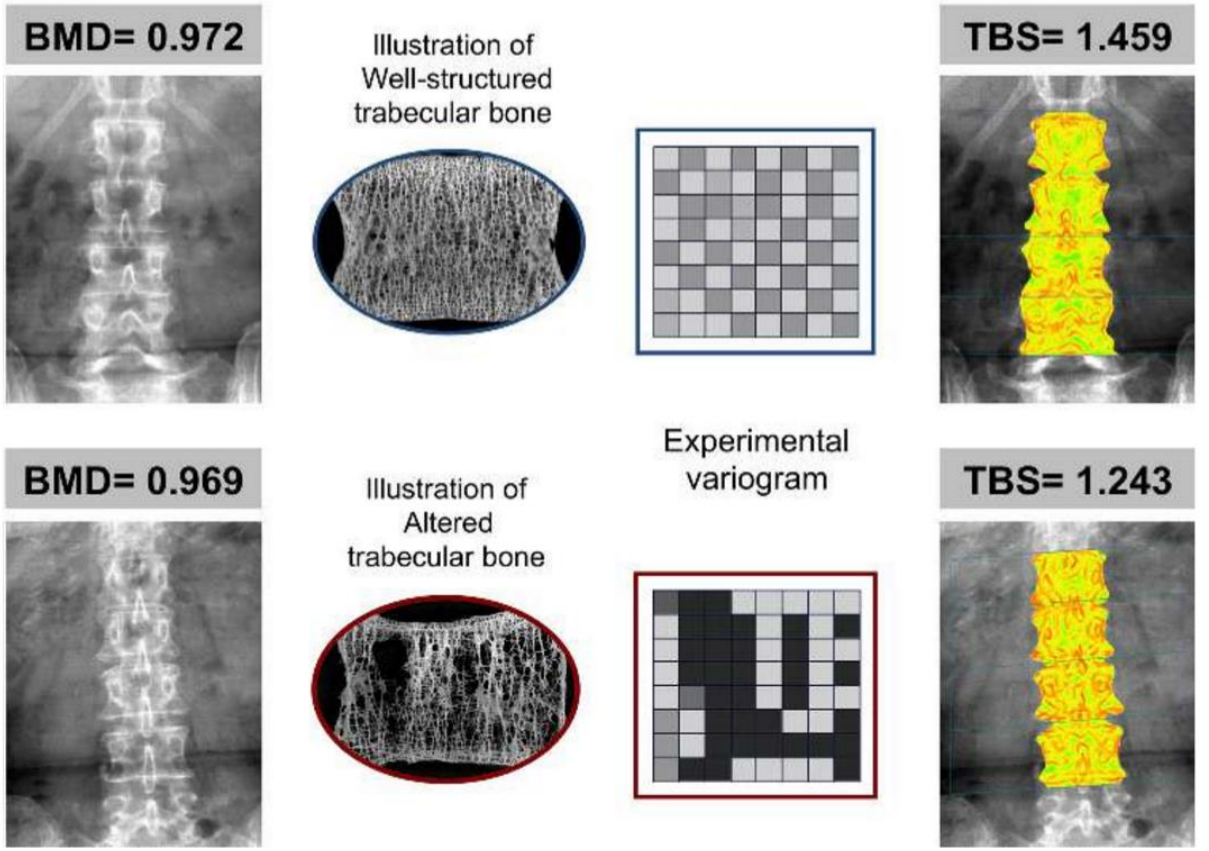


- Microarchitecture
  - High resolution peripheral quantitative CT (HR-pQCT)
  - Trabecular bone score (TBS)
- Turnover:
  - Bone biopsy with double tetracycline labeling
  - Serum, urine markers
- Accumulation of damage: ?
- Mineralization:
  - Ca, phos, 25OHD, PTH
- Collagen:
  - Genetic testing (osteogenesis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



# Trabecular Bone Score Estimates Microarchitecture

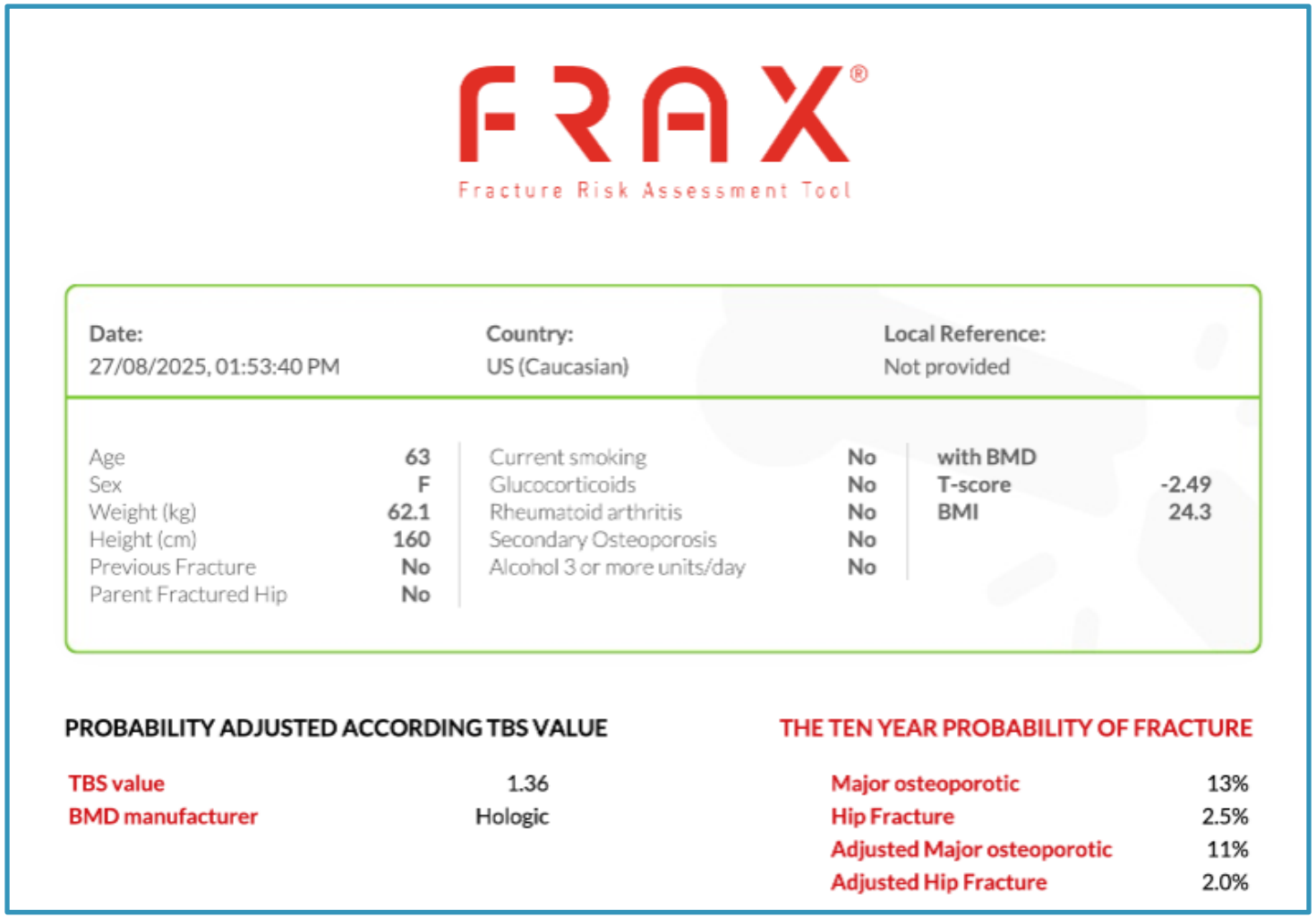
- Analytical, non-invasive measure of grey-level variation in lumbar spine DXA images to estimate 3D textural characteristics of vertebrae
- Higher TBS associated with better bone ***microarchitecture*** and lower risk of fractures




| | |
|---|---|
| **Normal** | **≥1.350** |
| **Partially degraded** | **1.2-1.350** |
| **Degraded** | **≤1.200** |

Silva et al. *J Bone Miner Res.* 2014;29(3).

# TBS predicts fracture risk independent of BMD and FRAX



FRAX®

Fracture Risk Assessment Tool

| Date: | Country: | Local Reference: |
|---|---|---|
| 27/08/2025, 01:53:40 PM | US (Caucasian) | Not provided |

| | | | | | |
|---|---|---|---|---|---|
| Age | 63 | Current smoking | No | with BMD | |
| Sex | F | Glucocorticoids | No | T-score | -2.49 |
| Weight (kg) | 62.1 | Rheumatoid arthritis | No | BMI | 24.3 |
| Height (cm) | 160 | Secondary Osteoporosis | No | | |
| Previous Fracture | No | Alcohol 3 or more units/day | No | | |
| Parent Fractured Hip | No | | | | |

**PROBABILITY ADJUSTED ACCORDING TBS VALUE**

| | |
|---|---|
| TBS value | 1.36 |
| BMD manufacturer | Hologic |

**THE TEN YEAR PROBABILITY OF FRACTURE**

| | |
|---|---|
| Major osteoporotic | 13% |
| Hip Fracture | 2.5% |
| Adjusted Major osteoporotic | 11% |
| Adjusted Hip Fracture | 2.0% |

***Particularly in patients with diabetes and long-term glucocorticoid use***

Leslie et al. *J Clin Endocrinol Metab.* 2013;98(2).
Iki et al. *J Bone Miner Res.* 2014;29(2).

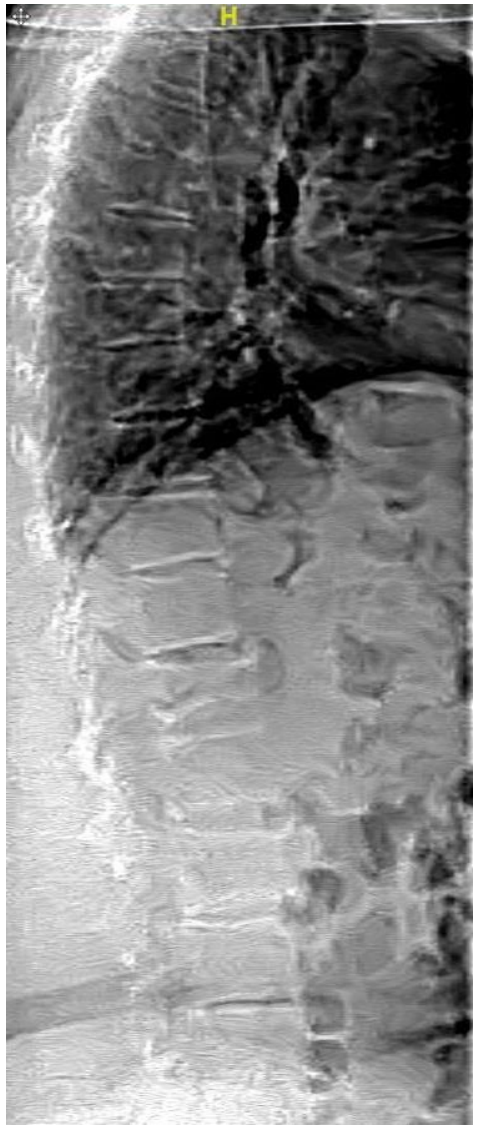
# Fraxplus.org

My FRAX | Free account | 4 Credits | Results | My Account | Purchase History | Log Out

## Price plans

| | VISITOR | FREE ACCOUNT | PRO | CLINICAL | DEVELOPER |
|---|---|---|---|---|---|
| FRAX® calculations | Unlimited<br>3 / minute | Unlimited<br>10 / minute | Unlimited<br>20 / minute | Unlimited<br>30 / minute | Unlimited |
| FRAXplus® adjustments | - | 5 | Unlimited<br>20 / minute | Unlimited<br>30 / minute | Unlimited |
| Adjustment history stored | - | ● | ● | ● | ● |
| Export as PDF | - | ● | ● | ● | ● |
| Multi-patient entry | - | - | - | 10,000 / year | 10,000 / year |
| API access to FRAX® | - | - | - | - | 5,000 / year |
| Number of users | - | 1 | 1 | 10 | 25 |
| **Price** | - | 0€ | 50€ / year<br>SUBSCRIBE | 400€ / year<br>CONTACT US | 4000€ / year<br>CONTACT US |

# 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

Rosen H. UpToDate. 2023.

# 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 ≥20%
  - 10-year probability of hip fracture ≥3%
- History of fragility fracture
  - **Hip or spine regardless of BMD**
  - Proximal humerus, pelvis, (wrist) if BMD is in the osteopenia range

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

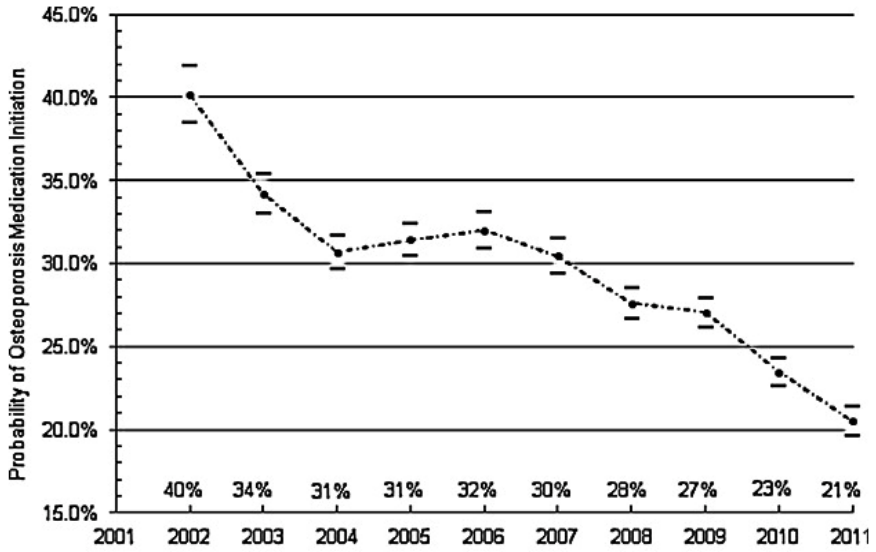
LeBoff et al. *Osteoporos Int.* 2022;33(10).
Camacho et al. *Endocr Pract.* 2020;26(Suppl 1).
Siris et al. *Osteoporos Int.* 2014;25(5).
Wainwright SA et al. *J Clin Endocrinol Metab.* 2005;90.

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

**Subsequent Fracture Rates, within 1 year of Index Fracture**

| Index fracture | Overall | Vertebral | Hip |
|---|---|---|---|
| **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?

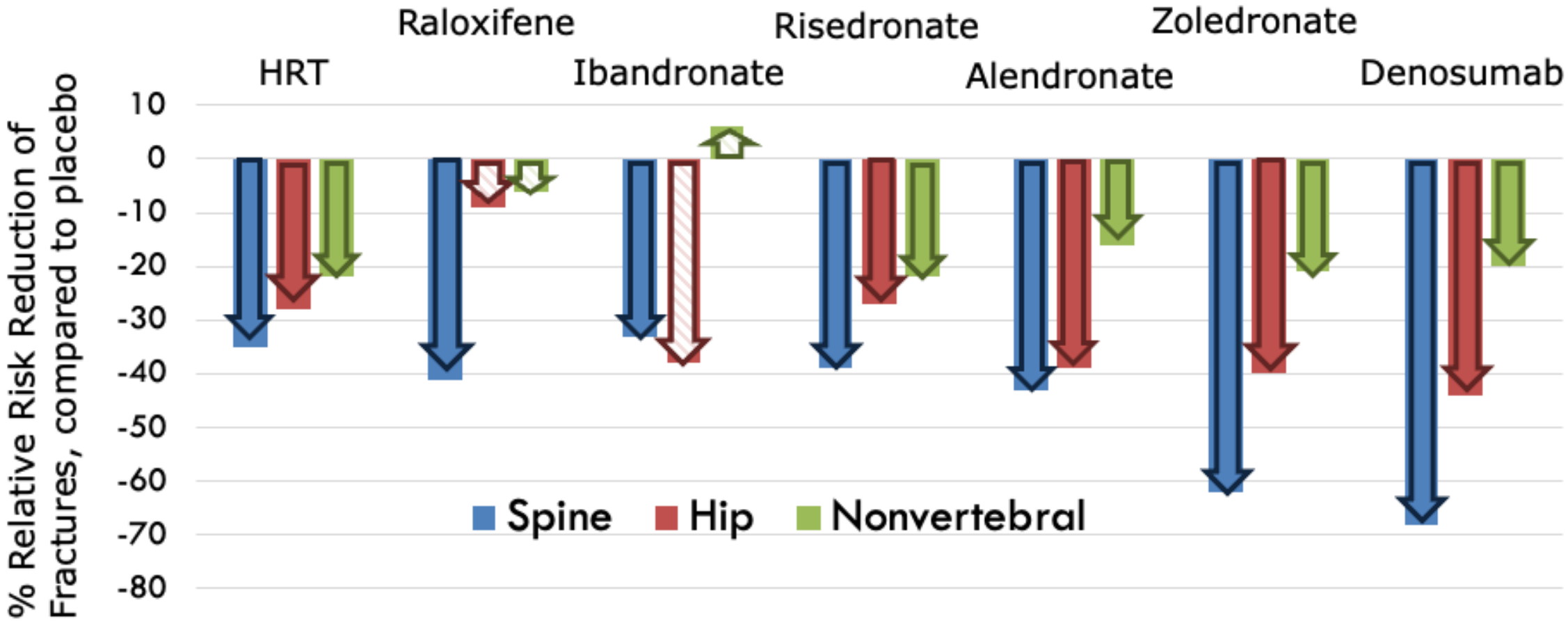
A) Hormone replacement therapy
B) Raloxifene
C) Alendronate
D) Zoledronic acid
E) Denosumab

# Case 1: 62-year-old postmenopausal woman

What do you now recommend?

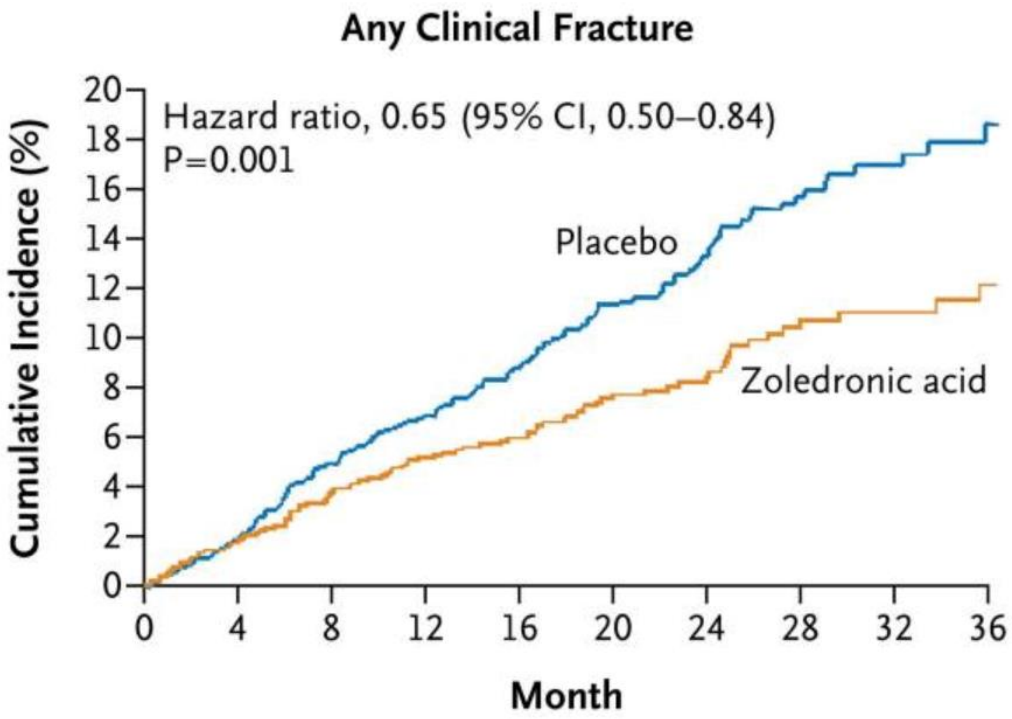
A) Hormone replacement therapy—>10 years out from menopause (and technically not FDA approved for osteoporosis treatment)
B) Raloxifene—has not been shown to reduce hip fractures
C) Alendronate—has a history of GERD
**D) Zoledronic acid**
E) Denosumab—an option but discontinuation remains a problem

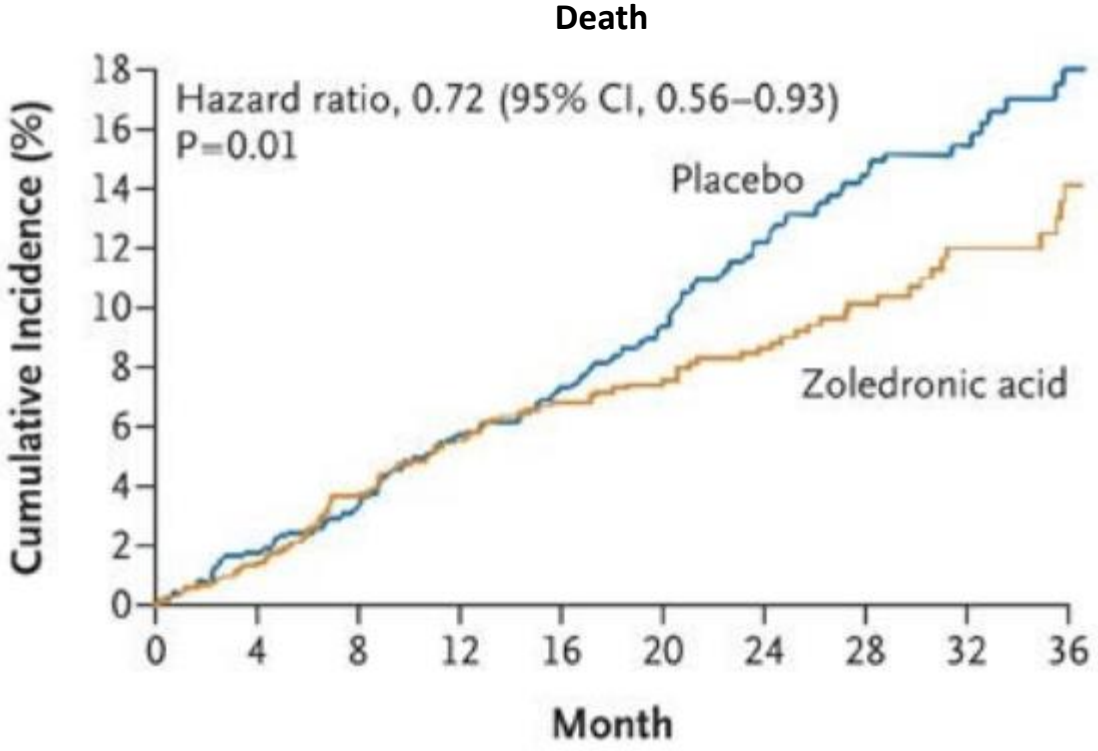
# Osteoporosis Medications are Very Effective at Preventing Fractures




Barrionuevo et al. *J Clin Endocrinol Metab.* 2019;104(5).

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




Reduced risks of:

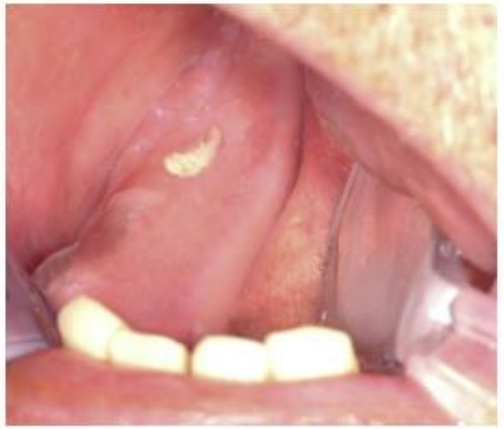
- Fractures by 35%
- Vertebral fractures by 46%

***Reduces mortality by 28%!***

Lyles KW, et al. *N Engl J Med*. 2007;357(18).

# 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: ≤0.05% (≤5 per 10,000)
  - IV bisphosphonates: ≤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

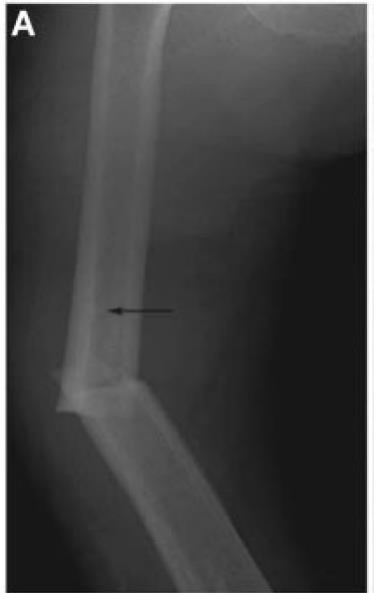
American Association of Oral and Maxillofacial Surgeons' Position Paper on ONJ, 2022:

- "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

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

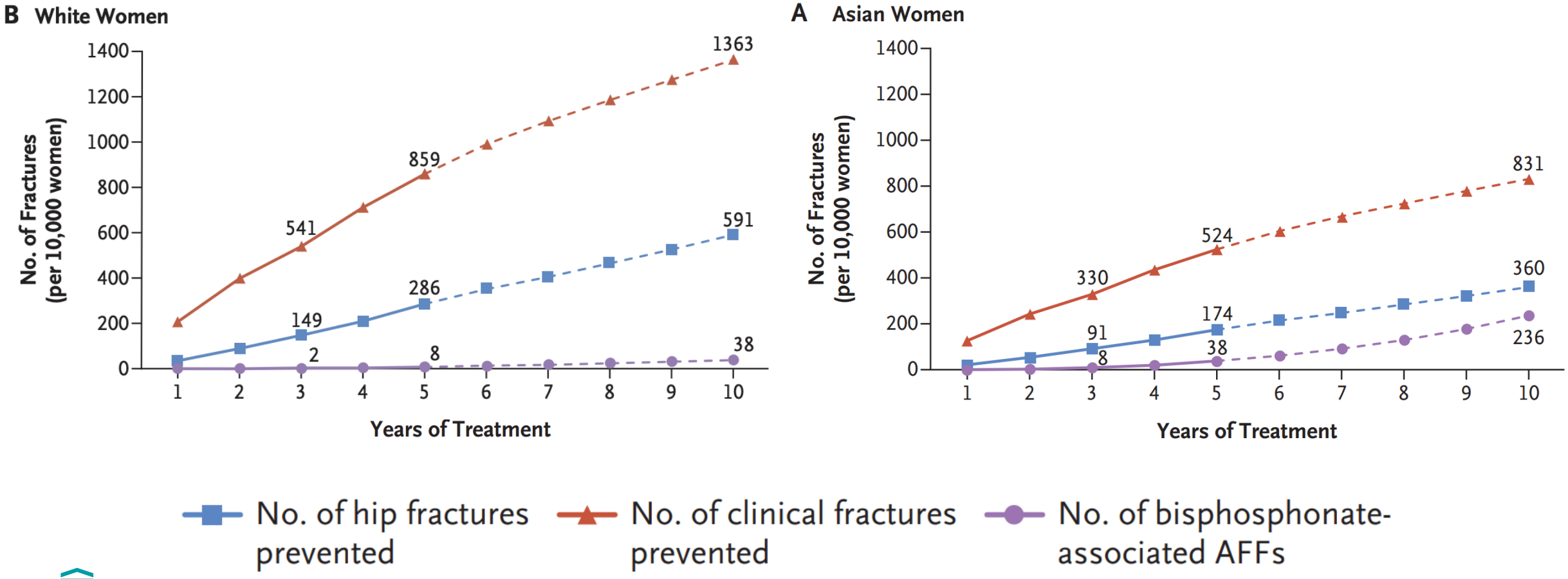
# Atypical Femur Fractures are Also Very Rare

- 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




Shane et al. *J Bone Miner Res.* 2014;29(1).

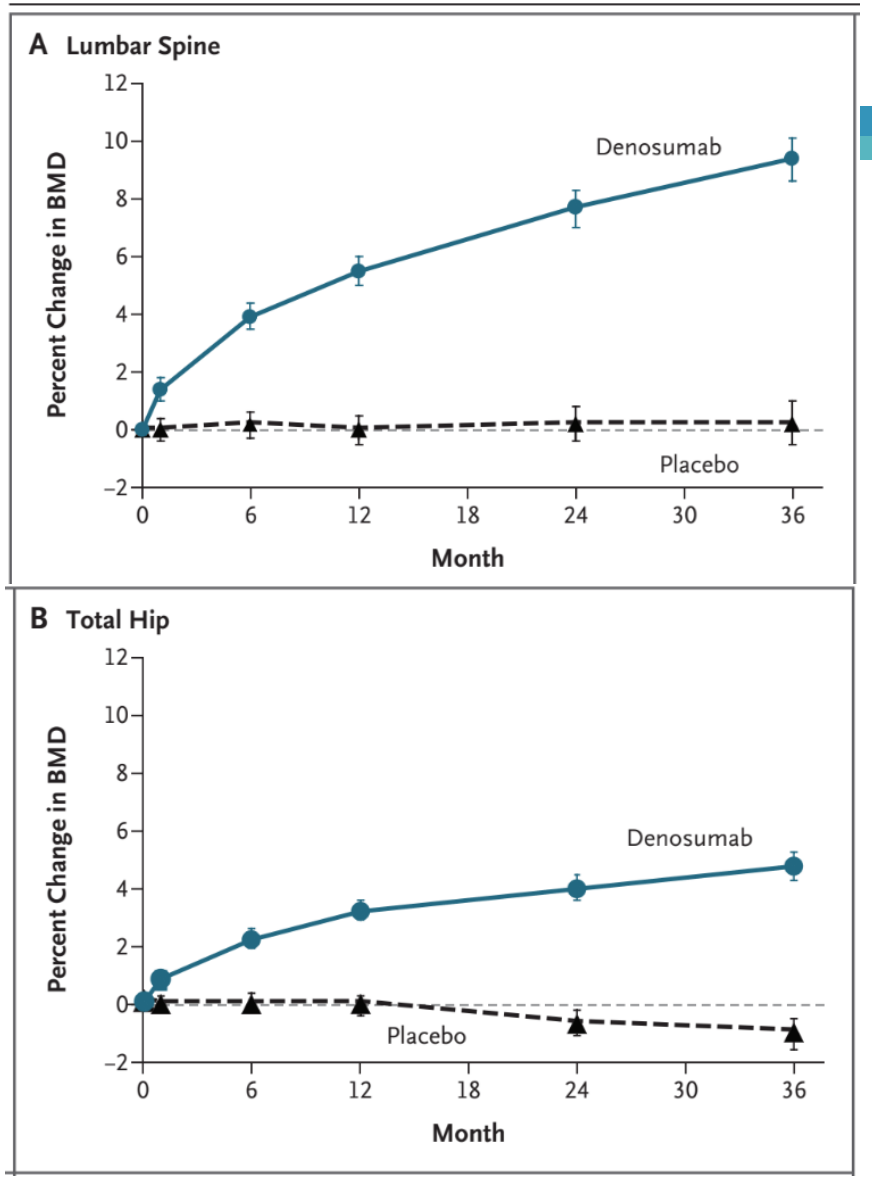
# Bisphosphonates prevent many more fractures than cause AFFs, but there are racial differences




Black et al. *N Engl J Med.* 2020;383(8).

# Denosumab

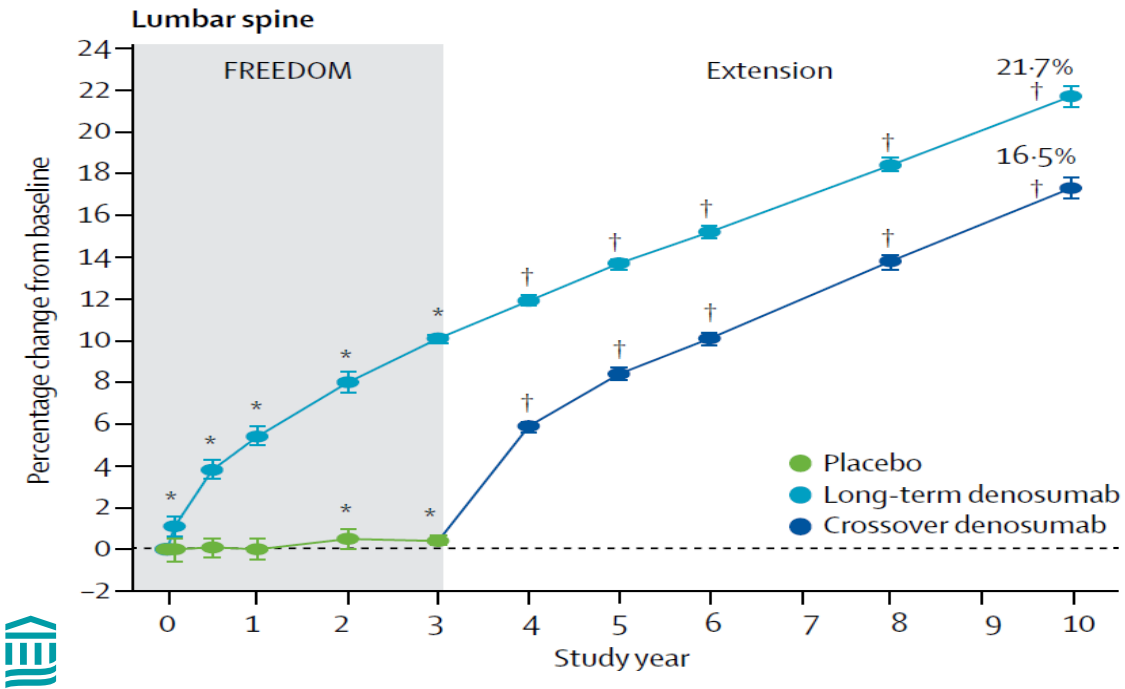
- Antibody that binds and inhibits RANKL, which regulates osteoclastic bone resorption
- Reduces risk of vertebral fractures by 68% and hip fractures by 40% over 3 years
- Okay to use in renal insufficiency
- Adverse events:
  - Hypocalcemia
  - Rashes
  - Cellulitis
  - ONJ, AFF



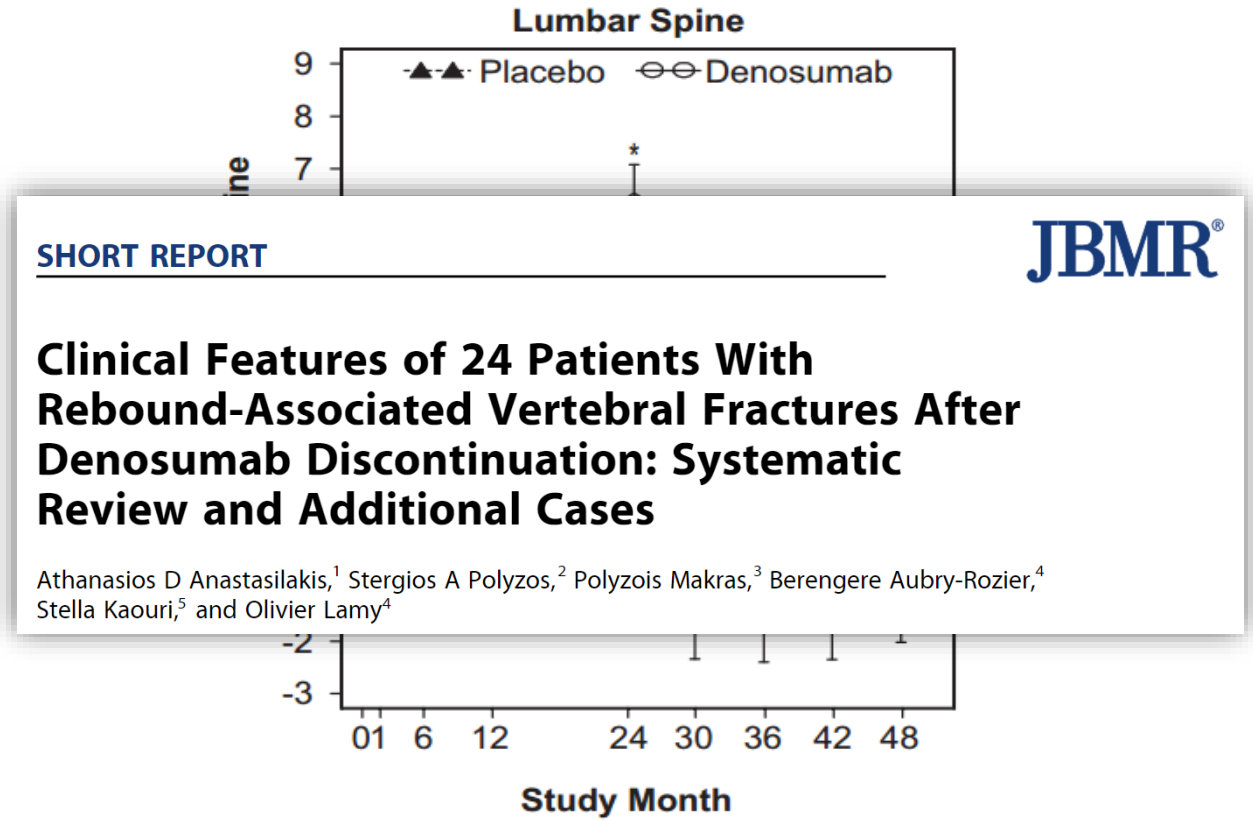

Cummings et al. *N Engl J Med.* 2009;361(8).

# Denosumab vs. Bisphosphonates

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




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




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 Lamy[4]

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

**For young patients, try to avoid or limit to ≤2 years.**

**For older patients (~80+ yo) at high risk of fracture, plan to continue denosumab indefinitely.**

Tsourdi et al. *J Clin Endocrinol Metab.* 2021;106(1)

# 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 |

- No further fractures

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

Adler et al. *J Bone Miner Res.* 2016;31(1).

# Case 2

# Case 2: 65 yo postmenopausal woman

- 65-year-old otherwise healthy postmenopausal woman referred for osteoporosis
  - DXA scan, 5/2021:

| | T-score |
|---|---|
| L1-L4 spine | -3.7 |
| L femoral neck | -2.9 |

  - Shortly afterwards, sustained a T12 compression fracture while learning how to golf

# Secondary Work-up is Recommended Prior to Osteoporosis Treatment

## Basic

- CBC: normal
- Chem: Ca 9.8, phos 3.1, Cr 0.99
- LFTs: alk phos 69, alb 4.0
- 25OHD: 54 ng/mL
- PTH: 40 (15-65)
- 24-hour urine calcium: 74 mg

## As clinically indicated

- TSH: 0.69
- TTg IgA: negative
- SPEP/UPEP: negative
- Iron/ferritin
- Homocysteine
- Prolactin
- Total testosterone (men)
- 24-hour urine free cortisol
- Tryptase: 2.8
- Urinary histamine
- Bone turnover markers

BHOF Bone Health & Osteoporosis FOUNDATION™

LeBoff et al. *Osteoporos Int.* 2022;33.

# Case 2: 65 yo postmenopausal woman

With an unremarkable secondary work up, what is the best treatment option?

A) Raloxifene
B) Alendronate
C) Zoledronic acid
D) Denosumab
E) Teriparatide/Abaloparatide

# Case 2: 65 yo postmenopausal woman

With an unremarkable secondary work up, what is the best treatment option?

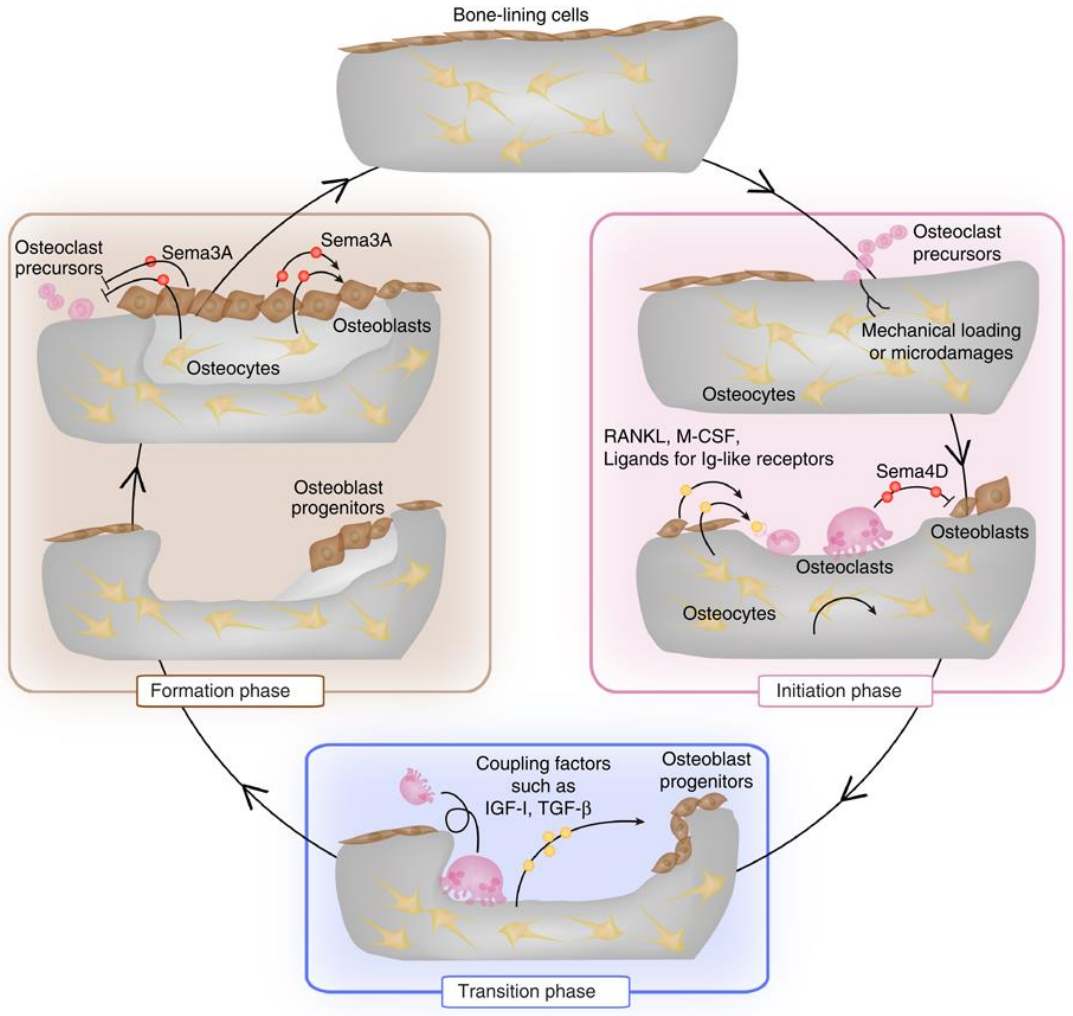
A) Raloxifene
B) Alendronate
C) Zoledronic acid
D) Denosumab
E) Teriparatide/Abaloparatide—starting with an anabolic agent first will maximize gains in BMD and teriparatide has been shown to be more effective than risedronate in reducing fractures in women with history of vertebral fractures

# Categories of Pharmacologic Treatment

***Antiresorptive therapies***
block osteoclastic bone resorption.

***Anabolic therapies***
promote osteoblastic bone formation.

***Dual action***

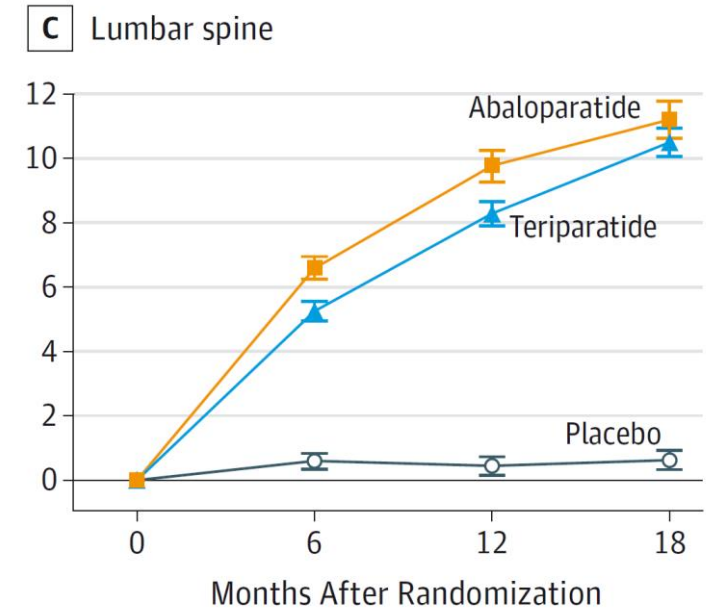


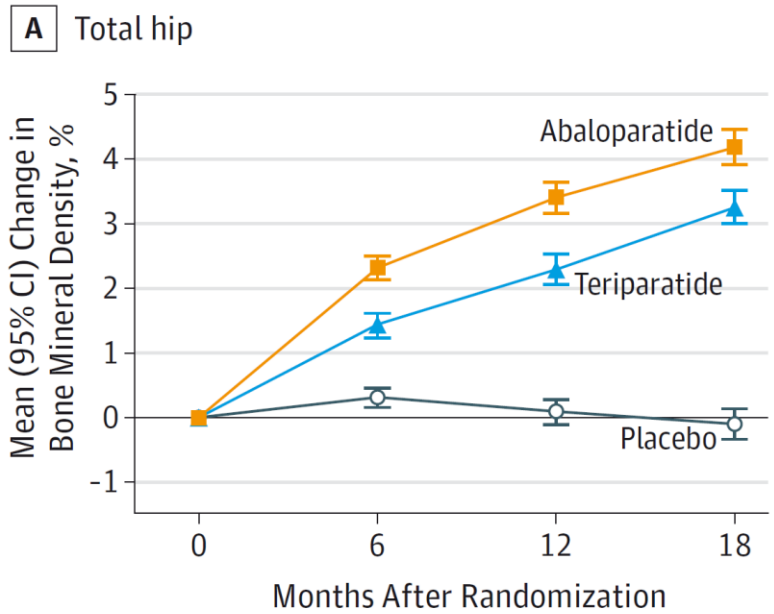

Negishi-Koga et al. *Bonekey Rep.* 2012.

# 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) |




Miller et al. *JAMA.* 2016;316(7).

# 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

***Must be followed by antiresorptive therapy!***

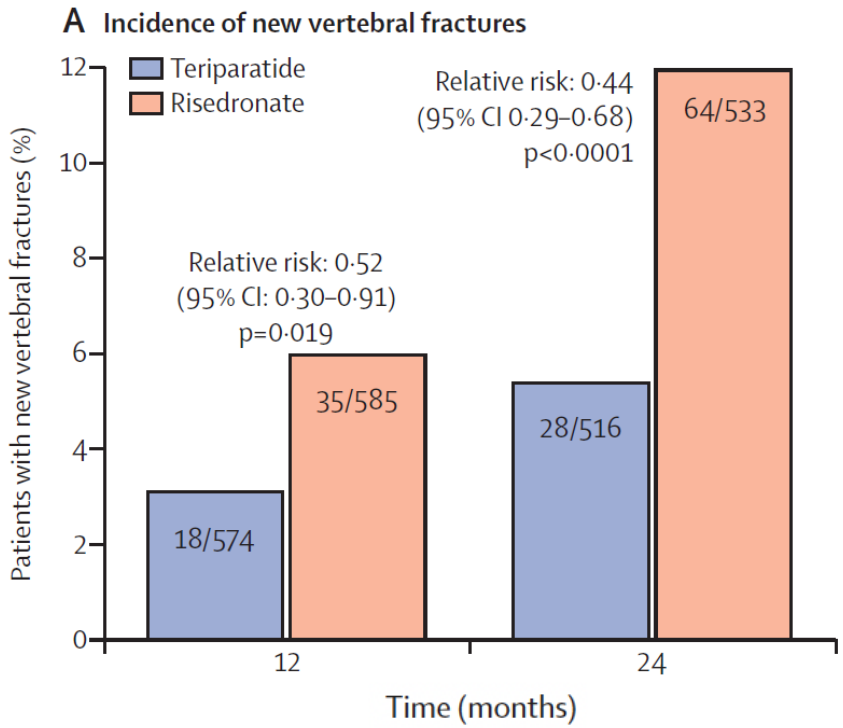
# Use Anabolic Agents *prior* to Anti-resorptive Agents to Get the Most Gains in BMD

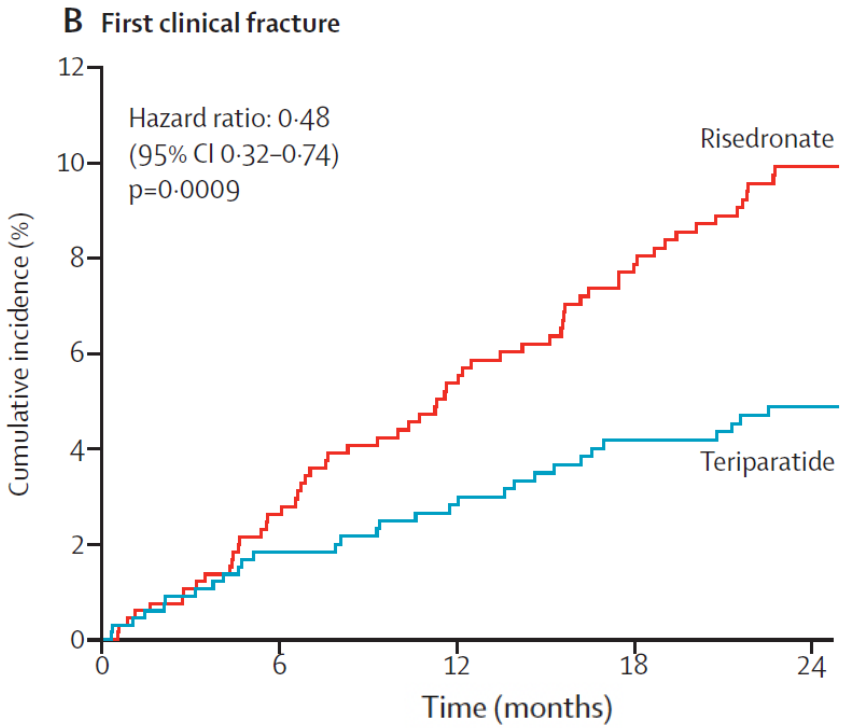
| Treatment paradigm | % Change in total hip BMD during TPTD/PTH treatment | | | |
|---|---|---|---|---|
| | 6 mo | 12 mo | 18 mo | 24 mo |
| Alendronate (mean 29.3 mo) → TPTD (18 mo) | −1.8% | −1.0% | +0.3% | – |
| Alendronate (median 29.2 mo) → TPTD (24 mo) | −1.2% | −0.6% | +0.6% | +2.1% |
| Risedronate (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%** | |

Cosman et al. *J Bone Miner Res*. 2017;32(2).

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

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




Kendler et al. *Lancet.* 2018;391(10117).

# Case 2: 65 yo postmenopausal woman

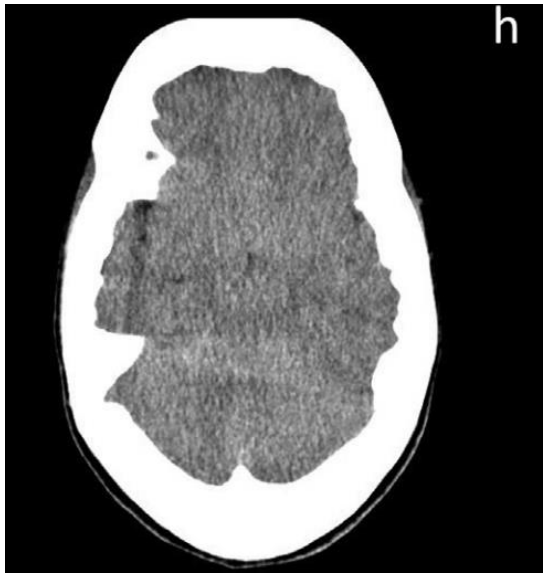
- Tried abaloparatide, stopped due to vomiting, dizziness, and headaches
- Also could not tolerate teriparatide

**What now?**

# The NEW Anabolic Agent (technically dual agent): Romosozumab

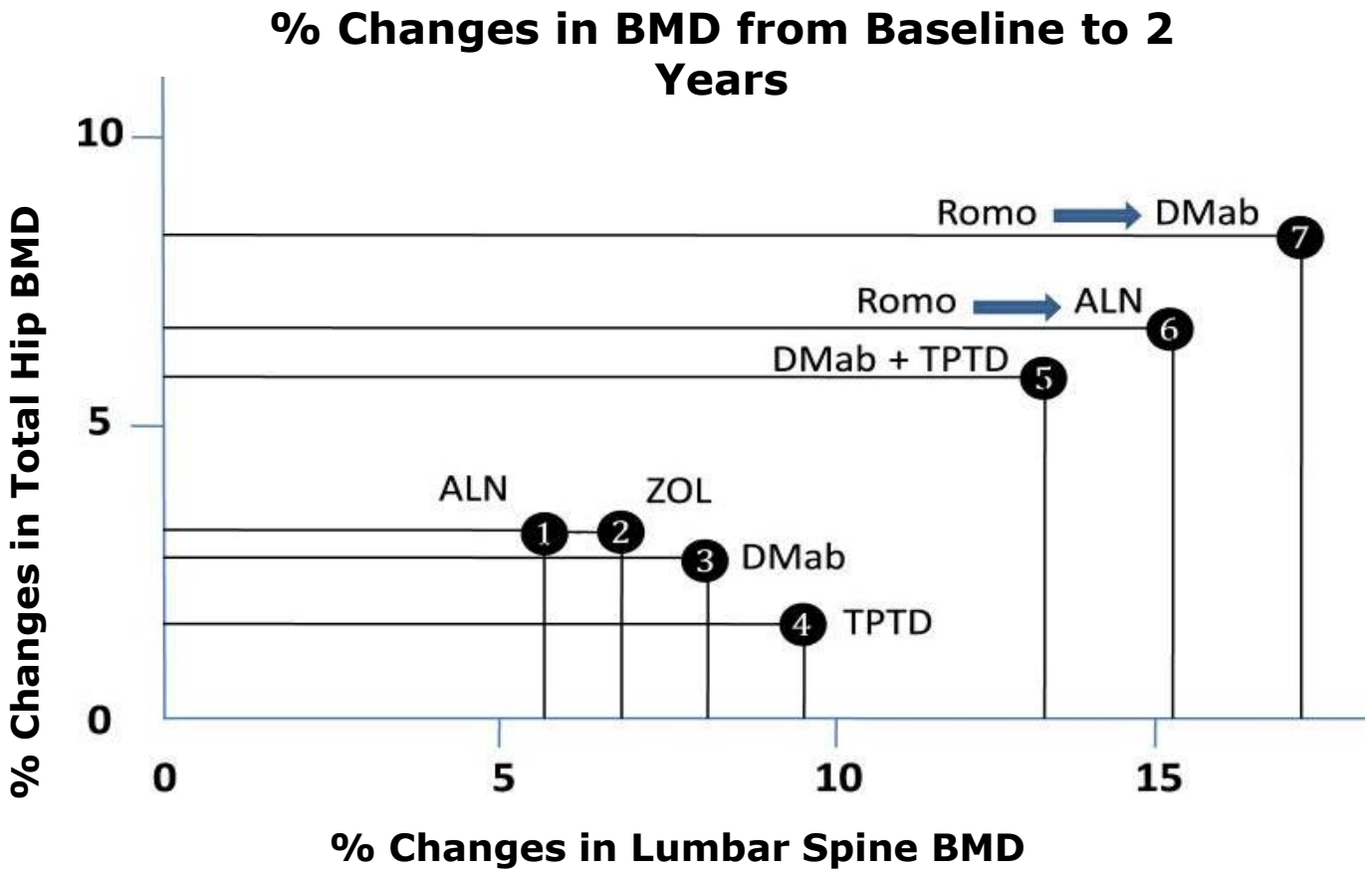
- FDA approved in 2019 *for women only*
- Monthly subcutaneous injection for 12 months
- Based on the disease sclerosteosis, a rare genetic disorder with high bone mass due to loss-of-function mutation in SOST
- Sclerostin is produced by osteocytes, inhibits bone formation and enhances bone resorption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

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


Whyte et al. *Bone.* 2018;116.

# Romosozumab Increases Bone Density the Most

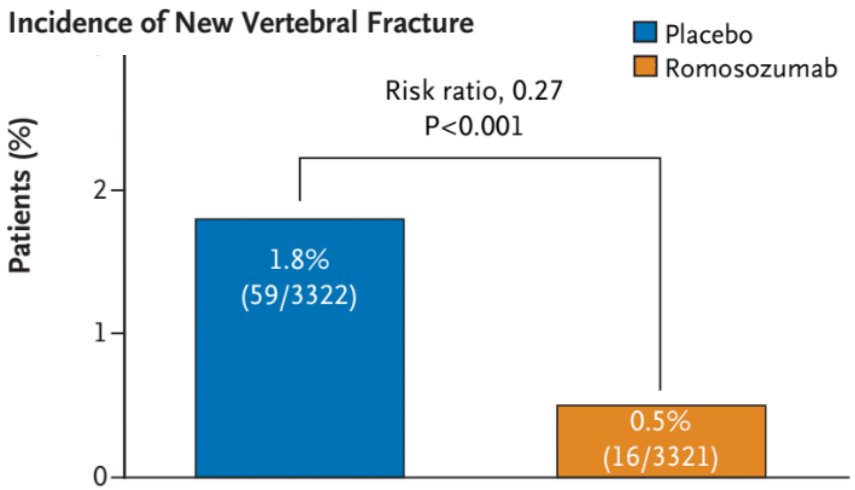



McClung et al. *Osteoporos Sarcopenia.* 2018; 4(1).

# Romosozumab Reduces Fractures Effectively

## FRAME

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

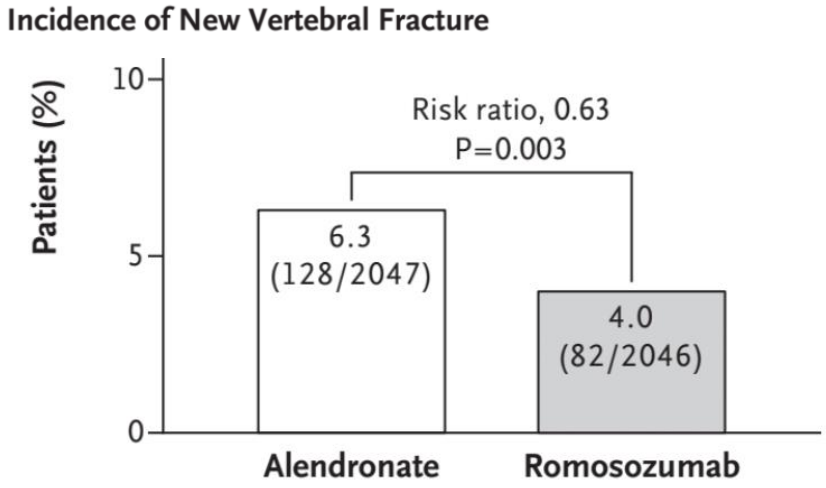



36% reduction in clinical fractures (1.6 v. 2.5%)

Cosman et al. *N Engl J Med.* 2016;375(16).

## ARCH

Vs. alendronate for 12 mo, followed by alendronate




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

Saag et al. *N Engl J Med*. 2017;377(15).

# 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.

Cosman et al. *N Engl J Med.* 2016;375(16).
Saag et al. *N Engl J Med*. 2017;377(15).

# Case 2: 65 yo postmenopausal woman

- Started romosozumab, completed 12- month course
- DXA scan, 4/2023:

| | T-score | Comparison to 5/2021 |
|---|---|---|
| L1-L4 spine | -2.9 | 13.5% increase |
| L total hip | | 6.6% increase (nonsig) |
| L femoral neck | -2.6 | |

- No new fractures

**What now?**

# Case 2:

- All anabolic therapies need to be followed by anti-resorptive agents
- Transitioned to zoledronate, which she received in 10/2023, 12/2024, and 1/2026
- DXA scan, 4/2024:

| | T-score | Comparison to 10/2021 |
|---|---|---|
| L1-L4 spine | -2.7 | Stable |
| L total hip | | Stable |
| L femoral neck | -2.4 | |

- No new fractures

# 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%)


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

# MOC Reflective Statement

- 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.
- Consider anabolic agents in patients with very low bone density (ideally prior to anti-resorptive treatments) or history of vertebral fractures.

# References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- Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2016;31(1).