



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

Osteoporosis and Metabolic Bone Disease

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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 - Clinical focus: osteoporosis



Disclosures

Shire Pharmaceuticals (not relevant)



Learning Objectives

- Identify patients who should be screened for osteoporosis
- Understand the rare complications of osteoporosis treatments
- Assess need for non-bisphosphonate osteoporosis treatments



Case 1

Case 1: 62 yo postmenopausal woman

- 62-year-old postmenopausal woman
 - Ankle fracture from a fall down the stairs in 1/2005 (at 51 years old)
 - 5th metatarsal fracture from a misstep in 12/2007 (at 53 years old)
 - Screening DXA, 4/2016:

	T-score	Z-score
L1-L4 spine	-1.6	0.0
R total hip	-1.6	-0.3
R femoral neck	-2.3	-0.3

When should we start screening?



DXA is Indicated in Patients at High Risk for Fractures

- All women ≥ 65 years old and men ≥ 70 years old
- Adults who have a fracture at age ≥ 50 years old
- Younger post/perimenopausal women and men aged 50-69 years with clinical risk factors
- Adults with a condition or taking a medication associated with low bone mass or bone loss



There are Many Risk Factors for Fractures

Table 1 Conditions, diseases, and medications that cause or contribute to osteoporosis and/or fractures [27]

Lifestyle factors	Hypogonadal states	Gastrointestinal disorders	Rheumatologic and autoimmune diseases	Medications
Alcohol abuse	Anorexia nervosa	Celiac disease	Ankylosing spondylitis	Aluminum-containing antacids
Excessive thinness	Androgen insensitivity	Bariatric surgery	Other rheumatic and autoimmune diseases	Androgen deprivation therapy
Excess vitamin A	Female athlete triad	Gastric bypass	Rheumatoid arthritis	Anticoagulants (unfractionated heparin)
Frequent falling	Hyperprolactinemia	Gastrointestinal surgery	Systemic lupus	Anticonvulsants (e.g. phenobarbital, phenytoin, valproate)
High salt intake	Hypogonadism	Inflammatory bowel disease including Crohn's disease and ulcerative colitis	Neurological and musculoskeletal risk factors	Aromatase inhibitors
Immobilization	Panhypopituitarism	Malabsorption syndromes	Epilepsy	Barbiturates
Inadequate physical activity	Premature menopause (<40 years)	Pancreatic disease	Muscular dystrophy	Cancer chemotherapeutic drugs
Low calcium intake	Turner's & Klinefelter's syndromes	Primary biliary cirrhosis	Multiple sclerosis	Cyclosporine A and tacrolimus
Smoking (active or passive)			Parkinson's disease	Glucocorticoids (≥ 5.0 mg/day prednisone or equivalent for ≥ 3 months)
Vitamin D insufficiency/deficiency			Spinal cord injury	GnRH (Gonadotropin releasing hormone) agonists and antagonists
			Stroke	Depot medroxyprogesterone acetate (Depo-Provera)
Genetic diseases	Endocrine disorders	Hematologic disorders	Miscellaneous conditions and diseases	Methotrexate
Cystic fibrosis	Obesity	Hemophilia	HIV/AIDS	Parenteral nutrition
Ehlers-Danlos	Cushing's syndrome	Leukemia and lymphomas	Amyloidosis	Proton pump Inhibitors
Gaucher's disease	Diabetes mellitus (Types 1 & 2)	Monoclonal gammopathies	Chronic metabolic acidosis	Selective serotonin reuptake inhibitors
Hemochromatosis	Hyperparathyroidism	Multiple myeloma	Chronic obstructive lung disease	Tamoxifen (premenopausal use for breast cancer treatment)
Hypophosphatasia	Thyrotoxicosis	Sickle cell disease	Congestive heart failure	Thiazolidinediones (such as pioglitazone and rosiglitazone)
Hypophosphatemia		Systemic mastocytosis	Depression	Thyroid replacement hormone (in excess)
Marfan syndrome		Thalassemia	Renal disease (CKD III– CKD V/ESRD)	
Menkes steely hair syndrome			Hypercalciuria	
Osteogenesis imperfecta			Idiopathic scoliosis	
Parental history of hip fracture			Post-transplant bone disease	
Porphyria			Sarcoidosis	
Homocystinuria			Weight loss	
			Hyponatremia	



These are the Most Important Risk Factors for Fractures

- Fragility fracture after age 50 years
- Osteopenia on x-ray
- Glucocorticoid therapy (≥ 3 mo)
- Low body weight (< 127 lbs or BMI < 20)
- Family history of osteoporotic fracture
- Early menopause
- Current smoking
- Excessive alcohol use



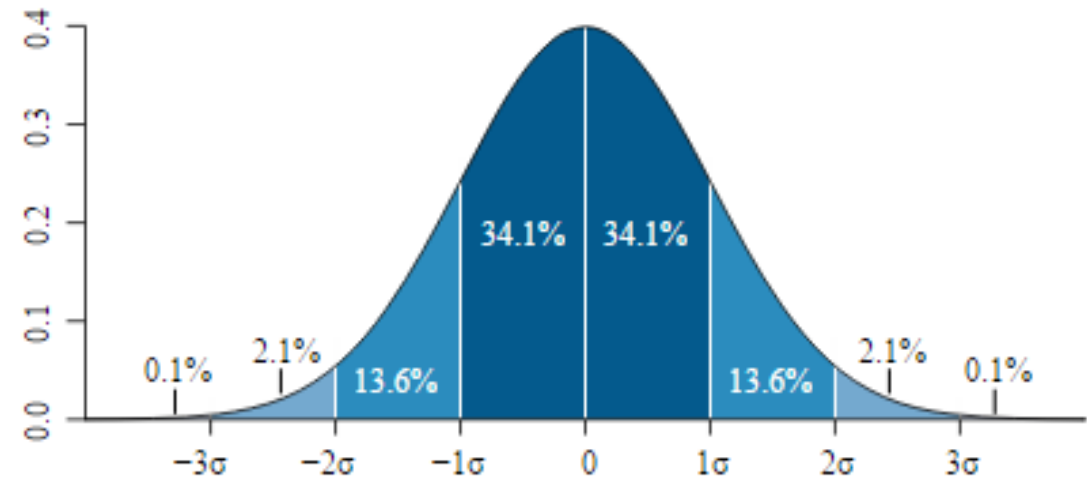
Case 1

- Medical History:
 - Roux-en-Y gastric bypass in 2009
- Medications:
 - Calcium 650 mg with vitamin D3 500 IU twice a day
 - Vitamin D3 1000 units daily
 - Vitamin B12
 - 2 chewable pediatric multivitamins
- Social History:
 - Non-smoker
 - No alcohol
- Family History:
 - No parental history of fractures
- Physical Exam:
 - Height: 4'10.5" (tallest 5')
 - Weight: 160 lbs
 - BMI: 32.9



DXA Interpretation

- Bone Mineral Density (BMD): g/cm²
- T-scores:
 - Standard deviation from mean of young normal
 - For diagnosis in *postmenopausal women* and *men ≥50 years old*
- Z-scores:
 - Matched for age, sex, race, (and weight)
 - For premenopausal women and men <50



	T-score	Z-score
L1-L4 spine	-1.6	0.2
R total hip	-1.6	-0.3
R femoral neck	-2.3	-0.3



Diagnosis of Osteoporosis

- WHO criteria: BMD at spine, total hip, femoral neck, or 1/3rd radius
- History of fragility fracture
 - Hip or spine regardless of BMD
 - Proximal humerus, pelvis, (wrist) if BMD is in the osteopenia range
- Elevated FRAX—*Most women with hip fractures do NOT have osteoporosis!*

	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.

Fraxplus.org/calculation-tool

- Indicated for those with BMD in the osteopenia range
 - Postmenopausal women and men age ≥ 50
 - NOT on pharmacologic treatment
- Recommend treatment if:
 - 10-year probability of major osteoporotic fracture $\geq 20\%$
 - 10-year probability of hip fracture $\geq 3\%$

The screenshot shows the Fraxplus.org/calculation-tool questionnaire interface. At the top, there are fields for 'Country: US (Caucasian)' and 'Name/ID:'. A link 'About the risk factors' is in the top right. The main section is titled 'Questionnaire:' and contains 12 numbered items. Items 1-4 are on the left, and items 10-12 are on the right. Item 5 is 'Previous Fracture', item 6 is 'Parent Fractured Hip', item 7 is 'Current Smoking', item 8 is 'Glucocorticoids', and item 9 is 'Rheumatoid arthritis'. Each item has radio buttons for 'No' (selected) and 'Yes'. Item 10 is 'Secondary osteoporosis', item 11 is 'Alcohol 3 or more units/day', and item 12 is 'Femoral neck BMD (g/cm²)'. Item 12 has a dropdown menu for 'Select BMF' and a text input field. At the bottom right of the questionnaire are 'Clear' and 'Calculate' buttons. Below the questionnaire, the results are displayed under the heading 'Patient:'. The results are: '- Major osteoporotic fracture: 18%' and '- Hip fracture: 2.9%'. The results are in a larger, bold font.

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)
Select BMF

Patient:

- Major osteoporotic fracture: 18%
- Hip fracture: 2.9%



Case 1

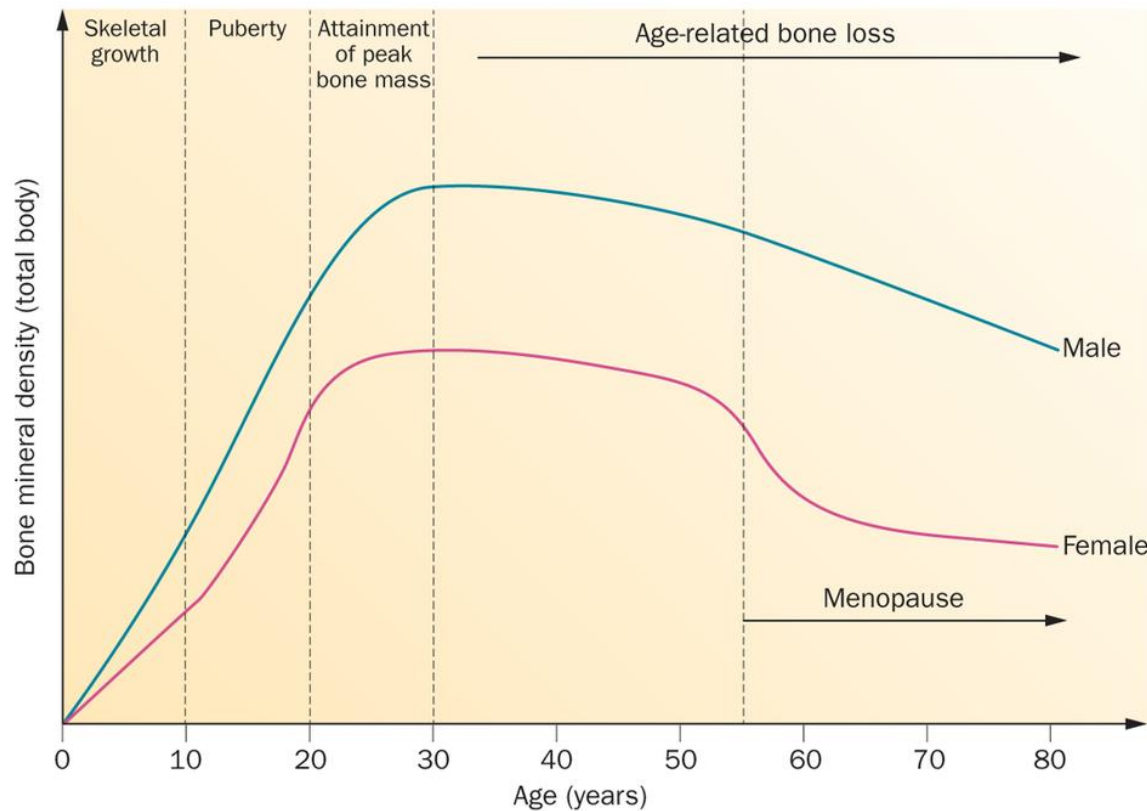
- Counseled on calcium, vitamin D, and exercise
- Repeat DXA scan, 11/2018:

	T-score	Z-score	Comparison to 4/2016
L1-L4 spine	-2.2	-0.2	-7.6%
R total hip	-2.4	-0.9	-11.9%
R femoral neck	-2.7	-0.9	

How much bone loss is expected with age?



How Much Bone Loss is Expected with Age?



- Age-related bone loss
 - Begins in 5th decade of life
 - 0.5-1% per year
- Menopause-related bone loss
 - Begins 3-5 years before LMP and continues for 3-5 years after cessation of menses
 - Averaged 1-2% per year
 - Up to 3-5% per year

Case 1

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	T-score	Z-score	Comparison to 4/2016
L1-L4 spine	-2.2	-0.2	-7.6%
R total hip	-2.4	-0.9	-11.9%
R femoral neck	-2.7	-0.9	

- Suffered a hemorrhagic stroke in 2017 with L sided muscle weakness and vision problems
- Referred to Endocrinology



Secondary Work-up is Recommended Prior to Osteoporosis Treatment

Basic

- CBC: normal
- Chem: Ca 9.0, phos 4.0, Cr 0.72
- LFTs: alk phos 67, alb 4.0
- 25OHD: 42 ng/mL
- PTH: 86 (30-65)
- 24-hour urine calcium: 42 mg

As clinically indicated

- TSH: 3.12
- TTg IgA: negative
- SPEP/UPEP
- Iron/ferritin
- Homocysteine
- Prolactin
- Total testosterone (men)
- 24-hour urine free cortisol
- Tryptase, urinary histamine
- Bone turnover markers

Case 1

Her PTH is elevated at 86 with normal calcium (9.0), normal phosphorus (4.0), and low 24-hour urinary calcium (42 mg/day). What does she most likely have?

- A. Primary hyperparathyroidism
- B. Normocalcemic hyperparathyroidism
- C. Secondary hyperparathyroidism
- D. Familial hypocalciuric hypercalcemia



Case 1

Her PTH is elevated at 86 with normal calcium (9.0), normal phosphorus (4.0), and low 24-hour urinary calcium (42 mg/day). What does she most likely have?

		Serum Ca	Urinary Ca	Serum Phos
A.	Primary hyperparathyroidism	↑	↑	↓
B.	Normocalcemic hyperparathyroidism	Normal	↑	↓ / normal
C.	Secondary hyperparathyroidism	Normal	↓ / ↑	↓ / nl / ↑
D.	Familial hypocalciuric hypercalcemia	↑	↓	↓



Case 1

- Increased calcium supplementation to 650 mg with vitamin D3 500 IU 3x/day
- Started calcitriol 0.25 mcg daily, titrated up to 1.0 mcg daily
- PTH finally normalized



Case 1

- DXA scan, 11/2018:

	T-score	Z-score	Comparison to 4/2016
L1-L4 spine	-2.2	-0.2	-7.6%
R total hip	-2.4	-0.9	-11.9%
R femoral neck	-2.7	-0.9	

What do you recommend beyond calcium/vitamin D?

- A. Nothing more
- B. Hormone replacement
- C. Raloxifene
- D. Alendronate
- E. Zoledronic acid
- F. Denosumab



Case 1

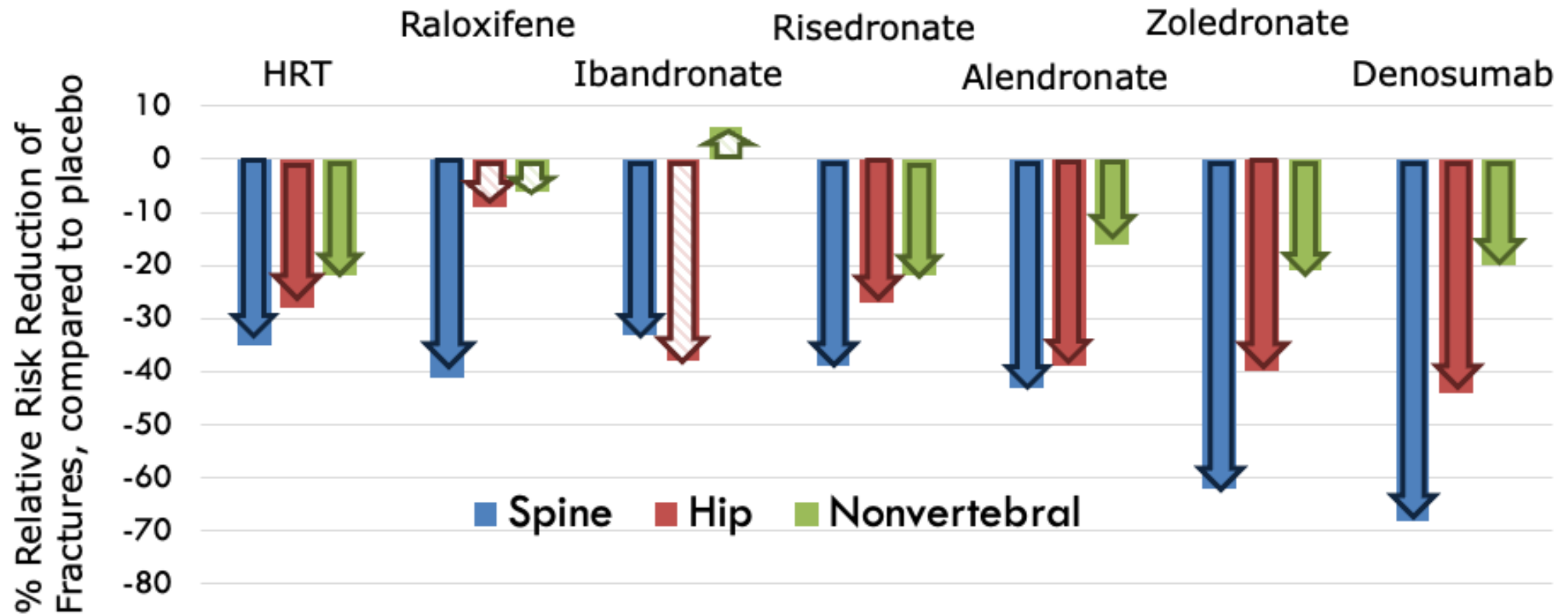
What do you recommend now?

- A. Nothing more—meets criteria for treatment, has very rapid bone loss, is at high fall risk
- B. Hormone replacement— >10 years out from menopause
- C. Raloxifene—does not reduce hip fractures where her T-score is the lowest
- D. Alendronate—concern for malabsorption with history of gastric bypass
- E. Zoledronic acid**
- F. Denosumab—discontinuation remains an issue



ACP Recommendation 1: Recommends bisphosphonates for initial treatment for postmenopausal females (high-certainty evidence) and *suggests* for males (low-certainty evidence).

Osteoporosis Medications are Very Effective at Preventing Fractures



Estrogen/Hormone Replacement

- FDA approved for *prevention* of osteoporosis with the caveat “for whom nonestrogen medications are not considered to be appropriate.”
- For young, recently menopausal women with low bone density, menopausal symptoms, and no contraindications.
 - Transdermal preparations

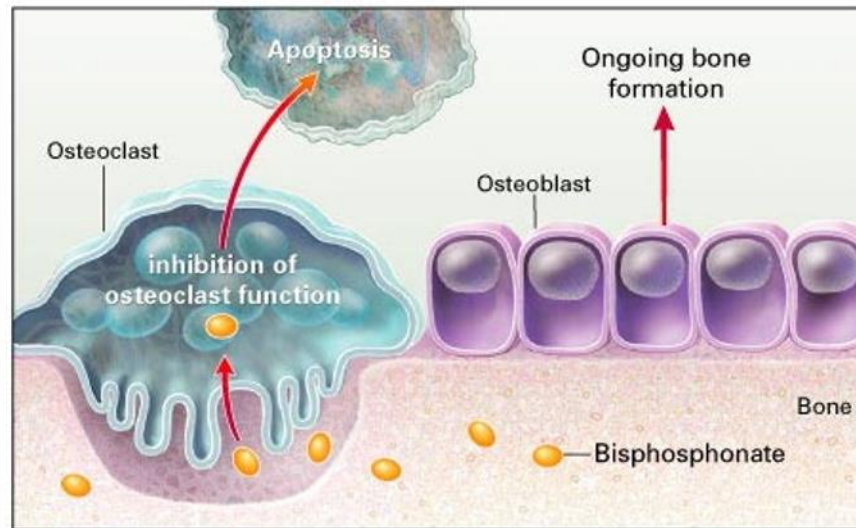
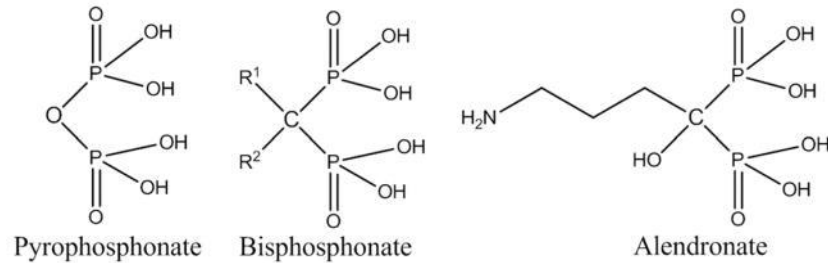


Raloxifene

- FDA approved for treatment of osteoporosis
- For postmenopausal women with low bone density at the spine, personal/family history of breast cancer, and low VTE/stroke risk.
 - Reduces vertebral but not hip or nonvertebral fractures
 - May exacerbate hot flashes



Bisphosphonates: mechanism of action



- Similar structure as pyrophosphate
- Attach to hydroxyapatite on bony surfaces
- Bisphosphonates released during resorption inhibit further osteoclastic activity

Bisphosphonates

Contraindications

- Esophageal disease, inability to be upright with oral agents
- Hypocalcemia
- CrCl <35 mL/min

Adverse Effects

- GI intolerance with oral agents
- Acute phase reaction with IV (pretreat with acetaminophen)
- Hypocalcemia (check vitamin D status)
- Musculoskeletal pain
- Iritis/uveitis/episcleritis: 0.1%
- Atrial fibrillation?



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



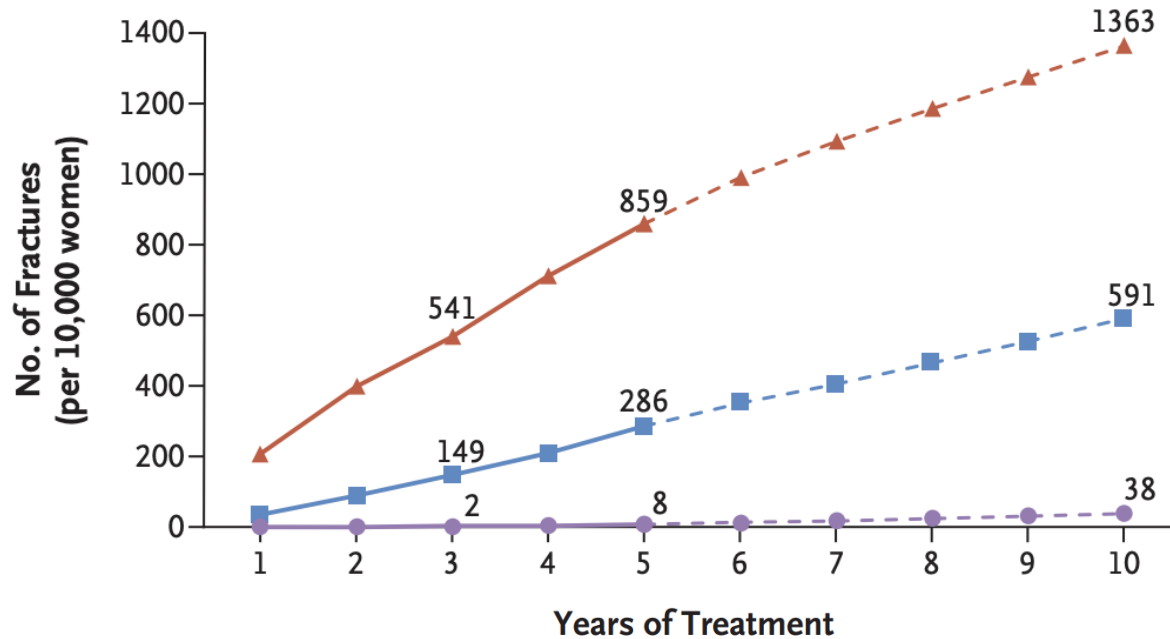
Atypical Femur Fractures are Also Very Rare

- 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

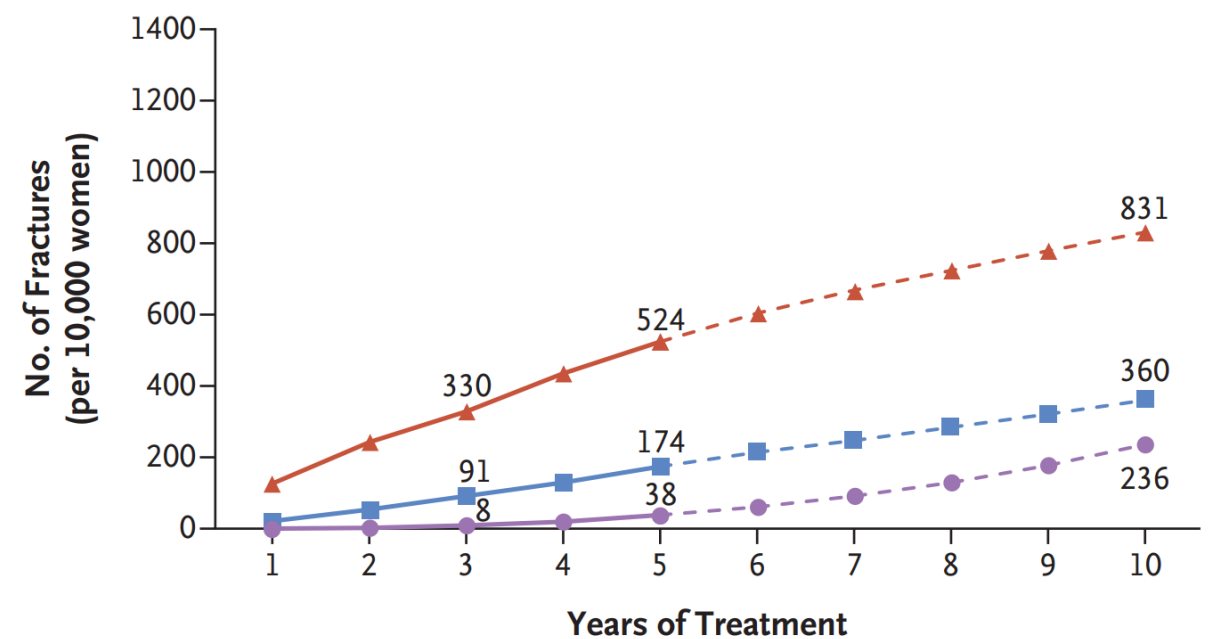


Bisphosphonates prevent many more fractures than cause AFFs, but there are racial differences

B White Women



A Asian Women



■ No. of hip fractures prevented

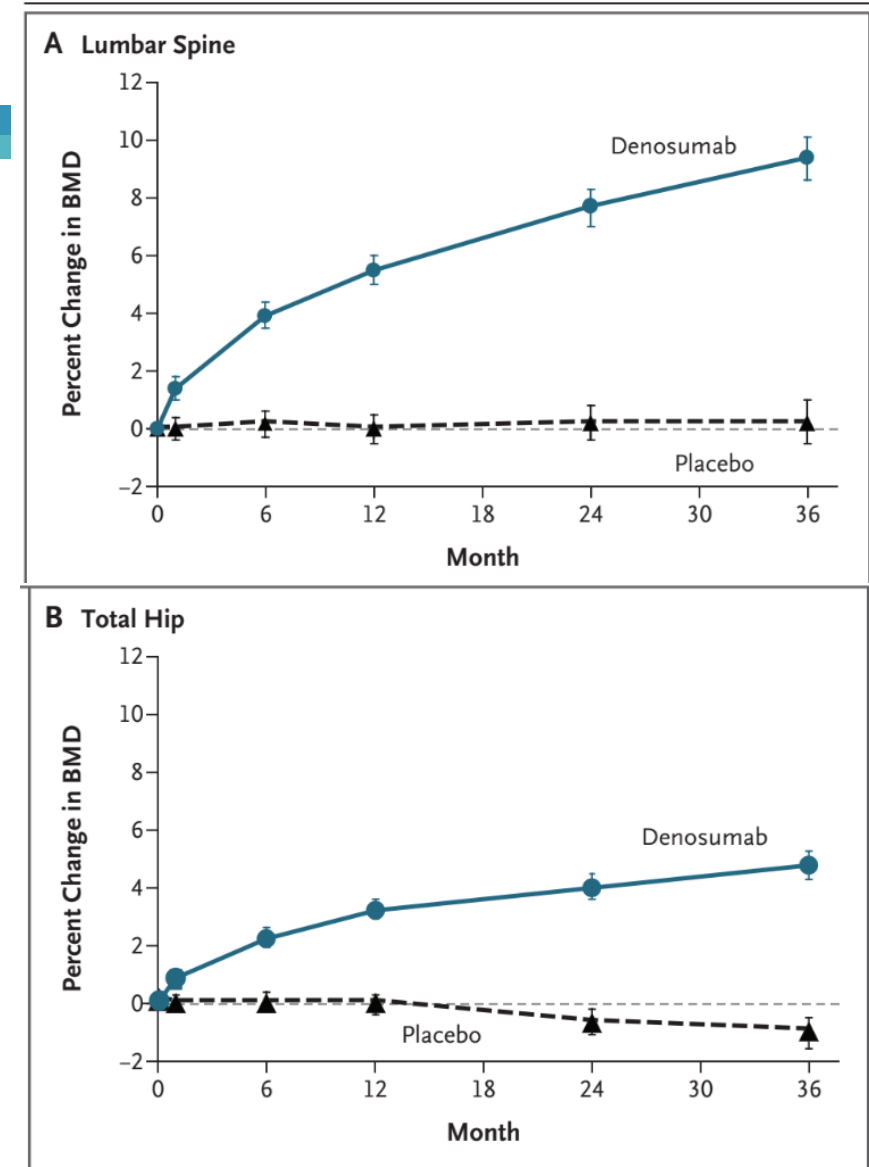
▲ No. of clinical fractures prevented

● No. of bisphosphonate-associated AAFs



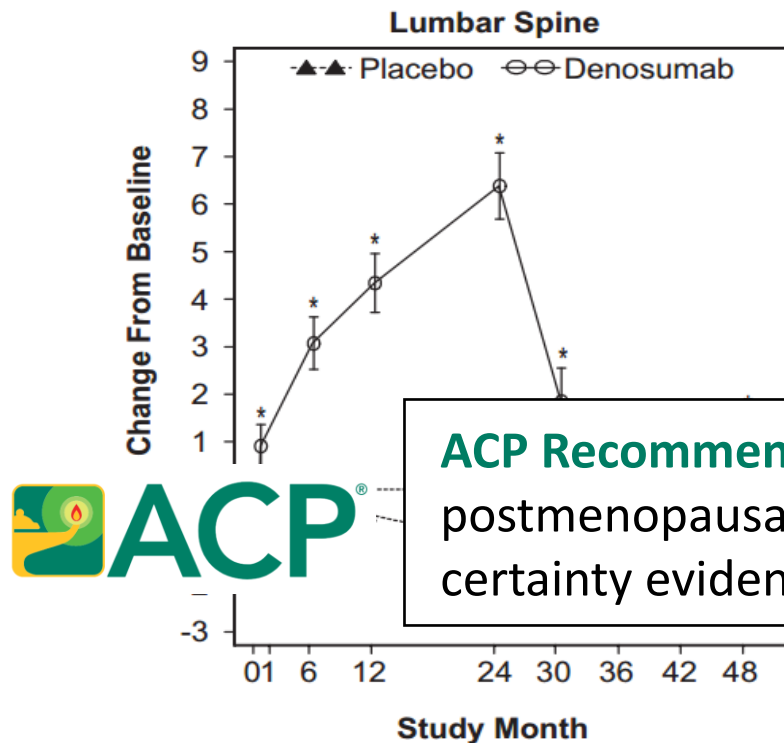
Denosumab

- 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



ACP Recommendation 2: Suggests denosumab as a second-line treatment in postmenopausal females (moderate-certainty evidence) and males (low-certainty evidence).

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:

- Received zoledronic acid 5 mg IV in 5/2019
 - Woke up with myalgias, stiffness, and diaphoresis, lasted for 1 day
- DXA scan, 11/2020:

	T-score	Z-score	Comparison to 11/2018
L1-L4 spine	-1.8	0.4	+6.4%
R total hip	-1.7	-0.2	+11.8%
R femoral neck	-2.5	-0.6	



Case 1:

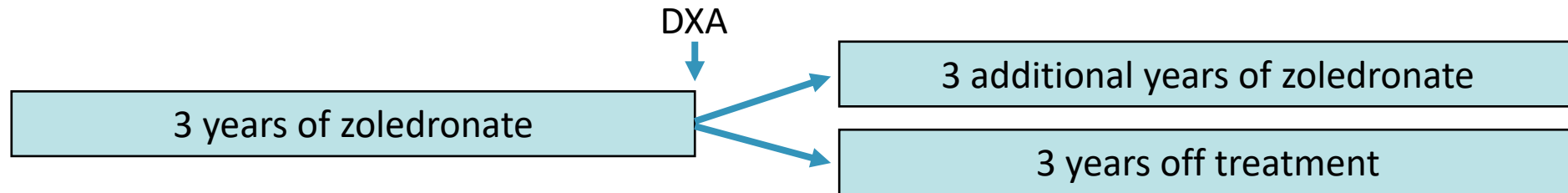
- Received subsequent doses of zoledronic acid 5 mg IV in 6/2020 and 7/2021, tolerated these well
- DXA scan, 6/2022:

	T-score	Z-score	Comparison to 11/2020
L1-L4 spine	-1.9	0.5	Stable
R total hip	-1.8	-0.2	Stable
R femoral neck	-2.4	-0.5	

She has completed 3 doses. Now what?



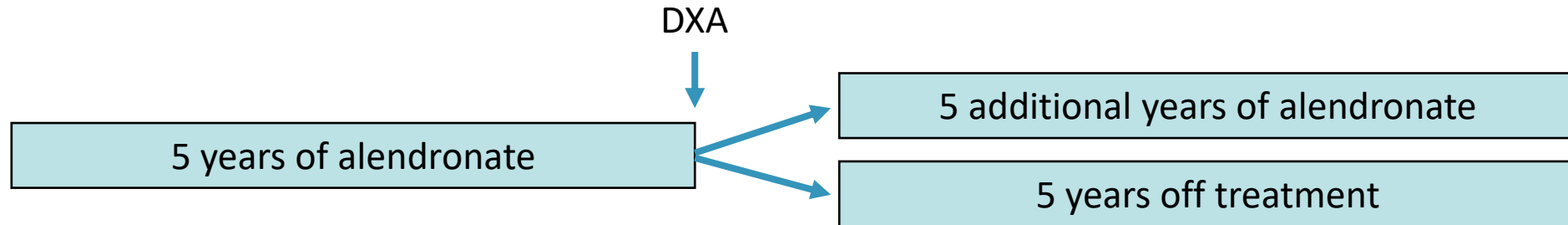
Zoledronic acid extension study: Z3P3 vs. Z6



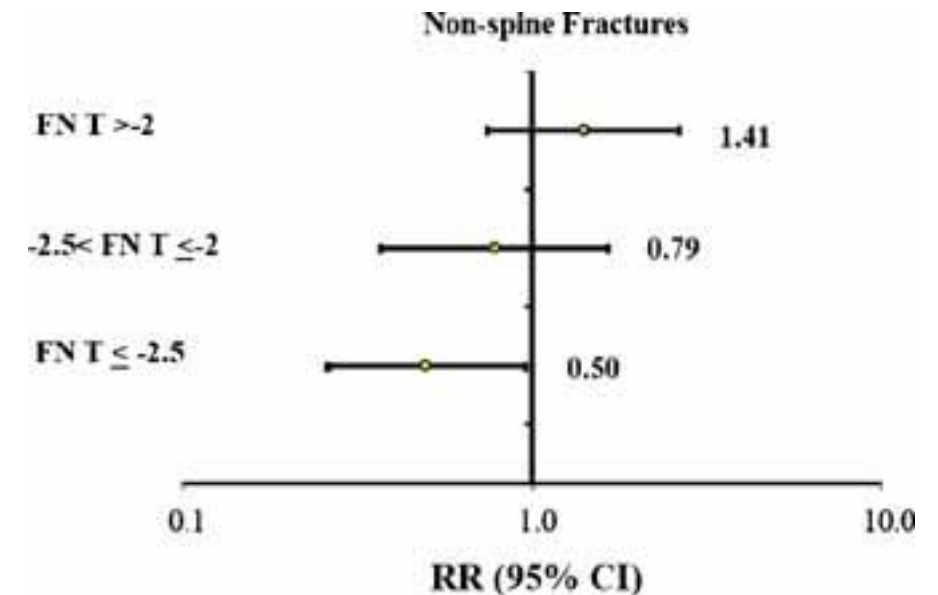
- No difference in hip fracture (1.4 vs 1.3%)
- No difference in non-vertebral fracture (7.6 vs. 8.2%)
- Sig. reduced risk of **vertebral fracture** (6.2% vs. 3.0%)
 - Total hip or femoral neck T-score ≤ -2.5
 - Incident vertebral fracture
- 1 ONJ, no AFF



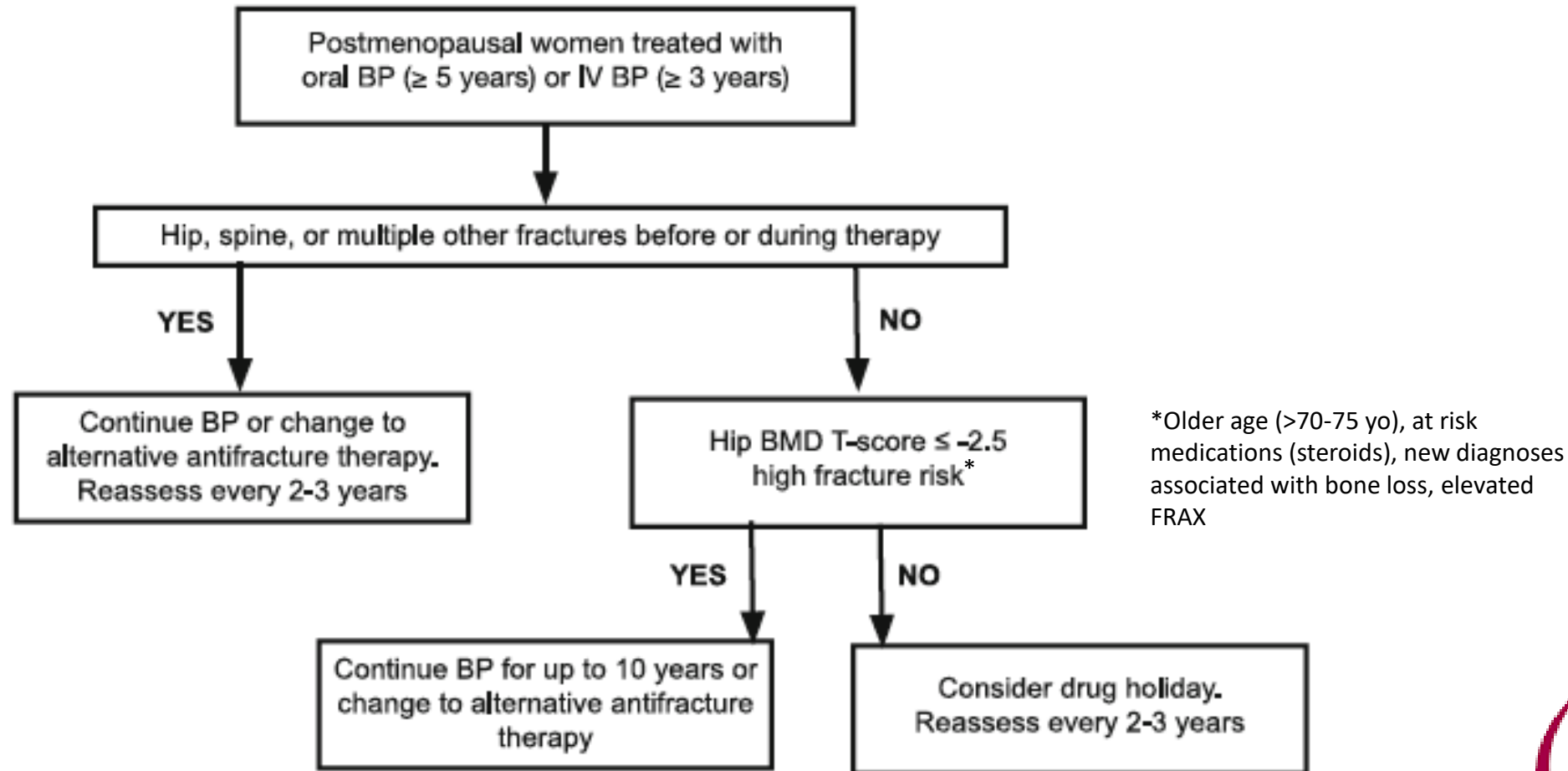
Alendronate extension study: 5A5P vs. 10A



- No difference in hip fractures (3% vs. 3%)
- No difference in nonvertebral fractures (19% vs. 19%)
- Sig. difference in clinical vertebral fractures (5% vs. 2%)
- 50% less fractures if femoral neck T-score ≤ -2.5 after initial 5 years of treatment



Who needs longer bisphosphonate therapy?



When to restart after a drug holiday?

- Reassess every 2-3 years
- Consider restarting if:
 - BMD decreases
 - Incident fracture
 - T-score ≤ -2.5
 - New risk factors
 - Rise in bone turnover markers to pretreatment levels

*Caveat: In the alendronate extension trial, only older age and lower hip BMD at time of discontinuation were predictive of fractures during the drug holiday (not 1 year change in BMD or bone turnover markers).



Bauer et al. *JAMA Intern Med.* 2014;174(7).

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

Camacho et al. *Endocr Pract.* 2016;22(Suppl 4).

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



Case 2: 65 yo postmenopausal woman

Secondary work up was unremarkable. What is the best treatment option for her?

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



Case 2: 65 yo postmenopausal woman

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ACP Recommendation 3: *Suggests recombinant PTH (low-certainty evidence) or sclerostin inhibitor (moderate—certainty evidence), followed by bisphosphonate, in females with very high risk of fracture.*

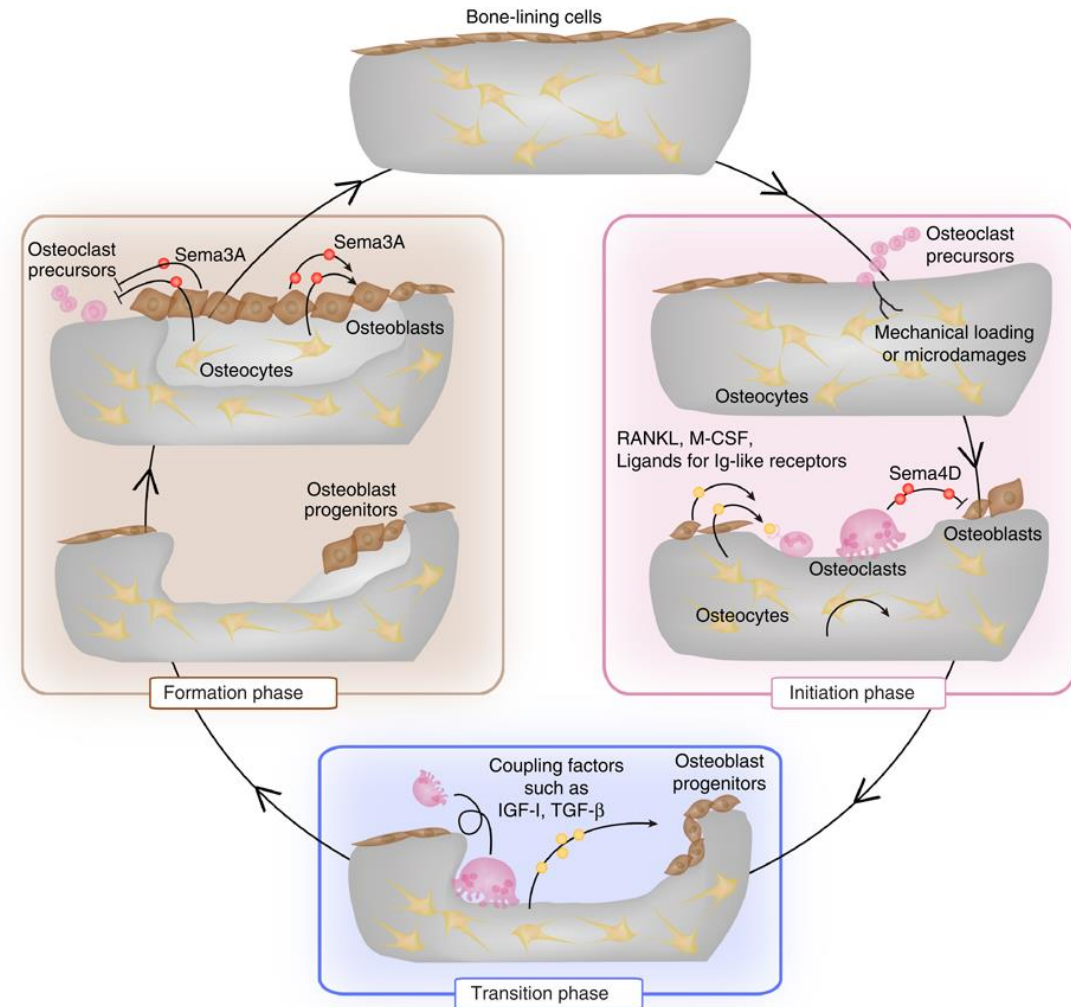


Categories of Pharmacologic Treatment

Antiresorptive therapies
block osteoclastic bone
resorption.

Anabolic therapies
promote osteoblastic bone
formation.

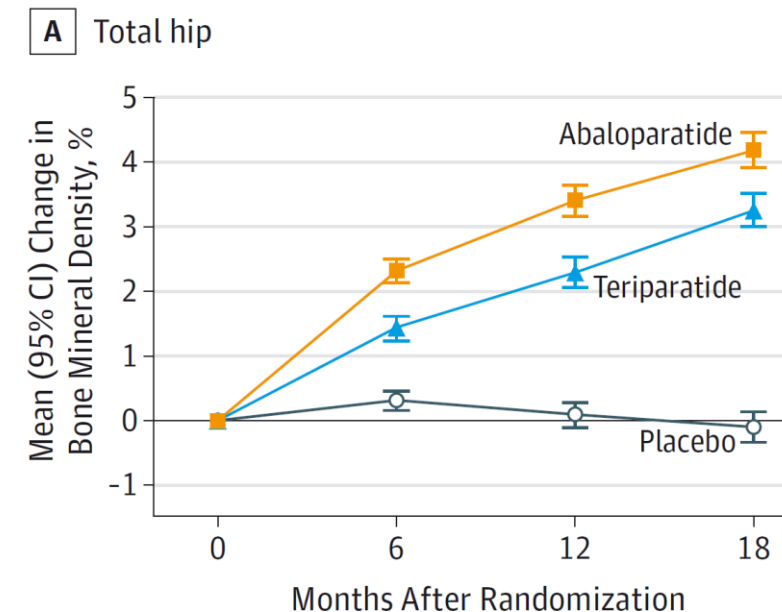
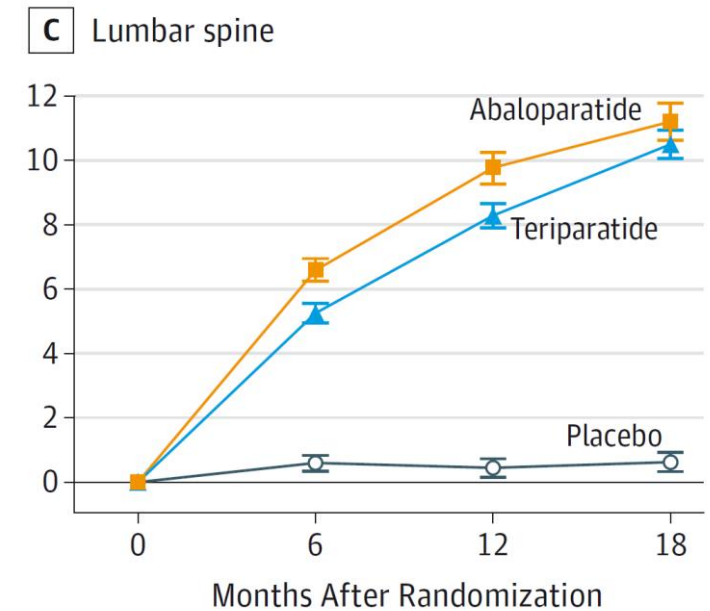
Dual action



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

Must be followed by antiresorptive therapy!



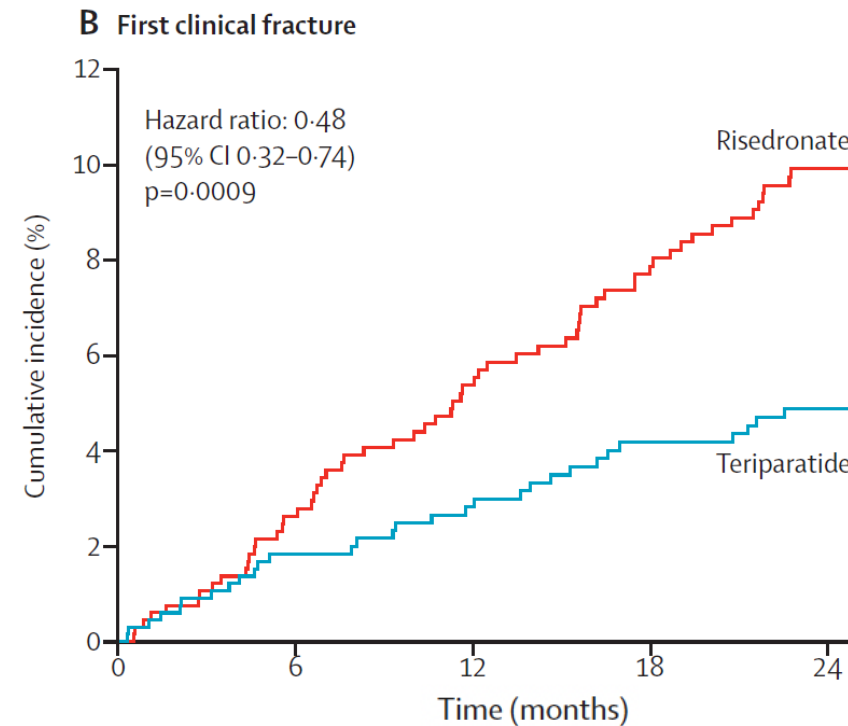
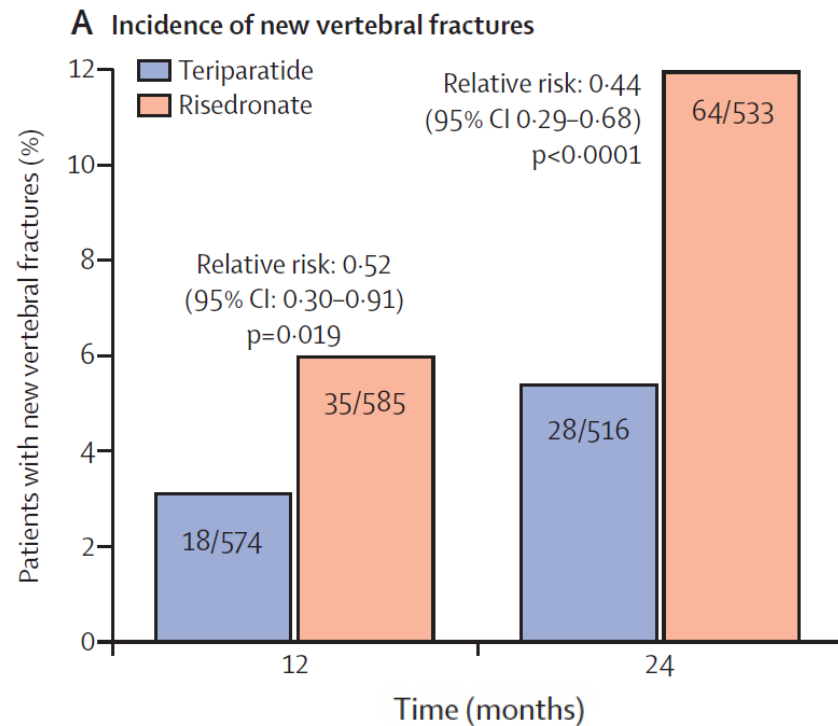
Use Anabolic Agents *prior* to Anti-resorptive Agents to Get the Most Gains in BMD

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%	



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)



Case 2: 65 yo postmenopausal woman

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

What now?



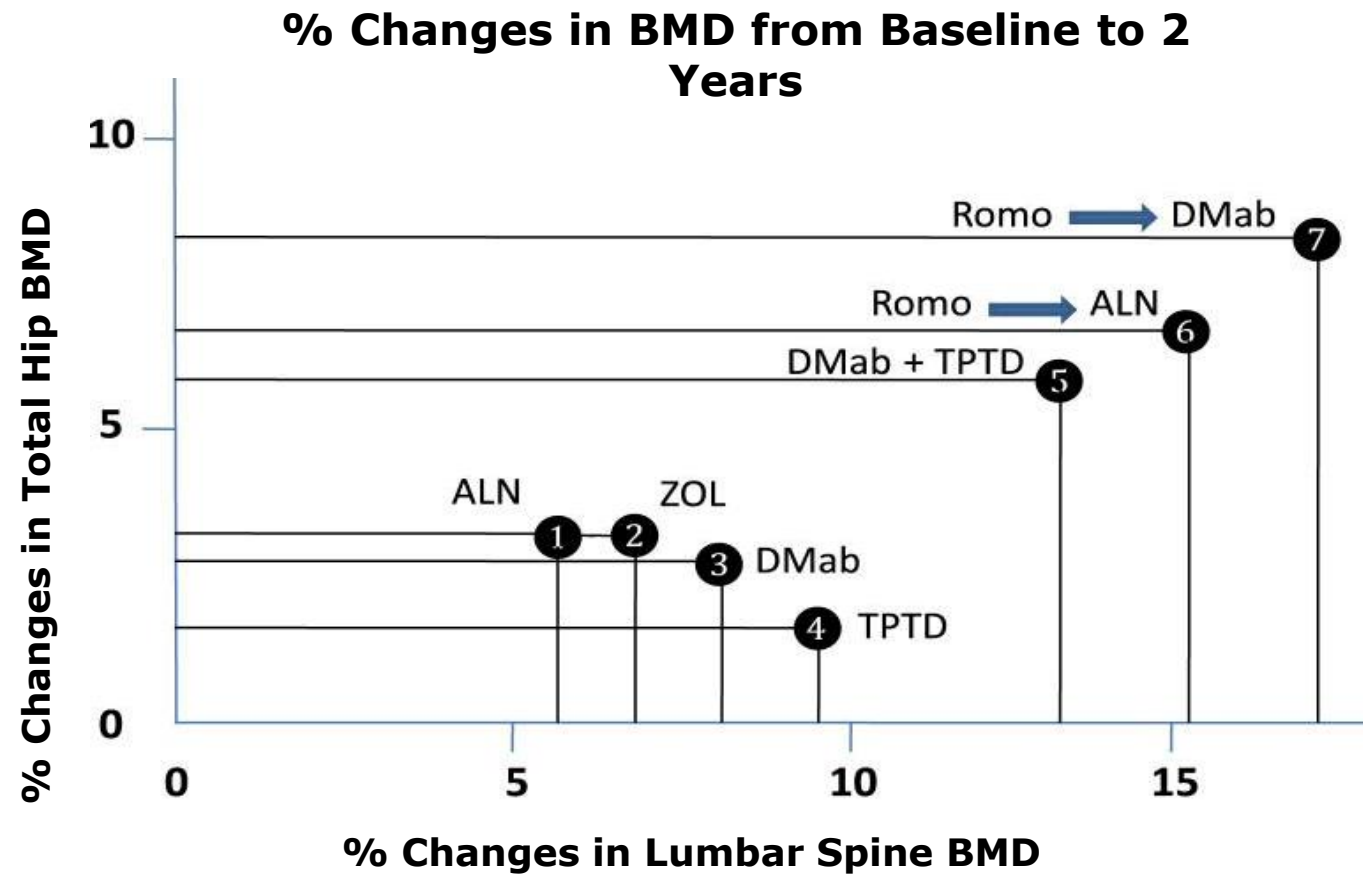
The NEW Anabolic Agent (technically dual agent): Romosozumab

- 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*



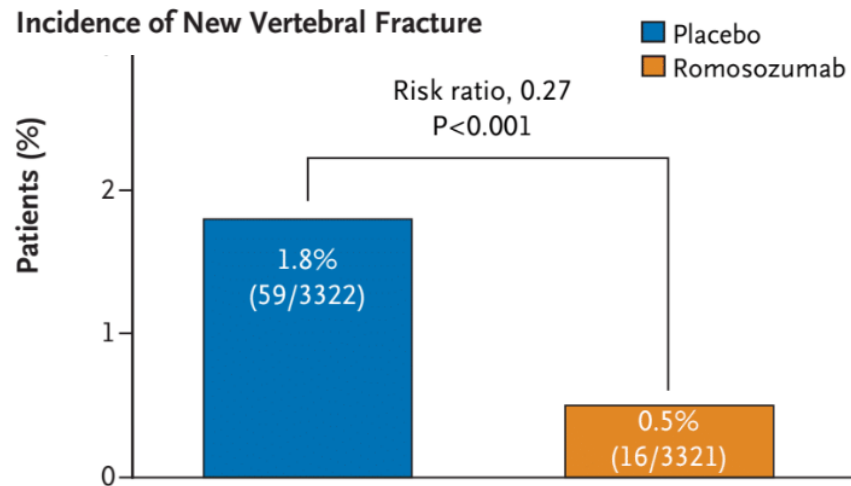
Romosozumab Increases Bone Density the Most



Romosozumab Reduces Fractures Effectively

FRAME

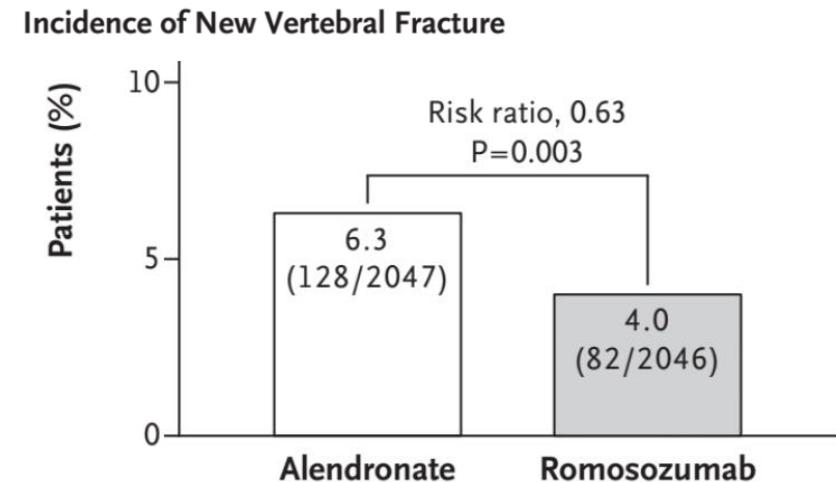
Vs. placebo for 12 mo, followed by denosumab for 12 mo



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

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: 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 ($>30\%$, $>4.5\%$)



MOC Take Home Summary

- Fragility fracture should trigger DXA testing.
- 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 or history of vertebral fractures.



References

- American College of Physicians: Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults. *Ann Intern Med.* 2023;176(2).
- Bone Health & Osteoporosis Foundation: The Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int.* 2022;33(10).
- AACE Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. *Endocr Pract.* 2020;26(Suppl 1).
- Endocrine Society: Pharmacological Management of Osteoporosis in Postmenopausal Women. *J Clin Endocrinol Metab.* 2020;105(3).
- 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).

