Osteoporosis: Latest in treatment recommendations

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Disclosures

- Sanofi, Pfizer, Moderna, Seqirus, and Merck:
  - Advisory Board and Speaker bureau
  - Vaccines
- AstraZeneca
  - Advisory Board and Speaker bureau
  - Asthma and COPD
- Exact Sciences
  - Advisory Board and Speaker bureau
  - Colorectal cancer
- Axsome
  - Speaker bureau
  - Migraines and Major Depressive Disorder
- AbbVie
  - Advisory Board
  - Migraines
- Pfizer
  - Speaker bureau
  - Migraines
- GSK
  - Consultant
  - OA and Pain; and Vaccines

All relevant financial disclosures have been mitigated.

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Objectives

- At the end of this presentation, the participant will be able to:

1. Discuss the pathophysiology of osteoporosis.
2. Identify the non-pharmacologic and pharmacologic agents available for the treatment of osteopenia and osteoporosis.
3. Compare and contrast newer pharmacologic agents with older agents with regard to benefits, risks, adverse effects, and drug interactions.

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Tips

- References
  - Listed throughout and at the end of the presentation

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Case Study

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Case Study Anna: 57-year-old Female: Well visit

- Family history
  - Mother with hip fracture at age 75 years related to a fall
- PMH
  - No personal history of fractures (fragility or traumatic)
  - Hypothyroid with replacement (TSH – 0.89 mIU/mL)
  - Asthma – Present since childhood
  - Total abdominal hysterectomy at age 40 years
  - Hypertension – Diagnosed at age 46 years

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Anna (continued)

- Social history
  - 4 ounces (118 mL) white wine daily for past 10 years
  - Smoker: 15-pack year history of smoking
    - Discontinued 10 yrs ago; no relapses
  - Exercise
    - Walks 20 minutes, approximately 4 times per week

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Anna (continued)

- Medications
  - Levothyroxine 125 mcg one daily for 20 years
  - HCTZ 12.5 mg one daily
  - Fluticasone/salmeterol (Advair®) 250/50 mcg 1-puff twice daily
  - Prednisone 0 – 1 time per year for asthma exacerbation

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Anna (continued)

- Physical examination
  - 65 inches (165 cm)
  - 111 pounds (50 kg)
- Labs
  - 25 (OH) vitamin D level:
    - 20.5 ng/mL (51.25 nmol/L)
  - Serum calcium: 8.9 mg/dL (2.2 mmol/L)

- DXA scan
  - Hip: T-score = -1.7
  - L-S spine: T-score = -2.0

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Anna (continued)

1. What are her risk factors?
2. Is she at an increased risk for fracture?

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Pharmacologic Treatment of Primary Osteoporosis

Qaseem, A., Hicks, L.A, Etxeandia-Ikobaltzeta, I., Shamliyan, T., Cooney, T.G.; Clinical Guidelines Committee of the American College of Physicians; Cross J.T. Jr., Fitterman, N., Lin, J.S., Maroto, M., Obley, A.J., Tice, J.A., Tufte, J.E. (2023). Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians. *Ann Intern Med*. 176(2):224-238. https://pubmed.ncbi.nlm.nih.gov/36592456/

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The Clinician's Guide to Prevention and Treatment of Osteoporosis

LeBoff, M.S., Greenspan, S.L., Insogna, K.L., Lewiecki, E.M., Saag, K.G., Singer, A.J. and Siris, E.S. (2022). *Osteoporos Int.,* 33, 2049–2102. https://doi.org/10.1007/s00198-021-05900-y ***or*** https://link.springer.com/content/pdf/10.1007/s00198-021-05900-y.pdf

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Updated ACOG Guidelines

Dakkak M, Banerjee M, White L. Osteoporosis Treatment: Updated Guidelines From ACOG. Am Fam Physician. 2023 Jul;108(1):100-104. PMID: 37440727.

https://www.aafp.org/pubs/afp/issues/2023/0700/practice-guidelines-osteoporosis-treatment.html

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Definition of Osteoporosis[1]

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

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Osteoporosis: Is there a problem?

- Over 44 million Americans have or are at risk for osteoporosis.[2]
  - 10 million people have osteoporosis.
  - 34 million more are estimated to have low bone mass, which puts them at increased risk of developing osteoporosis and related fractures.
- 80% of those affected are women; 20% are men.[3]
- The prevalence of osteoporosis is expected to continue to increase with the growth of the elderly population.[4]

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Osteoporotic Fractures[5]

- Two million osteoporotic fractures each year in the United States
- One in every two women will experience an osteoporotic fracture at some point in her lifetime.

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Osteoporosis in Men[2]

- Approximately, 20% of individuals with osteoporosis are men.
- 8–10 million men have osteopenia or osteoporosis.
- ~13% lifetime risk of sustaining a fracture of the hip, spine, or distal forearm (compared to 40% in women)
- Mortality is significantly higher in men than in women following fracture of the hip or spine.

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Hip fractures in men can lead to disability and death.

- Men are twice more likely to die within one-year of a hip fracture than are women.[6]
- Osteoporotic fractures are associated with a 3.2-fold increase in mortality in men.[7]

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Why is osteoporosis such a widespread problem?[3,8,9]

- Lack of education and awareness
- Sedentary lifestyles
- Calcium and vitamin D intake
- Alcohol intake
- Cigarette smoking

- Carbonated drinks
- Aging population
- Medications
- Underdiagnosis and undertreatment
- Poor medication adherence

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Underdiagnosed/Undertreated[3]

- Many patients are undiagnosed because this is often a silent disease until a fracture occurs.
  - Emphasis must be on early diagnosis and treatment, regardless of symptoms.

- Adherence to chronic medications is poor.
  - Many new treatment options are now available.
    - Routes of delivery: Oral, injection, IV, subcutaneous administration
    - Frequency options: Daily, weekly, monthly, quarterly, annually

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Incidence of Fracture Among Women

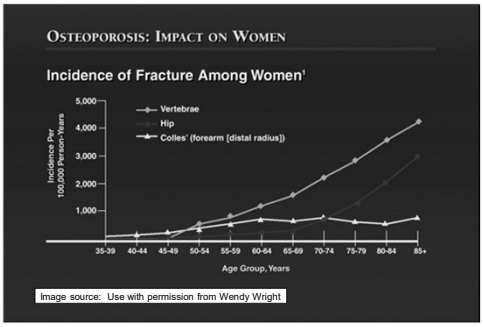

Image source: Use with permission from Wendy Wright

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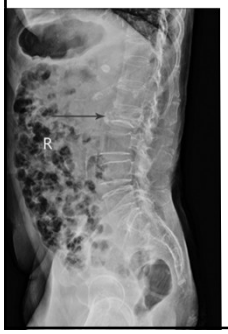
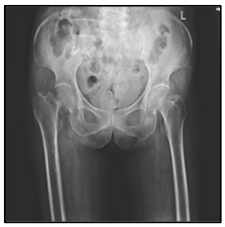
Incidence of Fractures: Vertebral vs. Hip[10]



- Vertebral fractures
  - 700,000 annually
- Hip fractures
  - 300,000 annually



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Osteoporotic Fractures[11]

- Although much of the discussion in the literature speaks to hip fractures and the increased risk of morbidity and mortality, there are important additional messages…
  - Hip fracture rates begin to increase significantly at the age of 70 years and are associated with significant morbidity and mortality.
  - Vertebral fractures, often silent, are also associated with significant morbidity and mortality yet tend to occur in the younger individual: Age 55+ years.

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Health Impact of Vertebral Fractures

- Vertebral fracture is often unrecognized.
- Patients who have a vertebral fracture…
  - Are at greater risk of any subsequent fracture
  - May become unable to walk unassisted
  - Lose height
  - May experience pain
  - Are at greater risk of death

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Pathophysiology of Osteoporosis

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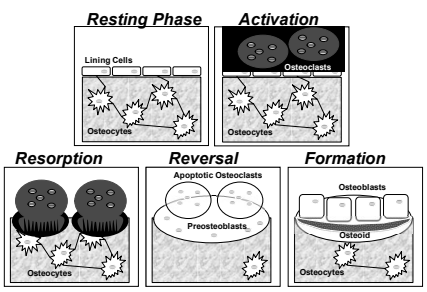
Bone Remodeling



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Bone Growth and Density[2]

- Childhood: Bones grow in length and density.
- Teen years: Maximum height is reached, but bones continue to become more dense
- Peak bone mass or density: Achieved at age 30 years
- After age 30 years: Bones slowly start to lose density or strength.

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Pathophysiology of Osteoporosis[12, 13]

- Bone remodeling occurs throughout an individual's lifetime.
  - **In adults, osteoclasts** (bone resorption) is balanced by that of **osteoblasts** (bone formation).
- Diminishing estrogen levels with menopause lead to excessive bone resorption.
  - Postmenopausal women lose 12% of bone mass over 6 years, beginning two years before the last menses, followed by 1–2% loss per year thereafter.

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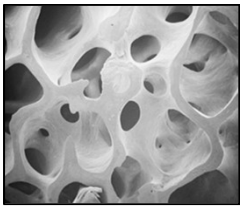
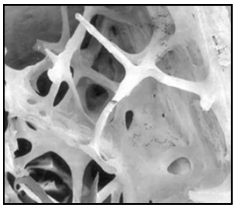
Contrast of Healthy and Osteoporotic Bone



Healthy Bone



Osteoporotic Bone

Image sources: Used with permission from Wendy Wright

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Assessment of the Individual at Risk for Osteoporosis

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Assessment of the Individual At Risk For Osteoporosis

- Clinical history
  - Risk factors
  - Physical symptoms
  - Perceived loss of height
- Physical examination

- DXA scans
- Additional testing
  - 25-hydroxyvitamin D levels: 25(OH)D
  - Additional testing dictated by comorbidities (i.e., TSH)

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Osteoporosis Risk Factors

- **Advanced age**
- **Personal history of fracture after age 50 years**
- History of a fracture in a primary relative
- BMI <19 kg/m^2
- Current low bone mass

- Female
- Family history of osteoporosis
- Estrogen deficiency
- Amenorrhea
- Anorexia
- Low lifetime calcium intake
- Vitamin D deficiency

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Osteoporosis Risk Factors (continued)

- Use of certain medications
- Oral corticosteroids
- Anticonvulsants
- Presence of certain chronic medical conditions

- Low testosterone levels in men
- An inactive lifestyle
- Cigarette smoking
- Excessive use of alcohol
- Being White or Asian

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Vitamin D Deficiency

- 50% of women with an osteoporotic hip fracture[14]
  - Severely deficient (≤12 ng/mL [30 nmol/L])
- 51% of healthy Black adolescents in Boston[15]
- 67% of Australian women in residential care had 25(OH)D levels below 10 ng/mL (25 nmol/L).[16]

14. Le LeBoff, M.S., Kohlmeier, L., Hurwitz, S., Franklin, J., Wright, J., Glowacki, J. Occult vitamin D deficiency in postmenopausal U.S. women with acute hip fracture. *JAMA*. 1999 Apr 28;281(16):1505-11. https://pubmed.ncbi.nlm.nih.gov/10227320/

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Vitamin D[17]

- Measure 25(OH)D (25-hydroxyvitamin D)
  - Current reference is >20 ng/mL (50 nmol/L).
  - Treatment target is 30–50 ng/mL (75–125 nmol/L).
- Healthy individuals with levels of 20 ng/mL (50 nmol/L), showed poor Ca^{+} absorption from a test meal.
- Individuals who are truly deficient will likely need large dosages of vitamin D.

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Physical Examination Findings[18, 19]

- Weight/body mass index
  - Weight <127 pounds (57 kg) and BMI <19 kg/m^2 are risk factors.

- Obtain yearly height.
  - Compare heights from year to year.
  - Ideally, measure heights with stadiometer.
  - Loss of >1.5 inch (3.8 cm) in lifetime is considered significant.
  - Loss of >1.0 inch (2.5 cm) in one-year signifies possible fracture.

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Physical Examination Findings[18, 19] (continued)

- Assess for dorsal kyphosis and cervical lordosis.
- Palpate spine for tender or painful areas.
- Assess for muscle strength and balance.

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Additional Testing as Indicated to Rule-out a Secondary Cause of Osteoporosis[1]

- CBC with differential
  - Cancer
- Comprehensive metabolic panel
  - Renal or liver disease
  - Serum calcium
- 25 (OH) D
  - Vitamin D deficiency

- TSH and free T4
  - Hyperthyroidism
- 24-hour urine for calcium excretion
- Free testosterone level (both free and total)
  - Hypogonadism
- PTH
  - Hyperparathyroidism

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Diagnosis of Osteoporosis

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Recognizing Osteoporosis: Usefulness of BMD Testing

- In clinical practice, bone mineral density (BMD)
  - Remains the gold standard[3]
  - One of the best determinants of bone strength[20]
  - Correlates with fracture risk[3,20]
- BMD predicts fracture as reliably as blood pressure predicts stroke.[3,21]

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Diagnosis of Osteoporosis

- DXA scan
  - Central DXA
  - Most accurate for serial measurements
  - Allows comparison between current and previous DXA scans
  - Perform at same locations

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BMD Testing[17]

- Recommended for…
  - Women aged ≥65 years and men aged ≥70 years
  - Postmenopausal women and men aged 50–69 years, based on risk profile
  - Postmenopausal women and men aged ≥50 years with history of adult-age fracture
  - The same facility and on the same densitometry device for each test whenever possible

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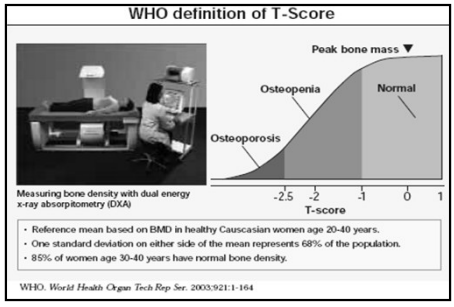
WHO Definition of T-score



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Anna (continued)

1. Does she meet the diagnostic criteria for osteopenia or osteoporosis?

T-scores:
-1.7 Hip
-2.0 L-S spine

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Treatment Options

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Summary of Revisions[22]

- Treatment recommendations
  - Treat all individuals with a T-score of -2.5 in the hip.
  - Those with T-scores of 1.0 to -2.5 (osteopenia) should be treated when the 10-year probability of a hip fracture is ≥3% (FRAX® model) ***or*** the 10-year probability of a major osteoporosis related fracture is ≥20% based upon the U.S. adapted WHO criteria (FRAX® model).

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Summary of Revisions[22] (continued)

- FRAX®
  - WHO fracture risk assessment model/tool
  - Provides 10-year probability of fracture risk
  - New risk assessment tool

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Fracture Risk Assessment Tool (FRAX®)

https://frax.shef.ac.uk/FRAX/tool.aspx?country=9

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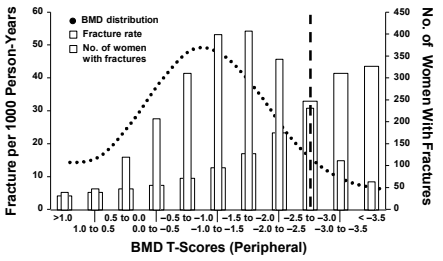
Population BMD Distribution, Fracture Rates, and Number of Women with Fractures



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Summary: Important To Remember…[23, 24]

- One-half or more of all fractures occur in individuals with T-scores better than -2.5 SD.
- Thus, treating by BMD alone may not be the answer.
- Hence, the new revisions to the guidelines.

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Nonpharmacologic Therapies[1]

- Improved dietary calcium and vitamin D
- Exercise
  - Aerobic
  - Weight bearing
  - Increase muscle strength and flexibility
- Discontinue smoking
- Moderation of alcohol
- Avoidance of medications which increase risk

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Summary of Recent Revisions[22]

- Calcium and vitamin D
  - Calcium
    - 1000 mg daily for men ages 50–70 years
    - 1200 mg/day for women ages ≥51 years and men ages ≥71 years
  - Vitamin D_3: 800–1000 international units per day for those over 50 years of age

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Clinical Pearls with Calcium

- Calcium supplements should be taken with meals and in divided doses with no more than 500–600 mg at one time.
  - The fraction of the oral dose of calcium that is absorbed diminishes above this dose.[13]
- If the patient is on a proton pump inhibitor (PPI), use a citrate preparation.
  - Calcium carbonate needs an acidic environment to activate absorption.[25]
- Viactiv®* contains vitamin K which may increase coagulability in patients taking anticoagulants.

*Calcium, elemental (as carbonate), vitamin D, vitamin K; soft chews

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Vitamin D Requirements

- 3,000–5,000 international units used each day[26]
- 1,000 international units intake **minimum** needed to satisfy daily needs[26, 27]

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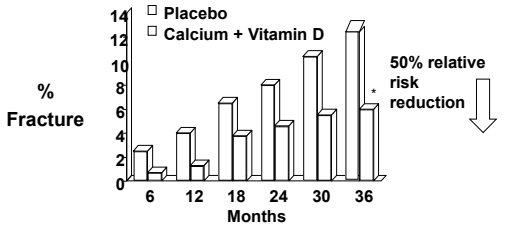
Reduction of Nonvertebral Fracture with Calcium and Vitamin D



p=0.02 (455 healthy men and women age 65+ years)

Image source: Used with permission from Wendy Wright. Adapted from Dawson-Hughes, B., Harris, S.S., Krall, E.A., Dallal, G.E. (1997). Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med.*, 337(10):670-6. https://pubmed.ncbi.nlm.nih.gov/9278463/

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Medications for Use Osteoporosis (Postmenopause and/or Male)

Drug	Prevention	Treatment
Estrogen/estrogen-progesterone	Yes	No
Alendronate	Yes	Yes
Ibandronate sodium tablets	Yes	Yes
Ibandronate sodium injection	No	Yes
Risedronate	Yes	Yes
Raloxifene	Yes	Yes
Calcitonin (IM/SC)	No	Yes
Teriparatide	No	Yes
Abaloparatide	No	Yes
Zoledronic acid (5 mg IV every 12 months)	No	Yes
Denosumab	No	Yes
Romosozumab	No	Yes

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Two Primary Types of Pharmacotherapy for Osteoporosis

Antiresporptive Agents (Reduce bone loss)	**Anabolic Agents** (Build bone)
• Bisphosphonates • Estrogen (HRT) • RANKL inhibitor • Selective estrogen modulators (SERMS) • Calcitonin	• Synthetic parathyroid hormone • Sclerostin inhibitor

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Bisphosphonates are the most used pharmacotherapy.

- Most commonly prescribed medication class for osteoporosis
- Increase in BMD at the hip and spine [28]
- Reduce the risk of fractures[1, 28]
- Have a demonstrated tolerability profile[29]

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ACP Guidelines

Bisphosphonates are considered first-line medications to reduce fractures of osteoporosis, both men and women.

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Oral Bisphosphonates…

Results are not from head-to-head clinical trials. Comparisons of efficacy should not be made.

Product	Alendronate (Fosamax®) FIT Study	Ibandronate (Boniva®) MOBILE Study	Risedronate (Actonel®) VERT* Trial
Non-vertebral fracture ↓	51–56%	69% BONE Study	
Vertebral fracture ↓	52%	52%	
L-S BMD ↑	6.5%	6.6%	
Fem neck BMD ↑	5.9%	2.8%	
Adverse effects	Dyspepsia Joint pain Flu-like syndrome	Dyspepsia Joint pain Flu-like syndrome	Dyspepsia Joint pain Flu-like syndrome
Cost	Generic	Generic	Generic

*Vertebral efficacy with risedronate therapy (VERT)

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What about patients who are intolerant of oral therapies?[30]

- Ibandronate (Boniva®) I.V. injection
  - FDA approved for the treatment of postmenopausal osteoporosis in women unable to tolerate oral regimens
  - Administered once every 3 months
  - 3 mg/every 3 months
    - Slow IV push (15–30 second injection).
  - Obtain creatinine prior to administration.

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Zoledronic Acid (Reclast®) Bisphosphonate Derivative[31]

- Indications
  - Treatment of postmenopausal osteoporosis
- Dosing
  - 5 mg IV every 12 months

- Infuse over 15–30 min; do not infuse <15 minutes
  - Dilute solution for injection in 100 mL NS or D5W prior to administration (good hydration prior to giving)
- Excretion
  - Urine 39% as unchanged drug within 24 hours

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Zoledronic Acid (Reclast®) – Three-year Clinical Fracture Data[31]

Outcome	Reclast® N=3875 Event Rate N (%)	Placebo N=3861	Absolute Reduction in Fracture Incidence	Relative Risk Reduction in Fracture Incidence
Any clinical fracture	308 (8.4)	456 (12.8)	4.4 (3.0)	33 (23.0)
Clinical vertebral fracture	19 (0.5)	84 (2.6)	2.1 (1.5)	77 (63.0)
Non-vertebral fracture	292 (8.0)	388 (10.7)	2.7 (1.4)	25 (13.0)

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Bone, Joint and/or Musculoskeletal Pain[32]

- The product inserts for all the bisphosphonates have a warning about bone, joint, and/or musculoskeletal pain.
- MedWatch safety summary suggests the association between bisphosphonates and musculoskeletal pain may be overlooked by healthcare professionals.
  - Delaying diagnosis
  - Prolonging pain and/or impairment
  - Necessitating the use of analgesics

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Bisphosphonates

- First line medications to treat osteoporosis
- Generally, used for five years orally or three years IV

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Other Therapies…[33, 34]

Product	Raloxifene HCL (Evista®)	Calcitonin-salmon (Miacalcin®)
Non-vertebral fracture ↓	NS	48%
Vertebral fracture ↓	55%	36%
L-S BMD ↑	2.6%	Not available
Femoral neck BMD ↑	2.1%	Not available
Route	Oral	Intranasal
Adverse effects	Thromboembolism Hot flashes	Nausea, diarrhea flushing, rhinorrhea
Cost	$71	$68

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ACP Guidelines

Denosumab is now considered 2nd-line pharmacologic agent in postmenopausal women and men diagnosed with osteoporosis who are unable to utilize a bisphosphonate.

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Denosumab[35, 36]

- Denosumab: Prolia®
- Class: Receptor activator of nuclear factor kappa-B ligand (RANKL)
  - Human IgG2 monoclonal antibody with affinity and specificity for human RANKL
  - Produced from genetically engineered mammalian (Chinese hamster ovary) cells

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Denosumab[35, 36] (continued)

- Indication
  - Postmenopausal women with osteoporosis at high risk for fracture
- Dosage
  - 60 mg administered as a single subcutaneous injection – Every 6 months
  - Administer into upper arm, upper thigh, or the abdomen.

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Denosumab[35, 36] (continued)

- Contraindications
  - Hypocalcemia
- Warnings and precautions
  - Hypocalcemia can be exacerbated by denosumab.
  - Serious infections (7800 patients in trial)
    - Infections were more common in individuals treated with this medications.
    - 3.3% in the placebo group; 4.0% in the treatment group
    - Endocarditis: 0–placebo; 3 in denosumab group

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Why Potential for Infection?[35, 36]

- Receptor activator of nuclear factor kappa-B ligand (RANKL) is expressed on T and B lymphocytes and in lymph nodes.
- RANKL inhibitor may increase risk of infection.

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Denosumab[35, 36] (continued)

- Warnings and precautions
  - Osteonecrosis of the jaw (ONJ)
  - Dermatologic adverse reactions
    - 2.0% placebo
    - 2.5% denosumab
  - Pancreatitis: Higher rates
  - Renal impairment: No dosage adjustment needed

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Efficacy[35, 36]

- New vertebral fractures
  - Placebo: 7.2%
  - Denosumab: 2.3% (ARR*: 4.8%, RR** reduction: 68%)
- Hip fractures
  - Placebo: 1.2%
  - Denosumab: 0.7% (ARR*: 0.3%, RRR**: 40%)
  - All at year 3

- Improvement in bone density over 3 years
  - 8.8%: Lumbar spine
  - 6.4%: Total hip
  - 5.2%: Femoral neck

*Absolute risk reduction
**Relative risk reduction

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Denosumab

- Improves bone density more quickly than bisphosphonates but bone losses are more quick after discontinuing
- Consider bisphosphonate after

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Denosumab

- Biosimilar approved by the FDA
  - Denosumab-nxxp, a biosimilar to Prolia, called Bildyos

https://www.endocrinologyadvisor.com/news/fda-approves-denosumab-biosimilars-bildyos-bilprevda/ accessed 10-18-2025

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ACP Guidelines

ACP recommends that sclerostin inhibitor or recombinant PTH, followed then by a bisphosphonate be used in women at very high risk of fracture.

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Teriparatide (FORTEO®)[37]

- Indications
  - Treatment of postmenopausal women with osteoporosis who are at high risk for fracture
  - Women who have failed or are intolerant of previous osteoporosis therapy
  - Men with primary or hypogonadal osteoporosis who are at high risk for fracture

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Teriparatide (FORTEO®)[37] (continued)

- Indications (cont.)
  - Dosage
    - Subcutaneous injection into the thigh or abdominal wall
    - Recommended dosage: 20 mcg once a day for up to 2 years
  - Adverse effects
    - Pain at injection site, arthralgias
    - Check serum calcium.
    - Boxed warning: osteosarcoma in rats

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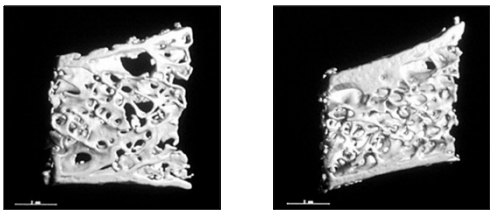
Trabecular Connectivity



Before

After

Image source: Used with permission from Wendy Wright. Dempster, D.W., Cosman, F., Kurland, E.S., Zhou, H., Nieves, J., Woelfert, L., Shane, E., Plavetić, K., Müller, R., Bilezikian, J., Lindsay, R. (2001). Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res.*, 16(10):1846-53. https://pubmed.ncbi.nlm.nih.gov/11585349/.

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Abaloparatide (Tymlos™)[38]

- Class
  - A human parathyroid hormone related peptide analog
- Indication
  - Treatment of postmenopausal women with osteoporosis at high risk for fracture

- Dosage
  - 80 mcg subcutaneously once daily
  - Subcutaneous injection into periumbilical region of abdomen

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Abaloparatide (Tymlos™)[38] (continued)

- Warnings and precautions
  - Instruct patients to lie down during administration due to reports of orthostatic symptoms (for first few doses).
  - Avoid in patients with hypercalcemia.
  - Not recommended in individuals with Paget's disease.
  - Limit use to two years

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Abaloparatide (Tymlos™)[38] (continued)

- Efficacy
  - 1139 patients exposed to medication over 18–25 months
  - Increased BMD (8.8% vertebral spine, 3.5% hip)
  - Significant reduction in new vertebral fractures (0.6% compared to 4.2% placebo, $p < 0.0001$) and non-vertebral fractures
- Drug-drug interactions: **None**
- Competition
  - Teriparatide (FORTEO®)

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Abaloparatide (Tymlos™)[38] (continued)

- Adverse effects
  - Hypercalciuria (11% vs. 9%)
  - Dizziness (10% vs. 6%)
  - Nausea (8% vs. 3%)
  - Headache (8% vs. 6%)
  - Injection site reactions (58% vs. 28%)
- Lab changes
  - Increase in calcium
  - Increase in uric acid

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Abaloparatide (Tymlos™)[38] (continued)

- Advantages
  - No dosage adjustment for mild to severe renal disease
- Disadvantages
  - Cost (approximately $1,600 per month)
  - Subcutaneous injection
  - Store in refrigerator

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Romosozumab-aqqg (Evenity®)[39]

- Indication
  - For the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy

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Romosozumab-aqqg (Evenity®)[39] (continued)

- Class
  - Sclerostin inhibitor
  - Inhibits the action of sclerostin, a regulatory factor in bone metabolism
  - Increases bone formation and, to a lesser extent, decreases bone resorption

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Romosozumab-aqqg (Evenity®)[39] (continued)

- Dosage
  - Two separate subcutaneous injections are needed to administer the total dose of 210 mg. Inject two syringes, one after the other.
  - Should be administered by a healthcare provider
  - Administer 210 mg subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm.

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Romosozumab-aqqg (Evenity®)[39] (continued)

- Warnings and precautions
  - May increase risk of MI, cardiovascular or cerebrovascular death
  - Should not be used in individual who has had MI or CVA in the past 1-year.
  - Limit to length of use: 1-year.
    - Effect wanes after 1-year.
  - Renal impairment: Patients with severe renal impairment or receiving dialysis are at greater risk of developing hypocalcemia.
  - Monitor serum calcium and supplement with calcium and vitamin D.

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Romosozumab-aqqg (Evenity®)[39] (continued)

- Contraindications
  - Hypocalcemia
  - Pregnancy and lactation

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Romosozumab-aqqg (Evenity®)[39] (continued)

- Efficacy
  - Significantly reduced the incidence of new vertebral fractures through month 12, compared to placebo
  - In addition, the significant reduction in fracture risk persisted through the second year in women who received romosozumab during the first year and transitioned to denosumab compared to those who transitioned from placebo to denosumab.
  - Increased BMD at month 12: 12.7% at the lumbar spine, 5.8% at the total hip, and 5.2% at the femoral neck

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Romosozumab-aqqg (Evenity®)[39] (continued)

- Adverse effects
  - Arthralgias (0.2%) and headache (0.1%)
  - In a randomized controlled trial in postmenopausal women, there was a higher rate of major adverse cardiac events (MACE), a composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, in patients treated with Evenity® compared to those treated with alendronate.

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Romosozumab-aqqg (Evenity®)[39] (continued)

- Adverse effects (cont.)
  - In a randomized controlled trial…(cont.)
    - MI: 0.2% placebo, 0.3% romosozumab
    - CVA: 0.3% placebo, 0.2% romosozumab
    - MI: 0.8% romosozumab, 0.2% alendronate
    - CVA: 0.6% romosozumab, 0.3% alendronate
  - Osteonecrosis of the jaw

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Romosozumab-aqqg (Evenity®)[39] (continued)

- Advantages
  - First in its class
- Competition
  - No other product within class
  - Another option for those with osteoporosis
- Cost
  - Approximately $1,825 per month

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Re-evaluation after Therapy[40]

- Monitoring of therapy has traditionally been with BMD every two years.
  - May be done at 1-year
- Remember: One does not need to show gains in BMD to have success.
- However, continuing loss suggests secondary cause or poor adherence.

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Osteonecrosis of the Jaw (ONJ)[40]

- Characterized clinically by an area of exposed bone in the mandible, maxilla or palate that typically heals poorly or does not heal over a period of 6 to 8 weeks.[1]
- ONJ has occurred in one in 100,000 individuals on oral bisphosphonates.[2]
- 95% of ONJ is related to IV bisphosphonates for cancer therapy.[2]

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Osteonecrosis of the Jaw (ONJ)[40] (continued)

- 60% of those with ONJ had a recent dental extraction as a predisposing factor.
  - The majority have an underlying malignancy as an added risk.
- In general, ONJ rates in these patients range from 1.3% to 7%.

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Osteonecrosis of the Jaw (ONJ)[41] (continued)

- Predisposing factors for the development of ONJ appear to be…
  - Dental surgery
  - Oral trauma
  - Periodontitis
  - Poor dental hygiene
  - Treatment with chemotherapy
  - Treatment with corticosteroids

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How should clinicians respond?[41]

- The documented benefits from the use of bisphosphonates for established indications clearly outweigh whatever small risk of ONJ documented in the literature.
- For the patient on nitrogen-containing bisphosphonates caution should be used in recommending elective invasive dental work such as dental-implant surgery.

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Pulse Therapy[42]

- Women who discontinued alendronate after 5 years showed…
  - A moderate decline in BMD
  - A gradual rise in biochemical markers
  - No higher hip fracture risk (although slightly higher clinical vertebral fractures) compared to those who continued alendronate
- Results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk.
- **Can we do this clinically?**

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Case Study

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Case Study Anna: 57-year-old Female

- Family history
  - Mother with hip fracture at age 75 years related to a fall
- PMH
  - No personal history of fractures (fragility or traumatic)
  - Hypothyroid with replacement (TSH – 0.89 mIU/mL)
  - Asthma – Present since childhood
  - Total abdominal hysterectomy (TAH) at age 40 years
  - Hypertension – Diagnosed at age 46 years

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Anna (continued)

- Social history
  - 4 ounces (118 mL) white wine daily for past 10 years
  - Smoker: 15-pack year history of smoking
    - Discontinued 10 yrs ago; no relapses
  - Exercise
    - Walks 20 minutes, approximately 4 times per week

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Anna (continued)

- Medications
  - Levothyroxine 125 mcg one daily for 20 years
  - HCTZ 12.5 mg one daily
  - Fluticasone/salmeterol (Advair®) 250/50 mcg 1-puff twice daily
  - Prednisone 1× per year for asthma exacerbation

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Anna (continued)

- Physical examination
  - 65 inches (165 cm)
  - 111 pounds (50 kg)
- Labs
  - 25 (OH) vitamin D level: 20.5 ng/mL (51.25 nmol/L)
  - Serum calcium: 8.9 mg/dL (2.2 mmol/L)

- DXA scan
  - Hip: T-score = -1.7
  - L-S spine: T-score = -2.0

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Anna (continued)

1. Would you treat Anna?

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Anna (continued)

2. If yes, with what?
   a. Calcium and vitamin D
   b. Estrogen therapy/ menopausal hormone therapy (ET/HT)
   c. Selective estrogen receptor modulators (SERMs)
   d. Calcitonin
   e. Bisphosphonate (weekly, monthly, every 3 months, once yearly)
   f. Parathyroid hormone
   g. Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor
   h. Sclerostin inhibitor

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Summary

- Osteoporosis is underdiagnosed and undertreated.
- Numerous options exist to treat and prevent this condition.
- Adherence to any chronic medication is often poor. Therefore, all techniques to improve outcomes should be entertained.

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I would be happy to entertain any questions you have!

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End of Presentation!
Thank you for your time, attention.

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