UPMC LIFE CHANGING MEDICINE

Updates in Management of Osteoporosis

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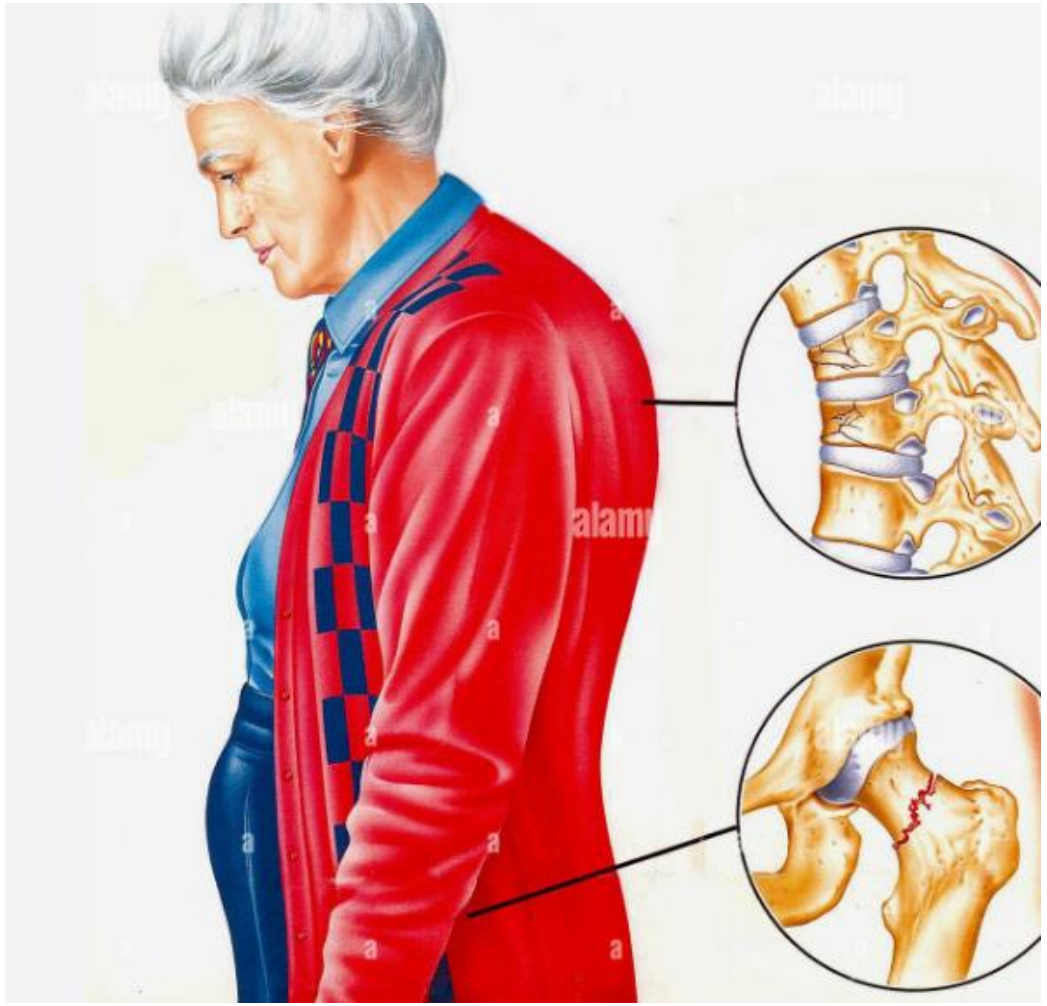
Disclosures

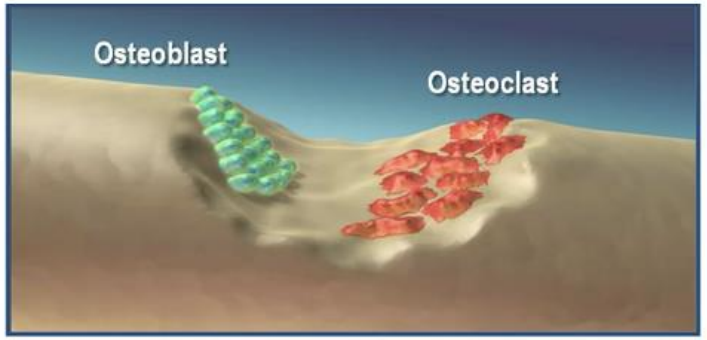
- None

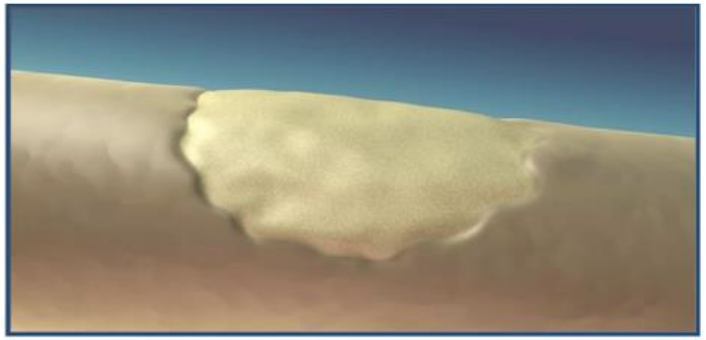
Objectives

- To highlight the morbidity and mortality associated with fragility fractures
- To determine who and how to screen for osteoporosis
- To review initial evaluation of secondary causes of osteoporosis
- To review pharmacological management and highlight more newly available options

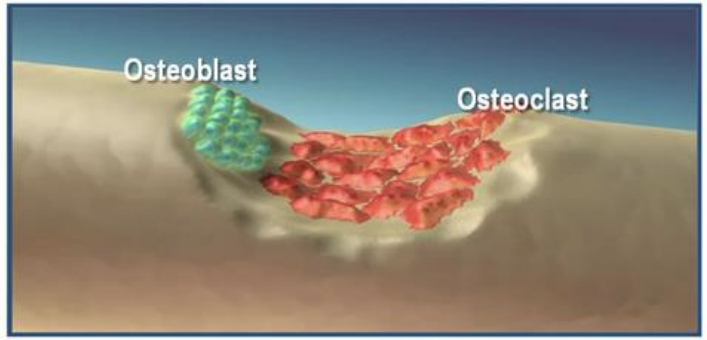


Normal Homeostasis

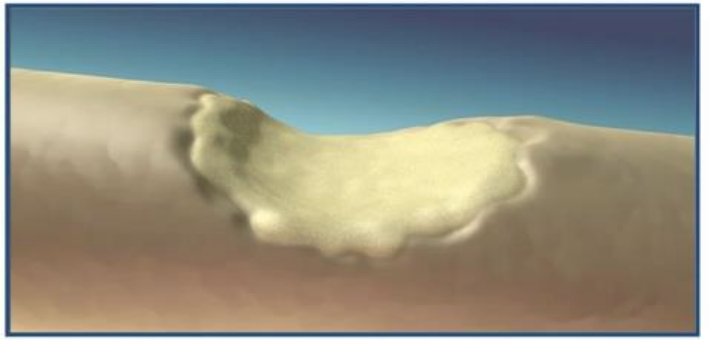




Postmenopausal Osteoporosis Results From Imbalanced Remodeling[3]



Negative Bone Balance[2]



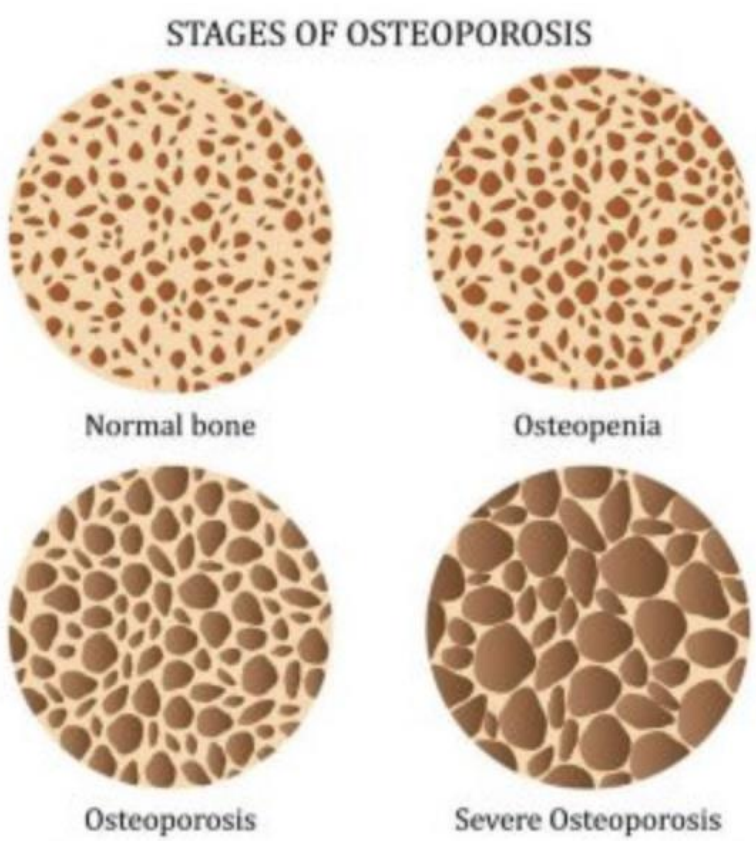
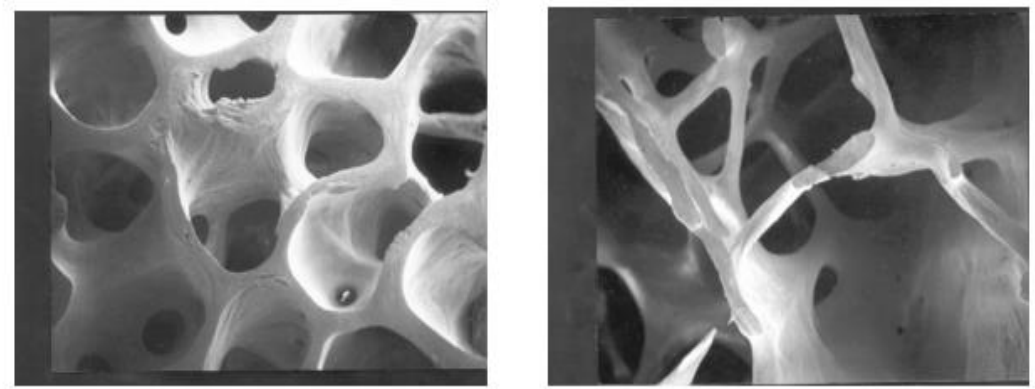


Fig. 3 Micrographs of normal (left) and osteoporotic (right) bone. As trabecular mineral is depleted, individual bony plates and connecting branches are lost, leaving less resilient, weaker bone that is more likely to fail under normally tolerated mechanical loads. Dempster, DW et al. (1986) *J Bone Miner Res* 1:15-27. Reprinted with permission [50]



Dempster, DW et al. (1986) J Bone Miner Res 1:15-27. reprinted with permission.[51]

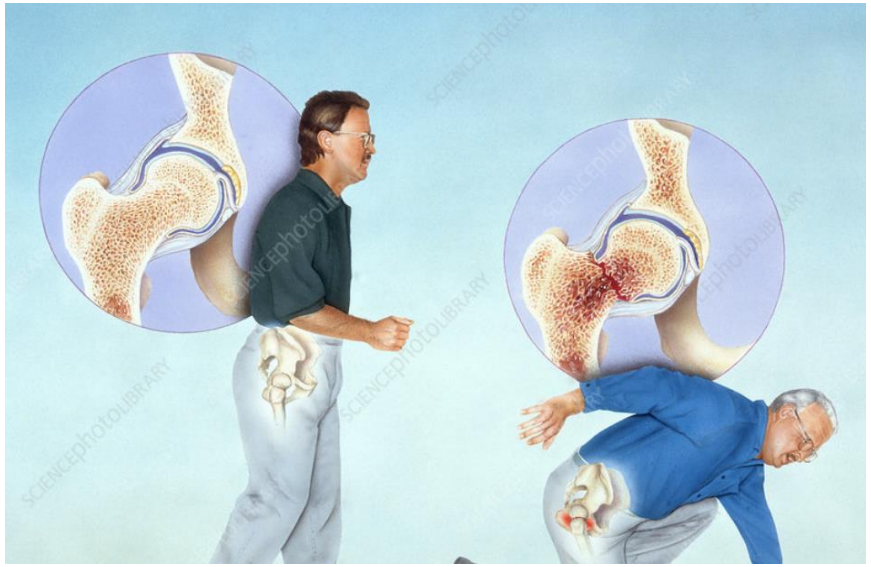
Introduction

- Osteoporosis is the most common metabolic bone disease in the USA and the world
- Any new fracture in an adult ≥ 50 years signifies imminent elevated risk for subsequent fractures
  - Particularly in the year following the initial fracture
- Untreated osteoporosis can lead to a vicious cycle of recurrent fracture(s), often resulting in disability and premature death
- **Primary care providers and medical specialists are critical gatekeepers** who can identify fractures and initiate proven osteoporosis interventions

M. S. LeBoff, et al., Osteoporosis International (2022)) 33:2049–2102

Disturbing Gap

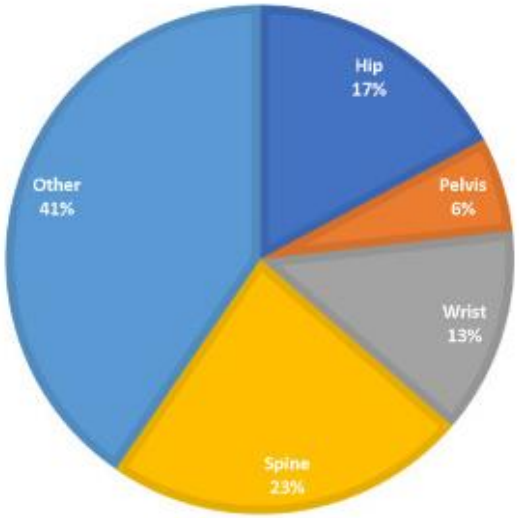
- At-risk patients are often not screened
- Majority of highest risk women and **men** who have a fracture(s) are not diagnosed and do not receive effective, FDA-approved therapies
- Even those prescribed appropriate therapy are unlikely to take the medication as prescribed



M. S. LeBoff, et al., Osteoporosis International (2022)) 33:2049–2102

Fractures

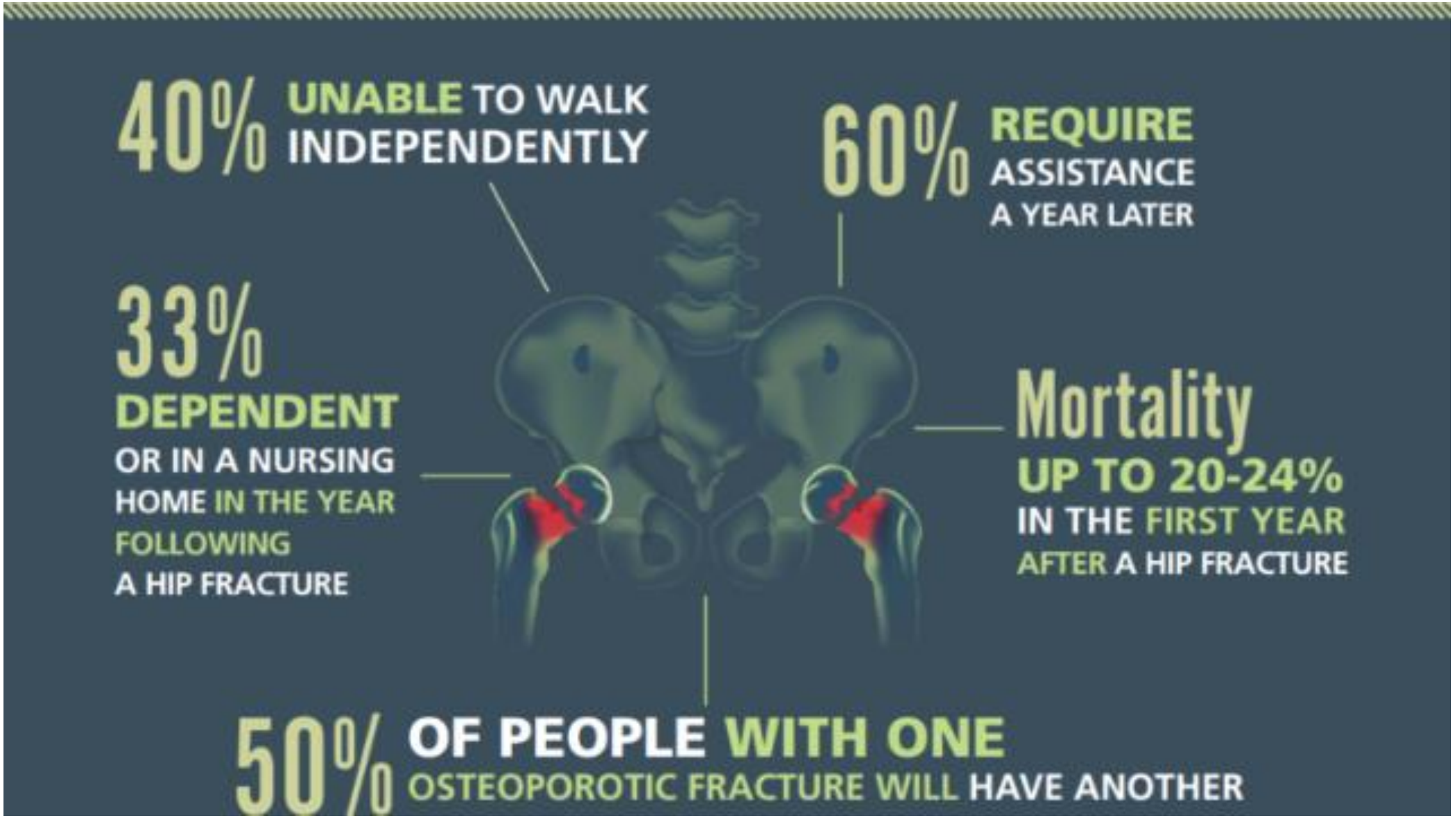
- Fractures can occur in any bone
  - Hip and spine fractures are most common, account
    of all osteoporotic fractures
- An estimated **10.2 million** persons aged ≥ 50 years in t
  States have osteoporosis
- About 43.3 million persons (**>40% of older U.S. adults**) have low bone mass associated with a high risk for progression to osteoporosis



Qaseem, MD, PhD, MHA, et al., Pharmacologic Treatment of Primary Osteoporosis or Low BoneMass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians., Ann Intern Med.2023;176:224-238

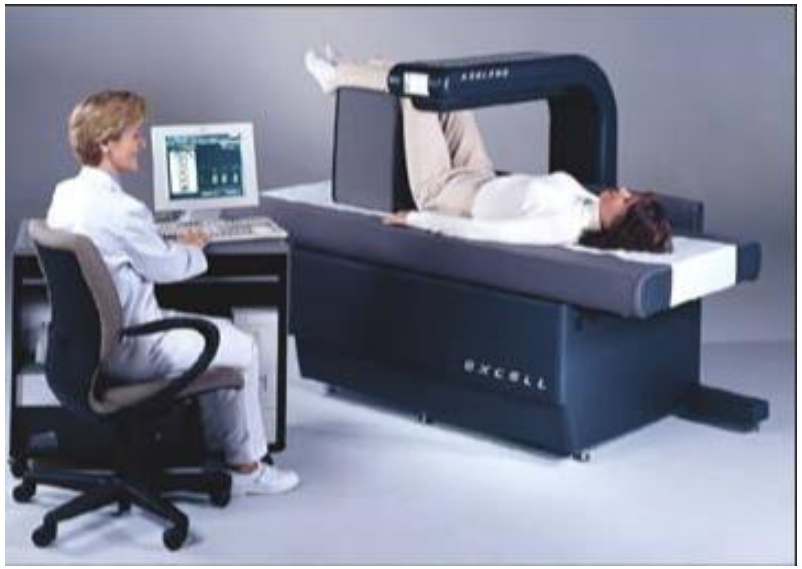
- At present the 2 million new cases of osteoporotic fracture per year
  - Exceeds the annual number of new cases of MI, breast cancer, and prostate cancer combined
- Annual fracture incidence is expected to increase 68%, to 3.2 million by 2040
- The personal and economic costs of fractures are enormous
  - Fractures result in more than 432,000 hospital admissions
  - Annual fracture related costs are expected to increase from $57 billion to over $95 billion by 2040
- This heavy toll could be significantly reduced with routine use of effective treatments and screenings

M. S. LeBoff, et al., Osteoporosis International (2022)) 33:2049–2102



Kagan, MD., et al., American Bone Health

Screening



- Perform BMD testing in the following:
  - **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
  - DXA facilities that employ accepted quality assurance measures
    - The same facility and on the same densitometry device for each test whenever possible

M. S. LeBoff, et al., Osteoporosis International (2022)) 33:2049–2102

Diagnostic categories for osteoporosis and low bone mass based upon BMD measurement by DXA

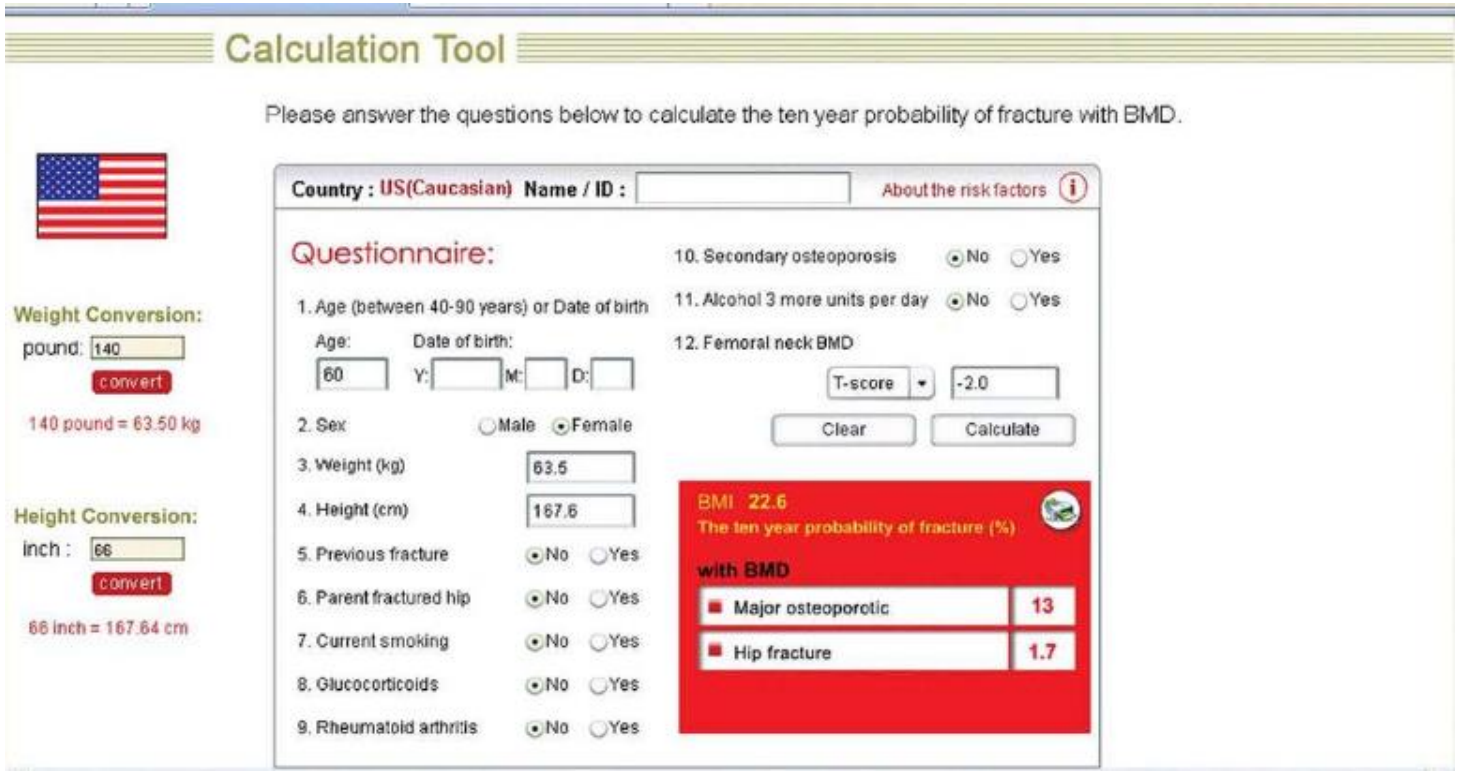
Category	Bone mass
Normal	A value for BMD within 1.0 SD of the young adult female reference mean (T-score greater than or equal to -1.0 SD).
Low bone mass (osteopenia)	A value for BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean (T-score less than -1 and greater than -2.5 SD).
Osteoporosis	A value for BMD 2.5 or more SD below the young adult female reference mean (T-score less than or equal to -2.5 SD).
Severe (established) osteoporosis	A value for BMD more than 2.5 SD below the young adult female reference mean in the presence of one or more fragility fractures.

BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; SD: standard deviation.

Data from: WHO scientific group on the assessment of osteoporosis at the primary health care level: Summary meeting report, 2004. Geneva: World Health Organization, 2007.

FRAX®

- The National Osteoporosis Foundation Clinician's Guide focuses on its utility in postmenopausal women and men aged >50 years
- Validated to be used in untreated patients only
- The current National Osteoporosis Foundation Guide recommends treating patients with FRAX 10-year risk scores of > or = 3% for hip fracture or > or = 20% for major osteoporotic fracture, to reduce their fracture risk

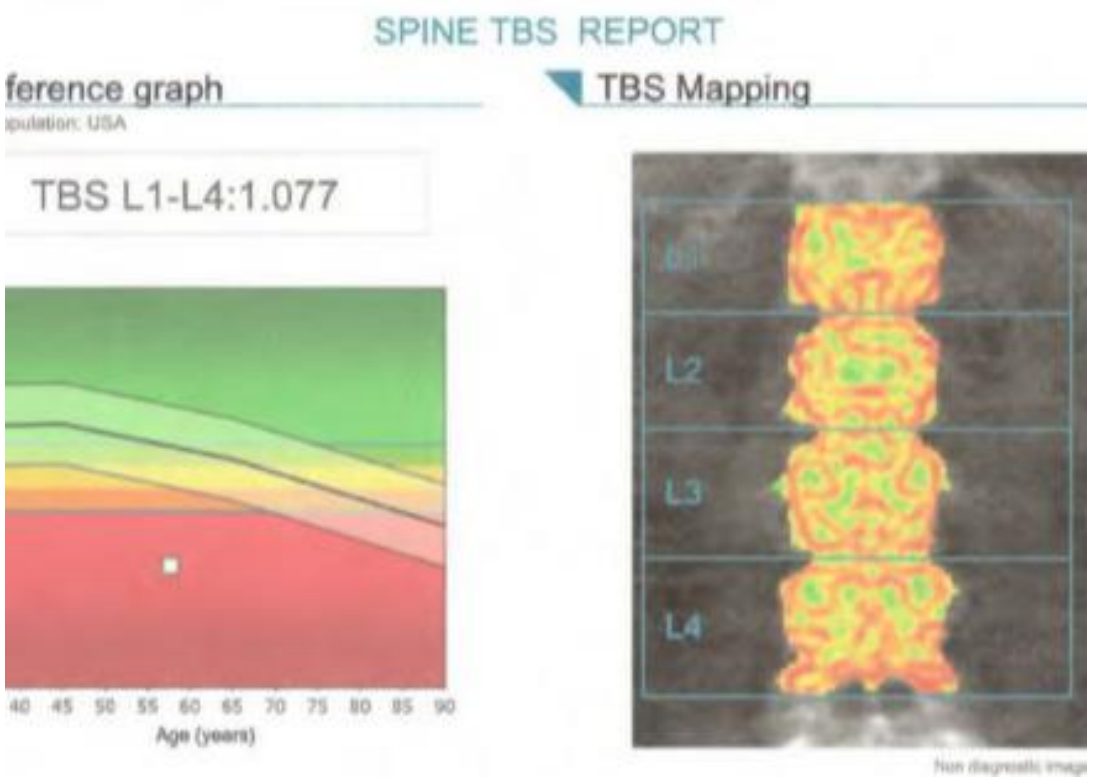


Siris, MD, et al., Primary Care Use of FRAX®: Absolute Fracture Risk Assessment in Postmenopausal Women and Older Men

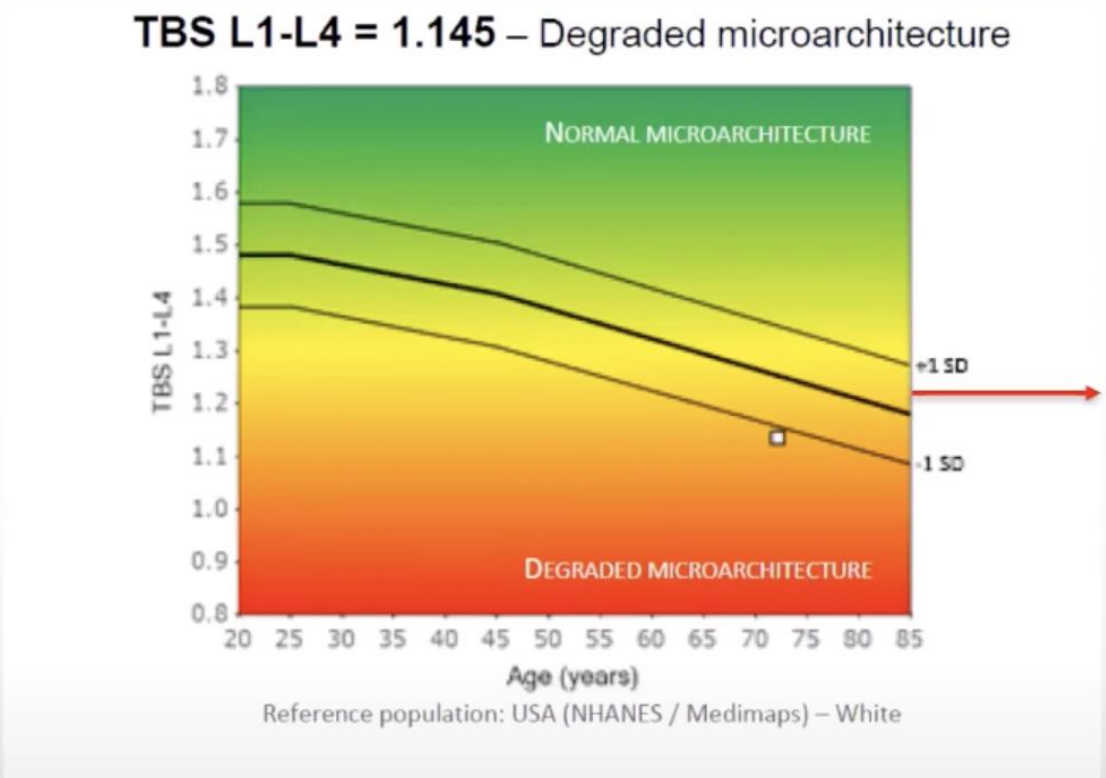
Pages 82-90 | Published online: 13 Mar 2015

FRAX® with trabecular bone score (TBS)

- An assessment of how evenly or unevenly mineral is structurally distributed in trabecular bone
- Adding TBS to FRAX®, which is possible on late-model densitometry devices, increases the ability of FRAX® to predict fractures (TBS-adjusted FRAX®)
- TBS is most applicable to patients who have low bone mass, rather than those with osteoporosis according to BMD criteria, for whom treatment is already indicated
- TBS is FDA approved



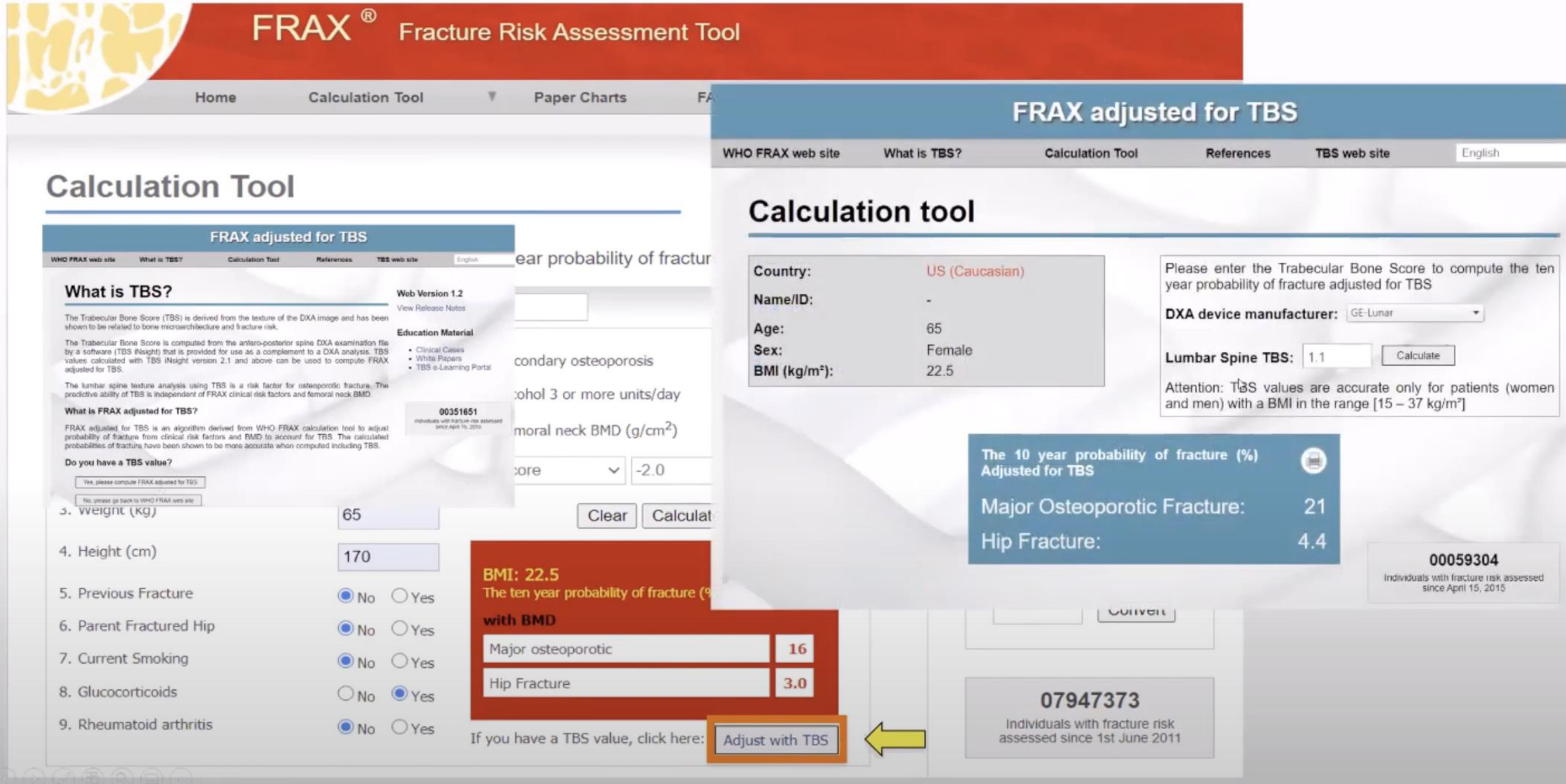
Characterize the bone structure



Spine TBS	TBS ≥ 1.310	Normal microarchitecture
	1.230 < TBS < 1.310	Partially degraded microarchitecture
	TBS ≤ 1.230	Degraded microarchitecture

McCloskey EV, Odén A, Harvey NC, et al. A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its Relationship to FRAX. J Bone Miner Res. 2016 May;31(5):940-8. doi: 10.1002/jbmr.2734. Epub 2015 Nov 19. PMID: 26498132 Free Article

Adjustment of FRAX Based on TBS



Causes of Secondary Osteoporosis

Medical conditions	Medications
Central nervous system disorders (e.g., epilepsy, multiple sclerosis, Parkinson disease, spinal cord injury, stroke)	Anticonvulsants (e.g., phenobarbital, phenytoin [Dilantin])
Chronic obstructive pulmonary disease	Chemotherapeutics
Endocrine/metabolic disorders (adrenal insufficiency, athletic amenorrhea, Cushing syndrome, hemochromatosis, homocystinuria, primary hyperparathyroidism, hyperprolactinemia, hyperthyroidism, primary or secondary hypogonadism, premature menopause, thyrotoxicosis, type 1 diabetes mellitus)	Cyclosporine (Sandimmune)
Gastrointestinal disorders (celiac disease, gastric bypass, inflammatory bowel disease, malabsorption, pancreatic insufficiency, primary biliary cirrhosis)	Depo-medroxyprogesterone (Depo-Provera)
Hematologic disorders (hemophilia, leukemia and lymphomas, monoclonal gammopathies, multiple myeloma, sickle cell disease, thalassemia)	Glucocorticoids
Human immunodeficiency virus infection or AIDS	Gonadotropin-releasing hormone agonists and antagonists
Liver disease (severe)	Heparin
Nutrition disorders (alcoholism, anorexia nervosa/bulimia, malnutrition, vitamin A excess, vitamin D deficiency)	Lithium
Renal insufficiency or renal failure	Methotrexate
Rheumatoid arthritis	Proton pump inhibitors
Systemic lupus erythematosus	Selective serotonin reuptake inhibitors
	Tacrolimus (Prograf)
	Tamoxifen
	Thiazolidinediones (e.g., pioglitazone [Actos])
	Thyroid hormone excess

Adapted from U.S. Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General. *Rockville, Md.: U.S. Department of Health and Human Services, Office of the Surgeon General; 2004:47,51.*

Evaluation

- **History and physical examination**
  - Most of the conditions causing osteoporosis can be excluded with a careful history and physical examination
  - Lifestyle factors that contribute to bone loss

Lifestyle factors
Alcohol abuse
Excessive thinness
Excess vitamin A
Frequent falling
High salt intake
Immobilization
Inadequate physical activity
Low calcium intake
Smoking (active or passive)
Vitamin D insufficiency/deficiency

Evaluation

Table 3 Diagnostic studies for exclusion of secondary causes of osteoporosis

Blood or serum

- Complete blood count (CBC)
- Albumin
- Chemistry levels (albumin-adjusted calcium, renal function, phosphorus, and magnesium)
- Liver function tests
- 25(OH) vitamin D
- Parathyroid hormone (PTH)
- Total testosterone and gonadotropin (men aged 50–69 years)

Consider in select patients

- Serum protein electrophoresis (SPEP), serum immunofixation, serum free kappa and lambda light chains
- Thyroid-stimulating hormone (TSH) +/− free T_4
- Tissue transglutaminase antibodies (and IgA levels)
- Iron and ferritin levels
- Homocysteine (to evaluate for homocystinuria)
- Prolactin level
- Tryptase
- Biochemical markers of bone turnover

Urine

- 24-h urinary calcium and creatinine

Consider in select patients

- Urinary protein electrophoresis (UPEP)
- Urinary free cortisol level (or salivary cortisol)
- Urinary histamine

Calcium and Vitamin D

- Recommend a diet with adequate total calcium intake
  - 1000 mg/day for men aged 50–70 years
  - 1200 mg/day for women ≥ 51 years and men ≥ 71 years
  - Incorporating calcium supplements if intake is insufficient
- Monitor serum 25-hydroxyvitamin D levels
  - Maintain serum vitamin D sufficiency (≥ 30 ng/mL but below ≤ 50 ng/mL)
  - Prescribe supplemental vitamin D (800–1000 units/day) as needed for individuals aged 50 years and older to achieve a sufficient vitamin D level
    - Higher doses may be necessary in some adults, especially those with malabsorption

Treatment

- STRONGLY consider initiating pharmacologic treatment in postmenopausal women and men ≥ 50 years of age who have the following:
  - **Primary fracture prevention**:
    - T-score ≤ − 2.5 at the femoral neck, total hip, lumbar spine, 33% radius (some uncertainty with existing data) by DXA
    - Low bone mass (osteopenia: T-score between − 1.0 and − 2.5) at the femoral neck or total hip by DXA with a 10-year hip fracture risk ≥ 3% or a 10-year major osteoporosis-related fracture risk ≥ 20% based on the US-adapted FRAX® model

M. S. LeBoff, et al., Osteoporosis International (2022)) 33:2049–2102

- STRONGLY Consider initiating pharmacologic treatment in postmenopausal women and men ≥ 50 years of age who have the following:
  - **Secondary fracture prevention**
    - Fracture of the hip or vertebra regardless of BMD
    - Fracture of proximal humerus, pelvis, or distal forearm in persons with low bone mass (osteopenia: T-score between − 1.0 and − 2.5)
    - The decision to treat should be individualized in persons with a fracture of the proximal humerus, pelvis, or distal forearm who do not have osteopenia or low BMD

M. S. LeBoff, et al., Osteoporosis International (2022)) 33:2049–2102

Table 11 FDA-approved drugs for osteoporosis [153]

Drug name	Brand name	Form/dosing	Approval for
Bisphosphonates			
Alendronate	Generic alendronate and Fosamax®, Fosamax Plus D™	Oral (tablet) Daily/weekly	Women and men
Alendronate	Binosto®	Effervescent tablet Weekly	Women and Men
Ibandronate	Boniva®	Oral (tablet) Monthly	Women
Ibandronate	Boniva®	Injection Quarterly	Women
Risedronate	Actonel®/Actonel® w/ calcium	Oral (tablet) Daily/weekly/twice monthly/monthly; monthly with calcium	Women and men
Risedronate	Atelvia™	Oral delayed-release (tablet) Weekly	Women
Zoledronic acid	Reclast®	IV infusion Once a year/once every 2 years	Women and men
Estrogen-related therapies			
Estrogen	Multiple brands	Oral (tablet) Daily	Women
Estrogen	Multiple brands	Transdermal (skin patch) Twice weekly/weekly	Women
Raloxifene	Evista®	Oral (tablet) Daily	Women
Conjugated	Duavee®	Oral (tablet)	Women

Parathyroid hormone analogs		
Abaloparatide	Tymlos®	Injection Daily (for 2 years)
Teriparatide	Forteo®	Injection Daily (for ≥ 2 years)*
RANKL inhibitor		
Denosumab	Prolia™	Injection Every 6 months
Sclerostin inhibitor		
Romosozumab	Evenity™	Injection (2) Monthly for 12 months
Calcitonin Salmon		
Calcitonin	Fortical®/Miacalcin®	Nasal spray Daily
Calcitonin	Miacalcin®	Injection Schedule varies

Alendronate (Fosamax®)

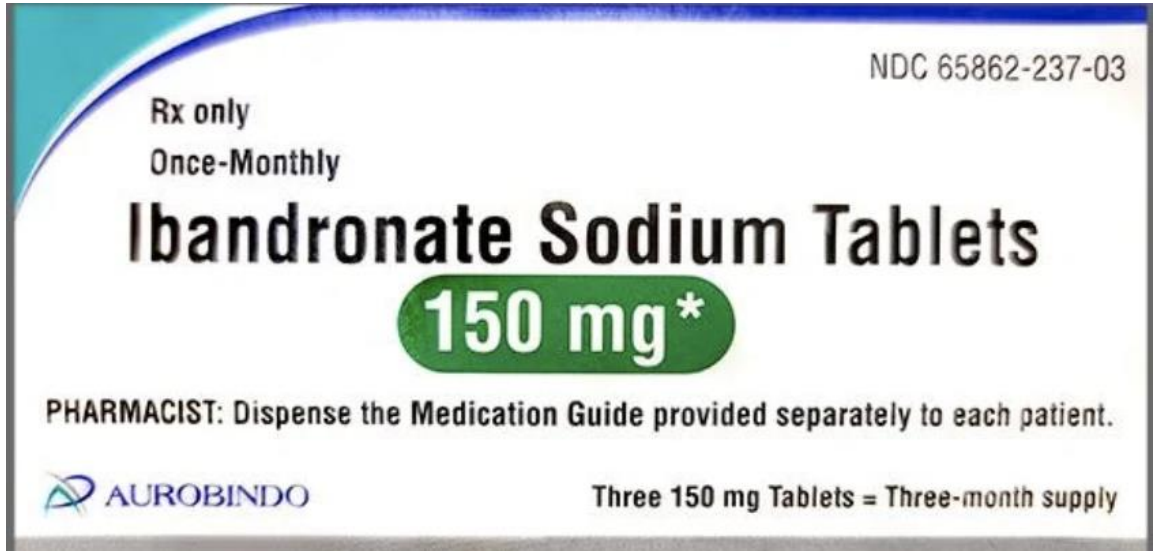
- Reduces incidence of spine and hip fractures by about 50% over 3 years in patients with prior vertebral fracture and in patients who have hip T scores diagnostic of osteoporosis (≤ − 2.5)

Side Effects

- Similar for all oral bisphosphonate medications and include:
  - Gastrointestinal problems such as difficulty swallowing
  - Esophageal inflammation
  - Rare cases of atypical femur fractures (AFF) and osteonecrosis of the jaw (ONJ)
  - Ocular inflammation (anterior uveitis and episcleritis) has been documented
  - **All bisphosphonates can affect renal function and are contraindicated in patients with estimated GFR below 30– 35 mL/min**

Ibandronate (Boniva®)

- Ibandronate reduces incidence of vertebral fractures by about 33–50% over 3 years **but does not reduce risk of non-vertebral fracture (hip/non-hip)**

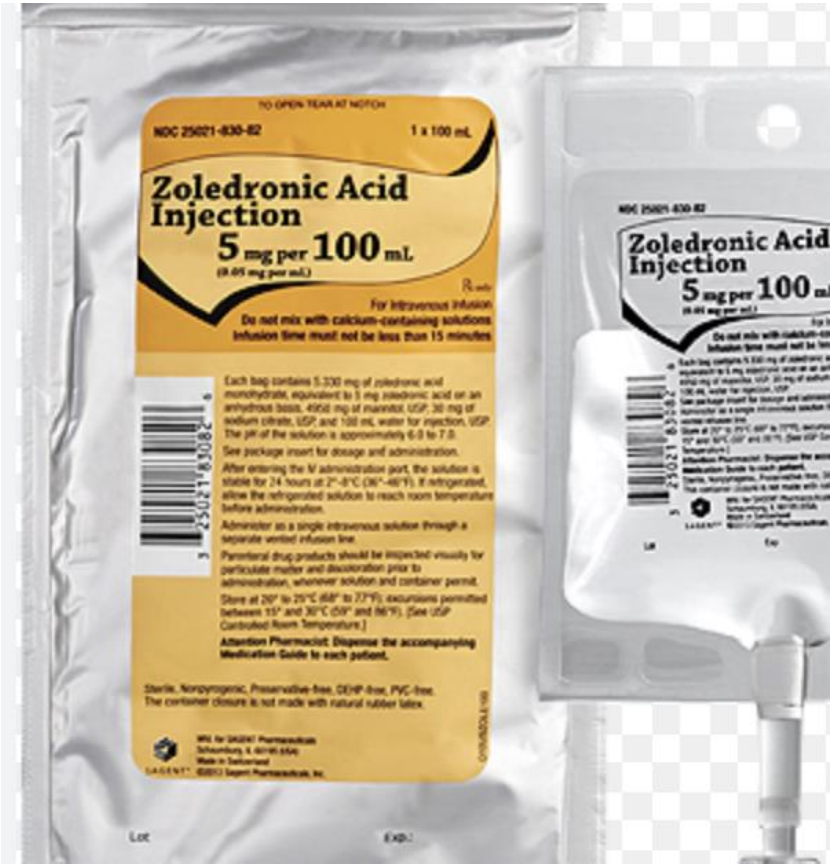


Risedronate (Actonel®, Atelvia™)

- Compared with placebo, risedronate reduced incidence of vertebral fractures by 39%, hip fractures by 27%, and non-vertebral fractures by 22%

Zoledronic acid, brand name: Reclast®

- Zoledronic acid is approved by the FDA for prevention and treatment of osteoporosis in postmenopausal women
  - (5 mg once yearly for treatment and once every 2 years for prevention)



Zoledronic acid, brand name: Reclast®

Reduces incidence of vertebral fractures by 62–70% (with significant reduction at 1 year), hip fractures by 41%, and non-vertebral fractures by 21–25% over 3 years in patients with osteoporosis

Zoledronic acid, brand name: Reclast®

5 mg in 100 mL, is given once yearly by intravenous infusion administered over at least 15 min

Flu-like symptoms (arthralgia, headache, myalgia, fever) have occurred in 32% of patients after the first dose, 7% after the second dose, and 3% after the third dose

- **To reduce likelihood of acute-phase reactions, patients should be well hydrated, drink 2 glasses of water before the infusion and pre-treat with acetaminophen**

Zoledronic acid, brand name: Reclast®

25(OH) vitamin D level should be replete before treatment

May cause or exacerbate hypocalcemia

Is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment

Bisphosphonate holiday

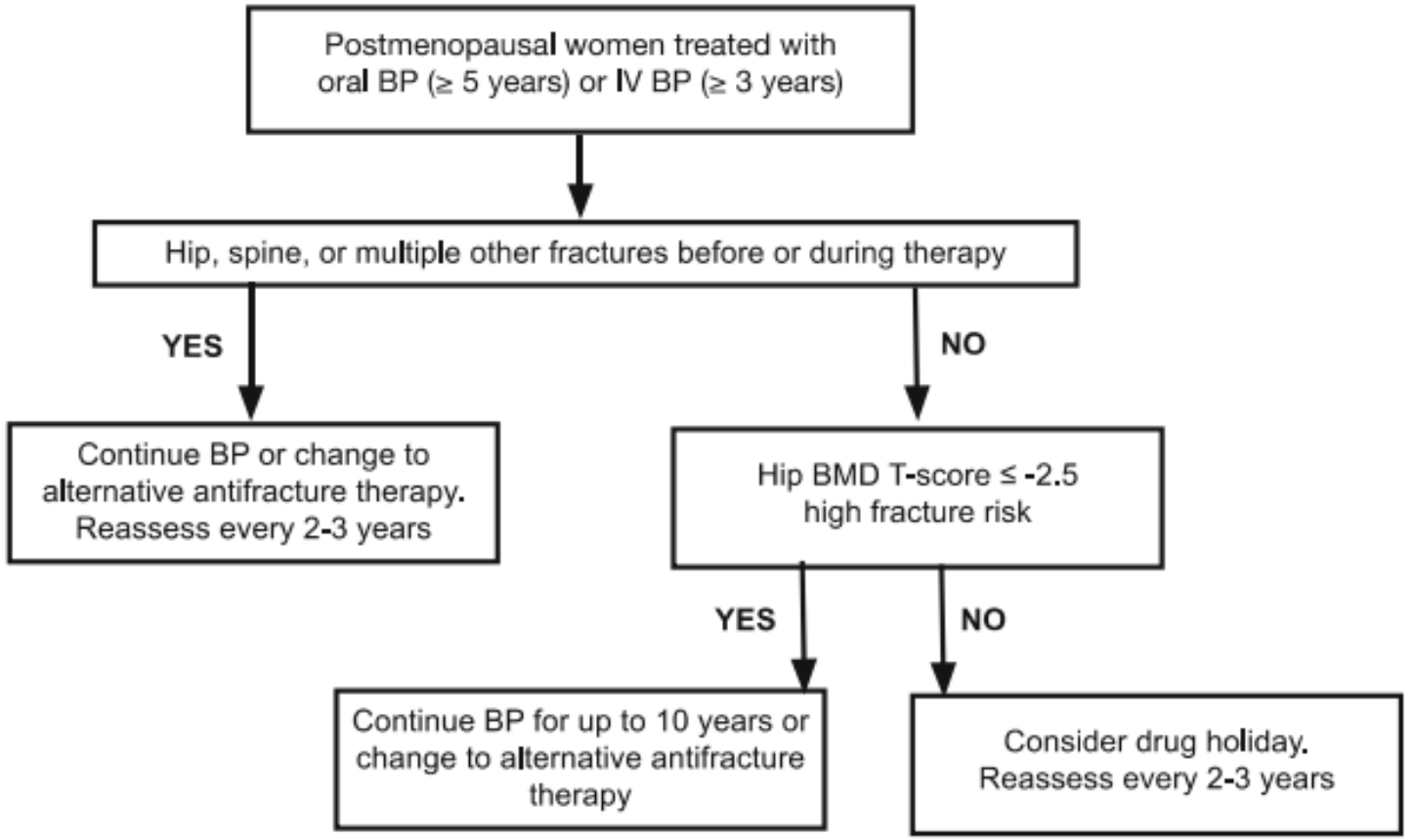


Fig. 6 Management of long-term bisphosphonate (BP) treatment in postmenopausal women. Note: This flowchart illustrates ASBMR task force recommendations for management of patients taking bisphosphonates. All other osteoporosis drugs lose effect rapidly when discontinued and must be promptly followed by alternative antifracture therapies. Adler RA, et al. (2016), *J Bone Miner Res* [14]

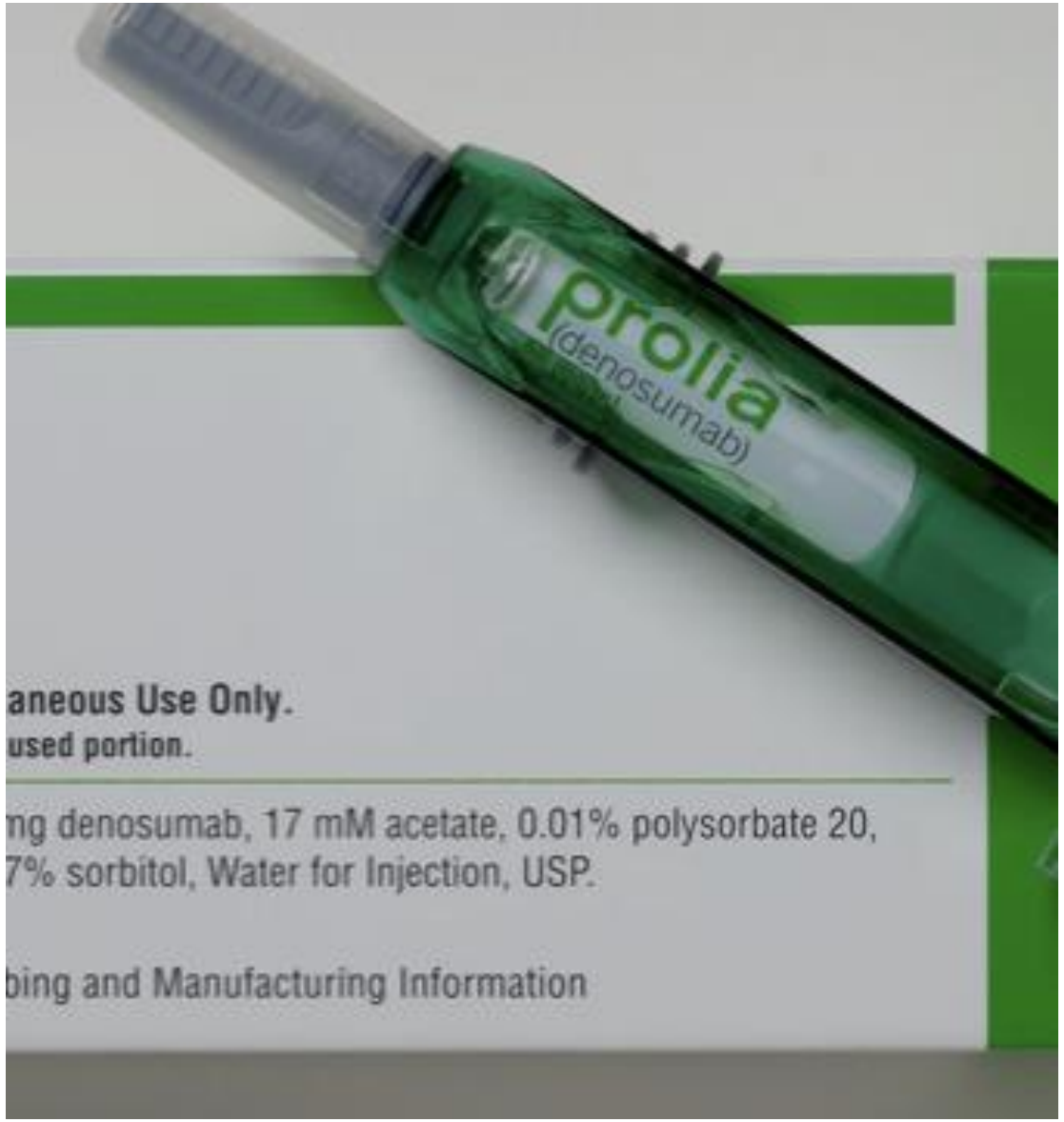
Please keep track of bisphosphonate start date

RANKL inhibitor (denosumab)

- The cytokine RANK-ligand (RANKL) produced by osteocytes is required for osteoclast formation
- Suppressing RANKL blocks osteoclast formation, leading to less bone resorption and higher bone density

Denosumab

- Denosumab is one of the most potent antiresorptive drugs available
- Denosumab reduces incidence of vertebral fractures by about 68% at 1 year, hip fractures by about 40% and non-vertebral fractures by about 20% at 3 years, with continued fracture reduction in studies extended to 5 years



Denosumab

- May cause or exacerbate hypocalcemia, and therefore, hypocalcemia must be corrected before treatment
- Has been associated with very rare cases of AFF and ONJ

Denosumab

- Discontinuation of denosumab treatment is associated with rapid bone loss that may result in multiple vertebral fractures, especially in patients with a prior vertebral fracture
- **A drug holiday is not appropriate with denosumab**
- During periods of suspended treatment, and as recommended by the FDA, alternate antiresorptive therapy should be considered to maintain gains in bone density.

Parathyroid hormone analogs (teriparatide, abaloparatide)

- Parathyroid hormone (PTH) regulates calcium homeostasis

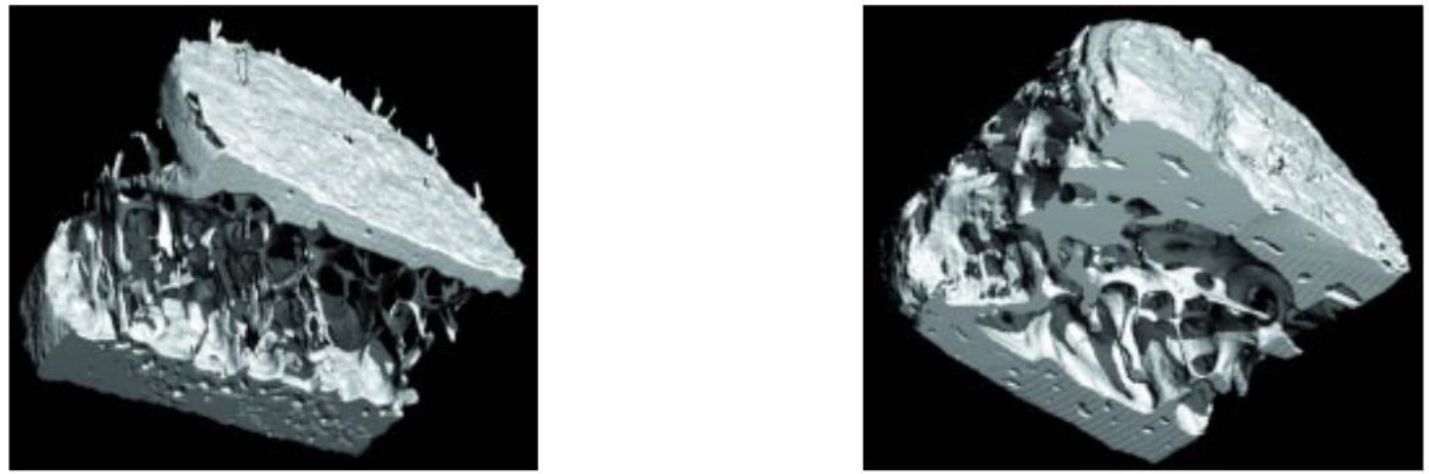
- Constant high exposure to PTH causes bone resorption, while intermittent administration of exogenous recombinant PTH stimulates bone formation

Teriparatide, brand name: Forteo® and the bioequivalent Bonsity

Reduces risk of vertebral fractures by 65–77%, and non-vertebral fractures by 35–53% in patients with osteoporosis, after an average of 18 months of therapy

It is important to follow teriparatide treatment with an antiresorptive agent, usually a bisphosphonate or denosumab, to maintain or further increase BMD

Anabolic Effect



After 21 months of Forteo

Neer et al. NEJM 2001

Teriparatide, brand name: Forteo® and the bioequivalent Bonsity

Teriparatide is administered by 20 µg daily subcutaneous injection.

When treatment is discontinued, bone loss can be rapid and alternative agents should be considered to maintain BMD

Treatment duration was previously restricted to 24 months, but this was recently changed to open the possibility of longer treatment in high-risk patients.

Teriparatide, brand name: Forteo® and the bioequivalent Bonsity

Side effects:

- Transient orthostatic hypotension
- Leg cramps and nausea
- Transiently increases serum calcium which may predispose patients to digitalis toxicity
- It should be used with caution in patients with active or recent kidney stones, hypercalcemia and hypercalcemic disorders, and/or cutaneous calcification
- Its use should be avoided in settings of increased risk for osteosarcoma

Abaloparatide, brand name: Tymlos®

- Reduces risk of new vertebral fractures by about 86% and non-vertebral fractures by about 43% in postmenopausal women with osteoporosis, after an average of 18 months of therapy

Abaloparatide, brand name: Tymlos®

- Administered by 80 µg daily subcutaneous injection in the periumbilical area of the abdomen
- Abaloparatide treatment duration is recommended not to exceed 24 months
- It is common practice to follow abaloparatide treatment with an antiresorptive agent, usually a bisphosphonate or denosumab, to maintain or further increase BMD

Sclerostin inhibitor (romosozumab) Romosozumab-aqqg, brand name **EVENITY™**

- Romosozumab is a fully human monoclonal antibody to sclerostin
- It is currently FDA-approved for 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 poor response or intolerance to other available osteoporosis therapies.

Sclerostin inhibitor (romosozumab) Romosozumab-aqqg, brand name EVENITY™

- **Reduces fractures and increases BMD at the lumbar spine and total hip more than placebo, alendronate, and teriparatide in postmenopausal women with low bone mass**

- In the pivotal FRAME trial, romosozumab compared to placebo for 12 months reduced risk of new vertebral fracture by 73% and clinical fractures by 36%

Sclerostin inhibitor (romosozumab) Romosozumab-aqqg, brand name EVENITY™

- Extension studies have reported BMD trending back towards pretreatment levels after discontinuing therapy
    - Follow-on therapy with denosumab and, to a lesser degree, alendronate preserve or continue to accrue BMD benefits following romosozumab therapy

Sclerostin inhibitor (romosozumab) Romosozumab-aqqg, brand name EVENITY™

- Received FDA approval with a boxed warning stating that it may increase risks for myocardial infarction, stroke, and cardiovascular (CV) death
  - **It should not be taken by women who experienced a stroke or CV event in the previous year**
- May cause hypocalcemia, and therefore, hypocalcemia must be corrected before treatment
- Has been associated with rare cases of AFF and ONJ (fewer cases than denosumab)

Monitoring treatment response

DXA is currently the preferred approach

Recommend monitoring the BMD by dual-energy X-ray absorptiometry at the spine and hip every 1 to 3 years to assess the response to treatment

Clinical assessment should be performed to identify new fractures, falls, and/or new or worsening comorbidities.

J Clin Endocrinol Metab, May 2019, 104(5):1595–1622

2023 ACP Guidelines

Bisphosphonates are recommended as first-line therapy for postmenopausal women and for men with primary osteoporosis

The RANK ligand inhibitor denosumab (Prolia) is recommended as second-line therapy for women or men with contraindications to — or adverse effects from — bisphosphonates

Romosozumab (Evenity) and the recombinant parathyroid hormone teriparatide (Forteo) — are recommended “conditionally” only for women with osteoporosis and very high fracture risk

- **These drugs are prescribed only for 1 and 2 years, respectively, and should be followed by a bisphosphonate to mitigate rebound bone loss.**

Qaseem A et al. Ann Intern Med 2023 Jan 3 Ott SM. Ann Intern Med 2023 Jan 3

Clinical Pearls

Perform BMD testing in women aged ≥ 65 years and men aged ≥ 70 years

Maintain serum vitamin D sufficiency (≥ 30 ng/mL but below ≤ 50 ng/mL) and ensure adequate calcium intake

Adding TBS to FRAX®, which is possible on late-model densitometry devices, increases the ability of FRAX® to predict fractures (TBS-adjusted FRAX®)

Bisphosphonates are first line but ensure that start date is clearly documented and treatment holiday is recommended after 5 years unless high risk of fracture

Please keep in mind that denosumab (Prolia) needs to be continued with NO holiday – if plan to stop then need to start alendronate or zoledronic acid infusion

Anabolic agents NEED to be followed by antiresorptive agents to maintain BMD gains

Do not use romosuzumab in women with a heart attack or stroke in the past 12 months

Primary care providers and medical specialists are critical gatekeepers who can identify fractures and initiate proven osteoporosis interventions

Thank you!