
بسم الله الرحمن الرحيم

In the Name of God

Postmenopausal Osteoporosis

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1403/07/25

References:

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- *N Engl J Med 2023;389:1979-91., Clinical Practice. Postmenopausal Osteoporosis*
- *OBSTETRICS & GYNECOLOGY, VOL. 139, NO. 4, APRIL 2022 .ACOG Committee on Cli nical Practice Guidelines. Management of Postmenopausal Osteoporosis.*
- *J Menopausal Med 2024;30:1-23,The 2024 Guidelines for Osteoporosis - Korean Society of Menopause.*
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Osteoporosis is a **silent disease** until a fracture occurs. Approximately 71% of osteoporotic fractures in people aged ≥50 years occur in **women**.

Postmenopausal osteoporosis is caused by estrogen deficiency, which leads to increased osteoclast differentiation and activation, accelerated bone resorption that outpaces formation, and rapid bone loss, particularly in the years immediately before and after menopause.

Individuals who fail to reach peak bone mass during childhood and adolescence can develop osteoporosis earlier in their 50s without aging factors and decreased estrogen levels.

women have an average life expectancy of approximately 87–88 years. Considering menopause typically occurs at roughly 50 years old, postmenopausal life spans over 37–38 years, accounting for more than **40%** of an individual's lifespan.

the overall prevalence of osteoporosis in adults over 50 was 22.4%, with 7.5% in men and 37.3% in women, showing that the rate is **over four times higher in women**. The prevalence of osteoporosis by age increased roughly two-fold for every 10-year increase, with 15.4% for women aged 50–59, 36.6% for 60–69, and 68.5% for those over 70.

Individuals with osteoporosis and an elevated or high risk of fracture can be identified through screening and risk assessment.

In addition to lifestyle and environmental interventions, such as aerobic and weight-bearing exercise, adequate intake of calcium and vitamin D, and fall-prevention strategies, pharmacologic therapy generally is indicated for individuals at high risk of fracture. Bone loss can be slowed or prevented with pharmacologic therapy.

The National Institutes of Health in the United States, defining osteoporosis as “a skeletal disorder characterized by **compromised bone strength** predisposing a person to an increased risk of fracture”. The term ‘bone strength’ is a term that reflects both **bone density and bone quality**.

At present, there are no specific ways to measure bone quality; thus, it could be said that there are no accurate methods to quantify overall bone strength. Consequently, BMD tests are primarily used as a substitute measure for evaluating bone strength. It is known that **BMD reflects about 70% of bone strength.**

Diagnosing osteoporosis using BMD has low sensitivity in predicting fractures; only about **20%** of female fractures are diagnosed as osteoporosis.

Postmenopausal osteoporosis is diagnosed on the basis of the occurrence of a **fragility fracture** (with no associated trauma or with trauma equivalent to falling from a standing height or less) or bone mineral density at the spine, total hip, or femoral neck that is at least 2.5 standard deviations below the mean of that in a young adult reference population (**T score of −2.5 or less**), as measured with the use of DXA.

Dual-energy x-ray absorptiometry (DXA) is recommended in postmenopausal women **65 years of age or older** and postmenopausal women **younger than 65 years of age who have risk factors** (table 1).

Table 1. Risk Factors for Postmenopausal Osteoporosis and Fracture.

Older age	
Low weight (<127 lb [<58 kg])	Or BMI less than 20 kg/m2
Previous fracture during adulthood (particularly hip, spine, or wrist); recent fracture indicates a higher risk than remote or unclear history	
Parental history of hip fracture	
Current or past glucocorticoid treatment (>5 mg prednisolone daily or equivalent for 3 mo or more)	
Other medications that cause bone loss*	
Current smoking	
Excess alcohol intake	more than three drinks per day
Causes of secondary osteoporosis†	
Rheumatoid arthritis	
Premature menopause (<40 yr of age) or hypogonadism	
Frequent falls	

Screening and Diagnosis

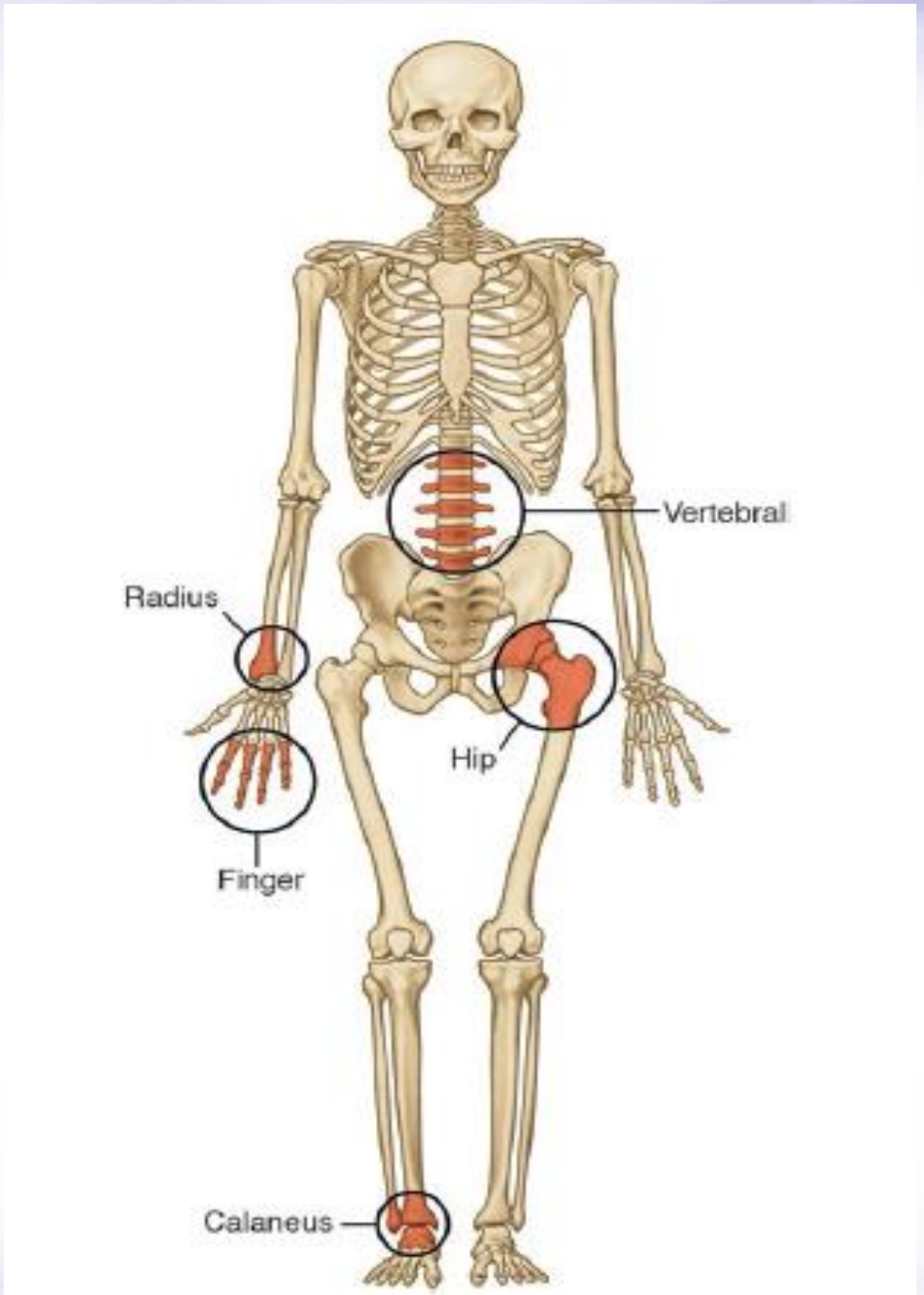
Evaluation for osteoporosis involves clinical examination (medical history, physical examination, height measurement), risk assessment with a formal risk assessment tool, and BMD testing (as indicated by age or risk assessment tool results).

Height loss can be an indicator of an asymptomatic vertebral fracture. Height loss also may indicate an increased risk of nonvertebral fracture. The National Osteoporosis Foundation recommends that patients who have lost 1.5 inches **(4 cm) or more from their peak height at age 20** years or 0.8 inches **(2 cm) or more from a previously documented** measurement or during 1–3 years should undergo vertebral imaging.

The **advantages** of DXA include

1) high accuracy,
2) minimal radiation exposure,
3) easy of use and interpretation,
4) easy assessment of response to treatment

it can also evaluate bone density in areas such as the forearm and the calcaneus. In situations where imaging of the lumbar spine and femur is not possible, in cases of hyperparathyroidism or extreme obesity in which the patient cannot get onto the imaging table, DXA captures images of the distal third of the radius.



Particular sites of the skeleton measured for diagnosis of osteoporosis

Osteoporosis is a lifelong problem that requires evolving management, which may include intervals on and off medical treatment. Considerations for the use of osteoporosis pharmacologic therapy include the following:

- type of treatment
- timing of initiation
- length of treatment
- use of drug holidays to reduce the risk of adverse events
- bone loss management when therapy is discontinued
- timing of therapy re-initiation
- indications for referral to an endocrinologist or other osteoporosis specialist

Before starting pharmacotherapy for osteoporosis, evaluate patients for **secondary causes** of bone loss. (GOOD PRACTICE POINT)

Secondary Causes of Bone Loss:

Evaluate patients for remediable secondary causes of bone loss. (GOOD PRACTICE POINT)

(Box 1 and Box 2), particularly in patients with very low BMD or with a history of multiple or recent fractures. Secondary causes should be corrected if possible. If bone loss persists, osteoporosis treatment should be initiated as necessary.

Box 1. Common Causes of Bone Loss or Secondary Osteoporosis*

Conditions, disorders, and diseases

- AIDS or HIV
- Anorexia nervosa
- Diabetes mellitus (type 1 and type 2)
- Diminished ovarian reserve
- Gastric bypass
- Hyperparathyroidism
- Hypocalcemia
- Premature menopause (induced or surgical)
- Primary ovarian insufficiency
- Renal impairment
- Rheumatoid arthritis
- Turner's syndrome
- Vitamin D deficiency

Medications

- Antiepileptic drugs (eg, phenytoin, carbamazepine, primidone, and phenobarbital)
- Antiretroviral drugs
- Aromatase inhibitors
- Cancer chemotherapeutic agents
- Depot medroxyprogesterone acetate†
- Glucocorticoids
- Gonadotropin-releasing hormone agonists
- Gonadotropin-releasing hormone antagonists
- Heparin

Causes: organ transplantation, hypopituitarism, malabsorption, bariatric surgery, immobility, untreated hyperthyroidism, chronic pulmonary disease, Cushing's disease, osteogenesis imperfecta, Gaucher's disease, and Marfan syndrome.

Other medications include, suppressive doses of thyroid hormone, cyclosporine, low-molecular-weight heparins, thiazolidinediones, antidepressants, and proton-pump inhibitors.

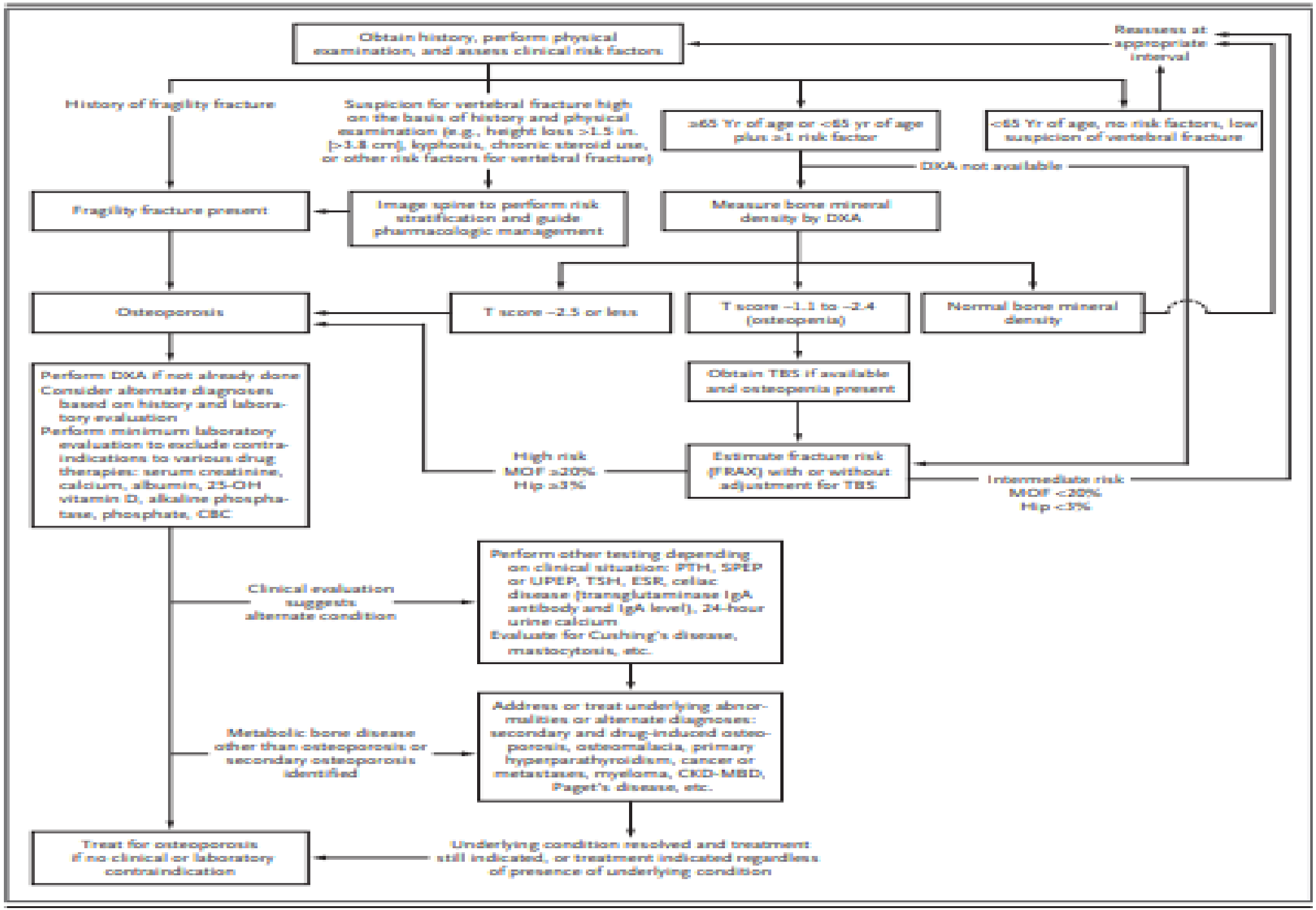
Some drug categories have been associated with higher fractures in epidemiologic studies but have not been causally linked.

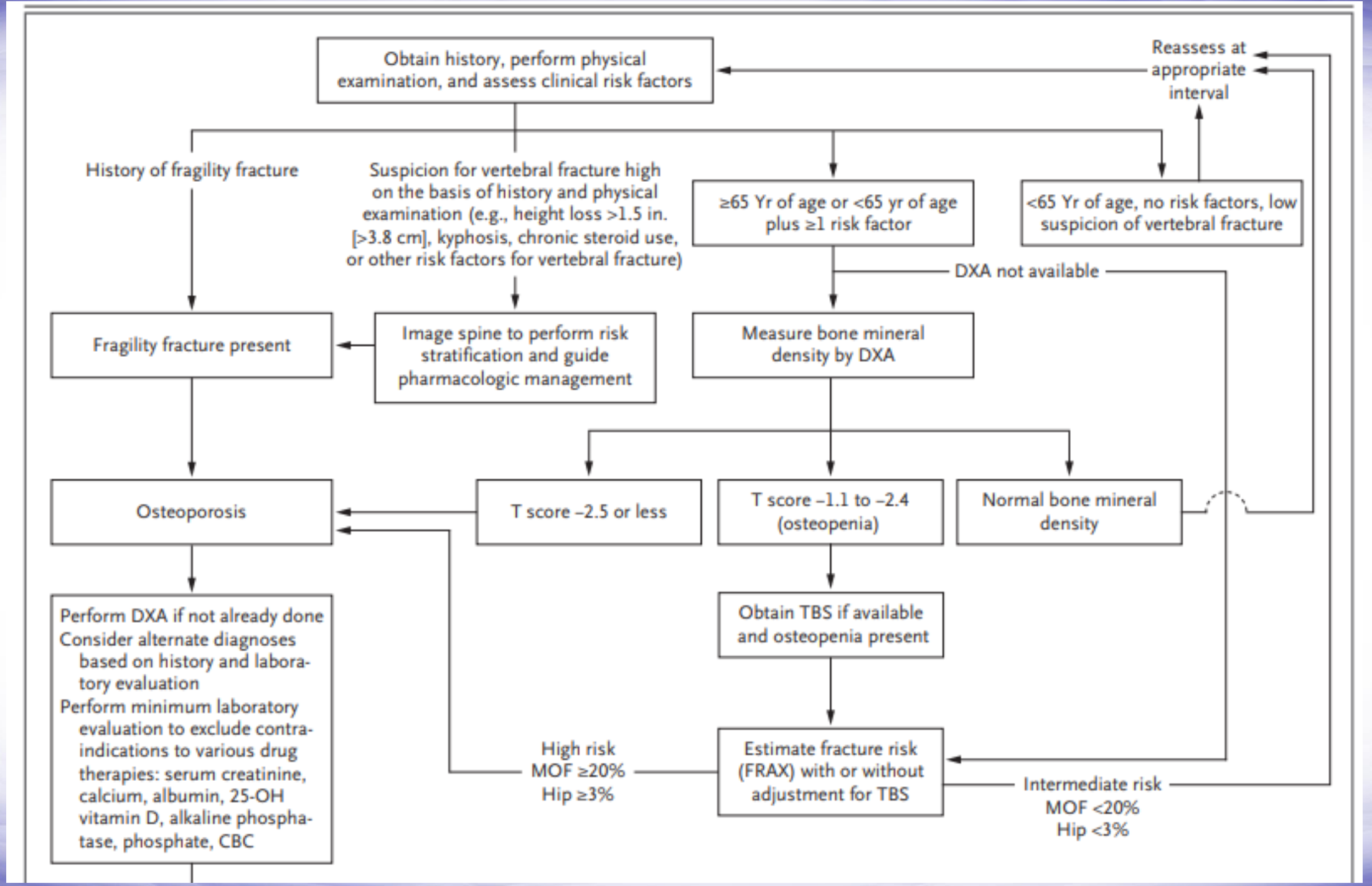
The use of **depot medroxyprogesterone** acetate is associated with loss of bone mineral density, available evidence suggests that decreases in bone density appear to be substantially or fully reversible after discontinuation.

Recommended risk assessment before initiation of **aromatase inhibitor** treatment or chemotherapy in patients with breast cancer includes BMD testing, a bone related medical history (eg, new back pain, occurrence of fractures or falls), use of a validated risk-assessment tool (eg, FRAX calculator), and a physical examination.

Box 2. Initial Evaluation for Secondary Osteoporosis

- Complete blood count
- Metabolic profile (calcium, renal function, phosphorus, and magnesium)
- 24-hour collection for calcium, sodium, and creatinine excretion
- Liver function tests
- Thyroid-stimulating hormone with or without free T4
- 25-hydroxyvitamin D


Obtain history, perform physical examination, and assess clinical risk factors
Reassess at appropriate interval
History of fragility fracture
Suspicion for vertebral fracture high on the basis of history and physical examination (e.g., height loss >1.5 in. [>3.8 cm], kyphosis, chronic steroid use, or other risk factors for vertebral fracture)
≥65 Yr of age or <65 yr of age plus ≥1 risk factor
<65 Yr of age, no risk factors, low suspicion of vertebral fracture
DXA not available
Fragility fracture present
Image spine to perform risk stratification and guide pharmacologic management
Measure bone mineral density by DXA
Osteoporosis
T score −2.5 or less
T score −1.1 to −2.4 (osteopenia)
Normal bone mineral density
Perform DXA if not already done
Consider alternate diagnoses based on history and laboratory evaluation
Perform minimum laboratory evaluation to exclude contraindications to various drug therapies: serum creatinine, calcium, albumin, 25-OH vitamin D, alkaline phosphatase, phosphate, CBC
Obtain TBS if available and osteopenia present
High risk
MOF ≥20%
Hip ≥3%
Estimate fracture risk (FRAX) with or without adjustment for TBS
Intermediate risk
MOF <20%
Hip <3%
Clinical evaluation suggests alternate condition
Perform other testing depending on clinical situation: PTH, SPEP or UPEP, TSH, ESR, celiac disease (transglutaminase IgA antibody and IgA level), 24-hour urine calcium
Evaluate for Cushing's disease, mastocytosis, etc.
Metabolic bone disease other than osteoporosis or secondary osteoporosis identified
Address or treat underlying abnormalities or alternate diagnoses: secondary and drug-induced osteoporosis, osteomalacia, primary hyperparathyroidism, cancer or metastases, myeloma, CKD-MBD, Paget's disease, etc.
Treat for osteoporosis if no clinical or laboratory contraindication
Underlying condition resolved and treatment still indicated, or treatment indicated regardless of presence of underlying condition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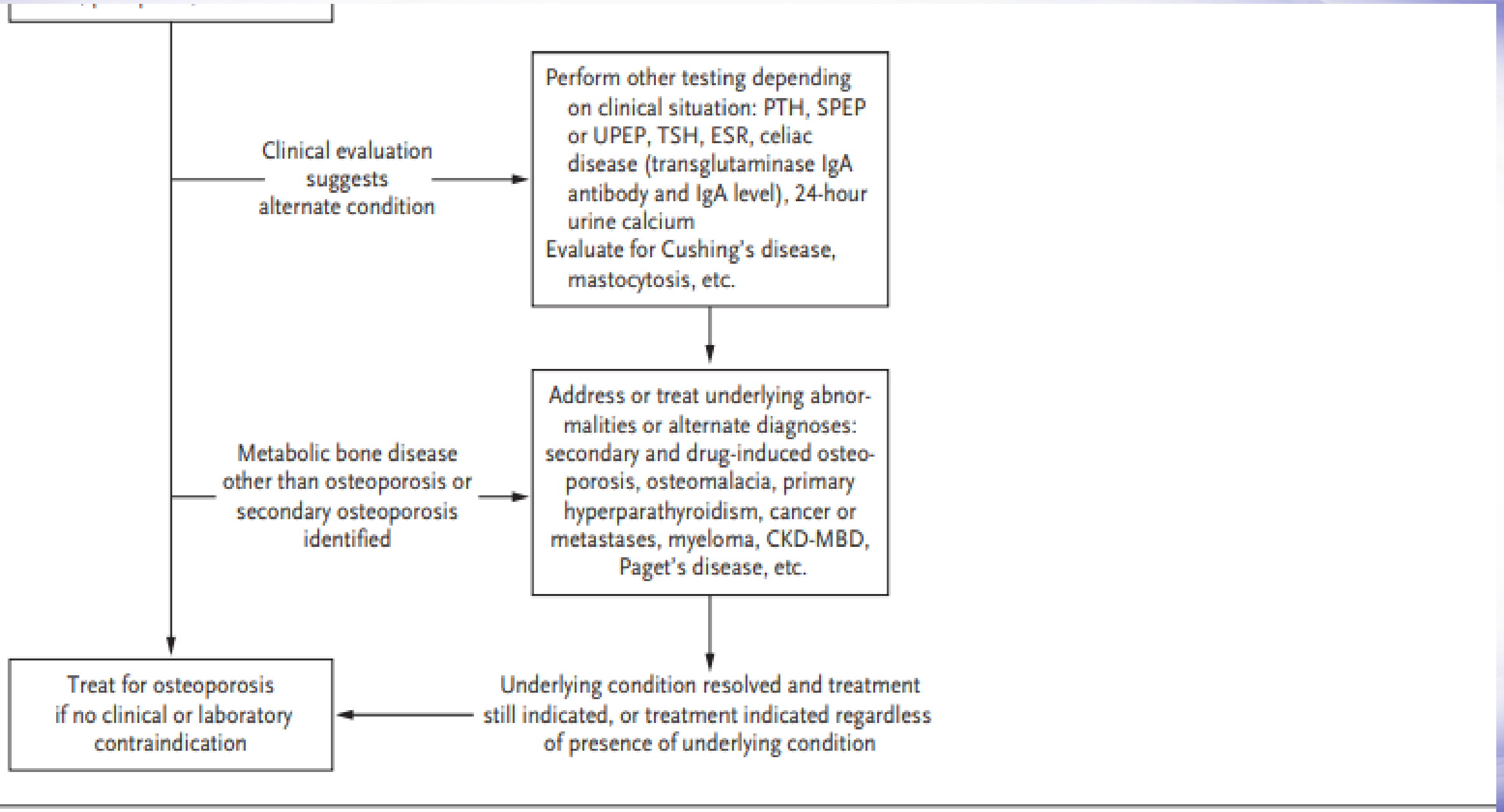
Perform DXA if not already done
Consider alternate diagnoses based on history and laboratory evaluation
Perform minimum laboratory evaluation to exclude contraindications to various drug therapies: serum creatinine, calcium, albumin, 25-OH vitamin D, alkaline phosphatase, phosphate, CBC
Obtain TBS if available and osteopenia present
High risk MOF ≥20% Hip ≥3%
Estimate fracture risk (FRAX) with or without adjustment for TBS
Intermediate risk MOF <20% Hip <3%


Clinical evaluation suggests alternate condition
Perform other testing depending on clinical situation: PTH, SPEP or UPEP, TSH, ESR, celiac disease (transglutaminase IgA antibody and IgA level), 24-hour urine calcium
Evaluate for Cushing's disease, mastocytosis, etc.
Metabolic bone disease other than osteoporosis or secondary osteoporosis identified
Address or treat underlying abnormalities or alternate diagnoses: secondary and drug-induced osteoporosis, osteomalacia, primary hyperparathyroidism, cancer or metastases, myeloma, CKD-MBD, Paget's disease, etc.
Underlying condition resolved and treatment still indicated, or treatment indicated regardless of presence of underlying condition
Treat for osteoporosis if no clinical or laboratory contraindication

Box 4. Suggested Indications for Subspecialist* Referral for Osteoporosis Management

- T-score less than −3.0
- New fragility fracture
- Normal bone mineral density and fragility fracture
- Recurrent fractures or progressive bone loss despite osteoporosis treatment
- Osteoporosis that is unusual or not responding to treatment
- Endocrine or metabolic causes of secondary osteoporosis (eg, hyperthyroidism, hyperparathyroidism, hypercalciuria, or elevated prolactin)
- Comorbidities that complicate treatment (eg, chronic kidney disease, low glomerular filtration rate, or malabsorption syndromes)

1. Low-risk group

Should satisfy all of the following criteria:

- No previous fragility fractures, especially hip or spine fractures.
- BMD T-score ≥-1.0.
- FRAX-calculated 10-year hip fracture risk <3% and major osteoporotic fractures <20%.

2. Moderate-risk group

Should satisfy all of the following criteria:

- No previous fragility fractures, especially hip or spine fractures.
- -2.5 <BMD T-score <-1.0.
- FRAX-calculated 10-year hip fracture risk <3% and major osteoporotic fractures <20%.

3. High-risk group

If at least one of the following criteria is satisfied:

- History of fragility fractures, especially hip or spine fractures >12 months ago .
- BMD T-score ≤-2.5.
- FRAX-calculated 10-year hip fracture risk ≥3%, or 10-year risk of major osteoporotic fracture risk ≥20%.

4. Very-high-risk group

If at least one of the following criteria is satisfied:
- Recent fragility fractures, especially hip or spine, within the past 12 months.
- Fractures occurring during approved osteoporosis treatment.
- Multiple fractures.
- Fracture occurred while on drugs that caused skeletal harm (e.g.,glucocorticoids).
- BMD T-score <-3.0.
- High risk of falls or history of injurious falls.
- FRAX-calculated 10-year hip fracture risk ≥4.5% or 10-year risk of major osteoporotic fracture risk ≥30%.

Candidates for Pharmacotherapy

ACOG recommends pharmacologic osteoporosis treatment in patients who have a high risk of fracture. (STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)

Box 3. Indications for Osteoporosis Pharmacotherapy

After evaluation for remediable secondary causes, pharmacotherapy for postmenopausal osteoporosis is recommended for patients who meet any of the following criteria:

- T-score −2.5 or lower by DXA of the femoral neck, total hip, lumbar spine, or distal 1/3 radius*
- History of fragility fracture, including asymptomatic vertebral fracture
- T-score between −1.0 and −2.5 and increased risk of fracture, as determined by a formal clinical risk-assessment tool†

For example, a high 10-year Fracture risk (hip fracture risk of ≥3% or major osteoporotic fracture risk of ≥20%) according to the fracture risk assessment tool (FRAX).

Fragility fractures can be classified into **major** (hip, spine, distal radius, and proximal humerus) and **minor** (sacrum, ribs, distal femur, humerus, and ankle), according to their anatomic sites.

FRAX estimated
fracture risk or T scores can be adjusted with the use of the **trabecular bone score** to enhance risk stratification. The trabecular bone score is most useful when it influences treatment decisions (e.g., for osteopenia or when the level of fracture risk is close to an intervention threshold) but should not be used alone for diagnosis.

2) Quantitative computed tomography

FDA-approved, clinically available software now permits opportunistic screening of volumetric bone mineral density, bone strength, and prevalent vertebral fractures with the use of routine clinical computed tomography (CT) to identify persons at risk for future fractures. the **advantage** of measuring regardless of body size. It can also exclude areas of the spine that influence BMD. it can evaluate the therapeutic effect of drugs and can exclude degenerative changes in the spine or aortic calcification. Evidence suggests that this technology performs at least as well as DXA.

The **pitfall** of QCT is that it exposes the patient to a higher radiation dose than DXA, WHO standards cannot be applied. Typically, osteoporosis is diagnosed when the BMD of the L2 and L3 areas is 80 mg/cm3 or less.

3) Quantitative ultrasound

QUS has the advantages of no radiation exposure, being easy to use, and occupying a small space for equipment; thus, it is widely used in many countries. The FDA approved QUS for predicting osteoporosis, and the International Society for Clinical Densitometry (ISCD) consensus recommends measurements only at the heel. The calcaneus, rich in trabecular bone, makes measuring changes in BMD easier than cortical bone. QUS does not show results that match BMD. In studies that measured BMD and QUS simultaneously, the correlation was moderate. However, it has been reported to predict fracture risk relatively well.

Fracture risk reassessment should be performed annually in all groups except the low-risk group. Depending on the results of fracture risk reassessment, appropriate sequential treatment is required.

In the low-risk group, osteoporosis medication is not required and fracture risk reassessment is performed every 2 years.

In the moderate-risk group, osteoporosis medication is not required and fracture risk reassessment is performed annually. Even in the moderate-risk group, if physicians determine that osteoporosis treatment is necessary, treatment with selective estrogen receptor modulators or bisphosphonates (BPs) (risedronate, etc.) might be considered.

In the high-risk group, alendronate, risedronate, zoledronic acid, and denosumab are recommended as first-line therapies.

While ibandronate and raloxifene reduced the vertebral fracture risk compared to placebo, they did not reduce non-vertebral and hip fracture risk significantly. Thus, ibandronate and raloxifene can be used to reduce the vertebral fracture risk.

Pharmacotherapy Options:

ACOG recommends bisphosphonates as initial therapy for most postmenopausal patients at increased risk of fracture. (STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)

Bisphosphonates prevent and treat osteoporosis by inhibiting osteoclast-mediated bone resorption.

Adverse effects of oral bisphosphonates include musculoskeletal pains, gastrointestinal irritation, and esophageal reflux and ulceration. Potential rare risks include osteonecrosis of the jaw, atypical fractures of the femoral shaft, and esophageal cancer. Patients should be cautioned that pain in the thigh or groin may be a prodrome to an atypical femoral fracture.

Bisphosphonates generally are contraindicated in patients with acute renal failure or reduced kidney function (ie, estimated glomerular filtration rate of less than **35** mL/min for zoledronic acid and alendronate or less than **30** mL/min for risedronate and ibandronate).

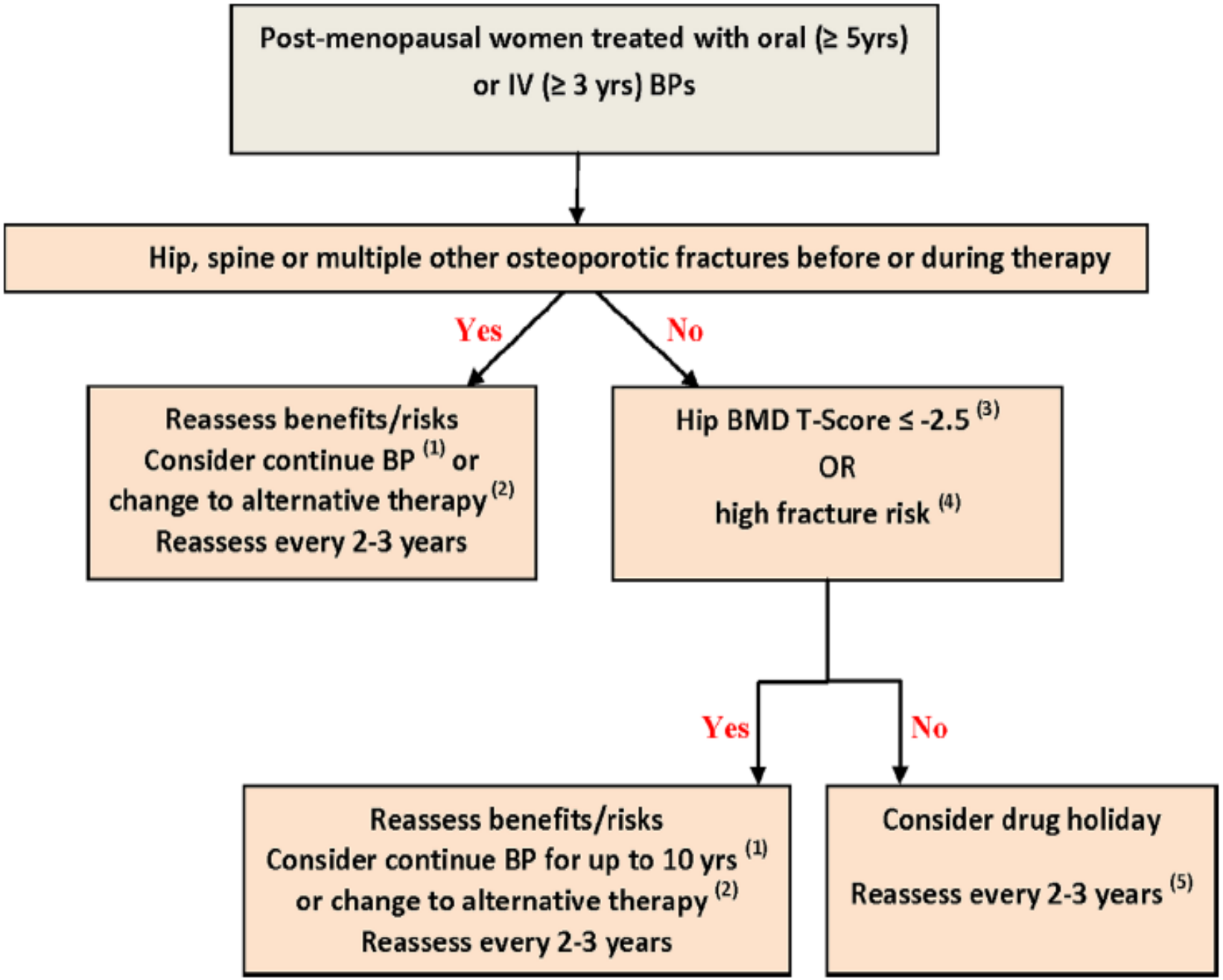
When BPs are used as a first-line therapy, BMD measurements and fracture risk reassessments should be performed **annually**. If the fracture risk is reduced to low-to-moderate or moderate-risk after drug treatment, a **drug holiday** may be considered if the patients are stable. The concept of drug holidays was developed because of the uncertainty about the antifracture benefits of long-term bisphosphonate use and concern that persistence of bisphosphonates in bone might increase the risk of atypical femoral fracture and osteonecrosis of the jaw.

ACOG suggests discontinuation of bisphosphonates to allow a drug holiday after 5 years of treatment with oral bisphosphonates or after 3 years of treatment with intravenous zoledronic acid. **Longer treatment**, of up to 10 years for oral bisphosphonates or up to 6 years for intravenous zoledronic acid, is suggested for patients at **high risk** of fracture. (CONDITIONAL RECOMMENDATION, LOW QUALITY EVIDENCE)

During drug holidays, fracture risk reassessment should be performed at intervals of **1 to 2 years**, and drug treatment should be resumed when the BMD T-score decreases significantly (T-score ≤-2.5) or a fracture occurs. Retreatment may be considered when bone resorption markers increase to pretreatment levels during drug holidays, but this is still controversial for general application.

If the fracture risk persists in patients classified as high-risk, BPs should be continued or switching to a more effective drug should be considered. If oral BPs are used, switching to injectable antiresorptive agents can be considered. If **injectable BPs agents** are used or the fracture risk increases to a very high level, switching to **anabolic agents** may be considered.

Teriparatide treatment in patients previously treated with BP or denosumab increased spinal BMD but decreased hip BMD.


Post-menopausal women treated with oral (≥ 5yrs) or IV (≥ 3 yrs) BPs
Hip, spine or multiple other osteoporotic fractures before or during therapy
Yes
No
Reassess benefits/risks
Consider continue BP (1) or change to alternative therapy (2)
Reassess every 2-3 years
Hip BMD T-Score ≤ -2.5 (3)
OR
high fracture risk (4)
Yes
No
Reassess benefits/risks
Consider continue BP for up to 10 yrs (1) or change to alternative therapy (2)
Reassess every 2-3 years
Consider drug holiday
Reassess every 2-3 years (5)

ACOG recommends using denosumab as initial therapy for postmenopausal patients at increased risk of fracture who prefer every 6-month subcutaneous administration. (STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE) Denosumab is a human monoclonal antibody that interferes with osteoclast production and activity by inhibition of the RANK ligand.

Patients who discontinue **denosumab** therapy should be transitioned to treatment with another **antiresorptive agent**. (GOOD PRACTICE POINT)

A drug holiday is not recommended for denosumab because of the increased risk of rapid bone loss and vertebral fractures within a few months of treatment cessation. The duration of continued treatment will depend on clinical factors, such as the patient's individual risk of fracture. Clinical data are available for up to 10 years of denosumab use.

Unlike bisphosphonates, denosumab can be used in patients with decreased glomerular filtration rates. However, as with bisphosphonates, denosumab is contraindicated in patients with **hypocalcemia**, and rare cases of osteonecrosis of the jaw and atypical femoral fractures have been reported.

the **discontinuation of denosumab** is associated with rapid bone loss. After denosumab discontinuation, BMD at all skeletal sites declines significantly and **returns to pretreatment values after 1 to 2 years**. Suppressed bone turnover markers, C-terminal telopeptide and propeptide of type I collagen, increase above pretreatment levels within 3 and 6 months. And it has been reported that the risk of multiple vertebral fractures is increased. In real-world settings, the risk of any fracture, vertebral fracture and multiple vertebral fractures increased.

Sequent BPs treatment (alendronate, zoledronic acid) after denosumab discontinuation effectively maintained the BMD gain obtained with denosumab treatment. Thus, if denosumab is used as first-line therapy, treatment is continued until the fracture risk is reduced to moderate; when discontinuation of denosumab is considered, subsequent BPs treatment is required. The evidence for sequential **raloxifene** treatment after denosumab discontinuation to prevent rebound phenomenon is **insufficient.**

Selective Estrogen Receptor Modulators

ACOG suggests raloxifene for postmenopausal patients at **increased risk of vertebral fracture** and **breast cancer** who are at **low risk of venous thromboembolism** and **do not have significant vasomotor symptoms**. (CONDITIONAL RECOMMENDATION, HIGH-QUALITY EVIDENCE)

Raloxifene, a selective estrogen receptor modulator, is indicated for the prevention and treatment of postmenopausal osteoporosis as well as for the prevention of invasive breast cancer. By acting as an estrogen agonist in bone, it reduces bone resorption and turnover. Raloxifene has been found to significantly reduce the risk of vertebral fractures, **no effect** has been demonstrated **on non vertebral or hip fractures.**

Raloxifene is associated with increases in BMD, which are maintained with long-term use of **up to 8 years**. Raloxifene also has been shown to reduce the risk of invasive breast cancer. Adverse effects of raloxifene include venous thromboembolism, death from stroke (observed in patients with coronary heart disease or at increased risk of major coronary events), leg cramps, and hot flash, worsening of pre-existing hypertriglyceridemia.

Raloxifene is contraindicated in patients with current or past venous thromboembolism and should be used with caution in individuals with **hepatic impairment**. Other selective estrogen receptor modulators that have been investigated for osteoporosis management but are not FDA-approved for this indication include tamoxifen, bazedoxifene (alone), and ospemifene.

Hormone Therapy

Estrogen therapy alone (for patients without a uterus) or combined with a progestogen can be considered as an option for the prevention of bone loss and fracture in women at increased risk who meet all the following criteria:

are younger than **60 years or within 10 years of menopause**; are at low risk of venous thromboembolism, breast cancer, and cardiovascular disease; have bothersome menopausal symptoms; and for whom other therapies such as bisphosphonates or denosumab are not appropriate.

In general, because of the associated risks, the use of hormone therapy should be limited to the **lowest effective dose** for the **shortest duration** necessary.

Discontinuation of hormone therapy should include an assessment of benefits and risks. Women without osteoporosis, estrogen alone or combined with progestin reduced the overall risk of clinical fracture compared with placebo.

Estrogen plus progestin increased the risk of coronary artery disease and cognitive impairment in women older than 60 years or more than 10 years from menopause, and it slightly increased the risk of breast cancer, stroke, and venous thromboembolism.

Relatively rapid bone loss and loss of protection from fracture occurs after discontinuation of hormone therapy. This can be prevented by **switching to a bisphosphonate or another antiresorptive agent**.

Conjugated Estrogen/Bazedoxifene

The combination of conjugated estrogen and the SERM bazedoxifene is FDA-approved for the prevention of bone loss and the treatment of vasomotor symptoms.

In RCTs, conjugated estrogen/bazedoxifene has been associated with a small but statistically significant increase in BMD at the lumbar spine and hip compared with placebo; however, no fracture data are available.

Calcitonin

Calcitonin nasal spray is indicated for the treatment of postmenopausal osteoporosis in individuals who are **more than 5 years past menopause** and for whom alternative treatments are not suitable. In a study, intranasal calcitonin spray was associated with a statistically significant increase in lumbar spine BMD from baseline and a reduced risk of recurrent vertebral fracture compared with placebo. However, a reduction in nonvertebral and hip fracture has not been demonstrated.

Calcitonin is rarely used because more effective osteoporosis therapies available. There have been safety concerns about a possible increased risk of **malignancy.** Although an FDA review found insufficient evidence of a causal association, it advises shared decision making regarding the benefits and risks for patients.

In very-high-risk patients, an immediate therapeutic response was required because the risk of subsequent fractures was high during the first year after the initial fracture. Thus, a more active and rapid osteoporosis treatment is recommended.

anabolic agents, such as teriparatide, abaloparatide or romosozumab, are strongly recommended as first-line therapies.

Parathyroid Hormone Analogs

ACOG recommends the parathyroid hormone analogs, teriparatide and abaloparatide, for the treatment of postmenopausal osteoporosis for up to 2 years in patients who are at very high risk of fracture as an initial treatment option or who continue to sustain fractures or have significant bone loss while taking antiresorptive therapy or for the treatment of osteoporosis that is unresponsive to antiresorptive therapy (STRONG RECOMMENDATION, HIGH-QUALITY EVIDENCE)

Unlike antiresorptive agents, anabolic medications such as teriparatide and abaloparatide can restore bone mass and structure that is already lost in patients with very advanced osteoporosis.

Anabolic therapy needs to be followed by treatment with an antiresorptive agent such as a bisphosphonate or denosumab to preserve the BMD gains. Treatment is restricted to 2 years in a patient's lifetime because research with high-dose teriparatide and abaloparatide in laboratory rats found an increased incidence of osteosarcoma.

Parathyroid hormone analogs should not be used in patients with **Paget's** disease, unexplained elevations of alkaline phosphatase, or **hypercalcemic** disorders such as primary hyperparathyroidism, and caution is advised when used in patients with **urolithiasis** or preexisting **hypercalciuria**.

Teriparatide

Teriparatide significantly reduces the risk of nonvertebral and vertebral fracture. There are **conflicting** data on teriparatide's efficacy to reduce the risk of **hip fracture**, which may have been due to the very low incidence of hip fractures in the in the analysis.

In a meta-analysis that compared teriparatide with bisphosphonates, teriparatide was found to be more effective in reducing the risk of vertebral fracture and in increasing BMD at the lumbar spine (at 6, 12, and 18 months) and femoral neck (at 18 months), with similar rates of adverse events.

BMD declines quickly after discontinuation of teriparatide, and sequent BPs or denosumab therapy prevent bone loss and further increase BMD.

Abaloparatide

A meta-analysis demonstrated that abaloparatide reduces the risk of vertebral fracture and nonvertebral fracture compared with placebo.

The reduction in **hip fracture** in the meta-analysis was **not statistically significant**.

In a prospective analysis of BMD response among participants in the Abaloparatide Comparator Trial In Vertebral Endpoint (ACTIVE) trial, a significantly greater proportion of patients treated with abaloparatide experienced increases in BMD than did those treated with placebo or teriparatide at months 6 (19.1% vs 0.9% for placebo and 6.5% for teriparatide), 12 (33.2% vs 1.5% and 19.8%), and 18 (44.5% vs 1.9% and 32.0%) (P,.001).

In an extension study of the ACTIVE trial on postmenopausal osteoporosis women at high risk of fracture, participants who received **18 months of treatment with abaloparatide followed by 24 months of alendronate** had a significantly decreased risk of vertebral fracture, nonvertebral fracture, clinical fracture, and major osteoporotic fracture and also experienced additional increases in BMD at the lumbar spine, total hip, and femoral neck compared with participants who received 18 months of placebo followed by 24 months of alendronate.

Sclerostin-Binding Inhibitors

ACOG recommends the sclerostin-binding inhibitor romosozumab for the treatment of postmenopausal osteoporosis for **up to 1 year** in patients who are **not at increased risk of cardiovascular disease or stroke** and have a very high risk of fracture or for whom other treatments have not been effective. (STRONG RECOMMENDATION, MODERATE-QUALITY EVIDENCE).

The anabolic agent romosozumab is a humanized monoclonal antibody that binds to and inhibits the activity of the protein sclerostin, which increases bone formation and decreases bone breakdown.

In the FRAME RCT 12-month treatment with romosozumab was associated with a significantly reduced risk of vertebral fracture and clinical fractures compared with placebo, with BMD increases of 13.3% in the lumbar spine and 6.8% in the total hip.

A systematic review that compared romosozumab with other therapies (alendronate, teriparatide) and placebo showed a similar **decreased risk of vertebral fracture, nonvertebral fracture, and hip fracture,** as well as a significant increase in BMD (at the lumbar spine, total hip, and femoral neck), with no significant difference in the incidence of adverse events.

As with other types of anabolic therapy, One year of romosozumab treatment should be **followed by denosumab or alendronate** to help maintains the fracture reduction benefit and increases the spine and hip BMD.

Although romosozumab is currently indicated for up to 12 months of treatment, RCT data from phase 2 extension trials suggest that a second 12-month course, particularly when followed by 12 months of denosumab, is associated with continued significant increases in BMD with no additional safety concerns.

Romosozumab may increase the risk of **myocardial infarction, stroke, and cardiovascular death,** and the drug label includes a black box warning against its use in patients with a recent history (within 1 year) of myocardial infarction or stroke and recommends caution for use in patients with other cardiovascular risk factors.

Administration of romosozumab is contraindicated in patients with **hypocalcemia**, which should be corrected before use. Other reported but rare adverse events include osteonecrosis of the jaw and atypical femoral fractures.

We favor for very high-risk groups therapy with anabolic agents. If anabolic therapy was declined, Denosumab or zoledronic acid, which are strong antiresorptive agents, can also be used as a first-line therapy in very high-risk groups. we would **favor denosumab** over bisphosphonates, because the greater effects of denosumab on bone mineral density. If denosumab or zoledronic acid is difficult to administer, other BPs (alendronate and risedronate) can be considered.

Administration of denosumab or zoledronic acid in the very high-risk group is the same as treatment in the high-risk group.

In the STRUCTURE trial, romosozumab increased hip and spine BMD and hip strength compared to teriparatide in women with postmenopausal osteoporosis transitioning from BP therapy.

Transitioning to romosozumab after 12 months of denosumab treatment improves spine BMD and maintains total hip BMD; however, the decreased levels of bone turnover markers during denosumab administration gradually return to baseline.

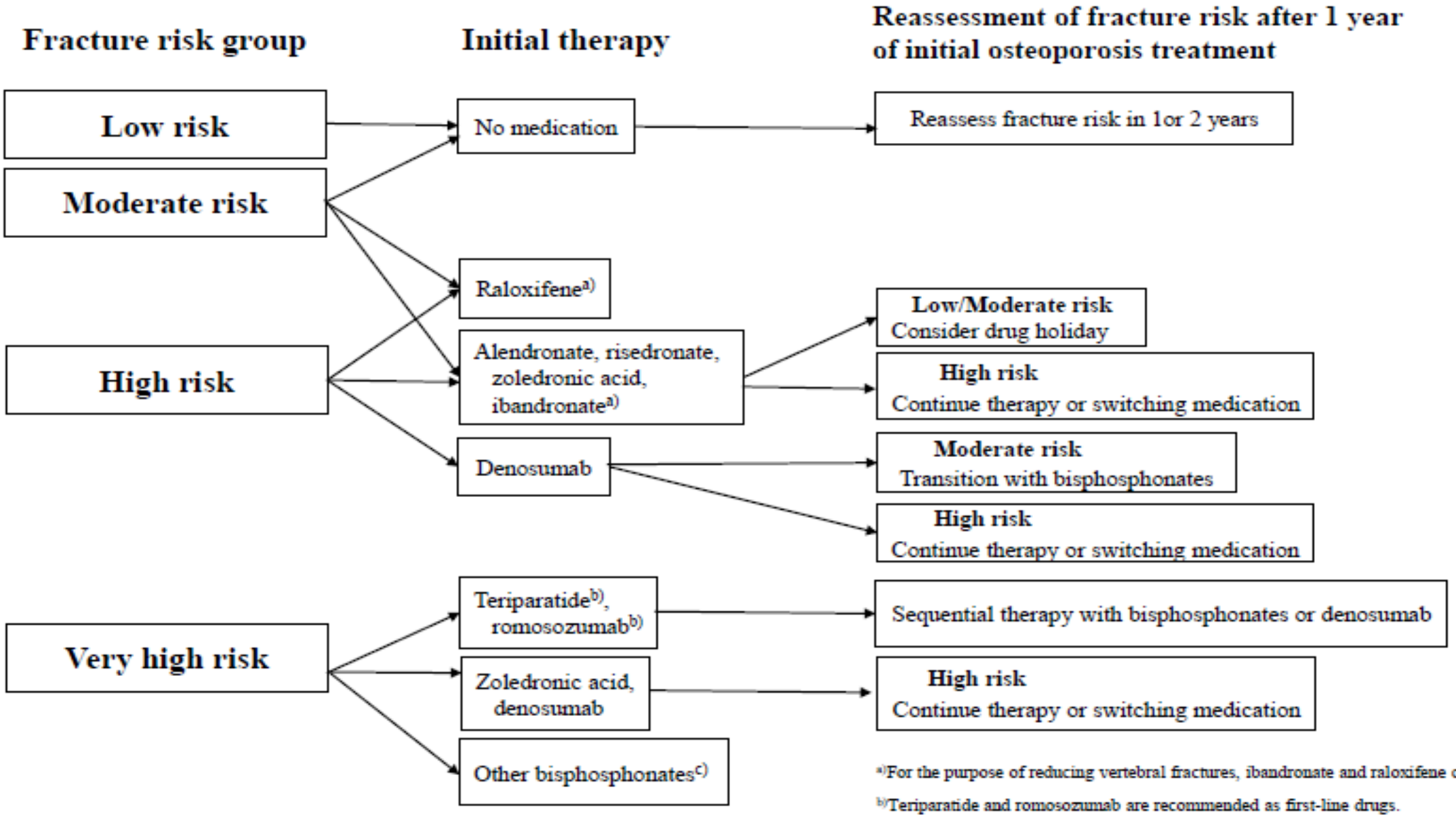
Switching from an anabolic agent to an antiresorptive agent is recommended in the very-high-risk group rather than switching from an antiresorptive agent to an anabolic agent, as it shows a much more effective increase in spine and hip BMD and a reduction in fracture risk.

Table 1. Medications for Postmenopausal Osteoporosis

Category	Examples (Mode of Administration)	Indication	Demonstrated Fracture Risk Reduction
Antiresorptive agents			
Bisphosphonate*†‡	Alendronate (PO) Risedronate (PO) Zoledronic acid (IV)	Prevention and treatment	Vertebral Nonvertebral Hip
	Ibandronate (PO)	Prevention and treatment	Vertebral
	Ibandronate (IV)	Treatment	
Targeted monoclonal-antibody RANK-ligand inhibitor*‡§	Denosumab (SQ)	Prevention‖ and treatment	Vertebral Nonvertebral Hip
Selective estrogen receptor modulator*‡§	Raloxifene (PO)	Prevention and treatment for patients at increased risk of breast cancer	Vertebral
Hormone therapy*¶#	Estrogen with or without progestogen (multiple regimens)	Prevention	Vertebral Nonvertebral Hip
	Conjugated estrogen plus bazedoxifene (PO)	Prevention	N/A
Calcitonin**	Salmon calcitonin (intranasally or SQ)	Treatment	Vertebral††
Anabolic agents			
Parathyroid hormone analog*§	Abaloparatide (SQ) Teriparatide (SQ)	Treatment for patients at very high risk of fracture	Vertebral Nonvertebral
Sclerostin-binding inhibitor*‡‡	Romosozumab (SQ)		Vertebral Nonvertebral Hip

Table 6.1 Drugs used and approved to treat osteoporosis. The new drug romosozumab is injected subcutaneously monthly for a year

	Oral daily	Oral weekly	Oral monthly	Subcutaneous daily	Subcutaneous every 6 months	Injection quarterly	Infusion annually
Alendronate	10 mg	70 mg					
Risedronate	5 mg	35 mg	150 mg				
Ibandronate			150 mg			3 mg	
Zoledronate							5 mg
Strontium ranelate	2 g						
Teriparatide				20 µg			
Abaloparatide				80 µg			
Denosumab					60 mg		



[a)]For the purpose of reducing vertebral fractures, ibandronate and raloxifene can be considered.

[b)]Teriparatide and romosozumab are recommended as first-line drugs.

[c)]If these drugs cannot be used, other bisphosphonates (alendronate, risdronate) can be considered.

Nonpharmacologic Interventions

Calcium and Vitamin D

Counsel patients who are receiving osteoporosis pharmacotherapy and patients with postmenopausal osteoporosis who cannot tolerate pharmacologic therapy to consume the recommended daily allowance of calcium and vitamin D through diet (preferably), supplementation, or both. (GOOD PRACTICE POINT)

Both the Endocrine Society and International Osteoporosis Foundation recommend calcium and vitamin D supplementation **as an adjunct to osteoporosis pharmacologic treatment** because nearly all validation studies of osteoporosis pharmacotherapy have included calcium and vitamin D supplementation in both the intervention and control groups.

The American Association of Clinical Endocrinologists and National Osteoporosis Foundation also acknowledge that **dietary intake** of the RDA of calcium is preferable to supplementation because excess intake has no proven benefit but is associated with an increased risk of renal calculi.

The RDA for calcium is 1,000 mg per day from ages 19 to 50 years and 1,200 mg per day in older women. For vitamin D, the RDA is 600 international units per day to age 70 years and 800 international units per day thereafter. The RDA of vitamin D is believed to maintain an adequate serum level of 25-hydroxyvitamin D (20 ng/mL) in 97.5% of the population.

A randomized trials of postmenopausal individuals found that compared with placebo, combined calcium (1,000–1,200 mg/d) and vitamin D (800 international units/d) was associated with a **reduction in hip fracture** but not a statistically significant decrease in nonvertebral fracture (RR 0.93; 95% CI 0.85–1.01) or vertebral fracture (RR 0.88; 95% CI 0.61–1.27).

In a more recent meta-analysis of six RCTs, combined calcium (1,000-1,200 mg/d) and vitamin D (400-800 international units/d) was associated with a reduced risk of hip fracture and a small decreased risk of any fracture.

In contrast to these findings, the U.S. Preventive Services Task Force systematic review found that supplementation with calcium and vitamin D **had no effect** on total fracture incidence.

However, the Task Force review focused on an average-risk population (ie, without vitamin D deficiency, osteoporosis, or prior fracture) and did not include high-risk patients, for whom combined supplementation appears to be effective.

Complementary and Nutritional Alternative Treatments

It is unclear soy isoflavones and other complementary and alternative nutritional therapies have a beneficial effect on BMD.

Isoflavones, a class of phytoestrogens, are the most studied nutritional approach for osteoporosis. Soybeans and soy products, the most common dietary sources of phytoestrogens, have estrogenic properties that have been hypothesized to have beneficial effects on bone. Studies have produced mixed results.

A 2011 report by the North American Menopause Society concluded that there was not significant evidence showing that isoflavones have a beneficial effect on bone density.

Flax seeds are another source of phytoestrogens that have been investigated for bone loss prevention. A systematic review that examined the effect of flax interventions on bone turnover markers and BMD found no clear benefit for either outcome.

Green tea extract, which has antioxidant properties hypothesized to be beneficial for bone health, also has been studied as an intervention to prevent bone loss. However, it was found to have no effect on BMD in postmenopausal women with BMI in the overweight or obese range.

A randomized placebo-controlled trial that included 131 postmenopausal women with T-scores of -1 or lower found that supplementation with **specific collagen peptide** (ie, small proteins that may accumulate in bone) was associated with a statistically significant improvement in BMD T-score at 12 months (spine, femoral neck) vs control group.

Lifestyle Interventions

Osteoporosis management should include patient counseling about **fall prevention and exercise**. Fractures often occur in older adults because of trips, slips, or falls, which underscores the importance of including fall-prevention strategies (such as vision assessment and treatment, balance training, and environmental assessment and modification) as part of osteoporosis management.

Routine aerobic physical activity (moderate-to-high impact) and weight-bearing exercises (muscle strengthening or exercise against resistance) are also recommended to prevent falls, maintain bone health, and prevent bone loss. Other lifestyle changes to help improve bone and overall health, such as **smoking cessation and reduction of alcohol intake.**

Treatment Monitoring

ACOG suggests DXA testing every 1–3 years during osteoporosis pharmacotherapy, depending on clinical circumstances, until findings are stable. (CONDITIONAL RECOMMENDATION, MODERATE–QUALITY EVIDENCE)

Osteoporosis treatment monitoring aims to identify patients who have progressive bone loss.

Expert guidelines on osteoporosis management generally recommend repeat BMD testing (ideally on the same DXA machine as prior measurements) after 1–3 years, depending on disease severity and clinical features. Patients with a progressive loss of BMD or a new or recurrent fragility fracture should be evaluated for causes of suboptimal response to therapy, such as poor medication adherence, secondary osteoporosis, or use of medications that can cause bone loss.

Expert guidelines also recommend evaluation of **renal function and serum calcium and vitamin D levels every 1–2 years** during osteoporosis pharmacotherapy.

Vertebral fracture assessment may be indicated in addition to BMD testing for patients with significant height loss or a self-reported prior vertebral fracture or who are receiving glucocorticoid therapy (eg, prednisone, 5 mg/d or more for 3 months or longer) Assessment can be performed using either lateral thoracic and spine X-ray or lateral vertebral fracture assessment, which is available on most DXA machines.

While BMD is used to decide treatment strategies and assess the rate of bone loss or the response to osteoporosis treatment, it still cannot comprehensively **predict** the risk of osteoporotic fractures. Furthermore, BMD measurements for assessing treatment response require lengthy measurement **intervals** of more than a year. Bone turnover, the process of resorbing old bone and forming new bone, is continuously taking place. Changes in the rate of bone turnover may affect bone quality. Considering the limitations of BMD and the characteristics of bone turnover markers that reflect bone quality, the attention given to the potential role of bone turnover markers for predicting fracture risk and monitoring treatment response in the clinical setting is constantly increasing.

THANKS FOR YOUR ATTENTION