A Specialty Networks Company

CLINICAL PRACTICE GUIDELINE

Adult Osteoporosis

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Table of Contents

List of Tables

Abbreviations

AACE	American Association of Clinical Endocrinologists
AAOMS	American Association of Oral and Maxillofacial Surgeons
ACE	American College of Endocrinology
ACR	American College of Rheumatology
ADA	American Dental Association
ADT	Androgen deprivation therapy
AFF(s)	Atypical femoral fracture(s)
AI	Aromatase inhibitor
ASBMR	American Society for Bone and Mineral Research
BMD	Bone mineral density
BMI	Body mass index
BP(s)	Bisphosphonate(s)
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DXA	Dual energy X-ray absorptiometry
FDA	Food and Drug Administration
FRAX®	Fracture Risk Assessment Tool
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
HEDIS	Healthcare Effectiveness Data and Information Set
ICER	Institute for Clinical and Economic Review
IOF	International Osteoporosis Foundation
ISCD	International Society for Clinical Densitometry
IV	Intravenous
LSC	Least significant change
MBD	Metabolic bone disease
MRI	Magnetic resonance imaging
MI	Myocardial infarction
MRONJ	Medication-related osteonecrosis of the jaw
NCQA	National Committee for Quality Assurance
NOF	National Osteoporosis Foundation
ONJ	Osteonecrosis of the jaw
PA	Posterior-anterior (e.g., view in a DXA scan)
PPI(s)	Proton pump inhibitor(s)
PTH	Parathyroid hormone
QC	Quality control

RA	Rheumatoid arthritis
RR	Relative risk
SD(s)	Standard deviation(s)
SDI	Spinal deformity index
TBS	Trabecular bone score
US	United States
VFA	Vertebral fracture assessment

Introduction

Osteoporosis is a skeletal disorder characterized by decreased bone strength, which predisposes individuals to an increased risk of fracture.[1, 2] It is often asymptomatic, under-recognized, and undertreated. According to the National Institutes of Health, as of 2018, more than 53 million Americans have osteoporosis or low bone mass (osteopenia).[3] It is projected that by 2020, the number of adults 50 years of age or older in the United States (US) with either low bone mass or osteoporosis at the femoral neck or lumbar spine will be 64.6 million, and of these, 12.3 million will have osteoporosis. In 2030, the number of adults with low bone mass or osteoporosis at these two sites will increase to 71.4 million.[4]

Fractures, especially of the hip and spine, are a significant health risk to the Medicare population. In addition, they are associated with significant morbidity and mortality.[5] A study conducted by Milliman for the National Osteoporosis Foundation (NOF),[6] estimated that in 2015, 2.3 million fractures occurred in the Medicare population (both fee for service and Medicare Advantage) and about 40% of these fractures involved either the hip or spine.

According to the New Jersey Department of Human Services, Division of Aging Services, 20% of patients who fracture their hip require long term care, 50% never regain the ability to walk without assistance, 20% die within one year from complications of the fracture or the surgery to repair the fracture, and a third are completely dependent on others.[7]

Melton reported on the morbidity and mortality of all osteoporotic fractures, citing an excess 12% to 20% mortality after hip fractures, with 19% of patients requiring placement in a nursing home.[8] Furthermore, 10% of patients with vertebral or distal forearm fractures will have chronic pain and others will have some functional loss in the forearm.

In 2002, the annual cost of treating osteoporosis and associated fractures in elderly Medicare patients was estimated to be approximately $16 billion.[9] By 2018, it was estimated that the cost of caring for fractures in this population was $57 billion ($48.8 billion in direct costs and $8.2 billion in indirect costs) and in 2040, the cost could be greater than $95 billion ($81.5 billion in direct costs and $13.5 billion in indirect costs).[10]

The *United Rheumatology Clinical Practice Guideline—Osteoporosis* is designed to assist clinicians in the management of patients who have, or are considered at risk for, osteoporosis. The Guideline is continually reviewed and modified as appropriate, based on current peer-reviewed literature.

Establishing the Diagnosis of Osteoporosis and Risk of Fracture(s)

Bone strength is determined by a combination of bone mineral density (BMD; measured in grams of mineral/per area or volume) and bone quality. Bone quality is determined by bone architecture, turnover, microfractures, and mineralization. Currently, no one test is available to determine bone strength; BMD is used as a "proxy measure and accounts for approximately 70% of bone strength" (Page 5).[1] Osteoporosis increases a patient's risk of fracture, but other risk factors include: a history of falls; decreased physical activity; slow gait; decreased muscle strength in the legs; poor vision; decreased cognition; and environmental hazards such as area rugs.[2]

BMD of the lumbar spine, total hip, and femoral neck is measured by central dual energy X-ray absorptiometry (DXA). In some patients, BMD cannot be measured in the lumbar spine and/or hips (e.g., prior spine surgery, metal implants, marked osteoarthritis of the spine, vertebral compression fractures,

or total hip arthroplasty), in which case the 33% radius, also known as the distal 1/3 radius, may be used as a substitute.[11] Ward's triangle or greater trochanter of the hip should not be used to calculate BMD.[12]

BMD is usually reported as a T-score, which compares the patient's BMD to young normal controls; Zscores compare the patient's BMD to age-matched controls. In postmenopausal women and men over the age of 50 years, a T-score of ≤-2.5 is consistent with the diagnosis of osteoporosis, and a T-score between -1.0 and -2.5 is consistent with low bone mass/osteopenia. A T-score ≥-1.0 is considered normal. Younger individuals who do not have secondary causes of metabolic bone disease (MBD) should not be given a diagnosis of osteoporosis. Instead, they might be labelled as having *low bone mass for age* if their Z-score is ≤-2.0.

The 2020 osteoporosis guidelines published in May, 2020 by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE)[13] indicate that osteoporosis may be diagnosed not only in patients with a T-score of <-2.5 but also in the following clinical scenarios:

- Low-trauma fracture of the hip or vertebra, if there is no MBD, and regardless of BMD
- Low-trauma fracture of the proximal humerus, distal forearm or pelvis with a T-score of <-1.0
- T-score between -1.0 and -2.5 and high Fracture Risk Assessment Tool (FRAX; or if available trabecular bone score [TBS]-adjusted FRAX) fracture probability based on country-wide specific thresholds

The majority of osteoporotic vertebral fractures are not clinically apparent but must be looked for by radiographic imaging.[14, 15] Termed morphometric or radiographic vertebral fractures, they are an essential part of the evaluation of patients with suspected osteoporosis. Studies of postmenopausal women in the US, who were referred for osteoporosis evaluation, have demonstrated that 10% to 17% of those with low bone mass/osteopenia on DXA had at least one moderate or severe morphometric vertebral fracture on vertebral fracture assessment (VFA).[16, 17] These individuals might not have been treated, if the 10-year fracture risk threshold was below the cut-off of 3% for hip fracture and 20% for major osteoporotic fracture as measured by FRAX. Morphometric fractures should not be viewed as less predictive of a future fracture than clinical vertebral fractures. Most major clinical trials of osteoporosis drug therapy designate morphometric vertebral fractures as one of the primary end points. Additionally, morphometric vertebral fractures can affect morbidity and when involving the thoracic spine are associated with decreased vital capacity on pulmonary function studies.[18]

By calculating the total number and grade of vertebral fractures present in the thoracic and lumbar spine, a spinal deformity index (SDI) can be determined.[19] Across the range of femoral neck BMD T-scores, prevalent spine fracture burden, as determined by SDI, increased the likelihood of incident vertebral fractures up to 12-fold, nonvertebral fractures 2-fold, and any fractures up to 7-fold.[20]

As discussed in the section, *Pharmacologic Treatment*, patients with two or more moderate (Grade 2) and one or more severe (Grade 3) vertebral fractures are assumed to have a very high fracture risk, which warrants anabolic drug therapy.[21]

As previously mentioned, an estimated 2.3 million fractures occurred in the Medicare population (both fee for service and Medicare Advantage) in 2015 and about 40% of these fractures involved either the hip or spine.[6] Less than 10% of the patients with fee for service Medicare had a DXA scan within 6 months of

the fracture. This is very important as it finds patients with recent fractures (especially of the spine and hip) that may be undertreated because a diagnosis of osteoporosis or low bone mass is never established.

The National Committee for Quality Assurance (NCQA) has developed a tool called the Healthcare Effectiveness Data and Information Set (HEDIS), which is used to evaluate the quality of care provided by different health plans. One measure that HEDIS looks at is the percentage of women with Medicare between 67 and 85 years of age who have had a fracture (any fracture including a fragility fracture) and a follow up DXA or treatment for osteoporosis within 6 months of the fracture or have an active prescription for osteoporosis medication within the prior 12 months of the fracture. The intent of this quality measure is to get older patients with a fracture treated for osteoporosis to prevent future fractures. According to NCQA, the rates of compliance to this measure for Medicare patients is poor. The average score by reporting Medicare plans was 44.9%, which represented an improvement of 9 percentage points since 2014 when it was 35.9%.[22]

Medical History and Appropriate Queries

1. All patients should be evaluated for the presence or absence of kyphosis.
2. Current height (using a wall-mounted stadiometer) and weight should be recorded.
3. Prior to starting pharmacologic treatment for osteoporosis with bisphosphonates (BPs) or denosumab, patients should have had a complete dental examination.
4. A complete physical examination is required for all patients.
5. Fracture risk assessment (see discussion below)
6. Special attention should be paid to the following, as appropriate:[12, 18, 23-25]
    a. Endocrine disorders that may cause secondary osteoporosis:
        i. Diabetes
        ii. Growth hormone deficiency
        iii. Hypercortisolism
        iv. Primary or secondary hyperparathyroidism
        v. Hyperthyroidism vi. Hypogonadism vii. Acromegaly viii. Hyperprolactinemia ix. Cushing's syndrome x. Acromegaly
    b. Gastrointestinal (GI) problems associated with secondary osteoporosis:
        i. Anorexia nervosa ii. Chronic liver disease iii. Chronic active hepatitis iv. Pancreatic insufficiency
        v. Malabsorption syndromes such as, but not limited to:

            - Celiac disease
            - Crohn's disease
            - Gastric resection or bypass
            - Total parenteral nutrition (TPN)

c. Renal disorders associated with secondary osteoporosis:
    i. Hypercalciuria ii. Renal tubular acidosis iii. Renal insufficiency
d. Other disorders associated with secondary osteoporosis:
    i. Ehlers Danlos or Marfan syndromes
    ii. Myeloma iii. Mastocytosis iv. Gaucher's disease
    v. Chronic obstructive pulmonary disease vi. Amyloidosis
    vii. Lymphoma viii. Sarcoidosis ix. Sickle cell anemia
    x. Rheumatoid arthritis (RA)
    xi. Multiple sclerosis xii. Vitamin D deficiency xiii. Immobilization
e. Organ transplantation
f. Drugs associated with secondary osteoporosis such as, but not limited to:
    i. Aromatase inhibitors ii. Glucocorticoids iii. Androgen deprivation therapy iv. Heparin
    v. Warfarin vi. Lithium
    vii. Thyroid hormone intake above normal physiologic doses
    viii. Thiazolidinediones ix. Depo-Provera®
    x. Anti-seizure medications

7. Laboratory tests, if no current values are available:[18, 23-28]
    a. Complete blood count, comprehensive metabolic panel, and serum phosphorus
    b. Erythrocyte sedimentation rate and C-reactive protein
    c. 25-hydroxyvitamin D
    d. 24-hour urine calcium
    e. Intact parathyroid hormone (PTH)
    f. Serum and urine protein electrophoresis, immunofixation/immunoelectrophoresis
    g. Anti-endomysial and anti-gliadin antibodies, if celiac disease is suspected

Fracture Risk Assessment

In the last decade, fracture risk assessment tools have been developed and used with increasing frequency. These have allowed providers to calculate a quantitative rather than qualitative risk of future fracture, which can more appropriately guide treatment decisions. The FRAX,[30] is recommended by United Rheumatology, and is the best-known and most widely utilized tool.

All risk assessment tools have limitations and clinical judgment is still important. At the 2010 FRAX Position Development Conference, the International Society for Clinical Densitometry (ISCD) and the International

Osteoporosis Foundation (IOF) agreed on several limitations of FRAX. The paper was then modified in 2019:[31]

- Falls are a risk factor for fracture but are not in the current FRAX model; fracture probability may be increased in individuals with frequent falls, but that risk cannot be quantified at the present time.
- Smoking may increase the risk of fracture, but that risk cannot be quantified.
- The model underestimates fracture risk in individuals with multiple prior fractures.
- FRAX does not consider the severity of prior vertebral fractures and may, therefore, underestimate the risk for future fractures.
- FRAX identifies parental history of hip fracture as increasing the risk of future fractures but likely underestimates the risk of fracture when this history is present.
- Fractures of the hip, vertebrae and humerus may increase an individual's risk for fracture more than other fractures.
- FRAX does not include bone turnover markers as risk factors because the evidence is considered to be inconclusive.
- The use of glucocorticoids as a risk factor for future fracture is complicated:
    - If the equivalent of a dose of prednisone between 2.5 and 7.5 mg/day is taken for ≥3 months, FRAX captures the risk for future fractures well. When the dose is greater than the equivalent of 7.5 mg/day, FRAX underestimates the risk of fracture. When the dose is equivalent of less than 2.5 mg/day the model probably overestimates the risk of fracture.
    - High dose inhaled glucocorticoids may be a risk factor for fracture and are not accounted for by FRAX.
    - In individuals with adrenal insufficiency, appropriate glucocorticoid replacement has not been documented to increase fracture risk and use of steroids in this setting should not be included in FRAX calculations.
- Only the BMD (T-score) of the femoral neck as determined by DXA should be used with FRAX.
- FRAX may under or overestimate major osteoporotic fracture risk when the lumbar spine T-score is much lower or higher (>1 standard deviation [SD]) than the femoral neck T-score.
- FRAX plus BMD predicts fracture risk better than clinical risk factors or BMD alone.
- FRAX should not be used to monitor response to treatment.
- The rate of bone loss is not included in FRAX because the evidence is inconsistent as to whether this represents an additional independent risk factor for fracture.

The value of fracture risk assessment tools is based on several important observations. First, more low-trauma fractures occur in individuals who do not meet the densitometric definition of osteoporosis than occur in those who do.[32] Furthermore, many of these patients will be found to have low bone mass.

Second, the single best predictor of a future fracture is a prior fracture. According to the NOF, approximately 25% of men and 50% of women over 50 years of age will suffer a fracture related to osteoporosis sometime during their lifetime.[33, 34]

A history of low-trauma vertebral, hip, proximal humerus, ankle, pelvis, or distal forearm fractures put both men and women at a higher-than-average risk for a future fracture.[29] Finally, factors in addition to BMD and fracture history, such as age, body mass index (BMI), frailty, alcohol and cigarette use, family history of osteoporotic fracture, steroid use, and RA are known to increase the risk of future fracture.

FRAX is included on newer DXA equipment but it can easily be accessed online.[35] This calculator integrates clinical risk factors for fracture (mentioned above) and BMD at the femoral neck to calculate the 10-year probability of hip fracture and of a major osteoporotic fracture (clinical spine, forearm, hip, or proximal humerus). The models used to develop the FRAX diagnostic tool were derived from studying patient populations in North America, Europe, Latin America, Asia, and Australia. Therefore, FRAX has been used in many countries to guide treatment decisions. In the US, the NOF *Clinician's Guide to Prevention and Treatment of Osteoporosis*[36] provides a framework that prioritizes using FRAX for those individuals who are not yet receiving Food and Drug Administration (FDA)-approved drug therapy, have not had (a) prior low-trauma fracture(s), and have low bone mass/osteopenia.

Recently, it has been reported that a patient with an acute fracture has a much higher risk for a subsequent osteoporotic fracture in the following 2 years than that calculated by FRAX. Such a patient is considered to have a very high risk of another fracture in the 2 years after the acute fracture. The risk decreases somewhat over time but does not return to baseline. This early phase of very high risk is also referred to as "imminent risk". The risk for a future fracture is also very high when the patient has a history of both a fracture of indeterminate age and a family history of hip fracture.[36-38] Kanis et al.[36] describe how to adjust the FRAX risk assessment for fractures of the hip and major osteoporotic fractures, which can be found at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7018677/pdf/198_2019_Article_5176.pdf. Calculating a more accurate FRAX risk is important in order to make the most appropriate treatment decisions. Patients are considered to be at very high risk if the corrected FRAX is above the upper FRAX thresholds. Providers should take into account that FRAX varies from country to country and the numbers in this paper reflect the average of five European countries.

United Rheumatology strongly encourages the use of anabolic treatments immediately following an index fracture for as long as permitted and then changing treatment to an anti-resorptive drug.[13]

Additional tools for the assessment of fracture risk include the TBS, hip axis length and other markers of bone turnover, such as serum C-telopeptide, urine N-telopeptide. Of these, the TBS has been studied most extensively and has the greatest value for further quantifying fracture risk. It can now be incorporated into the FRAX calculation and is offered as a software upgrade by many manufacturers of central DXA equipment.

In 1993, a consensus conference of the NOF, the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the European Foundation for Osteoporosis and Bone Disease (which is now known as the IOF) defined the components of osteoporosis. According to this definition, both low bone mass and deterioration of the microarchitecture of bone (measured as TBS) contribute to osteoporosis.[40]

Bone mass is determined by DXA imaging. The TBS determines the textural index of bone microarchitecture from DXA images of the spine.[27] According to Silva et al.,[41] a high TBS is consistent with

better bone structure that is more resistant to fracture, whereas a low TBS is consistent with weaker bone structure more likely to fracture. The normal range of the TBS for postmenopausal women is ≥ 1.350. Scores between 1.210 and 1.350 represent moderate deterioration of the trabecular microarchitecture, and scores ≤1.200 represent marked degradation of the bone microarchitecture. Normal range for TBS in men has not been determined. Silva et al. reviewed the current literature on TBS and concluded that:[41]

- TBS provides lower values in postmenopausal women and in men with previous fragility fractures than in their nonfractured peers.
- TBS results are lower in women who have sustained a fragility fracture but in whom DXA does not indicate osteoporosis or even low bone mass/osteopenia.
- TBS predicts fracture risk as well as lumbar-spine BMD measurements in postmenopausal women.
- Therapies for osteoporosis differ in the extent to which they influence the TBS.

A 2017 publication in the *Journal of Bone and Mineral Research*[42] concluded, that when TBS was added to FRAX, the resulting adjusted risk score for either a major osteoporotic fracture or a hip fracture showed a small but significant improvement in the prediction of fracture risk. The improvement was greatest for women with a FRAX score near a level for which treatment would be considered and for those under the age of 65 years.

United Rheumatology encourages the use of TBS plus FRAX, if TBS is installed on the DXA scanner.

Indications for Baseline Bone Mineral Density Testing[11, 30, 42-44]

United Rheumatology requires the use of central DXA for the evaluation of patients referred for BMD testing.[11]

Patients who meet one or more of the following risk factors should be referred for a **baseline BMD (DXA) study:**[26, 45]

- Women aged ≥65
- Men aged ≥70
- Postmenopausal women aged <65 with one or more of the following:
  - Low body weight (BMI <20) ○ Prior fracture as an adult ○ Parent with hip fracture
  - Alcohol intake of three or more drinks a day ○ High risk medication
  - Disease or condition associated with bone loss
- Men <70 if they have a risk factor for low bone mass or osteoporosis, including but not limited to:
  - Low body weight ○ Prior fracture as an adult
    - High risk medication
  - Disease or condition associated with bone loss

- Perimenopausal women with risk for fracture
- Adults >50 years of age with a low-trauma/fragility fracture without a condition that may cause secondary osteoporosis
- Adults taking glucocorticoid therapy for at least 3 months
- Adults taking medications associated with bone loss
- Adults with a disease or condition that is associated with bone loss
- Anyone considered for pharmacologic therapy
- Anyone on medication for osteoporosis to monitor results of treatment
- Anyone who is not currently treated for osteoporosis, but evidence of bone loss would lead to treatment

Indications for a Vertebral Fracture Assessment[30, 35, 42, 46]

A VFA is an important part of fracture risk assessment, because up to 20% of individuals with low bone mass/osteopenia have one or more previously undiagnosed vertebral body compression fractures.[46] The recognition of a morphometric fracture establishes the diagnosis of osteoporosis, regardless of BMD, and could alter decisions regarding the initiation of drug therapy for osteoporosis. Additionally, increasing numbers and higher grades of vertebral body fractures have been found to correlate with increasing fracture risk.[46] **Lateral views only** of the thoracic and lumbar spine can be performed, using either plain films or DXA equipment if VFA imaging is available on the unit.

United Rheumatology encourages the use of DXA equipment for VFA, because it is more cost effective[47] and has lower radiation exposure than plain films.

According to the recommendations of the NOF, VFA should be performed, in:[48]

- All women aged ≥70 years
- All men aged ≥80 years
- All women 65–69 with T score of ≤-1.5 in the lumbar spine, or total hip, or femoral neck • All men age 70–79 with T score of ≤-1.5 in the lumbar spine, or total hip, or femoral neck
- Postmenopausal women and men older than 50 with at least one of the following: ○ Fragility fracture at age 50 or older
    - Historical loss of height of ≥1.5 inches (4.0 cm), defined as the difference between the current height and peak height at the age of 20 years
    - Loss of height of ≥0.8 inches (2.0 cm), defined as the difference between the current height and a previously documented height measurement (preferably with the same stadiometer)
    - Glucocorticoid therapy of ≥5 mg of prednisone or equivalent per day for at least 3 months

The ability to measure the precise current height of a patient is essential for evaluating their potential loss of height and identifying patients at risk for vertebral fracture. Therefore, all healthcare providers should have a wall-mounted stadiometer.

A recent Canadian study[49] demonstrated that VFA (using DXA equipment) as part of osteoporosis screening was able to reliably detect moderate to severe vertebral fractures. Patients with a prevalent

fracture(s) are at increased risk for a future fracture(s) and need treatment despite a DXA score that is normal or showed low bone mass, or a FRAX score that was not consistent with a high risk for fracture. The study also found that patients with documented fractures were more likely to adhere to prescribed medications.

United Rheumatology strongly supports the use of the NOF indications for performing a VFA. In addition, United Rheumatology supports the use of VFA in patients being screened for osteoporosis. Patients with normal BMD, or with low bone mass and a previously undiagnosed vertebral fracture, should be treated.[47, 49]

Monitoring Bone Mineral Density

Follow-up BMD studies should be conducted at the same facility using the same equipment as the prior study, whenever possible. The recommended intervals for follow-up BMD studies are indicated in Table 1.

Table 1. Recommended monitoring intervals for BMD studies using DXA[50]

Patient Characteristics	Intervals for Follow-up Studies
Treatment with adequate calcium intake and vitamin D only OR If results would lead to initiation of drug therapy	• Every 1 to 2 years, if approaching intervention threshold based on T-score or FRAX • Every 3 to 5 years, if BMD is borderline low, and there are some clinical risks • Not more frequently than once every 5 years, if the patient is comfortably above the intervention threshold
Treatment with an FDA-approved drug for osteoporosis	• Initial follow up at 1 year, if significant risk factors for rapid bone loss; otherwise at 2 to 3 years, to exclude progression of disease, defined as significant decline in BMD based on LSC, non-compliance, secondary causes of osteoporosis or interference by other medications • Then every 2 years, until BMD stabilizes • Not less than every 2 years or more than every 5 years after BMD has stabilized
Completed FDA-approved drug therapy for osteoporosis (drug holiday)	• 1 year after starting a drug holiday, if significant risk factors for rapid bone loss; otherwise at 2 years

BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; FDA, Food and Drug Administration; FRAX, Fracture Risk Assessment Tool; LSC, least significant change

Treatment

Non-pharmacologic Recommendations[12, 13, 24, 25, 42, 43, 51, 52]

- Counsel patients on the risk of osteoporosis and related fractures.
- Suggest a diet that includes adequate amounts of total calcium (1000 mg/day for men aged 50 to 70 years; 1200 mg/day for women aged >50 years and men aged >70 years using dietary supplements, if needed).
- Suggest vitamin D intake in diet and supplements, if needed, for men and women aged >50 years to maintain a 25-hydroxyvitamin D level ≥30.
- Encourage adequate dietary protein and an overall balanced diet.

- Assess risk factors for falls and offer appropriate modifications (e.g., home-safety assessment, balance exercises, avoidance of central nervous system depressant medications, careful monitoring of antihypertensive medications, and visual correction if needed).
- Advise against smoking and excessive alcohol intake (three or more drinks per day).
- Patients should be counselled about the value of an exercise program specifically designed for people with osteoporosis. These programs can help decrease the progression of bone loss, improve balance and agility, and reduce the risk of falling and fractures. Before starting such a program, patients should be evaluated by a physician to determine if an exercise program is appropriate for them.

  Some exercises, such as swimming and cycling, can improve cardiovascular health but will not help to decrease bone loss or the risk of falling, because these are non-weight bearing exercises. Patients should be advised to avoid high impact exercises (involving jumping, running, skipping, heavy lifting, bending forward and twisting at the waist), including but not limited to, sit ups, touching toes, some yoga poses, golf, and tennis. Exercises that are suggested for this population include but are not limited to, balance training, walking, stair climbing, strength or resistance training, tai chi, Pilates, and yoga.[26, 35, 53, 54]

  If the patient is approved for an exercise program by a physician, the program should be supervised and ideally include at least 30 minutes of a combination of weight bearing and strength training exercises 5 days per week (but not less than twice weekly). Once patients have successfully mastered a program, they can sometimes be transitioned to a mix of supervised exercise and a home exercise program.[12]
- Review all medications that the patient is currently taking to assess for drugs that could be overly sedating or could lead to an increased risk of falls.

Pharmacologic Treatment[12, 13]

FDA-approved pharmacologic treatment (Table 2) should be initiated in the following settings:

- Low-trauma/fragility fractures of the spine and hip regardless of BMD
- Recent low-trauma/fragility fractures, except those in fingers, toes, skull, sternum, and face with a T-score between -1.0 and -2.5

- T-scores of ≤-2.5 by DXA at either the femoral neck, total hip, or lumbar spine. The 1/3 radius can be used if one is unable to utilize the lumbar spine and/or both hips
- Patients with T-scores between -1.0 and -2.5 by DXA (low bone mass/osteopenia) at the femoral neck, total hip, lumbar spine **AND** a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability of ≥20% based on FRAX.[55] The 1/3 radius can be used if one is unable to utilize the lumbar spine and/or both hips

Low vitamin D levels leading to secondary hyperparathyroidism and calcium levels should be corrected prior to starting any pharmacologic treatment for osteoporosis.
An oral BP can be the initial choice for those patients requiring drug therapy, unless the patient has a very high risk for fracture based on a history of multiple prior fractures, or a very low T-score of ≤-3.0 (see below), or an undiagnosed vertebral fracture(s) with normal or low bone mass.

Oral BPs are contraindicated in those with significant gastroesophageal reflux disease (GERD), esophageal motility disorders, or renal insufficiency with an estimated glomerular filtration rate (GFR) of ≤30 mL to 35 mL/min.

Generic BPs such as oral alendronate, oral ibandronate, and oral risedronate are significantly less expensive than their respective brand-name products (Fosamax®, Boniva®, and Actonel®). If the response to a generic oral BP is not adequate (as shown by a significant decline in bone density on a repeat DXA study at the 1-year follow-up), another therapy should be considered. Some studies have demonstrated variability in rates of disintegration and absorption among individual generic oral BPs that can affect tolerability, adherence, and possibly efficacy when compared to their brand-name equivalents.[55, 56] Thus, a decline in BMD may be seen in a patient compliant with a generic oral BP. Raloxifene (Evista®) is an appropriate alternative to oral BPs in younger women with a low risk of hip fracture, particularly those at increased risk for breast cancer and/or those with significant GERD that makes oral BPs problematic. Raloxifene is not be prescribed for men.

Parenterally administered medications include zoledronic acid (Reclast®; an intravenously administered BP) and denosumab (Prolia®; a RANKL inhibitor that is administered subcutaneously). Either of these two medications may be used as initial therapy, if oral medications are not tolerated. Zoledronate, administered as an annual 5 mg intravenous (IV) infusion for 3 to 6 years, can be used to treat osteoporosis and is also an attractive alternative in individuals with low bone mass/osteopenia who might only need one 5 mg infusion every 2 to 3 years. Like denosumab, it is often used in individuals with significant GI intolerance to oral BPs or in those with significant declines in BMD while on oral BP therapy. Zoledronate is contraindicated in patients with an estimated GFR ≤30 mL to 35 mL/min. Denosumab, 60 mg subcutaneously every 6 months, should be administered by a healthcare provider and is often used in individuals who are unable to take either an oral or parenteral BP due to renal insufficiency. When denosumab is discontinued and not replaced with an alternative anti-resorptive, a rapid decrease in BMD along with increased risk of vertebral fractures can be seen.[51, 57] Recently, the Prolia (denosumab) prescribing information has been amended to include the statement, “Multiple vertebral fractures have been reported following Prolia discontinuation. Consider transitioning to another anti-resorptive agent if Prolia [denosumab] is discontinued.” (Page 1).[59]

Additional drugs that are given parenterally include the PTH analogues teriparatide (Forteo®)[60], abaloparatide (Tymlos®),[61] and romosozumab (Evenity), which is a monoclonal antibody that has both strong anabolic properties and weak anti-resorptive properties. These drugs should be used as **initial therapy in patients who are considered to be at very high risk for fracture** (see below). They can also be used for patients who have failed treatment with other osteoporosis drugs. Forteo®, and Tymlos® are administered subcutaneously daily for 2 years. A cumulative total of 2 years of therapy with a PTH analogue should not be exceeded; if the patient requires continued treatment, a medication with a different mode of action such as an anti-resorptive should be prescribed.

Another option for the **initial treatment of postmenopausal women with a very high risk of fracture and osteoporosis or failed treatment with another osteoporosis drug** is romosozumab-aqqg (brand name Evenity),[62] which is a monoclonal antibody (IgG2) that binds to sclerostin leading to a potent anabolic and weaker anti-resorptive effect. According to the package insert romosozumab-aqqg is administered subcutaneously using two separate injections (one immediately following the other) of 105 mg for a total dose of 210 mg every month for a total of 12 monthly injections. After a year of treatment, this drug should be discontinued and an anti-resorptive drug should be prescribed in its place.[63] Romosozumabaqqg should not be given to patients who have had either a myocardial infarction (MI) or stroke in the past year or who have significant cardiovascular risk factors for an MI or stroke. In addition, it should be stopped immediately if the patient has either an MI or stroke while on the drug.[63] Romosozumab-aqqg is not currently approved for use in men or for treatment of glucocorticoid-induced osteoporosis.

Since the goal of therapy is to lower the risk of future fractures, it is important to stratify patients according to fracture risk. This can lead to the most appropriate initial course of drug therapy.[13] All patients regardless of risk category should be strongly advised to follow the non-pharmacologic recommendations listed above.[13]

Based on a recent review of evidence-based literature, United Rheumatology supports the use of the following four categories of fracture risk which can facilitate selecting the most appropriate treatment:[38, 63]

- **Low risk**: Patients with low bone mass **without a prior fracture history** who have 10-year FRAX scores for hip fracture of <3% and major osteoporotic fracture risk of <20% are assumed to be at low risk and can be treated with calcium and vitamin D along with lifestyle modifications described above.
- **Moderate risk**: Patients with low bone mass without prior history of fracture who score above these FRAX fracture thresholds are assumed to be at moderate risk and need medical therapy, including oral or IV BPs or raloxifene, if there are no significant contraindications, along with lifestyle modifications described above.
- **High risk**: Patients at high risk for fracture as defined by the FDA are patients with multiple risk factors for fracture, prior fragility fractures, and/or those failing to respond to prior drug therapies or are unable to tolerate previously prescribed medications. Drugs approved by the FDA for patients at high risk for fracture include denosumab and anabolic agents such as teriparatide, abaloparatide and romosozumab-aqqg. IV zoledronate (5 mg yearly for 1 to 5 years) can also be used. Patients with osteoporosis on DXA without a history of fragility fractures also need medical therapy along with lifestyle modifications described above. The more negative the T-scores, the higher the risk for fracture.

- **Very high risk**: Both AACE and ACE recommend using anabolic therapy initially in patients with the highest fracture risk or an especially high fracture risk, which is defined as those who have had a recent fracture (e.g., within the past 12 months), those that have fractures while on approved osteoporosis therapy, multiple fractures while on drugs causing skeletal harm (e.g., glucocorticoids), those with a very low T-score (e.g., <-3.0), those with a high risk of falls or history of injurious falls, and those with a very high fracture probability by FRAX (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm.[13]

In 2017, the Institute for Clinical and Economic Review (ICER) assessed the role of anabolic drugs for treatment of postmenopausal osteoporosis (*Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value)*.[65] They concluded that for the two anabolic agents available at the time, the evidence was "promising, but inconclusive (P/I) for net health benefit comparing abaloparatide and teriparatide to zoledronic acid." (Page 37).[65] Since the ICER report was published, two studies have demonstrated the superiority of anabolic drugs to oral BPs in lowering fracture risk in patients at the very highest risk for fracture.

- The VERO trial (**VER**tebral fracture treatment comparisons in **O**steoporotic women) published by Kendler et al.,[21] compared the anti-fracture efficacy of teriparatide 20 µg daily with risedronate 35 mg weekly in postmenopausal women at very high risk for fracture in a head-to-head study for 24 months. Patients were enrolled if they had a T-score of ≤-1.5 and radiographic evidence of at least two moderate or one severe vertebral fragility fracture(s). At the end of 2 years, patients treated with teriparatide had a clinically significant lower risk of new (morphometric) vertebral fractures and clinical fractures (defined as composite of both clinical vertebral and nonvertebral fractures) when compared to patients taking risedronate. There were no differences in the incidence of nonvertebral fractures between the two arms of the trial.
- Sagg et al.,[65] published the **ARCH** study of 4093 postmenopausal women between the ages of 55 and 90 years with BMD T-scores of ≤-2.5 at the total hip or femoral neck and either one moderate or severe vertebral fracture or two mild vertebral fractures. Patients could also be enrolled if their BMD T-score at the total hip or femoral neck was ≤-2.0 and they had either two moderate or severe vertebral fractures or a history of a proximal femoral fracture. The patients were equally divided into 2 groups, one of which received subcutaneous romosozumab (210 mg monthly for 12 months) and the other received oral alendronate (70 mg weekly for 12 months). At the end of one year both groups were given 70 mg alendronate weekly for another year. At the end of 2 years the group that had started with romosuzumab, had a significantly lower risk of new vertebral fractures (50%), non-vertebral fractures (19%) and hip fractures (38%) than the alendronate group.

Given the significant difference in cost between the currently available anabolic agents (teriparatide, abaloparatide, romosozumab-aqqg) and oral BPs, United Rheumatology recommends that anabolic drugs should be selectively prescribed as first-line therapy in patients who have a **very high risk** for fracture. United Rheumatology also recommends the use of anabolic agents as first-line therapy in patients with a T-score ≤-3.5 in the lumbar spine, total hip, and/or femoral neck with or without a prior fragility fracture. Anabolic drug therapy is also appropriate as second-line therapy in individuals who have failed to respond to anti-resorptive therapy with interval fragility fracture(s).

There is no fracture data to support the use of nasal or injectable calcitonin for the treatment of osteoporosis or increased fracture risk in postmenopausal women. Similarly, there are no fracture data to support the use of combination therapy (e.g., BP plus teriparatide, denosumab plus teriparatide, or raloxifene plus BP).

Chronic Kidney Disease (CKD) and Osteoporosis

The relationship between CKD and bone disease is complex. When osteoporosis is suspected in patients with CKD, collaboration with the patient's nephrologist is essential, because these patients can have other metabolic bone disorders that can be the cause of fragility fractures. An excellent review of this topic was authored by Paul Miller in 2014.[67] The FDA has indicated that BPs should not be used for patients with a GFR below 30 mL to 35 mL/min (Table 2) and suggests that generally, administering providers should take special care when prescribing BPs for elderly patients, because they are more likely to have impaired renal function than younger patients.

The 2017 Kidney Disease Improving Global Outcomes guidelines recommend that patients with Grade-1 and Grade-2 CKD be managed as those without renal impairment. Patients with Grade-3a and Grade-3b CKD and normal PTH levels with evidence of either osteoporosis on a BMD study and/or high risk for fracture should also be managed as those without renal disease.[68]

Table 2. Recommended pharmacologic treatments for patients with osteoporosis

Drug Classification	Generic Name	Brand Name	Route of Administration	Limitation on Treatment Duration	Contraindications	FDA-approved Indications
Anti-resorptive agents						
BPs	Alendronate Ibandronate Risedronate Zoledronate (zoledronic acid)	Fosamax® Boniva® Actonel® Atelvia® Reclast® Zometa® Aclasta®	Oral Oral Oral IV	See Drug Holiday, below	For BPs as a group: • Drug allergy • Hypocalcemia • Decreased renal function For oral BPs only: • Esophageal dysmotility (GERD) For all BPs (oral and IV): • Do not use in patients with CKD and GFR ≤30–35 mL/min	Alendronate • Osteoporosis in postmenopausal women • To increase bone mass in men with osteoporosis • Treatment of steroid-induced osteoporosis Ibandronate • Osteoporosis in postmenopausal women Risedronate • Osteoporosis in postmenopausal women • To increase bone mass in men with osteoporosis • Treatment of steroid-induced osteoporosis Zoledronate • Osteoporosis in postmenopausal women • To increase bone mass in men with osteoporosis

						• Treatment of steroidinduced osteoporosis

Drug Classification	Generic Name	Brand Name	Route of Administration	Limitation on Treatment Duration	Contraindications	FDA-approved Indications

RANKL inhibitor	Denosumab	Prolia®	SC	If discontinued at any time another anti-resorptive therapy should be prescribed	• Drug allergy • Hypocalcemia • Pregnancy	• Osteoporosis in postmenopausal women at high risk of fracture • Increase bone mass in men at high risk of fracture • Increase in bone mass in men at high risk of fracture on ADT for non-metastatic prostate cancer • Increase in bone mass in women at high risk of fracture receiving adjuvant AI therapy for breast cancer • Steroid-induced osteoporosis (GIO)
Estrogen agonist/antagonist	Raloxifene*	Evista®	SC	If discontinued at any time another anti-resorptive therapy should be prescribed	• Drug allergy • Hypocalcemia • Pregnancy	
Anabolic Agents						
PTH analogues	Teriparatide (PTH analog) Abaloparatide** (PTH related protein)	Forteo® Tymlos®	SC SC	For teriparatide and abaloparatide injection: • 2 years in a lifetime after which anti-resorptive	For teriparatide and abaloparatide: • Drug allergy • Increased risk of osteosarcoma in individuals with Paget's disease, unexplained high	Teriparatide • Osteoporosis in postmenopausal women at high risk for fracture • Men diagnosed with primary osteoporosis • Increase in bone mass in men with primary or

Drug Classification	Generic Name	Brand Name	Route of Administration	Limitation on Treatment Duration	Contraindications	FDA-approved Indications
				therapy should be prescribed	alkaline phosphatase, young patients with open epiphyses or prior external beam or implant radiation therapy involving the skeleton	hypogonadal osteoporosis with high risk of fracture • Men and women with steroid-associated osteoporosis and sustained steroid therapy at high risk of fracture Abaloparatide • Osteoporosis in postmenopausal women at high risk of fracture
Sclerostin inhibitor	Romosozumab-aqqg**	Evenity	SC	Monthly for a **total of 1 year** followed by an anti-resorptive agent if treatment for osteoporosis is still needed	• • Drug allergy • Hypocalcemia • MI or stroke in the past year If patient has a MI or stroke while on this drug it should be stopped	• Osteoporosis in postmenopausal women at high risk for fracture • Failed or intolerant to other drugs for osteoporosis

*Not recommended in men

**Not yet approved for use in men and not approved for use in patients on glucocorticoid therapy

AI, aromatase inhibitors; ADT, androgen deprivation therapy; BPs, bisphosphonates; CKD, chronic kidney disease; FDA, Food and Drug Administration; GFR, glomerular filtration rate; GIO, glucocorticoid-induced osteoporosis; IV, intravenous; MI, myocardial infarction; PTH, parathyroid hormone; SC, subcutaneous

Recommendations for Patients Receiving Glucocorticoids

No discussion of patients at very high risk for fracture is complete without consideration of those on glucocorticoids. The use of glucocorticoids is frequently necessary in the treatment of inflammatory conditions but is fraught with multiple comorbidities and potential mortality. Osteoporotic fractures are of significant concern in these patients. At any given T-score, the incidence of new vertebral fractures in postmenopausal women receiving glucocorticoids is increased when compared with nonusers. Fractures appear to occur at higher bone density than that seen in postmenopausal osteoporosis, perhaps due to the effect of glucocorticoids on the osteocyte.[68] Importantly, a rapid decline in BMD can begin within the first 3 months of glucocorticoid therapy and peak at 6 months, followed by a slower but steady loss of BMD with persistent steroid use.[70]

United Rheumatology supports the management of a patient receiving glucocorticoid therapy according to the American College of Rheumatology (ACR) 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-induced Osteoporosis.[44] According to these guidelines, fractures in patients on glucocorticoid therapy may occur without a decline in BMD. A FRAX risk assessment should be performed in all postmenopausal women and men over the age of 50 years who are treated with glucocorticoids. FRAX assigns a low (<10%), medium (between 10% and 20%), or high (>20%) risk to patients based on their calculated 10-year major osteoporotic fracture risk. All high-risk patients should be treated. Height loss is assessed with a wall-mounted stadiometer, and patients with a loss in height of ≥1.5 inches should undergo assessment for prevalent morphometric vertebral body compression fractures.

The management of postmenopausal women and men over the age of 50 years who will be given glucocorticoids or are already taking them is shown in Table 3.[44] The management of premenopausal women and men under the age of 50 years with a prevalent fragility fracture starting or receiving glucocorticoids is shown in Table 4.

Table 3. Management of postmenopausal women and men ≥50 years of age starting or receiving glucocorticoids based on FRAX

Glucocorticoid Dose	FRAX risk		
	Low	Medium	High
<7.5 mg/day for ≥3 months	No treatment	One of the following: • Alendronate • Risedronate	
≥7.5 mg/day for ≥3 months	One of the following: • Alendronate • Risedronate • Zoledronate	One of the following: • Alendronate • Risedronate • Zoledronate	One of the following: • Alendronate • Risedronate • Zoledronate

≤5 mg/day for ≤1 month			One of the following: • Alendronate • Risedronate • Zoledronate • Teriparatide
≥5 mg/day for ≤1 month OR Any dose used for >1 month			• Teriparatide is preferred

Table 4. Management of premenopausal women and men under the age of 50 years with a prevalent fragility fracture starting or receiving glucocorticoids

Glucocorticoid Dose	Women (No Childbearing Potential)	Women (Childbearing Potential)	Men <50 Years of Age
≥5 mg/day for 1 to 3 months	One of the following: • Alendronate • Risedronate	No consensus	One of the following: • Alendronate • Risedronate
≥7.5 mg/day for 1 to 3 months	• Zoledronate	No consensus	• zoledronate
Any dose for >3 months	One of the following: • Alendronate • Risedronate • Zoledronate • Teriparatide	One of the following: • Alendronate • Risedronate	One of the following: • Alendronate • Risedronate • Zoledronate • Teriparatide
≥7.5 mg/day for >3 months	One of the following: • Alendronate • Risedronate • Zoledronate • Teriparatide	One of the following: • Alendronate • Risedronate • Teriparatide	
≤7.5 mg/day		No consensus	

Drug Holiday

In the last decade, concern about the potential of medication-related osteonecrosis of the jaw (MRONJ) and atypical femoral fractures (AFFs) associated with long-term BP use has led to the recommendation that patients treated for osteoporosis stop BP therapy after a pre-specified period of time. This is based on the concern that the risk of long-term therapy might be greater than the potential benefit of fracture reduction.

The duration of treatment is dependent on the patient's fracture risk. For patients with no prior fragility fractures, including younger postmenopausal women and those with moderately low T-scores (termed moderate fracture risk by the AACE/ACE), a drug holiday should be considered after 3 years of oral or 5 years of IV BP therapy.[12, 70] In this group, a drug holiday for 2 to 5 years should be considered depending

on the patient and their BMD during the drug holiday.[50, 70] For patients with prior fragility fracture(s) and/or frail older women with increased risk of falls and/or very low T-scores (termed higher fracture risk by AACE/ACE), a drug holiday is recommended after a longer treatment period with BPs (10 years with oral therapy; 6 years with IV BP therapy).[12] These recommendations are consistent with those published by the American Society for Bone and Mineral Research (ASBMR) Task Force.[71] Hip T-scores between -2.0 and -2.5 in the **F**racture intervention trial **L**ong-term **EX**tension (FLEX) trial and below -2.5 in the **H**ealth **O**utcomes and **R**educed **I**ncidence with **Z**oledronic acid **ON**ce yearly (HORIZON) trial predicted a beneficial response to continued therapy.[71, 72] Based on these results, the Task Force recommended that fracture risk should be reassessed after 3 years of IV BP therapy or 5 years of oral BP therapy.[71] For those at higher risk, consideration of continued treatment for at least 6 years (IV BP) or 10 years (oral BP) was recommended. However, these patients require continued monitoring. In this population the risk of AFFs (discussed below) increases with the duration of BP treatment.[50] However, the Task Force stated that the benefit of decreased risk of vertebral fractures is far greater than the risk for AFFs.[50]

It is important to note that BPs have different binding affinities to bone, and only alendronate and zoledronate remain avidly bound to bone for several years or longer after the drug has been withdrawn.[50] Therefore, the concept of a drug holiday, where a drug is withdrawn and the benefit (fracture reduction) persists while risk is reduced, is only applicable to alendronate and zoledronate. Several researchers have provided more in-depth analyses of how to determine the need for a drug holiday as opposed to continued treatment.[73-75]

According to the 2019 guidelines from the Endocrine Society,[50] osteoporosis therapy should be restarted if there is a concerning decline in BMD, fracture or other increased fracture risks during the drug holiday.

A drug holiday is **not applicable with denosumab** treatment. In fact, both the 2016 AACE/ACE Guidelines[12] and the 2019 Guidelines from the Endocrine Society,[50] recommend against a drug holiday for patients on denosumab (also see the discussion on denosumab prescribing information under

Pharmacologic Treatment). If denosumab is discontinued the patient should immediately be given another anti-resorptive drug.[13]

Anabolic drugs such as teriparatide, and abaloparatide should not be used for more than 2 years cumulatively. In contrast, there are no cautions in the package insert about using romosozumab for more than one subsequent course or using it in an individual previously treated for 2 years with a PTH analogue. However, immediate sequential treatment with more than one anabolic drug is not currently recommended by United Rheumatology because of the belief that over stimulation of osteoblasts will have a diminishing anabolic effect. After treatment with any of these anabolic drugs, transitioning to an anti-resorptive is recommended to avoid loss of bone density gained while on anabolic therapy. Unlike denosumab, increased risk of fracture has not been reported after teriparatide or abaloparatide withdrawal.

Patients treated with raloxifene are not at risk for MRONJ or atypical fractures; therefore, duration of therapy is not an issue in younger postmenopausal women. Since the drug does not protect against hip fractures and other nonvertebral fractures, transitioning to an alternate osteoporosis drug is appropriate when the risk for these fractures becomes more significant.

Special Considerations in the Management of Osteoporosis

Special considerations in the treatment of osteoporosis include the potential correlation of calcium and cardiovascular risk, the use of proton pump inhibitors (PPIs) in patients with osteoporosis, and MRONJ or AFFs with the use of potent anti-resorptives.

Calcium and Cardiovascular Risk

There have been conflicting reports about calcium supplements and increased risk of cardiovascular events. Several meta-analyses and a subgroup analyses of the Women's Health Initiative raised the issue of a possible increased risk of cardiovascular disease (CVD) associated with calcium supplements.[76-78] However, others such as the Nurses' Health Study, a prospective cohort study with 74,245 women who were followed for 24 years, did not find that calcium supplements increased the risk of CVD.[79] In addition, another review of studies and meta-analyses of calcium supplements did not find an increased risk of CVD.[81] In fact, some studies have suggested a cardioprotective effect of calcium plus vitamin D.[81-83] Vitamin D itself has been demonstrated to be cardioprotective.

While it has been demonstrated in multiple trials that there is no effect on fracture reduction with either calcium or vitamin D independently, there are newer meta-analyses that suggest a potential for hip fracture reduction with the combination. The meta-analyses are limited by several factors, including, but not limited to, lack of standardization of assays, potential publications bias, and lack of data on gender differences. Likewise, the data on the potential deleterious effect of calcium on the cardiovascular system, remains controversial. Further studies, including prospective data, are needed to substantiate these issues.[85] Current Institute of Medicine recommendations advocate calcium supplements to promote bone health in patients who do not obtain the recommended calcium intake through dietary sources.[86]

Proton Pump Inhibitors and Osteoporosis

The relationship between PPI usage and a potential increase in osteoporotic fracture remains unclear. The Canadian Multicentre Osteoporosis Study showed that, while PPI users had lower BMD at baseline than nonusers, PPI use over 10 years did not appear to be associated with accelerated BMD loss.[86] The association between PPIs and osteoporosis-related fractures has been suggested in several retrospective analyses; the strength of the relationship varied from study to study. To date, no prospective analyses have been published, and no mechanism of action has been proposed by which PPI usage could increase the risk for fracture. Prior studies that have analyzed the association between PPI use and BMD have produced conflicting data so that the actual relationship between PPI use and BMD is poorly characterized.

Multiple meta-analyses assessing the risk of PPI use and fractures were published in 2011.[87-91] The majority of these studies showed that the risk of hip (relative risk [RR], 1.2 to 1.3) and spine (RR, 1.6) fractures was increased moderately in PPI users. These studies were limited by heterogeneity, and when the studies were adjusted for other risk factors for fracture, PPIs were no longer seen as the cause. Histamine H2 receptor antagonists were not associated with an increased risk for fracture. Based on these data, low BMD may be a marker for other comorbidities that predispose patients for PPI use rather than a direct effect of PPI therapy. One study published in 2011 calculated a 'refractory GERD score' that showed an association of higher PPI use and female gender, more comorbidities, and greater overall costs.[92] Further study is suggested, but currently no change in the prescribing habits for PPIs is required.

Medication-related Osteonecrosis of the Jaw

Medication-related osteonecrosis of the jaw (MRONJ) replaces the term *osteonecrosis of the jaw* (*ONJ)*. The change in nomenclature is supported by the American Association of Oral and Maxillofacial Surgeons (AAOMS), because there have been reports of ONJ not only related to BPs but to other anti-resorptive medications such as denosumab and antiangiogenic agents.[93-97] According to the package insert for romosozumab-aqqg, patients taking this drug may be at risk for MRONJ.[63] The AAOMS definition of MRONJ includes all of the following findings (Page 1940):[94]

- Current or previous treatment with anti-resorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease

Individuals at risk of developing this condition usually have either a malignancy, low bone mass/osteopenia, or osteoporosis and have been on treatment with anti-resorptive medications including BP, denosumab, or antiangiogenic agents.[93] In contrast, romosozumab is a weak anti-resorptive and it is not yet known whether the risk for ONJ will be lower than it is for BPs or denosumab. Although MRONJ can occur spontaneously in patients taking these medications, the risk is extremely low;[99] however, the risk increases after dental implants, periodontal interventions, and tooth extractions. A 2017 publication from the International Task Force on ONJ stated that, "The incidence of ONJ in the osteoporosis patient population is very low and may be only minimally higher than the frequency seen in the general population." (Page 13).[99]

In 2014, the AAOMS published a white paper on MRONJ[94]. In that paper the risk for cancer patients not exposed to anti-resorptive medications was found to range between 0% and 0.019%. In cancer patients exposed to zolendronate, the incidence of MRONJ the reported rate for MRONJ was between 0.7% and 6.7%. In patients with cancer treated with denosumab, the incidence rate was reported to be between 0.7% to 1.9%.[93, 100] A study published in 2010,[101] 13,946 patients who had been on BP for at least 4 years were asked to respond to a survey. The respondents consisted of 8572 patients. Of these about 25% reported dental symptoms but only 9 cases of MRONJ were identified resulting a prevalence rate of 0.10%.

The results of the 7-year extension of the **F**racture **RE**duction **E**valuation of **D**enosumab in **O**steoporosis every 6 **M**onths (FREEDOM)[103] are interesting. For the first 3 years, this was an international, randomized, placebo-controlled study to evaluate if denosumab decreased fracture risk. No cases of MRONJ were reported. The study was then extended for an additional 7 years and was able to investigate whether denosumab for 10 years increased the risk of MRONJ. In the additional 7 years, 13 cases of MRONJ were reported, with most patients responding to treatment (information was not available for one patient and was incomplete for another). Denosumab was not discontinued during MRONJ treatment in these patients. The incidence of MRONJ in women treated with denosumab was 0.68% for those who had dental procedures and 0.05% for those who did not.

If a patient develops MRONJ, the dentist and prescribing physician must work collaboratively. The American Dental Association (ADA) indicates that the decision to stop BPs or denosumab should be made by the treating physician after a discussion with the patient's dentist.[102] The decision to discontinue therapy should be based on the risk of complications of not treating osteoporosis and not on the risk of

MRONJ, because the risk of osteoporotic fracture without therapy is much higher than the risk of MRONJ with continued BP or denosumab treatment.

Although the risk of MRONJ is low, a common-sense approach to using potent anti-resorptives such as BPs and denosumab might be to follow recommendations in the *Warnings and Precautions* section of the
Prolia prescribing information (Section 5.4):[59]

> A routine oral exam should be performed by the prescriber prior to initiation of treatment. A dental examination with appropriate preventative dentistry is recommended prior to treatment in patients with risk factors for ONJ such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene and comorbid disorders (e.g., periodontal and/or pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment.

A similar recommendation is provided in the Reclast prescribing information (Section 5.4):[103, 104]

> A routine oral examination should be performed by the prescriber prior to initiation of bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be performed prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy angiogenesis inhibitors, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy).

Before a patient with low bone mass/osteopenia or osteoporosis or malignant bone disease is started on an oral or parenteral BP, denosumab, or romosozumab-aqqg, the patient should have a complete dental evaluation with optimization of dental health prior to starting these medications; including but not limited to treatment of acute and potential infections, removal of non-restorable teeth, treatment of periodontal disease, and completion of any planned elective dentialveolar surgery. If possible, medications associated with increased risk of MRONJ should not be started until there is healing of bone and/or there has been mucosalization of any extraction or surgical sites (after 2 to 3 weeks). Patients with dentures should be evaluated for any areas of mucosal trauma.[93, 102, 104]

Patient education is very important. Patients should be told that the risk of MRONJ is very low when they are treated with BPs, denosumab, or romosozumab. This risk can be decreased further with good dental hygiene and regular visits to a dentist. Patients should be encouraged to have a dental evaluation at least every 6 months to include an examination and cleaning.[93] In addition, patients should be advised to brush their teeth at least twice a day and floss daily.[99] The ADA recommends that patients with active dental problems should be treated; because the risk of complications from untreated cavities, periodontal disease, periapical abscess, or granulomas is higher than the risk of MRONJ.[102] Caring for patients on medications that have either a spontaneous risk for MRONJ or an increased risk for MRONJ as a result of a dental procedure requires excellent communication between the dentist and the prescribing physician.

Potent Anti-resorptives and Atypical Femoral Fractures

The recognition of potential atypical femoral fractures (AFFs) in postmenopausal women treated with long-term oral or parenteral BPs, romosozumab-aqqg and denosumab, has had a significant impact, not only on the prescribing patterns of providers but also the willingness of patients to take these drugs. The increasing use of a drug holiday is a direct result of these concerns. Although the absolute risk is low, ranging from 3.2 to 50 cases per 100,000 patient years,[105] the risk does increase with long-term use. Two studies suggest a risk of >100 cases per 100,000 patient years with 5 to 9 years of BP use.[100, 106] The fact that this risk is still quite low compared with the risk of common postmenopausal and age-related osteoporotic fractures has not helped to diminish patient anxiety.

The ASBMR Task Force published definitions of AFFs, AFF epidemiology, risk factors, and management in 2010,[107] with an update in 2014.[105] The revised case definition (Table 5) is helpful for distinguishing these fractures from the more common osteoporotic fragility fractures occurring in the femur.[107]

Table 5. The 2014 ASBMR definition of AFF

The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. AND At least four of the five major features listed must be present to diagnose an AFF. None of the minor features is required, but they have sometimes been associated with these fractures.	
Major Features	**Minor Features**
• Fracture is associated with minimal or no trauma, as in a fall from a standing height or less. • Fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur. • Completed fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex. • The fracture is noncomminuted or minimally comminuted. • Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (‘breaking’ or ‘flaring’).	• Generalized increase in cortical thickness of the femoral diaphysis. • Unilateral or bilateral prodromal symptoms such as dull or arching pain in the groin or thigh. • Bilateral incomplete or complete femoral diaphysis fractures. • Delayed fracture healing.

AFF, atypical femoral fracture; ASBMR, American Society for Bone and Mineral Research

To lower the likelihood of an AFF, United Rheumatology provides the following recommendations, based on expert consensus:

- AFFs appear to occur most commonly in younger more active women, perhaps due to microfractures and stress reactions that fail to heal and then propagate. In these women, a shorter duration of therapy of 3 to 5 years with a subsequent drug holiday until BMD declines significantly again or the use of IV zoledronate every 2 to 3 years is appropriate.
- Although the mechanism of action of denosumab is different from BPs, it is also a potent anti-resorptive. Accordingly, switching to denosumab after BP therapy may not lower the risk of AFFs. In contrast, romosozumab-aqqg has a weak anti-resorptive effect; however, it is not yet known whether this will translate into a lower risk of developing AFFs.
- Ask patients at each visit whether they are experiencing groin or thigh pain. If examination fails to identify a clear cause of their pain (e.g., trochanteric bursitis or hip osteoarthritis), obtain a radiograph(s) of the femur and look for signs of early stress reactions such as cortical breaking.
- Promptly withdraw BP, denosumab or romosozumab-aqqg therapy in those found to have an AFF and image the contralateral femur for signs of fracture (X-ray, bone scan, or magnetic resonance imaging [MRI]) as bilaterality is not uncommon.

Recommendations for the management of incomplete AFFs are provided in the 2010 and 2014 ASBMR Task Force recommendations.[105, 107] Prophylactic reconstruction (nail fixation) is recommended for painful incomplete AFFs. For minimal pain, conservative therapy with limited weight-bearing activity and possible use of teriparatide is suggested, based on positive outcomes in some reported cases, although placebo-controlled trials are not available.

The Appendix lists all the essential elements that the provider should collect at each clinical visit for osteoporosis screening.

Technique for Performing a Bone Mineral Density Scan

The best imaging modality for BMD is a central DXA study. It is the only modality accepted by United Rheumatology.

The DXA examination should include the following:[11, 108, 109]

1. Posterior-anterior (PA) view of the lumbar spine and of one or both hips. BMD of the spine and hip should be measured in all patients.
2. If the evaluation of the lumbar spine or hip cannot be done because of severe degenerative disease or heavy vascular calcifications, fractures, scoliosis, or metal implants; images of the nondominant forearm should be obtained for BMD measurement.
3. When evaluating the lumbar spine, it is preferable to use four vertebrae (L1 to L4); however, a minimum of two adjacent vertebrae can be used to calculate the T-score. BMD should not be measured in a single vertebra. Vertebrae with a difference in T-score of ≥1.0 compared with an adjacent vertebra may be excluded from the calculation. In addition, vertebrae with evidence of fractures, prior surgery, metal plates or screws, overlying tubing, or marked degenerative changes should be excluded from the calculation.

4. In a patient with known hyperparathyroidism, a PA BMD measurement of the nondominant forearm should be obtained.
5. BMD of the hip may be measured on either side or both sides and should include the lowest value obtained from the femoral neck or total hip.
6. Follow up DXA scans should be performed on the same machine as previously used (if possible) and compared to prior studies. The region of interest and area measured should be the same as on the previous scan. At times it may be necessary to use different DXA equipment (equipment replacement or different facility), the comparison is then qualitative and not quantitative.

Personnel and Facility Requirements[11, 71, 105]

1. Facility accreditation by ISCD is encouraged but not required.
2. All providers interpreting DXA scans must have passed the ISCD certification examination at least one time.
3. All technologists performing this examination must maintain current certification in bone densitometry from the American Registry of Radiologic Technologists or a qualification as a Certified Bone Densitometry Technologist from the ISCD.
4. Each facility must have a quality control (QC) program consistent with either the recommendations of the ISCD or the ACR–SPR-SSR practice parameters that should be designed in consultation with a qualified medical physicist.
5. All facilities must have a supervising physician who is responsible for the QC program.
6. All facilities must have a supervising technologist who is responsible for QC procedures.
7. These procedures should be performed at least three times per week prior to the first clinical examination. A permanent record of the QC tests must be available on site. The supervising technologist is also responsible for determining the precision error and the least significant change (LSC) that should represent pooled data from all technologists.
8. Any new technologist must perform a precision study and, if acceptable, the results must be pooled with the data from all the technologists at the facility.
9. Cross-calibration according to the recommendations of the ISCD should be performed when changing any hardware or when replacing the entire system.

Documentation

The information in this section is based on the ISCD 2015 Official Positions and the American College of Radiology's practice parameter for the performance of DXA.[11, 105]

A permanent record must be maintained according to appropriate state law for retention of records and imaging; including patient history forms (written or electronic), requests or referrals for the examination, printouts or the electronic equivalent of images (including regions of interest, if provided), and the BMD values. All images must include:

1. Patient demographics
2. Date of examination
3. Image orientation
4. Facility name
5. Unit manufacturer and model

Minimum DXA report requirements are:

1. Patient demographics, including but not limited to:
    a. Name
    b. Unique medical-record number
    c. Date of birth
    d. Gender
2. Name of the referring provider.
3. Indications for the test.
4. Name of the manufacturer and model number of the equipment used.
5. Risk factors, including fragility or low-trauma fractures. Although current software provided by DXA manufacturers includes a FRAX 10-year fracture risk prediction, this should not be applied to patients currently on FDA-approved drug therapy for osteoporosis.
6. Assessment of technical quality of the study, and the reason for exclusion of a specific site, if appropriate.
7. Skeletal sites scanned.
8. BMD in g/cm^2 for each site.
9. T-score and Z-score, if appropriate, for each site.
10. Classification according to the World Health Organization criteria. Only one classification is given per patient. The classification is based on the lowest T-score not to each site evaluated.
11. General recommendation for evaluation of secondary causes of low BMD, if the scan demonstrates osteoporosis and the work-up has not been done recently.
12. Recommendations for the necessity and timing of a follow-up DXA scan.
13. For premenopausal women and men under age 50 years, the BMD and Z-score should be reported. A Z-score lower (more negative) than ≤-2.0 is described as low bone density for age.
14. Comparison to prior DXA scans if available and documentation of whether or not there has been a significant change.

Optional items in a DXA report:

1. Specific recommendations for evaluation of secondary causes of MBD.
2. Recommendations for pharmacological and non-pharmacological interventions.
3. Recommendations for further non-BMD testing, such as X-ray, MRI, computed tomography etc.
4. TBS score, if available.
5. FRAX risk, if available.
6. FRAX risk with TBS value included in the calculation, if available.

Items that should ***not*** **be included in a DXA** report:

7. A statement that there has been bone loss without knowledge of previous bone density study.
8. Use of the terms 'mild', 'moderate', or 'marked' low bone mass/osteopenia or osteoporosis.
9. Separate diagnoses for different regions of interest (e.g., low bone mass/osteopenia at the hip and osteoporosis at the lumbar spine).

Minimum VFA report requirements are:[105, 108]

1. Patient demographics, including but not limited to:
   a. Name
   b. Unique medical record number
   c. Date of birth
   d. Gender
2. Name of referring provider.
3. Indications for the test.
4. Type of examination – X-rays or DXA.
5. Risk factors, including low-trauma/fragility fractures.
6. Assessment of technical quality of the study, including vertebrae that cannot be evaluated.
7. Vertebral deformities, and whether or not deformities are consistent with vertebral fracture.
8. Location and grade of each vertebral body compression fracture.
   The Genant visual semi-quantitative method[112] is the current clinical technique of choice for diagnosing vertebral fractures.
9. If the study is a follow-up, it should compare the prior studies and comment on the significance of changes, if any.

Glossary

1/3rd radius or 33% radius	Bone mineral density measured in the distal third of the radius in the nondominant arm.
Atypical femoral fracture (AFF)	Low-trauma fracture of the femur potentially associated with long-term use of BPs or denosumab. The earliest symptoms may be groin or thigh pain. X-rays may demonstrate findings suggestive of a stress fracture in the lateral cortex of the femoral shaft.
Bone mineral density (BMD)	Describes the amount of calcium and other mineral content in bone. The greater the calcium and mineral content, the higher the bone density. BMD is measured by DXA, which measures mineral content in g/cm^2 but is often reported as a T-score (see below) in adults.[11]

Central dual energy X-ray absorptiometry (DXA)	A technology using very low-dose X-rays to determine BMD. It is the preferred method for evaluating patients for osteoporosis of the lumbar spine and hip. Imaging of the lumbar spine and hip (axial skeleton or central DXA) is the best method to diagnose osteoporosis, monitor results of drug therapy, and predict the risk of fracture(s). The appendicular skeleton (wrist, radius, or forearm) is sometimes used (peripheral DXA) to supplement central imaging, when the evaluation of the lumbar spine or hip is compromised.[36, 43]
FRAX®	The Fracture Risk Assessment Tool, developed by the University of Sheffield in cooperation with other medical societies, to identify individuals at increased risk for a fracture. This computer-based algorithm is available on the Sheffield University website and determines the 10-year probability of any major osteoporotic fracture and the 10-year probability of a hip fracture.[52]
Genant semi-quantitative method	A technique recommended to assess for vertebral fracture whether using VFA or plain radiographs. The reader first visually scans all vertebrae for presence of deformity using loss of height as well as lack of parallelism of the end plates, cortical buckling, end-plate deformities, and loss of vertical continuity of vertebral morphology.[112] Vertebrae are then assigned a grade of 1 (mild), 2 (moderate) or 3 (severe), based on the degree of height loss between anterior-posterior dimensions (wedge), anterior-middle dimensions (biconcave) or posterior-anterior dimensions (crush).
Low-trauma/fragility facture	A fracture that occurs either spontaneously or as the result of a fall from a standing height or less. It also includes fractures that result from coughing, sneezing, or any quick movement such as opening a window.[29]
Low bone mass/osteopenia	The term low bone mass is preferred by both the NOF and the ISCD over osteopenia. Low bone mass describes a bone density measurement that is between -1.0 and -2.5 SDs below the mean BMD of a young-adult reference population.
Osteoporosis	There are two definitions of osteoporosis:[11] 1. A densitometric definition based on a T-score of -2.5 or lower 2. A clinical definition based on a history of a low-trauma/fragility fracture in an adult
T-score	A calculation used to report the results of BMD or bone densitometry tests. The T-score describes the number of SDs above or below the mean BMD of a young-adult reference population.[36]

Vertebral fracture	Grade 1 or mild fracture: • Reduction in vertebral height of 20% to 25% Grade 2 or moderate fracture • Reduction in vertebral height of 26% to 40% Grade 3 or severe fracture • Reduction in vertebral height of >40%

Appendix

Essential Elements from Osteoporosis Clinical Guidelines

Demographics	• Gender, age, race, height/weight/BMI
Social and Personal History	• Alcohol use of more than two units per day • Current cigarette use • Dietary calcium intake
Medications (to include current vs prior, and start/stop dates)	• Steroids for more than 3 months • Current thyroid hormone supplement, neuroleptics, aromatase inhibitors, androgen deprivation, estrogens, BPs (type), raloxifene, teriparatide, calcitonin, denosumab, vitamin D supplement, or calcium supplement
Past Medical History	• Maximum adult height (for historical height loss) • RA, systemic lupus erythematosus, inflammatory bowel disease, renal calculi, celiac disease, gastric bypass, anorexia, alcoholism, hypogonadism, insulin-dependent diabetes mellitus, multiple myeloma, hyperparathyroidism • Skeletal radiation, GERD, arterial/venous thrombotic events • MRONJ, AFF(s) • Low-trauma fracture as an adult ○ Type of fracture and date (excluding fingers, toes, and skull) ○ Vertebral fractures: number and grade
Review of Systems	• Acute/sub-acute back pain • Dental health • Frequent falls, frailty • Significant dysphagia
Family History	• Hip fracture in either parent • Diagnosis of osteoporosis in other family members • Renal calculi
Physical Examination	• Height: current ○ vs past height (for "measured height loss") ○ vs maximal height (for "historical height loss") • Kyphosis • Ability to stand on either leg for >6 seconds • Oral health/dental evaluation

DXA Data	• Machine type • Least significant change for spine and hip • Lowest T-score • BMD (g/cm^2) in femoral neck (to calculate FRAX®) ○ Lowest of two values, if both hips present • FRAX® result • Vertebral morphometry, if height loss or back pain; VFA, if available; lateral T and L spine radiographs, if not • Trabecular bone score, if available

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Document Updates

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1.1.2016	Creation of first version	Jun 2016
1.1.2017	Annual review incorporating most recent research	Mar 2017
1.1.2019	2018/19 update	Mar 2019
1.1.2021	2021 update	May 2021
1.1.2023	2023 Update	Feb 2023