



Clinical Practice Guideline

Adult Osteoporosis

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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
ARRT	American Registry of Radiologic Technologists
ASBMR	American Society for Bone and Mineral Research
BMD	Bone mineral density
BMI	Body mass index
BP(s)	Bisphosphonate(s)
BUN	Blood urea nitrogen
CBC	Complete blood count
CKD	Chronic kidney disease
CMP	Comprehensive metabolic panel
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CVD	Cardiovascular disease
DXA	Dual energy X-ray absorptiometry
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FRAX [®]	Fracture Risk Assessment Tool
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIO	Glucocorticoid-induced osteoporosis
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
ICER	Institute for Clinical and Economic Review
ICSI	Institute for Clinical Systems Improvement
IOF	International Osteoporosis Foundation
ISCD	International Society for Clinical Densitometry
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LSC	Least significant change
MBD	Metabolic bone disease
MRI	Magnetic resonance imaging
MRONJ	Medication-related osteonecrosis of the jaw
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
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
SLE	Systemic lupus erythematosus
TBS	Trabecular bone score
TPN	Total parenteral nutrition
TSH	Thyroid stimulating hormone
VFA	Vertebral fracture assessment
WHO	World Health Organization

Introduction

Osteoporosis is defined as a skeletal disorder characterized by decreased bone strength predisposing to an increased risk of fracture.^{1,2} It is often asymptomatic, under-recognized, and undertreated. Fractures, which can be a complication of osteoporosis, pose an enormous healthcare burden, with significant morbidity and mortality, and contribute to rising healthcare costs.³ In 2002 alone, the annual cost of treating osteoporosis and associated fractures in the Medicare population was estimated to be approximately \$16 billion.⁴

It is projected that by 2020, the number of adults 50 years of age or older in the United States with either low bone mass (osteopenia) 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 of these two sites will increase to 71.4 million, contributing to the ever-rising cost of healthcare.⁵

Individuals with osteoporosis are at increased risk of hip fractures. According to Brauer et al.⁶ and a Report of the Surgeon General,⁷ there is considerable confusion about the appropriate diagnosis, monitoring, and treatment of individuals with low bone mass/osteopenia or osteoporosis. Rheumatologists and other specialists are frequently called upon to diagnose and treat this disease. They routinely see patients at increased risk for osteoporosis; including postmenopausal women, older men and women, and individuals taking glucocorticoids. The indications for bone mineral density testing will be discussed later in this guideline.

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. At this time, there is no one test available to determine bone strength. Bone mineral density is used as a “proxy measure [for bone strength] and accounts for approximately 70% of bone strength” (Page 786).¹ Osteoporosis is one risk for 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

Bone mineral density of the lumbar spine, total hip, and femoral neck is measured by central dual energy X-ray absorptiometry (DXA). In some patients, the lumbar spine and/or hips cannot be used to measure BMD (e.g., in those with prior spine surgery with 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 substituted for either the lumbar spine and/or hips.⁸ Ward’s triangle and the greater trochanter of the hip should not be used to calculate BMD.⁹

In contrast to T-scores, which compare the patient's BMD to young normal controls, Z-scores 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 -2.5 and -1 is consistent with low bone mass/osteopenia. A T-score > -1 is considered normal. A diagnosis of osteoporosis should not be made in younger individuals without secondary causes of metabolic bone disease (MBD). Instead, they might be labelled as having *low bone mass for age* if their Z-score is < -2.0 .

Osteoporosis should be diagnosed in a postmenopausal woman or man over the age 50 years, regardless of BMD if she/he has had a fragility fracture of the hip, spine, pelvis, proximal humerus, or distal forearm.^{9,10}

The majority of osteoporotic vertebral fractures are not clinically apparent but must be looked for by radiographic imaging.^{11,12} 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 United States 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).^{13,14} 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. Morphometric fractures should not be viewed as less predictive of 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.¹⁵

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.¹⁶ Prevalent spine fracture burden as determined by SDI increased the likelihood of incident vertebral fractures up to 12-fold, nonvertebral fracture 2-fold, and any fracture 7-fold across the range of femoral neck BMD T-scores.¹⁷

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 often warrants anabolic drug therapy.¹⁸

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 a recent dental examination.
4. A complete physical examination is required for all patients.
5. Special attention should be paid to the following, as appropriate:^{9, 15, 19-21}
 - a. Risk factors for primary osteoporosis:
 - i. Age of 65 years or older
 - ii. Low body weight
 - iii. Early menopause
 - iv. Family history of osteoporosis or fractures
 - v. Smoking
 - vi. Excessive use of alcohol, defined as more than three drinks daily
 - vii. Balance problems and risk of falling (assess balance on exam by having patient attempt to stand on each leg for >6 seconds)
 - viii. Loss of height
 - ix. Kyphosis
 - x. Prior fragility fractures of the spine, hip, pelvis, upper humerus, or distal forearm after the age 50 years
 - b. Endocrine disorders that may cause secondary osteoporosis:
 - i. Diabetes (Type II)
 - ii. Growth hormone deficiency
 - iii. Hyperadrenalism
 - iv. Primary or secondary hyperparathyroidism
 - v. Hyperthyroidism
 - vi. Hypogonadism
 - vii. Acromegaly
 - viii. Hypercortisolism
 - ix. Endometriosis
 - x. Hyperprolactinemia
 - xi. Addison's disease
 - xii. Acromegaly
 - c. 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)
 - Vitamin D deficiency
- d. Renal disorders associated with secondary osteoporosis:
 - i. Hypercalciuria
 - ii. Renal tubular acidosis
 - iii. Renal insufficiency
 - e. 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 (COPD)
 - vi. Amyloidosis
 - vii. Lymphoma
 - viii. Sarcoidosis
 - ix. Sickle cell anemia
 - x. Rheumatoid arthritis (RA)
 - xi. Multiple sclerosis
 - xii. Vitamin D deficiency
 - f. Organ transplantation
 - g. 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
6. Laboratory tests, if no current values are available:^{15, 19-24}
- a. Complete blood count (CBC), comprehensive metabolic panel (CMP), and serum phosphorus
 - b. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
 - c. Serum calcium and 25-hydroxyvitamin D
 - d. Thyroid stimulating hormone (TSH), if hyperthyroidism is suspected
 - e. 24-hour urine calcium
 - f. Intact parathyroid hormone (PTH)
 - g. Serum and urine protein electrophoresis, immunofixation/immunoelectrophoresis
 - h. Anti-endomysial and anti-gliadin antibodies, if Crohn's 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 Fracture Risk Assessment Tool (FRAX®),²⁵ developed at the University of Sheffield, is the best-known and most widely utilized tool.

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.²⁶ Second, the single best predictor of future fracture is a prior fracture. According to the National Osteoporosis Foundation (NOF), approximately 25% of men over the age of 50 years and 50% of women over the age 50 years will suffer a fracture related to osteoporosis sometime during their lifetime.^{27, 28}

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.²⁴ 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 influence the risk of future fracture.

FRAX integrates clinical risk factors for fracture and BMD at the femoral neck to calculate the 10-year probability of hip fracture and the 10-year probability 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 different countries to guide treatment decisions. In the United States, the NOF *Clinician's Guide to Prevention and Treatment of Osteoporosis*¹⁰ 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.

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, including the following:²⁹

- Falls are a risk factor for fracture but are not included 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.
- The model underestimates fracture risk in individuals with multiple prior fractures.
- FRAX identifies only parental history of hip fracture but no other fragility fractures that may be a risk factor for fracture.
- The model underestimates fracture probability in patients on prednisone doses exceeding 7.5 mg/day.
 - High-dose inhaled glucocorticoids may be a risk factor for fracture and are not accounted for.
 - In individuals with adrenal insufficiency, appropriate glucocorticoid replacement has not been shown to increase fracture risk, and use of steroids in this setting should not be included in FRAX calculations.

- 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.

Additional tools for the assessment of fracture risk include the trabecular bone score (TBS), markers of bone turnover (serum C-telopeptide, urine N-telopeptide), and hip axis length. 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 on the University of Sheffield website](#) 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 (NIAMS) and the European Foundation for Osteoporosis and Bone Disease (later, this organization came to be 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.³⁰ and treatment of osteoporosis

Bone mass is determined by DXA imaging. The TBS determines the textural index of bone microarchitecture from DXA images of the spine.²³ According to Silva et al,³¹ 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 1.200 and 1.350 represent moderate deterioration of the trabecular microarchitecture, and scores ≤ 1.200 represent degradation of the bone microarchitecture. A normal TBS for men has not been determined. Silva et al. reviewed the current literature on TBS and concluded that:³¹

- 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*³² 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.

The University of Sheffield website allows for the calculation fracture risk using either [FRAX alone](#) or [FRAX adjusted for TBS](#). United Rheumatology encourages the use of TBS plus FRAX, if TBS is installed on the DXA scanner.

Indications for Baseline Bone Mineral Density Testing^{8, 24, 29, 33, 34}

United Rheumatology requires the use of central DXA for the evaluation of patients referred for BMD testing.⁸

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

- Women aged ≥ 65 years
- Men aged ≥ 70 years
- Postmenopausal women aged ≤ 65 years and men aged < 70 years, 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
 - Parental history of hip fracture
 - Excessive alcohol (3 drinks per day or more)
 - Use of medications known to be associated with secondary bone loss such as but not limited to:
 - Glucocorticoids
 - Aromatase inhibitors
 - Androgen deprivation therapy
 - Anticonvulsants such as phenytoin or phenobarbital
 - Chronic heparin
 - Chemotherapy
 - Aromatase inhibitors
 - Glucocorticoids
 - Androgen deprivation therapy
 - Heparin
 - Warfarin
 - Lithium
 - Thyroid hormone intake above normal physiologic doses
 - Thiazolidinediones
 - Depo-Provera
 - Anti-seizure medications
 - Adults with a disease or condition known to be associated with bone loss (see secondary causes of osteoporosis, above)
 - Chronic renal disease
 - Estrogen deficiency
 - Hyperparathyroidism
 - Systemic lupus erythematosus (SLE)
 - Malabsorption
 - Current smoking
- Adults with a low-trauma/fragility fracture without a condition that may cause secondary osteoporosis

Indications for a Vertebral Fracture Assessment^{10, 24, 29, 35}

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.³⁵ 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.³⁵ **Lateral views** only of the thoracic and lumbar spine can be performed, using either plain films or DXA equipment, if VFA imaging is available.

United Rheumatology encourages the use of DXA equipment for VFA, because it is associated with lower cost and lower exposure to radiation than plain films.

A VFA should be performed, in women aged ≥ 70 years or men aged ≥ 80 years who have a T-score of < -1.0 in the lumbar spine, total hip, or femoral neck **and** meet one of the following parameters:

- Self-reported but undocumented prior vertebral fracture
- Prospective height loss of ≥ 1.5 inches (4.0 cm), defined as the difference between the current height and peak height at the age of 20 years
- Prospective height loss of ≥ 0.8 inches (2.0 cm), defined as the difference between the current height and a previously documented height measurement
- 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 the potential loss of height and identifying patients at risk for vertebral fracture. Therefore, all healthcare providers should have a wall-mounted stadiometer.

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

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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Initial follow up at 1 year, if significant risk factors for rapid bone loss; otherwise at 2 years, to exclude progression of disease, defined as significant decline in BMD based on LSC • Then every 2 years, until BMD plateaus • 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)	<ul style="list-style-type: none"> • 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

General Recommendations^{9, 20, 21, 24, 33, 36, 37}

- Counsel patients on the risk of osteoporosis and related fractures.
- Suggest a diet that includes adequate amounts of total calcium (1000 mg per day for men aged 50 to 70 years; 1200 mg per 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 .
- Assess risk factors for falls and offer appropriate modifications (e.g., home-safety assessment, balance exercises, correction of vitamin D insufficiency, avoidance of central nervous system [CNS] depressant medications, careful monitoring of antihypertensive medications, and visual correction if needed).
- Advise against smoking and excessive alcohol intake.
- Patients should be counselled about the value of an exercise program specifically designed for people with osteoporosis. These programs may 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.^{10, 22, 38, 39}

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 on 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.⁹

Pharmacologic Treatment⁹

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

- Recent low-trauma/fragility fractures; except those in fingers, toes, skull, sternum, and face
- T-scores of ≤ -2.5 by DXA at the femoral neck, total hip, or lumbar spine
- Postmenopausal women and men aged ≥ 50 years with T-scores between -1 and -2.5 by DXA (low bone mass/osteopenia) at the femoral neck, total hip, or lumbar spine **AND** a 10-year hip fracture probability $\geq 3\%$ or a 10-year major osteoporosis-related fracture probability of $\geq 20\%$ based on FRAX

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 is at high risk for fracture based on a history of multiple prior fractures or a very low T-score of ≤ -3.0 (see below). 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 per minute.

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 recent studies have demonstrated variability in rates of disintegration and absorption among individual generic oral BPs that can affect tolerability, adherence, and possibly efficacy of generic oral BPs when compared to their brand-name equivalents.^{40, 41} Thus, a decline in BMD in a patient compliant with a generic oral BP may be seen.

Raloxifene (Evista[®]) is an appropriate alternative in younger women with a low risk of hip fracture, particularly in those at increased risk for breast cancer and/or those with significant GERD that makes oral BPs problematic. Raloxifene is not recommended in men.

Parenterally administered medications include zoledronic acid (Reclast®) and denosumab (Prolia®). These medications may be used as initial therapy, if oral medications are not tolerated. Zoledronate 5 mg IV yearly 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 \leq 30 mL to 35 mL per minute. Denosumab 60 mg subcutaneously every 6 months administered by a healthcare provider 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 antiresorptive, a rapid decrease in BMD along with increased fracture risk can be seen.³⁶ 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 antiresorptive agent if Prolia [denosumab] is discontinued.” (Page 1).⁴²

Additional parenterally administered drugs include the anabolic agents teriparatide (Forteo®) and abaloparatide (Tymlos®). Twenty micrograms of Forteo is given subcutaneous daily for 2 years; the dose for Tymlos is 40 micrograms subcutaneously, daily for 2 years. A cumulative total of 2 years of anabolic therapy should not be exceeded if the patient needed to be switched among the two anabolic agents. 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).

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 help lead to the most appropriate course of treatment.

- Patients with low bone mass **without prior fracture history** who have 10-year fracture risk scores for hip fracture of <3% and major fracture of <20% are assumed to be at low risk and may be treated with calcium and vitamin D alone.
- 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 BPs or raloxifene, if there are no significant contraindications.
- Patients with osteoporosis on DXA study without a history of fragility fractures need medical therapy. **The more negative the T-scores, the higher the risk for fracture.**
- 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 therapy. FDA-approved drugs for patients within this category include denosumab, teriparatide, and abaloparatide. Both the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend using teriparatide, zoledronic acid, or denosumab in individuals at especially high fracture risk/highest fracture risk.⁹ Of note, these guidelines were published before Tymlos (abaloparatide) gained FDA approval.

With the introduction of a second anabolic agent (Tymlos/abaloparatide) and the dramatic yearly price increases of Forteo/teriparatide, there has been greater scrutiny of when it is appropriate to use an anabolic agent as a first-line agent. The AACE/ACE guidelines suggest that anabolic therapy should be used

in patients with the highest fracture risk or an especially high fracture risk, defined as those who have had multiple vertebral or hip fractures or very low T-scores.⁹ The Institute for Clinical and Economic Review (ICER) recently addressed this topic in their Evidence Report entitled, *Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value*.⁴³ They concluded that for the two anabolic agents, the evidence was “promising, but inconclusive for net health benefit when compared to zoledronate in postmenopausal women with osteoporosis at high risk for fracture.” (Page 27).⁴³

Shortly after the ICER report was issued, a landmark paper was published by Kendler et al.,¹⁸ which was the first clinical trial (**VERtebral fracture treatment comparisons in Osteoporotic women [VERO]**) to specifically address the question of fracture efficacy when an anabolic drug (teriparatide 20 µg daily) was compared to a BP (risedronate 35 mg weekly) in a head-to-head study for 24 months in postmenopausal women at very high risk for fracture. 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 significantly 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.

Given the significant difference in cost between the anabolic agents currently available and oral BPs, United Rheumatology recommends that anabolic drugs should be selectively prescribed as first-line therapy in patients at **very high risk** for fracture (defined as per the VERO trial entry criteria: T-scores ≤ -1.5 and the presence of at least two moderate or one severe vertebral fragility fracture[s]). 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 no prior fragility fracture. Anabolic drug therapy is also appropriate as second-line therapy in individuals who have failed to respond to antiresorptive therapy with interval fragility fracture(s).

Currently, abaloparatide is not approved for use in men or glucocorticoid-associated osteoporosis.

Chronic Kidney Disease and Osteoporosis

The relationship between chronic kidney disease (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 2007.⁴⁴ The FDA has indicated that all BPs should not be used for patients with a GFR below 30 mL to 35 mL per minute (Table 2) and suggests that, generally, administering providers should take special care when prescribing BPs for elderly patients, because these patients are more likely to have impaired renal function than younger ones.

The 2017 Kidney Disease Improving Global Outcomes (KDIGO) 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.⁴⁵

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
BPs Antiresorptive agents	alendronate	Fosamax®	Oral	See Drug Holiday, below	<p>For BPs as a group:</p> <ul style="list-style-type: none"> • Drug allergy • Hypocalcemia • Decreased renal function <p>For oral BPs only:</p> <ul style="list-style-type: none"> • Esophageal dysmotility (GERD) <p>For all BPs (oral and IV):</p> <ul style="list-style-type: none"> • Do not use in patients with CKD and GFR ≤ 30-35mL/min 	<p>Alendronate</p> <ul style="list-style-type: none"> • Osteoporosis in postmenopausal women • Increase bone mass in men with osteoporosis • Treatment of steroid-induced osteoporosis
	ibandronate	Boniva®	Oral			<p>Ibandronate</p> <ul style="list-style-type: none"> • Osteoporosis in postmenopausal women
	risedronate	Actonel® Atelvia®	Oral			<p>Risedronate</p> <ul style="list-style-type: none"> • Osteoporosis in postmenopausal women • Increase bone mass in men with osteoporosis • Treatment of steroid-induced osteoporosis
	zoledronate	Reclast® Zometa® Aclasta®	IV			<p>Zoledronate</p> <ul style="list-style-type: none"> • Osteoporosis in postmenopausal women • Increase bone mass in men with osteoporosis • Treatment of steroid-induced osteoporosis

Drug Classification	Generic Name	Brand Name	Route of Administration	Limitation on Treatment Duration	Contraindications	FDA-approved Indications
Estrogen agonist/antagonist Antiresorptive agent	raloxifene*	Evista®	Oral	No limitations	<ul style="list-style-type: none"> • Drug allergy • Women of childbearing age • Hypercoagulable state 	Raloxifene <ul style="list-style-type: none"> • Osteoporosis in postmenopausal women
RANK ligand inhibitor Antiresorptive agent	denosumab	Prolia®	Subcutaneous	If discontinued at any time another antiresorptive therapy should be prescribed	<ul style="list-style-type: none"> • Drug allergy • Hypocalcemia • Pregnancy 	Denosumab <ul style="list-style-type: none"> • 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)

Drug Classification	Generic Name	Brand Name	Route of Administration	Limitation on Treatment Duration	Contraindications	FDA-approved Indications
Anabolic Agents Increase bone formation	teriparatide (PTH analog)	Forteo®	Subcutaneous	For both teriparatide and abaloparatide: <ul style="list-style-type: none"> • 2 years for anabolic agents, after which anti-resorptive therapy should be prescribed 	For both teriparatide and abaloparatide: <ul style="list-style-type: none"> • Drug allergy • Increased risk of osteosarcoma in individuals with Paget's disease, unexplained high alkaline phosphatase, young patients with open epiphyses or prior external beam or implant radiation therapy involving the skeleton 	Teriparatide <ul style="list-style-type: none"> • Osteoporosis in postmenopausal women at high risk for fracture • Increase in bone mass in men with primary or hypogonadal osteoporosis with high risk of fracture • Men and women with steroid associated osteoporosis and sustained steroid therapy at high risk of fracture Abaloparatide <ul style="list-style-type: none"> • Osteoporosis in postmenopausal women at high risk of fracture
	abaloparatide** (PTH related protein)	Tymlos®	Subcutaneous			

*Not recommended in men

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

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; PM, postmenopausal; PTH, parathyroid hormone; RANK, receptor activator of nuclear factor Kappa-B

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.⁴⁶ 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.⁴⁷

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 (GIO).³³ 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 the 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 3.³³ The management of premenopausal women and men aged 50 years or younger who will be given glucocorticoids or are taking them is outlined in Table 4.³³ At this time, there are no definitive published guidelines concerning the duration of treatment. Recommendations for patients at very high risk for fracture (i.e. those with two or more moderate and those with one or more severe vertebral fractures) include treatment with an anabolic agent such as teriparatide 20 micrograms daily for up to 2 years. Abaloparatide, a parathyroid related peptide, is not currently approved for the treatment of GIO.

Patients treated with anabolic agents should not be treated with these drugs for more than 2 years. Subsequently, an antiresorptive agent should be prescribed to prevent a decrease in BMD.⁹

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

Glucocorticoid Dose	Low FRAX Risk	Medium FRAX Risk	High FRAX Risk
<7.5 mg/day for ≥3 months	No treatment	One of the following: <ul style="list-style-type: none"> • alendronate • risedronate 	
≥7.5 mg/day for ≥3 months	One of the following: <ul style="list-style-type: none"> • alendronate • risedronate • zoledronate 	One of the following: <ul style="list-style-type: none"> • alendronate • risedronate • zoledronate 	
≤5 mg/day for ≤1 month			One of the following: <ul style="list-style-type: none"> • alendronate • risedronate • zoledronate
≥5 mg/day for ≤1 month OR Any dose used for >1 month			<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • alendronate • risedronate 	No consensus	One of the following: <ul style="list-style-type: none"> • alendronate • risedronate
≥7.5 mg/day for 1 to 3 months	<ul style="list-style-type: none"> • zoledronate 	No consensus	<ul style="list-style-type: none"> • zoledronate
Any dose for >3 months	One of the following: <ul style="list-style-type: none"> • alendronate • risedronate • zoledronate • teriparatide 		One of the following: <ul style="list-style-type: none"> • alendronate • risedronate • zoledronate • teriparatide
≥7.5 mg/day for >3 months		One of the following: <ul style="list-style-type: none"> • 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 intravenous (IV) BP therapy.⁹ 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 with BPs (6 years with IV BP therapy).⁹ These recommendations are consistent with those published by the American Society for Bone and Mineral Research (ASBMR) Task Force.⁴⁸ Hip T-scores between -2.0 and -2.5 in the Fracture intervention trial Long-term **EX**tension (FLEX) trial and below -2.5 in the **Health Outcomes and Reduced Incidence with Zoledronic acid ON**ce yearly (HORIZON) trial predicted a beneficial response to continued therapy.^{49, 50} 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.⁴⁸ For those at higher risk, continued treatment for at least 6 years (IV BP) or 10 years (oral BP) was recommended. It is important to realize 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. 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.⁵¹⁻⁵³

A drug holiday is not applicable with denosumab treatment. In fact, the 2016 AACE/ACE Guidelines⁹ recommend against a drug holiday for patients on denosumab (also see the discussion on denosumab prescribing information under Pharmacologic Treatment).

Anabolic drugs such as teriparatide and abaloparatide should not be used for more than 2 years cumulatively. After treatment with either of these drugs, transitioning to an antiresorptive is recommended to avoid loss of bone gained while on anabolic therapy. Unlike denosumab, increased risk of fracture has not been reported with teriparatide or abaloparatide withdrawal.

Patients treated with raloxifene are not at risk for MRONJ or atypical fractures, 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 antiresorptives.

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.⁵⁴⁻⁵⁶ 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.⁵⁷ In addition, another review of studies and meta-analyses of calcium supplements did not find an increased risk of CVD.⁵⁸ In fact, some studies⁵⁹⁻⁶¹ have suggested a cardioprotective effect of calcium plus vitamin D. Vitamin D itself has been demonstrated to be cardioprotective.

Further study in this area is needed to clarify this controversy. 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.⁶²

Proton Pump Inhibitors and Osteoporosis

The relationship between proton pump inhibitor (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.⁶³ The association between PPIs and osteoporosis-related fractures had 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 2011.⁶⁴⁻⁶⁸ 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 causal. 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.⁶⁹ 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 osteonecrosis of the jaw not only related to bisphosphonates but to other antiresorptive medications such as denosumab and antiangiogenic medications.⁷⁰⁻⁷⁴ The AAOMS definition of MRONJ includes all of the following findings (Page 1940):⁶⁷

- Current or previous treatment with antiresorptive 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

The individuals at risk of developing this condition usually have either a malignancy, low bone mass/osteopenia, or osteoporosis and have been on treatment with antiresorptive medications, denosumab, or antiangiogenic agents.⁷⁰ Although MRONJ can occur spontaneously in patients taking these medications, the risk is extremely low.⁷⁵ The risk, however, 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 slightly higher than the frequency seen in the general population.” (Page 13).⁷⁶

In 2011, the American Dental Association’s Council on Scientific Affairs summarized the findings of a systematic meta-analysis performed by an advisory committee of the Council on the dental management of patients treated with antiresorptive therapy for osteoporosis.⁷⁷ According to this review, the risk of MRONJ in patients with cancer exposed to IV BPs has been reported to be between 1.5% to 14.8%.⁷⁰ In patients with cancer treated with denosumab, the incidence rate was reported to be between 0.7% to 1.9%^{70, 78}

The results of the 7-year extension of the **F**racture **R**eduction **E**valuation of **D**enosumab in **O**steoporosis every 6 **M**onths (FREEDOM) study have become available.⁷⁹ 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 in the first 3 years. 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 .68% for those who had dental procedures and .05% for those who did not.

If a patient develops MRONJ, the dentist and prescribing physician must work collaboratively to care for this patient. 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.⁷⁷ 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 antiresorptives such as BPs and denosumab might be to follow recommendations in the *Warnings and Precautions* section of the Prolia prescribing information (Section 5.4):⁴²

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):^{80, 81}

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 antiresorptive medication or denosumab, 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 dentalveolar 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.^{70, 77, 78}

Patient education is very important. Patients should be told that the risk of MRONJ is very low when they are treated with BPs or denosumab. 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.⁷⁰ In addition, patients should be advised to brush their teeth at least twice a day and floss daily.⁷⁵ 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.⁷⁷ 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 and with 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,⁸² 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.^{78, 83} 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 2010,⁸⁴ with an update in 2014.⁸² The revised case definition (Table 5) is helpful for distinguishing these fractures from the more common osteoporotic fragility fractures occurring in the femur.⁸²

Table 5. The 2014 ASBMR definition of AFF

<p>The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.</p> <p>AND</p> <p>At least 4 of the 5 major features listed must be present to diagnose an AFF.</p> <p>None of the minor features is required, but they have sometimes been associated with these fractures.</p>	
Major Features	Minor Features
<ul style="list-style-type: none"> • 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'). 	<ul style="list-style-type: none"> • Generalized increase in cortical thickness of the femoral diaphyses. • 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 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 seems prudent.
- Although the mechanism of action of denosumab is different from BPs, it is also a potent antiresorptive. Accordingly, switching to denosumab after BP therapy may not lower the risk of AFFs.
- Query 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 of the femur and look for signs of early stress reactions such as a cortical breaking.
- Promptly withdraw BP or denosumab 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.^{82, 84} 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:⁸

1. Posterior-anterior (PA) view of the lumbar spine and of one or both hips. Bone mineral density of the spine and hip should be measured in all patients.
2. If the evaluation of the lumbar spine or hip is compromised by extensive degenerative disease or heavy vascular calcifications, fractures, scoliosis, or metal implants; images of the nondominant forearm should be obtained.
3. When evaluating the lumbar spine, it is preferable to use all four vertebrae (L1 to L4); however, a minimum of two adjacent vertebrae must be used to calculate the T-score. Bone mineral density should not be measured in a single vertebra. Vertebrae with a difference in T-score of ≥ 1.0 compared to 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. Bone mineral density of the hip may be measured on either side or both sides and should include the lowest value obtained of the femoral neck or total hip.

Personnel and Facility Requirements^{8,85}

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 (ARRT) or a qualification as a Certified Bone Densitometry Technologist from the ISCD.
4. Each facility must have a quality control (QC) program consistent with the recommendations of the ISCD 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.⁸

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 (WHO) criteria
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

Optional items in a DXA report:

1. Specific recommendations for evaluation of secondary causes of MBD
2. Recommendations for pharmacological and nonpharmacological interventions
3. Recommendations for further non-BMD testing such as X-ray, MRI, computed tomography (CT), 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:

1. A statement that there has been bone loss without knowledge of previous bone density study
2. Mention of 'mild', 'moderate', or 'marked' low bone mass/osteopenia or osteoporosis
3. 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:

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 (radiographs or absorptiometry)
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
9. The Genant visual semi-quantitative method⁸⁶ is the current clinical technique of choice for diagnosing vertebral fractures.
10. If the study is a follow-up, it should compare the prior studies and comment on the significance of changes, if any.

Glossary

1/3 rd 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. ⁸
Central dual energy X-ray absorptiometry (DXA)	<p>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).</p> <p>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.^{10, 24}</p>
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. ³⁷
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. ⁸⁶ 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 fracture	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. ²⁴
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	<p>There are two definitions of osteoporosis:⁸</p> <ol style="list-style-type: none"> 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	<p>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.¹⁰</p>
Vertebral fracture	<p>Grade 1 or mild fracture:</p> <ul style="list-style-type: none"> • Reduction in vertebral height of 20% to 25% <p>Grade 2 or moderate fracture</p> <ul style="list-style-type: none"> • Reduction in vertebral height of 26% to 40% <p>Grade 3 or severe fracture</p> <ul style="list-style-type: none"> • Reduction in vertebral height of >40%

Appendix

Essential Elements from Osteoporosis Clinical Guidelines

Demographics	<ul style="list-style-type: none"> • Gender, age, race, height/weight/BMI
Social and Personal History	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Maximum adult height (for historical height loss) • RA, SLE, IBD, 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 <ul style="list-style-type: none"> ○ Type of fracture and date (excluding fingers, toes, and skull) ○ Vertebral fractures: number and grade
Review of Systems	<ul style="list-style-type: none"> • Acute/sub-acute back pain • Dental health • Frequent falls, frailty • Significant dysphagia
Family History	<ul style="list-style-type: none"> • Hip fracture in either parent • Diagnosis of osteoporosis in other family members • Renal calculi
Physical Examination	<ul style="list-style-type: none"> • Height: current <ul style="list-style-type: none"> ○ 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	<ul style="list-style-type: none"> • Machine type • Least significant change for spine and hip • Lowest T-score • BMD (g/cm²) in femoral neck (to calculate FRAX®) <ul style="list-style-type: none"> ○ 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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