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Osteoporosis
A Review

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IMPORTANCE Osteoporosis is characterized by low bone mass, increased bone fragility, and increased susceptibility to fracture, which is associated with substantial morbidity, mortality, and economic costs. Worldwide, 1 in 3 women and 1 in 5 men older than 50 years of age experience osteoporotic fractures in their lifetime.

OBSERVATIONS Risk factors for osteoporosis include older age, female sex, prior fractures, prior falls, low body weight, history of hip fracture in a parent, glucocorticoid use, cigarette smoking, excess alcohol consumption, certain comorbidities (eg, inflammatory bowel disease, rheumatoid arthritis, and chronic liver and kidney disease), and low level of bone mineral density (BMD; measured by dual-energy x-ray absorptiometry). The fracture risk assessment algorithm combines these clinical risk factors and BMD measurement to estimate the 10-year absolute fracture risk for hip, spine, shoulder, and forearm fractures. For patients at high risk of fracture, such as those with a T score of −2.5 or less (equivalent to a bone mass that is ≥2.5 SDs below that of young adults) for BMD, history of vertebral or hip fracture, multiple fractures, or high 10-year absolute fracture risk (eg, ≥20%), antiresorptive agents (bisphosphonates or, if contraindicated, denosumab) are recommended to reduce vertebral fractures (risk difference, −52 [95% CI, −95 to −18 per 1000 person-years]) and hip fractures (risk difference, −6 [95% CI, −11 to −1 per 1000 person-years]). Anabolic medications (teriparatide, abaloparatide, and romosozumab) should be considered in very high-risk individuals (eg, recent vertebral fractures, hip fracture with a T score of ≤−2.5 for BMD), followed by an antiresorptive agent. The use of fracture liaison services (comprehensive inpatient or outpatient management program for patients after a fracture) was shown to increase medication initiation and adherence by 38% compared with 17% for patients who did not receive fracture liaison services (risk difference, 20% [95% CI, 16% to 25%]) and these benefits may reduce the rates of subsequent fracture. Patients are recommended to follow appropriate intake of calcium (1000 to 1200 mg) and vitamin D (600 to 800 IU) guidelines and to pursue a regimen of muscle resistance exercises (eg, squats, push-ups) and balance exercises (eg, heel raises, standing on 1 foot).

CONCLUSIONS AND RELEVANCE Osteoporosis is a common condition among older adults that leads to increased susceptibility to fracture, which is associated with substantial morbidity and mortality. Antiresorptive agents such as bisphosphonates or denosumab are recommended for patients at high fracture risk. Anabolic treatment with parathyroid hormone analogs (such as teriparatide and abaloparatide) and sclerostin inhibitors (such as romosozumab) can be considered for very high-risk individuals.

Multimedia

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The World Health Organization defines osteoporosis as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fracture.[1] Osteoporosis management focuses on preventing fractures, rather than treating low bone mineral density (BMD), which is measured with dual-energy x-ray absorptiometry (DXA).[2,3] Important clinical risk factors associated with new fractures, such as prior fractures and falls, have been incorporated in fracture risk assessment tools that help identify patients at high fracture risk who can benefit from treatments that reduce fracture risk.[3-6]

Fractures are a common cause of years lived with disability and are associated with subsequent fractures, loss of autonomy, and increased morbidity and mortality.[7] Although osteoporosis is often considered a disease of older females, one-third of all fractures occur in older males.[8] In 2019, 8.14 million women and 6.11 million men aged 50 years or older worldwide sustained a hip fracture, which is the most serious consequence of osteoporosis.[9] Hip fractures are associated with a mortality rate of 24% in the year following the fracture and lead to reduced mobility.[10]

This review summarizes the epidemiology, diagnosis, and treatment of osteoporosis in postmenopausal females and males aged 50 years or older.

Methods

We searched PubMed for English-language studies of the epidemiology, pathophysiology, diagnosis, fracture prediction tools, and treatment of osteoporosis published from January 31, 2014, to March 11, 2025. After 1237 articles were identified, an additional 97 articles were identified from reference lists. The 98 articles included in this review included 20 randomized clinical trials (RCTs), 15 reviews, 21 meta-analyses, 20 guidelines or position statements, and 22 observational (including 21 longitudinal and 1 cross-sectional) studies.

Discussion

Pathophysiology

Skeletal development in childhood and adolescence requires de novo bone formation and shaping (modeling). In contrast, the primary process for preserving bone mass after skeletal maturity involves resorption of damaged and older bone followed by formation of new bone (remodeling). Osteoblasts are cells that form bone and osteoclasts are cells that resorb bone. Osteoblasts and osteoclasts are regulated by the Wnt low-density lipoprotein receptor–related proteins 4 and 5/6 sclerostin system and the osteoprotegerin—the receptor activator of nuclear factor κB (RANK) and the RANK ligand (RANKL) system.[11]

Osteocytes, which are fully differentiated osteoblasts, are the most abundant cell type in bone.[12] Osteocytes are interconnected through canalicular networks (fluid-filled microchannels) that sense biomechanical strain and bone microdamage and initiate targeted bone remodeling to match bone mass to skeletal loading requirements during everyday activities (such as walking, climbing, jumping). Bones contain varying proportions of trabecular bone (most abundant in the vertebrae) and cortical bone (found in long bones such as the femur), which contribute to bone strength. Trabecular loss and greater cortical porosity (the amount of void space within the cortex) increase with age, leading to reduced bone strength.[13]

Risk Factors for Osteoporosis

Inadequate bone strength reflects a failure to achieve optimal peak bone mass during early adulthood, excessive bone loss at later ages, or both. Peak bone mass typically occurs in early adulthood by the end of the first 2 decades of life. Peak bone mass and subsequent rate of bone loss are influenced by multiple genes. Genomic-wide association studies have identified loci associated with BMD, bone strength, and fracture risk factors.[14] Nutrition (such as adequate calcium intake); physical activity; and levels of estrogen, progesterone, testosterone, growth hormone, and other hormones are also major regulators of peak bone mass.[15] Premature menopause (before 40 years of age), hypogonadism, nutritional deficiencies (eg, vitamin D or calcium), low body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of less than 20, weight loss, immobility, presence of certain comorbidities (eg, inflammatory bowel disease, rheumatoid arthritis, chronic liver or kidney disease), and use of certain medications (eg, glucocorticoid, aromatase inhibitors such anastrozole and letrozole, androgen deprivation agents such as leuprolide and bicalutamide) contribute to accelerated bone loss.[3,16-19] Current smoking and high alcohol consumption (≥3 drinks daily) are also risk factors for bone loss.[20,21]

Clinical Presentation

Osteoporosis may be asymptomatic or present as a painful fracture or as vertebral fractures identified on spine imaging. Approximately two-thirds of vertebral fractures are not identified due to absence of symptoms or because symptoms are attributed to chronic back conditions (such as osteoarthritis). These vertebral fractures are often identified incidentally on imaging completed for other purposes.

Previously, fractures attributed to osteoporosis were restricted to "fragility" or "low trauma" fractures, defined as falling from standing height or a similar minimally traumatic fall. However, fractures occurring in the setting of high trauma, such as falling down a flight of stairs, have the same association with reduced BMD as low-trauma fractures, predict future low-trauma fractures, and can be prevented by the same medications used to reduce osteoporotic fractures.[22] Therefore, only fractures associated with extreme trauma (eg, fall from a roof) or local pathology (eg, malignancy) should be discounted when considering prior fractures as a risk for future fractures.

The sites of fractures most associated with osteoporosis include the hip, spine, shoulder, forearm, and pelvis. In contrast, fractures of the hands, feet, and craniofacial bones are not considered to be related to osteoporosis.[23] Clinical features suggesting the presence of an undiagnosed vertebral fracture include height loss, increased horizontal distance (measured as a patient stands with heels and buttock against a wall) between the skull occiput and the wall due to kyphosis, and reduced space between the lower ribs and the pelvis due to vertebral height loss.[24]

Assessment and Diagnosis

Most clinical practice guidelines recommend screening for clinical risk factors for osteoporosis in postmenopausal females and males

older than 50 years.[3,5,6,24] A history of fracture or experiencing 1 fall or more during the prior year substantially increases the risk of fracture (hazard ratio [HR], 1.88 [95% CI, 1.72-2.07] for prior fracture; HR, 1.42 [95% CI, 1.33-1.51] for prior falls in women; and HR, 1.53 [95% CI, 1.41-1.67] for prior falls in men) (absolute rates not provided).[25,26] A clinical diagnosis of osteoporosis can be made in patients with a fall-related hip, vertebral, or multiple fracture events in the absence of another explanation (such as primary bone cancer or metastasis to bone) or metabolic bone disease, such as osteomalacia.[3,5]

The clinical utility of BMD screening is for fracture risk prediction[27]; a low BMD level is strongly associated with fracture risk in both sexes.[28] Patients with a T score of −2.5 or less for BMD (equivalent to a bone mass ≥2.5 SDs below that of young adults) are categorized as having osteoporosis.

Approximately 70% of osteoporotic fractures occur in females and males who do not have osteoporosis based on BMD level[29,30] (**Box**). Important clinical risk factors have been incorporated in fracture risk assessment tools to improve risk assessment in individual patients.[4] The most widely used risk assessment tool is the Fracture Risk Assessment Tool (FRAX); this tool is used to estimate 10-year fracture probability for the hip, spine, shoulder, and forearm using BMD of the femoral neck (optional) and the following risk factors: age, sex, BMI, prior fracture (excluding hands, feet, and craniofacial bones), parental history of hip fracture, current smoking, alcohol intake (≥3 drinks/d), secondary osteoporosis (such as hyperparathyroidism), glucocorticoid intake (≥5 mg/d of prednisone or an equivalent for >3 months), and rheumatoid arthritis.[31] Other fracture risk calculation tools include the Garvan Fracture Risk Calculator and QFracture.[4]

Spinal imaging is required to diagnose vertebral fractures. Severe vertebral fractures can appear as vertebral collapse or a wedge shape, but milder deformities of the vertebral body can be difficult to identify with a plain radiographic image or with DXA-based vertebral fracture assessment (lateral image of the spine).[32] Imaging techniques such as computed tomography and magnetic resonance imaging can help to confirm or exclude a vertebral fracture if there is diagnostic uncertainty. Presence of superior or inferior vertebral end plate depression in conjunction with vertebral body height loss is consistent with a fracture[33] (**Figure 1**). The trabecular bone score (derived from the local variations in spinal DXA image intensity) measures BMD-independent information on bone structure and fracture risk. When available, the trabecular bone score can be used with FRAX for improved fracture prediction (**Table 1**).

The age threshold at which universal BMD screening is recommended varies across different guidelines. Some guidelines recommend screening specific populations at increased risk,[3] whereas others recommend a fracture risk assessment of all individuals older than 50 years to identify those at increased risk.[6] For example, the Bone Health and Osteoporosis Foundation in the US recommends BMD screening in postmenopausal females aged 50 through 64 years and males aged 50 through 69 years with clinical risk factors such as a prior fracture, frequent falls, and in all females 65 years or older and males 70 years or older.[3] The 2025 US Preventive Services Task Force statement[34] recommended BMD screening for females 65 years or older and postmenopausal females younger than 65 years at increased risk of osteoporosis (as determined by a fracture risk assessment tool such as FRAX). The US Preventive Services Task Force concluded that the current evidence was insufficient to assess the balance of benefits and harms of BMD screening in men for osteoporosis.[34]

Box. Commonly Asked Questions About the Management of Osteoporosis

Bisphosphonates are typically discontinued after 3 to 5 years. When should a bisphosphonate be resumed, and for how long, after a drug holiday?
Typically, after 3 to 5 years of treatment, bisphosphonates are discontinued for approximately 2 to 3 years. Bisphosphonates can be resumed if new fractures or risk factors occur. The Fracture Risk Assessment Tool can be used to calculate absolute fracture risk after a drug holiday. When resuming bisphosphonates, the duration of therapy is similar to the initial recommendations.

Should monitoring with dual-energy x-ray absorptiometry (DXA) be performed in people who had a T score of less than −2.5?
The guidelines recommend repeated measurement of bone mineral density (BMD) in patients who initiate bisphosphonate therapy even if the initial T score is less than −2.5. Data from trials with antiresorptive and anabolic therapies show an inverse relationship between the BMD level attained with therapy and the subsequent fracture risk. A clinically meaningful reduction in fracture risk is expected when the increase in BMD level exceeds the measurement error reported by the DXA facility where the BMD test was performed (https://iscd.org/official-positions-2023/).

Should patients with a BMD level within the range for osteopenia (ie, a T score of −1.0 to −2.5) or within the normal range (ie, a T score >−1.0) ever be treated with medications for osteoporosis?
Patients with fall-related hip, vertebral, or multiple fractures are at high subsequent fracture risk even if their T score is not in the range for osteopenia. The use of osteoporosis drugs is associated with significant reductions in fracture risk even when a patient's T score is greater than −2.5 (high evidence certainty).

Treatment

Lifestyle Measures

General lifestyle measures should be encouraged in all adults to prevent fractures, including maintaining a BMI higher than 20. Cigarette smoking and daily alcohol intake should be avoided.[20,21,35] Reducing fall risk through exercise (balance, strength, and resistance training; flexibility exercises; and endurance training) and multifactorial interventions (including initial assessment of modifiable risk factors for falls and subsequent customized interventions) should be considered in older adults.[36,37]

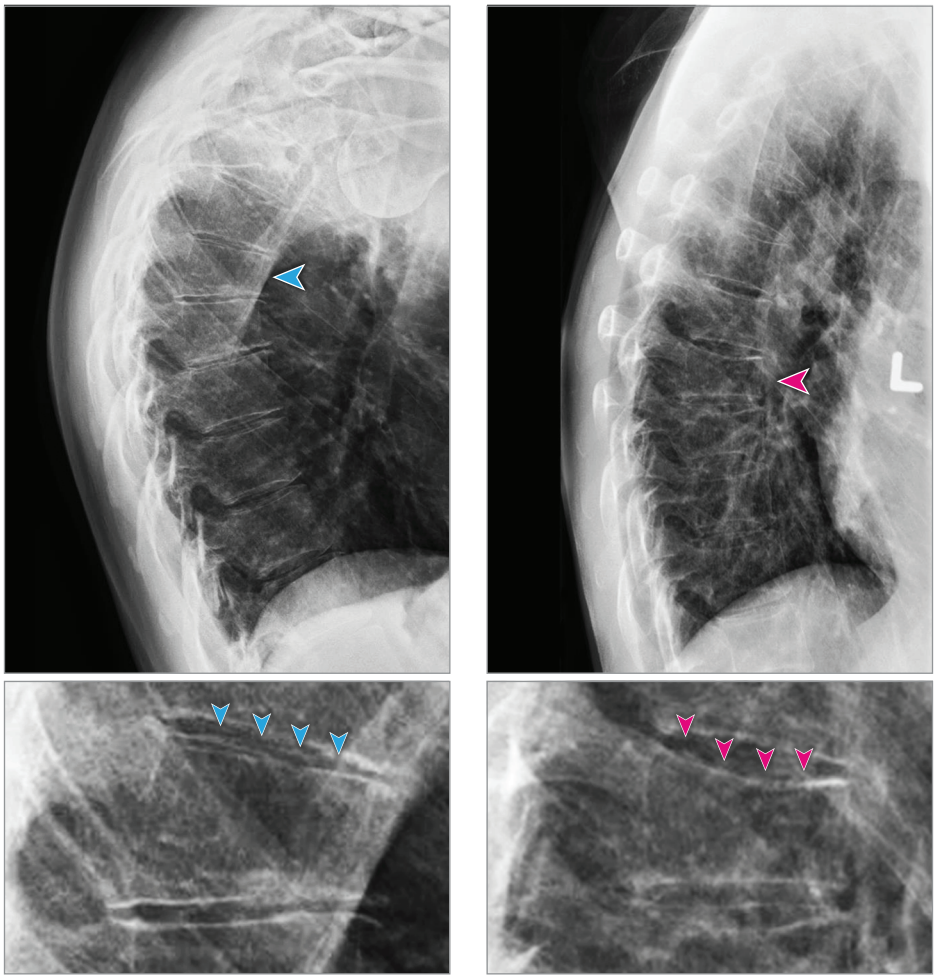
Exercise

In a systematic review and meta-analysis[38] of 5 RCTs including 521 people at increased fracture risk, progressive resistance training (eg, squats, lunges, and push-ups) for at least 8 months' duration was associated with improved BMD in the femoral neck (mean difference, 0.02 g/cm^2 [95% CI, 0.01-0.03 g/cm^2]; absolute rates not reported). In a systematic review and meta-analysis[38] of 13 clinical trials with 911 participants, a progressive resistance training program was associated with improved ability to perform daily tasks (mean difference in the Timed Up and Go test, −0.89 seconds [95% CI, −1.01 to −0.78 seconds]; absolute rates not reported).

Figure 1. Radiographic Images of the Thoracic Spine

A Lateral thoracic spine radiograph of nonfracture deformity (top) and close-up (bottom)

B Lateral thoracic spine radiograph of fracture deformity (top) and close-up (bottom)



A, Nonfracture deformity is shown with the wedge-shaped vertebral body (arrowheads) and without superior end plate depression (arrowheads). B, Fracture deformity is shown with the wedge-shaped vertebral body (arrowheads) and with a depressed superior end plate (arrowheads).

In a systematic review,[39] balance and functional exercises were associated with a decrease in the rate of falls by 24% in community-dwelling adults compared with control (rate ratio, 0.76 [95% CI, 0.70 to 0.81]) (39 RCTs including 7920 participants; 646 per 1000 person-years vs 850 per 1000 person-years) and a decrease by 13% in the number of people experiencing 1 or more falls compared with control (relative risk, 0.87 [95% CI, 0.82 to 0.91]) (37 RCTs including 8288 participants; absolute rates not reported).

Nutrition

Dietary calcium and vitamin D from food sources and supplements are important nutrients for bone health. Food sources rich in calcium include milk products and fortified beverages (plant-based soy milk, oat milk, or orange juice) and canned salmon (with bones). Fortified milk and plant-based beverages (such as soy or oat milk), eggs, and fatty fish are foods rich in vitamin D. The recommended Dietary Reference Intakes from the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (formerly the National Academy of Medicine[40]) for calcium consist of 1000 mg/d for males aged 19 to 70 years, 1000 mg/d for females aged 19 to 50 years, 1200 mg/d for females older than 51 years, and 1200 mg/d for males older than 71 years and for vitamin D are 600 IU/d until 70 years of age and 800 IU/d in people older than 70 years.

A systematic review and meta-analysis[41] including 33 RCTs and 51 145 community-dwelling participants (who were not selected for presence of osteoporosis or deficient dietary intake) found there was no significant association with hip fracture risk among those taking calcium supplements (20 per 1000 person-years) vs those taking a placebo (10 per 1000 person-years) (risk difference [RD], 10 [95% CI, 0 to 10]) nor among those taking vitamin D supplements (10 per 1000 person-years) vs those taking a placebo (17 per 1000 person-years) (RD, 0 [95% CI, −0 to 10]). Results were similar for combined calcium and vitamin D supplementation for hip fracture and other fracture sites (20 per 1000 person-years) compared with placebo (10 per 1000 person-years) (RD, 0 [95% CI, −0 to 0]).[41] Other recent meta-analyses that studied vitamin D supplementation in people without established osteoporosis reported no significant association of vitamin D with improved BMD or fracture risk in adults.[42,43] Calcium supplementation exceeding recommendations has been associated with adverse events such as kidney stones and possibly increased risk of cardiovascular events. Although a large

Table 1. Assessments Used in the Evaluation and Management of Osteoporosis

	Description	When should this test be used?	Other considerations
Laboratory investigations			
Blood testing	• Measure serum calcium, phosphate, alkaline phosphatase, and creatinine levels and assess thyroid function	Prior to initiating therapy to assess for • Potential secondary causes of osteoporosis (eg, hyperparathyroidism or chronic liver disease) • Potential contraindications to treatment when considering pharmacotherapy (eg, kidney dysfunction) in individuals with osteoporosis (if levels were not measured within prior year)	• Clinical guidelines vary in the extent of testing recommended
Test individuals at risk for vitamin D deficiency	• Measure serum 25-hydroxyvitamin D (25[OH]D) level	• When treating individuals at risk for vitamin D deficiency, including those with malabsorption, liver disease, chronic kidney disease, reduced sun exposure, and after gastric bypass surgery	• Routine follow-up (3 mo after initiation of supplementation) is not recommended for those without risk factors for vitamin D deficiency
Fracture risk assessment tools			
Fracture Risk Assessment Tool (FRAX)[a]	• All 3 tools predict probability of fracture over 1-10 y (depending on the tool used) based on clinical risk factors (with or without measurement of femoral neck for bone mineral density)	• All 3 tools assess absolute fracture risk in adults who are not currently receiving treatment for osteoporosis • Most guidelines recommend assessing fracture risk when ≥50 y of age in both postmenopausal females and in males	• Takes into consideration competing risk of mortality • Bone mineral density is an optional input variable
QFracture (assesses the risk of osteoporotic fracture)			• Bone mineral density is not an input variable
Garvan Fracture Risk Calculator			• Includes the number of falls and prior fractures • Bone mineral density is an optional input variable
Imaging			
Imaging of lateral spine	• Vertebral fracture assessment using conventional radiography or dual-energy x-ray absorptiometry	• To identify the presence of a vertebral fracture in individuals with signs or symptoms of acute vertebral fractures or of occult vertebral fractures (such as height loss and kyphosis)	• A confirmed vertebral fracture on imaging (even if the patient is asymptomatic or it is a remote fracture) is associated with a high fracture risk
Dual-energy x-ray absorptiometry	Areal bone mineral density assessment is • Expressed in g/cm^2 • Expressed as a T score (SDs above or below peak bone mass)	• To assess bone mineral density in both postmenopausal females and in males aged ≥50 y as part of the fracture risk assessment or for monitoring the response to osteoporosis therapy	• Patients are considered to have normal bone mass when the T score is ≥−1.0 • Patients are considered to have low bone mass (osteopenia) when the T score is between −1.0 and −2.5 • Patients are considered to have osteoporosis when the T score is ≤−2.5
Trabecular bone score	• Unitless texture measure derived from dual-energy x-ray absorptiometry images of the lumbar spine, which are only available when specific software is available for the densitometer	• The trabecular bone score can be entered in the FRAX prediction algorithm to assess fracture risk in adults • When available on the bone mineral density report, the trabecular bone score is useful in individuals close to the treatment threshold (indicates when the results are most likely to alter clinical management)	• Adding the trabecular bone score to FRAX improves fracture prediction

[a] Calibrated using individual population-specific fracture and mortality data by country. The country-specific tool is available at https://www.fraxplus.org.

RCT evaluating calcium supplements with vitamin D on health risks and benefits in 36 282 postmenopausal women[44] showed no evidence of an increased risk of cardiovascular events, a meta-analysis with 9 RCTs and 28 072 participants[45] reported that calcium supplementation was associated with an increased risk of cardiovascular events compared with placebo (HR, 1.15 [95% CI, 1.03-1.27]; absolute rates not reported).

The Endocrine Society does not recommend routine testing of vitamin D levels in healthy individuals.[46] The Bone Health and Osteoporosis Foundation and other societies recommend that vitamin D levels should be measured in individuals at risk of vitamin D deficiency including adults with chronic kidney or liver disease, malabsorption, limited sun exposure, or after bariatric surgery and in people with bone diseases such as osteomalacia or osteoporosis and fractures.[3,40] A dietary and supplemental intake of 800 to 1000 IU of vitamin D is adequate for most adults with osteoporosis, but should be individualized according to dietary intake and vitamin D level in those with a vitamin deficiency.

Pharmacotherapy

Pharmacological therapies for osteoporosis are categorized as antiresorptive (decreasing bone resorption), anabolic (stimulating bone formation), or both (**Table 2**). All agents approved by the US Food and Drug Administration reduce the incidence of vertebral fractures and some also reduce nonvertebral and hip fractures[47-50] (**Figure 2**). Although most studies have been performed in postmenopausal females, evidence from clinical trials in males with primary osteoporosis showed similar efficacy and safety as in females.[8,51]

Bisphosphonates

Oral bisphosphonates, specifically alendronate and risedronate, are first-line antiresorptive medications because of their efficacy, tolerability, and cost-effectiveness. Based on multiple studies over a follow-up of 3 to 4 years,[47,48,52,53] bisphosphonates reduced the incidence of vertebral fractures compared with placebo (45 per 1000 person-years vs 100 per 1000 person-years, respectively; RD, −56

Table 2. Pharmacological Fracture Prevention Therapies

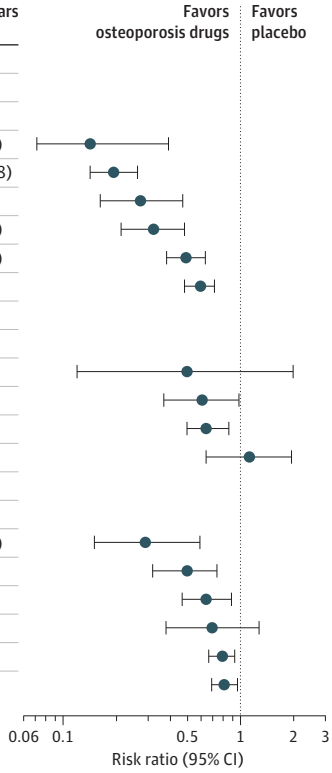
	Drug	Dosage	Mechanism of action	Contraindications	Potential adverse effects
Antiresorptive agents					
Oral bisphosphonate	Alendronate	70 mg/wk	• Direct osteoclast inhibition	Creatinine clearance <30-35 mL/min, hypocalcemia, or esophageal abnormalities (eg, esophagitis or peptic ulcer disease)	Dyspepsia (20%-30% of patients), myalgia (4% of patients), osteonecrosis of the jaw (<0.1% of patients), and atypical femoral fracture (0.02%-0.1% of patients)
	Risedronate	35 mg/wk			
	Ibandronate	150 mg/mo			
Intravenous bisphosphonate	Zoledronic acid	5 mg every 12-18 mo (administered intravenously)	• Direct osteoclast inhibition	Creatinine clearance <30-35 mL/min or hypocalcemia	Headache, myalgia, or fever (30% of patients); transient elevated level of creatinine (2% of patients); kidney failure (rare); hypocalcemia (<1% of patients); osteonecrosis of the jaw (<0.1% of patients); and atypical femur fracture (0.02%-0.1% of patients)
	Ibandronate	3 mg every 3 mo (administered intravenously)			Esophageal abnormalities are not a consideration with the intravenous formulation
RANKL inhibitor	Denosumab	60 mg every 6 mo (administered subcutaneously)	• Reduces osteoclast differentiation and activity due to inhibition of RANKL	Hypocalcemia	Eczema (3% of patients), cellulitis (0.3% of patients), osteonecrosis of the jaw (<0.1% of patients), and atypical femur fracture (0.02%-0.1% of patients)
					Increased risk of vertebral fracture if denosumab dosing is delayed by >1 mo or interrupted
Selective estrogen receptor modulator	Raloxifene	60 mg/d (administered orally)	• Estrogen receptor agonist on bone	Venous thromboembolism, stroke, or cardiovascular disease	Hot flashes (10% of patients), leg cramps (7% of patients), peripheral edema (5% of patients), and deep vein thrombosis (0.9% of patients)
Anabolic agents					
Parathyroid hormone analog	Teriparatide	20 µg/d for 1.5-2 y (administered subcutaneously)	• Stimulation of parathyroid hormone receptor • Increases bone remodeling (formation is greater than resorption)	Creatinine clearance <30 mL/min, bone malignancy, increased risk for osteosarcoma, or hypercalcemia	Nausea (20% of patients), headache (13% of patients), hypercalcemia (3%-6% of patients), and leg cramps (3% of patients)
	Abaloparatide	80 µg/d for 1.5-2 y (administered subcutaneously)			
Sclerostin inhibitor	Romosozumab	210 mg/mo for 12 mo (administered subcutaneously)	• Inhibits the sclerostin-activating Wnt signaling pathways • Increases bone formation • Reduces bone resorption	Myocardial infarction or stroke (within past 12 mo) or hypocalcemia	Injection site reactions (5% of patients), serious cardiovascular events (2.5% of patients treated with romosozumab vs 1.9% treated with alendronate), osteonecrosis of the jaw (rare[a]), and atypical femur fracture (rare[a])

Abbreviation: RANKL, receptor activator of nuclear factor κB ligand.

[a] There were 2 cases of osteonecrosis of the jaw and 3 cases of atypical femur fracture reported in 5621 participants who received romosozumab in the large romosozumab vs placebo trials.

Figure 2. Efficacy of Osteoporosis Medication Use for the Prevention of Vertebral, Hip, and Any Clinical Fractures

	No. of fractures/No. of participants		Risk difference per 1000 person-years (95% CI)[a]
	Placebo	Treatment	
Fracture location			
Vertebral fracture			
Drug class			
Abaloparatide	30/711	4/690	-36 (-52 to -21)
Teriparatide	122/1510	22/1504	-69 (-112 to -28)
Romosozumab	59/3322	16/3321	-13 (-18 to -8)
Denosumab	264/3691	86/3702	-48 (-58 to -39)
Bisphosphonates	799/7970	406/8932	-56 (-84 to -33)
Raloxifene	308/4177	315/6385	-28 (-57 to -1)
Hip fracture			
Drug class			
Teriparatide	4/544	4/1093	-4 (-12 to 4)
Denosumab	43/3906	26/3902	-4 (-8 to 0)
Bisphosphonates	160/8305	103/8329	-6 (-11 to -1)
Raloxifene	18/2576	26/3902	1 (-3 to 5)
Any clinical fracture			
Drug class			
Abaloparatide	34/821	10/824	-29 (-45 to -14)
Teriparatide	94/1716	61/2254	-27 (-56 to -7)
Romosozumab	90/3591	58/3589	-9 (-15 to -2)
Raloxifene	339/4461	526/6978	-6 (-18 to 6)
Bisphosphonates	1134/9280	964/10 283	-24 (-42 to -7)
Denosumab	293/3906	238/3902	-14 (-25 to -3)



[a]The data are from a systematic review and network meta-analysis conducted by Ayers et al.[47]

[95% CI, −95 to −18]) and hip fractures (13 per 1000 person-years vs 19 per 1000 person-years; RD, −6 [95% CI, −11 to −1]) with moderate to high evidence certainty. Oral and intravenous formulations of ibandronate also reduce risk of vertebral fractures compared with placebo, but there is no consistent evidence that ibandronate reduces the risk of nonvertebral fractures.[52,54] In meta-analyses,[47,53,55] intravenous zoledronic acid reduced the risk of vertebral fractures (RD, −71 [95% CI, −80 to −54] per 1000 person-years) compared with placebo, reduced the risk of hip fractures (RD, −9 [95% CI, −15 to −3] per 1000 person-years), and reduced the risk of any clinical fractures (RD, −24 [95% CI, −42 to −7] per 1000 person-years), which are defined as fractures at any skeletal site that require medical attention (additional data appear in Figure 2).

Bisphosphonates are contraindicated in those with an estimated glomerular filtration rate of less than 30 to 35 mL/min. Among individuals taking oral bisphosphonates, 20% to 30% experience upper gastrointestinal symptoms such as dyspepsia. Myalgia, arthralgia, headache, and transient flu-like symptoms can also occur in up to 30% of recipients, especially with intravenous zoledronic acid. The incidence of serious adverse events, such as osteonecrosis of the jaw and atypical femur fractures (fractures occurring in the femoral shaft under normal physiological loads), is not higher than placebo during bisphosphonate use for up to 2 years.[47] However, bisphosphonates are associated with an increased risk of jaw osteonecrosis if taken for longer than 2 years (range, 0.2-10 per 10 000 patient-years) compared with placebo and are associated with an increased risk of atypical femur fracture if taken for 3 years or longer (2.5 per 10 000 patient-years with 3-5 years of bisphosphonate use and 13 per 10 000 patient-years with >8 years of bisphosphonate use).[55] The risk of atypical femur fracture is higher in females who self-report Asian race or ethnicity.[56] Discontinuation of bisphosphonates leads to a decrease in atypical femur fracture risk by 50% in the first year and by 80% 3 years after stopping the medication.[56]

Denosumab

Denosumab is a monoclonal antibody that binds and inhibits RANKL (an activator of osteoclastogenesis and osteoclast activity).[57] Denosumab reduces the risk of vertebral fractures compared with placebo (23 per 1000 person-years vs 71 per 1000 person-years, respectively; RD, −48 [95% CI, −58 to −39]), hip fractures (7 per1000 person-years vs 11 per 1000 person-years; RD, −4 [95% CI, −8 to 0]), and any clinical fractures (61 per1000 person-years vs 75 per 1000 person-years; RD, −14 [95% CI, −25 to −3]) with moderate to high evidence certainty.[47,57] Although follow-up studies suggested continued fracture reduction efficacy up to 10 years,[58] the certainty of the evidence is low.[59,60]

Hypocalcemia can occur after denosumab injection in the setting of vitamin D deficiency or advanced kidney dysfunction.[55,61] Osteonecrosis of the jaw and atypical femur fractures have been reported with denosumab, but their incidence may be lower than with bisphosphonates.[62,63]

Rapid bone loss and increased risk of vertebral fractures have been observed after discontinuation of denosumab and after a dosing delay of more than 1 month.[64,65] In a post hoc analysis of 1001

participants who stopped denosumab as part of participation in an RCT, the rate of vertebral fracture increased from 1.2 per 100 participant-years during the treatment period to 7.1 per 100 participant-years after discontinuation, which was similar to the rate of vertebral fracture increase in participants who received and then discontinued placebo (n = 470; 8.5 per 100 participant-years).[64] Guidelines recommend that denosumab, once initiated, be continued indefinitely, or that bisphosphonates such as alendronate or intravenous zoledronic acid be prescribed to reduce the risk of vertebral fractures if denosumab is discontinued.[66] The risk of vertebral fractures after denosumab discontinuation is greater in those with preexisting vertebral fractures and longer duration of use.[67]

Estrogen Receptor Agonists

Raloxifene, a selective estrogen receptor modulator, is an estrogen receptor agonist in bone and estrogen receptor antagonist in breast and uterine tissue. In postmenopausal females, raloxifene modestly inhibits bone resorption. In a systematic review and network meta-analysis[47] that included 34 RCTs and 36 observational studies of patients with low bone mass or osteoporosis, raloxifene was associated with a lower incidence of vertebral fractures compared with placebo (49 per 1000 person-years vs 74 per 1000 person-years, respectively; RD, −28 [95% CI, −57 to −1]) with low evidence certainty, but did not reduce the risk of nonvertebral fractures. Compared with placebo, raloxifene is associated with an approximately 3-fold increased risk of thromboembolism and may also increase the risk of fatal stroke.[68] Hot flashes, leg cramps, and peripheral edema occur in approximately 5% to 15% of individuals who take raloxifene.[69]

Teriparatide and Abaloparatide

Teriparatide and abaloparatide are analogs of human parathyroid hormone and human parathyroid-related peptide that stimulate bone remodeling through their actions on osteoblasts and osteoclasts.[70,71] Teriparatide reduces vertebral fracture rates compared with placebo (13 per 1000 person-years vs 81 per 1000 person-years, respectively; RD, −69 [95% CI, −112 to −28]) and the risk of all clinical fractures (27 per 1000 person-years vs 54 per 1000 person-years; RD, −27 [95% CI, −56 to −7]) with low to moderate evidence certainty.[47] Teriparatide reduces risk of vertebral fracture compared with bisphosphonates (54 per 1000 person-years vs 120 per 1000 person-years, respectively; RD, −66 [95% CI, −100 to −32]) and any clinical fracture (44 per 1000 person-years vs 90 per 1000 person-years; RD, −45 [95% CI, −72 to −19]).[47]

Teriparatide and abaloparatide are contraindicated in patients with hyperparathyroidism because they may exacerbate hypercalcemia, and in individuals with skeletal malignancy or conditions that have increased osteosarcoma risk, such as prior skeletal radiation or Paget disease of bone. However, postmarketing surveillance studies have shown no excess osteosarcoma risk in people taking these medications, and therefore this risk no longer appears as a black box warning.[72] Transient hypotension infrequently occurs with the first dose of teriparatide or abaloparatide. Other potential adverse events include nausea, dizziness, palpitations, headache, myalgia, and hypercalcemia. Loss of bone mass occurs after discontinuation, so the use of antiresorptive therapy, such as bisphosphonates or denosumab, should be prescribed after discontinuation of teriparatide and abaloparatide.[73]

Romosozumab

Romosozumab is a monoclonal antibody that binds and inhibits sclerostin, an osteocyte-secreted inhibitor of the Wnt-signaling pathway, and thereby markedly increases bone formation and moderately reduces bone resorption.[74] In a systematic review and network meta-analysis,[47] the use of romosozumab was associated with lower rates of vertebral fracture compared with placebo (5 per 1000 person-years vs 18 per 1000 person-years, respectively; RD, −13 [95% CI, −18 to −8]) and lower rates of any clinical fracture (16 per 1000 person-years vs 25 per 1000 person-years; RD, −9 [95% CI, −15 to −2]) with moderate evidence certainty. In a network meta-analysis[47] that included 34 RCTs and 36 observational studies, romosozumab followed by 12 months of alendronate reduced the number of vertebral fractures compared with alendronate monotherapy (41 of 1000 person-years vs 80 per 1000 person-years, respectively; RD, 40 [95% CI, −55 to 24]) and reduced the occurrence of any clinical fractures (97 per 1000 person-years vs 130 per 1000 person-years; RD, −33 [95% CI, −53 to −14]). After 12 months of treatment with romosozumab, an antiresorptive therapy, such as bisphosphonates or denosumab, should be prescribed.[75] After discontinuing romosozumab, further increases in bone mass typically occur with denosumab,[76] and maintenance of bone mass occurs with alendronate.[77]

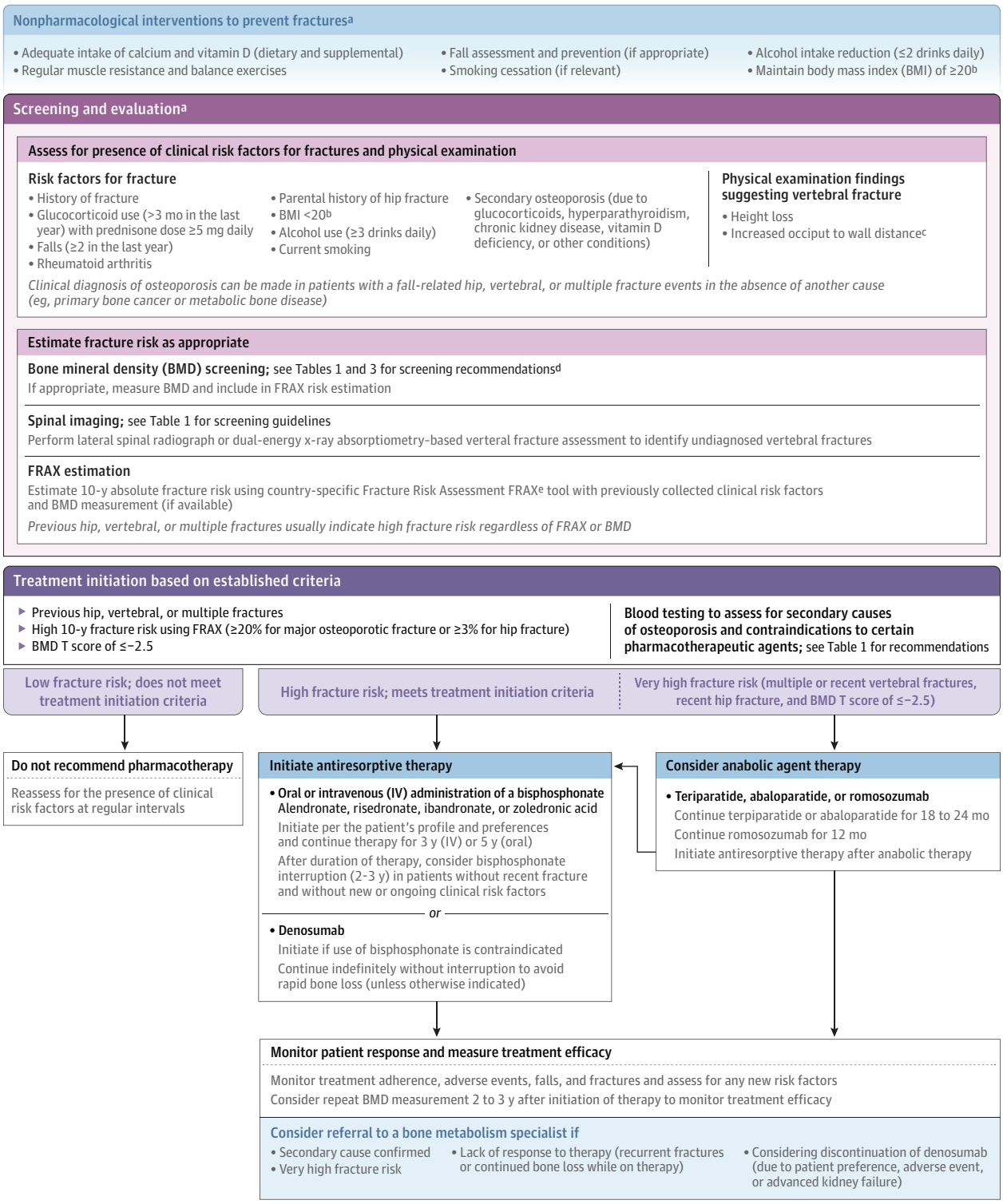
The adverse effects of romosozumab include injection site reactions (such as pain or skin discoloration) and rare cases of osteonecrosis of the jaw and atypical femur fractures.[74,77] A clinical trial[77] involving 4093 participants reported an increase in serious adverse cardiovascular events in those assigned to romosozumab compared with alendronate over a 12-month period (2.5% for romosozumab vs 1.9% for alendronate). In a larger clinical trial[74] involving 7180 participants, there was no increased rate of cardiovascular events in patients with osteoporosis randomized to romosozumab compared with placebo. The US Food and Drug Administration label for romosozumab includes a black box warning for increased risk of myocardial infarction, stroke, and cardiovascular mortality. Romosozumab should not be initiated in patients who have had a myocardial infarction or stroke in the past year.

Recommended Therapeutic Strategies

Most practice guidelines on osteoporosis management and fracture prevention recommend pharmacotherapy for postmenopausal females and males aged 50 years or older with osteoporosis based on BMD screening results or for those with a high fracture risk or with a history of hip, spinal, or multiple fractures (even if their BMD level is in the osteopenia or normal range)[3,5,24,78] (**Figure 3**).

For individuals at high fracture risk, either oral or intravenous bisphosphonates are appropriate primary treatment. For people who have contraindications or intolerance to bisphosphonates, denosumab is recommended. Raloxifene is a reasonable option for postmenopausal females who are not at increased risk of thromboembolism and who prefer not to initiate treatment with a bisphosphonate or who have contraindications to bisphosphonates. Anabolic therapy with parathyroid hormone analogs or romosozumab should be considered as the first-line agent in those at very high fracture risk. The Endocrine Society guideline[79] recommends use of anabolic medications, such as parathyroid hormone analogs or romosozumab, for postmenopausal females with a T score of −2.5 or less for BMD and prior fractures, or in those with multiple vertebral fractures.

Figure 3. Screening, Diagnosis, and Management of Osteoporosis and Fracture Prevention



[a]This algorithm summarizes general guidance in assessment and management of osteoporosis. It has not been validated. Consult local osteoporosis clinical practice guidelines for the approach to assessment and management of osteoporosis in postmenopausal females and in males aged ≥50 years.

[b]Calculated as weight in kilograms divided by height in meters squared.

[c]Refers to when the patient stands with heels and buttocks against the wall and the horizontal distance between the occiput and the wall is measured.

[d]The US Preventive Services Task Force recommends BMD screening for postmenopausal females aged ≥65 years to prevent osteoporotic fractures and postmenopausal females aged <65 years who are at increased risk of osteoporosis as determined by the Fracture Risk Assessment Tool (FRAX). The current evidence is insufficient to assess the balance of benefits and harms of BMD screening in men.

[e]Country-specific FRAX available at https://www.fraxplus.org.

Duration and Sequence of Therapy

Due to concerns about the adverse effects of long-term use, interruption of bisphosphonate therapy should be considered after 3 years of intravenous bisphosphonate use or 5 years of oral bisphosphonate use. The antifracture benefits of continuing bisphosphonate therapy beyond 5 years remain unclear. An RCT involving 1099 participants[80] reported that after 5 years of alendronate therapy, patients who continued taking alendronate had lower rates of clinically recognized vertebral fractures compared with those who discontinued therapy (24 per 1000 person-years vs 53 per 1000 person-years, respectively; RD, −29 [95% CI, −53 to −5]), although the rates of radiologically confirmed vertebral fracture did not differ (98 per 1000 person-years vs 113 per 1000 person-years; RD, −15 [95% CI, −52 to 22]). Another clinical trial of 1233 patients with osteoporosis[81] reported that those who continued intravenous zoledronic acid for more than 3 years had a significantly lower rate of radiologically confirmed vertebral fractures compared with those who discontinued intravenous zoledronic acid after 3 years (30 per 1000 person-years vs 62 per 1000 person-years, respectively; RD, −32 [95% CI, −55 to −9]), but not a lower rate for clinical vertebral fracture (risk ratio, 1.81 [95% CI, 0.53 to 6.20] for continuing with intravenous zoledronic acid vs placebo; absolute difference not provided).

For individuals at a moderate or low fracture risk who have not sustained a fracture while taking a bisphosphonate, interrupting therapy (ie, drug holiday) is appropriate, although the optimal duration of bisphosphonate interruption is uncertain. Fracture rates do not appear to increase for the first 1 to 2 years after bisphosphonate discontinuation but may increase 2 to 5 years later.[82-84]

For those who remain at high fracture risk after 3 to 5 years of treatment (eg, those who sustained a fracture while receiving bisphosphonate therapy), continuation of an intravenous bisphosphonate for 3 additional years or oral bisphosphonate for 5 additional years or switching to denosumab may be considered. Use of teriparatide, abaloparatide, or romosozumab may be considered if the patient remains at high risk after 3 to 5 years of bisphosphonate therapy. However, improvements in BMD and bone strength after anabolic therapy are smaller when anabolic therapy is used after antiresorptive agents compared with individuals not previously treated with bisphosphonates.[85,86] Transition from denosumab to teriparatide or abaloparatide is associated with transient bone loss and should be avoided.[87] Based on limited data, switching from denosumab to romosozumab may prevent transient bone loss.[88]

Additional studies are needed regarding the benefits vs harms of repeated cycles of anabolic therapy and for combined use of an anabolic and antiresorptive agent. This combination therapy is more costly than individual therapies, may cause more adverse events, and is usually reserved for selected patients at very high fracture risk.[3] There are no indications for combining 2 antiresorptive agents.

Monitoring

Regular clinical assessment should be performed to identify weight and height loss, fractures, falls, and adverse events and to assess adherence to management plans.[3,5,6,24] Repeat measurement of BMD can be performed after 2 to 3 years of pharmacotherapy to monitor treatment response, even if the initial T score for BMD was less than −2.5. Data from trials of antiresorptive and anabolic therapies show an inverse relationship between the achieved BMD level and subsequent fracture risk. Observational studies have reported that subsequent fracture risk is lower among patients whose BMD level increased after therapy initiation compared with those whose BMD level remained stable or decreased.[89] A clinically meaningful reduction in fracture risk is expected when the increase in BMD level exceeds the measurement error defined by the precision assessment of the DXA facility where the measurement of BMD was performed (precision assessments are performed by the DXA facilities, and this information is usually provided on the BMD report).

In the absence of treatment, fracture risk reassessment using FRAX should be performed after 3 to 10 years based on initial fracture risk.[90]

Practical Considerations

Most individuals in the US with osteoporosis who have sustained a fracture or who are at high risk of fracture do not receive guideline-recommended treatment.[91] Fracture liaison services are evidence-based programs that consist of a multidisciplinary team of clinicians that implement evidence-based diagnostic and treatment protocols after fractures. A systematic review and meta-analysis[92] of 16 RCTs and 58 observational studies involving 8399 participants reported that compared with patients with osteoporosis-related fractures without care from a fracture liaison service, patients who received fracture liaison services were more likely to have higher rates of treatment initiation (17% vs 38%, respectively; RD, 20% [95% CI, 16%-25%) and medication adherence (34% vs 57%; RD, 22% [95% CI, 13%-31%]). After a fracture, patients should receive pain control and rehabilitation and support via a multidisciplinary approach.[93]

Practice guidelines exist to guide clinicians in the identification and management of adults with osteoporosis and increased fracture risk (**Table 3** and Figure 3). Multifaceted strategies to implement practice recommendations, such as integration in electronic medical records or development of decision aid tools, have improved awareness of osteoporosis and its management.[94-96] A shared decision-making model for treatment is encouraged.[97,98]

Referral to a specialist with expertise in osteoporosis should be considered for patients if uncertainty exists about fracture risk or treatment, for the evaluation of secondary causes of osteoporosis, for comorbidities that complicate the treatment of osteoporosis, or for serious adverse events associated with medications used to treat osteoporosis.

Limitations

This review has several limitations. First, some relevant publications may have been missed. Second, the quality of evidence was not formally assessed. Third, some secondary causes of osteoporosis (ie, glucocorticoid-induced, chronic kidney disease) and osteoporosis in young individuals were not discussed.

Conclusions

Osteoporosis is a common condition among older adults that leads to increased susceptibility to fracture, which is associated with substantial morbidity and mortality. Antiresorptive agents such as bisphosphonates or denosumab are recommended for patients at high

Table 3. Summary of Guideline Recommendations for Management of Osteoporosis[a]

	Bone Health and Osteoporosis Foundation guideline,[3] 2022	UK Osteoporosis guideline,[6] 2022	Endocrine Society guideline updates,[78,79] 2019 and 2020	American Association of Clinical Endocrinologists/ American College of Endocrinology clinical practice guidelines,[5] 2020
Target population	• Postmenopausal females and males ≥50 y of age	• Postmenopausal females and males ≥50 y of age	• Postmenopausal females	• Postmenopausal females ≥50 y
Measurement of bone mineral density (BMD)	• Postmenopausal females aged 50-64 y and males aged 50-69 y with risk factors for osteoporosis • Females aged ≥65 y • Males aged ≥70 y	• FRAX assessment without BMD should be performed in postmenopausal females and in males ≥50 y of age • FRAX assessment with BMD should be performed in individuals at intermediate risk (close to the age-dependent treatment threshold) or in individuals at high or very high risk (if a baseline BMD measurement is needed for a subsequent monitoring purpose)		• Postmenopausal females aged 50-64 y with clinical risk factors for osteoporosis or history of fractures • Postmenopausal females aged ≥65 y
FRAX (a fracture risk assessment tool)	• Country specific	• Country specific	• Country specific	• Country specific
Treatment initiation	• In postmenopausal females and males aged ≥50 y with • Hip or vertebral fracture (regardless of T score) • Fracture of the pelvis, proximal humerus or distal forearm with T score between −1 and −2.5 • T score ≤−2.5 at the femoral neck, total hip, or lumbar spine or 33% radius • T score between −1 and −2.5 and a 10-y probability of ≥20% for major osteoporotic fractures or ≥3% for hip fractures (based on the country-specific[b] FRAX tool)	Postmenopausal females and males aged ≥50 y with • Prior or recent fragility fracture (particularly in older people) • A 10-y probability of high or very high fracture risk based on the country-specific[b] FRAX tool; intervention threshold increases with age until 70 y (after which it is constant)	• Postmenopausal females at high fracture risk with • Hip or vertebral fracture • Recent fracture (within 2 y) • T score ≤−2.5 for femoral neck BMD, total hip, or lumbar spine or distal radius • T score of −1 to −2.5 and a 10-y probability of ≥20% for major osteoporotic fractures or ≥3% for hip fractures (based on the country-specific[b] FRAX tool)	• Postmenopausal females with • Low bone mass (osteopenia) and a history of fracture of the hip or spine • T score ≤−2.5 for femoral neck BMD, total hip, or lumbar spine or one-third radius • T score of −1 to −2.5 and a 10-y probability of ≥20% for major osteoporotic fractures or ≥3% for hip fractures (based on the country-specific[b] FRAX tool)
Monitoring after initiation of treatment	• Measurement of BMD every 2 y	• No specific recommendation	• Measurement of BMD every 1 to 3 y	• Measurement of BMD every 1 to 2 y until stable
Interruption of bisphosphonate treatment (drug holiday)	• In those at modest risk of fracture (no recent fracture or T score >−2.5) after 3 y of intravenous or 5 y of oral bisphosphonate • Reassess fracture risk and BMD level every 2 to 3 y	• After 3 y of treatment with intravenous bisphosphonate or 5 y of treatment with oral bisphosphonate, reassess fracture risk and reconsider treatment every 1.5-3 y • Pause treatment for those at lower risk	• In those at low to moderate fracture risk, consider bisphosphonate interruption after 3 to 5 y of therapy	• For oral bisphosphonates, consider a bisphosphonate holiday after 5 y of treatment or 6 to 10 y in very high risk • For zoledronate, consider a bisphosphonate holiday after 3 y in patients at high risk and up to 6 y in those at very high risk

[a] The 2024 US Preventive Services Task Force[34] recommendations are to screen postmenopausal females aged 65 years or older for BMD level to prevent osteoporotic fractures and screen postmenopausal females younger than 65 years who are at increased risk of osteoporosis (as determined by a clinical risk assessment tool). The current evidence is insufficient to assess the balance of benefits and harms of BMD screening in men.

[b] Calibrated using individual country population-specific fracture and mortality data. When using FRAX to calculate absolute fracture risk, it is important to use the country-specific tool, which is easily identified on the website (https://www.fraxplus.org).

fracture risk. Anabolic treatment with parathyroid hormone analogs (such as teriparatide and abaloparatide) and sclerostin inhibitors (such as romosozumab) can be considered for individuals at very high fracture risk.

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