AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS — 2016

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The American Association of Clinical Endocrinologists/American College of Endocrinology Medical Guidelines for Practice are systematically developed statements to assist healthcare professionals in medical decision-making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **AFF** = atypical femur fracture; **ASBMR** = American Society for Bone and Mineral Research; **BEL** = best evidence level; **BMD** = bone mineral density; **BTM** = bone turnover marker; **CBC** = complete blood count; **CI** = confidence interval; **DXA** = dual-energy X-ray absorptiometry; **EL** = evidence level; **FDA** = U.S. Food and Drug Administration; **FLEX** = Fracture Intervention Trial (FIT) Long-term Extension; **FRAX®** = Fracture Risk Assessment Tool; **GFR** = glomerular filtration rate; **GI** = gastrointestinal; **HORIZON** = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; **IOF** = International Osteoporosis Foundation; **ISCD** = International Society for Clinical Densitometry; **IU** = international units; **IV** = intravenous; **LSC** = least significant change; **NBHA** = National Bone Health Alliance; **NOF** = National Osteoporosis Foundation; **25(OH)D** = 25-hydroxy vitamin D; **ONJ** = osteonecrosis of the jaw; **PINP** = serum carboxy-terminal propeptide of type I collagen; **PTH** = parathyroid hormone; **R** = recommendation; **RANK** = receptor activator of nuclear factor kappa-B; **RANKL** = receptor activator of nuclear factor kappa-B ligand; **RCT** = randomized controlled trial; **RR** = relative risk; **S-CTX** = serum C-terminal telopeptide; **SQ** = subcutaneous; **VFA** = vertebral fracture assessment; **WHO** = World Health Organization.

1. INTRODUCTION

Osteoporosis is a growing major public health problem with impacts on quality and quantity of life that cross medical, social, and economic lines. These guidelines were developed by the American Association of Clinical Endocrinologists (AACE) with hopes of reducing the risk of osteoporosis-related fractures and thereby maintaining the quality of life for people with osteoporosis. The guidelines use the best evidence, taking into consideration the economic impact of the disease and the need for efficient and effective evaluation and treatment of postmenopausal women with osteoporosis. The intent is to provide evidence-based information about the diagnosis, evaluation, and treatment of postmenopausal osteoporosis for endocrinologists, physicians in general, regulatory bodies, health-related organizations, and interested laypersons.

2. METHODS FOR DEVELOPMENT OF AACE CLINICAL PRACTICE GUIDELINES FOR POSTMENOPAUSAL OSTEOPOROSIS

Evidence was obtained through MEDLINE searches and other designated reference sources. Expert opinion was used to evaluate the available literature and to grade references relative to evidence level (EL) (Table 1), evidence analysis, and subjective factors (Table 2), based on the ratings of 1 through 4 from the 2010 and 2014 AACE protocols for standardized production of clinical practice guidelines (available online at https://www.aace.com/files/checklists_july_2014_ep.pdf) (1 [EL 4; CPG NE], 2 [EL 4; CPG NE]). Best evidence level (BEL) for evidence presented in the discussion of the evidence base is given for each recommendation in the Executive Summary. In addition, recommendations were graded A through D, in accordance with methods established by the AACE in 2004 and clarified in 2010 (Table 3) (1 [EL 4; CPG NE], 3 [EL 4; CPG NE]). Information pertaining to cost-effectiveness was included when available. Examples of qualifiers that are appropriate to append to recommendations include risk-benefit analyses, evidence gaps, alternative physician preferences (dissenting opinions), alternative recommendations (e.g., based on resource availability and cultural factors), expert consensus and relevance (i.e., patient-oriented evidence that matters) (1 [EL 4; CPG NE]). **(Endocr Pract. 2016;22:Suppl4;1-42)**

3. EXECUTIVE SUMMARY

To guide readers, recommendations are organized into the following questions:

- Q1. How is fracture risk assessed and osteoporosis diagnosed?
- Q2. When osteoporosis is diagnosed, what is an appropriate evaluation?
- Q3. What are the fundamental measures for bone health?
- Q4. Who needs pharmacologic therapy?
- Q5. What medication should be used to treat osteoporosis?
- Q6. How is treatment monitored?
- Q7. What is successful treatment of osteoporosis?
- Q8. How long should patients be treated?
- Q9. Is combination therapy better than treatment with a single agent?
- Q10. Should sequential use of therapeutic agents be considered?
- Q11. Should vertebral augmentation be considered for compression fractures?
- Q12. When should referral to a clinical endocrinologist or osteoporosis specialist be considered?

3.Q1. How Is Fracture Risk Assessed and Osteoporosis Diagnosed?

- **R1.** Evaluate all postmenopausal women aged ≥50 years for osteoporosis risk **(Grade B; BEL 1, downgraded due to gaps in evidence)**.
- **R2.** A detailed history, physical exam, and clinical

Table 1
2010 AACE Protocol for Production of Clinical Practice Guidelines
Step 1: Evidence Rating

1	Meta-analysis of randomized controlled trials (MRCT)
1	Randomized controlled trial (RCT)
2	Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT)
2	Nonrandomized controlled trial (NRCT)
2	Prospective cohort study (PCS)
2	Retrospective case-control study (RCCS)
3	Cross-sectional study (CSS)
3	Surveillance study (registries, surveys, epidemiologic study) (SS)
3	Consecutive case series (CCS)
3	Single case reports (SCR)
4	No evidence (theory, opinion, consensus, or review) (NE)

1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; 4 = no evidence.
Adapted from Mechanick et al. *Endocr Pract*. 2010;16:270-283.(1 [EL 4; CPG NE])

fracture risk assessment with the Fracture Risk Assessment Tool (FRAX®) should be included in the initial evaluation for osteoporosis **(Grade B; BEL 2)**.

- **R3.** Consider bone mineral density (BMD) testing based on clinical fracture risk profile **(Grade B; BEL 2)**.
- **R4.** When BMD is measured, axial dual-energy X-ray absorptiometry (DXA) measurement (spine and hip) should be used **(Grade B; BEL 2)**.
- **R5a.** Osteoporosis should be diagnosed based on presence of fragility fractures in the absence of other metabolic bone disorders **(Grade B; BEL 2)** or a T-score of –2.5 or lower in the lumbar spine (anteroposterior), femoral neck, total hip, and/or 33% (one-third) radius even in the absence of a prevalent fracture **(Grade B; BEL 2)**.
- **R5b.** Osteoporosis may also be diagnosed in patients with osteopenia and increased fracture risk using FRAX® country-specific thresholds **(Grade B; BEL 2)**.

3.Q2. When Osteoporosis Is Diagnosed, What Is an Appropriate Evaluation?

- **R6.** Evaluate for causes of secondary osteoporosis **(Grade B; BEL 2)**.
- **R7.** Evaluate for prevalent vertebral fractures **(Grade A; BEL 1)**.
- **R8.** Consider using bone turnover markers (BTMs) in the initial evaluation and follow-up of osteoporosis patients. Elevated levels can predict more rapid rates of bone loss and higher fracture risk **(Grade B; BEL 1, downgraded based on expert consensus)**.

3.Q3. What Are the Fundamental Measures for Bone Health?

- **R9.** Measure serum 25-hydroxyvitamin D (25[OH]D) in patients who are at risk for vitamin D insufficiency, particularly those with osteoporosis **(Grade B; BEL 2)**.
- **R10.** Maintain serum 25-hydroxyvitamin D (25[OH]D) ≥30 ng/mL in patients with osteoporosis (preferable range, 30-50 ng/mL) **(Grade B; BEL 3, upgraded based on expert consensus)**.
- **R11.** Supplement with vitamin D_3 if needed; 1,000 to 2,000 international units (IU) of daily maintenance therapy is typically needed to maintain an optimal serum 25(OH)D level **(Grade C, BEL 4; upgraded based on expert consensus)**.
- **R12.** Higher doses may be necessary in the presence of certain factors (e.g., obesity, malabsorption, transplant patients, certain ethnicities, older individuals) **(Grade A; BEL 1)**.
- **R13.** Counsel patients to maintain adequate dietary intake of calcium, to a total intake (including diet plus supplement, if needed) of 1,200 mg/day for women ≥50 years **(Grade B; BEL 2)**.
- **R14.** Counsel patients to limit alcohol intake to no more than 2 units per day. **(Grade B; BEL 2)**.
- **R15**. Counsel patients to avoid or stop smoking **(Grade B; BEL 2)**.
- **R16.** Counsel patients to maintain an active lifestyle, including weight-bearing, balance, and resistance exercises **(Grade B; BEL 2)**.
- **R17.** Provide counseling on reducing risk of falls, particularly among the elderly **(Grade A; BEL 1)**.

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Table 2
2010 AACE Protocol for Production of Clinical Practice Guidelines
Step 2: Evidence Analysis and Subjective Factors

Study design	Data analysis	Interpretation
Premise correctness	Intent-to-treat	Generalizability
Allocation concealment (randomization)	Appropriate statistics	Logical
Selection bias		Incompleteness
Appropriate blinding		Validity
Using surrogate end points (especially in "first-in-its-class" intervention)		
Sample size (beta error)		
Null hypothesis versus Bayesian statistics		
Adapted from Mechanick et al. *Endocr Pract*. 2010;16:270-283.(1 [EL 4; CPG NE])		

- **R18.** Consider recommending use of hip protectors in individuals with a high risk of falling **(Grade B; BEL 1, downgraded due to discrepancy in efficacy between studies)**.
- **R19.** Consider referral for physical therapy, which may reduce discomfort, prevent falls, and improve quality of life **(Grade A; BEL 1)**.

3.Q4. Who Needs Pharmacologic Therapy?

- **R20.** Strongly recommend pharmacologic therapy for patients with osteopenia or low bone mass and a history of fragility fracture of the hip or spine **(Grade A; BEL 1).**
- **R21.** Strongly recommend pharmacologic therapy for patients with a T-score of –2.5 or lower in the spine, femoral neck, total hip or 33% radius **(Grade A; BEL 1).**
- **R22.** Strongly recommend pharmacologic therapy for patients with a T-score between –1.0 and –2.5 if the FRAX® 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% in the U.S. or above the country-specific threshold in other countries or regions **(Grade B; BEL 2).**

3.Q5. What Medication Should Be Used to Treat Osteoporosis?

- **R23.** Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, risedronate, zoledronic acid, and denosumab are appropriate as initial therapy for most patients at high risk of fracture **(Grade A; BEL 1)**.
- **R24.** Teriparatide, denosumab, or zoledronic acid should be considered for patients unable to use oral therapy and as initial therapy for patients at especially high fracture risk **(Grade A; BEL 1)**.
- **R25.** Raloxifene or ibandronate may be appropriate initial therapy in some cases where patients requiring drugs with spine-specific efficacy **(Grade A; BEL 1)**.

3.Q6. How Is Treatment Monitored?

- **R26.** Obtain a baseline axial (spine and hip) DXA, and repeat DXA every 1 to 2 years until findings are stable. Continue with follow-up DXA every 1 to 2 years or at a less-frequent interval, depending on clinical circumstances **(Grade B; BEL 2)**.
- **R27.** Monitor serial changes in lumbar spine, total hip, or femoral neck BMD; if spine, hip, or both are not evaluable, consider monitoring using the 33% radius site **(Grade A; BEL 1)**.
- **R28.** Follow-up of patients should ideally be conducted in the same facility with the same machine **(Grade B; BEL 4, upgraded based on expert consensus)**.
- **R29.** Consider using BTMs for assessing patient compliance and therapy efficacy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction; significant increases indicate good response to anabolic therapy **(Grade B; BEL 1; downgraded based on expert consensus)**.

3.Q7. What Is Successful Treatment of Osteoporosis?

- **R30.** Successful treatment of osteoporosis is defined as stable or increasing BMD with no evidence of new fractures or fracture progression **(Grade A; BEL 1)**.
- **R31.** For patients taking antiresorptive agents, target for treatment success is BTMs at or below the median value for premenopausal women **(Grade A; BEL 1)**.
- **R32.** Consider alternative therapy or reassessment for causes of secondary osteoporosis in patients who have recurrent fractures or significant bone loss while on therapy **(Grade A; BEL 1)**. A single fracture while on

therapy is not necessarily evidence of treatment failure, but it does suggest that fracture risk is high.

3.Q8. How Long Should Patients Be Treated?

- **R33.** Treatment with teriparatide should be limited to 2 years **(Grade A; BEL 1)**.
- **R34a.** For oral bisphosphonates, consider a "bisphosphonate holiday" after 5 years of stability in moderate-risk patients **(Grade B; BEL 1, downgraded due to limitations of data)**.
- **R34b.** For oral bisphosphonates, consider a "bisphosphonate holiday" after 6 to 10 years of stability in higher-risk patients **(Grade B; BEL 1, downgraded due to limitations of data)**.
- **R34c.** For intravenous (IV) zoledronic acid, consider a drug holiday after 3 annual doses in moderate-risk patients and after 6 annual doses in higher-risk patients. **(Grade B, BEL 1, downgraded due to limitations of data)**.
- **R34d.** Teriparatide or raloxifene may be used during

Table 3
2010 AACE Protocol for Production of Clinical Practice Guidelines
Step 3: Grading Recommendations

2004 AACE Criteria for Grading Recommendations

Recommendation grade	Description
A	Homogeneous evidence from multiple, well-designed, randomized, controlled trials with sufficient statistical power Homogeneous evidence from multiple, well-designed, cohort-controlled trials with sufficient statistical power ≥1 conclusive level 1 publications demonstrating benefit >> risk
B	Evidence from ≥1 well-designed clinical trial, cohort- or case-controlled analytic study, or meta-analysis No conclusive level 1 publications; ≥1 conclusive level 2 publications demonstrating benefit >> risk
C	Evidence based on clinical experience, descriptive studies, or expert consensus opinion No conclusive level 1 or 2 publications; ≥1 conclusive level 3 publications demonstrating benefit >> risk No conclusive risk at all and no conclusive benefit demonstrated by evidence
D	Not rated No conclusive level 1, 2, or 3 publications demonstrating benefit >> risk Conclusive level 1, 2, or 3 publications demonstrating risk >> benefit

2010 AACE Update: Mapping Evidence Levels to Recommended Grading

BEL	Subject factor impact	Two-thirds consensus	Mapping	Recommended grading
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust Down	D
1, 2, 3, 4	NA	No	Adjust down	D

1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; 4 = no evidence.
Starting with the left column, best evidence level (BEL), subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact ("none"), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. NA = not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).
Adapted from Mechanick et al. *Endocr Pract*. 2010;16:270-283 (1 [EL 4; CPG NE])

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the "bisphosphonate holiday" period for higher-risk patients **(Grade D; BEL 4)**.

- **R34e.** A drug "holiday" is not recommended with denosumab **(Grade A; BEL 1)**.
- **R34f.** The ending of the "holiday" for bisphosphonate treatment should be based on individual patient circumstances (fracture risk or change in BMD or BTMs) **(Grade B; BEL 4, upgraded based on expert consensus)**.
- **R34g.** Other therapeutic agents should be continued for as long as clinically appropriate **(Grade D; BEL 4)**.

3.Q9. Is Combination Therapy Better Than Treatment With a Single Agent?

- **R35a.** Until the effect of combination therapy on fracture risk is demonstrated AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis **(Grade C; BEL 4; expert consensus, upgraded due to cost and potential increased side effects)**.
- **R35b.** If estrogen is being given for treatment of menopausal symptoms or raloxifene is administered to reduce the risk of breast cancer, an additional agent such as a bisphosphonate, denosumab, or teriparatide may be considered in higher-rise patients **(Grade D; BEL 4)**.
- **R35c.** Combined denosumab and teriparatide achieves a better BMD response versus either agent alone, but no fracture data are available. **(Grade B; BEL 1; downgraded due to potential increased side effects and increased cost)**.

3.Q10. Should Sequential Use of Therapeutic Agents Be Considered?

- **R36.** Treatment with teriparatide should always be followed by antiresorptive agents to prevent bone density decline and loss of fracture efficacy **(Grade A; BEL 1)**.

3.Q11. Should Vertebral Augmentation Be Considered for Compression Fractures?

- **R37.** Vertebroplasty and kyphoplasty are not recommended as first-line treatment of vertebral fractures given the unclear benefit on overall pain and the potential increased risk of vertebral fractures in adjacent vertebrae **(Grade B, BEL 1; downgraded due to limitations of published studies)**.

3.Q12. When Should Referral to a Clinical Endocrinologist or Osteoporosis Specialist Be Considered?

- **R38.** When a patient with normal BMD sustains a fracture without major trauma **(Grade C; BEL 4; upgraded due to expert consensus)**.
- **R39.** When recurrent fractures or continued bone loss occurs in a patient receiving therapy without obvious treatable causes of bone loss **(Grade C; BEL 4; upgraded due to expert consensus)**.
- **R40.** When osteoporosis is unexpectedly severe, has unusual features, or less common secondary conditions (e.g., hyperthyroidism, hyperparathyroidism, hypercalciuria, or elevated prolactin) are identified **(Grade C; BEL 4; upgraded due to expert consensus)**.
- **R41.** When a patient has a condition that complicates management (e.g., chronic kidney disease [CKD]: glomerular filtration rate [GFR] <35, hyperparathyroidism, or malabsorption) **(Grade C; BEL 4; upgraded due to expert consensus)**.
- **R42.** Patients who experience fragility fractures should be evaluated and treated. Referral to an osteoporosis specialist or a fracture liaison team, if available, should be considered **(Grade B; BEL 2)**.

4. EVIDENCE BASE

In this update, there are 321 reference citations, of which 115 (36%) are EL 1 (strong), 77 (24%) are EL 2 (intermediate), 39 (12%) are EL 3 (weak), and 90 (28%) are EL 4 (no clinical evidence). The majority of reference citations are EL 1 or 2: 192/321 (60%), which is slightly more than the 121/209 (58%) EL 1 and 2 references included in the 2010 AACE Clinical Practice Guidelines. The evidence base presented here provides relevant information for the recommendations in the Executive Summary.

Public Health Impact of Osteoporosis

Osteoporosis is a major public health problem. The National Osteoporosis Foundation (NOF) estimates that 10.2 million Americans have osteoporosis and that an additional 43.4 million have low bone mass. More than 2 million osteoporosis-related fractures occur annually in the U.S., more than 70% of these occur in women (Fig. 1) (4 [EL 3; SS], 5 [EL 3; SS]). In the U.S., Medicare currently pays for most of these costs, and as the population ages, the costs of these fractures are estimated to exceed $25 billion

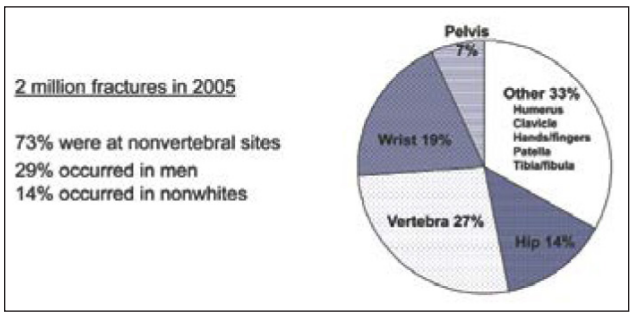

Fig. 1. Fractures attributable to osteoporosis in the United States in 2005. Distribution by skeletal site is shown. Adapted from Burge et al (5 [EL 3; SS]).

by 2025. Despite these significant costs, fewer than 1 in 4 women aged 67 years or older with an osteoporosis-related fracture undergoes bone density measurement or begins osteoporosis treatment (6 [EL 4; review NE]). A recent retrospective analysis demonstrated that the annual cost of caring for osteoporotic fracture exceeds the annual costs of caring for breast cancer, myocardial infarction, or stroke in women aged 55 years and older (7 [EL 2; RCCS]).

Osteoporosis is preventable and treatable, but only a small proportion of those at increased risk for fracture are evaluated and treated. Age is an important risk factor for bone loss; by age 60, half of white women have osteopenia or osteoporosis (8 [EL 3; SS]). The average femoral neck T-score by DXA for a 75-year-old women is –2.5, meaning that more than half of women age 75 and older meet the criterion for osteoporosis (9 [EL 3; SS]). More than 20% of postmenopausal women have prevalent vertebral fractures (10 [EL 3; CSS]). Although these guidelines focus on the evaluation and treatment of osteoporosis in postmenopausal women, osteoporosis may affect men and premenopausal women.

4.Q1. How Is Fracture Risk Assessed and Osteoporosis Diagnosed?

4.Q1.1. What Is the Definition of Postmenopausal Osteoporosis?

Osteoporosis is defined as "a [silent] skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality" (11 [EL 4; NE]).

In 1994, a Working Group of the WHO established an operational definition of postmenopausal osteoporosis (Table 4) (6 [EL 4; review NE]). The T-score is defined as the SD of an individual's BMD from the mean value for healthy young white women. Although the WHO diagnostic criteria were not intended to serve as thresholds for treatment decisions, they are often used for this purpose. In addition, the WHO criteria are useful for making public health and health policy decisions and are commonly accepted as standards for inclusion in clinical trials for research purposes.

4.Q1.2. What Are the Diagnostic Criteria?

Clinically, osteoporosis can be diagnosed if there is a low-trauma (i.e., fragility) fracture in the absence of other metabolic bone disease, independent of the BMD (T-score) value. Thus, patients with osteopenia or low bone mass (defined as T-score between –1.0 and –2.5, based on BMD testing) but with a low-trauma (fragility) fracture of the spine, hip, proximal humerus, pelvis, or possibly distal forearm are also at an increased risk for future fractures and should be diagnosed with osteoporosis and considered for pharmacologic therapy (see **R20-R22**) (Table 5) (12 [EL 4; NE], 13 [EL 2; RCCS], 14 [EL 4; review NE], 15 [EL 4; NE], 16 [EL 4; NE]). While osteoporosis has traditionally been diagnosed based on T-scores less than –2.5 in the lumbar spine, total hip, femoral neck and/or 33% radius (6 [EL 4; review NE]), the AACE agrees with the proposed new clinical diagnosis by the National Bone Health Alliance that osteoporosis may also be diagnosed in patients with osteopenia and increased fracture risk using FRAX® country-specific thresholds (12 [EL 4; NE], 13 [EL 2; RCCS], 14 [EL 4; review NE], 17 [EL 2; PCS]).

All postmenopausal women ≥50 years should undergo clinical assessment for osteoporosis and fracture risk, including a detailed history and physical examination (Table 6) (18 [EL 3; SS], 19 [EL 4; CPG NE], 20 [EL 3; SS], 21 [EL 4; review NE], 22 [EL 1; RCT; incomplete follow-up; 60% response rate]). Tools such as the clinical fracture risk assessment (FRAX®) should be utilized when available (23 [EL 4; NE], 24 [EL 4; opinion NE]). The U.S.

Table 4
World Health Organization Criteria for Classification of Osteopenia and Osteoporosis

Category	T-score
Normal	–1.0 or above
Low bone mass (osteopenia)[a]	Between –1.0 and –2.5
Osteoporosis	–2.5 or below

[a] Fracture rates within this category vary widely. The category of "osteopenia" is useful for epidemiology studies and clinical research but is problematic when applied to individual patients and must be combined with clinical information to make treatment decisions.

Table 5
2016 AACE Diagnosis of Osteoporosis in Postmenopausal Women

1. T-score –2.5 or below in the lumbar spine, femoral neck, total, and/or 33% (one-third) radius
2. Low-trauma spine or hip fracture (*regardless of BMD*)
3. Osteopenia or low bone mass (T-score between –1 and –2.5) **with** a fragility fracture of proximal humerus, pelvis, or possibly distal forearm
4. Low bone mass or osteopenia and high FRAX® fracture probability based on country-specific thresholds

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Preventive Services Task Force recommends BMD testing for all women aged ≥65 and younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors (18 [EL 3; SS], 19 [EL 4; CPG NE]).

4.Q1.3. What Are the Clinical Features and Complications of Postmenopausal Osteoporosis?

4.Q1.3.1. Low BMD

As noted above, low BMD can be used to define postmenopausal osteoporosis. There is a strong inverse relationship between BMD and fracture risk. Therefore, low BMD is a major indicator of fracture risk, although it is important to realize that individual patients may sustain fractures at different BMD levels and factors other than bone density influence fracture risk (see **4.Q2. What Are the Risk Factors for Osteoporosis-Related Fractures?**). Low BMD and/or bone loss are not associated with symptoms prior to fracture.

4.Q1.3.2. Fracture

Fracture is the single most important manifestation of postmenopausal osteoporosis. Osteoporotic fractures are usually precipitated by low-energy injuries such as a fall from standing height. Osteoporosis can also be diagnosed in patients with or without fragility fractures. Vertebral fractures, however, may occur during routine daily activities, without a specific fall or injury. In clinical practice, it may be difficult or impossible to reconstruct the mechanical force applied to bone in a particular fall.

Osteoporosis-related fractures often lead to pain, disability, and deformity and reduce quality and quantity of life. Hip fractures are the most serious consequence of osteoporosis. Women with hip fracture have an increased mortality of 12 to 20% during the following 2 years. More than 50% of hip fracture survivors are unable to return to independent living; many require long-term nursing home care (25 [EL 4; review NE]). Other low-trauma fractures that are considered osteoporosis-related include those of the proximal humerus and pelvis and in some cases of the distal forearm.

Table 6
Assessment for Fracture Risk and Osteoporosis in Postmenopausal Women

- Medical history and physical examination to identify:
  - Prior fracture without major trauma (other than fingers, toes, skull) after age 50
  - Clinical risk factors for osteoporosis
    - Age ≥65
    - Low body weight (<57.6 kg [127 lb])
    - Family history of osteoporosis or fractures
    - Smoking
    - Early menopause
    - Excessive alcohol intake (≥3 drinks daily)
  - Secondary osteoporosis
  - Height loss or kyphosis
  - Risk factors for falling
  - Patient's reliability, understanding, and willingness to accept interventions
- Lateral spine imaging with standard radiography or vertebral fracture assessment in patients with unexplained height loss, self-reported but undocumented prior spine fractures, or glucocorticoid therapy equivalent to ≥5 mg prednisone daily for 3 months or more
- Bone mineral density measurements in those at increased risk for osteoporosis and fractures and willing to consider pharmacologic treatment if low bone mass is documented:
  - All women ≥65 y of age
  - Younger postmenopausal women
    - With a history of fracture(s) without major trauma
    - Starting or taking long-term systemic glucocorticoid therapy
    - With radiographic osteopenia
    - With clinical risk factors for osteoporosis (low body weight, cigarette smoking, family history of spine or hip fractures, early menopause, or secondary osteoporosis)
- In women who are candidates for pharmacologic therapy, laboratory evaluation to identify coexisting conditions that may contribute to bone loss and/or interfere with therapy

4.Q1.4. What Are the Risk Factors for Osteoporosis-Related Fractures?

BMD testing is a powerful tool, but clinical risk factors also significantly influence fracture risk in individual patients. The FRAX® tool is widely available (www.shef.ac.uk/FRAX) and incorporates multiple clinical risk factors that predict fracture risk, largely independent of BMD (26 [EL 4; NE], 27 [EL 4; NE], 28 [EL 3; SS], 29 [EL 4; review NE], 30 [EL 2; PCS]). Clinical risk factors in FRAX® include age, sex, body mass index, smoking, alcohol use, prior fracture, parental history of hip fracture, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and femoral neck BMD (when available). FRAX® predicts the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, humerus, or forearm). Postmenopausal women aged 50 years or older with osteopenia (T-score between –1.0 and –2.5) with a 10-year probability ≥3% for hip fracture or ≥20% for major osteoporotic fracture in the U.S. or above country-specific threshold) are recommended to consider osteoporosis treatment (Table 7).

It is important to note that FRAX® underestimates future fracture risk as it reports risk for only hip and major fractures, which comprise approximately half of all fragility fractures. FRAX® also underestimates risk in patients with multiple osteoporosis-related fractures, recent fractures, lumbar spine BMD much lower than femoral neck BMD, those with secondary osteoporosis, and those at increased risk of falling (31 [EL 4; review NE], 32 [EL 4; review NE], 33 [EL 4; NE], 34 [EL 4; review NE], 35 [EL 3; CSS], 36 [EL 2; PCS], 37 [EL 2; RCCS], 38 [EL 3; CSS]). Fall events are not directly captured in the FRAX® tool. Falls magnify the risk due to other factors and are the proximate cause of most fractures in older adults (39 [EL 2; PCS]). Table 8 shows factors that increase the risk of falls and fractures.

4.Q1.5. Bone Densitometry

4.Q1.5.1. Bone density scores

Bone density results are reported as grams of mineral per square cm of projected bone area and are converted to T- and Z-scores. The T-score represents the number of SDs from the normal young-adult mean values, whereas the Z-score represents the number of SDs from the normal mean value for age-, race- or ethnicity-, and sex-matched control subjects. T-scores are used for diagnostic classification in postmenopausal women. Z-scores are recommended for premenopausal women, with a Z-score –2.0 or lower defined as "below the expected range for age" and >–2.0 as "within the expected range for age." Postmenopausal women with very low Z scores often have secondary osteoporosis and should undergo comprehensive evaluation to identify the causes.

4.Q1.5.2. Indications for BMD measurement

BMD testing is useful for screening and monitoring therapy in people at high risk for osteoporosis (e.g., postmenopausal women, patients with hyperparathyroidism or

Table 7
Risk Factors Included in FRAX®

Country of residence
Ethnicity (US models only—white, black, Hispanic, and Asian)
Age (accepts ages between 40 and 90 y)
Sex
Weight (kg) and height (cm) used to calculate body mass index; a converter from English to metric units is provided within the FRAX® tool
Family history (either parent with a hip fracture)
Personal history of fragility fracture, including radiographic vertebral fracture
Glucocorticoid use (prednisolone ≥5 mg daily for 3 mo or longer, current or past)
Rheumatoid arthritis (confirmed diagnosis)
Smoking (current)
Alcohol use (>3 units daily)
Secondary osteoporosis[a] (specifically mentioned are type 1 diabetes, osteogenesis imperfect in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption and chronic liver disease)
BMD[b]. Either T-score or femoral neck BMD can be entered. The model also works without BMD.

Abbreviations: BMD = bone mineral density; FRAX® = Fracture Risk Assessment Tool.
[a] Because the effects of causes of secondary osteoporosis on fracture risk are assumed to be mediated through changes in BMD, a "yes" answer to this question does not change fracture risk if BMD is entered into the risk tool.
[b] If the T-score is used, prior correction with the "FRAX® patch" is required. If BMD is used, data are entered as g/cm^2 after identification of the densitometer manufacturer.
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other bone disorders, or those being treated with medications associated with bone loss [e.g., glucocorticoids]), if evidence of bone loss would result in modification of therapy. A list of indications for BMD testing is shown in Table 9.

BMD testing is the gold standard in diagnosing osteoporosis; however, not everyone has access to this evaluation. Therefore, the decision to measure BMD should be based on an individual's clinical fracture risk profile and skeletal health assessment (40 [EL 2; MNRCT]). The AACE recommends BMD testing for women aged 65 and older and younger postmenopausal women at increased risk for bone loss and fracture based on fracture risk analysis. BMD measurement is not recommended in children, adolescents, or healthy young men or premenopausal women, unless there is a significant fracture history or there are specific risk factors for bone loss (e.g., long-term glucocorticoid therapy).

In addition to its role in diagnosis, BMD measurement is useful in monitoring response to therapy, as shown in Table 10.

4.Q1.5.3. BMD measurement sites and techniques

DXA of the lumbar spine and proximal femur (hip) provides accurate and reproducible BMD measurements at important osteoporosis-associated fracture sites. Optimally, both hips should be initially measured to prevent misclassification and to have a baseline for both hips in case a fracture or replacement occurs in 1 hip. These axial sites are preferred over peripheral sites for both baseline and serial measurements. The most reliable comparative results are obtained when the same instrument and, ideally, the same technologist are used for serial measurements (41 [EL 4; position statement]).

Diagnostic criteria, therapeutic studies, and cost-effectiveness data have been primarily based on DXA measurements of the total hip, femoral neck, and/or lumbar spine (L1-L4), and are the preferred measurement sites (42 [EL 2; PCS], 43 [EL 2; PCS], 44 [EL 2; PCS]). The distal one-third radius (33%) can also be used as a diagnostic site, particularly when other preferred sites are not available. Use of other subregions within the proximal femur (i.e., Ward's triangle or trochanter) or of an individual vertebra has not been validated and is not recommended.

Several other techniques are available for BMD measurement, including quantitative computed tomography for measurement of both central and peripheral sites, quantitative ultrasonometry, radiographic absorptiometry, and single-energy x-ray absorptiometry. Peripheral bone density measurements can identify patients at increased risk for fracture; however, the diagnostic DXA criteria established by the WHO and recommended by the AACE apply only to the axial measurements (i.e., lumbar spine, femoral neck,

Table 8
Factors That Increase Risk of Falling and Fracture

Neurologic disorders
Parkinson disease
Seizure disorder
Peripheral neuropathy
Prior stroke
Dementia
Impaired gait and/or balance
Autonomic dysfunction with orthostatic hypotension
Impaired vision
Impaired hearing
Frailty and deconditioning
Proximal myopathy
Sarcopenia
Medications
Sedatives and hypnotics
Antihypertensive agents
Narcotic analgesics
Environmental factors
Poor lighting
Stairs
Slippery floors
Wet, icy, or uneven pavement
Uneven roadways
Electric or telephone cords
Walking large dogs, being tripped up by small dogs
Throw rugs
Positioning in a wet or dry bathtub

Table 9
Indications for Bone Mineral Density Testing

All women ≥65 years old
All postmenopausal women
With a history of fracture(s) without major trauma
With osteopenia identified radiographically
Starting or taking long-term systemic glucocorticoid therapy (≥3 mo)
Other peri- or postmenopausal women with risk factors for osteoporosis if willing to consider pharmacologic interventions
Low body weight (<127 lb or body mass index <20 kg/m^2)
Long-term systemic glucocorticoid therapy (≥3 mo)
Family history of osteoporotic fracture
Early menopause (<40 years old)
Current smoking
Excessive alcohol consumption
Secondary osteoporosis

Table 10
Bone Mineral Density Measurements: Potential Uses in Postmenopausal Women

Screening for osteoporosis
Establishing the severity of osteoporosis or bone loss in patients with suspected osteoporosis (e.g., patients with fractures or radiographic evidence of osteopenia)
Determining fracture risk—especially when combined with other risk factors for fractures
Identifying candidates for pharmacologic intervention
Assessing changes in bone density over time in treated and untreated patients
Enhancing acceptance of, and perhaps adherence with, treatment
Assessing skeletal consequences of diseases, conditions, or medications known to cause bone loss

and total hip) and the distal one-third of the radius. Thus, other technologies should not be used to diagnose osteoporosis but may be used to assess fracture risk.

4.Q1.5.4. Role of BMD in diagnosis and clinical decision-making

For women without prior fragility fractures, BMD is the single best predictor of osteoporotic fracture risk (for every 1-SD decrease in age-adjusted BMD, the relative risk [RR] of fracture increases 1.6- to 2.6-fold) (45 [EL 2; MNRCT]). The relationship between bone density and fracture risk, however, is a continuum, without a clear "fracture threshold." The WHO has defined T-score criteria for the classification of osteoporosis (T-score at or below –2.5) and low BMD (i.e., "osteopenia" with a T-score between –1.0 and –2.5) (Table 4) based on DXA measurements. Evidence supporting the association of BMD by DXA and fracture risk is well established, and a relationship between BMD change with therapy and fracture risk reduction has also been shown (46 [EL 1; RCT]). These criteria are useful for classification and risk stratification in individual patients, epidemiologic studies, and therapeutic trial design, but they are not intended as treatment thresholds. Although there is good evidence that fracture risk is sufficiently high in most postmenopausal women with osteoporosis to merit pharmacologic intervention, cost-effective management of women with osteopenia is less clear. While their overall rate of fractures is lower than that of patients with osteoporosis, more than 50% of fragility fractures occur in women with BMD in the "osteopenia" range. It is now recommended that treatment decisions include consideration of fracture probability. Thus, BMD results should be combined with other clinical fracture risk factors for accurate fracture risk assessment and to guide treatment decisions. FRAX® integrates the contribution of BMD and other clinical risk factors and calculates an individual's probability of fracture over 10 years. Other fracture tools of varying complexity have been proposed, but FRAX® is the most widely used.

4.Q1.5.5. Inaccuracies in bone density reports

Inaccuracies in BMD readings can result from a variety of factors. These include the following: inadequate training in DXA testing and interpretation; positioning errors (of the patient as well as of the region of interest), inadequate knowledge of how to eliminate fractured vertebrae or vertebrae with more severe osteoarthritis and extra-articular calcification from the field, nonadherence to the International Society for Clinical Densitometry (ISCD) guideline recommending measurement of at least 2 consecutive vertebrae, inclusion of artifacts in the analysis, errors in use of ethnic- or sex-specific databases, faulty data input to the FRAX® calculator, failure to exclude extraskeletal calcifications, inaccurate reporting of results (e.g., "patient has lost 30% of BMD" or "bones are equivalent to an 80-year-old"), and failure to compare results or comparing results from different machines or following major software changes without appropriate adjustment or recalibration. Clinicians need to be aware of these potential pitfalls in DXA report interpretation.

4.Q2. When Osteoporosis Is Diagnosed, What Is an Appropriate Evaluation?

4.Q2.1. What Laboratory Testing Is Recommended to Assess for Causes of Secondary Osteoporosis?

An appropriate medical evaluation is indicated in all women with postmenopausal osteoporosis and at high fracture risk to identify coexisting medical conditions that cause or contribute to bone loss. Some of these disorders may be asymptomatic and require laboratory testing for detection. Some causes of osteoporosis in adults are summarized in Table 11.

Because of the high prevalence of causes of secondary osteoporosis even in apparently healthy, postmenopausal women, laboratory testing should be considered for all women with osteoporosis (24 [EL 4; opinion NE]). In a retrospective study, a few simple laboratory tests provided

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useful information in at least 40% of women who did not have clinical evidence of secondary osteoporosis. (47 [EL 4; opinion NE], 48 [EL 3; CSS], 49 [EL 1; MRCT], 50 [EL 3; SS], 51 [EL 2; RCCS], 52 [EL 2; RCCS], 53 [EL 4; opinion NE]). If medical history, physical findings, or laboratory test results suggest causes of secondary osteoporosis, additional laboratory evaluation is warranted and may include, but is not limited to, the tests listed in Table 12.

Laboratory evaluation should include a complete blood count (CBC); comprehensive metabolic panel; 25(OH)D, intact parathyroid hormone (PTH); phosphate; and a 24-hour urine collection for calcium, sodium, and creatinine. The 24-hour urine calcium collection must occur after the patient is vitamin D replete and has been on a reasonable calcium intake (1,000-1,200 mg/day) for at least 2 weeks. If the patient is receiving thyroid hormone or there is a suspicion for hyperthyroidism, thyroid-stimulating hormone should also be measured. If there is clinical or biochemical evidence of malabsorption, celiac antibodies should be obtained. Serum and urine protein electrophoresis could be obtained if there is a suspicion for multiple myeloma (e.g., non-PTH mediated hypercalcemia).

4.Q2.2. Vertebral Fracture Detection

Vertebral fracture is the most common osteoporotic fracture and indicates a high risk for future fractures, even when the T-score does not meet the threshold for osteoporosis. Prevalent fractures, therefore, may change an individual's diagnostic classification, estimated risk of future fractures, and clinical management. The majority of vertebral fractures, however, remain undetected unless specifically sought by imaging techniques (spine x-ray or vertebral fracture assessment, VFA) (54 [EL 4; review NE]). VFA, a technique to assess vertebral fractures with DXA technology, can often be done at the same time with DXA (55 [EL 3; CSS], 56 [EL 3; CSS], 57 [EL 3; CSS]). Both historical and prospective height loss have been associated with a new vertebral fracture (58 [EL 2; PCS], 59 [EL 3; CSS]). Lateral spine imaging with standard radiography or VFA with DXA is indicated when T-score is <–1.0 and 1 or more of the following is present:

- Women aged ≥70 years or men aged ≥80 years
- Historical height loss >4 cm (>1.5 inches)
- Self-reported but undocumented prior vertebral fracture
- Glucocorticoid therapy equivalent to ≥5 mg prednisone or equivalent per day for ≥3 months (https://iscd.app.box.com/OP-ISCD-2015-Adult)

In patients with unexplained height loss or back pain, thoracic and lumbar spine radiography or VFA by DXA is indicated if prevalent vertebral fractures would alter clinical management. Although these height loss thresholds have >90% specificity, the sensitivity for detecting prevalent vertebral fractures is low. Other indications for vertebral radiographs include kyphosis and systemic glucocorticoid therapy, both of which are associated with

Table 11
Causes of Secondary Osteoporosis in Adults

Endocrine or metabolic causes	Nutritional/GI conditions	Drugs	Disorders of collagen metabolism	Other
Acromegaly Diabetes mellitus Type 1 Type 2 Growth hormone deficiency Hypercortisolism Hyperparathyroidism Hyperthyroidism Hypogonadism Hypophosphatasia Porphyria Pregnancy	Alcoholism Anorexia nervosa Calcium deficiency Chronic liver disease Malabsorption syndromes/ malnutrition (including celiac disease, cystic fibrosis, Crohn's disease, and gastric resection or bypass) Total parenteral nutrition Vitamin D deficiency	Antiepileptic drugs[a] Aromatase inhibitors Chemotherapy/ immunosuppressants Depo-Provera Glucocorticoids Gonadotropin-releasing hormone agents Heparin Lithium Proton pump inhibitors Selective serotonin reuptake inhibitors Thiazolidinediones Thyroid hormone (in supraphysiologic doses)	Ehlers-Danlos syndrome Homocystinuria due to cystathionine deficiency Marfan syndrome Osteogenesis imperfect	AIDS/HIV[a] Ankylosing spondylitis Chronic obstructive pulmonary disease Gaucher disease Hemophilia Hypercalciuria Immobilization Major depression Myeloma and some cancers Organ transplantation Renal insufficiency/ failure Renal tubular acidosis Rheumatoid arthritis Systemic mastocytosis Thalassemia

Abbreviations: AIDS = acquired immunodeficiency syndrome; GI = gastrointestinal; HIV = human immunodeficiency virus; GI = gastrointestinal.
[a] Phenobarbital, phenytoin, primidone, valproate, and carbamazepine have been associated with low bone mass.

Table 12
Laboratory Tests to Consider in Detecting Secondary Osteoporosis

Complete blood cell count
Serum chemistry, including calcium, phosphate, total protein, albumin, liver enzymes, alkaline phosphatase, creatinine, and electrolytes
24-h collection for calcium, sodium, and creatinine excretion (to identify calcium malabsorption or hypercalciuria)
Serum 25-hydroxyvitamin D
Additional tests if clinically indicated might include (but not limited to):
Serum intact parathyroid hormone concentration for possible primary or secondary hyperparathyroidism
Serum thyrotropin
Tissue transglutaminase antibodies for suspected celiac disease
Serum protein electrophoresis and free kappa and lambda light chains for suspected myeloma
Urinary free cortisol or other tests for suspected adrenal hypersecretion
Serum tryptase, urine N-methylhistidine, or other tests for mastocytosis
Bone marrow aspiration and biopsy to look for marrow-based diseases
Undecalcified iliac crest bone biopsy with double tetracycline labeling
Recommended for patients with bone disease and renal failure to establish the correct diagnosis and direct management
May be helpful in the assessment of patients with the following:
Suspected osteomalacia or mastocytosis when laboratory test results are inconclusive
Fracture without major trauma despite normal or high bone density
Vitamin D-resistant osteomalacia and similar disorders to assess response to treatment
Genetic testing for unusual features that suggest rare metabolic bone diseases

increased vertebral fracture risk. The sensitivity and reliability of standard radiography to assess BMD are poor, and this technique should not be used to diagnose osteoporosis in the absence of vertebral fractures.

4.Q2.3. How Are BTMs Used in the Initial Evaluation and Follow-up of Postmenopausal Osteoporosis?

BTMs provide a dynamic assessment of skeletal activity and are useful modalities for skeletal assessment. Although they cannot be used to diagnose osteoporosis, elevated levels can predict more rapid rates of bone loss (60 [EL 1; RCT, no blinding], 61 [EL 2; PCS], 62 [EL 2; PCS]) and are associated with increased fracture risk independent of BMD (63 [EL 2; PCS], 64 [EL 2; PCS]). In addition, these markers respond quickly to therapeutic intervention, and changes in markers have been associated with bone response to therapy and fracture risk reduction (65 [EL 1; RCT]). Their use in clinical practice, however, is limited by high in vivo and assay variability (e.g., urinary resorption markers), poor predictive ability in individual patients, and lack of evidence-based thresholds for clinical decision-making. In 2010, the International Osteoporosis Foundation (IOF) proposed that serum C-terminal telopeptide (S-CTX) and serum carboxy-terminal propeptide of type I collagen (PINP) be used as reference analytes for BTMs in clinical and observational studies (66 [EL 2; MNRCT]). Recently, the National Bone Health Alliance (NBHA) working in association with the American Association for Clinical Chemistry (AACC) have established that the preferred resorption marker is S-CTX and the preferred formation marker is PINP and have defined the steps necessary to enhance the science and clinical utility of BTMs (67 [EL 4; consensus NE]).

The most useful BTMs include the bone formation osteoblast-derived products and the bone resorption products of collagen degradation. Clinical trials have shown that early changes in BTMs are associated with long-term BMD changes in women taking antiresorptive (68 [EL 1; RCT]) or anabolic (69 [EL 1; RCT]) drugs. Significant reductions in BTMs have also been associated with fracture reduction (70 [EL 1; MRCT], 71 [EL 1; RCT], 72 [EL 2; PCS]). Antiresorptive therapy can likely be deemed effective if BTMs during therapy are at or below the median value for premenopausal women. The decrease in BTMs compared to pretreatment levels with oral and IV bisphosphonates can range from 30 to 50% (73 [EL 1; RCT]) and from 40 to 80% with denosumab (74 [EL 1; RCT]). Use of a bone resorption marker such as a fasting morning S-CTX may be helpful in evaluating nonresponders with bone loss or fractures on therapy or to identify patients with high bone turnover. An elevated S-CTX level is associated with high bone turnover and could represent malabsorption or poor compliance and the need for evaluation for causes of secondary osteoporosis. It must be noted, however, that a recent fracture will transiently raise BTMs. In summary, BTMs may be useful in certain situations for fracture risk assessment or determining medication compliance, drug absorption, or therapeutic efficacy.

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4.Q3. What Are Fundamental Factors for Bone Health?

4.Q3.1. How Can Bone Loss and Fractures Be Prevented?

Several lifestyle modifications may improve musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures. These include an adequate intake of calcium and vitamin D; lifelong participation in regular, weight-bearing, resistance exercise and balance-improving exercises to minimize falls; avoiding use of tobacco and excessive use of alcohol; and elimination of potential risk factors for falling. This "bone healthy" lifestyle is important for everyone, not just patients with osteopenia and osteoporosis.

Patients with osteoporosis may benefit from physical therapy or other activities and other nonpharmacologic measures to improve strength and reduce the risk of falls and fractures. Goals include the following:

- Optimize skeletal development and maximize peak bone mass at skeletal maturity
- Maintain skeletal mass and prevent age-related bone loss
- Preserve the structural integrity of the skeleton
- Prevent falls and fractures

4.Q3.2. Vitamin D

Vitamin D plays a major role in calcium absorption and bone health and may be important in muscle performance, balance, and falling risk. Moreover, optimal vitamin D status may enhance the response to bisphosphonate therapy (75 [EL 2; PCS]), increase BMD, and prevent fractures (76 [EL 3; CSS]). Many scientific organizations recommend intake of at least 1,000 IU of vitamin D per day for adults aged 50 years and older. The Institute of Medicine (IOM) suggests 4,000 IU of vitamin D per day as the safe upper limit in the general population (77 [EL 4; consensus NE], 78 [EL 4; consensus NE]).

Vitamin D deficiency is common in patients with osteoporosis (79 [EL 3; CSS]) and hip fracture (80 [EL 2; PCS]). It is advisable to measure serum 25(OH)D levels in patients at risk of deficiency, especially in those with osteoporosis (Grade B, BEL 2). The effectiveness of anti-osteoporosis treatment may be hindered by vitamin D deficiency. The dose of vitamin D needed to correct deficiency varies among individuals (81 [EL 4; review NE]). Recent results suggest doses greater than 1,000 IU or even 4,000 IU of vitamin D per day may be needed (82 [EL 1; RCT], 83 [EL 1; RCT]). In addition, patient factors including obesity, race or ethnicity, and history of transplant may influence vitamin D status and increase the necessary vitamin D dose to achieve adequate levels (84 [EL 1; RCT], 85 [EL 1; RCT], 86 [EL 1; RCT], 87 [EL 1; RCT], 88 [EL 2; retrospective analysis], 89 [EL 2; retrospective analysis], 90 [EL 2; PCS]).

An individual's vitamin D status is assessed by measuring serum 25(OH)D. The optimal 25(OH)D level is controversial; the AACE and Endocrine Society recommend serum 25(OH)D ≥30 ng/mL to define vitamin D sufficiency based on evidence that secondary hyperparathyroidism is increasingly common as 25(OH)D levels fall below 30 ng/mL (91 [EL 3; CSS], 92 [EL 1; MRCT]). Controversy about the optimal upper limit for serum 25(OH)D remains, and evidence of the safety of higher levels in different populations is not conclusive. Until further evidence is available, a reasonable upper limit is 50 ng/mL, based on levels in sun-exposed healthy young adults. Evidence from another randomized controlled trial (RCT) suggests no benefit in exceeding serum levels of 30 ng/mL (93 [EL 1; RCT])

A meta-analysis of studies in postmenopausal women found a significant reduction in hip and nonvertebral fractures with vitamin D supplementation at doses ≥700 to 800 IU/day (94 [EL 1; MRCT]). The Women's Health Initiative (WHI) study showed a small but significant increase in hip BMD (1%) in the group that received 1,000 mg of calcium and 400 IU of vitamin D per day (95 [EL 1; RCT]). In addition to the skeletal effects of vitamin D, some studies have also shown improvement in muscle strength, balance, and fall risk (96 [EL 2; MNRCT], 97 [EL 1; RCT], 98 [EL 1; RCT]), as well as survival (99 [EL 1; MRCT]).

Adults who are vitamin D insufficient or deficient (serum 25(OH)D 20-29 or <20 ng/mL, respectively) may be treated with 50,000 IU of vitamin D_2 or vitamin D_3 once a week or 5,000 IU vitamin D_2 or vitamin D_3 daily for 8 to 12 weeks to achieve a 25(OH)D blood level >30 ng/mL (78 [EL 4; consensus NE], 81 [EL 4; review NE]). This regimen should be followed by maintenance therapy of vitamin D_3 1,000 IU to 2,000 IU daily (or an appropriate dose to maintain an adequate target 25(OH)D blood level). A higher dose may be required in patients with obesity or malabsorption and those on medications affecting vitamin D metabolism, and may also be needed in other individuals. Alternatively, single, large doses of vitamin D (bolus dosing of vitamin D_3 ≥300,000 IU) may rapidly correct deficiencies and improve vitamin D status for up to 3 months (100 [EL 2; MNRCT]). Due to the limited amount of food products containing sufficient vitamin D (fresh salmon with up to 1,000 IU and shitake mushrooms with 1,600 IU), the authors recommend vitamin D supplementation.

4.Q3.3. Calcium

Adequate calcium intake is a fundamental aspect of any osteoporosis prevention or treatment program and part of a lifestyle for healthy bones at any age. The recommended daily calcium intake for various populations is outlined in Table 13 (77 [EL 4; consensus NE]). For adults aged 50 years and older, the recommended calcium intake

(including diet, plus calcium supplements, if necessary if dietary intake is insufficient) is 1,200 mg/day. Calcium supplementation has been shown to slightly increase BMD, and a recent meta-analysis from the NOF showed a 15% reduced risk of total fractures (summary relative risk estimate [SRRE], 0.85; 95% confidence interval [CI], 0.73-0.98) and a 30% reduced risk of hip fractures (SRRE, 0.70; 95% CI, 0.56-0.87) (101 [EL 1; MRCT]). Other studies have shown mixed results as far as calcium and fracture efficacy. This is likely due in part to problems with study design and patient compliance (95 [EL 1; RCT], 102 [EL 1; RCT], 103 [EL 1; MRCT], 104 [EL 1; RCT]).

The optimal intake and utility of calcium supplements is controversial. In a Swedish prospective longitudinal cohort, calcium intake (both dietary and supplemental) of more than 1,500 mg/day was associated with a hazard ratio of 1.40 (95% CI, 1.17-1.67) for all-cause mortality (105 [EL 2; PCS]). Three prospective cohort studies and a meta-analysis suggested increased risk of cardiovascular disease among calcium supplement users (106 [EL 1; RCT], 107 [EL 1; RCT], 108 [EL 1; RCT]). In contrast, low dietary calcium intake (<700 mg/day compared with 1,400 mg/day) has been associated with increased cardiovascular risks (109 [EL 2; PCS]). Other studies found no effect of calcium supplements on cardiovascular risk (110 [EL 1; RCT], 111 [EL 1; RCT]). A recent study of more than 9,000 participants followed for 10 years found that postmenopausal women taking 500 to 1,000 mg of supplemental calcium had a significant survival advantage over women not taking supplements (112 [EL 2; PCS]). Moreover, there was no increase or decrease in mortality in women taking more than 1,000 mg of supplemental calcium. A large study raised concerns about the risk of nephrolithiasis from calcium supplementation (95 [EL 1; RCT]); however, hypercalciuria may worsen with calcium supplementation, and participants in the study were not evaluated for renal calcium wasting. Also, the absolute risk of kidney stones was small (2.5% in the calcium-supplemented group versus 2.1% in the control group). In addition, the mean total calcium intake from diet and supplements in these subjects was higher than currently recommended. Patients with a history of nephrolithiasis should be evaluated for the etiology for renal stone formation or hypercalciuria prior to deciding about calcium supplementation. In summary, existing studies suggest that dietary calcium may be preferred over supplemental calcium and that total calcium intake should not exceed 1,500 mg/day (113 [EL 4; consensus NE]). Increasing calcium intake beyond the recommended levels has not been shown to be useful and may be harmful (114 [EL 4; review NE], 115 [EL 1; RCT], 116 [EL 4; NE], 117 [EL 1; RCT], 118 [EL 4; consensus NE]). The AACE, NOF, IOM, and Endocrine Society recommend that women aged 51 years or older consume 1,200 mg of calcium per day (77 [EL 4; consensus NE], 119 [EL 4; NE]).

It is important to obtain a dietary history to assess calcium intake prior to recommending calcium supplements. The average daily calcium intake among American adults is about half of what is recommended, with a median of approximately 600 mg/day (120 [EL 3; SS]). Patients with low dietary intake may increase their daily intake by consuming extra calcium-rich foods including dairy products. For individuals who are unable to increase dietary calcium due to lactose intolerance or lack of access to calcium-rich foods, calcium supplementation is an option.

Numerous calcium supplements are available. Calcium carbonate is generally the least expensive and requires the smallest number of tablets, due to a generous calcium content (40%). Calcium carbonate, however, may cause more gastrointestinal (GI) complaints (e.g., constipation and bloating) than calcium citrate, in the expert opinion of task force members. In addition, it requires gastric acid for absorption and is best absorbed when taken with meals. Calcium citrate is often more expensive than calcium carbonate, and requires more tablets to achieve the desired dose due to a lower calcium content (21%), but its absorption is not dependent on gastric acid, and it may be less likely to cause GI complaints. In addition to tablets, which can be large and difficult for some patients to swallow, calcium supplements are available as soft chews and gummy preparations. For optimal absorption, calcium supplementation should not exceed 500 to 600 mg per dose, irrespective of the preparation. The dose should be divided for patients requiring more than 600 mg calcium supplement daily.

It is advisable to assess calcium and vitamin D adequacy through laboratory evaluation prior to initiation of pharmacologic therapy for osteoporosis.

Table 13
Recommended Dietary Allowance for Calcium

Age	Sex	Recommended dietary allowance (mg/d)
0-6 mo	M + F	200
6-12 mo	M + F	260
1-3 y	M + F	700
4-8 y	M + F	1,000
9-18 y	M + F	1,300
19-50 y	M + F	1,000
51-70 y	M	1,000
51-70 y	F	1,200
71+ y	M + F	1,200

From Ross et al (77 [EL 4; consensus NE]). Reproduced with permission.

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4.Q3.3.1. Other supplements and nutrition considerations

Magnesium: Patients frequently question whether magnesium supplementation is needed, but no RCT has evaluated the effect of magnesium intake on fracture risk or BMD. Most people have adequate dietary intake of magnesium; however, individuals who are at risk for hypomagnesemia (e.g., those with GI malabsorption, chronic liver disease [including alcoholics], or renal tubular loss or those using proton pump inhibitors or diuretics long term) may benefit from magnesium supplementation. Magnesium may also help counteract constipation associated with calcium supplementation.

Although magnesium is required for adequate calcium absorption, if body stores are adequate, magnesium supplementation does not increase BMD (121 [EL 4; NE]). In fact, there is no evidence that adding magnesium to calcium tablets increases the absorption of calcium. One study showed that adding 789 to 826 mg of magnesium per day did not increase the rates of calcium absorption (122 [EL 3; CCS]).

Vitamins A and K and phytoestrogens: Excessive chronic intake of vitamin A (i.e., more than 10,000 IU daily) should be avoided, as this has been shown to have detrimental effects on bone (123 [EL 4; review NE]). Some data suggest that vitamin K (1 mg/day) may reduce bone turnover and loss in postmenopausal women (124 [EL 1; RCT]). However, not all studies replicate this finding, and further investigation is needed before vitamin K can be considered a part of the standard recommendation for osteoporosis prevention. "Natural" estrogens (isoflavones) are promoted to prevent bone loss, but there are no conclusive data to support the use of these agents for increasing bone density or decreasing fracture risk (125 [EL 1; RCT], 126 [EL 1; RCT], 127 [EL 1; RCT, small sample size, no placebo]).

Caffeine: Patients should be advised to limit caffeine intake to less than 1 to 2 servings (8-12 ounces/serving) of caffeinated drinks per day. Several observational studies have shown an association between caffeinated beverage consumption and fractures (128 [EL 2; PCS], 129 [EL 2; PCS], 130 [EL 2; NRCT]). Caffeine intake leads to a slight decrease in intestinal calcium absorption and increase in urinary calcium excretion, but the most important effect of caffeinated beverages is that, by replacing milk in the diet, they contribute to overall inadequate calcium intake in the U.S. population.

Protein: Adequate protein intake (U.S. recommended daily allowance, 0.8 g/kg) helps minimize bone loss among patients who have suffered hip fractures (131 [EL 4; review NE], 132 [EL 1; RCT, small sample size]). In one study, patients who received supplemental protein after hip fracture had shorter hospital stays and better functional recovery (132 [EL 1; RCT, small sample size]).

4.Q3.4. Alcohol

Excessive intake of alcohol is associated with increased fracture risk (133 [EL 2; PCS]). The mechanisms of increased fractures from alcohol are multifactorial and include a negative effect on bone formation, a predisposition to falls, calcium deficiency, and chronic liver disease. Chronic liver disease, in turn, predisposes to vitamin D deficiency. Postmenopausal women at risk for osteoporosis should be advised against consuming more than 3 drinks daily, with 1 drink equivalent to 120 mL of wine, 30 mL of liquor, or 260 mL of beer (133 [EL 2; PCS], http://www.shef.ac.uk/FRAX/).

4.Q3.5. Smoking

Multiple studies have shown that cigarette smoking increases osteoporotic fracture risk and should therefore be avoided (134 [EL 2; CCS], 135 [EL 3; CSS]). The exact mechanism is unclear but may relate to increased metabolism of endogenous estrogen or direct effects of cadmium on bone metabolism. No prospective studies have been performed to determine whether smoking cessation reduces fracture risk, but a meta-analysis showed a higher risk of fractures in current smokers compared with previous smokers (136 [EL 2; MNRCT]). All smokers should be counseled on smoking cessation. The use of tobacco products is detrimental to the skeleton, as well as to overall health.

4.Q3.6. Exercise

Regular weight-bearing exercise (e.g., walking 30-40 minutes per session, plus back and posture exercises for a few minutes, 3-4 days per week) should be advocated throughout life. Studies on early postmenopausal women have shown that strength training leads to small yet significant changes in BMD; a meta-analysis of 16 trials including 699 subjects showed a 2% improvement in lumbar spine BMD in the group that exercised compared with the group that did not (137 [EL 2; MNRCT]). Among the elderly, these exercises help slow bone loss attributable to disuse, improve balance and muscle strength, and ultimately help reduce the risk of falls (138 [EL 2; PCS], 139 [EL 2; MNRCT], 140 [EL 2; MNRCT], 141 [EL 1; MRCT], 142 [EL 1; MRCT]).

Effects of exercise on BMD are modest, but a recent meta-analysis concluded that the exercise induced improvements in lumbar spine and femoral neck BMD would reduce osteoporosis fracture risk by approximately 10% (143 [EL 1; MRCT]). The reduction in fall risk is likely more important than the effects of exercise on BMD, as approximately 95% of hip fractures are due to a fall (144 [EL 4; NE]). Both home and group exercise programs

reduce falls (145 [EL 1; MRCT]); exercises that challenge balance and improve trunk muscle strength produce a greater reduction in fall risk (142 [EL 1; MRCT], 146 [EL 2; MNRCT]).

Individuals with severe osteoporosis should use caution when engaging in activities that involve forward spine flexion and rotation, lifting heavy weights, or even side bending of the trunk, because these maneuvers exert compressive forces on the spine that may lead to fracture.

Weight-bearing and resistance exercise can improve agility, strength, posture, and balance, which may reduce the risk of falls. In addition, exercise may modestly increase bone density. The AACE strongly endorses lifelong physical activity for cardiovascular health, osteoporosis prevention, and overall health. Weight-bearing exercise includes walking, jogging, tai chi, stair climbing, dancing, and other activities. Muscle-strengthening exercise includes weight training and other resistive movements. A clinician's evaluation is recommended before initiating an exercise program in an individual with osteoporosis. Physical therapy plays an important role in the effort to mitigate sarcopenia and reduce fall risk.

4.Q3.7. Fall Prevention

Falls are the precipitating cause of most fractures, and an effective osteoporosis treatment regimen must include a program for fall prevention. All patients should be counseled on fall prevention. Particularly predisposed are individuals who are older or frail, have a stroke history, or are on medications that decrease mental alertness. Although several interventions have been shown to reduce the risk of falling, none have been shown to reduce the risk of fractures, though it seems logical that they would.

Approximately one-third of people aged 65 years or older and roughly half of those aged 80 years or older fall each year (147 [EL 2; PCS], 148 [EL 2; PCS]). An estimated 20 to 30% of persons who fall suffer moderate-to-severe injuries (149 [EL 4; NE], 150 [EL 3; SS]). A higher percentage of women with osteoporosis have a history of falling within the prior year than women without osteoporosis (151 [EL 3; CSS]). This association has been ascribed to shared risk factors such as age, muscle weakness, and sedentary lifestyle (152 [EL 4; NE]). Indeed, a recent French guideline supports BMD measurement in individuals at high risk of falling (152 [EL 4; NE], 153 [EL 4; consensus, NE]).

Table 14 lists measures that can be taken to avoid falls at home. Individuals who are older or frail, have recently been hospitalized, have suffered a prior stroke, are receiving medications that decrease mental alertness, or have cognitive impairment are particularly vulnerable (154 [EL 2; PCS]). In addition to minimizing the use of medications that impair balance, appropriate correction of visual impairment may improve mobility and reduce risk of falls. Several interventions reduce risk of falls (141 [EL 1; MRCT], 145 [EL 1; MRCT], 155 [EL 1; MRCT]), and a meta-analysis found decreased fracture risk with exercise, but fracture numbers were small and the possibility of publication bias was raised (156 [EL 2; MNRCT]). The relationship of vitamin D with falls is unclear; some, but not all, meta-analyses found that vitamin D supplementation reduced fall risk (96 [EL 2; MNRCT], 157 [EL 1; MRCT]), and an RCT failed to find a decrease in falls with vitamin D (158 [EL 1; RCT]). Annual high-dose vitamin D, however, was associated with an increased risk of falls (159 [EL 1; RCT]). Rigorous prospective studies are needed to clarify the effect of vitamin D deficiency on fall risk. In the interim, assurance of a normal 25(OH)D status in patients with osteoporosis is appropriate.

4.Q3.8. Hip Protectors

Hip protectors do not reduce the risk of falling, but they should reduce the risk of fracture. Positive results have been seen in some but not all trials, and compliance is poor (160 [EL 2; MNRCT, quasi-randomized included], 161 [EL 1; MRCT], 162 [EL 3; SS], 163 [EL 2; PCS], 164 [EL 2; RCCS], 165 [EL 2; MNRCT, quasi-randomized included]). A recent Cochrane review found poor long-term adherence with no effect on hip fracture risk in community-dwelling adults. This review suggested that hip protectors probably reduce hip fracture risk among people in nursing care or residential care settings (166 [EL 2; MNRCT, quasi-randomized included]). Hip protectors may be considered for patients with prior hip fracture and those who are slender or frail, have fallen in the past, and have significant risk factors for falling due to postural hypotension or imbalance, regardless of whether they have osteoporosis.

Hip protectors may protect an individual from injuring the hip in the event of a fall (162 [EL 3; SS]), but whether they effectively reduce hip fractures is inconclusive (167 [EL 2; MRCT, quasi-RCTs included]). There is additional

Table 14
Measures for Prevention of Falls

Anchor rugs
Minimize clutter
Remove loose wires
Use nonskid mats
Install handrails in bathrooms, halls, and long stairways
Light hallways, stairwells, and entrances
Encourage patient to wear sturdy, low-heeled shoes
Recommend hip protectors for patients who are predisposed to falling
Keep all items within reach and avoid using stepstools

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uncertainty regarding which hip protector to use, as most marketed products have not been tested in RCTs. Several studies have illustrated the usefulness of improving balance and BMD using vibration stands, although the results are conflicting (168 [EL 4; NE], 169 [EL 4; review NE], 170 [EL 2; NRCT]).

4.Q3.9. Physical Therapy

Elderly patients with significant kyphosis, back discomfort, and gait instability may benefit from referral for physical therapy. A treatment plan that focuses on weight-bearing exercises, back strengthening, and balance training with selective orthotic use may help reduce discomfort, prevent falls and fractures, and improve quality of life (171 [EL 1; MRCT]). Table 15 summarizes the recommendations for lifestyle modifications.

Table 15
Recommendations Regarding Lifestyle Issues

Ensure adequate calcium intake
Ensure adequate vitamin D intake
Consume a balanced diet
Regularly perform weight-bearing and balance exercises
Avoid tobacco use
Limit alcohol consumption
Take measures to avoid falls
Consider use of hip protectors

4.Q4. Who Needs Pharmacologic Therapy?

The AACE strongly recommends pharmacologic therapy for the following patients:

a. Those with osteopenia or low bone mass and a history of fragility fracture of the hip or spine.
b. Those with a T-score of –2.5 or lower in the spine, femoral neck, total hip, or 33% radius.
c. Those with a T-score between –1.0 and –2.5 in the spine, femoral neck, total hip, or 33% radius, if the FRAX® 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% (in the U.S.) or above the country-specific threshold in other countries or regions.

References:

a. (172 [EL 1; RCT], 173 [EL 1; RCT], 174 [EL 1; RCT], 175 [EL 1; RCT], 176 [EL 1; RCT], 177 [EL 1; RCT], 178 [EL 1; RCT], 179 [EL 1; RCT], 180 [EL 1; RCT, partial blinding], 181 [EL 1; RCT])
b. (175 [EL 1; RCT], 179 [EL 1; RCT], 180 [EL 1; RCT, partial blinding], 182 [EL 2; PCS], 183 [EL 1; RCT], 184 [EL 4; NE], 185 [EL 1; RCT], 186 [EL 1; RCT], 187 [EL 1; RCT], 188 [EL 1; RCT], 189 [EL 1; RCT], 190 [EL 1; RCT], 191 [EL 1; RCT])
c. (192 [EL 4; opinion NE], 193 [EL 4; guideline], 194 [EL 3; SS], 195 [EL 3; SS])

4.Q4.1. Decision-making on Pharmacologic Therapy

Therapeutic intervention thresholds vary among countries based on the cost-effectiveness of treatments, the approach taken to setting the intervention threshold, and available therapeutic modalities and resources (192 [EL 4; opinion NE], 196 [EL 3; CSS]). To be most effective, the clinical experience of the treating physician is incorporated with best practices in a given country and locally available resources. Potential risks and benefits of available osteoporosis interventions should be reviewed and incorporated into local guidelines, while allowing physicians to individualize treatment decisions for patient preferences and circumstances.

4.Q5. What Medication Should Be Used to Treat Osteoporosis?

A number of agents are approved by the U.S. Food and Drug Administration (FDA) for prevention and/or treatment of postmenopausal osteoporosis as shown in Table 16. Full prescribing information should be reviewed before recommending any specific agent.

There are no-head-to-head trials with a preplanned endpoint of fractures comparing one drug with another. Four agents (alendronate, risedronate, zoledronic acid, and denosumab) have evidence for "broad spectrum" antifracture efficacy (spine, hip, and nonvertebral fracture risk reduction) and should generally be considered as initial options for most patients who are candidates for treatment (Table 17) (174 [EL 1; RCT], 175 [EL 1; RCT], 189 [EL 1; RCT], 197 [EL 1; RCT], 198 [EL 1; RCT]). Those who have lower or moderate fracture risk (e.g., younger postmenopausal women with no prior fractures and moderately low T-scores) can be started on oral agents. Injectable agents such as teriparatide, denosumab, or zoledronic acid can be considered as initial therapy for those who have the highest fracture risk (e.g., older women who have had multiple vertebral fractures or hip fractures, or who have very low T-scores), those who have upper GI problems and might not tolerate oral medication, those who have lower GI problems and might not absorb oral medications, and for patients who have trouble remembering to take oral medications or coordinating an oral bisphosphonate with other oral medications or their daily routine. For patients at high risk of spine fracture but not at risk for hip or nonvertebral fractures, ibandronate and raloxifene may be appropriate, and raloxifene has a "side benefit" of reducing breast cancer risk. (179 [EL 1; RCT], 180 [EL 1; RCT, partial blinding], 189 [EL 1; RCT], 199 [EL 1; RCT], 200

[EL 1; RCT], 201 [EL 1; RCT], 202 [EL 1; RCT], 203 [EL 2; RCCS]).

Denosumab is the agent of choice for patients with renal insufficiency, but this agent is not recommended for dialysis patients or those with stage 5 kidney disease due to the high risk of hypocalcemia.

4.Q5.1. How Are Bisphosphonates Used?

First introduced in the 1990s, bisphosphonates have been the most widely used drugs for treating osteoporosis. Bisphosphonates bind to hydroxyapatite in bone, particularly at sites of active bone remodeling, and reduce the activity of bone-resorbing osteoclasts. In the U.S., 4 bisphosphonates are available (alendronate, ibandronate, risedronate, and zoledronic acid) (173 [EL 1; RCT], 174 [EL 1; RCT], 175 [EL 1; RCT], 189 [EL 1; RCT], 197 [EL 1; RCT], 204 [EL 1; RCT]); 3 of the 4 (alendronate, risedronate, and zoledronic acid) have evidence for broad-spectrum antifracture efficacy (174 [EL 1; RCT], 175 [EL 1; RCT], 189 [EL 1; RCT], 197 [EL 1; RCT]). All of these agents are available as generic preparations.

Orally administered bisphosphonates (most commonly used are alendronate 70 mg weekly and risedronate 35 mg weekly or 150 mg monthly) must be taken after a prolonged fast (usually fasting overnight and taken in the morning soon after arising) and swallowed with a full glass of water (with at least a 30-minute wait after ingestion before other medications, food, or beverages other than water). Orally administered bisphosphonates should be used with caution in patients with active esophageal disease. Other contraindications to oral bisphosphonate administration include the inability to follow the dosing regimen for oral use (i.e., inability to remain upright for 30-60 minutes), the presence of anatomic or functional esophageal abnormalities that might delay tablet transit (e.g., achalasia, stricture, or dysmotility), and the presence of documented or potential GI malabsorption (e.g., gastric bypass procedures, celiac disease, Crohn's disease, infiltrative disorders, etc.). A special formulation of risedronate (Atelvia®) can be taken with or after food and, because the delayed-release coating does not dissolve until after exiting the stomach, may be considered for patients with upper GI problems. The incidence of upper GI adverse events, however, is not lower with the coated preparation compared with the conventional preparation (205 [EL 4; NE]).

Contraindications to oral or IV bisphosphonate therapy include drug hypersensitivity or hypocalcemia. Bisphosphonates should be used with caution, if at all, in patients with reduced kidney function (GFR <30 mL/min for risedronate and ibandronate or <35 mL/min for alendronate and zoledronic acid) (206 [EL 4; CPG NE]). Rapid IV administration of nitrogen-containing bisphosphonates may cause transient or permanent decreases in kidney

Table 16
Drugs Approved by the US Food and Drug Administration for Prevention and Treatment of Postmenopausal Osteoporosis[a]

	Postmenopausal osteoporosis	
Drug	**Prevention**	**Treatment**
Alendronate (Fosamax)	5 mg PO daily 35 mg PO weekly	10 mg PO daily 70 mg PO weekly[b] 70 mg + D[c]
Calcitonin (Miacalcin, Fortical)	—	200 IU intranasally once daily, or 100 IU SQ qod
Denosumab (Prolia)	—	60 mg SQ every 6 mo
Estrogen (multiple formulations)	Multiple regimens	—
Ibandronate (Boniva, generic form)	2.5 mg PO daily 150 mg PO monthly	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 mo
Raloxifene (Evista)	60 mg PO daily	60 mg PO daily
Risedronate (Actonel, Atelvia, generic form)[a]	5 mg PO daily 35 mg PO weekly 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 150 mg PO monthly
Teriparatide (Forteo)	—	20 μg SQ daily
Zoledronic acid (Reclast, generic infusion form)	5 mg IV every 2nd y	5 mg IV once yearly

Abbreviations: IV = intravenous; PO = per os; qod = every other day; SQ = subcutaneous.
[a] Please review the package inserts for specific prescribing information.
[b] Fosamax 70 mg is available as both a tablet and a unit dose liquid. Alendronate (generic Fosamax) is available.
[c] Fosamax Plus D is a tablet containing 70 mg of alendronate and 2,800 IU or 5,600 IU of vitamin D for weekly administration.
[d] Risedronate 150 mg once monthly tablet is available.

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function, especially in older patients, with dehydration, or in those using diuretics or potentially nephrotoxic drugs (207 [EL 4; NE], 208 [EL 3; SS], 209 [EL 4; NE]).

IV or high-dose oral administration of nitrogen-containing bisphosphonates may cause acute-phase reactions in up to 30% of patients receiving their first dose (210 [EL 2; PCS]). These reactions are characterized by fever and muscle aches—a flu-like illness—lasting several days. Acetaminophen given 1 to 2 hours before treatment may reduce the likelihood of these reactions and can also be given to treat the symptoms.

Although not seen in clinical trials, there are postmarketing reports of patients treated with an oral or IV bisphosphonate who experienced bone, joint, or muscle complaints that may be severe (211 [EL 3; SS]) but usually resolve on discontinuation. The possible association between orally administered bisphosphonates and esophageal cancer has been explored. One study suggested no increased risk (212 [EL 2; PCS]), and another suggested that risk was increased with long-term use but small in absolute terms—from 1 case per 1,000 in untreated subjects to 2 cases per 1,000 with bisphosphonate use of 5 years or more (213 [EL 2; RCCS]). The FDA concluded that there is no definite association between bisphosphonate use and esophageal cancer (214 [EL 4; review NE]). Atrial fibrillation as a serious adverse event was noted in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (189 [EL 1; RCT]) but was not seen in other trials of zoledronic acid or other bisphosphonates and is thought by the FDA to be a chance finding (215 [EL 4; NE]).

Osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFFs) are safety concerns with bisphosphonates but with other agents as well and will be discussed elsewhere.

4.Q5.2. How Is Denosumab Used?

Denosumab is a fully human monoclonal antibody that prevents receptor activator of nuclear factor kappa-B ligand (RANKL) from binding to its receptor, RANK, thereby reducing the differentiation of precursor cells into mature osteoclasts and decreasing the function and survival of activated osteoclasts. For treatment of osteoporosis, the dose is 60 mg by subcutaneous (SQ) injection every 6 months. In the pivotal clinical trial of 7,808 women, denosumab showed "broad spectrum" antifracture efficacy. Studies of up to 8 years' duration indicate a good safety profile. Calcium deficiency, vitamin D deficiency, and secondary hyperparathyroidism should be corrected prior to initiating denosumab treatment to avoid precipitating hypocalcemia (179 [EL 1; RCT], 199 [EL 1; RCT], 200 [EL 1; RCT], 201 [EL 1; RCT], 202 [EL 1; RCT]). In a 3-year, pivotal, placebo-controlled trial there was an imbalance in some low-frequency events (cellulitis, pancreatitis, and endocarditis) that did not seem causally related to denosumab treatment (198 [EL 1; RCT]) and have not been reported with higher-dose denosumab (Xgeva®) used to treat patients with advanced cancer.

When treatment with denosumab was stopped after 2 years, BMD decreased to baseline values and BTMs increased to values above baseline by 12 months after discontinuation (200 [EL 1; RCT]), so a "drug holiday" is not recommended with denosumab.

4.Q5.3. How Is Raloxifene Used?

Raloxifene is approved by the FDA for prevention and treatment of postmenopausal osteoporosis, as well as for the reduction of risk of breast cancer in women with postmenopausal osteoporosis or at high risk of breast cancer

Table 17
Summary of Evidence for Fracture Risk Reduction

	Fracture risk reduction		
Drug	**Vertebral**	**Nonvertebral**	**Hip**
Alendronate (Fosamax) (197 [EL 1; RCT])	Yes	Yes	Yes
Calcitonin (Miacalcin, Fortical) (177 [EL 1; RCT])	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Denosumab (Prolia) (198 [EL 1; RCT])	Yes	Yes	Yes
Ibandronate (Boniva) (173 [EL 1; RCT], 204 [EL 1; RCT])	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Raloxifene (Evista) (178 [EL 1; RCT])	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Risedronate (Actonel, Atelvia) (174 [EL 1; RCT], 175 [EL 1; RCT])	Yes	Yes	Yes
Teriparatide (Forteo) (180 [EL 1; RCT, partial blinding], 203 [EL 2; RCCS])	Yes	Yes	No effect demonstrated[a]
Zoledronic acid (Reclast) (189 [EL 1; RCT])	Yes	Yes	Yes

[a] The lack of demonstrable effect at these sites should be considered in the context that the studies may not have been adequately powered.

(216 [EL 4, NE]) and is available in a generic formulation. The approved dose is 60 mg daily. Raloxifene is contraindicated in women of childbearing potential, those who have had venous thromboembolic disease, and those who are known to be hypersensitive to any component of raloxifene tablets (216 [EL 4, NE]). Raloxifene has been shown to reduce the risk of spine fracture (178 [EL 1; RCT]), but neither nonvertebral nor hip fracture efficacy has been demonstrated (178 [EL 1; RCT], 217 [EL 1; RCT]).

A significant reduction in breast cancer was seen in an osteoporosis trial with raloxifene (178 [EL 1; RCT], 218 [EL 1; RCT]). This finding was confirmed in a larger trial of women at high risk of breast cancer (219 [EL 1; RCT]). Of note, raloxifene is not indicated for the treatment of invasive breast cancer, for reduction of the risk of recurrence of breast cancer, or for reduction of the risk of noninvasive breast cancer.

Because raloxifene has not been shown to reduce hip or nonvertebral fracture, it may not be the best treatment option in many patients with osteoporosis. However, for patients with low BMD in the spine but not in the hip (discordance), it may be an acceptable initial choice, and it may be particularly attractive in these patients who are also at high risk of breast cancer. Although we recommend against the combined use of 2 antiresorptive drugs for treatment of osteoporosis, patients at high risk of hip fracture who are taking raloxifene with the main goal of reducing their risk of breast cancer can reasonably have a bisphosphonate or denosumab added for hip fracture risk reduction. The risk-benefit ratio of combined treatment with raloxifene and bisphosphonate or denosumab is unclear, as data on fracture risk reduction and adverse events such as ONJ and AFF are lacking.

Raloxifene is associated with an approximately 3-fold increase in occurrence of venous thromboembolic diseases (similar to estrogen), although the absolute risk is low (220 [EL 1; RCT]). Other side effects include menopausal symptoms (e.g., hot flashes and night sweats) and leg cramps (220 [EL 1; RCT]).

When use of raloxifene is stopped, the skeletal benefits appear to be lost fairly quickly, during the following 1 or 2 years.

4.Q5.4. How Is Calcitonin Used?

Injectable and nasal spray recombinant salmon calcitonin are approved by the FDA for treatment of postmenopausal osteoporosis (221 [EL 4; NE], 222 [EL 4; NE]). The approved dosage of injectable calcitonin for treatment of postmenopausal osteoporosis is 100 IU daily given SQ or intramuscularly. The approved dose of nasal spray calcitonin is 200 IU (1 spray) daily. Injectable calcitonin is available in a sterile solution. The main contraindication to use of calcitonin is drug hypersensitivity (221 [EL 4; NE], 222 [EL 4; NE]). Skin testing is recommended before use in patients with suspected sensitivity to the drug.

There are no published studies with injectable calcitonin that show antifracture efficacy. Nasal spray calcitonin (200 IU daily) has been shown to reduce the risk of new vertebral fractures in women with postmenopausal osteoporosis, but neither a lower dose (100 IU daily) nor a higher dose (400 IU daily) was effective in reducing vertebral fractures and the approved dose was not shown to reduce hip or nonvertebral fracture risk (177 [EL 1; RCT]). Calcitonin produces a minimal increase in BMD in the spine in women >5 years after menopause onset but does not increase BMD at sites other than the spine (177 [EL 1; RCT]).

A 5-year clinical study indicated a good safety profile (177 [EL 1; RCT]). Common side effects of parenterally administered calcitonin include nausea, local inflammatory reactions at the injection site, and vasomotor symptoms including sweating and flushing. The most common side effect of nasally administered calcitonin is nasal discomfort including rhinitis, irritation of the nasal mucosa, and occasional epistaxis. Use of calcitonin with either route of administration is well tolerated (221 [EL 4; NE], 222 [EL 4; NE]).

Safety and efficacy data are available through 5 years (177 [EL 1; RCT]). When calcitonin is stopped, the skeletal benefits are lost fairly quickly, during the subsequent 1 or 2 years.

Primarily because more effective agents are available to increase bone density and reduce fracture risk, few patients are using calcitonin as long-term treatment for osteoporosis. Because of a suggested analgesic effect (223 [EL 2; NRCT], 224 [EL 1; RCT, small sample], 225 [EL 1; RCT, no placebo, small sample], 226 [EL 1; RCT, small sample], 227 [EL 1; RCT]), short-term prescriptions are often given to patients with acute painful vertebral fractures with hopes of an analgesic effect.

A meta-analysis of 21 RCTs of nasal spray calcitonin and an investigational oral calcitonin formulation showed a higher incidence of malignancy in the calcitonin-treated patients (215 [EL 4; NE]). The FDA did not find sufficient evidence to establish a causal relationship between calcitonin administration and cancer risk, but they urged that the risks and benefits of the various osteoporosis treatment options be weighed for individual patients.

4.Q5.5. What Is the Role of Estrogen and Menopausal Hormone Therapy in Treatment of Postmenopausal Osteoporosis?

Although once considered the "treatment of choice" for postmenopausal osteoporosis, estrogen was never specifically approved for this use. It is approved by the FDA for prevention of postmenopausal osteoporosis with the

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added caveat, "when prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom nonestrogen medications are not considered to be appropriate" (228 [EL 4; NE]). This agent improved bone density and vasomotor symptoms without stimulating breast or uterine tissue.

When estrogen is prescribed for a patient with an intact uterus, a progestin should also be used, either daily or cyclically, to protect against endometrial stimulation. A combination of conjugated equine estrogens (0.45 mg) and the selective estrogen receptor modulator bazedoxifene (20 mg) has now been approved by the FDA for the prevention of postmenopausal osteoporosis (229 [EL 1; RCT]). In the WHI, conjugated equine estrogen (0.625 mg daily) with or without medroxyprogesterone acetate was shown to reduce the risk of fractures of the spine, hip, and nonvertebral sites in postmenopausal women (230 [EL 1; RCT], 231 [EL 1; RCT]). There has been considerable controversy regarding the extraskeletal effects of estrogen, particularly with regard to cardiovascular disease and breast cancer. Current recommendations are to use estrogen for the relief of menopausal symptoms in the lowest dose necessary and for the shortest time possible. For women who are appropriately treated with long-term estrogen (or combination estrogen/progestin) therapy, these agents may be sufficient, but they can also be used in conjunction with other medications for osteoporosis (e.g., bisphosphonates, denosumab, or teriparatide) based on clinical needs and judgment.

4.Q5.6. How Is Teriparatide Used?

Teriparatide—recombinant human PTH(1-34)—is considered an "anabolic" agent; by contrast, the medications discussed above appear to work by reducing bone resorption. It is approved by the FDA for initial treatment of women with postmenopausal osteoporosis who are at high risk of fracture or have failed or been intolerant of previous osteoporosis therapy (232 [EL 4; NE]). Teriparatide is also approved for treatment of glucocorticoid-induced osteoporosis. The dose is 20 mcg once daily SQ. It is prudent to measure serum calcium, PTH, and 25(OH)D levels before treatment with the drug.

Teriparatide has been shown to reduce the risk of vertebral and nonvertebral fractures in women with postmenopausal osteoporosis (180 [EL 1; RCT, partial blinding]). The incidence of hip fracture was low in this trial, so whether teriparatide protects against hip fracture is unknown. Teriparatide dramatically increases BMD in the spine but has little effect on BMD in the hip or forearm (180 [EL 1; RCT, partial blinding]). Patients who lose BMD in the hip with teriparatide treatment are still protected against vertebral fracture compared with placebo (203 [EL 2; RCCS]).

Side effects of teriparatide are mild and transient and include nausea, orthostatic hypotension (which usually does not necessitate discontinuation of the drug, occurs in association with the first few doses, and responds to assumption of a recumbent posture), and leg cramps. Hypercalcemia, usually mild, asymptomatic, and transient, has been observed but is not common (232 [EL 4; NE]). Hypercalciuria may also rarely occur and may respond to calcium supplement dose modification. Serum calcium level should be drawn at least 16 hours after teriparatide administration.

Teriparatide has a boxed warning because of the occurrence of osteosarcomas in 1 strain of rats treated with very high doses (3-50 times higher than the human equivalent dose), starting at 2 weeks of age, and continued for their lifetimes (approximately 75 human-year equivalents) (233 [EL 4; NE]). Subsequent studies in the same strain of rats showed no development of malignant bone tumors with use of doses of teriparatide up to 3 times higher than the human equivalent dose (234 [EL 4; NE]). Because teriparatide caused an increased incidence of osteosarcomas in rats, it should not be used in patients at increased risk of osteosarcoma (those with Paget disease of bone, open epiphyses, a history of irradiation involving the skeleton, or an unexplained elevation of alkaline phosphatase level of skeletal origin) (232 [EL 4; NE]). The annual incidence of osteosarcoma in women aged 50 years or older in the general population is approximately 1 in 250,000. The actual incidence of osteosarcoma in users of teriparatide is unknown; there are rare reports, consistent with the background incidence (235 [EL 4; NE], 236 [EL 3; SCR]). Teriparatide should also not be administered to patients with primary or any form of secondary untreated or unresolved hyperparathyroidism (232 [EL 4; NE]). Teriparatide is not approved for use longer than 2 years' total duration (232 [EL 4; NE]).

When treatment with teriparatide is stopped, bone density declines quickly during the following year, although fracture reduction may persist for 1 or 2 years (237 [EL 2; PCS]). Use of alendronate after teriparatide therapy has been shown to prevent this loss and in some cases will be associated with a further increase in BMD (238 [EL 1; RCT]). Likely, other agents (e.g., zoledronic acid or denosumab) would work as well as alendronate and perhaps better.

4.Q5.7. What Is the Role of Strontium?

Strontium ranelate is approved for the treatment of osteoporosis in some countries but not the U.S. Due to evidence of increased cardiovascular risk and occurrence of severe Stevens-Johnson reactions, the European Medicines Agency (EMA) has recommended that strontium ranelate use be restricted to patients who cannot be treated with

other medicines approved for osteoporosis, and that these patients be evaluated regularly by their doctor and that treatment be stopped if patients develop heart or circulatory problems such as uncontrolled high blood pressure or angina. An increased risk of myocardial infarction was observed in pooled analyses of safety data from RCTs with strontium ranelate (239 [EL 4; NE], 240 [EL 3; SS]). This was not however, seen in postmarketing studies, prescription event monitoring, an observational cohort study (241 [EL 2; PCS]) or studies in prescription databases in the U.K. and Denmark (242 [EL 2; RCCS], 243 [EL 3; SS], 244 [EL 3; SS]).

Some patients in the U.S. are taking over-the-counter preparations that contain other salts of strontium (e.g., strontium citrate) in the hope that this might be useful to prevent or treat osteoporosis. Some of these products contain trivial doses of strontium or combine strontium with other compounds that compete for absorption. If a sufficient amount of strontium is absorbed and incorporated into the skeleton, a measurable increase in BMD may occur. However, the efficacy and safety of these products have not been evaluated in rigorous clinical trials. Although strontium ranelate has reasonable evidence for antifracture efficacy, much of the BMD increase observed in strontium-treated patients is attributable to incorporation of strontium (a heavy element) in bone matrix, rather than to any putative bone building effect of strontium (245 [EL 4; NE]). Therefore, the AACE recommends against the use of over-the-counter strontium products in osteoporosis management.

4.Q6. How Is Treatment Monitored?

Serial BMD testing may be done to determine if or when to initiate treatment and to monitor the response to treatment. In untreated patients, the frequency of testing depends on the results of the initial test (e.g., how close the patient is to an intervention threshold) and the likelihood of significant future bone loss. Age-related bone loss, which begins in the fifth decade of life, occurs at an average rate of 0.5 to 1.0% per year (246 [EL 2; PCS, small sample size]). Menopause-related bone loss, which begins 3 to 5 years before the last menstrual period and continues for 3 to 5 years after the cessation of menses, occurs at an average rate of 1 to 2% per year (247 [EL 2; PCS]). A more rapid bone loss (3 to 5% in a year) may occur in some women after natural menopause, after stopping postmenopausal estrogen therapy, or after initiation of glucocorticoid or aromatase inhibitor therapy (53 [EL 4; opinion NE]). A bone-loss calculator can be found at the ISCD website (www.iscd.org). One SD is a ~10% deviation from the young-adult mean. Thus, a 10% bone loss (which typically occurs over 10 to 20 years of age-related bone loss or 5 to 10 years of menopause-related bone loss) will result in a decrease of ~1.0 T-score unit.

For patients on treatment or with a baseline evaluation near a fracture intervention threshold, BMD testing every 1 to 2 years is often appropriate. This frequency of BMD testing may be appropriate in recently postmenopausal women, for whom rates of bone loss are increased, and in women of any age with other disorders or medications that adversely affect bone. The frequency of testing is individualized depending on the patient's clinical state (248 [EL 2; PCS]).

The goal of monitoring osteoporosis therapy is to identify those who have significant bone loss. In patients on treatment, stable or increasing BMD at the spine and hip indicates a satisfactory response (249 [EL 4; review NE]). If BMD decreases significantly in treated patients, they should be evaluated for noncompliance, secondary causes of osteoporosis, or use of medications that might cause bone loss (250 [EL 4; NE]).

Differences between BMD results may simply reflect the inherent variability of the test measurement; thus, testing facilities must calculate the least significant change (LSC) for relevant measurement sites to determine the magnitude of difference that represents a real change. This is determined using a facility's regular technologist(s), patients, and device (251 [EL 4; NE], 252 [EL 4; NE]). The ISCD has established guidelines for determining the number of patients and repetitive scans needed to determine the LSC (30 patients in duplicate or 15 patients in triplicate) (251 [EL 4; NE], 252 [EL 4; NE]). The LSC is usually set at the 95% confidence limit for change. The manufacturer's LSC should not be used, because it does not account for differences in patients who will be tested and the performance and skill of the technologist. If serial studies show a difference that exceeds the LSC, the probability that the difference is real is greater than 95%.

In addition to knowing the LSC, it is important to note that differences in regions of interest, local structural change, or skeletal artifacts may result in an apparent "change" in BMD that does not reflect true progression of bone loss or gain. Before accepting a report of significant loss, images and numeric results of the studies should be viewed to assess comparability.

The definition of a "nonresponder" to therapy is complex, and the proportion of nonresponders for different therapies varies. Treatment failure may be defined by a significant decrease in BMD or recurrent fractures in a patient who is compliant to therapy. In clinical trials, some patients experienced bone loss and/or fractures; however, these patients may still have benefited from treatment by preventing even greater bone loss or postponing the occurrence of fractures (249 [EL 4; review NE]). Nevertheless, it is reasonable that a patient with significant bone loss or 1 or more new fragility fractures be evaluated for compliance with medication, secondary causes of bone loss, and new medications or diseases that can cause bone loss.

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Furthermore, studies have shown that the change in BMD accounts for <20% of the fracture risk reduction following antiresorptive therapy (70 [EL 1; MRCT], 253 [EL 4; NE]). Finally, although it has been suggested that BMD monitoring might improve patient compliance, nonadherence to therapy usually occurs early (after 6-7 months), before the second BMD would be performed (254 [EL 3; survey SS]).

Ideally, BMD monitoring should occur at the same facility, using the same machine and, if possible, the same technologist as the previous DXA and should involve the same regions of interest (ROIs) for both the spine and hip. The distal one-third radius site is also acceptable, when spine and hip sites are not evaluable (6 [EL 4; review NE], 255 [EL 1; MRCT], 256 [EL 1; RCT]). Other peripheral sites (e.g., heel, finger, and tibia) should not be used for monitoring. Most third-party payers and some Medicare carriers financially support yearly BMD testing in appropriate circumstances (e.g., with a diagnosis of osteoporosis or high risk for rapid bone loss); all Medicare carriers financially support testing every 2 years. The AACE recommends a repeat DXA 1 to 2 years after initiation of therapy until bone density is stable, and longer intervals between testing with evidence of continued BMD stability, based on expert opinion. Because sites rich in trabecular bone such as the posterior-anterior spine are more metabolically active, a significant change is likely to occur earlier at the spine than at the hip.

Skeletal status can also be examined by assessing the development or progression of asymptomatic vertebral fractures, using lateral x-rays of the thoracic and lumbar spine or VFA. (55 [EL 3; CSS], 56 [EL 3; CSS], 57 [EL 3; CSS], 58 [EL 2; PCS], 59 [EL 3; CSS], 257 [EL 4; consensus NE], 258 [EL 4; consensus NE])

BTMs are useful for assessing patient compliance and efficacy of therapy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction, and significant increases indicate good response to anabolic therapy (249 [EL 4; review NE]).

4.Q7. What Is Successful Treatment of Osteoporosis?

Pharmacologic and nonpharmacologic treatments for osteoporosis aim to prevent fractures by improving bone strength, preventing falls, and reducing the impact force of falls. RCTs have demonstrated a reduction in fracture risk in patients with stable or increasing BMD receiving pharmacological therapy, in particular, use of bisphosphonates for osteoporosis treatment compared with those receiving placebo (174 [EL 1; RCT], 175 [EL 1; RCT], 189 [EL 1; RCT], 197 [EL 1; RCT]). In addition, larger increases in BMD may result in increased reduction of fracture risk; however, this association has not been consistently shown (259 [EL 1; RCT], 260 [EL 1; MRCT], 261 [EL 1; RCT]).

The goal of treatment is fracture prevention, but no treatment can completely eliminate the risk. A fracture during therapy is not necessarily a treatment failure, but it should trigger reconsideration of risk factors for fracture and possibly a change in treatment strategies. The risk of fracture is highest after a recent fracture and diminishes over time (34 [EL 4; review NE], 262 [EL 2; PCS]). The number, severity, and recency of vertebral fractures are directly correlated with the future fracture risk (263 [EL 2; PCS], 264 [EL 1; RCT]).

The concept that response to therapy is not necessarily the same as achieving an acceptable level of fracture risk has led to proposals for the development of osteoporosis treatment targets (265 [EL 4; opinion NE], 266 [EL 4; opinion NE]), as are used in the management of some other chronic silent diseases such as hypertension and diabetes. As a consequence, an American Society for Bone and Mineral Research (ASBMR)/NOF task force was formed to review the medical evidence, determine the feasibility of developing osteoporosis treatment targets, propose targets (if possible), and recommend an agenda for further study. At this time, treatment targets have not been identified.

When treatment is initiated due to a low DXA T-score (such as ≤–2.5) it is intuitive that the treatment target be a higher T-score. When treatment is started due to high fracture probability with an algorithm such as FRAX®, it is also intuitive that fracture probability should be reduced to a level that is less than the threshold for starting treatment, perhaps to a level that is similar to an age-matched person with normal BMD by WHO criteria and no clinical risk factors for fracture. A change in BTM is also a possible treatment target. There are strengths and weaknesses to each of these strategies, which have been described in detail elsewhere (265 [EL 4; opinion NE]). There are many challenges to identifying 1 or more treatment targets, including limited data on comparative effectiveness of therapeutic agents in reducing fracture risk, lack of consensus on what an acceptable level of fracture risk should be, and limited effectiveness of current therapeutic agents to reduce risk of fracture, particularly nonvertebral fractures. Osteoporosis treatment targets may achieve greater clinical utility as more data comparing fracture risk with different agents become available and drugs with a more robust antifracture effect are developed.

4.Q8. How Long Should Patients Be Treated?

4.Q8.1. What Are the Safety Concerns of Antiresorptive Therapy?

ONJ was first reported in patients with advanced cancer receiving high-dose bisphosphonate therapy. More recently, head-to-head trials in advanced cancer patients showed an incidence of 1 to 2% per year with zoledronic acid (at an annual dose 10 times higher than that used to

treat osteoporosis) and denosumab (at an annual dose 12 times higher than that used to treat osteoporosis). The incidence of ONJ is much lower with oral or IV bisphosphonate therapy for osteoporosis, on the order of 1/10,000 to 1/100,000 patients per year (267 [EL 4; review NE], 268 [EL 4; review NE], 269 [EL 4; consensus NE], 270 [EL 4; review NE]) and appears to be low with denosumab therapy for osteoporosis (179 [EL 1; RCT]). Risk factors include dental pathologic conditions, invasive dental procedures, and poor dental hygiene. An oral examination should be done in patients being considered for treatment with these agents; if significant dental issues are present, delaying the initiation of bisphosphonate or denosumab therapy until the dental issues have been corrected should be considered. For patients already receiving bisphosphonates or denosumab who require invasive dental procedures, there is no evidence that discontinuing or interrupting treatment will change the outcome or reduce the risk of ONJ. Nonetheless, stopping treatment should at least be considered for patients undergoing extensive invasive dental procedures (e.g., extraction of several teeth).

AFF of the subtrochanteric region is another rare event that seems to be increased with long-term bisphosphonate therapy (>5 years duration) but is rarely (if at all) seen with the higher doses used in advanced cancer (271 [EL 1; RCT], 272 [EL 2; RCCS], 273 [EL 4; review NE]). Such fractures are sometimes described as "chalk stick" because of their radiologic appearance. They occur after little or no trauma. A literature review of AFF cases by the ASBMR reported a history of prodromal groin or thigh pain in approximately 70% of patients with AFF, bilateral fractures and bilateral radiographic abnormalities in 28%, and delayed healing in 26% (273 [EL 4; review NE]). Any patient with a history of bisphosphonate therapy who presents with persistent thigh or groin pain should interrupt bisphosphonate treatment while appropriate imaging studies are performed. In the early stages, a lateral periosteal stress reaction may be seen radiologically. It has been hypothesized that these patients may have very low bone turnover, although this point has not been rigorously substantiated. Whether a direct etiologic relationship exists between ONJ or AFFs and bisphosphonate use is not clear (274 [EL 4; review NE], 275 [EL 3; CCS]). Evidence for atypical femoral shaft fractures was recently reviewed by an ASBMR task force (273 [EL 4; review NE], 276 [EL 4; review NE]). Subtrochanteric femur fractures are also seen in patients with low BMD not on bisphosphonates and with other therapies for osteoporosis, such as denosumab. A causal relationship has not been established (277 [EL 2; PCS]). Because these fractures can occur in patients not on any treatment, "atypical" fractures will be seen eventually with any agent, unless a new drug for osteoporosis prevents this type of fracture. Definitions and diagnostic criteria for ONJ and AFF are given in Table 18.

Table 18
ONJ and AFF: Definitions and Diagnostic Criteria (269 [EL 4; consensus NE], 273 [EL 4; review NE], 318 [EL 2; RCCS])

(ONJ)	The presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a healthcare professional
(AFF)	The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare
	Major features (at least 4 of 5) • The fracture is associated with minimal or no trauma, as in a fall from a standing height or less • The 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 • Complete 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 ("beaking" or "flaring")
	Minor features (none required) • Generalized increase in cortical thickness of the femoral diaphyses • Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh • Bilateral incomplete or complete femoral diaphysis fractures • Delayed fracture healing

Abbreviations: AFF = atypical femur fracture; ONJ = osteonecrosis of the jaw.

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A recent meta-analysis found an increased risk of new-onset atrial fibrillation among users of oral and IV bisphosphonates. Caution and close monitoring is advised among elderly patients with pre-existing cardiovascular disease, especially when IV bisphosphonates are used (278 [EL 2; MNRCT], 279 [EL 2; MNRCT]).

4.Q8.2. Bisphosphonate Holidays

Because bisphosphonates accumulate and may have a prolonged residence time in bone (and residual therapeutic effect after stopping), "bisphosphonate holidays" may be considered. A post hoc analysis of results from Fracture Intervention Trial (FIT) Long Term Extension (FLEX) Trial of 10 versus 5 years of alendronate assessed the influence of fracture status and T-score on treatment effect. Higher-risk women (those with T-score ≤–2.5) who stopped treatment had nearly twice as many nonvertebral fractures: 21 (28%) versus 16 (15%) with continued treatment (280 [EL 1; RCT]), suggesting that longer treatment is better for higher-risk patients. However, in the first 2 years, the Kaplan-Meier curves for clinical vertebral fractures showed no difference between those who stopped and those who continued, indicating a residual benefit. In the second extension of the HORIZON trial, postmenopausal women previously treated with zoledronic acid for 6 years were randomized to continue treatment or switched to placebo for an additional 3 years. Three morphometric vertebral fractures were reported with 9 years of treatments compared with 5 reported with 6 years of treatment. Clinical fractures were similar between the 2 groups, reported in 10 of the patients who continued treatment for 9 years and in 9 patients who received 6 years of therapy (71 [EL 1; RCT], 183 [EL 1; RCT], 281 [EL 1; RCT]). A 3-year extension study of the zoledronic acid arms of the HORIZON study showed significantly fewer morphometric spine fractures in patients who continued yearly zoledronic acid for 6 years versus those who switched to placebo after 3 years of treatment. No differences in clinical vertebral fractures or nonvertebral fractures, however, were noted (282 [EL 1; RCT]).

The AACE agrees with the recently published ASBMR algorithm for managements of patients on long-term bisphosphonate treatment that recommends that patients who are initially at high risk and remain at high risk receive a treatment duration of 10 years for an oral bisphosphonate (280 [EL 1; RCT], 283 [EL 4; consensus]) or 6 years for IV zoledronic acid (281 [EL 1; RCT], 282 [EL 1; RCT], 284 [EL 1; RCT]). The risk-benefit ratio for treatment beyond 10 years has not been investigated and remains unknown. For lower risk patients, a drug holiday can be considered after 5 years of stability on oral bisphosphonates or 3 years on IV zoledronic acid. No other treatment is needed during the bisphosphonate "holiday" for lower-risk patients but for higher-risk patients, teriparatide or a weaker antiresorptive drug such as raloxifene might be appropriate.

The optimal duration of a "bisphosphonate holiday" has not been established. Patient selection and monitoring during "bisphosphonate holidays" is important. The rank order for binding affinity for bone is zoledronic acid>alendronate>risedronate; logic suggests that the "holiday" might be longest after treatment with zoledronic acid, shortest after treatment with risedronate, and intermediate after treatment with alendronate (285 [EL 4; review]). In addition, consider resuming therapy in patients who experience fracture or show significant BMD loss. The rise in bone resorption markers (e.g., C- and N-terminal telopeptides) to pretreatment levels might be a signal that the "holiday" should be over, but this may not apply to patients with osteoporosis who had low bone resorption markers before treatment initiation.

4.Q9. What Is the Role of Concomitant Use of Therapeutic Agents?

There are no studies showing that combination treatment with two or more osteoporosis drugs has a greater effect on fracture reduction than treatment with a single agent (286 [EL 4; review NE]). Modest additive effects on BMD and bone turnover have been observed with combinations of two antiresorptive agents. The combined use of an antiresorptive drug and teriparatide or PTH may alter BMD and the bone turnover response, depending on which antiresorptive agent is used (287 [EL 1; RCT]).

There is evidence some combinations may enhance the rapidity of BMD changes. For example, while teriparatide increases lumbar spine BMD more than zoledronic acid and zoledronic acid increases hip BMD more than teriparatide, a single dose of IV zoledronic acid given at the same time as starting teriparatide leads to the most rapid BMD increase at both the lumbar spine and hip (288 [EL 1; RCT, partial blinding]). Perhaps the most robust additive BMD effect is seen with the combination of teriparatide and denosumab, which results in a larger increase in BMD than either agent alone (289 [EL 1; RCT]); however, no fracture data are available.

Combination therapy substantially raises the cost and probably increases the potential for side effects. Until the effect of combination therapy on fracture risk is better understood, the AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis. However, in certain situations when the patient needs a stronger agent because fracture risk is especially high or there is demonstrated suboptimal effect from raloxifene or hormone replacement therapy (i.e., recurrent fractures, high bone resorption markers, or progression of BMD loss), yet the patient has specific nonbone reasons to continue with these agents, another antiresorptive agent or anabolic therapy could be added to the therapy.

4.Q10. What Is the Role of Sequential Use of Therapeutic Agents?

Treatment with teriparatide should always be followed by antiresorptive agents to prevent bone density decline and loss of fracture efficacy (287 [EL 1; RCT], 288 [EL 1; RCT, partial blinding], 290 [EL 1; RCT], 291 [EL 1; RCT], 292 [EL 1; RCT], 293 [EL 4; review NE]). The rationale for using an antiresorptive agent after anabolic therapy is based both on the limited period that anabolic therapy with teriparatide is used and on data showing that, lumbar spine BMD declines if antiresorptive therapy is not initiated after teriparatide therapy (294 [EL 2; PCS]).

4.Q11. What Is the Role of Vertebral Augmentation for Compression Fractures?

Vertebral fractures can be associated with pain and limit mobility. Surgical procedures including vertebroplasty and kyphoplasty have been considered for relief of vertebral fracture pain. Initial data on 2 RCTs comparing vertebroplasty versus a control procedure on a primary outcome of overall pain showed no significant benefit from vertebroplasty up to 1 month (295 [EL 1; RCT]) and up to 6 months; however, the control group had a high rate of crossover to the vertebroplasty group (296 [EL 1; RCT]). A meta-analysis of individual patient data from 2 blinded trials of vertebroplasty failed to show an advantage of vertebroplasty over placebo for participants with acute fractures (<6 weeks) or severe pain (297 [EL 1; MRCT, small sample size]). Recently published 2-year follow-up data of patients with acute osteoporotic vertebral fractures found no beneficial effects of vertebroplasty over a sham procedure at 12 or 24 months (298 [EL 1; RCT]).

Both vertebroplasty and kyphoplasty have been suggested to increase the risk of vertebral fractures in the adjacent vertebrae. Despite a potential benefit with faster pain relief, a significantly increased incidence of additional vertebral fractures in patients undergoing vertebroplasty compared with placebo was noted in an RCT of 125 patients with vertebral fractures at 12 months' follow-up (299 [EL 1; RCT]). In contrast, another study found no difference in new fractures in patients receiving vertebroplasty versus usual care at a mean of 11.4 months, with decreased severity of further height loss in treated vertebrae (300 [EL 1; RCT]). In a meta-analysis assessing the safety of balloon kyphoplasty in patients with symptomatic osteoporotic vertebral fractures, new vertebral fractures were detected in 20.7% of treated patients, and more than half of the cases had fractures adjacent to the treated level (301 [EL 1; RCT]). Given the limitations to these published studies, the role for surgical procedures in treatment of vertebral fractures remains uncertain.

4.Q12. When Should Referral to a Clinical Endocrinologist or Osteoporosis Specialist Be Considered?

Referral to a clinical endocrinologist or osteoporosis specialist may be important in patients with normal BMD and fracture without major trauma, those with recurrent fractures or continued bone loss while receiving therapy without obvious treatable causes of bone loss, those with less common secondary conditions (e.g., hyperthyroidism, hyperparathyroidism, hypercalciuria, or elevated prolactin), those with osteoporosis with unexpectedly severe or unusual features, and those with a condition that complicates management (e.g., chronic kidney disease [CKD]: GFR <35, hyperparathyroidism, or malabsorption). Patients who experience fragility fractures should be evaluated and treated. Referral to an osteoporosis specialist or a fracture liaison team, if available, should be considered (302 [EL 3; SS], 303 [EL 2; MNRCT]).

5. COMMUNICATING RISK TO PATIENTS

Risk communication has been defined in general terms as "the study and practice of collectively and effectively understanding risks" (304 [EL 4; NE]). When applied to healthcare interactions, including those concerned with the management of osteoporosis, it can be characterized as "one-to-one communication in which the intervention includes a stimulus to patients to weigh the risks and benefits of a treatment choice or behavioral (risk reducing) change" (305 [EL 4; review NE]). In addition to understanding the potential risk and expected benefits of osteoporosis treatments, patients must fully appreciate the risk of fractures and their consequences (e.g., pain, disability, loss of independence, and death) when no treatment is given (306 [EL 4; review NE]). It is incumbent on the clinician to provide this information to each patient in a manner that is fully understood, and it is equally important to learn from the patient about cultural beliefs, previous treatment experiences, fears, and concerns. With effective risk communication, the clinician and the patient are both privy to the same information. This is the first step toward shared decision-making (307 [EL 3; SS], 308 [EL 4; review NE], 309 [EL 4; review NE]), a process by which a management plan is developed with active patient participation. Shared decision-making often begins with a recommendation from the clinician followed by a response, perhaps with an alternative plan, from the patient. In the end, the desired result is a treatment plan that is medically reasonable and acceptable to the patient, often involving compromises from both participants.

There are many obstacles to risk communication (310 [EL 4; review NE]). The medical evidence on efficacy and safety of treatment options may be complex, incomplete,

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and uncertain. Patients often distrust medical experts and pharmaceutical companies. Statistical illiteracy is common in both clinicians and patients. The risk of fracture and its consequences may not be fully appreciated. Clinicians may lack the necessary skills or time needed to explain the balance of benefits and risks. Competing healthcare priorities may detract from attention paid to osteoporosis. Patients may be reluctant to reveal their fears and concerns. Risks that may seem trivial or nonexistent to the clinician may nevertheless be frightening for the patient. News media reports of rare possible adverse effects of osteoporosis treatment and questionable overuse of diagnostic procedures sometimes generate concern that osteoporosis treatment is dangerous or overused. Postmarketing case reports of undesirable medical occurrences in patients treated for osteoporosis do not necessarily represent a causal relationship with the medication being used. For a variety of reasons, patients may fail to fill a prescription when it is written. When treatment is started, it may not be taken correctly or for a sufficient length of time to achieve the desired reduction in fracture risk.

Strategies to overcome obstacles to effective risk communication include recognition and acceptance of the limitations of medical evidence (310 [EL 4; review NE]). Treatment decisions for osteoporosis must be individualized with the understanding that many or most patients would not qualify for participation in the clinical trial that demonstrated efficacy and safety of the medications under consideration (311 [EL 2; RCCS]). Patients can be educated on the current state of medical knowledge using credible information sources. Media reports can be put in perspective by describing the benefits of treatment in proportion to the possible risks. Data can be presented in simple language that is understandable to the patient, sometimes with the use of decision aids such as brochures, graphs, videos, and models to enhance what is spoken and facilitate treatment decisions. The concerns of the patient must be considered and validated. Finally, shared decision-making allows the patient to be an active participant in osteoporosis management.

Studies to evaluate the effectiveness of communication interventions have been difficult to compare due to the diversity of measured outcomes. Study endpoints have included those that are behavioral (e.g., compliance and persistence), cognitive (e.g., knowledge and risk perception), and affective (e.g., anxiety and satisfaction) (305 [EL 4; review NE]). A systematic review of RCTs of communication tools found that most formats (verbal, written, video, provider-delivered, and computer-based) increased patients' understanding of the medical evidence (312 [EL 1; MRCT]). Understanding was enhanced when the methods were individualized and/or interactive, with decision aids such as cartoons or graphs also helping. It was concluded that increasing evidence supports the design of evidence-based communication tools, although there is limited access to these tools in clinical practice. Attentive listening to patients is an important component of risk communication and shared decision-making, with evidence that this a skill can be learned (313 [EL 4; review NE]). An RCT of risk communication for treatment to prevent hip fractures for patients in primary care practices found that presentation of treatment benefit and harm using absolute risk estimates (expressed by icon array graphs with human figures with hip fracture risk calculated by FRAX®) led to greater treatment acceptance than presentation of the same information as RRs (314 [EL 1; RCT]). Another RCT evaluated postmenopausal women with low BMD receiving a decision aid (a tailored pictograph of 10-year fracture probability, absolute risk reduction with bisphosphonates, side effects, and cost) compared with controls receiving a standard brochure (315 [EL 1; RCT]). The decision aid improved the quality of clinical decisions (i.e., patient understanding of benefit and risk) and may have improved adherence but did not affect rates of initiating treatment. Regular contact with a healthcare professional after starting osteoporosis treatment appears to be one of a few interventions that improves adherence (316 [EL 1; RCT], 317 [EL 2; PCS]). Examples of decision aids that illustrate risk in a visual, patient-friendly manner are given in Figure 2. Figure 3 provides risk comparisons for osteoporosis, fracture, ONJ, and other events.

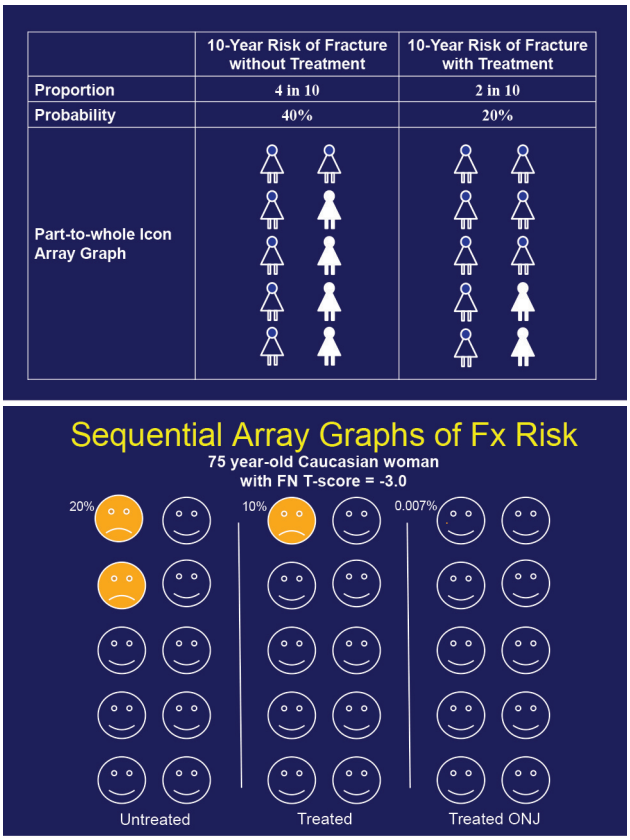

Fig. 2. Examples of visual depictions of fracture risk for use with patients.

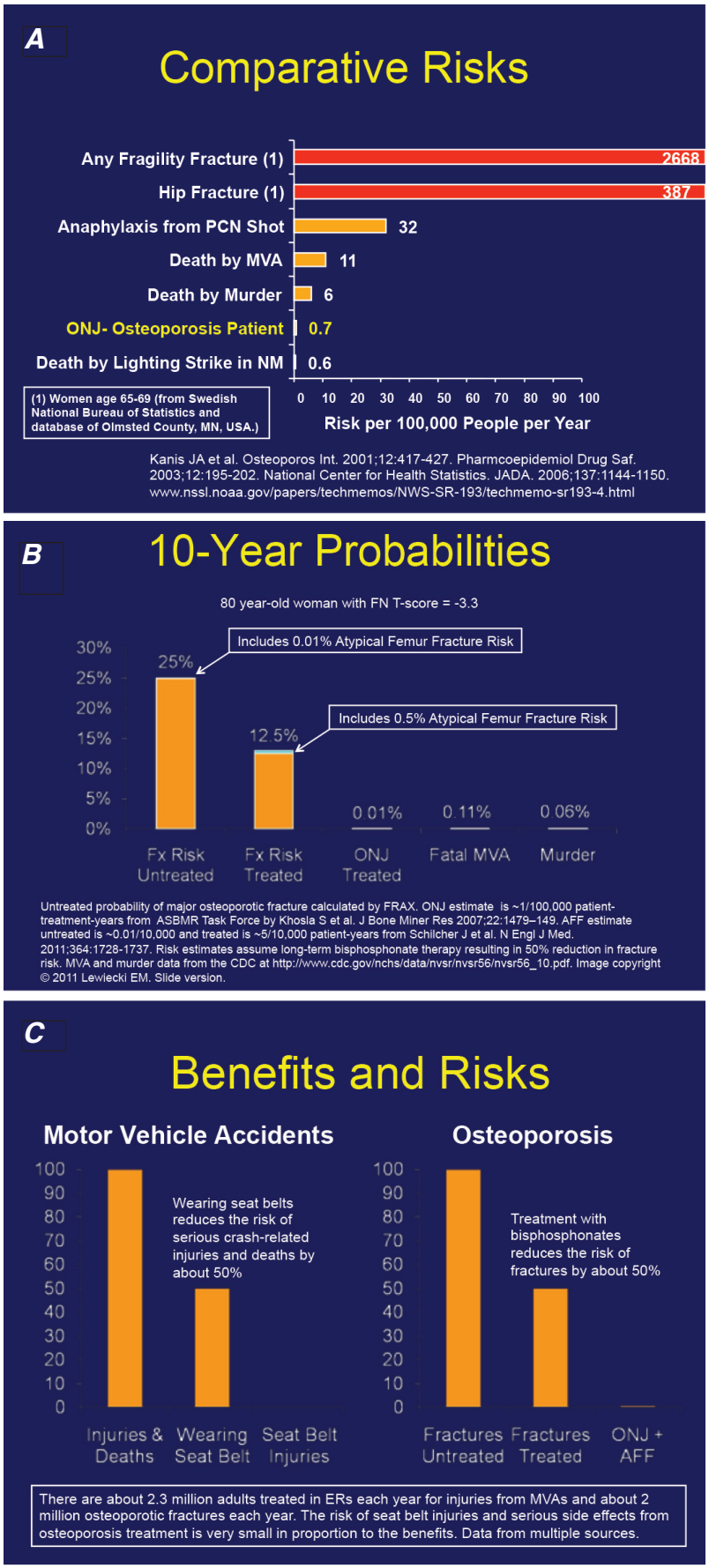

Fig. 3. *(A)* Comparative risk of fracture, ONJ, and other events in women aged 65-69 (319 [EL 3; SS], 320 [EL 2; RCCS], 321 [EL 4; consensus recommendations]); *(B)* 10-year probability of fracture in treated and untreated patients, ONJ in treated patients, and other events in an 80-year-old woman (269 [EL 4; consensus NE], 318 [EL 2; RCCS]); *(C)* benefits and risks of treatment in osteoporosis compared with seat belt intervention in MVAs. AFF = atypical femur fracture; Fx = fracture; MVA = motor vehicle accident; ONJ = osteonecrosis of the jaw; PCN = penicillin.

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Further study is needed to determine the most effective means of communicating benefit and risk in osteoporosis management. The best available evidence at this time suggests that communication skills can be learned, decision aids may be helpful, and that shared decision-making may improve clinical outcomes.

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Note: Reference sources are followed by an evidence level [EL] rating of 1, 2, 3, or 4. The strongest evidence levels (EL 1 and EL 2) appear in red for easier recognition.

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AACE/ACE 2016 Postmenopausal Osteoporosis Treatment Algorithm

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

No prior fragility fractures or moderate fracture risk**

- Alendronate, denosumab, risedronate, zoledronic acid***
- **Alternate therapy:** Ibandronate, raloxifene

Reassess at least yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to teriparatide if on injectable antiresorptive or at very high risk of fracture

Prior fragility fractures or indicators of higher fracture risk**

- Denosumab, teriparatide, zoledronic acid***
- **Alternate therapy:** Alendronate, risedronate

Reassess at least yearly for response to therapy and fracture risk

Denosumab

Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

Teriparatide for up to 2 years

Sequential therapy with oral or injectable antiresorptive agent

Zoledronic acid

- If stable, continue therapy for 6 years****
- If progression of bone loss or recurrent fractures, consider switching to teriparatide

* 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.

** Indicators of higher fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.

*** Medications are listed alphabetically.

**** Consider a drug holiday after 6 years of IV zoledronic acid. During the holiday, another agent such as teriparatide or raloxifene could be used.