Clinical Practice Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/ AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS— 2020 UPDATE

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The American Association of Clinical Endocrinologists' Medical Guidelines for Practice are systematically developed statements to assist health-care 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 reflect 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 considering local resources and individual patient circumstances.

Abbreviations:
25(OH)D = 25-hydroxyvitamin D; **AACE** = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **AFF** = atypical femoral fracture; **ASBMR** = American Society for Bone and Mineral Research; **BEL** = best evidence level; **BMD** = bone mineral density; **BTM** = bone turnover marker; **CI** = confidence interval; **CPG** = clinical practice guideline; **CTX** = C-terminal telopeptide type-I collagen; **DXA** = dual-energy X-ray absorptiometry; **EL** = evidence level; **FDA** = U.S. Food and Drug Administration; **FRAX®** = Fracture Risk Assessment Tool; **GI** = gastrointestinal; **HORIZON** = Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial (zoledronic acid and zoledronate are equivalent terms); **ISCD** = International Society for Clinical Densitometry; **IU** = international units; **IV** = intravenous; **LSC** = least significant change; **NOF** = National Osteoporosis Foundation; **ONJ** = osteonecrosis of the jaw; **PINP** = serum amino-terminal propeptide of type-I collagen; **PTH** = parathyroid hormone; **R** = recommendation; **ROI** = region of interest; **RR** = relative risk; **SD** = standard deviation; **TBS** = trabecular bone score; **VFA** = vertebral fracture assessment; **WHO** = World Health Organization

ABSTRACT

Objective: The development of these guidelines is sponsored by the American Association of Clinical Endocrinologists (AACE) Board of Directors and American College of Endocrinology (ACE) Board of Trustees and adheres with published AACE protocols for the standardized production of clinical practice guidelines (CPGs).

Methods: Recommendations are based on diligent reviews of the clinical evidence with transparent incorporation of subjective factors, according to established AACE/ACE guidelines for guidelines protocols.

Results: The Executive Summary of this 2020 updated guideline contains 52 recommendations: 21 Grade A (40%), 24 Grade B (46%), 7 Grade C (14%), and no Grade D (0%). These detailed, evidence-based recommendations allow for nuance-based clinical decision-making that addresses multiple aspects of real-world care of patients. The evidence base presented in the subsequent Appendix provides relevant supporting information for the Executive Summary recommendations. This update contains 368 citations: 123 (33.5%) evidence level (EL) 1 (highest), 132 (36%) EL 2 (intermediate), 20 (5.5%) EL 3 (weak), and 93 (25%) EL 4 (lowest). New or updated topics in this CPG include: clarification of the diagnosis of osteoporosis, stratification of the patient according to high-risk and very-high-risk features, a new dual-action therapy option, and transitions from therapeutic options.

Conclusion: This guideline is a practical tool for endocrinologists, physicians in general, regulatory bodies, health-related organizations, and interested laypersons regarding the diagnosis, evaluation, and treatment of postmenopausal osteoporosis. **(Endocr Pract. 2020;26 (Suppl 1):1-44)**

INTRODUCTION

Osteoporosis is a growing major public health problem, with an impact on quality and quantity of life that crosses medical, social, and economic lines. These guidelines have been 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.

METHODS

The AACE Board of Directors approved this 2020 update of the 2016 AACE/American College of Endocrinology (ACE) Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. Selection of the co-chairs, primary writers, and expert reviewers as well as the logistics for creating this guideline update were conducted in adherence with the AACE Protocol for Standardized Production of Clinical Practice Guidelines, Algorithms, and Checklists–2017 Update (2017 Guidelines for Guidelines; 2017 G4G) (Tables 1 through 4) (1). Methods established by AACE in 2004 and clarified in 2010, 2014, and 2017 more clearly delineate the mapping of recommendation grades for transparency and allow for more interpretative flexibility (Tables 1 through 4) (1-4). This updated methodology provides for patient-first language, greater detail regarding ratings for evidence, and general oversight of the entire clinical practice guideline (CPG) production process.

All members of the appointed task force and reviewers made disclosures regarding multiplicities of interests and attested that they are not employed by industry. Primary writers submitted contributions to specific clinical questions, which were subsequently reviewed, discussed, and integrated into the final document. This input provides the basis for the recommendations herein. This CPG was

approved by all primary writers, invited expert reviewers, the AACE CPG Oversight Committee, and the AACE Board of Directors before submission to *Endocrine Practice* for peer review.

Evidence was obtained through literature searches using the MEDLINE® database through PubMed® and other designated reference sources. Based on the 2017 AACE protocols for standardized production of CPGs (1), the appointed task force of medical experts evaluated available literature and graded references with numerical descriptors (evidence level [EL] 1 [highest] to 4 [lowest]) according to semantic descriptors of study type (Table 1), analyzed the graded evidence in consideration of subjective factors related to interpretation of the quality of each individual study's design and data analysis (Table 2), and then assessed recommendation qualifiers (such as risks and benefits, gaps in evidence, and cost-effectiveness when available) for the aggregate evidence base of an individual recommendation (Tables 3) (1). Based on identified subjective factors and qualifiers, the task force assigned recommendations with grades A through D (strong, intermediate, weak, no conclusive evidence/expert opinion) by expert consensus, mapping to the best evidence level (BEL), or highest quality rating, of supporting literature (Table 4). The process leading to a final recommendation and grade is not rigid but incorporates expert integration of objective and subjective factors meant to reflect optimal real-life clinical decision-making, options, and individualization of care. This document is a guideline; since individual circumstances and clinical presentations differ from patient to patient, ultimate clinical management is based on what is in the best interest of the patient that would also involve the patient's input ("patient-centered care") and reasonable clinical judgment by the treating clinician.

The Executive Summary lists 12 clinical questions related to postmenopausal osteoporosis and 52 recommendations, organized by corresponding question; some recommendations include multiple statements. Recommendation grade and BEL are provided after each recommendation (labeled R and numbered) in the Executive Summary. The relevant evidence base with discussion to support each recommendation as well as tables and figures for the updated recommendations follow the Executive Summary in an Appendix.

KEY UPDATES FOR 2020

The following key updates highlight the most important new recommendations in this CPG. See also the updated AACE/ACE Postmenopausal Osteoporosis Treatment Algorithm included at the end of the Executive Summary.
- Postmenopausal women with osteoporosis can be stratified according to high-risk and very-high-risk features, which includes prior fractures. Stratification of the patient drives the choice of the initial agent as

well as the duration of therapy.
- The new anabolic agent romosozumab is included in the treatment algorithm.
- Transitions from therapeutic agents, including denosumab, are further elucidated.

EXECUTIVE SUMMARY

To guide readers, recommendations (R) 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. What is the role of concomitant use of therapeutic agents?
- Q10. What is the role of sequential use of therapeutic agents?
- Q11. What is the role of vertebral augmentation for compression fractures?
- Q12. When should referral to a clinical endocrinologist or other osteoporosis specialist be considered?

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 fracture risk assessment with fracture risk assessment tool (FRAX®) or other fracture risk assessment tool should be included in the initial evaluation for osteoporosis (**Grade B; BEL 1**).

R3. Consider bone mineral density testing based on clinical fracture risk profile (**Grade B; BEL 2**).

R4. When bone mineral density is measured, axial dual-energy X-ray absorptiometry (DXA) measurement (lumbar spine and hip; 1/3 radius if indicated) should be used (**Grade B; BEL 2**).

R5. Osteoporosis is diagnosed based on presence of fragility fractures in the absence of other metabolic bone disorders and even with a normal bone mineral density (T-score)

Table 1
2017 AACE Protocol for Production of Clinical Practice Guidelines
Revised Logical Ranking of Scientific Methodologies (Step I: Evidence Rating)

Numerical Descriptor	Semantic Descriptor	Methodology Descriptor
STRONG EVIDENCE		
1 (1)	RCT	Randomized controlled trial
1 (1)	MRCT	Meta-analysis of only randomized controlled trials
INTERMEDIATE EVIDENCE		
2 (2)	MNRCT	Meta-analysis including nonrandomized prospective or case-controlled trials
2 (new)	NMA	Network meta-analysis
2(2)	NRCT	Nonrandomized controlled trial (or unconfirmed randomization)
2 (2)	PCS	Prospective cohort study (does not include open-label extension study)
2 (2)	RCCS	Retrospective case-control study
2 (new)	NCCS	Nested case-control study
2 (3; reassigned)	ES	Epidemiological study (hypothesis driven; includes survey, registry, data-mining, with or without retrospective uni-multivariate analyses or propensity matching)
2 (new)	OLES	Open-label extension study
2 (new)	PHAS	Post hoc analysis study
WEAK EVIDENCE		
3 (new)	DS	Discovery science (explorative/inductive; includes -omics, "big data," network analysis, systems biology, Bayesian inference, modeling) (48)
3 (new)	ECON	Economic study (includes Markov models, pharmacoeconomics) (49-53)
3 (3)	CCS	Consecutive case series (N > 1)
3 (3)	SCR	Single case report (N = 1)
3 (new)	PRECLIN	Preclinical study (e.g., feasibility, safety)
3 (new)	BR	Basic research (must be high impact and relevant)
NO EVIDENCE		
4 (4)	NE	No evidence (theory, opinion, consensus, review, position, policy, guideline)
4 (new)	O	Other (e.g., lower impact/relevant basic research; any highly flawed study)

Abbreviations: EBM = evidence-based methodology; EL = evidence level.
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Table 2
2017 AACE Protocol for Production of Clinical Practice Guidelines
Revised Evaluation of Studies (Step II: Scientific Analysis and Subjective Factors)

Study design	Data analysis	Interpretation
Allocation concealment (randomization)	Intent-to-treat	Generalizability
Blinding	Modeling (e.g., Markov)	Incompleteness
Comparator group	Network analysis	Logical
Endpoints (real clinical vs. surrogate)	Statistics	Overstated
Hypothesis	Appropriate follow-up	Validity
Power analysis (too small sample size)	Appropriate trial termination	
Premise		
Type 1 error (e.g., adjusted for PHAS)		

Abbreviations: AACE = American Association of Clinical Endocrinologists; PHAS = post hoc analysis study.
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Table 3
2017 AACE Protocol for Production of Clinical Practice Guidelines
Revised Evaluation of Recommendations (Step III: Recommendation Qualifiers)
Cascades (are there other recommendation versions based on ethnocultural factors?)
Dissenting opinions (based on health-care professional and patient preferences)
Economic (e.g., cost-effectiveness, cost-benefit, value)
Evidence base (are there significant gaps or is there overwhelming evidence?)
Relevance (patient-oriented evidence that matters vs. disease-oriented evidence; social acceptability)
Resource availability (limited or sufficient)
Risk to benefit
Abbreviation: AACE = American Association of Clinical Endocrinologists. Reprinted with permission from Mechanick et al. *Endocr Pract*. 2017;23:1006-1021 (1).

Table 4
2017 AACE Protocol for Production of Clinical Practice Guidelines
Revised and Detail Mapping Protocol (Step IV: Creating Initial Recommendation Grades)[a]

Best Evidence Level	Predominantly Negative SF and/or RQ	Predominantly Positive SF and/or RQ	Consensus for Recommendation and for Grade	EL to Grade Mapping	Map to Final Recommendation Grade
1	No	No	>66%	Direct	1 → A
Any[b]	No	No	100%	Rule	Any → A (new)
2	No	Yes	>66%	Adjust up	2 → A
2	No	No	>66%	Direct	2 → B
1	Yes	No	>66%	Adjust down	1 → B
3	No	Yes	>66%	Adjust up	3 → B
3	No	No	>66%	Direct	3 → C
2	Yes	No	>66%	Adjust down	2 → C
4	No	Yes	>66%	Adjust up	4 → C
4	No	No	>66%	Direct	4 → D
3	Yes	No	>66%	Adjust down	3 → D
Any[b]	Yes/no	Yes/no	>66%	Rule	Any → AD (new)

Abbreviations: AACE = American Association of Clinical Endocrinologists; BEL = best evidence level; EL = evidence level; RQ = recommendation qualifiers; SF = subjective factors.
[a]Recommendation Grade A = "Very Strong"; B = "Strong"; C = "Not Strong"; D = "Primarily Based on Expert Opinion." Mappings are provided in online supplementary material from (1).
[b]Rule-based adjustment wherein any recommendation can be a "Very Strong" Grade A if there is 100% consensus to use this designation. Similarly, if >66% consensus is not reached, even with some degree of scientific substantiation, a "Primarily Based on Expert Opinion" Grade D designation is assigned. The reasons for downgrading to D may be an inconclusive or inconsistent evidence base or simply failure of the expert writing committee to sufficiently agree. Note that any formulated recommendation is omitted from the document if sufficiently flawed, so any Grade D recommendation in the final document must be deemed sufficiently important. Rule-based adjustments are provided in online supplementary material from (1).
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(Grade B; BEL 2). Osteoporosis is also diagnosed based on a T-score of −2.5 or lower in the lumbar spine (antero-posterior), femoral neck, total hip, or 1/3 radius (33% radius), even in the absence of a prevalent fracture **(Grade B; BEL 4, upgraded by consensus)**. When the initial diagnosis of osteoporosis is made according to a T-score of −2.5 or below, the diagnosis persists even when a subsequent dual-energy X-ray absorptiometry (DXA) measurement shows a T-score better than −2.5 **(Grade B; BEL 4, upgraded by consensus)**.

R6. Osteoporosis may also be diagnosed in patients with a T-score between −1.0 and −2.5 and increased fracture risk using FRAX® (fracture risk assessment tool) country-specific thresholds **(Grade B; BEL 2)**.

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

R7. Evaluate for causes of secondary osteoporosis **(Grade B; BEL 1, downgraded due to limited evidence)**.

R8. Evaluate for prevalent vertebral fractures **(Grade B; BEL 2)**.

R9. Consider using bone turnover markers 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 A; BEL 1)**.

Q3. What Are the Fundamental Measures for Bone Health?

R10. 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)**.

R11. Maintain serum 25-hydroxyvitamin D (25[OH]D) ≥30 ng/mL in patients with osteoporosis (preferable range, 30 to 50 ng/mL) **(Grade A; BEL 1)**.

R12. Supplement with vitamin D3 if needed, with a daily dose of 1,000 to 2,000 international units (IU) typically required to maintain an optimal serum 25(OH)D level **(Grade A; BEL 1)**.

R13. Higher doses of vitamin D3 may be necessary in patients with present factors such as obesity, malabsorption, and older age **(Grade A; BEL 1)**.

R14. 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 age ≥50 years **(Grade B; BEL 1, downgraded due to limited evidence)**.

R15. Counsel patients to limit alcohol intake to no more than 2 units per day **(Grade B; BEL 2)**.

R16. Counsel patients to avoid or stop smoking **(Grade B; BEL 1, downgraded due to limited evidence)**.

R17. Counsel patients to maintain an active lifestyle, including weight-bearing, balance, and resistance exercises **(Grade A; BEL 1)**.

R18. Provide counseling on reducing risk of falls, particularly among the elderly **(Grade B; BEL 1, downgraded due to limited evidence)**.

R19. Consider referral for physical therapy, which may reduce discomfort, prevent falls, and improve quality of life **(Grade A; BEL 1)**.

Q4. Who Needs Pharmacologic Therapy?

R20. Pharmacologic therapy is strongly recommended for patients with osteopenia or low bone mass and a history of fragility fracture of the hip or spine **(Grade A; BEL 1)**.

R21. Pharmacologic therapy is strongly recommended for patients with a T-score of −2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius **(Grade A; BEL 1)**.

R22. Pharmacologic therapy is strongly recommended for patients with a T-score between −1.0 and −2.5 if the FRAX® (fracture risk assessment tool) (or if available, trabecular bone score [TBS]-adjusted 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 A; BEL 1)**.

R23. Consider patients with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than −3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm to be at very high fracture risk. Consider patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, to be high risk **(Grade B; BEL 1; downgraded due to limited evidence)**.

Q5. What Medication Should Be Used to Treat Osteoporosis?

R24. Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, denosumab, risedronate, and zoledronate are appropriate as initial therapy for most osteoporotic patients with high fracture risk, as defined in R23 **(Grade A; BEL 1)**.

R25. Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronate should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk, as defined in R23 **(Grade A; BEL 1)**.

R26. Ibandronate or raloxifene may be appropriate initial therapy in some cases for patients requiring drugs with spine-specific efficacy **(Grade B; BEL 1, downgraded due to limited evidence)**.

Q6. How Is Treatment Monitored?

R27. Obtain a baseline axial (lumbar spine and hip; 1/3 radius if indicated) dual-energy X-ray absorptiometry (DXA) and repeat DXA every 1 to 2 years until findings are stable. The 1/3 radius may be considered as an alternate site when the lumbar spine/hip are not evaluable or as an additional site in patients with primary hyperparathyroidism. Continue with follow-up DXA every 1 to 2 years or at a less frequent interval, depending on clinical circumstances **(Grade B; BEL 2)**.

R28. Monitor serial changes in lumbar spine, total hip, or femoral neck bone mineral density; if lumbar spine, hip, or both are not evaluable, monitoring with 1/3 radius site may be acceptable but is limited by a small area and a very large least significant change (LSC) **(Grade B; BEL 1, downgraded due to limited evidence)**.

R29. Follow-up of patients should ideally be conducted in the same facility with the same dual-energy X-ray absorptiometry (DXA) system, provided the acquisition, analysis, and interpretation adhere to International Society for Clinical Densitometry DXA best practices **(Grade C; BEL 2, downgraded due to limited evidence)**.

R30. Consider using bone turnover markers (BTMs) for assessment of 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 **(Grade B; BEL 1, adjusted down due to limited evidence)**.

Q7. What Is Successful Treatment of Osteoporosis?

R31. Consider stable or increasing bone mineral density, with no evidence of new fractures or vertebral fracture progression as a response to therapy for osteoporosis **(Grade A; BEL 1)**.

R32. Consider bone turnover markers at or below the median value for premenopausal women as a target for response to therapy for patients taking antiresorptive agents.

Consider significant increases in bone formation markers as a pharmacologic response to anabolic therapy **(Grade B; BEL 1, adjusted down due to limited evidence)**.

R33. Consider alternative therapy or reassessment for causes of secondary osteoporosis in patients who have recurrent fractures or significant bone loss while on therapy. Although a single fracture while on therapy is not necessarily evidence of treatment failure, consider two or more fragility fractures are evidence of treatment failure **(Grade B; BEL 1, downgraded due to limited evidence)**.

Q8. How Long Should Patients Be Treated?

R34. Limit treatment with abaloparatide and teriparatide to 2 years and follow abaloparatide or teriparatide therapy with a bisphosphonate or denosumab **(Grade A; BEL 1)**.

R35. Limit treatment with romosozumab to 1 year and follow with a drug intended for long-term use, such as a bisphosphonate or denosumab **(Grade B; BEL 1, downgraded due to limited evidence)**.

R36. For oral bisphosphonates, consider a bisphosphonate holiday after 5 years of treatment if fracture risk is no longer high (such as when the T score is greater than -2.5, or the patient has remained fracture free), but continue treatment up to an additional 5 years if fracture risk remains high **(Grade B; BEL 2)**.

R37. For oral bisphosphonates, consider a bisphosphonate holiday after 6 to 10 years of stability in patients with very high fracture risk **(Grade B; BEL 2)**.

R38. For zoledronate, consider a bisphosphonate holiday after 3 years in high-risk patients or until fracture risk is no longer high, and continue for up to 6 years in very-high-risk patients **(Grade A; BEL 1)**.

R39. The ending of a bisphosphonate holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in bone mineral density beyond the least significant change (LSC) of the dual-energy X-ray absorptiometry (DXA) machine, or an increase in bone turnover markers **(Grade A; BEL 1)**.

R40. A holiday is not recommended for non-bisphosphonate antiresorptive drugs **(Grade A; BEL 1)**, and treatment with such agents should be continued for as long as clinically appropriate **(Grade A; BEL 1)**.

R41. If denosumab therapy is discontinued, patients should be transitioned to another antiresorptive **(Grade A; BEL 1)**.

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

R42. Until the effect of combination therapy on fracture risk is better understood, AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis **(Grade A; BEL 1)**.

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

R43. Follow treatment with an anabolic agent (e.g., abaloparatide, romosozumab, teriparatide) with a bisphosphonate or denosumab to prevent bone density decline and loss of fracture efficacy **(Grade A; BEL 1)**.

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

R44. Vertebroplasty and kyphoplasty are not recommended as first-line treatment of vertebral fractures, given an unclear benefit on overall pain and a potential increased risk of vertebral fractures in adjacent vertebrae **(Grade A, BEL 1)**.

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

R45. 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 C; BEL 2, downgraded due to limited evidence)**.

R46. When a patient with normal bone mineral density sustains a fracture without major trauma, referral to a clinical endocrinologist or other osteoporosis specialist should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

R47. When recurrent fractures or continued bone loss occur(s) in a patient receiving therapy without obvious treatable causes of bone loss, referral to a clinical endocrinologist or other osteoporosis specialist should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

R48. When bone mineral density is unexpectedly low or when osteoporosis has unusual features such as young age, unexplained artifacts on bone density, and unexplained laboratory studies, including high or low alkaline phosphatase and/or low phosphorus, referral to a clinical endocrinologist or other osteoporosis specialist should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

R49. When a patient has a condition that complicates management (e.g., decreased kidney function, hyperparathyroidism, or malabsorption), referral to a clinical endocrinologist or other osteoporosis specialist should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

UPDATED EVIDENCE BASE FOR 2020

In this update, there are 368 reference citations, of which 125 (33.5%) are EL 1 (strong), 133 (36%) are EL 2 (intermediate), 20 (5.5%) are EL 3 (weak), and 95 (25%) are EL 4 (no clinical evidence). 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) (5,6). In the U.S., Medicare currently pays for most of these costs; with an aging population, the costs of these fractures are estimated to be more than $25 billion by 2025. Despite these significant costs, less than 1 in 4 women aged 67 years or older with an osteoporosis-related fracture gets their bone density measured or begins osteoporosis treatment (7). A recent retrospective analysis demonstrated that the annual cost of caring for osteoporotic fractures exceeds the annual costs of caring for breast cancer, myocardial infarction, or stroke in women aged 55 years and older (8).

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 years, half of white women have low bone mass (osteopenia) or osteoporosis (9). The average femoral neck T-score by dual-energy X-ray absorptiometry (DXA) for 75-year-old women is –2.5, meaning that more than half of women age 75 and older meet the criterion for osteoporosis (10). More than 20% of postmenopausal women have prevalent vertebral fractures (11). Although these guidelines focus only on the evaluation and treatment of osteoporosis in postmenopausal women, osteoporosis may affect men as well as women before and after menopause.

Q1. How Is Fracture Risk Assessed and Osteoporosis Diagnosed?

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" (12).

In 1994, a Working Group of the World Health Organization (WHO) established an operational definition of postmenopausal osteoporosis (Table 5) (7). The T-score is defined as the standard deviation of an individual's bone mineral density (BMD) from the mean value for young normal 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 decisions about public health and health policy and are commonly accepted as standards for inclusion in clinical trials for research purposes.

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. A fragility fracture is usually a fracture sustained from force similar to a fall from a standing position or less

that would not have occurred in healthy bone, excepting fractures of the skull, face, fingers, and toes. Thus, patients with low bone mass (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 6) (12-16). While osteoporosis has traditionally been diagnosed based on low bone density in the absence of fracture (7), AACE agrees that osteoporosis may also be diagnosed in patients with osteopenia and increased fracture risk using FRAX® (Fracture Risk Assessment Tool) country-specific thresholds (14-17). Patients diagnosed with osteoporosis should be treated. Indications for pharmacologic therapy are low T-score, increased fracture risk based on FRAX®, or fragility fracture. Once the diagnosis of osteoporosis is made, the diagnosis remains even if treatment results in a T-score better than −2.5.

All postmenopausal women age ≥50 years of age should undergo clinical assessment for osteoporosis and

Table 5 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
Severe or established osteoporosis	−2.5 or below with fragility fracture
[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.	
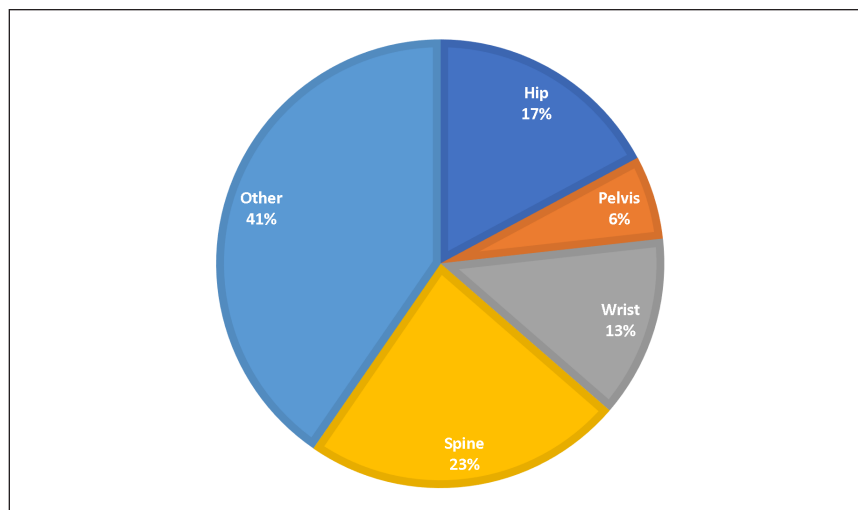
Fig. 1. Incidence of new osteoporotic fractures among Medicare beneficiaries by fracture type in 2015. Over 1.6 million new osteoporotic fractures were diagnosed in Medicare beneficiaries in 2015. Estimates of fracture incidence were based on diagnosis codes on medical claims for Medicare beneficiaries. Adapted with permission from Hansen D, Bazell C, Pelizzari P, Pyenson B. Medicare cost of osteoporotic fractures: The clinical and cost burden of an important consequence of osteoporosis.

Table 6 **2020 AACE Diagnosis of Osteoporosis in Postmenopausal Women**
1. T-score –2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius
2. Low-trauma spine or hip fracture (*regardless of bone mineral density*)
3. T-score between –1.0 and –2.5 **and** a fragility fracture of proximal humerus, pelvis, or distal forearm
4. T-score between –1.0 and –2.5 **and** high FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds
Abbreviations: AACE = American Association of Clinical Endocrinologists; FRAX® = fracture risk assessment tool; TBS = trabecular bone score.

fracture risk, including a detailed history and physical examination (Table 7) (18-25). Tools such as FRAX® should be utilized when available (26). The U.S. Preventive Services Task Force recommends BMD testing for all women aged 65 years or older 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 (20,21).

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

Q1.3.1 Low BMD

Low BMD, as noted above, can be used to define postmenopausal osteoporosis. A strong inverse relationship between BMD and risk of fracture exists. 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 **Q1.4 What Are the Risk Factors for Osteoporosis-related Fractures?**). Low BMD and/or bone loss are not associated with symptoms prior to fracture.

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 fall.

Osteoporosis-related fractures often lead to pain, disability, and deformity and reduce quality and quantity of life. Hip fractures are the most serious consequences of osteoporosis. Women have an increased mortality of 12 to 20% during the 2 years following hip fracture. More than 50% of survivors of hip fractures are unable to return to independent living; many require long-term nursing-home care (27). Other low-trauma fractures that are considered related to osteoporosis include those of the proximal humerus and pelvis and some cases of distal forearm.

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 readily available (www.shef.ac.uk/FRAX) and incorporates multiple clinical risk factors that predict fracture risk, largely independent of BMD (28-36). Clinical risk factors in FRAX® include age, sex, body mass index (BMI), 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 8).

It is important to note that FRAX® underestimates future fracture risk, as it reports risk for only hip fracture and major fractures, which comprise approximately half of all fragility fractures. Additionally, FRAX® 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 in those at increased risk of falling (37-44). 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 (45). For individuals with a history of falls, the Garvan fracture risk calculator, though based on much less data than FRAX®, can be utilized to gain insight into fracture risk. Table 9 shows factors that increase the risk of falls and fractures.

Q1.5. Bone Densitometry

Q1.5.1. Bone Density Scores

Bone density results are reported as grams of mineral per square centimeter of projected bone area and are converted to T- and Z-scores. The T-score represents the number of standard deviations (SDs) from the normal

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Table 7
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 years
  Clinical risk factors for osteoporosis
    Age ≥65 years
    Low body weight (<57.6 kg [127 lb])
    Smoking
    Early menopause
    Excessive alcohol intake (more than 3 drinks daily)
  Secondary osteoporosis
  Height loss of kyphosis
  Risk factors for falling (see Table 9)
  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 of prednisone per day for 3 months or more
- Bone mineral density measurements in those at increased risk for osteoporosis and fractures and willing to consider pharmaco-logic treatment if low bone mass is documented:
  All women 65 years of age or older
  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 or interfere with therapy (or both).

Table 8
Risk Factors Included in FRAX®

Country of residence
Ethnicity (U.S. models only—white, black, Hispanic, and Asian)
Age (accepts ages between 40 and 90 years)
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 or more for 3 months or longer, current or past)
Rheumatoid arthritis (confirmed diagnosis)
Smoking (current)
Alcohol use (2 or more units daily)
Secondary osteoporosis[a] (specifically mentioned are type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption, and chronic liver disease)
BMD. Femoral neck BMD should 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.
Reproduced with permission from Watts NB, et al. *J Bone Miner R*es. 2009;24:975-979 (274).

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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 greater than –2.0 defined as "within the expected range for age." Postmenopausal women with very low Z-scores often have secondary osteoporosis and should undergo comprehensive evaluation for these causes.

Q1.5.2. Indications for BMD measurement

Testing of BMD is useful for screening and monitoring therapy in people at high risk for osteoporosis (e.g., postmenopausal women, patients with hyperparathyroidism or 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 10.

Testing of BMD is the gold standard in diagnosing osteoporosis; however, not everyone has access to BMD

Table 9
Factors that Increase Risk of Falling and Fracture

Neurologic disorders
    Parkinson disease
    Seizure disorder
    Peripheral neuropathy
    Prior stroke
    Dementia
    Impaired gait or balance (or both)
    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

testing. Therefore, the decision to measure BMD should be based on an individual's clinical fracture risk profile and skeletal health assessment (46). AACE recommends BMD testing for women aged 65 years and older and younger postmenopausal women at increased risk for bone loss and fracture, based on analysis of fracture risk. Measurement of BMD 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, such as long-term glucocorticoid therapy.

In addition to its role in diagnosis, BMD measurement is useful in monitoring response to therapy, as shown in Table 11.

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 sites of osteoporosis-associated fracture. 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 one 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 at a high-quality DXA facility (47).

Diagnostic criteria, therapeutic studies, and cost-effectiveness data have been based primarily on DXA measurements of the total hip, femoral neck, and/or lumbar spine (L1 to L4) and are the preferred measurement sites (36,48,49). The 1/3 radius can also be used as a diagnostic site, particularly when other preferred sites are not available (50). 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. For BMD measurement, several other techniques are available, 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 AACE apply only to the axial measurements (i.e., lumbar spine, femoral neck, and total hip) and distal 1/3 of the radius. Thus, other technologies should not be used to diagnose osteoporosis but may be used to assess fracture risk.

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–standard deviation [SD] decrease in age-adjusted BMD, the relative risk [RR] of fracture increases 1.6- to 2.6-fold) (51). The relationship between bone density and fracture risk, however, is a continuum, without a clear "fracture threshold." The WHO has defined T-score criteria

Table 10
Indications for Bone Mineral Density Testing

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

Table 11
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 (for example, 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

for the classification of osteoporosis (T-score at or below –2.5) and low BMD (i.e., low bone mass or "osteopenia"; T-score between –1.0 and –2.5) (Table 5) 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 reduction of fracture risk has also been shown (52). 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 the risk for fractures is sufficiently high in most postmenopausal women with osteoporosis to merit pharmacologic intervention, cost-effective management of women with low bone mass (osteopenia) is less clear. While their overall rate of fractures is lower than that of patients with osteoporosis, more than 80% 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 risk factors for fractures for accurate assessment of fracture risk 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.

Role of Trabecular Bone Score in Adjusting FRAX® Risk

Trabecular bone score (TBS) is a textural index that measures pixel gray-level variations in the lumbar-spine DXA image, providing an indirect index of trabecular microarchitecture. Variability in the 2-dimensional projected DXA image is presumed to correlate with absorption parameters in 3-dimensional bone according to a mathematical relationship (53). TBS is obtained using commercially available U.S. Food and Drug Administration (FDA)-approved software that is installed in compatible DXA systems. High TBS values (note that TBS is unitless) correlate with homogeneous (i.e., normal) bone texture, while low values are indicative of more variable (i.e., weaker) bone texture. Numerous studies have shown that TBS predicts fracture risk independent of BMD (54) and that it enhances fracture risk prediction capabilities of FRAX® (55,56). Low TBS values increase FRAX® estimated risk, while high TBS values reduce it. TBS adjustment of FRAX® has been validated in 14 prospective international cohorts (56).

Age substantially alters the impact of TBS on FRAX® estimated risk, with the effect of TBS on fracture risk being much greater for younger women. Why TBS has less of an impact on FRAX® risk in older women is unclear, but a logical hypothesis is that falls become more common with advancing age and play a greater role in fracture risk. It is likely that bone strength is more important for fracture

risk in younger women while falls play a greater role with advancing age. Adjustment of TBS in FRAX® may have greatest clinical utility in patients whose fracture risk is close to the therapeutic intervention threshold. In patients with low bone mass (osteopenia), TBS-adjusted FRAX®, which can be included with the DXA printout, can sometimes be the deciding factor in making treatment decisions. TBS may be especially useful in clinical situations, such as type 2 diabetes and primary hyperparathyroidism, where FRAX® without TBS may underestimate fracture risk.

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 guideline published by the International Society for Clinical Densitometry (ISCD) recommending measurement of at least two consecutive vertebrae, inclusion of artifacts in the analysis, errors in use of ethnic- or gender-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 the interpretation of DXA reports, which are described in the "Consensus Statement by the AACE/ACE on the Quality of DXA Scans and Reports" (57). Best Practices for high-quality technical performance and interpretation of DXA scans have been published by the ISCD (58).

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

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 secondary osteoporosis in adults are summarized in Table 12

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 (59). This is reasonable, as a few simple laboratory tests provided useful information in 40 to 85% of women who did not have clinical evidence

of secondary osteoporosis in several studies (60-64). 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 13.

Laboratory evaluation should include a complete blood count, comprehensive metabolic panel, 25-hydroxyvitamin D (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 replete of vitamin D and has been on a reasonable calcium intake (1,000 to 1,200 mg/d) 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 obtained. Celiac antibodies or serum/urine protein electrophoresis could also be obtained.

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. Most vertebral fractures, however, remain undetected unless specifically sought by imaging techniques (spine X-ray or vertebral fracture assessment [VFA]) (65). VFA, a technique to assess vertebral fractures with DXA technology, can often be done at the same time with DXA (66-68). Both historical and prospective height loss have been associated with a new vertebral fracture (69,70). Lateral spine imaging with standard radiography or VFA with DXA is indicated when T-score is less than −1.0 and one 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 of 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 thresholds for height loss 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 increased risk of vertebral fracture. The sensitivity and reliability of standard radiography to assess BMD are poor, and in the absence of vertebral fractures, this technique should not be used to diagnose osteoporosis. If fracture is diagnosed by VFA, then additional imaging should be done to confirm the impression of fracture.

Table 12
Causes of Secondary Osteoporosis in Adults[a]

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
	  disease, and gastric
	  resection or bypass)
	Total parenteral
	  nutrition
	Vitamin D deficiency
		Anti-epileptic drugs[b]
		Aromatase inhibitors
		Chemotherapy/
		  immunosuppressants
		Medroxyprogesterone
		  acetate
		Glucocorticoids
		Gonadotropin-releasing
		  hormone agents
		Heparin
		Lithium
		Proton pump inhibitors
		Selective serotonin- reuptake
		  inhibitors
		SGLT2-inhibitors
		Thiazolidinediones
		Thyroid hormone (in
		  supraphysiologic doses)
			Ehlers-Danlos
			  syndrome
			Homocystinuria due
			  to cystathionine
			  deficiency
			Marfan syndrome
			Osteogenesis
			  imperfecta
				AIDS/HIV
				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

AIDS = acquired immunodeficiency syndrome; GI = gastrointestinal; HIV = human immunodeficiency virus; SGLT2 = sodium-glucose cotransporter 2.
[a]Not meant to be a complete list.
[b]Phenobarbital, phenytoin, primidone, valproate, and carbamazepine have been associated with low bone mass.

Table 13
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-hour 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

Q2.3. How Are Bone Turnover Markers Used in the Initial Evaluation and Follow-up of Postmenopausal Osteoporosis?

Bone turnover markers (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 (71-73) and are associated with increased fracture risk independent of BMD in some studies (74-76). One recent study without data for BMD failed to verify prediction of hip fractures with BTMs (77). Automated immunoassays have improved reproducibility of BTMs. In addition, these markers respond quickly to therapeutic intervention; changes in markers have been associated with bone response to therapy and reduction of fracture risk (78-83). In 2010, the International Osteoporosis Foundation proposed that serum C-terminal telopeptide type-1 collagen (CTX) and serum carboxy-terminal propeptide of type-I collagen (PINP) be used as reference analytes for BTMs in clinical and observational studies (76). The National Bone Health Alliance, working in association with the American Association for Clinical Chemistry, established that the preferred resorption marker is CTX and the preferred formation marker is PINP and defined the steps necessary to enhance the science and clinical utility of BTMs (84). Serum CTX must be drawn in the fasting state and ideally at the same time in the morning every time. Recommendations to reduce pre-analytical variability of BTMs have been published (85). Problems with the use of BTMs include their high cost (and variable insurance coverage), lack of appropriate reference ranges reported by commercial labs, and the influence of renal insufficiency on all markers except bone-specific alkaline phosphatase. Some experts routinely utilize BTMs in clinical practice, while others do not.

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 (86) or anabolic (87) drugs. Thus, clinicians might use the results of BTMs obtained after 3 to 6 months of oral bisphosphonate therapy to counsel patients that the therapy is effective and to maintain their compliance, rather than waiting 2 years for a DXA result. Significant reductions in BTMs for up to several months have also been shown to explain more of the fracture reductions associated with antiresorptive therapy than do increases in BMD (82,88,89). The preferred BTMs for monitoring are PINP for bone formation and CTX for bone resorption, except in the setting of renal insufficiency or if there are insurance issues, then bone-specific alkaline phosphatase may be used. Use of a bone resorption marker, such as a fasting-morning CTX, may be helpful in determining the reason for bone loss despite antiresorptive therapy. For example, an elevated CTX level is associated with high bone turnover and could represent malabsorption of medication or poor compliance and the need for further evaluation for causes of secondary osteoporosis and/or the need to change to parenteral osteoporosis therapy. It must be noted, however, that a recent fracture will transiently raise BTMs, and thus, such elevations after an acute fracture should not be interpreted as treatment failure. Conversely, loss of BMD in the face of well-suppressed BTMs (greater than the least significant change [LSC] of the BTMs) and stable body weight might raise concern for factors that may confound DXA interpretation and prompt further scrutiny of DXA images (see section **Q6**). An additional potential use of BTMs is in the setting of a bisphosphonate drug holiday, where highly suppressed bone turnover (as compared with a baseline value) indicates continued antiresorptive effect and, theoretically, continued antifracture benefit. However, presently, there are no peer-reviewed trials supporting or refuting this approach. In summary, BTMs are useful in certain situations, such as assessment of fracture risk and to provide early feedback to patients that their drug is or is not working, which leads to discussions pertaining to medication compliance, drug absorption, and/or therapeutic efficacy. BTMs do not need to be assessed in all osteoporosis patients.

Q3. What Are the Fundamental Measures for Bone Health?

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, 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 only 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

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 risk of falling. Moreover, optimal

vitamin D status may increase response to bisphosphonate therapy (90), increase BMD, and prevent fractures (91). 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) (now the National Academy of Medicine [NAM]) suggest 4,000 IU of vitamin D per day as the safe upper limit in the general population (92,93).

Vitamin D deficiency is common in patients with osteoporosis (94) and hip fracture (95). It is advisable to measure serum 25(OH)D levels in patients at risk of deficiency, especially in those with osteoporosis. The effectiveness of anti-osteoporosis treatment may be hindered by vitamin D deficiency. The dose of vitamin D needed to correct vitamin D deficiency varies among individuals (96,97), with recent data suggesting daily vitamin D doses greater than 1,000 IU or even 4,000 IU may be needed (98,99). In addition, patient factors, including obesity and history of malabsorption, may influence vitamin D status and increase the vitamin D dose necessary to achieve adequate levels (100-105).

An individual's vitamin D status is assessed by measurement of serum 25(OH)D—not by measurement of 1,25-dihydroxyvitamin D. The optimal 25(OH)D level is controversial; AACE and the 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 (93,106-108). Other groups recommend that 25(OH)D values ≥20 ng/mL be considered adequate (109,110). 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. A reasonable upper limit, based on levels in sun-exposed healthy young adults, is 50 ng/mL until further evidence is available. Evidence from one randomized trial suggested no benefit to exceeding serum levels of 30 ng/mL (111). However, in patients with stage 3 or 4 chronic kidney disease, treatment with the calcifediol form of vitamin D (25[OH]D) to levels of 50 ng/mL has been shown to improve secondary hyperparathyroidism (112).

A meta-analysis of randomized studies in postmenopausal women found a significant reduction in hip and nonvertebral fractures with vitamin D supplementation at doses of 700 to 800 IU/day or more (113). 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 (114). In addition to the skeletal effects of vitamin D, some studies have also shown improvement in muscle strength, balance and fall risk (113,115,116), and survival (117). However, a randomized trial in frail elderly patients with baseline mean 25(OH)D levels of 18.4 to 20.9 ng/mL comparing three different *monthly* doses of vitamin D (a low-dose control group receiving 24,000 IU of vita-

min D₃, a group receiving 60,000 IU of vitamin D₃, and a group receiving 24,000 IU of vitamin D₃ plus 300 μg of calcifediol) showed an increase in falls with the two more-aggressive doses of vitamin D, demonstrating that caution should be used with bolus dosing in this patient population until the optimal dose and schedule are known (118). Single, larger annual bolus doses of vitamin D are also not recommended based on a placebo-controlled randomized trial in women with risk factors for hip fracture (median age of 76 years and baseline median 25[OH]D level of 21 ng/mL), where 500,000 IU of vitamin D₃ was given annually (119). Daily dosing has been hypothesized to more closely replicate serum vitamin D₃ (cholecalciferol) levels achieved by cutaneous production (120). Additionally, the high vitamin D₃ (cholecalciferol) concentrations obtained with bolus dosing may induce 24-hydroxylation, resulting in inactive vitamin D (121)—a concept supported by work finding that a single vitamin D₃ dose of 150,000 IU led to greater 24,25-dihydroxyvitamin D₃ than daily dosing of 5,000 IU for 1 month (122). The possibility that daily and intermittent bolus dosing might have different effects on vitamin D metabolism raises the question whether these supplementation approaches should be considered equivalent in randomized controlled trials.

Adults who are vitamin D insufficient or deficient (serum 25[OH]D 20 to 29 or <20 ng/mL, respectively) may be treated with 5,000 IU vitamin D₃ daily for 8 to 12 weeks to achieve a 25(OH)D blood level >30 ng/mL (93,96). Vitamin D₃ (cholecalciferol) rather than vitamin D₂ should be used for replacement (123). Not every 25(OH)D assay measures 25(OH)D₂. Moreover, due to unequal cross-reactivity for 25(OH)D₂, many current assays are inaccurate if there is a significant amount of 25(OH)D₂ (124,125). As such, when substantial amounts of 25(OH)D₂ are present, a spuriously low total 25(OH)D level will be reported. It should be noted that vegetarians may refuse to take vitamin D₃ given its animal source. In such individuals, and in those receiving high-dose ergocalciferol, use of an appropriate assay, generally one performed using liquid chromatography–tandem mass spectrometry that accurately quantifies both 25(OH)D₂ and 25(OH)D₃ with the sum of these defining the individual's vitamin D status, is essential.

The above-noted repletion regimen should be followed by maintenance therapy of 1,000 to 2,000 IU of vitamin D₃ 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 metabolism of vitamin D, as well as other individuals. Only in uncommon clinical situations is there a need to prescribe high-dose (e.g., 50,000 IU) treatment with vitamin D.

In patients with active granulomatous disease, repletion of vitamin D must be undertaken with caution due to risk for hypercalciuria and/or hypercalcemia (96).

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 14 (92). For adults aged 50 years and older, the recommended calcium intake (including diet, plus calcium supplements if necessary when dietary intake is insufficient) is 1,200 mg/day. Calcium supplementation has been shown to increase BMD slightly. 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 to 0.98) and a 30% reduced risk of hip fractures (SRRE, 0.70; 95% CI, 0.56 to 0.87) (126). 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 (114,127-129).

The optimal intake and utility of calcium supplements are 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 to 1.67) for all-cause mortality (130). Three prospective cohort studies and a meta-analysis, all from one group, suggested increased risk of cardiovascular disease and stroke among calcium supplement users (131-134). The meta-analysis involved trials that did not collect cardiovascular outcomes as primary or secondary study endpoints, and thus, these events were not adjudicated. In contrast, low dietary calcium intake (<700 mg/day compared with 1,400 mg/day) has been associated with increased cardiovascular risks (135). Other studies found no effect of calcium supplements on cardiovascular risk (136,137). A 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 (138). 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 (114); 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, in these subjects, the mean total calcium intake from diet and supplements was much higher (~2,100 mg) than currently recommended. Patients with a history of nephrolithiasis should be evaluated for the etiology of renal stone formation or hypercalciuria prior to deciding about calcium supplementation. Patients who are found to have idiopathic hypercalciuria may be treated with thiazide diuretics. Patients with kidney stones that have hyperoxaluria should be treated with calcium citrate. In summary, studies to date suggest that dietary calcium may be preferred over supplemental calcium and that total calcium intake should not exceed 1,500 mg/day (139). Increasing calcium intake beyond the recommended levels has not been shown to be useful and may be harmful (140-144). AACE, NOF, the IOM (now NAM), and the Endocrine Society recommend that women aged 51 years or older consume 1,200 mg per day of calcium from all sources (93,108,109,139).

A dietary history to assess calcium intake prior to recommending calcium supplements is important. The average daily calcium intake among American adults is about half of what is recommended, with a median of approximately 600 mg/day (145). Patients with low dietary intake may increase their daily intake by consuming extra calcium-rich foods, including dairy products, nuts, and seeds. For individuals who are unable to increase dietary calcium due to lactose intolerance or lack of access to calcium-rich foods, use of calcium supplements 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 gastrointestinal (GI) complaints (e.g., constipation and bloating). 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. For patients requiring more than 600 mg calcium supplement daily, the dose should be divided.

It is advisable to assess adequacy of calcium and vitamin D through laboratory evaluation prior to initiation of pharmacologic therapy for osteoporosis. It should be noted that a 24-hour urine calcium collection is the best commercially available method of evaluating adequacy of calcium intake and absorption. Urinary creatinine excretion may be assessed in the same 24-hour urine collection as a gauge of the completeness of the collection. Urinary sodium excretion may be measured as well if hypercalciuria is suspected. High sodium intake may increase urine calcium.

Q3.3.1. Other Supplements and Nutrition Considerations

Magnesium: Patients frequently question whether supplementation of magnesium is needed, but no randomized controlled study has evaluated the effect of magnesium intake on fracture risk or BMD. Most people have adequate dietary intake of magnesium. Individuals who are at risk for hypomagnesemia (e.g., those with GI malabsorption, chronic liver disease [including alcoholics], or renal tubu-

Table 14 Recommended Dietary Allowance for Calcium		
Age	**Sex**	**Recommended dietary allowance (mg/day)**
0-6 months	M + F	200
6-12 months	M + F	260
1-3 years	M + F	700
4-8 years	M + F	1,000
9-18 years	M + F	1,300
19-50 years	M + F	1,000
51-70 years	M	1,000
51-70 years	F	1,200
71+ years	M + F	1,200
Reproduced with permission from Ross AC, et al. *J Clin Endocrinol Metab*. 2011;96:53-58 (109).		

lar loss or those using proton-pump inhibitors or diuretics long term), however, may benefit from supplementation of magnesium. 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 (146). 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 rates of calcium absorption (147).

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 (148). Some data suggest that vitamin K (1 mg/day) may reduce bone turnover and bone loss in postmenopausal women (149). However, not all studies replicate this finding, and further studies are needed before vitamin K can be considered a part of the standard recommendation for osteoporosis prevention. "Natural" estrogen-receptor agonists, 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 (150-152).

Caffeine: Patients should be advised to limit caffeine intake to less than 1 to 2 servings (8 to 12 ounces/serving) of caffeinated drinks per day. Several observational studies have shown an association between consumption of caffeinated beverages and fractures (153-155). Caffeine intake leads to a slight decrease in intestinal calcium absorption and increase in urinary calcium excretion.

Protein: Adequate protein intake (U.S. recommended daily allowance, 0.8 g/kg) helps minimize bone loss among patients who have suffered hip fractures (156,157). In one study, patients who received supplemental protein after hip fracture had shorter hospital stays and better functional recovery (157).

Q3.4. Alcohol

Excessive intake of alcohol is associated with increased fracture risk (158). 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 2 drinks daily, with 1 drink equivalent to 120 mL of wine, 30 mL of liquor, or 260 mL of beer (158) (http://www.shef.ac.uk/FRAX/).

Q3.5. Smoking

Cigarette smoking has been validated by multiple studies to increase osteoporotic fracture risk and thus should be avoided (159,160). 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 done 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 (161). All smokers should be counseled on smoking cessation. The use of tobacco products is detrimental to the skeleton, as well as to overall health.

Q3.6. Exercise

Regular weight-bearing exercise (e.g., walking 30 to 40 minutes per session, plus back and posture exercises for a few minutes, 3 to 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 (162). 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 (163-167).

BMD effects of exercise are modest, but a meta-analysis concluded that the exercise-induced improvement in lumbar spine and femoral neck BMD would reduce osteoporosis fracture risk by approximately 10% (168). 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 (169). Both home and group exercise programs reduce falls (170); exercises that challenge balance and improve trunk muscle strength produce a greater reduction in risk of falls (167,171).

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.

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 (172,173). Twenty to 30% of persons who fall suffer moderate-to-severe injury (174,175). A higher percentage of women with osteoporosis have a history of falling within the prior year than women without osteoporosis (176). This association has been ascribed to shared risk factors, such as age, muscle weakness, and sedentary lifestyle (177). Indeed, a French guideline supported BMD measurement in individuals at high risk of falling (177,178).

Table 15 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 (179). 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 (166,170,180); a meta-analysis found decreased fracture risk with exercise, but fracture numbers were small and the possibility of publication bias was raised (181). The relationship of vitamin D with falls is unclear; some, but not all, meta-analyses found vitamin D supplementation reduced fall risk (182,183), and a randomized controlled trial failed to find a decrease in falls with vitamin D (184). Annual high-dose vitamin D, however, was associated with an increased risk of falls (119). Rigorous prospective studies are needed to clarify the role of vitamin D deficiency in risk of falls. In the interim, assurance of a normal 25(OH)D status in patients with osteoporosis is appropriate.

Q3.8. Exercises and Proper Body Mechanics

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. AACE strongly endorses lifelong physical activity for cardiovascular health, osteoporosis prevention, and overall health. Weight-bearing exercise includes walking, jogging, Tai Chi, stair climbing, and dancing, among other activities. Muscle-strengthening exercise includes

weight training and other resistive exercises. Before initiating an exercise program in an individual with osteoporosis, a clinician's evaluation is recommended. Physical therapy plays an important role in the effort to mitigate sarcopenia and reduce risk of falls.

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 use of orthotics may help reduce discomfort, prevent falls and fractures, and improve quality of life (185). Table 16 summarizes the recommendations for lifestyle modifications.

Q4. Who Needs Pharmacologic Therapy?

AACE strongly recommends pharmacologic therapy for the following patients:
a. Those with a T-score between −1.0 and −2.5 in the spine, femoral neck, total hip, or 1/3 radius and a history of fragility fracture of the hip or spine (186-195).
b. Those with a T-score of −2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius (189,193,194,196-205).
c. Those with a T-score between −1.0 and −2.5 in the spine, femoral neck, total hip, or 1/3 radius, if the FRAX® (or if available, TBS-adjusted 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 (206-208).

Table 15
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

Table 16
Recommendations Regarding Lifestyle Issues
Ensure adequate intake of calcium
Ensure adequacy of vitamin D intake
Consume a balanced diet
Regularly perform weight-bearing and balance exercises
Avoid use of tobacco
Limit alcohol consumption
Take measures to avoid falls

Q4.1. Decision-Making on Pharmacologic Therapy

Therapeutic intervention thresholds vary from country to country based on the cost of treatments, the approach taken to setting the intervention threshold, and available therapeutic modalities and resources (206,209). To be most effective, 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.

Q4.2. Stratification of Fracture-Risk Categories

Pharmacologic therapy to reduce fracture risk is indicated when fracture risk is high based on T-scores between −1.0 and −2.5 and a history of fragility fracture of the hip or spine, and T-scores between −1.0 and −2.5 and a FRAX® 10-year probability of major osteoporotic fracture ≥20% or 10-year probability of hip fracture ≥3% in the U.S. or above country-specific threshold in other countries or regions. It is important to note that these criteria were based on a pharmacoeconomic analysis from a decade ago. Were the same quality-adjusted life year criterion applied today, the treatment thresholds would be notably lower.

When starting treatment, it is appropriate to stratify patients by level of fracture risk, since this may influence selection of initial treatment. Most patients are started on treatment because of high fracture risk. Some who are at very high fracture risk may require more aggressive treatment to achieve an acceptable level of fracture risk. There is evidence supporting superiority of anabolic agents over antiresorptive agents in reducing vertebral fracture risk in very high fracture risk patients (210-213). Patients at very high fracture risk include those with a recent fracture (e.g., within the past 12 months), those that have fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), those with a very low T-score (e.g., less than −3.0), high risk of falls or history of injurious falls, and those with a very high fracture probability by FRAX® (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm (214-217).

Q4.3. Assessment of Fracture Risk in Special Populations

FRAX® underestimates fracture risk among patients with diabetes mellitus (218). Analyses from three prospective cohort studies (Study of Osteoporotic Fractures, Osteoporotic Fractures in Men Study, and the Health, Aging, and Body Composition study) found that for the same T-score, age, and FRAX® score, those with diabetes had higher fracture risks than those without. Conversely, for similar fracture risks, individuals with diabetes had higher T-scores than those without diabetes (219). This could be due to several pathophysiologic processes that occur in diabetes and could even be medication induced (thiazolidinediones, canagliflozin).

Significantly lower TBS and higher TBS-adjusted FRAX® scores are found in patients with type 2 diabetes mellitus with prevalent vertebral fractures compared with patients with type 2 diabetes mellitus without vertebral fractures; however, no BMD differences were found between these two groups (220).

Rheumatoid arthritis may be entered into the FRAX® algorithm as a surrogate for fracture risk associated with type 2 diabetes mellitus (221). Additionally, adjusting FRAX® scores using TBS could be a useful tool for this population.

Q4.4. Review of Evidence or Expert Opinion to Support Recommendations for Medication Based on Category of Fracture Risk

Many large randomized trials have documented the efficacy of various pharmaceutical agents in reducing fracture risk (186-189,192-194,201,202,222-224). It is intuitive that agents which stimulate bone formation (anabolic treatment) and restore degraded bone microarchitecture could be expected to have greater effects on BMD and fracture reduction than those that inhibit bone breakdown (antiresorptive therapies). Consistent with this, an increasing body of evidence documents superiority of anabolic agents. For example, from results among patients treated with glucocorticoids, teriparatide produced a greater lumbar spine BMD increase (7%) than did alendronate (3.4%) and a greater reduction in vertebral fracture incidence (6.1% vs. 0.6%) (210). Similarly, in high-risk patients, teriparatide produced greater increase in BMD and greater reduction in incidence of vertebral fracture than risedronate (211,212). Providing further support for the superiority of anabolic therapy, patients who received 1 year of an anti-sclerostin agent (romosozumab) experienced substantially reduced vertebral fracture and incidence of clinical fracture than alendronate (213). Moreover, in the setting of prior antiresorptive therapy, initiation of teriparatide is followed by a reduction in hip BMD, causing some experts to advocate anabolic therapy as initial osteoporosis treatment for high-risk patients or any patient with a T-score of −2.5 or worse, followed by antiresorptive therapy (225).

Q5. What Medication Should Be Used to Treat Osteoporosis?

Several agents are approved by the FDA for prevention and/or treatment of postmenopausal osteoporosis, as shown in Table 17. Full prescribing information should be reviewed before recommending any specific agent.

Head-to-head trial data are limited (212). Four agents (alendronate, risedronate, zoledronate, and denosumab)

have evidence for "broad-spectrum" antifracture efficacy (spine, hip, and nonvertebral fracture risk reduction) and should, in the absence of contraindications, be considered as initial options for most patients who are candidates for treatment (Table 18) (52,188,189,202,212,223,226). Those who have "high fracture risk" (for example, postmenopausal women with no prior fractures and moderately low T-scores) can be started on oral agents. Injectable agents such as abaloparatide, denosumab, romosozumab, teriparatide, or zoledronate can be considered as initial therapy for those who are at very high fracture risk (for example, older women who have had multiple vertebral fractures or hip fractures, or who have very low T-scores), those who have GI problems and might not tolerate or absorb oral medication, and for patients who have trouble remembering to take oral medications or coordinating an oral bisphosphonate with other oral medications or daily routine. Importantly, patients taking the anabolic agents or denosumab are advised to transition to an oral bisphosphonate when the course of therapy is complete to avoid bone loss after stopping those drugs. Anabolic and dual-action agents may be preferable for patients at very high risk of fracture as initial therapy. For patients at high risk of spine fracture but not at risk for hip or nonvertebral fractures, raloxifene may be appropriate and has a "side benefit" of reducing the risk of breast cancer.

Denosumab is not contraindicated in patients with renal insufficiency, and no dose adjustment is required in these patients. However, the risk of hypocalcemia upon starting denosumab appears to be greater in patients with significantly impaired renal function. There is minimal experience with the use of denosumab in dialysis patients.

Q5.1. How Are Bisphosphonates Used?

Bisphosphonates, first introduced in the 1990s, have been the most widely used drugs for treatment of 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., four bisphosphonates are available (alendronate, ibandronate, risedronate, and zoledronate) (187-189,202,223,227); three of the four (alendronate, risedronate, and zoledronate) have evidence for broad-spectrum antifracture efficacy (188,189,202,223). 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 to 60 minutes), the presence of anatomic or functional esophageal abnormalities that might delay transit of the tablet (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.) (228). 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 (229).

Contraindications to oral or intravenous (IV) bisphosphonate therapy include drug hypersensitivity or hypocalcemia. Bisphosphonates should be used with caution, if at all, in patients with reduced kidney function (glomerular filtration rate [GFR] <30 mL/min for risedronate and ibandronate or <35 mL/min for alendronate). Prior to the administration of zoledronate, a creatinine clearance should be calculated based on the serum creatinine and actual body weight using the Cockcroft-Gault formula before each dose. For most patients, there is little difference between estimated GFR and Cockcroft-Gault, but it can be significant. The prescribing information says not to give to "patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment" (230). Rapid IV administration of nitrogen-containing bisphosphonates may cause transient or permanent decreases in kidney function, especially in older patients, with dehydration or those using diuretics or potentially nephrotoxic drugs (231,232).

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 (233). 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 (234) but usually resolve on discontinuation. The possible association between orally administered bisphosphonates and esophageal cancer has been explored. One study suggested no increased risk (235), and one 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 (236). The FDA concluded that there is no definite association between bisphosphonate use and esophageal cancer (237). Atrial fibrillation as a serious adverse event was noted in the Health Outcomes

and Reduced Incidence with Zoledronic acid (zoledronate) ONce yearly (HORIZON) Pivotal Fracture Trial (202), but was not seen in other trials of zoledronate or other bisphosphonates and is thought by the FDA to be a chance finding.

Osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFFs) are safety concerns not only with bisphosphonates but with other agents as well and will be discussed elsewhere.

Q5.2. How Is Denosumab Used?

Denosumab is a fully humanized monoclonal antibody that prevents receptor activator of nuclear factor kappa-B ligand from binding to its receptor, receptor activator of nuclear factor kappa-B, 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 injection every 6 months. In a 3-year, pivotal placebo-controlled clinical trial of 7,808 women with postmenopausal osteoporosis (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months [FREEDOM] Trial), denosumab showed "broad-spectrum" antifracture efficacy as early as 12 months after starting therapy. Studies

of denosumab treatment with duration of up to 10 years indicate persistent fracture protection and a good safety profile (238). Switching from bisphosphonates to denosumab results in additional gains in BMD (239). Denosumab is contraindicated in patients with hypocalcemia, who often have hypoparathyroidism or osteomalacia (240). Intakes of calcium and vitamin D should be adequate upon starting denosumab treatment to minimize the risk of hypocalcemia (193,226,240-242). In the FREEDOM study, there was an imbalance in some low-frequency events (skin rash and cellulitis, serious adverse events related to infection) that did not seem causally related to denosumab treatment (243), did not increase in frequency with long-term therapy (238), 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 or 8 years, BMD decreased rapidly, and BTMs increased to values above baseline by 12 months after discontinuation (237,240). Protection from vertebral fractures is quickly lost, but the risk does not usually exceed that in untreated patients (244). Case reports of multiple vertebral fractures upon stopping denosumab therapy have been reported (245,246). Drug holidays from denosumab are

Table 17 **Drugs Approved by the U.S. Food and Drug Administration for Prevention and Treatment of Postmenopausal Osteoporosis**[a]		
	Postmenopausal Osteoporosis	
Drug	**Prevention**	**Treatment**
Abaloparatide (Tymlos)	—	80 μg SQ daily
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 months
Estrogen (multiple formulations; estrogen-bazodoxifene)	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 months
Raloxifene (Evista)	60 mg PO daily	60 mg PO daily
Risedronate (Actonel, Atelvia, generic form)[d]	5 mg PO daily 35 mg PO weekly 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 150 mg PO monthly
Romosozumab (Evenity) Teriparatide (Forteo)	— —	20 μg SQ daily 210 mg SQ monthly
Zoledronate (Reclast, generic infusion form)	5 mg IV every 2nd year	5 mg IV once yearly
Abbreviations: IV = intravenously; PO = orally; qod = every other day; SQ = subcutaneously. [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.		

Table 18 Summary of Evidence for Reduction of Fracture Risk with Pharmacologic Agents			
	Reduction of Fracture Risk		
Drug	**Vertebral**	**Nonvertebral**	**Hip**
Abaloparatide (Tymlos) (273, 282) Alendronate (Fosamax) (223)	Yes Yes	Yes Yes	No effect demonstrated[a] Yes
Calcitonin (Miacalcin, Fortical) (191)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Denosumab (Prolia) (193, 242)	Yes	Yes	Yes
Ibandronate (Boniva) (187, 227)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Raloxifene (Evista) (192)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Risedronate (Actonel, Atelvia) (188, 189) Romosozumab (Evenity) (213, 283)	Yes Yes	Yes [b]	Yes [b]
Teriparatide (Forteo) (194, 306)	Yes	Yes	No effect demonstrated[a]
Zoledronate (Reclast) (202)	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.
[b]Clinical fracture reduction was shown in both trials. Nonvertebral and hip fracture reductions were shown at month 24 for patients receiving 12 months of romosozumab followed by 12 months of alendronate compared with patients receiving 24 months of alendronate (213).

not recommended due to this potential increased fracture risk. However, it should be noted that it is uncertain how commonly multiple vertebral fractures occur and how best to optimally prevent this phenomenon.

Although much more data are needed to determine the clinical magnitude of this issue, patients should be informed about the importance of not missing a dose of denosumab. If treatment is discontinued, patients should be transitioned to an alternative antiresporptive therapy. There is concern that using an IV antiresorptive may not be effective if it is given before the inhibitory effect of the denosumab has worn off.

Q5.3. How Is Calcitonin Used?

Injectable and nasal spray recombinant salmon calcitonin are approved by the FDA for treatment of postmenopausal osteoporosis (247,248). The approved dosage of injectable calcitonin for treatment of postmenopausal osteoporosis is 100 IU daily given subcutaneously 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 (247,248). For patients with suspected sensitivity to the drug, skin testing is recommended before treatment.

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 (191). Calcitonin produces a minimal increase in BMD in the spine in women >5 years after onset of menopause but does not increase BMD at sites other than the spine (191,249).

A clinical study of 5 years' duration indicated a good safety profile (191). 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 (247,248).

Safety and efficacy data are available through 5 years (191). When use of calcitonin is stopped, the skeletal benefits are lost relatively quickly during the subsequent 1 or 2 years.

Primarily because more effective agents are available to increase bone density and reduce fracture risk, we recommend limiting the use of calcitonin as long-term treatment for osteoporosis. Because of a suggestive analgesic effect (250-254), short-term prescriptions are often given to patients with acute painful vertebral fractures with hopes of an analgesic effect.

A meta-analysis of 21 randomized clinical trials of nasal spray calcitonin and an investigational oral calcitonin formulation showed a higher incidence of malignancy in the calcitonin-treated patients (255,256). The FDA did not find sufficient evidence to establish a causal relationship between calcitonin administration and cancer risk but urged that the risks and benefits of the various osteoporosis treatment options be weighed for individual patients.

Q5.4. 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 (257) 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 (257). Raloxifene has been shown to reduce the risk of fractures of the spine (192), but neither nonvertebral nor hip fracture efficacy has been demonstrated (238).

In an osteoporosis trial with raloxifene, a significant reduction in breast cancer was seen (258). This finding was confirmed in a larger trial of women at high risk of breast cancer (259). 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. For patients with low BMD in the spine but not in the hip (discordance), however, 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 use of two antiresorptive drugs in combination 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 (259). Other side effects include menopausal symptoms (e.g., hot flashes and night sweats) and leg cramps (260).

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

Q5.5. Selective Estrogen-Receptor Modulators/Conjugated Equine Estrogens

The selective estrogen-receptor modulator, bazedoxifene, has been studied and is FDA approved in a combination pill with conjugated equine estrogen. The rationale was that such a combination would improve BMD and reduce hot flashes, but without some of the other adverse effects on the endometrium and breast associated with estrogen therapy alone (261,262). In a study by Lindsey et al (263), the combination of bazedoxifene and estrogen in 3,997 postmenopausal women showed a statistically significant increase in BMD at multiple sites over 2 years compared with placebo, along with a decrease in BTMs. In addition to the favorable effects on bone, bazedoxifene-conjugated estrogen therapy significantly reduced the frequency and severity of hot flushes and improved vulvar-vaginal atrophy and its symptoms compared with placebo, with a good tolerability profile (264).

A 3-year, randomized, double-blind study performed in 7,492 postmenopausal women with osteoporosis showed a reduction in new vertebral fractures with bazedoxifene but not in nonvertebral fractures (265). An extension of this study demonstrated the efficacy and safety of bazedoxifene over 7 years in this group with similar fracture data (266). The bazedoxifene-conjugated estrogen combination comes as a once-a-day tablet. It carries a boxed warning that there is an increased risk for endometrial cancer in women with a uterus who take unopposed estrogens. There are data that this medication reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Other warnings that come with estrogen therapy alone also apply, including that this medication should be given for the shortest duration necessary consistent with the goals and risks for the individual patient. Unlike raloxifene, the effect of treatment with this combination medication on the risk of breast cancer is unknown. A recent review of this formulation concluded that there was a significant reduction in vasomotor symptoms, improved sleep, protection of bone tissue, and improvement in vaginal atrophy with no stimulation of breast tissue, endometrial tissue, or increase in cardiovascular risk (267). This medication has not been studied in patients over 75 years of age.

Indications for bazedoxifene-conjugated estrogens are for women with a uterus with moderate-to-severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis. The package insert states that when this medication is prescribed solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis, and non-estrogen medication should be carefully considered (268). Based on its data and mechanism of action, this medication serves a very limited use in the prevention or treatment of postmenopausal osteoporosis and likely would not be selected except for in very specific situations and ideally in conjunction with a gynecologist.

Q5.6. 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. Estrogen is approved by the FDA for prevention of postmenopausal osteoporosis with the 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 non-estrogen medications are not considered to be appropriate" (268).

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. 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 (269,270). The extraskeletal effects of estrogen have generated considerable controversy, particularly regarding 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.

Q5.7. How Are Anabolic Agents (Abaloparatide and Teriparatide) Used?

Abaloparatide (modified PTH-related peptide 1-34) (271) and teriparatide (recombinant human PTH1-34) are considered "anabolic" agents (by contrast, the medications discussed above work by reducing bone resorption). Both are 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 (271,272). Teriparatide is also approved for treatment of glucocorticoid-induced osteoporosis and treatment of osteoporosis in men. Both are injected subcutaneously. Abaloparatide does not require refrigeration after use. The dose of abaloparatide is 80 μg daily, while teriparatide is given at 20 μg daily. It is prudent to measure serum calcium, PTH, and 25(OH)D levels, and alkaline phosphatase (to rule out Paget disease) before treatment with either medication.

Both abaloparatide and teriparatide have been shown to increase BMD and reduce the risk of vertebral and nonvertebral fractures in women with postmenopausal osteoporosis in randomized controlled trials (194,273), but the incidence of hip fracture was low in these trials; whether anabolic agents protect against hip fracture is not known. In a head-to-head trial, gains in BMD were greater with abaloparatide compared with teriparatide, especially in the femoral neck, total hip, and 1/3 radius. Fracture reduction was numerically greater with abaloparatide than with teriparatide, although the difference between active arms was only significant for major osteoporosis-related fractures. Patients who lose BMD in the hip with teriparatide treatment are still protected against vertebral fracture compared with placebo related to improvements in bone geometry and microarchitecture (274).

Side effects of both abaloparatide and teriparatide have been 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 (271,272) and less likely with abaloparatide than with teriparatide. If serum calcium is measured, the blood should be drawn at least 16 hours after drug administration.

Both abaloparatide and teriparatide have boxed warnings because of the occurrence of osteosarcomas in rats treated with very high doses (275). Subsequent studies in the same strain of rats showed no development of malignant bone tumors with doses of teriparatide up to 3 times higher than the human equivalent dose (276). Because of the increased incidence of osteosarcomas in rats, abaloparatide and teriparatide 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) (271,272). 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 (277,278). Abaloparatide and teriparatide also should not be administered to patients with primary or any form of secondary untreated or unresolved hyperparathyroidism (271,272). Both abaloparatide and teriparatide are limited to no longer than 2 years in total duration (271,272).

When treatment with teriparatide is stopped, bone density declines quickly during the following year, although fracture reduction may persist for 1 or 2 years (279). Use of bisphosphonates or denosumab after teriparatide therapy prevents this loss and may result in a further increase in BMD (272,280,281). Alendronate has also been studied after abaloparatide, with similar results (282). Available data demonstrate that treatment with either teriparatide or abaloparatide should routinely be followed by antiresorptive therapy, typically with either a bisphosphonate or denosumab followed by an oral bisphosphonate. There is no apparent rationale for a "washout period" or "drug holiday" between the end of anabolic therapy and the initiation of antiresorptive treatment.

There are several studies in which teriparatide was used in patients treated with oral bisphosphonates, either previously or concurrently. None were large enough to assess fracture risk reduction, but BMD and BTM changes appeared to be "blunted" because of the previous bisphosphonate therapy. In a small study in which patients first received 2 years of denosumab, BMD decreased for 6 to 12 months after they were changed to teriparatide (281). It is probably not advisable to use teriparatide (or abaloparatide) if denosumab is stopped, but teriparatide (and probably abaloparatide) may be added to ongoing denosumab therapy.

Q5.8. What Is Romosozumab and What Is Its Role?

Romosozumab is a monoclonal antibody directed against sclerostin. Sclerostin binds with the Wnt receptor and inhibits the differentiation of precursor cells into

mature bone-forming osteoblasts. Blocking sclerostin binding to osteoblasts allows osteoblast activity to increase. BTMs suggest an early anabolic effect, bone density increases are dramatic, and biopsies indicate an anabolic effect through both modeling (increase in cross-sectional area) and remodeling (bone repair). Approval of romosozumab for postmenopausal women at high risk of fracture was based on two large trials. In the larger of the two trials (N = 7,180) (283), patients received either subcutaneous romosozumab 210 mg monthly or placebo for 12 months; then, all patients received denosumab. In the other trial (N = 4,093) (213), patients received monthly romosozumab or oral alendronate (double-blind, double-dummy) for 12 months; then, all received open-label alendronate. Both trials showed significant reductions in radiographic vertebral fractures at 12 months (73% reduction vs. placebo, 34% reduction vs. alendronate) and 24 months (75% for romosozumab followed by denosumab compared with placebo followed by denosumab, 48% for denosumab followed by alendronate compared with alendronate for 2 years). Clinical fractures were also significantly reduced in both trials at 12 and 24 months by 27 to 33%. Nonvertebral fracture reduction (19%) and hip fracture reduction (38%) were significant only in the smaller trial at 24 months (213). In a 12-month study of romosozumab versus teriparatide versus placebo (N = 367), Genant et al (284) found changes in total spine (17.7%, 12.9%, –0.8%, respectively) and total hip (4.1%, 1.2%, and 0.3%, respectively) with QCT (high-resolution computed tomography scan). Langdahl et al (285) enrolled 436 patients with at least 3 years of oral bisphosphonate therapy (mean, 6.2 years) who were then assigned to 12 months of either romosozumab or teriparatide. Greater gains in BMD were seen with romosozumab in the lumbar spine (9.8% vs. 5.4%), femoral neck (3.2% vs. –0.2%), and total hip (2.9% vs. –0.5%).

Romosozumab will likely be viewed as a "rescue drug" for patients at very high fracture risk" in the near term. It is an option for patients previously treated with teriparatide or abaloparatide, and future retreatment with romosozumab may be possible. Romosozumab can be used in patients with prior radiation exposure. In the smaller of the phase 3 trials (N = 4,093), serious cardiovascular events were significantly more common with romosozumab compared with the alendronate control group (213), but the increased risk did not persist and was small. Because of this, the black-box warning for romosozumab states that it should not be used in patients at high risk for cardiovascular events or who have had recent myocardial infarction or stroke.

Romosozumab has also been studied in men (286) but is not currently approved for male osteoporosis.

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 (287). 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 (288). 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 (64,289,290). A bone-loss calculator can be found on the ISCD website (www.iscd.org). One SD is about 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 about 1.0 T-score units. Serial monitoring is based on absolute BMD and not T-scores.

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 (291).

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 (292). In treated patients, if BMD decreases significantly, patients should be evaluated for noncompliance, secondary causes of osteoporosis, or use of medications that might cause bone loss (293).

Differences between BMD results may simply reflect the inherent variability of the test measurement; thus, testing facilities must calculate the 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 (294,295). 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) (294,295). 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 (ROIs), 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.

Ideally, BMD monitoring should occur at the same facility, using the same DXA machine and, if possible, the same technologist as the previous DXA and should involve the same ROIs for both the spine and hip (58,296). The 1/3 radius site is also acceptable, when spine and hip sites are not evaluable (7,297,298). It must be noted that two of the three manufacturers of DXA instruments calibrate their spine BMD for the same ROI (spine), so that, for the same patient, GE's Lunar DXA gives a BMD 20% higher than Hologic's DXA. 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. 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 postero-anterior spine, are more metabolically active, a significant change is likely to occur earlier at the spine than at the hip.

Skeletal status also can be examined by assessing the development or progression of asymptomatic vertebral fractures, using lateral X-rays of the thoracic and lumbar spine or VFA (66-70,299,300).

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 (292).

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. Randomized trials have demonstrated a reduction in fracture risk in patients with stable or increasing BMD receiving pharmacologic therapy, in particular, use of bisphosphonates for osteoporosis treatment compared with those receiving placebo (188,189,202,223). In addition, larger increases in BMD may result in increased reduction of fracture risk; however, this association has not been consistently shown (301-303).

The goal of treatment is prevention of fractures, but no treatment can eliminate risk of fracture. A fracture during therapy is not necessarily a treatment failure but 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 (40,304). The number, severity, and recency of vertebral fractures are directly correlated with the risk of future fractures (305,306).

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 treat-to-target goals (307,308), as are used in the management of some other chronic silent diseases, such as hypertension and diabetes. Consequently, an American Society for Bone and Mineral Research (ASBMR)/NOF task force was formed to review the medical evidence, determine the feasibility of developing treat-to-target goals, propose targets (if possible), and recommend an agenda for further study. At this time, treatment targets have not been identified.

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 (292). Nevertheless, it is reasonable that a patient with significant bone loss or one 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. Furthermore, the change in BMD accounts for <20% of the fracture risk reduction following antiresorptive therapy (88, 309). Finally, although it has been suggested that BMD monitoring might improve patient compliance, nonadherence to therapy usually occurs early (after 6 to 7 months), before the second BMD would be performed (310).

When treatment is initiated due to a low DXA T-score (such as −2.5 or lower), 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 BTMs is also a possible treatment target. There are strengths and weaknesses to each of these strategies, which have been described in detail elsewhere (307). There are many challenges to identifying one 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. Treat-to-target goals 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.

Q8. How Long Should Patients Be Treated?

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

ONJ was first reported in patients with advanced cancer receiving high-dose bisphosphonate therapy. Head-to-head trials in advanced cancer patients showed an incidence of 1 to 2% per year with zoledronate (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 in patients who do not have cancer). 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 (311-314) and appears to be low with denosumab therapy for osteoporosis, with 5.2 cases per 10,000 patient-years (193,315). 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 should at least be considered for patients undergoing extensive invasive dental procedures such as extraction of several teeth (316).

AFF of the subtrochanteric region is another rare event that seems to be increased with long-term bisphosphonate therapy (>5 years duration) and is also rarely seen with the higher dosing frequencies used in advanced cancer treatment (317-320). It is estimated that treatment of 1,000 women with osteoporosis for up to 3 years would be associated with fewer than 1 AFF per 100 osteoporotic fractures prevented (321). 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% (322). 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 obtained. 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 the use of bisphosphonates is not clear. Evidence for AFFs has been reviewed by a task force of the ASBMR (318,322). 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 (323). Because these fractures can occur in patients not on any treatment, unless a new drug for osteoporosis prevents this type of fracture, "atypical" fractures will be seen eventually with any agent. Interestingly, a recent cohort study suggested that these fractures are not associated with excess mortality (324). There is evidence that using anabolic therapy when AFF is diagnosed accelerates fracture healing (325-327).

Definitions and diagnostic criteria for ONJ and AFF are given in Table 19. It is important to remember that the number of fractures that are prevented with osteoporosis treatment far outweighs the risk of ONJ or AFFs (see section on risk communication, Fig. 2 (328).

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 a T-score –2.5 or lower) who stopped treatment had nearly twice as many nonvertebral fractures: 21 (28%) versus 16 (15%) with continued treatment (329), suggesting that longer treatment is better for higher-risk patients. In the first 2 years, the Kaplan-Meier curve for clinical vertebral fractures, however, showed no difference between those who stopped and those who continued, indicating a residual benefit. A 3-year extension study of the zoledronate arms of the HORIZON study showed significantly fewer morphometric spine fractures in patients who continued yearly zoledronate 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 (330). In the second extension of the HORIZON trial, postmenopausal women previously treated with zoledronate 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 treatment compared with 5 reported with 6 years of treatment. Clinical fractures were similar between the two groups, reported in 10 of the patients who continued treatment for 9 years and in 9 patients who received 6 years of therapy (331).

AACE agrees with the ASBMR algorithm for management of patients on long-term bisphosphonate treatment that recommends that patients who are initially at very high

risk and remain at high risk receive a treatment duration of 10 years for an oral bisphosphonate (328,329) or 6 years for IV zoledronate (330-332). The risk-benefit ratio for treatment beyond 10 years has not been investigated and remains unknown. For patients at "high fracture risk," a drug holiday can be considered after 5 years of stability on oral bisphosphonates or 3 years of IV zoledronate. For patients at very high fracture risk, a non-bisphosphonate treatment (teriparatide) may be offered during the holiday from the bisphosphonate.

The optimal duration of a bisphosphonate holiday has not been established. Two recent retrospective studies have suggested that the risk of new clinical fractures is higher in patients on a bisphosphonate holiday (333,334), especially if their T-scores equal or are worse than –2.5 (283). Patient selection and monitoring during bisphosphonate holidays are important. The rank order for binding affinity for bone is zoledronate > alendronate > risedronate; logic suggests that the holiday might be longest after treatment with zoledronate, shortest after treatment with risedronate, and intermediate after treatment with alendronate (335). In addition, consider resuming therapy in patients who experience fracture or show significant BMD loss. Some experts feel that a rise in bone resorption markers (e.g., CTX or N-terminal telopeptide type-I collagen) to pretreatment levels might be a signal that the holiday should be over, but this is debatable and may not apply to patients with osteoporosis who had low bone resorption markers before treatment was started.

## 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 (336). 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 the BMD and bone turnover response, depending on which antiresorptive agent is used (337).

There is evidence that some combinations may enhance the rapidity of BMD changes. For example, while teriparatide increases lumbar spine BMD more than zoledronate and zoledronate increases hip BMD more than teriparatide, a single dose of IV zoledronate given at the same time as starting teriparatide results in the most rapid increase in BMD at both the lumbar spine and hip (222). 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 (338). However, in contrast to the effects of teriparatide monotherapy, markers of bone formation are reduced with combination therapy, and no fracture data are available.

Combination therapy substantially increases the cost and probably increases the potential for side effects. Until the effect of combination therapy on fracture risk is better understood, AACE does not recommend concomitant use

Table 19 ONJ and AFF: Definitions and Diagnostic Criteria (313, 318, 369)	
Osteonecrosis of the jaw (ONJ)	The presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health-care professional.
Atypical femoral fracture (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 diaphysis. • 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.
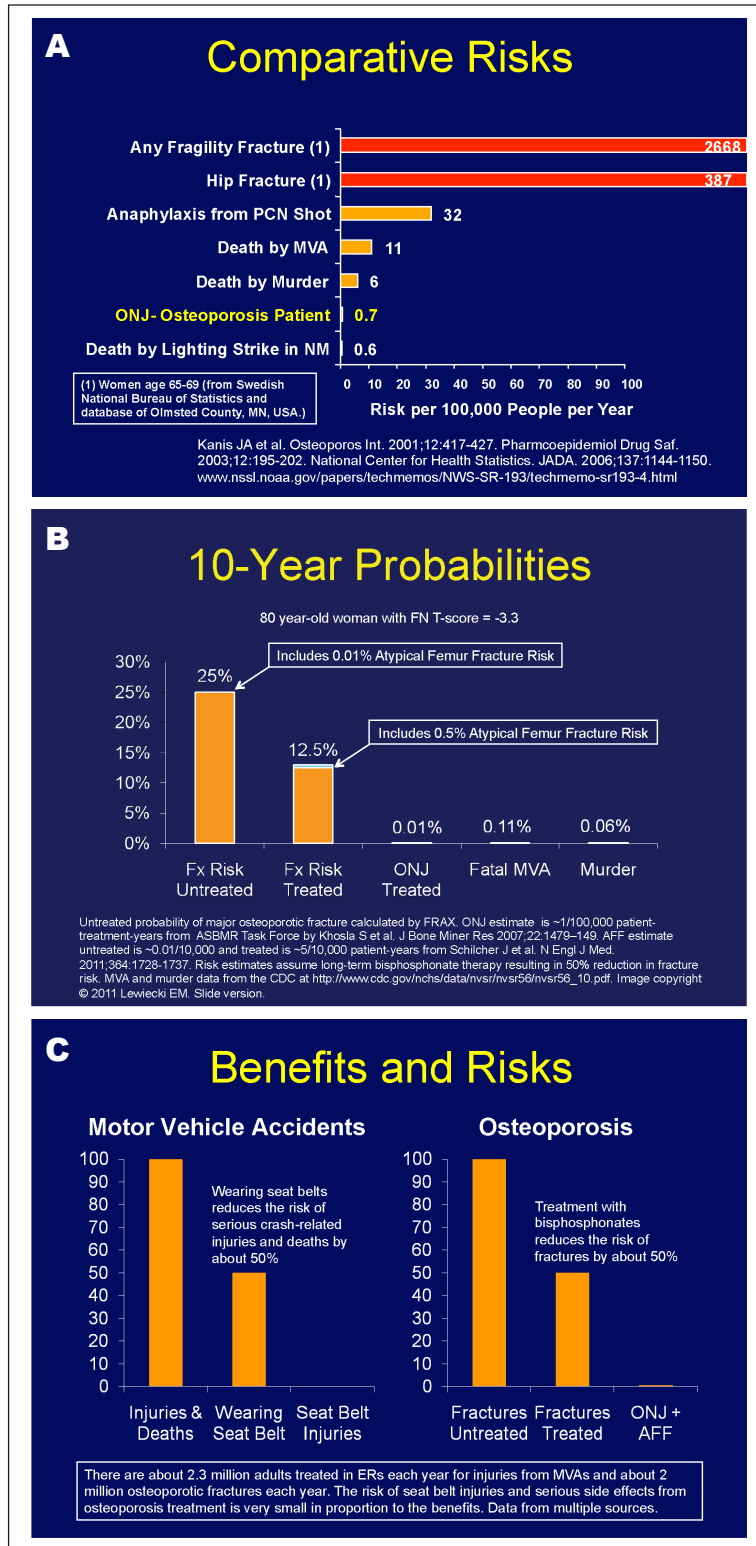
Fig. 2. Comparative risk of fracture, osteonecrosis of the jaw (ONJ), and other events in women age 65 to 69 years (*A*) (371-373); 10-year probability of fracture in treated and untreated patients, ONJ in treated patients, and other events in an 80-year-old woman (*B*) (313, 369); and benefits and risks of treatment in osteoporosis compared with seat-belt intervention in motor vehicle accidents (*C*). *AFF* = atypical femoral fracture; *ERs* = emergency rooms; *FN* = femoral neck; *Fx* = fracture; *MVA* = motor vehicle accident; *NM* = New Mexico; *PCN* = penicillin.

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 non-bone reasons, such as breast protection with raloxifene, to continue with these agents, another antiresorptive agent or anabolic therapy could be added to the therapy.

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

Upon discontinuation of an anabolic agent (i.e., abaloparatide, romosozumab, teriparatide), therapy with an antiresorptive agent, such as denosumab, bisphosphonates, or raloxifene, is recommended to prevent loss of BMD and fracture efficacy (222,224,337,339-345). Switching from a bisphosphonate to an anabolic agent can be done, but switching from denosumab to a currently available anabolic agent is associated with loss of hip BMD and is not recommended (281,346).

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 two randomized, controlled studies comparing vertebroplasty versus a control procedure on a primary outcome of overall pain showed no significant benefit from vertebroplasty up to 1 month (347) and up to 6 months (348). A meta-analysis of individual patient data from two blinded trials of vertebroplasty failed to show an advantage of vertebroplasty over placebo for participants with acute fractures (<6 weeks) or severe pain (349). A study with 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 (350).

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 a randomized, controlled trial of 125 patients with vertebral fractures at 12 months' follow-up (351). By 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 (352). In a meta-analysis assessing the safety of balloon kyphoplasty in patients with symptomatic osteo-porotic 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 (353). Given the limitations to these published studies, the role for surgical procedures in treatment of vertebral fractures remains uncertain.

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

Referral to a clinical endocrinologist or other 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 such as young age or abnormal laboratory testing (e.g., low phosphorus, high or low alkaline phosphatase), artifacts on DXA that are unexplained, and those with a condition that complicates management (e.g., decreased kidney function, 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 (354,355).

COMMUNICATING RISK TO PATIENTS

Risk communication has been defined in general terms as "the study and practice of collectively and effectively understanding risks" (356). When applied to health-care 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" (357). 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 (358). 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. Estimation of fracture risk should consider that T-score must be combined with clinical risk factors, especially advanced age and previous fracture, and recognize that absolute fracture risk is more useful than RR in developing treatment plans. Treatment recommendations may be quite different; an early postmenopausal woman with a T-score of –2.5 has osteoporosis, although fracture risk is much lower than an

80-year-old woman with the same T-score. Effective risk communication imparts to the patient a good understanding of fracture risk with no treatment compared with the balance of benefits and risks with treatment.

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 (358-360), a process by which a plan of management is developed with active participation of the patient. 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 (361). The medical evidence on efficacy and safety of treatment options may be complex, incomplete, 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 health-care 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 (361). 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 (362). 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 for 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 the management of osteoporosis.

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) (357). A systematic review of randomized controlled trials of communication tools found that most formats (verbal, written, video, provider-delivered, and computer-based) increased patients' understanding of the medical evidence (363). Understanding was enhanced when the methods were individualized and/or interactive, with decision aids such as cartoons or graphs helping, as well. It was concluded that there is increasing evidence supporting the design of evidence-based communication tools, although access to these tools in clinical practice was limited. Attentive listening to patients is an important component of risk communication and shared decision-making, with evidence that this is a skill that can be learned (364). A randomized controlled trial 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 (365). Another randomized controlled trial 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 (366). 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 health-care professional after starting osteoporosis treatment appears to be one of the few interventions shown to improve adherence (367,368). Examples of decision aids that illustrate risk in a visual, patient-friendly manner are given in Figure 2. Figure 3 *A* through *C* provides comparisons of risk for osteoporosis, fracture, ONJ, and other events.

More study is needed to determine the most effective means of communicating benefit and risk in the management of osteoporosis. 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.
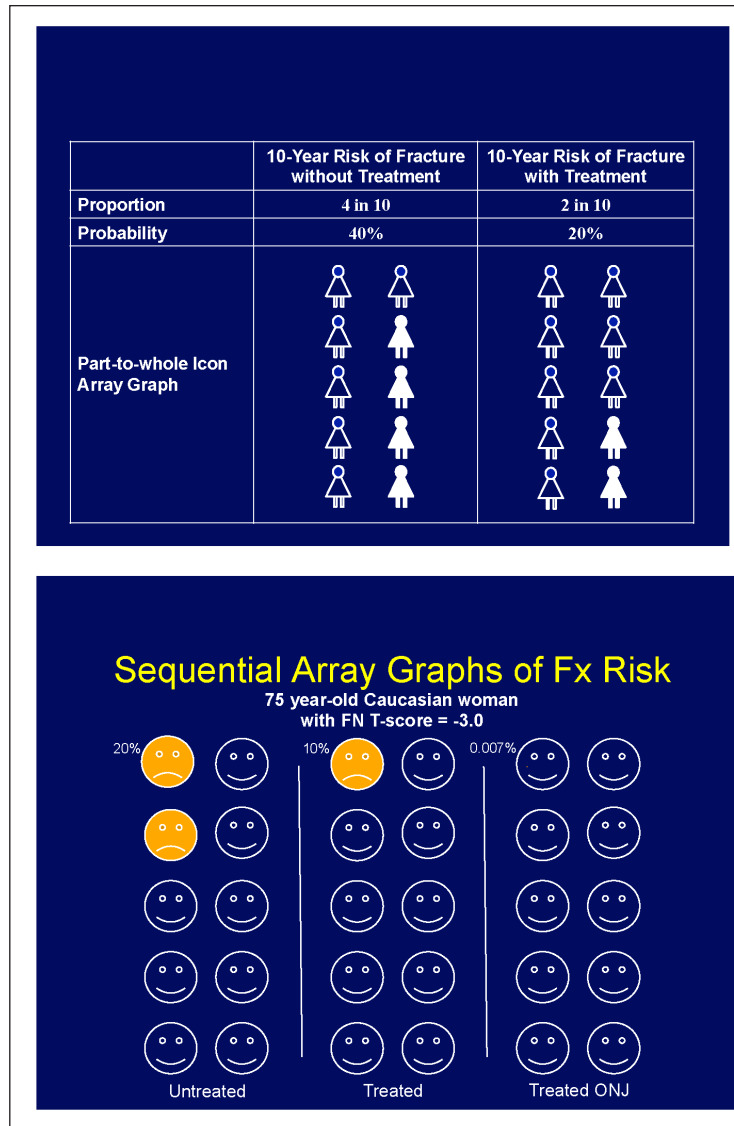
Fig. 3. Examples of visual depictions of fracture risk for use with patients.

AACE/ACE 2020 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

High risk/no prior fractures**

- Alendronate, denosumab, risedronate, zoledronate***
- **Alternate therapy:** Ibandronate, raloxifene

Reasses 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 abaloparatide, romosozumab, or teriparatide if on injectable antiresorptive or at very high risk of fracture
- Factors leading to suboptimal response

Very high risk/prior fractures**

- Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate***
- **Alternate therapy:** Alendronate, risedronate

Reasses yearly for response to therapy and fracture risk

Denosumab	Romosozumab for 1 year	Abaloparatide or teriparatide for up to 2 years	Zoledronate
Continue therapy until the patient is no longer high risk and ensure transition with another antiresorptive agent.	Sequential therapy with oral or injectable antiresorptive agent	Sequential therapy with oral or injectable antiresorptive agent	• If stable, continue therapy for 6 years**** • If progression of bone loss or recurrent fractures, consider switching to abaloparatide, teriparatide or romosozumab

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

** Indicators of very high 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 zoledronate. During the holiday, an anabolic agent or a weaker antiresorptive such as raloxifene could be used.

ABBREVIATIONS GUIDE

BMD – bone mineral density
LSC – least significant change
BTM – bone turnover marker

REFERENCES

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.

1. **Mechanick JI, Pessah-Pollack R, Camacho P, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology protocol for standardized prodcution of clinical practice guidelines, algorithms, and checklists -- 2017 update. *Endocr Pract.* 2017;23:1006-1021.[EL 4; NE]

2. **Mechanick JI, Camacho PM, Garber AJ, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology protocol for standardized production of clinical practice guidelines, algorithms, and checklists--2014 update and the AACE G4G program. *Endocr Pract.* 2014;20:692-702.[EL 4; NE]

3. **Mechanick JI, Camacho PM, Cobin RH, et al.** American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines--2010 update. *Endocr Pract.* 2010;16:270-283.[EL 4; NE]

4. **Mechanick JI, Bergman DA, Braithwaite SS, Palumbo PJ.** American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines. *Endocr Pract.* 2004;10:353-361.[EL 4; NE]

5. **Wright NC, Looker AC, Saag KG, et al.** The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res.* 2014;29:2520-2526.[EL 2; ES]

6. **Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A.** Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res.* 2007;22:465-475.[EL 3; DS]

7. **Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N.** The diagnosis of osteoporosis. *J Bone Miner Res.* 1994;9:1137-1141.[EL 4; NE]

8. **Singer A, Exuzides A, Spangler L, et al.** Burden of illness for osteoporotic fractures compared with other serious diseases among postmenopausal women in the United States. *Mayo Clin Proc.* 2015;90:53-62.[EL 2; ES]

9. **Looker AC, Orwoll ES, Johnston CC Jr, et al.** Prevalence of low femoral bone density in older U.S. adults from NHANES III. *J Bone Miner Res.* 1997;12:1761-1768.[EL 2; ES]

10. **Faulkner KG, von Stetten E, Miller P.** Discordance in patient classification using T-scores. *J Clin Densitom.* 1999;2:343-350.[EL 2; ES]

11. **Melton LJ, 3rd, Lane AW, Cooper C, Eastell R, O'Fallon WM, Riggs BL.** Prevalence and incidence of vertebral deformities. *Osteoporos Int.* 1993;3:113-119.[EL 2; ES]

12. **NIH Consensus Development Panel on Osteoporosis Prevention D, and Therapy.** Osteoporosis prevention, diagnosis, and therapy. *JAMA.* 2001;285:785-795.[EL 4; NE]

13. **Guglielmi G, Muscarella S, Bazzocchi A.** Integrated imaging approach to osteoporosis: state-of-the-art review and update. *Radiographics.* 2011;31:1343-1364.[EL 4; NE]

14. **Leslie WD, Majumdar SR, Lix LM, et al.** High fracture probability with FRAX usually indicates densitometric osteoporosis: implications for clinical practice. *Osteoporos Int.* 2012;23:391-397.[EL 2; ES]

15. **Siris ES, Adler R, Bilezikian J, et al.** The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. *Osteoporos Int.* 2014;25:1439-1443.[EL 4; NE]

16. **Siris ES, Boonen S, Mitchell PJ, Bilezikian J, Silverman S.** What's in a name? What constitutes the clinical diagnosis of osteoporosis? *Osteoporos Int.* 2012;23:2093-2097.[EL 4; NE]

17. **Wainwright SA, Marshall LM, Ensrud KE, et al.** Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab.* 2005;90:2787-2793.[EL 2; PCS]

18. **Barr RJ, Stewart A, Torgerson DJ, Reid DM.** Population screening for osteoporosis risk: a randomised control trial of medication use and fracture risk. *Osteoporos Int.* 2010;21:561-568.[EL 1; RCT]

19. **Hiligsmann M, Gathon HJ, Bruyère O, Ethgen O, Rabenda V, Reginster JY.** Cost-effectiveness of osteoporosis screening followed by treatment: the impact of medication adherence. *Value Health.* 2010;13:394-401.[EL 3; ECON]

20. **Nayak S, Roberts MS, Chang CC, Greenspan SL.** Health beliefs about osteoporosis and osteoporosis screening in older women and men. *Health Educ J.* 2010;69:267-276.[EL 2; ES]

21. **Nelson HD, Haney EM, Dana T, Bougatsos C, Chou R.** Screening for osteoporosis: an update for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2010;153:99-111.[EL 4; NE]

22. **Thompson M, Evitt CP, Whaley MM.** Screening for falls and osteoporosis: prevention practice for the hand therapist. *J Hand Ther.* 2010;23:212-228; quiz 229.[EL 4; NE]

23. **Rubin KH, Rothmann MJ, Holmberg T, et al.** Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study. *Osteoporos Int.* 2018;29:567-578.[EL 1; RCT]

24. **Shepstone L, Lenaghan E, Cooper C, et al.** Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. *Lancet.* 2018;391:741-747.[EL 1; RCT]

25. **Viswanathan M, Reddy S, Berkman N, et al.** Screening to prevent osteoporotic fractures: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2018;319:2532-2551.[EL 2; MNRCT]

26. **Kanis JA, Group obotWHOS.** Assessment of osteoporosis at the primary health care level. *WHO Collaborating Center for Metabolic Bone Disease Technical Report:* University of Sheffield, UK, 2008.[EL 4; NE]

27. **Orwig DL, Chan J, Magaziner J.** Hip fracture and its consequences: differences between men and women. *Orthop Clin North Am.* 2006;37:611-622.[EL 4; NE]

28. **Kanis JA, Hans D, Cooper C, et al.** Interpretation and use of FRAX in clinical practice. *Osteoporos Int.* 2011;22:2395-2411.[EL 4; NE]

29. **Lewiecki EM, Compston JE, Miller PD, et al.** FRAX® Bone Mineral Density Task Force of the 2010 Joint International Society for Clinical Densitometry & International Osteoporosis Foundation position development conference. *J Clin Densitom.* 2011;14:223-225.[EL 4; NE]

30. **Kanis JA, Johansson H, Oden A, Cooper C, McCloskey EV.** Worldwide uptake of FRAX. *Arch Osteoporos.* 2014;9:166.[EL 2; ES]

31. **Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD.** FRAX® with and without bone mineral density. *Calcif Tissue Int.* 2012;90:1-13.[EL 4; NE]

32. **Hillier TA, Cauley JA, Rizzo JH, et al.** WHO absolute fracture risk models (FRAX): do clinical risk factors improve fracture prediction in older women without osteoporosis? *J Bone Miner Res.* 2011;26:1774-1782.[EL 2; ES]

33. **van Staa TP, Leufkens HG, Cooper C.** Does a fracture at one site predict later fractures at other sites? A British cohort study. *Osteoporos Int.* 2002;13:624-629.[EL 2; ES]

34. **Gehlbach S, Saag KG, Adachi JD, et al.** Previous fractures at multiple sites increase the risk for subsequent fractures: the Global Longitudinal Study of Osteoporosis in Women. *J Bone Miner Res.* 2012;27:645-653.[EL 2; PCS]

35. **Lindsay R, Silverman SL, Cooper C, et al.** Risk of new vertebral fracture in the year following a fracture. *JAMA.* 2001;285:320-323.[EL 2; PHAS]

36. **Johnell O, Kanis JA, Oden A, et al.** Predictive value of BMD for hip and other fractures. *J Bone Miner Res.* 2005;20:1185-1194.[EL 2; MNRCT]

37. **McCloskey E, Kanis JA.** FRAX updates 2012. *Curr Opin Rheumatol.* 2012;24:554-560.[EL 4; NE]

38. **Silverman SL, Calderon AD.** The utility and limitations of FRAX: A US perspective. *Curr Osteoporos Rep.* 2010;8:192-197.[EL 4; NE]

39. **Watts NB, Ettinger B, LeBoff MS.** FRAX facts. *J Bone Miner Res.* 2009;24:975-979.[EL 4; NE]

40. **van den Bergh JP, van Geel TA, Lems WF, Geusens PP.** Assessment of individual fracture risk: FRAX and beyond. *Curr Osteoporos Rep.* 2010;8:131-137.[EL 4; NE]

41. **Kreidieh OI, El-Hajj Fuleihan G.** Impact of changes in mortality on FRAX-derived fracture probabilities. *Bone.* 2014;62:43-50.[EL 2; ES]

42. **Kanis JA, Johansson H, Oden A, McCloskey EV.** Guidance for the adjustment of FRAX according to the dose of glucocorticoids. *Osteoporos Int*. 2011;22:809-816.[EL 2; ES]

43. **Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA.** Spine-hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. *Osteoporos Int*. 2011;22:839-847.[EL 2; ES]

44. **Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA.** Does osteoporosis therapy invalidate FRAX for fracture prediction? *J Bone Miner Res*. 2012;27:1243-1251.[EL 2; ES]

45. **Sambrook PN, Cameron ID, Chen JS, et al.** Influence of fall related factors and bone strength on fracture risk in the frail elderly. *Osteoporos Int*. 2007;18:603-610.[EL 2; PCS]

46. **Kanis JA, Oden A, Johnell O, et al.** The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int*. 2007;18:1033-1046.[EL 3; DS]

47. **Densitometry TISfC.** 2015 ISCD Official Positions--Adult. Accessed October 7, 2015. https://www.iscd.org/official-positions/2015-iscd-official-positions-adult/. [EL 4; NE]

48. **Stone KL, Seeley DG, Lui LY, et al.** BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. *J Bone Miner Res*. 2003;18:1947-1954. [EL 2; PCS]

49. **Cummings SR, Black DM, Nevitt MC, et al.** Bone density at various sites for prediction of hip fractures. The study of osteoporotic fractures research group. *Lancet*. 1993;341:72-75.[EL 2; PCS]

50. **Black DM, Cummings SR, Genant HK, Nevitt MC, Palermo L, Browner W.** Axial and appendicular bone density predict fractures in older women. *J Bone Miner Res*. 1992;7:633-638.[EL 2; PCS]

51. **Marshall D, Johnell O, Wedel H.** Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ*. 1996;312:1254-1259.[EL 2; MNRCT]

52. **Austin M, Yang YC, Vittinghoff E, et al.** Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res*. 2012;27:687-693.[EL 2; ES]

53. **Pothuaud L, Carceller P, Hans D.** Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture. *Bone*. 2008;42:775-787.[EL 3; DS]

54. **Silva BC, Leslie WD, Resch H, et al.** Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J Bone Miner Res*. 2014;29:518-530.[EL 4; NE]

55. **Harvey NC, Gluer CC, Binkley N, et al.** Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. *Bone*. 2015;78:216-224.[EL 4; NE]

56. **McCloskey EV, Odén A, Harvey NC, et al.** A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. *J Bone Miner Res*. 2016;31:940-948.[EL 2; MNRCT]

57. **Licata A, Binkley N, Petak SM, Camacho P.** Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the quality of DXA scans and reports. *Endocr Pract*. 2018;24:220-229.[EL 4; NE]

58. **Lewiecki EM, Binkley N, Morgan SL, et al.** Best practices for dual-energy X-ray absorptiometry measurement and reporting: International Society for Clinical Densitometry Guidance. *J Clin Densitom*. 2016;19:127-140.[EL 4; NE]

59. **Gallagher JC, Sai AJ.** Bone: is screening for secondary causes of osteoporosis worthwhile? *Nat Rev Endocrinol*. 2010;6:360-362. [EL 4; NE]

60. **Barzel US.** Recommended testing in patients with low bone density. *J Clin Endocrinol Metab*. 2003;88:1404-1405; author reply 1405.[EL 2; ES]

61. **Tannenbaum C, Clark J, Schwartzman K, et al.** Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. *J Clin Endocrinol Metab*. 2002;87:4431-4437.[EL 2; CSS]

62. **Edwards BJ, Bunta AD, Simonelli C, Bolander M, Fitzpatrick LA.** Prior fractures are common in patients with subsequent hip fractures. *Clin Orthop Relat Res*. 2007;461:226-230.[EL 3; ECON]

63. **Camacho PM, Dayal AS, Diaz JL, et al.** Prevalence of secondary causes of bone loss among breast cancer patients with osteopenia and osteoporosis. *J Clin Oncol*. 2008;26:5380-5385.[EL 2; RCCS]

64. **Lane NE.** An update on glucocorticoid-induced osteoporosis. *Rheum Dis Clin North Am*. 2001;27:235-253.[EL 4; NE]

65. **Lewiecki EM, Laster AJ.** Clinical review: Clinical applications of vertebral fracture assessment by dual-energy X-ray absorptiometry. *J Clin Endocrinol Metab*. 2006;91:4215-4222.[EL 4; NE]

66. **Greenspan SL, von Stetten E, Emond SK, Jones L, Parker RA.** Instant vertebral assessment: a noninvasive dual X-ray absorptiometry technique to avoid misclassification and clinical mismanagement of osteoporosis. *J Clin Densitom*. 2001;4:373-380.[EL 2; ES]

67. **Schousboe JT, Debold CR.** Reliability and accuracy of vertebral fracture assessment with densitometry compared to radiography in clinical practice. *Osteoporos Int*. 2006;17:281-289.[EL 2; PCS]

68. **Binkley N, Krueger D, Gangnon R, Genant HK, Drezner MK.** Lateral vertebral assessment: a valuable technique to detect clinically significant vertebral fractures. *Osteoporos Int*. 2005;16:1513-1518.[EL 2; PCS]

69. **Siminoski K, Jiang G, Adachi JD, et al.** Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures. *Osteoporos Int*. 2005;16:403-410.[EL 2; PCS]

70. **Siminoski K, Warshawski RS, Jen H, Lee K.** The accuracy of historical height loss for the detection of vertebral fractures in postmenopausal women. *Osteoporos Int*. 2006;17:290-296.[EL 2; PCS]

71. **Chesnut CH, 3rd, Bell NH, Clark GS, et al.** Hormone replacement therapy in postmenopausal women: urinary N-telopeptide of type I collagen monitors therapeutic effect and predicts response of bone mineral density. *Am J Med*. 1997;102:29-37.[EL 1; RCT]

72. **Ross PD, Knowlton W.** Rapid bone loss is associated with increased levels of biochemical markers. *J Bone Miner Res*. 1998;13:297-302.[EL 2; PHAS]

73. **Garnero P, Sornay-Rendu E, Duboeuf F, Delmas PD.** Markers of bone turnover predict postmenopausal forearm bone loss over 4 years: the OFELY study. *J Bone Miner Res*. 1999;14:1614-1621. [EL 2; PCS]

74. **Garnero P, Hausherr E, Chapuy MC, et al.** Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study. *J Bone Miner Res*. 1996;11:1531-1538.[EL 2; PCS]

75. **Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD.** Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. *J Bone Miner Res*. 2000;15:1526-1536.[EL 2; PCS]

76. **Vasikaran S, Eastell R, Bruyère O, et al.** Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int*. 2011;22:391-420.[EL 2; MNRCT]

77. **Crandall CJ, Vasan S, LaCroix A, et al.** Bone turnover markers are not associated with hip fracture risk: a case-control study in the Women's Health Initiative. *J Bone Miner Res*. 2018;33:1199-1208.[EL 2; NCCS]

78. **Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD.** Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res*. 2003;18:1051-1056.[EL 2; PHAS]

79. **Bauer DC, Black DM, Garnero P, et al.** Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the Fracture Intervention Trial. *J Bone Miner Res*. 2004;19:1250-1258.[EL 2; ES]

80. **Naylor KE, Jacques RM, Paggiosi M, et al.** Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: the TRIO study. *Osteoporos Int*. 2016;27:21-31.[EL 1; RCT]

81. **Glover SJ, Eastell R, MCloskey EV, et al.** Rapid and robust response of biochemical markers of bone formation to teriparatide therapy. *Bone*. 2009;45:1053-1058.[EL 2; PCS]

82. **Eastell R, Vrijens B, Cahall DL, Ringe JD, Garnero P, Watts NB.** Bone turnover markers and bone mineral density response with risedronate therapy: relationship with fracture risk and patient adherence. *J Bone Miner Res*. 2011;26:1662-1669.[EL 2; PHAS]

83. **Eastell R, Christiansen C, Grauer A, et al.** Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. *J Bone Miner Res*. 2011;26:530-537.[EL 1; RCT]

84. **Bauer D, Krege J, Lane N, et al.** National Bone Health Alliance Bone Turnover Marker Project: current practices and the need for

US harmonization, standardization, and common reference ranges. *Osteoporos Int*. 2012;23:2425-2433.[EL 4; NE]

85. **Szulc P, Naylor K, Pickering ME, Hoyle N, Eastell R, Leary E.** Use of CTX-I and PINP as bone turnover markers: Nationall Bone Health Alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability. *Ann Biol Clin (Paris)*. 2018;76:373-391.[EL 4; NE]

86. **Greenspan SL, Resnick NM, Parker RA.** Early changes in biochemical markers of bone turnover are associated with long-term changes in bone mineral density in elderly women on alendronate, hormone replacement therapy, or combination therapy: a three-year, double-blind, placebo-controlled, randomized clinical trial. *J Clin Endocrinol Metab*. 2005;90:2762-2767.[EL 1; RCT]

87. **Bauer DC, Garnero P, Bilezikian JP, et al.** Short-term changes in bone turnover markers and bone mineral density response to parathyroid hormone in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2006;91:1370-1375.[EL 1; RCT]

88. **Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD.** Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab*. 2002;87:1586-1592.[EL 1; MRCT]

89. **Bauer DC, Schwartz A, Palermo L, et al.** Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. *JAMA Intern Med*. 2014;174:1126-1134.[EL 2; PHAS]

90. **Carmel AS, Shieh A, Bang H, Bockman RS.** The 25(OH)D level needed to maintain a favorable bisphosphonate response is ≥33 ng/ml. *Osteoporos Int*. 2012;23:2479-2487.[EL 2; ES]

91. **Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B.** Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med*. 2004;116:634-639.[EL 2; ES]

92. **Ross AC.** The 2011 report on dietary reference intakes for calcium and vitamin D. *Public Health Nutr*. 2011;14:938-939.[EL 4; NE]

93. **Holick MF, Binkley NC, Bischoff-Ferrari HA, et al.** Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911-1930.[EL 4; NE]

94. **Holick MF, Siris ES, Binkley N, et al.** Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab*. 2005;90:3215-3224.[EL 2; PCS]

95. **LeBoff MS, Hawkes WG, Glowacki J, Yu-Yahiro J, Hurwitz S, Magaziner J.** Vitamin D-deficiency and post-fracture changes in lower extremity function and falls in women with hip fractures. *Osteoporos Int*. 2008;19:1283-1290.[EL 2; PCS]

96. **Wimalawansa SJ.** Vitamin D in the new millennium. *Curr Osteoporos Rep*. 2012;10:4-15.[EL 4; NE]

97. **Wimalawansa SJ.** Non-musculoskeletal benefits of vitamin D. *J Steroid Biochem Mol Biol*. 2018;175:60-81.[EL 4; NE]

98. **Baron JA, Barry EL, Mott LA, et al.** A trial of calcium and vitamin D for the prevention of colorectal adenomas. *N Engl J Med*. 2015;373:1519-1530.[EL 1; RCT]

99. **Arora P, Song Y, Dusek J, et al.** Vitamin D therapy in individuals with prehypertension or hypertension: the DAYLIGHT trial. *Circulation*. 2015;131:254-262.[EL 1; RCT]

100. **Mason C, Xiao L, Imayama I, et al.** Vitamin D3 supplementation during weight loss: a double-blind randomized controlled trial. *Am J Clin Nutr*. 2014;99:1015-1025.[EL 1; RCT]

101. **Dhaliwal R, Mikhail M, Feuerman M, Aloia JF.** The vitamin d dose response in obesity. *Endocr Pract*. 2014;20:1258-1264.[EL 1; RCT]

102. **Knutsen KV, Madar AA, Lagerløv P, et al.** Does vitamin D improve muscle strength in adults? A randomized, double-blind, placebo-controlled trial among ethnic minorities in Norway. *J Clin Endocrinol Metab*. 2014;99:194-202.[EL 1; RCT]

103. **Chaney A, Heckman MG, Diehl NN, Meek S, Keaveny AP.** Effectiveness and outcomes of current practice in treating vitamin D deficiency in patients listed for liver transplantation. *Endocr Pract*. 2015;21:761-769.[EL 2; ES]

104. **Farahati J, Nagarajah J, Gilman E, et al.** Ethnicity, clothing style, and body mass index are significant predictors of vitamin D

insufficiency in Germany. *Endocr Pract*. 2015;21:122-127.[EL 2; ES]

105. **Li Y, Chen C, Liu HL, Qian G.** Vitamin D, parathyroid hormone, and heart failure in a Chinese elderly population. *Endocr Pract*. 2015;21:30-40.[EL 2; CSS]

106. **Chapuy MC, Preziosi P, Maamer M, et al.** Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int*. 1997;7:439-443.[EL 2; ES]

107. **Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P.** Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocrinol Metab*. 2007;92:1415-1423. [EL 1; MRCT]

108. **Camacho PM, Petak SM, Binkley N, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2016. *Endocr Pract*. 2016;22(suppl 4):1-42.[EL 4; NE]

109. **Ross AC, Manson JE, Abrams SA, et al.** The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;96:53-58.[EL 4; NE]

110. **Manson JE, Brannon PM, Rosen CJ, Taylor CL.** Vitamin D deficiency-is there really a pandemic? *N Engl J Med*. 2016;375:1817-1820.[EL 4; NE]

111. **Hansen KE, Johnson RE, Chambers KR, et al.** Treatment of vitamin D insufficiency in postmenopausal women: a randomized clinical trial. *JAMA Intern Med*. 2015;175:1612-1621.[EL 1; RCT]

112. **Sprague SM, Crawford PW, Melnick JZ, et al.** Use of extended-release calcifediol to treat secondary hyperparathyroidism in stages 3 and 4 chronic kidney disease. *Am J Nephrol*. 2016;44:316-325[EL 1; RCT]

113. **Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B.** Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA*. 2005;293:2257-2264.[EL 1; MRCT]

114. **Jackson RD, LaCroix AZ, Gass M, et al.** Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354:669-683.[EL 1; RCT]

115. **Bischoff-Ferrari HA, Conzelmann M, Stahelin HB, et al.** Is fall prevention by vitamin D mediated by a change in postural or dynamic balance? *Osteoporos Int*. 2006;17:656-663.[EL 2; PHAS]

116. **Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C.** Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res*. 2000;15:1113-1118.[EL 2; NRCT]

117. **Autier P, Gandini S.** Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007;167:1730-1737.[EL 1; MRCT]

118. **Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al.** Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. *JAMA Intern Med*. 2016;176:175-183.[EL 1; RCT]

119. **Sanders KM, Stuart AL, Williamson EJ, et al.** Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010;303:1815-1822.[EL 1; RCT]

120. **Heaney RP, Armas LA.** Quantifying the vitamin D economy. *Nutr Rev*. 2015;73:51-67.[EL 4; NE]

121. **Vieth R.** How to optimize vitamin D supplementation to prevent cancer, based on cellular adaptation and hydroxylase enzymology. *Anticancer Res*. 2009;29:3675-3684.[EL 4; NE]

122. **Ketha H, Thacher TD, Oberhelman SS, Fischer PR, Singh RJ, Kumar R.** Comparison of the effect of daily versus bolus dose maternal vitamin D3 supplementation on the 24,25-dihydroxyvitamin D3 25-hydroxyvitamin D3 ratio. *Bone*. 2018;110:321-325.[EL 1; RCT]

123. **Binkley NC, Wiebe DA.** It's time to stop prescribing ergocalciferol. *Endocr Pract*. 2018;24:1099-1102.[EL 4; NE]

124. **Tolan NV, Yoon EJ, Brady AR, Horowitz GL.** Price of high-throughput 25-hydroxyvitamin D immunoassays: frequency of inaccurate results. *J Appl Lab Med*. 2018;2:868-879.[EL 3; BR]

125. **Wyness SP, Straseski JA.** Performance characteristics of six automated 25-hydroxyvitamin D assays: mind your 3s and 2s. *Clin Biochem*. 2015;48:1089-1096.[EL 3; BR]

126. **Weaver CM, Alexander DD, Boushey CJ, et al.** Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int*. 2016;27:367-376.[EL 1; MRCT]

127. **Porthouse J, Cockayne S, King C, et al.** Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ*. 2005;330:1003.[EL 1; RCT]

128. **Shea B, Wells G, Cranney A, et al.** Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev*. 2002;23:552-559.[EL 1; MRCT]

129. **Grant AM, Avenell A, Campbell MK, et al.** Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet*. 2005;365:1621-1628.[EL 1; RCT]

130. **Michaëlsson K, Melhus H, Warensjö Lemming E, Wolk A, Byberg L.** Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. *BMJ*. 2013;346:f228.[EL 2; PCS]

131. **Bolland MJ, Barber PA, Doughty RN, et al.** Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008;336:262-266.[EL 1; RCT]

132. **Bolland MJ, Avenell A, Baron JA, et al.** Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691.[EL 1; MRCT]

133. **Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR.** Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ*. 2011;342:d2040.[EL 1; MRCT]

134. **Khan SU, Khan MU, Riaz H, et al.** Effects of nutritional supplements and dietary intervention on cardiovascular outcomes: an umbrella review and evidence map. *Ann Intern Med*. 2019;171:190-198.[EL 1; MRCT]

135. **Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR.** Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. *Am J Epidemiol*. 1999;149:151-161.[EL 2; ES]

136. **Zhu K, Devine A, Dick IM, Wilson SG, Prince RL.** Effects of calcium and vitamin D supplementation on hip bone mineral density and calcium-related analytes in elderly ambulatory Australian women: a five-year randomized controlled trial. *J Clin Endocrinol Metab*. 2008;93:743-749.[EL 1; RCT]

137. **Zhu K, Bruce D, Austin N, Devine A, Ebeling PR, Prince RL.** Randomized controlled trial of the effects of calcium with or without vitamin D on bone structure and bone-related chemistry in elderly women with vitamin D insufficiency. *J Bone Miner Res*. 2008;23:1343-1348.[EL 1; RCT]

138. **Langsetmo L, Berger C, Kreiger N, et al.** Calcium and vitamin D intake and mortality: results from the Canadian Multicentre Osteoporosis Study (CaMos). *J Clin Endocrinol Metab*. 2013;98:3010-3018.[EL 2; PCS]

139. **Silverman SL, Cummings SR, Watts NB.** Recommendations for the clinical evaluation of agents for treatment of osteoporosis: consensus of an expert panel representing the American Society for Bone and Mineral Research (ASBMR), the International Society for Clinical Densitometry (ISCD), and the National Osteoporosis Foundation (NOF). *J Bone Miner Res*. 2008;23:159-165.[EL 4; NE]

140. **Bauer DC.** Clinical practice. Calcium supplements and fracture prevention. *N Engl J Med*. 2013;369:1537-1543.[EL 4; NE]

141. **Prentice RL, Pettinger MB, Jackson RD, et al.** Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. *Osteoporos Int*. 2013;24:567-580.[EL 2; PHAS]

142. **Reid IR, Bolland MJ.** Calcium supplements: bad for the heart? *Heart (British Cardiac Society)*. 2012;98:895-896.[EL 4; NE]

143. **Bolland MJ, Grey A, Gamble GD, Reid IR.** Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. *Am J Clin Nutr*. 2011;94:1144-1149.[EL 1; RCT]

144. **Moyer VA.** Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2013;158:691-696.[EL 2; MNRCT]

145. **Alaimo K, McDowell MA, Briefel RR, et al.** Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988-91. *Adv Data*. 1994:1-28.[EL 2; ES]

146. **Kim MH, Kim EJ, Jung JY, Choi MK.** Effect of water-soluble silicon supplementation on bone status and balance of calcium and magnesium in male mice. *Biol Trace Elem Res*. 2014;158:238-242.[EL 3; BR]

147. **Spencer H, Fuller H, Norris C, Williams D.** Effect of magnesium on the intestinal absorption of calcium in man. *J Am Coll Nutr*. 1994;13:485-492.[EL 2; NRCT]

148. **Jackson HA, Sheehan AH.** Effect of vitamin A on fracture risk. *Ann Pharmacother*. 2005;39:2086-2090.[EL 4; NE]

149. **Braam LA, Knapen MH, Geusens P, et al.** Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. *Calcif Tissue Int*. 2003;73:21-26.[EL 1; RCT]

150. **Alexandersen P, Toussaint A, Christiansen C, et al.** Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. *JAMA*. 2001;285:1482-1488.[EL 1; RCT]

151. **Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA.** The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2004;79:326-333.[EL 1; RCT]

152. **Gallagher JC, Satpathy R, Rafferty K, Haynatzka V.** The effect of soy protein isolate on bone metabolism. *Menopause*. 2004;11:290-298.[EL 1; RCT]

153. **Hallstrom H, Wolk A, Glynn A, Michaelsson K.** Coffee, tea and caffeine consumption in relation to osteoporotic fracture risk in a cohort of Swedish women. *Osteoporos Int*. 2006;17:1055-1064.[EL 2; ES]

154. **Kiel DP, Felson DT, Hannan MT, Anderson JJ, Wilson PW.** Caffeine and the risk of hip fracture: the Framingham Study. *Am J Epidemiol*. 1990;132:675-684.[EL 2; ES]

155. **Barrett-Connor E, Chang JC, Edelstein SL.** Coffee-associated osteoporosis offset by daily milk consumption. The Rancho Bernardo Study. *JAMA*. 1994;271:280-283.[EL 2; ES]

156. **Rizzoli R, Ammann P, Chevalley T, Bonjour JP.** Protein intake and bone disorders in the elderly. *Joint Bone Spine*. 2001;68:383-392.[EL 4; NE]

157. **Schürch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP.** Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. **Ann Intern Med.** 1998;128:801-809.[EL 1; RCT]

158. **Kanis JA, Johansson H, Johnell O, et al.** Alcohol intake as a risk factor for fracture. *Osteoporos Int*. 2005;16:737-742.[EL 2; ES]

159. **Giampietro PF, McCarty C, Mukesh B, et al.** The role of cigarette smoking and statins in the development of postmenopausal osteoporosis: a pilot study utilizing the Marshfield Clinic Personalized Medicine Cohort. *Osteoporos Int*. 2010;21:467-477.[EL 3; DS]

160. **Daniell HW.** Osteoporosis of the slender smoker. Vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. *Arch Intern Med*. 1976;136:298-304.[EL 2; ES]

161. **Kanis JA, Johnell O, Oden A, et al.** Smoking and fracture risk: a meta-analysis. *Osteoporos Int*. 2005;16:155-162.[EL 2; MNRCT]

162. **Kelley GA, Kelley KS, Tran ZV.** Exercise and lumbar spine bone mineral density in postmenopausal women: a meta-analysis of individual patient data. *J Gerontol A Biol Sci Med Sci*. 2002;57:M599-M604.[EL 2; ES]

163. **Gardner MM, Phty M, Robertson MC, McGee R, Campbell AJ.** Application of a falls prevention program for older people to primary health care practice. *Prev Med*. 2002;34:546-553.[EL 2; PCS]

164. **Robertson MC, Campbell AJ, Gardner MM, Devlin N.** Preventing injuries in older people by preventing falls: a meta-analysis of individual-level data. *J Am Geriatr Soc*. 2002;50:905-911.[EL 2; MNRCT]

165. **Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW.** The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos Int*. 1999;9:1-12.[EL 2; MNRCT]

166. **Choi M, Hector M.** Effectiveness of intervention programs in preventing falls: a systematic review of recent 10 years and meta-analysis. *J Am Med Dir Assoc*. 2012;13:188.e113-121.[EL 1; MRCT]

167. **Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC.** Effective exercise for the prevention of falls: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2008;56:2234-2243.[EL 1; MRCT]

168. **Kelley GA, Kelley KS, Kohrt WM.** Effects of ground and joint reaction force exercise on lumbar spine and femoral neck bone mineral density in postmenopausal women: a meta-analysis of randomized controlled trials. *BMC Musculoskel Disord*. 2012;13:177.[EL 1; MRCT]

169. **Scott V, Wagar L, Elliott S.** Falls & related injuries among older Canadians. Canada.2010. Prepared on behalf of the Public Health Agency of Canada, Division of Aging and Seniors. 2011; Victoria, BC: Victoria Scott Consulting.[EL 2; ES]

170. **Gillespie LD, Robertson MC, Gillespie WJ, et al.** Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2012: CD007146.[EL 4; NE]

171. **Granacher U, Gollhofer A, Hortobágyi T, Kressig RW, Muehlbauer T.** The importance of trunk muscle strength for balance, functional performance, and fall prevention in seniors: a systematic review. *Sports Med*. 2013;43:627-641.[EL 2; MNRCT]

172. **Tinetti ME, Speechley M, Ginter SF.** Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319:1701-1707.[EL 2; PCS]

173. **Hausdorff JM, Rios DA, Edelberg HK.** Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil*. 2001;82:1050-1056.[EL 2; PCS]

174. **Prevention. CfDCa.** Web-based Injury Statistics Query System (WISQARS): Injury Prevention & Control. Accessed January 15, 2007. https://www.cdc.gov/injury/wisqars/index.html.[EL 2; ES]

175. **Centers for Disease Control and Prevention.** Fatalities and injuries from falls among older adults-United States, 1993-2003 and 2001-2005. *Morb Mortal Wkly Rep*. 2006;55:1221-1224.[EL 2; ES]

176. **da Silva RB, Costa-Paiva L, Morais SS, Mezzalira R, Ferreira Nde O, Pinto-Neto AM.** Predictors of falls in women with and without osteoporosis. *J Orthop Sports Phys Ther*. 2010;40:582-588.[EL 2; ES]

177. **Blain H, Rolland Y, Beauchet O, et al.** Usefulness of bone density measurement in fallers. *Joint Bone Spine*. 2014;81:403-408.[EL 4; NE]

178. **Briot K, Cortet B, Thomas T, et al.** 2012 update of French guidelines for the pharmacological treatment of postmenopausal osteoporosis. *Joint Bone Spine*. 2012;79:304-313.[EL 4; NE]

179. **van Doorn C, Gruber-Baldini AL, Zimmerman S, et al.** Dementia as a risk factor for falls and fall injuries among nursing home residents. *J Am Geriatr Soc*. 2003;51:1213-1218.[EL 2; PCS]

180. **Goodwin VA, Abbott RA, Whear R, et al.** Multiple component interventions for preventing falls and fall-related injuries among older people: systematic review and meta-analysis. *BMC Geriatr*. 2014;14:15.[EL 1; MRCT]

181. **Kemmler W, Häberle L, von Stengel S.** Effects of exercise on fracture reduction in older adults: a systematic review and meta-analysis. *Osteoporos Int*. 2013;24:1937-1950.[EL 2; MNRCT]

182. **Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al.** Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ*. 2009;339:b3692.[EL 1; MRCT]

183. **Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al.** Effect of vitamin D on falls: a meta-analysis. *JAMA*. 2004;291:1999-2006.[EL 1; MRCT]

184. **Uusi-Rasi K, Patil R, Karinkanta S, et al.** Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. *JAMA Intern Med*. 2015;175:703-711.[EL 1; RCT]

185. **Li WC, Chen YC, Yang RS, Tsauo JY.** Effects of exercise programmes on quality of life in osteoporotic and osteopenic postmenopausal women: a systematic review and meta-analysis. *Clin Rehabil*. 2009;23:888-896.[EL 1; MRCT]

186. **Black DM, Cummings SR, Karpf DB, et al.** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Fracture Intervention Trial Research Group*. Lancet. 1996;348:1535-1541.[EL 1; RCT]

187. **Chesnut CH, 3rd, Skag A, Christiansen C, et al.** Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res*. 2004;19:1241-1249.[EL 1; RCT]

188. **Harris ST, Watts NB, Genant HK, et al.** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA*. 1999;282:1344-1352.[EL 1; RCT]

189. **Reginster J, Minne HW, Sorensen OH, et al.** Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int*. 2000;11:83-91.[EL 1; RCT]

190. **Kanis JA, Barton IP, Johnell O.** Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. *Osteoporos Int*. 2005;16:475-482.[EL 2; PHAS]

191. **Chesnut CH, 3rd, Silverman S, Andriano K, et al.** A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med*. 2000;109:267-276.[EL 1; RCT]

192. **Ettinger B, Black DM, Mitlak BH, et al.** Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282:637-645.[EL 1; RCT]

193. **Cummings SR, San Martin J, McClung MR, et al.** Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.[EL 1; RCT]

194. **Neer RM, Arnaud CD, Zanchetta JR, et al.** Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344:1434-1441.[EL 1; RCT]

195. **Lyles KW, Cólon-Emeric CS, Magaziner JS, et al.** Zoledronic acid in reducing clinical fracture and mortality after hip fracture. *N Engl J Med*. 2007;357:1799-1809.[EL 1; RCT]

196. **Black DM, Thompson DE, Bauer DC, et al.** Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. *J Clin Endocrinol Metab*. 2000;85:4118-4124.[EL 2; PCS]

197. **Bone HG, Hosking D, Devogelaer JP, et al.** Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med*. 2004;350:1189-1199.[EL 1; RCT]

198. **Miller PD, McClung MR, Macovei L, et al.** Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res*. 2005;20:1315-1322. [EL 1; RCT]

199. **Reginster JY, Adami S, Lakatos P, et al.** Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. *Ann Rheum Dis*. 2006;65:654-661.[EL 1; RCT]

200. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol*. 2008;35:488-497.[EL 1; RCT]

201. **McClung MR, Geusens P, Miller PD, et al.** Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med*. 2001;344:333-340.[EL 1; RCT]

202. **Black DM, Delmas PD, Eastell R, et al.** Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356:1809-1822.[EL 1; RCT]

203. **Sorensen OH, Crawford GM, Mulder H, et al.** Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone*. 2003;32:120-126.[EL 1; RCT]

204. **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.[EL 1; RCT]

205. **Black DM, Schwartz AV, Ensrud KE, et al.** Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296:2927-2938.[EL 1; RCT]

206. **Dawson-Hughes B, Tosteson AN, Melton LJ, 3rd, et al.** Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. *Osteoporos Int*. 2008;19:449-458. [EL 3; ECON]

207. **Kanis JA, Johansson H, Oden A, Dawson-Hughes B, Melton LJ 3rd, McCloskey EV.** The effects of a FRAX revision for the USA. *Osteoporos Int*. 2010;21:35-40.[EL 3; DS]

208. **Ettinger B, Black DM, Dawson-Hughes B, Pressman AR, Melton LJ, 3rd.** Updated fracture incidence rates for the US version of FRAX. *Osteoporos Int*. 2010;21:25-33.[EL 3; DS]

209. **Tosteson AN, Melton LJ, 3rd, Dawson-Hughes B, et al.** Cost-effective osteoporosis treatment thresholds: the United States perspective. *Osteoporos Int*. 2008;19:437-447.[EL 3; ECON]

210. **Saag KG, Shane E, Boonen S, et al.** Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med*. 2007;357:2028-2039.[EL 1; RCT]

211. **Hadji P, Zanchetta JR, Russo L, et al.** The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporos Int*. 2012;23:2141-2150.[EL 1; RCT]

212. **Kendler DL, Marin F, Zerbini CA, et al.** Effects of teriparatide and risedronate on new fractures in post-menopausal women with sever osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2017;391:230-240. [EL 1; RCT]

213. **Saag KG, Petersen J, Brandi ML, et al.** Romosozumab or alendronate for fracture prevention in women with osteoporosis. *New Engl J Med*. 2017;377:1417-1427.[EL 1; RCT]

214. **Roux C, Briot K.** Imminent fracture risk. *Osteoporos Int*. 2017;28:1765-1769.[EL 4; NE]

215. **Johansson H, Siggeirsdóttir K, Harvey NC, et al.** Imminent risk of fracture after fracture. *Osteoporos Int*. 2017;28:775-780.[EL 2; ES]

216. **Bonafede M, Shi N, Barron R, Li X, Crittenden DB, Chandler D.** Predicting imminent risk for fracture in patients aged 50 or older with osteoporosis using US claims data. *Arch Osteoporos*. 2016;11:26-33.[EL 2; ES]

217. **Deloumeau A, Moltó A, Roux C, Briot K.** Determinants of short term fracture risk in patients with a recent history of low-trauma non-vertebral fracture. *Bone*. 2017;105:287-291.[EL 2; ES]

218. **Giangregorio LM, Leslie WD, Lix LM, et al.** FRAX underestimates fracture risk in patients with diabetes. *J Bone Miner Res*. 2012;27:301-308.[EL 2; ES]

219. **Schwartz AV, Vittinghoff E, Bauer DC, et al.** Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA*. 2011;305:2184-2192.[EL 2; PCS]

220. **Choi YJ, Ock SY, Chung YS.** Trabecular Bone Score (TBS) and TBS-adjusted Fracture Risk Assessment Tool are potential supplementary tools for the discrimination of morphometric vertebral fractures in postmenopausal women with type 2 diabetes. *J Clin Densitom*. 2016;19:507-514.[EL 2; ES]

221. **Schacter GI, Leslie WD.** DXA-based measurements in diabetes: can they predict fracture risk? *Calcif Tissue Int*. 2017;100:150-164. [EL 4; NE]

222. **Cosman F, Eriksen EF, Recknor C, et al.** Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res*. 2011;26:503-511.[EL 1; RCT]

223. **Cummings SR, Black DM, Thompson DE, et al.** Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*. 1998;280:2077-2082.[EL 1; RCT]

224. **Watts NB, Harris ST, Genant HK, et al.** Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med*. 1990;323:73-79.[EL 1; RCT]

225. **Cosman F, Nieves JW, Dempster DW.** Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis. *J Bone Miner Res*. 2017;32:198-202.[EL 4; NE]

226. **Bone HG, Bolognese MA, Yuen CK, et al.** Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab*. 2008;93:2149-2157.[EL 1; RCT]

227. **McClung MR, Wasnich RD, Recker R, et al.** Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. *J Bonoe Miner Res*. 2004;19:11-18.[EL 1; RCT]

228. **Bauer DC, Black D, Ensrud K, et al.** Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. *Arch Intern Med*. 2000;160:517-525.[EL 1; RCT]

229. Atelvia (risedronate sodium) delayed-release tablets. North Norwich, NY: Norwich Pharmaceuticals, 2015.[EL 4; O]

230. **Kidney Disease Improving Global Ooutcomes Work Group.** KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2009:S1-130.[EL 4; NE]

231. **Jones SG, Dolan G, Lengyel K, Myers B.** Severe increase in creatinine with hypocalcaemia in thalidomide-treated myeloma patients receiving zoledronic acid infusions. *Br J Haematol*. 2002;119:576-577.[EL 3; CCS]

232. **Chang JT, Green L, Beitz J.** Renal failure with the use of zoledronic acid. *N Engl J Med*. 2003;349:1676-1679; discussion 1676-1679.[EL 4; NE]

233. **Adami S, Bhalla AK, Dorizzi R, et al.** The acute-phase response after bisphosphonate administration. *Calcif Tissue Int*. 1987;41:326-331.[EL 2; PCS]

234. **Wysowski DK, Chang JT.** Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med*. 2005;165:346-347.[EL 4; NE]

235. **Cardwell CR, Abnet CC, Cantwell MM, Murray LJ.** Exposure to oral bisphosphonates and risk of esophageal cancer. *JAMA*. 2010;304:657-663.[EL 2; ES]

236. **Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V.** Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. *BMJ*. 2010;341:c4444.[EL 2; RCCS]

237. **McClung M, Harris ST, Miller PD, et al.** Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. *Am J Med*. 2013;126:13-20.[EL 4; NE]

238. **Bone HG, Wagman RB, Brandi ML, et al.** 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;5:513-523.[EL 1; RCT]

239. **Miller PD, Pannacciulli N, Brown JP, et al.** Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. *J Clin Endocrinol Metab*. 2016;101:3163-3170.[EL 1; RCT]

240. **Miller PD, Bolognese MA, Lewiecki EM, et al.** Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone*. 2008;43:222-229.[EL 1; RCT]

241. **McClung MR, Lewiecki EM, Geller ML, et al.** Effect of denosumab on bone mineral density and biochemical markers of bone turnover: 8-year results of a phase 2 clinical trial. *Osteoporos Int*. 2013;24:227-235.[EL 2; OLES]

242. **Bone HG, Chapurlat R, Brandi ML, et al.** The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. *J Clin Endocrinol Metab*. 2013;98:4483-4492.[EL 2; OLES]

243. **Watts NB, Roux C, Modlin JF, et al.** Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: coincidence or causal association? *Osteoporos Int*. 2012;23:327-337.[EL 2; ES]

244. **Cummings SR, Ferrari S, Eastell R, et al.** Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM Trial and its extension. *J Bone Miner Res*. 2018;33:190-198.[EL 2; PHAS]

245. **Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O.** Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res*. 2017;32:1291-1296.[EL 3; CCS]

246. **Lamy O, Gonzalez-Rodriguez E, Stoll D, Hans D, Aubry-Rozier B.** Severe rebound-associated vertebral fractures after denosumab discontinuation: 9 clinical case reports. *J Clin Endocrinol Metab*. 2017;102:354-358.[EL 3; CCS]

247. Fortical (calcitonin-salmon [rDNA origin] Nasal spray for intra-nasal use [package insert]. Maple Grove, MN: Upsher-Smith Laboratories, Inc, 2014.[EL 4; O]

248. Miacalcin (calcitonin-salmon) for injection and nasal spray [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp, 2014.[EL 4; O]

249. **Wimalawansa SJ.** Physiology of calcitonin and its therapeutic uses. *Encyclopedia of Endocrine Diseases: Second Edition*. 2018: 178-191.[EL 4; NE]

250. **Pun KK, Chan LW.** Analgesic effect of intranasal salmon calcitonin in the treatment of osteoporotic vertebral fractures. *Clin Ther*. 1989;11:205-209.[EL 3; CCS]

251. **Ofluoglu D, Akyuz G, Unay O, Kayhan O.** The effect of calcitonin on beta-endorphin levels in postmenopausal osteoporotic patients with back pain. *Clin Rheumatol*. 2007;26:44-49.[EL 1; RCT]

252. **Laroche M, Cantogrel S, Jamard B, et al.** Comparison of the analgesic efficacy of pamidronate and synthetic human calcitonin in osteoporotic vertebral fractures: a double-blind controlled study. *Clin Rheumatol*. 2006;25:683-686.[EL 1; RCT]

253. **Lyritis GP, Paspati I, Karachalios T, Ioakimidis D, Skarantavos G, Lyritis PG.** Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures. A double blind, placebo-controlled clinical study. *Acta Orthop Scand Suppl*. 1997;275:112-114.[EL 1; RCT]

254. **Lyritis GP, Ioannidis GV, Karachalios T, et al.** Analgesic effect of salmon calcitonin suppositories in patients with acute pain due to recent osteoporotic vertebral crush fractures: a prospective double-blind, randomized, placebo-controlled clinical study. *Clin J Pain*. 1999;15:284-289.[EL 1; RCT]

255. **U.S. Food and Drug Administration.** Questions and answers: changes to the indicated population for miacalcin (calcitonin-salmon). December 15, 2014.[EL 4; NE]

256. **Wells G, Chernoff J, Gilligan JP, Drause DS.** Does salmon calcitonin cuase cancer? A review and meta-analysis. *Osteoporos Int*. 2016;27:13-19.[EL 1; MRCT]

257. Evista (raloxifene hydrochloride) tablet for oral use [package insert]. Eli Lilly and Co, 2011.[EL 4; O]

258. **Vogel VG, Costantino JP, Wickerham DL, et al.** Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295:2727-2741.[EL 1; RCT]

259. **Barrett-Connor E, Mosca L, Collins P, et al.** Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006;355:125-137.[EL 1; RCT]

260. **Delmas PD, Bjarnason NH, Mitlak BH, et al.** Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med*. 1997;337:1641-1647.[EL 1; RCT]

261. **Kawai M, Modder UI, Khosla S, Rosen CJ.** Emerging therapeutic opportunities for skeletal restoration. *Nat Rev Drug Discov*. 2011;10:141-156.[EL 4; NE]

262. **Pinkerton JV, Harvey JA, Lindsay R, et al.** Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. *J Clin Endocrinol Metab*. 2014;99:E189-198. [EL 1; RCT]

263. **Lindsey R, Gallagher JC, Kagan R, Pickar JH, Constantine G.** Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril*. 2009;92:1045-1052.[EL 1; RCT]

264. **Kawate H, Takayanagi R.** Efficacy and safety of bazedonxifene for postmenopausal osteoporosis. *Clin Interv Aging*. 2011;6:151-160.[EL 4; NE]

265. **Silverman SL, Christiansen C, Genant HK, et al.** Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res*. 2008;23:1923-1934.[EL 1; RCT]

266. **Palacios S, Silverman SL, de Villiers TJ, et al.** A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. *Menopause (New York, NY)*. 2015;22:806-813.[EL 1; RCT]

267. **Lello S, Capozzi A, Scambia G.** The tissue-selective estrogen complex (bazedoxifene/conjugated estrogens) for the treatment of menopause. *Int J Endocrinol*. 2017;2017:5064725.[EL 4; NE]

268. Premarin (conjugated estrogens) tablets, USP for oral use [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc., 2014.[EL 4; O]

269. **Cauley JA, Robbins J, Chen Z, et al.** Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003;290:1729-1738. [EL 1; RCT]

270. **Jackson RD, Wactawski-Wende J, LaCroix AZ, et al.** Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. *J Bone Miner Res*. 2006;21:817-828.[EL 1; RCT]

271. Tymlos (abaloparatide injection, for subcutaneous use. Waltham, MA: Radius Health, Inc., 2017.[EL 4; O]

272. Forteo (teriparatide [rDNA origin] injection) for subcutaneous use [package insert]. Indianapolis, IN: Eli Lilly and Co, 2012.[EL 4; O]

273. **Miller PD, Hattersley G, Riis BJ, et al.** Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA*. 2016;316:722-733.[EL 1; RCT]

274. **Watts NB, Miller PD, Kohlmeier LA, et al.** Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment. *J Bone Miner Res*. 2009;24:1125-1131.[EL 2; PHAS]

275. **Vahle JL, Sato M, Long GG, et al.** Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. *Toxicol Pathol*. 2002;30:312-321.[EL 3; BR]

276. **Vahle JL, Long GG, Sandusky G, Westmore M, Ma YL, Sato M.** Bone neoplasms in F344 rats given teriparatide [rhPTH(1-34)] are dependent on duration of treatment and dose. *Toxicol Pathol*. 2004;32:426-438.[EL 3; BR]

277. **Harper KD, Krege JH, Marcus R, Mitlak BH.** Osteosarcoma and teriparatide? *J Bone Miner Res*. 2007;22:334.[EL 4; NE]

278. **Subbiah V, Madsen VS, Raymond AK, Benjamin RS, Ludwig JA.** Of mice and men: divergent risks of teriparatide-induced osteosarcoma. *Osteoporos Int*. 2010;21:1041-1045.[EL 3; SCR]

279. **Lindsay R, Scheele WH, Neer R, et al.** Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. *Arch Intern Med*. 2004;164:2024-2030. [EL 2; OLES]

280. **Black DM, Bilezikian JP, Ensrud KE, et al.** One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med*. 2005;353:555-565.[EL 1; RCT]

281. **Leder BZ, Tsai JN, Uihlein AV, et al.** Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet*. 2015;386:1147-1155.[EL 2; OLES]

282. **Bone HG, Cosman F, Miller PD, et al.** ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. *J Clin Endocrinol Metab*. 2018;103:2949-2957.[EL 2; OLES]

283. **Cosman F, Crittenden DB, Adachi JD, et al.** Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375:1532-1543.[EL 1; RCT]

284. **Genant HK, Engelke K, Bolognese MA, et al.** Effects of romosozumab compared with teriparatide on bone density and mass at the spine and hip in postmenopausal women with low bone mass. *J Bone Miner Res*. 2017;32:181-187.[EL 1; RCT]

285. **Langdahl BL, Libanati C, Crittenden DB, et al.** Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet*. 2017;390:1585-1594.[EL 1; RCT]

286. **Lewiecki EM, Blicharski T, Goemaeire S, et al.** A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab*. 2018;103:3183-3193.[EL 1; RCT]

287. **Greenspan SL, Maitland LA, Myers ER, Krasnow MB, Kido TH.** Femoral bone loss progresses with age: a longitudinal study in women over age 65. *J Bone Miner Res*. 1994;9:1959-1965.[EL 2; CSS]

288. **Ooms ME, Lips P, Roos JC, et al.** Vitamin D status and sex hormone binding globulin: determinants of bone turnover and bone mineral density in elderly women. *J Bone Miner Res*. 1995;10:1177-1184.[EL 2; ES]

289. **Wasnich RD, Bagger YZ, Hosking DJ, et al.** Changes in bone density and turnover after alendronate or estrogen withdrawal. *Menopause*. 2004;11:622-630.[EL 1; RCT]

290. **Gallagher JC, Rapuri PB, Haynatzki G, Detter JR.** Effect of discontinuation of estrogen, calcitriol, and the combination of both on bone density and bone markers. *J Clin Endocrinol Metab*. 2002;87:4914-4923.[EL 1; RCT]

291. **Gourlay ML, Fine JP, Preisser JS, et al.** Bone-density testing interval and transition to osteoporosis in older women. *N Engl J Med*. 2012;366:225-233.[EL 2; PCS]

292. **Lewiecki EM, Watts N.** Assessing response to osteoporosis therapy. *Osteoporos Int*. 2008;19:1363-1368.[EL 4; NE]

293. **Lewiecki EM, Randolph LA.** How common is loss of bone mineral density in elderly clinical practice patients receiving oral bisphosphonate therapy for osteoporosis. *J Bone Miner Res*. 2002;17:S367.[EL 2; ES]

294. **Lenchik L, Kiebzak GM, Blunt BA.** What is the role of serial bone mineral density measurements in patient management? *J Clin Densitom*. 2002;5 suppl:S29-S38.[EL 4; NE]

295. **Baim S, Wilson CR, Lewiecki EM, Luckey MM, Downs RW Jr, Lentle BC.** Precision assessment and radiation safety for dual-energy X-ray absorptiometry: position paper of the International Society for Clinical Densitometry. *J Clin Densitom*. 2005;8:371-378.[EL 4; NE]

296. **Kolta S, Ravaud P, Fechtenbaum J, Dougados M, Roux C.** Follow-up of individual patients on two DXA scanners of the same manufacturer. *Osteoporos Int*. 2000;11:709-713.[EL 2; PCS]

297. **Shen L, Xie X, Su Y, Luo C, Zhang C, Zeng B.** Parathyroid hormone versus bisphosphonate treatment on bone mineral density in osteoporosis therapy: a meta-analysis of randomized controlled trials. *PLoS One*. 2011;6:e26267.[EL 1; MRCT]

298. **Simon BR, Parlee SD, Learman BS, et al.** Artificial sweeteners stimulate adipogenesis and suppress lipolysis independently of sweet taste receptors. *J Biol Chem*. 2013;288:32475-32489.[EL 2; PHAS]

299. **Schousboe JT, Vokes T, Broy SB, et al.** Vertebral fracture assessment: the 2007 ISCD official positions. *J Clin Densitom*. 2008;11:92-108.[EL 4; NE]

300. **Schousboe JT, Shepherd JA, Bilezikian JP, Baim S.** Executive summary of the 2013 International Society for Clinical Densitometry position development conference on bone densitometry. *J Clin Densitom*. 2013;16:455-466.[EL 4; NE]

301. **Hochberg MC, Ross PD, Black D, et al.** Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group. *Arthritis Rheum*. 1999;42:1246-1254.[EL 2; PCS]

302. **Watts NB, Cooper C, Lindsay R, et al.** Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. *J Clin Densitom*. 2004;7:255-261.[EL 1; MRCT]

303. **Chapurlat RD, Palermo L, Ramsay P, Cummings SR.** Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. *Osteoporos Int*. 2005;16:842-848.[EL 1; RCT]

304. **Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P.** Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977-2001. *J Bone Miner Res*. 2009;24:1299-1307.[EL 2; ES]

305. **Black DM, Arden NK, Palermo L, Pearson J, Cummings SR.** Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Mineral Res*. 1999;14:821-828. [EL 2; PCS]

306. **Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH.** Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. *J Clin Endocrinol Metab*. 2005;90:1583-1587.[EL 2; PHAS]

307. **Lewiecki EM, Cummings SR, Cosman F.** Treat-to-target for osteoporosis: is now the time? *J Clin Endocrinol Metab*. 2013;98:946-953.[EL 4; NE]

308. **Cummings SR, Cosman F, Eastell R, Reid IR, Mehta M, Lewiecki EM.** Goal-directed treatment of osteoporosis. *J Bone Miner Res*. 2013;28:433-438.[EL 4; NE]

309. **Bouxsein ML.** Mechanisms of osteoporosis therapy: a bone strength perspective. *Clin Cornerstone*. 2003;Suppl 2:S13-21.[EL 4; NE]

310. **Tosteson AN, Grove MR, Hammond CS, et al.** Early discontinuation of treatment for osteoporosis. *Am J Med*. 2003;115:209-216. [EL 2; ES]

311. **Woo SB, Hellstein JW, Kalmar JR.** Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med*. 2006;144:753-761.[EL 4; NE]

312. **Bilezikian JP.** Osteonecrosis of the jaw--do bisphosphonates pose a risk? *N Engl J Med*. 2006;355:2278-2281.[EL 4; NE]

313. **Khosla S, Burr D, Cauley J, et al.** Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2007;22:1479-1491.[EL 4; NE]

314. **Khan AA, Morrison A, Hanley DA, et al.** Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res*. 2015;30:3-23.[EL 4; NE]

315. **Watts N, Grbic JT, Binkley N, et al.** Invasive oral procedures and events in postmenopausal women with osteoporosis treated with denosumab for up to 10 years. *J Clin Endocrinol Metab*. 2019;104:2443-2452.[EL 1; RCT]

316. **Ruggiero SL, Dodson TB, Fantasia J, et al.** American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. *J Oral Maxillofac Surg*. 2014;72:1938-1956.[EL 4; NE]

317. **Lenart BA, Neviaser AS, Lyman S, et al.** Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporos Int*. 2009;20:1353-1362.[EL 2; RCCS]

318. **Shane E, Burr D, Abrahamsen B, et al.** Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2014;29:1-23.[EL 4; NE]

319. **Schilcher J, Koeppen V, Aspenberg P, Michëelsson K.** Risk of atypical femoral fracture during and after bisphosphonate use. *N Engl J Med*. 2014;371:974-976.[EL 4; NE]

320. **Adler R.** Management of endocrine disease: Atypical femoral fractures: risks and benefits of long-term treatment of osteoporosis with anti-resorptive therapy. *Eur J Endocrinol*. 2018;178:R81-R87.[EL 4; NE]

321. **Black DM, Rosen CJ.** Clinical Practice. Postmenopausal Osteoporosis. *N Engl J Med*. 2016;374:254-262.[EL 4; NE]

322. **Shane E, Burr D, Ebeling PR, et al.** Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2010;25:2267-2294.[EL 4; NE]

323. **Kim SY, Schneeweiss S, Katz JN, Levin R, Solomon DH.** Oral bisphosphonates and risk of subtrochanteric or diaphyseal femur fractures in a population-based cohort. *J Bone Miner Res*. 2011;26:993-1001.[EL 2; ES]

324. **Kharazmi M, Hallberg P, Schilcher J, Aspenberg P, Michëelsson K.** Mortality after atypical femoral fractures: a cohort study. *J Bone Miner Res.* 2016;31:491-497.[EL 2; ES]

325. **Chiang CY, Zebaze RM, Ghasem-Zadeh A, Juliano-Burns S, Hardidge A, Seeman E.** Teriparatide improves bone quality and healing of atypical femoral fractures associated with bisphosphonate therapy. *Bone.* 2013;52:360-365.[EL 2; PCS]

326. **Miyakoshi N, Alzawa T, Sasaki S, et al.** Healting of bisphosphonate-associated atypical femoral fractures in patients with osteoporosis: a comparison between treatment with and without teriparatide. *J Bone Miner Metab.* 2015;33:553-559.[EL 2; ES]

327. **Watts NB, Aggers D, McCarthy EF, et al.** Responses to treatment with teriparatide in patients with atypical femur fractures previously treated with bisphosphonates. *J Bone Miner Res.* 2017;32:1027-1033.[EL 2; PCS]

328. **Adler RA, El-Hajj Fuleihan G, Bauer DC, et al.** Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2016;31:16-35.[EL 4; NE]

329. **Schwartz AV, Bauer DC, Cummings SR, et al.** Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. *J Bone Miner Res.* 2010;25:976-982.[EL 2; PHAS]

330. **Cosman F, Cauley JA, Eastell R, et al.** Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? *J Clin Endocrinol Metab.* 2014;99:4546-4554.[EL 1; RCT]

331. **Black DM, Reid IR, Cauley JA, et al.** The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res.* 2015;30:934-944.[EL 1; RCT]

332. **Black DM, Reid IR, Boonen S, et al.** The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res.* 2012;27:243-254.[EL 1; RCT]

333. **Mignot MA, Taisne N, Legroux I, Cortet B, Paccou J.** Bisphosphonate drug holidays in postmenopausal osteoporosis: effect on clinical fracture risk. *Osteoporos Int.* 2017;28:3431-3438.[EL 2; ES]

334. **Bindon B, Adams W, Balasubramanian N, Sandhu J, Camacho P.** Osteoporotic fractures during bisphosphonate drug holiday. *Endocr Pract.* 2018;24:163-169.[EL 2; ES]

335. **Russell RG.** Bisphosphonates: the first 40 years. *Bone.* 2011;49:2-19.[EL 4; NE]

336. **Compston JE, Watts NB.** Combination therapy for postmenopausal osteoporosis. *Clin Endocrinol.* 2002;56:565-569.[EL 1; MRCT]

337. **Black DM, Greenspan SL, Ensrud KE, et al.** The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med.* 2003;349:1207-1215.[EL 1; RCT]

338. **Leder BZ, Tsai JN, Uihlein AV, et al.** Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab.* 2014;99:1694-1700.[EL 1; RCT]

339. **Rittmaster RS, Bolognese M, Ettinger MP, et al.** Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab.* 2000;85:2129-2134.[EL 1; RCT]

340. **Deal C, Omizo M, Schwartz EN, et al.** Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. *J Bone Miner Res.* 2005;20:1905-1911.[EL 1; RCT]

341. **Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM.** The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med.* 2003;349:1216-1226.[EL 1; RCT]

342. **Bone HG, Bolognese M, Yuen CK, et al.** Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab.* 2011;96:972-980.[EL 1; RCT]

343. **Freemantle S, Satram-Hoang S, Tang E-T, et al.** Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int.* 2012;23:317-326.[EL 1; RCT]

344. **Diab DL, Watts NB.** Postmenopausal osteoporosis. *Curr Opin Endocrinol Diabetes Obes.* 2013;20:501-509.[EL 4; NE]

345. **Cummings SR, Ferrari S, Eastell R, et al.** Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM Trial and its extension. *J Bone Miner Res.* 2018;33:190-198.[EL 2; PHAS]

346. **Boonen S, Marin F, Obermayer-Pietsch B, et al.** Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab.* 2008;93:852-860.[EL 2; ES]

347. **Kallmes DF, Comstock BA, Heagerty PJ, et al.** A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med.* 2009;361:569-579.[EL 1; RCT]

348. **Buchbinder R, Osborne RH, Ebeling PR, et al.** A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med.* 2009;361:557-568.[EL 1; RCT]

349. **Staples MP, Kallmes DF, Comstock BA, et al.** Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis. *BMJ.* 2011;343:d3952. [EL 1; MRCT]

350. **Kroon F, Staples M, Ebeling PR, et al.** Two-year results of a randomized placebo-controlled trial of vertebroplasty for acute osteoporotic vertebral fractures. *J Bone Miner Res.* 2014;29:1346-1355.[EL 1; RCT]

351. **Blasco J, Martinez-Ferrer A, Macho J, et al.** Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: a 12-month randomized follow-up, controlled trial. *J Bone Miner Res.* 2012;27:1159-1166.[EL 1; RCT]

352. **Klazen CA, Venmans A, de Vries J, et al.** Percutaneous vertebroplasty is not a risk factor for new osteoporotic compression fractures: results from VERTOS II. *Am J Neuroradiol.* 2010;31:1447-1450.[EL 1; RCT]

353. **Bóuza C, Lopez-Cuadrado T, Almendro N, Amate JM.** Safety of balloon kyphoplasty in the treatment of osteoporotic vertebral compression fractures in Europe: a meta-analysis of randomized controlled trials. *Eur Spine J.* 2015;24:715-723.[EL 1; MRCT]

354. **Aghamirsalim M, Sorbi R.** Do the hospitalized patients with osteoporotic fractures require endocrinologists' help? *J Endocrinol Invest.* 2012;35:992-995.[EL 2; ES]

355. **Bell K, Strand H, Inder WJ.** Effect of a dedicated osteoporosis health professional on screening and treatment in outpatients presenting with acute low trauma non-hip fracture: a systematic review. *Arch Osteoporos.* 2014;9:167.[EL 4; NE]

356. **Radonich M.** Communicating radiation risk to the public. *Community Environmental Monitoring Program 25th Anniversary Annual Workshop:* National Service Center Publications (NSCEP), 2006.[EL 4; NE]

357. **Edwards A, Elwyn G.** How should effectiveness of risk communication to aid patients' decisions be judged? A review of the literature. *Med Decis Making.* 1999;19:428-434.[EL 4; NE]

358. **Charles CA, Whelan T, Gafni A, Willan A, Farrell S.** Shared treatment decision making: what does it mean to physicians? *J Clin Oncol.* 2003;21:932-936.[EL 2; ES]

359. **Charles C, Gafni A, Whelan T.** Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. *Social science & medicine (1982).* 1999;49:651-661.[EL 4; NE]

360. **Charles C, Gafni A, Whelan T.** Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). *Soc Sci Med.* 1997;44:681-692.[EL 4; NE]

361. **Lewiecki EM.** Risk communication and shared decision making in the care of patients with osteoporosis. *J Clin Densitom.* 2010;13:335-345.[EL 4; NE]

362. **Dowd R, Recker RR, Heaney RP.** Study subjects and ordinary patients. *Osteoporos Int.* 2000;11:533-536.[EL 2; ES]

363. **Trevena LJ, Davey HM, Barratt A, Butow P, Caldwell P.** A systematic review on communicating with patients about evidence. *J Eval Clin Pract.* 2006;12.[EL 2; MNRCT]

364. **Boudreau JD, Cassell E, Fuks A.** Preparing medical students to become attentive listeners. *Med Teach.* 2009;31:22-29.[EL 4; NE]

365. **Hudson B, Toop L, Mangin D, Pearson J.** Risk communication methods in hip fracture prevention: a randomised trial in primary care. *Br J Gen Pract*. 2011;61:e469-e476.[EL 1; RCT]

366. **Montori VM, Shah ND, Pencille LJ, et al.** Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. *Am J Med*. 2011;124:549-556.[EL 1; RCT]

367. **Clowes JA, Peel NF, Eastell R.** The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. *J Clin Endocrinol Metab*. 2004;89:1117-1123.[EL 1; RCT]

368. **Briot K, Ravaud P, Dargent-Molina P, Zylberman M, Liu-Leage S, Roux C.** Persistence with teriparatide in postmenopausal osteoporosis; impact of a patient education and follow-up program: the French experience. *Osteoporos Int*. 2009;20:625-630.[EL 2; PCS]

369. **Schilcher J, Michaëlsson K, Aspenberg P.** Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med*. 2011;364:1728-1737.[EL 2; ES]

370. **Hansen D, Bazell C, Pelizzari P, Pyenson B.** Medicare cost of osteoporotic fractures: The clinical and cost burden of an important consequence of osteoporosis. Available at: http://www.milliman.com/insight/2019/Medicare-cost-of-osteoporotic-fractures. Accessed October 2019.[EL 4; NE]

371. **Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A.** The burden of osteoporotic fractures: a method for setting intervention thresholds. *Osteoporos Int*. 2001;12:417-427.[EL 2; ES]

372. **International Collaborative Study of Severe Anaphylaxis.** Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoepidemiol Drug Saf*. 2003;12:195-202.[EL 2; RCCS]

373. **American Dental Association Council on Scientific Affairs.** Dental management of patients receiving oral bisphosphonate therapy: expert panel recommendations. *J Am Dent Assoc*. 2006;137:1144-1150.[EL 4; NE]