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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

EXECUTIVE SUMMARY

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DISCLAIMER

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.

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ABBREVIATIONS

25(OH)D = 25-hydroxyvitamin D; **AACC** = American Association for Clinical Chemistry; **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; **BMI** = body mass index ; **BTM** = bone turnover marker; **CBC** = complete blood count; **CI** = confidence interval; **CPG** = clinical practice guideline; **CTX** = C-terminal telopeptide type-I collagen; **DXA** = dual-energy X-ray absorptiometry; **EL** = evidence level; **FDA** = US Food and Drug Administration; **FLEX** = Fracture Intervention Trial (FIT) Long-term Extension; **FRAX**[®] = Fracture Risk Assessment Tool; **FREEDOM** Trial = Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months Trial; **GFR** = glomerular filtration rate; **GI** = gastrointestinal; **HF** = hip fracture; **HORIZON** = Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial (zoledronic acid and zoledronate are equivalent terms); **HRT** = hormone replacement therapy; **IOF** = International Osteoporosis Foundation; **IOM** = Institute of Medicine; **ISCD** = International Society for Clinical Densitometry; **IU** = international units; **IV** = intravenous; **LSC** = least significant change; **MOF** = major osteoporosis fracture; **NAM** = National Academy of Medicine; **NBHA** = National Bone Health Alliance; **NOF** = National Osteoporosis Foundation; **NTX** = N-terminal telopeptide type-I collagen; **ONJ** = osteonecrosis of the jaw; **PINP** = serum amino-terminal propeptide of type-I collagen; **PTH** = parathyroid hormone; **R** = recommendation; **RANK** = receptor activator of nuclear factor kappa B; **RANKL** = receptor activator of nuclear

factor kappa-B ligand; **ROI** = region of interest; **RR** = relative risk; **SD** = standard deviation; **SRRE**
= summary relative risk estimate; **TBS** = trabecular bone score; **TSH** = thyroid-stimulating
hormone; **VFA** = vertebral fracture assessment; **WHI** = Women's Health Initiative; **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 (CPG).

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%) 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.

LAY ABSTRACT

Osteoporosis is preventable and treatable, but only a small proportion of those at increased risk for fracture are evaluated. This updated guideline provides recommendations based on scientific evidence to reduce the risk of osteoporosis-related fractures, and for health-care professionals to efficiently and effectively evaluate, diagnose, and treat osteoporosis in postmenopausal women, based on assessment of fracture risk, measurement of bone mineral density or bone mass, and a patient's history, presence and probability of fracture, among other factors. Several lifestyle modifications, such as adequate intake of calcium and vitamin D, regular exercise, a balanced diet, avoiding tobacco and limiting alcohol consumption, and removing potential risk factors to avoid falls, may improve balance, preserve bone strength, and prevent future fractures. All postmenopausal women aged 50 years and older should undergo clinical assessment for osteoporosis and fracture risk, using a fracture risk assessment tool when available. This update indicates numerous approved medications that could be used to reduce fractures and treat osteoporosis and for which appropriate groups of patients, depending on their level of risk factors. Decision-making regarding choice of medication can depend on fracture risk, location of fractures, benefits, cost, availability, patient preferences, and individual health history and circumstances. Based on the evidence and recommendations presented, physicians may determine when to initiate treatment, how to monitor response to

therapy and identify those who have significant bone loss, and how to determine the success and duration of treatments for osteoporosis.

KEY UPDATES FOR 2020

The following key updates highlight the most important new recommendations in this CPG.

- 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 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) (**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, 30–50 ng/mL) **(Grade A; BEL 1)**.

R12. Supplement with vitamin D₃ if needed, with a daily dose of 1,000–2,000 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, TBS-adjusted FRAX[®]) 10-year probability for major osteoporotic fracture is $\geq 20\%$ or the 10-year probability of hip fracture is $\geq 3\%$ in the US 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., < -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 highest 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 is limited by small area and very large least significant change (**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 pharmacological 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 alendronate 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 (T-score > -2.5, no fractures, etc.), 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 anti-resorptive 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, treatment with another antiresorptive agent is recommended if there are no contraindications. (**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)**.

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