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

EXECUTIVE SUMMARY

Complete Guidelines available at http://journals.aace.com

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

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

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

1. INTRODUCTION

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

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

Evidence was obtained through MEDLINE searches and other designated reference sources. Expert opinion was used to evaluate the available literature and to grade references relative to evidence level (EL) (Table 1), evidence analysis, and subjective factors (Table 2), based on the ratings of 1 through 4 from the 2010 and 2014 AACE protocols for standardized production of clinical practice guidelines (available online at https://www.aace.com/files/checklists_july_2014_ep.pdf) (1 [EL 4; CPG NE], 2 [EL 4; CPG NE]). Best evidence level (BEL) for evidence presented in the discussion of the evidence base is given for each recommendation in the Executive Summary. In addition, recommendations were graded A through D, in accordance with methods established by the AACE in 2004 and clarified in 2010 (Table 3) (1 [EL 4; CPG NE], 3 [EL 4; CPG NE]). Information pertaining to cost-effectiveness was included when available. Examples of qualifiers that are appropriate to append to recommendations include risk-benefit analyses, evidence gaps, alternative physician preferences (dissenting opinions), alternative recommendations (e.g., based on resource availability and cultural factors), expert consensus and relevance (i.e., patient-oriented evidence that matters) (1 [EL 4; CPG NE]). **(Endocr Pract. 2016;22:1111-1118)**

3. EXECUTIVE SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Study design	Data analysis	Interpretation
Premise correctness	Intent-to-treat	Generalizability
Allocation concealment (randomization)	Appropriate statistics	Logical
Selection bias		Incompleteness
Appropriate blinding		Validity
Using surrogate end points (especially in "first-in-its-class" intervention)		
Sample size (beta error)		
Null hypothesis versus Bayesian statistics		

Adapted from Mechanick et al. *Endocr Pract*. 2010;16:270-283.(1 [EL 4; CPG NE])

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

3.Q4. Who Needs Pharmacologic Therapy?

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

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

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

3.Q6. How Is Treatment Monitored?

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

3.Q7. What Is Successful Treatment of Osteoporosis?

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

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

3.Q8. How Long Should Patients Be Treated?

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

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

2004 AACE Criteria for Grading Recommendations

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

2010 AACE Update: Mapping Evidence Levels to Recommended Grading

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

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

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

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

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

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

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

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

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

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

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

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

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DISCLOSURE

Co-Chairs

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Task Force Members

Dr. Neil Binkley reports that he has received advisory/consultant honoraria from Merck, Amgen, Eli Lilly and Company, Bristol-Myers Squibb, and Nestle. He has also received research support from Amgen, Merck, Eli Lilly and Company, Opko Health, Novartis, and GE Healthcare Lunar.

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AACE/ACE 2016 Postmenopausal Osteoporosis Treatment Algorithm

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

Evaluate for causes of secondary osteoporosis

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

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

No prior fragility fractures or moderate fracture risk**

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

Reassess at least yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

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

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

Progression of bone loss or recurrent fractures

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

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

Prior fragility fractures or indicators of higher fracture risk**

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

Reassess at least yearly for response to therapy and fracture risk

Denosumab

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

Teriparatide for up to 2 years

Sequential therapy with oral or injectable antiresorptive agent

Zoledronic acid

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

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

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

*** Medications are listed alphabetically.

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