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CLINICAL GUIDELINE

Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians

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Description: This guideline updates the 2008 American College of Physicians (ACP) recommendations on treatment of low bone density and osteoporosis to prevent fractures in men and women. This guideline is endorsed by the American Academy of Family Physicians.

Methods: The ACP Clinical Guidelines Committee based these recommendations on a systematic review of randomized controlled trials; systematic reviews; large observational studies (for adverse events); and case reports (for rare events) that were published between 2 January 2005 and 3 June 2011. The review was updated to July 2016 by using a machine-learning method, and a limited update to October 2016 was done. Clinical outcomes evaluated were fractures and adverse events. This guideline focuses on the comparative benefits and risks of short- and long-term pharmacologic treatments for low bone density, including pharmaceutical prescriptions, calcium, vitamin D, and estrogen. Evidence was graded according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians. The target patient population includes men and women with low bone density and osteoporosis.

Recommendations: Recommendation 1: *ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)*

Recommendation 2: *ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years. (Grade: weak recommendation; low-quality evidence)*

Recommendation 3: *ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)*

Recommendation 4: *ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women. (Grade: weak recommendation; low-quality evidence)*

Recommendation 5: *ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)*

Recommendation 6: *ACP recommends that clinicians should make the decision whether to treat osteopenic women 65 years of age or older who are at a high risk for fracture based on a discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medications. (Grade: weak recommendation; low-quality evidence)*

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Osteoporosis is a systemic skeletal disease characterized by decreasing bone mass and microarchitectural deterioration of bone tissue that leads to an increased risk for bone fragility and fracture (1). Although osteoporosis can be present in any bone, the hip, spine, and wrist are most likely to be affected. Osteoporosis is found in an estimated 200 million people worldwide (2), and an estimated 54 million men and women in the United States have osteoporosis or low bone density (3). Approximately 50% of Americans older than 50 years are at risk for osteoporotic fracture (4). The economic impact of osteoporosis on the health care system is estimated to be $25.3 billion per year by 2025 (3).

* This paper, written by Amir Qaseem, MD, PhD, MHA; Mary Ann Forciea, MD; Robert M. McLean, MD; and Thomas D. Denberg, MD, PhD, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Thomas D. Denberg, MD, PhD (*Chair during development of the guideline*)†; Mary Ann Forciea, MD (*current Chair*)†; Michael J. Barry, MD†; Molly Cooke, MD†; Nick Fitterman, MD†; Russell P. Harris, MD, MPH†; Linda L. Humphrey, MD, MPH†; Devan Kansagara, MD, MCR†; Robert M. McLean, MD†; Tanveer P. Mir, MD†; Holger J. Schünemann, MD, PhD†; and Timothy J. Wilt, MD, MPH‡. Approved by the ACP Board of Regents on 27 April 2015.

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Table 1. The American College of Physicians Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	**Benefits Finely Balanced With Risks and Burden**
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) workgroup.

Risk factors for osteoporotic fracture include (but are not limited to) increasing age, female sex, postmenopause for women, hypogonadism or premature ovarian failure, low body weight, history of parental hip fracture, ethnic background (white persons are at higher risk than black persons), previous clinical or morphometric vertebral fracture, previous fracture due to minimal trauma (that is, previous osteoporotic fracture), rheumatoid arthritis, current smoking, alcohol intake (3 or more drinks daily), low bone mineral density (BMD), vitamin D deficiency, low calcium intake, hyperkyphosis, falling, and immobilization (5). Another risk factor for osteoporotic fracture is long-term use of certain medications, the most commonly implicated being glucocorticoids, anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadotropin-releasing hormone agonists (5).

Osteoporosis can be diagnosed by the occurrence of fragility fracture. In patients without fragility fracture, osteoporosis is often diagnosed by low BMD. Dual-energy x-ray absorptiometry (DXA) is the current gold standard test for diagnosing osteoporosis in people without an osteoporotic fracture. Results of DXA are scored as SDs from a young, healthy norm (usually female) and reported as T scores. For example, a T score of –2 indicates a BMD that is 2 SDs below the comparative norm. The international reference standard for the description of osteoporosis in postmenopausal women and in men aged 50 years or older is a femoral neck BMD of 2.5 SD or more below the young female adult mean (2). Low BMD as measured by DXA is an imperfect predictor of fracture risk, identifying less than one half of the people who go on to have an osteoporotic fracture.

Bone density can also be classified according to the *Z* score, the number of SD above or below the expected BMD for the patient's age and sex. A *Z* score of –2.0 or lower is defined as either "low BMD for chronological age" or "below the expected range for age," and those above –2.0 are "within the expected range for age" (6). Risk scores that combine clinical risk factors with BMD testing results, such as FRAX (the World Health Organization Fracture Risk Assessment Tool), can be used to predict fracture risk among people with low bone density.

Pharmacologic treatments for osteoporosis include bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), peptide hormones (teriparatide [the 1,3,4 amino acid fragment of parathyroid hormone] and calcitonin), estrogen (in the form of menopausal hormone therapy) for postmenopausal women, and selective estrogen receptor modulators (SERMs) (raloxifene for postmenopausal women). Most of the treatments aim to prevent bone resorption. Denosumab (a new biologic agent), dietary and supplemental calcium, and vitamin D are also used for treatment. Bazedoxifene, a SERM, has recently been approved by the U.S. Food and Drug Administration (FDA) with conjugated estrogen for prevention of osteoporosis.

GUIDELINE FOCUS AND TARGET POPULATION

This updated guideline presents additional available evidence on treatments, including new medications and biologic agents, to prevent fractures in men and women with low bone density or osteoporosis since publication of the ACP 2008 guideline, and replaces the 2008 guideline (7). Several therapies included in the 2008 guideline have been excluded from the update, including calcitonin, which is no longer widely used for osteoporosis treatment, and both etidronate and pamidronate, neither of which are FDA-approved for the prevention of fractures or treatment of osteoporosis. One new biologic, denosumab, a human monoclonal antibody approved by the FDA for treatment of osteoporosis, has been added since publication of the 2008 guideline. Different medications for the treatment of osteoporosis may affect various parts of the skeletal system differently. The target audience for this guideline includes all clinicians and the target patient population includes men and women with low bone density and osteoporosis. These recommendations are based on a systematic evidence review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (6, 8). This guideline is endorsed by the American Academy of Family Physicians.

METHODS

Systematic Review of the Evidence

The evidence review was conducted by AHRQ's Southern California Evidence-based Practice Center–RAND Corporation. **Appendix 1** (available at Annals.org) summarizes the methods for the evidence review, and additional details can be found in the reports (6, 8).

Reviewers searched databases from 2 January 2005 to 3 June 2011. A machine-learning method was used to update the searches, once in 2014 and then specifically on bisphosphonates, calcium, vitamin D, and estrogen through 12 July 2016 (9). **Appendix 2** (available at Annals.org) shows the search methodology for the update. Reviewers also did a limited search on the recently FDA-approved drug bazedoxifene from 1 January 2013 to 26 October 2016. Evidence tables for studies identified in the 2016 update search are

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found in Appendix Tables 1 and 2 (available at Annals .org).

Grading the Evidence and Developing Recommendations

This guideline was developed by ACP's Clinical Guidelines Committee (CGC) according to ACP's guideline development process, details of which can be found in ACP's methods paper (10). The CGC used the evidence tables in the accompanying systematic review (8), full report (6), and update when reporting the evidence and graded the recommendations by using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology (Table 1).

Peer Review

The AHRQ systematic review was peer-reviewed and posted on the AHRQ Web site for public comments. The 2014 evidence review was also peer-reviewed through the journal. The guideline was peer-reviewed through the journal and posted online for comments from ACP Regents and ACP Governors, who represent physician members at the national and international level.

Comparative Benefits of Treatment Versus Placebo for Reducing Fractures in Patients With Osteoporosis

Bisphosphonates

High-quality evidence showed that bisphosphonates, including alendronate (11–42-43–45), risedronate (34–36, 42, 46–77-78), and zoledronic acid (79–85), reduce vertebral, nonvertebral, and hip fractures compared with placebo in postmenopausal osteoporotic women. High-quality evidence also showed that ibandronate reduces the risk for radiographic vertebral fractures, although evidence is insufficient to determine the effect of ibandronate on hip fractures (38, 86–94). Moderate-quality evidence showed that zoledronic acid reduces radiographic vertebral fractures in osteoporotic men (95).

Denosumab

High-quality evidence showed that treatment with denosumab reduces radiographic vertebral, nonvertebral, and hip fractures compared with placebo in postmenopausal osteoporotic women (96–108). One Japanese trial and its 1-year open-label extension study included postmenopausal osteoporotic women with prevalent radiographic vertebral fractures and showed that denosumab protected against radiographic vertebral fractures (101, 109).

Teriparatide

High-quality evidence showed that treatment with teriparatide reduces radiographic vertebral and nonvertebral fractures compared with placebo in postmenopausal osteoporotic women (34, 110–120).

SERMs

High-quality evidence showed that raloxifene reduces vertebral fractures in osteoporotic women; however, it did not statistically significantly decrease the risk for nonvertebral or hip fractures compared with placebo (34, 121–127).

Bazedoxifene is FDA-approved in combination with conjugated estrogens for the prevention of osteoporosis (20 mg, with 0.45 mg conjugated estrogen). The systematic review did not find any randomized controlled trials (RCTs) with this combination that had primary fracture outcomes.

Estrogen Therapy for Postmenopausal Women

Moderate-quality evidence showed no difference in reduced fracture with estrogen treatment in postmenopausal women with established osteoporosis (40, 41, 123, 128–130). This differs from the 2008 guideline, which reported high-quality evidence that estrogen therapy was associated with reduced risk for vertebral, nonvertebral, and hip fractures in postmenopausal women (7, 131). Studies included in the 2008 guideline focused on postmenopausal women or those with low bone density as opposed to the newer data, which focused on postmenopausal women with established osteoporosis.

Calcium or Vitamin D

Moderate-quality evidence showed that the overall effect of calcium or vitamin D alone on fracture risk is uncertain. Studies showed no difference between calcium alone and placebo for reduced vertebral and nonvertebral fracture risk (132–157), although adherence was low. Data on the efficacy of vitamin D alone for reducing fracture risk are mixed, and the overall effect is uncertain (34, 129, 134–139, 142–144, 146, 148, 149, 152, 158–189-190–209).

Physical Activity

Evidence is insufficient to conclusively show the effect of physical activity on fracture risk (210–218). There are no studies that evaluated the comparative effectiveness of physical activity with that of other interventions.

Comparative Benefits of Treatment Within and Among Classes for Reducing Fractures in Patients With Osteoporosis

Evidence is insufficient to determine the comparative effectiveness of pharmacologic therapy or the superiority of one medication over another, within the same class or among classes, for prevention of fractures (21, 29, 40–42, 123, 129, 130, 139, 149, 156, 175, 199, 201, 208, 219–234). Network meta-analyses addressing the lack of head-to-head comparisons between the drugs mostly show no statistically significant differences among the various therapies (235–239).

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BENEFITS OF TREATMENT FOR FRACTURE RISK REDUCTION IN INDIVIDUALS WITH DIFFERENT FRACTURE RISKS

Bone Mineral Density

Moderate-quality evidence from post hoc analysis of 1 RCT showed that low femoral neck BMD did not predict the effect of alendronate on clinical vertebral or nonvertebral fracture risk (240).

FRAX Risk Assessment

Moderate-quality evidence from post hoc analysis of 1 RCT showed no significant interaction between fracture risk as assessed by FRAX and the efficacy of raloxifene for reducing the relative risk for vertebral fractures in women older than 75 years (241).

Prior Fractures (Prevention vs. Treatment)

Evidence is insufficient for prevalent fractures to predict the efficacy of alendronate or raloxifene treatment in reducing risk for fractures in postmenopausal women, because studies reported conflicting results (240, 242–244). Moderate-quality evidence from post hoc analysis of 1 RCT showed that postmenopausal women with prevalent vertebral fractures benefited more from teriparatide treatment than those without prevalent fractures (245).

Age

High-quality evidence showed that bisphosphonates and teriparatide are at least as effective for older patients as they are for younger patients (246–249).

Sex

Evidence is insufficient regarding the effectiveness of therapies to prevent fractures or treat osteoporosis in men, because few relevant studies have been published (28, 50–52, 82, 90, 136, 157, 166). Two RCTs evaluated vitamin D treatment in men and women and reported on fractures (136, 166). One study showed that calcium plus vitamin D_3 reduced the risk for fracture among elderly women but not elderly men (136). The other study showed no difference in fracture reduction for elderly men treated with intramuscular injection of ergocalciferol, whereas women had increased risk for wrist fractures (166).

Race/Ethnicity

High-quality evidence from post hoc analysis of 2 RCTs showed that compared with placebo, raloxifene decreases the relative risk for vertebral fracture but not nonvertebral or hip fracture among Asian women (250), consistent with findings from U.S. studies.

Glucocorticoid Treatment

Moderate-quality evidence showed that alendronate, risedronate, and teriparatide reduced fracture risk in patients taking glucocorticoids (30, 219).

Renal Insufficiency

Evidence is insufficient from trials assessing the effect of renal function on the efficacy of alendronate, raloxifene, and teriparatide in preventing fractures in osteoporotic women (251–254).

HARMS OF PHARMACOLOGIC TREATMENT FOR REDUCING FRACTURES

Bisphosphonates

Low-quality evidence showed that bisphosphonates are associated with atypical subtrochanteric fractures, and the FDA has issued a warning for these drugs (255). Evidence suggests that this adverse event may be related to treatment duration, because the rate of atypical fractures for women taking bisphosphonates for less than 2 years was 1.78 per 100 000 and increased to over 100 per 100 000 in women taking the drugs for 8 years or more (256).

Low-quality evidence also showed that bisphosphonates are associated with osteonecrosis of the jaw, although this side effect is rare (257–282).

The 2008 guideline reported that bisphosphonates may be associated with atrial fibrillation; however, most new evidence suggests that there is no increased risk (126, 283–288). A recent post hoc double-blind extension of the HORIZON-PFT trial found no difference in atrial fibrillation with 9 years versus 6 years of treatment with zoledronic acid in osteoporotic postmenopausal women, although women treated for 9 years had a higher incidence of any arrhythmia (14.1% vs. 4.2%; $P = 0.02$) (85). One study showed that bisphosphonates were associated with increased risk for incident acute myocardial infarction (hazard ratio [HR], 1.38 [95% CI, 1.08 to 1.77], after cardiovascular disease risk factors were controlled for) after a median 3.6 years of follow-up (289). A population-based cohort study also showed that bisphosphonates were associated with increased risk for cardiovascular events, including atrial fibrillation (adjusted HR, 1.55 [CI, 1.04 to 2.39]) and congestive heart failure (adjusted HR, 1.65 [CI, 1.36 to 1.99]) (290). In contrast, a recent meta-analysis concluded that there is no significant association between oral or intravenous bisphosphonate use and total cardiovascular events, stroke, myocardial infarction, or cardiovascular death (287).

High-quality evidence showed that bisphosphonates are associated with mild upper gastrointestinal symptoms (83, 291–303), and a network meta-analysis did not show statistically significant differences between the various bisphosphonates for gastrointestinal symptoms (304).

High-quality evidence showed that zoledronic acid is associated with hypocalcemia (odds ratio [OR], 7.22 [CI, 1.81 to 42.7]) (81, 305). High-quality evidence also showed that zoledronic acid is associated with influenza-like symptoms (OR, 6.39 [CI, 5.76 to 7.09]) (79, 81, 82, 306–308). A recent secondary analysis of a double-blind RCT showed an increased incidence of uveitis (1.1% [CI, 0.5% to 2.1%]) and episcleritis (0.1% [CI, 0.0% to 0.7%]) in women treated with zoledronic acid (309).

Ibandronate is associated with myalgias, cramps, and limb pain (OR, 2.25 [CI, 1.57 to 3.29]) (92, 310), and zoledronic acid is associated with adverse effects including atrial fibrillation (OR, 1.45 [CI, 1.14 to 1.86]) (81), arthritis and arthralgias (OR, 2.82 [CI, 2.32 to

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3.45]), headaches (OR, 3.18 [CI, 2.57 to 3.97]), and uveitis (OR, 12.1 [CI, 1.78 to 516]).

Evidence is insufficient to associate bisphosphonates with increased cancer risk, because studies report conflicting results (292, 311–326).

Denosumab

High-quality evidence showed that denosumab is associated with mild upper gastrointestinal symptoms (OR, 1.74 [CI, 1.29 to 2.38]) (43, 327). Moderate-quality evidence showed that denosumab is associated with increased risk for infection (risk ratio [RR], 1.26 [CI, 1.01 to 1.57]) (328). One small RCT reported a slight increase in bacterial cellulitis with patients treated with denosumab compared with placebo (1.3% vs. 0.6%), but no increase in serious infection (1.1% vs. 1.5%) (109). Denosumab has also been associated with rash/eczema (OR, 1.96 [CI, 1.46 to 2.66]) (43, 96, 97). A post hoc analysis of the open-label extension of FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) confirmed 2 events of atypical femoral fracture and 8 events of osteonecrosis of the jaw through 8 years of denosumab therapy (100).

Teriparatide

High-quality evidence showed that teriparatide is associated with mild upper gastrointestinal symptoms (OR, 3.26 [CI, 2.82 to 3.78]) (113, 117, 329, 330), headache (OR, 1.46 [CI, 1.27 to 1.69]) (113, 117, 331), and hypercalcemia (OR, 12.9 [CI, 10.5 to 16]) (116, 117, 331, 332). Other adverse effects include renal side effects (OR, 2.36 [CI, 2.01 to 2.77]) and hypercalciuria (OR, 2.44 [CI, 2.08 to 2.86]) (254). There were no incident cases of osteosarcoma associated with use of this medication in the first 4 years of the voluntary Forteo Patient Registry safety study (333), and in a postmarketing case series study encompassing 9 years of osteosarcoma cases, no patient reported use of teriparatide before diagnosis of osteosarcoma (334).

SERMs

High-quality evidence showed that raloxifene is associated with hot flashes (OR, 1.58 [CI, 1.35 to 1.84]) (122, 123, 335–340) and thromboembolic events (OR, 1.63 [CI, 1.36 to 1.98]) (122, 336, 341–346). Raloxifene is also associated with pulmonary embolism (OR, 1.82 [CI, 1.16 to 2.92) (122, 341, 345, 347) and cerebrovascular death (OR, 1.56 [CI, 1.04 to 2.39]) (122, 341, 342, 348–350). A study comparing postmarketing surveillance of raloxifene in younger women (aged < 75 y) versus older women (aged ≥75 y) showed no difference in overall adverse effects from raloxifene (351).

Estrogen Therapy for Postmenopausal Women

High-quality evidence from the Women's Health Initiative showed that menopausal hormone therapy was associated with increased risk for cerebrovascular accidents and venous thromboembolic events (7, 352). One subsequent assessment of the trial showed that the higher incidence of breast cancer decreased after therapy was discontinued (353). Another study showed that estrogen plus progestin therapy was associated with more invasive breast cancer, more node-positive tumors, and more deaths due to breast cancer than placebo (354).

Calcium and Vitamin D

Although previous data suggested an association between calcium supplementation and increased risk for myocardial infarction, moderate-quality evidence shows no association (355). One study showed increased risk for hypercalciuria with vitamin D supplementation (356).

Monitoring of Patients With Osteoporosis

There is no evidence from RCTs regarding how often to monitor BMD during osteoporosis treatment. Moderate-quality evidence suggests that most women do not need regular monitoring (357–368). Data from 1 study (365) showed that only 10% of women with normal or mildly osteopenic DXA scores (T score > –1.49) develop osteoporosis within 15 years; 10% of women with moderate osteopenia (T score, –1.50 to –1.99) develop osteoporosis within 5 years; and 10% of women with advanced osteopenia (T score, –2.0 to –2.49) develop osteoporosis within 1 year. Another study showed no improvement in prediction of hip or major fractures in women who had BMD measured 4 years after baseline (357). Overall data from several studies (358–363) showed that women treated with antiresorptive treatment (including bisphosphonates, raloxifene, and teriparatide) benefited from reduced fractures with treatment even if BMD did not increase.

Duration of Pharmacologic Therapy

Low-quality evidence showed that the appropriate duration of treatment is uncertain, although high-risk patients may benefit from more than 5 years of treatment (240, 242, 369–371). One study showed no cumulative difference in the risk for nonvertebral fractures in women continuing alendronate therapy for 5 versus 10 years (18.9% vs. 19%) (240). Post hoc analysis of this study showed that women with femoral neck T scores of –2.5 or worse and baseline prevalent vertebral fracture had reduced fracture risk by continuing alendronate therapy for 10 years versus stopping after 5 years compared with placebo (11.1% to 5.3%) (242). Another study on zoledronic acid showed no difference for clinical vertebral fractures, hip fractures, nonvertebral fractures, or all clinical fractures in women who continued to receive the drug for 3 versus 6 years (369).

The Figure provides a summary of the recommendations and clinical considerations.

Future Research

Most of the evidence for treating osteoporotic men is based on trials that included women, and further research is needed on the treatment of men. Studies directly addressing the efficacy of pharmacologic treatments for reducing fractures in patients with osteopenia are also needed.

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Figure. Summary of the American College of Physicians Guideline on the treatment of low bone density or osteoporosis to prevent fractures in men and women.

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Summary of the American College of Physicians Guideline on the Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women

Disease/Condition	Low BMD or osteoporosis
Target Audience	All clinicians
Target Patient Population	Adults with low BMD or osteoporosis
Interventions Evaluated	Bisphosphonates: alendronate, risedronate, ibandronate, zoledronic acid; denosumab; teriparatide; selective estrogen receptor modulators (raloxifene, bazedoxifene); estrogen, calcium, vitamin D
Outcomes Evaluated	Reduction in fracture (total, vertebral, nonvertebral, spine, hip, wrist, other), adverse events
Benefits of Treatment	Bisphosphonates, denosumab, teriparatide, raloxifene: reduction in vertebral fracture Alendronate, risedronate, zoledronic acid, denosumab, teriparatide: reduction in nonvertebral fracture Alendronate, risedronate, zoledronic acid, denosumab: reduction in hip fracture
Harms of Treatment	Bisphosphonates in general: mild upper GI symptoms, atypical subtrochanteric fracture, osteonecrosis of the jaw Raloxifene: cardiovascular (serious), thromboembolic events, pulmonary embolism, cerebrovascular death, hot flashes Ibandronate: myalgias, cramps and limb pain Zoledronic acid: atrial fibrillation, arthritis and arthralgias, headaches, hypocalcemia, uveitis or ocular events possibly or probably related to the study drug, influenza-like symptoms Denosumab: mild upper GI symptoms, rash/eczema Teriparatide: upper GI symptoms, renal, headaches, hypercalcemia, hypercalciuria
Recommendations	*Recommendation 1: ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)* *Recommendation 2: ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years. (Grade: weak recommendation; low-quality evidence)* *Recommendation 3: ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)* *Recommendation 4: ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women. (Grade: weak recommendation; low-quality evidence)* *Recommendation 5: ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)* *Recommendation 6: ACP recommends that clinicians should make the decision whether to treat osteopenic women 65 years of age or older who are at a high risk for fracture based on a discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medications. (Grade: weak recommendation; low-quality evidence)*
Inconclusive Areas of Evidence	Comparative effectiveness trials evaluating pharmacologic treatments for low bone density or osteoporosis are lacking. In addition, although FRAX scores are widely used, there is a lack of evidence linking FRAX scores to treatment efficacy.
High Value Care	The current evidence does not support frequent monitoring of women with normal BMD for osteoporosis, because data showed that most women with normal DXA scores did not progress to osteoporosis within 15 years. Data also does not support monitoring BMD during the initial 5 years of treatment in patients taking pharmacologic agents to treat osteoporosis. Clinicians should select generic drugs to treat osteoporotic patients when possible.
Clinical Considerations	Comparative effectiveness of the different treatments is unknown. Treatment duration is unknown, although high-risk patients may benefit from longer treatments.

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; FRAX = World Health Organization Fracture Risk Assessment Tool; GI = gastrointestinal.

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RECOMMENDATIONS

Recommendation 1: ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)

High-quality evidence showed that pharmacologic treatment in postmenopausal women who have osteoporosis (T scores ≤ –2.5 or those who have experienced fragility fractures) is beneficial for preventing further bone loss and reducing the risk for initial or subsequent fractures. Some bisphosphonates (alendronate, risedronate, and zoledronic acid) and the newer biologic agent denosumab reduce radiographic vertebral as well as clinical, nonvertebral, and hip fractures.

Both bisphosphonates and denosumab are associated with mild gastrointestinal symptoms. Denosumab is also associated with increased risk for infection and rash or eczema. Bisphosphonates are associated with atypical subtrochanteric fractures and osteonecrosis of the jaw. Although there is no association between bisphosphonates and atrial fibrillation, some studies have reported increased cardiovascular events. Zoledronic acid is associated with hypocalcemia, influenza-like symptoms, arthritis and arthralgias, headache, and uveitis.

When prescribing bisphosphonates, clinicians should discuss the importance of adherence. Factors associated with poor adherence include side effects and the inconvenience of taking medications, absence of symptoms for underlying disease, comorbid conditions, age, and socioeconomic status.

Although evidence showed that raloxifene and ibandronate reduce radiographic vertebral fractures, and teriparatide reduces vertebral and nonvertebral fractures, studies have shown no benefit for these drugs to reduce all fracture types; therefore, they are not recommended as a first-line pharmacologic treatment. Raloxifene is associated with serious harms, such as thromboembolism. Calcitonin, which is no longer widely used for osteoporosis treatment, was not considered in this guideline.

Calcium and vitamin D may be added as dietary supplements to osteoporosis treatment regimens, although the effectiveness of these regimens on fracture prevention is unclear. The majority of trials with bisphosphonate therapy gave women calcium supplements and many also gave vitamin D; therefore, supplementation with these agents may be considered. However, dosages should be carefully considered, because excess dosing has been associated with hypercalcemia (221, 372–377). Moderate-quality evidence showed no association between calcium supplementation and increased risk for myocardial infarction (355), but a large trial demonstrated an increase in kidney stones (137).

Recommendation 2: ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years. (Grade: weak recommendation; low-quality evidence)

Although the direct evidence is insufficient to determine the appropriate duration of pharmacologic therapy, most studies that evaluated the benefit of treatment continued therapy for up to 5 years. Continuing treatment after the initial 5 years may be beneficial for some patients and may be appropriate after reassessing the risks and benefits of continuing therapy. Post hoc analysis from an RCT (242) suggested that patients treated with alendronate who had preexisting fractures or those with a BMD of –2.5 or less after 5 years of initial therapy may benefit from continued treatment, because these patients experienced a decreased incidence of new clinical vertebral fractures.

Recommendation 3: ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)

Data that specifically apply to men are sparse. However, no evidence suggests that outcomes associated with pharmacologic treatment would differ between men and women if based on similar BMDs. Data for men are extrapolated from studies that included women with T scores of –2.5 or less or those who have experienced fragility fractures. Moderate-quality evidence from 1 study that detected fractures radiographically showed that zoledronic acid reduced vertebral fractures in osteoporotic men (95). In women, some bisphosphonates (alendronate, risedronate, and zoledronic acid) reduce vertebral, nonvertebral, and hip fractures. The overall quality of evidence was downgraded to low owing to indirectness. Bisphosphonates are associated with adverse effects, including mild gastrointestinal symptoms, atypical subtrochanteric fractures, and osteonecrosis of the jaw.

Recommendation 4: ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women. (Grade: weak recommendation; low-quality evidence)

Current evidence does not show any benefit for bone density monitoring during treatment. Moderate-quality evidence showed that women treated with antiresorptive treatment (including bisphosphonates, raloxifene, and teriparatide) benefited from reduced fractures with treatment, even if there was no increase in BMD or if BMD decreased. There was no evidence for BMD monitoring for men.

Recommendation 5: ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)

Moderate-quality evidence showed that menopausal estrogen treatment did not reduce fracture risk in postmenopausal women with established osteoporosis. Evidence from a previous systematic review (131) showed that estrogen decreased fracture risk; however, many of these studies focused on postmenopausal women with low bone density, or on postmenopausal women in general rather than those with established osteoporosis. Estrogen treatment is associ-

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Table 2. Summary of Evidence on Pharmacologic Treatments for Low Bone Density and Osteoporosis

Treatment	Effect on Fracture Risk in Osteoporotic Women and Evidence Quality			Adverse Events and Evidence Quality	Fair Price for 1-Day Supply*
	Vertebral	Nonvertebral	Hip		
Bisphosphonates	Summarized individually below	Summarized individually below	Summarized individually below	As a class: atypical subtrochanteric fracture, osteonecrosis of the jaw (low-quality)	Summarized individually below
Alendronate	Improves; high-quality	Improves; high-quality	Improves; high-quality	Mild upper GI symptoms (high-quality)	Generic: $9 Brand-name (Fosamax): $130
Ibandronate	Improves; high-quality	Uncertain	Uncertain	Mild upper GI symptoms (high-quality); myalgias, cramps and limb pain	Generic: $60 Brand-name (Boniva): $588
Risedronate	Improves; high-quality	Improves; high-quality	Improves; high-quality	Mild upper GI symptoms (high-quality)	Generic: $136 Brand-name (Actonel): $337
Zoledronic acid	Improves; high-quality Improves in osteoporotic men; moderate quality	Improves; high-quality	Improves; high-quality	Mild upper GI symptoms, hypocalcaemia, influenza-like symptoms (high-quality); atrial fibrillation; arthritis and arthralgias, headaches, uveitis	Generic: $66 Brand-name (Reclast): $1105
Denosumab (injectable)	Improves; high-quality	Improves; high-quality	Improves; high-quality	Mild upper GI symptoms (high-quality), infection (moderate-quality); rash	Brand-name (Prolia): $1047
Teriparatide (injectable)	Improves; high-quality	Improves; high-quality	Unknown	Mild upper GI symptoms, headache, hypercalcemia (high-quality); hypercalciuria, renal adverse effects	Brand-name (Forteo): $2767
Raloxifene	Improves; high-quality	No effect	No effect	Hot flashes, thromboembolic events (high-quality); pulmonary embolism, cerebrovascular death	Generic: $2.40 Brand-name (Evista): $70
Calcium and vitamin D	Uncertain	Uncertain	Uncertain	Increased risk for hypercalcemia	NA
Menopausal hormone therapy	Improves in postmenopausal women (not selected for having osteoporosis in the studies); high-quality Does not improve in postmenopausal women with established osteoporosis; moderate-quality	Uncertain	Improves in postmenopausal women (not selected for having osteoporosis in the studies); high-quality	Increased risk for cerebrovascular accidents and thromboembolic events (high-quality)	NA

GI, gastrointestinal; NA = not available.
* Formulation and dosing vary. Generics are available where indicated. Data were obtained from the Healthcare Bluebook (www.healthcarebluebook.com).

ated with serious harms, such as increased risk for cerebrovascular accidents and venous thromboembolism, and these harms significantly outweigh the potential benefits. Although raloxifene has some benefit in reducing vertebral fractures, it does not reduce hip fracture or nonvertebral fractures and is associated with serious harms, including thromboembolism.

Recommendation 6: ACP recommends that clinicians should make the decision whether to treat osteopenic women 65 years of age or older who are at a high risk for fracture based on a discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medications. (Grade: weak recommendation; low-quality evidence)

Low-quality evidence showed that treatment with risedronate in women with osteopenia (defined as a T score of –1.0 to –2.5) near the osteoporosis threshold (T score of –2.5) may reduce their fracture risk. This evidence comes from a post hoc analysis of 2-year follow-up data from 4 large RCTs of postmenopausal women with advanced osteopenia and no prevalent vertebral fractures that showed that treatment with risedronate significantly reduced the risk for fragility fracture compared with placebo (73% lower than placebo) (378). This effect is similar to fracture reductions seen in women with osteoporosis undergoing the similar treatment. Duration of treatment in these studies was 1.5 to 3 years.

Although the current evidence is limited to a post hoc evaluation of risedronate in women with advanced osteopenia, the CGC believes that the benefit of fracture reduction is likely to be similar across all bisphosphonates, on the basis of data in osteoporotic women. However, the efficacy of other bisphosphonates has

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not been directly evaluated in osteopenic women, and no study has been conducted to primarily assess the effects of fracture prevention in women with osteopenia.

The rate of progressive bone loss and the risk for fracture range widely across the osteopenic spectrum and according to additional factors, such as age. The risk for severe adverse effects increases with prolonged use of bisphosphonates. Given the limited evidence supporting benefit, the balance of benefits and harms of treating osteopenic women is most favorable when the risk for fracture is high. Women younger than 65 years with osteopenia and women older than 65 years with mild osteopenia (T score between –1.0 and –1.5) will benefit less than women 65 years of age or older with severe osteopenia (T score < –2.0).

Clinicians can use their own judgment based on risk factors for fracture, or they can use a risk assessment tool. Several risk assessment tools, such as FRAX (World Health Organization Fracture Risk Assessment Tool), are available to predict fracture risk among untreated people with low bone density (379). Although FRAX is widely used, there is no evidence from RCTs demonstrating a benefit of fracture reduction when FRAX scores are used for treatment decision making. Factors that increase the risk for fracture in women include lower body weight, smoking, weight loss, family history of fractures, decreased physical activity, alcohol or caffeine use, low calcium and vitamin D intake, and corticosteroid use (7, 380, 381).

Inconclusive Areas of Evidence

Comparative effectiveness trials evaluating pharmacologic treatments for low bone density or osteoporosis are lacking. In addition, although FRAX scores are widely used, evidence linking FRAX scores to treatment efficacy is lacking. One post hoc analysis of a trial with raloxifene showed that treatment efficacy did not vary according to FRAX score (241), and at age 75 years, the risk reduction for vertebral fracture was similar across FRAX scores.

High-Value Care

The current evidence does not support frequent monitoring of women with normal bone density for osteoporosis, because data showed that most women with normal DXA scores did not progress to osteoporosis within 15 years. The data also do not support monitoring BMD during the initial 5 years of treatment in patients receiving pharmacologic agents to treat osteoporosis. Clinicians should select generic drugs to treat osteoporotic patients when possible (Table 2).

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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Appendix 1: Methods

This guideline update is based on an AHRQ evidence report and an update of the systematic review (131, 382). The key questions addressed are:

1. What are the comparative benefits in fracture reduction among various pharmacologic treatments for low bone density?

- Bisphosphonate medications: alendronate, risedronate, ibandronate, zoledronic acid
- Denosumab
- Menopausal estrogen therapy for women (numerous brands and routes of administration)
- Parathyroid hormone 1,3,4: teriparatide
- SERMs: raloxifene
- Calcium
- Vitamin D
- Combinations or sequential use of the above agents
- Exercise compared with the above agents

2. How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture, as determined by the following factors:

- BMD
- FRAX or other risk assessment score
- Prior fractures (prevention vs. treatment)
- Age
- Sex
- Race/ethnicity
- Glucocorticoid use
- Other factors (e.g., whether the individuals were community dwelling vs. institutionalized, vitamin D deficient vs. not)

3. What are the short- and long-term harms of the various treatments when used specifically to treat or prevent low bone density or osteoporotic fracture? Do these vary by any specific subpopulations?

4. How often should patients be monitored (via measurement of BMD) during therapy, and how does the antifracture benefit vary with long term continued use of pharmacotherapy?

Search Strategy

The literature search included identified trials published in the English language by searching MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, the American College of Physicians Journal Club database, the National Institute of Clinical Excellence, the NHA Technology Assessment Program, the FDA's MedWatch database, and relevant pharmacologic databases from 2 January 2005 to 3 June 2011 and was updated to March 2014 by using a machine-learning method (9). Evidence was further updated specifically for bisphosphonates, calcium, vitamin D, and estrogen through 12 July 2016. Reviewers also did a limited search on the recently FDA-approved drug bazedoxifene from 1 January 2013 to 26 October 2016 (see **Appendix 2** for the search strategy). Only RCTs and published systematic reviews of RCTs that met inclusion criteria were included in the assessment of effectiveness. Where no RCTs were available, large observational studies (with more than 1000 participants), systematic reviews, and case reports (for rare events) were included (for example, assessment of effects in subgroups or assessment of particular serious adverse events).

Quality Assessment

The quality of RCTs, observational studies, and meta-analyses was assessed by using the Jadad scale, the Newcastle–Ottawa Scale, and the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) criteria, respectively (383–385). The overall quality of evidence and strength of recommendations was graded according to ACPs' clinical practice guidelines grading system (10).

Population

Studies were limited to those conducted in adults older than 18 years, healthy adults, those with low bone density, or those with osteoporosis.

Interventions Evaluated

Pharmacologic agents approved for use in the United States including bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid), teriparatide, raloxifene, and menopausal estrogen therapy; the biologic agent denosumab; dietary and supplemental calcium and vitamin D; and physical activity.

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Comparators

The efficacy or effectiveness of the intervention in question were compared with that of placebo or another potency or dosing schedule for the same agent or another agent in the same or another class.

Outcomes

Outcomes evaluated include reduction in fracture (total, vertebral, nonvertebral, spine, hip, wrist, other) and adverse events.

Target Audience

The target audience for this guideline is all clinicians.

Target Patient Population

The target patient population is all adult men and women with low bone density or osteoporosis.

Peer Review

The AHRQ systematic review was peer-reviewed and posted on the AHRQ website for public comments. The 2014 evidence reviews also underwent a peer review process through the journal. The guideline underwent a peer review process through the journal and was posted online for comments from ACP Regents and ACP Governors, who represent physician members at the national and international level.

Appendix 2: Update Search Methodology

Database Searched and Period Covered

PubMed: 1 January 2014 to 12 July 2016

Language

English

Search Strategy 1 (Bisphosphonates)

osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density

AND

alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate*

Search Strategy 2 (SERMs)

osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density

AND

raloxifene* OR evista OR tamoxifen* OR nolvadex OR embo OR fendamex OR soltamov OR tamofen OR bazedoxifene* OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms

Search Strategy 3 (Monitoring)

osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density

AND

monitor*

Search Strategy 4 (FRAX)

osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density

AND

frax

Search Strategy 5 (Other Treatments)

osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density

AND

strontium OR tibolone OR pth OR parathyroid hormone* OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR calcium OR vitamin d OR teriparatide OR forteo OR preos

Database Searched and Period Covered

PubMed: 1 January 2014 to 12 July 2016

Language

English

Search Strategy 6 (Adverse Events)

osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density

AND

adverse effects[Subheading] OR Drug Toxicity-[Mesh] OR toxicity[Subheading] OR adverse[tiab] OR harm OR harmful OR safe[ti] OR safety[ti] OR toxic*[tiab]

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Appendix Table 1. Evidence Table for New Randomized, Controlled Trials Identified in the Update

Study, Year (Reference); Drug	Study Characteristics	Sample Characteristics	Eligibility	Interventions	Outcomes	Results
Silverman et al, 2008 (122)*; bazedoxifene	Design: randomized, double-blind, placebo-controlled Setting: multicenter Location: 206 sites in Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the United States Jadad scale score: 3	Mean age: 67 y (range NR) Women: 100% Race/ethnicity: 87% white Screened: 26 749 Eligible: NR Enrolled: 7492 Withdrawn: NR Lost to follow-up: NR Analyzed: 6847	Inclusion criteria: generally healthy postmenopausal women aged 55–85 y with osteoporosis by BMD or prevalent vertebral fracture Exclusion criteria: diseases that affect bone metabolism, interfere with bone mineral densitometry, pathologic vertebral fracture, vasomotor symptoms requiring treatment, endometrial hyperplasia or carcinoma, abnormal vaginal bleeding, cancer within 10 y of study, endocrine disorders requiring treatment, untreated malabsorption disorders, history of DVT, elevated cholesterol or triglyceride level, use of androgen, estrogen, progestogen, or osteoporosis medication	Interventions: Bazedoxifene, 20 mg/d Bazedoxifene, 40 mg/d Raloxifene, 60 mg/d Placebo Given for 36 mo All participants received oral daily calcium up to 1200 mg and vitamin D, 400–800 IU	Primary: incidence of new radiographically confirmed vertebral fractures after 36 mo of treatment in bazedoxifene and placebo groups Secondary: incidence of clinical vertebral fractures and nonvertebral fractures, BMD change, bone resorption markers Method of AE assessment: monitored by investigators regularly	Number of participants with new clinical vertebral fractures (no between-group differences were observed): Bazedoxifene, 20 mg/d: 11 Bazedoxifene, 40 mg/d: 11 Raloxifene: 13 Placebo group: 14 Incidence of nonvertebral osteoporosis-related fractures (no difference among groups): Bazedoxifene, 20 mg/d: 5.7% Bazedoxifene, 40 mg/d: 5.6% Raloxifene: 5.9% Placebo: 6.3% Post hoc analysis performed in women at high risk for fracture (BMD T score ≤ –3.0 and/or ≥1 moderate or severe vertebral fracture, or multiple mild vertebral fractures, in whom nonvertebral fracture risk was demonstrated) compared with placebo: 50% reduction in nonvertebral fracture risk with bazedoxifene, 20 mg/d, vs. placebo ($P = 0.02$)
Nakamura et al, 2014 (109); denosumab	Design: randomized, double-blind placebo-controlled with open-label active comparator (DIRECT study) Setting: multicenter Location: Japan Jadad scale score: 2	Mean age: 69.9 y (range NR) Women: 95% Race/ethnicity: Japanese Screened: 2650 Eligible: NR Enrolled: 1262 Withdrawn: NR Lost to follow-up: unclear Analyzed: 1194	Inclusion criteria: Japanese postmenopausal women and men aged ≥50 y with 1 to 4 prevalent vertebral fractures and BMD T score < –1.7 at lumbar spine or –1.6 at the total hip Exclusion criteria: >2 moderate and/or any severe vertebral fractures on lateral spine radiography, hyperparathyroidism, hypocalcemia, rheumatoid arthritis, Paget disease of bone, oral bisphosphonate use for > 3 y, use of osteoporosis medication within 6 wk before study enrollment (6 mo for bisphosphonates), creatinine concentration ≥2.0 mg/dL, elevated values on liver function tests	Denosumab, 60 mg SC every 6 mo Placebo Open-label alendronate, 35 mg/wk Calcium and vitamin D were also given daily Randomized was performed in a 2:2:1 ratio and stratified by sex	Primary: radiographic morphometric new or worsening vertebral fracture for denosumab vs. placebo at 24 mo Secondary: new clinical vertebral fracture, nonvertebral fracture, change in BMD, bone turnover markers	New or worsening vertebral fracture at 24 mo: Denosumab: 3.6% Placebo: 10.3% Denosumab vs. placebo decreased risk for new or worsening vertebral fracture: HR, 0.343 (95% CI, 0.194–0.606) Incidence of new vertebral fracture at 24 mo: Denosumab: 2.2% Placebo: 8.6% Reduction in risk of 74% ($P < 0.001$) Incidence of nonvertebral fracture at 24 mo: 4.1% in both the denosumab and placebo groups HR for incidence of new vertebral fracture with denosumab vs. alendronate at 24 mo: 0.416 (CI, 0.180–0.962); $P = 0.03$

AE = adverse event; BMD = bone mineral density; DVT = deep venous thrombosis; HR = hazard ratio; NR = not reported; SC = subcutaneously.

* This study was initially included in the 2012 report for the raloxifene arm. We have abstracted the data here for bazedoxifene, which was newly approved by the U.S. Food and Drug Administration.

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Appendix Table 2. Evidence Table for Post hoc and Subgroup Analyses and Follow-up Studies Identified in the Update

Study, Year (Reference); Drug	Study Characteristics	Sample Characteristics	Interventions	Outcomes	Results	Conclusions
Ito et al, 2017 (233); ibandronate, risedronate	Per protocol analysis among subgroup of persons with prevalent vertebral fractures MOVER study	RCT inclusion criteria: ambulatory men and women with primary osteoporosis aged ≥60 y with BMD of lumbar spine or proximal femur <80% of young adult mean and 1 to 5 prevalent vertebral fractures Analyzed: 1134	RCT: IV ibandronate, 1 mg/mo, vs. oral risedronate, 2.5 mg/d No mention of calcium and vitamin D	Vertebral and nonvertebral fracture at 6, 12, 24, and 36 mo	**Incidence of vertebral fractures** Patients with 1 prevalent vertebral fracture: Ibandronate: 11.2% Risedronate: 12.6% Patients with ≥2 prevalent vertebral fractures: Ibandronate: 20.4% Risedronate: 22.1 % Patients with femoral neck BMD T scores ≥−2.5: Ibandronate: 13.7% Risedronate: 17.3% Patients with femoral neck BMD T scores >−2.5: Ibandronate: 16.4% Risedronate: 19.1% **Incidence of nonvertebral fractures** Patients with ≥2 prevalent vertebral fractures: Ibandronate: 7.6% Risedronate: 9.5% Nonvertebral fractures in patients with femoral neck BMD T score >−2.5: Ibandronate: 7.6% Risedronate: 9.4%	Fracture reduction efficacy of ibandronate, 1 mg/mo, was consistent across subgroups examined, independent of number of prevalent fractures and baseline BMD values, and did not significantly differ from that of oral risedronate, 2.5 mg/d IV ibandronate, 1 mg/mo, is roughly equivalent to the dosage of 3 mg/quarter that is currently FDA-approved
Palacios et al, 2015 (99); denosumab	Post hoc analysis of the FREEDOM RC	7808 women aged 60–90 y with BMD T-score >–2.5 but ≥-4.0 at lumbar spine or total hip Subgroups: prior fracture status, age, prior medication use Prior fragility fracture was present in 45% of the study population	RCT: denosumab, 60 mg SC, vs. placebo every 6 mo for 36 mo At least 1000 mg calcium and 400 IU vitamin D daily	Fragility fracture at 36 mo	Compared with placebo, denosumab decreased risk for secondary fragility fracture by 39% (incidence, 17.3% vs. 10.5%; P <0.001) In overall study population, denosumab decreased risk for fragility fracture by 40% (13.3% vs. 8.0%; P < 0.001) Similar results were seen in subgroup analyses of prior osteoporotic medication use. age, prior fracture site	Denosumab decreased risk for fragility fractures similarly in all risk subgroups
Papapoulos et al, 2015 (100); denosumab	Open-label extension of all participants in the FREEDOM RCT who did not miss >1 dose of investigational product; all participants to receive denosumab with daily calcium and vitamin D for 5 y (total of 8 y of denosumab exposure for women originally assigned to receive 3 y of denosumab in initial RCT)	4550 postmenopausal women aged 60–90 y with lumbar spine or total hip BMD T score >–2.5 but ≥–4.0	Initial RCT Denosumab, 60 mg SC, or placebo every 6 mo for 3 y All participants received calcium, >1 g/d, and vitamin D, ≥400 IU/d	Primary: safety and tolerability Secondary: bone turnover markers, BMD, new vertebral and nonvertebral fractures	Annualized incidence of new vertebral fractures with denosumab: Years 4 and 5: 1.5% Year 6: 1.3% Years 7 and 8: 1.3% Annualized incidence of new nonvertebral fractures with denosumab: Year 4: 1.5% Year 5: 1.2% Year 6: 1.8% Year 7: 1.6% Year 8: 0.7% Number of women with new fractures over 8 y of denosumab therapy: Wrist: 57 Rib: 17 Hip: 13 Ankle: 12	Yearly incidence of new vertebral and nonvertebral fractures remained low during open-label extension of total of 8 y of denosumab therapy
Sugimoto et al, 2015 (101); denosumab	1-year open-label extension phase of DIRECT in which all participants received denosumab	Japanese postmenopausal women and men aged ≥50 y with 1 to 4 prevalent vertebral fractures, and BMD T score –1.7 at lumbar spine or >–1.6 at the total hip	RCT: denosumab, 60 mg SC every 6 mo, vs. placebo for 2 y All participants received supplements: calcium, ≥600 mg/d, and vitamin D, 400 IU/d	Vertebral and nonvertebral fractures at baseline and at 6, 12, 18, 24, and 36 mo; BMD; bone turnover markers	At 36 mo of denosumab therapy: New vertebral fracture in year 3 vs year 1: rate ratio vs. placebo, 0.192 (95% CI 0.023–1.591); P = 0.1261 Cumulative incidence of nonvertebral fracture: 5.1% (CI, 3.4–7.7) Cumulative incidence of major nonvertebral fracture: 2.1% (CI, 1.1–4.0) Crossover group (placebo year 1, then denosumab years 2 and 3): New vertebral fracture in year 3 vs year 2: rate ratio, 0.231 (CI, 0.104–0.516); P < 0.001 Cumulative incidence of nonvertebral fracture at 36 mo: 6.6 % (CI, 4.6–9.5) Cumulative incidence of major nonvertebral fracture at 36 mo: 5.5 % (CI, 3.7–8.1)	Denosumab treatment for 3 y was associated with a favorable benefit–risk profile

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***Appendix Table 2*—Continued**

Study, Year (Reference); Drug	Study Characteristics	Sample Characteristics	Interventions	Outcomes	Results	Conclusions
Black et al, 2015 (85); zoledronic acid	Second extension of HORIZON-PFT	Women with postmenopausal osteoporosis	Initial RCT: Women with postmenopausal osteoporosis randomly assigned to receive annual zoledronic acid, 5 mg IV (n = 3889) vs. placebo (n = 3876) for 3 y First extension: randomly assigned to 3 additional annual infusions of zoledronic acid vs. placebo Second extension, double-blind: women who received first and third doses of zoledronic acid during the first extension, and had completed first extension, were randomly assigned to receive zoledronic acid once yearly or placebo for 3 additional years All participants received oral calcium, 1000–1500 mg/d, and vitamin D, 400–1200 IU/d, as supplements	Primary end point: BMD change Secondary end point: fracture, bone turnover markers, safety	Clinical fractures at year 9 vs. year 6: Number of fractures was low and did not significantly differ by treatment.; too few for meaningful comparison Incidence with zoledronic acid for 9 y: 12.2% Incidence with zoledronic acid for 6 y, followed by placebo for 3 y: 9.5% HR, 1.11 (CI, 0.45–2.73)	Nearly all patients who have completed 6 annual zoledronic acid infusions can discontinue medication for up to 3 y with maintenance of benefits
Ferrari et al, 2015 (98); denosumab	Open-label extension of FREEDOM	Postmenopausal women aged 60–90 y with lumbar spine or total hip T-score >–2.5 at the lumbar spine or hip but ≥–4.0 at both locations Long-term therapy group: 2343 Crossover group: 1731	Initial RCT: Denosumab, 60 mg SC every 6 mo for 3 y, vs placebo All participants received calcium, ≥1 g/d, and vitamin D, ≥400 IU/d Open-label extension: 4074 participants who missed ≤1 dose of denosumab during the first 3 y of denosumab treatment continued into the fourth year (long-term group), and the placebo group started denosumab therapy (cross-over group) through year 7	Nonvertebral fractures, BMD	Nonvertebral fractures: Crossover group: reduction of 49% (rate ratio, 0.51; P = 0.005) for year 4 vs. years 1–3 Long-term therapy group (up to 7 y of denosumab): reduction of 21 % (rate ratio, 0.79; P = 0.0046) during years 4–7 vs. years 1–3	There was a further reduction in the nonvertebral fracture rate that persisted through 7 y of denosumab therapy
Harvey et al, 2015 (119); teriparatide	Post hoc analysis according to baseline fracture risk by FRAX prediction tool in 1537 women	Postmenopausal women aged 42–86 y	Teriparatide, 40 µg/d (n = 544), vs. teriparatide, 20 µg/d (n = 541), vs. placebo (n = 544) for 18 mo The 2 teriparatide dosage groups were combined owing to similar effects on fracture occurrence No mention of calcium or vitamin D dose	Morphometric vertebral fractures; nonvertebral fractures	Morphometric vertebral fractures: Teriparatide treatment was associated with a statistically significant 66 % decrease in (HR, 0.34 [CI, 0.23–0.50]) Any nonvertebral fractures: Teriparatide treatment based on the pooled doses was associated with an HR of 0.63 [CI, 0.44–0.90]	Teriparatide significantly reduced the risk for nonvertebral and morphometric vertebral fractures by a similar extent, regardless of baseline fracture probability
Silverman et al, 2012 (386); bazedoxifene	Preplanned 2-y extension of the 3-y study in 4216 postmenopausal women	Postmenopausal women aged 55–85 y with osteoporosis by BMD or prevalent vertebral fracture	Bazedoxifene, 20 mg/d, was continued; participants receiving bazedoxifene, 40 mg/d group were transitioned to 20 mg/d after 4 y ("40/20 mg"); placebo was continued	5-year findings: new vertebral fractures (primary) and non-vertebral fractures, changes in BMD, bone turnover markers Subgroup analyses were performed in the high-risk subgroup, defined as women with femoral neck T score ≤–3.0 and/or ≥1 moderate or severe or ≥2 mild vertebral fractures	Incidence of new vertebral fractures at 5 y: Bazedoxifene, 20 mg/d: 4.5% Bazedoxifene, 40/20 mg/d: 3.9% Placebo: 6.8% P < 0.05 Relative risk reduction: Bazedoxifene, 20 mg/d: 35% Bazedoxifene, 40/20 mg/d: 40% High-risk subgroup: bazedoxifene, 20 mg/d, reduced nonvertebral fracture risk vs. placebo (37%; P = 0.06); combined data for bazedoxifene, 20 mg/d and 40/20 mg/d, reached statistical significance (34% reduction; P < 0.05)	The antifracture efficacy of bazedoxifene on new vertebral fractures continued during 5 y, and there was antifracture efficacy against nonvertebral fractures in the high-risk subgroup
Palacios et al, 2015 (387); bazedoxifene	Second extension of Silverman et al, 2012 (386): years 6–7	Postmenopausal women aged 55-85 y with osteoporosis by BMD or prevalent vertebral fractures	The bazedoxifene group from Silverman et al (386) continued to receive bazedoxifene, 20 mg/d	Incidence of new vertebral and nonvertebral fractures; BMD change; safety assessment	Cumulative incidence of new vertebral fractures at 7 y: Bazedoxifene, 40/20 mg: 6.4% (36.5% relative risk reduction vs. placebo) Bazedoxifene, 20 mg: 7.6% (relative risk reduction) 30.4%) Placebo: 9.9% P < 0.001 for both bazedoxifene groups vs. placebo Overall incidence of nonvertebral fracture: Bazedoxifene, 40/20 mg: 11.2% Bazedoxifene, 20 mg: 12.0% Placebo, 10.8%	The efficacy of bazedoxifene against new vertebral fractures was sustained over 7 y, but there was no effect on overall incidence of nonvertebral fracture

BMD = bone mineral density; DIRECT = Denosumab Fracture Intervention Randomized Placebo Controlled Trial; FDA = U.S. Food and Drug Administration; FREEDOM = Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months; HORIZON-PFT = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial; HR = hazard ratio; IV = intravenous; MOVER = MOnthly intraVenous ibandronatE versus daily oral Risedronate; RCT = randomized, controlled trial; SC = subcutaneous.