CLINICAL GUIDELINE

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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.

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)*

Ann Intern Med. 2017;166:818-839. doi:10.7326/M15-1361 **Annals.org**
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This article was published at Annals.org on 9 May 2017.

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).

See also:

Editorial comment 852
Summary for Patients I-24

Web-Only
CME/MOC activity

* 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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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.

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.

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

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).

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

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.

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.

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-

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

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.

Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations.

Financial Support: Financial support for the development of this guideline comes exclusively from the ACP operating budget.

Disclosures: Dr. Fitterman chairs the test writing committee for internal medicine for the American Board of Internal Medicine and receives a consultation fee for this work. Authors not named here have disclosed no conflicts of interest. Authors followed the policy regarding conflicts of interest described at www.annals.org/aim/article/745942. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-1361. All financial and intellectual disclosures of interest were declared, and potential conflicts were discussed and managed. Dr. Wilt participated in the discussion for this guideline but was recused from voting on the recommendations because of active indirect financial and intellectual conflicts. A record of disclosures and management of conflicts of interest is kept for each CGC meeting and conference call and can be viewed at www.acponline.org/about-acp/who-we-are/leadership/committees-boards-councils/clinical-guidelines-committee/disclosure-of-interests-for-clinical-guidelines-committee.

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References

1. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement Online. 2000;17:1-36. Accessed at https://consensus.nih.gov/2000/2000osteoporosis111html.htm on 5 April 2017.
2. **Kanis JA, on behalf of the World Health Organization Scientific Group.** Assessment of osteoporosis at the primary health-care level. Technical Report. University of Sheffield, UK: World Health Organization Collaborating Centre for Metabolic Bone Diseases. University of Sheffield; 2007.
3. **National Osteoporosis Foundation.** What is osteoporosis and what causes it? Accessed at http://nof.org/articles/7 on 22 July 2014.
4. **U.S. Department of Health and Human Services.** Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General, 2004. Accessed at https://www.ncbi.nlm.nih.gov/books/NBK45513/ on 5 April 2017.
5. **Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al.** Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporosis International. 2014;25:2359-81. [PMID: 25182228] doi:10.1007/s00198-014-2794-2
6. **Crandall C, Newberry SJ, Diamant A, Lim YW, Gellad WF, Suttorp MJ, et al.** Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of a 2007 Report. Comparative Effectiveness Review no. 53. Prepared by the Southern Cal-

ifornia Evidence-based Practice Center under contract no. HHSA-290-2007-10062-I. Rockville, MD: Agency for Healthcare Research and Quality; March 2012. Accessed at www.effectivehealthcare.ahrq.gov/ on 20 March 2017.

7. **Qaseem A, Snow V, Shekelle P, Hopkins R Jr, Forciea MA, Owens DK; Clinical Efficacy Assessment Subcommittee of the American College of Physicians.** Pharmacologic treatment of low bone density or osteoporosis to prevent fractures: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;149:404-15. [PMID: 18794560]

8. **Crandall CJ, Newberry SJ, Diamant A, Lim YW, Gellad WF, Booth MJ, et al.** Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. Ann Intern Med. 2014;161:711-23. [PMID: 25199883] doi:10.7326/M14-0317

9. **Dalal SR, Shekelle PG, Hempel S, Newberry SJ, Motala A, Shetty KD.** A pilot study using machine learning and domain knowledge to facilitate comparative effectiveness review updating. Rockville, MD: Agency for Healthcare Research and Quality; September 2012. Accessed at https://www.ncbi.nlm.nih.gov/books/NBK109161/ on 20 March 2017.

10. **Qaseem A, Snow V, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians.** The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010;153:194-9. [PMID: 20679562] doi:10.7326/0003-4819-153-3-201008030-00010

11. **Adami S, Passeri M, Ortolani S, Broggini M, Carratelli L, Caruso I, et al.** Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. Bone. 1995;17:383-90. [PMID: 8573412]

12. **Ascott-Evans BH, Guanabens N, Kivinen S, Stuckey BG, Magaril CH, Vandormael K, et al.** Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. Arch Intern Med. 2003;163:789-94. [PMID: 12695269] doi:10.1001/archinte.163.7.789

13. **Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al.** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348:1535-41. [PMID: 8950879]

14. **Bone HG, Downs RW Jr, Tucci JR, Harris ST, Weinstein RS, Licata AA, et al.** Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. J Clin Endocrinol Metab. 1997;82:265-74. [PMID: 8989272] doi:10.1210/jcem.82.1.3682

15. **Bonnick S, Rosen C, Mako B, DeLucca P, Byrnes C, Melton M.** Alendronate vs calcium for treatment of osteoporosis in postmenopausal women [abstract]. Bone. 1998;23(Suppl 5):S476.

16. **Chesnut CH 3rd, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST, et al.** Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. Am J Med. 1995;99:144-52. [PMID: 7625419]

17. **Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al.** Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280:2077-82. [PMID: 9875874]

18. **Dursun N, Dursun E, Yalçin S.** Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. Int J Clin Pract. 2001;55:505-9. [PMID: 11695068]

19. **Greenspan SL, Parker RA, Ferguson L, Rosen HN, Maitland-Ramsey L, Karpf DB.** Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. J Bone Miner Res. 1998;13:1431-8. [PMID: 9738515] doi:10.1359/jbmr.1998.13.9.1431

20. **Greenspan SL, Schneider DL, McClung MR, Miller PD, Schnitzer TJ, Bonin R, et al.** Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002;136:742-6. [PMID: 12020142]

21. **Hosking D, Chilvers CE, Christiansen C, Ravn P, Wasnich R, Ross P, et al.** Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. N Engl J Med. 1998;338:485-92. [PMID: 9443925] doi:10.1056/NEJM199802193380801

22. **Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, et al.** Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med. 1995;333:1437-43. [PMID: 7477143] doi:10.1056/NEJM199511303332201

23. **McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J, Weinstein RS, et al.** Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. Ann Intern Med. 1998;128:253-61. [PMID: 9471927]

24. **Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al.** Alendronate for the treatment of osteoporosis in men. N Engl J Med. 2000;343:604-10. [PMID: 10979796] doi:10.1056/NEJM200008313430902

25. **Pols HA, Felsenberg D, Hanley DA, Stepán J, Muñoz-Torres M, Wilkin TJ, et al.** Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int. 1999;9:461-8. [PMID: 10550467]

26. **Ringe JD, Dorst A, Faber H, Ibach K.** Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. Rheumatol Int. 2004;24:110-3. [PMID: 13680141] doi:10.1007/s00296-003-0388-y

27. **Weinstein R, Bone H, Tucci J, Downs R, Harris S, Licata A, et al.** Alendronate treatment of osteoporosis in elderly women [abstract]. J Bone Miner Res. 1994;9(Suppl 1):S144.

28. **Papaioannou A, Kennedy CC, Freitag A, Ioannidis G, O'Neill J, Webber C, et al.** Alendronate once weekly for the prevention and treatment of bone loss in Canadian adult cystic fibrosis patients (CFOS trial). Chest. 2008;134:794-800. [PMID: 18641106] doi:10.1378/chest.08-0608

29. **Ringe JD, Farahmand P, Schacht E, Rozehnal A.** Superiority of a combined treatment of alendronate and alfacalcidol compared to the combination of alendronate and plain vitamin D or alfacalcidol alone in established postmenopausal or male osteoporosis (AAC-Trial). Rheumatol Int. 2007;27:425-34. [PMID: 17216477] doi:10.1007/s00296-006-0288-z

30. **de Nijs RN, Jacobs JW, Lems WF, Laan RF, Algra A, Huisman AM, et al; STOP Investigators.** Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. N Engl J Med. 2006;355:675-84. [PMID: 16914703] doi:10.1056/NEJMoa053569

31. **Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group.** Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev. 2002;23:508-16. [PMID: 12202465] doi:10.1210/er.2001-2002

32. **Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston CC Jr, Adami S, et al.** Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. JAMA. 1997;277:1159-64. [PMID: 9087473]

33. **Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE.** Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. Osteoporos Int. 2005;16:468-74. [PMID: 15448985] doi:10.1007/s00198-004-1725-z

34. **Stevenson M, Jones ML, De Nigris E, Brewer N, Davis S, Oakley J.** A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess. 2005;9:1-160. [PMID: 15929857]

35. **Boonen S, Laan RF, Barton IP, Watts NB.** Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies. Osteoporos Int. 2005;16:1291-8. [PMID: 15986101] doi:10.1007/s00198-005-1945-x
36. **Nguyen ND, Eisman JA, Nguyen TV.** Anti-hip fracture efficacy of biophosphonates: a Bayesian analysis of clinical trials. J Bone Miner Res. 2006;21:340-9. [PMID: 16526127] doi:10.1359/JBMR.050903
37. **Sawka AM, Papaioannou A, Adachi JD, Gafni A, Hanley DA, Thabane L.** Does alendronate reduce the risk of fracture in men? A meta-analysis incorporating prior knowledge of anti-fracture efficacy in women. BMC Musculoskelet Disord. 2005;6:39. [PMID: 16008835] doi:10.1186/1471-2474-6-39
38. **Jansen JP, Bergman GJ, Huels J, Olson M.** Prevention of vertebral fractures in osteoporosis: mixed treatment comparison of bisphosphonate therapies. Curr Med Res Opin. 2009;25:1861-8. [PMID: 19530978] doi:10.1185/03007990903035281
39. **Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al.** Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008;CD001155. [PMID: 18253985] doi:10.1002/14651858.CD001155.pub2
40. **Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al.** Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab. 2000;85:720-6. [PMID: 10690882] doi:10.1210/jcem.85.2.6393
41. **Greenspan SL, Resnick NM, Parker RA.** Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA. 2003;289:2525-33. [PMID: 12759324] doi:10.1001/jama.289.19.2525
42. **Hosking D, Adami S, Felsenberg D, et al.** Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. Curr Med Res Opin 2003;19:383-94.
43. **Hosking D, Adami S, Felsenberg D, Andia JC, Välimäki M, Benhamou L, et al.** Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. Curr Med Res Opin. 2003;19:383-94. [PMID: 13678475] doi:10.1185/030079903125002009
44. **Quandt SA, Thompson DE, Schneider DL, Nevitt MC, Black DM; Fracture Intervention Trial Research Group.** Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of-1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. Mayo Clin Proc. 2005;80:343-9. [PMID: 15757015]
45. **Zein CO, Jorgensen RA, Clarke B, Wenger DE, Keach JC, Angulo P, et al.** Alendronate improves bone mineral density in primary biliary cirrhosis: a randomized placebo-controlled trial. Hepatology. 2005;42:762-71. [PMID: 16175618] doi:10.1002/hep.20866
46. **Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group.** Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev. 2002;23:517-23. [PMID: 12202466] doi:10.1210/er.2001-3002
47. **Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE.** Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. J Bone Miner Res. 2005;20:2105-15. [PMID: 16294264] doi:10.1359/JBMR.050817
48. **Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al.** Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008;CD004523. [PMID: 18254053] doi:10.1002/14651858.CD004523.pub3
49. **Zhong ZM, Chen JT.** Anti-fracture efficacy of risedronic acid in men: A meta-analysis of randomized controlled trials. Clin Drug Investig. 2009;29:349-57. [PMID: 19366276] doi:10.2165/00044011-200929050-00007
50. **Sato Y, Honda Y, Iwamoto J.** Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease. Neurology. 2007;68:911-5. [PMID: 17372126] doi:10.1212/01.wnl.0000257089.50476.92
51. **Ringe JD, Farahmand P, Faber H, Dorst A.** Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. Rheumatol Int. 2009;29:311-5. [PMID: 18762944] doi:10.1007/s00296-008-0689-2
52. **Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD.** Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. J Bone Miner Res. 2009;24:719-25. [PMID: 19049326] doi:10.1359/jbmr.081214
53. **Palomba S, Manguso F, Orio F Jr, Russo T, Oppedisano R, Sacchinelli A, et al.** Effectiveness of risedronate in osteoporotic postmenopausal women with inflammatory bowel disease: a prospective, parallel, open-label, two-year extension study. Menopause. 2008;15(4 Pt 1):730-6. [PMID: 18698280] doi:10.1097/gme.0b013e318159f190
54. **Sato Y, Kanoko T, Satoh K, Iwamoto J.** The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Arch Intern Med. 2005;165:1737-42. [PMID: 16087821] doi:10.1001/archinte.165.15.1737
55. **Ringe JD, Faber H, Farahmand P, Dorst A.** Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. Rheumatol Int. 2006;26:427-31. [PMID: 16001181] doi:10.1007/s00296-005-0004-4
56. **Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY.** A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. Osteoporos Int. 1997;7:488-95. [PMID: 9425508]
57. **Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, et al.** Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 1999;42:2309-18. [PMID: 10555025] doi:10.1002/1529-0131(199911)42:11<2309::AID-ANR8>3.0.CO;2-K
58. **Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY.** Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. J Clin Endocrinol Metab. 2000;85:1895-900. [PMID: 10843171] doi:10.1210/jcem.85.5.6603
59. **Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al.** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999;282:1344-52. [PMID: 10527181]
60. **Hooper MJ, Ebeling PR, Roberts AP, Graham JJ, Nicholson GC, D'Emden M, et al.** Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. Climacteric. 2005;8:251-62. [PMID: 16390757] doi:10.1080/13697130500118126
61. **McClung M, Bensen W, Bolognese M, Bonnick S, Ettinger M, Harris S, et al.** Risedronate increases bone mineral density at the hip, spine and radius in postmenopausal women with low bone mass [abstract]. Osteoporos Int. 1998;8(Suppl 3):111.
62. **McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al; Hip Intervention Program Study Group.** Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344:333-40. [PMID: 11172164] doi:10.1056/NEJM200102013440503
63. **Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC Jr.** Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. J Clin Endocrinol Metab. 1998;83:396-402. [PMID: 9467547] doi:10.1210/jcem.83.2.4586
64. **Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al.** Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis.

Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11:83-91. [PMID: 10663363]
65. **Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, et al.** Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res. 2000;15:1006-13. [PMID: 10841169] doi:10.1359/jbmr.2000.15.6.1006
66. **Reid DM, Adami S, Devogelaer JP, Chines AA.** Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy. Calcif Tissue Int. 2001;69: 242-7. [PMID: 11730260]
67. **Watts NB, Josse RG, Hamdy RC, Hughes RA, Manhart MD, Barton I, et al.** Risedronate prevents new vertebral fractures in postmenopausal women at high risk. J Clin Endocrinol Metab. 2003;88: 542-9. [PMID: 12574177] doi:10.1210/jc.2002-020400
68. **Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al.** Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int. 2000; 67:277-85. [PMID: 11000340]
69. **Bianchi G, Sambrook P.** Oral nitrogen-containing bisphosphonates: a systematic review of randomized clinical trials and vertebral fractures. Curr Med Res Opin. 2008;24:2669-77. [PMID: 18694543] doi:10.1185/03007990802370912
70. **Greenspan SL, Bhattacharya RK, Sereika SM, Brufsky A, Vogel VG.** Prevention of bone loss in survivors of breast cancer: A randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2007;92:131-6. [PMID: 17047022] doi:10.1210/jc.2006-1272
71. **Milgrom C, Finestone A, Novack V, Pereg D, Goldich Y, Kreiss Y, et al.** The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits. Bone. 2004;35:418-24. [PMID: 15268892] doi:10.1016/j.bone.2004.04.016
72. **Kanaji A, Higashi M, Namisato M, Nishio M, Ando K, Yamada H.** Effects of risedronate on lumbar bone mineral density, bone resorption, and incidence of vertebral fracture in elderly male patients with leprosy. Lepr Rev. 2006;77:147-53. [PMID: 16895071]
73. **Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, et al.** Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003;32:120-6. [PMID: 12633783]
74. **Palomba S, Orio F Jr, Manguso F, Falbo A, Russo T, Tolino A, et al.** Efficacy of risedronate administration in osteoporotic postmenopausal women affected by inflammatory bowel disease. Osteoporos Int. 2005;16:1141-9. [PMID: 15928801] doi:10.1007/s00198-005-1927-z
75. **Kishimoto H, Fukunaga M, Kushida K, Shiraki M, Itabashi A, Nawata H, et al; Risedronate Phase III Research Group.** Efficacy and tolerability of once-weekly administration of 17.5 mg risedronate in Japanese patients with involutional osteoporosis: a comparison with 2.5-mg once-daily dosage regimen. J Bone Miner Metab. 2006;24: 405-13. [PMID: 16937274] doi:10.1007/s00774-006-0706-z
76. **Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al.** The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int. 2002;71:103-11. [PMID: 12085156] doi:10.1007/s00223-002-2011-8
77. **Harris ST, Watts NB, Li Z, Chines AA, Hanley DA, Brown JP.** Two-year efficacy and tolerability of risedronate once a week for the treatment of women with postmenopausal osteoporosis. Curr Med Res Opin. 2004;20:757-64. [PMID: 15140343] doi:10.1185/030079904125003566
78. **Delmas PD, Benhamou CL, Man Z, Tlustochowicz W, Matzkin E, Eusebio R, et al.** Monthly dosing of 75 mg risedronate on 2 consecutive days a month: efficacy and safety results. Osteoporos Int. 2008; 19:1039-45. [PMID: 18087660] doi:10.1007/s00198-007-0531-9
79. **Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al; HORIZON Pivotal Fracture Trial.** Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007; 356:1809-22. [PMID: 17476007] doi:10.1056/NEJMoa067312
80. **Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al.** Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med. 2002;346:653-61. [PMID: 11870242] doi:10.1056/NEJMoa011807
81. **Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al; HORIZON Recurrent Fracture Trial.** Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357:1799-809. [PMID: 17878149] doi:10.1056/NEJMoa074941
82. **Chapman I, Greville H, Ebeling PR, King SJ, Kotsimbos T, Nugent P, et al.** Intravenous zoledronate improves bone density in adults with cystic fibrosis (CF). Clin Endocrinol (Oxf). 2009;70:838-46. [PMID: 18823395] doi:10.1111/j.1365-2265.2008.03434.x
83. **Bai H, Jing D, Guo A, Yin S.** Randomized controlled trial of zoledronic acid for treatment of osteoporosis in women. J Int Med Res. 2013;41:697-704. [PMID: 23669294] doi:10.1177/0300060513480917
84. **Chao M, Hua Q, Yingfeng Z, Guang W, Shufeng S, Yuzhen D, et al.** Study on the role of zoledronic acid in treatment of postmenopausal osteoporosis women. Pak J Med Sci. 2013;29:1381-4. [PMID: 24550958]
85. **Black DM, Reid IR, Cauley JA, Cosman F, Leung PC, Lakatos P, et al.** The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2015;30:934-44. [PMID: 25545380] doi:10.1002/jbmr.2442
86. **Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, et al.** Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. Osteoporos Int. 2009;20: 291-7. [PMID: 18663402] doi:10.1007/s00198-008-0653-8
87. **Harris ST, Blumentals WA, Miller PD.** Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Curr Med Res Opin. 2008;24:237-45. [PMID: 18047776] doi:10.1185/030079908X253717
88. **Ravn P, Clemmesen B, Riis BJ, Christiansen C.** The effect on bone mass and bone markers of different doses of ibandronate: a new bisphosphonate for prevention and treatment of postmenopausal osteoporosis: a 1-year, randomized, double-blind, placebo-controlled dose-finding study. Bone. 1996;19:527-33. [PMID: 8922653]
89. **Grotz W, Nagel C, Poeschel D, Cybulla M, Petersen KG, Uhl M, et al.** Effect of ibandronate on bone loss and renal function after kidney transplantation. J Am Soc Nephrol. 2001;12:1530-7. [PMID: 11423583]
90. **Fahrleitner-Pammer A, Piswanger-Soelkner JC, Pieber TR, Obermayer-Pietsch BM, Pilz S, Dimai HP, et al.** Ibandronate prevents bone loss and reduces vertebral fracture risk in male cardiac transplant patients: a randomized double-blind, placebo-controlled trial. J Bone Miner Res. 2009;24:1335-44. [PMID: 19257824] doi:10.1359/jbmr.090216
91. **Chesnut CH 3rd, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al; Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE).** Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19:1241-9. [PMID: 15231010] doi:10.1359/JBMR.040325
92. **Recker R, Stakkestad JA, Chesnut CH 3rd, Christiansen C, Skag A, Hoiseth A, et al.** Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone. 2004;34:890-9. [PMID: 15121021] doi:10.1016/j.bone.2004.01.008
93. **Miller PD, McClung MR, Macovei L, Stakkestad JA, Luckey M, Bonvoisin B, et al.** Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res. 2005;20:1315-22. [PMID: 16007327] doi:10.1359/JBMR.050313
94. **Delmas PD, Adami S, Strugala C, Stakkestad JA, Reginster JY, Felsenberg D, et al.** Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing

intravenous administration study. Arthritis Rheum. 2006;54:1838-46. [PMID: 16729277] doi:10.1002/art.21918
95. **Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J, Langdahl B, et al.** Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med. 2012;367:1714-23. [PMID: 23113482] doi:10.1056/NEJMoa1204061
96. **Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, et al.** Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab. 2008;93:2149-57. [PMID: 18381571] doi:10.1210/jc.2007-2814
97. **Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al; FREEDOM Trial.** Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756-65. [PMID: 19671655] doi:10.1056/NEJMoa0809493
98. **Ferrari S, Adachi JD, Lippuner K, Zapalowski C, Miller PD, Reginster JY, et al.** Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. Osteoporos Int. 2015;26:2763-71. [PMID: 26068295] doi:10.1007/s00198-015-3179-x
99. **Palacios S, Kalouche-Khalil L, Rizzoli R, Zapalowski C, Resch H, Adachi JD, et al.** Treatment with denosumab reduces secondary fracture risk in women with postmenopausal osteoporosis. Climacteric.2015;18:805-12.[PMID:26029985]doi:10.3109/13697137.2015.1045484
100. **Papapoulos S, Lippuner K, Roux C, Lin CJ, Kendler DL, Lewiecki EM, et al.** The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study. Osteoporos Int. 2015;26:2773-83. [PMID: 26202488] doi:10.1007/s00198-015-3234-7
101. **Sugimoto T, Matsumoto T, Hosoi T, Miki T, Gorai I, Yoshikawa H, et al.** Three-year denosumab treatment in postmenopausal Japanese women and men with osteoporosis: results from a 1-year open-label extension of the Denosumab Fracture Intervention Randomized Placebo Controlled Trial (DIRECT). Osteoporos Int. 2015;26:765-74. [PMID: 25403903] doi:10.1007/s00198-014-2964-2
102. **Kendler D.** Sustainability of anti-fracture efficacy and safety of denosumab in postmenopausal osteoporosis [abstract]. Osteoporosis Int. 2013;24 Suppl 4:S653-4.
103. **Lippuner K, Roux C, Bone HG, Zapalowski C, Minisola S, Franek E, et al.** Denosumab treatment of postmenopausal women with osteoporosis for 7 years: clinical fracture results from the first 4 years of the freedom extension [abstract]. Osteoporosis Int. 2013;24(1 Suppl 1):S39-40.
104. **Palacios S, Rizzoli R, Zapalowski C, Resch H, Adami S, Adachi JD, et al.** Denosumab reduced osteoporotic fractures in postmenopausal women with osteoporosis with prior fracture: results from FREEDOM [abstract]. Osteoporosis Int. 2013;24(1 Suppl 1):S299-300.
105. **Papapoulos S, McClung MR, Franchimont N, Adachi JD, Bone HG, Benhamou CL, et al.** Denosumab (DMab) treatment for 6 years maintains low fracture incidence in women (greater-than or equal to)75 years with postmenopausal osteoporosis (PMO) [abstract]. Osteoporosis Int. 2013;24(1 Suppl 1):S45-6.
106. **Bone HG, Chapurlat R, Brandi ML, Brown JP, Czerwinski E, Krieg MA, et al.** The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. J Clin Endocrinol Metab. 2013;98:4483-92. [PMID: 23979955] doi:10.1210/jc.2013-1597
107. **Brown JP, Roux C, Törring O, Ho PR, Beck Jensen JE, Gilchrist N, et al.** Discontinuation of denosumab and associated fracture incidence: analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. J Bone Miner Res. 2013;28:746-52. [PMID: 23109251] doi:10.1002/jbmr.1808
108. Discontinuing denosumab treatment does not increase fracture risk. Bonekey Rep. 2013;2:269. [PMID: 24422041] doi:10.1038/bonekey.2013.3
109. **Nakamura T, Matsumoto T, Sugimoto T, Hosoi T, Miki T, Gorai I, et al.** Clinical Trials Express: fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: denosumab fracture intervention randomized placebo controlled trial (DIRECT). J Clin Endocrinol Metab. 2014;99:2599-607. [PMID: 24646104] doi:10.1210/jc.2013-4175
110. **Vestergaard P, Jorgensen NR, Mosekilde L, Schwarz P.** Effects of parathyroid hormone alone or in combination with antiresorptive therapy on bone mineral density and fracture risk—a meta-analysis. Osteoporos Int. 2007;18:45-57. PMID: 16951908 doi:10.1007/s00198-006-0204-0
111. **Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH.** Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. J Clin Endocrinol Metab. 2005;90:1583-7. [PMID: 15613428] doi:10.1210/jc.2004-0826
112. **Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, et al.** Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int. 2005;16:510-6. [PMID: 15322742] doi:10.1007/s00198-004-1713-3
113. **Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al.** The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003;18:9-17. [PMID: 12510800] doi:10.1359/jbmr.2003.18.1.9
114. **Cosman F, Lindsay R.** Therapeutic potential of parathyroid hormone. Curr Osteoporos Rep. 2004;2:5-11. [PMID: 16036076]
115. **Greenspan S, Bone H, Marriott T.** Preventing the first vertebral fracture in postmenopausal women with low bone mass usting PTH(1-84): results from the TOP study [abstract]. J Bone Miner Res. 2005;20:S56.
116. **Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP.** Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab. 2000;85:3069-76. [PMID: 10999788] doi:10.1210/jcem.85.9.6818
117. **Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al.** Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434-41. [PMID: 11346808] doi:10.1056/NEJM200105103441904
118. **Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al.** The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003;18:9-17. [PMID: 12510800] doi:10.1359/jbmr.2003.18.1.9
119. **Harvey NC, Kanis JA, Odén A, Burge RT, Mitlak BH, Johansson H, et al.** FRAX and the effect of teriparatide on vertebral and non-vertebral fracture. Osteoporos Int. 2015;26:2677-84. [PMID: 26092063] doi:10.1007/s00198-015-3173-3
120. **Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, et al.** Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. J Bone Miner Res. 2001;16:925-31. [PMID: 11341338] doi:10.1359/jbmr.2001.16.5.925
121. **Ensrud KE, Stock JL, Barrett-Connor E, Grady D, Mosca L, Khaw KT, et al.** Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. J Bone Miner Res. 2008;23:112-20. [PMID: 17892376] doi:10.1359/jbmr.070904
122. **Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, et al.** Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res. 2008;23:1923-34. [PMID: 18665787] doi:10.1359/jbmr.080710
123. **Reid IR, Eastell R, Fogelman I, Adachi JD, Rosen A, Netelenbos C, et al.** A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. Arch Intern Med. 2004;164:871-9. [PMID: 15111373] doi:10.1001/archinte.164.8.871

124. **Schachter HM, Clifford TJ, Cranney A, Barrowman NJ, Moher D.** Raloxifene for primary and secondary prevention of osteoporotic fractures in postmenopausal women: a systematic review of efficacy and safety evidence. Report no. 50. Ottawa, Ontario, Canada: Canadian Coordinating Office for Health Technology Assessment; 2005.
125. **Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD.** Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int. 2006;17:313-6. [PMID: 16217588] doi:10.1007/s00198-005-2030-1
126. **Barrett-Connor E, Swern AS, Hustad CM, Bone HG, Liberman UA, Papapoulos S, et al.** Alendronate and atrial fibrillation: a meta-analysis of randomized placebo-controlled clinical trials. Osteoporos Int. 2012;23:233-45. [PMID: 21369791] doi:10.1007/s00198-011-1546-9
127. **Bischoff-Ferrari HA, Rees JR, Grau MV, Barry E, Gui J, Baron JA.** Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. Am J Clin Nutr. 2008;87:1945-51. [PMID: 18541589]
128. **Boone RH, Cheung AM, Girlan LM, Heathcote EJ.** Osteoporosis in primary biliary cirrhosis: a randomized trial of the efficacy and feasibility of estrogen/progestin. Dig Dis Sci. 2006;51:1103-12. [PMID: 16865577] doi:10.1007/s10620-006-8015-x
129. **Ishida Y, Kawai S.** Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: the Yamaguchi Osteoporosis Prevention Study. Am J Med. 2004;117:549-55. [PMID: 15465502] doi:10.1016/j.amjmed.2004.05.019
130. **Wimalawansa SJ.** A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med. 1998;104:219-26. [PMID: 9552083]
131. **MacLean C, Alexander A, Carter J, Chen S, Desai SB, Grossman J, et al.** Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis. AHRQ Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2007.
132. **Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, et al.** Randomized controlled trial of calcium in healthy older women. Am J Med. 2006;119:777-85. [PMID: 16945613] doi:10.1016/j.amjmed.2006.02.038
133. **Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al.** Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr. 2007;86:1780-90. [PMID: 18065599]
134. **Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P.** Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab. 2007;92:1415-23. [PMID: 17264183] doi:10.1210/jc.2006-1404
135. **Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A.** Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007;370:657-66. [PMID: 17720017] doi:10.1016/S0140-6736(07)61342-7
136. **Larsen ER, Mosekilde L, Foldspang A.** Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res. 2004;19:370-8. [PMID: 15040824] doi:10.1359/JBMR.0301240
137. **Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al; Women's Health Initiative Investigators.** Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669-83.
138. **Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al.** Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care. BMJ. 2005;330:1003. [PMID: 15860827] doi:10.1136/bmj.330.7498.1003
139. **Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al; RECORD Trial Group.** Oral vitamin D_3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet. 2005;365:1621-8. [PMID: 15885294] doi:10.1016/S0140-6736(05)63013-9
140. **Prince RL, Devine A, Dhaliwal SS, Dick IM.** Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med. 2006;166:869-75. [PMID: 16636212] doi:10.1001/archinte.166.8.869
141. **Fujita T, Ohue M, Fujii Y, Miyauchi A, Takagi Y.** Reappraisal of Katsuragi calcium study, a prospective, double-blind, placebo-controlled study of the effect of active absorbable algal calcium (AAACa) on vertebral deformity and fracture. J Bone Miner Metab. 2004;22:32-8. [PMID: 14691684] doi:10.1007/s00774-003-0445-3
142. **Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al.** Vitamin D_3 and calcium to prevent hip fractures in elderly women. N Engl J Med. 1992;327:1637-42. [PMID: 1331788] doi:10.1056/NEJM199212033272305
143. **Chapuy MC, Arlot ME, Delmas PD, Meunier PJ.** Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ. 1994;308:1081-2. [PMID: 8173430]
144. **Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, et al.** Combined calcium and vitamin D_3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int. 2002;13:257-64. [PMID: 11991447] doi:10.1007/s001980200023
145. **Chevalley T, Rizzoli R, Nydegger V, Slosman D, Rapin CH, Michel JP, et al.** Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int. 1994;4:245-52. [PMID: 7812072]
146. **Dawson-Hughes B, Harris SS, Krall EA, Dallal GE.** Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337:670-6. [PMID: 9278463] doi:10.1056/NEJM199709043371003
147. **Hansson T, Roos B.** The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. Calcif Tissue Int. 1987;40:315-7. [PMID: 3111669]
148. **Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ; Nottingham Neck of Femur (NONOF) Study.** A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: the Nottingham Neck of Femur (NONOF) Study. Age Ageing. 2004;33:45-51. [PMID: 14695863]
149. **Peacock M, Liu G, Carey M, McClintock R, Ambrosius W, Hui S, et al.** Effect of calcium or 25OH vitamin D_3 dietary supplementation on bone loss at the hip in men and women over the age of 60. J Clin Endocrinol Metab. 2000;85:3011-9. [PMID: 10999778] doi:10.1210/jcem.85.9.6836
150. **Prince R, Devine A, Dick I, Criddle A, Kerr D, Kent N, et al.** The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. J Bone Miner Res. 1995;10:1068-75. [PMID: 7484282] doi:10.1002/jbmr.5650100711
151. **Recker RR, Hinders S, Davies KM, Heaney RP, Stegman MR, Lappe JM, et al.** Correcting calcium nutritional deficiency prevents spine fractures in elderly women. J Bone Miner Res. 1996;11:1961-6. [PMID: 8970899] doi:10.1002/jbmr.5650111218
152. **Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ.** Effect of calcium supplementation on bone loss in postmenopausal women. N Engl J Med. 1993;328:460-4. [PMID: 8421475] doi:10.1056/NEJM199302183280702
153. **Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ.** Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. Am J Med. 1995;98:331-5. [PMID: 7709944] doi:10.1016/S0002-9343(99)80310-6
154. **Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ 3rd.** Long-term effects of calcium supplementation on se-

rum parathyroid hormone level, bone turnover, and bone loss in elderly women. J Bone Miner Res. 1998;13:168-74. [PMID: 9495509] doi:10.1359/jbmr.1998.13.2.168

155. **Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group.** Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev. 2002;23:552-9. [PMID: 12202470] doi:10.1210/er.2001-7002

156. **Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM; Research Committee of the British Thoracic Society.** Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. Thorax. 2004;59:761-8. [PMID: 15333852] doi:10.1136/thx.2003.013839

157. **Frost RJ, Sonne C, Wehr U, Stempfle HU.** Effects of calcium supplementation on bone loss and fractures in congestive heart failure. Eur J Endocrinol. 2007;156:309-14. PMID: 17322490 doi:10.1530/EJE-06-0614

158. **Richy F, Schacht E, Bruyere O, Ethgen O, Gourlay M, Reginster JY.** Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. Calcif Tissue Int. 2005;76:176-86. [PMID: 15692726] doi:10.1007/s00223-004-0005-4

159. **Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL.** Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2005;CD000227. [PMID: 16034849] doi:10.1002/14651858.CD000227.pub2

160. **O'Donnell S, Moher D, Thomas K, Hanley DA, Cranney A.** Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. J Bone Miner Metab. 2008;26:531-42. [PMID: 18979152] doi:10.1007/s00774-008-0868-y

161. **Avenell A, Gillespie WJ, Gillespie LD, O'Connell D.** Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2009;CD000227. [PMID: 19370554] doi:10.1002/14651858.CD000227.pub3

162. **DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group.** Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010;340:b5463. [PMID: 20068257] doi:10.1136/bmj.b5463

163. **Bergman GJ, Fan T, McFetridge JT, Sen SS.** Efficacy of vitamin D_3 supplementation in preventing fractures in elderly women: a meta-analysis. Curr Med Res Opin. 2010;26:1193-201. [PMID: 20302551] doi:10.1185/03007991003659814

164. **Izaks GJ.** Fracture prevention with vitamin D supplementation: considering the inconsistent results. BMC Musculoskelet Disord. 2007;8:26. [PMID: 17349055] doi:10.1186/1471-2474-8-26

165. **Lai JK, Lucas RM, Clements MS, Roddam AW, Banks E.** Hip fracture risk in relation to vitamin D supplementation and serum 25-hydroxyvitamin D levels: a systematic review and meta-analysis of randomised controlled trials and observational studies. BMC Public Health. 2010;10:331. [PMID: 20540727] doi:10.1186/1471-2458-10-331

166. **Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C.** Effect of annual intramuscular vitamin D on fracture risk in elderly men and women–a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford). 2007;46:1852-7. [PMID: 17998225] doi:10.1093/rheumatology/kem240

167. **Law M, Withers H, Morris J, Anderson F.** Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. Age Ageing. 2006;35:482-6. [PMID: 16641143] doi:10.1093/ageing/afj080

168. **Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B.** Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293:2257-64. [PMID: 15886381] doi:10.1001/jama.293.18.2257

169. **Papadimitropoulos E, Wells G, Shea B, Gillespie W, Weaver B, Zytaruk N, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group.** Meta-analyses of therapies for postmenopausal osteoporosis. VIII: meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev. 2002;23:560-9. [PMID: 12202471] doi:10.1210/er.2001-8002

170. **Richy F, Ethgen O, Bruyere O, Reginster JY.** Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int. 2004;15:301-10. [PMID: 14740153] doi:10.1007/s00198-003-1570-5

171. **Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al.** Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009;169:551-61. [PMID: 19307517] doi:10.1001/archinternmed.2008.600.

172. **Jackson C, Gaugris S, Sen SS, Hosking D.** The effect of cholecalciferol (vitamin D_3) on the risk of fall and fracture: a meta-analysis. QJM. 2007;100:185-92. [PMID: 17308327] doi:10.1093/qjmed/hcm005

173. **Adachi JD, Bensen WG, Bianchi F, Cividino A, Pillersdorf S, Sebaldt RJ, et al.** Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year followup. J Rheumatol. 1996;23:995-1000. [PMID: 8782129]

174. **Aloia JF, Vaswani A, Ellis K, Yuen K, Cohn SH.** A model for involutional bone loss. J Lab Clin Med. 1985;106:630-7. [PMID: 4067377]

175. **Avenell A, Grant AM, McGee M, McPherson G, Campbell MK, McGee MA; RECORD Trial Management Group.** The effects of an open design on trial participant recruitment, compliance and retention–a randomized controlled trial comparison with a blinded, placebo-controlled design. Clin Trials. 2004;1:490-8. [PMID: 16279289] doi:10.1191/1740774504cn053oa

176. **Baeksgaard L, Andersen KP, Hyldstrup L.** Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. Osteoporos Int. 1998;8:255-60. [PMID: 9797910] doi:10.1007/s001980050062

177. **Bolton-Smith C, McMurdo ME, Paterson CR, Mole PA, Harvey JM, Fenton ST, et al.** Two-year randomized controlled trial of vitamin K_1 (phylloquinone) and vitamin D_3 plus calcium on the bone health of older women. J Bone Miner Res. 2007;22:509-19. [PMID: 17243866] doi:10.1359/jbmr.070116

178. **Caniggia A, Delling G, Nuti R, Lorè F, Vattimo A.** Clinical, biochemical and histological results of a double-blind trial with 1,25-dihydroxyvitamin D_3, estradiol and placebo in post-menopausal osteoporosis. Acta Vitaminol Enzymol. 1984;6:117-28. [PMID: 6388277]

179. **Dukas L, Bischoff HA, Lindpaintner LS, Schacht E, Birkner-Binder D, Damm TN, et al.** Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc. 2004;52:230-6. [PMID: 14728632]

180. **Ebeling PR, Russell RG.** Teriparatide (rhPTH 1-34) for the treatment of osteoporosis. Int J Clin Pract. 2003;57:710-8. [PMID: 14627183]

181. **Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA, et al.** Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. J Am Geriatr Soc. 2005;53:1881-8. [PMID: 16274368] doi:10.1111/j.1532-5415.2005.00468.x

182. **Gallagher JC, Riggs BL, Recker RR, Goldgar D.** The effect of calcitriol on patients with postmenopausal osteoporosis with special reference to fracture frequency. Proc Soc Exp Biol Med. 1989;191:287-92. [PMID: 2740360]

183. **Gallagher JC, Goldgar D.** Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol. A randomized controlled study. Ann Intern Med. 1990;113:649-55. [PMID: 2221645]

184. **Gallagher JC, Fowler SE, Detter JR, Sherman SS.** Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab. 2001;86:3618-28.
185. **Gorai I, Chaki O, Taguchi Y, Nakayama M, Osada H, Suzuki N, et al.** Early postmenopausal bone loss is prevented by estrogen and partially by 1alpha-OH-vitamin D_3: therapeutic effects of estrogen and/or 1alpha-OH-vitamin D_3. Calcif Tissue Int. 1999;65:16-22. [PMID: 10369728]
186. **Geusens P, Dequeker J.** Long-term effect of nandrolone decanoate, 1 alpha-hydroxyvitamin D_3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: a double-blind controlled study. Bone Miner. 1986;1:347-57. [PMID: 3333018]
187. **Hayashi Y, Fujita T, Inoue T.** Decrease of vertebral fracture in osteoporotics by administration of 1α-hydroxy-vitamin D_3. J Bone Mineral Metab. 1992;10:50-4. doi:10.1007/BF02378983
188. **Jensen GF, Meinecke B, Boesen J, Transbøl I.** Does $1,25(OH)_2D_3$ accelerate spinal bone loss? A controlled therapeutic trial in 70-year-old women. Clin Orthop Relat Res. 1985;215-21. [PMID: 3881203]
189. **Komulainen MH, Kröger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, et al.** HRT and vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. Maturitas. 1998;31:45-54. [PMID: 10091204]
190. **Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM.** Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med. 1996;124:400-6. [PMID: 8554248]
191. **Lyons RA, Johansen A, Brophy S, Newcombe RG, Phillips CJ, Lervy B, et al.** Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int. 2007;18:811-8. [PMID: 17473911] doi:10.1007/s00198-006-0309-5
192. **Menczel J, Foldes J, Steinberg R, Leichter I, Shalita B, Bdolah-Abram T, et al.** Alfacalcidol (alpha D_3) and calcium in osteoporosis. Clin Orthop Relat Res. 1994; 241-7. [PMID: 8131343]
193. **Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI.** Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res. 2002;17:709-15. [PMID: 11918228] doi:10.1359/jbmr.2002.17.4.709
194. **Orimo H, Shiraki M, Hayashi T, Nakamura T.** Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D_3. Bone Miner. 1987;3:47-52. [PMID: 3505192]
195. **Orimo H, Shiraki M, Hayashi Y, Hoshino T, Onaya T, Miyazaki S, et al.** Effects of 1 alpha-hydroxyvitamin D_3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. Calcif Tissue Int. 1994;54:370-6. [PMID: 8062152]
196. **Ott SM, Chesnut CH 3rd.** Calcitriol treatment is not effective in postmenopausal osteoporosis. Ann Intern Med. 1989;110:267-74. [PMID: 2913914]
197. **Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H.** Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009;20:315-22. [PMID: 18629569] doi:10.1007/s00198-008-0662-7
198. **Sato Y, Kuno H, Kaji M, Saruwatari N, Oizumi K.** Effect of ipriflavone on bone in elderly hemiplegic stroke patients with hypovitaminosis D. Am J Phys Med Rehabil. 1999;78:457-63. [PMID: 10493456]
199. **Sato Y, Manabe S, Kuno H, Oizumi K.** Amelioration of osteopenia and hypovitaminosis D by 1alpha-hydroxyvitamin D_3 in elderly patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;66:64-8. [PMID: 9886454]
200. **Tilyard MW, Spears GF, Thomson J, Dovey S.** Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med. 1992;326:357-62. [PMID: 1729617] doi:10.1056/NEJM199202063260601
201. **Trivedi DP, Doll R, Khaw KT.** Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003;326:469. [PMID: 12609940] doi:10.1136/bmj.326.7387.469
202. **Ushiroyama T, Ikeda A, Sakai M, Higashiyama T, Ueki M.** Effects of the combined use of calcitonin and 1 alpha-hydroxycholecalciferol on vertebral bone loss and bone turnover in women with postmenopausal osteopenia and osteoporosis: a prospective study of long-term and continuous administration with low dose calcitonin. Maturitas. 2001;40:229-38. [PMID: 11731184]
203. **Bolland MJ, Grey A.** A case study of discordant overlapping meta-analyses: vitamin d supplements and fracture. PLoS One. 2014;9:e115934. [PMID: 25551377] doi:10.1371/journal.pone.0115934
204. **Zheng YT, Cui QQ, Hong YM, Yao WG.** A meta-analysis of high dose, intermittent vitamin D supplementation among older adults. PLoS One. 2015;10:e0115850. [PMID: 25602255] doi:10.1371/journal.pone.0115850
205. **Avenell A, Mak JC, O'Connell D.** Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014;CD000227. [PMID: 24729336] doi:10.1002/14651858.CD000227.pub4
206. **Torres A, García S, Gómez A, González A, Barrios Y, Concepción MT, et al.** Treatment with intermittent calcitriol and calcium reduces bone loss after renal transplantation. Kidney Int. 2004;65:705-12. PMID: 14717945 doi:10.1111/j.1523-1755.2004.00432.x
207. **Sato Y, Iwamoto J, Kanoko T, Satoh K.** Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovasc Dis. 2005;20:187-92. [PMID: 16088114] doi:10.1159/000087203
208. **Shikari M, Kushida K, Yamazaki K, Nagai T, Inoue T, Orimo H.** Effects of 2 years' treatment of osteoporosis with 1 alpha-hydroxy vitamin D_3 on bone mineral density and incidence of fracture: a placebo-controlled, double-blind prospective study. Endocr J. 1996;43:211-20. [PMID: 9026268]
209. **Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al.** Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010;303:1815-22. [PMID: 20460620] doi:10.1001/jama.2010.594
210. **Korpelainen R, Keinänen-Kiukaanniemi S, Nieminen P, Heikkinen J, Väänänen K, Korpelainen J.** Long-term outcomes of exercise: follow-up of a randomized trial in older women with osteopenia. Arch Intern Med. 2010;170:1548-56. [PMID: 20876406] doi:10.1001/archinternmed.2010.311
211. **Lock CA, Lecouturier J, Mason JM, Dickinson HO.** Lifestyle interventions to prevent osteoporotic fractures: a systematic review. Osteoporos Int. 2006;17:20-8. [PMID: 15928799] doi:10.1007/s00198-005-1942-0
212. **Ebrahim S, Thompson PW, Baskaran V, Evans K.** Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. Age Ageing. 1997;26:253-60. [PMID: 9271287]
213. **Jensen J, Lundin-Olsson L, Nyberg L, Gustafson Y.** Fall and injury prevention in older people living in residential care facilities. A cluster randomized trial. Ann Intern Med. 2002;136:733-41. [PMID: 12020141]
214. **Preisinger E, Alacamlioglu Y, Pils K, Bosina E, Metka M, Schneider B, et al.** Exercise therapy for osteoporosis: results of a randomised controlled trial. Br J Sports Med. 1996;30:209-12. [PMID: 8889112]
215. **Sato Y, Metoki N, Iwamoto J, Satoh K.** Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients. Neurology. 2003;61:338-42. [PMID: 12913194]
216. **Sinaki M, Wahner HW, Offord KP, Hodgson SF.** Efficacy of non-loading exercises in prevention of vertebral bone loss in postmenopausal women: a controlled trial. Mayo Clin Proc. 1989;64:762-9. [PMID: 2671517]
217. **Sinaki M, Itoi E, Wahner HW, Wollan P, Gelzcer R, Mullan BP, et al.** Stronger back muscles reduce the incidence of vertebral frac-

tures: a prospective 10 year follow-up of postmenopausal women. Bone. 2002;30:836-41. [PMID: 12052450]
218. **Vetter NJ, Lewis PA, Ford D.** Can health visitors prevent fractures in elderly people? BMJ. 1992;304:888-90. [PMID: 1392755]
219. **Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, et al.** Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009;60:3346-55. [PMID: 19877063] doi:10.1002/art.24879
220. **Bonnick S, Broy S, Kaiser F, Teutsch C, Rosenberg E, DeLucca P, Melton M.** Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. Curr Med Res Opin. 2007;23:1341-9. [PMID: 17594775] doi:10.1185/030079907X188035
221. **Xia WB, Zhang ZL, Wang HF, Meng XW, Zhang Y, Zhu GY, et al.** The efficacy and safety of calcitriol and/or Caltrate D in elderly Chinese women with low bone mass. Acta Pharmacol Sin. 2009;30:372-8. [PMID: 19262561] PMCID: PMC4085656 doi:10.1038/aps.2009.12
222. **Tauchmanovà L, De Simone G, Musella T, Orio F, Ricci P, Nappi C, et al.** Effects of various antireabsorptive treatments on bone mineral density in hypogonadal young women after allogeneic stem cell transplantation. Bone Marrow Transplant. 2006;37:81-8. PMID: 16247420 doi:10.1038/sj.bmt.1705196
223. **Garcia-Delgado I, Prieto S, Gil-Fraguas L, Robles E, Rufilanchas JJ, Hawkins F.** Calcitonin, etidronate, and calcidiol treatment in bone loss after cardiac transplantation. Calcif Tissue Int. 1997;60:155-9. [PMID: 9056163]
224. **Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM; Research Committee of the British Thoracic Society.** Hormone replacement therapy (HRT) or etidronate for osteoporosis in postmenopausal asthmatics on glucocorticoids: a randomised factorial trial. Scott Med J. 2009;54:21-5. [PMID: 19291931] doi:10.1258/rsmsmj.54.1.21
225. **Boutsen Y, Jamart J, Esselinckx W, Stoffel M, Devogelaer JP.** Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. Calcif Tissue Int. 1997;61:266-71. [PMID: 9312195]
226. **Luckey M, Kagan R, Greenspan S, Bone H, Kiel RD, Simon J, et al.** Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause. 2004;11:405-15. [PMID: 15243278]
227. **Uchida S, Taniguchi T, Shimizu T, Kakikawa T, Okuyama K, Okaniwa M, et al.** Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: a double-blind, randomized study. J Bone Miner Metab. 2005;23:382-8. [PMID: 16133688] doi:10.1007/s00774-005-0616-5
228. **Muscoso E, Puglisi N, Mamazza C, Lo Giudice F, Testai M, Abbate S, et al.** Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study. Eur Rev Med Pharmacol Sci. 2004;8:97-102. [PMID: 15267123]
229. **Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SM, et al.** Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. J Clin Endocrinol Metab. 2006;91:2631-7. [PMID: 16636120] doi:10.1210/jc.2005-2602
230. **Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S, et al; Fosamax Actonel Comparison Trial Investigators.** Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res. 2005;20:141-51. [PMID: 15619680] doi:10.1359/JBMR.040920
231. **Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, et al.** A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87:4528-35. [PMID: 12364430] doi:10.1210/jc.2002-020334
232. **Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C.** Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res. 2000;15:1113-8. [PMID: 10841179] doi:10.1359/jbmr.2000.15.6.1113
233. **Ito M, Tobinai M, Yoshida S, Hashimoto J, Nakamura T.** Effect of monthly intravenous ibandronate injections on vertebral or non-vertebral fracture risk in Japanese patients with high-risk osteoporosis in the MOVER study. J Bone Miner Metab. 2017;35:58-64. [PMID: 26614597] doi:10.1007/s00774-015-0723-x
234. **Okada Y, Nawata M, Nakayamada S, Saito K, Tanaka Y.** Alendronate protects premenopausal women from bone loss and fracture associated with high-dose glucocorticoid therapy. J Rheumatol. 2008;35:2249-54. [PMID: 19031508]
235. **Murad MH, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA, et al.** Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. J Clin Endocrinol Metab. 2012;97:1871-80. doi:10.1210/jc.2011-3060. [PMID: 22466336] doi:10.1210/jc.2011-3060
236. **Hopkins RB, Goeree R, Pullenayegum E, Adachi JD, Papaioannou A, Xie F, et al.** The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. BMC Musculoskelet Disord. 2011;12:209. [PMID: 21943363] doi:10.1186/1471-2474-12-209
237. **Freemantle N, Cooper C, Diez-Perez A, Gitlin M, Radcliffe H, Shepherd S, et al.** Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. Osteoporos Int. 2013;24:209-17. [PMID: 22832638] doi:10.1007/s00198-012-2068-9
238. **Migliore A, Broccoli S, Massafra U, Cassol M, Frediani B.** Ranking antireabsorptive agents to prevent vertebral fractures in postmenopausal osteoporosis by mixed treatment comparison meta-analysis. Eur Rev Med Pharmacol Sci. 2013;17:658-67. [PMID: 23543450]
239. **Jansen JP, Bergman GJ, Huels J, Olson M.** The efficacy of bisphosphonates in the prevention of vertebral, hip, and nonvertebral-nonhip fractures in osteoporosis: a network meta-analysis. Semin Arthritis Rheum. 2011;40:275-84.e1-2. [PMID: 20828791] doi:10.1016/j.semarthrit.2010.06.001
240. **Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al; FLEX Research Group.** Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006;296:2927-38. [PMID: 17190893] doi:10.1001/jama.296.24.2927
241. **Kanis JA, Johansson H, Oden A, McCloskey EV.** A meta-analysis of the efficacy of raloxifene on all clinical and vertebral fractures and its dependency on FRAX. Bone. 2010;47:729-35. [PMID: 20601292] doi:10.1016/j.bone.2010.06.009
242. **Schwartz AV, Bauer DC, Cummings SR, Cauley JA, Ensrud KE, Palermo L, et al; FLEX Research Group.** Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. J Bone Miner Res. 2010;25:976-82. [PMID: 20200926] doi:10.1002/jbmr.11
243. **Siris ES, Harris ST, Eastell R, Zanchetta JR, Goemaere S, Diez-Perez A, et al; Continuing Outcomes Relevant to Evista (CORE) Investigators.** Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res. 2005;20:1514-24. [PMID: 16059623] doi:10.1359/JBMR.050509
244. **Sontag A, Wan X, Krege JH.** Benefits and risks of raloxifene by vertebral fracture status. Curr Med Res Opin. 2010;26:71-6. [PMID: 19908937] doi:10.1185/03007990903427082
245. **Prevrhal S, Krege JH, Chen P, Genant H, Black DM.** Teriparatide vertebral fracture risk reduction determined by quantitative and qualitative radiographic assessment. Curr Med Res Opin. 2009;25:921-8. [PMID: 19250060] doi:10.1185/03007990902790993
246. **Boonen S, Klemes AB, Zhou X, Lindsay R.** Assessment of the relationship between age and the effect of risedronate treatment in women with postmenopausal osteoporosis: a pooled analysis of four studies. J Am Geriatr Soc. 2010;58:658-63. [PMID: 20345865] doi:10.1111/j.1532-5415.2010.02763.x

247. **Boonen S, Black DM, Colón-Emeric CS, Eastell R, Magaziner JS, Eriksen EF, et al.** Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. J Am Geriatr Soc. 2010;58:292-9. [PMID: 20070415] doi:10.1111/j.1532-5415.2009.02673.x
248. **Boonen S, Marin F, Mellstrom D, Xie L, Desaiah D, Krege JH, et al.** Safety and efficacy of teriparatide in elderly women with established osteoporosis: bone anabolic therapy from a geriatric perspective. J Am Geriatr Soc. 2006;54:782-9. [PMID: 16696744]
249. **Eastell R, Black DM, Boonen S, Adami S, Felsenberg D, Lippuner K, et al; HORIZON Pivotal Fracture Trial.** Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density. J Clin Endocrinol Metab. 2009;94:3215-25. [PMID: 19567517] doi:10.1210/jc.2008-2765
250. **Nakamura T, Liu JL, Morii H, Huang QR, Zhu HM, Qu Y, et al.** Effect of raloxifene on clinical fractures in Asian women with postmenopausal osteoporosis. J Bone Miner Metab. 2006;24:414-8. [PMID: 16937275] doi:10.1007/s00774-006-0702-3
251. **Warriner AH, Outman RC, Saag KG, Berry SD, Colón-Emeric C, Flood KL, et al.** Management of osteoporosis among home health and long-term care patients with a prior fracture. South Med J. 2009;102:397-404. [PMID: 19279529] doi:10.1097/SMJ.0b013e31819bc1d3
252. **Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, et al.** Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. J Bone Miner Res. 2007;22:503-8. [PMID: 17243862] doi:10.1359/jbmr.070112
253. **Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE; MORE Investigators.** The effect of raloxifene treatment in postmenopausal women with CKD. J Am Soc Nephrol. 2008;19:1430-8. [PMID: 18400939] doi:10.1681/ASN.2007050555
254. **Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH.** Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. Osteoporos Int. 2007;18:59-68. [PMID: 17013567] doi:10.1007/s00198-006-0189-8
255. U.S. Food and Drug Administration. FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures-Safety Announcement. October 13. 2010. Accessed at https://www.fda.gov/Drugs/DrugSafety/ucm229009.htm on 5 April 2017.
256. **Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, et al.** Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res. 2012;27:2544-50. [PMID: 22836783] doi:10.1002/jbmr.1719
257. **Abrahamsen B.** Bisphosphonate adverse effects, lessons from large databases. Curr Opin Rheumatol. 2010;22:404-9. [PMID: 20473174] doi:10.1097/BOR.0b013e32833ad677
258. **Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, et al; Predicting Risk of Osteonecrosis of the Jaw with Oral Bisphosphonate Exposure (PROBE) Investigators.** Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg. 2010;68:243-53. [PMID: 19772941] doi:10.1016/j.joms.2009.03.050
259. **Grbic JT, Landesberg R, Lin SQ, Mesenbrink P, Reid IR, Leung PC, et al; Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial Research Group.** Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. J Am Dent Assoc. 2008;139:32-40. [PMID: 18167382]
260. **Khan AA, Sándor GK, Dore E, Morrison AD, Alsahli M, Amin F, et al; Canadian Taskforce on Osteonecrosis of the Jaw.** Bisphosphonate associated osteonecrosis of the jaw. J Rheumatol. 2009;36:478-90. [PMID: 19286860] doi:10.3899/jrheum.080759
261. **Lapi F, Cipriani F, Caputi AP, Corrao G, Vaccheri A, Sturkenboom MC, et al; Bisphosphonates Efficacy-Safety Tradeoff (BEST) study group.** Assessing the risk of osteonecrosis of the jaw due to bisphosphonate therapy in the secondary prevention of osteoporotic fractures. Osteoporos Int. 2013;24:697-705. [PMID: 22618266] doi:10.1007/s00198-012-2013-y
262. **Fitzpatrick SG, Stavropoulos MF, Bowers LM, Neuman AN, Hinkson DW, Green JG, et al.** Bisphosphonate-related osteonecrosis of jaws in 3 osteoporotic patients with history of oral bisphosphonate use treated with single yearly zoledronic acid infusion. J Oral Maxillofac Surg. 2012;70:325-30. [PMID: 21723015] doi:10.1016/j.joms.2011.02.049
263. **O'Ryan FS, Lo JC.** Bisphosphonate-related osteonecrosis of the jaw in patients with oral bisphosphonate exposure: clinical course and outcomes. J Oral Maxillofac Surg. 2012;70:1844-53. PMID: 22595135 doi:10.1016/j.joms.2011.08.033
264. **Otto S, Schreyer C, Hafner S, Mast G, Ehrenfeld M, Sturzenbaum S, et al.** Bisphosphonate-related osteonecrosis of the jaws–characteristics, risk factors, clinical features, localization and impact on oncological treatment. J Craniomaxillofac Surg. 2012;40:303-9.
265. **Bocanegra-Pérez MS, Vicente-Barrero M, Sosa-Henríquez M, Rodríguez-Bocanegra E, Limiñana-Cañal JM, López-Márquez A, et al.** Bone metabolism and clinical study of 44 patients with bisphosphonate-related osteonecrosis of the jaws. Med Oral Patol Oral Cir Bucal. 2012;17:e948-55. [PMID: 22926469]
266. **Park W, Lee SH, Park KR, Rho SH, Chung WY, Kim HJ.** Characteristics of bisphosphonate-related osteonecrosis of the jaw after kidney transplantation. J Craniofac Surg. 2012;23:e510-4. [PMID: 22976726] doi:10.1097/SCS.0b013e31825b33f6
267. **Tennis P, Rothman KJ, Bohn RL, Tan H, Zavras A, Laskarides C, et al.** Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis. Pharmacoepidemiol Drug Saf. 2012;21:810-7. [PMID: 22711458] doi:10.1002/pds.3292
268. **Urade M, Tanaka N, Furusawa K, Shimada J, Shibata T, Kirita T, et al.** Nationwide survey for bisphosphonate-related osteonecrosis of the jaws in Japan. J Oral Maxillofac Surg. 2011;69:e364-71. [PMID: 21782307] doi:10.1016/j.joms.2011.03.051
269. **Diniz-Freitas M, López-Cedrún JL, Fernández-Sanromán J, García-García A, Fernández-Feijoo J, Diz-Dios P.** Oral bisphosphonate-related osteonecrosis of the jaws: Clinical characteristics of a series of 20 cases in Spain. Med Oral Patol Oral Cir Bucal. 2012;17:e751-8. [PMID: 22549688]
270. **Baillargeon J, Kuo YF, Lin YL, Wilkinson GS, Goodwin JS.** Osteonecrosis of the jaw in older osteoporosis patients treated with intravenous bisphosphonates. Ann Pharmacother. 2011;45:1199-206. [PMID: 21954448] doi:10.1345/aph.1Q239
271. **Almăşan HA, Băciut M, Rotaru H, Bran S, Almăşan OC, Băciut G.** Osteonecrosis of the jaws associated with the use of bisphosphonates. Discussion over 52 cases. Rom J Morphol Embryol. 2011;52:1233-41. [PMID: 22203928]
272. **Villa A, Castiglioni S, Peretti A, Omodei M, Ferrieri GB, Abati S.** Osteoporosis and bisphosphonate-related osteonecrosis of the jaw bone. ISRN Rheumatol. 2011;2011:654027. [PMID: 22389800] doi:10.5402/2011/654027
273. **Otto S, Abu-Id MH, Fedele S, Warnke PH, Becker ST, Kolk A, et al.** Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: not just a sporadic coincidence–a multi-centre study. J Craniomaxillofac Surg. 2011;39:272-7. [PMID: 20580566] doi:10.1016/j.jcms.2010.05.009
274. **Vescovi P, Campisi G, Fusco V, Mergoni G, Manfredi M, Merigo E, et al.** Surgery-triggered and non surgery-triggered Bisphosphonate-related Osteonecrosis of the Jaws (BRONJ): A retrospective analysis of 567 cases in an Italian multicenter study. Oral Oncol. 2011;47:191-4. [PMID: 21292541] doi:10.1016/j.oraloncology.2010.11.007
275. **Grbic JT, Black DM, Lyles KW, Reid DM, Orwoll E, McClung M, et al.** The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. J Am Dent Assoc. 2010;141:1365-70. [PMID: 21037195]
276. **Solomon DH, Mercer E, Woo SB, Avorn J, Schneeweiss S, Treister N.** Defining the epidemiology of bisphosphonate-associated osteonecrosis of the jaw: prior work and current challenges. Osteo-

poros Int. 2013;24:237-44. [PMID: 22707065] doi:10.1007/s00198-012-2042-6
277. **Lee SH, Chang SS, Lee M, Chan RC, Lee CC.** Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis. Osteoporos Int. 2014;25:1131-9. [PMID: 24343364] doi:10.1007/s00198-013-2575-3
278. **Hansen PJ, Knitschke M, Draenert FG, Irle S, Neff A.** Incidence of bisphosphonate-related osteonecrosis of the jaws (BRONJ) in patients taking bisphosphonates for osteoporosis treatment - a grossly underestimated risk? Clin Oral Investig. 2013;17:1829-37. [PMID: 23114879] doi:10.1007/s00784-012-0873-3
279. **Chamizo Carmona E, Gallego Flores A, Loza Santamaría E, Herrero Olea A, Rosario Lozano MP.** Systematic literature review of bisphosphonates and osteonecrosis of the jaw in patients with osteoporosis. Reumatol Clin. 2013;9:172-7. [PMID: 22784630] doi:10.1016/j.reuma.2012.05.005
280. **Gaudin E, Seidel L, Bacevic M, Rompen E, Lambert F.** Occurrence and risk indicators of medication-related osteonecrosis of the jaw after dental extraction: a systematic review and meta-analysis. J Clin Periodontol. 2015;42:922-32. [PMID: 26362756] doi:10.1111/jcpe.12455
281. **Gu JM, Wang L, Lin H, Chen DC, Tang H, Jin XL, et al.** The efficacy and safety of weekly 35-mg risedronate dosing regimen for Chinese postmenopausal women with osteoporosis or osteopenia: 1-year data. Acta Pharmacol Sin. 2015;36:841-6. [PMID: 26051110] doi:10.1038/aps.2015.30
282. **Filleul O, Crompot E, Saussez S.** Bisphosphonate-induced osteonecrosis of the jaw: a review of 2,400 patient cases. J Cancer Res Clin Oncol. 2010;136:1117-24. [PMID: 20508948] doi:10.1007/s00432-010-0907-7
283. **Arslan C, Aksoy S, Dizdar O, Dede DS, Harputluoglu H, Altundag K.** Zoledronic acid and atrial fibrillation in cancer patients. Support Care Cancer. 2011;19:425-30. [PMID: 20358384] doi:10.1007/s00520-010-0868-z
284. **Rhee CW, Lee J, Oh S, Choi NK, Park BJ.** Use of bisphosphonate and risk of atrial fibrillation in older women with osteoporosis. Osteoporos Int. 2012;23:247-54. [PMID: 21431993] doi:10.1007/s00198-011-1608-z
285. **Kim SY, Kim MJ, Cadarette SM, Solomon DH.** Bisphosphonates and risk of atrial fibrillation: a meta-analysis. Arthritis Res Ther. 2010;12:R30. [PMID: 20170505] doi:10.1186/ar2938
286. **Loke YK, Jeevanantham V, Singh S.** Bisphosphonates and atrial fibrillation: systematic review and meta-analysis. Drug Saf. 2009;32:219-28. [PMID: 19338379] doi:10.2165/00002018-200932030-00004
287. **Kim DH, Rogers JR, Fulchino LA, Kim CA, Solomon DH, Kim SC.** Bisphosphonates and risk of cardiovascular events: a meta-analysis. PLoS One. 2015;10:e0122646. [PMID: 25884398] doi:10.1371/journal.pone.0122646
288. **Thadani SR, Ristow B, Blackwell T, Mehra R, Stone KL, Marcus GM, et al; Osteoporotic Fractures in Men Study (MrOS) Research Group.** Relationship of Bisphosphonate Therapy and Atrial Fibrillation/Flutter: Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. Chest. 2016;149:1173-80. [PMID: 26836889] doi:10.1016/j.chest.2015.11.022
289. **Pittman CB, Davis LA, Zeringue AL, Caplan L, Wehmeier KR, Scherrer JF, et al.** Myocardial infarction risk among patients with fractures receiving bisphosphonates. Mayo Clin Proc. 2014;89:43-51. [PMID: 24388021] doi:10.1016/j.mayocp.2013.08.021
290. **Wang JC, Chien WC, Chung CH, Liao WI, Tsai SH.** Adverse cardiovascular effects of nitrogen-containing bisphosphonates in patients with osteoporosis: A nationwide population-based retrospective study. Int J Cardiol. 2016;215:232-7. [PMID: 27128537] doi:10.1016/j.ijcard.2016.04.088
291. **Nakamura T, Nakano T, Ito M, Hagino H, Hashimoto J, Tobinai M, et al; MOVER Study Group.** Clinical efficacy on fracture risk and safety of 0.5 mg or 1 mg/month intravenous ibandronate versus 2.5 mg/day oral risedronate in patients with primary osteoporosis. Calcif Tissue Int. 2013;93:137-46. [PMID: 23644930] doi:10.1007/s00223-013-9734-6
292. **Cardwell CR, Abnet CC, Veal P, Hughes CM, Cantwell MM, Murray LJ.** Exposure to oral bisphosphonates and risk of cancer. Int J Cancer. 2012;131:E717-25. [PMID: 22161552] doi:10.1002/ijc.27389
293. **Chen YM, Chen DY, Chen LK, Tsai YW, Chang LC, Huang WF, et al.** Alendronate and risk of esophageal cancer: a nationwide population-based study in Taiwan. J Am Geriatr Soc. 2011;59:2379-81. [PMID: 22188086] doi:10.1111/j.1532-5415.2011.03693.x
294. **Hartle JE, Tang X, Kirchner HL, Bucaloiu ID, Sartorius JA, Pogrebnaya ZV, et al.** Bisphosphonate therapy, death, and cardiovascular events among female patients with CKD: a retrospective cohort study. Am J Kidney Dis. 2012;59:636-44. [PMID: 22244796] doi:10.1053/j.ajkd.2011.11.037
295. **Schwartz AV, Schafer AL, Grey A, Vittinghoff E, Palermo L, Lui LY, et al.** Effects of antiresorptive therapies on glucose metabolism: results from the FIT, HORIZON-PFT, and FREEDOM trials. J Bone Miner Res. 2013;28:1348-54. [PMID: 23322676] doi:10.1002/jbmr.1865
296. **Lee WY, Sun LM, Lin MC, Liang JA, Chang SN, Sung FC, et al.** A higher dosage of oral alendronate will increase the subsequent cancer risk of osteoporosis patients in Taiwan: a population-based cohort study. PLoS One. 2012;7:e53032. [PMID: 23300854] doi:10.1371/journal.pone.0053032
297. **Etminan M, Forooghian F, Maberley D.** Inflammatory ocular adverse events with the use of oral bisphosphonates: a retrospective cohort study. CMAJ. 2012;184:E431-4. [PMID: 22470169] doi:10.1503/cmaj.111752
298. **Vestergaard P.** Occurrence of gastrointestinal cancer in users of bisphosphonates and other antiresorptive drugs against osteoporosis. Calcif Tissue Int. 2011;89:434-41. [PMID: 22002678] doi:10.1007/s00223-011-9539-4
299. **Chiang CH, Huang CC, Chan WL, Huang PH, Chen TJ, Chung CM, et al.** Oral alendronate use and risk of cancer in postmenopausal women with osteoporosis: A nationwide study. J Bone Miner Res. 2012;27:1951-8. [PMID: 22532232] doi:10.1002/jbmr.1645
300. **Shih AW, Weir MA, Clemens KK, Yao Z, Gomes T, Mamdani MM, et al.** Oral bisphosphonate use in the elderly is not associated with acute kidney injury. Kidney Int. 2012;82:903-8. [PMID: 22695327] doi:10.1038/ki.2012.227
301. **Christensen S, Mehnert F, Chapurlat RD, Baron JA, Sørensen HT.** Oral bisphosphonates and risk of ischemic stroke: a case-control study. Osteoporos Int. 2011;22:1773-9. [PMID: 20945149] doi:10.1007/s00198-010-1395-y
302. **Kang JH, Keller JJ, Lin HC.** A population-based 2-year follow-up study on the relationship between bisphosphonates and the risk of stroke. Osteoporos Int. 2012;23:2551-7. [PMID: 22270858] doi:10.1007/s00198-012-1894-0
303. **Khalili H, Huang ES, Ogino S, Fuchs CS, Chan AT.** A prospective study of bisphosphonate use and risk of colorectal cancer. J Clin Oncol. 2012;30:3229-33. [PMID: 22649131] doi:10.1200/JCO.2011.39.2670
304. **Tadrous M, Wong L, Mamdani MM, Juurlink DN, Krahn MD, Lévesque LE, et al.** Comparative gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis. Osteoporos Int. 2014;25:1225-35. [PMID: 24287510] doi:10.1007/s00198-013-2576-2
305. **Crawford BA, Kam C, Pavlovic J, Byth K, Handelsman DJ, Angus PW, et al.** Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2006;144:239-48. [PMID: 16490909]
306. **Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al.** Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med. 2002;346:653-61. [PMID: 11870242] doi:10.1056/NEJMoa011807
307. **Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N.** Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol. 2003;169:2008-12. [PMID: 12771706] doi:10.1097/01.ju.0000063820.94994.95

308. **McClung M, Miller P, Recknor C, Mesenbrink P, Bucci-Rechtweg C, Benhamou CL.** Zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass: a randomized controlled trial. Obstet Gynecol. 2009;114:999-1007. [PMID: 20168099] doi:10.1097/AOG.0b013e3181bdce0a
309. **Patel DV, Bolland M, Nisa Z, Al-Abuwsi F, Singh M, Horne A, et al.** Incidence of ocular side effects with intravenous zoledronate: secondary analysis of a randomized controlled trial. Osteoporos Int. 2015;26:499-503. [PMID: 25187119] doi:10.1007/s00198-014-2872-5
310. **Stakkestad JA, Benevolenskaya LI, Stepan JJ, Skag A, Nordby A, Oefjord E, et al; Ibandronate Intravenous Study Group.** Intravenous ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. Ann Rheum Dis. 2003;62:969-75. [PMID: 12972476]
311. **Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V.** Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ. 2010;341:c4444. [PMID: 20813820] doi:10.1136/bmj.c4444
312. **Wright E, Seed PT, Schofield P, Jones R.** Bisphosphonates and cancer. More data using same database. BMJ. 2010;341:c5315. [PMID: 20880919] doi:10.1136/bmj.c5315
313. **Cardwell CR, Abnet CC, Cantwell MM, Murray LJ.** Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA. 2010;304:657-63. [PMID: 20699457] doi:10.1001/jama.2010.1098
314. **Nguyen DM, Schwartz J, Richardson P, El-Serag HB.** Oral bisphosphonate prescriptions and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Dig Dis Sci. 2010;55:3404-7. [PMID: 20397052] doi:10.1007/s10620-010-1198-1
315. **Vinogradova Y, Coupland C, Hippisley-Cox J.** Exposure to bisphosphonates and risk of common non-gastrointestinal cancers: series of nested case-control studies using two primary-care databases. Br J Cancer. 2013;109:795-806. [PMID: 23868009] doi:10.1038/bjc.2013.383
316. **Andrici J, Tio M, Eslick GD.** Bisphosphonate use and the risk of colorectal cancer: a meta-analysis [abstract]. Gastroenterology. 2013;144(5 Suppl 1):S385.
317. **Pazianas M, Abrahamsen B, Eiken PA, Eastell R, Russell RG.** Reduced colon cancer incidence and mortality in postmenopausal women treated with an oral bisphosphonate–Danish National Register Based Cohort Study. Osteoporos Int. 2012;23:2693-701. [PMID: 22392160] doi:10.1007/s00198-012-1902-4
318. **Vinogradova Y, Coupland C, Hippisley-Cox J.** Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data. BMJ. 2013;346:f114. [PMID: 23325866] doi:10.1136/bmj.f114
319. **Andrici J, Tio M, Eslick GD.** Meta-analysis: oral bisphosphonates and the risk of oesophageal cancer. Aliment Pharmacol Ther. 2012;36:708-16. [PMID: 22966908] doi:10.1111/apt.12041
320. **Sun K, Liu JM, Sun HX, Lu N, Ning G.** Bisphosphonate treatment and risk of esophageal cancer: a meta-analysis of observational studies. Osteoporos Int. 2013;24:279-86. PMID: 23052941 doi:10.1007/s00198-012-2158-8
321. **Chen LX, Ning GZ, Zhou ZR, Li YL, Zhang D, Wu QL, et al.** The carcinogenicity of alendronate in patients with osteoporosis: evidence from cohort studies. PLoS One. 2015;10:e0123080. [PMID: 25881304] doi:10.1371/journal.pone.0123080
322. **Jung SY, Sohn HS, Park EJ, Suh HS, Park JW, Kwon JW.** Oral bisphosphonates and upper gastrointestinal cancer risks in Asians with osteoporosis: a nested case-control study using national retrospective cohort sample data from Korea. PLoS One. 2016;11:e0150531. [PMID: 26937968] doi:10.1371/journal.pone.0150531
323. **Morden NE, Munson JC, Smith J, Mackenzie TA, Liu SK, Tosteson AN.** Oral bisphosphonates and upper gastrointestinal toxicity: a study of cancer and early signals of esophageal injury. Osteoporos Int. 2015;26:663-72. [PMID: 25349053] doi:10.1007/s00198-014-2925-9
324. **Newcomb PA, Passarelli MN, Phipps AI, Anderson GL, Wactawski-Wende J, Ho GY, et al.** Oral bisphosphonate use and risk of postmenopausal endometrial cancer. J Clin Oncol. 2015;33:1186-90. [PMID: 25713431] doi:10.1200/JCO.2014.58.6842
325. **Rennert G, Rennert HS, Pinchev M, Lavie O.** The effect of bisphosphonates on the risk of endometrial and ovarian malignancies. Gynecol Oncol. 2014;133:309-13. [PMID: 24556062] doi:10.1016/j.ygyno.2014.02.014
326. **Vogtmann E, Corley DA, Almers LM, Cardwell CR, Murray LJ, Abnet CC.** Oral PMID: 26445463. PLoS One. 2015;10:e0140180. [PMID: 26445463] doi:10.1371/journal.pone.0140180
327. **Kumagai Y, Hasunuma T, Padhi D.** A randomized, double-blind, placebo-controlled, single-dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of denosumab administered subcutaneously to postmenopausal Japanese women. Bone. 2011;49:1101-7. [PMID: 21871589] doi:10.1016/j.bone.2011.08.007
328. **Toulis KA, Anastasilakis AD.** Increased risk of serious infections in women with osteopenia or osteoporosis treated with denosumab. Osteoporos Int. 2010;21:1963-4. [PMID: 20012939] doi:10.1007/s00198-009-1145-1
329. **Nakamura T, Sugimoto T, Nakano T, Kishimoto H, Ito M, Fukunaga M, et al.** Randomized Teriparatide [human parathyroid hormone (PTH) 1-34] Once-Weekly Efficacy Research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. J Clin Endocrinol Metab. 2012;97:3097-106. [PMID: 22723322] doi:10.1210/jc.2011-3479
330. **Fujita T, Fukunaga M, Itabashi A, Tsutani K, Nakamura T.** Once-weekly injection of low-dose teriparatide (28.2 μg) reduced the risk of vertebral fracture in patients with primary osteoporosis. Calcif Tissue Int. 2014;94:170-5. [PMID: 23963633] doi:10.1007/s00223-013-9777-8
331. **Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, et al; Treatment of Osteoporosis with Parathyroid Hormone Study Group.** Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med. 2007;146:326-39. [PMID: 17339618]
332. **Miller PD, Bilezikian JP, Diaz-Curiel M, Chen P, Marin F, Krege JH, et al.** Occurrence of hypercalciuria in patients with osteoporosis treated with teriparatide. J Clin Endocrinol Metab. 2007;92:3535-41. [PMID: 17609307] doi:10.1210/jc.2006-2439
333. **Krohn K, Kellier N, Masica D, Gilsenan A, Harding A, Andrews E.** Forteo voluntary patient registry: 4-year progress on a prospective osteosarcoma surveillance study [abstract]. Osteoporosis Int. 2014;25(1 Suppl. 1):S61.
334. **Krohn K, Kellier N, Masica D, Midkiff K, Harris D, Andrews E.** Post-marketing case series study of adult osteosarcoma and for-(S)TEO: study findings from the first 9 years [abstract]. Osteoporosis Int. 2014;25(1 Suppl 1):S61-2.
335. **Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E.** Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87:985-92. [PMID: 11889149] doi:10.1210/jcem.87.3.8325
336. **Johnston CC Jr, Bjarnason NH, Cohen FJ, Shah A, Lindsay R, Mitlak BH, et al.** Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women: three-year data from 2 double-blind, randomized, placebo-controlled trials. Arch Intern Med. 2000;160:3444-50. [PMID: 11112238]
337. **Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, et al.** Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med. 1997;337:1641-7. [PMID: 9385122] doi:10.1056/NEJM199712043372301
338. **Kung AW, Chao HT, Huang KE, Need AG, Taechakraichana N, Loh FH, et al.** Efficacy and safety of raloxifene 60 milligrams/day in postmenopausal Asian women. J Clin Endocrinol Metab. 2003;88:3130-6. [PMID: 12843154] doi:10.1210/jc.2002-021855
339. **Jolly EE, Bjarnason NH, Neven P, Plouffe L Jr, Johnston CC Jr, Watts SD, et al.** Prevention of osteoporosis and uterine effects in

postmenopausal women taking raloxifene for 5 years. Menopause. 2003;10:337-44. [PMID: 12851517] doi:10.1097/01.GME.0000058772.59606.2A

340. **Nickelsen T, Lufkin EG, Riggs BL, Cox DA, Crook TH.** Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in postmenopausal women. Psychoneuroendocrinology. 1999;24:115-28. [PMID: 10098223]

341. **Mosca L, Grady D, Barrett-Connor E, Collins P, Wenger N, Abramson BL, et al.** Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. Stroke. 2009;40:147-55. [PMID: 18948611] doi:10.1161/STROKEAHA.108.518621

342. **Miller PD, Chines AA, Christiansen C, Hoeck HC, Kendler DL, Lewiecki EM, et al.** Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res. 2008;23:525-35. [PMID: 18072873] doi:10.1359/jbmr.071206

343. **McClung MR, Siris E, Cummings S, Bolognese M, Ettinger M, Moffett A, et al.** Prevention of bone loss in postmenopausal women treated with lasofoxifene compared with raloxifene. Menopause. 2006;13:377-86. [PMID: 16735934] doi:10.1097/01.gme.0000188736.69617.4f

344. **Michalská D, Stepan JJ, Basson BR, Pavo I.** The effect of raloxifene after discontinuation of long-term alendronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2006 Ma; 91:870-7. [PMID: 16352692] doi:10.1210/jc.2004-2212

345. **Grady D, Ettinger B, Moscarelli E, Plouffe L Jr, Sarkar S, Ciaccia A, et al; Multiple Outcomes of Raloxifene Evaluation Investigators.** Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. Obstet Gynecol. 2004;104:837-44.

346. **Meunier PJ, Vignot E, Garnero P, Confavreux E, Paris E, Liu-Leage S, et al.** Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene Study Group. Osteoporos Int. 1999;10:330-6. [PMID: 10692984]

347. **Smith MR, Fallon MA, Lee H, Finkelstein JS.** Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. J Clin Endocrinol Metab. 2004;89:3841-6. [PMID: 15292315] doi:10.1210/jc.2003-032058

348. **Zheng S, Wu Y, Zhang Z, Yang X, Hui Y, Zhang Y, et al.** Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in postmenopausal women: a randomized clinical trial in Beijing. Chin Med J (Engl). 2003;116:1127-33. [PMID: 12935394]

349. **Ensrud K, Genazzani AR, Geiger MJ, McNabb M, Dowsett SA, Cox DA, et al.** Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. Am J Cardiol. 2006;97:520-7. [PMID: 16461049] doi:10.1016/j.amjcard.2005.09.083

350. **Liu JL, Zhu HM, Huang QR, Zhang ZL, Li HL, Qin YJ, et al.** Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in Chinese postmenopausal women with osteoporosis: a multi-center, randomized, placebo-controlled clinical trial. Chin Med J (Engl). 2004;117:1029-35. [PMID: 15265377]

351. **Takeuchi Y, Hamaya E, Taketsuna M, Sowa H.** Safety of 3-year raloxifene treatment in Japanese postmenopausal women aged 75 years or older with osteoporosis: a postmarketing surveillance study. Menopause. 2015;22:1134-7. [PMID: 25756692] doi:10.1097/GME.0000000000000441

352. **Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al; Writing Group for the Women's Health Initiative Investigators.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321-33. [PMID: 12117397]

353. **Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, Manson JE, Gass M, et al; WHI Investigators.** Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med. 2009;360:573-87. [PMID: 19196674] doi:10.1056/NEJMoa0807684

354. **Chlebowski RT, Anderson GL, Gass M, Lane DS, Aragaki AK, Kuller LH, et al; WHI Investigators.** Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010;304:1684-92. [PMID: 20959578] doi:10.1001/jama.2010.1500

355. **Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ.** Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. Ann Intern Med. 2016;165:856-866. [PMID: 27776363] doi:10.7326/M16-1165

356. **Matsumoto T, Miki T, Hagino H, Sugimoto T, Okamoto S, Hirota T, et al.** A new active vitamin D, ED-71, increases bone mass in osteoporotic patients under vitamin D supplementation: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2005;90:5031-6. [PMID: 15972580] doi:10.1210/jc.2004-2552

357. **Berry SD, Samelson EJ, Pencina MJ, McLean RR, Cupples LA, Broe KE, et al.** Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture. JAMA. 2013;310:1256-62. [PMID: 24065012] doi:10.1001/jama.2013.277817

358. **Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, et al.** Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med. 2002;112:281-9. [PMID: 11893367]

359. **Chapurlat RD, Palermo L, Ramsay P, Cummings SR.** Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. Osteoporos Int. 2005;16:842-8. [PMID: 15580479] doi:10.1007/s00198-004-1770-7

360. **Watts NB, Geusens P, Barton IP, Felsenberg D.** Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. J Bone Miner Res. 2005;20:2097-104. [PMID: 16294263] doi:10.1359/JBMR.050814

361. **Miller PD, Delmas PD, Huss H, Patel KM, Schimmer RC, Adami S, et al.** Increases in hip and spine bone mineral density are predictive for vertebral antifracture efficacy with ibandronate. Calcif Tissue Int. 2010;87:305-13. [PMID: 20737140] doi:10.1007/s00223-010-9403-y

362. **Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD.** Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res. 2002;17:1-10. [PMID: 11771654] doi:10.1359/jbmr.2002.17.1.1

363. **Chen P, Miller PD, Delmas PD, Misurski DA, Krege JH.** Change in lumbar spine BMD and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. J Bone Miner Res. 2006;21:1785-90. [PMID: 17002571] doi:10.1359/jbmr.060802

364. **Gourlay ML, Fine JP, Preisser JS, May RC, Li C, Lui LY, et al; Study of Osteoporotic Fractures Research Group.** Bone-density testing interval and transition to osteoporosis in older women. N Engl J Med. 2012;366:225-33. [PMID: 22256806] doi:10.1056/NEJMoa1107142

365. **Bell KJ, Hayen A, Macaskill P, Irwig L, Craig JC, Ensrud K, Bauer DC.** Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. BMJ. 2009;338:b2266. [PMID: 19549996] doi:10.1136/bmj.b2266

366. **Rabenda V, Bruyère O, Reginster JY.** Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression. Osteoporos Int. 2011;22:893-901. [PMID: 21060990] doi:10.1007/s00198-010-1469-x

367. **Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, et al.** Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. J Clin Densitom. 2004;7:255-61. [PMID: 15319494]

368. **Watts NB, Miller PD, Kohlmeier LA, Sebba A, Chen P, Wong M, et al.** Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment. J Bone Miner Res. 2009;24:1125-31. [PMID: 19113918] doi:10.1359/jbmr.081256

369. **Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, et al.** The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2012;27:243-54. [PMID: 22161728] doi:10.1002/jbmr.1494
370. **Mellström DD, Sörensen OH, Goemaere S, Roux C, Johnson TD, Chines AA.** Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int. 2004;75:462-8. [PMID: 15455188] doi:10.1007/s00223-004-0286-7
371. **Whitaker M, Guo J, Kehoe T, Benson G.** Bisphosphonates for osteoporosis–where do we go from here? N Engl J Med. 2012;366:2048-51. [PMID: 22571168] doi:10.1056/NEJMp1202619
372. **Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al.** Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ. 2008;336:262-6. [PMID: 18198394] doi:10.1136/bmj.39440.525752.BE
373. **Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al.** Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691. [PMID: 20671013] doi:10.1136/bmj.c3691
374. **Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR.** Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011;342:d2040. [PMID: 21505219] doi:10.1136/bmj.d2040
375. **Li K, Kaaks R, Linseisen J, Rohrmann S.** Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart. 2012;98:920-5. [PMID: 22626900] doi:10.1136/heartjnl-2011-301345
376. **Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y.** Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health–AARP diet and health study. JAMA Intern Med. 2013;173:639-46. [PMID: 23381719] doi:10.1001/jamainternmed.2013.3283
377. **Michaëlsson K, Melhus H, Warensjö Lemming E, Wolk A, Byberg L.** Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. 2013;346:f228. [PMID: 23403980] doi:10.1136/bmj.f228
378. **Siris ES, Simon JA, Barton IP, McClung MR, Grauer A.** Effects of risedronate on fracture risk in postmenopausal women with osteopenia. Osteoporos Int. 2008;19:681-6. [PMID: 17968610] doi:10.1007/s00198-007-0493-y
379. **World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield.** WHO Fracture Risk Assessment Tool. Accessed at www.shef.ac.uk/FRAX/ on 31 March 2015.
380. **U.S. Preventive Services Task Force.** Screening for osteoporosis: U.S. preventive services task force recommendation statement. Ann Intern Med. 2011;154:356-64. [PMID: 21242341] doi:10.7326/0003-4819-154-5-201103010-00307
381. **McCloskey E.** FRAX: identifying people at high risk of fracture. International Osteoporosis Foundation. 2009. Accessed at www.iofbonehealth.org/sites/default/files/PDFs/WOD%20Reports/FRAX_report_09.pdf on 23 March 2015.

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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), teri-

paratide, raloxifene, and menopausal estrogen therapy; the biologic agent denosumab; dietary and supplemental calcium and vitamin D; and physical activity.

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]

Web-Only References

382. **Crandall CJ, Newberry SJ, Diamant A, Lim YW, Gellad WF, Suttorp MJ, et al.** Treatment to Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report. AHRQ Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2012.

383. **Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV.** Effect of fluoroscopically guided caudal epidural steroid or local anesthetic injections in the treatment of lumbar disc herniation and radiculitis: a randomized, controlled, double blind trial with a two-year follow-up. Pain Physician. 2012;15:273-86.

384. **Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al.** The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.asp on 5 April 2017.

385. **Moore C, Holland J, Shaib F, Ceridan E, Schonard C, Marasa M.** Prevention of low back pain in sedentary healthy workers: a pilot study. Am J Med Sci. 2012;344:90-5. [PMID: 22173041] doi:10.1097/MAJ.0b013e3182364942

386. **Silverman SL, Chines AA, Kendler DL, Kung AW, Teglbjærg CS, Felsenberg D, et al; Bazedoxifene Study Group.** Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. Osteoporos Int. 2012;23:351-63. [PMID: 21779819] doi:10.1007/s00198-011-1691-1

387. **Palacios S, Silverman SL, de Villiers TJ, Levine AB, Goemaere S, Brown JP, et al; Bazedoxifene Study Group.** A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. Menopause. 2015;22:806-13. [PMID: 25668306] doi:10.1097/GME.0000000000000419

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 group. We have abstracted the data here for bazedoxifene, which was newly approved by the U.S. Food and Drug Administration.

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.