ACP Clinical Practice
American College of Physicians
GUIDELINES

Pharmacologic Treatment of Low Bone Density or Osteoporosis to Prevent Fractures: A Clinical Practice Guideline from the American College of Physicians

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Description: The American College of Physicians (ACP) developed this guideline to present the available evidence on various pharmacologic treatments to prevent fractures in men and women with low bone density or osteoporosis.

Methods: Published literature on this topic was identified by using MEDLINE (1966 to December 2006), the *ACP Journal Club* database, the Cochrane Central Register of Controlled Trials (no date limits), the Cochrane Database of Systematic Reviews (no date limits), Web sites of the United Kingdom National Institute of Health and Clinical Excellence (no date limits), and the United Kingdom Health Technology Assessment Program (January 1998 to December 2006). Searches were limited to English-language publications and human studies. Keywords for search included terms for osteoporosis, osteopenia, low bone density, and the drugs listed in the key questions. This guideline grades the evidence and recommendations according to the ACP's clinical practice guidelines grading system.

Recommendation 1: *ACP recommends that clinicians offer pharmacologic treatment to men and women who have known osteoporosis and to those who have experienced fragility fractures (Grade: strong recommendation; high-quality evidence).*

Recommendation 2: *ACP recommends that clinicians consider pharmacologic treatment for men and women who are at risk for developing osteoporosis (Grade: weak recommendation; moderate-quality evidence).*

Recommendation 3: *ACP recommends that clinicians choose among pharmacologic treatment options for osteoporosis in men and women on the basis of an assessment of risk and benefits in individual patients (Grade: strong recommendation; moderate-quality evidence).*

Recommendation 4: *ACP recommends further research to evaluate treatment of osteoporosis in men and women.*

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The National Institutes of Health's consensus conference (1) defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk for fracture. Bone strength reflects the integration of two main features: bone density and bone quality. . . . Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures), and mineralization." Although osteoporosis can affect any bone, the hip, spine, and wrist are most likely to be affected. Osteoporosis affects an estimated 44 million Americans or 55% of people 50 years of age or older. Another 34 million Americans are estimated to have low bone mass, meaning that they are at an increased risk for osteoporosis.

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Osteoporosis can be diagnosed by the occurrence of fragility fracture. In patients without fragility fracture, osteoporosis is often diagnosed by low bone density. Dual x-ray absorptiometry (DXA) is the current gold standard test for diagnosing osteoporosis in people without an osteoporotic fracture. Dual x-ray absorptiometry results are scored as standard deviations (SDs) from a young healthy norm (usually female) and reported as T-scores. For example, a T-score of −2 indicates a bone mineral density that is 2 SDs below the comparative norm. The international reference standard for the description of osteoporosis in postmenopausal women and in men age 50 years or older is a femoral neck bone mineral density of 2.5 SD or more below the young female adult mean (2). Low bone density, as measured by DXA, is an imperfect predictor of fracture risk, identifying fewer than half the people who go on to have an osteoporotic fracture. Screening guidelines for women are well established (3), and

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the American College of Physicians (ACP) recently published guidelines on screening for men (4).

This guideline presents the available evidence on various pharmacologic treatments to prevent fractures in men and women with low bone density or osteoporosis. Medications used to treat osteoporosis may affect different parts of the skeletal system differently, and efficacy for vertebral fractures does not necessarily imply efficacy for nonvertebral fractures. The target audience for this guideline is all clinicians and the target patient population is all adult men and women with low bone density or osteoporosis. These recommendations are based on the systematic evidence review by MacLean and colleagues (5) and the Agency for Healthcare Research and Quality–sponsored Southern California Evidence-Based Practice Center evidence report (6).

The drugs currently approved for prevention of osteoporosis include alendronate, ibandronate, risedronate, zoledronic acid, estrogen, and raloxifene. The drugs currently approved for treatment of osteoporosis include alendronate, ibandronate, risedronate, calcitonin, teriparatide, zoledronic acid (in postmenopausal women), and raloxifene. Testosterone, pamidronate, and etidronate are not approved by the U.S. Food and Drug Administration for the treatment or prevention of osteoporosis.

METHODS

The literature search done by MacLean and colleagues for the systematic review (5) included studies from MEDLINE (1966 to December 2006), the *ACP Journal Club* database, the Cochrane Central Register of Controlled Trials (no date limits), the Cochrane Database of Systematic Reviews (no date limits), Web sites of the United Kingdom National Institute of Health and Clinical Excellence (no date limits), and the United Kingdom Health Technology Assessment Program (January 1998 to December 2006). The reviewers limited their search to English-language publications and human studies. They derived evidence for comparative benefits of various treatments exclusively from randomized, controlled trials, whereas they included evidence from other types of studies for short- and long-term harms.

Two physicians independently abstracted data about study populations, interventions, follow-up, and outcome ascertainment by using a structured form. For each group within a randomized trial, a statistician extracted the sample size and number of persons reporting fractures. Two reviewers, under the supervision of the statistician, independently abstracted information about adverse events. The statistician or the principal investigator resolved disagreements.

This guideline is based on an evaluation of 76 randomized, controlled trials, 4 of which were identified in the updated search, and 24 meta-analyses that were included in the efficacy analyses. The analyses of adverse events included 491 articles, representing 417 randomized trials, 25 other controlled clinical trials, 11 open-label trials, 31 large observational studies, and 9 case reports of osteonecrosis among bisphosphonate users. MacLean and colleagues' background article (5) includes details about the methods used for the systematic evidence review.

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	I-recommendation	

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

The ACP rates the evidence and recommendations by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system with minor modifications (**Table 1**). In addition, the evidence reviewers used predefined criteria to assess the quality of systematic reviews and randomized trials, based on internal and external validity assessments detailed in the Quality of Reporting of Meta-Analyses (QUOROM) statement (7).

The objective of this guideline is to synthesize the evidence for the following questions:

1. What are the comparative benefits in fracture reduction among and also within the following treatments for low bone density: bisphosphonates, specifically alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid; calcitonin; estrogen for women; teriparatide; selective estrogen receptor modulators (SERMs), specifically raloxifene and tamoxifen; testosterone for men; vitamins and minerals, specifically vitamin D and calcium; and the combination of calcium plus vitamin D?

2. How does fracture reduction resulting from treatments vary among individuals with different risks for fracture as determined by bone mineral density (borderline, low, or severe), previous fractures (prevention vs. treatment), age, sex, glucocorticoid use, and other factors (such as community-dwelling vs. institutionalized or vitamin D–deficient vs. not)?

3. What are the short- and long-term harms (adverse effects) of these therapies, and do these vary by specific subpopulations?

COMPARATIVE BENEFITS OF DRUGS VERSUS PLACEBO IN FRACTURE REDUCTION

Evidence from 24 meta-analyses (8–30) and 35 additional randomized trials published after the meta-analyses

(31–65) described the effect of 9 of the 14 agents (alendronate, etidronate, risedronate, calcitonin, estrogen, teriparatide, raloxifene, calcium, and vitamin D) on fracture incidence. For 4 agents (ibandronate, pamidronate, zoledronic acid, and tamoxifen), the reviewers found no meta-analyses and instead gathered the evidence from 14 randomized trials (66–79). No studies were found that reported fracture rates for testosterone. Three randomized trials (35, 80, 81) and 1 meta-analysis (82) evaluated the combination of calcium plus vitamin D on fractures.

Bisphosphonates

Good-quality evidence showed that alendronate, etidronate, ibandronate, and risedronate prevent vertebral fractures. In addition, evidence from good-quality studies demonstrated that both alendronate and risedronate prevent nonvertebral and hip fractures. Two large randomized trials showed that zoledronic acid prevents vertebral and nonvertebral fractures in high-risk populations and reduces the risk for hip fracture (67, 74). Ibandronate has not been shown to reduce nonvertebral fractures (68). Of the 6 fairly small trials that looked at vertebral fractures, 1 demonstrated a statistically significant reduction in fractures with pamidronate relative to placebo (0.14 [95% CI, 0.03 to 0.72]) (73). However, after these data were pooled, the pooled risk estimate for fractures for pamidronate relative to placebo was not significant (0.52 [CI, 0.21 to 1.24]) (6).

Calcitonin

Fair-quality evidence shows that calcitonin reduces vertebral fractures (83, 84). Good-quality evidence indicates that calcitonin does not reduce nonvertebral fractures (13, 16).

Estrogen

Good-quality evidence shows that estrogen reduces the incidence of vertebral (29, 85), nonvertebral (86), and hip fractures (85).

Teriparatide

Good-quality evidence shows that teriparatide prevents vertebral fractures. The evidence related to teriparatide preventing nonvertebral fractures is mixed; 1 large randomized trial showed a reduction in nonvertebral fractures (34) but 2 small trials did not (87, 88).

SERMs

Good-quality evidence shows that raloxifene prevents vertebral fractures, but that tamoxifen has no effect on vertebral fractures (89–91). In addition, both raloxifene and tamoxifen had no effect on hip fractures (91). Tamoxifen is not approved by the U.S. Food and Drug Administration for the treatment or prevention of osteoporosis.

Testosterone

No studies reported fracture rates for testosterone.

Calcium and Vitamin D

In the studies evaluated by MacLean and colleagues (5), the evidence for the effect of calcium alone on reduction of fractures is complex. Most studies of pharmacologic agents for osteoporosis include calcium and vitamin D as part of the treatment regimen. Evidence from 1 meta-analysis (27) and several randomized trials (35, 48, 51, 92) showed no significant difference between calcium and placebo in preventing vertebral, nonvertebral, and hip fractures in postmenopausal women. However, nonadherence to therapy may influence this result, and 1 trial with a prespecified analysis of adherent patients found a reduction in fracture risk (48). A recent meta-analysis (82) concluded that the relative risk (RR) for fracture with calcium alone was 0.90 (CI, 0.80 to 1.00), but it did not include a modestly large trial with negative results (35).

MacLean and colleagues (5) included 5 systematic reviews that evaluated vitamin D. Four meta-analyses (8, 21, 24, 28) found that standard vitamin D (D_2, D_3, or 25-hydroxyvitamin [25(OH)]D) did not have any effect on risk for vertebral, nonvertebral, or hip fractures; a fifth (35) showed a statistically significant reduction in the pooled risk for nonvertebral and hip fractures for vitamin D_2 or D_3. In addition, MacLean and colleagues identified 3 meta-analyses (21, 23, 24) that showed that vitamin D analogues [1,25(OH)D and 1(OH)D] significantly reduced the risk for vertebral, nonvertebral, and hip fractures. A meta-analysis published after MacLean and colleagues' review concluded that vitamin D and calcium reduced fractures by 13% (RR, 0.87 [CI, 0.77 to 0.97]) (82).

In summary, for evaluating the comparative benefits of drugs versus placebo in fracture reduction, good-quality evidence shows that alendronate, etidronate, ibandronate, risedronate, calcitonin, teriparatide, and raloxifene prevent vertebral fractures. The reviewers also found good-quality evidence that alendronate and risedronate prevent nonvertebral and hip fractures. No clear evidence demonstrates the appropriate duration of treatment with bisphosphonates; however, bisphosphonate trials ranged from 3 months to 60 months. Good evidence shows that estrogen reduced the incidence of vertebral, nonvertebral, and hip fractures. The effect of calcium alone is less certain. Systematic reviews of the effectiveness of vitamin D and calcium have reached different conclusions, with the most recent systematic review (82) finding a modest reduction in fracture risk.

Comparative Benefits of Drugs within and among Classes in Fracture Reduction

Evidence from 9 randomized trials comparing different bisphosphonates (41, 93–100), 1 study comparing different SERMs (101), and 16 studies with head-to-head comparisons of agents from different classes (31, 32, 35, 37, 42, 50, 64, 98, 100, 102–108) evaluated intermediate outcomes, such as bone mineral density and changes in markers of bone turnover. These studies were too short to detect clinically important differences in fracture incidence.

The 2 head-to-head trials that compared fracture incidence outcomes (risedronate vs. etidronate [97] and raloxifene vs. alendronate [107]) were underpowered and showed no statistically significant differences.

In summary, evidence is insufficient to determine whether one bisphosphonate is superior to another, with the exception that ibandronate did not reduce nonvertebral fractures in a relatively large trial (68). Little evidence comparing drugs from different classes is available.

Benefits of Drugs in Different Risk Groups for Fracture Reduction

Low-Risk Populations

We defined "low risk" as a 10-year risk for osteoporotic fracture (vertebral, nonvertebral, or hip) of up to 2% and a lifetime risk of up to 21%. The reviewers gathered evidence from 4 meta-analyses (14, 15, 28, 107). Summary estimates for alendronate showed a statistically nonsignificant reduction in the risk for vertebral fracture (RR, 0.45 [CI, 0.06 to 3.15]) and nonvertebral fracture (RR, 0.79 [CI, 0.28 to 2.24]) (15). Estrogen did not reduce the risk for vertebral fracture (28) but reduced nonvertebral fractures (28, 109). However, raloxifene and vitamin D did reduce the risk for vertebral fractures (raloxifene RR, 0.53 [CI, 0.35 to 0.79]; vitamin D RR, 0.86 [CI, 0.72 to 1.02]) (28). Evidence from 2 randomized trials did not show any difference between raloxifene and tamoxifen for reducing fractures (63, 101).

Special Populations

Men

Studies showed that risedronate decreased the risk for hip fractures (RR, 0.25 [CI, 0.08 to 0.78]) (56), calcitonin decreased the risk for vertebral fractures (RR, 0.09 [CI, 0.01 to 0.96]) (61), and teriparatide decreased the risk for total fractures (RR, 0.16 [CI, 0.01 to 0.96]) and possibly the risk for vertebral fractures (odds ratio [OR], 0.44 [CI, 0.18 to 1.09]) (44). Evidence is insufficient to evaluate the effect of calcium alone in men (35).

Populations at Increased Risk for Falls

Populations studied included patients with stroke and hemiplegia, Alzheimer disease, a recent hip fracture, or Parkinson disease. Zoledronic acid reduced the risk for vertebral fractures (hazard ratio, 0.54 [CI, 0.32 to 0.92]) and nonvertebral fractures (hazard ratio, 0.73 [CI, 0.55 to 0.98]) in patients with a recent hip fracture (74). In patients with Alzheimer disease, risedronate reduced the risk for nonvertebral fracture (RR, 0.29 [CI, 0.15 to 0.57]) (53) and hip fracture (RR, 0.29 [CI, 0.13 to 0.66]) (58). Risedronate also reduced the risk for hip fracture in patients with stroke (RR, 0.22 [CI, 0.05 to 0.88]) and hemiparesis (RR, 0.25 [CI, 0.08 to 0.78]) (55, 56). In patients with Parkinson disease, alendronate (RR, 0.30 [CI, 0.12 to 0.78]) reduced the risk for hip fracture (57). Vitamin D also reduced the risk for hip fracture in patients with stroke and hemiparesis (RR, 0.12 [CI, 0.02 to 0.90]).

Populations with Renal Insufficiency

One trial (110) showed that alendronate reduced the risk for fractures to a similar degree in patients with and those without reduced renal function.

Populations with Long-Term Glucocorticoid Use

Evidence from 3 studies included in a systematic review (111) showed a possible reduction in vertebral fracture rate with bisphosphonate treatment (112–114). Six additional trials have been published since this systematic review. Three of these randomized trials (115–117) showed that bisphosphonates reduced the fracture rate. Results from 2 studies also showed that risedronate treatment led to a statistically significant reduction in the absolute risk (11%) and RR (70%) of incident radiographic vertebral fractures after 1 year (117) and in vertebral fractures (116). In another trial (115), alendronate was associated with a reduction in the risk for incident radiographic vertebral fractures. However, 3 additional trials showed no significant effect on fracture risk for etidronate (32, 53), from calcium (32), between calcium and a combination of etidronate and calcium (32), or between calcium and pamidronate (103).

To summarize the overall fracture reduction benefits of drug treatments in special populations in different risk groups, a SERM (raloxifene) and vitamin D both reduced the risk for vertebral fracture in low-risk patients. Far fewer men than women have been included in these trials, resulting in less evidence about the effectiveness of treatment in men. In men, risedronate decreased hip fractures and calcitonin decreased vertebral fractures. Teriparatide decreased total fractures and possibly vertebral fractures. In patients with a previous hip fracture, zoledronic acid reduced the risk for vertebral and nonvertebral fractures. Risedronate reduced the hip and nonvertebral fracture risk among patients with Alzheimer disease. Bisphosphonates (risedronate and alendronate) also reduced the clinical and radiographic fracture rate in patients receiving glucocorticoids.

Adverse Effects of Drugs

Bisphosphonates

The most common adverse effects of bisphosphonates are gastrointestinal. Trials reported esophageal ulcerations from all bisphosphonates except zoledronic acid. One trial of etidronate versus placebo showed a statistically significant increase in esophageal ulceration (OR, 1.33 [CI, 1.05 to 1.68]) (118). Mild upper gastrointestinal events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn) were more common with etidronate in a pooled analysis (OR, 1.33 [CI, 1.21 to 1.46]) (32, 42, 53, 54, 64, 112, 118–128) and with pamidronate (OR, 3.14 [CI, 1.93

to 5.21]) (75, 79, 129–133). Pooled analysis showed no difference in occurrence of mild upper gastrointestinal events between alendronate, ibandronate, risedronate, or zoledronic acid and placebo. However, pooled analysis of head-to-head trials showed a higher risk for mild upper gastrointestinal events with alendronate than with etidronate (OR, 5.89 [CI, 1.61 to 32.7]), calcitonin (OR, 3.42 [CI, 1.79 to 7.00]), or estrogen (OR, 1.57 [CI, 1.00 to 2.46]). The pooled estimate from 3 studies showed that etidronate users were at increased risk for perforations, ulcerations, and gastrointestinal bleeding events (OR, 1.32 [CI, 1.04 to 1.67]) (59, 118, 134), whereas the pooled estimate from 2 studies showed that ibandronate had a lower risk for serious gastrointestinal adverse events (OR, 0.33 [CI, 0.14 to 0.74]) (68, 135). Case reports and case series have documented increased osteonecrosis of the jaw in patients receiving bisphosphonates, but the most cases of osteonecrosis have occurred in patients with cancer who received high doses of intravenous bisphosphonates (136). However, we could not calculate the risk for this event from the available studies. Some studies showed a link between atrial fibrillation and either zoledronic acid or alendronate (5, 137).

Calcitonin

Evidence from randomized trials showed no clinically important serious adverse events associated with the use of calcitonin.

Estrogen

Estrogen was associated with an increased risk for thromboembolic events versus placebo in pooled results from 4 studies (OR, 1.36 [CI, 1.01 to 1.86]) (37, 85, 138, 139). In addition, pooled results for estrogen–progestin also showed a higher risk for thromboembolic events versus placebo (OR, 2.27 [CI, 1.72 to 3.02]) (52, 140, 141). Pooled odds of stroke were increased with estrogen (OR, 1.28 [CI, 1.05 to 1.57]) (83, 138, 139) and combined estrogen–progestin (OR, 1.28 [CI, 1.05 to 1.57]) relative to placebo (52, 140). Women who received estrogen had a lower pooled risk for breast cancer than those who received placebo (OR, 0.79 [CI, 0.66 to 0.93]) (83, 138, 142–144). However, pooled analysis showed that women who received an estrogen–progestin combination had an increased risk for breast cancer (OR, 1.28 [CI, 1.03 to 1.60]) (52, 131, 140). One study showed a lower risk for colon cancer among women who received an estrogen–progestin combination (OR, 0.64 [CI, 0.43 to 0.95]) (85).

Teriparatide

Evidence from randomized trials showed no clinically important serious adverse events associated with the use of teriparatide.

SERMs

Raloxifene increased the pooled risk for pulmonary embolism (OR, 6.26 [CI, 1.55 to 54.80]) (145, 146). In addition, pooled results showed that raloxifene increased the risk for thromboembolic events (OR, 2.08 [CI, 1.47 to 3.02) (145, 147–152) and mild cardiac events, including chest pain, palpitations, tachycardia, and vasodilatation (OR, 1.53 [CI, 1.01 to 2.35]) (147, 149, 152–155).

Testosterone

No trials of testosterone reported adverse events; however, testosterone has well-known side effects.

Calcium and Vitamin D

Evidence from randomized trials showed no clinically important serious adverse events associated with the use of calcium and vitamin D.

To summarize the adverse effects of drugs, estrogen increased the risk for stroke and thromboembolic events; estrogen–progestin increased the risk for stroke and breast cancer; and raloxifene increased the risk for pulmonary embolism, thromboembolic events, and mild cardiac events. Etidronate was associated with increased risk for esophageal ulcerations and, in addition to mild upper gastrointestinal events, increased the risk for perforations, ulcerations, and bleeding events. Alendronate was associated with a higher risk for mild upper gastrointestinal events than were etidronate, calcitonin, and estrogen.

Summary

Good evidence shows that bisphosphonates (alendronate, etidronate, and risedronate) reduce the risk for vertebral, nonvertebral, and hip fractures. Ibandronate reduces vertebral fractures. No clear evidence indicates the appropriate duration of treatment with bisphosphonates; however, bisphosphonate trials ranged from 3 months to 60 months. Estrogen reduces the risk for vertebral, nonvertebral, and hip fractures. Whereas evidence for fracture risk reduction from calcium alone is less clear, it is stronger for vitamin D and calcium in combination (82). Evidence showed a statistically significant reduction in the risk for vertebral fractures from vitamin D analogues [1,25(OH)D and 1(OH)D] but mixed results for nonvertebral and hip fractures.

Oral bisphosphonates increase the risk for such gastrointestinal adverse events as acid reflux. However, pooled analyses showed no differences in occurrence of mild upper gastrointestinal events among alendronate, ibandronate, risedronate, or zoledronic acid versus placebo; however, pooled analyses of 18 trials of etidronate versus placebo indicated an increased risk for mild gastrointestinal events. The evidence linking zoledronic acid infusion with atrial fibrillation is contradictory. Raloxifene increased the pooled risk for pulmonary embolism and thromboembolic events. Estrogen was linked to an increased risk for cerebrovascular and thromboembolic events.

Recommendations

Recommendation 1: ACP recommends that clinicians offer pharmacologic treatment to men and women who have known

osteoporosis and to those who have experienced fragility fractures (Grade: strong recommendation; high-quality evidence).

Good evidence supports the treatment of patients who have osteoporosis to prevent further loss of bone and to reduce the risk for initial or subsequent fracture. Randomized, controlled trials offer good evidence that, compared with placebo, alendronate, ibandronate, risedronate, calcitonin, teriparatide, and raloxifene prevent vertebral fractures. Evidence is also good that teriparatide prevents nonvertebral fractures compared with placebo and that risedronate and alendronate prevent both nonvertebral and hip fractures compared with placebo. Estrogen has been shown to be associated with reduced vertebral, nonvertebral, and hip fractures. The evidence on use of calcium with or without vitamin D is mixed, and the effectiveness is modest. Because most trials of other pharmacologic therapy included their use, we recommend adding calcium and vitamin D to osteoporosis treatment regimens. Evidence is insufficient to determine the appropriate duration of therapy.

Recommendation 2: ACP recommends that clinicians consider pharmacologic treatment for men and women who are at risk for developing osteoporosis (Grade: weak recommendation; moderate-quality evidence).

Evidence supports the treatment of selected patients who are at risk for osteoporosis but who do not have a T-score on DXA less than −2.5. Evidence supporting preventive treatment is stronger for patients who are at moderate risk for osteoporosis, which includes patients who have a T-score from −1.5 to −2.5, are receiving glucocorticoids, or are older than 62 years of age.

Factors that increase the risk for osteoporosis in men include age (>70 years), low body weight (body mass index <20 to 25 kg/m^2), weight loss (>10% [compared with the usual young or adult weight or weight loss in recent years]), physical inactivity (no physical activities performed regularly, such as walking, climbing stairs, carrying weights, housework, or gardening), corticosteroid use, and androgen deprivation therapy (4). Risk factors for women include lower body weight, the single best predictor of low bone mineral density; smoking; weight loss; family history; decreased physical activity; alcohol or caffeine use; and low calcium and vitamin D intake (3). In certain circumstances, a single risk factor (for example, androgen deprivation therapy in men) is enough for clinicians to consider pharmacologic treatment.

Research groups are developing calculators, such as the World Health Organization's Fracture Risk Assessment Tool (available at www.shef.ac.uk/FRAX/), to predict the risk for osteoporotic fracture. Such tools will help guide both clinician and patient decisions.

Recommendation 3: ACP recommends that clinicians choose among pharmacologic treatment options for osteoporosis in men and women on the basis of an assessment of the risk and benefits to individual patients (Grade: strong recommendation; moderate-quality evidence).

We recommend that the choice of therapy for patients who are candidates for pharmacologic treatment be guided by judgment of the risks, benefits, and adverse effects of drug options for each individual patient. **Table 2** summarizes the benefits and harms of pharmacologic agents for fracture risk. Because good-quality evidence shows that bisphosphonates reduce the risk for vertebral, nonvertebral, and hip fractures, they are reasonable options to consider as first-line therapy, particularly for patients who have a high risk for hip fracture. Evidence from head-to-head trials is insufficient to demonstrate the superiority of one bisphosphonate over another. Alendronate and risedronate have been studied more than other bisphosphonates (**Table 2**). Ibandronate has not been shown to reduce nonvertebral or hip fractures, which may be an important consideration for some patients. In a recent trial, zoledronic acid administered to patients with a recent hip fracture reduced subsequent fracture and improved survival (74). Of the other agents available for treatment of osteoporosis, estrogen has efficacy for vertebral, nonvertebral, and hip fractures but is associated with other serious risks; calcitonin has not been demonstrated to reduce nonvertebral and hip fractures; and calcium and vitamin D are part of the treatment regimen in most studies of pharmacologic agents for osteoporosis.

Gastrointestinal events are the most common adverse effects associated with bisphosphonate therapy. No evidence was found that bisphosphonates, calcium, vitamin D, calcitonin, or teriparatide differ regarding risk for serious cardiac events. Etidronate is associated with an increased risk for esophageal ulcers, bleeding events, and mild upper gastrointestinal events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn). Raloxifene is associated with a higher risk for pulmonary embolism, thromboembolic events, and mild cardiac events (including chest pain, palpitations, tachycardia, and vasodilatation). Estrogen is associated with a greater risk for stroke, and the estrogen–progestin combination is associated with a greater probability of stroke and higher odds of breast cancer. In trials, perforations, ulcerations, and bleeding events occurred with all of the bisphosphonates except zoledronic acid.

Recommendation 4: ACP recommends further research to evaluate treatment of osteoporosis in men and women.

Current evidence is mostly concentrated on postmenopausal women; more research on other patient populations, including men, is needed. Comparative effectiveness data on preventing fractures from head-to-head

Table 2. **Summary of Evidence about Drugs and Fracture Risk**

Agent	Effect on Risk and Level of Evidence			Adverse Effects	FDA Approval
	Vertebral Fracture	Nonvertebral Fracture	Hip Fracture		
Bisphosphonates					
Alendronate	↓; strong evidence	↓; strong evidence	↓; strong evidence	Mild upper GI events, esophageal ulcerations, perforations, and bleeding events	Prevention or treatment
Etidronate	↓; strong evidence	↔; fair evidence	↔; strong evidence	Mild upper GI events, esophageal ulcerations, perforations, and bleeding events	Not FDA-approved for prevention or treatment
Ibandronate	↓; strong evidence	↔; strong evidence	Not studied	Esophageal ulcerations, perforations, and bleeding events	Prevention or treatment
Pamidronate	↔; weak evidence	↔; weak evidence	↔; weak evidence	Mild upper GI events, esophageal ulcerations, perforations, and bleeding events	Not FDA-approved for prevention or treatment
Risedronate	↓; strong evidence	↓; strong evidence	↓; strong evidence	Esophageal ulcerations, perforations, and bleeding events	Prevention or treatment
Zoledronic acid	↓; strong evidence	↓; strong evidence	↓; strong evidence	Muscular and joint pain	Prevention
Calcitonin	↓; fair evidence	↔; strong evidence	Not studied	No clinically significant adverse effects	Treatment
Estrogen	↓; strong evidence	↓; strong evidence	↓; strong evidence	Thromboembolic events; cerebrovascular accident, stroke, and breast cancer (when combined with progestin); gynecologic problems (endometrial bleeding); breast abnormalities (pain, tenderness, and fibrocytosis)	Prevention
Teriparatide	↓; strong evidence	↓; fair evidence	↔; weak evidence	No clinically significant adverse effects	Treatment
SERMs					
Raloxifene	↓; strong evidence	↔; strong evidence	↔; strong evidence	Pulmonary embolism, thromboembolic events	Prevention or treatment
Tamoxifen	↔; strong evidence	Not studied	↔; strong evidence	Pulmonary embolism	Not FDA-approved for prevention or treatment
Testosterone	Not studied	Not studied	Not studied	No clinically significant adverse effects	Not FDA-approved for prevention or treatment
Calcium and vitamin D	Modest effect*; strong evidence	Modest effect*; strong evidence	Modest effect*; strong evidence	No clinically significant adverse effects	Over the counter

↓ = decreased; ↔ = no effect; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; SERM = selective estrogen receptor modulator.
* Pooled estimate across fracture sites.

studies with sufficient power to detect differences would be helpful. The association between bisphosphonates and osteonecrosis of the jaw also needs to be studied. Finally, further research is needed on prevention strategies in both men and women and on the appropriate duration of treatment for osteoporosis.

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

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