



# Effective Health Care

## Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis

### Executive Summary

#### Background

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The clinical complications of osteoporosis include fractures, disability, and chronic pain. Approximately 44 million people in the United States are affected by osteoporosis or low bone density. It is especially common in postmenopausal women.

This report summarizes the available evidence comparing the efficacy and safety of agents used to prevent or treat low bone density, including osteoporosis. The following questions are addressed in this report:

**Key Question 1.** What are the comparative benefits in fracture reduction among and also within the following treatments for low bone density:

- Bisphosphonate medications, specifically alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid.
- Calcitonin.
- Calcium.
- Estrogen for women.

#### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm)



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- Parathyroid hormone (PTH).
- Selective estrogen receptor modulators (SERMs), specifically raloxifene and tamoxifen.
- Testosterone for men.
- Vitamin D.
- Combinations of above.
- Exercise in comparison to above agents.

**Key Question 2.** How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), prior fractures (prevention vs. treatment), age, gender, glucocorticoid use, and other factors (e.g., community dwelling vs. institutionalized, vitamin D deficient vs. not)?

**Key Question 3.** What are the adherence and persistence to medications for the treatment and prevention of osteoporosis, the factors that affect adherence and persistence, and the effects of adherence and persistence on the risk of fractures?

**Key Question 4.** What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?

## Conclusions

### Key Question 1

- There is good evidence from randomized controlled trials (RCTs) that alendronate, etidronate, ibandronate, risedronate, calcitonin, 1-34 PTH, and raloxifene prevent vertebral fractures compared with placebo.
- There is good evidence from RCTs that risedronate and alendronate prevent both nonvertebral and hip fractures compared with placebo.
- There is good evidence that zoledronic acid prevents vertebral and nonvertebral fractures, and fair evidence (see addendum) that it prevents hip fractures.
- There is evidence from one RCT that 1-34 PTH prevents nonvertebral fractures compared with placebo.
- There is good evidence that estrogen is associated with a reduced incidence of vertebral, nonvertebral, and hip fractures.

- There are no data from RCTs on the effect of testosterone on the prevention of fractures.
- There is evidence from a meta-analysis and several large RCTs that there is no difference between calcium alone and placebo in preventing vertebral, nonvertebral, hip, and wrist fractures in postmenopausal women.
- According to a large body of literature, vitamin D had varying effects on fracture prevention, depending on dose, analogs, and population. One meta-analysis found that 700 to 800 I.U. daily was necessary to reduce hip and nonvertebral fractures.
- Based on limited data from head-to-head trials, superiority for the prevention of fractures has not been demonstrated for any agent within the bisphosphonate class.
- Based on limited data from head-to-head trials, superiority for the prevention of vertebral fractures has not been demonstrated for bisphosphonates in comparison with calcitonin, calcium, or raloxifene. However, these studies were not designed or powered to detect fractures.
- Based on six head-to-head RCTs, there was no difference in fracture incidence between bisphosphonates and estrogen. However, none of the trials were powered to detect differences in fracture rates.
- There are no data from RCTs on the effect on fracture prevention of exercise relative to the effect of agents used to treat or prevent osteoporosis.

### Key Question 2

- Alendronate, etidronate, ibandronate, risedronate, teriparatide, and raloxifene reduce the risk of fractures among high-risk groups, including postmenopausal women with osteoporosis.
- Calcitonin has been demonstrated to reduce the risk of fracture among postmenopausal women.
- There are insufficient data to determine whether etidronate or ibandronate prevents fractures among groups at intermediate or low risk for osteoporosis, including postmenopausal women without osteoporosis or men.
- There are insufficient data to determine whether alendronate prevents fractures among groups at low risk for osteoporosis, including postmenopausal women without osteoporosis and men.

- Raloxifene prevents fractures in postmenopausal women at low risk for fracture.
- The effect of estrogen on fracture prevention for women at low risk is uncertain.
- Calcitonin, risedronate, and teriparatide reduce the risk of fracture among men.
- Among subjects treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate.
- There is good evidence that tamoxifen does not prevent fractures among women at risk for breast cancer.
- Reduction in fracture risk for subjects treated with alendronate, risedronate, or vitamin D has been demonstrated in populations at increased risk for fracture due to conditions that increase the risk of falling, including stroke with hemiplegia, Alzheimer's disease, and Parkinson's disease.
- There are limited and inconclusive data on the effect of agents for the prevention and treatment of osteoporosis on transplant recipients and patients treated with chronic corticosteroids.
- Based on evidence from observational studies, factors that affect adherence and persistence with medications include side effects of medications, absence of symptoms related to the underlying disease, comorbid conditions, ethnicity, socioeconomic status, and dosing regimens.
- In four observational studies comparing weekly and daily bisphosphonates, weekly users had higher persistence and adherence rates.
- There is evidence from one RCT that postmenopausal women who are nonadherent to treatment with calcium have a higher risk of fracture than women who are adherent to therapy.
- There is evidence from RCTs and observational studies that postmenopausal women who are nonadherent to treatment with alendronate, risedronate, HRT, calcium, or calcitonin have a higher risk of fracture than women who are adherent to therapy.
- There is evidence from one observational study that postmenopausal women with osteoporosis who are nonpersistent with alendronate and risedronate therapy have a higher risk of fracture than women persistent with these medications.

### Key Question 3

- Only 10 fracture trials reported rates of adherence to therapy. Five trials of calcium reported low rates of adherence. In two studies of daily oral bisphosphonates, more than 80 percent of patients took at least 70 percent of the drug. The other three trials reported high rates of adherence with risedronate therapy.
- There is evidence from 10 observational studies that adherence to therapy with alendronate, etidronate, risedronate, calcitonin, hormone replacement therapy (HRT), raloxifene, calcium, and vitamin D is poor among many postmenopausal women with osteoporosis.
- There is evidence from one observational study that adherence to therapy with alendronate and risedronate is poor in many chronic glucocorticoid users.
- There is evidence from 12 observational studies that persistence with therapy with alendronate, etidronate, risedronate, calcitonin, HRT, raloxifene, calcium, and vitamin D is poor in many men and postmenopausal women with osteoporosis.

### Key Question 4

- Across a large body of randomized controlled trials, there were no differences in the rates of serious cardiac events among bisphosphonates, calcium, vitamin D, calcitonin, PTH, and placebo.
- A significant increase in the risk of atrial fibrillation for zoledronic acid relative to placebo has been reported in one large RCT but not in another. (See addendum.) A trend toward increased risk for alendronate relative to placebo has been reported in a single large RCT.
- Relative to placebo, raloxifene had increased pooled risk for pulmonary embolism (PE), thromboembolic events, and mild cardiac events (including chest pain, palpitations, tachycardia, and vasodilation).
- Relative to placebo, the risk of PE for tamoxifen was elevated in one trial; the risk of thromboembolic events did not differ in this trial.
- In the three placebo-controlled trials of estrogen that reported cerebrovascular accident, estrogen participants had higher odds than did participants who took a placebo. In the two trials that

compared an estrogen-progestin combination with placebo, the combination participants had greater odds of stroke than did placebo patients. When four estrogen studies reporting thromboembolic events were pooled, estrogen participants had greater odds of reporting them than did placebo participants. Similar results were found when three studies comparing an estrogen-progestin combination with placebo were pooled.

- Esophageal ulcerations were reported in trials of all the bisphosphonates except zoledronic acid. The only significant difference from placebo was found in one trial in which etidronate participants had higher odds of esophageal ulcers.
- Perforations, ulcerations, and bleeds (PUBs) were reported in trials of all the bisphosphonates except zoledronic acid. Etidronate participants had higher odds of PUBs than did placebo participants in three pooled studies. In two pooled trials of oral daily ibandronate, treated participants had lower odds of PUBs than did placebo participants. Differences between other bisphosphonates and placebo were not statistically significant in pooled analyses.
- We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as “mild upper gastrointestinal (GI) events.” Pooled analyses of 18 trials of etidronate showed greater odds for treated participants than for placebo participants. Seven pooled trials of pamidronate also showed greater odds for the drug than for placebo. Our pooled analyses found no difference between alendronate, ibandronate, risedronate, or zoledronic acid and placebo regarding mild upper GI events. In contrast, alendronate participants had higher odds of mild upper GI events than did etidronate participants in three pooled head-to-head trials. Alendronate participants also had higher odds of mild upper GI events in four head-to-head trials vs. calcitonin and four head-to-head trials vs. estrogen. Etidronate participants had higher odds of mild upper GI events in three head-to-head trials vs. estrogen.
- In five pooled trials of estrogen vs. placebo, estrogen participants had lower odds of breast cancer. Conversely, in three pooled studies of estrogen-progestin combination vs. placebo, treatment participants had higher odds of breast cancer. One estrogen-progestin study showed that

treated participants had lower odds of colon cancer than did placebo participants.

- In three pooled studies of tamoxifen vs. placebo, tamoxifen participants had lower odds of breast cancer. Differences between raloxifene and placebo were not significant.
- In a pooled analysis of seven trials, estrogen participants had more gynecological problems (such as uterine bleeding) than placebo participants. The same was true for users of estrogen-progestin combination in three pooled trials.
- In three pooled trials, tamoxifen participants had greater odds of gynecological problems than did placebo patients.
- Osteosarcoma was reported in only one study, a head-to-head trial of raloxifene vs. tamoxifen; differences between groups were not significant.
- There are no data from osteoporosis trials that describe an association between bisphosphonates or any other agents and the development of osteonecrosis. In case reports and case series articles, we found 41 cases of osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates. Cases involved pamidronate, zoledronic acid, and alendronate.

## Remaining Issues

We did not identify any studies that demonstrated the superiority of any drug over another for the prevention of fractures. However, none of the head-to-head comparisons between agents had large enough sample sizes to detect differences between agents. Thus, more large head-to-head studies are needed both within and between classes.

There are limited data on whether these treatments reduce the risk of fracture in lower risk populations, such as women with mildly reduced bone density and men. Demonstration of fracture risk reduction could lead to broader use of the agents in these populations and reduced fracture rates. Demonstration that fracture risk is not reduced in these populations could lead to the discontinuation of their use in these populations, with a concomitant reduction in adverse events and unnecessary health care spending.

We did not find any studies that assessed the effect of testosterone in men on the development of fractures.

The impact of testosterone on fracture reduction could be clarified by tracking fractures in large placebo-enrolled trials.

Cancer patients taking intravenous bisphosphonates should be carefully monitored for osteonecrosis. Physicians are encouraged to report cases through the scientific literature.

## Addendum

The search for studies relevant to this report was updated in the preparation of a manuscript summarizing the findings of this report ([www.acponline.org](http://www.acponline.org)). The search was updated for the manuscript, but not this full report, by searching MEDLINE® (January 1, 2007, to November 10, 2007) for large clinical trials that reported fracture outcomes for each of the agents described in this report. In that search 263 titles were identified and among those, 4 were relevant to this analysis.<sup>1-4</sup> The main findings from those studies are as follows.

*Lyons et al.*<sup>1</sup>—This 3-year randomized, double-blind, placebo-controlled study evaluated the effect of oral supplementation with vitamin D on fractures among 3,440 older adults in residential care facilities. There was no significant difference in fracture incidence between vitamin D and control groups: hazards ratio, 0.95; 95-percent confidence interval (CI), 0.79, 1.15. These findings are consistent with the data summarized in this report.

*Recker et al.*<sup>2</sup>—This 5-year randomized, double-blind study was designed to evaluate the relative effects of raloxifene and alendronate on fracture risk among postmenopausal women. The prespecified analyses required 3,000 subjects, but investigators were able to

recruit only 1,835. This study found no difference in the incidence of hip, wrist, or total vertebral fractures, but it was not powered to do so. However, a significant difference in moderate to severe vertebral fractures (3/713 for alendronate, 0/699 for raloxifene;  $p=0.04$ ) was found in a prespecified analysis. No other head-to-head studies that compared raloxifene and alendronate were identified for this report. However, the addition of this single study, which did not have sufficient sample size to perform prespecified analyses, does not change the conclusion of this report that there are insufficient data to draw conclusions about the relative efficacy of agents used to treat or prevent osteoporotic fractures.

*Lyles et al.*<sup>3</sup>—This 5-year randomized, double-blind, placebo-controlled study evaluated the effect of once-yearly infusions with zoledronic acid on fractures among 1,065 adults who had undergone repair of a hip fracture within 90 days of enrollment. The risks of vertebral (hazards ratio 0.54; 95-percent CI, 0.32, 0.92) and nonvertebral fractures were significantly reduced (hazards ratio 0.73; 95-percent CI, 0.55, 0.98). Risk of an additional hip fracture was reduced, though not significantly, for zoledronic acid relative to placebo in one study (hazards ratio 0.70; 95-percent CI, 0.41-1.19). These findings are consistent with the data summarized in this report.

This study also provided data on the effect of zoledronic acid on atrial fibrillation. The incidence of serious atrial fibrillation was 1.3 percent for placebo vs. 1.1 percent for zoledronic acid ( $p = 0.84$ ). This is in contrast to the findings of one placebo-controlled trial described in this report, which reported an increased risk of serious atrial fibrillation for zoledronic acid—0.5 percent for placebo vs. 1.3 percent for zoledronic acid (absolute risk, 144/3,889 vs. 93/3,876;  $p<0.001$ ).<sup>5</sup> Another placebo-controlled trial described in this report suggested a possible increased risk of atrial fibrillation for alendronate (absolute risk, 128/3,236 vs. 102/3,223; odds ratio = 1.26; 95-percent CI, 0.96, 1.66).<sup>6</sup>

<sup>1</sup>Lyons RA, Johansen A, Brophy S, 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.

<sup>2</sup>Recker RR, Kendler D, Recknor CP, et al. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone* 2007 Apr;40(4):843-51. Epub 2006 Dec 19.

<sup>3</sup>Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357:1799-809.

<sup>4</sup>Jamal SA, Bauer DC, Ensrud KE, 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.

<sup>5</sup>Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.

<sup>6</sup>Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. *N Engl J Med* 2007;356:1895-6.

*Jamal et al.*<sup>4</sup>—This retrospective analysis of the Fracture Intervention Trial (FIT) compared the efficacy of alendronate on fracture prevention for patients with renal insufficiency relative to those without. Treatment with alendronate reduced the risk of clinical fractures to a similar degree in those with reduced renal function (relative risk, 0.78; 95-percent CI, 0.51, 1.21) and those without reduced renal function (relative risk, 0.80; 95-percent CI, 0.70, 0.93; p for interaction = 0.89). Treatment with alendronate reduced the risk of spine fractures to a similar degree in those with reduced renal function (relative risk, 0.72; 95-percent CI, 0.31, 1.70) and those without reduced renal function (relative risk, 0.50; 95-percent CI, 0.32, 0.76; p for interaction = 0.44). No other studies included in this report describe a direct comparison of the effects of agents used to treat or prevent osteoporosis between subjects with or without renal insufficiency.

## Full Report

This executive summary is part of the following document: MacLean C, Alexander A, Carter J, Chen S, Desai SB, Grossman J, Maglione M, McMahon M, McNamara M, Mojica W, Newberry S, Ranganath V, Suttrop M, Timmer M, Tringale C, Valentine D, Zhou A. Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density

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