Comparative Effectiveness Review
Number 12

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

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Comparative Effectiveness Review
Number 12

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

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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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.
- 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 to executive summary) 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.

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.

- 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 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 to executive summary.) 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 probems 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). 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.[1,2,3,4] The main findings from those studies are as follows.

Lyons et al.[1]—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.[2]—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.[3]—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 =

[1] 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.
[2] 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.
[3] 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.
[4] 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.

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).[5] 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).[6]

Jamal et al.[4]—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.

[5] 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.
[6] Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. N Engl J Med 2007;356:1895-6.

Introduction

Background

Osteoporosis (OP) 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.[1] Approximately 44 million people in the United States are affected by OP and low bone mass.[2] The clinical complications include fractures, disability, and chronic pain. It is estimated that 54% of women age 50 and older will sustain an osteoporotic fracture during their lifetime.[3] Further, approximately 4% of patients older than 50 who experience a hip fracture will die while in the hospital, and 24% will die within a year after experiencing the hip fracture.[4]

The economic burden of OP is large and growing. Most estimates are based on the cost of fracture alone: A 1995 estimate of costs due to osteoporotic fracture in the United States produced a figure of $13.8 billion.[5] A 2003 review estimated the total costs in the United States at $17 billion.[6] Although the bulk of these costs were incurred by individuals older than 65 who are retired, direct costs and work-loss are significant among employed postmenopausal women.[7] The increasing prevalence and cost of OP has heightened interest in the efficacy and safety of the many agents currently available to treat the loss of bone mineral associated with osteoporosis.

Definition of Osteoporosis

The clinical definition of osteoporosis is based either on clinical evidence of fracture or on densitometric measurement of bone mineral density (expressed as grams [gms] per centimeter $[cm]^2$). The National Osteoporosis Foundation (NOF) defines osteoporosis as a disease characterized by increased bone fragility and risk for fracture; of special concern are fractures of the hip and spine.[8] The World Health Organization (WHO) defines osteoporotic bone as bone that is more than 2.5 standard deviations lower in BMD than that of the average 25-year-old adult (called the young-adult mean).[a9] Thus, the number of standard deviations below normal, also known as the T-score (e.g., a T-score of -1 indicates a BMD that is 1 SD below the young-adult mean) can be used to define osteoporosis. Osteopenia, considered a precursor to osteoporosis, is defined as a T-score between -1 and -2.5. (WHO). Severe osteoporosis can be defined as a BMD of -2.5 or below that is accompanied by at least one fragility fracture (NOF).

Osteoporosis can be further categorized based on its etiology. Primary, or involutional, osteoporosis, the most common form, is applied to any diagnosis in which a disease or disorder known to result in osteoporosis is not present. Primary osteoporosis can be further categorized as juvenile, postmenopausal, age-related, and idiopathic (diagnosed in a young adult with no known contributing disorder) osteoporosis. Secondary osteoporosis is diagnosed when the cause of the

[a] Because the majority of the population used to derive this average consisted of white females and because it is known that bone density differs between men and women (a difference that increases with age past 50) as well as among whites, blacks, and people of Asian origin, some concern exists regarding its application to men and to nonwhites.

bone loss can be attributed to another disease or use of particular types of medication, as described below.

Risk Factors for Low BMD, Osteoporosis, and Fractures

Osteoporosis is a major cause of morbidity and mortality in older persons. The difficulty and cost of treating osteoporosis necessitate developing a method to identify those who are most at risk and therefore candidates for preventive interventions. However, whereas low BMD is associated with an increased risk for fracture, it is not a perfect predictor. Further, clinical risk factors alone do not adequately predict low BMD. Current evidence does not support the use of densitometry as a screening tool for low risk population because of its cost, as well as its inability to predict who will sustain fractures.[10] However, when its use is restricted to those with known risk factors for low BMD and fracture, its prognostic value improves.

Of additional concern is the relationship between bone mineral density (BMD) and fracture risk, which is imperfect. While loss of bone mineral is associated with an increased risk of fracture, it is not a perfect predictor. Nevertheless, several agents for treatment of OP and all agents indicated for prevention of OP have been approved based on data on their ability to preserve or increase BMD. Thus, it is important to evaluate the evidence regarding the effect of these drugs on fracture risk.

Risk Factors for Low BMD and Osteoporosis

The major risk factors for osteoporosis include age, sex, body size, lifestyle, and family history. Peak bone mass is achieved by late adolescence and maintained throughout the 20s, 30s, and 40s with adequate intakes of calcium and vitamin D and exercise. Bone loss begins to accelerate after the age of 50, particularly in postmenopausal women.[11] Low body weight, loss of weight (in older individuals), sedentary lifestyle, and a history of anorexia nervosa or athletic amenorrhea increase the risk for osteoporosis. Additional factors that are associated with an increased risk for osteoporosis include having a disease that requires treatment with glucocorticoids, family history of bone disease, and hypogonadism (in men). The design and validation of risk assessment tools is an active area of research.[12]

Risk Factors for Fracture

The evidence supporting a link between a large number of potential factors and risk for fracture was reviewed in a 2001 meta-analysis.[10] The outcome assessed in the majority of studies was hip fracture. The following factors had the strongest predictive value for fracture risk (as evidenced by a RR greater than 2.00): older age (older than 70-80); low body weight or body mass index or loss of weight; prior osteoporotic fracture; use of glucocorticoids; use of the older anticonvulsants (that interfere with vitamin D metabolism); sedentary lifestyle; primary hyperparathyroidism; type I diabetes; anorexia nervosa; gastrectomy; pernicious anemia; and male hypogonadism. Menopause and family history of osteoporotic fracture were moderate risk factors. Caveats discussed by the authors were that various populations have not been studied equally; most studies included only whites and only persons older than 50; and only half of the

studies included men. Additional meta-analyses on the effects of alcohol and of smoking on fracture risk identified a considerable increase in risk that could not be attributed to BMD.[10, 13, 14]

The Role of Falls

Osteoporotic fractures are sustained through falls. Thus, it is also important to consider the factors that increase the risk for falling, particularly among elderly people, and the evidence base for fall management.

The risk for falling increases with age, as do the consequences. Among community-dwelling elderly, five percent of falls result in a fracture or other cause for hospitalization. In nursing homes and hospitals, the risk for falling and the risk for complications are considerably higher: 10 to 25 percent of institutional falls result in fracture, laceration, or other need for hospital care. The most important risk factors for falls are gait and balance disorders, functional impairment, visual deficits, cognitive impairment, and use of psychotropic medications.[15-18] When these factors are combined, the effect on falls is synergistic.

Treatment and Prevention of Osteoporosis

For individuals identified to be at risk for developing osteoporosis, intervention measures are aimed at preventing the condition from developing, whereas in those who have already presented with low BMD or fractures, treatment is aimed at preventing further bone loss to reduce the risk of initial or subsequent fracture.

The NOF has issued a set of evidence-based guidelines for the diagnosis, treatment, and prevention of osteoporosis; first issued in 1999, the guidelines have since been updated.[8] Prevention recommendations include adequate intakes of calcium and vitamin D, maintenance of regular weight-bearing exercise, fall prevention, and avoidance/limitation of tobacco and alcohol use. Several of these recommendations are discussed in greater detail below. Indications and recommendations for pharmacologic treatment are also included in the guidelines. The NOF recommends pharmacologic intervention for women with T-scores of -2.0 or less but with no other risk factors; for women with T-scores of -1.5 or less with other risk factors; and for any woman with a prior vertebral or hip fracture. Treatment methods are discussed below.

Nutrition and Use of Supplements

Although many nutrients are involved in bone formation and maintenance, calcium and vitamin D appear to play the most central role. In 1997, as part of the periodic update of the recommended dietary allowances (RDAs, now known collectively as the dietary reference intakes or DRIs), the Institute of Medicine systematically reviewed the literature on nutrition and bone health and developed a set of evidence-based recommendations for intake of calcium and vitamin D. This review also found that the average American does not consume a diet that is adequate in calcium and that many Americans, especially those at highest risk for osteoporotic fractures, do not obtain adequate vitamin D from the diet or through sun exposure.[19] Thus, the Surgeon General's Report on Bone Health and Osteoporosis, among others, recommends the routine use of calcium and vitamin D supplements.

Physical Activity and Falls Prevention

Physical activity contributes to the reduction of fracture risk in two ways. First, the biomechanical pull of muscles on bones has been shown to increase bone density; thus, weight-bearing exercise appears to play an important role in increasing and preserving bone mass. Second, regular physical activity has been shown to help prevent falls due to balance problems and decreased strength and endurance. Recommendations for management of falls consist of measures aimed at detection, evaluation, and intervention.[20] The Surgeon General's Report on Bone Health and Osteoporosis recommends strength and weight-bearing activities in addition to 30 minutes per day of regular exercise.

Pharmacologic Agents Other Than Supplements

Various pharmaceutical agents have been approved by the Food and Drug Administration (FDA) for the treatment and/or prevention of osteoporosis. This section provides a brief review of the FDA approval process for agents intended to treat and prevent osteoporosis and its relationship to fracture prevention, followed by a description of the agents that have received FDA approval.

The FDA Approval Process. In 1979, the FDA published its first guidance document for the clinical evaluation of the safety and efficacy of drugs to treat osteoporosis.[21] From the outset, the FDA acknowledged certain difficulties, including quantitative assessment of skeletal bone, the inexact relationship between bone mass and fracture risk, and the size and duration of studies that would be required to detect changes in bone density and/or fracture risk. Inclusion criteria for clinical trials were defined as objective evidence of disease (that is, history of an osteoporosis-related fracture) or the less objective criterion of low bone mass, as determined by any one of six methods, all imperfect. In an effort to ease the process of trial implementation, the Guidance Document permitted efficacy to be defined as improvement in bone mass during therapy if the process of new bone formation could be demonstrated to be normal, rather than requiring evidence of significant decrease in fracture risk. If new bone formation did not prove normal or if it was not possible to determine normalcy, fracture studies would be required.

Operating under the initial guidance document--which did not require demonstration of fracture risk reduction--calcitonin was approved as an injectable drug for the treatment of osteoporosis in 1984, conditional upon the initiation and eventual completion of a trial to assess fracture risk. Calcitonin is a peptide hormone synthesized in the thyroid that participates in the physiological regulation of calcium and phosphorus; it had previously been approved for the treatment of Paget's disease (a disease characterized by abnormal bone remodeling). Upon completion of the study, it became apparent that enrollment and retention of patients in this fracture trial was problematic, and the fracture reduction efficacy of calcitonin remained in doubt. In the early 1990s, the Prevent Reoccurrence of Osteoporotic Fracture (PROOF) trial tested the ability of a nasally administered form of calcitonin (100, 200, and 400 IU) to prevent fracture. Although fracture prevention was seen with 200 IU, none was seen at the higher or lower dose; this lack of dose response, combined with a lack of effect on BMD suggested either that the positive effect of the 200 IU dose was an artifact or that BMD and fracture risk are not well correlated. Nevertheless, the drug is still widely prescribed.

During the 1980s, two additional agents–sodium fluoride (NaF) and the bisphosphonate (see below) etidronate--were evaluated for the treatment of osteoporosis under the initial guidance document, which did not require fracture risk reduction. Although both agents increased bone density significantly when tested in large scale trials of postmenopausal women, evidence suggested that neither reduced the risk for vertebral fracture and that at least one (NaF) may have increased fracture risk. Based on this experience, the Osteoporosis Guidance document was updated in 1994 to include the following requirements for approval of a new drug to treat postmenopausal osteoporosis: 1) demonstration of normal bone quality in preclinical studies with two laboratory animal species, including the ovariectomized rat model; 2) normal bone quality in a subset of clinical trial participants; 3) significant increase in BMD; and 4) at least a positive trend in 3-year fracture risk decrease. The 1994 Guidance document also provided requirements for approval of agents for *prevention* of osteoporosis (in individuals at high risk but without history of osteoporotic fracture). Only agents that have already been approved for *treatment* of osteoporosis can be approved for *prevention*. For *prevention*, BMD may serve as an appropriate–and sufficient–outcome measure for efficacy in double-blind RCTs of at least 2 years duration with multiple dosage arms (to establish a minimum effective dose). The guidance also provided recommendations for the appropriate sample population.

Based on extensive data from observational studies, estrogen was exempted from the fourth requirement and was approved for prevention based on BMD alone. Subsequently, however, the FDA has required evidence of fracture efficacy for approval of selective estrogen receptor modulators (SERMS). In 1997, the first SERM, raloxifene, was approved. The bisphosphonate alendronate was the first nonestrogenic agent to be evaluated and approved for treatment of postmenopausal osteoporosis.

In 2004, the FDA began soliciting comments on the 1994 Guidance document in preparation for its revision. Two issues of particular interest were the continued use of placebo (as opposed to active) controls (an issue with both ethical and technical implications) and the minimum acceptable duration for treatment trials.

Thus, not all drugs currently approved for treatment of osteoporosis were required to demonstrate reduction in fracture risk (e.g., calcitonin). With the exception of estrogen products all agents approved for prevention of osteoporosis have demonstrated fracture reduction, as they were approved first for osteoporosis treatment. Further, approval of an indication for a different dose, frequency, or route of administration does not require demonstration of reduced fracture risk. These implications of the current guidance have heightened interest in evaluating the efficacy data for drugs approved to treat and prevent osteoporosis.

The Agents. The agents currently approved for treatment and/or prevention of osteoporosis include bisphosphonates; hormone replacement therapy with estrogen or combination estrogen/progesterone preparations; calcitonin; raloxifene; and parathyroid hormone. In addition, testosterone has been tested but is not approved for this indication.

Bisphosphonates are compounds that permanently bind to mineralized bone surfaces and disrupt bone resorption by at least two different mechanisms. The non-nitrogenous bisphosphonate

etidronate is taken up by osteoclasts (the cells responsible for resorption), where it competes with ATP, inducing apoptosis (programmed cell death). The nitrogenous bisphosphonates alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid inhibit a step in the HMG CoA Reductase pathway (the enzymatic pathway responsible for cholesterol synthesis), resulting in the disruption of attachment of several subcellular proteins to the cell membrane. Other mechanisms implicated in bisphosphonates' inhibition of bone resorption include interference with cytoskeletal lipoproteins. Bisphosphonates approved by the FDA for both treatment and prevention of osteoporosis are alendronate, ibandronate, and risedronate (see Table 1 for dosages). Alendronate and risedronate are approved for treatment of men with osteoporosis as well as men and women with glucocorticoid-induced osteoporosis. Etidronate, pamidronate, and zoledronic acid are not approved for the prevention or treatment of osteoporosis, but are used off-label for this purpose. Several other bisphosphonates, such as tiludronate and clodronate, have been tested in clinical trials of osteoporosis but are not yet approved for the treatment of osteoporosis in the United States. Therefore, they will not be reviewed at this time.

Calcitonin is a peptide hormone produced by the follicular cells of the thyroid gland that suppresses osteoclast activity. As described above, calcitonin was approved for the treatment of osteoporosis prior to the requirement for demonstration of reduction in fracture risk. Calcitonin is available in several forms for different routes of administration.

SERMs exhibit a pharmacologic profile characterized by estrogen agonist activity in some tissues with estrogen antagonist activity in other tissues.[22] The first widely used SERM, tamoxifen, has estrogen antagonist activity in breast tissue and is approved for treatment of breast cancer. Another SERM, raloxifene, exhibits an estrogen agonist profile in the skeletal system. This agent is FDA-approved for the prevention and treatment of postmenopausal osteoporosis.

One of the newest treatments for osteoporosis is human parathyroid hormone (PTH), which helps to regulate calcium metabolism and promotes the growth of new bone. Two analogs of human PTH have been developed for use in the treatment of osteoporosis. Teriparatide (brand name Forteo) is a synthetic form of the first 34 amino acids of human PTH (PTH 1-34). This drug is administered by injection and is FDA-approved for up to 24 months of use for the treatment of osteoporosis among postmenopausal women and hypogonadal men. Full-length PTH (brand name PReOs) contains all 84 amino acids in human PTH (PTH 1-84). This agent is under review for FDA approval. Because it is not FDA-approved, full-length PTH is not reviewed in this report.

Adherence to Treatment. In spite of demonstrated efficacy in clinical trials, the effectiveness of medications in daily clinical practice is affected by adherence (also known as compliance) and persistence. It is well established that long-term adherence to medication regimens for many chronic diseases such as hypertension,[23, 24] and hyperlipidemia[25, 26] is inadequate. This knowledge, coupled with concerns regarding the side-effect profile of some treatments for osteoporosis, led to interest in assessing what is known about adherence to these treatments in daily practice.

This Report

Under Section 1013 of the Medicare Modernization Act, the Agency for Healthcare Research and Quality (AHRQ) was instructed to conduct comparative-effectiveness reviews (CER) on medications, devices, and other interventions. The CERs aim to concisely synthesize the evidence, clearly state conclusions about the evidence, and identify research gaps.

This CER compares the benefits in fracture reduction and the harms from adverse events (AE) among and within the various classes of treatment for low bone density. Our outcomes of interest for measuring benefits are vertebral, non-vertebral, hip, and radial fractures. The studies collect vertebral fracture outcomes in one of two ways. In some studies, all participants undergo radiography at pre-determined intervals. Other studies use clinical criteria, i.e. whether a fracture has been diagnosed by a clinician during the time interval. Trials that radiograph all participants will by nature detect more fractures. However the higher detection rate will apply to both treatment and placebo groups. Thus, the relative differences found should be similar that found in studies that use clinical criteria.

To characterize harms, we examine cardiac, dermatologic, endocrine, gastrointestinal, genitourinary, hematological, immunologic, metabolic, musculoskeletal, neurological, psychiatric, and respiratory adverse events armory the treatment and placebo groups.

Table 1 describes current FDA-approved indications and the evidence base for these indications for the treatments evaluated in this review.

Scope and Key Questions

Key Question 1. What are the comparative benefits in fracture reduction (including vertebral and nonvertebral sites [hip, radius, and proximal humerus]) among and also within (particularly for parts a and b) the following treatments for low bone density:

a. Bisphosphonate medications, specifically: alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid; and between intravenous and orally administered forms

b. Selective estrogen receptor modulators, specifically: raloxifene and tamoxifen

c. Calcitonin

d. Parathyriod hormone (PTH)

e. Testosterone for men

f. Estrogen for women

g. Calcium

h. Vitamin D in comparison to alternate therapies[b]

i. Exercise in comparison to alternate therapies

j. Combinations of above

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 to and persistence with 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?

[b] Will summarize recent meta-analyses on vitamin D, but will not search for, evaluate, or summarize individual studies on vitamin D unless vitamin D is a comparator arm in studies of other drugs noted above.

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts

Drug	Trade Name (s)	FDA-Labeled Indications and Dosing	BMD Data Evaluated for FDA Approval		Fracture Data Evaluated for FDA Approval	
Bisphosphonates						
Alendronate	**Fosamax**	**Treatment of osteoporosis in postmenopausal women**				
		10 mg/d	% Increase relative to placebo at 3 years[a,b]		US and Multinational Combined Study: Decrease in RVF in **5,10 mg/d x 3yr** or **20 mg/d x 2yr + 5 mg/d x 1yr** relative to placebo (% Relative reduction in fracture risk)[b]	
			LS	7-10 (6-10)[c]	at least 1 new VF	3.2% vs. 6.2% (48) [a]
			FN	6-6.5	at least 2 new VF	0.6% vs. 4.2% (87) [a]
			T	8-Jul	Total new VF	4.2 vs. 11.3/100 pts
			% Increase relative to baseline at 1 year			
			LS	5.4	3-year FIT (pts with ? 1 baseline RVF): % (Relative reduction in fracture risk)	
					RVF	
					1 new RVF	15.0% vs. 7.9% (47)[a]
					2 new RVF	0.5% vs. 4.9% (90) [a]
					CVF	
					Any CVF	13.8 vs. 18.1% (26) [a]
					1 CVF	2.3% vs. 5.0% (54) [a]
					Hip fracture	1.1% vs. 2.2% (51) [a]
					Wrist fracture	2.2% vs. 4.1% (48) [a]
					4-year FIT (pts with low BM, no baseline RVF): % (Relative reduction in fracture risk)	
					RVF	
					1 new RVF	4.8% vs. 2.5% (48) [a]
					2 new RVF	0.1% vs. 0.6% (78) [a]
					CVF	
					Any CVF	12.9 vs. 16.2% (22) [a]
					1 CVF	1.0% vs. 1.6% (41)
					Hip fracture	1.0% vs. 1.4% (29)
					Wrist fracture	3.9% vs. 3.8% (0)
		70 mg/wk	% Increase relative to baseline at 1 year			
			LS	5.1		

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts (continued)

Drug	Trade Name (s)	FDA-Labeled Indications and Dosing	BMD Data Evaluated for FDA Approval		Fracture Data Evaluated for FDA Approval	
Bisphosphonates						
Alendronate	**Fosamax**	**Prevention of postmenopausal osteoporosis**				
		5 mg/d	% Increase relative to baseline at 2 years, 3 years (change in placebo)[b]			
			LS	3.5(-2.0), 2.8 (-3.5)		
			FN	1.0 (-1.0), 1.0 (-4.0)		
			T	3.0 (-0.8), 2.5 (-2.5)		
			TB	0.5 (-2.0), 0.3 (-2.0)		
		35 mg/wk	% Increase for LS relative to baseline at 1 year (other sites also comparable)			
			10 mg/d	3.2		
			35 mg/wk	2.9		
		Treatment to increase BMD in men with LBD or OP fracture				
		5 mg/d	% Increase relative to placebo at 1 year[b]			
			LS	2.2-2.5[a]		
			FN	1.5-2.6[a]		
			T	1.3-2.0[a]		
			TB	maintained		
		Treatment to increase BMD in adults with GC-induced osteoporosis				
		5 mg/d	% increase relative to placebo at 1 year[b]			
			LS	2.2-2.5[a]		
			FN	1.5-2.6[a]		
			T	1.3-2.0[a]		
			TB	maintained		
		10 mg/d	% increase relative to placebo at 1 year[b]			
			LS	4.1 vs. 1.6[c]		
			FN	Same as 5 mg		
			T	2.g vs. 1.7[c]		
			TB	Same as 5 mg		

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts (continued)

Drug	Trade Name (s)	FDA-Labeled Indications and Dosing	BMD Data Evaluated for FDA Approval		Fracture Data Evaluated for FDA Approval	
Bisphosphonates						
Etidronate	**Didronel**	**Not FDA-approved for the prevention or treatment of osteoporosis**				
		Prevention of heterotopic Ossification secondary to total hip replacement				
		20 mg/kg/day ORALLY for 1 month before and 3 months after surgery	2/3 decrease in clinically important heterotopic bone formation; Retards progression of immature lesions and decreases severity by 50%, persisting through 9 mos.			
		Prevention of hypercalcemia of malignancy				
		7.5 mg/kg/day administered IV over a period of at least 2 hours on 3 successive days	ND			
		5-10 mg/kg/day ORALLY, not to exceed 6 months, or 11-20 mg/kg/day, not to exceed 3 months	ND			
Ibandronate	**Boniva**	**Treatment of osteoporosis in postmenopausal women**				
			% Change at 3 yrs. relative to baseline vs. placebo		Incidence of VF relative to placebo (over 3 yrs.)	
		2.5 mg/d po	LS	6.4 vs. 1.4 [a]	New VF	4.7% vs. 9.6% (52)[a]
			Hip	3.1 vs. -0.7 [a]	New/worsening VF	5.1 vs. 10.4% (52)[a]
			FN	2.6 vs. -0.7 [a]	CVF	2.8% vs. 5.3% (49) [a]
			T	5.3 vs. 0.2 [a]	NonVF	9.1% vs. 8.2%
			% Change at 1 yr. relative to baseline (vs. 2.5 mg/d)			
		150 mg monthly po	LS	4.85 vs. 3.86 [a,d]		
		3 mg every 3 months IV	No data			
		Prevention of osteoporosis in postmenopausal women				
			% Change from baseline after 2 yrs. compared w/ placebo			
		2.5 mg/d po	LS	3.1 [a]		
			Hip	1.8		
			FN	2		
			T	2.1		
		150 mg monthly po	Evaluation in progress			

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts (continued)

Drug	Trade Name (s)	FDA-Labeled Indications and Dosing	BMD Data Evaluated for FDA Approval		Fracture Data Evaluated for FDA Approval	
Bisphosphonates						
Pamidronate	**Aredia**	**Not FDA-approved for the prevention or treatment of osteoporosis**				
		Prevention of bone metastasis, osteolytic				
		90 mg IV administered as a 2-hour infusion every 3-4 weeks; optimal duration of therapy is not known	No data on BMD or fracture in package insert			
		Prevention of hypercalcemia of malignancy				
		60-90 mg IV as a single dose infused over 2 to 24hr				
Risedronate	**Actonel**	**Treatment of osteoporosis in postmenopausal women**				
			% increase from baseline vs. placebo in 4 trials at 3 years (VF NAA, VF MNA) or 1.5-2 years (BMD NAA, BMD MNA)		% of postmenopausal women w/ ? 1 VF at baseline w/ new or worsening VF over 3 years vs. placebo alone in two RCTs (% rel risk reduction)	
		5 mg/d po	VF MNA		New and worsening VF NAA	
			LS	6.6 vs. 1.0 [a]	0-1 yr	3.9 vs. 7.2[a] (49)
			FN	1.6 vs. -1.4 [a]	0-2 yrs	8.0 vs. 12.8 [a] (42)
			Femoral T	3.9 vs. -1.9 [a]	0-3 yrs	13.9 vs. 18.5 [a] (33)
			Midshaft radius	0.2 vs. -1.5 [a]	New VF NAA	
			VF NAA		0-1 yr	2.4 vs. 6.4 [a] (65)
			LS	5.0 vs. 0.8 [a]	0-2 yrs	5.8 vs. 11.7 [a] (55)
			FN	1.4 vs. -1.0 [a]	0-3 yrs	11.3 vs. 16.3 [a] (41)
			Femoral T	3.0 vs. -0.5 [a]	New and worsening VF MNA	
			Midshaft radius	0.1 vs. -1.2 [a]	0-1 yr	8.2 vs. 15.3 [a] (50)
			BMD MNA		0-2 yrs	13.9 vs. 28.3 [a] (56)
			LS	4.0 vs. 0.0 [a]	0-3 yrs	21.8 vs. 34.0 [a] (46)
			FN	1.3 vs. -1.1 [a]	New VF MNA	
			Femoral T	2.5 vs. -0.6 [a]	0-1 yr	5.6 vs. 13.3 [a] (61)
			BMD NAA		0-2 yrs	11.6 vs. 24.7 [a] (59)
			LS	4.8 vs. 0.2 [a]	0-3 yrs	18.1 vs. 29.0 [a] (49)
			FN	2.4 vs. 0.1 [a]		
			Femoral T	4.0 vs. 1.3 [a]		
		35 mg/wk *po*			35 mg/wk comparable to effects of 5 mg/d	

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts (continued)

Drug	Trade Name (s)	FDA-Labeled Indications and Dosing	BMD Data Evaluated for FDA Approval		Fracture Data Evaluated for FDA Approval	
Risedronate	**Actonel**	**Prevention of osteoporosis in postmenopausal women**				
			% change from baseline vs. placebo at 2 years			
		5 mg/d *po*	LS	1.8 vs. -2.5		
			FN	0.6 vs. -2.5		
			T	2.5 vs. -1.7		
		35 mg/wk *po*	ND			
			% change from baseline in estrogen vs. estrogen+Actonel at 1 year ±SE			
		Estrogen 0.625mg ±Actonel 5mg/d	LS	4.6±0.20 vs. 5.2±0.23		
			FN	1.8±0.25 vs. 2.7±0.25		
			FT	3.2±0.28 vs. 3.7±0.25		
			Midshaft radius	0.4±0.14 vs. 0.7±0.17		
			Distal Radius	1.7±0.24 vs. 1.6±0.28		
		Treatment of osteoporosis due to glucocorticoids				
			% Change from baseline cf. placebo at 1 yr (patients with long-term GC use and low LS BMD at baseline)		% incidence RVF vs. placebo at 1 yr	
		5 mg/d	LS	2.9 vs. 0.2[a]	RVF	5 vs. 15
			FN	1.8 vs. -0.1 [a]		
			T	2.4 vs. 0.8		
		Prevention of osteoporosis due to glucocorticoids				
			% Change from baseline cf. placebo at 1 yr (in patients with GC use of recent onset and normal LS BMD at baseline)		% incidence RVF vs. placebo at 1 yr (relative risk reduction)	
		5 mg/d	LS	3.8[a]	RVF	6 vs. 17 (70%)
			FN	4.1 [a]		
			T	4.6 [a]		
			Distal radius	NS		
Zoledronic acid	**Zometa**	**Not FDA-approved for the prevention or treatment of osteoporosis**				
		Treatment of hypercalcemia of malignancy				
		4 mg IV infused **over 15 min**; may repeat in 7 days	4 mg IV infused **over 5 min** in two RCTs vs. pamindronate			
			ND		Determined only as skeletal-related events	
		Treatment of bone resorption due to Multiple myeloma or bone metastasis of solid tumors				
		4 mg IV infused **over 15 min** every 3-4 weeks	ND		Determined only as skeletal-related events	

NOTE: Zoledronic acid labeled as 'Reclast' was approved by the FDA for the treatment of osteoporosis in post-menopausal women on 8/17/07.

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts (continued)

Drug	Trade Name (s)	FDA-Labeled Indications and Dosing	BMD Data Evaluated for FDA Approval		Fracture Data Evaluated for FDA Approval	
Hormonal Agents and SERMS						
Calcitonin	**Miacalcin,**	**Treatment of osteoporosis in postmenopausal women**				
	Fortical	100 IU SC or IM				
		every other day				
		200 IU IN/d	Increase relative to placebo (0.5 to 2 years)			
		Alternating nostrils	LS	Signif		
			Forearm	NS		
			Hip	NS		
Estrogen	**Premarin**	**Prevention of postmenopausal osteoporosis**				
	Premarin IV	0.3, 0.45, 0.625 mg/d	HOPE Study: 0.625,0.45, 0.3mg/d Premarin, % change from baseline ±SE vs. placebo at 26 months		WHI: 0.625 mg/d, relative risk of fracture vs. placebo at mean follow-up time of 6.8 yrs. (95% CI)	
			LS		Hip	0.61 (0.41-0.91)
			0.625	2.46±0.37 vs. -2.45±0.36[a]	LS	0.62 (0.42-0.93)
			0.45	2.26±0.35 [a]	Total	0.70 (0.63-0.79)
			0.3	1.13±0.36 [a]		
			TB			
			0.625	0.68±0.17 vs. -1.50±0.17 [a]		
			0.45	0.74±0.16 [a]		
			0.3	0.40±0.17 [a]		
			FN			
			0.625	1.82±0.45 vs. -1.72±0.45 [a]		
			0.45	1.84±0.44 [a]		
			0.3	0.62±0.45 [a]		
			Femoral T			
			0.625	3.82±0.58 vs. 0.81±0.58 [a]		
			0.45	3.16±0.56 [a]		
			0.3	3.05±0.57 [a]		

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts (continued)

Drug	Trade Name (s)	FDA-Labeled Indications and Dosing	BMD Data Evaluated for FDA Approval		Fracture Data Evaluated for FDA Approval	
Hormonal Agents and SERMS						
Estrogen plus MPA	**Prempro** **Premphase**	0.3/1.5 mg/d E/MPA 0.45/1.5 0.625/2.5	HOPE Study: 0.625/2.5, 0.45/1.5, 0.3/1.5 mg, % change from baseline ±SE vs. placebo at 26 months		WHI: 0.625/2.5 mg/d, relative risk of fracture vs. placebo at mean follow-up time of 5.2 yrs. (95% CI)	
			LS		Hip	0.67 (0.47-0.96)
			0.625/2.5	3.28±0.37 vs. -2.45±0.36 [a]	LS	0.65 (0.46-0.92)
			0.45/1.5	2.18±0.35 [a]	Wrist/forearm	0.71 (0.59-0.85)
			0.3/1.5	1.71±0.35 [a]	Total	0.76 (0.69-0.87)
			TB			
			0.625/2.5	0.87±0.17 vs. -1.50±0.17 [a]		
			0.45/1.5	0.59±0.17 [a]		
			0.3/1.5	0.60±0.16 [a]		
			FN			
			0.625/2.5	1.62±0.46 vs. -1.72±0.45 [a]		
			0.45/1.5	1.48±0.44 [a]		
			0.3/1.5	1.31±0.43 [a]		
			Femoral T			
			0.625/2.5	3.35±0.59 vs. 0.81±0.58 [a]		
			0.45/1.5	2.84±0.57 [a]		
			0.3/1.5	3.93±0.56 [a]		
Parathyroid Hormone	**Forteo** **Teriparatide**	**Treatment of osteoporosis in postmenopausal women who are at high risk for fracture (90% had baseline RVF)**				
			% change from baseline to 19 mos vs. placebo		% of women w/ new fractures at 19 mos vs. placebo alone (Ca and Vit D) (% rel risk reduction)	
		20 mcg/d	LS	9.7 vs. 1.1 [a]	New RVF (≥ 1)	5.0 vs. 14.3[a] (65)
			FN	2.8 vs. -0.7 [a]	1 RVF	3.8 vs. 9.4
			TH	2.6 vs. -1.0	2 RVF	0.9 vs. 2.9
			T	3.5 vs. -0.2 [a]	≥3 RVF	0.2 vs. 2.0
			Intertrochanter	2.6 vs. -1.3 [a]	Other sites	2.6 vs. 5.5[a]
			Ward's triangle	4.2 vs. -0.8 [a]		
			TB	0.6 vs. -0.5 [a]		
			Distal 1/3 radius	-2.1 vs. -1.3		
			Ultradistal radius	-0.1 vs. -1.6		

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts (continued)

Drug	Trade Name (s)	FDA-Labeled Indications and Dosing	BMD Data Evaluated for FDA Approval		Fracture Data Evaluated for FDA Approval	
Hormonal Agents and SERMS						
Parathyroid Hormone	**Forteo Teriparatide**	**Treatment of osteoporosis in men with primary or hypogonadal osteoporosis who are at high risk for fracture**				
			% change from baseline to median of 10 mos. vs. placebo		Effect on Frx risk not studied in men	
		20 mcg/d	LS	5.9 vs. 0.5 [a]		
			FN	1.5 vs. 0.3 [a]		
			TH	1.2 vs. 0.5		
			T	1.3 vs. 1.1		
			Intertrochanter	1.2 vs. 0.6		
			Ward's triangle	2.8 vs. 1.1		
			TB	0.4 vs. -0.4		
			Distal 1/3 radius	-0.5 vs. -0.2		
			Ultradistal radius	-0.5 vs. -0.3		
Raloxifine	**Evista**	**Treatment of osteoporosis in postmenopausal women**				
		60 mg/d po	% increase at 24 mos. vs. placebo		% of women w/ new fractures at 19 mos vs. placebo alone (Ca and Vit D) (% rel risk reduction)	
			LS	2.6 [a]	No baseline frx:	
			FN	1.9 [a]	≥ 1 new RVF	1.9 vs. 4.3 (55)
			Ultradistal radius	2.2 [a]	≥ 1 baseline frx:	
			Distal radius	0.9 [a]	≥ 1 new RVF	14.1 vs. 20.2 (30)
			TB	1.1 [a]	≥ 1 new CVF	1.8 vs. 3.1 (41)
		Prevention of osteoporosis in postmenopausal women				
			% increase by DXA at 24 mos. vs. placebo in 3 trials: NAE, EU, INT			
			TH	2.0, 2.4, 1.3 [a]		
			FN	2.1, 2.5, 1.6 [a]		
			T	2.2, 2.7, 1.3 [a]		
			Intertrochanter	2.3, 2.4, 1.3 [a]		
			LS	2.0, 2.4, 1.8 [a]		
			Ward's triangle	3.1-4.0		
			Ultradistal radius	Signif. only for EU		

Table 1. FDA-approved indications for agents used to prevent or treat osteoporosis by BMD and fracture data used for approval or detailed in package inserts (continued)

Raloxefine	**Evista**	**Treatment of osteoporosis in postmenopausal women**					
		60 mg/d po	% increase at 24 mos. vs. placebo			% of women w/ new fractures at 19 mos vs. placebo alone (Ca and Vit D) (% rel risk reduction)	
			LS	2.6 [a]		No baseline frx:	
			FN	1.9 [a]		≥ 1 new RVF	1.9 vs. 4.3 (55)
			Ultradistal radius	2.2 [a]		≥ 1 baseline frx:	
			Distal radius	0.9 [a]		≥ 1 new RVF	14.1 vs. 20.2 (30)
			TB	1.1 [a]		≥ 1 new CVF	1.8 vs. 3.1 (41)
		Prevention of osteoporosis in postmenopausal women					
			% increase by DXA at 24 mos. vs. placebo in 3 trials: NAE, EU, INT				
			TH	2.0, 2.4, 1.3 [a]			
			FN	2.1, 2.5, 1.6 [a]			
			T	2.2, 2.7, 1.3 [a]			
			Intertrochanter	2.3, 2.4, 1.3 [a]			

Abbreviations: BMD bone mineral density; **CVF** vertebral fracture diagnosed clinically**; DXA** dual energy x-ray absorptiometry; **EU** European Evista trial; **GC** glucocorticoid; **FIT** Fracture Intervention Trial**; FN** femoral neck; **HOPE** Health and Osteoporosis Progestin and Estrogen Study; **IM** intramuscular; **IN** intranasal; **INT** International Evista trial; **IU** international units; **LBD** low bone density; **LS** lumbar spine; **MNA** Multinational Actonel trial; **MPA** Medroxyprogesterone acetate; **NAA** North American Actonel trial; **NAE** North American Evista trial; **ND** not described; **po** oral; **SC** subcutaneous administration; **T** trochanter; **TB** total body; **TH** total hip; **RVF** vertebral fracture diagnosed radiographically; **VF** vertebral fracture; **WHI** Women's Health Initiative

[a] Significant; exact test not reported.

[b] Two separate studies.

[c] Only in postmenopausal women not receiving estrogen therapy; rest same between 5mg and 10 mg.

[d] BMD also higher in 150 mg/mo group at other sites.

Methods

Topic Development and Technical Expert Panel

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) located at Oregon Health and Science University (OHSU) drafted the initial key questions and, after approval from AHRQ, posted them to a public web site. The public was invited to comment on these questions. After reviewing the public commentary, the SRC drafted final key questions and submitted them to AHRQ for approval.

The key questions subsequently went through several revisions. An original question on whether change in bone density is an adequate intermediate endpoint for treatment effectiveness was removed in October, 2005, based on discussion with AHRQ and our Technical Expert Panel (TEP). In addition, an original question asking for review of practical and validated tools that can be used by patients or clinicians to predict the risk of fracture and the benefits of treatment was declared beyond the scope of this review in December, 2005. In response to comments on the first draft of this report, a key question about the effect of treatment adherence and persistence of medications on fracture was added.

Our TEP met by conference call on October 12, 2005, January 11, 2006, and September 12, 2006. Additionally, we conferred with the FDA by teleconference on September 26, 2006. At the October meeting, the TEP suggested we focus on the bisphosphonates, SERMs, Calcitonin, and PTH. They noted that calcium, vitamin D, hormones, and exercise had already been reviewed extensively; thus, they suggested that we summarize existing reviews on these interventions and incorporate study-level data for these interventions only in comparison to agents of primary interest. At the January 2006 meeting, due to the amount of literature found and time constraints, we suggested limiting the efficacy analyses to trials with fracture outcomes. The TEP found this suggestion acceptable but advised us not to pool data across different fracture types. Thus, we do not analyze intermediate outcomes such as bone mineral density or markers of bone turnover.

The September 2006 TEP meeting focused on adverse events (AE) and risk groups. The September 2006 call with the FDA focused on AE analysis. Based on these calls and discussions with AHRQ, the following AE were defined as particularly important for one or more of the agents being reviewed in this report: 1) cardiovascular: myocardial infarction, stroke; 2) thromboembolic events: pulmonary embolism, venous thrombo-embolic events; 3) malignancies: breast cancer, colon cancer, lung cancer, osteosarcoma; 4) upper GI events: perforations, ulcers, bleeds, esophageal ulcerations; 5) osteonecrosis; 6) inflammatory eye reactions: uveitis, scleritis; 6) acute phase reactions. It was decided to expand the search strategy for these key AE (see below).

Risk groups (high, intermediate, low, and unknown) were defined based on combinations of risk factors that would be reported in clinical trials, including BMD, fracture history, age, comorbidities, or treatment with drugs that increase the risk for fracture. The risk groups are also defined below.

Search Strategy

This report incorporated three main searches: one to identify studies of the drugs of interest to this report, one to identify key AE associated with these drugs, and one to identify studies that described adherence to and persistence with the drugs. We also performed a targeted search to identify studies from the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study (HERS).

Given the large volume of literature in this area and the fact that a number of systematic reviews and meta-analyses had previously been published, we used a two-pronged approach to identify articles for this report. First we identified any systematic reviews and meta-analyses that reported on the effect of agents of interest on fracture risk. When relevant systematic reviews or meta-analyses were identified for specific agents, we truncated our search for those specific agents to include dates after the last search date used in the review/meta-analysis.

For the three main searches, our basic search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) key word nomenclature developed for MEDLINE® and was adapted for use in the other databases. We searched MEDLINE® for the period from 1966 to December 2006. We also searched the American College of Physicians (ACP) Journal Club database and the Cochrane controlled trials register. Our search was not limited by publication type (e.g. reports of randomized controlled trials, systematic reviews). Nevertheless, to identify additional systematic reviews and meta-analyses not captured in our primary search strategy, we also searched MEDLINE®, the Cochrane Database of Systematic Reviews, the websites of the National Institute for Clinical Excellence, and the NHA Health Technology Assessment Programme. We also manually searched reference lists of review articles obtained as part of our search. (We refer to this process as "reference mining.") The texts of the major search strategies are shown in Appendix A.

In our search to identify clinical studies of drugs of interest to this review, we used terms for osteoporosis, osteopenia, low bone density, and the drugs listed in the key questions. In our search for the key AE, we used terms for the AE and each of the drugs of interest for this report. In our search for adherence and persistence we used terms for adherence and persistence and the drugs of interest for this report. In all cases both generic and trade names were used. The texts of the major search strategies are shown in Appendix A. To supplement the information in systematic reviews on the effects of estrogen on fracture and on AE associated with estrogen, we were asked to review studies from the Women's Health Initiative (WHI) and Heart and Estrogen-progestin Replacement Study (HERS) trials. The WHI studies were identified from a website (http://www.nhlbi.nih.gov/whi/references.htm) that provides a comprehensive list of manuscripts published from this study. Reports from the HERS trial were identified through a MEDLINE® search.

We invited TEP members to provide additional studies. Studies suggested by stakeholders during the public review period were also reviewed. In addition, we received the following materials from the Scientific Resource Center:

- Medical and statistical reviews of all FDA-approved drugs listed in the key questions, obtained from the FDA web site;
- Scientific information packets from:

Auxilium Pharmaceuticals	- Testum® (Testosterone)
Novartis	- Miacalcin® (Calcitonin)
Merck	- Fosamax® (Alendronate)
Eli Lilly	- Evista® (Raloxifene)
	- Forteo® (Teriparatide)
Roche	- Boniva® (Ibandronate)
Proctor & Gamble	- Actonel® (Risedronate).

All citations were imported into an electronic database using ProCite.

Study Selection

Three sets of inclusion criteria were developed: one each for the efficacy, AE, and adherence/persistence analyses. For titles obtained through the searches for studies of drugs and osteoporosis/osteopenia and low bone density, we accepted any title that suggested the manuscript might include information on fracture, BMD, markers of bone turnover, or any AE. For titles obtained from the search for AEs by drug of interest, titles were accepted if they suggested that the manuscript included information on the relationship between the AE and the drug. Likewise, for the titles identified from the search for adherence and compliance, titles were accepted if they suggested that the manuscript might include information on adherence and compliance. Titles identified for the first two searches were reviewed independently by two reviewers. All titles selected by either reviewer went on to the screening phase. Titles identified for the adherence/persistence search were reviewed by a single reviewer. Full text articles were obtained for all articles that were accepted for the screening phase.

At the screening phase, all articles identified through the searches for efficacy or AE were reviewed independently by two physicians using a structured screening form (Appendix B). Reviewers reconciled their answers from the review form and came to consensus on any disagreements. The principal investigator resolved any disagreements between reviewers. Articles identified through the search for adherence/persistence were screened by a single reviewer.

At this stage, articles could be accepted for further review for either the efficacy (fracture) or adverse events analysis. Controlled clinical trials that reported fracture outcomes for one or more of the drugs of interest were accepted for the efficacy analysis and went on to data extraction. Controlled clinical trials and large case control or cohort studies ($n \geq 1000$) that reported fracture *or BMD or markers of bone turnover* for one or more of the drugs of interest and that reported one or more AE went on for AE analyses. Also included in AE analysis were articles that were identified through the search for specific AE, if any AE for any of the drugs of interest was reported. Articles of any study design that reported on adherence/persistence for any of the drugs of interest went on for further evaluation.

Data Extraction

Articles that met screening criteria for the efficacy analysis were further reviewed using the "quality review form" included in Appendix B. We extracted the following data from the controlled clinical trials: setting; geographic region; population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); concurrent medications or supplements; number screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and type of outcome reported. We also abstracted run-in period and wash-out period where applicable. Data from each article were independently abstracted by two physicians trained in the critical assessment of evidence. They resolved disagreements by consensus; the principal investigator resolved any disagreements that remained after their discussion.

A statistician extracted the fracture outcome data. For each treatment or placebo arm within an RCT, the sample size and number of persons reporting fractures were extracted.

Articles that screened in for the adverse events analysis were each abstracted independently by two reviewers under the supervision of the statistician. Disagreements were resolved by the statistician and/or the principal investigator. Adverse events were recorded onto a spreadsheet that identified each trial group, the description of the adverse event as listed in the original article, and the number of subjects in each group. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event. If a trial mentioned a particular type of adverse event in the discussion but did not report data on that adverse event, we did not include that trial in that particular event's analysis. In other words, we did not assume zero events occurred unless the trial report specifically stated that zero events were observed. By taking this approach, we may have overestimated the number of patients for whom a particular adverse event was observed.

Articles that screened in for the adherence/persistence analysis were further reviewed by a single reviewer who abstracted relevant data from each article in a qualitative fashion. Per the Scientific Resource Center, we abstracted the aims, time period covered, eligibility criteria, study designs included, interventions studied, populations, and results from systematic reviews and meta-analyses. These data are presented in the evidence tables (Appendix C).

Quality Assessment

We used predefined criteria to assess the quality of systematic reviews and individual RCTs. As observational studies were not used for efficacy analyses, we felt that quality rating was unnecessary.

Before we assessed the quality of systematic reviews and meta-analyses, we reviewed the QUOROM statement,[27] which consists of a checklist of 18 items and a flow diagram. The statement's authors were able to identify scientific evidence for only eight items. As the authors did not suggest a specific scoring mechanism for the checklist, we focused on aspects of internal and external validity as suggested in the Medicare Modernization Act (MMA) Drug Review Methods Manual distributed in March, 2005. These items, which include search strategy, inclusion criteria for individual studies, and method of synthesis, among others, are presented in the evidence table for systematic reviews in Appendix C. Each systematic review or meta-analyses is discussed in detail in its corresponding section of the results.

We assessed the quality of individual RCTs using the Jadad scale, which was developed for drug trials and which we feel is well suited to the evaluation of quality in this report. The Jadad scale ranges from 0-5 based on points given for randomization, blinding, and accounting for withdrawals and dropouts.[28] Across a broad array of meta-analyses, an evaluation found that studies scoring 0-2 report exaggerated results compared with studies scoring 3-5.[29] The latter have been called "good" quality and the former called "poor" quality.

Applicability

Effectiveness studies compare a new drug with viable alternatives rather than with placebos and produce health, quality of life, and economic outcomes data under real-world conditions. For example, an effectiveness trial of a new asthma drug would include asthma-related emergency room visits, the frequency and costs of physician visits, patients' quality of life, patient compliance with the medications, acquisition costs of the medications, and frequency and costs of short- and long-term adverse events."[30]

Clinicians and policymakers often distinguish between the efficacy of an intervention (the extent to which the treatment works under ideal circumstances) and the effectiveness of the intervention (the extent to which the treatment works on average patients in average settings). Efficacy studies tend to be smaller, to be performed on referred patients and in specialty settings, and to exclude patients with comorbidities. Effectiveness studies are larger and more generalizable to practice. The vast majority of studies included in our report are efficacy studies. However, our analysis of adherence and persistence provides some information about effectiveness in that adherence and persistence influence effectiveness.

Rating the Body of Evidence

We assessed the overall strength of evidence for outcomes using a method developed by the Grade Working Group, which classified the grade of evidence across outcomes according to the following criteria:[31]

- **High** = Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very Low** = Any estimate of effect is very uncertain.

Data Synthesis

We performed three main analyses: one to evaluate efficacy, one to evaluate adherence, and one to evaluate AE. Comparisons of interest for all analyses were single drug versus placebo for each of the drugs of interest, and single drug versus single drug comparisons for drugs within the same class and across classes. In addition we evaluated comparisons between estrogen combined with progesterone and placebo or single drugs. Studies that included either calcium or vitamin D in both study arms were classified as being comparisons between the other agents in each arm, e.g., alendronate plus calcium versus risedronate plus calcium would be classified as alendronate versus risedronate.

Efficacy

The efficacy outcome of interest for this report is fractures. We report data about the following types of fractures (as reported in the studies reviewed)--vertebral, non-vertebral, hip, wrist, and humerus. For each of the drug comparisons, we summarized fracture data from published systematic reviews and meta-analyses in tables. Data abstracted from individual controlled clinical trials were grouped by fracture type within each drug comparison of interest. Based on a recommendation from the TEP, we did not combine data on different types of fracture; hence we report findings for total fractures only if a study reported data on total fractures (likewise for non-vertebral fractures). The primary outcome for our efficacy analysis is the number of people who reported at least one fracture. Because the occurrence of a fracture was fairly rare, and zero events were often observed in at least one of the treatment groups, odds-ratios (OR) were calculated using the Peto method.[32] An OR with a value less than one indicates that the odds of having a fracture is less in the intervention group than in the comparison group. Trials that report zeros in both groups have an undefined OR. Because fractures are rare events, the OR approximates the relative risk (RR) of fracture. In some instances, we combined data from multiple study arms in an individual study to calculate a single OR for comparisons of interest. In these instances, the same outcome had been reported for each of the arms, and the individuals in each arm were unique. For example, to develop on OR for the risk of vertebral fractures

regardless of dose, subjects in the various dose groups were combined and compared with subjects in the placebo group.

Among comparisons that had not previously been pooled in other meta-analyses and that had at least three trials that were judged to be clinically similar enough to warrant meta-analysis, we estimated a pooled OR using the Peto method.[32] When analyzing outcomes with rare events, the Peto method has been shown to give the least biased estimate.[33] Forest plots are provided when trials were pooled. The OR for each trial is illustrated by a box, where the size of the box is proportional to the trial's sample size. The 95% confidence interval (CI) is depicted as a horizontal line on each side of the box. A diamond on the bottom of each graph represents the pooled estimate and CI. A vertical solid line at one indicates no treatment effect.

We also report the chi-squared test of heterogeneity p-value based on Cochran's Q[34] and the I^2 statistic.[35] A significant Q statistic or I^2 values close to 100% represent very high degrees of heterogeneity. I^2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity.

All efficacy meta-analyses were conducted with Stata statistical software.[36]

Recognizing that the risk of fracture may be affected by characteristics of the study population, we defined risk groups for fracture and assigned each of the controlled clinical trials to one risk group. Published meta-analyses that are summarized in this report typically used similar criteria to define risk groups, which we detail in the tables summarizing the meta-analyses. The criteria we used to define risk groups are as follows:

High-risk:

1) transplant population, or
2) study entry criteria require T score ≤ -2.5, *or*
3) study entry criteria require ≥1 fracture, *or*
4) ≥50% population has 1 or more fractures at baseline or
5) Significant neuromuscular impairment

Intermediate-risk:

1) study entry criteria require T score ≤1.5, *or*
2) 10-49.99% of population has one or more fracture at baseline, *or*
3) study population has chronic disease that is commonly treated with glucocorticoids *or*
4) in the absence of data on BMD or fractures, mean age of population ≥ 62 years.

Low-risk:

1) study entry criteria require T score ≤0.0, *or*
2) < 10% of population has BMD =8 g/cm2 at baseline, *or*
3) < 10% of population has one or more fracture at baseline, *or*
4) in the absence of data on BMD or fracture, mean age of population <62 years.

Unknown risk:

BMD, fracture history, and age not reported as entry criteria or in baseline characteristics of population.

Adherence

The term *adherence* is defined as the extent to which a person's health behavior is consistent with medical advice.[37] Health behavior refers not only a patient's decision to take a medication at the prescribed frequency, but also to their conformity to recommended dosages, timing (e.g., each morning, 30 minutes prior to eating), and instructions (e.g., with or without food, remain upright for 1 hour, etc.). Adherence is synonymous with the term *compliance*. *Persistence* is defined as the duration of treatment, while *nonpersistence* is defined as treatment discontinuation without medical recommendation.[37]

A qualitative summary of the literature on adherence and persistence with medications for osteoporosis was developed focusing on 1) the effect of adherence and persistence of medications for osteoporosis on fractures, 2) rates of adherence and persistence of medications to treat or prevent osteoporosis, and 3) the factors that affect adherence and persistence of medications to treat or prevent osteoporosis.

Adverse Events

Two main analyses were performed for adverse events: analyses to assess the relationship between a group of adverse events that were identified *a priori* as particularly relevant and exploratory analyses of all adverse events that were reported for any of the drugs. For the analyses of adverse events, we examined (where possible given the available data) comparisons of drug versus placebo, and comparisons of drug versus drug, for drugs within the same class and across classes.

A list of all unique adverse events that were reported in any of the studies was compiled, and a physician grouped adverse events into clinically sensible categories and subcategories, including a category for each of the adverse events that were identified *a priori* as being of interest. For groups of events that occurred in three or more trials, we performed a meta-analysis to estimate the pooled OR and its associated 95% confidence interval. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed; generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analyses using the statistical software package StatXact Procs for SAS Users.[38] For events that were reported in only one trial, an OR is calculated and reported.

Any significant OR greater than one indicates the odds of the adverse event associated with the bone density drug is larger than the odds associated with an adverse event among patients in the comparison group (placebo, vitamin D, estrogen, calcium, or other bone density drug). We note that if no events were observed in the comparison group, but events were observed in the intervention group, the OR is infinity and the associated confidence interval is bounded from below only. In such a case, we report the lower bound of the confidence interval.

Peer Review

A draft version of the report was submitted for peer review and public comment in May, 2006. This final report includes the revisions and additional analyses conducted in response to those comments.

Results

We identified 1,794 titles through our electronic library searches, 97 titles through scientific information packets from pharmaceutical companies, 484 titles through reference mining, and three titles through peer reviewers, for a total of 2,378 titles. After reviewing titles and/or abstracts where available, we ordered 1,831 articles and were unable to obtain 10.

Of the 1,821 articles screened, 1,720 were excluded from our efficacy analyses for the reasons detailed in Figure 1. Appendix D contains a list of these excluded studies. Because systematic reviews already existed for alendronate, risedronate, etidronate, raloxifene, calcitonin, PTH, and estrogen, we did not re-analyze trials of these drugs versus placebo in our efficacy analyses. This means that 166 articles on RCTs were excluded from further efficacy analyses. In total, 76 articles reporting on RCTs and 25 meta-analyses were considered for the efficacy analyses.

Our analyses of adverse events included 490 articles, representing 416 randomized controlled trials, 25 other controlled clinical trials, one open-label trial, and 31 observational studies (case control or cohort). Seven articles reporting cases of osteonecrosis among bisphosphonate users were also described.

Figure 1. Literature Flow

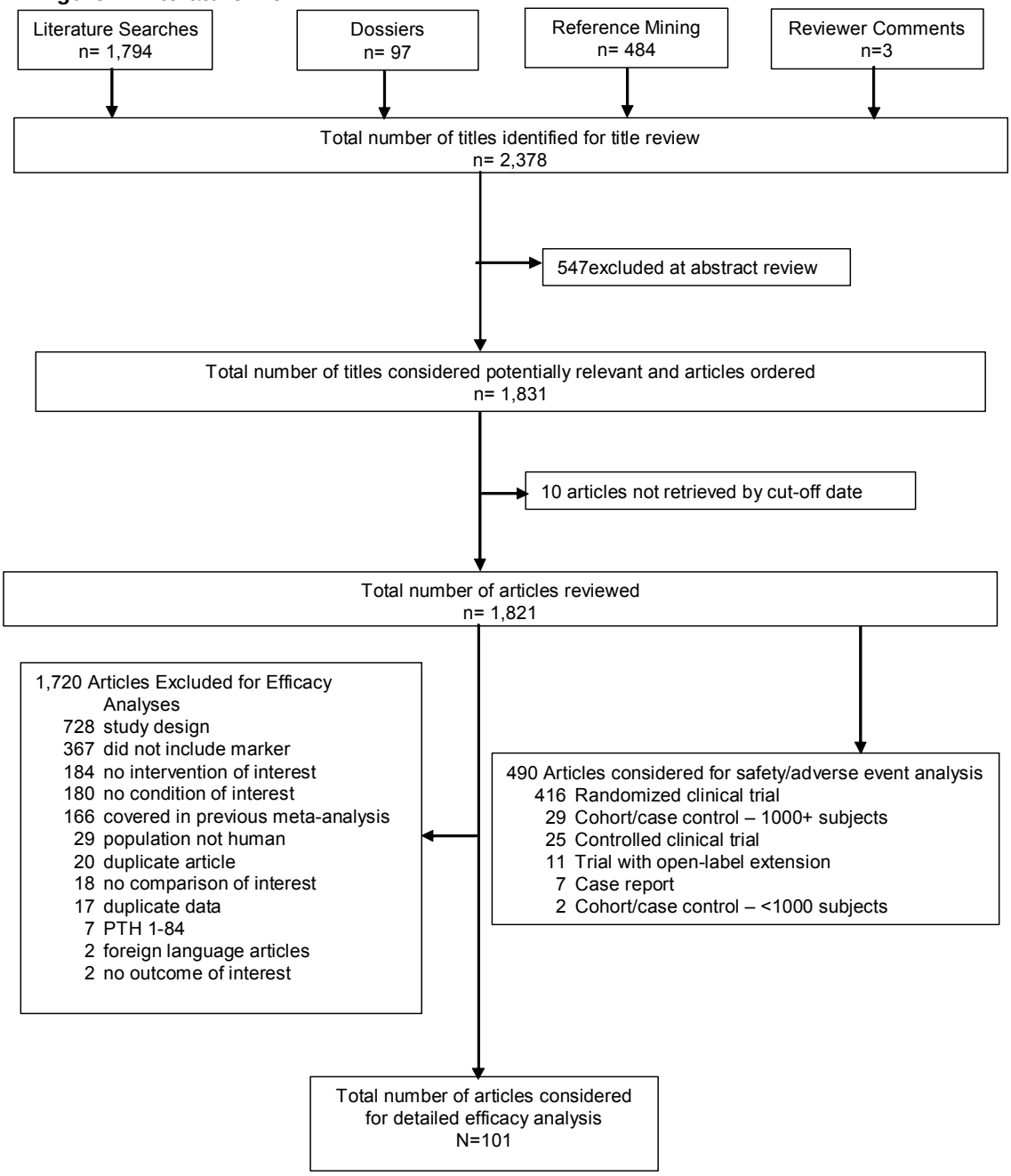
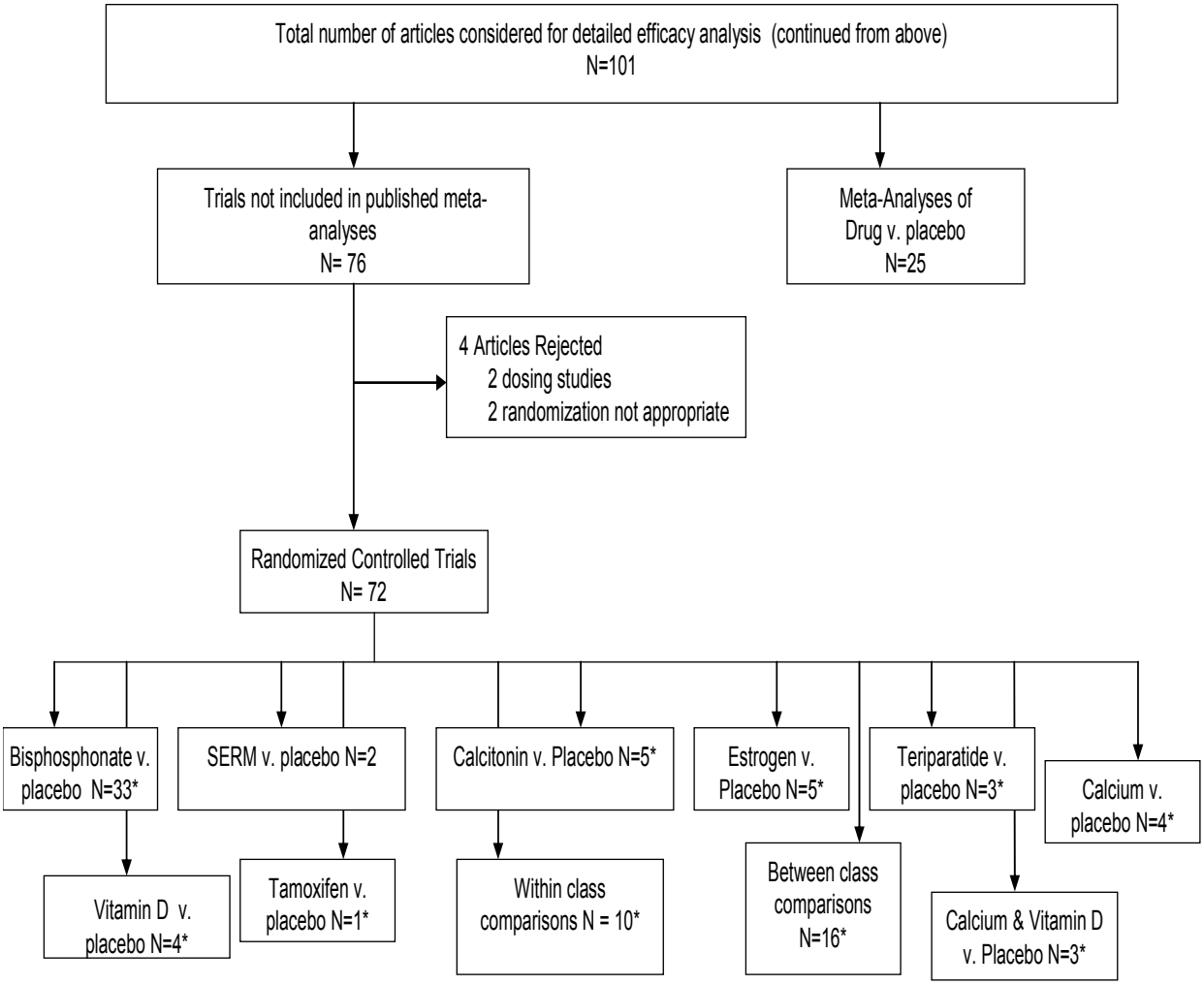


Figure 1. Literature Flow (continued)



*articles considered are not mutually exclusive

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, etidronate, ibandronate, pamidronate, risedronate,and zoledronic acid
- Calcitonin
- Calcium
- Estrogen for women
- 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 Points

- There is good evidence from RCTs that, compared with placebo, alendronate, etidronate, ibandronate, risedronate, calcitonin, 1-34 PTH, and raloxifene prevent vertebral fractures.
- There is good evidence from RCTs that both risedronate and alendronate prevent both non-vertebral and hip fractures--compared with placebo.
- There is good evidence that zoledronic acid prevents vertebral and nonvertebral fractures, and fair evidence (see addendum to executive summary) that it prevents hip fractures.
- There is evidence from one RCT that 1-34 PTH prevents non-vertebral fractures--compared with placebo.
- There is good evidence that estrogen is associated with a reduced incidence of vertebral, non-vertebral and hip fractures.
- There are no data from RCTs on the effect of testosterone on the prevention of fractures.

- There is evidence from a published meta-analysis and several RCTs that there is no difference between calcium alone and placebo in preventing vertebral, non-vertebral, hip and wrist fractures in postmenopausal women.

- According to a large body of literature, vitamin D had varying results 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, within the bisphosphonate class, superiority for the prevention of fractures has not been demonstrated for any agent.

- Based on limited head-to-head trial data, 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 of exercise relative to agents used to treat or prevent osteoporosis on fracture prevention.

Detailed Analyses

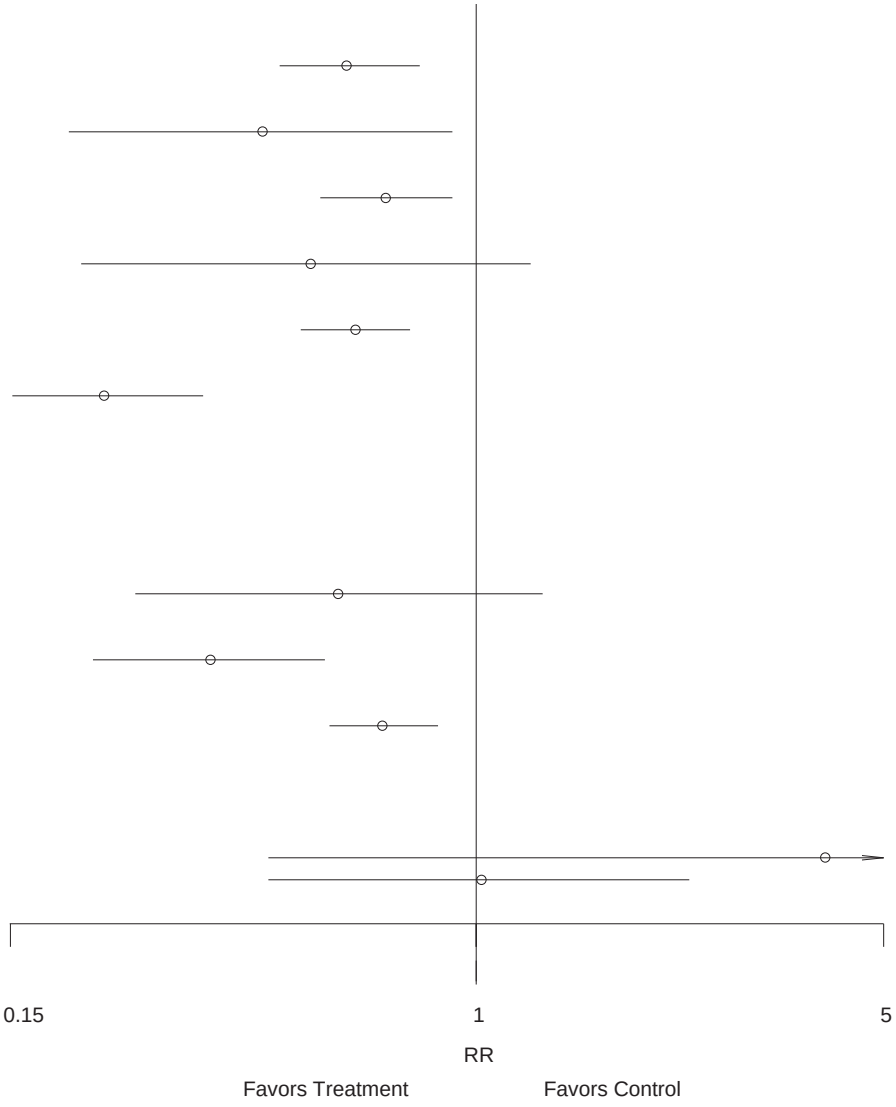
Drug vs. placebo comparisons

For nine of the 14 agents for the prevention or treatment of osteoporosis that were reviewed in this report (alendronate, etidronate, risedronate, calcitonin, estrogen, PTH, raloxifene, calcium, vitamin D), we identified 25 meta-analyses that described the effect of the agent relative to placebo on fracture incidence.[39-57, 57-62] Many RCTs not included in the meta-analyses described the risk of fracture for these single agents relative to placebo. For four of the five agents for which we did not identify meta-analses (ibandronte, pamidronate, zoledronic acid, tamoxifen) we identified 15 RCTs that described the risk of fracture relative to placebo. We did not find any meta-analyses or RCTs that reported fracture rates for testosterone relative to placebo. For the only agent combination evaluated for this report, i.e., calcium plus vitamin D, we identified three RCTs that evaluated the risk of fracture for combined calium and vitamin D relative to placebo.[63-65]

Figures 2-9 and the following text summarize from the available data the risk (relative to placebo) of developing fracture while taking the agents in question.

Figure 2. Risk of vertebral fracture relative to placebo for subjects at high risk for fracture, by agent*

Study	# Studies	# Fractures, agent	Sample Size, agent	# Fractures, placebo	Sample Size, placebo	Total Sample Size
BISPHOSPHONATES: Alendronate						
Stevenson, 2005[21]	2	95	1507	167	1320	2827
BISPHOSPHONATES: Etidronate						
Stevenson, 2005[21]	2	9	137	19	126	263
BISPHOSPHONATES: Ibandronate*	3	125	2955	137	1964	4919
BISPHOSPHONATES: Pamidronate*	4	8	123	14	122	245
BISPHOSPHONATES: Risedronate						
Stevenson, 2005[21]	2	114	1040	182	1024	2064
BISPHOSPHONATES: Zolendronic Acid						
Black, 2007[83]	1	19	3800	84	3231	7031
CALCITONIN**			. . . . .			
CALCIUM**			. . . . .			
ESTROGEN						
Stevenson, 2005[21]	2	8	51	12	53	104
PTH						
Stevenson, 2005[21]	1	22	444	64	448	892
SERMS: Raloxifene						
Stevenson, 2005[21]	1	113	769	163	770	153
TESTOSTERONE**			. . . . .			
VITAMIN D						
Avenell, 2005[25]	2	4	1378	1	1367	2745
Stevenson, 2005[21]	3	12	52	13	57	109



FOOTNOTES FOR FIGURES 2-9 APPEAR ON THE PAGE FOLLOWING FIGURE 9.

Figure 3. Risk of vertebral fracture relative to placebo for subjects not at high risk for fracture, by agent*

Study	# Studies	# Fractures, agent	Sample Size, agent	# Fractures, placebo	Sample Size, placebo	Total Sample Size
BISPHOSPHONATES: Alendronate						
Cranney, 2002[13]	2	NR	NR	NR	NR	1355
Sawka, 2005[31]	2	11	214	23	161	375
Stevenson, 2005[21]	3	72	2621	114	2472	5093
BISPHOSPHONATES: Etidronate						
Cranney, 2005[15]	10	32	538	54	538	1076
BISPHOSPHONATES: Ibandronate**						
BISPHOSPHONATES: Pamidronate**						
BISPHOSPHONATES: Risedronate						
Cranney, 2002[18]	5	NR	NR	NR	NR	2604
Miller, 2005[34]						
Subjects with severe renal impairment	9	NR	301	NR	271	572
Subjects with moderate renal impairment	9	NR	2034	NR	2037	4071
Subjects with mild renal impairment	9	NR	2161	NR	2192	4353
BISPHOSPHONATES: Zolendronic Acid**						
CALCITONIN						
Cranney, 2002[19]	4	NR	NR	NR	NR	1404
Kanis, 1999[20]	10	237	1309	271	678	1987
CALCIUM						
Shea, 2002[23]	5	NR	NR	NR	NR	576
ESTROGEN						
Torgerson, 2001[103]	13	NR	NR	NR	NR	6723
Stevenson, 2005[21]	2	10	602	5	616	1218
Wells, 2002[28]	5	NR	NR	NR	NR	3385
WHI						
Estrogen only[104]	1	39	5310	64	5429	10739
Estrogen + Progestin[65]	1	41	8506	60	8102	16608
PTH						
SERMS: Raloxifine						
Seeman, 2006[29]						
60 mg	4	172	2583	255	2624	5207
120/150 mg	5	147	2682	257	2739	5421
Schachter, 2005[22]	2	NR	NR	NR	NR	7848
Stevenson, 2005[21]	1	35	1490	68	1522	3012
TESTOSTERONE**						
VITAMIN D						
Avenell, 2005[25]	2	37	1477	41	1476	2953
Papadimitropoulos, 2002[24]						
Standard	1	NR	NR	NR	NR	160
Calcitrol	7	NR	NR	NR	NR	970
Richy, 2004[35]	9	NR	NR	NR	NR	1665
Stevenson, 2005[21]	1	8	18	9	22	40

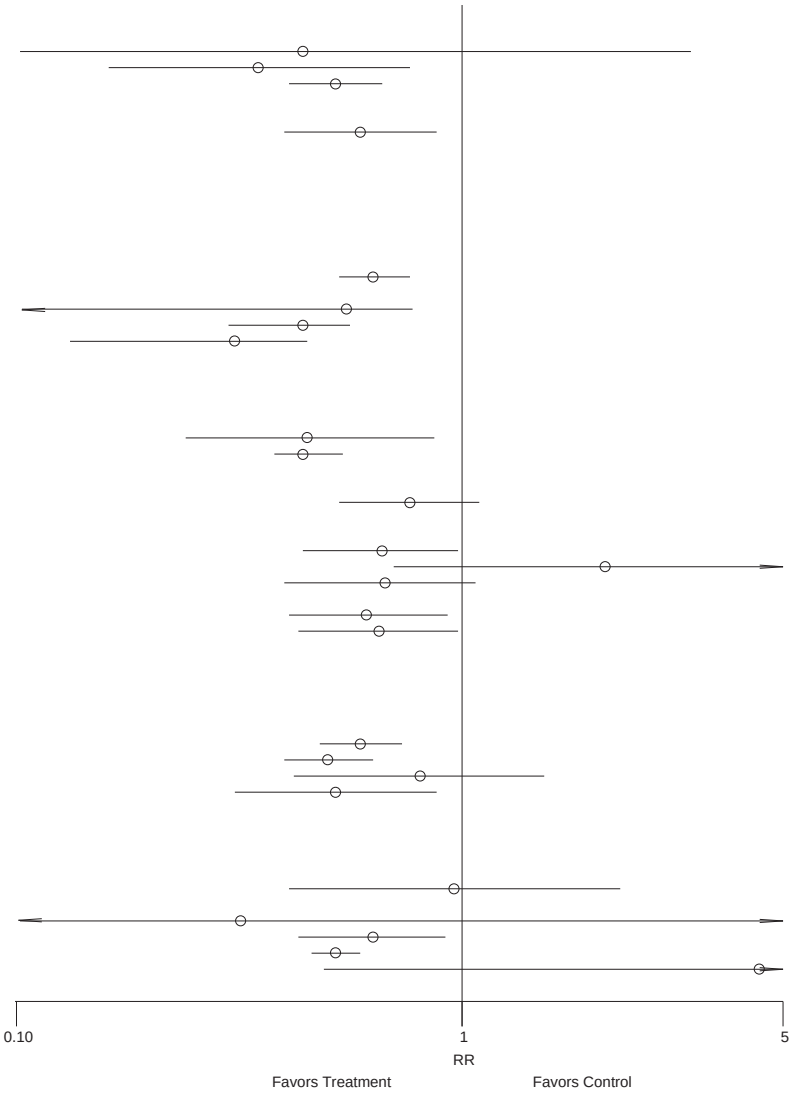


Figure 4. Risk of non-vertebral fracture relative to placebo for subjects at high risk for fracture, by agent*

Study	# Studies	# Fractures, agent	Sample Size, agent	# Fractures, placebo	Sample Size, placebo	Total Sample Size
BISPHOSPHONATES: Alendronate						
Stevenson, 2005[21]	2	167	1619	186	1402	3021
BISPHOSPHONATES: Etidronate						
Stevenson, 2005[21]	4	29	205	28	205	410
BISPHOSPHONATES: Ibandronate**						
	1	176	1954	89	975	2929
BISPHOSPHONATES: Pamidronate**						
	2	4	50	7	59	109
BISPHOSPHONATES: Risedronate						
Stevenson, 2005[21]	2	69	1218	103	1221	2439
BISPHOSPHONATES: Zolendronic Acid						
Black,2007[83]	1	292	3650	388	3626	7276
ESTROGEN						
Stevenson, 2005[21]	2	2	43	3	43	86
Torgerson, 2001[103]	8	NR	NR	NR	NR	NR
PTH						
Stevenson, 2005[21]	1	34	541	53	544	1085
SERMS: Raloxifene						
Stevenson, 2005[21]	1	437	4536	240	2292	6828
TESTOSTERONE**						
			.....			
VITAMIN D						
Stevenson, 2005[21]	1	5	101	12	112	213

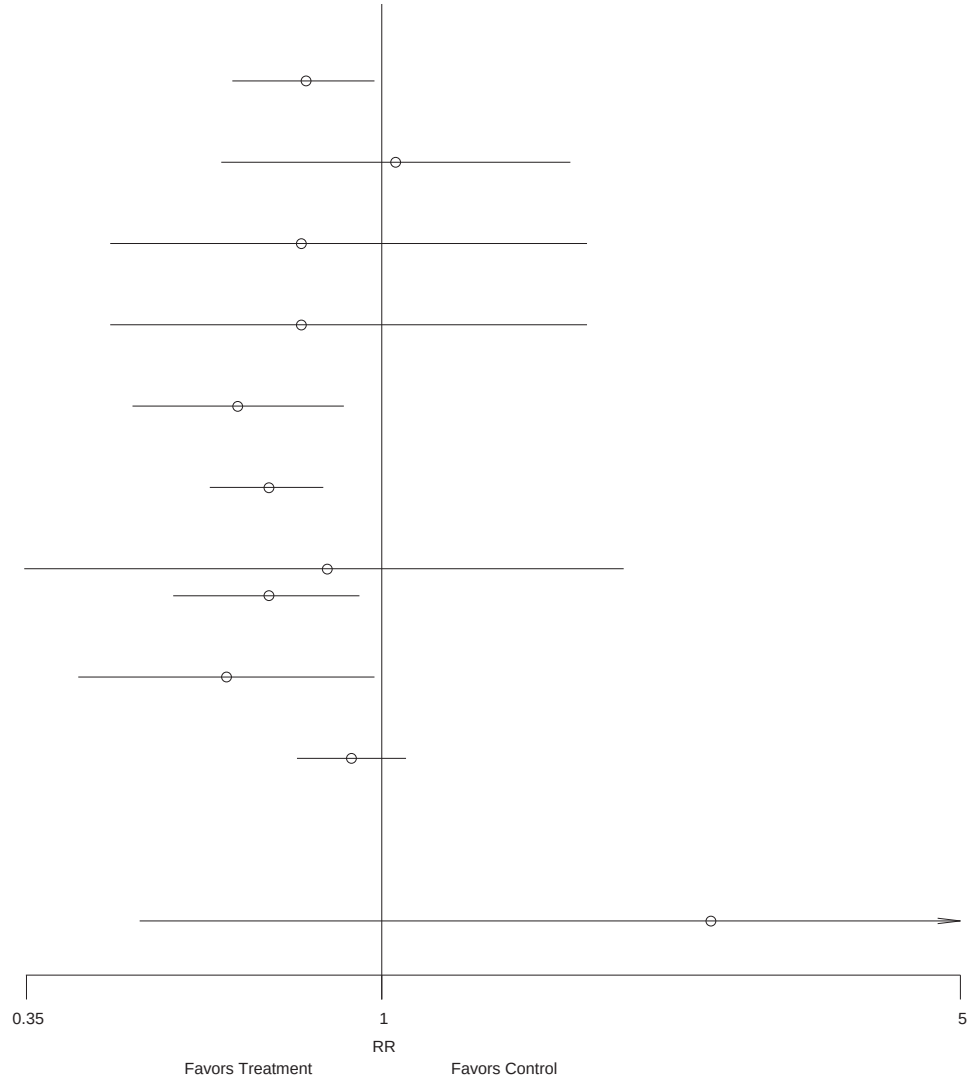


Figure 5. Risk of non-vertebral fracture relative to placebo for subjects not at high risk for fracture, by agent*

Study	# Studies	# Fractures, agent	Sample Size, agent	# Fractures, placebo	Sample Size, placebo	Total Sample Size
BISPHOSPHONATES: Alendronate						
Boonen, 2005[36]	3	NR	3833	NR	3620	7453
Cranney, 2002[13]	6	NR	NR	NR	NR	3723
Karpf, 1997[14]	5	73	1012	60	590	1602
Sawka, 2005[31]	2	12	214	13	161	375
Stevenson, 2005[21]	3	287	3258	352	3368	6626
BISPHOSPHONATES: Etidronate						
Cranney, 2005[15]	8	48	433	49	434	867
BISPHOSPHONATES:Ibandronate**				. . . . .		
BISPHOSPHONATES:Pamidronate**				. . . . .		
BISPHOSPHONATES:Risedronate						
Boonen, 2005[36]	3	NR	7416	NR	4355	11771
Cranney, 2002[18]	7	NR	NR	NR	NR	12958
BISPHOSPHONATES:Zolendronic acid						
Reid, 2007[82]	1	1	60	1	59	119
CALCITONIN						
Cranney, 2002[19]	3	NR	NR	NR	NR	1482
Kanis, 1999[20]	10	NR	NR	NR	NR	1744
CALCIUM						
Shea, 2002[23]	2	NR	NR	NR	NR	222
ESTROGEN						
Stevenson, 2005[21]	13	229	4112	261	3204	7316
Torgenson, 2001[103]	6	NR	NR	NR	NR	5383
Wells, 2002[28]	22	NR	NR	NR	NR	8774
PTH**				. . . . .		
SERMS: Raloxifene**				. . . . .		
TESTOSTERONE**				. . . . .		
VITAMIN D						
Avenell, 2005[25]				. . . . .		
Alphacalcidol	2	5	236	12	230	466
Calcitrol	1	6	123	13	123	246
Bischoff-Ferrari, 2005[26]	7	613	5046	655	4774	9820
Stevenson, 2005[21]	1	NR	18	NR	22	40
Papadimitropoulos, 2002[24]				. . . . .		
Standard Vitamin D	3	NR	NR	NR	NR	5399
Calcitriol	3	NR	NR	NR	NR	788
Either	6	NR	NR	NR	NR	6187
Richy, 2004[35]				. . . . .		
Calcitriol	5	NR	NR	NR	NR	381
Alphacalcidol	6	NR	NR	NR	NR	929

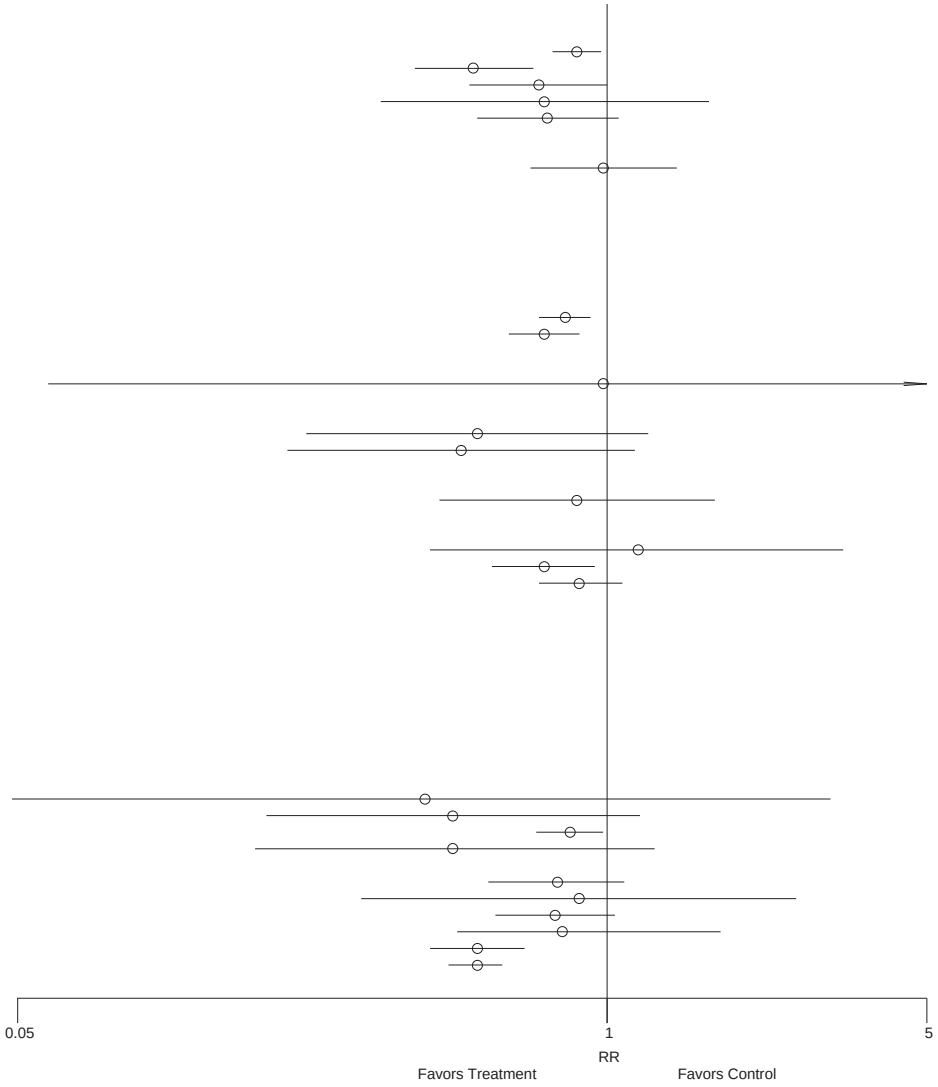


Figure 6. Risk of hip fracture relative to placebo for subjects at high risk for fracture, by agent*

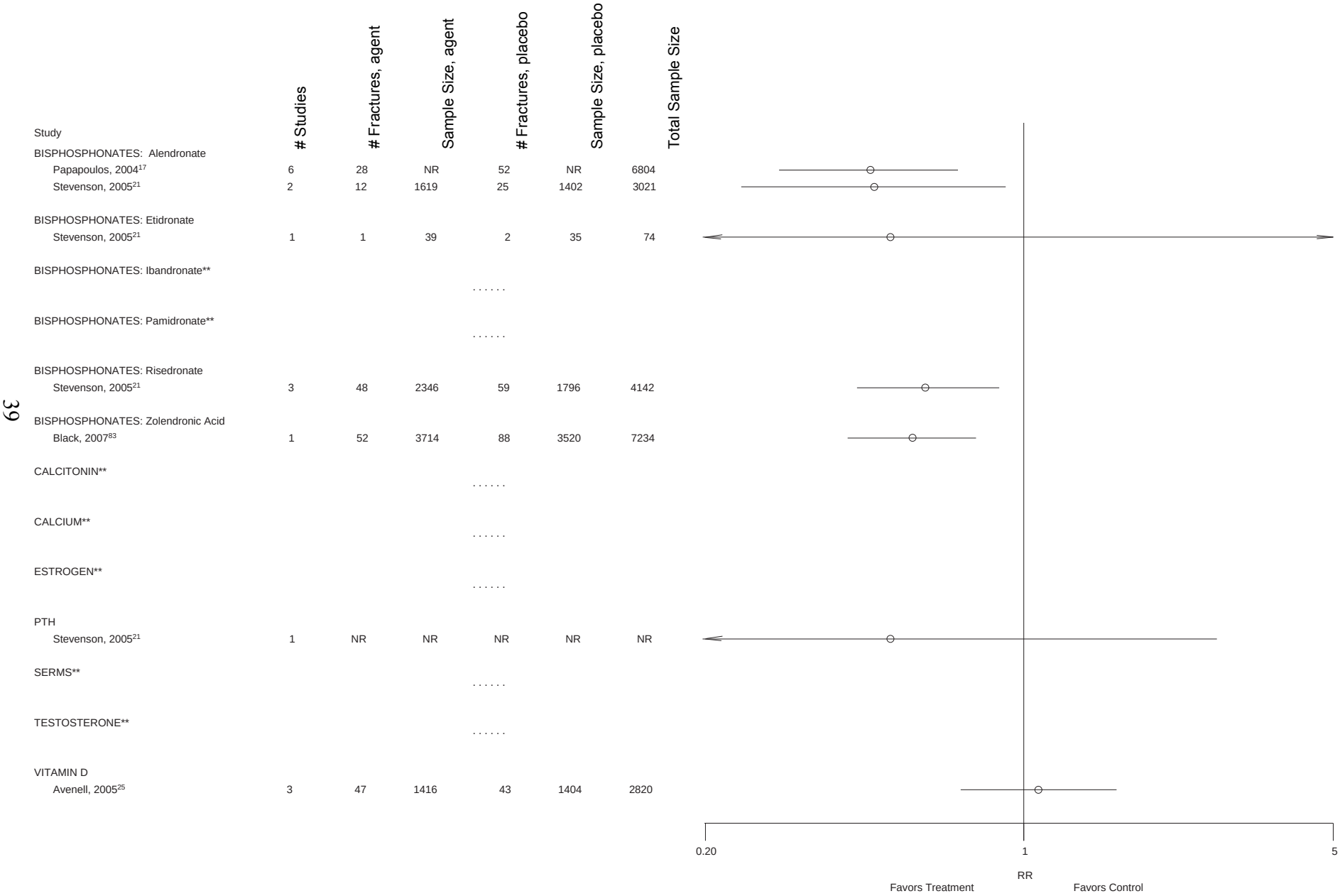


Figure 7. Risk of hip fracture relative to placebo for subjects not at high risk for fracture, by agent*

Study	# Studies	# Fractures, agent	Sample Size, agent	# Fractures, placebo	Sample Size, placebo	Total Sample Size
BISPHOSPHONATES: Alendronate						
Cranney, 2002[13]	8	NR	NR	NR	NR	8603
Karpf, 1997[14]	5	6	1012	7	590	1602
Nguyen, 2005[30]	6	40	5511	59	4878	10389
Papapoulos, 2004[17]	6	37	NR	57	NR	6804
Stevenson, 2005[21]	2	20	2811	27	2615	5426
BISPHOSPHONATES: Etidronate						
Cranney, 2001[15]	4	5	295	4	294	589
Nguyen, 2006[30]	2	2	245	4	244	489
BISPHOSPHONATES: Ibandronate**						
BISPHOSPHONATES: Pamidronate**						
BISPHOSPHONATES: Risedronate						
Nguyen, 2006[30]	3	76	4519	75	2677	7196
Stevenson, 2005[21]	3	81	4842	80	3042	7884
BISPHOSPHONATES: Zolendronic Acid**						
CALCITONIN**						
CALCIUM**						
ESTROGEN						
Stevenson, 2005[21]	5	59	10588	78	10210	20798
WHI						
Estrogen Only[104]	1	38	5310	64	5429	10739
Estrogen + Progestin[65]	1	52	8506	73	8102	16608
PTH**						
SERMS: Raloxifine						
Stevenson, 2005[21]	1	40	4536	18	2292	6828
TESTOSTERONE**						
VITAMIN D						
Avenell, 2005[25]						
Alphacalciferol	3	1	122	11	117	239
Calcitriol	1	0	123	1	123	246
Standard D	4	195	7932	163	7916	15848
BischoffFerrari, 2005[26]	5	293	4774	318	4520	9294

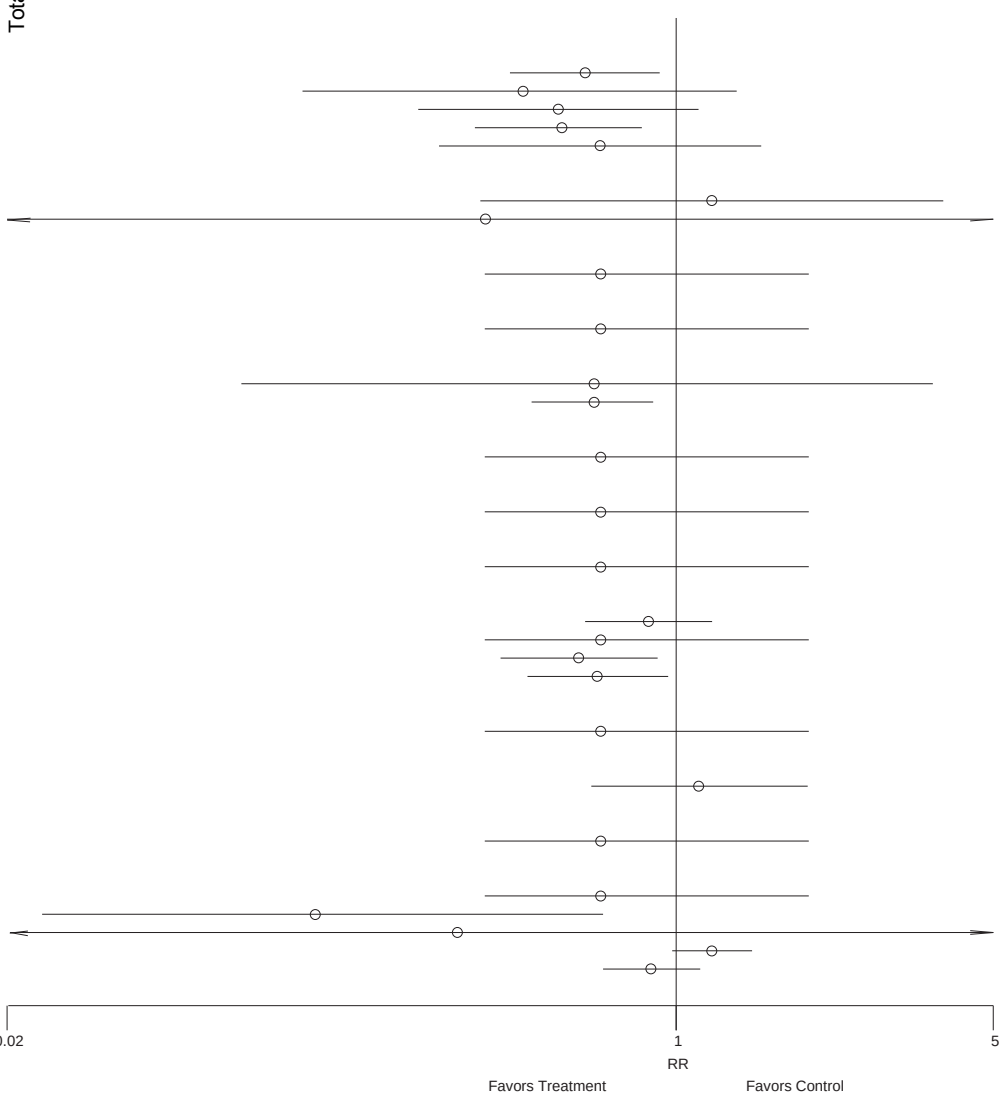


Figure 8. Pooled risk of wrist fracture among populations at high risk for fracture for agents used to treat or prevent osteoporosis relative to placebo*

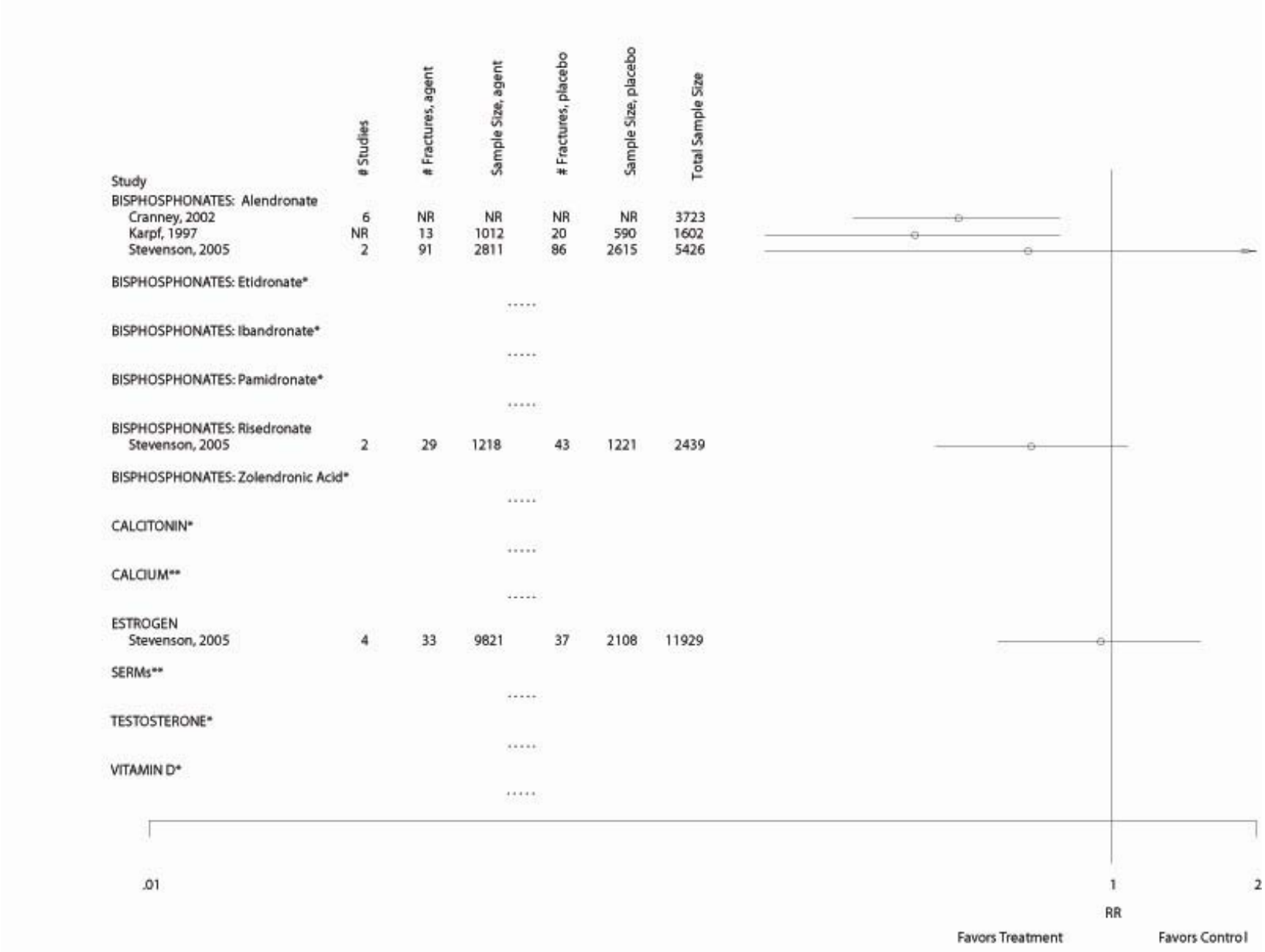
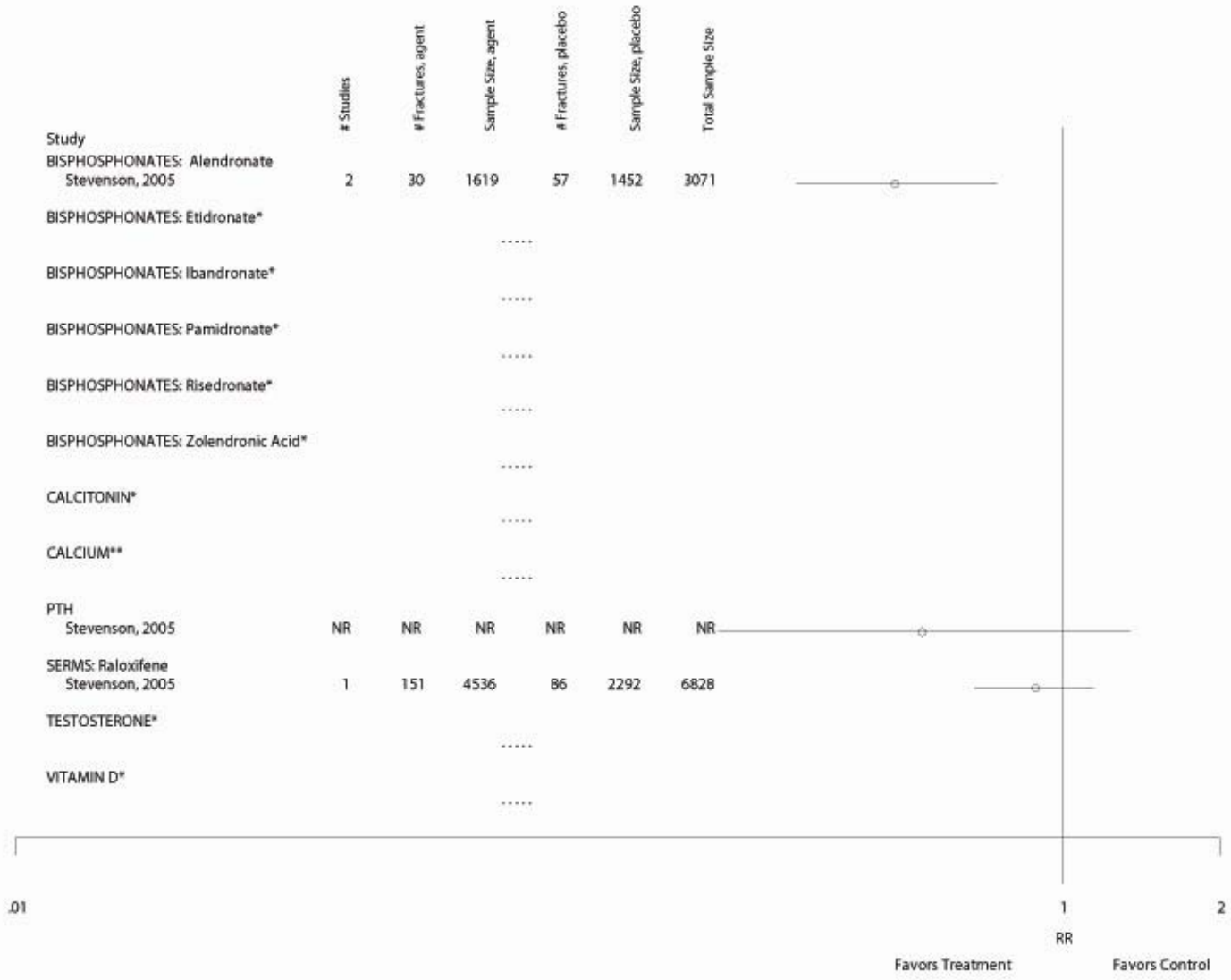


Figure 9. Pooled risk of wrist fracture among populations not defined as at high risk for fracture for agents used to treat or prevent osteoporosis relative to placebo*



FOOTNOTES FOR FIGURES 2-9

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years.
† Pooled risk estimate from cited meta-analys(is)(es) or systematic review(s).
‡ Pooled risk estimate calculated by authors; restricted to studies with ≥ 12 months of follow-up.
§ Risk estimate calculated from cited individual study.
** Insufficient data to calculate risk.

Bisphosphonates

Alendronate:

We identified seven meta-analyses[39, 40, 43, 47, 56, 57, 62] that pooled data from 17 different RCTs to estimate the effect of alendronate on fracture risk reduction relative to placebo (or no treatment) among postmenopausal women. The studies that were included in each of the meta-analyses are detailed in Table 2. These meta-analyses reported pooled risk estimates for vertebral, non-vertebral, hip, and wrist fractures (Table 3).

We identified seven RCTs[66-72] not included in the meta-analyses that describe the number of fractures among subjects treated with alendronate and placebo (Table 4). The study population in six of these studies was postmenopausal women with intermediate[67, 69, 70, 72] or high[66, 68] risk for fracture. In one of these studies, the postmenopausal women also had Parkinson's disease.[72] The population in the other study comprised men and women with primary biliary cirrhosis, who had an intermediate risk for fracture.[71]

Fracture prevention was the primary outcome in one study, which assessed the effect of alendronate on fracture risk among postmenopausal women at intermediate risk for fracture.[70] The risk for vertebral fracture for women treated with alendronate relative to placebo was 0.43 (95% CI 0.23, 0.79). The risk of fracture was significantly lower for alendronate compared with placebo in one other study, which assessed risk among postmenopausal women with Parkinson's disease.[72] In this study, fracture was a secondary outcome. The risk of hip fracture for women treated with alendronate relative to placebo was 0.30 (95% CI, 0.12, 0.78).

The risk of fracture was not significantly different between alendronate and placebo in any of the other studies. However, in all other studies, fractures were assessed either as secondary outcomes[67, 71] or adverse events.[66, 68, 69] The sample sizes in these studies were not sufficiently large to detect differences in fracture risk among study groups.

Table 2. Randomized controlled trials included in meta-analyses of effect of alendronate on fracture relative to placebo or no treatment, by fracture type*

RCTs (Author, year)	Meta-analysis (Author, year)															
	Cranney, 2002[39]				Karpf, 1997[40]			Papapoulos, 2004[43]	Stevenson, 2005[47]				Boonen, 2005[62]	Nguyen, 2006[56]	Sawka, 2005[57]	
	Fracture type*															
	V	NV	H	W	NV	H	W	H	V	NV	H	W	NV	H	V	NV
Adami, 1995[73]	X	X			X	X	X									
Black, 1996[74]	X	X	X	X				X	X	X	X	X	X	X		
Bone, 1997[75]	X	X														
Bonnick, 1998[76]		X						X						X		
Chesnut, 1995[77]	X	X			X	X	X									
Cummings, 1998[78]	X	X						X	X		X	X	X	X		
Dursun, 2001[79]									X							
Greenspan, 1998[80]								X								
Greenspan, 2002[81]														X		
Hosking, 1998[82]	X	X														
Liberman, 1995[83]	X	X			X	X	X	X	X	X	X	X	X	X		
McClung, 1998[84]	X	X														
Orwoll, 2000[85]															X	X
Pols, 1999[86]		X								X				X		
Ringe, 2004[87]															X	X
Unpublished data					X	X	X									
Weinstein, 1994[88]					X	X	X									

* V=vertebral, NV=non-vertebral, H=hip, W=wrist/forearm; X= Included in pooled analysis.

Table 3. Pooled risk estimates of fracture for alendronate, relative to placebo or no treatment, among postmenopausal women*

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral				
Cranney, 2002[39]				
Prevention trials, dose ≥ 5 mg/d	2	1,355	0.45	(0.06, 3.15)
Treatment trials, dose ≥ 5 mg/d	7	8,005	0.53	(0.43, 0.65)
Sawka, 2005[57]		375	0.36	(0.17, 0.77)
Stevenson, 2005[47]				
Subjects with osteoporosis or osteopenia	3	5,093	0.60	(0.46, 0.80)
Subjects with osteoporosis or severe osteoporosis	2	2,827	0.53	(0.42, 0.67)
Non-vertebral				
Boonen, 2005[62]	3	7,453	0.86	(0.76, 0.97)
Cranney, 2002[39]				
All trials, 5 mg/d	8	8,603	0.87	(0.73, 1.02)
All trials, 10-40 mg/d	6	3,723	0.51	(0.38, 0.69)
Treatment trials, 10-40 mg/d			0.51	(0.38, 0.69)
Karpf, 1997[40]	5	1,602	0.71	(0.50, 1.00)
Sawka, 2005[57]	2	375	0.73	(0.32, 1.67)
Stevenson, 2005[47]				
Subjects with osteoporosis or osteopenia	3	6,626	0.74	(0.52, 1.06)
Subjects with osteoporosis or severe osteoporosis	2	3,021	0.81	(0.66, 0.98)
Hip				
Cranney, 2002[39]				
All trials, 5 mg/d	8	8,603	0.70	(0.46, 1.05)
All trials, 10-40 mg/d	6	3,723	0.45	(0.18, 1.13)
All trials, 5-40 mg/d	11	11,808	0.63	(0.43, 0.92)
Karpf, 1997[40]	5	1,602	0.46	(0.15, 1.36)
Nguyen, 2005[56]	6	10389	0.55	(0.27, 1.12)
Papapoulos, 2004[43]				
Subjects with T score ≤ 2.0 or with vertebral fracture	6	9,023	0.55	(0.36, 0.84)
Subjects with T score ≤ 2.5 or with vertebral fracture	6	6,804	0.45	(0.28, 0.71)
Stevenson, 2005[47]				
Subjects with osteoporosis or osteopenia	2	5,426	0.68	(0.30, 1.54)
Subjects with osteoporosis or severe osteoporosis	2	3,021	0.46	(0.23, 0.91)
Forearm/Wrist				
Cranney, 2002[39]				
All trials, 5 mg/d	8	8,603	0.84	(0.51, 1.40)
All trials, 10-40 mg/d	6	3,723	0.48	(0.29, 0.78)
Karpf, 1997[40]	5	1,602	0.39	(0.19, 0.78)
Stevenson, 2005[47]				
Subjects with osteoporosis or osteopenia	2	5,426	0.67	(0.19, 2.32)
Subjects with osteoporosis or established osteoporosis	2	3,071	0.48	(0.31, 0.75)

* Cranney: 'treatment trial' population has T-score < -2 SD and/or baseline prevalence of fracture is >20% and/or average age is >62; 'prevention trial' population has T-score ≥ -2 SD and/or baseline prevalence of fracture is ≤20% and/or average age is ≤62. Stevenson: severe osteoporosis defined as T score <- 2.5 SD AND at least one documented fracture; osteoporosis defined as T score <- 2.5 SD without prior fracture; osteopenia defined as T-score between -1 and -2.5 SD.

Table 4. Risk of fracture for alendronate, any dose, relative to placebo, by fracture group

Author, year	Study duration	Type of fracture	Risk level*	Number of fractures, alendronate	Number of fractures, placebo	Odds ratio (95% CI)
TOTAL FRACTURES						
Bone, 2000[66]	24 months	any clinical fracture	High	5/92	4/50	0.65 (0.16, 2.66)
Greenspan, 2003[67]	36 months	clinical fracture	Intermediate	7/93	9/93	0.76 (0.27, 2.12)
Hosking, 2003[68]	12 months	clinically diagnosed vertebral or nonvertebral	High	6/172	2/89	1.52 (0.34, 6.67)
VERTEBRAL FRACTURES						
McClung, 2006[69]	12 months	clinical vertebral fracture	Intermediate	1/46	1/46	1.00 (0.06, 16.23)
Quandt, 2005[70]	54 months	clinical vertebral fracture	Intermediate	12/1878	29/1859	0.43 (0.23, 0.79)
Zein, 2005[71]	12 months	new compression/vertebral fracture	Intermediate	1/14	0/13	6.88 (0.14, 347.7)
NON-VERTEBRAL FRACTURES						
Zein, 2005[71]	12 months	peripheral fracture	Intermediate	0/14	1/13	0.13 (0.00, 6.33)
HIP						
Sato, 2006[72]	48 months	hip fracture	Intermediate	4/131	14/129	0.30 (0.12, 0.78)
WRIST						
McClung, 2006[69]	12 months	Radius, ulna, or both	Intermediate	0/46	0/46	NC
HUMERUS						
McClung, 2006[69]	12 months	Humerus	Intermediate	0/46	0/46	NC

*High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.
NC=not calculable.

Etidronate:

We identified three meta-analyses[41, 47, 56] that pooled data from 11 different RCTs to estimate the effect of etidronate on fracture risk reduction relative to placebo or no treatment among postmenopausal women (Table 5). These meta-analyses reported pooled risk estimates for vertebral, non-vertebral, hip, and wrist fractures (Table 6).

We identified six RCTs[89-94] not included in the meta-analyses that describe the number of fractures among subjects treated with etidronate and placebo (Table 7). The study population in three of these studies was postmenopausal women with high[89, 91, 93] risk for fracture. The populations in the other three studies were at intermediate risk for fracture and included men and women with asthma[92] or connective tissue disease[94] requiring treatment with glucocorticoids or amyotrophic lateral sclerosis (ALS).[90]

Although fracture was the primary outcome at the start of one study,[92] enrollment was lower than anticipated and the final sample size was not sufficiently large to detect differences in fracture risk between etidronate and placebo. In another study,[90] the primary and secondary outcomes were not clearly stated, although this study likewise had insufficient sample size to detect differences in fracture risk between etidronate and placebo. In all other studies, fractures were assessed either as secondary outcomes[91, 93, 94] or adverse events.[89] The sample sizes in these studies were not sufficiently large to detect differences in fracture risk among study groups.

Among all of these studies, the risk of fracture for etidronate relative to placebo was significant in one.[93] In this study, which assessed the risk of vertebral fracture among postmenopausal women at high risk for fracture, the risk of fracture for etidronate relative to placebo was 0.41 (95% CI, 0.17, 0.99).

Table 5. Randomized controlled trials included in meta-analyses of effect of etidronate on fracture relative to placebo or no treatment

	Meta-analyses (Author, year)						
RCTs (Author, year)	Cranney, 2001[41]			Stevenson, 2005[47]			Nguyen, 2006[56]
	Fracture type*						
	V	NV	H	V	NV	H	H
Harris, 1995*							X
Herd, 1997[95]	X						
Iwamoto, 2001[96]					X		
Lyritis, 1997[97]	X	X	X	X	X	X	
Meunier, 1997[98]	X	X					
Montessori, 1997[99]	X	X					
Pacifici, 1988[100]	X						
Pouilles, 1997[101]	X	X					
Storm, 1990[102]	X	X	X		X		X
Watts, 1990[103]	X	X	X	X	X	X	
Wilmalawansa, 1998[91]	X	X			X		

* V=vertebral, NV=nonvertebral, H=hip, W=wrist/forearm; X= Included in pooled analysis.

Table 6. Pooled risk estimates of fracture for etidronate, relative to placebo or no treatment, among postmenopausal women*

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Cranney, 2001[41]				
All trials	10	1,076	0.60	(0.41, 0.88)
Prevention trials	5	738	0.61	(0.29, 1.26)
Treatment trials	5	338	0.59	(0.38, 0.94)
Stevenson, 2005[47]				
Subjects with established osteoporosis	2	263	0.43	(0.20, 0.91)
Non-vertebral				
Cranney, 2001[41]				
All trials	8	867	0.98	(0.68, 1.42)
Prevention trials	4	586	1.05	(0.69, 1.60)
Treatment trials	4	281	0.75	(0.34, 1.70)
Stevenson, 2005[47]				
Subjects with established osteoporosis	4	410	1.04	(0.64, 1.69)
Hip				
Cranney, 2001[41]				
All trials	4	589	1.20	(0.37, 3.88)
Nguyen, 2006[56]	2	489	0.38	(0.004-171.8)
Stevenson, 2005[47]				
Subjects with severe osteoporosis	1	309	0.50	(0.05, 5.34)

* Cranney: 'treatment trial' population has T-score < -2 SD and/or baseline prevalence of fracture is >20% and/or average age is >62; 'prevention trial' population has T-score ≥ -2 SD and/or baseline prevalence of fracture is ≤20% and/or average age is ≤62. Stevenson: severe osteoporosis defined as T score <- 2.5 SD AND at least one documented fracture; osteoporosis defined as T score <- 2.5 SD without prior fracture; osteopenia defined as T-score between -1 and -2.5 SD.

Table 7. Risk of fracture for etidronate, any dose, relative to placebo or control, by fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, etidronate	Number of fractures, placebo or control†	Odds ratio (95% CI)
VERTEBRAL FRACTURES						
Campbell, 2004[92]	60 months	new symptomatic or semi-quantative vertebral fractures	Intermediate	13/81	19/95†	0.77 (0.36, 1.65)
Ishida, 2004[93]	24 months	vertebral	High	8/66	17/66†	0.41 (0.17, 0.99)
Sato, 2003[94]	36 months	New vertebral	Intermediate	0/30	2/31	0.14 (0.01, 2.21)
Sato, 2006[90]	24 months	vertebral	Intermediate	0/41	3/41	0.13 (0.01, 1.27)
Wimalawansa, 1998[91]	48 months	vertebral	High	3/14	5/14†	0.51 (0.10, 2.55)
NON-VERTEBRAL FRACTURES						
Wimalawansa, 1998[91]	48 months	nonvertebral	High	1/14	1/14	1.00 (0.06, 16.85)
HIP						
Sato, 2004[89]	3 months	hip fracture	High	0/36	0/37	NC
HUMERUS						
Sato, 2006[90]	24 months	proximal humerus fracture	Intermediate	1/41	1/41	1.00 (0.06, 16.27)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

† Versus control.

Ibandronate:

We identified four RCTs[104-107] that reported the effects of ibandronate relative to placebo or control on the incidence of fractures (Table 8). The study population in three of these studies was postmenopausal women with osteoporosis or osteopenia.[104-106] The study population in the other study was male and female kidney transplant recipients.[107] In two of these studies, fracture prevention was the primary outcome and the studies had sufficiently large sample sizes to detect differences in fracture risk among study groups.[105, 106] In the other two studies,[104, 107, 108] fracture data were reported as adverse events among samples not large enough to detect differences in fracture rates among study groups.

Among the studies that evaluated fracture risk as a primary outcome, one assessed the effect of daily and intermittent ibandronate on vertebral (primary outcome) and non-vertebral (secondary outcome) fractures among 1,952 subjects.[105] In this study, the risks of clinical vertebral fractures for daily and intermittent ibandronate relative to placebo were the same, 0.54 (95% CI, 0.32, 0.88). The relative risks of clinical non-vertebral fractures for daily and intermittent ibandronate relative to placebo were 1.0 (95% CI, 0.73, 1.36) and 1.09 (95% CI, 0.80, 1.50), respectively. The other study found no association between ibandronate and morphometric vertebral fractures among 2,862 subjects.[106]

Among the studies that reported fracture data as secondary outcomes[107] or adverse events[104], one was performed among 180 postmenopausal women[104] and the other among 80 kidney transplant recipients.[107] The first of these studies included 5 different dosage groups for ibandronate. Fracture risk for ibandronate relative to placebo was not statistically significant for any individual dose group. However, when all dose groups were pooled, the risk of fracture for ibandronate relative to placebo was slightly but significantly reduced (Table 8). The data reported in these studies did not demonstrate an association between ibandronate and either arm- or vertebral fractures, but the studies were not powered to do so.

Among the four studies that reported rates of vertebral fractures, the pooled risk of fracture for ibandronate relative to placebo was 0.70 (95% CI 0.54, 0.91).

Table 8. Risk of fracture for ibandronate, any dose, relative to placebo, by fracture group*

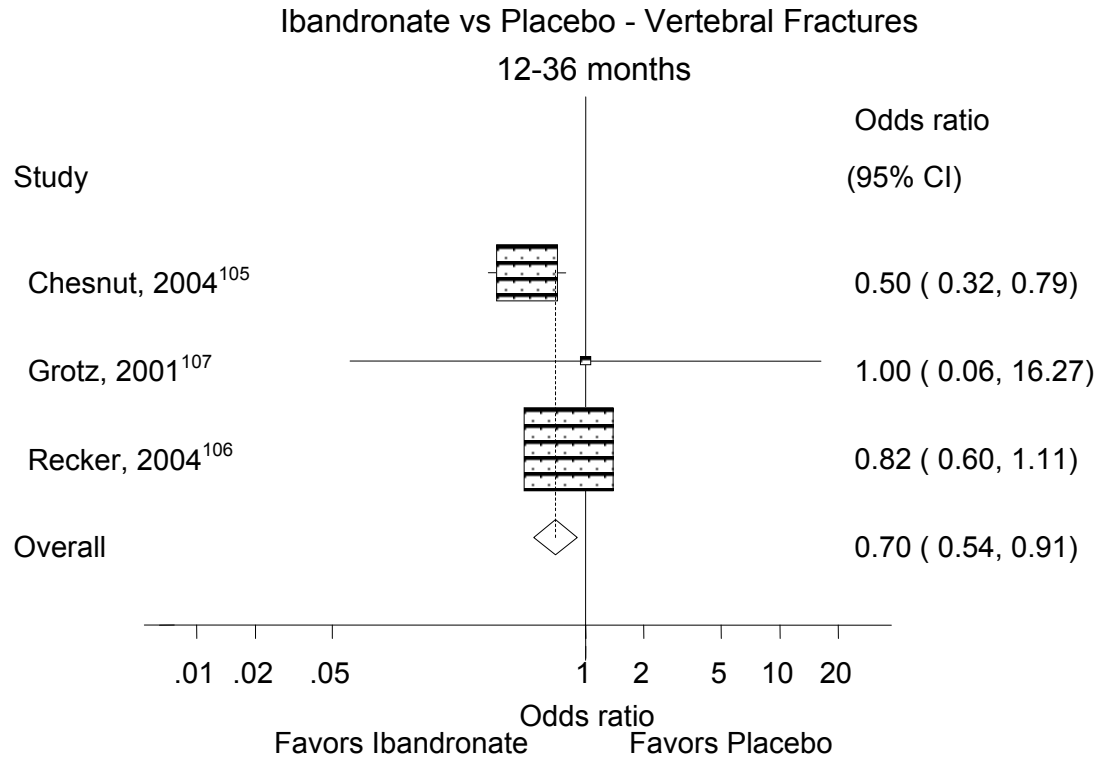
Author, year	Study duration	Type of fracture	Risk level	Number of fractures, ibandronate	Number of fractures, placebo	Odds ratio (95% CI)
ALL FRACTURES						
Ravn, 1996[104]	12 months	fracture	Intermediate	0/150†	1/30	0.002 (0.00, 0.477)
VERTEBRAL						
Chesnut, 2004[105]	36 months	clinical vertebral	High	44/1954‡	41/975	0.50 (0.32, 0.79)
Grotz, 2001[107]	12 months	vertebral	High	1/40	1/40	1.00 (0.006, 16.27)
Recker, 2004[106]	36 months	morphometric vertebral fractures	High	80/961	95/949	0.82 (0.60, 1.11)
NON-VERTEBRAL						
Chesnut, 2004[105]	36 months	clinical osteoporotic nonvertebral	High	176/1954†	89/975	0.995 (0.76, 1.30)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

† 0.25mg , 0.50mg, 1.0mg, 2.5mg and 5.0 mg dose groups combined.

‡ daily and intermittent dose groups combined.

Figure 10. Pooled risk of vertebral fractures for ibandronate relative to placebo or control



Heterogeneity chi-squared = 3.08 (d.f. = 2) p = 0.214
I-squared (variation in OR attributable to heterogeneity) = 35.1%

Test of OR=1 : z= 2.71 p = 0.007

Pamidronate:

We identified six RCTs[109-114] that reported the effects of pamidronate relative to placebo or control on the incidence of fractures (Table 9). Four of these studies were performed among male and female organ transplant recipients,[110, 111, 113, 114] one among men or women receiving chemotherapy for lymphoma[109] and one among postmenopausal women with osteoporosis or osteopenia.[112] The occurrence of new fractures was a secondary outcome in all of the studies. These studies reported the following types of fractures: hip, long bone, non-vertebral and vertebral. In the one study that assessed hip fractures, none occurred in either the pamidronate or control groups.[114] Relative to control, there was no significant association between pamidronate and long bone fractures (OR 0.48, 95% CI 0.11, 2.17). Likewise, relative to placebo, there was no significant association between pamidronate and non-vertebral fractures (OR 1.21, 95% CI 0.07, 19.96). However, none of the studies had sample sizes large enough to detect a difference in fracture rates between groups.

There were sufficient data to perform a pooled analysis only of vertebral fractures. Among the four studies with a 12-month study duration,[109, 110, 113, 114] the pooled odds of vertebral fractures for pamidronate relative to placebo or control among 269 subjects was 0.52 (95% CI, 0.21, 1.24). However, this pooled sample size is not large enough to detect a difference in fracture rates between study groups (Table 9 and Figure11). There are no data on use of pamidronate for postmenopausal osteoporosis.

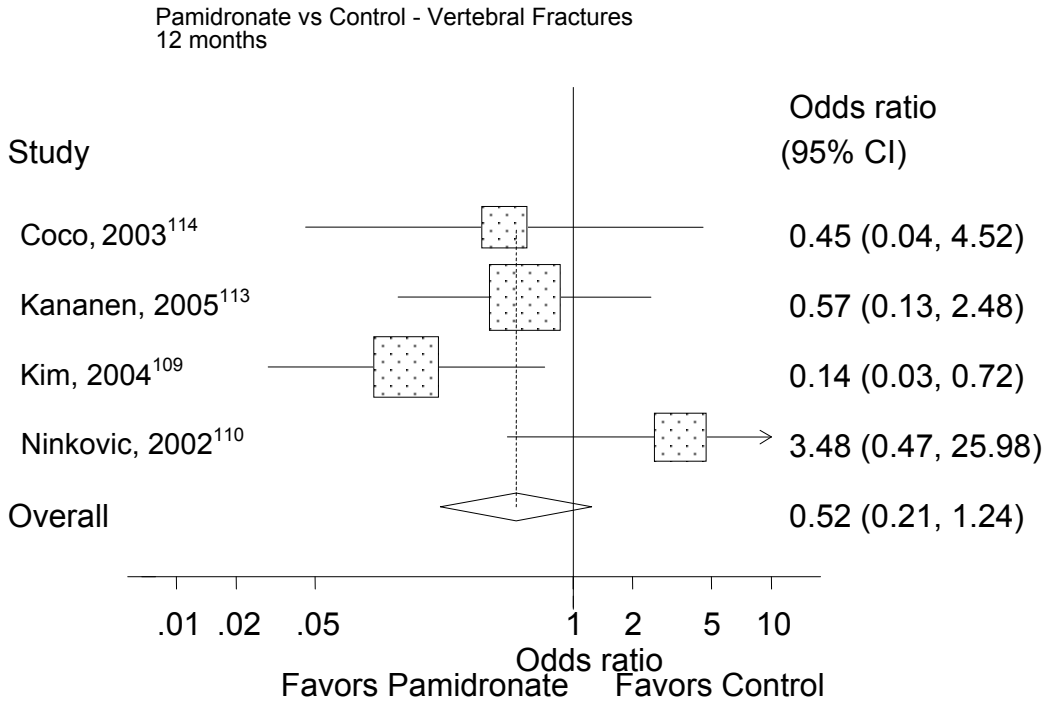
Table 9. Risk of fracture for pamidronate, any dose, relative to placebo, by fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, pamidronate	Number of fractures, placebo or control†	Odds ratio (95% CI)
VERTEBRAL						
Aris, 2000[111]	24 months	Vertebral	High	3/16	1/18†	3.43 (0.44, 26.92)
Coco, 2003[114]	12 months	Vertebral	High	1/31	2/28†	0.45 (0.04, 4.52)
Kananen, 2005[113]	12 months	Vertebral	High	3/33	5/33†	0.57 (0.13, 2.48)
Kim, 2004[109]	12 months	vertebral	High	1/25	6/20†	0.14 (0.03, 0.72)
Ninkovic, 2002[110]	12 months	vertebral	High	3/34	1/41	3.48 (0.47, 25.98)
Reid, 1994[112]	24 months	vertebral	High	7/26	10/22	0.45 (0.14, 1.46)
NONVERTEBRAL						
Aris, 2000[111]	24 months	long bone fracture	High	3/16	6/18†	0.48 (0.11, 2.17)
Ninkovic, 2002[110]	12 months	nonvertebral	High	1/34	1/41	1.21 (0.07, 19.96)
HIP						
Coco, 2003[114]	12 months	hip fractures	High	0/31	0/28†	NC

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

† Control group.

Figure 11. Pooled risk of vertebral fractures for pamidronate relative to placebo or control among subjects with organ transplants or undergoing chemotherapy



Heterogeneity chi-squared = 5.92 (d.f. = 3) p = 0.116
I-squared (variation in OR attributable to heterogeneity) = 49.3%

Risedronate:

We identified five meta-analyses[44, 47, 56, 60, 62] that pooled data from 10 different RCTs to describe the effect of risedronate on fracture risk reduction relative to placebo or no treatment, among postmenopausal women. We also identified two manuscripts each that pooled results from two RCTs, one which evaluated post-menopausal women,[115] and which evaluated men and women treated with corticosteroids.[116] The pooled analysis among post-menopausal women[115] is described in this section; the pooled analysis among subjects treated with glucocorticoids[116] is described in the section on glucocorticoids in this report (Table 57). The studies that were included in each of the meta-analyses and the pooled analysis among post-menopausal women are detailed in Table 10. The meta-analyses analyses reported pooled risk estimates for vertebral, non-vertebral, hip, and wrist fractures (Table 11). The pooled analysis reported a 47% (95% CI 23% to 63%) and 62% (95% CI 44%, 75%) risk reduction in vertebral fractures for risidronate relative to placebo after one year for doses of 2.5 mg/d and 5.0 mg/d of risedronate, respectively.

We identified ten RCTs[68, 117-125] not included in the meta-analyses that describe the number of fractures among subjects treated with risedronate and placebo (Table 12). The study population in six of these studies was postmenopausal women with high risk for fracture;[68, 117-120, 122, 125] in one it was postmenopausal women with intermediate risk of fracture.[121] The populations in the other three studies were male or predominantly male subjects at increased risk for fracture due to stroke,[124] leprosy[125] or marching (military recruits at risk for stress fractures).[123]

Fracture was the primary outcome in six of the studies. Significant reductions in the risk of vertebral and non-vertebral fractures for risedronate relative to placebo were reported in five of these studies, all of which included populations at high risk for fracture.[117-120, 124] In one of these studies there was a significant reduction in risk for vertebral but not non-vertebral or humeral fractures.[117] The study population and fracture risk was unique in the one study for which fracture risk was a primary outcome, but there was no difference in risk between the arms. This study assessed the risk of stress fractures induced by marching in health military recruits with mean age 19 years.[123]

None of the studies that assessed fracture as secondary outcomes or adverse events demonstrated a significant difference in fracture risk between risedronate and placebo.[121, 125, 126] None of these studies has sufficient sample size to detect a difference.

We identified three studies that reported fractures for different doses of risedronate (Table 13).[126-128] The risk of fracture did not differ between dose groups. However, fracture data were collected as secondary outcomes or adverse events in all of these studies and none had sufficient sample size to detect differences between dose groups. Among studies that compared various doses to placebo (but did not have different doses within the same study) and for which fracture was a primary outcome, there were reductions in the risks of all fractures, non-vertebral, and hip fractures with 2.5 mg daily dosing and reductions in the risk of vertebral fractures for 5.0 mg daily and 30 mg weekly dosing.

Table 10. Randomized controlled trials included in meta-analyses of effect of risedronate on fracture relative to placebo or no treatment

RCTs (Author, year)	Meta-analyses (Author, year)										
	Cranney, 2002[44]		Stevenson, 2005[47]				Boonen, 2005[62]	Miller, 2005[60]	Nguyen, 2006[56]	Watts, 2003[115]	Wallach, 2000[116]
	Fracture Type										
	Vertebral	Non-vertebral	Vertebral	Non-vertebral	Hip	Wrist	Non-vertebral	Vertebral	Hip	Vertebral	Vertebral
Clemmensen, 1997[129]	X	X									
Fogelman, 2000[130]	X	X						X			
Harris, 1999[131]	X	X	X	X	X	X	X	X	X	X	
Hooper, 2005[121]								X			
McClung, 1998[132]*		X						X			
McClung 1998[132]*											
McClung, 2001[133]*		X			X			X			
McClung, 2001[133]*		X					X	X	X		
Mortensen, 1998[134]	X	X									
Reginster, 2000[135]	X	X	X	X	X	X	X	X	X	X	
Reid, 2000[136]											X
Cohen, 1999[137]											X

X= Included in pooled analysis.
* Same study reported in two different abstracts.
** This study combines data from two RCTs, one of which is the study by Cohen[137] included in the sytematic review.

Table 11. Pooled risk estimates of fracture for risedronate, relative to placebo or no treatment, among postmenopausal women*

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral				
Cranney, 2002[44]	5	2,604	0.64	(0.54, 0.77)
Miller, 2005[60] Subjects with severe renal impairment	9	232	0.56	(0.11, 0.78)
Subjects with moderate renal impairment	9	2426	0.45	(0.31, 0.57)
Subjects with mild renal impairment	9	3088	0.32	(0.14, 0.46)
Stevenson, 2005[47]	2	2,064	0.62	(0.50, 0.77)
Non-vertebral				
Boonen, 2005[62]	3	11,770	0.81	(0.71, 0.92)
Cranney, 2002[44]	7	12,958	0.73	(0.61, 0.87)
Stevenson, 2005[47]	2	2,439	0.67	(0.50, 0.90)
Hip				
Nguyen, 2006[56]	3	7,196	0.66	(0.11, 3.68)
Stevenson, 2005[47]				
Subjects with established osteoporosis	3	4,142	0.60	(0.42, 0.88)
Subjects with severe osteoporosis or osteoporosis	3	7,884	0.66	(0.48, 0.89)
Wrist				
Stevenson, 2005[47]				
Subjects with severe osteoporosis	2	2,439	0.68	(0.43, 1.08)

* Stevenson: severe osteoporosis defined as T score <- 2.5 SD AND at least one documented fracture; osteoporosis defined as T score <- 2.5 SD without prior fracture; osteopenia defined as T-score between -1 and -2.5 SD.

Table 12. Risk of fracture for risedronate, relative to placebo, by dose and fracture group

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, risedronate	Number of fractures, placebo	Odds ratio (95% CI)
ANY DOSE, ALL FRACTURES						
Greenspan, 2006[122]	12 months	fracture	High	2/43	0/44	7.75 (0.48, 125.9)
Hosking, 2003[68]	12 months	clinically diagnosed vertebral or nonvertebral	High	6/178	2/89	1.47 (0.33, 6.52)
Milgrom, 2004[123]	14 weeks	all stress fracture	Unknown	24/165	21/159	1.12 (0.60, 2.10)
2.5 MG DAILY, VERTEBRAL						
Hooper, 2005[121]	24 months	vertebral fracture	High	11/127	10/125	1.09 (0.45, 2.66)
Kanaji, 2006[125]	12 months	vertebral fractures	Intermediate	0/12	0/11	NC
2.5 MG DAILY, NON-VERTEBRAL						
Hooper, 2005[121]	24 months	nonvertebral fracture	High	3/127	6/127	0.5 (0.13, 1.9)
Sato, 2005[118]	18 months	nonvertebral fracture	High	8/231	29/230	0.29 (0.15, 0.57)
2.5 MG DAILY, HIP						
Sato, 2005[118]	18 months	hip fracture	High	5/231	19/230	0.29 (0.13, 0.66)
Sato, 2005[124]	18 months	hip fracture	High	2/134	10/133	0.25 (0.08, 0.78)
Sato, 2005[119]	12 months	hip fracture	High	1/172	7/173	0.22 (0.05, 0.88)
5.0 MG DAILY, VERTEBRAL						
Sorensen, 2003[117]	24 months	vertebral fracture	High	15/109	29/103	0.42 (0.22, 0.81)
Hooper, 2005[121]	24 months	vertebral fracture	High	10/129	10/125	0.97 (0.39, 2.40)
5.0 MG DAILY, NON-VERTEBRAL						
Sorensen, 2003[117]	24 months	nonvertebral fracture	High	7/135	11/129	0.59(0.23, 1.54)
Hooper, 2005[121]	24 months	non vertebral fracture	High	5/129	6/129	0.83 (0.25, 2.76)
5.0 MG DAILY, HUMERUS						
Sorensen, 2003[117]	24 months	humerus	High	3/136	6/130	0.48 (0.13, 1.81)
30-35 MG WEEKLY, ALL FRACTURES						
Greenspan, 2006[122]	12 months	fracture	High	2/43	0/44	7.75 (0.48, 125.9)
Milgrom, 2004[123]	14 weeks	all stress fracture	Unknown	24/165	21/159	1.12 (0.60, 2.10)
35 MG WEEKLY, VERTEBRAL						
Palomba, 2005[120]	12 months	vertebral fracture	High	5/40	14/41	0.30 (0.11, 0.84)
35 MG WEEKLY, NON-VERTEBRAL						
Palomba, 2005[120]	12 months	non-vertebral fracture	High	0/40	4/41	0.13 (0.02, 0.95)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Table 13. Risk of fracture for risedronate, relative to different doses of risedronate, by fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, risedronate, weekly	Number of fractures, risedronate, daily	Odds ratio (95% CI)
RISEDRONATE 2.5 MG/D COMPARED TO RISEDRONATE 17.5MG/WEEK						
VERTEBRAL						
Kishimoto, 2006[126]	48 weeks	vertebral fracture	Intermediate	6/222	5/227	1.23 (0.37, 4.00)
RISEDRONATE 5 MG/D VERSUS RISEDRONATE 35MG/WEEK						
VERTEBRAL						
Brown, 2002[128]	24 months	new morphometric vertebral fractures	High	6/480	5/485	1.21 (0.37, 3.98)
Harris, 2004[127]	24 months	morphometric vertebral fractures	High	12/415	7/422	1.92 (0.75, 4.88)
NON-VERTEBRAL						
Brown, 2002[128]	24 months	any nonvertebral fractures	High	24/480	28/485	0.86 (0.49, 1.50)
RISEDRONATE 5 MG/D VERSUS RISEDRONATE 50MG/WEEK,						
VERTEBRAL						
Brown, 2002[128]	24 months	new morphometric vertebral fractures	High	6/480	2/491	2.8 (0.7, 11.26)
Harris, 2004[127]	24 months	morphometric vertebral fractures	High	12/415	7/422	1.74 (0.70, 4.32)
NON-VERTEBRAL						
Brown, 2002[128]	24 months	any nonvertebral fractures	High	24/480	24/491	1.02 (0.57, 1.83)
RISEDRONATE 35 MG/WEEK VERSUS RISEDRONATE 50MG/WEEK,						
VERTEBRAL						
Brown, 2002[128]	24 months	new morphometric vertebral fractures	High	5/485	2/491	1.19 (0.68, 2.08)
Harris, 2004[127]	24 months	morphometric vertebral fractures	High	12/415	7/422	0.9 (0.30, 2.68)
NON-VERTEBRAL						
Brown, 2002[128]	24 months	any nonvertebral fractures	High	28/485	24/491	1.19 (0.68, 2.08)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, OR 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Zoledronic acid:

We identified two RCTs[138, 139] that reported the effect of zoledronic acid relative to placebo on the incidence of vertebral and non-vertebral fractures among postmenopausal women at intermediate risk for fracture. In one study 351 postmenopausal women were randomized to different doses and frequencies of zoledronic acid ranging from 1-4 milligrams given in 1-4 doses over a one-year period. Fracture incidence was a secondary outcome in this study. Among 59 subjects randomized to placebo and 292 subjects randomized to zoledronic acid, none sustained vertebral fractures during the 1-year study period. There were five non-vertebral fractures each in the zoledronic acid and placebo groups. There was no significant association between any dose of zoledronic acid and non-vertebral fractures relative to placebo (Table 14). However, this study does not have sufficient statistical power to detect differences in fracture among study arms.

In the other study, 7,765 postmenopausal women at high risk for fracture were randomized to a single infusion of zoledronic acid at baseline or placebo and followed over three years.[139] The primary end points in this study were new vertebral and hip fractures; nonvertebral fractures, any clinical fractures, and clinical vertebral fractures were secondary outcomes. There were significant reductions in the risk of each of these types of fractures for zoledronic acid relative to placebo at 36 months (Table 14).

Table 14. Risk of fracture for zoledronic acid, relative to placebo, by dose, frequency, and fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, zoledronic acid	Number of fractures, placebo	Odds ratio (95% CI)
5 MILLIGRAMS ONCE						
Black, 2007[139]	36 months	Any clinical; fracture	High	308/3667	456/3563	0.63 (0.54, 0.72)
Black, 2007[139]	36 months	Nonvertebral fracture	High	292/3650	388/3626	0.73 (0.62, 0.85)
Black, 2007[139]	36 months	Morphometric vertebral fracture	High	92/2788	310/2844	0.32 (0.26, 0.39)
Black, 2007[139]	36 months	Clinical vertebral fracture	High	19/3800	84/3231	0.23 (0.16, 0.34)
Black, 2007[139]	36 months	Hip fracture	High	52/3714	88/3520	0.56 (0.40, 0.78)
4 MILLIGRAMS ONCE						
Reid, 2002[138]	12 months	Nonvertebral fracture	Intermediate	1/60	1/59	0.98 (0.06, 15.91)
Reid, 2002[138]	12 months	Vertebral fractures	Intermediate	0/60	0/59	NC
2 MILLIGRAMS, EVERY 6 MONTHS						
Reid, 2002[138]	12 months	Nonvertebral fracture	Intermediate	1/61	1/59	0.97 (0.06, 15.65)
Reid, 2002[138]	12 months	Vertebral fractures	Intermediate	0/61	0/59	NC
0.25 MILLIGRAMS, EVERY 3 MONTHS						
Reid, 2002[138]	12 months	Nonvertebral fracture	Intermediate	0/60	1/59	0.13 (0.00, 6.71)
Reid, 2002[138]	12 months	Vertebral fractures	Intermediate	0/60	0/59	NC
0.5 MILLIGRAMS, EVERY 3 MONTHS						
Reid, 2002[138]	12 months	Nonvertebral fracture	Intermediate	1/58	1/59	1.02 (0.06, 16.46)
Reid, 2002[138]	12 months	Vertebral fractures	Intermediate	0/58	0/59	NC
1 MILLIGRAM, EVERY 3 MONTHS						
Reid, 2002[138]	12 months	Nonvertebral fracture	Intermediate	2/53	1/59	2.2 (0.22, 21.7)
Reid, 2002[138]	12 months	Vertebral fractures	Intermediate	0/53	0/59	NC

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population. NC= not calculable.

Calcitonin:

We identified four meta-analyses[42, 45, 46, 59] that describe the effect of calcitonin on fracture risk reduction relative to placebo or no treatment. One focused on the use of calcitonin for the prevention and treatment of glucocorticoid-incuded osteoporosis[42] and is described in the section on glucocorticoid-induced osteoporosis in this report. The RCTs included in the remaining three meta-analyses are detailed in Table 15. These meta-analyses reported pooled risk estimates for vertebral and non-vertebral fractures (Table 16). One of the meta-analyses was restricted to postmenopausal women;[45] one to renal transplant recipients;[59]and the other was not restricted to a specific population and included postmenopausal women, men and women with osteoporosis, as well as men and women taking corticosteroids.[46]

We identified five RCTs[93, 140-143] not included in the meta-analyses that describe the number of fractures among subjects treated with calcitonin and placebo (Table 17). The study population in two of these studies was postmenopausal women with high risk for fracture;[93, 140] and in one, it was postmenopausal women with low risk of fracture.[141] The population in the fourth study[142] was men with osteoporosis at high risk for fracture. The population in the last of these studies was liver transplant recipients.[143]

Fracture was a secondary outcome in all of the studies. Significant reductions in the risk of vertebral fractures for calcitonin relative to placebo were reported in two studies, one among postmenopausal women at high risk for fracture (OR 0.41, 95% CI 0.17, 0.99),[93] the other among men with osteoporosis at high risk for fracture (OR 0.09, 95% CI 0.01, 0.96).[142] The risk of vertebral fracture for calcitonin relative to placebo was not significant in the other two studies.[140, 141]

Table 15. Randomized controlled trials included in meta-analyses of effect of calcitonin on fracture relative to placebo or no treatment

RCTs (Author, year)	Meta-analyses (Author, year)				
	Cranney, 2002[45]		Kanis, 1999[46]		Palmer, 2005[59]
	Fracture Type				
	Vertebral	Non-vertebral	Vertebral	Non-vertebral	Any
Arnala, 1996[144]			X	X	
Agrawal, 1980[145]			X	X	
Chesnut, 2000[146]	X	X			
Gennari, 1985[147]			X		
Grotz, 1998[148]					X
Gruber, 1984[149]			X		
Healey, 1996[150]			X		
Hizmetli, 1996[151]	X				
Luengo, 1994[152]			X	X	
Nordal, 1996[153]					X
Overgaard, 1992[154]	X	X	X	X	
Peyron, 1980[155]			X		
Rico, 1992[156]			X	X	
Rico, 1995[157]		X	X		
Ringe, 1990[158]			X	X	
Ringe, 1987[159]			X	X	
Sambrook, 1993[160]			X	X	
Stock, 1997[161]			X		

X=Included in pooled analysis.

Table 16. Pooled risk estimates of fracture for calcitonin relative to placebo or no treatment

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral				
Cranney, 2002[45]	4	1,404	0.46	(0.25, 0.87)
Kanis, 1999[46]	10	1,744	0.80	(0.64, 1.01)
Non-vertebral				
Cranney, 2002[45]	3	1,481	0.52	(0.22, 1.23)
Kanis, 1999[46]	10	1,744	0.48	(0.20, 1.15)
Any Site				
Palmer, 2005[59]	2	93	0.33	(0.04, 3.05)

Table 17. Risk of fracture for calcitonin, relative to placebo, by dose and fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, calcitonin	Number of fractures, placebo or control†	Odds ratio (95% CI)
100 IU DAILY						
Hay, 2001[143]	12 months	Spine fracture	High	5/27	8/28	0.58 (0.17, 1.99)
20 IU WEEKLY						
Ishida, 2004[93]	24 months	vertebral	High	8/66	17/66†	0.41 (0.17, 0.99)
200 IU DAILY						
Trovas, 2002[140]	12 months	vertebral fracture	High	1/13	2/11	0.40 (0.04, 4.30)
200 IU DAILY DURING ALTERNATE MONTHS						
Toth, 2005[142]	18 months	vertebral fracture	High	0/40	3/31†	0.09 (0.01, 0.96)
10 IU TWICE MONTHLY						
Ushiroyama, 2001[141]	12 months	vertebral fracture	Low	0/49	2/52†	0.14 (0.01, 2.28)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population. IU = international units

† Versus control group

Estrogen

We identified four meta-analyses[47, 53, 54, 162] and two publications from the Women's Health Initiative (WHI)[163, 164] published after the meta-analyses that evaluated the effect of estrogen on fracture risk. The meta-analyses pooled data from 31 different RCTs. The RCTs included in these meta-analyses are detailed in Table 18.

Among three meta-analyses that evaluated risk for vertebral fracture, one demonstrated a statistically significant risk reduction (Table 19). Likewise, among three meta-analyses that evaluated risk for non-vertebral fracture, one demonstrated a statistically significant risk reduction (Table 19).

Although some data from the WHI are included in one of the meta-analyses[47], the results from this trial are noteworthy. In the estrogen plus progestin component of the WHI, 16,608 postmenopausal women aged 50-79 years were randomized to received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in one tablet or placebo. Estrogen plus medroxyprogesterone was associated with a 33% reduction in vertebral fractures, 33% reduction in hip fractures, and 24% overall reduction in fracture compared with placebo, all of which were statistically significant (Table 19)[163, 164] The estrogen alone arm of the WHI also showed a significant reduction in total, vertebral and hipfractures, compared to placebo (Table 19).[165] Data on this risk of hip fracture from the estrogen plus progesterone component of WHI were included in the Stevenson meta-analysis;[47] data from the estrogen alone component of the WHI and data on vertebral fractures from the WHI were not used to calculate risk estimates in the Stevenson meta-analysis.

We identified five RCTs[66, 67, 91, 93, 166] not included in the meta-analyses that describe the number of fractures among subjects treated with estrogen and placebo or control (Table 20). The study population in three of these studies was postmenopausal women with high risk for fracture;[66, 91, 93] and in two, it was postmenopausal women with intermediate risk of fracture.[67, 166] Data on fracture were collected as secondary in two studies[91, 93] or adverse events[66, 67, 166] in each of three studies. None of these studies had sufficient sample size to detect a difference in fracture risk between study arms.

Table 18. Randomized controlled trials included in meta-analyses of effect of estrogen on fracture relative to placebo or no treatment*

RCTs (Author, year)	Meta-analyses (Author, year)							
	Stevenson, 2005[47]				Torgerson, 2001[53]	Torgerson, 2001[162]	Wells, 2002[54]	
	Fracture type†							
	V	NV	H	W	V	NV	V	NV
Aitken, 1973[167]						X		
Alexandersen, 1999[168]	X	X			X	X	X	X
Bjarnason, 2000[169]		X				X		
Cauley, 2001[170]			X	X				
Cheng, 2000[171]						X		
Delmas, 2000[172]		X			X	X		
Eiken, 1997[173]		X				X		
Eli Lily, 2001‡						X		
Gallagher, 2001[174]	X	X			X			
Genant, 1997[175]		X				X		
Greenspan, 1998[176]							X	X
Herrington (HERS), 2000[177]		X	X	X	X	X		
Hosking, 1998[82]						X		X
Hully, 1998[178]						X	X	X
Ishida, 2001[179]					X			
Komulainen, 1997[180]								X
Komulainen, 1998[181]						X		
Lees, 2001[182]		X	X	X				
Lindsay, 1990[183]		X			X	X		
Lufkin, 1992[184]	X	X			X		X	
Mosekilde, 2000[185]	X	X			X	X		
Mulnard, 2000[186]						X		
Nachtigall, 1979[187]						X		
Orr-Walker, 2000[188]		X				X		
PEPI, 1996[189]					X	X		
Ravn (EPIC), 1999[190]			X	X	X	X		
Recker, 1999[191]		X			X	X		
Rossouw (WHI), 2002[164]			X	X				
Stevenson, 2000[192]						X		
Wimalawamsa, 1998[91]		X			X	X	X	X
Weiss, 1999[193]		X				X		

* HERS= Heart and Estrogen/progestin Study, WHI = Women's Health Initiative.
† V=vertebral, NV=nonvertebral, H=hip, W=wrist/forearm X= Included in pooled analysis.
‡ Citation not provided.

Table 19. Risk estimates of fracture for estrogen relative to placebo or no treatment among postmenopausal women from pooled analyses and from the Women's Health Initiative*

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Torgerson, 2001[53]	13	6,723	0.67	(0.45, 0.98)
Stevenson, 2005[47]				
Women with severe osteoporosis*	1	68	0.58	(0.26, 1.30)
Women with severe osteoporosis, osteoporosis or osteopenia	2	104	0.71	(0.24, 2.12)
Women not selected for low BMD	2	1,218	2.05	(0.71, 5.97)
Wells, 2002[54]	5	3,385	0.66	(0.41, 1.07)
Women's Health Initiative, 2003[165] Estrogen only	1	10,739	0.62†	(0.42, 0.93)
Women's Health Initiative, 2003[164] Estrogen plus progesterone	1	16,608	0.66†	(0.44, 0.98)
Non-vertebral				
Torgerson, 2001[162]				
All women	22	8,774	0.73	(0.56, 0.94)
Women < 60	14	ND	0.67	(0.46, 0.98)
Women ≥ 60	88	ND	0.88	(0.71, 1.08)
Stevenson, 2005[47]				
Women with severe osteoporosis	2	86	0.67	(0.12, 3.93)
Women with severe osteoporosis, osteoporosis or osteopenia	4	264	0.86	(0.37, 1.96)
Women with osteoporosis or osteopenia	1	128	1.17	(0.41, 3.28)
Women not selected for low BMD	13	7,316	0.86	(0.72, 1.02)
Wells, 2002[54]	6	5,383	0.87	(0.71, 1.08)
Hip				
Stevenson, 2005[47]				
Women not selected for low BMD	4	20,798	0.74	(0.53, 1.03)
Women's Health Initiative, 2003[165] Estrogen only	1	10,739	0.61†	(0.41, 0.91)
Women's Health Initiative, 2003[164] Estrogen plus progesterone	1	16,608	0.67†	(0.47, 0.96)
Forearm/Wrist				
Stevenson, 2005[47]				
Women not selected for low BMD	4	4,160	0.95	(0.58, 1.53)

* Stevenson: severe osteoporosis defined as T score <- 2.5 SD AND at least one documented fracture; osteoporosis defined as T score <- 2.5 SD without prior fracture; osteopenia defined as T-score between -1 and -2.5 SD; ND = not described. † Hazards ratio as reported in cited studies.

Table 20. Risk of fracture for estrogen, relative to placebo, by fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, estrogen	Number of fractures, placebo or control	Odds ratio (95% CI)
ALL FRACTURES						
Bone, 2000[66]	24 months	any clinical fracture	High	10/143	4/50	0.86 (0.25, 2.97)
Greenspan, 2003[67]	36 months	clinical fracture	Intermediate	5/93	9/93	0.54 (0.18, 1.60)
VERTEBRAL						
Ishida, 2004[93]	24 months	vertebral	High	7/66†	17/66‡	0.36 (0.15, 0.88)
Reid, 2004[166]	36 months	vertebral	Intermediate	1/102	1/90	0.88 (0.05, 14.27)
Wimalawansa, 1998[91]	48 months	vertebral	High	2/15†	5/14‡	0.31 (0.06, 1.64)
NONVERTEBRAL						
Wimalawansa, 1998[91]	48 months	Nonvertebral	High	1/15†	1/14‡	0.93 (0.06, 15.69)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, OR 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

† Estrogen plus progesterone.

‡ Control group.

1-34 Parathyroid Hormone

Teriparatide:

We identified one systematic review[47] that summarized data about the effect of teriparatide on fracture relative to placebo or no treatment among postmenopausal women. The RCTs included in this systematic review are detailed in Table 21. This systematic review reported risk estimates for vertebral, non-vertebral, hip, wrist, and humerus fractures (Table 22).

We identified three RCTs[194-196] not included in the review that describe the number of fractures among subjects treated with teriparatide and placebo (Table 23). The study population in one of these studies was postmenopausal women with high risk for fracture.[194] The population in the other two studies was men with osteoporosis at intermediate risk for fracture participating in the same trial.[195, 196]

Fracture was the primary outcome in the study among postmenopausal females. This study demonstrated a reduced risk of vertebral (OR 0.34, 95% CI 0.22, 0.54) and non-vertebral (OR 0.63, 95% CI 0.39, 1.00) fractures for teriparatide relative to placebo at 21 months.

The other two studies report data at 11[195] and 18[196] months from the same trial. Fracture data were reported as adverse events and as secondary outcomes at the 11- and 18-month points, respectively. No significant difference in non-vertebral fractures between teriparatide and placebo was found at 11 months. A significant reduction in the risk of combined fractures (OR 0.16, 95% CI 0.04, 0.65) and a non-significant reduction in vertebral fractures (OR 0.44, 95% CI, 0.18, 1.09) for teriparatide relative to placebo was reported at 18 months.

Table 21. Randomized controlled trials included in systematic review of the effect of teriparatide on fracture relative to placebo or no treatment

RCTs (Author, year)	Systematic review (Author, year)				
	Stevenson, 2005[47]				
	Vertebral	Non-vertebral	Hip	Wrist	Humerus
Cosman, 2001[197]	X				
Neer, 2001[198]	X	X	X	X	X

Table 22. Pooled risk estimates of fracture for teriparatide relative to placebo or no treatment among postmenopausal women*

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Stevenson, 2005[47]				
All subjects, dose 20 μg/d	1	892	0.35	(0.22, 0.55)
All subjects, dose 40 μg/d	1	882	0.31	(0.19, 0.50)
Subjects with severe osteoporosis	1	892	0.35	(0.22, 0.55)
Non-vertebral				
Stevenson, 2005[47]				
All subjects, dose 20 μg/d	1	1,085	0.65	(0.43, 0.98)
All subjects, dose 40 μg/d	1	1,096	0.60	(0.39, 0.91)
Subjects with severe osteoporosis	1	1,085	0.65	(0.43, 0.98)
Hip				
Stevenson, 2005[47]				
Subjects with severe osteoporosis	1	NR	0.50	(0.09, 2.73)
Wrist				
Stevenson, 2005[47]				
Subjects with severe osteoporosis	1	NR	0.54	(0.22, 1.35)
Humerus				
Stevenson, 2005[47]				
Subjects with severe osteoporosis	1	NR	0.80	(0.22, 2.98)

* Stevenson: severe osteoporosis defined as T score <- 2.5 SD AND at least one documented fracture; osteoporosis defined as T score <- 2.5 SD without prior fracture; osteopenia defined as T-score between -1 and -2.5 SD.

Table 23. Risk of fracture for teriparatide, relative to placebo, by fracture group

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, teriparatide	Number of fractures, placebo	Odds ratio (95% CI)
ALL FRACTURES						
Kaufman, 2005[196]	30 months	moderate or severe facture	Intermediate	2/176†	7/103	0.16 (0.04, 0.65)
VERTEBRAL						
Gallagher, 2005[194]	21 months	vertebral fracture	High	22/403	62/398	0.34 (0.22, 0.54)
Kaufman, 2005[196]	30 months	vertebral fracture	Intermediate	10/176†	12/103	0.44 (0.18, 1.09)
NON-VERTEBRAL						
Gallagher, 2005[194]	21 months	nonvertebral fracture	High	30/467	46/464	0.63 (0.39, 1.00)
Orwoll, 2003[195]	11 months	nonvertebral fractures	Intermediate	3/290†	3/147	0.48 (0.09, 2.62)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, OR 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

† 20ug and 40ug dose groups combined.

Selective Estrogen Receptor Modulators (SERM)

Raloxifene:

We identified three meta-analyses[47, 48, 55] that pooled data from four different RCTs to describe the effect of raloxifene on fracture risk reduction relative to placebo or no treatment among postmenopausal women. The RCTs included in these meta-analyses are detailed in Table 24. These meta-analyses reported risk estimates for vertebral, non-vertebral, hip, and wrist fractures (Table 25).

We identified two RCTs not included in the meta-analysis that describe the number of fractures among subjects treated with raloxifene relative to placebo (Table 26). One study population was postmenopausal women with intermediate risk for fracture.[166] Fracture data were collected as adverse events. There was no statistical difference in fracture risk between raloxifene and placebo, but the study was not powered to detect such a difference.

The other study was the RUTH (Raloxifene Use for The Heart) trial.[199] This trial was designed to study the effects of raloxifene on cardiovascular events and breast cancer in post-menopausal women. Fractures were a secondary outcome. Raloxifene subjects had lower odds of clinical vertebral fractures relative to placebo (OR 0.66, 95% CI 0.48, 0.90). There was no substantial difference in clinical nonvertebral fractures.

Table 24. Randomized controlled trials included in meta-analyses of effect of raloxifene on fracture relative to placebo or no treatment

RCTs (Author, year)	Meta-analyses (Author, year)						
	Schachter, 2005[48]		Stevenson, 2005[47]				Seeman, 2006[55]
	Fracture Type						
	Vertebral	Non-vertebral	Vertebral	Non-vertebral	Hip	Wrist	Vertebral
Ettinger, 1999[200]	X		*	*	*	*	X
Jolly, 2003[201]							X
Lufkin, 1998[202]	X		*	*	*		X
Morii , 2003[203]							X

X= Included in pooled analysis; * identified but not included in pooled analysis.

Table 25. Risk estimates of fracture for raloxifene relative to placebo or no treatment among postmenopausal women*

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Schachter, 2005[48]				
Ettinger study at four years	1	7,705	0.60	(0.52, 0.69)
Ettinger and Lufkin studies at four years	2	7,848	0.81	(0.43, 1.51)
Stevenson, 2005[47]				
Women with severe osteoporosis	1	NR	0.69	(0.56, 0.86)
Women with severe osteoporosis or osteoporosis	1	4,551	0.65	(0.53, 0.79)
Women with osteoporosis	1	NR	0.53	(0.35, 0.79)
Women with osteopenia	1	NR	0.53	(0.32, 0.88)
Seeman, 2006[55]				
60 mg	5	5,600	0.60	(0.49, 0.74)
120/150mg	4	5,403	0.51	(0.41, 0.64)
Non-vertebral				
Stevenson, 2005[47]				
Women with severe osteoporosis or osteoporosis	1	6,828	0.92	(0.79, 1.07)
Hip				
Stevenson, 2005[47]				
Women with severe osteoporosis or osteoporosis	1	6,828	1.12	(0.65, 1.95)
Wrist				
Stevenson, 2005[47]				
Women with severe osteoporosis or osteoporosis	1	6,828	0.89	(0.68, 1.15)

* Stevenson: severe osteoporosis defined as T score <- 2.5 SD AND at least one documented fracture; osteoporosis defined as T score <- 2.5 SD without prior fracture; osteopenia defined as T-score between -1 and -2.5 SD.

Table 26. Risk of vertebral fracture for raloxifene, relative to placebo*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, serm	Number of fractures, placebo	Odds ratio (95% CI)
Reid, 2004[166]	36 months	Vertebral fracture	Intermediate	4/193†	1/90	1.72 (0.26, 11.05)
Barrett-Connor, 2006[199]	5.6 years	Clinical vertebral	Unknown risk	64/5,044	97/5,057	0.66 (0.48. 0.90)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.
† 60 mg and 150 mg dose groups combined.

Tamoxifen:

We identified one RCT[204] that describes the number of fractures among subjects treated with tamoxifen relative to placebo (Table 27). The study population in this study comprised women older than 60 or women aged 35-59 with increased risk for breast cancer. Fracture was a secondary outcome for this study. There was no statistical difference in fracture risk between tamoxifen and placebo, for any type of fracture (Table 27).

Table 27. Risk of vertebral fracture for tamoxifen, relative to placebo*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, /SERM	Number of fractures, placebo	Odds ratio (95% CI)
Fisher, 1998[204]	60 months	spine fracture	4	12/6576	22/6599	0.56 (0.28, 1.09)
Fisher, 1998[204]	60 months	Radius, Colle's	4	14/6576	23/6599	0.62 (0.32, 1.17)
Fisher, 1998[204]	60 months	other lower radius	4	66/6576	63/6599	1.05 (0.74, 1.49)
Fisher, 1998[204]	60 months	hip	4	12/6576	22/6599	0.56 (0.28, 1.09)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Testosterone:

We did not identify any studies that evaluated the risk of fracture with testosterone relative to placebo. Studies of testosterone use and its effects on bone health have been limited in their outcome measures to that of bone density.

Vitamins and Minerals

Calcium:

We identified one meta-analysis[49] that describes the effect of calcium supplementation on fracture risk reduction relative to placebo or no treatment, among postmenopausal women. The meta-analysis pooled data from five different RCTs (Table 28). Vitamin D was given to all subjects in one of the studies (single 300,000 IU dose at study inception)[205] but was not used in any of the other studies. This meta-analysis reported pooled risk estimates for vertebral and non-vertebral fractures, neither of which were statistically significant (Table 29).

We identified four RCTs[65, 92, 206, 207] not included in the meta-analysis that describe the number of fractures among subjects treated with calcium relative to placebo (Table 30). The study population in three of these studies was postmenopausal women with high[65, 206] or intermediate[207] risk for fracture. The populations in the other study included men and women with asthma[92] who had an intermediate risk for fracture.

Although fracture was the primary outcome for all of these studies, enrollment was lower than anticipated and the sample size was not sufficiently large to detect differences in fracture risk between calcium and placebo in one study.[92]

There were no statistically significant differences in the risk of fracture for calcium relative to placebo in the remaining three trials using intention to treat analyses. However, two of the studies[65, 206] reported high rates of non-compliance with calcium. In one study,[206] in which 57% of the subjects took at least 80% of their calcium pills, the participants in the calcium group had reduced fracture incidence compared with the placebo group (10.2% vs. 15.4%; hazard ratio, 0.66; 95% CI, 0.45-0.97). In the other study,[65] 78% took at least 80% of the calcium pills; however an analysis of compliant subjects was not performed for this study.

Table 28. Randomized controlled trials included in meta-analysis of effect of calcium on fracture relative to placebo or no treatment

Meta-analysis (Author, year)		
RCTs (Author, year)	Shea, 2002[49]	
	Vertebral	Non-vertebral
Chevally, 1994[205]	X	X
Hansson, 1987[208]	X	
Recker, 1996[209]	X	
Reid, 1993[210]	X	
Riggs, 1998[211]	X	X

X= Included in pooled analysis.

Table 29. Pooled risk estimates of fracture for calcium relative to placebo or no treatment among postmenopausal women

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Shea, 2002[49]	5	576	0.77	(0.54, 1.09)
Non-vertebral				
Shea, 2002[49]	2	222	0.86	(0.43, 1.72)

Table 30. Risk of fracture for calcium, relative to placebo, by fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, calcium	Number of fractures, placebo or control†	Odds ratio (95% CI)
ALL FRACTURES						
Campbell, 2004[92]	60 months	New symptomatic vertebral and non-vertebral fractures	Intermediate	7/85	7/95†	1.13 (0.38, 3.35)
Prince, 2006[206]**	60 months	Any site fracture	High	110/728	126/728	0.85 (0.64, 1.12)
Prince, 2006[206]***	60 months	Any site fracture	High	43/422	63/409	0.63 (0.42, 0.94)
Grant, 2005[65]	62 months	New fractures	High	189/1311	196/1332	0.98 (0.79, 1.21)
VERTEBRAL FRACTURES						
Campbell, 2004[92]	60 months	New symptomatic or semi-quantittive vertebral fractures	Intermediate	15/85	19/95†	0.86 (0.41, 1.81)
Grant, 2005[65]	62 months	Clinical vertebral fracture	High	3/1311	1/1332	2.77 (0.39, 19.65)
Prince, 2006[206]**	60 months	Vertebral deformity	High	44/431	50/450	0.91 (0.59, 1.40)
Prince, 2006[206]***	60 months	Vertebral deformity	High	22/306	32/305	0.66 (0.38, 1.16)
Reid, 2006[207]	60 months	Vertebral fracture	Intermediate	27/739	38/732	0.70 (0.42, 1.14)
NON-VERTEBRAL						
Prince, 2006[206]**	60 months	Any appedicular site fracture	High	83/728	94/729	0.87 (0.64, 1.19)
Prince, 2006[206]***	60 months	Any appredicular site fracture	High	39/419	58/411	0.63 (0.41, 0.96)
HIP						
Grant, 2005[65]	62 months	Proximal femur fracture	High	49/1311	41/1332	1.22 (0.80, 1.86)
Prince, 2006[206]**	60 months	Proximal femur	High	11/733	6/750	1.86 (071, 4.83)
Prince, 2006[206]***	60 months	Proximal femur	High	5/417	3/429	1.70 (0.42, 6.85)
Reid, 2006[207]	60 months	hip fracture		17/739	5/732	3.0 (1.29, 6.95)
WRIST						
Grant, 2005[65]	62 months	Distal forearm fracture	High	33/1311	28/1332	1.20 (0.72, 2.00)
Prince, 2006[206]**	60 months	Wrist or hand	High	21/724	20/741	1.08 (0.58, 2.00)
Prince, 2006[206]***	60 months	Wrist or hand	High	10/417	12/414	0.82 (0.35, 1.92)
Reid, 2006[207]	60 months	Distal forearm fracture	Intermediate	28/739	44/732	0.62 (0.39, 1.00)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

** Intention to treat analysis.

*** Compliant with medication.

† Control group.

Vitamin D:

We identified six meta-analyses[47, 50-52, 58, 61] that pooled data from 39 different RCTs to describe the effect of vitamin D on fracture risk reduction relative to placebo or no treatment. The populations included in these meta-analyses were men or women with osteoporosis,[51, 58, 61] older adults,[52] and postmenopausal women.[50, 58, 61, 212] The RCTs included in these meta-analyses are detailed in Table 31. These meta-analyses reported risk estimates for vertebral, non-vertebral, and hip fractures (Table 32).

One meta-analysis,[51] which included RCTs and quasi-randomized trials of vitamin D and its analogues, found that vitamin D alone had no statistically significant effect on hip, vertebral, or any new fracture. Vitamin D with calcium marginally reduced hip fractures (RR 0.81, 95% C.I. 0.68-0.96) but did not have any effect on vertebral fractures. The effect appeared to be restricted to those living in institutional care.

A second meta-analysis evaluated the efficacy of vitamin D treatment in preventing postmenopausal osteoporosis and included 25 RCTs--published between 1966 and 1999--of standard or hydroxylated vitamin D with or without calcium supplementation or a control.[50] This analysis concluded that vitamin D reduced the risk of vertebral fractures (RR=0.63, 95% C.I. 0.45-0.88). A non-significant trend was seen for nonvertebral fractures (RR=0.77, p=0.09). The authors acknowledge that inferences from these analyses are limited by variability in design, difference in vitamin D formulation, differences in populations studied, and inconsistent outcome measures.

The third meta-analysis evaluated fracture prevention with vitamin D supplementation and included studies with men.[52] Five RCTs with hip fracture as an outcome and seven RCTs with nonvertebral fracture as an outcome were included. All trials used standard vitamin D_3 (cholecalciferol). A vitamin D dose of 700 to 800 I.U. daily was associated with a reduced risk of hip fracture (RR=0.74, 95% C.I. 0.61-0.88) and a reduced risk of any nonvertebral fracture (RR=0.77, 95% C.I. 0.68-0.8). Doses of 400 I.U. daily were not effective in preventing hip and nonvertebral fractures.

The fourth meta-analysis[47] evaluated the effect of vitamin D on fractures in postmenopausal women. This meta-analyses stratified findings based on whether subjects had osteopososis at study enrollment (according to BMD). In this meta-analysis, vitamin-D had no effect on fracture in either stratum.

The fifth meta-analysis[61] evaluated the effects of two vitamin D analogs - alfacalcitol and calcitriol – on the risk for fracture in men and women with osteoporosis. Both analogs reduced the risk of overall fracture rate, vertebral fracture rate, and nonvertebral fracture rate. Calcitriol had similar efficacy to alphacalcidol; however, no study included in the meta-analysis tested them head to head. Participants were also stratified based on whether the osteoporosis was primary or secondary (glucocorticoid-induced [GC]): vitamin D analogs did not significantly decrease the risk for fracture in participants with GC-induced osteoporosis.

The sixth meta-analysis[58] evaluated the effects of the two vitamin D analogs as well as native vitamin D on men and women's fracture risk (expressed as rate difference – RD – the difference

in fracture rate between the treatment and placebo groups). The RDs for the analogs and native vitamin D were significant at 24 and 36 months. Although the RDs for the analogues were greater than for native vitamin D, there were no head-to-head comparisons. No significant effect was seen on participants with GC-induced osteoporosis.

We identified four RCTs[65, 93, 213, 214] not included in the meta-analyses that described the number of fractures among subjects treated with vitamin D compared with placebo (Table 33). The study population in all of these studies was at high risk for fracture. The majority of the patients in three of these were postmenopausal women,[65, 93, 214] although one large study included 793 men.[65] The other study include male and female renal transplant recipients.[213] Fracture was the primary outcome in one[65] and a secondary outcome in the others.

No difference in the risk for fracture for vitamin D relative to placebo was detected in the single study with sufficient sample size to detect such a difference.[65] One study that included postmenopausal women with hemiplegia after stroke did demonstrate a significant reduction in risk for hip fracture for vitamin D relative to placebo (OR 0.12, 95% CI 0.016, 0.89).[214] The other two studies[93, 213] did not detect a difference but were not powered to do so.

Table 31. Randomized controlled trials included in meta-analyses of effect of vitamin D on fracture relative to placebo or no treatment

RCTs (Author, year)	Meta-analyses (Author, year)												
	Avenell, 2005[51]			Bischoff-Ferrari, 2005[52]		Papadimitropoulos, 2002[50]		Stevenson, 2005[47]		Richy, 2004[61]		Richy, 2005[58]	
	Fracture Type												
	V	NV	H	NV	H	V	NV	V	NV	V	NV	V	NV
Adachi, 1996[215]												X	
Aloia, 1988[216]								X		X			
Avenell, 2004[217]	X		X										
Baeksgaard, 1998[218]						X							
Cannigia, 1984[219]						X		X					
Chapuy, 1994[220]				X	X								
Chapuy, 1992[221]							X						X
Chapuy, 2002[222]				X	X								
Dawson-Hughes, 1997[223]				X	X		X					X	
Dukas, 2004[224]		X											
Ebeling, 2001[225]										X		X	
Gallegher, 1989[226]										X			X
Gallegher, 1990[227]										X		X	
Gallagher, 2001[174]			X			X			X	X	X	X	X
Gorai,1999[228]		X											
Grant, 2005[229]	X												
Guesens, 1986[230]						X							
Harwood, 2004[231]			X										
Hayashi, 1992[232]										X		X	
Komulainen, 1998[181]													X
Lipps, 1996[233]			X	X	X		X						X
Menczel, 1994[234]											X		X
Meyer, 2002[235]			X	X	X								X
Oriomo, 1987[236]						X							

X= Included in pooled analysis; * identified but not included in pooled analysis

Table 31. Randomized controlled trials included in meta-analyses of effect of vitamin D on fracture relative to placebo or no treatment (continued)

RCTs (Author, year)	Avenell, 2005[51]			Bischoff-Ferrari, 2005[52]		Papadimitropoulos, 2002[50]		Stevenson, 2005[47]		Richy, 2004[61]		Richy, 2005[58]	
	Fracture Type												
	V	NV	H	NV	H	V	NV	V	NV	V	NV	V	NV
Oriomo, 1994[237]						X	X			X		X	
Ott, 1989[238]						X	X	X	X				
Peacock, 2000[239]	X												
Pfeifer, 2000[240]				X	X								X
Sambrook, 2000[241]										X		X	
Sato, 1997[242]			X								X		X
Sato, 1999a[243]		X	X								X		X
Sato, 1999b[244]			X										
Shiraki, 1996[245]										X			X
Smith, 2004[246]			X										
Stempfle, 1999[247]												X	
Tilyard, 1992[248]						X	X			X		X	
Trivedi, 2003[249]	X		X	X	X							X	X
Ushirooyama, 2001[141]		X											

X= Included in pooled analysis; * identified but not included in pooled analysis

Table 32. Risk estimates of fracture for vitamin D relative to placebo or no treatment*

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Avenell, 2005[51]				
Standard vitamin-D [D2, D3, or 25(OH)D]				
Not selected on basis of prior osteoporotic fracture	2	2,953	0.96	(0.42, 2.21)
Selected on basis of prior osteoporotic fracture	1	2745	3.97	(0.44, 35.45)
Either selected or not selected on basis of prior osteoporotic fracture	3	5698	1.13	(0.50, 2.55)
Papadimitropoulos, 2002[50]				
Standard vitamin-D [D2, D3, or 25(OH)D]	1	160	0.33	(0.01, 8.05)
Calcitriol (1,25-OH vitamin D)	7	970	0.64	(0.44, 0.92)
Either Standard vitamin-D or Calcitriol	8	1130	0.63	(0.45, 0.88)
Richy, 2004[61]				
Primary osteoporosis	9	1665	0.53	(0.47, 0.60)
Calcitriol	6	896	0.52	(0.41, 0.67)
Alphacalcidol	3	769	0.53	(0.46, 0.61)
GC-induced (calcitriol only)	2	106	0.33	(0.07, 1.51)
Richy, 2005[58]				
Primary osteoporosis (24 mos)				
Vitamin D analogues	5	1972	15%†	(10, 20%)
Standard vitamin D	2	3075	1.6%†	(0.4, 2.6%)
GC treatment				
Vitamin D analogues	3	300	9%	(-2, 22%)
Standard vitamin D	1	62	6%	(-23, 10%)
Stevenson, 2005[47]				
Women with severe osteoporosis	3	109	1.02	(0.44, 2.32)
Elderly women not selected for BMD	1	NR	4.44	(0.50, 39.03)
Non-vertebral				
Avenell, 2005[51]				
Alphacalcidiol				
Not selected on basis of prior osteoporotic fracture	2	466	0.40	(0.05, 3.08)
Bischoff-Ferrari, 2005[52]				
All doses (D2, D3)	7	9820	0.83	(0.70, 0.98)
700-800IU/d	5	6098	0.77	(0.68, 0.87)
400IU/d	2	3722	1.03	(0.86, 1.24)
Stevenson, 2005[47]				
Women with severe osteoporosis or osteoporosis	1	86	2.50	(0.51, 12.19)
Elderly women not selected for BMD	1	213	0.46	(0.17, 1.27)
Papadimitropoulos, 2002[50]				
Standard vitamin-D [D2, D3, or 25(OH)D]	3	5399	0.78	(0.55, 1.09)
Calcitriol (1,25-OH vitamin D)	3	788	0.87	(0.29, 2.59)
Either Standard vitamin-D or Calcitriol	6	6187	0.77	(0.57, 1.04)
Richy, 2004[61]	11	1310	0.52	(0.46, 0.59)
Calcitriol	5	381	0.52	(0.41, 0.66)
Alphacalcidol	6	929	0.52	(0.45, 0.59)
Richy, 2005[58]				
Primary osteoporosis				
Vitamin D analogues	7	913	8%†	(2, 13%)
Standard vitamin D	6	7058	2%†	(1, 3%)

Table 32. Risk estimates of fracture for vitamin D relative to placebo or no treatment* (continued)

Type of fracture	# studies	Sample size	RR	(95% CI)
Hip				
Avenell, 2005[51]				
Standard vitamin-D [D2, D3, or 25(OH)D]				
Not selected on basis of prior osteoporotic fracture	4	15948	1.20	(0.98, 1.47)
Selected on basis of prior osteoporotic fracture	3	2820	1.08	(0.72, 1.62)
Either selected or not selected on basis of prior osteoporotic fracture	7	18668	1.17	(0.98, 1.41)
Alphacalcidiol				
Not selected on basis of prior osteoporotic fracture	3	239	0.16	(0.04, 0.69)
Calcitriol (1,25-OH vitamin D)				
Not selected on basis of prior osteoporotic fracture	1	246	0.33	(0.01, 8.10)
Bischoff-Ferrari, 2005[52]				
All doses (D2, D3)	5	9294	0.88	(0.69, 1.13)
700-800IU/d	3	5572	0.74	(0.61, 0.88)
400IU/d	2	3722	1.15	(0.88, 1.50)

* Stevenson: severe osteoporosis defined as T score <- 2.5 SD AND at least one documented fracture; osteoporosis defined as T score <- 2.5 SD without prior fracture; osteopenia defined as T-score between -1 and -2.5 SD. †Results expressed as rate difference (difference in fracture rate between treatment and placebo or no treatment).

Table 33. Risk of vertebral fracture for vitamin D, relative to placebo*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, vit d	Number of fractures, placebo	Odds ratio (95% CI)
ALL FRACTURES						
Grant, 2005[65]	62 months	New fractures	High	212/1343	196/1332	1.09 (0.88, 1.34)
Torres, 2004[213]	12 months	symptomatic fracture	High	0/41	0/45	NC
VERTEBRAL						
Grant, 2005[65]	62 months	Clinical vertebral	High	4/1343	1/1332	1.17 (0.71, 1.95)
Ishida, 2004[93]	24 months	vertebral	High	11/66	17/66	0.58 (0.25, 1.34)
HIP						
Grant, 2005[65]	62 months	Proximal femur	High	47/1343	41/1332	1.14 (0.75, 1.75)
Sato, 2005[214]	24 months	Hip	High	0/24	4/24	0.12 (0.01, 0.90)
WRIST						
Grant, 2005[65]	62 months	Distal forearm	High	33/1343	28/1332	1.17 (0.71, 1.95)
Ishida, 2004[93]	24 months	vertebral	High	11/66	17/66	0.58 (0.25, 1.34)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Calcium plus Vitamin D:

We identified three RCTs[63-65] that described the number of fractures among subjects treated with calcium plus vitamin D compared with placebo (Table 34). The study population in each of these studies was predominantly postmenopausal women with high[65] or intermediate[63, 64] risk for fracture. Fracture was a primary outcome in each of these studies, and all were powered to detect differences in fracture risk between study arms. Fracture risk did not differ significantly for calcium plus vitamin D compared with placebo for any type of fracture in any of the studies (Table 34).

Table 34. Risk of vertebral fracture for calcium plus vitamin D, relative to placebo*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, Calcium plus vit D	Number of fractures, placebo or control	Odds ratio (95% CI)
ALL FRACTURES						
Grant, 2005[65]	62 months	New fractures	High	104/1306	196/1332	0.95 (0.76, 1.18)
Jackson, 2006[63]	84 months	Total fracture	Intermediate	2101/18176	2158/18106	0.97 (0.91, 1.03)
Porthouse, 2005[64]	24 months	All fractures	Intermediate	24/607	22/602	1.09 (0.6, 1.96)
VERTEBRAL						
Grant, 2005[65]	62 months	Clinical vertebral	High	0/1306	1/1332	0.14 (0, 6.96)
Jackson R, 2006[63]	84 months	Clinical vertebral	Intermediate	181/18176	197/18106	0.91 (0.75, 1.12)
HIP						
Grant, 2005[65]	62 months	Proximal femur	High	46/1306	41/1332	1.15 (0.75, 1.76)
Jackson, 2006[63]	84 months	Hip fracture	Intermediate	175/18176	199/18106	0.87 (0.71, 1.07)
Porthouse, 2005[64]	24 months	Hip fracture	Intermediate	5/607	2/602	2.35 (0.53, 10.36)
WRIST						
Grant, 2005[65]	62 months	Distal forearm	High	33/1306	28/1332	1.21 (0.73, 2.01)
Jackson, 2006[63]	84 months	Lower arm or wrist	Intermediate	565/18176	557/18106	1.01 (0.9, 1.14)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Within class comparisons

Among the classes of drugs included in this report, two include two or more drugs that were considered in this report: the bisphosphonates and SERM. We identified nine RCTs with comparisons across different bisphosphonates and one with a comparison across different SERMs.

Bisphosphonates

We identified nine RCTs[68, 250-257] that included head-to-head comparisons of four different bisphosphonates pairs (Table 35). For the most part, these studies were not designed or powered to compare fracture outcomes but rather to compare changes in intermediate outcomes such as bone mineral density and changes in markers of bone turnover. Only one of the head-to-head trials[250] was designed to compare facture outcomes; this study was designed to compare risedronate to etidronate for the prevention of vertebral fractures.

Table 35. Head to head trials of bisphosphonates with fracture outcomes

	Alendronate	Etidronate	Ibandronate	Pamidronate	Risedronate	Zoledronic acid
Alendronate	**********					
Etidronate	2	**********				
Ibandronate	0	0	**********			
Pamidronate	0	0	0	**********		
Risedronate	4	2	1	0	**********	
Zoledronic acid	0	0	0	0	1	**********

Alendronate *vs.* Etidronate:

We identified two RCTs[252, 253] that compared fracture risk between treatment with alendronate and etidronate. Fracture was a secondary outcome in each of these studies and neither was powered to detect differences in fracture across groups. The study populations were postmenopausal women with osteoporosis[253] and osteopenic women with primary biliary cirrhosis.[252] Both studies were small and neither demonstrated any difference in fracture risk between alendronate and etidronate (Table 36).

Alendronate *vs.* Risedronate:

We identified four RCTs[68, 254, 255, 257] that compared fracture risk between treatment with alendronate and risedronate. Fracture data were collected as a secondary outcome in one of these studies[255] and as adverse events in the other three;[68, 254, 257] none were powered to detect differences in fracture across groups. All studies were restricted to women with osteoporosis or osteopenia. Three of the studies specified that the women were postmenopausal.[68, 254, 257] Across all doses and all type of fractures that were assessed, there were no differences in fracture risk between alendronate and risedronate (Table 37).

Table 36. Fractures with alendronate relative to etidronate, by fracture type*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, alendronate	Number of fractures, etidronate	Odds ratio (95% CI)
VERTEBRAL						
Guanabens, 2003[252]	24 months	vertebral	Intermediate	0/13	0/13	NC
Iwamoto, 2003[253]	6 months	vertebral	High	0/25	1/25	0.14 (0.00, 6.82)
NONVERTEBRAL						
Guanabens, 2003[252]	24 months	non-vertebral	Intermediate	2/13	1/13	2.06 (0.19, 21.85)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, *or* in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.
NC=not calculable

Table 37. Fractures with alendronate relative to risedronate, by fracture type among women with osteoporosis*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, alendronate	Number of fractures, risedronate	Odds ratio (95% CI)
ALL FRACTURES						
Bonnick, 2006[257]	24 months	clinical fracture	Intermediate	34/410	34/415	1.01 (0.62, 1.66)
Hosking, 2003[68]	12 months	fracture, clinical	High	6/172	6/178	1.04 (0.33, 3.27)
Rosen, 2005[254]	12 months	fracture	Intermediate	26/520	20/533	1.35 (0.75, 2.43)
Muscoso, 2004[255]	12 months	total fractures	High	2/1000	0/100	3.01 (0.02, 373.9)
VERTEBRAL						
Muscoso, 2004[255]	12 months	vertebral	High	2/1000	0/100	NC
Muscoso, 2004[255]	24 months	vertebral	High	4/1000	0/100	NC
HIP						
Muscoso, 2004[255]	12 months	femoral	High	1/1000	0/100	NC
Muscoso, 2004[255]	24 months	femoral	High	2/1000	0/100	NC
WRIST						
Muscoso, 2004[255]	12 months	radial	High	1/1000	0/100	NC
Muscoso, 2004[255]	24 months	radial	High	0/1000	0/100	NC

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.
NC=not calculable

Etidronate *vs.* Risedronate:

We identified two RCTs[250, 251] that compared fracture risk between treatment with etidronate and risedronate. In one study,[250] incidence of new vertebral fractures was the primary outcome; this study had sufficient sample size to demonstrate noninferiority of risedronate to etidronate for the prevention of vertebral fractures. Fracture incidence was a secondary outcome in the other study[251] and it did not have power to detect differences in fracture incidence across groups. The inclusion criteria were postmenopausal women with osteoporosis for one study,[250] and men or women with osteoporosis for the other, although only 1% of the sample was male.[251] Neither study demonstrated any difference in fracture risk between etidronate and risedronate (Table 38).

Table 38. Fractures with etidronate relative to risedronate, by fracture type

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, etidronate	Number of fractures, risedronate	Odds ratio (95% CI)
Fukunaga, 2002[251]	11 months	non-vertebral	High	4/117	7/118	0.57 (0.17,1.91)
Fukunaga, 2002[251]	11 months	vertebral	High	2/111	0/101	6.81 (0.42, 110)
Kushida, 2004[250]	96 weeks	vertebral	High	13/217	19/216	0.66 (0.32, 1.36)

Risedronate *vs.* Zoledronic Acid:

We identified one RCT[256]that compared fracture risk between treatment with risedronate and with zoledronic acid. This study evaluated the effects of several antiresorptive treatments on bone mineral density among women with ovarian failure after allogeneic stem cell transplantation; fracture was a secondary outcome. There was no difference in fracture risk between risedronate and zoledronic acid, but the sample sizes were small and the study was not powered to detect differences (Table 39).

Table 39. Risk of fracture for risedronate relative to zoledronic acid, by fracture type

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, risedroante	Number of fractures, zoledronic acid	Odds ratio (95% CI)
Tauchmanova, 2006[256]	12 months	subclinical vertebral fractures	Intermediate	2/15	3/15	0.63 (0.10, 4.15)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, *or* 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Selective Estrogen Receptor Modulators

Raloxifene *vs.* Tamoxifen:

We identified one RCT[258] that compared fracture risk between treatment with raloxifene and treatment with tamoxifen. This RCT evaluated the effects of raloxifene and tamoxifen on a number of outcomes including fracture among 19,747 postmenopausal women with increased risk for breast cancer. There was no difference in fracture risk between the agents (Table 40); the study was powered to detect differences.

Table 40. Risk of fracture for raloxifene relative to tamoxifen, by fracture type*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, raloxifene	Number of fractures, tamoxifen	Odds ratio (95% CI)
Vogel, 2006[258]	60 months	osteoporotic fractures	Low	104/9726	96/9745	1.09 (0.82, 1.44)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, OR 3) 0-10% of population has one or more fracture at baseline, *or* in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Between class comparisons

We identified 16 RCTs[65-67, 82, 91-93, 166, 255, 256, 259-264] that included head-to-head comparisons of 11 different drug pairs (Table 41).

Table 41. Head to head trials between classes of agents used to treat or prevent osteoporosis that examined fracture outcomes

	BIsphosphonate	Calcitonin	Calcium	Estrogen	PTH	SERMS	Testosterone	Vitamin D	Exercise
BIsphosphonate	**********								
Calcitonin	2	**********							
Calcium	2	0	*********						
Estrogen	6	1	0	**********					
PTH	1	0	0	0	********				
SERMS	3	0	0	1	0	**********			
Testosterone	0	0	0	0	0	0	**********		
Vitamin D	2	3	1	1	0	0	0	*********	

Bisphosphonate *vs.* Calcitonin:

We identified two studies[93, 261] that compared the effects of a bisphosphonate and calcitonin on fracture incidence. Fractures were secondary outcomes in each, and neither was powered to detect differences in fracture rate across arms. In one study, the population was postmenopausal women with osteoporosis;[93] in the other, organ transplant recipients that were primarily male.[261] The bisphosphonate in both studies was etidronate. Both studies were small, and no difference in fracture incidence between etidronate and calcitonin was found in either (Table 42).

Table 42. Fractures with etidronate relative to calcitonin, by fracture type*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, etidronate	Number of fractures, calcitonin	Odds ratio (95% CI)
Ishida, 2004[93]	24 months	vertebral	High	8/66	8/66	1.00 (0. 35, 2.83)
Garcia-Delgado, 1997[261]	18 months	vertebral	High	3/14	4/13	0.63 (0. 12, 3.39)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline OR 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, *or* in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Bisphosphonate *vs.* Calcium:

We identified two studies[92, 263] that compared the effects of a bisphosphonate and calcium on fracture incidence (Table 43). One study assessed etidronate,[92] the other pamidronate.[263] The study populations comprised individuals who required long-term glucocorticoids; in one study, they were required for asthma[92], and in the other study, they were required primarily for connective tissue disease.[263] Although fracture was the primary outcome of one study,[92] it did not reach target enrollment. Fracture was the secondary outcome of the other study.[263] There were no significant differences in the risk of fracture for bisphosphonates relative to calcium in either study. Neither study had sufficient sample size to detect such a difference in risk across study arms.

Table 43. Fractures with bisphosphonates relative to calcium, by bisphosphonate*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, etidronate	Number of fractures, calcium	Odds ratio (95% CI)
ETIDRONATE						
Campbell, 2004[92]	60 months	New symptomatic vertebral or non-vertebral	Intermediate	5/81	7/85	0.74 (0. 23, 2.38)
PAMIDRONATE						
Boutsen, 1997[263]	12 months	Atraumatic vertebral fracture	Intermediate	1/14	0/13	6.88 (0.14, 347.65)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, *or* 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Bisphosphonate *vs.* Estrogen:

We identified six studies that compared a bisphosphonate alone with estrogen: three compared alendronate and estrogen,[66, 67, 82] two compared etidronate and estrogen,[91, 93] and one compared both risedronate and zoledronic acid to estrogen.[256] There was no difference in fracture incidence between any of the bisphosphonates and estrogen (Table 44). Fracture data were collected as adverse events in the three studies that compared alendronate and estrogen;[66, 67, 82] they were collected as secondary endpoints in the studies that compared etidronate, risedronate, or zoledronic acid and estrogen.[91, 93, 256] None of the studies was powered to detect differences in fracture rates across study arms.

Table 44. Fractures with bisphosphonate relative to estrogen, among postmenopausal women*

Author, year	Study duration	Fracture type	Risk level	Number of fractures, bisphosphonate	Number of fractures, estrogen	Odds ratio (95% CI)
ALENDRONATE						
Hosking, 1998[82]	24 months	non-vertebral	1	44/897	6/204†	1.58 (0. 56, 4.43)
Bone, 2000[66]	24 months	clinical fracture	1	5/92	10/143	0.77 (0. 26, 2.25)
Greenspan, 2003[67]	34 months	clinical fracture	2	7/93	5/93	1.43 (0. 44, 4.58)
ETIDRONATE						
Ishida, 2004[93]	24 months	vertebral	1	8/66	7/66†	1.16 (0. 40, 3.39)
Wimalawansa, 1998[91]	48 months	non-vertebral	1	1/14	1/15	1.07 (0. 06, 18.10)
Wimalawansa, 1998[91]	48 months	vertebral	1	3/14	2/15	1.73 (0. 26, 11.50)
RISEDRONATE						
Tauchmanova, 2006[256]	12 months	Subclinical vertebral	2	2/15	1/15	2.05 (0.20, 21.36)
ZOLEDRONIC ACID						
Tauchmanova, 2006[256]	12 months	Subclinical vertebral	2	3/15	1/15	3.05 (0.38, 24.18)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids *or* 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

† Estrogen plus progesterone.

Bisphosphonate *vs.* PTH:

We identified one study[259] on fracture incidence among postmenopausal women that compared a bisphosphonate–alendronate–with PTH. In this study, the likelihood of non-vertebral fracture was higher with alendronate than with PTH (OR 3.24, 95% CI 1.04-10.07). Fractures were secondary outcomes; the study was not powered to detect differences in fracture rates across arms (Table 45).

Table 45. Fractures with alendronate relative to PTH among postmenopausal women*

Author, year	Study duration	Fracture type	Risk level	Number of fractures, Alendronate	Number of fractures, PTH	Odds ratio (95% CI)
Body, 2002[259]	14 months	non-vertebral	1	10/73	3/73	3.24 (1.04, 10.07)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Bisphosphonate *vs.* SERMS:

We identified three studies[255, 260, 262] that compared the effects of a bisphosphonate and a SERM on fracture incidence among women with osteoporosis. Two of the studies specified osteoporosis as an inclusion criterion;[260, 262] the average age of the women enrolled in the other study was 68 years.[255] The SERM in all studies was raloxifene. Alendronate was compared with raloxifene in each of the studies. Risedronate was compared with raloxifene in one study.[255] There was no difference in fracture incidence between either of the bisphosphonates and raloxifene (Table 46). Data on fractures were collected as adverse events in two of the studies[137, 262] and as secondary outcomes in the other.[255] Neither study was powered to detect differences in fracture rates across study arms.

Table 46. Fractures with bisphosphonates relative to raloxifene*

Author, year	Study duration	Fracture type	Risk level	Number of fractures, bisphosphonate	Number of fractures, raloxifene	Odds ratio (95% CI)
ALENDRONATE						
TOTAL FRACTURES						
Luckey, 2004[260]	12 months	all clinical fractures	HIgh	5/221	8/230	0.65 (0.22, 1.95)
Uchida, 2005[264]	12 months	Vertebral or nonvertebral	Intermediate	22/713	20/699	1.08 (0.59, 2.0)
VERTEBRAL						
Muscoso, 2004[255]	24 months	vertebral	High	6/1000	0/100	NC
Uchida, 2005[264]	12 months	Vertebral	Intermediate	8/713	5/699	1.56 (0.52, 4.65)
NONVERTEBRAL						
Uchida, 2005[264]	12 months	Nonvertebral	Intermediate	14/713	15/699	0.94 (0.44, 1.91)
HIP						
Muscoso, 2004[255]	24 months	femoral	High	3/1000	0/100	NC
Uchida, 2005[264]	12 months	Hip fracture	Intermediate	1/713	2/699	0.5 (0.05, 4.84)
WRIST						
Muscoso, 2004[255]	24 months	radial	High	1/1000	0/100	NC
Uchida, 2005[264]	12 months	Wrist	Intermediate	6/713	8/699	0.74 (0.26, 2.11)
RISEDRONATE						
VERTEBRAL						
Muscoso, 2004[255]	24 months	vertebral	High	0/100	0/100	NC
HIP						
Muscoso, 2004[255]	24 months	femoral	High	0/100	0/100	NC
WRIST						
Muscoso, 2004[255]	24 months	radial	High	0/100	0/100	NC

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.

Bisphosphonate *vs.* Testosterone:

We did not identify any studies that evaluated the risk of fracture for any bisphosphonate relative to testosterone.

Bisphosphonate *vs.* Vitamin D:

We identified one meta-analysis[265] and two original studies[93, 261] not included in the meta-analysis that compared the effects of a bisphosphonate and a vitamin D preparation on fracture incidence. The meta-analysis[265] pooled five studies that compared the effect of bisphosphonates with that of vitamin D analogs in decreasing the risk for vertebral fractures in patients taking glucocorticoids (Table 47). Data on fractures were collected as secondary outcomes in all studies, and no two studies compared the same bisphosphonate-vitamin D analog pair. Bisphosphonates were more effective than vitamin D analogs (RR 1.20 95% CI 0.32, 4.55).

In one original study, the population comprised postmenopausal women with osteoporosis, and[93] the other study was composed of primarily male organ transplant recipients.[261] The bisphosphonate in both original studies was etidronate. Etidronate was compared with alfacalcidol in one study[93] and with calcidiol[261] in the other. There was no difference in fracture incidence between etidronate and either of the vitamin D preparations (Table 48). Data on fractures were collected as secondary outcomes in both studies; neither was powered to detect differences in fracture rates across study arms.

Table 47. Randomized controlled trials included in meta-analysis of effect of vitamin D on fracture relative to bisphosphonates

RCTs	Meta-analysis
	De Nijs, 2004[265]
	Fracture Type
	Vertebral
Bianda, 2000[266]	X
Henderson, 2001[267]	X
Ringe, 2003[268]	X
Sambrook, 2003[269]	X
Van Cleemput, 1996[270]	X

Table 48. Fractures with etidronate relative to vitamin D, by vitamin D preparation

Author, year	Study duration	Fracture type	Risk level	Number of fractures, etidronate	Number of fractures, vitamin D	Odds ratio (95% CI)
ALPHACALCIDIOL						
Ishida, 2004[93]	24 months	Vertebral	High	8/66	11/66	0.69 (0.26, 1.83)
CALCIDIOL						
Garcia-Delgado, 1997[261]	18 months	Vertebral	High	3/14	0/13	8.08 (0.76, 85.33)

Calcitonin *vs.* Estrogen:

We identified one study[93] that compared the effect of calcitonin and estrogen on fracture incidence among postmenopausal women. There was no difference in fracture incidence between calcitonin and estrogen (Table 49). Fracture incidence was a secondary outcome in this study, and it was not powered to detect differences in fracture rates across study arms.

Table 49. Fractures with calcitonin relative to estrogen among postmenopausal women*

Author, year	Study duration	Fracture type	Risk level	Number of fractures, calcitonin	Number of fractures, estrogen	Odds ratio (95% CI)
Ishida, 2004[93]	24 months	Vertebral	High	8/66	7/66†	1.16 (0.4, 3.39)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤≤2.5, or 3) study entry criteria require≥≥1 fracture, or 4) ≥≥50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history, and age not reported as entry criteria or in baseline characteristics of population.
† Estrogen combined with progesterone.

Calcitonin *vs.* Teriparatide (PTH):

We did not identify any studies that compared the effects of calcitonin and teriparatide on fracture risk.

Calcitonin *vs.* Vitamin D:

We identified three studies[93, 141, 261] that compared the effects of calcitonin and vitamin D on fracture incidence. The study population in two studies was postmenopausal women at high[93] or low[141] risk for fracture and in the other study consisted predominantly of male organ transplant recipients at high risk for fracture.[261] One study demonstrated an increased risk of vertebral fracture with calcitonin relative to vitamin D.[261] Although the result was statistically significant, the confidence interval was very wide and the sample size was small. In the other studies, there was no difference in fracture incidence between groups (Table 50). Fracture incidence was a secondary outcome in each study; none were powered to detect differences in fracture rates across study arms.

Table 50. Fractures with calcitonin relative to vitamin D*

Author, year	Study duration	Fracture type	Risk level	Number of fractures, calcitonin	Number of fractures, vitamin D	Odds ratio (95% CI)
Ishida, 2004[93]	24 months	Vertebral	High	8/66	11/66	0.69 (0.26, 1.83)
Garcia-Delgado, 1997[261]	18 months	Vertebral	High	4/13	0/13	9.71 (1.20, 78.42)
Ushiroyama T, 2001[141]	24 months	Vertebral	Low	0/49	0/50	NC

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤≤-2.5, or 3) study entry criteria require≥≥1 fracture, or 4) ≥≥50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤≤ 1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history, and age not reported as entry criteria or in baseline characteristics of population.
NC=not calculable.

Calcium *vs.* Vitamin D:

We identified one RCT[65] that describes the number of fractures among subjects treated with calcium relative to vitamin D (Table 51). The study population was postmenopausal women with prior osteoporotic fractures at high risk for fracture. Fracture was the primary outcome for this study. There were no statistically significant differences in the risk of fracture for calcium relative to vitamin D for any type of fracture (Table 51).

Table 51. Risk of fracture for calcium, relative to vitamin D, by fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, calcium	Number of fractures, vitamin D†	Odds ratio (95% CI)
ALL FRACTURES						
Grant, 2005[65]	62 months	New fractures	High	189/1311	212/1343	0.90 (0.73, 1.11)
VERTEBRAL FRACTURES						
Grant, 2005[65]	62 months	Clinical vertebral fractures	High	3/1311	4/1343	0.77 (0.17, 3.39)
HIP						
Grant, 2005[65]	62 months	Proximal femur fracture	High	49/1311	47/1343	1.07 (0.71, 1.60)
WRIST						
Grant, 2005[65]	62 months	Distal forearm fracture	High	33/1311	33/1343	1.02 (0.63, 1.67)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤≤-2.5, or 3) study entry criteria require ≥≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history and age not reported as entry criteria or in baseline characteristics of population.
† Control group.

Estrogen *vs.* Vitamin D:

We identified one RCT[93] that described the number of fractures among subjects treated with estrogen relative to vitamin D (Table 52). The study population in this study was postmenopausal women with intermediate risk for fracture. Fracture was a secondary outcome for this study. There was no statistically significant difference in the risk of fracture for estrogen relative to vitamin D for vertebral fractures (Table 52). However, the study was not powered to detect such differences.

Table 52. Risk of fracture for estrogen, relative to vitamin D, by fracture group*

Author, year	Study duration	Type of fracture	Risk level	Number of fractures, estrogen	Number of fractures, vitamin D†	Odds ratio (95% CI)
VERTEBRAL						
Ishida, 2004[93]	24 months	Vertebral	High	7/66†	11/66	0.6 (0.22, 1.62)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤≤-2.5, or 3) study entry criteria require≥≥1 fracture, or 4) ≥≥50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history, and age not reported as entry criteria or in baseline characteristics of population.
† Estrogen plus medroxyprogesterone.

Estrogen *vs.* Teriparatide

We did not identify any studies that compared the effects of estrogen and teriparatide on fracture risk.

SERM *vs.* Estrogen

We identified one study[166] that compared the effects of raloxifene and estrogen on fracture incidence among postmenopausal women. There was no difference in fracture incidence between these groups (Table 53). Data on fracture incidence were collected as adverse events. This study was not powered to detect differences in fracture rates between study arms.

Table 53. Fractures with raloxifene, relative to estrogen, among postmenopausal women*

Author, year	Study duration	Fracture type	Risk level	Number of fractures, etidronate	Number of fractures, estrogen	Odds ratio (95% CI)
Reid, 2004[166]	36 months	Vertebral	Intermediate	4/193†	1/102	1.9 (0.03, 12.22)

* High-risk: 1) transplant population, or 2) study entry criteria require T score ≤-2.5, or 3) study entry criteria require≥1 fracture, or 4) ≥ 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score ≤1.5, or 2) 10-50% of population has one or more fracture at baseline, or 3) study population has chronic disease that is commonly treated with glucocorticoids or 4) in the absence of data on BMD or fractures, mean age of population > 62 years. Low-risk: 1) study entry criteria require T score ≤0.0, or 2) < 10% of population has BMD =8 g/cm2 at baseline, or 3) 0-10% of population has one or more fracture at baseline, or in the absence of data on BMD or fracture, mean age of population <62 years. Unknown risk: BMD, fracture history, and age not reported as entry criteria or in baseline characteristics of population.
† 60 and 150 mg dose groups combined.

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 Points

- 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 post-menopausal women.
- There are insufficient data to determine whether etidronate or ibandronate prevent fractures among groups at intermediate or low risk for osteoporosis including postmenopausal women without osteoporosis or among men.
- There are insufficient data to determine whether alendronate prevents fractures among groups at low risk for osteoporosis including postmenopausal women without osteoporosis or among 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.

- 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.

Detailed Analyses

Fracture risk

Among the 24 meta-analyses reviewed for this report, six performed analyses that evaluated the effect of therapy for different groupings of fracture risk.[39, 41, 43, 47, 51, 162] The criteria used to define risk groups for these studies overlapped but were not identical. Likewise, they overlapped with but were not identical to the risk groups defined for this report, which are as follows:

High-risk:

1) transplant population, *or*
2) study entry criteria require T score ≤ -2.5, *or*
3) study entry criteria require≥1 fracture, *or*
4) ≥50% of population has 1 or more fractures at baseline, *or*
5) Significant neuromuscular impairment

Intermediate-risk:

1) study entry criteria require T score ≤1.5, *or*
2) 10-49.99% of population has one or more fracture at baseline, *or*
3) study population has chronic disease that is commonly treated with glucocorticoids, *or*
4) in the absence of data on BMD or fractures, mean age of population ≥60 years.

Low-risk:

1) study entry criteria require T score ≤0.0, *or*
2) < 10% of population has BMD =8 g/cm2 at baseline, *or*
3) < 10% of population has one or more fracture at baseline, *or*
4) in the absence of data on BMD or fracture, mean age of population <60 years.

The risk groups defined in each of the meta-analyses were each categorized into the best fitting risk group for this report. The criteria used to define risk groups in each of the meta-analyses and how they fit into the risk groups defined for this report are detailed in Table 54. The risk estimates from each meta-analysis, by the risk groups defined for this report, are displayed in Table 55. The risk categories for subgroups detailed in the Women's Health Initiative[163] are also detailed. Among the three studies that contributed data to the pooled risk estimate of vertebral fractures for ibandronate that was calculated for this report (Figure 10), all were among high risk subjects. We assigned a high risk designation to the pooled study population. Among the four studies that contributed data to the pooled risk estimate of vertebral fractures for pamidronate that was calculated for this report (Figure 11), three were among high risk subjects and two were among intermediate risk subjects. We assigned a high risk designation to the pooled study population.

Table 54. Risk groups from published meta-analyses and from the Women's Health Initiative

Risk groups in other reports	Risk groups for this report		
Author	High	Intermediate	Low
Avenell[51]			
Not selected for prior fracture		X	
Selected for prior fracture	X		
Cauley (WHI)[163]			
Age at screening 50-59			X
Age at screening 60-69		X	
History of fracture	X		
No history of fracture‡		X	
Cranney[39, 41]*			
Prevention			X
Treatment		X	
Papapoulos[43]			
T-score ≤2.0 or vertebral fracture		X	
T-score ≤2.5 or vertebral fracture	X		
Stevenson[47]†			
Not selected for low BMD			X
Osteopenia			X
Elderly women not selected for BMD		X	
Osteoporosis		X	
Severe Osteoporosis	X		
Torgerson[162]			
Women <60			X
Women ≥60		X	

* Cranney: 'treatment trial' population has T-score < -2 SD and/or baseline prevalence of fracture is >20% and/or average age is >62; 'prevention trial' population has T-score ≥ -2 SD and/or baseline prevalence of fracture is ≤20% and/or average age is ≤62. †Stevenson: severe osteoporosis defined as T score <- 2.5 SD AND at least one documented fracture; osteoporosis defined as T score <- 2.5 SD without prior fracture; osteopenia defined as T-score between -1 and -2.5 SD. ‡ Classified as intermediate based on no fracture and mean age of overall population , which was 63.

Table 55 compares the effects of agents on various risk groups. In some instances, pooled estimate for fracture risk of the population with a higher risk for fracture reached statistical significance when a pooled estimate of the population with less severe osteoporosis or osteopenia did not. Similarly, in some instances, the pooled estimate for fracture risk for the population with a higher fracture risk was higher than the estimate for the population with lower risk. However, in all instances the point estimates for the groups with the higher fracture risk fell within the 95% confidence intervals for the estimates for the group with lower fracture risk.

Table 55. Risk of developing fracture for populations with more severe osteoporosis or osteopenia, by fracture risk, drug, and fracture type

	Fracture risk		
	High	Intermediate	Low
Author, year	OR (95% CI)		
Alendronate			
Vertebral Fractures			
Cranney, 2002[39]		0.53	0.45
		(0.43, 0.65)	(0.06, 3.15)
Stevenson, 2005[47]	0.53	0.60	
	(0.42, 0.67)	(0.46, 0.80)	
Non-Vertebral Fractures			
Cranney, 2002[39]		0.49	0.79*
		(0.36, 0.67)	(0.28, 2.24)
Stevenson, 2005[47]	0.81	0.74|	
	(0.66, 0.98)	(0.52, 1.06)	
Hip Fractures			
Papapoulos, 2004[43]	0.45	0.56	
	(0.28, 0.71)	(0.36, 0.84)	
Stevenson, 2005[47]	0.46	0.68	
	(0.23, 0.91)	(0.30, 1.54)	
Wrist Fractures			
Stevenson, 2005[47]	0.48	0.67	
	(0.31, 0.75)	(0.19, 2.32)	
Etidronate			
Vertebral Fractures			
Cranney, 2001[41]		0.59	0.61
		(0.38, 0.94)	(0.29, 1.26)
Stevenson, 2005[47]	0.43		
	(0.20, 0.91)		
Non-vertebral Fracture			
Cranney, 2001[41]		0.75	
		(0.34, 1.70)	
Hip Fracture			
Stevenson, 2005[47]	0.50		
	(0.05, 5.34)		
Ibandronate			
Vertebral Fractures			
Current report, Figure 10	0.70		
	(0.54, 0.91)		
Pamidronate			
Vertebral Fractures			
Current report, Figure 11	0.52		
	(0.21, 1.24)		

Table 55. Risk of developing fracture for populations with more severe osteoporosis or osteopenia, by fracture risk, drug, and fracture type (continued)

	Fracture risk		
	High	Intermediate	Low
Author, year	OR (95% CI)		
Risedronate			
Vertebral Fractures			
Stevenson, 2005[47]	0.62		
	(0.50, 0.77)		
Non-vertebral Fractures			
Stevenson, 2005[47]	0.67		
	(0.50, 0.90)		
Hip Fracture			
Stevenson, 2005[47]	0.66	0.60	
	(0.48, 0.89)	(0.42, 0.88)	
Wrist Fracture			
Stevenson, 2005[47]	0.68		
	(0.43, 1.08)		
Estrogen			
Vertebral Fractures			
Stevenson, 2005[47]	0.58		2.05
	(0.26, 1.30)		(0.71, 5.97)
Non-vertebral Fractures			
Stevenson, 2005[47]	0.67	1.17	0.86
	(0.12, 3.93)	(0.41, 3.28)	(0.72, 1.02)
Torgerson, 2001[162]		0.88	0.67
		(0.71, 1.08)	(0.46, 0.98)
Hip Fracture			
Cauley, 2003[163]†		0.76‡	0.17‡
		(0.41, 1.39)	(0.02, 1.43)
Cauley, 2003[163]†	0.77§	0.52§	
	(0.48, 1.22)	(0.28, 0.98)	
Stevenson, 2005[47]			0.74
			(0.53, 1.03)
Wrist			
Stevenson, 2005[47]			0.95
			(0.58, 1.53)
Teriparatide			
Vertebral Fractures			
Stevenson, 2005[47]	0.35		
	(0.22, 0.55)		
Non-vertebral Fractures			
Stevenson, 2005[47]	0.65		
	(0.43, 0.98)		
Stevenson, 2005[47]	0.50		
	(0.09, 2.73)		
Wrist			
Stevenson, 2005[47]	0.54		
	(0.22, 1.35)		
Humerus			
Stevenson, 2005[47]	0.80		
	(0.22, 2.98)		

Table 55. Risk of developing fracture for populations with more severe osteoporosis or osteopenia, by fracture risk, drug, and fracture type (continued)

	Fracture risk		
	High	Intermediate	Low
Author, year	OR (95% CI)		
Raloxifene			
Vertebral Fractures			
Stevenson, 2005[47]	0.69		0.53
	(0.56, 0.86)		(0.35, 0.79)
Non-vertebral Fractures			
Stevenson, 2005[47]	0.92		
	(0.79, 1.07)		
Hip Fracture			
Stevenson, 2005[47]	1.12		
	(0.65, 1.95)		
Wrist Fracture			
Stevenson, 2005[47]	0.89		
	(0.68, 1.15)		
Vitamin D			
Vertebral Fractures			
Avenell, 2005[51]	3.97	0.96|	
	(0.44, 35.45)	(0.42, 2.21)	
Stevenson, 2005[47]	1.02	4.44	
	(0.44, 2.32)	(0.50, 39.03)	
Non-vertebral Fractures			
Avenell, 2005[51]		0.40	
		(0.05, 3.08)	
Stevenson, 2005[47]		0.46	0.86
		(0.17, 1.27)	(0.72, 1.02)
Hip Fracture			
Avenell, 2005[51]	1.08	1.20	
	(0.72, 1.62)	(0.98, 1.47)	

* Risk estimate based on single study.
† RCT comparing estrogen plus progestin, Hazards ratios reported in study.
‡ Based on age strata. See Table 54.
§ Based on history of fracture. See table 54.

Three of the six meta-analyses that reported fracture risk according to risk groups included a risk group that could be categorized as"low risk" according to our criteria.[41, 47, 162] The Women's Health Initiative also reported fracture rates by risk groups.[163] The meta-analyses report pooled risk estimates among low risk populations for bisphosphonates, estrogen, raloxifene and vitamin D. Among the bisphosponates alendronate and etidronate, no significant risk reduction for fracture relative to placebo was demonstrated for low risk subjects in one meta-analysis.[39] For estrogen, no significant reductions in risk for vertebral or wrist fractures relative to placebo were reported for low risk subjects in one meta-analysis.[47] The risk of non-vertebral fractures for estrogen relative to placebo for low risk subjects was significantly reduced in one meta-analysis;[162] in another it was reduced, but not significantly.[47] For raloxifene, a significant reduction in risk for vertebral fractures relative to placebo was reported for low risk subjects in one meta-analysis.[47] There was no significant risk reduction for low risk subjects treated wih vitamin D relative to placebo in one meta-analysis.[47] The Women's Health Initiative evaluated risk of fracture for a number risk categories and did not find any significant differences in fracture risk across the different categories for hip[163, 165] or total[163] fractures. In addition to history of fracture and age, both of which fit into the classification scheme used for this analysis (Table 55), the WHI also assessed fracture risk based on a composite fracture risk score and found no difference in risk across categories for hip or total fractures. Two additional RCTs in low-risk groups were published after these meta-analyses. In one trial[141] none of 49 calcitonin users had fractures at 24 months, compared to two of 52 control subjects. Another RCT among women at increased risk for breast cancer (but not selected for fracture risk) showed no difference in fractures between raloxifene and tamoxifen at 60 months.[256]

Special Populations

Post-menopausal women, not classified into risk groups: An additional meta-analysis[45] that evaluated the effect of calcitonin relative to placebo was restricted to post-menopausal women, but did not provide other information to allow classification into one of the risk categories above. This meta-analysis reported a reduced risk of vertebral fractures with calcitonin relative to placebo (RR 0.46, 95% CI 0.25, 0.87). The risk of non-vertebral fractures was not significantly reduced with calcitonin relative to placebo (RR 0.52, 95% CI 0.22, 1.23).

Men: Few studies assessed the effect of agents to reduce fracture risk among men. Among nine studies that included men,[65, 92, 123-125, 140, 142, 195, 196] three demonstrated a reduction in fracture risk: one for total fractures with teriparatide,[196] one for hip fractures with risedronate,[124] and one for vertebral fractures with calcitonin.[142] Among the remaining studies, only one had sufficient sample size to assess the effect of agents on fracture.[65] In this study, which included men and women, there was no reduction in the rate of fractures for calcium relative to placebo; subgroup analyses found no difference in risk among men and women.

Breast cancer: We identified one large RCT[204] that evaluated the effect of tamoxifen relative to placebo on fracture risk among women older than 60 or women aged 35-59 with increased risk for breast cancer. There was no statistical difference in fracture risk between tamoxifen and placebo, for any type of fracture (Table 27).

Differences in fracture risk due to BMD-lowering medications or conditions. Eighteen RCTs were performed in special populations with increased risk for fractures as a result of medications or diseases that reduce BMD. There were 13 studies with populations at increased risk for fractures due to medications that decrease BMD: eight were performed among recipients of solid organ transplants;[107, 110-112, 114, 143, 213, 261] two among bone marrow transplant recipients;[113, 256] one among subjects with asthma;[123] and two among patients undergoing chemotherapy for lymphoma[109] and breast cancer.[122] Among 24 comparisons between drug and placebo or between two drugs, two demonstrated a significant difference in fracture risk for one study arm compared with another, although both have very wide 95% confidence intervals. In one, the risk of vertebral fracture was reduced for pamidronate relative to placebo (OR 0.14, 95% CI 0.03, 0.72) among patients receiving chemotherapy for lymphoma.[109] In the other, the risk of vertebral fracture for calcitonin relative to calcidiol was 9.71 (95% CI 1.2, 78.42) among lung transplant recipients.[261] Among all 23 studies, fracture data were collected as secondary outcomes or adverse events; none were powered to detect differences in fracture rates across study arms.

There were four studies among populations at increased risk for fracture due to a disease that is associated with low BMD: two among subjects with primary biliary cirrhosis;[71, 252] one among subjects with leoprosy;[125] and one among subjects with inflammatory bowel disease in remission.[120] Among six comparisons between drug and placebo or between two drugs, one demonstrated a significant difference in fracture risk for one study arm compared with another. In this study,[120] the risk of vertebral fracture among subjects with inflammatory bowel disease in remission was reduced for risedronate relative to placebo (OR 0.3, 95% CI 0.11, 0.84). There were no significant differences in risk between alendronate and placebo or risedronate and placebo in studies of subjects with primary biliary cirrhosis or leprosy. Fracture was a secondary outcome in all of these studies and none were powered to detect differences in fracture rates across study arms.

Differences in Fracture Risk due to Increased Risk for Falls. There were six studies among populations at increased risk for fracture due to conditions that increase the risk of falling: three among subjects with stroke and hemiplegia;[119, 124, 214] one among subjects with Alzheimer's disease;[118] one among subjects with a recent hip fracture;[89] and one among subjects with Parkinson's disease in remission.[72] Across these studies, there were seven comparisons between alendronate, etidronate, risedronate, or vitamin D and placebo, six of which demonstrated significant reductions in fracture risk for the agent relative to placebo (Table 56). Fracture was the primary outcome in three of these studies and a secondary outcome in two.[72, 214] All but two[72, 214] had sufficient sample size to detect differences in fracture risk across arms, although one of these two studies demonstrated a significant difference in risk across arms.[214]

Table 56. Risk of fracture among populations at increased risk for falling, by drug

Author, year	Study duration	Type of fracture	Number of fractures, agent	Number of fractures, placebo or control	Odds ratio (95% CI)
Alendronate					
Sato, 2006[72]	48 months	Hip fracture	4/131	14/129	0.3 (0.12, 0.78)
Etidronate					
Sato, 2004[89]	3 months	Hip fracture	0/36	0/37	NA
Risedronate					
Sato, 2005[119]	12 months	Hip fracture	1/172	7/173	0.22 (0.05, 0.88)
Sato, 2005[118]	18 months	Hip fracture	5/231	19/230	0.29 (0.13, 0.66)
Sato, 2005[118]	18 months	Nonvertebral fracture	8/231	29/230	0.29 (0.15, 0.57)
Sato, 2005[124]	18 months	Hip fracture	2/134	10/133	0.25 (0.08, 0.78)
Vitamin D					
Sato, 2005[214]	24 months	Hip fractures	0/24	4/24	0.12 (0.02, 0.90)

Glucocorticoid-induced osteoporosis

Bisphosphonates: We identified one systematic review[271] and six studies published subsequent to the review[92, 94, 136, 263, 272, 273] that evaluated the effect of bisphosphonates on fracture incidence among subjects treated with glucocorticoids. The systematic review identified nine studies[137, 274-281] published before 1999 that reported fracture data, although not as the primary outcome (Table 57). The authors of the systematic review report that six of the studies[137, 274-277, 280] analyzed the difference between treatment and control group with regard to fracture risk; three found a trend in reduced fracture rate[137, 274, 276] and one demonstrated a 10.1% reduction in vertebral fractures among patients treated with risedronate compared with control.[137]

Among the studies published after the systematic review, three demonstrated significant reductions in the risk of fracture for bisphosphonates relative to placebo and three did not. One study[273] that compared risedronate and placebo demonstrated a statistically significant reduction in the absolute risk and relative risk of incident radiographic vertebral fractures (11% and 70%, respectively) after 1 year. This study included data from the Cohen trial,[137] which was included in the systematic review. Another,[272] which compared alendronate and placebo, demonstrated a significant reduction in the risk of incident radiographic vertebral fractures (0.7% with alendronate versus 6.8% with placebo; $p < 0.05$). The third trial with significant results[136] compared two different daily doses of risedronate with placebo. A significant reduction in the incidence of vertebral fractures of 70% was found for the combined risedronate groups. In the remaining three trials, there was no significant difference in fracture risk between etidronate and control,[92, 94] calcium and control,[92] or calcium and etidronate.[92]

Table 57. RCTs of bisphosphonates used to treat or prevent glucocorticoid-induced osteoporosis that report fracture data included in prior systematic review*

Author, year	Bisphosphonate	Control	N	Mean daily steroid dose	Population	Results
Studies included in systematic review						
Adachi, 1997[274]	Cyclical etidronate: 400 mg/d X 2weeks, then 500 mg/d Ca X 11 weeks; could use 1000 u/d vit D	Cyclical placebo, then 500 mg/d Ca; could use 1000 u/d vitamin D	117	11 mg prednisone	Primary; 42 men/75 women Mean age 58 years with primarily RA, PMR	Trend toward reduced fracture risk for etidronate.
Cohen, 1999[137]	Risedronate 2.5 or 5 mg/d + 1000mg/d Ca + 400 u/d vit D	Placebo + 1000 mg/d Ca + 400u/d vit D	290	15 mg prednisone	Secondary, men and women Mean age 58.4, primarily RA, PMR	Trend toward reduced fracture risk for risedronate.
Cortet, 1999[281]	Cyclical etidronate 400 mg/d X 2 weeks then 500 mg/d Ca X 11 weeks	500 mg/d Ca	12	Nr	Primary, 3 men/ 9 women (33% postmenopausal) with primary biliary cirrhosis	Fractures reported but not analyzed.
Geusens, 1998[280]	Cyclical etidronate 400 mg/d X 2 weeks then 500 mg/d Ca X 11 weeks; could use 1000 u/d vit D	Cyclical placebo, then 500 mg/d Ca; could use 1000 u/d vitamin D	83	12.5 mg prednisone	Primary, 28 men/ 55 women (84% postmenopausal) with primary RA and PMR	No significant difference in fracture rate but not powered to detect.
Jenkins, 1999[279]	Cyclical etidronate 400 mg/d X 2 weeks then 97 mg/d Ca + 400 u/d vit D X 11 weeks	Cyclical placebo then 97 mg/d Ca + 400400 u/d vit D	49	7.5 mg prednisolone	Secondary 19 men/ 30 women, mean age 59 years, with asthma, PMR, and SLE	Fractures reported but not analyzed.
Jensen, 1998[277]	Risedronate	1000 mg/d Ca	55	8.5 mg prednisone	Unknown combination 11 men/ 44 women (mean age 64) with primarily PMR, TA, asthma	Significant reduction in fracture risk for risedronate relative to placebo.
Roux, 1998[275]	Clodronate 800, 1600, or 2400 mg/d	Placebo	74	8 mg prednisolone	Secondary 33 men/ 41 women (73% postmenopausal) age range 39-73, with asthma or COPD	No significant difference in fracture rate but not powered to detect.

* Systematic review by Blair et al., 2000[271]

Table 57. RCTs of bisphosphonates used to treat or prevent glucocorticoid-induced osteoporosis that report fracture data included in prior systematic review* (continued)

Author, year	Bisphosphonate	Control	N	Mean daily steroid dose	Population	Results
Studies included in systematic review						
Saag, 1998[276]	Risedronate 2.5, 5, or 10 mg/d + 500 mg/d Ca	Placebo + 500 mg/d Ca	477	21 mg prednisone	Primary 477 men and women (70% postmenopausal) mean age 59.4±14.3, primarily RA, PMR, SLE	Trend toward reduced fracture risk for risedronate.
Skingle, 1999[278]	Cyclical etidronate 400 mg/d X 2 wks then 500 mg/d Ca 11 wks	Cyclical placebo then 500 mg/d Ca	28	9 mg/d prednisolone	Primary 11 men/ 17 women with PMR or RA	Fractures reported but not analyzed.
Studies published after systematic review						
Adachi, 2001[272]	Alendronate 5 or 10 mg X 24 mos (or 2.5 mg for 12 mos and 10 mg for 12 mos) + 800-1000 mg/d Ca + 250-500 u/d vit D	Placebo + 800-1000 mg/d Ca + 250-500 u/d vit D	208	7.5 mg prednisone (10 mg in year 2)	66 men/ 142 women (63% postmenopausal), age range 21-79	90% reduction in vertebral fractures (2 years); 70% reduction in nonvertebral fractures.
Reid, 2000[136]	Risedronate 2.5 or 5 mg/d + 1g/d Ca + 400 u/d vit D X 12 mos	Placebo + 1g/d Ca + 400 u/d vit D	290	≥7.5 mg prednisone	Ambulatory men and women, age 18-85, primarily RA, dermatologic, respiratory diseases	70% reduction in vertebral fractures.
Wallach, 2000[273]	Risedronate 2.5 or 5 mg/d + 1000 mg/d Ca + 400 u/d vit D X 12 mos	Placebo + 1000 mg/d Ca + 400 u/d vit D	509	7.5 mg prednisone equivalent	184 Men/ 325 women (78% postmenopausal), age range 18-85 years, primarily RA, PMR, TA, CILD, COPD, asthma, and others	2.5 mg risedronate: 58% reduction in vertebral fractures; 5 mg risedronate: 70% reduction in vertebral fractures.

* Systematic review by Blair et al., 2000[271]; CILD Chronic infiltrative lung disease, COPD chronic obstructive pulmonary disease, PMR polymyalgia rheumatica, RA rheumatoid arthritis, SLE Systemic Lupus Erythematosus

Calcitonin: We identified one meta-analysis[42] that evaluated the effect of calcitonin relative to placebo for the prevention and treatment of glucocorticoid-induced osteoporosis. Among four trials and a total of 256 subjects, the pooled risk for vertebral fractures for calcitonin relative to placebo was 0.71 (95% CI, 0.26, 1.89). Among four trials and a total of 208 subjects, the pooled risk for non-vertebral fractures was 0.52 (95% CI 0.14, 1.96).

Other risk groups

We did not identify any studies that evaluated the effect of treatments for osteoporosis for different age groups, levels of vitamin D deficiency, or residence in the community compared with residence in a nursing home.

Key Question 3. What are the adherence to and persistence with 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 Points

- Only 10 fracture trials reported rates of adherence to therapy. Five trials of calcium reported high rates of non-adherence. In studies that defined "adherence" as taking at least 80% of pills, from 32% to 78% of subjects were adherent. In two studies of daily oral bisphosphonates, more than 80% of patients took at least 70% of the drug. The other three trials reported high rates of adherence with weekly risedronate therapy.

- There is evidence from 10 observational studies that adherence to therapy with alendronate, etidronate, risedronate, calcitonin, HRT, raloxifene, and calcium and vitamin D is poor in 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, and calcium and vitamin D is poor in many men and postmenopausal women with osteoporosis.

- Based on evidence from observational studies, factors that affect adherence and persistence include side effects of medications, absence of symptoms related to the underlying disease, co-morbid 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 RCTs and observational studies that postmenopausal women who are non-adherent to treatment with alendronate, risedronate, HRT, calcium, or calcitonin have an increased risk of fracture compared with women who are adherent to therapy.

- There is evidence from one observational study that postmenopausal women with osteoporosis who are non-persistent with alendronate and risedronate therapy have an increased risk of fracture compared with women persistent with these medications.

Detailed Analyses

Effect of adherence and persistence of medications for osteoporosis on fractures in RCTs

Among the RCTs included in this report that assessed the effect of agents on the prevention of fractures, 27 reported that they measured subject adherence to therapy. However, among these studies, only 10 reported rates of adherence to therapy.[63-65, 127, 128, 206, 207, 262, 282, 283] Of these, only five included an analysis of outcomes that considered adherence to therapy.[63, 64, 206, 207, 282]

Five RCTs[63-65, 206, 207] reported high rates of non-adherence with calcium. In one study,[206] 57% of the subjects took at least 80% of their calcium pills. Reduced fracture incidence was seen in the calcium compared with the placebo groups (10.2% vs 15.4%; hazard ratio, 0.66; 95% CI 0.45-0.97). In a second study,[63] 59% of subjects took at least 80% of their calcium and vitamin D pills. These subjects had a 29% reduction in hip fractures compared with placebo groups (hazard ratio 0.71; 95% CI 0.52 – 0.97). In another study,[64] 12-month adherence rates were only 63% among women participating in a trial of calcium plus vitamin D vs. placebo. The definition of adherence used in this study was not described, and adherence was calculated only for women known to be alive at the 12-month timepoint. There was no difference in fracture incidence among women who adhered to treatment compared with placebo. In another study,[207] 32% of subjects had at least one 6-month period of compliance less than 60%. When these non-adherent patients were excluded from the analysis, there was no significant difference in hip or vetebral fracture risk among women taking calcium compared with those taking placebo. In another study,[65] 78% of subjects took at least 80% of their calcium pills. An analysis of adherent subjects was not performed.

Five RCTs reported rates of adherence with bisphosphonate treatments.[127, 128, 262, 282, 283] We identified a study that reported rates of adherence with alendronate.[282] In this study, 81% of patients took at least 70% of their study drug. Fracture risk was reported by stratifying patients into three categories based on their change in BMD over the course of the study. Adherent subjects taking alendronate who had a 0-4% decrease in lumbar spine BMD over the course of the study had a reduction of 60% in vertebral fracture risk compared with those taking placebo (OR 0.40 95% CI 0.16 – 0.99). Those who "gained" BMD (0% to 4%) during treatment had a reduction of risk of 51% (OR 0.49 95% CI 0.30 – 0.78). Those who lost more than 4% of BMD over the course of the study did not have a significant change in fracture risk. In a separate study,[262] rates of adherence were reported among patients randomized to either raloxifene or alendronate. Overall, 84.3% of subjects took at least 70% of their study medication, with no difference between treatment groups. An analysis of adherent subjects was not performed for this study.

We also identified three RCTs that reported high rates of adherence with weekly risedronate therapy.[127, 128, 283] One study[128] reported that 98% of subjects randomized to weekly risedronate or to placebo took at least 80% of their study medications. Another study[283] reported that 100% of subjects in the risedronate group and 99.3% taking placebo were adherent, defined as "receiving the study drug at the correct time and in the appropriate manner." A third study reported that 98% of subjects were adherent with weekly risedronate therapy.[127] An analysis of adherent subjects was not performed for any of these three studies.

Effect of adherence and persistence of medications for osteoporosis on fractures in observational studies

We identified three observational studies[284-286] that assessed the effect of adherence or persistence on fracture risk (Table 58). Rates of fracture prevention in all three studies were shown to vary according to levels of adherence to therapy. Huybrechts and colleagues identified a cohort of 38,120 women with osteoporosis from a large US managed care database who were administered alendronate, risedronate, or hormone replacement therapy (HRT) over a 5-year period.[286] They found that three quarters of the women had low adherence, defined as a medication possession ratio (MPR) below 80% over the entire course of their follow-up. After adjusting for other known risk factors, low adherence was associated with a 17% increased risk of fracture. Low adherence was also associated with a 37% increase in all-cause hospitalization, and with higher average monthly costs for all medical services. Siris used two large US commercial claims databases to examine refill adherence (defined as MPR > 80%) among all women in a 5-year period who received a prescription for either alendronate or risedronate.[285] Adherence to medications was associated with a 25% relative reduction in risk for all osteoporotic fractures compared with noncompliant patients. Persistence with therapy (nonpersistence was defined as a refill gap of more than 30 days during the period of the study) was associated with a 29% reduction in the risk of nonvertebral fractures and a 45% reduction in the risk of hip fractures. Another study, which used data obtained from the health services databases of Saskatchewan, Canada, found that among 11,249 women who were treated with alendronate, risedronate, etidronate ±calcium, calcitonin, or HRT for osteoporosis, those with a MPR ≥ 80% experienced a 16% lower fracture rate.[284]

Table 58. Effect of adherence to and persistence with osteoporosis medications on fractures

Author, year	Sample size	Study duration	Medications	Effect of adherence or persistence
Huybrechts, 2006[286]	38,120	5 years	Alendronate Risedronate HRT	17% increase in fracture rate with low adherence.
Siris, 2006[285]	35,537	24 months	Alendronate Risedronate	Relative risk reduction 25% for all osteoporotic fractures in refill adherent patients; 29% risk reduction for non-vertebral fractures, 45% risk reduction for hip fractures in persistent patients
Caro,2004[284]	11,249	5 years	Alendronate Etidronate ± calcium Risedronate Calcitonin HRT	16% decrease in fracture rate in patients with good adherence (MPR>80%)

Rates of adherence and persistence–medications to treat or prevent osteoporosis

We identified 18 observational studies that reported rates of adherence (Table 59) or persistence (Table 60) for medications used to treat or prevent osteoporosis.

Adherence

Ten studies assessed adherence to osteoporosis medications.[284-293] We identified eight studies that examined adherence among cohorts of patients identified using large retrospective clinical databases. A Canadian health services database was used to examine adherence of all women during a 5-year period who were diagnosed with osteoporosis and who were prescribed at least one treatment medication (including bisphosphonates, HRT, or calcitonin).[284] In this study, fewer than 50% of patients had a MPR greater than 80% over the 5-year period. Another study examined data from 49 US health plans to identify 18,882 women with osteoporosis who initiated therapy with a bisphosphonate, calcitonin, raloxifene, or estrogen during a 5-year period.[288] Adherence failure in this study was defined as a MPR less than 80%. Overall, the investigators found that the rate of adherence failure was 47% at 3 months, 70% at 1 year, and 77% at 3 years. In another study, refill compliance (defined as MPR > 80%) among all women enrolled in one of two large US commercial insurance plans and receiving a prescription for either alendronate or risedronate[285] was 43% over 5 years.[285]

A large US managed care database was used to identify 38,120 women with osteoporosis who were treated with alendronate, risedronate, or HRT over a 5-year period.[286] Among these women, 75% had an MPR below 80% over their entire follow-up period. Another study examined a general United Kingdom (UK) practice computer database of 97,992 women to identify 1,286 women who received a prescription for either alendronate or risedronate in a 1-year period.[289] They found that 45% of women were adherent at 1 year (defined as a MPR > 80%). Finally, 10,566 women from a US national managed care administrative claims database who were prescribed risedronate, alendronate, or raloxifene were followed over a 6-month period.[291] They identified the MPR for each individual patient and found a mean adherence rate of 61% for alendronate, 58% for risedronate, and 54% for raloxifene.

A single study reported adherence rates for one individual drug. Using a large US prescription claims database to identify 28,718 women initiated on HRT, Faulkner and colleagues found that 55% were non-compliant with therapy (defined as MPR < 75%) at 1 year.[287]

Rates of adherence to osteoporosis prevention therapies were also examined in a study of glucocorticoid users. A large US national managed care database was examined to identify 6,282 chronic glucocorticoid users who were prescribed alendronate or risedronate during a 3-year period.[292] The mean adherence rates were not statistically different between users of alendronate (72%) and risedronate (74%).

We also identified two studies that examined adherence rates in controlled clinical trials. In one study, women were randomized to either placebo plus calcium and vitamin D or HRT plus calcium and vitamin D.[290] Patients taking ≥80% of their pills were considered adherent. At 6 months, 81% of subjects were adherent to HRT/placebo, while 78% of subjects were adherent to calcium and vitamin D. Another study used a prospective non-randomized cohort to examine adherence among Spanish women who were treated with raloxifene or alendronate.[293] Overall, patients in the raloxifene group reported signficantly better adherence than did women in the alendronate group (95% vs. 91%); however, it should be noted that this study was sponsored and co-authored by the makers of raloxifene.

Table 59. Rates of adherence with osteoporosis medications

Author, year	Sample size	Study duration	Medications	Adherence*
Caro* 2004[284]	11,249	5 years	Alendronate Etidronate ± calcium Risedronate Calcitonin HRT	49.4% adherence over course of study; mean follow-up 2 years
Faulkner, 1998[287]†	28,718	1year	HRT	46% adherence at 1 year
Siris,* 2006[285]	35,537	2 year	Alendronate Risedronate	43% adherence at 2 years
Weycker*, 2006[288]	18,882	3 years	Alendronate Risedronate Calcitonin HRT Raloxifene	53% at 3 months 30% at 1 year 26% at 3 years
Huybrechts* 2006[286]	38,120	5 years	Alendronate Risedronate HRT	25% adherence over course of study; mean follow-up 1.7 years
deLusignan* 2006[289]	1,286	1 year	Alendronate Risedronate	45% adherence at 1 year
Unson* 2006[290]	107	6 month	Calcium + Vitamin D plus Estrogen or placebo	81% adherence at 6 months for HRT/placebo; 78% adherence at 6 months for calcium + vitamin D
Downey‡ 2006[291]	10,566	1 year	Alendronate Risedronate Raloxifene	61% mean adherence rate for alendronate; 58% mean adherence rate for risedronate; 54% mean adherence rate for raloxifene
Curtis ‡ 2006[292]	1,158	3 year	Alendronate Risedronate	Mean adherence rate 72% alendronate, 74% risedronate; study of chronic glucocorticoid users
Turbi* 2003[293]	902	12 months	Raloxifene Alendronate	95% adherence in raloxifene group; 91% adherence in alendronate at 1 year

* Defined by attaining specific MPR of 80%.
† Defined by attaining specific MPR of 75%.
‡ Defined as mean MPR attained by individual patients over the study period.

Poor adherence to treatment instructions has also been demonstrated in two studies. Hamilton and coworkers studied 219 UK patients attending an osteoporosis clinic to determine compliance with risedronate therapy.[294] Although all participants were given detailed oral instructions and a leaflet detailing the proper administration of risedronate, the investigators discovered using follow-up questionnaires that 26% of patients took their medication incorrectly, and 28% of these experienced adverse events. In a separate study, 10 inpatients and 30 outpatients were administered alendronate for osteoporosis.[295] Both inpatients and outpatients took the medication incorrectly: 37% of inpatients and 7% of outpatients received other medications with the alendronate, and 12% of inpatients did not sit upright after receiving alendronate. Thus, even when patients are technically taking their medications, improper techniques may inhibit absorption of the correct dose or may increase the likelihood of side-effects.

Persistence

We identified 12 studies that reported persistence rates for osteoporosis medications.[284, 288, 291, 293, 296-303] These studies are displayed in Table 60. Nine of these studies used large claims databases. One study used a database of all Medicare beneficiaries participating in a state-run drug benefits program to identify a cohort of patients who initiated treatment for osteoporosis.[303] Treatments included bisphosphonates, calcitonin, HRT, or raloxifene. The investigators found that after 1 year of therapy, 45% of subjects were no longer taking osteoporosis medications, a figure that increased to 52% of patients at 5 years. Another study that examined a prospective observational Canadian database, CANDOO, found that among men and women who initiated therapy with etidronate, alendronate (daily), or HRT in a 10.5-year time period, 86% were still taking any one of these three therapies at 1 year; 77% and 70% of patients continued therapy at 2 and 3 years, respectively.[302] Alendronate-treated patients were 40% more likely to discontinue therapy than were etidronate-treated patients. There were no differences in discontinuation rates between HRT and either alendronate or etidronate. In the study noted above by Weycker and coworkers, the rate of persistence failure among patients prescribed a bisphosphonate, calcitionin, HRT, or raloxifene was 47% at 1 year and 77% at 3 years.[288] In a separate study, there was a 79% 1-year discontinuation rate with alendronate, an 81% discontinuation rate with risedronate, and an 84% discontinuation rate with raloxifene.[291] A telephone survey of 956 women from the Kaiser Permanente Northern California database who initiated treatment with HRT, raloxifene, or alendronate over a 3-year period was conducted.[296] A mean of 7 months of treatment, 26% of subjects taking HRT had discontinued therapy, which was significantly higher than the proportion who discontinued raloxifene (19%) or alendronate (19%). A study by Caro and coworkers, 60% of subjects treated with a bisphosphonate, calcitonin, or HRT discontinued therapy within 5 years.[284] Rossini and coworkers identified 9,851 postmenopausal Italian women who were prescribed calcium + vitamin D, HRT, raloxifene, risedronate, clodronate, or alendronate for osteoporosis.[297] Using a follow-up questionnaire, the investigators found that 19.1% of subjects had discontinued their medications, at a mean follow-up time of 14 months.

Two studies used a large clinical database to assess the persistence rates of individual medications for osteoporosis. The Kaiser Permanente of Northern California database was examined to determine persistence rates among women prescribed weekly oral alendronate.[300] The 1-year discontinuation rate was 50%, although 1/3 of women discontinuing therapy restarted within 6 months. In a prospective cohort study of 6,282 UK women prescribed HRT for osteoporosis, approximately 34% of women discontinued HRT in the first 2 years of use.[301]

Two smaller cohort studies have also examined rates of persistence with osteoporosis therapy. One study identified 178 consecutive patients prescribed either daily alendronate or raloxifene for osteoporosis.[298] They found that 23% of patients had discontinued therapy within 6 months. In the pharmaceutical company-sponsored prospective randomized cohort study (described above), 26% of subjects in the alendronate group and 16% of subjects in the raloxifene group discontinued therapy at 1 year.[293]

One study examined rates of persistence in a controlled clinical trial. Among 6,459 postmenopausal women randomized to either alendronate or placebo in the FIT trial,[299] the 1-year overall discontinuation rate was 11%.

Several studies have revealed that the rate of discontinuation for osteoporosis therapies is highest during the first 2 years of treatment. In a study of women prescribed HRT for osteoporosis, 34% discontinued HRT in the first 2 years of use; however, after 2 years, the rates of further discontinuation were low.[301] In studies by Solomon[303] and Weycker,[288] rates of discontinuation and adherence failure were also greatest in the first 2 years following initiation of therapy.

Table 60. Rates of non-persistence with osteoporosis medications

Author, year	Sample size	Study duration	Medications	Percent discontinuing medication
Caro, 2004[284]	11,249	5 years	Alendronate Etidronate ± calcium Risedronate Calcitonin HRT	60% at 5 years
Downey, 2006[291]	10,566	1 year	Alendronate Risedronate Raloxifene	79% discontinuation at 1 year with alendronate; 81% discontinuation at 1 year with risedronate; 84% discontinuation with raloxifene
Tosteson, 2003[296]	956	4-12 months	HRT Raloxifene Alendronate	26% discontinuation in HRT; 19% discontinuation raloxifene; 19% alendronate, all at mean of 7 months
Rossini, 2006[297]	9,851	11-18 months	Calcium + Vitamin D HRT Raloxifene Risedronate Clodronate Alendronate	19.1% discontinuation at mean of 14 months
Segal, 2003[298]	178	6 months	Raloxifene Alendronate	23% discontinuation rate at 6 months
Turbi, 2003[293]	902	1 year	Raloxifene Alendronate	26% discontinuation in alendronate group; 16% discontinuation in raloxifene group at 1 year
Buist, 2000[299]	6,459	12 months	Alendronate Placebo	2.2% discontinuation at 1 month 4.8% at 3 months 11.1% at 12 months
Weycker, 2006[288]	18,882	3 years	Alendronate Risedronate Calcitonin HRT Raloxifene	47% discontinuation at 1 year; 77% discontinuation at 3 year
Lo, 2006[300]	13,455	1 year	Alendronate	50% discontinuation at 1 year
Steel, 2003[301]	838	5 years	HRT	34% discontinuation at 2 years 39% discontinuation at 5 years
Papaioannou, 2003[302]	1,967		Etidronate Alendronate HRT	14% discontinuation at 1 year 23% discontinuation at 2 years 30% discontinuation at 3 years,
Solomon, 2005[303]	40,042	5 years	Alendronate Risedronate Calcitonin Raloxifene HRT	45.2% discontinuation at 1 year 52.1% discontinuation at 5 years

Factors that affect adherence and persistence to osteoporosis medications

We identified 25 studies[286, 287, 290, 292, 293, 296-299, 302, 303, 303-315] that identified factors that may affect adherence or persistence with medications for osteoporosis: side effects, absence of symptoms, comorbid conditions, age, ethnicity, socioeconomic status, and dosing regimen.

Side effects of medications

We identified five studies that documented side effects as a contributing factor to non-persistence with medications.[293, 296-298, 304] In two separate non-randomized observational studies comparing raloxifene and alendronate,[293, 298] the most frequent cause identified for medication discontinuation was medication side effects. Similarly, in the telephone survey of a cohort of women who had been started on HRT, raloxifene, or alendronate for osteopenia or osteoporosis, two-thirds of patients who had discontinued therapy cited side effects as the primary reason for discontinuance.[296]

Fear of side effects can also affect adherence to osteoporosis medications. Questionnaires were used to assess reasons for medication discontinuation among women who had been prescribed calcium ± vitamin D, HRT, raloxifene, or bisphosphonates for osteoporosis.[297] Although 25% of women in the cohort listed side effects as the primary reason for medication discontinuation, 20% named fear of side effects as their motivation. Similarly, a questionnaire study of a US cohort of 816 women starting HRT revealed that women who were concerned about the side effects of HRT were 3.7 times more likely to discontinue therapy within 2 years than were women who did not express these concerns.[304]

Absence of symptoms

We identified four studies that documented absence of symptoms as a reason for non-persistence with osteoporosis therapy.[292, 299, 303, 305] Patients with osteoporosis who have not experienced an osteoporotic fracture do not suffer from symptoms of the disease and frequently are unaware of their diagnosis until bone densitometry is performed. Women who have not been shown documentation of their osteoporosis, or who have not experienced effects from their osteoporosis (i.e., fracture) may be less likely to persist with therapy. In a retrospective cohort study, a multivariate analysis found that a history of a fracture before or after initiation of osteoporosis therapy or a history of BMD testing before and after initiating therapy were both independently associated with increased persistence.[303] Similarly, a managed care database study of glucocorticoid users initiating therapy with bisphosphonates found that a lack of previous BMD testing was significantly associated with an increased risk of non-persistence.[292] In one focus group study of postmenopausal women who were educated about osteoporosis treatments and asked to choose a therapy, women who thought they were unlikely to sustain a fracture, or who perceived fracture outcomes as not severe were likely to choose no treatment for osteoporosis.[305] However, a history of previous fracture was not associated with study medicine discontinuation among participants in the FIT RCT.[299]

Co-Morbid Conditions

Patients with multiple co-morbid conditions may also be less likely to adhere to osteoporosis therapy. We found two studies[299, 303] that implicated co-morbid conditions in reduced

persistence with osteoporosis therapy. Solomon and coworkers found that in their cohort, smaller numbers of comorbid conditions independently predicted increased persistence.[303] In a sub-analysis of adherence data from the FIT trial found that the strongest predictors of study medicine discontinuation were fair-to-poor self-rated health and the presence of four or more depressive symptoms.[299]

Age

Findings on the effect of age on adherence to osteoporosis therapy varied.[287, 299, 302, 303] Two studies implicated younger age in poorer compliance. In a retrospective cohort study of the CANDOO database, increasing age was an independent predictor of medication adherence.[302] In another retrospective cohort analysis, younger age was associated with non-compliance with HRT.[287] In contrast, Solomon and coworkers found that younger age independently predicted increased persistence,[303] no association between age and study medicine discontinuation was found in the FIT trial.[299]

Ethnicity and Socioeconomic Status

We found four articles that studied ethnicity and socioeconomic status (SES) as factors that affect adherence and persistence to osteoporosis therapy.[290, 306-308] Several aspects of SES, such as income and education level, may influence the likelihood that a patient will remain adherent to osteoporosis therapy. Additionally, ethnicity and cultural beliefs may also influence adherence. Unson and coworkers examined the influence of SES and ethnicity on medication adherence (calculated using MPR) in a placebo-controlled trial of calcium, vitamin D, and estrogen.[290] They demonstrated that minority participants and those with lower income and educational levels had lower adherence rates than white participants and those with higher SES.

Three studies have examined the role of SES in persistence with HRT therapy. A follow up study to the PEPI trial, which compared the effects of estrogen alone or in combination with progestin with placebo,[316] examined determinants of estrogen continuation after participation in the trial.[306] Education and non-white ethnicity predicted lower post-trial persistence with hormone use. Similarly, in a cross-sectional study of 50-70 year old women in Vermont, women of moderate to high income were three times more likely than those with low income to initate therapy with HRT.[307] A separate cross-sectional study of postmenopausal women in Turkey demonstrated that higher educational status was directly related to the likelihood that a patient will begin HRT, but is not related to discontinuation of HRT.[308]

Dosing regimen

We identified eight articles that studied the frequency of medication dosing and non-adherence to and non-persistence with osteoporosis therapy.[291, 309-315] In a national telephone survey of women taking bisphosphonates for osteoporosis in the UK, non-persistence with therapy was significantly associated with self-reported "difficulty taking medications because of too frequent dosing." A complaint of too frequent dosing was associated with increased likelihood of discontinuation in both the daily and weekly bisphosphonate doses in this study.[309] We also identified two patient preference studies that reported a patient preference for less frequent dosing of medications. In one open-label trial of women taking daily alendronate who were switched to weekly alendronate, 96% of patients preferred the weekly dosage.[310] In another

similar patient preference study, 86% of women preferred the once weekly dose of alendronate to the once daily regimen, and most patients also expressed that the once weekly dosing would allow them to achieve better long-term adherence (87.5% vs. 8.5%).[311]

We also identified five studies that compared adherence or persistence rates between different dosing regimens. In the cohort study noted above by Downey, weekly bisphosphonate users had slightly higher 12-month adherence (63% vs. 54%) and persistence rates (22% vs. 19%) than did daily users.[291] Similarly, a study that used an administrative claims database from 30 US health plans revealed that weekly bisphosphonate users had a significantly higher mean MPR than did daily users (69% vs. 58%).[312] In that study, persistence rates were also higher among weekly bisphosphonate users (44% vs. 32%), and in multivariate analysis adjusting for other risk factors, dosing frequency was the strongest predictor of time to discontinuation. In a separate review of three UK databases, patients on weekly bisphosphonate regimens had a consistently higher mean MPR and longer persistence than did those taking daily bisphosphonates.[313] Another review of 211,319 patients in a US pharmacy database demonstrated that only about one third of patients receiving daily bisphosphonates, compared with 45% of weekly users, achieved adequate adherence, defined as MPR > 80%.[314]

We found one open-label study that compared monthly ibandronate with weekly alendronate.[315] In that study, the investigators found that 6-month persistence rates were higher in the monthly ibandronate group (57% vs. 37%). It should be noted, however, that the trial was co-authored by the manufacturers of ibandronate, and that only the ibandronate group participated in a patient-support program, which may have influenced persistence rates.

Monitoring programs

Patient monitoring programs can also be used to identify at-risk patients who are non-adherent with their osteoporosis treatments. One approach to increased patient monitoring is to increase contact between health care providers and patients. This approach can be used not only to monitor adherence to therapy directly, but also to provide patients with additional opportunities to discuss questions or problems related to therapy. One study randomized 75 women with osteopenia on raloxifene to one of three groups: 1) no monitoring, 2) monitoring with three nurse visits to assess well being, record adverse events, and assist with medication problems (but not adherence), or 3) monitoring with both nurses visits and with assessment of markers of bone turnover.[317] They found that patients in both monitored groups increased cumulative adherence by 57% and persisted with therapy 25% longer than did non-monitored patients. In addition, adherence at 1 year was correlated with a significant improvement in hip BMD. The addition of marker measurements did not improve adherence or persistence compared with nurse monitoring alone.

In the future, computer monitoring may also be used to improve patient adherence with therapy. In the study detailed above, a computerized data extraction program was used to identify women in a population who are at risk for osteoporotic fractures and who should be targeted for osteoporosis therapy. They also used the program to calculate adherence to therapy. The authors noted that a program such as this could be used in the future to identify non-adherent

patients.[289] However, in the United States, the use of such programs may be limited by privacy issues and compliance with HIPAA guidelines.

Non-adherence and non-persistence to osteoporosis therapies may severely reduce the effectiveness of these medications and may lead to unnecessary fractures and ultimately to an increase in the public health burden. Strategies to improve adherence should be investigated and implemented.

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

Key Points

- 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 to executive summary); 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 vasodilatation).

- 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 (CVA), 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 thromboemoblic 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 where 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 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 probems 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.

Detailed Analyses

Our first analyses include the controlled trials and large cohort studies ($N \geq 1{,}000$) found through our primary electronic searches. We focus on the adverse events that were identified as most important by our Technical Expert Panel (TEP): cardiovascular, malignancy, upper gastrointestinal, and osteonecrosis. The TEP selected specific sub-categories to focus upon, as listed below. We were specifically asked by AHRQ to include results from the Women's Health Initiative (WHI) and Heart and Estrogen-Progestin Replacement Study (HERS) trials for cardiovascular and cancer risks, although these studies did not always focus on bone-density patients.

A table that displays all the adverse events from the entire analysis is included as Appendix E. That table includes information on cancer, cardiac, dermatologic, gastrointestinal, gynecologic, immunologic, metabolic, musculoskeletal, neurological, psychiatric, and respiratory events.

To further evaluate the prevalence of selected adverse events, we were asked to perform broader post-hoc literature searches for each drug and each of the TEP's "most important" adverse events, regardless of whether the drugs were being used for bone-density treatment. Reports were selected for inclusion hierarchically by the highest level study design in the following order: meta-analysis, systematic review, observational cohort, case-control study, case series, case reports. Hence, if large cohort studies existed, there was no need to examine individual case reports. The results from these post-hoc analyses will be discussed separately, after the initial analyses.

Bisphosphonates

Cardiovascular

Acute coronary syndrome, including myocardial infarction. Acute coronary syndrome includes myocardial infarctions, coronary events, acute coronary syndromes, unstable angina, ischemic cardiac events, cardiac events requiring acute angioplasty, and cardiac events requiring coronary artery bypass graft surgery.

As shown in Table 61, there were no significant differences between any of the bisphosphonates and placebo regarding acute coronary syndrome.[67, 91, 104, 112, 139, 283, 318-322] However, two reports show an increased incidence of atrial fibrillation with bisphosphonates. In the HORIZON trial[139] the risk of serious atrial fibrillation was significantly increased for once-yearly zolendronic acid relative to placebo (50 versus 20 patients, $p<0.001$). In a letter to the editor[323] the authors of the FIT trial, which was included in this report reanalyzed data from that trial and reported a trend toward increased risk of atrial fibrillation with alendronate (OR = 1.26, 95% CI 0.96, 1.66); data on the atrial fibrillation were not included in the original publication.

Cardiac death. We found no trials of ibandronate or zoledronic acid that reported cardiac death. In trials of alendronate,[318, 319] etidronate,[321] pamidronate,[112] risedronate,[283] and zoledronic acid[139]that reported cardiac death, there were no differences between drugs and placebo.

Cerebrovascular events (CVA). We found no trials of alendronate, etidronate, or risedronate that reported CVAs. In trials of ibandronate,[104, 106] pamidronate,[324] and zoledronic acid[139] that reported CVA, there were no significant differences between the drugs and placebo.

Pulmonary embolism (PE). We found no trials of alendronate, etidronate, ibandronate, or zoledronic acid that reported PE. In one trial of risedronate,[137] difference between drug and placebo was not significant.

Venous thromboembolic events. We found no trials of etidronate, ibandronate, pamidronate, risedronate, or zoledronic acid that reported thromboembolic events. In two pooled trials of alendronate,[67, 325] there were no significant differences between drug and placebo.

Malignancy

Breast Cancer. We found one placebo-controlled study each of etidronate[326] and ibandronate[104] that reported breast cancer incidence. The study found no significant differences between these drugs and placebo. Breast cancer was not reported in trials of the other bisphosphonates.

Colon Cancer. One trial of pamidronate[327] reported colon cancer incidence; there was no difference between the drug and placebo groups. No trials of other bisphosphonates reported colon cancer.

Lung Cancer. We found one placebo-controlled study each of etidronate[326] and pamidronate[324] that reported lung cancer. There were no significant differences between these drugs and placebo. Lung cancer was not reported in trials of the other bisphosphonates.

Osteosarcoma. Osteosarcoma was not reported in any bisphosphonate trials.

Upper gastro-intestinal

Esophageal ulcerations. Esophageal ulcerations were reported in trials of all the bisphosphonates except zoledronic acid. The only significant difference was found in one study,[328] where etidronate participants had higher odds of esophageal ulcers than did the placebo group (OR 1.33, 95% CI 1.05, 1.68).

Perforations, ulcerations, and bleeds (PUBs). These were reported in trials of all the bisphosphonates except zoledronic acid. Etidronate participants had higher odds of PUBs than did placebo participants in three[89, 328, 329] pooled studies (OR 1.32, 95% CI 1.04, 1.67). In two pooled trials of oral daily ibandronate,[105, 330] participants had lower odds than did placebo participants (OR 0.33, 95% CI 0.14, 0.74).

Other upper GI, mild. We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as "upper GI events, mild." Pooled analyses of 18 studies of etidronate[90-95, 98, 101, 274, 275, 280, 281, 326, 328, 331-334] showed greater odds of mild upper GI events than did placebo (OR 1.33, 95% CI 1.21, 1.46). Seven pooled trials of pamidronate[110, 112, 324, 327, 335-337] also showed greater odds than did placebo (OR 3.14, 95% CI 1.93, 5.21). There were no differences between alendronate, ibandronate, risedronate, or zoledronic acid and placebo regarding mild upper GI events.

There were also significant results in head-to-head studies (not shown, see Appendix E). Alendronate participants had higher odds of mild upper GI events than did etidronate participants in three pooled head-to-head studies.[252, 338, 339] Alendronate participants also had higher odds of mild upper GI events in four head-to-head trials vs. calcitonin[73, 320, 340, 341] and four vs. estrogen.[66, 67, 342, 343] Etidronate participants had higher odds of mild upper GI events in seven head-to-head trials vs. calcium[92, 96, 344-348] and three head-to-head trials vs. estrogen.[91, 93, 345]

Other statistically significant results (Not shown, see Appendix E).

Musculoskeletal. This category includes muscular and joint pain, arthritis, and muscle cramps. Risedronate participants had lower odds of musculoskeletal events than did placebo participants in nine pooled trials[120, 123, 134, 136, 137, 273, 349, 349, 350, 350-352](OR 0.40, 95% CI 0.29, 0.54). In three pooled trials,[138, 139, 353] zoledronic acid participants had higher odds of these events than did placebo participants (OR 4.52, 95% CI 3.78, 5.43). In two head-to-head trials,[259, 354] alendronate participants had greater odds of these events than did participants taking PTH (OR 3.84, 95% CI 2.22, 6.80).

Metabolic. In two trials, alendronate patients had increased odds of hypocalcemia relative to placebo patients (nine of 301 treatment patients versus none of 207 placebo patients). Increased odds of hypercalcemia were also reported in a trial of zoledronic acid.[139]

Table 61. Bisphosphonates-adverse events vs. placebo

Event Group	Alendronate		Etidronate		Ibandronate		Pamidronate		Risedronate		Zoledronic acid	
	# of Trials	OR (95% CI)	# of Trials	OR (95% CI)	# of Trials	OR (95% CI)	# of Trials	OR (95% CI)	# of Trials	OR (95% CI)	# of Trials	OR (95% CI)
Cardiovascular												
Acute Coronary Syndrome	4	3.59 (0.35, 180)	2	Inf+ (0.21, Inf+)	1	Inf+ (0.01, Inf+)	1	0(0, 37.7)	2	0.38 (0.01, 7.62)	1	0.98 (0.71, 1.37)
Cardiac Death	2	Inf+(0.13, Inf+)	1	Inf+ (0.03, Inf+)	0	NR	1	0(0, 37.7)	1	Inf+ (0.02, Inf+)	1	1.18 (0.71, 1.94)
Atrial Fibrillation	1	1.26 (0.96, 1.66)	0	NR	0	NR	0	NR	1	Inf+ (0.02, Inf+)	1	1.56 (1.19, 2.06)
Cerebrovascular Events (serious)	0	NR	0	NR	2	0.32 (0, 27.3)	1	Inf+(0.09, Inf+)	0	NR	1	0.98 (0.72, 1.34)
Pulmonary Embolism	0	NR	0	NR	0	NR	0	NR	1	Inf+(0.01, Inf+)	0	NR
Thromboembolic Events	2	Inf+ (0.03, Inf+)	0	NR	0	NR	0	NR	0	NR	0	NR
Cancer												
Cancer	2	Inf+ (0.03, Inf+)	3	3.12 (0.25, 165)	3	Inf+ (0.12, Inf+)	2	Inf+(0.4, Inf+)	1	0(0, 34.5)	0	NR
Breast Cancer	0	NR	1	Inf+ (0.03, Inf+)	1	Inf+ (0.01, Inf+)	0	NR	0	NR	0	NR
Colon Cancer	0	NR	0	NR	0	NR	1	Inf+(0.03, Inf+)	0	NR	0	NR
Lung Cancer	0	NR	1	0(0, 41)	0	NR	1	Inf+(0.01, Inf+)	0	NR	0	NR
Osteosarcoma	0	NR	0	NR	0	NR	0	NR	0	NR	0	NR
GI												
GI (mild)	54	1.05 (0.99, 1.13)	18	1.33 (1.21, 1.46)*	10	1.02(0.92, 1.13)	7	3.14 (1.93, 5.21)*	22	1.03 (0.95, 1.13)	3	1.34 (0.6, 3.21)
Upper GI (excluding esophagus)	39	1(0.92, 1.07)	15	1.53 (1.25, 1.88)*	5	1.04(0.89, 1.22)	4	4.73 (2.53, 9.35)*	20	1.07 (0.96, 1.19)	2	1.82 (0.53, 9.73)
Reflux and Esophageal	27	1.11 (0.99, 1.23)	0	NR	2	1.35(0.68, 2.88)	3	1.49 (0.33, 9.24)	13	0.90 (0.69, 1.19)	0	NR
GI (serious)	20	1.01 (0.83, 1.24)	7	1.32 (1.12, 1.55)*	3	0.77(0.55, 1.08)	4	2.7(0.66, 15.9)	12	0.93 (0.72, 1.19)	0	NR
Esophageal (serious)	8	1.42 (0.89, 2.29)	1	1.33 (1.05, 1.68)*	1	1.25(0.2, 13.1)	1	Inf+(0.46, Inf+)	6	0.69 (0.37, 1.32)	0	NR
Upper GI Perforations, Ulcers, or Bleeds (not esophageal)	12	0.88 (0.66, 1.18)	3	1.32 (1.04, 1.67)*	2	0.33 (0.14, 0.74)*	3	1.67 (0.31, 11.2)	7	0.64 (0.27, 1.53)	0	NR

* =statistically significant

SERMS

Cardiovascular

Acute coronary syndrome, including myocardial infarction. As displayed in Table 62, in three trials of raloxifene[166, 355, 356] and one trial of tamoxifen,[204] there were no significant differences between either drug and placebo.

Cardiac death. Two trials of raloxifene[355, 356] and one of tamoxifen[204] reported cardiac deaths. There were no significant differences between either drug and placebo.

CVA. Three trials of raloxifene[356-358]and one of tamoxifen[204] reported CVA. There were no significant differences between either drug and placebo.

PE. Two large studies[355, 359] showed higher odds for PE among raloxifene participants than among placebo participants (OR 6.26, 95% CI 1.55, 54.80). Tamoxifen[204] also showed higher odds of PE than did placebo in one study (OR 3.52, 95% CI 1.37, 10.70).

Venous thromboembolic events. Raloxifene participants had greater odds of thromboembolic events than did placebo participants in seven pooled studies[201, 325, 355, 358, 360-362] (OR 2.08, 95% CI 1.47, 3.02). In one study of tamoxifen, differences with placebo were not significant.[204]

Malignancy

Breast Cancer. In three pooled studies of tamoxifen vs. placebo,[204, 363, 364] tamoxifen participants had lower odds of breast cancer (OR 0.60, 95% CI 0.53, 0.69). Differences between raloxifene and placebo were not significant in two pooled trials.[355, 360]

Colon Cancer. One placebo-controlled study of tamoxifen reported colon cancer.[204] Differences between groups were not significant. No studies of raloxifene reported colon cancer. A study comparing raloxifene with tamoxifen also reported colon cancer; differences between the drugs were not significant (not shown).

Lung Cancer. We found two placebo-controlled trials of raloxifene,[355, 359] and one of tamoxifen[204] that reported lung cancer, as did one study comparing raloxifene with tamoxifen. There were no significant differences in any studies.

Osteosarcoma. We found one head-to-head study of raloxifene vs. tamoxifen that reported bone cancer. Differences between groups were not significant (see Appendix E).

Upper gastro-intestinal

Esophageal ulcerations and ii. PUBs. These events were not reported in trials of raloxifene and tamoxifen.

Other upper GI, mild. In eight pooled trials of raloxifene[166, 203, 325, 355, 357, 360, 362, 365] and one trial of tamoxifen,[366] differences between drug and placebo were not significant.

Other statistically significant results (Not shown, see Appendix E).

Cardiac, mild. This category includes chest pain, palpitations, tachycardia, and vasodilatation. In a pooled analysis of six trials, raloxifene participants had higher odds of mild cardiac events than did placebo participants (OR 1.53, 95% CI 1.01, 2.25).

Musculoskeletal. This category includes muscular and joint pain, arthritis, and muscle cramps. In three head-to-head trials,[166, 367, 368] raloxifene participants had greater odds of these events than did participants taking estrogen (OR 2.44, 95% CI 1.27, 5.02).

Gynecologic. This category includes uterine problems such as endometrial bleeding. In three pooled trials,[204, 366, 369] tamoxifen participants had greater odds of gynecological problems than did placebo participants (OR 2.33, 95% CI 2.17, 2.50).

Table 62. SERM-adverse events vs. placebo

	Raloxifene		Tamoxifen	
Event Group	Number of Trials	OR (95% CI)	Number of Trials	OR (95% CI)
Cardiovascular				
Acute Coronary Syndrome	3	1.23(0.92, 1.66)	1	1.19(0.9, 1.58)
Cardiac Death	2	1.25(0.6, 2.78)	1	1.26(0.79, 2.03)
Cerebrovascular Events (serious)	3	1.22(0.89, 1.68)	1	1.16(0.79, 1.72)
Pulmonary Embolism	2	6.26(1.55, 54.8)*	1	3.52(1.37, 10.7)*
Thromboembolic Events	7	2.08(1.47, 3.02)*	1	1.6(0.91, 2.87)
Cancer				
Cancer	5	0.9(0.42, 2.04)	5	0.6(0.53, 0.69)*
Breast Cancer	2	0.71(0.1, 7.97)	3	0.49(0.42, 0.57)*
Colon Cancer	0	NR	1	1.24(0.56, 2.8)
Lung Cancer	2	0.39(0.01, 7.87)	1	1(0.57, 1.76)
Osteosarcoma	0	NR	0	NR
GI				
GI (mild)	8	0.97(0.78, 1.21)	1	1(0.01, 82)
Upper GI (excluding esophagus)	3	1.1(0.68, 1.81)	0	NR
Reflux and Esophageal	0	NR	0	NR
GI (serious)	1	0.49(0.01, 39.1)	0	NR
Esophageal (serious)	0	NR	0	NR
Upper GI Perforations, Ulcers, or Bleeds (not esophageal)	0	NR	0	NR

* =statistically significant

Estrogen or estrogen plus progestin

Cardiovascular

Acute coronary syndrome, including myocardial infarction. As displayed in Table 63, in the five trials of estrogen[67, 91, 165, 166, 370] and two trials of estrogen plus progestin[164, 371] that reported these events, there were no significant differences between treatment and placebo groups.

Cardiac death. In the two trials of estrogen[165, 370] and two trials of estrogen plus progestin[164, 371]that reported cardiac deaths, there were no significant differences between treatment and placebo groups.

CVA. We pooled three trials comparing estrogen with placebo;[165, 185, 370] the estrogen group had an odds ratio of 1.34 (95% CI, 1.07, 1.68) for CVA . We also pooled two trials comparing an estrogen-progestin combination with placebo;[164, 371] the combination participants had greater odds of stroke than did placebo participants (OR 1.28, 95% CI, 1.05, 1.57).

PE. In one trial of estrogen[370] and one trial of estrogen plus progestin,[371] there were no significant differences between treatment and placebo groups.

Venous thromboembolic events. Estrogen participants had greater odds of thromboembolic events than did placebo participants in four pooled studies[67, 165, 185, 370] (OR 1.36, 95% CI, 1.01, 1.86). Similar results were found when three studies comparing an estrogen-progestin combination with placebo[164, 191, 371] were pooled (OR 2.27, 95% CI, 1.72, 3.02).

Malignancy

Breast Cancer. In five pooled trials of estrogen vs. placebo,[165, 185, 370, 372, 373] estrogen participants had lower odds of breast cancer (OR 0.79, 95% CI, 0.66, 0.93). Conversely, in three pooled studies of estrogen-progestin combination vs. placebo,[164, 184, 371] treatment participants had higher odds of breast cancer (OR 1.28, 95% CI, 1.03, 1.60).

Colon Cancer. We found one placebo-controlled trial each of estrogen[165] and estrogen-progestin combined[164] that reported on colon cancer. Only the estrogen-progestin study showed a significant difference: treated participants had lower odds of colon cancer than did placebo participants (OR 0.64, 95% CI, 0.43, 0.95).

Lung Cancer. No trials of estrogen or progestin reported lung cancer.

Osteosarcoma. No trials of estrogen or progestin reported osteosarcoma.

Upper gastro-intestinal

Esophageal ulcerations and ii. PUBs. These events were not reported in trials of estrogen or estrogen-progestin combination.

Other upper GI, mild. Combination estrogen-progestin participants had lower odds than did placebo participants of mild reflux and esophageal events in two studies[256, 371](OR 0.0, 95% CI, 0.0, 0.81). Other comparisons were not significant. Alendronate and etidronate participants had higher odds of mild upper GI events in head-to-head trials vs. estrogen (see Appendix E).

Other statistically significant results (Not shown, see Appendix E)

Genitourinary. This category includes prostate problems, erectile dysfunction, dysuria, and urinary incontinence. Two trials each showed greater odds for estrogen and estrogen-progestin combination participants than for placebo participants.[82, 166]

Gynecologic. This category includes uterine problems such as endometrial bleeding. In a pooled analysis of seven trials,[67, 168, 185, 367, 370, 374, 375] estrogen participants had greater odds of gynecological problems than did placebo participants (OR 7.18, 95% CI, 5.31, 9.82). Similarly, estrogen-progestin combination participants had greater odds of these problems than did placebo participants in three pooled trials (OR 58.10, 95% CI, 9.03, 245.20).[184, 191, 375]

Breast abnormality, other than cancer. This category includes pain, tenderness, and fibrocysts. In a pooled analysis of seven trials,[67, 93, 166, 168, 367, 372, 376] estrogen participants had greater odds of

breast abnormalities than did placebo participants (OR 3.79, 95% CI, 2.64, 5.50). Similarly, estrogen-progestin combination participants had greater odds of these problems than did placebo participants in three pooled trials (OR 7.42, 95% CI, 3.79, 15.20).[184, 191, 256] In four head-to-head trials,[166, 367, 368, 376] raloxifene participants had far lower odds of breast abnormalities than did estrogen participants (OR 0.09, 95% CI, 0.07, 0.13). Two head-to-head trials each of alendronate[67, 342] and etidronate[93, 345] vs. estrogen and one trial of risedronate[256] and zoledronic acid[256] vs. estrogen-progestin all showed that participants taking the bisphosphonates had lower odds of breast abnormalities than did participants taking estrogen.

Table 63. Estrogen-adverse events vs. placebo

	Estrogen		Estrogen with progesterone	
Event Group	Number of Trials	OR (95% CI)	Number of Trials	OR (95% CI)
Cardiovascular				
Acute Coronary Syndrome	5	0.94(0.76, 1.18)	2	0.96(0.86, 1.09)
Cardiac Death	2	0.92(0.71, 1.2)	2	1.18(0.91, 1.54)
Cerebrovascular Events (serious)	3	1.34(1.07, 1.68)*	2	1.28(1.05, 1.57)*
Pulmonary Embolism	1	0.98(0.13, 7.37)	1	2.77(0.82, 12)
Thromboembolic Events	4	1.36(1.01, 1.86)*	3	2.27(1.72, 3.02)*
Cancer				
Cancer	5	0.86(0.75, 0.99)*	5	1.07(0.94, 1.22)
Breast Cancer	5	0.79(0.66, 0.93)*	3	1.28(1.03, 1.6)*
Colon Cancer	1	1.08(0.74, 1.57)	1	0.64(0.43, 0.95)*
Lung Cancer	0	NR	0	NR
Osteosarcoma	0	NR	0	NR
GI				
GI (mild)	6	1(0.65, 1.52)	2	1.38(0.97, 1.97)
Upper GI (excluding esophagus)	2	1.05(0.25, 6.29)	2	0.71(0.38, 1.26)
Reflux and Esophageal	2	0.68(0.37, 1.24)	1	0(0, 0.81)*
GI (serious)	0	NR	0	NR
Esophageal (serious)	0	NR	0	NR
Upper GI Perforations, Ulcers, or Bleeds (not esophageal)	0	NR	0	NR

* =statistically significant

Vitamin D and calcium

Cardiovascular. Serious cardiovascular adverse events were not reported in trials of vitamin D or calcium (Table 64).

Malignancy. Cancers were not reported in any trials of vitamin D or calcium.

Upper gastro-intestinal
Esophageal ulcerations and ii. PUBs. These events were not reported in trials of vitamin D or calcium.

Other upper GI, mild . In two trials of calcium[92, 269] and two trials of vitamin D,[93, 377] there were no significant differences between treatment and placebo groups regarding mild upper GI adverse events.

Table 64. Calcium & vitamin D–adverse events vs. placebo

	Calcium		Vitamin D	
Event Group	Number of Trials	OR (95% CI)	Number of Trials	OR (95% CI)
Cardiovascular				
Acute Coronary Syndrome	0	NR	0	NR
Cardiac Death	0	NR	0	NR
Cerebrovascular Events (serious)	0	NR	0	NR
Pulmonary Embolism	0	NR	0	NR
Thromboembolic Events	0	NR	0	NR
Cancer				
Cancer	0	NR	0	NR
Breast Cancer	0	NR	0	NR
Colon Cancer	0	NR	0	NR
Lung Cancer	0	NR	0	NR
Osteosarcoma	0	NR	0	NR
GI				
GI (mild)	2	0.79(0.33, 1.87)	3	0.27(0.04, 1.11)
Upper GI (excluding esophagus)	2	0.79(0.33, 1.87)	2	0.27(0.04, 1.11)
Reflux and Esophageal	0	NR	0	NR
GI (serious)	0	NR	0	NR
Esophageal (serious)	0	NR	0	NR
Upper GI Perforations, Ulcers or Bleeds (not esophageal)	0	NR	0	NR

Calcitonin, testosterone, and PTH

Cardiovascular

Acute coronary syndrome, including myocardial infarction. As displayed in Table 65, there were no trials of testosterone or PTH that reported these events. Three trials of calcitonin[148, 320, 378] reported acute coronary syndrome; the differences between calcitonin and placebo were not significant.

Cardiac death. There were no trials of testosterone or PTH that reported cardiac death. One trial of calcitonin reported cardiac death;[148] the difference between calcitonin and placebo was not significant.

CVA. One trial of calcitonin[378] and one trial of testosterone[379] reported CVA. Differences were not significant from placebo. No trials of PTH reported CVA.

PE and v. venous thromboembolic events. We found no trials of calcitonin, testosterone, or PTH that reported PE or thromboembolic events.

Malignancy. Cancers were reported in one trial of calcitonin,[380] two trials of testosterone,[379, 381] and three trials of PTH.[196, 198, 382] PTH participants had lower odds of cancer than did placebo participants (OR 0.49, 95% CI, 0.27, 0.90). Incidences for specific types of cancers such as breast cancer, colon cancer, lung cancer, or osteosarcoma were not reported in these trials.

Upper gastro-intestinal

Esophageal ulcerations and ii. PUBs. These events were not reported in trials of calcitonin, testosterone, and PTH.

Other upper GI, mild. In 15 trials of calcitonin[73, 93, 143, 148, 152, 320, 340, 341, 380, 383-388] and two trials of PTH,[198, 382] there were no significant differences between treatment and placebo groups regarding mild upper GI adverse events.

Other statistically significant results (Not shown, see Appendix E)

Cardiac, mild. This category includes chest pain, palpitations, tachycardia, and vasodilatation. In two pooled head-to-head trials,[389, 390] calcitonin participants had greater odds of mild cardiac events than did PTH participants (no events in 81 PTH participants, five events in 86 calcitonin participants).

Musculoskeletal. In two head-to-head trials,[259, 354] alendronate participants had greater odds of these events than did participants taking PTH (OR 3.84, 95% CI, 2.22, 6.80).

Dermatological. This category includes itching, rash, and injection site reactions. In eight pooled trials,[148, 149, 152, 386, 388, 391-393] calcitonin participants had greater odds of these symptoms than did placebo participants (OR 6.13, 95% CI, 2.81, 14.90). In two pooled trials,[394, 395] testosterone participants had greater odds of dermatological symptoms than did placebo participants (OR 8.64, 95% CI, 2.94, 29.70).

Ear, nose, and throat. In nine pooled trials,[152, 340, 341, 378, 380, 384, 386, 387, 392] calcitonin participants had greater odds of these events than did placebo participants (OR 2.31, 95% CI, 1.13, 4.99).

Table 65. Calcitonin, PTH, and testosterone-adverse events vs. placebo

	Calcitonin		Testosterone		PTH	
Event Group	Number of Trials	OR (95% CI)	Number of Trials	OR (95% CI)	Number of Trials	OR (95% CI)
Cardiovascular						
Acute Coronary Syndrome	3	0.98 (0.07, 13.7)	0	NR	0	NR
Cardiac Death	1	0 (0, 36.6)	0	NR	0	NR
Cerebrovascular Events (serious)	1	1.03 (0.07, 14.9)	1	Inf+ (0.03, Inf+)	0	NR
Pulmonary Embolism	0	NR	0	NR	0	NR
Thromboembolic Events	0	NR	0	NR	0	NR
Cancer						
Cancer	1	Inf+ (0.02, Inf+)	2	3.1 (0.24, 168)	3	0.49 (0.27, 0.9)*
Breast Cancer	0	NR	0	NR	0	NR
Colon Cancer	0	NR	0	NR	0	NR
Lung Cancer	0	NR	0	NR	0	NR
Osteosarcoma	0	NR	0	NR	0	NR
GI						
GI (mild)	15	0.96 (0.63, 1.48)	0	NR	2	1.39(0.98, 2)
Upper GI (excluding esophagus)	8	1.07 (0.55, 2.1)	0	NR	2	1.39(0.98, 2)
Reflux and Esophageal	1	0(0, 0.69)*	0	NR	0	NR
GI (serious)	0	NR	0	NR	0	NR
Esophageal (serious)	0	NR	0	NR	0	NR
Upper GI Perforations, Ulcers or Bleeds (not esophageal)	0	NR	0	NR	0	NR

* =statistically significant

Additional cohort, case-control, case series, and case report studies

To further evaluate the prevalence of selected adverse events, we performed broader literature searches for each low bone density treatment and cancers, cardiovascular events, gastrointestinal problems, and osteonecrosis. The "treatments" were not necessarily being used for low bone density. We found many additional cohort studies involving cancer, and several case series/case reports on osteonecrosis. We found no additional studies of cardiovascular events or gastrointestinal problems.

Cancer

We found eight large cohort or case-control studies examining the effect of calcium and/or vitamin D intake on the incidence of cancer. Results are displayed below in Table 66. In one study of breast cancer among women, increased dietary calcium was associated with lower risk (RR 0.80, CI 0.67-0.95). In contrast, one study of prostate cancer showed that increased dietary calcium was associated with higher risk (RR 2.2, CI 1.2-3.9). Vitamin D intake was not associated with either breast or prostate cancer.

In six studies, greater calcium intake was found to be either inversely associated with colorectal cancers or not statistically related. Vitamin D was not associated with these cancers, except in one study that showed an inverse relationship with increasing intake.

Table 66. Calcium/vitamin D observational studies

Study	Medications	Findings
Cancer Prevention Study II[396]	Calcium, Vitamin D	Women with the highest intake of dietary calcium were at lower risk of **breast cancer** than were those with the lowest intake (RR 0.80, CI 0.67-0.95). Neither use of supplemental calcium or vitamin D intake was associated with risk.
NHANES Follow-up[397]	Calcium, Vitamin D	Men with the highest intake of dairy food were at higher risk of **prostate cancer** than were those with the lowest intake (RR 2.2, CI 1.2-3.9). Dietary calcium was also strongly associated with increased risk (RR 2.2, CI 1.4-3.5). After adjustment for calcium intake, vitamin D was not associated with risk.
Veterans Affairs cohort[398]	Calcium, Vitamin D	In multivariate analyses, inverse associations were found for vitamin D intake (OR 0.94, CI 0.90-0.99) and colorectal cancer. Calcium intake was not significantly associated with **colorectal cancer**.
Nurses Health Study & Health Professionals Follow-up Study[399]	Calcium	In men and women, an inverse association was found between higher calcium intake and **distal colon cancer** (RR 0.65, CI 0.43-0.98).
Swedish Cancer Foundation[400]	Calcium, Vitamin D	Consumption of milk and total milk products was inversely related to **colon cancer,** but not at traditionally accepted significance levels (p=.06). No association was found for **rectal cancer**. Vitamin D intake and total dietary calcium were not related to colorectal cancer risk.
Iowa Women's Study[401]	Calcium, Vitamin D	Total calcium intake was inversely associated with **colon cancer** among women with a negative family history (RR 0.50) but unrelated to incidence for women with a positive family history.
Netherlands Cohort Study[402]	Calcium	For men and women, totally dietary calcium intake and calcium from fermented dairy products were not significantly associated with **colorectal cancer** risk. Calcium from unfermented dairy projects was inversely associated with **rectal cancer** risk (RR 0.55, CI 0.30-1.04).
Hawai'i Japanese Men[403]	Calcium	Total calcium intake was not related to risk of colon cancer, and separation of calcium into dairy and nondairy sources did not alter the result. However, there was a significant monotonic increase in *sigmoid* **colon cancer** risk with decreasing total calcium intake.

We found four large cohort or case-control studies regarding estrogen and estrogen-progestin combinations and colorectal cancers among women. Results are summarized in Table 67. In three studies, use of estrogen as hormone replacement therapy was inversely associated with these cancers. One study showed no association.

Table 67. Estrogen observational studies on colorectal cancer

Study	Medications	Findings
Leisure World Cohort, U.S.[404]	Estrogen - hormone replacement therapy	Elderly women who used hormone replacement therapy had age adjusted incidence rate of 2.67 per 1,000 persons compared with 3.30 per 1,000 persons for non-users.
Italy[405]	Estrogen - hormone replacement therapy	Ever-use of hormone replacement therapy was inversely associated with colon cancer (OR 0.64, CI 0.46-0.88) and rectal cancer (OR 0.46, CI 0.29-0.72). Increased duration of use was associated with decreasing risk for both cancers (p for trend < .01)
Cancer II Prevention Study, U.S.[406]	Estrogen - hormone replacement therapy	Ever-use of hormone replacement therapy was inversely associated with fatal colon cancer (RR 0.71, CI 0.61-0.83). Increased duration of use was associated with decreasing risk for colon cancer (p for trend < .001)
Saskatchewan Health Plan, Canada[407]	Estrogen, progestin, or combination	No association between colon cancer risk and the medications.

We found other observation studies of bisphosphonates, SERMs, calcitonin, testosterone, or PTH and cancer incidence or prevalence.

Osteonecrosis

We found seven articles reporting a total of 41 separate cases of osteonecrosis of the jaw in patients taking bisphosphonates. Cases involved pamidronate, zoledronic acid, and alendronate. The vast majority of cases were found in cancer patients taking the medications intravenously. All patients were advised to cease taking the medications. Surgical treatments varied in type and result.

We found no reports of other low bone density treatments and osteonecrosis.

Summary and Discussion

In this chapter, we describe the limitations of our review and then present our conclusions. We also discuss the implications of our findings for future research.

Limitations

Publication Bias

Our literature search procedures were extensive and included canvassing experts from academia and industry for studies. However, it is possible that other unpublished trial results exist for the treatments included in our report. Publication bias may occur, resulting in an overestimation of the efficacy of these treatments.

Study Quality

An important limitation common to systematic reviews is the quality of the original studies. Recent attempts to assess which elements of study design and execution are related to bias have shown that in many cases, such efforts are not reproducible. Therefore, the current approach is to avoid rejecting studies or using quality criteria to adjust the meta-analysis results. However, we did use as a measure of quality the Jadad scale, which is the only validated set of quality criteria for trials. As there is a lack of empirical evidence regarding other study characteristics and their relationship to bias, we did not attempt to use other criteria.

Conclusions

With the above limitations in mind, we reached the conclusions displayed in the table below.

Table 68. Summary of evidence

Key Question	Level of Evidence	Conclusion
1. What are the comparative benefits in fracture reduction among and also within the following treatments for low bone density:		
a. Bisphosphonates	High	Vertebral fractures: alendronate, etidronate, ibandronate, risedronate and zoledronic acid reduce the risk of vertebral fractures among postmenopausal women with osteoporosis.
	High	Nonvertebral fractures: alendronate, risedronate and zoledronic acid reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis.
	High	Hip: alendronate, risedronate and zoledronic acid reduce the risk of hip fractures among postmenopausal women with osteoporosis.
	Low	Wrist: alendronate reduces the risk of wrist fractures among postmenopausal women with osteoporosis.
	Low	Based on limited data from head-to-head trials, within the bisphosphonate class, superiority for the prevention of fractures has not been demonstrated for any agent.
	Low	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.
	Moderate	Based on six RCTs, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison with estrogen.
b. Calcitonin	Moderate	Vertebral fractures: calcitonin reduces the risk of vertebral fractures among postmenopausal women with osteoporosis.
c. Calcium	Moderate	The effect of calcium alone on fracture risk is uncertain. Several large, high quality RCTs were unable to demonstrate a reduction in fracture among postmenopausal women. However, a number of studies have demonstrated that compliance with calcium is low, and a subanalysis in one of the RCTs demonstrated a reduction in fracture risk with calcium relative to placebo among compliant subjects.
d. Estrogen	High	Estrogen reduces the risk of vertebral and hip fractures.
e. PTH (teriparatide)	Moderate/High	Teriparatide is effective in preventing vertebral and non-vertebral fractures.

Table 68. Summary of Evidence (continued)

Key Question	Level of Evidence	Conclusion
f. SERMs (raloxifene, tamoxifen)	High	Raloxifene is effective in preventing vertebral fractures.
g. Testosterone	None	There are no data from RCTs to inform this question.
h. Vitamin D	Moderate	The effect of vitamin D on fracture risk is uncertain. Among a number of meta-analyses, some reported a reduced risk for vitamin D relative to placebo, some did not. There was no reduction in fracture risk for vitamin D relative to placebo in a large, high quality RCT published after the meta-analyses.
i. Exercise in comparison to above agents.	None	There are no data from RCTs to inform this 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)?	High Moderate High Low High Moderate Low	Alendronate, etidronate, ibandronate, risedronate, teriparatide, and raloxifene reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis. Calcitonin reduces the risk of fracture among postmenopausal women. Raloxifene prevents fractures in postmenopausal women at low risk for fracture. Teriparatide, risedronate, and calcitonin reduce risk of fracture among men. Among subjects treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate. 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. 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.

Table 68. Summary of Evidence (continued)

Key Question	Level of Evidence	Conclusion
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?	Moderate	Only 10 RCTs reported rates of adherence to therapy. Five trials of calcium reported high rates of non-adherence. In two studies of daily oral bisphosphonates, more than 80% of patients took at least 70% of the drug. The other three trials reported high rates of adherence with weekly risedronate therapy.
	Moderate	There is evidence from 10 observational studies that adherence to therapy with alendronate, etidronate, risedronate, calcitonin, HRT, raloxifine, and calcium and vitamin D is poor in many postmenopausal women with osteoporosis.
	Low	There is evidence from one observational study that adherence to therapy with alendronate and risedronate is poor in many chronic glucocorticoid users.
	Moderate	There is evidence from 12 observational studies that persistence with therapy with alendronate, etidronate, risedronate, calcitonin, HRT, raloxifene, and calcium and vitamin D is poor in many men and postmenopausal women with osteoporosis.
	Moderate	Based on evidence from observational studies, factors that affect adherence and persistence to medications include side effects of medications, absence of symptoms related to the underlying disease, co-morbid conditions, ethnicity, socioeconomic status, and dosing regimens.
	High	In four observational studies comparing weekly and daily bisphosphonates, weekly users had higher persistence and adherence rates.
	Moderate	There is evidence from RCTs and observational studies that postmenopausal women who are non-adherent to treatment with alendronate, risedronate, HRT, calcium, or calcitonin have an increased risk of fracture compared with women who are adherent to therapy.
	Low	There is evidence from one observational study that postmenopausal women with osteoporosis who are non-persistent with alendronate and risedronate therapy have an increased risk of fracture compared with women persistent with these medications.

Table 68. Summary of Evidence (continued)

Key Question	Level of Evidence	Conclusion
4. What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?	High	There were no differences among bisphosphonates, calcium, vitamin D, calcitonin, PTH, and placebo regarding serious cardiac events.
	High	Zoledronic acid is associated with an increased risk of atrial fibrillation relative to placebo.
	High	Estrogen and estrogen-progestin combination participants had higher odds of cerebrovascular accident (CVA) and thromboembolic events than did placebo participants.
	High	Participants who took raloxifene or tamoxifen showed higher odds for pulmonary embolism than did participants who took a placebo. Raloxifene participants also had greater odds of thromboembolic events.
	Moderate	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.
	Moderate	Perforations, ulcerations (non-esophageal), and bleeds (PUBs) were reported in trials of all the bisphosphonates except zoledronic acid. Etidronate participants had higher odds of PUBs than did placebo patients. Patients taking oral daily ibandronate had lower odds of PUBs than did those taking placebo. Differences between other bisphosphonates and placebo were not statistically significant in pooled analyses.
	Moderate	We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as “mild upper GI events.” Etidronate and pamidronate users had greater odds of these events than did placebo participants. 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 pooled head-to-head trials. Alendronate participants also had higher odds of mild upper GI events in head-to-head trials vs. calcitonin and head-to-head trials vs. estrogen. Etidronate participants had higher odds of mild upper GI events in head-to-head trials vs. estrogen.
	Moderate	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.
	Low	Osteosarcoma was reported in only one study, a head-to-head trial of raloxifene vs. tamoxifen; differences between groups were not significant.

Table 68. Summary of Evidence (continued)

Key Question	Level of Evidence	Conclusion
	Low	We found 41 published cases of osteonecrosis of the jaw in patients taking bisphosphonates. Cases involved pamidronate, zoledronic acid, and alendronate. The vast majority of cases were found in cancer patients taking the medications intravenously.

Discussion

This report provides a comprehensive summary of the meta-analyses and RCTs that have evaluated the effect of various agents on fracture risk. Consistent with FDA requirements to demonstrate a reduced fracture risk in order to obtain approval of an agent for the *treatment* of osteoporosis, a number of RCTs have been performed that used fracture as the primary outcome and that were powered to detect a difference in fracture risk among postmenopausal osteoporotic women at high risk for fracture. Across these studies there is a high level of evidence that alendronate, etidronate, ibandronate, risedronate, calcitonin, teriparatide, and raloxifene prevent vertebral and/or nonvertebral (total, hip and/or wrist) fractures in this population. Each of these agents, with the exception of etidronate, has been approved by the FDA for the treatment of osteoporosis. Also, consistent with FDA requirements to obtain approval for the *prevention* of osteoporosis, i.e., demonstration of an improvement in BMD, *not* fracture risk reduction, there have been few studies performed that assessed fracture as a primary outcome and had sufficient sample size to detect a difference in fracture risk among subjects at lower risk for fracture. A meta-analysis report that raloxifene[55] reduces the risk of vertebral fractures in low-risk populations; one study demonstrated a reduction in the risk of any fracture for ibandronate relative to placebo.[104] Each of these agents has been approved by the FDA for the prevention of osteoporotic fractures.

Estrogen is likewise approved by the FDA for the prevention of osteoporotic fractures in postmenopausal women. However, data on fracture risk reduction for estrogen are more complex. The data describing the effect of estrogen on fracture risk suggest that estrogen reduces the risk of vertebral and hip fracture; the effect of estrogen on non-vertebral fractures is less clear. Among three meta-analyses that assessed the risk of vertebral fracture in postmenopausal women, the pooled sample size in one was too small to detect differences in fracture risk across arms.[47] The one with the largest pooled sample size (6,723) demonstrated a reduced fracture risk relative to placebo (OR 0.45, 95% CI, 0.45, 0.98)[53] and the other[54] with a large sample size demonstrated a risk reduction that was nearly statistically significant. (OR 0.68, 95% CI 0.41, 1.07) Likewise, data on the risk for hip fracture demonstrate a significantly reduced risk in the WHI, a large, high quality RCT,[164] and a nearly significant risk reduction in a meta-analysis[47] that included data from the WHI. Among the three meta-analyses that evaluated the risk of non-vertebral fractures, all reported point estimates for reduced risk, but the 95% confidence intervals varied in relation to sample size. The analysis with the largest sample size (8,774)[162] had the narrowest confidence interval and it did not cross null. The other two had smaller sample sizes (7,316[47] and 5,383[54]) and wider confidence intervals that crossed null.

Tamoxifen and testosterone are not approved by the FDA for the treatment or prevention of osteoporosis. Consistent with this fact, we did not identify any evidence that these agents reduce the risk of fractures. For tamoxifen, there is evidence from one large RCT that tamoxifen is not associated with fracture risk reduction.[204] We did not identify any studies that assessed the effect of testosterone on fracture. ~~In contrast, though not approved by the FDA for the prevention or treatment of osteoporosis, the effect of zoledronic acid on fractures is under active investigation, likely in preparation for a petition to the FDA for an approved indication for the treatment of osteoporosis. To this end a large RCT that evaluated the effect of zoledronic acid on fracture among post-menopausal women at high risk for fracture was recently published and~~

~~demonstrated a reduced risk relative to placebo at three years.~~[139] NOTE: Text redlined to reflect that Zoledronic acid labeled as 'Reclast' was approved by the FDA for the treatment of osteoporosis in post-menopausal women on 8/17/07.

The evidence for fracture risk reduction is less clear for the other agents assessed in this report. For calcium, several large, high quality RCTs[65, 206, 207] were unable to demonstrate a reduction in fracture among postmenopausal women. However, a number of studies have demonstrated that compliance with calcium is low,[63-65, 206, 207] and a sub-analysis in one of the RCTs demonstrated a reduction in fracture risk with calcium relative to placebo among subjects who were compliant with therapy.[206]

Data on the effect of vitamin D on fracture risk are likewise unclear. Among a number of meta-analyses, some reported a reduced risk for vitamin D relative to placebo,[50, 52, 58, 61] and some did not.[47, 50, 51] There was some overlap between the studies included in the meta-analyses, although each included some unique studies. The finding of a significant reduction in fracture risk was not related to the size of the pooled sample in the meta-analyses. Notably, one meta-analysis reported a reduction in fracture risk for vitamin D relative to placebo for doses $\geq$ 800 IU per day, but not for 400 IU per day. However, in a large, high quality RCT published after the meta-analyses, no reduction in fracture risk was observed for 1,000 IU vitamin D relative to placebo among ambulatory people ages 70 and older with a history of prior fracture.[65] In another RCT published after the meta-analyses, there was a reduction in fracture risk with 1,000 IU vitamin D relative to placebo for postmenopausal women with hemiplegia due to stroke. Together these data do not prove that vitamin D prevents fractures. However, these data do suggest that in high enough doses, vitamin D might prevent fractures in some high-risk populations. That fracture risk reduction was observed among postmenopausal women with hemiplegia suggests that one mechanism through which vitamin D might prevent fractures is by reducing falls. Indeed, vitamin D-treated subjects in this study had a 59% reduction in falls relative to placebo, consistent with the reduction in falls associated with vitamin D that has been reported in other studies.[408]

We did not identify any studies that demonstrated 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.

This report also evaluated whether fracture risk reduction varies among individuals with different risks for fracture. Special populations identified in the studies include men, populations with increased risk for fractures as a result of medications or diseases that reduce BMD, and people living with conditions that increase the risk of falling. None of the studies that included subjects at low risk for fracture had sample sizes large enough to detect significant risk reductions for the agents assessed.

Few studies assessed the effect of agents to reduce fracture risk among men. Among nine studies that included men,[65, 92, 123-125, 140, 142, 195, 196] three demonstrated a reduction in fracture risk: one for total fractures with teriparatide,[196] one for hip fractures with risedronate,[124] and one for vertebral fractures with calcitonin.[142] Among the remaining studies, only one had sufficient sample size to assess the effect of agents on fracture.[65] In this study, which included men and

women, there was no reduction in the rate of fractures for calcium relative to placebo; subgroup analyses found no difference in risk among men and women.

Special populations with increased risk for fractures as a result of medications that were identified included patients on long-term glucocorticoids,[92, 94, 136, 263, 271-273] recipients of solid organ transplants,[107, 110-112, 114, 143, 213, 261] and bone marrow transplant recipients.[113, 256] Among subjects treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate[136, 137, 273] and alendronate.[272] Fracture risk reductions were not demonstrated for any other agents. Both risedronate and alendronate are approved by the FDA for the treatment of glucocorticoid-induced osteoporosis.

Populations at increased risk for fracture due to a disease that is associated with low BMD that were identified included those with primary biliary cirrhosis,[71, 252] leprosy,[125] and inflammatory bowel disease in remission.[120] Among these groups, fracture risk reduction relative to placebo was demonstrated only for patients with inflammatory bowel disease treated with risedronate.[120] However, none of the other studies was large enough to detect significant differences across study arms.

Populations identified as being at increased risk for fracture due to conditions that increase the risk of falling included those with stroke with hemiplegia,[119, 124, 214] Alzheimer's disease,[118], Parkinson's disease in remission,[72] and recent hip fracture.[89] Across these studies, there were seven comparisons between alendronate, etidronate, risedronate, or vitamin D and placebo; six of these demonstrated significant reductions in fracture risk for the agent relative to placebo.

The data described in this report also demonstrate that adherence to and persistence with medications for osteoporosis is low and suggests that low adherence is associated with less favorable reductions in fracture risk. Of note, among the RCTs identified to assess the effect of agents on fracture risk, 27 studies reported that adherence to therapy was measured, but only 10 of these reported the rates of adherence to therapy.[63-65, 127, 128, 206, 207, 262, 282, 283] Of these 10, only five included an analysis of outcomes that considered adherence to therapy.[63, 64, 206, 207, 282] The effect of adherence on fracture risk was variable in these studies. However, among three large observational studies,[284-286] adherence was inversely related to fracture risk. Factors associated with poor adherence include side effects of medications, absence of symptoms for underlying disease (i.e., osteoporosis or osteopenia), comorbid conditions, age, and socioeconomic status.

Future Research

Although there is good evidence that a number of the agents reviewed in this report reduce the risk of fracture among postmenopausal women with high risk for fracture, i.e., women with T-scores < -2.5 SD and/or a prior osteoporotic fracture, data on the effect of osteoporosis agents in reducing fracture risk in other populations are limited. Among populations at high risk for fracture, solid-organ and bone marrow transplant recipients comprise a significant and growing population. Further, because the underlying cause of osteoporosis is different than that in postmenopausal women, data on the efficacy of osteoporosis agents in postmenopausal women may not be applicable to this population. Hence, research is needed to determine if/which osteoporosis agents reduce fracture risk among transplant recipients. Among lower risk populations, there are limited data on whether osteoporosis agents reduce the risk of fracture among postmenopausal women with osteopenia and among men. Coupled with good evidence that all osteoporosis agents are associated with side effects that range from mild to serious, further research is needed to determine whether the benefits of treatment in these lower risk populations outweighs the risks. Further, because these groups comprise a large population, results from such studies have the potential to have a large impact … regardless of the results. Demonstration of fracture risk reduction could lead to broader use of these agents in these populations and reduced fracture rates. Demonstration that fracture risk is not reduced in these populations could lead to the discontinuance of these agents in these populations with a concomitant reduction in adverse events and unnecessary health care spending. A practical challenge in determining whether osteoporosis agents reduce the risk of fracture in lower risk populations is that large sample sizes will be required. Given that the baseline fracture risk is lower and that the time to develop fractures is longer in these lower risk populations, RCTs designed to assess fracture risk would require larger sample sizes and longer follow-up periods than those performed among high-risk postmenopausal women.

Regarding comparative effect of osteoporosis agents on preventing fractures, head-to-head studies of the different agent that have sufficient power to detect differences across study arms are needed. We did not find any studies that assessed the effect of testosterone in men on the development of fractures; fractures could be tracked in large placebo-controlled trials designed to access other outcomes.

Although a number of studies suggested that inconvenient dosing regimens reduced adherence and persistence, we did not identify any studies that specifically assessed the effect of changing dosing regimens on adherence or persistence. Additionally, although studies demonstrate that weekly dosing of osteoporosis medications achieves higher adherence rates than does daily dosing, overall compliance rates are still far below desirable levels. Additional studies will be required to demonstrate whether a change to less frequent medication dosing regimens will improve patient adherence and persistence.

Patients with osteoporosis are more likely to adhere to osteoporosis therapies if they have better understanding of their individual risks for complications of the disease.[409] Additionally, patients often do not follow prescribed instructions for taking their medications, and improper medication

use may lead to increased side effects.[294] Thus, patient education programs may improve adherence to osteoporosis therapy.

Robbins et al. used a patient-education intervention in a cohort of black and Hispanic women who were already participating in a RCT of HRT vs. placebo for osteoporosis. All minority participants received the educational intervention. One year after the educational intervention was implemented, the mean MPR improved significantly in black women from 80% to 88%, and in Hispanic women from 83% to 86%.[410] In one other controlled observational study, young postmenopausal women with osteoporosis did not show improvement in adherence rates after receiving an educational leaflet.[411] Given these results, more research on patient education, adherence, and outcomes is suggested.

Finally, the recent series of reports of osteonecrosis of the jaw among patients taking bisphosphonates point to the immediate need for epidemiologic research to define whether there is a significant association between bisphosphonates and jaw osteonecrosis, the magnitude of the association and the specific population(s) in which any association exists. Confirmation and definition of such an association could direct the appropriate use of these agents among specific patient populations. Additionally, should such an association be demonstrated, this could direct basic research into possible mechanisms, which might provide insight into the basic pathophysiology of osteoporosis and bone metabolism.

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Abbreviations

Alendr	Alendronate
Calcit	Calcitonin
CI	Confidence Interval
Esoph	Esophagus
Estrog	Estrogen
Etidro	Etidronate
GI	Gastrointestinal
HERS	Heart and Estrogen-Progestin Replacement Study
Ibandr	Ibandronate
Inj/app site rxns	Injection/ application site
Iu or IU	International Units
IV	Intravenous
LFTs	Liver function tests
MPR	Medication possession ratio
N/V	Nausea/vomiting
OR	Odds ratio
Pamidr	Pamidronate
PTH	Parathyroid hormone
Ralox	Raloxifene
RCT	Randomized Controlled Trial
RD	Rate difference
Rflx or esoph sx	Reflux or esophageal symptoms
Risedr	Risedonate
RR	Relative risk
Tamox	Tamoxifen
Testos	Testosterone
UGI	Upper Gastrointestinal
Vit D	Vitamin D
WHI	Women's Health Initiative
Zoledr	Zoledronic Acid