

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 problems than did placebo patients.
- Osteosarcoma was reported in only one study, a head-to-head trial of raloxifene vs. tamoxifen; differences between groups were not significant.
- There are no data from osteoporosis trials that describe an association between bisphosphonates or any other agents and the development of osteonecrosis. In case reports and case series articles, we found 41 cases of osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates. Cases involved pamidronate, zoledronic acid, and alendronate.

Remaining Issues

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

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

We did not find any studies that assessed the effect of testosterone in men on the development of fractures. The impact of testosterone on fracture reduction could be clarified by tracking fractures in large placebo-enrolled trials.

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

Addendum

The search for studies relevant to this report was updated in the preparation of a manuscript summarizing the findings of this report (www.acponline.org). 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 involuntal, 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 among 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. Parathyroid 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)				
		% Increase relative to baseline at 1 year					
70 mg/wk		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 <i>po</i>	LS	1.8 vs. -2.5		
			FN	0.6 vs. -2.5		
			T	2.5 vs. -1.7		
		35 mg/wk <i>po</i>	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. pamidronate			
			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, Fortical	Treatment of osteoporosis in postmenopausal women				
		100 IU SC or IM every other day				
		200 IU IN/d Alternating nostrils	Increase relative to placebo (0.5 to 2 years)			
			LS Signif			
			Forearm NS Hip NS			
Estrogen	Premarin Premarin IV	Prevention of postmenopausal osteoporosis				
		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				
Raloxifene	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-analysis 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 an 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 Q³⁴ and the I² statistic.³⁵ A significant Q statistic or I² values close to 100% represent very high degrees of heterogeneity. I² 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) $\geq 50\%$ 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

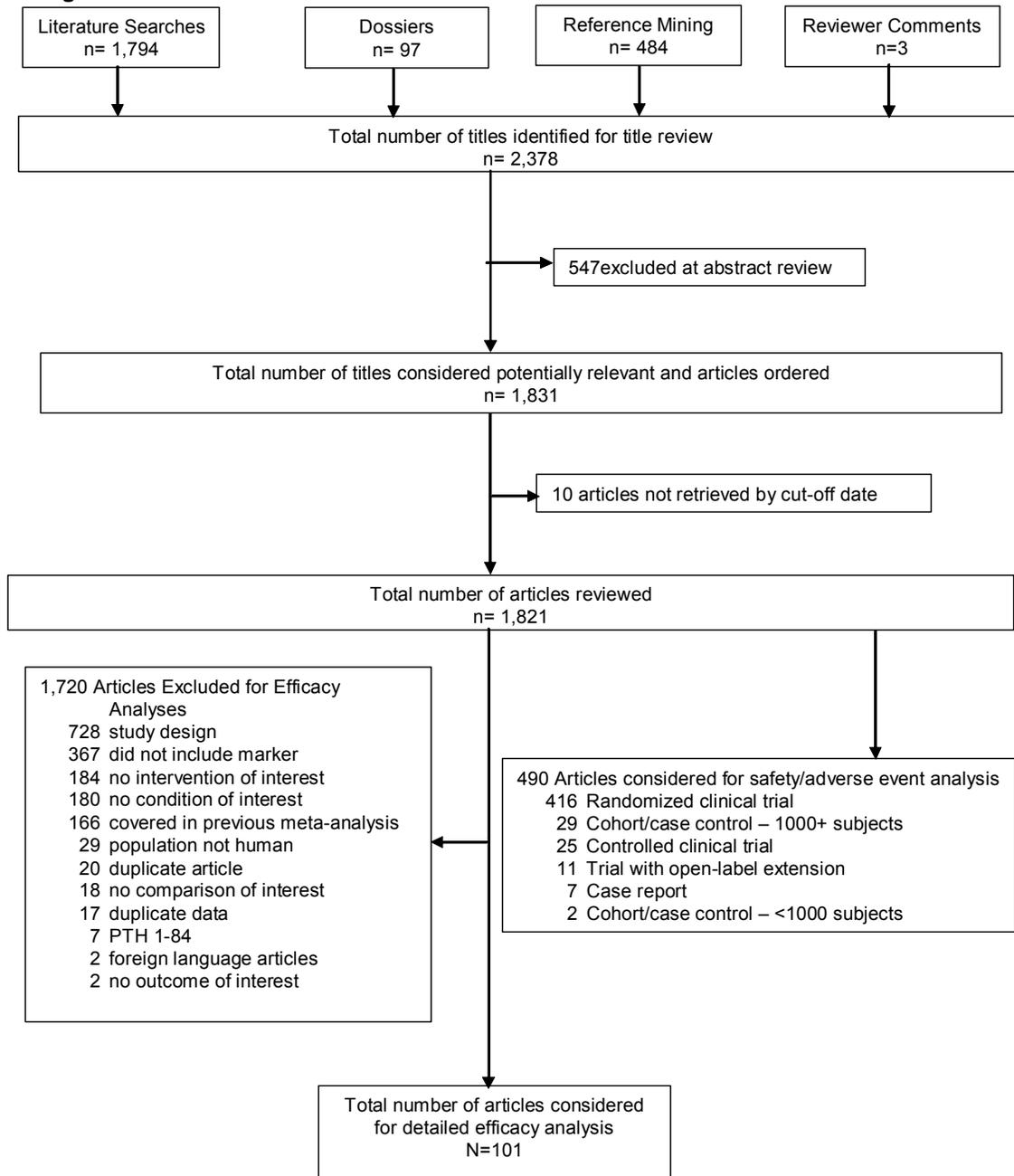
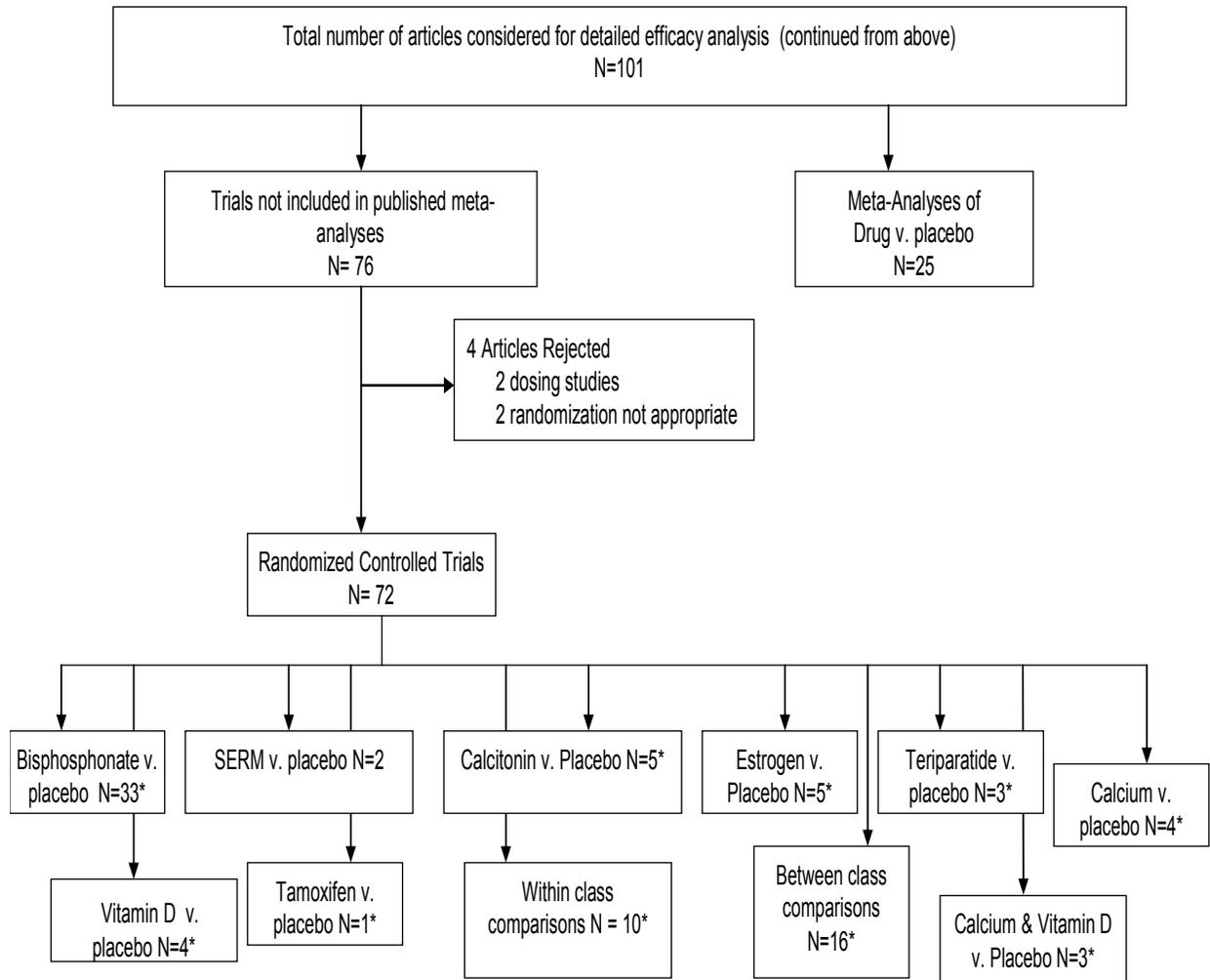


Figure 1. Literature Flow (continued)



*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-analyses (ibandronate, 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 calcium 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.

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*

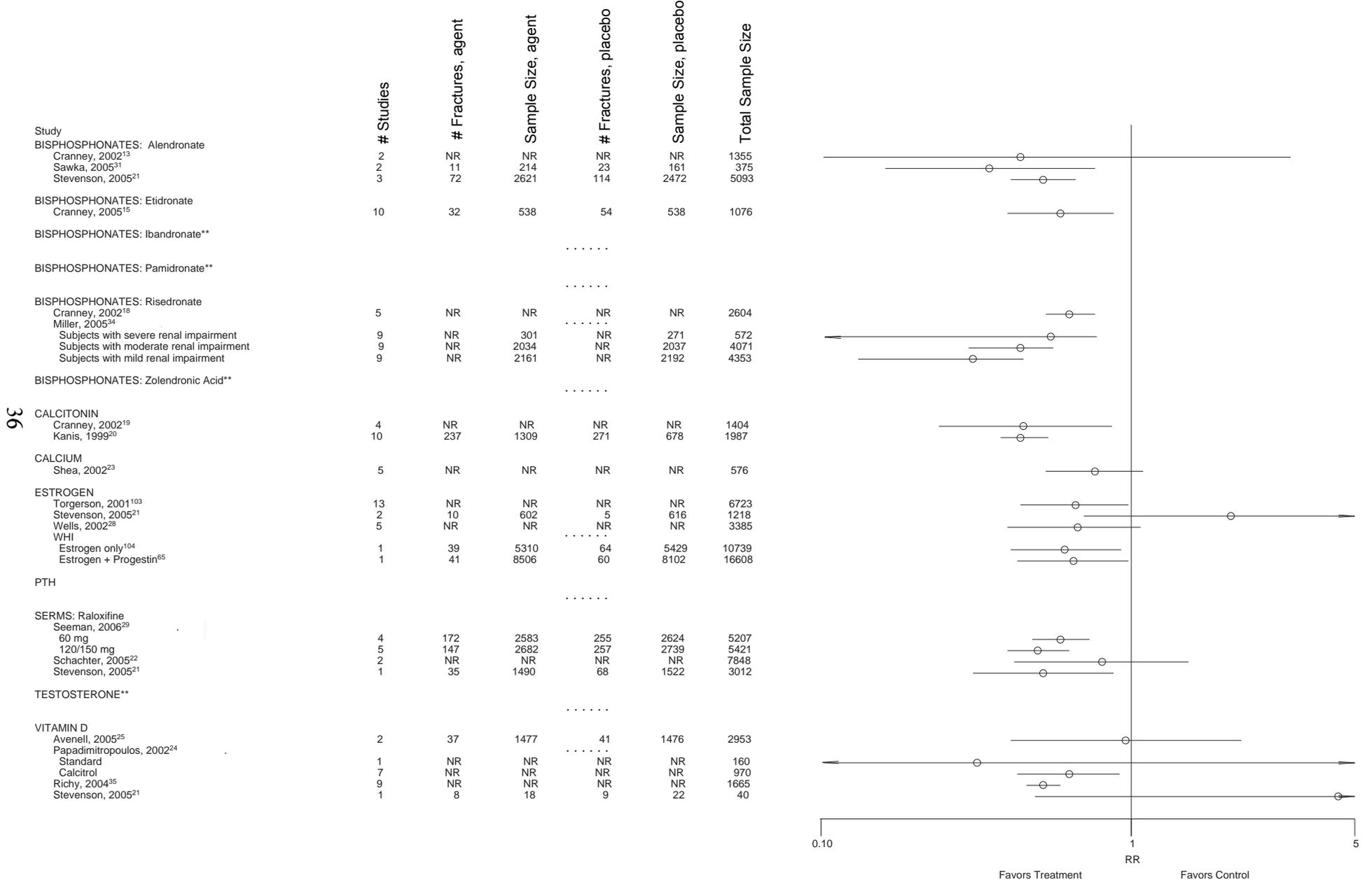


Figure 4. Risk of non-vertebral fracture relative to placebo for subjects at high risk for fracture, by agent*

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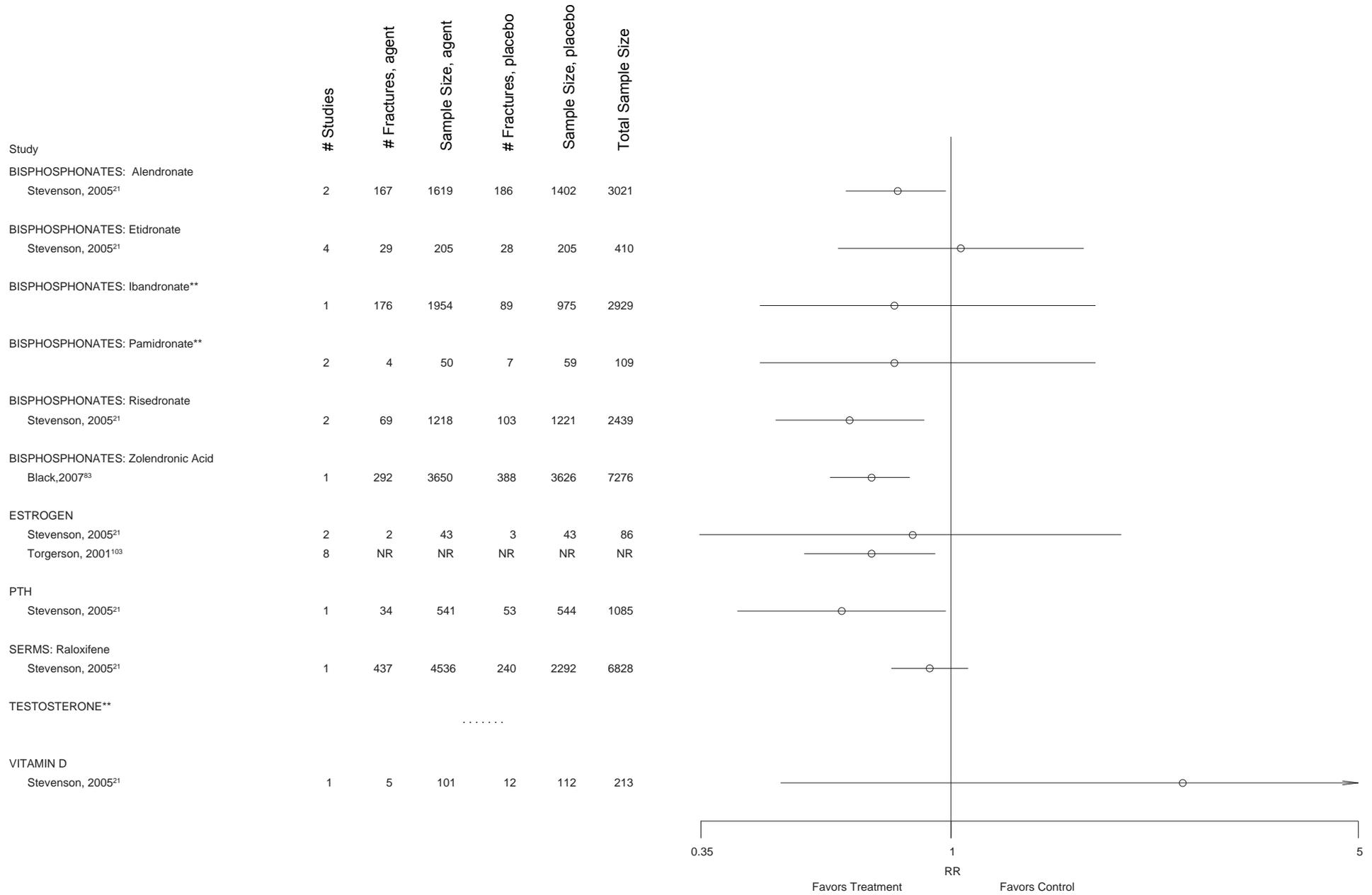


Figure 5. Risk of non-vertebral fracture relative to placebo for subjects not at high risk for fracture, by agent*

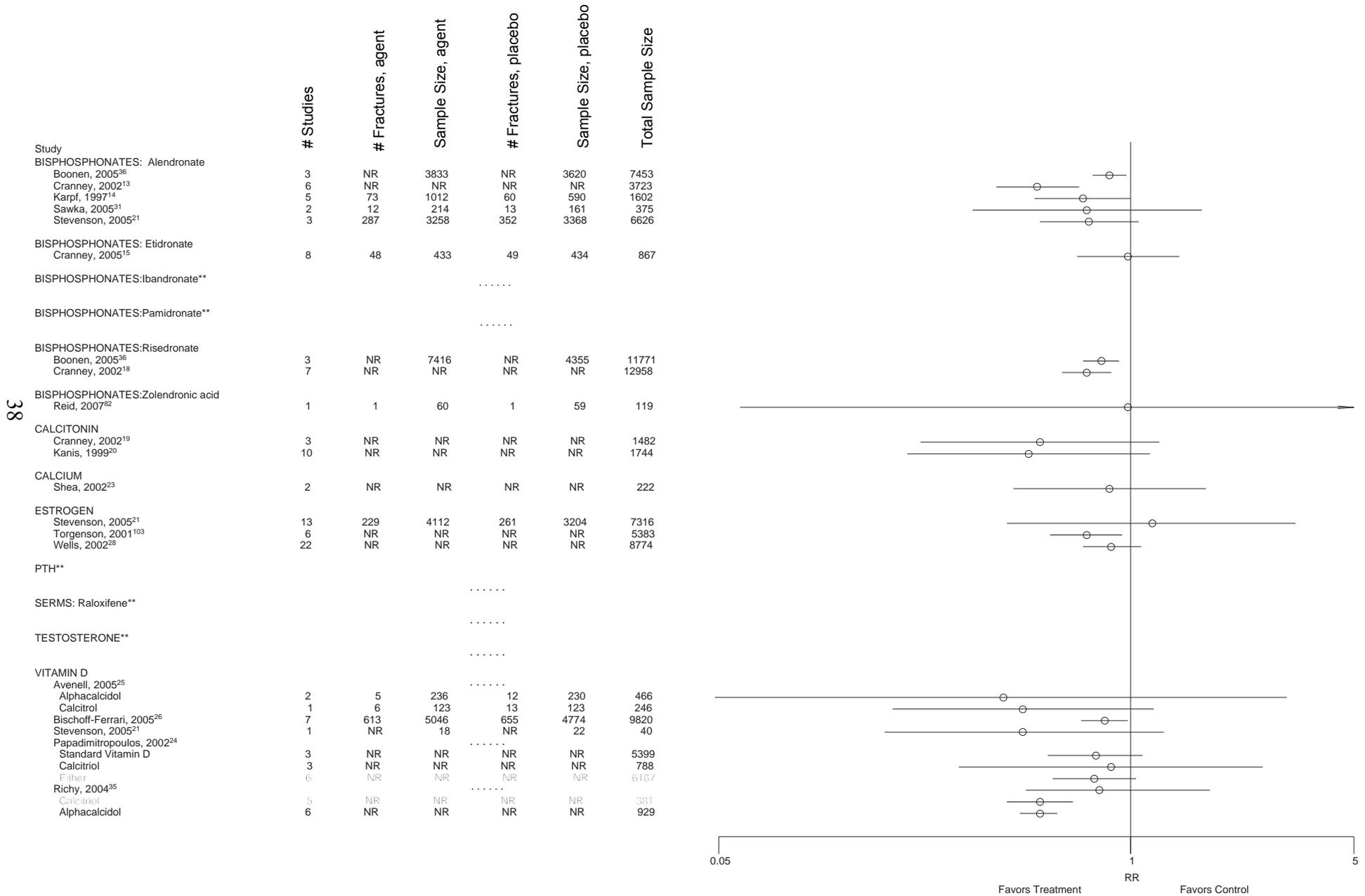


Figure 6. Risk of hip fracture relative to placebo for subjects at high risk for fracture, by agent*

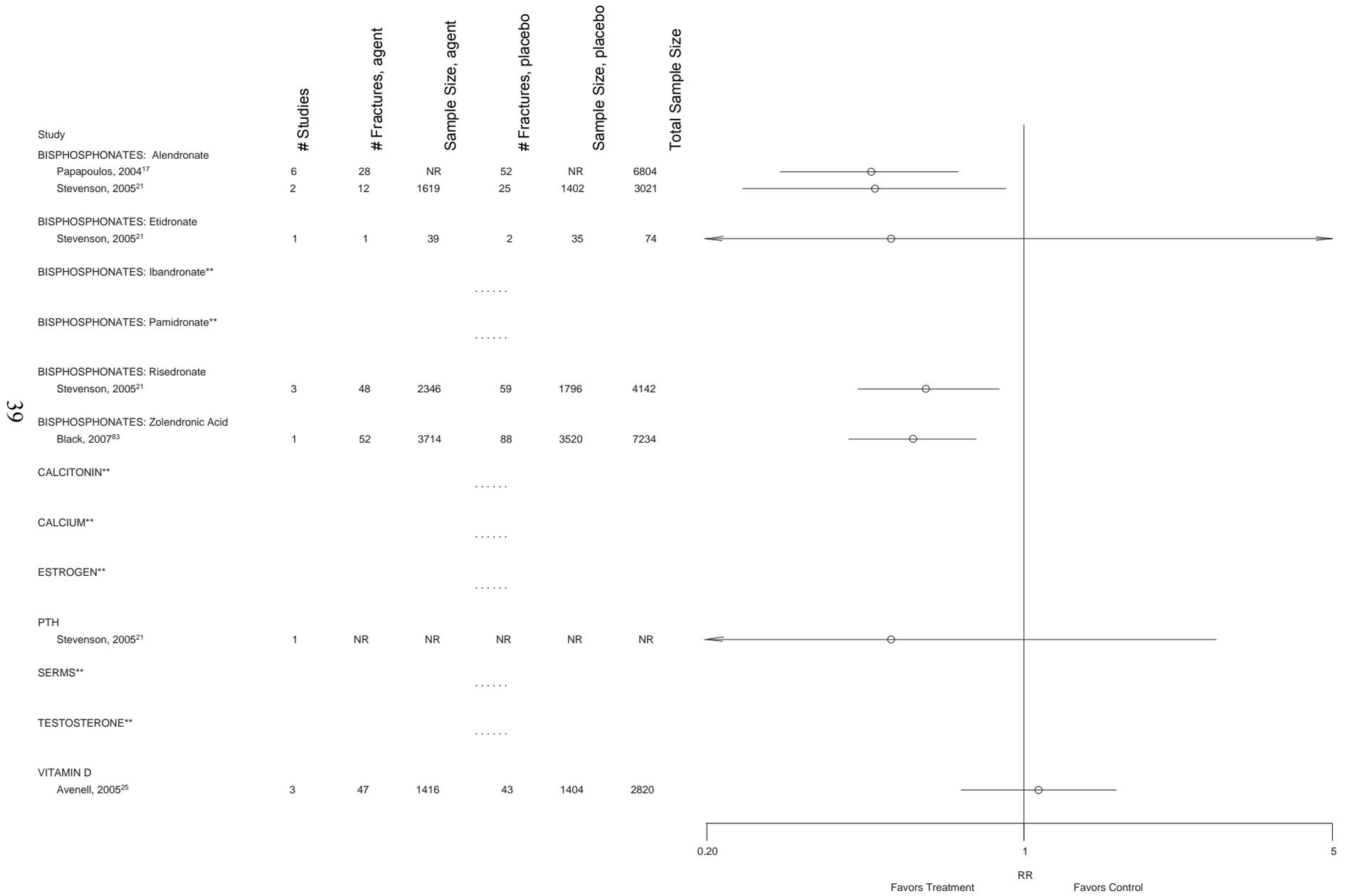
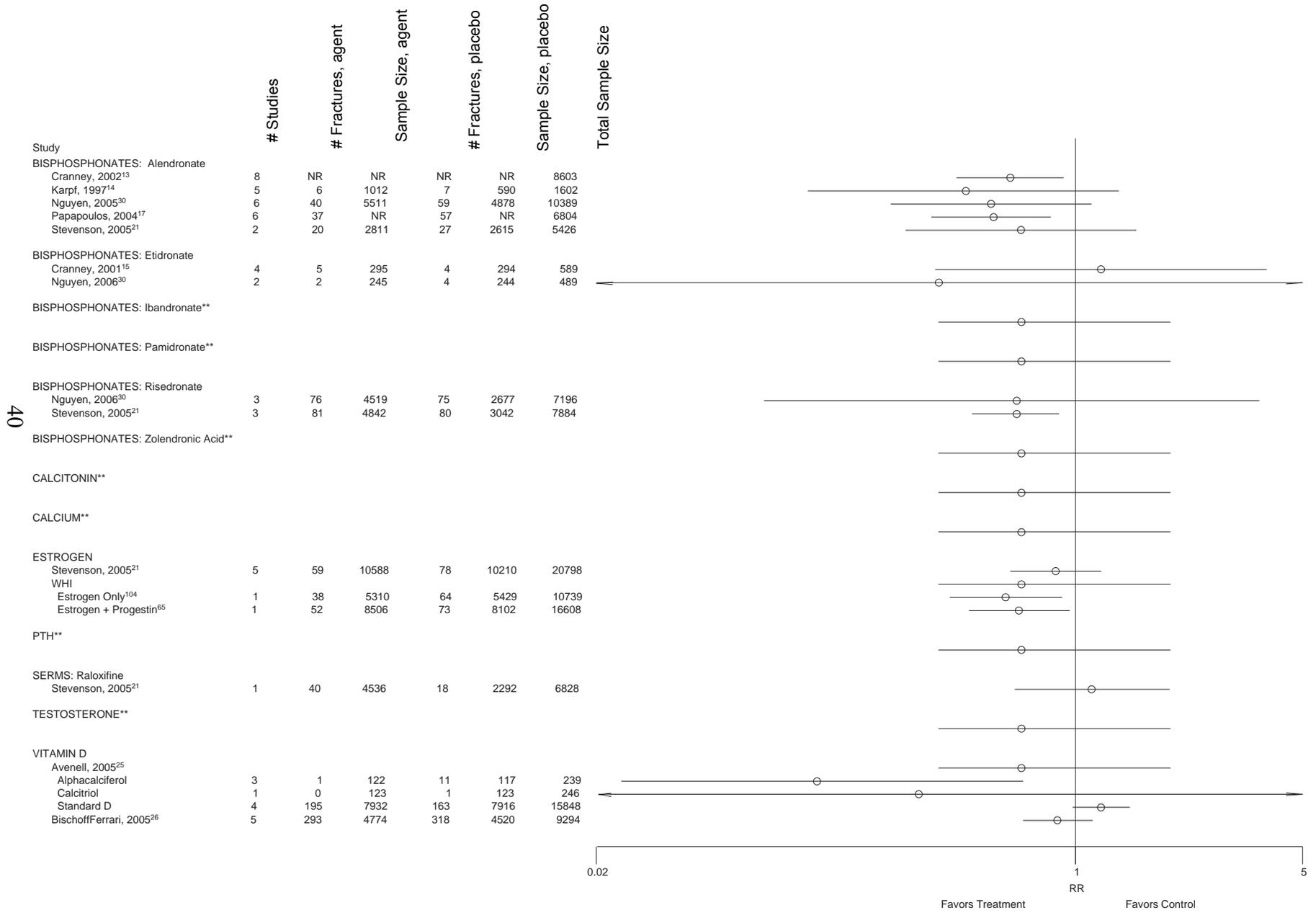


Figure 7. Risk of hip fracture relative to placebo for subjects not at high risk for fracture, by agent*



40

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*

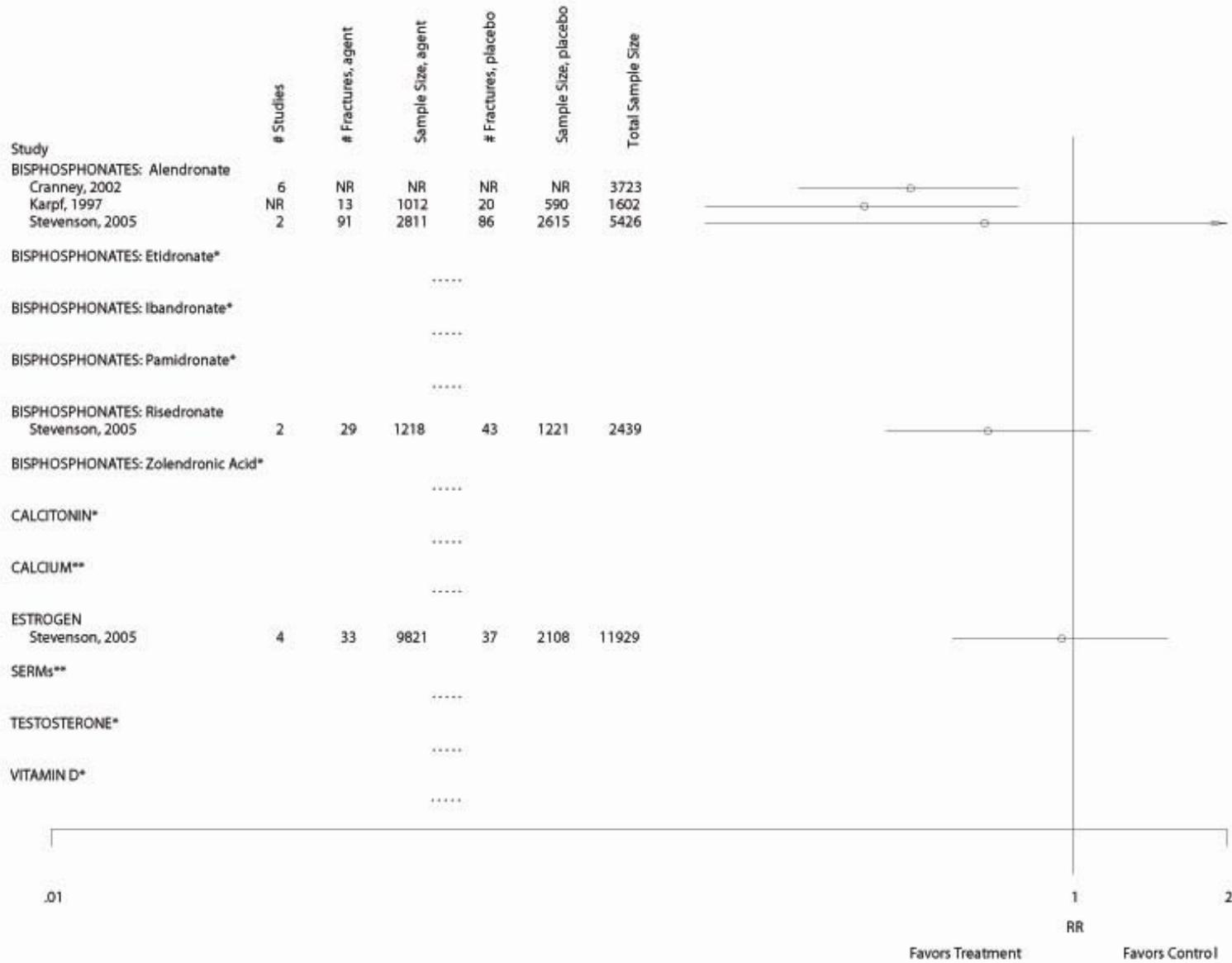
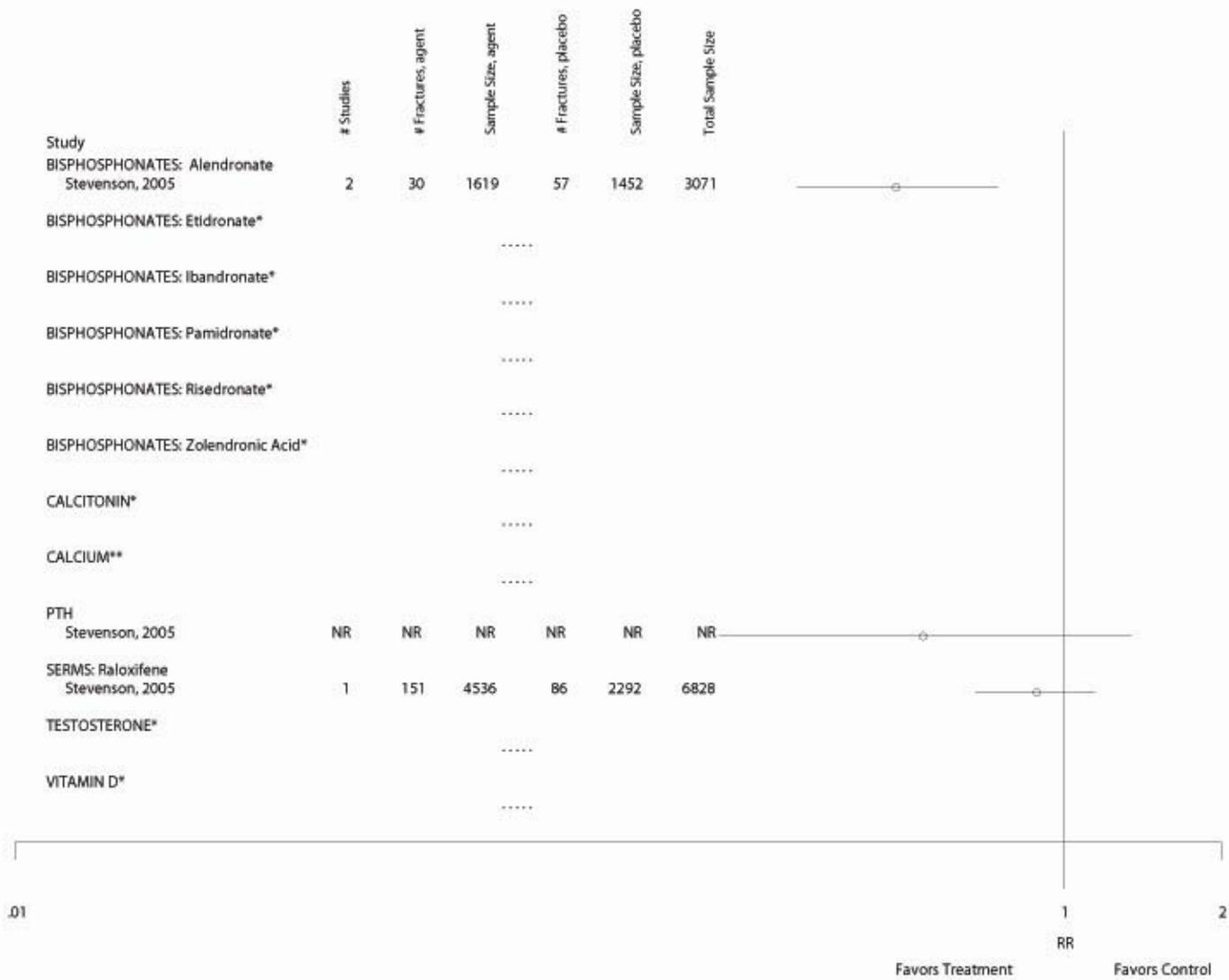


Figure 9. Pooled risk of wrist fracture among populations not defined as at high risk for fracture for agents used to treat or prevent osteoporosis relative to placebo*



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) $\geq 50\%$ 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 RCTs⁶⁶⁻⁷² 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 \geq 5 mg/d	2	1,355	0.45	(0.06, 3.15)
Treatment trials, dose \geq 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 \leq 2.0 or with vertebral fracture	6	9,023	0.55	(0.36, 0.84)
Subjects with T score \leq 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 \geq -2 SD and/or baseline prevalence of fracture is \leq 20% and/or average age is \leq 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) $\geq 50\%$ 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 RCTs⁸⁹⁻⁹⁴ 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 asthma⁹² or connective tissue disease⁹⁴ 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

RCTs (Author, year)	Meta-analyses (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		
Lyritys, 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	
Wimalawansa, 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-quantitative 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) $\geq 50\%$ 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 RCTs¹⁰⁴⁻¹⁰⁷ 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 outcomes¹⁰⁷ or adverse events¹⁰⁴, one was performed among 180 postmenopausal women¹⁰⁴ 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*

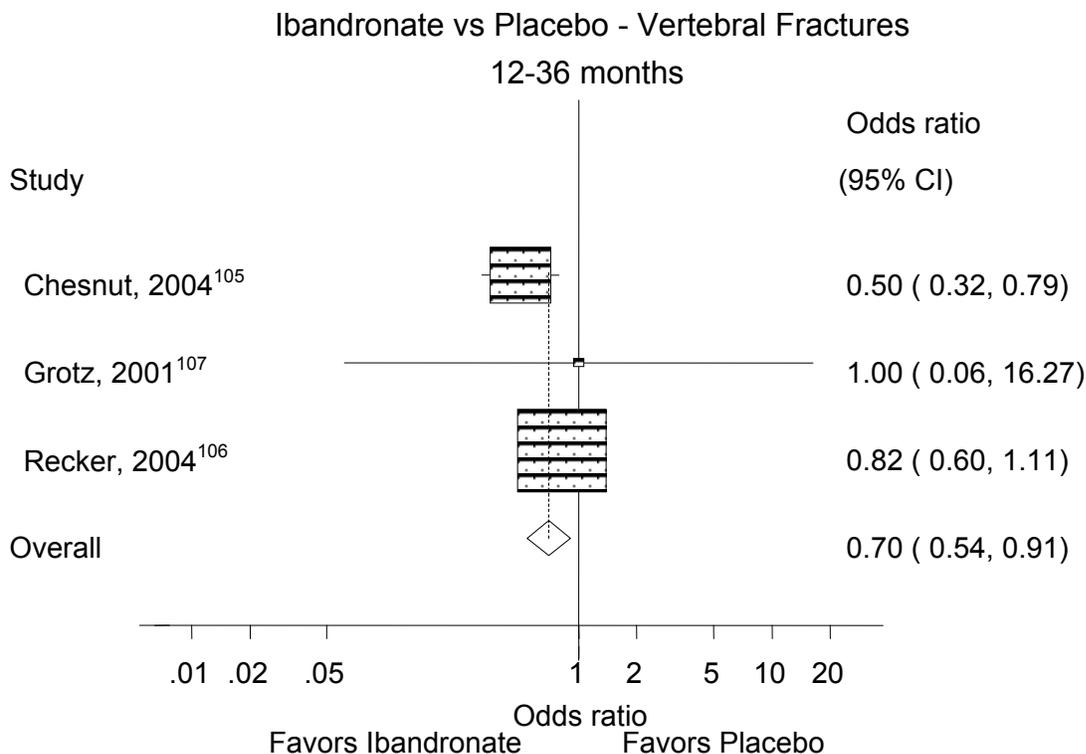
Author, year	Study duration	Type of fracture	Risk level	Number of fractures, ibandronate	Number of fractures, placebo	Odds ratio (95% CI)
ALL FRACTURES						
Ravn, 1996 ¹⁰⁴	12 months	fracture	Intermediate	0/150†	1/30	0.002 (0.00, 0.477)
VERTEBRAL						
Chesnut, 2004 ¹⁰⁵	36 months	clinical vertebral	High	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) $\geq 50\%$ 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 RCTs¹⁰⁹⁻¹¹⁴ 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 lymphoma¹⁰⁹ 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.

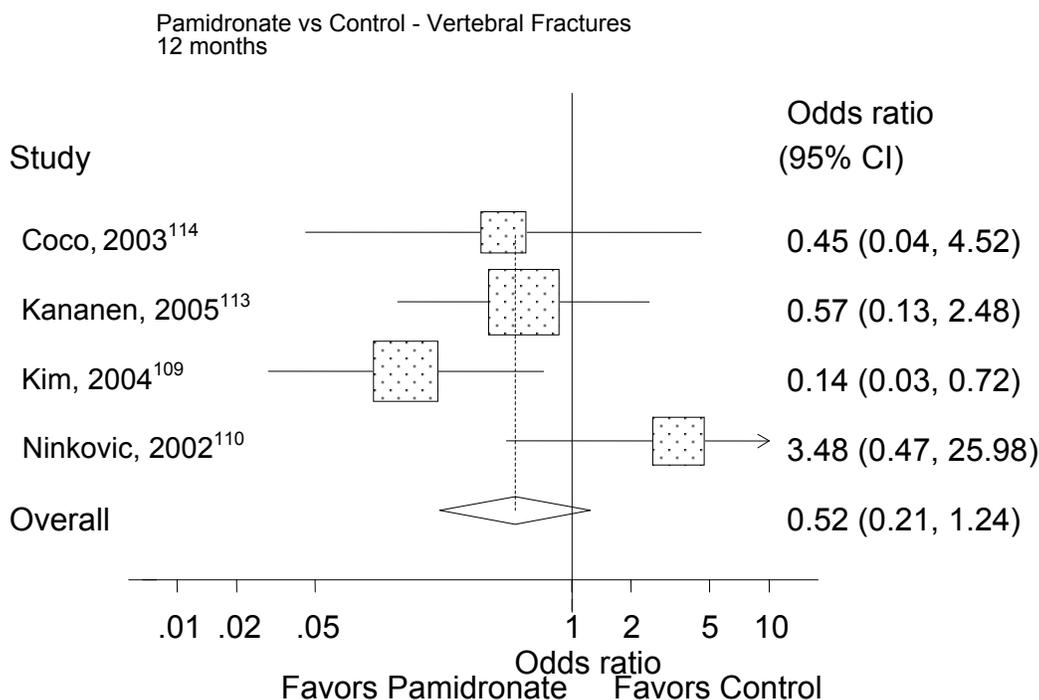
Table 9. Risk of fracture for pamidronate, any dose, relative to placebo, by fracture group*

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) $\geq 50\%$ 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 women¹¹⁵ is described in this section; the pooled analysis among subjects treated with glucocorticoids¹¹⁶ 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 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 risedronate 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 leprosy¹²⁵ 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 Cohen¹³⁷ included in the systematic 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) $\geq 50\%$ 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) $\geq 50\%$ 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) $\geq 50\%$ 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-induced osteoporosis⁴² 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 study¹⁴² 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) $\geq 50\%$ 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-analyses⁴⁷, 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 Lilly, 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		
Wimalawansa, 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=wrists/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) $\geq 50\%$ 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 review⁴⁷ 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 RCTs¹⁹⁴⁻¹⁹⁶ 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 11¹⁹⁵ and 18¹⁹⁶ 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 fracture	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) $\geq 50\%$ 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 ⁹⁵				
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 \leq -2.5, or 3) study entry criteria require \geq 1 fracture, or 4) \geq 50% population has 1 or more fractures at baseline or 5) Significant neuromuscular impairment. Intermediate-risk: 1) study entry criteria require T score \leq 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 \leq 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 RCT²⁰⁴ 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) $\geq 50\%$ 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-analysis⁴⁹ 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 intermediate²⁰⁷ risk for fracture. The populations in the other study included men and women with asthma⁹² 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-quantitative 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 appedicular 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 (0.71, 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) $\geq 50\%$ 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 D₃ (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-analysis⁴⁷ evaluated the effect of vitamin D on fractures in postmenopausal women. This meta-analyses stratified findings based on whether subjects had osteoporosis at study enrollment (according to BMD). In this meta-analysis, vitamin-D had no effect on fracture in either stratum.

The fifth meta-analysis⁶¹ 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-analysis⁵⁸ 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 one⁶⁵ 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]				
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				
Calcitriol	9	1665	0.53	(0.47, 0.60)
Alphacalcidol	6	896	0.52	(0.41, 0.67)
GC-induced (calcitriol only)	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				
Elderly women not selected for BMD	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				
Alphacalcidol				
Not selected on basis of prior osteoporotic fracture	2	466	0.40	(0.05, 3.08)
Bischoff-Ferrari, 2005 ⁵²				
All doses (D2, D3)				
700-800IU/d	7	9820	0.83	(0.70, 0.98)
400IU/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				
Elderly women not selected for BMD	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]				
Calcitriol (1,25-OH vitamin 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				
Calcitriol				
Alphacalcidol	11	1310	0.52	(0.46, 0.59)
Alphacalcidol	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)
Alphacalcidol				
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)				
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 RCTs⁶³⁻⁶⁵ 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 high⁶⁵ 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) $\geq 50\%$ 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 trials²⁵⁰ was designed to compare fracture 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 osteoporosis²⁵³ 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 studies²⁵⁵ 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) $\geq 50\%$ 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) $\geq 50\%$ 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 study²⁵¹ 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 RCT²⁵⁶ 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, risedronate	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) $\geq 50\%$ 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 RCT²⁵⁸ 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) $\geq 50\%$ 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) $\geq 50\%$ 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 asthma⁹², 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) $\geq 50\%$ 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) $\geq 50\%$ 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 study²⁵⁹ 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) $\geq 50\%$ 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) $\geq 50\%$ 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-analysis²⁶⁵ 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-analysis²⁶⁵ 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, and⁹³ 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 study⁹³ and with calcidiol²⁶¹ 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 study⁹³ 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) $\geq 50\%$ 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 high⁹³ or low¹⁴¹ 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) $\geq 50\%$ 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 RCT⁶⁵ 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) $\geq 50\%$ 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 RCT⁹³ 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) $\geq 50\%$ 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 study¹⁶⁶ 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) $\geq 50\%$ 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) $\geq 50\%$ 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 Initiative¹⁶³ 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

Author, year	Fracture risk		
	High	Intermediate	Low
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 ^{4†}	0.69 (0.56, 0.86)		0.53 (0.35, 0.79)
Non-vertebral Fractures			
Stevenson, 2005 ^{4†}	0.92 (0.79, 1.07)		
Hip Fracture			
Stevenson, 2005 ^{4†}	1.12 (0.65, 1.95)		
Wrist Fracture			
Stevenson, 2005 ^{4†}	0.89 (0.68, 1.15)		
Vitamin D			
Vertebral Fractures			
Avenell, 2005 ⁵¹	3.97 (0.44, 35.45)	0.96 (0.42, 2.21)	
Stevenson, 2005 ^{4†}	1.02 (0.44, 2.32)	4.44 (0.50, 39.03)	
Non-vertebral Fractures			
Avenell, 2005 ⁵¹		0.40 (0.05, 3.08)	
Stevenson, 2005 ^{4†}		0.46 (0.17, 1.27)	0.86 (0.72, 1.02)
Hip Fracture			
Avenell, 2005 ⁵¹	1.08 (0.72, 1.62)	1.20 (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 bisphosphonates 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 with 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 total¹⁶³ 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 trial¹⁴¹ 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-analysis⁴⁵ 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 RCT²⁰⁴ 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 lymphoma¹⁰⁹ 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 leprosy;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 review²⁷¹ 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 study²⁷³ 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 results¹³⁶ 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 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	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., 2000²⁷¹

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., 2000²⁷¹; 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-analysis⁴² 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 vertebral 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 study¹²⁸ reported that 98% of subjects randomized to weekly risedronate or to placebo took at least 80% of their study medications. Another study²⁸³ 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 studies²⁸⁴⁻²⁸⁶ 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 risedronate²⁸⁵ 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 $\geq 80\%$ 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 significantly 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	1 year	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, calcitonin, 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 Solomon³⁰³ 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 initiate 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 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 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 problems than did placebo patients.
- Osteosarcoma was reported in only one study, a head-to-head trial of raloxifene vs. tamoxifen; differences between groups were not significant.
- There are no data from osteoporosis trials that describe an association between bisphosphonates or any other agents and the development of osteonecrosis. In case reports and case series articles, we found 41 cases of osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates. Cases involved pamidronate, zoledronic acid, and alendronate.

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 trial¹³⁹ the risk of serious atrial fibrillation was significantly increased for once-yearly zoledronic acid relative to placebo (50 versus 20 patients, $p < 0.001$). In a letter to the editor³²³ 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 acid¹³⁹ 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 acid¹³⁹ 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 etidronate³²⁶ and ibandronate¹⁰⁴ 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 pamidronate³²⁷ 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 etidronate³²⁶ and pamidronate³²⁴ 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 tamoxifen²⁰⁴ reported cardiac deaths. There were no significant differences between either drug and placebo.

CVA. Three trials of raloxifene³⁵⁶⁻³⁵⁸ and one of tamoxifen²⁰⁴ 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). Tamoxifen²⁰⁴ 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 tamoxifen²⁰⁴ 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

Event Group	Raloxifene		Tamoxifen	
	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 estrogen³⁷⁰ 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 estrogen¹⁶⁵ and estrogen-progestin combined¹⁶⁴ 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 risedronate²⁵⁶ and zoledronic acid²⁵⁶ 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

Event Group	Estrogen		Estrogen with progesterone	
	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

Event Group	Calcium		Vitamin D	
	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 calcitonin³⁷⁸ and one trial of testosterone³⁷⁹ 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

Event Group	Calcitonin		Testosterone		PTH	
	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 products 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 High High Low Low Low Moderate	Vertebral fractures: alendronate, etidronate, ibandronate, risedronate and zoledronic acid reduce the risk of vertebral fractures among postmenopausal women with osteoporosis. Nonvertebral fractures: alendronate, risedronate and zoledronic acid reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis. Hip: alendronate, risedronate and zoledronic acid reduce the risk of hip fractures among postmenopausal women with osteoporosis. Wrist: alendronate reduces the risk of wrist fractures among postmenopausal women with osteoporosis. 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 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 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	Alendronate, etidronate, ibandronate, risedronate, teriparatide, and raloxifene reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis.
	Moderate	Calcitonin reduces the risk of fracture among postmenopausal women.
	High	Raloxifene prevents fractures in postmenopausal women at low risk for fracture.
	Low	Teriparatide, risedronate, and calcitonin reduce risk of fracture among men.
	High	Among subjects treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate.
	Moderate	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.
	Low	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
<p>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?</p>	Moderate	<p>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.</p>
	Moderate	<p>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.</p>
	Low	<p>There is evidence from one observational study that adherence to therapy with alendronate and risedronate is poor in many chronic glucocorticoid users.</p>
	Moderate	<p>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.</p>
	Moderate	<p>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.</p>
	High	<p>In four observational studies comparing weekly and daily bisphosphonates, weekly users had higher persistence and adherence rates.</p>
	Moderate	<p>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.</p>
	Low	<p>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.</p>

Table 68. Summary of Evidence (continued)

Key Question	Level of Evidence	Conclusion
<p>4. What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?</p>	High	<p>There were no differences among bisphosphonates, calcium, vitamin D, calcitonin, PTH, and placebo regarding serious cardiac events.</p>
	High	<p>Zoledronic acid is associated with an increased risk of atrial fibrillation relative to placebo.</p>
	High	<p>Estrogen and estrogen-progestin combination participants had higher odds of cerebrovascular accident (CVA) and thromboembolic events than did placebo participants.</p>
	High	<p>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.</p>
	Moderate	<p>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.</p>
	Moderate	<p>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.</p>
	Moderate	<p>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.</p>
	Moderate	<p>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.</p>
	Low	<p>Osteosarcoma was reported in only one study, a head-to-head trial of raloxifene vs. tamoxifen; differences between groups were not significant.</p>

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 raloxifene⁵⁵ 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 other⁵⁴ 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-analysis⁴⁷ 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 (7,316⁴⁷ and 5,383⁵⁴) 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 ≥ 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.

References

1. Christiansen C. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 1993;94(6):646-50.
2. Lindsay R. Osteoporosis. A guide to Diagnosis, Prevention, and Treatment. New York: Raven Press; 1992.
3. Chrischilles EA, Butler CD, Davis CS, et al. A model of lifetime osteoporosis impact. *Arch Intern Med* 1991;151(10):2026-32.
4. US Congress OoTA. Hip Fracture Outcomes in People Age 50 and Over-Background Paper. Washington, DC: US Government Printing Office. 1994.
5. Ray NF, Chan JK, Thamer M, et al. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res* 1997;12(1):24-35.
6. Keen RW. Burden of osteoporosis and fractures. *Curr Osteoporos Rep* 2003;1(2):66-70.
7. Sasser AC, Rousculp MD, Birnbaum HG, et al. Economic burden of osteoporosis, breast cancer, and cardiovascular disease among postmenopausal women in an employed population. *Womens Health Issues* 2005;15(3):97-108.
8. National Osteoporosis Foundation. Physicians Guide to Prevention and Treatment of Osteoporosis. Washington, D.C: National Osteoporosis Foundation; 2006.
9. World Health Organization. Assessment of fracture risk and its implication to screening for postmenopausal osteoporosis: Technical report series 843. Geneva: World Health Organization; 1994.
10. Espallargues M, Sampietro-Colom L, Estrada MD, et al. Identifying bone-mass-related risk factors for fracture to guide bone densitometry measurements: a systematic review of the literature. *Osteoporos Int* 2001;12(10):811-22.
11. Riggs BL, Khosla S, Melton LJ 3rd. Sex steroids and the construction and conservation of the adult skeleton. *Endocr Rev* 2002;23(3):279-302.
12. U.S Department of Health and Human Services. Bone Health and Osteoporosis; A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General. 2004.
13. Kanis JA, Johnell O, Oden A, et al. Smoking and fracture risk: a meta-analysis. *Osteoporos Int* 2005;16(2):155-62.
14. Kanis JA, Johansson H, Johnell O, et al. Alcohol intake as a risk factor for fracture. *Osteoporos Int* 2005;16(7):737-42.
15. Tromp AM, Pluijm SM, Smit JH, et al. Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. *J Clin Epidemiol* 2001;54(8):837-44.
16. Chu LW, Chi I, Chiu AY. Incidence and predictors of falls in the chinese elderly. *Ann Acad Med Singapore* 2005;34 (1):60-72.
17. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988;319(26):1701-7.
18. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. *J Gerontol* 1989;44(4):M112-7.
19. Institute of Medicine. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board. Washington, D.C: National Academy Press; 1997.
20. Rubenstein LZ, Powers CM, MacLean CH. Quality indicators for the management and prevention of falls and mobility problems in vulnerable elders. *Ann Intern Med* 2001;135(8 Pt 2):686-93.
21. Colman EG. The Food and Drug Administration's Osteoporosis Guidance Document: past, present, and future. *J Bone Miner Res* 2003;18(6):1125-8.
22. Muchmore DB. Raloxifene: A selective estrogen receptor modulator (SERM) with multiple target system effects. *Oncologist* 2000;5(5):388-92.
23. Wetzels GE, Nelemans P, Schouten JS, et al. Facts and fiction of poor compliance as a cause of inadequate blood pressure control: a systematic review. *J Hypertens* 2004;22(10):1849-55.
24. Caro JJ, Salas M, Speckman JL, et al. Persistence

- with treatment for hypertension in actual practice. *CMAJ* 1999;160(1):31-7.
25. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA* 1998;279(18):1458-62.
 26. Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;288(4):455-61.
 27. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Quality of Reporting of Meta-analyses. Lancet* 1999;354(9193):1896-900.
 28. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996 ;17(1):1-12.
 29. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352(9128):609-13.
 30. Fullerton DS, Atherly DS. Formularies, therapeutics, and outcomes: new opportunities. *Med Care* 2004;42(4 Suppl):III39-44.
 31. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454):1490.
 32. Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27(5):335-71.
 33. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2006.
 34. Hedges LV, Olkin I. *Statistical Methods for Meta-Analysis*. San Deigo, CA: Academic Press Inc; 1985.
 35. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60.
 36. Version 9.0. College Station, Texas: Stata Corp.; 2005.
 37. Gass M, Dawson-Hughes B. Preventing osteoporosis-related fractures: an overview. *Am J Med* 2006;119(4 Suppl 1):S3-S11 .
 38. StatXact 7 for Windows [computer program]. Version Version 7.0.1. Cambridge, MA: Cytel Software Corporation; 2005.
 39. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 2002;23(4):508-16.
 40. Karpf DB, Shapiro DR, Seeman E, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. *Alendronate Osteoporosis Treatment Study Groups. JAMA* 1997;277(14):1159-64.
 41. Cranney A, Welch V, Adachi JD, et al. Etidronate for treating and preventing postmenopausal osteoporosis. *Cochrane Database of Systematic Reviews* 2005;(3)
 42. Cranney A, Adachi JD, Homik JJEH, et al. Calcitonin for preventing and treating corticosteroid-induced osteoporosis. *Cochrane Database of Systematic Reviews* 2005;(3)
 43. Papapoulos SE, Quandt SA, Liberman UA, et al. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. *Osteoporos Int* 2005;16(5):468-74.
 44. Cranney A, Tugwell P, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev* 2002;23(4):517-23.
 45. Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. *Endocr Rev* 2002;23(4):540-51.
 46. Kanis JA, McCloskey EV. Effect of calcitonin on vertebral and other fractures. *QJM* 1999;92(3):143-9.
 47. Stevenson M, Lloyd Jones M, De Nigris E, et al. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess* 2005;9(22):1-160.
 48. Schachter HM, Clifford TJ, Cranney A, Barrowman NJ, Moher D. Raloxifene for primary and secondary prevention of osteoporotic fractures in postmenopausal women: a systematic review of efficacy and safety evidence. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment. 2005.
 49. Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII.

- Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev* 2002;23(4):552-9.
50. Papadimitropoulos E, Wells G, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocr Rev* 2002;23(4):560-9.
 51. Avenell A, Gillespie WJ, Gillespie LD, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2005;(3):CD000227.
 52. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005;293(18):2257-64.
 53. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. *BMC Musculoskelet Disord* 2001;2(1):7.
 54. Wells G, Tugwell P, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr Rev* 2002;23(4):529-39.
 55. Seeman E, Crans GG, Diez-Perez A, et al. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. *Osteoporos Int* 2006;17(2):313-6.
 56. Nguyen ND, Eisman JA, Nguyen TV. Anti-hip fracture efficacy of biophosphonates: a Bayesian analysis of clinical trials. *J Bone Miner Res* 2006;21(2):340-9.
 57. Sawka AM, Papaioannou A, Adachi JD, et al. Does alendronate reduce the risk of fracture in men? A meta-analysis incorporating prior knowledge of anti-fracture efficacy in women. *BMC Musculoskelet Disord* 2005;6:39.
 58. Richy F, Schacht E, Bruyere O, et al. Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. *Calcif Tissue Int* 2005;76(3):176-86.
 59. Palmer S, McGregor DO, Strippoli GF. Interventions for preventing bone disease in kidney transplant recipients. *Cochrane Database Syst Rev* 2005;(2):CD005015 .
 60. Miller PD, Roux C, Boonen S, et al. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 2005;20(12):2105-15.
 61. Richy F, Ethgen O, Bruyere O, et al. Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. *Osteoporos Int* 2004;15(4):301-10.
 62. Boonen S, Laan RF, Barton IP, et al. Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies. *Osteoporos Int* 2005;16(10):1291-8.
 63. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354(7):669-83.
 64. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ* 2005;330(7498):1003.
 65. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005;365(9471):1621-8.
 66. Bone HG, Greenspan SL, McKeever C, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. *J Clin Endocrinol Metab* 2000;85 (2):720-6.
 67. Greenspan SL , Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. *JAMA* 2003;289(19):2525-33.
 68. Hosking D, Adami S, Felsenberg D, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. *Current medical research and opinion* 2003;19(5):383-94.
 69. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006;354(8):821-31.
 70. Quandt SA, Thompson DE, Schneider DL, et al. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of -1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. *Mayo Clin Proc* 2005;80(3):343-9.

71. Zein CO, Jorgensen RA, Clarke B, et al. Alendronate improves bone mineral density in primary biliary cirrhosis: a randomized placebo-controlled trial. *Hepatology* 2005;42(4):762-71.
72. Sato Y, Iwamoto J, Kanoko T, et al. Alendronate and vitamin D2 for prevention of hip fracture in Parkinson's disease: A randomized controlled trial. *Mov Disord* 2006.
73. Adami S, Passeri M, Ortolani S, et al. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *Bone* 1995;17(4):383-90.
74. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 1996;348(9041):1535-41.
75. Bone HG, Downs RW Jr, Tucci JR, et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. *J Clin Endocrinol Metab* 1997;82(1):265-74.
76. Bonnick S, Rosen C, Mako B, et al. Alendronate vs calcium for treatment of osteoporosis in postmenopausal women. *Bone* 1998;23(Suppl 5):S476.
77. Chesnut CH, McClung MR, Ensrud KE, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *The American journal of medicine* 1995;99(2):144-52.
78. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280(24):2077-82.
79. Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. *Int J Clin Pract* 2001;55(8):505-9.
80. Greenspan SL, Parker RA, Ferguson L, et al. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. *J Bone Miner Res* 1998;13(9):1431-8.
81. Greenspan SL, Schneider DL, McClung MR, et al. Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial.[summary for patients in *Ann Intern Med*. 2002 May 21;136(10):154; PMID: 12020160]. *Annals of Internal Medicine* 2002;136(10): 742-6.
82. Hosking D, Chilvers CE, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med* 1998;338(8):485-92.
83. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995;333(22):1437-43.
84. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. *Annals of internal medicine* 1998;128(4):253-61.
85. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000;343(9):604-10.
86. Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Foxamax International Trial Study Group. *Osteoporos Int* 1999;9(5):461-8.
87. Ringe JD, Dorst A, Faber H, et al. Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. *Rheumatol Int* 2004;24(2):110-3.
88. Weinstein RS, Bone H, Tucci J, et al. Alendronate treatment of osteoporosis in elderly women. *J Bone Miner Res* 1994;9(Suppl 1):S144.
89. Sato Y, Kanoko T, Yasuda H, et al. Beneficial effect of etidronate therapy in immobilized hip fracture patients. *Am J Phys Med Rehabil* 2004;83(4):298-303.
90. Sato Y, Honda Y, Iwamoto J. Etidronate for fracture prevention in amyotrophic lateral sclerosis: A randomized controlled trial. *Bone* 2006.
91. Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. *Am J Med* 1998;104(3):219-26.

92. Campbell IA, Douglas JG, Francis RM, et al. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. *Thorax* 2004;59(9):761-8.
93. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. *The American Journal of Medicine* 2004;117(8):549-55.
94. Sato S, Ohosone Y, Suwa A, et al. Effect of intermittent cyclical etidronate therapy on corticosteroid induced osteoporosis in Japanese patients with connective tissue disease: 3 year followup. *J Rheumatol* 2003;30(12):2673-9.
95. Herd RJ, Balena R, Blake GM, et al. The prevention of early postmenopausal bone loss by cyclical etidronate therapy: a 2-year, double-blind, placebo-controlled study. *Am J Med* 1997;103(2):92-9.
96. Iwamoto J TTIS. Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate. *Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association* 2001;6(6):487-92.
97. Lyritis GP, Tsakalagos N, Paspatis I, et al. The effect of a modified etidronate cyclical regimen on postmenopausal osteoporosis: a four-year study. *Clin Rheumatol* 1997;16(4):354-60.
98. Meunier PJ, Confavreux E, Tupinon I, et al. Prevention of early postmenopausal bone loss with cyclical etidronate therapy (a double-blind, placebo-controlled study and 1-year follow-up). *J Clin Endocrinol Metab* 1997;82(9):2784-91.
99. Montessori ML, Scheele WH, Netelenbos JC, et al. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 1997;7(1):52-8.
100. Pacifici R, McMurtry C, Vered I, et al. Coherence therapy does not prevent axial bone loss in osteoporotic women: a preliminary comparative study. *J Clin Endocrinol Metab* 1988;66(4):747-53.
101. Pouilles JM, Tremollieres F, Roux C, et al. Effects of cyclical etidronate therapy on bone loss in early postmenopausal women who are not undergoing hormonal replacement therapy. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 1997;7(3):213-8.
102. Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990;322(18):1265-71.
103. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990; 323(2):73-9.
104. Ravn P, Clemmesen B, Riis BJ, et al. The effect on bone mass and bone markers of different doses of ibandronate: a new bisphosphonate for prevention and treatment of postmenopausal osteoporosis: a 1-year, randomized, double-blind, placebo-controlled dose-finding study. *Bone* 1996;19(5):527-33.
105. Chesnut III CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2004;19(8):1241-9.
106. Recker R, Stakkestad JA, Chesnut CH 3rd, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. *Bone* 2004;34(5):890-9.
107. Grotz W, Nagel C, Poeschel D, et al. Effect of ibandronate on bone loss and renal function after kidney transplantation. *Journal of the American Society of Nephrology : JASN* 2001;12(7):1530-7.
108. Jiang Y, Zhao JJ, Mitlak BH, et al. Recombinant human parathyroid hormone (1-34) teriparatide improves both cortical and cancellous bone structure. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2003;18(11):1932-41.
109. Kim SH, Lim SK, Hahn JS. Effect of pamidronate on new vertebral fractures and bone mineral density in patients with malignant lymphoma receiving chemotherapy. *The American journal of medicine* 2004;116(8):524-8.
110. Ninkovic M, Love S, Tom BD, et al. Lack of effect of intravenous pamidronate on fracture incidence and bone mineral density after orthotopic liver transplantation. *J Hepatol* 2002;37(1):93-100.
111. Aris RM, Lester GE, Renner JB, et al. Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. *American journal of respiratory and critical care medicine* 2000;162(3 Pt 1):941-6.

112. Reid IR, Wattie DJ, Evans MC, et al. Continuous therapy with pamidronate, a potent bisphosphonate, in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 1994;79(6):1595-9.
113. Kananen K, Volin L, Laitinen K, et al. Prevention of bone loss after allogeneic stem cell transplantation by calcium, vitamin D, and sex hormone replacement with or without pamidronate. *J Clin Endocrinol Metab* 2005;90(7):3877-85.
114. Coco M, Glicklich D, Faugere MC, et al. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. *Journal of the American Society of Nephrology : JASN* 2003;14(10):2669-76.
115. Watts NB, Josse RG, Hamdy RC, et al. Risedronate prevents new vertebral fractures in postmenopausal women at high risk. *J Clin Endocrinol Metab* 2003;88(2):542-9.
116. Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int* 2000;67(4): 277-85.
117. Sorensen OH, Crawford GM, Mulder H, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003;32(2):120-6.
118. Sato Y, Kanoko T, Satoh K, et al. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. *Arch Intern Med* 2005;165(15):1737-42.
119. Sato Y, Iwamoto J, Kanoko T, et al. Risedronate therapy for prevention of hip fracture after stroke in elderly women. *Neurology* 2005;64(5):811-6.
120. Palomba S, Orio F Jr, Manguso F, et al. Efficacy of risedronate administration in osteoporotic postmenopausal women affected by inflammatory bowel disease. *Osteoporos Int* 2005;16(9):1141-9.
121. Hooper MJ, Ebeling PR, Roberts AP, et al. Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. *Climacteric* 2005;8(3):251-62.
122. Greenspan SL, Bhattacharya RK, Sereika SM, et al. Prevention of Bone Loss in Survivors of Breast Cancer: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *J Clin Endocrinol Metab* 2006.
123. Milgrom C, Finestone A, Novack V, et al. The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits. *Bone* 2004;35(2):418-24.
124. Sato Y, Iwamoto J, Kanoko T, et al. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. *Arch Intern Med* 2005;165(15):1743-8.
125. Kanaji A, Higashi M, Namisato M, et al. Effects of risedronate on lumbar bone mineral density, bone resorption, and incidence of vertebral fracture in elderly male patients with leprosy. *Lepr Rev* 2006;77(2):147-53.
126. Kishimoto H, Fukunaga M, Kushida K, et al. Efficacy and tolerability of once-weekly administration of 17.5 mg risedronate in Japanese patients with involutinal osteoporosis: a comparison with 2.5-mg once-daily dosage regimen. *J Bone Miner Metab* 2006;24(5):405-13.
127. Harris ST, Watts NB, Li Z, et al. Two-year efficacy and tolerability of risedronate once a week for the treatment of women with postmenopausal osteoporosis. *Curr Med Res Opin* 2004;20(5):757-64.
128. Brown JP, Kendler DL, McClung MR, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcif Tissue Int* 2002;71(2):103-11.
129. Clemmesen B, Ravn P, Zegels B, et al. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. *Osteoporos Int* 1997;7(5):488-95.
130. Fogelman I, Ribot C, Smith R, et al. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. *J Clin Endocrinol Metab* 2000;85(5):1895-900.
131. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 1999;282(14):1344-52.
132. McClung M, Bensen W, Bolognese M, et al. Risedronate increases bone mineral density at the hip, spine and radius in postmenopausal women with low bone mass. *Osteoporosis International* 1998;8(Suppl 3):111.
133. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001;344(5):333-40.

134. Mortensen L, Charles P, Bekker PJ, et al. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab* 1998;83 (2):396-402.
135. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int* 2000;11(1):83-91.
136. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. *J Bone Miner Res* 2000;15(6):1006-13.
137. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 1999;42(11):2309-18.
138. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med* 2002;346(9):653-61.
139. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356(18):1809-22.
140. Trovas GP, Lyritis GP, Galanos A, et al. A randomized trial of nasal spray salmon calcitonin in men with idiopathic osteoporosis: effects on bone mineral density and bone markers. *J Bone Miner Res* 2002;17(3):521-7.
141. Ushiroyama T, Ikeda A, Sakai M, et al. Effects of the combined use of calcitonin and 1 alpha-hydroxycholecalciferol on vertebral bone loss and bone turnover in women with postmenopausal osteopenia and osteoporosis: a prospective study of long-term and continuous administration with low dose calcitonin. *Maturitas* 2001;40(3):229-38.
142. Toth E, Csupor E, Meszaros S, et al. The effect of intranasal salmon calcitonin therapy on bone mineral density in idiopathic male osteoporosis without vertebral fractures--an open label study. *Bone* 2005;36(1):47-51.
143. Hay JE, Malinchoc M, Dickson ER. A controlled trial of calcitonin therapy for the prevention of post-liver transplantation atraumatic fractures in patients with primary biliary cirrhosis and primary sclerosing cholangitis. *J Hepatol* 2001;34(2):292-8.
144. Arnala I, Saastamoinen J, Alhava EM. Salmon calcitonin in the prevention of bone loss at perimenopause. *Bone* 1996;18(6):629-32.
145. Agrawal R, Wallach S, Cohn S, et al. Calcitonin treatment in osteoporosis. In: *Calcitonin 1980. Proceedings of an international symposium held in Milan, October 1980.* Excerpta Medica 1980;237-46.
146. Chesnut CH 3rd, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med* 2000;109(4):267-76.
147. Gennari C, Chierichetti SM, Bigazzi S, et al. Comparative effects on bone mineral content of calcium and calcium plus salmon calcitonin given in two different regimens in postmenopausal osteoporosis. *Curr 1985;THER. RES., CLIN. EXP.* 38(3):455-464.
148. Grotz WH, Rump LC, Niessen A, et al. Treatment of osteopenia and osteoporosis after kidney transplantation. *Transplantation* 1998;66(8):1004-8.
149. Gruber HE, Ivey JL, Baylink DJ, et al. Long-term calcitonin therapy in postmenopausal osteoporosis. *Metabolism* 1984;33(4):295-303.
150. Healey JH, Paget SA, Williams-Russo P, et al. A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. *Calcif Tissue Int* 1996;58(2):73-80.
151. Hizmetli S, Elden H, Kaptanoglu E, et al. The effect of different doses of calcitonin on bone mineral density and fracture risk in postmenopausal osteoporosis. *Int J Clin Pract* 1998;52(7):453-5.
152. Luengo M, Pons F, Martinez de Osaba MJ, et al. Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy for asthma: a two year follow up study. *Thorax* 1994;49(11):1099-102.
153. Nordal KP, Halse J, Dahl E. The effect of nasal calcitonin on bone mineral density in renal transplant recipients. 1996;
154. Overgaard K, Hansen MA, Jensen SB, et al. Effect of salmon calcitonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. *BMJ* 1992;305(6853):556-61.
155. Peyron R, Serrurier D, Edouard C, Ghozlan R, Mayoux-Benhamon A, Meunier PJ. Treatment of high remodelling vertebral osteoporosis with human

- calcitonin: a two year double-blind placebo-controlled trial in 93 patients. In: Christiansen C, Overgaard Ke. Osteoporosis. Copenhagen: Osteopress; 1990. p. 1430-3.
156. Rico H, Hernandez ER, Revilla M, et al. Salmon calcitonin reduces vertebral fracture rate in postmenopausal crush fracture syndrome. *Bone Miner* 1992;16(2):131-8.
 157. Rico H, Revilla M, Hernandez ER, et al. Total and regional bone mineral content and fracture rate in postmenopausal osteoporosis treated with salmon calcitonin: a prospective study. *Calcif Tissue Int* 1995;56(3):181-5.
 158. Ringe JD. [Treatment of primary osteoporosis with calcium and salmon calcitonin]. *Deutsche medizinische Wochenschrift* 1990;115(31-32):1176-82.
 159. Ringe JD, Welzel D. Salmon calcitonin in the therapy of corticoid-induced osteoporosis. *European journal of clinical pharmacology* 1987;33(1):35-9.
 160. Sambrook P, Birmingham J, Kelly P. Prevention of corticosteroid-induced osteoporosis. *NEJM* 1993;328(24):1747-52.
 161. Stock JL, Avioli LV, Baylink DJ. Calcitonin-salmon nasal spray reduces the incidence of new vertebral fractures in post-menopausal women: three-year interim results of the PROOF study. *J Bone Miner Res* 1997;12(suppl 1):S149.
 162. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001;285(22):2891-7.
 163. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003;290(13):1729-38.
 164. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321-33.
 165. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291(14):1701-12.
 166. Reid IR, Eastell R, Fogelman I, et al. A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. *Arch Intern Med* 2004;164(8):871-9.
 167. Aitken JM, Hart DM, Lindsay R. Oestrogen replacement therapy for prevention of osteoporosis after oophorectomy. *Br Med J* 1973;3(5879): 515-8.
 168. Alexandersen P, Riis BJ, Christiansen C. Monofluorophosphate combined with hormone replacement therapy induces a synergistic effect on bone mass by dissociating bone formation and resorption in postmenopausal women: a randomized study. *J Clin Endocrinol Metab* 1999;84 (9):3013-20.
 169. Bjarnason NH, Byrjalsen I, Hassager C, et al. Low doses of estradiol in combination with gestodene to prevent early postmenopausal bone loss. *Am J Obstet Gynecol* 2000;183(3):550-60.
 170. Cauley JA, Black DM, Barrett-Connor E, et al. Effects of hormone replacement therapy on clinical fractures and height loss: The Heart and Estrogen/Progestin Replacement Study (HERS). *Am J Med* 2001;110(6):442-50.
 171. Cheng S, Sipila S, Puolakka H, et al. Effects of hormone replacement therapy and high impact physical exercise on bone/muscle ratio in postmenopausal women. *Osteoporos Int* 2000;11(suppl 2):175.
 172. Delmas PD, Confavreux E, Garnero P, et al. A combination of low doses of 17 beta-estradiol and norethisterone acetate prevents bone loss and normalizes bone turnover in postmenopausal women. *Osteoporos Int* 2000;11(2):177-87.
 173. Eiken P, Nielsen SP, Kolthoff N. Effects on bone mass after eight years of hormonal replacement therapy. *Br J Obstet Gynaecol* 1997;104(6):702-7.
 174. Gallagher JC, Fowler SE, Detter JR, et al. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab* 2001;86(8):3618-28.
 175. Genant HK, Lucas J, Weiss S, et al. Low-dose esterified estrogen therapy: effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. *Estratab/Osteoporosis Study Group. Arch Intern Med* 1997;157(22):2609-15.
 176. Greenspan S, Bankhurst A, Bell N. Effects of alendronate and estrogen alone and in combination on bone mass and turnover in postmenopausal osteoporosis. *J Bone Miner Res* 1998;S174 (Abstract 1107).
 177. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of

- coronary-artery atherosclerosis. *N Engl J Med* 2000 ;343(8):522-9.
178. Hully S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-13.
 179. Ishida Y, Soh H, Tsuchida M, et al. Comparison of the effectiveness of hormone replacement therapy, bisphosphonate, calcitonin, vitamin D and vitamin K in postmenopausal . *Bone* 2001;28(Suppl 1):S224.
 180. Komulainen M, Tuppurainen MT, Kroger H, et al. Vitamin D and HRT: no benefit additional to that of HRT alone in prevention of bone loss in early postmenopausal women. A 2.5-year randomized placebo-controlled study. *Osteoporosis Int* 1997;7:126-32.
 181. Komulainen MH, Kroger H, Tuppurainen MT, et al. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. *Maturitas* 1998;31(1):45-54.
 182. Lees B, Stevenson JC. The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17 beta and dydrogesterone. *Osteoporosis Int* 2001;12(4):251-8.
 183. Lindsay R, Tohme JF. Estrogen treatment of patients with established postmenopausal osteoporosis. *Obstet Gynecol* 1990;76(2):290-5.
 184. Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;117(1):1-9.
 185. Mosekilde L, Beck-Nielsen H, Sorensen OH, et al. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women - results of the Danish Osteoporosis Prevention Study. *Maturitas* 2000;36(3):181-93.
 186. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *Alzheimer's Disease Cooperative Study*. *JAMA* 2000;283(8):1007-15.
 187. Nachtigall LE, Nachtigall RH, Nachtigall RD, et al. Estrogen replacement therapy I: a 10-year prospective study in the relationship to osteoporosis. *Obstet Gynecol* 1979;53(3):277-81.
 188. Orr-Walker BJ, Evans MC, Clearwater JM, et al. Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women. *Arch Intern Med* 2000;160(14):2161-6.
 189. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. The Writing Group for the PEPI. *JAMA* 1996;276(17):1389-96.
 190. Ravn P, Bidstrup M, Wasnich RD, et al. Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study. A randomized, controlled trial. *Annals of internal medicine* 1999;131(12):935-42.
 191. Recker RR, Davies KM, Dowd RM, et al. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. *Ann Intern Med* 1999; 130(11):897-904.
 192. Stevenson JC, Lees B. Bone conserving effects of oestrogen are dose-dependent for age and time since menopause. *Osteoporosis Int* 2000;11(Suppl 1):25.
 193. Weiss SR, Ellman H, Dolker M. A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. *Transdermal Estradiol Investigator Group*. *Obstet Gynecol* 1999;94(3):330-6.
 194. Gallagher JC, Genant HK, Crans GG, et al. Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. *The Journal of clinical endocrinology and metabolism* 2005;90(3):1583-7.
 195. Orwoll ES, Scheele WH, Paul S. The effects of teriparatide[human parathyroid hormone(1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003;18:9-17.
 196. Kaufman JM, Orwoll E, Goemaere S, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporosis Int* 2005;16(5):510-6.
 197. Cosman F, Nieves J, Woelfert L, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 2001;16(5):925-31.
 198. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344(19):1434-41.
 199. Barrett-Connor E, Mosca L, Collins P, et al. Effects

- of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006 ;355(2):125-37.
200. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999;282(7):637-45.
 201. Jolly EE, Bjarnason NH, Neven P, et al. Prevention of osteoporosis and uterine effects in postmenopausal women taking raloxifene for 5 years. *Menopause* 2003;10(4):337-44.
 202. Lufkin EG, Whitaker MD, Nickelsen T, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res* 1998;13(11):1747-54.
 203. Morii H, Ohashi Y, Taketani Y, et al. Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. *Osteoporos Int* 2003;14(10):793-800.
 204. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90(18):1371-88.
 205. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int* 1994;4(5):245-52.
 206. Prince RL, Devine A, Dhaliwal SS, et al. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med* 2006;166(8):869-75.
 207. Reid IR, Mason B, Horne A, et al. Randomized controlled trial of calcium in healthy older women. *Am J Med* 2006;119(9):777-85.
 208. Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. *Calcif Tissue Int* 1987;40(6):315-7.
 209. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* 1996;11(12):1961-6.
 210. Reid IR, Ames RW, Evans MC, et al. Effect of calcium supplementation on bone loss in postmenopausal women. *N Engl J Med* 1993;328(7):460-4.
 211. Riggs BL, O'Fallon WM, Muhs J, et al. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *J Bone Miner Res* 1998;13(2):168-74.
 212. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. *JAMA* 2002;288(7):872-81.
 213. Torres A, Garcia S, Gomez A, et al. Treatment with intermittent calcitriol and calcium reduces bone loss after renal transplantation. *Kidney Int* 2004;65(2):705-12.
 214. Sato Y IJKTSK. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis* 2005;20(3):187-92.
 215. Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year followup. *J Rheumatol* 1996;23(6):995-1000.
 216. Aloia JF, Vaswani A, Ellis K, et al. A model for involutional bone loss. *J Lab Clin Med* 1985;106(6):630-7.
 217. Avenell A, Grant AM, McGee M, et al. The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. *Clin Trials* 2004;1(6):490-8.
 218. Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. *Osteoporos Int* 1998;8(3):255-60.
 219. Caniggia A, Delling G, Nuti R, et al. Clinical, biochemical and histological results of a double-blind trial with 1,25-dihydroxyvitamin D3, estradiol and placebo in post-menopausal osteoporosis. *Acta Vitaminol Enzymol* 1984;6(2):117-28.
 220. Chapuy MC, Arlot ME, Delmas PD, et al. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *BMJ* 1994;308(6936):1081-2.
 221. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 1992;327(23):1637-42.

222. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalys II study. *Osteoporos Int* 2002;13(3):257-64.
223. Dawson-Hughes B, Harris SS, Krall EA, et al. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997;337(10):670-6.
224. Dukas L, Bischoff HA, Lindpaintner LS, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. *J Am Geriatr Soc* 2004;52(2):230-6.
225. Ebeling PR, Russell RG. Teriparatide (rhPTH 1-34) for the treatment of osteoporosis. *Int J Clin Pract* 2003;57 (8):710-8.
226. Gallagher JC, Riggs BL, Recker RR, et al. The effect of calcitriol on patients with postmenopausal osteoporosis with special reference to fracture frequency. *Proc Soc Exp Biol Med* 1989;191(3):287-92.
227. Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol. A randomized controlled study. *Ann Intern Med* 1990;113(9):649-55.
228. Gorai I, Chaki O, Taguchi Y, et al. Early postmenopausal bone loss is prevented by estrogen and partially by 1alpha-OH-vitamin D3: therapeutic effects of estrogen and/or 1alpha-OH-vitamin D3. *Calcif Tissue Int* 1999;65(1):16-22.
229. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005;365(9471):1621-8.
230. Geusens P, Dequeker J. Long-term effect of nandrolone decanoate, 1 alpha-hydroxyvitamin D3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: a double-blind controlled study. *Bone Miner* 1986;1(4):347-57.
231. Harwood RH, Sahota O, Gaynor K, et al. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. *Age Ageing* 2004;33(1):45-51.
232. Hayashi Y, Fujita T, Inoue T. Decrease of vertebral fracture in osteoporotics by administration of 1 α -hydroxy-vitamin D₃. *Journal of Bone and Mineral Metabolism* 1992;10(2):50-4.
233. Lips P, Graafmans WC, Ooms ME, et al. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996;124(4):400-6.
234. Menczel J, Foldes J, Steinberg R, et al. Alfacalcidol (alpha D3) and calcium in osteoporosis. *Clin Orthop Relat Res* 1994;(300):241-7.
235. Meyer HE, Smedshaug GB, Kvaavik E, et al. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. *J Bone Miner Res* 2002;17(4):709-15.
236. Orimo H, Shiraki M, Hayashi T, et al. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D₃. *Bone Miner* 1987;3(1):47-52.
237. Orimo H, Shiraki M, Hayashi Y, et al. Effects of 1 alpha-hydroxyvitamin D₃ on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. *Calcif Tissue Int* 1994;54(5):370-6.
238. Ott SM, Chesnut CH 3rd. Calcitriol treatment is not effective in postmenopausal osteoporosis. *Ann Intern Med* 1989;110(4):267-74.
239. Peacock M, Liu G, Carey M, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab* 2000;85(9):3011-9.
240. Pfeifer M, Begerow B, Minne HW, et al. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res* 2000;15 (6):1113-8.
241. Sambrook P, Henderson NK, Keogh A, et al. Effect of calcitriol on bone loss after cardiac or lung transplantation. *J Bone Miner Res* 2000;15(9):1818-24.
242. Sato Y, Maruoka H, Oizumi K. Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1 alpha-hydroxyvitamin D₃ and calcium supplementation. *Stroke* 1997;28(4):736-9.
243. Sato Y, Manabe S, Kuno H, et al. Amelioration of osteopenia and hypovitaminosis D by 1alpha-hydroxyvitamin D₃ in elderly patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999;66(1):64-8.
244. Sato Y, Kuno H, Kaji M, et al. Effect of ipriflavone

- on bone in elderly hemiplegic stroke patients with hypovitaminosis D. *Am J Phys Med Rehabil* 1999;78(5):457-63.
245. Shikari M, Kushida K, Yamazaki K, et al. Effects of 2 years' treatment of osteoporosis with 1 alpha-hydroxy vitamin D3 on bone mineral density and incidence of fracture: a placebo-controlled, double-blind prospective study. *Endocr J* 1996;43(2):211-20.
 246. Smith H, Anderson F, Raphael H, et al. Effect of annual intramuscular vitamin D supplementation on fracture risk: population-based, randomised, double-blind, placebo-controlled trial [abstract]. *Osteoporosis International* 2004;15(1):S8.
 247. Stempfle HU, Werner C, Echtler S, et al. Prevention of osteoporosis after cardiac transplantation: a prospective, longitudinal, randomized, double-blind trial with calcitriol. *Transplantation* 1999;68(4):523-30.
 248. Tilyard MW, Spears GF, Thomson J, et al. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992;326(6):357-62.
 249. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003;326(7387):469.
 250. Kushida K, Fukunaga M, Kishimoto H, et al. A comparison of incidences of vertebral fracture in Japanese patients with involutional osteoporosis treated with risedronate and etidronate: a randomized, double-masked trial. *Journal of Bone and Mineral Metabolism* 2004;22(5):469-78.
 251. Fukunaga M, Kushida K, Kishimoto H, et al. A comparison of the effect of risedronate and etidronate on lumbar bone mineral density in Japanese patients with osteoporosis: a randomized controlled trial. *Osteoporos Int* 2002;13(12):971-9.
 252. Guanabens N PARIALPFCLMAMdOMRMPPRJ. Alendronate is more effective than etidronate for increasing bone mass in osteopenic patients with primary biliary cirrhosis. *The American journal of gastroenterology* 2003;98(10):2268-74.
 253. Iwamoto J, Takeda T, Ichimura S, et al. Comparative effects of treatment with etidronate and alendronate on bone resorption, back pain, and activities of daily living in elderly women with vertebral fractures. *Keio J Med* 2003;52(4):230-5.
 254. Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res* 2005;20(1):141-51.
 255. Muscoso E, Puglisi N, Mamazza C, et al. Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study. *Eur Rev Med Pharmacol Sci* 2004;8(2):97-102.
 256. Tauchmanova L, De Simone G, Musella T, et al. Effects of various antiresorptive treatments on bone mineral density in hypogonadal young women after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2006;37(1):81-8.
 257. Bonnick S, Saag KG, Kiel DP, et al. Comparison of Weekly Treatment of Postmenopausal Osteoporosis with Alendronate versus Risedronate Over Two Years. *J Clin Endocrinol Metab* 2006.
 258. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *Jama* 2006;295(23):2727-41.
 259. Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide. *J Clin Endocrinol Metab* 2002;87(10):4528-35.
 260. Luckey M, Kagan R, Greenspan S, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. *Menopause* 2004;11(4):405-15.
 261. Garcia-Delgado I PSG-FLRERJHF . Calcitonin, etidronate, and calcidiol treatment in bone loss after cardiac transplantation. *Calcified tissue international* 1997;60(2):155-9.
 262. 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* 2006.
 263. Boutsen Y, Jamart J, Esselinckx W, et al. Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. *Calcif Tissue Int* 1997;61(4):266-71.
 264. Uchida S, Taniguchi T, Shimizu T, et al. Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: a double-blind, randomized study. *J Bone Miner Metab* 2005;23(5):382-8.

265. de Nijs RN, Jacobs JW, Algra A, et al. Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D3 analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies. *Osteoporos Int* 2004;15(8):589-602.
266. Bianda T LAJGBHSHKWSC. Prevention of osteoporosis in heart transplant recipients: a comparison of calcitriol with calcitonin and pamidronate. *Calcified tissue international* 2000;67(2):116-21.
267. Henderson K, Eisman J, Keogh A, et al. Protective effect of short-term calcitriol or cyclical etidronate on bone loss after cardiac or lung transplantation. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2001;16(3):565-71.
268. Ringe JD, Dorst A, Faber H, et al. Three-monthly ibandronate bolus injection offers favourable tolerability and sustained efficacy advantage over two years in established corticosteroid-induced osteoporosis. *Rheumatology (Oxford)* 2003;42(6):743-9.
269. Sambrook PN, Kotowicz M, Nash P, et al. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. *J Bone Miner Res* 2003;18(5):919-24.
270. Van Cleemput J, Daenen W, Geusens P, et al. Prevention of bone loss in cardiac transplant recipients. A comparison of bisphosphonates and vitamin D. *Transplantation* 1996;61(10):1495-9.
271. Blair MM, Carson DS, Barrington R. Bisphosphonates in the prevention and treatment of glucocorticoid-induced osteoporosis. *J Fam Pract* 2000;49(9):839-48.
272. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum* 2001;44(1):202-11.
273. Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int* 2000;67(4):277-85.
274. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;337(6):382-7.
275. Roux C, Oriente P, Laan R, et al. Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. *Ciblos Study Group. J Clin Endocrinol Metab* 1998;83(4):1128-33.
276. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med* 1998;339(5):292-9.
277. Jencen D, Reid D, Devogelaer JP, et al. Risedronate is safe and well tolerated in treating corticosteroid-induced osteoporosis. 2nd Meeting of the ASBMR-IBMS; San Francisco, CA. *Marathon Multimedia*.
278. Skingle SJ, Moore DJ, Crisp AJ. Cyclical etidronate increases lumbar spine bone density in patients on long-term glucocorticosteroid therapy. *Int J Clin Pract* 1997;51(6):364-7.
279. Jenkins EA, Walker-Bone KE, Wood A, et al. The prevention of corticosteroid-induced bone loss with intermittent cyclical etidronate. *Scandinavian journal of rheumatology* 1999;28(3):152-6.
280. Geusens P, Dequeker J, Vanhoof J, et al. Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study. *Ann Rheum Dis* 1998;57(12):724-7.
281. Cortet B, Hachulla E, Barton I, et al. Evaluation of the efficacy of etidronate therapy in preventing glucocorticoid-induced bone loss in patients with inflammatory rheumatic diseases. A randomized study. *Rev Rhum Engl Ed* 1999;66(4):214-9.
282. Chapurlat RD, Palermo L, Ramsay P, et al. Risk of fracture among women who lose bone density during treatment with alendronate. *The Fracture Intervention Trial. Osteoporos Int* 2005;16(7):842-8.
283. Agrawal S, Krueger DC, Engelke JA, et al. Between-meal risedronate does not alter bone turnover in nursing home residents. *J Am Geriatr Soc* 2006;54(5):790-5.
284. Caro JJ, Ishak KJ, Huybrechts KF, et al. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int* 2004;15(12):1003-8.
285. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc* 2006;81(8):1013-22.
286. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its

- consequences in a managed care population. *Bone* 2006;38(6):922-8.
287. Faulkner DL, Young C, Hutchins D, et al. Patient noncompliance with hormone replacement therapy: a nationwide estimate using a large prescription claims database. *Menopause* 1998;5(4):226-9.
 288. Weycker D, Macarios D, Edelsberg J, et al. Compliance with drug therapy for postmenopausal osteoporosis. *Osteoporos Int* 2006.
 289. de Lusignan S, van Vlymen J, Hague N, et al. Using computers to identify non-compliant people at increased risk of osteoporotic fractures in general practice: a cross-sectional study. *Osteoporos Int* 2006.
 290. Unson CG, Litt M, Reisine S, et al. Adherence to calcium/vitamin D and estrogen protocols among diverse older participants enrolled in a clinical trial. *Contemp Clin Trials* 2006;27(3):215-26.
 291. Downey TW, Foltz SH, Boccuzzi SJ, et al. Adherence and persistence associated with the pharmacologic treatment of osteoporosis in a managed care setting. *South Med J* 2006;99(6):570-5.
 292. Curtis JR, Westfall AO, Allison JJ, et al. Channeling and adherence with alendronate and risedronate among chronic glucocorticoid users. *Osteoporos Int* 2006.
 293. Turbi C, Herrero-Beaumont G, Acebes JC, et al. Compliance and satisfaction with raloxifene versus alendronate for the treatment of postmenopausal osteoporosis in clinical practice: An open-label, prospective, nonrandomized, observational study. *Clin Ther* 2004;26(2):245-56.
 294. Hodsman AB, Lindsay R. Effects of 1-84 PTH over 1 year. *J Clin Endocrinol Metab* 2003.
 295. Mersfelder T, Armitstead JA, Ivey MF, et al. A medication use evaluation of alendronate: compliance with administration guidelines. *Pharm Pract Manag Q* 1999;18(4):50-8.
 296. Tosteson AN, Grove MR, Hammond CS, et al. Early discontinuation of treatment for osteoporosis. *Am J Med* 2003;115(3):209-16.
 297. Rossini M, Bianchi G, Di Munno O, et al. Determinants of adherence to osteoporosis treatment in clinical practice. *Osteoporos Int* 2006;17(6):914-21.
 298. Segal E, Tamir A, Ish-Shalom S. Compliance of osteoporotic patients with different treatment regimens. *Isr Med Assoc J* 2003;5(12):859-62.
 299. Buist DS, LaCroix AZ, Black DM, et al. Inclusion of older women in randomized clinical trials: factors associated with taking study medication in the fracture intervention trial. *J Am Geriatr Soc* 2000;48(9):1126-31.
 300. Lo JC, Pressman AR, Omar MA, et al. Persistence with weekly alendronate therapy among postmenopausal women. *Osteoporos Int* 2006;17(6):922-8.
 301. Steel SA, Albertazzi P, Howarth EM, et al. Factors affecting long-term adherence to hormone replacement therapy after screening for osteoporosis. *Climacteric* 2003;6(2):96-103.
 302. Papaioannou A, Ioannidis G, Adachi JD, et al. Adherence to bisphosphonates and hormone replacement therapy in a tertiary care setting of patients in the CANDOO database. *Osteoporos Int* 2003;14 (10):808-13.
 303. Solomon DH, Avorn J, Katz JN, et al. Compliance with osteoporosis medications. *Arch Intern Med* 2005;165(20):2414-9.
 304. Reynolds RF, Obermeyer CM, Walker AM, et al. The role of treatment intentions and concerns about side effects in women's decision to discontinue postmenopausal hormone therapy. *Maturitas* 2002;43 (3):183-94.
 305. Unson CG, Siccione E, Gaztambide J, et al. Nonadherence and osteoporosis treatment preferences of older women: a qualitative study. *J Womens Health (Larchmt)* 2003;12(10):1037-45.
 306. Barrett-Connor E, Espeland MA, Greendale GA, et al. Postmenopausal hormone use following a 3-year randomized clinical trial. *J Womens Health Gend Based Med* 2000;9(6):633-43.
 307. Finley C, Gregg EW, Solomon LJ, et al. Disparities in hormone replacement therapy use by socioeconomic status in a primary care population. *J Community Health* 2001;26(1):39-50.
 308. Karakoc B, Erenus M. Compliance considerations with hormone replacement therapy. *Menopause* 1998;5(2):102-6.
 309. Carr AJ, Thompson PW, Cooper C. Factors associated with adherence and persistence to bisphosphonate therapy in osteoporosis: a cross-sectional survey. *Osteoporos Int* 2006.
 310. Weiss M, Vered I, Foldes AJ, et al. Treatment preference and tolerability with alendronate once weekly over a 3-month period: an Israeli multi-center study. *Aging Clin Exp Res* 2005;17(2):143-9.

311. Simon JA, Lewiecki EM, Smith ME, et al. Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. *Clin Ther* 2002;24(11):1871-86.
312. Cramer JA, Amonkar MM, Hebborn A, et al. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin* 2005;21(9):1453-60.
313. Brankin E, Walker M, Lynch N, et al. The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases. *Curr Med Res Opin* 2006;22(7):1249-56.
314. Recker RR, Gallagher R, MacCosbe PE. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. *Mayo Clin Proc* 2005;80(7):856-61.
315. Cooper A, Drake J, Brankin E. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. *Int J Clin Pract* 2006;60(8):896-905.
316. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* 1995;273(3):199-208.
317. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. *J Clin Endocrinol Metab* 2004;89(3):1117-23.
318. Chailurkit LO, Jongjaroenprasert W, Rungbunnapun S, et al. Effect of alendronate on bone mineral density and bone turnover in Thai postmenopausal osteoporosis. *Journal of bone and mineral metabolism* 2003;21(6):421-7.
319. Palomba S, Orio F Jr, Colao A, et al. Effect of estrogen replacement plus low-dose alendronate treatment on bone density in surgically postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;87(4):1502-8.
320. Adami S, Baroni MC, Brogini M, et al. Treatment of postmenopausal osteoporosis with continuous daily oral alendronate in comparison with either placebo or intranasal salmon calcitonin. *Osteoporos Int* 1993;3 Suppl 3:S21-7.
321. Storm T, Kollerup G, Thamsborg G, et al. Five years of clinical experience with intermittent cyclical etidronate for postmenopausal osteoporosis. *J Rheumatol* 1996;23(9):1560-4.
322. Zegels B, Eastell R, Russell RG, et al. Effect of high doses of oral risedronate (20 mg/day) on serum parathyroid hormone levels and urinary collagen cross-link excretion in postmenopausal women with spinal osteoporosis. *Bone* 2001;28(1):108-12.
323. Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. *N Engl J Med* 2007;356(18):1895-6.
324. Ryan PJ, Blake GM, Davie M, et al. Intermittent oral disodium pamidronate in established osteoporosis: a 2 year double-masked placebo-controlled study of efficacy and safety. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 2000;11(2):171-6.
325. Michalska D, Stepan JJ, Basson BR, et al. The effect of raloxifene after discontinuation of long-term alendronate treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2006;91(3):870-7.
326. Heath DA, Bullivant BG, Boiven C, et al. The effects of cyclical etidronate on early postmenopausal bone loss: an open, randomized controlled study. *J Clin Densitom* 2000;3(1):27-33.
327. Brumsen C, Papapoulos SE, Lips P, et al. Daily oral pamidronate in women and men with osteoporosis: a 3-year randomized placebo-controlled clinical trial with a 2-year open extension. *J Bone Miner Res* 2002;17(6):1057-64.
328. van Staa T, Abenhaim L, Cooper C. Upper gastrointestinal adverse events and cyclical etidronate. *Am J Med* 1997;103(6):462-7.
329. Sato Y, Asoh T, Kaji M, et al. Beneficial effect of intermittent cyclical etidronate therapy in hemiplegic patients following an acute stroke. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2000;15(12):2487-94.
330. McClung MR, Wasnich RD, Recker R, et al. Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. *J Bone Miner Res* 2004;19(1):11-8.
331. Adami S, Bruni V, Bianchini D, et al. Prevention of early postmenopausal bone loss with cyclical etidronate. *J Endocrinol Invest* 2000;23(5):310-6.
332. Pitt P, Li F, Todd P, et al. A double blind placebo controlled study to determine the effects of

- intermittent cyclical etidronate on bone mineral density in patients on long-term oral corticosteroid treatment. *Thorax* 1998;53(5):351-6.
333. Silberstein EB, Schnur W. Cyclic oral phosphate and etidronate increase femoral and lumbar bone mineral density and reduce lumbar spine fracture rate over three years. *J Nucl Med* 1992;33(1):1-5.
 334. Geusens P, Vanhoof JSR, Joly J, et al. Cyclic etidronate increases bone density in the spine and hip in postmenopausal women on chronic corticosteroid treatment. A double-blind controlled study. *Bone* 1997;20(Supp 4):9S.
 335. Reid IR, King AR, Alexander CJ, et al. Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Lancet* 1988;1(8578):143-6.
 336. Lees B, Garland SW, Walton C, et al. Role of oral pamidronate in preventing bone loss in postmenopausal women. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 1996;6(6):480-5.
 337. Lufkin EG ARWMCWVEKOWRB. Pamidronate: an unrecognized problem in gastrointestinal tolerability. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 1994;4(6):320-2.
 338. Cortet B, Bera-Louville A, Gauthier P, et al. Comparative efficacy and safety study of etidronate and alendronate in postmenopausal osteoporosis. effect of adding hormone replacement therapy. *Joint Bone Spine* 2001;68(5):410-5.
 339. Sahota O, Fowler I, Blackwell PJ, et al. A comparison of continuous alendronate, cyclical alendronate and cyclical etidronate with calcitriol in the treatment of postmenopausal vertebral osteoporosis: a randomized controlled trial. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 2000;11(11):959-66.
 340. Downs RW Jr, Bell NH, Ettinger MP, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. *J Clin Endocrinol Metab* 2000;85(5):1783-8.
 341. El-Agroudy AE, El-Husseini AA, El-Sayed M, et al. A prospective randomized study for prevention of postrenal transplantation bone loss. *Kidney Int* 2005;67(5):2039-45.
 342. Evio S, Tiitinen A, Laitinen K, et al. Effects of alendronate and hormone replacement therapy, alone and in combination, on bone mass and markers of bone turnover in elderly women with osteoporosis. *J Clin Endocrinol Metab* 2004;89(2):626-31.
 343. Tiras MB, Noyan V, Yildiz A, et al. Effects of alendronate and hormone replacement therapy, alone or in combination, on bone mass in postmenopausal women with osteoporosis: a prospective, randomized study. *Hum Reprod* 2000;15(10):2087-92.
 344. Miller PD, Watts NB, Licata AA, et al. Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment. *Am J Med* 1997;103(6):468-76.
 345. Wimalawansa SJ. Combined therapy with estrogen and etidronate has an additive effect on bone mineral density in the hip and vertebrae: four-year randomized study. *Am J Med* 1995;99(1):36-42.
 346. Struys A, Snelder AA, Mulder H. Cyclical etidronate reverses bone loss of the spine and proximal femur in patients with established corticosteroid-induced osteoporosis. *Am J Med* 1995;99(3):235-42.
 347. Hasling C, Charles P, Jensen FT, et al. A comparison of the effects of oestrogen/progestogen, high-dose oral calcium, intermittent cyclic etidronate and an ADFR regime on calcium kinetics and bone mass in postmenopausal women with spinal osteoporosis. *Osteoporos Int* 1994;4(4):191-203.
 348. Evans RA, Somers NM, Dunstan CR, et al. The effect of low-dose cyclical etidronate and calcium on bone mass in early postmenopausal women. *Osteoporos Int* 1993;3(2):71-5.
 349. Ringe JD, Faber H, Farahmand P, et al. Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. *Rheumatol Int* 2006;26(5):427-31.
 350. Henderson S, Hoffman N, Prince R. A double-blind placebo-controlled study of the effects of the bisphosphonate risedronate on bone mass in patients with inflammatory bowel disease. *Am J Gastroenterol* 2006;101(1):119-23.
 351. Tauchmanova L, Selleri C, Esposito M, et al. Beneficial treatment with risedronate in long-term survivors after allogeneic stem cell transplantation for hematological malignancies. *Osteoporos Int* 2003;14(12):1013-9.
 352. Shiraki M, Fukunaga M, Kushida K, et al. A double-blind dose-ranging study of risedronate in Japanese

- patients with osteoporosis (a study by the Risedronate Late Phase II Research Group). *Osteoporos Int* 2003;14(3):225-34.
353. Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *The Journal of urology* 2003;169(6):2008-12.
 354. McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. *Arch Intern Med* 2005;165(15):1762-8.
 355. Grady D, Ettinger B, Moscarelli E, et al. Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. *Obstet Gynecol* 2004;104(4):837-44.
 356. Ensrud K, Genazzani AR, Geiger MJ, et al. Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol* 2006;97(4):520-7.
 357. Liu JL, Zhu HM, Huang QR, et al. Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in Chinese postmenopausal women with osteoporosis: a multicenter, randomized, placebo-controlled clinical trial. *Chin Med J (Engl)* 2004;117(7):1029-35.
 358. Zheng S, Wu Y, Zhang Z, et al. Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in postmenopausal women: a randomized clinical trial in Beijing. *Chin Med J (Engl)* 2003;116(8):1127-33.
 359. Smith MR, Fallon MA, Lee H, et al. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *The Journal of clinical endocrinology and metabolism* 2004;89(8):3841-6.
 360. Johnston CC Jr, Bjarnason NH, Cohen FJ, et al. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women: three-year data from 2 double-blind, randomized, placebo-controlled trials. *Arch Intern Med* 2000;160(22):3444-50.
 361. Meunier PJ, Vignot E, Garnero P, et al. Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. *Raloxifene Study Group. Osteoporos Int* 1999;10(4):330-6.
 362. Kung AW, Chao HT, Huang KE, et al. Efficacy and safety of raloxifene 60 milligrams/day in postmenopausal Asian women. *J Clin Endocrinol Metab* 2003;88(7):3130-6.
 363. Kristensen B, Ejlersten B, Dalgaard P, et al. Tamoxifen and bone metabolism in postmenopausal low-risk breast cancer patients: a randomized study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1994;12(5):992-7.
 364. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992;326(13):852-6.
 365. Johnell O, Scheele WH, Lu Y, et al. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;87(3):985-92.
 366. Grey AB, Stapleton JP, Evans MC, et al. The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. *Am J Med* 1995;99(6):636-41.
 367. Draper MW, Flowers DE, Huster WJ, et al. A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. *J Bone Miner Res* 1996;11(6):835-42.
 368. Neven P, Lunde T, Benedetti-Panici P, et al. A multicentre randomised trial to compare uterine safety of raloxifene with a continuous combined hormone replacement therapy containing oestradiol and norethisterone acetate. *BJOG* 2003;110(2):157-67.
 369. Decensi A, Robertson C, Viale G, et al. A randomized trial of low-dose tamoxifen on breast cancer proliferation and blood estrogenic biomarkers. *Journal of the National Cancer Institute* 2003;95(11):779-90.
 370. Cherry N, Gilmour K, Hannaford P, et al. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002;360(9350):2001-8.
 371. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA* 1998;280(7):605-13.
 372. Notelovitz M, John VA, Good WR. Effectiveness of Alora estradiol matrix transdermal delivery system in improving lumbar bone mineral density in healthy, postmenopausal women. *Menopause* 2002;9(5):343-53.
 373. Stefanick ML, Anderson GL, Margolis KL, et al.

- Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;295(14):1647-57.
374. Miller RG. The treatment of osteoporosis. A report of a double blind clinical therapeutic trial. *Gerontol Clin (Basel)* 1969;11(4):244-52.
 375. Greenwald MW, Gluck OS, Lang E, et al. Oral hormone therapy with 17beta-estradiol and 17beta-estradiol in combination with norethindrone acetate in the prevention of bone loss in early postmenopausal women: dose-dependent effects. *Menopause* 2005;12(6):741-8.
 376. Freedman M, San Martin J, O'Gorman J, et al. Digitized mammography: a clinical trial of postmenopausal women randomly assigned to receive raloxifene, estrogen, or placebo. *J Natl Cancer Inst* 2001;93(1):51-6.
 377. Frediani B, Allegri A, Bisogno S, et al. Effects of combined treatment with calcitriol plus alendronate on bone mass and bone turnover in postmenopausal osteoporosis: Two years of continuous treatment. *Clinical Drug Investigation* 1998;15(3):235-244.
 378. Peichl P, Marteau R, Griesmacher A, et al. Salmon calcitonin nasal spray treatment for postmenopausal women after hip fracture with total hip arthroplasty. *J Bone Miner Metab* 2005;23(3):243-52.
 379. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *The Journal of clinical endocrinology and metabolism* 2004;89(2):503-10.
 380. Kotaniemi A, Piirainen H, Paimela L, et al. Is continuous intranasal salmon calcitonin effective in treating axial bone loss in patients with active rheumatoid arthritis receiving low dose glucocorticoid therapy? *J Rheumatol* 1996;23(11):1875-9.
 381. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84(6):1966-72.
 382. Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide. *J Bone Miner Res* 2003;18(1):9-17.
 383. Lyritis GP, Ioannidis GV, Karachalios T, et al. Analgesic effect of salmon calcitonin suppositories in patients with acute pain due to recent osteoporotic vertebral crush fractures: a prospective double-blind, randomized, placebo-controlled clinical study. *The Clinical journal of pain* 1999;15(4):284-9.
 384. Reginster JY, Deroisy R, Lecart MP, et al. A double-blind, placebo-controlled, dose-finding trial of intermittent nasal salmon calcitonin for prevention of postmenopausal lumbar spine bone loss. *Am J Med* 1995;98(5):452-8.
 385. Abellan PM, Bayina GFJ, Calabozo M, et al. Multicentric comparative study of synthetic salmon calcitonin nasally administered in the treatment of established postmenopausal osteoporosis. *Anales De Medicina Interna* 1995;12(1):12-16.
 386. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. *N Engl J Med* 1993;328(24):1747-52.
 387. Reginster JY, Denis D, Albert A, et al. 1-Year controlled randomised trial of prevention of early postmenopausal bone loss by intranasal calcitonin. *Lancet* 1987;2(8574):1481-3.
 388. Gnudi S, Mongiorgi R, Moroni A, et al. Densitometric analysis in vivo evaluation of synthetic salmon calcitonin activity. *J Clin Pharm Ther* 1988;13(2):125-30.
 389. Kung AW, Pasion EG, Sofiyan M, et al. A comparison of teriparatide and calcitonin therapy in postmenopausal Asian women with osteoporosis: a 6-month study. *Curr Med Res Opin* 2006;22(5):929-37.
 390. Hwang JS, Tu ST, Yang TS, et al. Teriparatide vs. calcitonin in the treatment of Asian postmenopausal women with established osteoporosis. *Osteoporos Int* 2006;17(3):373-8.
 391. Huusko TM, Karppi P, Kautiainen H, et al. Randomized, double-blind, clinically controlled trial of intranasal calcitonin treatment in patients with hip fracture. *Calcif Tissue Int* 2002;71(6):478-84.
 392. Flicker L, Hopper JL, Larkins RG, et al. Nandrolone decanoate and intranasal calcitonin as therapy in established osteoporosis. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 1997;7(1):29-35.
 393. Adachi JD, Bensen WG, Bell MJ, et al. Salmon calcitonin nasal spray in the prevention of corticosteroid-induced osteoporosis. *Br J Rheumatol* 1997;36(2):255-9.
 394. Kenny AM, Prestwood KM, Gruman CA, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *The journals of gerontology Series A, Biological sciences and medical sciences* 2001;56(5):M266-72.

395. Howell SJ, Radford JA, Adams JE, et al. Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. *Clinical Endocrinology* 2001;55(3):315-24.
396. McCullough ML, Rodriguez C, Diver WR, et al. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Preventino Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev* 2005;14(12):2898-904.
397. Tseng M, Breslow RA, Graubard BI, et al. Dairy, calcium, and vitamin D intake and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr*. 2005;81(5):1147-54.
398. Lieberman DA, Prindiville S, Weiss DG, et al. Risk factors for advance colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA* 2003;290(22):2959-67.
399. Wu K, Willett WC, Fuchs CS, et al. Calcium intake and risk of colon cancer in women and men. *J Natl Cancer Inst* 2002;94(6):437-46.
400. Jarvinen R, Knekt P, Hakulinen T, et al. Prospective study on milk products, calcium and cancers of the colon and rectum. *Eur J Clin Nutr* 2001;55(11):1000-7.
401. Sellers TA, Bazyk AE, Bostick RM, et al. Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). *Cancer Causes Control* 1998;9(4):357-67.
402. Kampman E, Goldbohm RA, van den Brandt PA, et al. Fermented dairy products, calcium, and colorectal cancer in The Netherlands Cohort Study. *Cancer Res* 1994;54(12):3186-90.
403. Stemmermann GN, Nomura A, Chyou PH. The influence of dairy and nondairy calcium on subsite large-bowel cancer risk. *Dis Colon Rectum* 1990;33(3):190-4.
404. Paganini-Hill A. Estrogen replacement therapy and colorectal cancer risk in elderly women. *Dis Colon Rectum* 1999;42(10):1300-5.
405. Fernandez E, La Vecchia C, Braga C, et al. Hormone replacement therapy and risk of colon and rectal cancer. *Cancer Epidemiol Biomarkers Prev* 1998;7(4):329-33.
406. Calle EE, Miracle-McMahill HL, Thun MJ, et al. Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* 1995;87(7):517-23.
407. Risch HA, Howe GR. Menopausal hormone use and colorectal cancer in Saskatchewan: a record linkage cohort study. *Cancer Epidemiol Biomarkers Prev* 1995;4(1):21-8.
408. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. *JAMA* 2004;291(16):1999-2006.
409. Pickney CS, Arnason JA. Correlation between patient recall of bone densitometry results and subsequent treatment adherence. *Osteoporos Int* 2005;16(9):1156-60.
410. Robbins B, Rausch KJ, Garcia RI, et al. Multicultural medication adherence: a comparative study. *J Gerontol Nurs* 2004;30(7):25-32.
411. Guilera M, Fuentes M, Grifols M, et al. Does an educational leaflet improve self-reported adherence to therapy in osteoporosis? The OPTIMA study. *Osteoporos Int* 2006;17(5):664-71.

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