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Comparative Effectiveness Review
Number 53

Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report

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Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report

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Prepared by:
Southern California Evidence-based Practice Center—RAND Corporation
Santa Monica, CA

Investigators:
Carolyn J. Crandall, M.D., M.S.
Sydne J. Newberry, Ph.D.
Allison Diamant, M.D., M.S.H.S.
Yee-Wei Lim, M.D., Ph.D.
Walid F. Gellad, M.D., M.P.H.
Marika J. Suttorp, M.S.
Aneesa Motala, B.A.
Brett Ewing, M.S.
Beth Roth, M.A.
Roberta Shanman, M.L.S.
Martha Timmer, M.S.
Paul G. Shekelle, M.D., Ph.D.

Note: Several studies in this report have been retracted. They are indicated in the References section. More information is located on the journals' websites and the Retraction Watch database.

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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 Children's Health Insurance Program (CHIP).

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 (CERs) 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 strength 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 CERs 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 email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Supriya Janakiraman, M.D, M.P.H
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Technical Expert Panel

Roberta Biegel
Senior Director
Public Policy and Government Relations
National Osteoporosis Foundation
Washington, DC

Bruce Ettinger, M.D.
Clinical Professor
University of California San Francisco
San Francisco, CA

Theodore Hahn, M.D.
Professor in Residence
UCLA Medical Center,
Geriatric Research Education and Clinical Center
and VA Greater Los Angeles Healthcare System
Los Angeles, CA

Marc Hochberg, M.D., M.P.H.
Professor of Medicine
Head, Division of Rheumatology and Clinical Immunology
Professor of Epidemiology and Preventive Medicine
University of Maryland
Baltimore, MD

Hau Liu, M.D.
Director, Chronic Care Management
Associate Chief, Endocrinology and Metabolism
Santa Clara Valley
Clinical Assistant Professor of Medicine
Stanford University
San Jose and Stanford, CA

Catherine Maclean, M.D., Ph.D.
Staff Vice President, Performance Measurement
WellPoint, Inc.
Thousand Oaks, CA

Paul Miller, M.D.
Medical Director
Colorado Center for Bone Research
Lakewood, CO

Eric Orwoll, M.D.
Endocrinologist
Oregon Health and Science University
Portland, OR

Marcel Salive, M.D., M.P.H.
Director, Division of Medical and Surgical Services
Centers for Medicare and Medicaid Services
Baltimore, MD

William Schwab, M.D., Ph.D., AGSF
Chief of Geriatric Services
Kaiser Permanente of Ohio
Cleveland Heights, OH

Daniel Solomon, M.D., M.P.H,
Associate Professor of Medicine
Harvard Medical School
Brigham and Women's Hospital
Division of Rheumatology, Immunology and Allergy
Boston, MA

Peer Reviewers

Steve Cummings, M.D., FACP
San Francisco Coordinating Center
California Pacific Medical Center
California Pacific Medical Center Research Institute
University of California, San Francisco
San Francisco, CA

Rochelle Fu, Ph.D.
Oregon Health and Science University
Portland, OR

Conrad C. Johnston, M.D.
Indiana University School of Medicine
Indianapolis, IN

Ethel Siris, M.D.
Columbia University Medical Center
New York, NY

Disclosure: Service as a TEP member or peer reviewer should not be construed as agreeing with or endorsing the content of the report.

Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report

Structured Abstract

Objectives. To update a 2007 systematic review on the effectiveness and safety of treatments to prevent fractures in persons with low bone density or osteoporosis and factors affecting adherence to these treatments, and to assess whether monitoring helps identify those most likely to benefit from treatment and the benefits of long-term treatment.

Data Sources. MEDLINE®, Embase, the Cochrane Database of Systematic Reviews, and Clinical Trials.gov were searched from January 2005 through March 2011.

Review Methods. After review by two investigators against predetermined inclusion/exclusion criteria, we included existing systematic reviews, randomized controlled clinical trials, and large observational studies, where appropriate, for assessment of treatment efficacy, safety, and adherence.

Results. Alendronate, risedronate, zoledronic acid, denosumab, and teriparatide reduce the risk of vertebral and nonvertebral fractures among postmenopausal women with osteoporosis. Ibandronate and raloxifene reduce the risk of vertebral but not nonvertebral fractures. Alendronate, risedronate, zoledronic acid, and denosumab prevent hip fractures among postmenopausal women with osteoporosis. Risedronate decreases the risk of vertebral and nonvertebral fracture among men with osteoporosis.

Among those treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate compared to placebo; and for teriparatide compared to alendronate.

Few studies have compared osteoporosis therapies head-to-head.

Adherence to pharmacotherapy is poor in patients with osteoporosis, as with other chronic conditions. Many factors affect adherence to medications, including dosing frequency, side effects of medications, knowledge about osteoporosis, and cost. Age, prior history of fracture, and concomitant medication use do not appear to have an independent association with adherence. Dosing frequency appears to affect adherence: Adherence is improved with weekly compared to daily regimens, but evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens. Decreased adherence to bisphosphonates is associated with less than optimal reduction in the risk of fracture. Insufficient evidence is available to make conclusions about how adherence to and persistence with newer osteoporosis therapies compare to that with bisphosphonates.

Assessment of adverse effects finds that raloxifene is associated with an increased risk for pulmonary embolism and vasomotor flushing; and limited data support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Evidence is limited on the utility of monitoring and long-term treatment.

Conclusions. There is a high level of evidence that shows that fracture risk reduction is greatest in women with a diagnosis of osteoporosis and/or prevalent fractures. The level of evidence is low to moderate for fracture risk reduction in postmenopausal women with osteopenia and without prevalent fractures. The evidence is low for benefits of treatment for other populations, including men; for the benefits and risks of long-term treatment; and for the need (if any) for monitoring bone density; and mixed with regard to factors that influence adherence.

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Executive Summary

Background

Osteoporosis is a systemic skeletal disease characterized by decreasing bone mass and microarchitectural deterioration of bone tissue, with consequent increases in bone fragility and susceptibility to fracture.[1] In addition to fractures, the clinical complications of osteoporosis include disability and chronic pain. Approximately 52 million people in the United States are affected by osteoporosis or low bone density. It is especially common in postmenopausal women,[2] but one in five men will experience an osteoporosis-related fracture at some point in his lifetime.[3]

The economic burden of osteoporosis is large and growing: the most recent estimate of U.S. annual costs due to fractures alone have been nearly $20 billion.[2] A recent projection of the burden and costs of incident osteoporosis-related fractures in the United States from 2005 to 2025 estimates more than 2 million fractures in 2010, with direct medical costs of more than $18 billion (more than 25 percent attributable to men).[4] Although the bulk of these costs are incurred by individuals 65 and older, direct costs and productivity loss among working women under 65 are considerable.[2]

Target Audience

This report is intended for health care decisionmakers—patients and clinicians, health system leaders, and policymakers.

Diagnosis and Risk Factors

The clinical diagnosis of osteoporosis may be based on results of bone mineral density (BMD) measurement with dual energy x-ray absorptiometry (DXA).[3,5,6] In postmenopausal women and men over 50 years of age, BMD is classified according to the T-score. The T-score is the number of standard deviations above or below the mean for healthy 20- to 29-year-old adults, as determined by DXA. Osteoporosis is defined as a T-score of -2.5 or less.[3,6] A T-score between -2.5 and -1.0 is defined as “low bone density.” A T-score of -1 or greater is considered normal. Bone density can also be classified according to the Z-score, the number of standard deviations above or below the expected BMD for the patient’s age and sex. A Z-score of -2.0 or lower is defined as either “low BMD for chronological age” or “below the expected range for age,” and those above -2.0 are “within the expected range for age.” Individuals who have already had minimal trauma fracture are at increased risk of future osteoporotic fracture, independent of BMD.[3] Because the majority of fractures occur in patients with low bone mass rather than osteoporosis,[3] risk scores that combine clinical risk factors with BMD testing results, such as FRAX® (World Health Organization Fracture Risk Assessment Tool), have recently been developed to refine the ability to predict fracture risk among people with low bone density.

Risk factors for osteoporotic fracture include (but are not limited to) increasing age, female sex, postmenopause for women, hypogonadism or premature ovarian failure, low body weight, history of parental hip fracture, ethnic background (whites are at higher risk than blacks), previous clinical or morphometric vertebral fracture, previous fracture due to minimal trauma (i.e. previous osteoporotic fracture), rheumatoid arthritis, current smoking, alcohol intake (3 or more drinks/day), low BMD, vitamin D deficiency, low calcium intake, hyperkyphosis, falling,

and immobilization, along with chronic use of certain medications, the most commonly implicated being glucocorticoids (GC), anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadatropin-releasing hormone agonists.[3]

Several algorithms have been devised and validated for the prediction of osteoporotic fracture risk. Current National Osteoporosis Foundation guidelines as well as others endorse the use of the FRAX to select candidates for treatment.[7-9] The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women.[9,10] FRAX is a set of race- and nationality-specific algorithms that take into account an individual's age, sex, weight, height, previous fracture, parental history of osteoporotic fracture, smoking status, alcohol use, history of use of glucocorticoids, history of rheumatoid arthritis, secondary causes of osteoporosis, and femoral neck BMD to estimate the absolute 10-year risk of major osteoporotic fractures (i.e., clinical vertebral, hip, forearm, or proximal humerus fractures). Risk for osteoporosis may be viewed as a continuum that depends on all of these factors. A question of considerable interest is whether antifracture response to treatment is affected by (or predicted by) FRAX score.[3,11]

Therapy

The most recent National Osteoporosis Foundation Clinician's Guide recommended considering therapy for postmenopausal women and men aged 50 and older presenting with the following: a hip or vertebral (clinical or morphometric) fracture; T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes; low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3 percent or a 10-year probability of a major osteoporosis-related fracture ≥ 20 percent based on the U.S.-adapted World Health Organization (WHO) algorithm.[3]

The increasing prevalence and cost of osteoporosis have heightened interest in the effectiveness and safety of the many interventions currently available to prevent osteoporotic fracture. These interventions include pharmacologic agents, a biological agent, dietary and supplemental vitamin D and calcium, and weight-bearing exercise.

Pharmacologic agents include the bisphosphonate class of drugs, peptide hormones (parathyroid hormone and calcitonin), estrogen (in the form of menopausal hormone therapy) for postmenopausal women, and selective estrogen receptor modulators (raloxifene for postmenopausal women). With the exception of parathyroid hormone, each of these agents acts to prevent bone resorption. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical periosteal and/or endosteal bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. The bisphosphonates are compounds that bind reversibly to mineralized bone surfaces and disrupt resorption by the osteoclasts.

A newer therapeutic agent, denosumab, was approved by the Food and Drug Administration (FDA) in June 2010. Denosumab is a monoclonal antibody that inhibits the Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL), a stimulator of osteoclast differentiation and activation. By inhibiting osteoclast formation, function, and survival, denosumab decreases bone resorption. Although denosumab is classified by the FDA as a biological agent, it will be considered a pharmacological agent for the purposes of this report.

Besides pharmacologic agents, dietary and supplemental calcium and vitamin D, as well as weight bearing exercise, play important roles in preserving bone mass.[3] Lifelong calcium intake is required for the acquisition of peak bone mass and for the subsequent maintenance of bone

health. When serum calcium levels are inadequate, bone tissue is resorbed from the skeleton to maintain serum calcium at a constant level. Adequate vitamin D levels play a key role in calcium absorption, bone health, muscle performance, balance, and fall prevention.[3]

The various agents used to prevent and treat osteoporosis have been linked with a range of adverse effects, from the more common, mild effects (such as minor gastrointestinal complaints) to potentially serious issues. Some evidence suggests that these minor complaints, coupled with concerns about more serious effects, may affect the level of compliance with and persistence of treatment. Poor adherence and persistence may, in turn, affect the effectiveness of the treatments. These issues form the scope of this report and its predecessor.

The FDA Approval Process

In 1979, the FDA published its first Guidance Document for the clinical evaluation of the safety and effectiveness of drugs to treat osteoporosis.[12] 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 study size and duration needed to detect changes in bone density and/or fracture risk. Patient inclusion criteria for FDA clinical trials consisted of objective evidence of disease (i.e., 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, rather than requiring evidence of significant decrease in fracture risk, permitted effectiveness to be defined as improvement in bone mass during therapy if the process of new bone formation could be demonstrated to be normal. If new bone formation did not prove normal or if it was not possible to determine normalcy, fracture studies would be required.

The 1984 Guidance Document included several noteworthy changes. It recommended studies that would establish an indication for the prevention of postmenopausal osteoporosis. In addition, it described DXA as providing a valid measure of spinal bone mass, and it recommended that all participants in trials of agents for osteoporosis therapy be supplemented with calcium and vitamin D.

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. It 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 effect 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-related response, combined with a lack of effect on BMD, suggested either that the positive effect of the 200 IU dose was an experimental 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 agent 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 again in 1994 to include the following requirements for approval of a new drug to treat postmenopausal osteoporosis: (1) demonstration that treatment resulted in preservation or improvement in bone density while retaining normal bone quality[a] in preclinical studies with two laboratory animal species, including an ovariectomized rat model; (2) normal bone quality in a subset of clinical trial participants; (3) significant increase in BMD; and (4) at least a trend toward decreased fracture risk after three years (up from two years) of treatment. The 1994 Guidance Document also affirmed the use of DXA and bone turnover markers for phase I and II trials and provided requirements for approval of agents for prevention of osteoporosis (in individuals at high risk but without history of osteoporotic fracture).[13]It stipulated that only agents that have already been approved for treatment of osteoporosis can be approved for prevention. It suggested further that, for prevention, BMD may serve as an appropriate—and sufficient—outcome measure for efficacy in double-blind randomized controlled trials (RCT) 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 (of estrogen as used to treat menopausal symptoms), estrogen was approved for treatment of postmenopausal osteoporosis. Thus, it was exempted from the requirement that it demonstrate effectiveness for fracture prevention, and was approved for both treatment and prevention based on BMD alone. Subsequently, however, the FDA has required evidence of effectiveness in preventing fracture 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. (However, approval for a different indication, such as glucocorticoid-induced osteoporosis, does require demonstration of reduction in fracture risk.) These implications of the current guidance have heightened interest in evaluating the effectiveness data for drugs approved to treat and prevent osteoporosis.

[a] The FDA recognizes that components of bone strength include bone mineral density and bone quality; some aspects of bone quality that might affect fracture risk have been identified but are difficult to measure. Nevertheless, the requirements for approval specify that drugs must not result in accretion of new bone (or preservation of existing bone) with abnormal morphology.

In December 2007, the Evidence-based Practice Center (EPC) completed the first Comparative Effectiveness Review (CER) on the efficacy/effectiveness of these interventions in preventing osteoporosis-related fracture, their safety, and compliance with their use.[14]

The review found a high level of evidence suggesting that, compared with placebo, alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, a fragment of parathyroid hormone (PTH) that contains the first 34 of 84 amino acids (referred to as PTH [1-34] or teriparatide), and raloxifene prevent vertebral fractures; the evidence for calcitonin compared with placebo was fair. The report also found a high level of evidence to suggest that alendronate, risedronate, and estrogen prevent hip fractures, compared with placebo; the evidence for zoledronic acid was fair. No studies were identified that assessed the effect of testosterone on fracture risk. The evidence for an effect of vitamin D on both vertebral and hip fractures varied with dose, analogue, and study population. No antifracture evidence was available for calcium or physical activity.

Further, the evidence was insufficient to ascertain the relative superiority of any agent or to determine whether the agents were more effective in some populations than others.

Regarding adverse events associated with the pharmacologic agents, raloxifene, estrogen, and combined estrogen-progestin increased the risk for thromboembolic events, and etidronate increased the risk for esophageal ulcerations and gastrointestinal perforations, ulcerations, and bleeding. The use of menopausal hormone therapy was associated with an increased risk of breast cancer, heart disease, and stroke in the Women's Health Initiative, a 15-year trial sponsored by the National Heart, Lung, and Blood Institute, that enrolled and tracked more than 150,000 women; the trial comprised an observational study of the effects of postmenopausal hormone therapy and a clinical trial of the effects of dietary modification on cardiovascular disease, cancer, bone health, and other clinical conditions. Clinical trials reported mixed findings regarding an association of zoledronic acid with the risk for atrial fibrillation. No data were found from osteoporosis trials to suggest an association between bisphosphonates or any other agents and the development of osteonecrosis: A number of case reports and case series articles reported osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates.

Although fracture trials that reported data on adherence/compliance tended to find relatively good adherence to medication use, observational studies tended to report poor adherence with osteoporotic medications, as with other chronic conditions. Poor adherence was associated with lower effectiveness.

Scope and Key Questions

Since the release of the original report, several of the bisphosphonates have become available in new, less frequently administered, forms, and a new biological agent, denosumab, is now available. In addition, new data have been released on adverse events associated with bisphosphonates. Thus, in 2008, the EPC was asked to conduct an assessment of the need to update the original report (as well as the other CER reports released up to that time point); this report was submitted in March 2009.[15] For this report, the EPC conducted an abbreviated search and review of the literature addressing the topics of the first review. The abbreviated search consisted of a survey of experts in the field and a MEDLINE® search (using the same search terms as the original report) of 5 of the leading medical journals and 5 leading specialty journals dating from 2006 to mid-2008. The studies identified in this search that addressed the Key Questions of the original report were reviewed and abstracted, and their findings qualitatively

assessed using a process devised by the EPC to determine whether they confirmed, contradicted, or augmented the conclusions of the original report.

The update search identified new data on effectiveness and adverse effects. New studies were found for several agents, including denosumab, that were not included in the original report. In addition, studies were found on the effects of calcium and vitamin D and for novel dosing schedules or routes of administration of the bisphosphonates, ibandronate, and zoledronic acid. Based on this evidence, the assessment concluded that at least some of the conclusions of the first report regarding effectiveness may need to be updated (Key Question 1—see below). In addition, the assessment found new evidence on the safety of some agents that might warrant an update. For example, new evidence was found on the risk of atrial fibrillation with the use of some bisphosphonates and the risk of osteosarcoma with the use of teriparatide. Also, the FDA issued a labeling revision in December 2007 regarding the possible association of the use of pamidronate with deterioration of renal function (http://effectivehealthcare.ahrq.gov/ehc/products/125/331/2009_0923UpdatingReports.pdf).

Based on these findings, the Update Assessment suggested an updated review of the adverse effect evidence (Key Question 4).

In July 2009, the EPC was asked by AHRQ to conduct a full update of the original CER. We modified Key Question 1 to include medications that were not approved for the treatment of osteoporosis prior to the release of the original report but have since been approved, including zoledronic acid (IV) (Reclast®; Novartis; once-a-year infusion) and the monoclonal antibody, denosumab (Prolia®; Amgen; every-six-months injection); as well as agents for which no or few data were available for inclusion in the original report, such as injectable ibandronate sodium (Boniva®; Roche Laboratories/Hoffman laRoche; once every three months). We also omitted several agents—etidronate, pamidronate, tamoxifen, and testosterone—based on their not being indicated or used for osteoporosis treatment, and also modified the question to include consideration of the sequential or combined use of different agents. Although new evidence was found for strontium ranelate, this agent is not likely to be considered for FDA approval in the near future, so it was not included.

Key Question 2 originally assessed the evidence for efficacy and effectiveness among particular subpopulations of clinical interest. The subpopulations to be considered in the evidence review update were also augmented to include racial/ethnic differences because of the evidence for potential group differences in BMD and risk for osteoporosis. The subject matter experts also recommended considering the comparative utility of existing risk assessment algorithms for predicting antifracture effects of osteoporosis pharmacotherapy, i.e., whether differences in antifracture effects would be found among groups with different FRAX (or other) risk assessment cutoffs.

Key Question 3, which addresses compliance and adherence, remains as it was originally.

Key Question 4, which assesses adverse effects of the pharmacologic agents, was modified to exclude uses of the agents for any condition other than osteoporosis/low bone density so as to be congruent with the scope of the report.

The subject matter experts also recommended that an additional question be added. Because the optimal duration for therapy (and the role of monitoring in determining how long to treat) remains unknown, a question was added to address therapy duration and monitoring of effectiveness. Key Question 5 has two parts. The first part aims to assess the evidence that antifracture effect is predicted by DXA monitoring of BMD. The second part (which is really a subquestion to Key Question 1) aims to assess the evidence for comparative effectiveness of

long-term therapy (defined by consensus of the technical expert panel as therapy of 5 years or more). Thus the following questions guided the current report. (Figure A shows the report's analytic framework.)

Key Question 1: What are the comparative benefits in fracture risk reduction among the following therapeutic modalities for low bone density:

- Bisphosphonate medications, specifically:
    - Alendronate (Fosamax®, oral)
    - Risedronate (Actonel®; oral once-a-week)
    - Ibandronate (Boniva®)
    - Zoledronic acid (Reclast®IV).
- Denosumab (Prolia®)
- Menopausal estrogen therapy for women (numerous brands and routes of administration)
- Parathyroid hormone (PTH)
    - 1-34 (teriparatide) (Forteo®)
- Selective estrogen receptor modulators (SERMs), specifically
    - Raloxifene (Evista®)
- Calcium
- Vitamin D
- Combinations or sequential use of above
- Exercise in comparison to above agents

Key Question 2: How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by the following factors:

- Bone mineral density
- FRAX or other risk assessment score
- Prior fractures (prevention vs. treatment)
- Age
- Sex
- Race/ethnicity
- Glucocorticoid use
- Other factors (e.g., whether the individuals were community dwelling vs. institutionalized, vitamin D deficient vs. not)

Key Question 3: Regarding treatment adherence and persistence,[b]

- What are the levels of adherence to and persistence with medications for the treatment and prevention of osteoporosis?
- What factors affect adherence and persistence?

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[b] The terms adherence and persistence are defined based on principles outlined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). (Cramer, 2008) Adherence (or compliance) is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen." Although not specifically stated in the ISPOR definition, we view adherence to specific dosing instructions (which for bisphosphonates can affect both effectiveness and risk of adverse events) as an important component of adherence. Persistence is defined as "the duration of time from initiation to discontinuation of therapy."(Cramer, 2008)

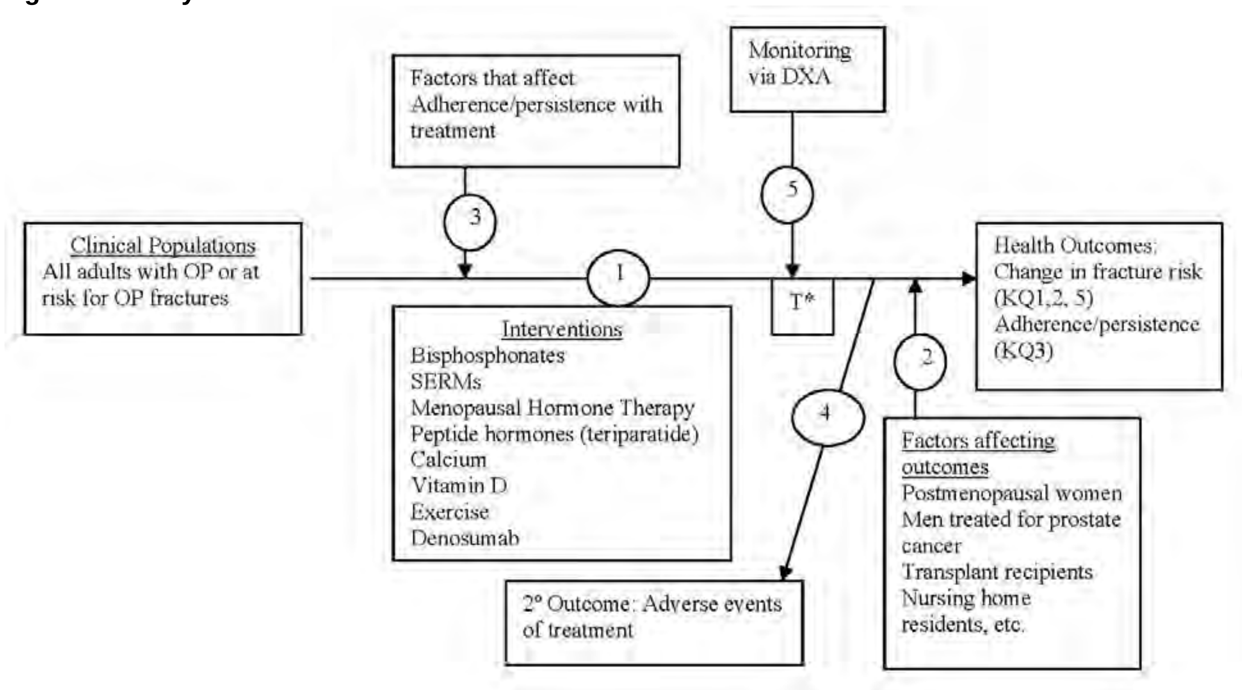
- What are the effects of adherence and persistence on the risk of fractures?

Key Question 4: What are the short- and long-term harms (adverse effects) of the above therapies (when used specifically to treat or prevent low bone density/osteoporotic fracture); and do these vary by any specific subpopulations (e.g., the subpopulations identified in Key Question 2)?

Key Question 5: With regard to treatment for preventing osteoporotic fracture:

- How often should patients be monitored (via measurement of bone mineral density) during therapy; how does bone density monitoring predict antifracture benefits during pharmacotherapy; and does the ability of monitoring to predict antifracture effects of a particular pharmacologic agent vary among the pharmacotherapies?
- How does the antifracture benefit vary with long-term continued use of pharmacotherapy, and what are the comparative antifracture effects of continued long-term therapy with the various pharmacotherapies?

Figure A. Analytic framework



BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; KQ = Key Question; OP = osteoporosis; SERMs = selective estrogen receptor modulators
*T connotes the timing of outcome measurement for studies that will be included, which will vary by KQ.

Methods

Search Strategy

Our basic search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature. Using the same basic search rules used for the original report (with the addition of several new terms for additional drugs), we searched MEDLINE® for the period from January 2005 through March 2011. We also searched Embase, the American

College of Physicians (ACP) Journal Club database, the Cochrane controlled trials register, and relevant pharmacological databases.

In searching for efficacy and effectiveness studies, we used terms for osteoporosis, osteopenia, low bone density, and the drugs listed in Key Question 1. In our search for the key adverse events (AE), we used terms for the AE and each of the drugs of interest. In our search for studies of adherence and persistence, we used terms for adherence and persistence and the drugs of interest. In all cases, both generic and trade names were used. In our search for studies on the effects of monitoring, we searched on terms related to monitoring and DXA in combination with the drugs of interest.

For new drugs, we reviewed the list of excluded studies from the original report to retrieve articles that had been rejected on the basis of drugs that were now included within the scope of the update, to find studies prior to 2005. The search was not limited to English-language publications and not limited by study design (e.g., reports of randomized controlled trials (RCT), observational studies, systematic reviews). The texts of the major search strategies are given in Appendix A.

To identify additional systematic reviews 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 the reference lists of review articles obtained as part of our search (“reference mining”).

To augment those searches, the EPC’s Scientific Resource Center (SRC) conducted several “grey literature” searches, including a search of relevant trials in the NIH Clinical Trials database, the Web of Science, FDA Medwatch files, and Health Canada files.

Study Eligibility Criteria

To identify studies for this report, we used the following inclusion criteria:

- **Populations:** Studies were limited to those recruiting the following individuals: adults over 18 (not children); healthy adults, those with low bone density, or those with osteoporosis (but not those with Paget’s disease, cancer, or any other disease of bone metabolism); those using drugs indicated for the treatment of osteoporosis (but not if the drugs were being used to treat cancer); adults who had low bone density or were at high risk of developing low bone density as a result of chronic use of glucocorticoids (GC) or a condition associated with the chronic use of glucocorticoids (such as asthma, organ transplant, rheumatoid arthritis; adults who had low bone density or were at high risk of developing low bone density as a result of having a condition associated with low bone density (e.g., rheumatoid arthritis, cystic fibrosis, Parkinson’s disease).
- **Interventions:** Studies were included if they examined pharmacological interventions for prevention or treatment of osteoporosis approved for use in the United States (or expected to be soon approved for use) or if they assessed the effects of calcium, vitamin D, or physical activity.
- **Comparators:** Studies included for assessing efficacy or effectiveness were those that compared the effectiveness of the intervention in question to that of placebo or another potency or dosing schedule for the same agent or another agent in the same or another class.
- **Outcomes:** For efficacy and effectiveness analysis, only studies that assessed vertebral, hip, and/or total fractures (and did not state that they lacked power to detect a change in

risk for fracture) were included. Studies that reported fracture only as an adverse event were excluded from effectiveness analysis; however, studies that reported atypical (low-stress subtrochanteric or femur) fractures as adverse outcomes were included in the adverse event analysis.

- **Duration:** Studies that had a minimum followup time of 6 months were included.
- **Design:** Only RCTs and published systematic reviews of RCTs that met inclusion criteria were included in the assessment of effectiveness;[16] however, for the assessment of effects in subgroups for which no RCTs were available, for the assessment of the effect of adherence on effectiveness, and for the assessment of particular serious adverse events, large observational studies (with more than 1,000 participants) and systematic reviews were included.

Study Selection

Each title list was screened separately by two reviewers with clinical training and experience in systematic review to eliminate obviously irrelevant titles. Abstracts were obtained for all selected titles. Full text articles were then obtained for all selected abstracts. The reviewers then conducted a second round of screening to ascertain which articles met the inclusion criteria and would go on to data abstraction. Selections at this stage were reconciled, and disagreements were settled by consensus (with the project leaders resolving remaining disagreements).

During the second round of screening, we imposed inclusion criteria based on the particular Key Question(s) addressed by the study. For effectiveness/efficacy questions (Key Questions 1, 2, and 5), we accepted any abstracts that indicated the manuscript might include information on the treatment/prevention of osteoporotic fracture (but not bone density alone). Controlled clinical trials and large observational studies (N>1,000) 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.

For assessing comparative effectiveness, we included only studies that compared two or more interventions within the same study, rather than attempting to compare treatment effects across studies. The differences in study design and baseline participant characteristics between studies would make interpretation of such comparisons suspect.

For Key Question 2, we identified studies that analyzed treatment efficacy and effectiveness by subgroups by noting, during the initial screening of full-text articles, any articles that reported the results of post hoc analyses of trial efficacy data by a subgroup of interest; by noting whether subgroup analyses were reported while extracting primary effectiveness results from clinical trial reports and large observational studies (over 1,000 participants); and we sought observational studies of any size that assessed effects of the agents of interest in populations not well represented in controlled trials. As with the head-to-head comparisons for Key Question 1, we did not attempt to compare treatment effects across studies because of the vast baseline differences between populations in characteristics considered to be potentially important, such as average age, body mass index, and race/ethnicity.

For Key Question 3 (adherence), articles of any study design that reported rates of adherence/persistence, factors influencing adherence/persistence, or the effects of adherence on effectiveness for any of the drugs of interest were included for further evaluation.

For Key Question 4 (adverse events), any articles were accepted if they suggested that the manuscript included information on the relationship between the adverse event and the drug. Controlled clinical trials and large case control or cohort studies (over 1,000 participants) 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, as well as studies of any design that described any of a number of rare adverse events (e.g., osteonecrosis of the jaw, atrial fibrillation, low stress subtrochanteric and femur fracture) in association with any of the drugs of interest, were initially included in adverse event analyses.

For Key Question 5 (effects of monitoring and long-term use), to ensure that we identified all articles that examined the effect of bone density monitoring in predicting treatment effectiveness or efficacy, we searched for these articles in the following ways: During the initial screening of articles, we included any clinical trials that reported fracture results and mentioned monitoring. We also included any trials that reported both BMD and fracture and subsequently assessed whether changes in BMD were compared to fracture outcomes. Where they existed, we also included reports of followups to trials included in the original report to assess the effect of long-term use.

Data Extraction

Study level details, such as population characteristics, comorbidities, inclusion and exclusion criteria, interventions, and outcomes assessed, were extracted and recorded onto specially designed forms.

Data Synthesis

We performed three main analyses: one to evaluate efficacy and effectiveness, one to evaluate adherence, and one to evaluate adverse events. 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.

The outcome of interest for assessing effectiveness for this report is fractures, based on FDA requirements. We report data about the following types of fractures (as reported in the studies reviewed): vertebral, nonvertebral, hip, wrist, and humerus. For each of the drug comparisons, we first summarized fracture data from published systematic reviews in tables. Data abstracted from individual controlled clinical trials were grouped by fracture type within each drug comparison of interest. Based on the recommendation of subject matter experts, 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 nonvertebral fractures). The primary outcome for our analysis of effectiveness is the number of people who reported at least one fracture.

To assess adherence, we extracted reported rates of adherence or persistence from trials and observational studies separately, as the rates of adherence and persistence reported for trials are likely to be higher than would be observed in practice. For those studies that provided information on the potential barriers and/or predictors to medication adherence in osteoporosis, we identified those barriers and predictors, using a data abstraction form designed especially for studies of adherence, and determined the number of studies discussing each factor and the characteristics of the study, including population characteristics, specifics on how adherence/persistence are measured, and funding source. For the analysis of adherence/persistence and fracture, we qualitatively reviewed each of these studies and prior systematic reviews addressing this topic.

For adverse events, two main analyses were performed: 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 was compiled of all unique adverse events that were reported in any of the studies, 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 (including those in the original report), we performed meta-analysis to estimate the pooled OR and its associated 95 percent confidence interval.

Assessments of Quality and Applicability and Rating the Body of Evidence

The methods used for quality assessment were determined by the design of included studies. The quality of RCTs was assessed using the Jadad scale,[17] 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 to 5 based on points given for randomization, blinding, and accounting for withdrawals and dropouts. (Two points are awarded for randomization and two for double blinding.) We also added an assessment of concealment of allocation.

The need to include observational studies was carefully assessed according to the guidelines presented in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. Specifically, we assessed whether clinical trials provided sufficient data to reach conclusions, and where they did not we included observational data. In practice, this meant that we included observational data in two topic areas: adverse events and the assessment of adherence and outcomes. The quality of prospective cohort and case-control studies that addressed adverse events was assessed using the relevant portions of the Newcastle-Ottawa Scales, as follows:[18]

- Are primary outcomes assessed using valid and reliable measures?
- Are outcome measures implemented consistently across all study participants?
- Were the important confounding and modifying variables taken into account in the design and analysis?
- How was the non-exposed cohort selected?
- How was exposure to drugs/exercise ascertained?
- Was it demonstrated that the outcome of interest was not present at the start of the study?

Assessing the quality of observational studies that measure adherence is a challenge, as no such metric currently exists and the items included in other metrics used to rate the quality of observational studies do not apply to most studies that assess adherence. Thus, for each such study, we listed those objective factors that might be related to both quality and generalizability/applicability, such as how adherence was measured and the size and location of the study.

As was done for the original report, we assessed the applicability of each included study based on the similarity of the target populations to those for which this report is intended. This assessment was separate from other quality assessments. The characteristics we used to distinguish efficacy from effectiveness, and therefore to rate applicability, were study setting,

study population (stringency of eligibility criteria), duration and attempt to assess treatment compliance, health outcome assessment, adverse event assessment, sample size, and use of intention-to-treat analysis.[19]

The overall strength of evidence for intervention effectiveness using guidance suggested by the U.S. Agency for Healthcare Research and Quality (AHRQ) for its Effective Healthcare Program.[20] This method is based on one developed by the Grade Working Group,[21] and classifies the grade of evidence according to the following criteria:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence on the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Evidence either is unavailable or does not permit a conclusion.

The evidence grade is based on four primary domains (required) and four optional domains. The required domains are risk of bias, consistency, directness, and precision; the additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias.

Conclusions

Key Question 1: What are the Comparative Benefits in Fracture Risk Reduction Among and Within the Included Therapeutic Modalities?

For this question, we identified 55 RCTs and 10 observational studies in addition to 58 systematic reviews (from both the original and current report) that assessed the effects of interventions compared to placebo: 9 systematic reviews and 10 RCTs for alendronate, 10 systematic reviews and 13 RCTs for risedronate, 3 systematic reviews and 3 RCTs for ibandronate, 4 RCTs for zoledronic acid, 1 systematic review and 2 RCTs for denosumab, 3 systematic reviews and 3 RCTs for raloxifene, 2 systematic reviews and 3 RCTs for teriparatide, 6 RCTs for menopausal estrogen therapy, 4 systematic reviews and 6 RCTs for calcium alone, 15 systematic reviews and 7 RCTs for vitamin D alone, 4 RCTs for vitamin D plus calcium, and 1 systematic review and 1 RCT for physical activity. (Studies that addressed more than one Key Question were counted more than once.) We reached the following conclusions:

- There is a high level of evidence from RCTs that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.
- There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid and denosumab reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis, and moderate evidence that teriparatide reduces the risk of nonvertebral fractures.
- There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip fractures in postmenopausal women with osteoporosis.

- The original report found a high level of evidence that estrogen is associated with a reduced incidence of vertebral, nonvertebral, and hip fractures; however, studies identified for this report, which tended to focus on postmenopausal women with established osteoporosis (rather than on postmenopausal women with low bone density only or postmenopausal women in general) did not show significant reductions in fracture risk.
- There is moderate evidence, based on a published systematic review and several RCTs, that there is no difference between calcium alone and placebo in reducing the risk for vertebral and nonvertebral fractures; however, calcium significantly reduced hip fracture risk in one pooled analysis, and overall fracture risk in another pooled analysis.
- A large body of literature showed mixed results for an effect of vitamin D in lowering the risk for fracture, varying with dose, fracture site, analogs (the various molecular and chemical forms of the vitamin, each of which has different biological activity), and population. Evidence is moderate that Vitamin D, 700 to 800 I.U. daily, particularly when given with calcium, reduces the risk of hip and nonvertebral fractures among institutionalized populations (one systematic review) and the overall risk of fractures (a second systematic review).
- There is a high level of evidence, based on six previously published systematic reviews, that there is no difference in vertebral, nonvertebral, or hip fracture risk with administration of vitamin D alone compared to administration of calcium alone.
- The evidence is insufficient to low regarding the effect of physical activity on fracture risk, compared to placebo: One study showed a small effect on fracture prevention. No studies compared the effect of physical activity to that of other interventions.
- The evidence is insufficient from head-to-head trials of bisphosphonates to prove or disprove any agent's superiority for the prevention of fractures.
- The evidence is insufficient, from three head-to-head trials of bisphosphonates compared to calcium, teriparatide, or raloxifene to prove or disprove superiority for the prevention of fractures.
- Evidence is moderate, based on six head-to-head RCTs, that there is no difference in fracture incidence between bisphosphonates and menopausal hormone therapy.
- The evidence is low, based on one head-to-head trial, that the combination of alendronate and calcium significantly decrease the risk for any type of clinical fracture compared with alendronate alone.
- The evidence is low, based on limited head-to-head trial data (two trials), for a difference in fracture incidence between menopausal hormone therapy and raloxifene or vitamin D.
- The evidence is insufficient regarding the use of combinations of osteoporosis therapies or sequential use of osteoporosis therapies in relation to fracture outcomes.

Key Question 2: How Does Fracture Risk Reduction Resulting From Treatments Vary Between Individuals With Different Risks for Fracture as Determined by Bone Mineral Density, Risk Assessment Score, Prior Fractures, age, sex, Race/Ethnicity, and Glucocorticoid use?

Our analysis yielded the following conclusions:

- **Bone mineral density:** Moderate evidence (post hoc analysis of one large RCT) showed that low femoral neck BMD did not predict the effect of alendronate on clinical vertebral or non-vertebral fracture risk. Post hoc analysis of two-year followup data from a large RCT of postmenopausal women with osteopenia and no prevalent vertebral fractures showed that risedronate significantly reduced the risk of fragility fracture in this group, comparable to reductions seen in women with osteoporosis.
- **FRAX risk assessment:** Moderate evidence (post hoc analysis of data from one large RCT) showed no effect of fracture risk as assessed by the WHO's FRAX on the effects of raloxifene in reducing risk for morphometric vertebral fracture among elderly women.
- **Prevalent fractures:**
    - Evidence is insufficient regarding the association between the presence of prevalent fractures (i.e., fractures that predated the start of pharmacological therapy) and the efficacy of alendronate in reducing the risk for fractures. Post hoc analysis of a large RCT showed that prevalent vertebral fractures do not predict the efficacy of alendronate; however another post hoc analysis of data from the same trial found that alendronate reduced the risk of incident nonvertebral fractures to a greater extent among women without prevalent fractures (but with T-scores ≤-2.5) than among women *with* prevalent fractures or without prevalent fractures and with T-score -2 to -2.5.
    - Evidence is insufficient regarding prevalent fracture and the efficacy of raloxifene. A post hoc analysis of one large RCT showed that raloxifene decreased the risk of major nonvertebral fracture among women with prevalent vertebral fracture, but not among women without prevalent vertebral fracture. However, two other RCTs found no influence of prevalent fracture.
    - Evidence is moderate (a post hoc analysis of one RCT) that prevalent fractures increased the relative efficacy of teriparatide in preventing fractures in postmenopausal women.
- **Age:**
    - In general, a high level of evidence suggests that bisphosphonates are at least as effective for older persons as for younger.
    - One RCT found no effect of age on the efficacy of risedronate.
    - One RCT found no influence of age on the effect of zoledronic acid in lowering the risk for vertebral or nonvertebral fractures but found that only women under 75 experienced a benefit in reduced risk for hip fracture. Another RCT found that age influences the effect of zoledronic acid on the risk for vertebral fracture risk but not the risk for nonvertebral or hip fracture. However these studies were not powered to detect differences across age groups.

- The relative effect of teriparatide on reducing the incidence of new vertebral fractures and nonvertebral fragility fractures was statistically indistinguishable in younger and older patients.
- **Sex:**
  - Evidence is insufficient regarding the effectiveness of therapies to prevent or treat osteoporosis in men. Only one RCT was identified that actually assessed the effect of sex on response to treatment. This study found that calcium plus vitamin D_3 reduced the risk of fracture among elderly women but not elderly men.
- **Race/Ethnicity:**
  - A high level of evidence (one post hoc pooled analysis of two RCTs) showed that raloxifene decreases the risk of vertebral fracture but not nonvertebral or hip fracture among Asian women; this finding is similar to that of U.S. and international studies of raloxifene.
- **Glucocorticoid treatment:**
  - Evidence is insufficient regarding the effect of glucocorticoid treatment on response to therapies. One new RCT found that teriparatide treatment was more effective in reducing risk of vertebral fractures than alendronate but equally effective in reducing risk for nonvertebral fractures.
- **Renal function:**
  - Evidence is insufficient from trials assessing the effect of renal function on the efficacy of alendronate, raloxifene, and teriparatide. Two trials report no effect of renal function on the effects of these agents. However, in a third trial, impaired renal function reduced the efficacy of zoledronic acid in preventing vertebral (but not nonvertebral or hip) fractures.

Key Question 3: What are the Adherence 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?

For this question, we identified two new systematic reviews, 18 RCTs, and 59 observational studies. We reached the following conclusions:

- Definitions of adherence and persistence vary widely across studies and over time.
- Adherence rates are higher in clinical trials than in real life, likely reflecting the select populations and controlled environments in trials; in contrast, adherence rates in observational studies tend to resemble those in real life.
- The rates of adherence and persistence observed in the studies reviewed for this report reflect closely the rates seen and examined in prior systematic reviews on the topic, as well as in the previous report. Adherence and persistence as measured in observational studies is poor. In the U.S. studies overall, about half of patients appeared to show persistence with osteoporosis treatment at 1 year, with adherence ranging widely across studies.
- Many potential barriers to adherence and persistence have been identified. Five of the most commonly assessed in published studies include age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of the

osteoporosis medications. The frequency with which these potential barriers appear in the literature does not necessarily correspond to their importance as barriers/factors related to adherence.

- Age, history of fracture, and number of concurrent medications do not appear to have an important independent association with adherence/persistence.
- Dosing frequency appears to affect adherence/persistence to a point: adherence is improved with weekly compared to daily regimens, but current evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens.
- Adverse effects—and concerns about adverse effects—appear to be important predictors of adherence and persistence. Evidence from a systematic review and 15 out of 17 observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral or both).
- The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.

Key Question 4: What are the Short- and Long-term Harms (Adverse Effects) of the Included Therapies; and do These Vary by any Specific Subpopulations?

For this question, we included 11 systematic reviews, 67 RCTs, 12 large observational studies, and six post hoc analyses. We reached the following conclusions:

- **Acute coronary syndrome, including myocardial infarction (MI):** Evidence is low (a new meta-analysis of 15 placebo-controlled trials of calcium (administered for bone health in all cases but one) for a small but significant increase in the risk for myocardial infarction in pooled results of five trials that contributed patient-level data; however serious concerns have been raised about methodological issues that may have led to bias.
- **Atrial fibrillation:** Evidence is insufficient regarding the risk for this event. The original report identified one study that showed a significant increase in the risk of atrial fibrillation for zoledronic acid relative to placebo but another that did not; the current report identified one additional trial that, when pooled with the two earlier trials of zoledronic acid, showed a significant increase in the risk for atrial fibrillation. A large Bayesian meta-analysis among users of bisphosphonates that did not reach statistical significance and several additional meta-analyses showed mixed results. In March 2010, the FDA issued a followup to its 2007 safety review, noting the inconsistency in the data and requesting that providers and patients report such side effects. Thus, a relationship between zoledronic acid and atrial fibrillation is unproven but still an area of active surveillance.
- **Pulmonary embolism (PE):** The original report identified two large studies that showed higher odds for PE among raloxifene participants than among placebo participants. The current report identified two additional studies that, when pooled with the original two, showed even higher risk for PE. Evidence is high for an increased risk for this event.
- **Venous thromboembolic events:** The original report identified four studies that showed higher risk of thromboembolic events for raloxifene-treated participants than for placebo participants. For the current report, four additional studies were identified that narrowed the confidence interval. Evidence is high for an increased risk for this event.

- **Vasomotor flushing (hot flashes):** A pooled analysis of eight studies, three from the original report and five identified for the current report, that compared raloxifene and placebo found a significant increase in vasomotor flushing among raloxifene users. Evidence is high for an increased risk for this event.
- **Esophageal cancer:** Four large observational studies identified for this report examined the risk of esophageal cancer among users of bisphosphonates. A prospective cohort study using a UK database found no increase in the risk for esophageal cancer, but two nested case control studies using the same dataset did identify an increased risk. A nested case control study of patients with Barrett's Esophagus who developed esophageal cancer also found no association with use of bisphosphonates. Evidence is insufficient regarding the risk for this event.
- **Mild upper gastrointestinal (GI) events:** We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as "mild upper GI events." Pooled analysis of 50 studies of alendronate showed greater odds of all mild upper gastrointestinal (GI) events for alendronate than for placebo. In a head-to-head comparison of alendronate with denosumab, alendronate was also more strongly associated with mild upper GI events than was denosumab. Evidence is high regarding the risk for alendronate and mild upper GI events.
- **Osteonecrosis of the jaw:** The original report identified case series and case reports describing 41 cases of osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates. One trial, two large observational studies, a post hoc analysis, and a systematic review that reported on the incidence of osteonecrosis of the jaw among individuals taking bisphosphonates to prevent or treat osteoporosis were identified for the current report. Cohort and case control studies range in their estimates of the incidence of osteonecrosis of the jaw associated with the use of bisphosphonates to prevent or treat osteoporosis from fewer than one case to 28 cases per 100,000 person-years of treatment. Thus evidence is high that the prevention and treatment of osteoporosis remains a relatively minor contributor to the development of osteonecrosis of the jaw.
- **Atypical fractures of the femur:** Seven observational studies, a pooled analysis of three trials, and a comprehensive review identified a small increase in the risk for atypical, low-trauma subtrochanteric fragility fractures of the femur with long-term use of bisphosphonates for prevention or treatment of osteoporosis. Based on this American Society of Bone and Mineral Research review, on 13 October 2010, the Food and Drug Administration, which has been conducting its own ongoing review of atypical subtrochanteric femur fracture, updated the risk of atypical fractures to the Warnings and Precautions level, acknowledging that the risk remains low compared with the numbers of osteoporotic fractures prevented by the drugs. Evidence is low for this conclusion.
- **Rashes, injection site reactions, and infection:** Pooled analysis of four trials of denosumab found an increased rate of rash but no increase in the rate of injection site reactions for the biological agent denosumab, compared with placebo. Based on evidence for an increased risk of infection, the FDA has issued a Risk Evaluation and Mitigation Strategy for the drug. A systematic review of four trials confirms the increased risk for infection. Evidence is high for these conclusions.

Key Question 5: How Often Should Patients be Monitored (via Measurement of BMD) During Therapy? How Does the Antifracture Benefit Vary With Long-term Continued use of Therapy?

For this question, we identified one systematic review and 4 RCTs. We reached the following conclusions:

- No evidence exists from RCTs regarding how often patients' BMD should be monitored during osteoporosis therapy.
- A high level of evidence exists from RCTs that lumbar spine and femoral neck BMD changes from serial monitoring predict only a small percentage of the change or do not predict the change in fracture risk from treatment with antiresorptives, including alendronate, risedronate, raloxifene, and teriparatide.
- In RCTs, even people who lose BMD during antiresorptive therapy benefit from a substantial reduction in risk of vertebral fracture. Greater increases in BMD did not necessarily predict greater decreases in fracture risk. Thus, improvement in spine bone mineral density during treatment with currently available osteoporosis medications accounts for a predictable but small part of the observed reduction in the risk of vertebral fracture. Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment. Evidence is high for this conclusion.
- Evidence is moderate (one large RCT) that, compared to using alendronate for 5 years followed by discontinuation after 5 years, continuous use of alendronate for 10 years resulted in a lower risk of vertebral fracture.

To aid the readers in identifying "what's new?" we also present these conclusions in Table A, with new conclusions (relative to the original report) identified in **bold**.

Table A. Summary of evidence

Strength of Evidence		Conclusion
Key Question 1. What are the comparative benefits in fracture risk reduction among the following treatments for low bone density:		
a. Bisphosphonates	High	Vertebral fractures: alendronate, risedronate, ibandronate, and zoledronic acid reduce the risk of vertebral fractures among postmenopausal women with osteoporosis.
	High	Non-vertebral fractures: alendronate, risedronate, and zoledronic acid reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis.
	High	Hip fractures: alendronate, risedronate and zoledronic acid reduce the risk of hip fractures among postmenopausal women with osteoporosis. **The effect of ibandronate is unclear, since hip fracture risk reduction was not a separately reported outcome in trials reporting nonvertebral fractures.**
	Low	Wrist fractures: alendronate reduces the risk of wrist fractures among postmenopausal women with osteoporosis. **Risedronate in a pooled analysis of two trials was associated with a lower risk of wrist fractures, but this did not quite reach the conventional level of statistical significance.**
	Insufficient	Data are insufficient from head-to-head trials of bisphosphonates to prove or disprove superiority for the prevention of fractures for any agent.
	Insufficient	Data are insufficient from head-to-head trials of bisphosphonates compared to calcium, **teriparatide,** or raloxifene to prove or disprove superiority for the prevention of fractures.
	Moderate	Based on six RCTs, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison with menopausal hormone therapy.

Table A. Summary of evidence (continued)

Strength of Evidence		Conclusion
b. 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.
c. Denosumab	**High**	**Denosumab reduces the risk of vertebral, nonvertebral and hip fractures in postmenopausal women with osteoporosis.**
d. Menopausal hormone therapy	**High**	Menopausal hormone therapy reduces the risk of vertebral and hip fractures in postmenopausal women.
	Moderate	**Menopausal hormone therapy does not reduce fracture risk significantly in postmenopausal women with established osteoporosis.**
e. PTH (teriparatide)	**High**	**Teriparatide reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.**
	Moderate	**Teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.**
f. SERMs (raloxifene)	High	Raloxifene **reduces the risk of** vertebral fractures among postmenopausal women with osteoporosis.
g. Vitamin D	**Low-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.
h. Exercise in comparison to above agents	**Insufficient**	There are no data from RCTs to inform this question. **One RCT that assessed the effect of a brief exercise program on fracture risk found a small decrease in risk of fractures among exercisers but the study was not powered to detect differences in fracture risk.**
Key Question 2. How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), *risk assessment score,* ***prior fractures (prevention vs. treatment),[c] age, sex, race/ethnicity, and glucocorticoid use?***		
High		Alendronate, ibandronate, risedronate, teriparatide, raloxifene, **zoledronic acid,** and **denosumab** reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis.
Moderate		**Low femoral neck BMD does not predict the effects of alendronate on clinical vertebral or nonvertebral fracture risk.**
Insufficient		**Prevalent fracture predicted the effect of alendronate on fracture risk in one study but not another.**
Low-moderate		**Risedronate reduces the risk of fragility fracture among postmenopausal women with osteopenia who do not have prevalent vertebral fractures.**
Insufficient		**Prevalent fracture predicts the efficacy of raloxifene for fracture prevention in some studies but not others.**
Moderate		**Prevalent fractures increase the relative efficacy of teriparatide in preventing fractures.**

[c] Prevention vs. treatment: If a person begins pharmacotherapy after having sustained fractures (i.e., the person has prevalent fractures), the therapy is considered treatment because the person, by definition, has osteoporosis and the medication is being administered to treat the condition. When these medications are administered to individuals with no prior fractures, these are individuals who have been identified as being at risk for osteoporosis (due to low bone density), but who don't actually (yet) have osteoporosis. They are being given the medication to prevent the onset of osteoporosis (i.e., further lowering of bone density and/or a first fracture).

Strength of Evidence	Conclusion
Moderate	Raloxifene prevents fractures in postmenopausal women at low risk for fracture **as assessed by FRAX.**
Insufficient	Teriparatide and risedronate **but not calcium and vitamin D** reduce risk of fracture among *men*.
High	**In general age does not predict the efficacy of bisphosphonates or teriparatide.**
High	**Raloxifene decreases the risk for vertebral fracture but not nonvertebral or hip fracture among postmenopausal Asian women, similar to other postmenopausal women.**
Moderate-High	Among *subjects treated with glucocorticoids*, fracture risk reduction was demonstrated for alendronate, risedronate, and **teriparatide.**
Insufficient	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*.
Insufficient	**Evidence is inconclusive on the effects of renal function on the efficacy of alendronate, raloxifene, and teriparatide in preventing fractures.**
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*.
Key Question 3. What are the adherence 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?	
Moderate	**Eighteen RCTs reported rates of adherence to therapy. Twelve trials with bisphosphonates and two trials with denosumab reported high levels of adherence (majority with over 90% adherence). Two trials with raloxifene had adherence rates 65-70%.**
High	**There is evidence from 58 observational studies, including 24 using U.S. data, that adherence and persistence with therapy with bisphosphonates, calcium, and vitamin D is poor in many patients with osteoporosis. One study described adherence with teriparatide. No studies describe primary nonadherence (i.e. nonfulfillment).**
Moderate	**Based on evidence from 41 observational studies, many factors affect adherence and persistence with medications including, but not limited to, dosing frequency, side effects of medications, co-morbid conditions, knowledge about osteoporosis, and cost. Age, prior history of fracture, and concomitant medication use do not appear to have an independent association with adherence or persistence.**
High	**Based on 20 observational studies, dosing frequency appears to affect adherence/persistence: adherence is improved with weekly compared to daily regimens, but current evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens.**
Moderate	**Evidence from a systematic review and 15 out of 17 observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral or both).**
Low	**The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.**

Strength of Evidence	Conclusion
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?	
High	Participants who took raloxifene showed higher odds for pulmonary embolism than did participants who took a placebo. Raloxifene participants also had greater odds of thromboembolic events.
High	Estrogen and estrogen-progestin combination participants had higher odds of cerebrovascular accident (CVA) and thromboembolic events than did placebo participants.
High	**A pooled analysis of ten trials found an increased risk with raloxifene for myalgias, cramps, and limb pain.**
High	We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as “mild upper GI events.” Our pooled analyses **showed alendronate had a slightly increased risk of** mild upper GI events. Alendronate participants also had higher odds of mild upper GI events in head-to-head trials vs. menopausal hormone therapy. **Pooled analysis also showed alendronate users to be at an increased risk for mild GI events compared to denosumab. Denosumab was also associated with an increase in mild GI events.**
Low	**A new systematic review of 15 placebo-controlled trials of calcium (administered for bone health in all trials but one) identified a statistically significant increase in the risk of myocardial infarction; however serious concerns have been expressed about possible bias.**
Moderate	**Teriparatide-treated participants showed a significant increase in hypercalcemia.**
Insufficient	The literature is equivocal on the potential association between bisphosphonates and the risk of atrial fibrillation.
High	**One trial, one post hoc analysis of three trials, two large observational studies, and a review of 2,408 cases of osteonecrosis of the jaw in patients taking bisphosphonates for osteoporosis prevention or treatment found that the incidence of osteonecrosis of the jaw in this group was small, ranging from less than one to 28 cases per 100,000 person-years of treatment.**
High	**Our pooled analysis of eight trials found an increased risk with raloxifene of hot flashes.**
Low	**Limited data from clinical trials and observational studies support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Data are not consistent, nevertheless these data were sufficient for FDA to issue a Warning regarding this possible adverse event.**
Moderate	**A pooled analysis of three trials of teriparatide found an increased risk of headaches.**
High	**A pooled analysis of four trials of denosumab found an increased risk of rash but no increase in the risk for injection-site reactions.**
Moderate	**A small number of clinical trials have reported an increased risk of hypocalcemia in patients treated with alendronate and zoledronic acid.**
Insufficient	**Four observational studies that assessed whether the use of an oral bisphosphonate is associated with an increased risk of esophageal cancer had mixed findings.**
High	**A pooled analysis of four trials of denosumab found an increased risk for infection.**

Strength of Evidence	Conclusion
Key Question 5a. How often should patients be monitored (via measurement of bone mineral density) during therapy?	
Insufficient	The role of BMD monitoring during therapy has not been explicitly studied; therefore any conclusions must be based on indirect evidence.
High	Changes in BMD during therapy account for only a small proportion of the decrease in fracture risk; while some studies suggest that greater change in BMD in active therapy groups predicts greater antifracture efficacy, these changes have not been demonstrated to apply to individuals. Even patients who continue to lose BMD during therapy have had statistically significant benefits in fracture reduction. Clinical guidance is lacking on appropriate responses to declines in BMD under active therapy, such as increasing medication dose, or the influence of discontinuing therapy among individuals who experience declines in BMD under active therapy but may nonetheless derive fracture protection.
Key Question 5b. How does the antifracture benefit vary with long-term continued use of pharmacotherapy?	
Moderate	One large RCT showed that after 5 years of initial alendronate therapy, vertebral fracture risk and nonvertebral fracture risk were lower if alendronate was continued for an additional 5 years instead of discontinued.
Low	A post hoc analysis of this same trial reported that there were statistically significant nonvertebral fracture risk reductions for women who at baseline had no vertebral fracture but had a BMD score of –2.5 or less.

What We Know About Whom To Treat and How

For clinicians, this report contributes information that may inform prescribing decisions:

- Evidence for antifracture effects of currently available osteoporosis therapies is greatest among those with established osteoporosis, meaning with existing fracture, or with T-score less than -2.5. Because at least half of osteoporotic fractures occur in individuals with T scores between -1 and -2.5, individuals with T-scores between -1 and -2.5 who are likely to experience fracture need to be identified.
- With the advent of tools such as the WHO’s FRAX, selection of treatment candidates will likely be refined. Emerging research is judging the antifracture effects of medications according to level of multivariable risk prediction instruments.
- Older individuals are as likely, or may be even more likely, to benefit from treatment as younger individuals, in terms of reduced fracture risk.
- Bisphosphonates and denosumab are the only agents for which there is a high level of evidence for reduction in hip fracture risk.
- For reduction in vertebral fracture risk, there is a high level of evidence supporting the use of bisphosphonates, raloxifene, teriparatide, and denosumab.
- Raloxifene has been shown to be not effective in reducing the risk of hip or nonvertebral fractures.
- To date, the comparative efficacy of available treatments has not been assessed among men with idiopathic osteoporosis.
- Although not definitive proof of who is likely to benefit from prolonged alendronate therapy, post hoc analyses of open-label extension data support the thesis that certain features predict continued fracture reduction with a 10-year instead of 5-year duration of alendronate therapy: BMD T-score of -1 to -2 (if women have baseline fractures), and BMD T-score <-2 if women do not have baseline fractures. These same factors have not

been evaluated with other osteoporosis pharmacotherapies. Studies have not directly compared the antifracture effects of longer durations of therapy among various therapies.
- Clinicians should be aware that, among people taking FDA-approved osteoporosis pharmacotherapy, changes in BMD are not good predictors of antifracture effects. Studies are currently examining whether serial BMD monitoring may be useful for other purposes.

Remaining Issues

Compared with the evidence available at the time of the prior report, additional evidence has emerged to clarify differences in anti-fracture efficacy between pharmacologic agents used to treat osteoporosis (e.g., hip fracture reduction only demonstrated for bisphosphonates and denosumab), and even among bisphosphonates (e.g., hip fracture reduction demonstrated for zoledronic acid, alendronate, and risedronate, but not ibandronate) among postmenopausal women with established osteoporosis. Nonetheless, data are thin regarding the comparative effectiveness or efficacy between different agents, and several concerns remain:

1. Whom should we treat? What is the balance of benefits and harms for postmenopausal women without established osteoporosis? The existing evidence shows that the strength of evidence for a benefit of treatment (in terms of fracture risk reduction) is low to moderate for postmenopausal women with osteopenia and without prevalent fractures and for men compared with postmenopausal women with established osteoporosis for whom the evidence is high. Given the established adverse events associated with treatment, and newly identified risks such as atypical subtrochanteric femur fractures, the question of whom to treat outside of postmenopausal women with established osteoporosis is perhaps less clear now than it was before. One way forward is to move away from BMD-based measures of risk and conduct trials that use a risk assessment-based method of identifying patients, such as the FRAX. Such risk assessment methods can incorporate other variables known to be associated with risk of fracture that go beyond bone mineral density. Re-analysis of existing trials should assess whether application of FRAX estimates post hoc allows for identification of subgroups of subjects at higher or lower risk than the typical subjects.
2. How long should we treat? The evidence base here is especially thin—the existing evidence is really just one trial, and one post hoc analysis of that trial, which suggests that treatment beyond five years with alendronate does not have a benefit in nonvertebral fracture risk reduction, except possibly in women with low BMD at baseline. Should treatment be for three years, four years, five years, or more? And what patient factors are important (such as the aforementioned low BMD at baseline) in terms of determining length of treatment? “Drug holidays” have been advocated by some clinicians—what are the benefits and harms of such holidays? When should they be timed? For how long should the “holiday” last? Could the efficacy of drug holidays vary according to pharmacologic profiles (e.g., route or frequency of administration) of the various bisphosphonates? And should all therapies be subject to a holiday, a point raised by a recent basic science analysis of denosumab?[22]
3. For people who are good candidates for treatment, how can we improve adherence? There is a moderate to high level of evidence that adherence is commonly poor, and that poor adherence is associated with worse fracture outcomes. This work needs to consider not just the dosing barriers to adherence, but the other factors reported

in the evidence (e.g., side effects, knowledge about osteoporosis, and cost.) The role of newer therapies administered once or twice yearly in improving adherence and persistence, and their cost-effectiveness, should be investigated.

4. For patients on treatment, should we monitor changes in BMD, and if so, how often? While no studies have examined explicitly the benefits and harms of BMD monitoring while on therapy, the practice remains popular, although the rationale for it is not clear. Post hoc analyses of trials of treatment show that changes in BMD while on treatment only modestly predict fracture risk reduction, and even patients whose BMD declines while on treatment have statistically significant reductions in fracture risk.
5. What is the comparative effectiveness of sequential treatment (following treatment with one class of agent by treatment with another)? We identified no clinical trials on the use of sequential treatment, although anecdotal evidence suggests that it is done in clinical practice (either intentionally, in the belief that it is superior to continued treatment with a single agent, or because some individuals do not respond to or cannot tolerate a particular agent). Thus studies are needed to assess the effectiveness of sequential regimens.
6. We need to remain vigilant for possible rare side effects. The identification—since our prior 2007 report—of an association between bisphosphonate use and atypical subtrochanteric fractures of the femur demonstrates the importance of the continuing need for surveillance, as this identification was not widely reported until after well more than a decade of widespread use.

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Introduction

Background

Osteoporosis is a systemic skeletal disease characterized by decreasing bone mass and microarchitectural deterioration of bone tissue, with consequent increases in bone fragility and susceptibility to fracture.[1] In addition to fractures, the clinical complications of osteoporosis include disability and chronic pain. Approximately 52 million people in the United States are affected by osteoporosis or low bone density. It is especially common in postmenopausal women,[2] but one in five men will experience an osteoporosis-related fracture at some point in his lifetime.[3]

The economic burden of osteoporosis is large and growing: the most recent estimate of US annual costs due to fractures alone have been nearly $20 billion.[2]A recent projection of the burden and costs of incident osteoporosis-related fractures in the United States from 2005 to 2025 estimates more than 2 million fractures in 2010 with direct medical costs of more than $18 billion (more than 25 percent attributable to men).[4] Although the bulk of these costs are incurred by individuals 65 and older, direct costs and productivity loss among working women under 65 are considerable.[2]

Diagnosis and Risk Factors

The clinical diagnosis of osteoporosis may be based on results of bone mineral density (BMD) testing[3,5,6] BMD is measured with dual energy x-ray absorptiometry (DXA). In postmenopausal women and men over 50 years, BMD is classified according to the T-score. The T-score is the number of standard deviations above or below the mean for healthy 20–29 year old adults[a], as determined by DXA. Osteoporosis is defined as a T-score of -2.5 or less. A T-score between -2.5 and -1.0 is defined as “low bone density.” A T-score of -1 or greater is considered normal. Bone density can also be classified according to the Z-score, the number of standard deviations above or below the expected BMD for the patient’s age and sex. A Z-score of -2.0 or lower is defined as either “low bone mineral density for chronological age” or “below the expected range for age,” and those above -2.0 are “within the expected range for age.” Individuals who have already had minimal trauma fracture are at increased risk of future osteoporotic fracture, independent of BMD.[3] Because the majority of fractures occur in patients with low bone mass rather than osteoporosis,[3] risk scores that combine clinical risk factors with BMD testing results, such as FRAX, have recently been developed to refine the ability to predict fracture risk among people with low bone density.

Risk factors for osteoporotic fracture include (but are not limited to) increasing age, female sex, postmenopause for women, hypogonadism or premature ovarian failure, low body weight, history of parental hip fracture, ethnic background (whites are at higher risk than blacks), previous clinical or morphometric vertebral fracture, previous fracture due to minimal trauma

[a] Note: Authorities disagree about whether to use young males or young females as the reference group to assess T scores in men.

(i.e. previous osteoporotic fracture), rheumatoid arthritis, current smoking, alcohol intake (3 or more drinks/day), low BMD, vitamin D deficiency, low calcium intake, hyperkyphosis, falling, and immobilization, along with chronic use of certain medications, the most commonly implicated being glucocorticoids, anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadatropin-releasing hormone agonists.[3]

Several algorithms have been devised and validated for the prediction of osteoporotic fracture risk. Current National Osteoporosis Foundation guidelines as well as others endorse the use of the FRAX to select candidates for treatment.[7-9] The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women.[9,10] FRAX is a set of race- and nationality-specific algorithms that take into account an individual's age, sex, weight, height, previous fracture, parental history of osteoporotic fracture, smoking status, alcohol use, history of use of glucocorticoids, history of rheumatoid arthritis, secondary causes of osteoporosis, and femoral neck BMD to estimate the absolute 10-year risk of major osteoporotic fractures (i.e. clinical vertebral, hip, forearm, or proximal humerus fractures). Risk for osteoporosis may be viewed as a continuum that depends on all of these factors. A question of considerable interest is whether antifracture response to treatment is affected by (or predicted by) FRAX score.[3,11]

Therapy

The most recent National Osteoporosis Foundation Clinician's Guide recommends considering therapy for postmenopausal women and men age 50 and older presenting with the following: a hip or vertebral (clinical or morphometric) fracture; T-score $\leq$ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes; Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture $\geq$ 3 percent or a 10-year probability of a major osteoporosis-related fracture $\geq$ 20% based on the US-adapted WHO algorithm[3].

The increasing prevalence and cost of osteoporosis have heightened interest in the effectiveness and safety of the many interventions currently available to prevent osteoporotic fracture. These interventions include pharmacologic agents, a biological agent, dietary and supplemental vitamin D and calcium, and weight-bearing exercise.

Pharmacologic agents include the bisphosphonate class of drugs, peptide hormones (parathyroid hormone and calcitonin), estrogen (in the form of menopausal hormone therapy[b]) for postmenopausal women, and selective estrogen receptor modulators (raloxifene for postmenopausal women). With the exception of parathyroid hormone (teriparatide), each of these agents acts to prevent bone resorption: Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical periosteal and/or endosteal bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. The bisphosphonates, are compounds that bind reversibly to mineralized bone surfaces and disrupt resorption by the

[b] The North American Menopause Society has established the following terminology for menopausal hormone therapy (formerly referred to as hormone replacement therapy): EPT=combined estrogen-progestogen therapy; ET=estrogen therapy; HT=therapy that encompasses both EPT and ET.

osteoclasts. The original bisphosphonates, etidronate and clodronate, were short-chain molecules that inhibited bone resorption by disrupting the oxidative phosphorylation pathway. The second generation, which includes alendronate and pamidronate, and the third generation, which includes risedronate and zoledronic acid, contain an amino group; these molecules inhibit bone resorption by inhibiting fatty acid; they may be associated with fewer adverse effects than the first generation. A newer therapeutic agent, denosumab, was approved by the FDA in June 2010. Denosumab is a monoclonal antibody that inhibits the Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL), a stimulator of osteoclast differentiation and activation. By inhibiting osteoclast formation, function, and survival, denosumab decreases bone resorption. Although denosumab is classified by the FDA as a biological, it will be considered a pharmacological agent for the purposes of this report.

Besides pharmacologic agents, dietary and supplemental calcium and vitamin D, as well as weight bearing exercise, play important roles in preserving bone mass. Lifelong calcium intake is required for the acquisition of peak bone mass and for the subsequent maintenance of bone health.[3] When serum calcium levels are inadequate, bone tissue is resorbed from the skeleton to maintain serum calcium at a constant level. Adequate vitamin D levels play a key role in calcium absorption, bone health, muscle performance, balance, and fall prevention.[3]

The various agents used to prevent and treat osteoporosis have been linked with adverse effects, from the more common, mild effects (such as minor gastrointestinal complaints) to potentially serious issues. Some evidence suggests that these minor complaints, coupled with concerns about more serious effects, may affect the level of compliance with and persistence of treatment level of compliance with and persistence of treatment. Poor adherence and persistence may, in turn, affect the effectiveness of the treatments. These issues drove the scope of this report and its predecessor.

The FDA Approval Process

In 1979, the FDA published its first Guidance Document for the clinical evaluation of the safety and effectiveness of drugs to treat osteoporosis.[12] 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 study size and duration needed to detect changes in bone density and/or fracture risk. Inclusion criteria for FDA clinical trials consisted of objective evidence of participant disease (i.e., 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 effectiveness 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.

The 1984 Guidance Document included several noteworthy changes. Studies were recommended that would establish an indication for the prevention of postmenopausal osteoporosis. In addition, DXA was described as providing a valid measure of spinal bone mass, and it was recommended that all participants in trials of agents for osteoporosis therapy be supplemented with calcium and vitamin D.

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 effects 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 that treatment resulted in preservation or improvement in bone density while retaining normal bone quality[b] 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 trend toward decreased fracture risk after three years (not two years) of treatment. The 1994 Guidance Document also affirmed the use of DXA and bone turnover markers for phase I and II trials and provided requirements for approval of agents for prevention of osteoporosis (in individuals at high risk but without history of osteoporotic fracture).[13] 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 effectiveness 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 (of estrogen as used to treat menopausal symptoms), estrogen was approved for treatment of postmenopausal osteoporosis. Thus it was exempted from the requirement that it demonstrate effectiveness for fracture prevention, and was approved for both treatment and prevention based on BMD alone. Subsequently, however, the FDA has required evidence of fracture effectiveness or 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.

[b] The FDA recognizes that components of bone strength include bone mineral density and bone quality; some aspects of bone quality that might affect fracture risk have been identified but are difficult to measure. Nevertheless, the requirements for approval specify that drugs must not result in accretion of new bone (or preservation of existing bone) with abnormal morphology.

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 (however, approval for a different indication, such as glucocorticoid-induced osteoporosis, does require demonstration of reduction in fracture risk). These implications of the current guidance have heightened interest in evaluating the data on the effects of drugs approved to treat and prevent osteoporosis.

The 2007 Comparative Effectiveness Review

In December, 2007, the Evidence-based Practice Center (EPC) completed the first Comparative Effectiveness Review (CER) on the efficacy/effectiveness of these interventions in preventing osteoporosis-related fracture, their safety, and compliance with their use.[14]

The review found a high level of evidence suggesting that, compared with placebo, alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, teriparatide, and raloxifene prevent vertebral fractures; the evidence for calcitonin compared with placebo was fair. The report also found a high level of evidence to suggest that alendronate, risedronate, and estrogen prevent hip fractures, compared with placebo; the evidence for zoledronic acid was fair. No studies were identified that assessed the effect of testosterone on fracture risk. The evidence for an effect of vitamin D on both vertebral and hip fractures varied with dose, analogue, and study population. No antifracture evidence was available for calcium or physical activity.

Further, the evidence was insufficient to determine the relative superiority of any agent or whether the agents were more effective in some populations than others.

Regarding adverse events associated with the pharmacologic agents, raloxifene, estrogen, and estrogen–progestin increased the risk for thromboembolic events, and etidronate increased the risk for esophageal ulcerations and gastrointestinal perforations, ulcerations, and bleeding. The use of menopausal hormone therapy was associated with an increased risk of breast cancer, heart disease, and stroke in the Women’s Health Initiative trial. Clinical trials reported mixed findings regarding an association of zoledronic acid with the risk for atrial fibrillation. No data were found from osteoporosis trials to suggest an association between bisphosphonates or any other agents and the development of osteonecrosis: A number of case reports and case series articles reported osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates.

Although fracture trials that reported data on adherence/compliance tended to find relatively good adherence to medication use, observational studies tended to report poor adherence with osteoporotic medications, as with other chronic conditions. Poor adherence was associated with lower effectiveness.

This Report

Since the release of the original report, several of the bisphosphonates have become available in new, less frequently administered, forms, and a new biological agent (denosumab) is now available. In addition, new data have been released on adverse events associated with

bisphosphonates. Thus, in 2008, the EPC was asked to conduct an assessment of the need to update the original report (as well as the other CER reports released up to that time point); that report was submitted in March, 2009.[15] For that report, the EPC conducted an abbreviated search and review of the literature addressing the topics of the first review. The abbreviated search consisted of a survey of experts in the field and a MEDLINE® search (using the same search terms as the original report) of 5 of the leading medical journals and 5 leading specialty journals dating from 2006 to mid-2008. The studies identified in this search that addressed the key questions were reviewed and abstracted, and their findings qualitatively assessed using a process devised by the EPC to determine whether they confirmed, contradicted, or augmented the conclusions of the original report.

The update search identified new data on effectiveness and adverse effects. New studies were found for several agents, including denosumab, that were not included in the original report. In addition new data were found for the effects of calcium and vitamin D and for novel dosing schedules or routes of administration of the bisphosphonates, ibandronate and zoledronic acid. Based on this evidence, the assessment concluded that at least some of the conclusions of the first report regarding effectiveness may need to be updated (Key Question 1 – see below). In addition, the assessment found new evidence on the safety of some agents that might warrant an update. For example, new evidence was found on the risk of atrial fibrillation with the use of some bisphosphonates and the risk of osteosarcoma with the use of teriparatide. Also, the FDA issued a labeling revision in December 2007 regarding the possible association of the use of pamidronate with deterioration of renal function (CER Updates Assessment, 2009 - unpublished). Based on these findings, the Update Assessment suggested an updated review of the adverse effect evidence (Key Question 4).

Scope and Key Questions

In July 2009, the EPC was asked by AHRQ to conduct a full update of the original CER. Key question 1 has been modified to include medications that were not approved for the treatment of osteoporosis prior to the release of the original report but have since been approved, including zoledronic acid (IV) (Reclast®; Novartis; once-a-year infusion) and the monoclonal antibody, denosumab (Prolia®; Amgen; every-six-months injection) and agents for which no or few data were available for inclusion in the original report, such as injectable ibandronate sodium (Boniva®; Roche Laboratories/Hoffman laRoche; once every three months). We also omitted several agents—etidronate, pamidronate, tamoxifen, and testosterone—based on their not being indicated or used for osteoporosis treatment, and also modified the question to include consideration of the sequential or combined use of different agents. Although new evidence was found for strontium ranelate, it is not likely to be considered for FDA approval in the near future, so it was not included.

Key Question 2 originally assessed the evidence for effectiveness among particular subpopulations of clinical interest. The subpopulations to be considered in the evidence review update were also augmented to include racial/ethnic differences based on evidence of differences in BMD and potential risk for osteoporosis. The subject matter experts also recommended considering the comparative utility of existing risk assessment algorithms for predicting antifracture effects of osteoporosis pharmacotherapy, i.e., whether differences in antifracture effects would be found among groups with different FRAX (or other) risk assessment cutoffs.

Key Question 3, which addresses compliance and adherence, remains as it was originally.

Key Question 4, which assesses adverse effects of the pharmacologic agents, was modified in keeping with the scope to exclude uses of the agents for any condition other than osteoporosis/low bone density.

The subject matter experts also recommended that an additional question be added. Because the optimal duration for therapy (and the role of monitoring in determining how long to treat) remains unknown, a question was added to address therapy duration and efficacy and effectiveness monitoring. Key Question 5 has two parts. The first part aims to assess the evidence that antifracture effects are predicted by DXA monitoring of BMD. The second part which is really a sub-question to Key Question 1 aims to assess the evidence for comparative efficacy and effectiveness of long-term therapy (defined by the consensus of the technical expert panel as therapy of 5 years or more). Thus the following questions guided the current report (Figure 1 shows the analytic framework).

Key Question 1. What are the comparative benefits in *fracture risk reduction* among the following therapeutic modalities for low bone density:

- Bisphosphonate medications, specifically:
  - Alendronate (Fosamax®, oral)
  - Risedronate (Actonel®; oral once-a-week)
  - Ibandronate (Boniva®)
  - Zoledronic acid (Reclast®, Zometa®, oral and IV).
- Denosumab (Prolia®)
- Menopausal Estrogen therapy for women (numerous brands and routes of administration)
- Parathyroid hormone (PTH)
  - 1-34 (teriparatide) (Forteo®)
- Selective estrogen receptor modulators (SERMs), specifically
  - Raloxifene (Evista®)
- Calcium
- Vitamin D
- Combinations or sequential use of above
- Exercise in comparison to above agents

Key Question 2. How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by the following factors:

- Bone mineral density
- FRAX or other risk assessment score.
- Prior fractures (prevention vs. treatment).
- Age
- Sex
- Race/ethnicity
- Glucocorticoid use
- Other factors (e.g., community dwelling vs. institutionalized, vitamin D deficient vs. not)

Key Question 3: Regarding treatment adherence and persistence,[c]

- a. What are the levels of adherence and persistence with medications for the treatment and prevention of osteoporosis?
- b. What factors affect adherence and persistence?
- c. What are 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 (when used specifically to treat or prevent low bone density/osteoporotic fracture), and do these vary by any specific subpopulations (e.g., the subpopulations identified in Key Question 2)?

Key Question 5: With regard to treatment for preventing osteoporotic fracture:

- a. How often should patients be monitored (via measurement of bone mineral density) during therapy, how does bone density monitoring predict antifracture benefits during pharmacotherapy, and does the ability of monitoring to predict antifracture effects of a particular pharmacologic agent vary among the pharmacotherapies?
- b. How does the antifracture benefit vary with long-term continued use of pharmacotherapy, and what are the comparative antifracture effects of continued long-term therapy with the various pharmacotherapies?

Table 1 describes selected characteristics of, and current indications for, the drugs evaluated in this review.

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[c] The terms adherence and persistence are defined based on principles outlined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).(Cramer, 2008) Adherence (or compliance) is defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.” Although not specifically stated in the ISPOR definition, we view adherence to specific dosing instructions (which for bisphosphonates can affect both effectiveness and risk of adverse events) as an important component of adherence. Persistence is defined as “the duration of time from initiation to discontinuation of therapy.”(Cramer, 2008)

Table 1. Prescription drugs indicated for prevention and treatment of low bone density/osteoporosis

Drug	Trade Name(s)	Labeled Indications	Dosing	Dose Adjustments for Special Populations
		Bisphosphonates		
Alendronate Source: Merck & Co., Inc., March 2010	Fosamax®	Indicated for treatment and prevention of osteoporosis in postmenopausal women; increasing bone mass in men with osteoporosis; treatment of glucocorticoid(GC)-induced osteoporosis in men and women with low bone mass	One 10 mg tablet, once daily, or 70mg (as tablet or oral solution) once weekly 70 mg (as tablet or oral solution) once weekly, or one 10 mg tablet daily One 35 mg tablet weekly or one 5 mg tablet daily One 5mg tablet daily	Treatment of postmenopausal women with osteoporosis Treatment of men with osteoporosis Prevention of osteoporosis in postmenopausal women Treatment of glucocorticoid-induced osteoporosis
Ibandronate Source: Genentech, Jan. 2010	Boniva®	Indicated for treatment and prevention of osteoporosis in postmenopausal women	One 150 mg tablet once monthly or one 2.5 mg tablet once daily or 3 mg injectable every 3 months	No dose adjustment necessary
Risedronate	Actonel® Actonel w/ calcium® Atelvia®	Indicated for treatment and prevention of osteoporosis in postmenopausal women and glucocorticoid-induced osteoporosis; Treatment to increase bone mass in men with osteoporosis	Treatment of postmenopausal women: 5 mg daily; 35 mg, weekly; 75 mg taken on two consecutive days each month; or 150 mg once monthly; Actonel with calcium is packaged as the once weekly 35mg with 1,250 mg calcium carbonate tablets to be taken daily; Atelvia is taken once weekly after breakfast	Prevention in postmenopausal women: 5 mg daily or 35 mg weekly; Men: 35 mg weekly; Treatment and prevention of glucocorticoid-induced osteoporosis: 5 mg daily
Zoledronic Acid	Reclast®	Indicated for treatment and prevention of osteoporosis in postmenopausal women and glucocorticoid-induced osteoporosis; Treatment to increase bone mass in men with osteoporosis	Treatment of postmenopausal women: 5mg infusion annually; prevention in postmenopausal women: 5 mg infusion biennially	Treatment of men with osteoporosis and treatment and prevention of glucocorticoid-induced osteoporosis: 5 mg infusion annually

Table 1. Prescription drugs indicated for prevention and treatment of low bone density/osteoporosis (continued)

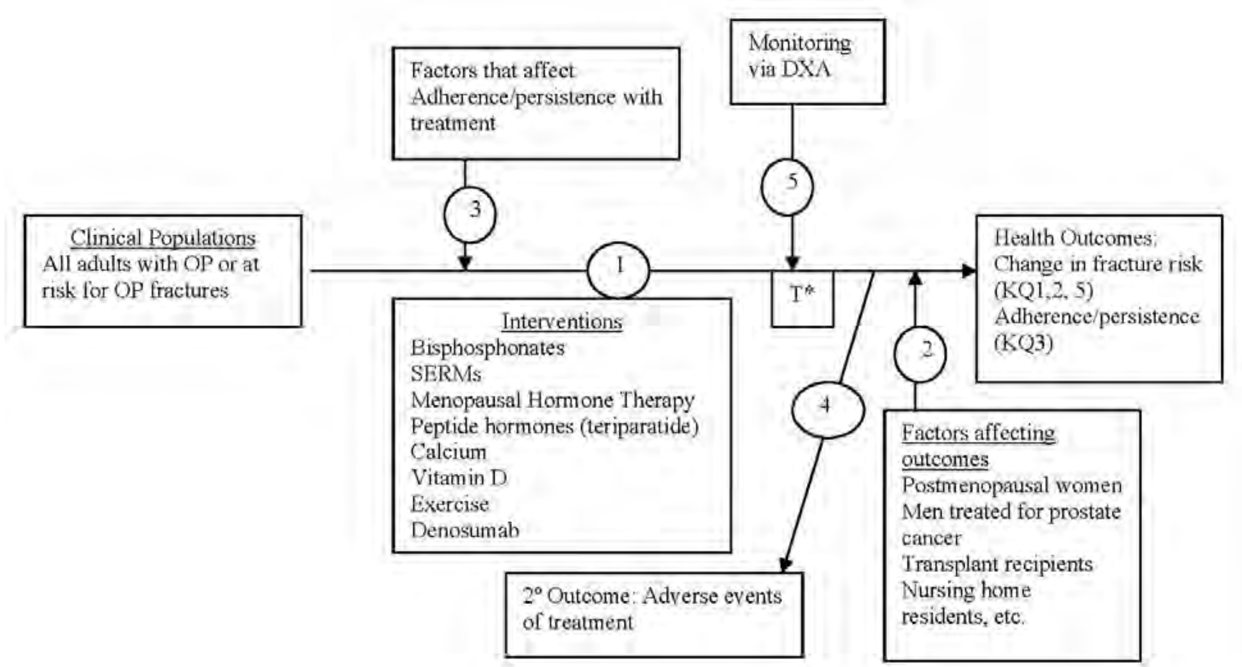
Drug	Trade Name(s)	Labeled Indications	Dosing	Dose Adjustments for Special Populations
Selective Estrogen Receptor Modulators (SERMs)				
Raloxifene	Evista®	Indicated for treatment and prevention of osteoporosis in postmenopausal women	60 mg tablet once daily	n/a
Peptide Hormones				
Teriparatide	Forteo®	Indicated for treatment of osteoporosis in postmenopausal women at high risk for fracture	20 mcg subcutaneously once daily	To increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or to treat men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture: same dose
Steroid Hormones				
Conjugated equine estrogen	Premarin®	Indicated for prevention of postmenopausal osteoporosis	0.3 mg tablet daily	n/a
Conjugated estrogen (CEE)/Medroxyprogeste rone (MPA)	Prempro®	Indicated for prevention of postmenopausal osteoporosis	0.3 mg CEE/1.5 mg MPA daily;0.45 CEE/1.5 mg MPA; 0.625 mg CE/2.5 mg MPA; 0.625 CEE/5 mg MPA	n/a
Estradiol(E)/norgestimat e(NE)	Prefest®	Indicated for prevention of postmenopausal osteoporosis	1.0 mg E daily for 3 consecutive days; 1.0 mg E/ 0.09 mg NE daily for next 3 consecutive days	n/a
17β Estradiol/norethindrone acetate	Activella® femhrt® etc.	Indicated for prevention of postmenopausal osteoporosis	Activella: 1.0 mg E.0.5 mg NE or 0.5 mg E/0.1 mg NE daily Femhrt: 1/0.5 mg or 0.5/0.25 mg daily	n/a
17β Estradiol/levonorgestrel transdermal	ClimaraPro®	Indicated for prevention of postmenopausal osteoporosis	0.045mg estradiol/ 0.015 mg levonorgestrel delivered daily	n/a
Estradiol oral	Estrace Oral®	Indicated for prevention of postmenopausal osteoporosis	0.5, 1 or 2 mg daily	
Estradiol transdermal	Vivelle® Climara® menostar®	Indicated for prevention of postmenopausal osteoporosis	Variable	n/a

Table 1. Prescription drugs indicated for prevention and treatment of low bone density/osteoporosis (continued)

Drug	Trade Name(s)	Labeled Indications	Dosing	Dose Adjustments for Special Populations
Biologicals				
Denosumab	ProliaTM®	Indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.	60 mg injected subcutaneously every six months	n/a

Figure 1 shows the inter-relationships of study-level factors and outcomes addressed by the key questions. The population of interest is all adults with osteoporosis or who are at risk for osteoporosis, with the exception of those with cancer and those with other diseases of the bone. Key Question 1 addresses the effectiveness of drugs, dietary supplements (vitamin D and calcium), and exercise in preventing fractures. Key Question 2 addresses factors that might affect the effectiveness of the treatments addressed in Key Question 1 (effects of the agents in subpopulations) in terms of fracture risk. Key Question 3 addresses the specific effect of adherence to and persistence with medication on the effects of these medications as well as factors that affect adherence and persistence. Key Question 4 addresses adverse events associated with treatment. Key Question 5 addresses the effects of monitoring and treatment duration on the effects of treatment.

Figure 1. Analytic framework



BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; OP = osteoporosis; SERMs = selective estrogen receptor modulators
*T connotes the timing of outcome measurement for studies that will be included, which will vary by KQ.

Methods

Topic Development

The topic for the original report was nominated in a public process involving input from technical experts and the AHRQ Effective Health Care Program. For this update, a new technical expert panel reviewed the key questions that guided the original report and suggested modifications as well as the addition of a new question. After approval from AHRQ, these revised questions were posted to a public Web site to permit public comment. Comments were reviewed by the research team and the technical expert panel; although no changes were made to the questions (except to clarify the parameters of long-term treatment), the comments are addressed within this report.

Search Strategy

As described in the first report[14] we used a three-pronged approach to searching for relevant literature. First, we conducted 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 adapted for use in the other databases. Using the same basic search rules used for the original report (with the addition of several new terms for additional drugs), we searched MEDLINE® for the period from January 2005 to March 2011. We also searched Embase, the American College of Physicians (ACP) Journal Club database, the Cochrane controlled trials register, and relevant pharmacological databases. For the drugs not included in the original report, we also rescreened titles from the searches conducted for that report and mined references from articles identified in the update searches.

In searching for efficacy and effectiveness studies, we used terms for osteoporosis, osteopenia, low bone density, and the drugs listed in Key Question 1. In our search for the key adverse events (AE), we used terms for the AE and each of the drugs of interest. In our search for studies of adherence and persistence, we used terms for adherence and persistence and the drugs of interest. In all cases, both generic and trade names were used. In our search for studies on the effects of monitoring, we searched on terms related to monitoring and DXA in combination with the drugs of interest.

Searches for all KQ1–5 commenced from 2006. For new drugs, we reviewed the list of excluded studies from the original report to retrieve articles that had been rejected on the basis of drugs that were now included within the scope of the update, to find studies prior to 2006. The search was not limited to English-language publications and not limited by study design (e.g., reports of randomized controlled trials (RCT), observational studies, systematic reviews). The texts of the major search strategies are given in Appendix A.

To identify additional systematic reviews 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 the reference lists of review articles obtained as part of our search ("reference mining.")

To augment those searches, the EPC's Scientific Resource Center (SRC), which provides a variety of scientific support services for the comparative effectiveness reviews, conducted several "grey literature" searches for us. First, they conducted a search of relevant trials in the

NIH Clinical Trials database. For completed clinical trials of interest, we noted any reported publications; if no publications were mentioned, we searched MEDLINE® for published results. All such publications were checked against the results of our MEDLINE® searches. Second, they searched the Web of Science to identify abstracts presented at relevant meetings; although we would not include meeting abstracts in the report, we identified relevant abstracts and searched MEDLINE® for peer-reviewed publications of the results. Finally, the SRC searched the FDA Medwatch and Health Canada files for warnings and changes in indications.

For the third prong of our approach, we identified any relevant systematic reviews that have appeared since the original report was released and added the pooled findings of new meta-analyses to the tables of pooled results created for the original report.

Study Eligibility Criteria

Populations: Studies were limited to those recruiting adults over 18 (not children); healthy adults, those with low bone density, or those with osteoporosis (but not those with Paget's disease, cancer, or any other disease of bone metabolism); those using drugs indicated for the treatment of osteoporosis (but not if the drugs were being used to treat cancer); adults who had low bone density or were at high risk of developing low bone density as a result of chronic use of glucocorticoids (GC) or a condition associated with the chronic use of glucocorticoids (such as asthma, organ transplant, rheumatoid arthritis); adults who had low bone density or were at high risk of developing low bone density as a result of having a condition associated with low bone density (e.g., rheumatoid arthritis, cystic fibrosis, Parkinson's disease).

Interventions: Studies were included if they examined pharmacological interventions for prevention or treatment of osteoporosis approved (or expected to be soon approved for use in the United States) or if they assessed the effects of calcium, vitamin D, or physical activity.

Comparators: Studies included for assessing effectiveness were those that compared the effects of the intervention in question to that of placebo or another potency or dosing schedule for the same agent or another agent in the same or another class.

Outcomes: For effectiveness analysis, only studies that assessed vertebral, hip, and/or total fractures (and did not state that they were not powered to detect a change in risk for fracture) were included. Studies that reported fracture as an adverse event were excluded from effectiveness analysis because the way that adverse events are typically ascertained does not ensure systematic identification of these events across or even within study groups; however, fractures reported as adverse events for example atypical (low-stress subtrochanteric or femur) fractures, were included in the adverse event analysis.

Duration: Studies that had a minimum followup time of 6 months were included.

Design: Only RCTs and published systematic reviews of RCTs that met inclusion criteria were included in the assessment of effectiveness; however, for the assessment of effects in subgroups for which no RCTs were available, for the assessment of the effect of adherence on effectiveness, and for the assessment of particular serious adverse events, large (more than 1,000 participants) observational studies and systematic reviews were included.

Study Selection

Each title list was screened separately by two reviewers with clinical training and experience in systematic review to eliminate obviously irrelevant titles e.g., a study pertaining to treatment of Paget's disease or a study of dietary calcium requirements in children. Abstracts were obtained for all selected titles. Full text articles were then obtained for all selected abstracts. The

reviewers then conducted a second round of screening, using a specially designed screening form (Appendix B) to ascertain which articles met the inclusion criteria and would go on to data abstraction. Selections at this stage were reconciled, and disagreements were settled by consensus (with the project leaders resolving remaining disagreements).

During the second round of screening, we imposed inclusion criteria based on the particular key question(s) addressed by the study. For effectiveness/efficacy questions (KQ1, 2, and 5), we accepted any abstracts that indicated the manuscript might include information on the treatment/prevention of osteoporotic fracture (but not bone density alone). Controlled clinical trials and large observational studies (N>1,000) 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.

For assessing comparative effectiveness, we included only studies that compared two or more interventions within the same study, rather than attempting to compare treatment effects across studies. The differences in study design and baseline participant characteristics between studies would make interpretation of such comparisons suspect.

For KQ2, we identified studies that analyzed treatment efficacy and effectiveness by subgroups in several different ways. First, during the initial screening of full-text articles, we noted any articles that reported the results of post hoc analyses of trial efficacy data by a subgroup of interest (e.g., age, sex, menopausal status, comorbidity such as prior or concurrent treatment with glucocorticoids, presence or absence of prevalent fractures, baseline T-score, lag time between hip fracture and treatment initiation). In some cases, these articles analyzed pooled data from multiple studies. Second, while extracting primary effectiveness results from clinical trial reports and large observational studies (over 1,000 participants), we assessed whether any subgroup analyses were reported and extracted those data separately. To ensure no subgroup analyses were missed, we rescreened all articles that included any subgroup of interest to assess whether data were reported for those particular subgroups. Finally, we sought observational studies of any size that assessed effects of the agents of interest in populations not well represented in controlled trials and included reports of post hoc analyses and open-label extensions of trials. As with the head-to-head comparisons for KQ1, we did not attempt to compare treatment effects across studies because of the vast baseline differences between populations in characteristics considered to be potentially important, such as average age, body mass index, and race/ethnicity.

For KQ3 (adherence), articles of any study design that reported rates of adherence/persistence, factors influencing adherence/persistence, or the effects of adherence on effectiveness for any of the drugs of interest were included for further evaluation.

For KQ4 (adverse events), any articles were accepted if they suggested that the manuscript included information on the relationship between the adverse event and the drug. Controlled clinical trials and large case control or cohort studies (n > 1,000) 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, as well as studies of any design that described any of a number of rare adverse events (e.g., osteonecrosis of the jaw, atrial fibrillation, low stress subtrochanteric and femur fracture) in association with any of the drugs of interest, were initially included in adverse event analyses.

For KQ5 (Effects of Monitoring and Long-term Use), to ensure we identified all articles that examined the effect of bone density monitoring in predicting treatment effectiveness or efficacy, we searched for these articles in the following ways. During the initial screening of articles, we included any clinical trials that reported fracture results and mentioned monitoring. We also included any trials that reported both BMD and fracture and subsequently assessed whether

changes in BMD were compared to fracture outcomes. Where they existed, we also included reports of followups to trials included in the original report to assess the effect of long-term use.

Data Extraction

Using forms specially created for each study design, we extracted the following data. From included trials, we extracted study name (if named trial); setting (treatment and/or residential, e.g., long-term care facilities); population characteristics (including sex, age, race/ethnicity, diagnosis [osteoporosis/low bone density], comorbidities); eligibility and exclusion criteria; interventions (dose and duration); participant numbers screened, eligible, enrolled, and lost to followup; method and schedule of outcome ascertainment; description and adequacy of randomization and blinding; description and adequacy of concealment of allocation; funding source and role of funder; monitoring of adherence/persistence and cross-over; and results for each outcome. From observational studies, we extracted study name (if named trial); setting; population characteristics (including sex, age, ethnicity, diagnosis, comorbidities); eligibility and exclusion criteria; interventions (dose and duration); recruitment method; numbers screened, eligible, enrolled, and lost to followup; method and schedule of outcome or diagnosis ascertainment; funding source and role of funder; monitoring of adherence and contamination; method of adjustment for confounders; and results for each outcome. For studies of adherence, we extracted, in addition to the above, whether measures included adherence, compliance, and/or persistence; the method of assessment of adherence; barriers to adherence; and effects of adherence on fracture risk.

Data Synthesis

We performed three main analyses: one to evaluate efficacy and effectiveness, one to evaluate adherence, and one to evaluate adverse events. 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 and Effectiveness

The outcome of interest for assessing effectiveness for this report is fractures, based on FDA requirements. We report data about the following types of fractures (as reported in the studies reviewed): vertebral, nonvertebral, hip, wrist, and humerus. For each of the drug comparisons, we first summarized fracture data from published systematic reviews in tables. Data abstracted from individual controlled clinical trials were grouped by fracture type within each drug comparison of interest. Based on the recommendation of subject matter experts, 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 nonvertebral fractures). The primary outcome for our analysis of effectiveness is the number of people who reported at least one fracture. Wherever possible, data were presented separately for subgroups of interest. We provide narrative descriptions of the outcomes of each study not included in a prior (published) meta-

analysis in Chapter 3. The data relevant to each outcome are presented in individual tables and subsequently in an evidence table (Appendix C).

Adherence

The terms adherence and persistence are defined based on principles outlined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[16] Adherence (or compliance) is defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.” Although not specifically stated in the ISPOR definition, we view adherence to specific dosing instructions (which for bisphosphonates can affect both effectiveness and risk of adverse events) as an important component of adherence. Persistence is defined as “the duration of time from initiation to discontinuation of therapy.”[16]

Studies that included information on adherence and/or persistence of medications for osteoporosis, as indicated in the initial article screening, formed the basis for this section of the review. Each of these studies was reviewed by one investigator to determine which adherence key question is discussed. Observational studies went on to the adherence long form, collecting detailed information on how adherence was defined, assessed, and measured and what barriers or predictors were included in each study. The investigators also abstracted the rates of adherence and persistence from each study.

The randomized and controlled clinical trials contributed evidence to the adherence analysis but did not go on to an adherence long form. Conclusions about adherence and persistence in all randomized trials are severely limited for three reasons: (1) trials restrict their patient populations in several ways, which often creates a group of patients who would be more adherent to a medicine than the general population; (2) patients are, by definition, in a clinical trial and therefore receive added attention and information that is not commonly received by the general population; (3) patients in a clinical trial who would otherwise be termed nonadherent to their medications may instead simply drop out of the trial, and thus adherence rates reported in trials may not account for patient drop out from the study. We summarized the rates of adherence in clinical trials and included any trials that discussed adherence and fracture risk, but the clinical trials were not searched for information about barriers/predictors of adherence using the detailed adherence long form.

Systematic reviews on the topic of adherence/persistence with osteoporosis medications that were identified in the literature search were reviewed by an investigator, and the most recent and relevant reviews were qualitatively summarized. Because each of these reviews was limited to very specific populations and study types, we did not eliminate studies from our review of adherence simply because they were mentioned in the prior systematic reviews.

We collected adherence and persistence rates from the randomized trials and observational studies and review them qualitatively, without any meta-analyses or pooling because of the substantial heterogeneity in measurements and definitions of adherence in each study and population differences across studies.

Several methods of measuring adherence are used in the medical literature. Self-reported adherence is commonly used, although self-report measures suffer from recall bias and may overestimate adherence. Electronic devices can monitor medication adherence and are quite accurate but expensive. Pill counts are another method of measuring the amount of medication taken: Patients bring in their pill bottles, and study staff will count pills that are remaining; this

method is limited in that the use of pills is assumed if not counted in the bottle, and the method can overestimate adherence and cannot give any information about timing or pattern

of doses taken.[17] Another commonly used method to measure adherence uses administrative databases from pharmacies or health plans to capture the amount of medication obtained by patients. These methods have the advantage of being objective and providing information over a large time span, but they are limited in that they include only what is in the database: If patients fill their prescriptions by mail, or at another pharmacy, or another health plan, or receive samples, these fills will not be captured. There are several different ways to measure adherence from these databases. Commonly used is the medication possession ratio (MPR), which is a ratio of the days of medication supplied divided by the days between the first fill and the last fill of the medication. Also measured are the proportion of days covered (PDC), for which pharmacy fills are used to determine what proportion of all days within a specified time period a patient had enough medication, and the percentage of doses taken as prescribed, which is the percentage of prescribed doses taken as directed by the patient during a specified time. Persistence, on the other hand, is typically measured either as a continuous variable and reported as the number of days on a medication until discontinuation or as a dichotomous variable, reporting the proportion of study subjects still on the medication after a period of time.

For those studies that provided information on the barriers and/or predictors to medication adherence in osteoporosis, we identified those barriers and predictors using the adherence long form and determined the number of studies discussing each factor and the characteristics of the study, including population characteristics, specifics on how adherence/persistence are measured, and funding source. For the analysis of adherence/persistence and fracture, we qualitatively review each of these studies and prior systematic reviews addressing this topic.

The methodologic quality of each article was assessed based on the study characteristics above, although there were no formal criteria or scales used for quality assessment of these articles. To our knowledge, there are no accepted quality metrics for grading the quality of adherence measurement. Many of these observational studies use prescription claims data in a retrospective fashion. As discussed above, these studies varied in their methods of analysis, study population, and outcome variables (adherence/persistence). The result is tremendous heterogeneity in these studies, so no attempt was made to combine these results into a meta-analysis, and our results are thus qualitative.

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 an exact logistic regression 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.[18] 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 (denoted in the tables as Inf+) and the associated confidence interval is bounded from below only. In such a case, we report the lower bound of the confidence interval.

Because the occurrence of adverse events 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.[19] When analyzing outcomes with rare events, the Peto method has been shown to give the least biased estimate.[20] 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. Because fractures are rare events, the OR approximates the relative risk (RR) of fracture.

Some adverse events are so rare that the relative risks may not accurately portray differences between active- and placebo-treated groups. Thus, we calculated the risk differences for each of the adverse event reports, which take into account the proportions of participants reporting the events.

Quality Assessment

The methods used for quality assessment were determined by the design of included studies. The quality of RCTs was assessed 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 (two points are awarded for randomization and two for double-blinding).[21] Across a broad array of meta-analyses, an evaluation found that studies scoring 0–2 report exaggerated results compared with studies scoring 3–5.[22] The latter have been called “good” quality and the former called “poor” quality. We also added an assessment of concealment of allocation.

The need to include observational studies was carefully assessed according to the guidelines presented in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. Specifically, we assessed whether clinical trials provided sufficient data to reach conclusions and where they did not we included observational data. In practice, this meant we included observational data in two topic areas: adverse events and the assessment of adherence and outcomes. The quality of prospective cohort and case-control studies that reported rare adverse events of particular concern was assessed using relevant portions of the Newcastle-Ottawa Scales for cohort and for case-control studies.[23] Items assessed for cohort studies included the following:

- Are primary outcomes assessed using valid and reliable measures?
- Are outcome measures implemented consistently across all study participants?
- Were the important confounding and modifying variables taken into account in the design and analysis?
- How was the nonexposed cohort selected?
- How was exposure to drugs/exercise ascertained?

- Was it demonstrated that the outcome of interest was not present at the start of the study?

Items assessed for case-control studies included the following:

- Was the case definition adequate?
- Were cases representative?
- How were controls selected and defined?
- On what basis were cases matched to controls?
- How were outcomes assessed?
- Was followup of adequate length?
- What proportion of cases was followed up completely?

For observational studies of adherence, no standardized assessment of quality currently exists. The Newcastle-Ottawa for observational cohorts does not apply to most of the adherence studies. Thus we abstracted and report objective factors for each study that might be related to both quality and generalizability, such as how adherence (outcome) was measured and size and location of study (generalizability); however, we did not apply particular scales to those studies that focused solely on adherence.

Applicability

As was done for the original report, we assessed the applicability of each included study based on the similarity of the target populations to those for which this report is intended. This assessment was separate from other quality assessments.

Although people may use the terms “efficacy” and “effectiveness” interchangeably when describing whether an intervention works, these terms have important differences both clinically and for policy. The fundamental distinction between efficacy and effectiveness studies lies in the populations enrolled and control over the intervention(s). Efficacy studies tend 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 efficacy of an intervention is the extent to which the treatment works under ideal circumstances, and the effectiveness of the intervention is the extent to which the treatment works on average patients in average settings.

Comparative Effectiveness Reviews (CERs) assess internal validity and external validity (e.g., applicability or generalizability) of included studies. Efficacy studies emphasize internal validity, whereas effectiveness studies emphasize applicability.

Ideally, 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-term and long-term adverse events.[24]

Based on the method of Gartlehner et al.,[25] the characteristics we used to distinguish efficacy from effectiveness, and therefore to rate applicability were study setting, study population (stringency of eligibility criteria), duration and attempt to assess treatment compliance, health outcome assessment, adverse event assessment, sample size, and use of intention-to-treat analysis (see Appendix C).

In addition, it should be noted that the majority of studies included in our report are efficacy studies to the extent that they were large clinical trials. 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 intervention effectiveness using guidance suggested by the U.S. Agency for Healthcare Research and Quality (AHRQ) for its Effective Healthcare Program.[26] This method is based on one developed by the Grade Working Group,[27] and classifies the grade of evidence according to the following criteria:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence on the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Evidence either is unavailable or does not permit a conclusion.

The evidence grade is based on four primary domains (required) and four optional domains. The required domains are risk of bias, consistency, directness, and precision; the additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias. A brief description of the required domains is displayed in Table 2 below. For this report, we used both this explicit scoring scheme and the global implicit judgment about "confidence" in the result. Where the two disagreed, we went with the lower classification.

Table 2. Grading the strength of a body of evidence: Required domains and their definitions

Domain	Definition and Elements	Score and Application
Risk of Bias	Risk of bias is the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies	Use one of three levels of aggregate risk of bias: • Low risk of bias • Medium risk of bias • High risk of bias
Consistency	The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements: • Effect sizes have the same sign (i.e., are on the same side of "no effect") • The range of effect sizes is narrow.	Use one of three levels of consistency: • Consistent (i.e., no inconsistency) • Inconsistent • Unknown or not applicable (e.g., single study) As noted in the text, single-study evidence bases (even mega-trials) cannot be judged with respect to consistency. In that instance, use "Consistency unknown (single study)."

Table 2. Grading the strength of a body of evidence: Required domains and their definitions (continued)

Domain	Definition and Elements	Score and Application
Directness	The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes. Two types of directness, which can coexist, may be of concern. Evidence is indirect if: • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B, e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not A vs. B. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes. Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain.	Score dichotomously as one of two levels of directness: • Direct • Indirect If indirect, specify which of the two types of indirectness account for the rating (or both, if that is the case), namely, use of intermediate/ surrogate outcomes rather than health outcomes, and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.
Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately) If a meta-analysis was performed, this will be the confidence interval around the summary effect size.	Score dichotomously as one of two levels of precision: • Precise • Imprecise A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.

Peer Review and Public Commentary

Experts on osteoporosis therapy and various stakeholder communities performed an external peer review of this CER. The AHRQ Effective Healthcare Program Scientific Resource Center (SRC) located at Oregon Health Sciences University (OHSU) oversaw the peer review process. Peer reviewers were charged with commenting on the content, structure, and format of the evidence report and encouraged to suggest any relevant studies we may have missed. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ and the SRC also requested review from its own staff. The draft report was posted on the EHC website for public comment. We also requested review from each member of our Technical Expert Panel (TEP).

Results

Literature Search

The initial searches done in September 2009 covering the period from January 2005-December 2009 found a total of 18,667 titles. A further search was done on PubMed alerts which produced 178 total citations. Reference mining contributed an additional 217 citations. In October and November 2010 an update search was done and then a final update search was done in March 2011 which produced a total of 7,304 hits. All 26,366 citations were imported into EndNote and screened. In total, reviewers selected 2,440 relevant titles for abstract review out of 26,366 titles identified in the searches (see Figure 2). Abstract review resulted in rejection of 1,644 articles. Reasons for abstract exclusion included the following: articles were not on osteoporosis (535), design (772), fracture not reported (only in effectiveness analyses) (262), population (75). Eight articles were not found, and 127 were already in the original report. Thus, 661 full-text articles were available for the next stage of screening (short form).

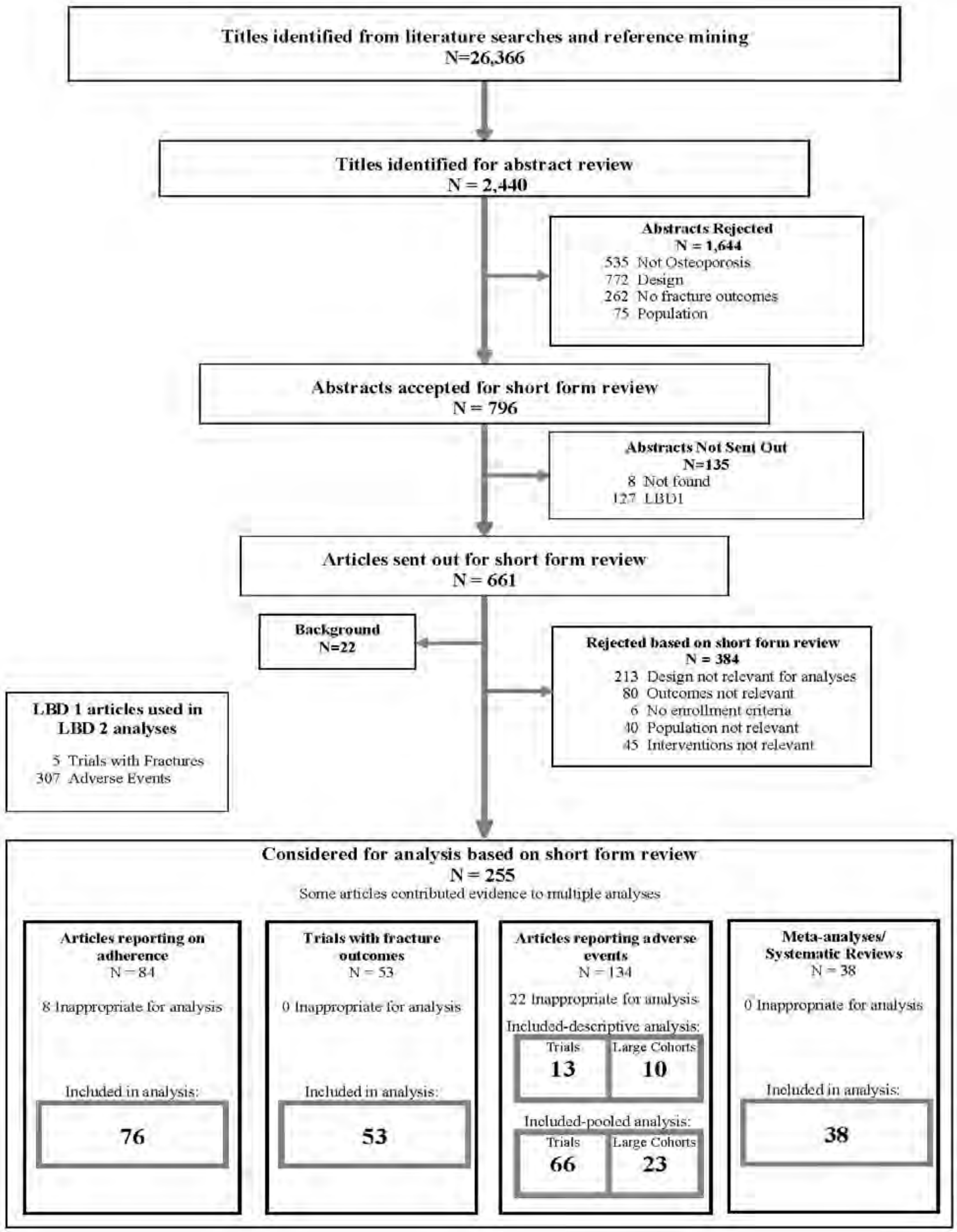
Screening of retrieved articles resulted in further exclusion of 384. Reasons for exclusion included the following: design not relevant for analyses (213 articles), outcomes not relevant to project (80 articles), no enrollment criteria (six articles), population not relevant to project (40 articles), interventions not relevant to project (45 articles). Twenty-two background articles were not included in any of the analyses but are narratively described in the report. Appendix D lists all citations that were excluded, by reason.

Among the 255 articles accepted based on short form review, 84 articles reported on adherence, of which 7 were subsequently rejected for not answering a key question and one was rejected for duplicate data. Of 53 trials with fracture outcomes, all were accepted for inclusion in the efficacy analysis. Of 134 articles that reported adverse events, 89 were trials and 45 were observational (large cohort) studies. Of the 89 trials, 10 were subsequently rejected for either design (crossover), reporting no actual adverse event data, or not reporting relevant outcomes. Of the remaining 79 trials, 66 were included in meta-analyses conducted for this report, and 13 were described narratively. Among the 45 large observational studies, 12 were subsequently rejected for either design (crossover), not actually reporting adverse event data, or not reporting relevant outcomes. Of the remaining 35 observational studies, 23 were included in meta-analyses conducted for this report, and 10 were described narratively.

The analysis of studies on efficacy and effectiveness included 5 articles from the original report (referred to as LBD1 in Figure 2), and the adverse events analysis included 307 articles from the original report.[14]

Figure 2 below displays the flow as described above.

Figure 2. Literature flow



LBD = Low Bone Density

Key Question 1: What Are the Comparative Benefits in Fracture Risk Reduction Among the Following Therapeutic Modalities for low Bone Density: Bisphosphonates, Denosumab, Menopausal Hormone Therapy, Selective Estrogen Receptor Modulators (Raloxifene), Parathyroid Hormone, Calcium, Vitamin D, and Physical Activity?

For this question, we identified 55 RCTs and 10 observational studies in addition to 58 systematic reviews (from both the original and current report) that assessed the effects of interventions compared to placebo: nine systematic reviews and 10 RCTs for alendronate, 10 systematic reviews and 13 RCTs for risedronate, three systematic reviews and three RCTs for ibandronate, four RCTs for zoledronic acid, one systematic review and two RCTs for denosumab, three systematic review and three RCTs for raloxifene, two systematic reviews and three RCTs for teriparatide, six RCTs for menopausal estrogen therapy, four systematic reviews and six RCTs for calcium alone, 15 systematic reviews and seven RCTs for vitamin D alone, four RCTs for vitamin D plus calcium, and one systematic review and one RCT for physical activity.

Key Findings for Key Question 1

- There is a high level of evidence from RCTs that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.
- There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid and denosumab reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis and moderate evidence that teriparatide reduces the risk of nonvertebral fractures.
- There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip fractures in postmenopausal women with osteoporosis.
- The original report found a high level of evidence that estrogen is associated with a reduced incidence of vertebral, nonvertebral, and hip fractures; however studies identified for this report, which tended to focus on postmenopausal women with established osteoporosis (rather than on postmenopausal women with low bone density only or postmenopausal women in general) did not show significant reductions in fracture risk.
- The evidence is moderate, based on a published systematic review and several RCTs, that there is no difference between calcium alone and placebo in reducing the risk for vertebral and nonvertebral fractures; however, calcium significantly reduced hip fracture risk in one pooled analysis, and overall fracture risk in another pooled analysis.
- A large body of literature showed mixed results for an effect of vitamin D in lowering the risk for fracture, varying with dose, fracture site, analogs, and population. Evidence is moderate that Vitamin D, 700 to 800 I.U. daily, particularly when given with calcium, reduces the risk of hip and nonvertebral fractures among institutionalized populations (one systematic review) and the overall risk of fractures (a second systematic review).
- There is a high level of evidence, based on six previously published systematic reviews, that there is no difference in vertebral, nonvertebral, or hip fracture risk with administration of vitamin D alone compared to administration of calcium alone.

- The evidence is insufficient to low regarding the effect of physical activity on fracture risk compared to placebo: One study showed a small effect on fracture prevention. No studies compared the effect of physical activity to that of other interventions.
- The evidence is insufficient from head-to-head trials of bisphosphonates to prove or disprove superiority for the prevention of fractures for any agent.
- The evidence is insufficient from head-to-head trials of bisphosphonates compared to calcium, teriparatide, or raloxifene to prove or disprove superiority for the prevention of fractures. (three trials)
- Evidence is moderate, based on six head-to-head RCTs, that there is no difference in fracture incidence between bisphosphonates and menopausal hormone therapy.
- The evidence is low, based on one head-to-head trial, that the combination of alendronate and calcium significantly decreased the risk for any type of clinical fracture compared with alendronate alone.
- The evidence is low, based on limited head-to-head trial data (two trials), for a difference in fracture incidence between menopausal hormone therapy and raloxifene or vitamin D.
- The evidence is insufficient regarding the use of combinations of osteoporosis therapies or sequential use of osteoporosis therapies in relation to fracture outcomes.

Overview of Results for Key Question 1

The results presented here are an update of the findings of the original 2007 report. For each osteoporosis medication (Table 1), we first describe previously published systematic reviews presented in the original report as well as systematic reviews published subsequent to the original report consistent with the incorporation of prior systematic reviews into new complex systematic reviews as articulated by Whitlock and colleagues.[28] Subsequently, for each medication, we present results of original studies published subsequent to the systematic reviews. This information will be presented in the following sequence: effectiveness of individual agents compared with placebo (bisphosphonates, biologics, selective estrogen receptor modulators (SERMs), peptide hormones, menopausal hormone therapy, dietary supplements, and lifestyle interventions), head-to-head comparisons of medications, and sequential or combination use of medications.

Agents Compared With Placebo

In this section, we present the findings of systematic reviews and original studies not included in a prior systematic review that compared the effects of an active intervention with those of a placebo.

For each drug/placebo combination, we first show the matrix of all the prior systematic reviews and the original studies they included; then we show the actual findings of meta-analyses; then we describe the results of any original studies not included in prior meta-analyses.

Bisphosphonates

This section presents the results of prior systematic reviews and original studies not included in a prior systematic review on the bisphosphonates alendronate, risedronate, ibandronate, and zoledronic acid. Although the original report also included etidronate and pamidronate, these agents have been excluded from the current report as they are not indicated for the prevention/treatment of primary osteoporosis in the U.S.

Alendronate

Prior Systematic Reviews

We identified nine systematic reviews evaluating the antifracture efficacy of alendronate compared to placebo or no treatment[29-37] (Table 3). In aggregate, the systematic reviews included data from 17 RCTs, the characteristics of which are summarized in Table 3. Of the nine, five assessed vertebral fracture risk, six assessed non-vertebral fracture risk, six assessed hip fracture risk, and four assessed wrist fracture risk.

Table 4 lists the systematic reviews that reported pooled risk estimates for fracture risk associated with alendronate relative to placebo or no treatment. For vertebral fractures, we found two new pooled estimates in addition to the three pooled estimates included in the original 2007 report. For non-vertebral fractures, we found one new pooled estimate in addition to the five pooled estimates included in the original 2007 report. For hip fractures, we found one new pooled estimate in addition to the five estimates included in the original 2007 report. For wrist fractures, we found one new estimate in addition to the three estimates included in the original 2007 report.

Vertebral fracture risk reduction associated with alendronate relative to placebo ranged from 40 percent to 64 percent; with one exception (a study testing a lower preventive 5 mg alendronate dose that found no significant increase or decrease in fracture risk with alendronate versus placebo), all studies showed a statistically significantly lower relative risk of vertebral fracture associated with alendronate compared to placebo or no treatment (Table 4).

The reduction in nonvertebral fracture risk with 10 mg or more alendronate vs. placebo ranged from 11 percent to 49 percent, and all but one study showed statistically significant reduction in nonvertebral fracture risk with a dose of 10 mg or more of alendronate versus placebo or no treatment. In contrast, nonvertebral fracture risk was not statistically significantly reduced with 5 mg doses of alendronate relative to placebo or no treatment.

The reduction in hip fracture risk associated with alendronate vs. placebo or no treatment ranged from 21 percent to 55 percent, and was statistically significant in 6 of the 12 pooled estimates. There was a suggestion that the effect was not statistically significant in the primary prevention setting (osteopenia as opposed to osteoporosis), and with doses lower than 10 mg daily. Thus, differences in baseline disease severity and alendronate doses across trials may explain heterogeneity in magnitudes and statistical significance of estimates of hip fracture reduction associated with alendronate use.

Alendronate in doses of 10 mg or more daily versus placebo or no treatment was associated with a statistically significant reduction in risk of wrist fracture, but reduction in risk of wrist fractures was not statistically significant with alendronate dosing of 5 mg daily, or with less severe pre-existing disease (primary prevention, osteopenia).

Table 3. Randomized controlled trials included in systematic reviews of effect of alendronate on fracture relative to placebo or no treatment, by fracture type

	Systematic Review (Author, Year)																				
	Cra, 2002[29]				Kar, 1997[30]			Pap, 2004[31]	Ste, 2005[32]				Boo, 2005[34]	Ngu, 2006[33]	Saw, 2005[35]		Jan, 2009[36]	Wel, 2008[37]			
	Fracture Type																				
RCTs (Author, Year)	**V**	**NV**	**H**	**W**	**NV**	**H**	**W**	**H**	**V**	**NV**	**H**	**W**	**NV**	**H**	**V**	**NV**	**V**	**V**	**NV**	**H**	**W**
Adami,1995[38]	X	X			X	X	X														
Ascott Evans, 2003[39]																		X	X	X	
Black, 1996[40]	X	X	X	X				X	X	X	X	X	X	X			X	X	X	X	X
Bone, 1997[41]	X	X																X	X		
Bonnick, 1998[42]		X						X						X							
Chesnut, 1995[43]	X	X			X	X	X											X	X		
Cummings, 1998[44]	X	X						X	X		X	X	X	X			X	X	X	X	X
Dursun, 2001[45]									X									X			
Greenspan, 1998[46]								X											X	X	X
Greenspan, 2002[47]														X						X	
Hosking, 1998[48]	X	X																X	X		
Liberman, 1995[49]	X	X			X	X	X	X	X	X	X	X	X	X			X		X	X	X
McClung, 1998[50]	X	X																			
Orwoll, 2000[51]																				X	X
Pols, 1999[52]		X								X				X				X	X	X	X
Ringe, 2004[53]															X	X					
Weinstein, 1994[54]					X	X	X														

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

References for systematic reviews: Cranney, Endocr Rev, 2002[29]; Karpf, JAMA, 1997[30]; Papapoulous, Osteoporos Int, 2004[31]; Stevenson, Health Technol Assess, 2005[32]; Boonen, Osteoporos Int, 2005[34]; Nguyen, J Bone Miner Res, 2006[33]; Sawka, BMC Musculoskelet Disord, 2005[35]; Jansen, Curr Med Res Opin, 2009[36]; Wells, Cochrane Database Syst Rev, 2008[37]

New Original Placebo-Controlled Studies

Characteristics of RCTs that examined fracture risk with alendronate (and were not included in a prior systematic review) vs. placebo are displayed in Table 5. Seven studies were included in the original report and three studies were newly identified for this report.[55-57] The quality of the newly identified studies, assessed according to the method of Jadad, scores of the new studies were 5, 0, and 5. In addition to possible differences in effect by dose and baseline disease severity (primary vs. secondary prevention, osteopenia vs. osteoporosis) noted in the pooled estimates (above), other study characteristics may explain differences in estimates of fracture risk reduction across alendronate studies (Table 5). Although longer alendronate treatment was not associated with a statistically significant decrease in overall fracture risk, only the study with a longer alendronate treatment duration (54 months) was associated with a statistically significant (57 percent) reduction in vertebral fracture risk (Table 5). Small absolute numbers of fracture events and small numbers of participants in several of the studies (ranging from 1 to 9 fracture events in all but one study) may contribute to the lack of statistical significance of the reduction in vertebral fracture risk associated with alendronate vs. placebo. Similarly, the estimates of reductions in nonvertebral fracture risk with alendronate vs. placebo were not statistically significant, but total numbers of fractures in the three studies were low, ranging from 1 event to 10 events. Compared to placebo, alendronate was associated with a 70 percent statistically significant reduction in hip fracture risk. Because no wrist or humerus fractures occurred in studies of alendronate vs. placebo, we do not display estimates of reduction in risk of wrist or humerus fracture associated with alendronate.

Using the criteria of Gartlehner and colleagues[25] to assess the applicability of the three new studies, we determined that they were moderately applicable: In particular, two studies were small, and one enrolled only individuals using glucocorticoids to control autoimmune diseases.

In summary, pooled analyses and RCTs provide a high level of evidence that treatment of osteoporosis with alendronate 10 mg daily compared to placebo significantly reduces the risk of vertebral fracture, nonvertebral fracture, and hip fracture in patients with osteoporosis. Data are less compelling about nonvertebral and hip fractures in patients without osteoporosis.

Table 4. Pooled risk estimates of fracture risk associated with alendronate, relative to placebo or no treatment, among postmenopausal women*

Author, Year	# Trials	Sample Size	RR	(95% CI)
Vertebral Fractures				
Original 2007 Report				
Cranney, 2002[29]				
Prevention trials, dose > 5 mg/d	2	1,355	0.45	(0.06, 3.15)
Treatment trials, dose > 5 mg/d	7	8,005	0.53	(0.43, 0.65)
Sawka, 2005[35]	2	375	0.36	(0.17, 0.77)
Stevenson, 2005[32]				
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)
Update Report				
Jansen, 2009[36] 5–20mg/d	3	7,453	0.47	(0.35, 0.57)
Wells, 2008[37]				
All trials 5 mg	3	1,314/1,493	0.40	(0.29, 0.55)
10 mg	4	3,486/3,670	0.55	(0.45, 0. 67)
Primary Prevention 5 mg	0	n/a	n/a	n/a
10 mg	1	2,214/2,218	0.55	(0.38, 0.80)
Secondary Prevention 5 mg	3	1,314/1,493	0.40	(0.29, 0.55)
10 mg	3	1,272/1,452	0.55	(0.43, 0.69)
Nonvertebral Fractures				
Original 2007 Report				
Boonen, 2005[34]	3	7,453	0.86	(0.76, 0.97)
Cranney, 2002[29]				
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[30]	5	1,602	0.71	(0.50, 1.00)
Sawka, 2005[35]	2	375	0.73	(0.32, 1.67)
Stevenson, 2005[32]				
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)
Update Report				
Wells, 2008[37]				
All trials 5 mg	2	591/592	0.95	(0.34, 2.67)
10 mg	5	4,843/4,638	0.84	(0.74, 0.94)
Primary Prevention 5 mg	1	498/501	1.50	(0.82, 3.05)
10 mg	1	2,214/2,218	0.89	(0.76, 1.04)
Secondary Prevention 5 mg	1	93/91	0.55	(0.26, 1.18)
10 mg	4	2,629/2,420	0.77	(0.64, 0.92)

Table 4. Pooled risk estimates of fracture risk associated with alendronate, relative to placebo or no treatment, among postmenopausal women* (continued)

Type of Fracture	# Trials	Sample Size	RR	(95% CI)
Hip Fractures				
Original 2007 Report				
Cranney, 2002[29]				
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[30]	5	1,602	0.46	(0.15, 1.36)
Nguyen, 2006[33]	6	10,389	0.55	(0.27, 1.12)
Papapoulos, 2005[31]				
Subjects with T score < 2.0 or with vertebral fracture	6	9,023	0.55	(0.36, 0.84)
Subjects with T score < 2.5 or with vertebral fracture	6	6,804	0.45	(0.28, 0.71)
Stevenson, 2005[32]				
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)
Update Report				
Wells, 2008[37]				
All trials 5 mg	0	n/a	n/a	n/a
10 mg	6	5,005/4,802	0.61	(0.40, 0.92)
Primary Prevention 5 mg	0	n/a	n/a	n/a
10mg	1	2,214/2,218	0.79	(0.44, 1.44)
Secondary Prevention 5 mg	0	n/a	n/a	n/a
10 mg	5	2,792/2,584	0.47	(0.26, 0.85)
Forearm/Wrist Fractures				
Original 2007 Report				
Cranney, 2002[29]				
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[30]	5	1,602	0.39	(0.19, 0.78)
Stevenson, 2005[32]				
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)
Update Report				
Wells, 2008[37]				
All trials 5 mg	0	n/a	n/a	n/a
10 mg	5	4,843/4,638	0.68	(0.34, 1.37)
Primary Prevention 5 mg	0	n/a	n/a	n/a
10 mg	1	2,214/2,218	1.19	(0.87, 1.62)
Secondary Prevention 5 mg	0	n/a	n/a	n/a
10 mg	4	2,629/2,420	0.50	(0.34, 0.73)

*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 5. Randomized controlled trials assessing risk of fracture for alendronate, any dose, relative to placebo, by anatomical site of fracture group (not included in prior meta-analyses)

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Alendronate	Number of Fractures, Placebo	Odds Ratio (95% CI)
Total Fractures					
Original 2007 Report					
Bone, 2000[58]	24 months	Any clinical fracture	5/92	4/50	0.65 (0.16, 2.66)
Greenspan, 2003[59]	36 months	Clinical fracture	7/93	9/93	0.76 (0.27, 2.12)
Hosking, 2003[60]	12 months	Clinically diagnosed vertebral or nonvertebral	6/172	2/89	1.52 (0.34, 6.67)
Update report: *No new studies*					
Vertebral Fractures					
Original 2007 Report					
McClung, 2006[61]	12 months	Clinical vertebral fracture	1/46	1/46	1.00 (0.06, 16.23)
Quandt, 2005[62]	54 months	Clinical vertebral fracture	12/1,878	29/1,859	0.43 (0.23, 0.79)
Zein, 2005[63]	12 months	New compression/vertebral fracture	1/14	0/13	6.88 (0.14, 347.7)
Update Report					
Papaioannou,2008[55]	12 months	Vertebral	0/23	2/24	0.14 (0.01, 2.23)
Ringe, 2007[56a]	24 months	Vertebral	4/30	5/30	0.77 (0.19, 3.15)
Nonvertebral Fractures					
Original 2007 Report					
Zein, 2005[63]	12 months	Peripheral fracture	0/14	1/13	0.13 (0.00, 6.33)
Update Report					
de Nijs, 2006[57]	18 months	Nonvertebral	2/99	3/101	0.68 (0.12,3.99)
Ringe, 2007[56]*	24 months	Nonvertebral	6/30	4/30	1.6 (0.42,6.16)
Hip Fractures					
Original 2007 Report					
Sato, 2006[64]	48 months	Hip fracture	4/131	14/129	0.30 (0.12, 0.78)
Update Report: *No new studies*					
Wrist Fractures					
Original 2007 Report					
McClung, 2006[61]	12 months	Radius, ulna, or both	0/46	0/46	NC
Update Report: *No new studies*					
Humerus Fractures (Original 2007 report, no new studies for current report)					
McClung, 2006[61]	12 months	Humerus	0/46	0/46	NC
Update Report: *No new studies*					

NC = not calculable

*Numbers of fractures are presented for the group assigned to receive alendronate + calcium + vitamin D in comparison to the group assigned to receive alfacalcidol + calcium.

Risedronate

Prior Systematic Reviews

We found 10 systematic reviews that reported the relative risk of fracture with risedronate vs. placebo or no treatment[32-34,65-71] (Table 6). Together, these systematic reviews encompassed 14 RCTs. Of the 10 systematic reviews, eight addressed vertebral fracture risk, five addressed non-vertebral fracture risk, three addressed hip fracture risk, and two addressed wrist fracture risk.

Compared to the original 2007 report, we found additional pooled estimates of the relative risk of fracture with risedronate vs. placebo or no treatment: two new estimates for vertebral fractures, two for nonvertebral fractures, one for hip fractures, and one for wrist fractures (Table 7).

The two meta-analyses of primary prevention studies revealed no statistically significant reductions in vertebral fracture associated with risedronate vs. placebo or no treatment, but the remainder of the pooled estimates suggested reductions of 46 percent to 69 percent in risk of vertebral fractures with risedronate relative to placebo or no treatment. Among subgroups with mild, moderate, and severe renal impairment, risedronate was associated with statistically significant (44 percent to 68 percent) reduction in vertebral fracture risk, but overlapping confidence internals do not allow assessment of whether effects vary by degree of renal impairment.

Except in the primary prevention setting, compared to placebo or no treatment, risedronate was associated with a statistically significant 19 percent to 60 percent reduction in nonvertebral fracture risk. In the primary prevention setting, and with dosing of 2.5 mg daily, risedronate was not associated with reduction in nonvertebral fractures.

Four of the five available pooled estimates reported statistically significant reductions (ranging from 36-40 percent) in hip fracture risk with risedronate therapy vs. placebo or no treatment. The association of risedronate with reduced hip fracture risk was not estimable separately in the primary prevention setting.

Pooled estimates show no statistically significant reduction in risk of wrist fractures with risedronate relative to placebo or no treatment.

New Original Placebo Controlled Studies

The original report included nine RCTs not included in a prior systematic review that compared the effects of risedronate on fracture risk with that of placebo. Four additional studies were identified for the current report, with Jadad scores ranging from 1 to 5.[72-75] Characteristics of RCTs that analyzed the relative reductions in fracture risk with risedronate vs. placebo are displayed in Table 8 according to anatomical site of fracture. Risedronate (all doses in aggregate) was not associated with reduction in fractures in aggregate. Here we describe the results by dose compared with placebo.

Risedronate 2.5 mg Daily Dose. Vertebral fracture risk reduction associated with the 2.5 mg dose of risedronate was not evaluable due to inadequate numbers of events in the one available RCT.[76] Compared to placebo, risedronate 2.5 mg daily was associated with 71 percent reduced risk of nonvertebral fracture.[77] Three of four RCTs reported statistically significantly decreased risk of hip fracture with risedronate 2.5 mg daily vs. placebo, ranging from 71 percent to 78 percent.[72,77-79]

Risedronate 5.0 mg Daily Dose. In one RCT, compared to placebo, risedronate 5 mg daily was associated with a statistically significant 58 percent reduction in vertebral fracture risk, but no statistically significant reduction in humerus fracture risk.[80] The reduction of nonvertebral fracture risk associated with risedronate 5 mg daily vs. placebo was not statistically significant in two comparisons,[80,81] including one 12-month study of men with primary or secondary osteoporosis,[81] but was significant in the same study at 24-months.[73]

Risedronate 30-35 mg Weekly Dose. Overall fracture risk was not statistically different with risedronate 30-35 mg weekly compared to placebo.[82,83] In three of four comparisons, risedronate 35 mg weekly vs. placebo was not associated with a statistically significant reduction in risk of vertebral fractures.[74,75,84] In two of three comparisons involving the same population of postmenopausal women at 12, 24, and 36 months, the relative risk of nonvertebral fracture with risedronate 35 mg weekly vs. placebo was significantly decreased (0.13-0.20).[75,84]
Using the criteria of Gartlehner et al.[25], to assess the applicability of the four new studies, we determined that they were moderately to highly applicable. However, two of the studies enrolled only men, a third enrolled only patients with inflammatory bowel disease, and the largest excluded many comorbid disorders.

New Original Head-to-Head Dosing Comparisons

Five studies compared dosing regimens head to head: three from the original report and two identified for this report.[85] [86] The Jadad scores for these two studies were 1 and 2. Table 9 shows the head-to-head comparisons of various doses of risedronate, including 2.5 mg daily, 5 mg daily, 17.5 mg weekly, 35 mg weekly, 50 mg weekly, and 150 mg monthly on two consecutive days per month. The combination of the studies from the original report and the newly identified studies provide 12 comparisons among different doses of risedronate in relation to vertebral and nonvertebral fracture risk. In general, all of the direct comparisons among various doses of risedronate showed no statistically significant differences in the relative risk of vertebral or nonvertebral fracture among the different doses although the 95% confidence intervals for some estimates are quite wide, meaning that clinically important differences could not be excluded. Using the criteria of Gartlehner et al.,[25] to assess the applicability of the two new studies identified for this report, we determined that their applicability was moderately high.

In summary, for treatment of osteoporosis, compared to placebo, risedronate in any currently FDA-approved dosing regimen decreases the risk of vertebral, nonvertebral, and hip fractures.

Table 6. Randomized controlled trials included in systematic reviews of effect of risedronate on fracture relative to placebo or no treatment

	Systematic Review (Author, Year)																	
	Cra, 2002[65]		Ste, 2005[32]				Boo, 2005[34]	Mil, 2005[66]	Ngu, 2006[33]	Wat, 2003[87]	Wal, 2000[68]	Bia, 2008[69]	Wel, 2008[70]				Zho, 2009[71]	
	Fracture Type																	
RCTs (Author, Year)	**V**	**NV**	**V**	**NV**	**H**	**W**	**NV**	**V**	**H**	**V**	**V**	**V**	**V**	**NV**	**H**	**W**	**V**	**NV**
Clemmensen, 1997[88]	X	X											X	X				
Cohen, 1999[89]											X							
Fogelman, 2000[90]	X	X						X					X	X				
Harris, 1999[91]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		
Hooper, 2005[92]								X										
McClung, 1998[93*]		X						X					X	X				
McClung, 2001[94*]		X			X		X	X	X					X	X			
Mortensen, 1998[95]	X	X																
Reginster, 2000[96]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		
Reid, 2000[97]											X	X	X	X	X			
Reid, 2001[98]																	X	
Ringe, 2006[81]																	X	X
Sato, 2005[78]																		X
Sato, 2007[72]																		X

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

[*]Same study reported in two different abstracts.

References for systematic reviews: Cranney, Endocr Rev, 2002[29]; Stevenson, Health Technol Assess, 2005[32]; Boonen, Osteoporos Int, 2005[34]; Miller, J Bone Miner Res, 2005[66]; Nguyen, J Bone Miner Res, 2006[33]; Watts, J Clin Endocrinol Metab, 2003[87]; Wallach, Calcif Tissue Int, 2000[68]; Bianchi, Curr Med Res Opin, 2008[69]; Wells, Cochrane Database Syst Rev, 2008[70]; Zhong, Clin Drug Investig, 2009[71]

Table 7. Pooled risk estimates of fracture for risedronate, relative to placebo or no treatment[*]

Author, Year	# Studies	Sample Size	RR	(95% CI)
		Vertebral Fractures		
Original 2007 Report				
Cranney, 2002[65]	5	2,604	0.64	(0.54, 0.77)
Miller, 2005[66]				
Subjects with severe renal impairment	9	232	0.56	(0.11, 0.78)
Subjects with moderate renal impairment	9	2,426	0.45	(0.31, 0.57)
Subjects with mild renal impairment	9	3,088	0.32	(0.14, 0.46)
Stevenson, 2005[32]	2	2,064	0.62	(0.50, 0.77)
Update Report				
Zhong, 2009[71†]	4	1,022	0.31	(0.16, 0.60)
Wells, 2008[70]				
Overall 2.5mg[‡]	4	1,460/1,532	0.62	(0.46, 0.83)
5 mg	4	1,534/1,532	0.63	(0.51, 0.77)
Primary 2.5 mg[‡]	1	127/135	1.08	(0.48, 2.46)
5 mg	2	166/161	0.97	(0.42, 2.25)
Secondary 2.5 mg[‡]	3	1,333/1,407	0.57	(0.42, 0.78)
5 mg	3	1,405/1,407	0.61	(0.50, 0.76)
		Nonvertebral Fractures		
Original 2007 Report				
Boonen, 2005[34]	3	11,770	0.81	(0.71, 0.92)
Cranney, 2002[65]	7	12,958	0.73	(0.61, 0.87)
Stevenson, 2005[32]	2	2,439	0.67	(0.50, 0.90)
Update Report				
Zhong, 2009[71†]	4	1,022	0.40	(0.23, 0.70)
Wells, 2008[70]				
Overall 2.5mg[‡]	2	235/305	0.50	(0.21, 1.19)
5 mg	5	7,731/4,666	0.80	(0.72, 0.90)
Primary 2.5 mg[‡]	1	127/125	0.49	(0.1, 1.92)
5 mg	1	129/125	0.81	(0.25, 2.58)
Secondary 2.5 mg[‡]	1	108/180	0.51	(0.17, 1.53)
5 mg	4	7,602/4,541	0.80	(0.72, 0.90)

Table 7. Pooled risk estimates of fracture for risedronate, relative to placebo or no treatment* (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)
Hip Fractures				
Original 2007 Report				
Nguyen, 2006[33]	3	7,196	0.66	(0.11, 3.68)
Stevenson, 2005[32]				
Subjects with osteoporosis or osteopenia	3	4,142	0.60	(0.42, 0.88)
Subjects with osteoporosis or severe osteoporosis	3	7,884	0.66	(0.48, 0.89)
Update Report				
Wells, 2008[70]				
Overall 5 mg	3	7,425/4,361	0.74	(0.59,0.94)
Primary 5 mg	1	37/36	NE[b]	
Secondary 5 mg	3	7,425/4,361	0.74	(0.59,0.94)
Wrist Fractures				
Original 2007 Report				
Stevenson, 2005[32]				
Subjects with severe osteoporosis	2	2,439	0.68	(0.43, 1.08)
Update Report				
Wells, 2008[70]				
Overall 5mg	2	1,265/1,263	0.67	(0.42, 1.07)
Primary 5 mg	1	37/36	NE	
Secondary 5 mg	2	1,228/1,227	0.67	(0.42, 1.07)

NE = not estimable

*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.

†Men.

‡The 2.5mg dose is no longer available.

Table 8. Risk of fracture for risedronate, relative to placebo, by dose and fracture group

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Risedronate	Number of Fractures, Placebo	Odds Ratio (95% CI)
Any Dose, All Fractures					
Original 2007 Report					
Greenspan, 2006[83]	12 months	Fracture	2/43	0/44	7.75 (0.48, 125.9)
Hosking, 2003[60]	12 months	Clinically diagnosed vertebral or nonvertebral	6/178	2/89	1.47 (0.33, 6.52)
Milgrom, 2004[82]	14 weeks	All stress fracture	24/165	21/159	1.12 (0.60, 2.10)
Update Report: ***No new studies***					
2.5 mg Daily, Vertebral					
Original 2007 Report					
Kanaji, 2006[76]	12 months	Vertebral	0/12	0/11	NC
Update Report: ***No new studies***					
2.5 mg Daily, Nonvertebral					
Original 2007 Report					
Sato, 2005[77]	18 months	Nonvertebral	8/231	29/230	0.29 (0.15, 0.57)
Update Report: ***No new studies***					
2.5 mg* Daily, Hip					
Original 2007 Report					
Sato, 2005[77]	18 months	Hip	5/231	19/230	0.29 (0.13, 0.66)
Sato, 2005[78]	18 months	Hip	2/134	10/133	0.25 (0.08, 0.78)
Sato, 2005[79]	12 months	Hip	1/172	7/173	0.22 (0.05, 0.88)
Update Report					
Sato, 2007[72]	24 months	Hip	3/121	9/121	0.35 (0.11, 1.12)
5.0 mg Daily, Vertebral					
Original 2007 Report					
Sorensen, 2003[80]	24 months	Vertebral	15/109	29/103	0.42 (0.22, 0.81)
Update Report: ***No new studies***					
5.0 mg Daily, Nonvertebral					
Original 2007 Report					
Sorensen, 2003[80]	24 months	Nonvertebral	7/135	11/129	0.59 (0.23, 1.54)
Update Report					
Ringe, 2009[73]	24 months	Nonvertebral	18/152	33/148	0.48 (0.26, 0.87)
Ringe, 2006[81]	12 months	Nonvertebral	10/158	17/158	0.57 (0.26, 1.25)
5.0 mg Daily, Humerus					
Original 2007 Report					
Sorensen, 2003[80]	24 months	Humerus	3/136	6/130	0.48 (0.13, 1.81)
Update Report: ***No new studies***					

Table 8. Risk of fracture for risedronate, relative to placebo, by dose and fracture group (continued)

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Risedronate	Number of Fractures, Placebo	Odds Ratio (95% CI)
30-35 mg Weekly, All Fractures					
Greenspan, 2006[83]	12 months	Fracture	2/43	0/44	7.75 (0.48, 125.9)
Milgrom, 2004[82]	14 weeks	All stress fractures	24/165	21/159	1.12 (0.60, 2.10)
Update report: ***no new studies***					
35 mg Weekly, Vertebral					
Original 2007 report					
Palomba, 2005[84]	12 months	Vertebral	5/40	14/41	0.30 (0.11, 0.84)
Update Report					
Boonen, 2009[74]	2 years	Vertebral	2/191	0/93	4.45 (0.23, 85.68)
Palomba, 2008[75]	2 years	Vertebral	4/40	7/41	0.55 (0.16, 1.95)
Palomba, 2008[75]	3 years	Vertebral	3/40	9/41	0.32 (0.1, 1.09)
35 mg Weekly, Nonvertebral					
Original 2007 Report					
Palomba, 2005[84]	12 months	Nonvertebral	0/40	4/41	0.13 (0.02, 0.95)
Update Report					
Palomba, 2008[75]	2 years	Nonvertebral	1/40	7/41	0.2 (0.05, 0.85)
Palomba, 2008[75]	3 years	Nonvertebral	1/40	4/41	0.29 (0.05, 1.75)

NC = not calculable
*The 2.5mg dose is no longer available.

Table 9. Randomized controlled trials assessing risk of fracture for risedronate, relative to different doses of risedronate, by fracture group (not included in prior systematic reviews)

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Risedronate, Weekly*	Number of Fractures, Risedronate, Daily	Odds Ratio (95% CI)†
Risedronate 2.5 Mg/D vs. Risedronate 17.5 mg/Week					
Vertebral					
Original 2007 report					
Kishimoto, 2006[99]	48 weeks	Vertebral	6/222	5/227	1.23 (0.37, 4.00)
Update report: ***No new studies***					
Risedronate 5 Mg/D vs. Risedronate 35 mg/Week					
Vertebral					
Original 2007 report					
Brown, 2002[100]	24 months	New morphometric vertebral	6/480	5/485	1.21 (0.37, 3.98)
Harris, 2004[101]	24 months	Morphometric vertebral	12/415	7/422	1.92 (0.75, 4.88)
Update report: ***No new studies***					
Nonvertebral					
Original 2007 report					
Brown, 2002[100]	24 months	Any non-vertebral	24/480	28/485	0.86 (0.49, 1.50)
Update report: ***No new studies***					
Risedronate 5 Mg/D vs. Risedronate 50 mg/Week					
Vertebral					
Original 2007 report					
Brown, 2002[100]	24 months	New morphometric vertebral	6/480	2/491	2.8 (0.7, 11.26)
Harris, 2004[101]	24 months	Morphometric vertebral	12/415	7/422	1.74 (0.70, 4.32)
Update report: ***No new studies***					
Nonvertebral					
Original 2007 report					
Brown, 2002[100]	24 months	Any non-vertebral	24/480	24/491	1.02 (0.57, 1.83)
Update report: ***No new studies***					
Risedronate 35 Mg/Week vs. Risedronate 50 mg/Week					
Vertebral					
Original 2007 report					
Brown, 2002[100]	24 months	New morphometric vertebral	5/485	2/491	1.19 (0.68, 2.08)
Harris, 2004[101]	24 months	Morphometric vertebral	12/415	7/422	0.9 (0.30, 2.68)
Update report: No new studies					
Non-Vertebral					
Original 2007 report					
Brown, 2002[100]	24 months	Any nonvertebral	28/485	24/491	1.19 (0.68, 2.08)
Update report: ***No new studies***					

Table 9. Randomized controlled trials assessing risk of fracture for risedronate, relative to different doses of risedronate, by fracture group (not included in prior systematic reviews) (continued)

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Risedronate, Weekly*	Number of Fractures, Risedronate, Daily	Odds Ratio (95% CI)†
Risedronate 150 mg Daily for 2 Consecutive Days per Month vs. Risedronate 5 mg/D					
Vertebral					
Original 2007 report: ***No comparable studies from the original report***					
Update report					
Delmas, 2008[85]	12 months	Vertebral	6/616	7/613	0.85 (0.29, 2.54)
Delmas, 2008[86]	12 months	Vertebral	8/650	8/642	0.99 (0.37, 2.65)

NC=not calculable

*Number of fractures/number of participants included in treatment arm.

†An odds ratio greater than 1 indicates higher risk of fracture in the group receiving active treatment.

Ibandronate

Prior Systematic Reviews

The antifracture effects of ibandronate vs. placebo or no treatment was examined in three meta-analyses (two specific to ibandronate[102,103] and the third covering multiple bisphosphonates)[36] (Table 10).

Pooled estimates of the effects of ibandronate among postmenopausal women from the three meta-analyses are summarized in Table 11, including separate pooled estimates by tertile of annual cumulative exposure for one of the meta-analyses.[103] We include RCT evidence for the effect of ibandronate vs. placebo in reducing vertebral fracture risk (51 percent statistically significant). In postmenopausal women, the RR of nonvertebral fracture was not significantly different with ibandronate less than 7.2 mg daily (lower annual cumulative exposure, which includes the 2.5 mg daily oral dose) vs. placebo. A statistically significant reduction in RR of nonvertebral fracture and of clinical fracture, of approximately 30 percent, was apparent only with higher annual cumulative exposure, i.e. 10.8 mg or more, a dosing regimen that includes 150 mg monthly oral dose and the 3 mg quarterly IV dose.

Original Placebo-Controlled Studies

We classified fracture risk associated with ibandronate vs. placebo according to anatomical fracture site from the three original studies (Table 12) not included in existing systematic reviews (two included in the first report [104,105] and one identified for this report[106]). The latter study had a Jadad score of 5. After 12 months, ibandronate was associated with a statistically significantly reduction in relative risk of overall fractures compared to placebo (OR 0.002, 95% CI: 0.00, 0.48).[104] However, results were conflicting regarding the relative risk of vertebral fracture associated with ibandronate vs. placebo after 12 months, with one trial showing no reduction in risk, and the other showing a statistically significant 85 percent reduction (RR 0.15, 95% CI 0.04, 0. 60). The confidence intervals of these two studies overlap and their numbers of fracture events were small, so that their apparently discrepant conclusions may be due to random variation.

The pooled analyses encompassed thousands of participants, whereas the RCTs not included in original meta-analyses had 35-180 participants and few fracture events (ranging from only 1 to 12 fractures). Using the criteria of Gartlehner et al.[25] to assess the applicability of the one study newly identified for this report, we determined that its applicability to the general population was moderately low. The population comprised a small group of men who were heart transplant recipients and the analysis was not intention-to-treat.[106]

If the results of the pooled analysis are classified in terms of the currently available FDA-approved doses of ibandronate, statistically significant reductions in fracture risk are associated with ibandronate doses of 150 mg monthly orally or 3 mg IV quarterly for 3 years (nonvertebral and overall clinical fracture), and for 2.5 mg orally daily for 2 years (overall clinical fractures).

In summary, compared to placebo, ibandronate in currently FDA-approved doses reduces the risk of vertebral, nonvertebral fractures, and overall clinical fractures, in individuals with osteoporosis.

Table 10. Randomized controlled trials included in systematic review of effect of ibandronate on fracture relative to placebo or no treatment by fracture type

	Systematic Review (Author, Year)			
	Cranney, 2009[102*]	Harris, 2008[103]		Jansen, 2009[36]
	Fracture Type			
RCTs (Author, Year)	NV	A	NV	V
Chestnut, 2004 [107]	X	X	X	X
Recker, 2004[108]	X	X	X	
Miller, 2005[109]	X			
Delmas, 2006[110]	X			

V = vertebral; A = all; NV = nonvertebral; X = included in pooled analysis
*Studies within drug comparison.

Table 11. Pooled risk estimates of fracture for ibandronate, relative to lower dose, placebo, or no treatment, among postmenopausal women

Author, Year	# Studies	Sample Size	RR	(95% CI)
Vertebral Fractures				
Original Report: ***No comparable studies from the original report***				
Update Report:				
Jansen, 2009[36]				
2.5 mg/d or 20 mg every other day	1	2.946	0.49	(0.26, 0.66)
Nonvertebral Fractures				
Original Report: ***No comparable studies from the original report***				
Update Report				
Cranney, 2009 [102]				
Lower ACE (5.5 mg) vs. placebo*	3	3,212	1.073†	(0.79, 1.46)
Harris, 2008 [103]				
Key Nonvertebral Site Fractures				
Higher ACE (≥10.8 mg) all-years‡	4	8,710	0.66§,**	(0.45. 0.96)
Higher ACE (≥10.8 mg) two-years	4	8,710	0.72	(0.48, 1.08)
Mid ACE (5.5-7.2 mg) all-years	4	8,710	1.15	(0.90, 1.46)
Mid ACE (5.5-7.2 mg) two-years	4	8,710	1.23	(0.93, 1.64)
Low ACE (≤4.0 mg) all years	4	8,710	0.87	(0.66, 1.15)
Low ACE (≤4.0 mg) two-years	4	8,710	0.93	(0.66, 1.31)
All Nonvertebral Fractures				
Higher ACE (≥10.8 mg) all-years	4	8,710	0.70**	(0.50, 0.99)
Higher ACE (≥10.8 mg) two-years	4	8,710	0.73	(0.51, 1.04)
Mid ACE (5.5-7.2 mg) all-years	4	8,710	1.04	(0.83, 1.20)
Mid ACE (5.5-7.2 mg) two-years	4	8,710	1.06	(0.82, 1.38)
Low ACE (≤4.0 mg) all-years	4	8,710	0.89	(0.69, 1.15)
Low ACE (≤4.0 mg) two-years	4	8,710	0.87	(0.64, 1.18)

Table 11. Pooled risk estimates of fracture for ibandronate, relative to lower dose, placebo, or no treatment, among postmenopausal women (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)
Clinical Vertebral and Nonvertebral Fractures[††]				
Original Report: ***No comparable studies from the original report***				
Update Report				
Harris, 2008[103]				
Higher ACE (≥10.8 mg) all-years	4	8,710	0.73[**]	(0.56, 0.95)
Higher ACE (≥10.8 mg) two-years	4	8,710	0.71[**]	(0.54, 0.93)
Mid ACE (5.5-7.2 mg) all-years	4	8,710	0.92	(0.77, 1.09)
Mid ACE (5.5-7.2 mg) two-years	4	8,710	0.88	(0.72, 1.08)
Low ACE (≤4.0 mg) all years	4	8,710	0.82	(0.67, 1.00)
Low ACE (≤4.0 mg) two years	4	8,710	0.76[**]	(0.60, 0.97)

[*]ACE: annual cumulative exposure (annual dose [mg] x bioavailability [0.6% for oral; 100% for IV]), Higher ACE (>10.8mg) vs. lower ACE (<7.2mg) described in head-to-head comparisons; 150 mg oral once- monthly and 3 mg IV quarterly are both approved, marketed dosages and fall within the high-dose group. The 2.5 mg daily approved dose fell within the low-ACE group.
[†]Unadjusted hazard ratio.
[‡]4 trials were pooled: two 2-year trials and two 3-year trials; the all-years comparisons included data from all available study years (both 2-year and 3-year). Also, oral and IV routes of administration were pooled.
[§]Adjusted hazard ratio.
[**]Significantly different.
[††]Clinical trials include nonvertebral and symptomatic vertebral, all ascertained by x-ray.

Table 12. Randomized controlled trials assessing risk of fracture for ibandronate, any dose, relative to placebo, by anatomical fracture site (not included in prior systematic reviews)

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Ibandronate*	Number of Fractures, Placebo*	Odds Ratio (95% CI)
All Fractures					
Original 2007 Report					
Ravn, 1996[104]	12 months	Fracture	0/150†	1/30	0.002 (0.00, 0.477)
Update report: *No new studies*					
Vertebral Fractures					
Original 2007 Report					
Grotz, 2001[105]	12 months	Vertebral	1/40	1/40	1.00 (0.006, 16.27)
Update Report					
Fahrleitner-Pammer, 2009[106]	12 months	Morphometric vertebral	2/17	10/18	0.15 (.04,.60)

*Number of fractures/number of participants included in treatment arm.
†.0.25mg , 0.50mg, 1.0mg, 2.5mg and 5.0 mg dose groups combined.

Zoledronic Acid

Prior Systematic Reviews

We identified no prior systematic reviews of studies assessing the effects of zoledronic acid.

Original Placebo-Controlled Studies

Table 13 shows the results of RCTs of intravenous zoledronic acid vs. placebo in postmenopausal women. Two studies were identified from the original report.[111,112] Since that report, two additional publications were identified for inclusion in this update (Jadad scores of 5 and 2).[113,114] Included RCTs were 12, 24, or 36 months in duration. Doses and dosing intervals tested were 4 mg (single dose), 5 mg (single dose), 2 mg twice yearly, 0.25 mg quarterly, 0.5 mg quarterly, and 1 mg quarterly

5 mg Single Dose. RCTs showed statistically significant reduction in any clinical fracture among postmenopausal women (RR 0.63, one RCT),[111] nonvertebral fracture among postmenopausal women and men and women post-hip fracture (RR 0.72-0.73, two RCTs),[111,113] morphometric vertebral fracture (RR 0.32, one RCT), clinical vertebral fracture (0.23, one RCT),[111], and vertebral fracture among men and women post-hip fracture (RR 0.54, one RCT)[113] with zoledronic acid vs. placebo. A 36-month RCT reported statistically significant reductions in hip fracture with zoledronic acid vs. placebo among postmenopausal women (RR 0.56, 95% CI: 0.40, 0.78),[111] but the shorter trial of 24-month duration in the post-hip fracture population found that hip fracture risk was not statistically significantly decreased with zoledronic acid vs. placebo (RR 0.69, 95% CI: 0.41, 1.17).[113]

4 mg Single Dose. Among postmenopausal women, only one RCT testing the 4 mg single dose was available; this study was included in the original report.[112] The trial recorded 2 fracture events, and had small numbers of participants. Risk of nonvertebral fracture was not statistically significantly different with zoledronic acid vs. placebo. Fractures of other types did not occur in the RCT of this dose of zoledronic acid, prohibiting estimates of the effect of this dose in relation to other types of fracture.

2 mg Every 6 Months. Among postmenopausal women, only two RCTs that tested a 2 mg dose every 6 months were identified, one in the original report[112] and one for the current report;[114] only the older study reported any fractures. The trial recorded two fracture events, and had small numbers of participants. Risk of nonvertebral fracture was not statistically significantly different with zoledronic acid vs. placebo. Fractures of other types did not occur in RCTs of this dose of zoledronic acid, prohibiting estimates of the effect of this dose in relation to other types of fracture.

0.25 mg Every 3 Months. Among postmenopausal women, only one RCT testing a 0.25 mg dose every 3 months was available.[112] The trial recorded one fracture event and had small numbers of participants. Risk of nonvertebral fracture was not statistically significantly different with zoledronic acid vs. placebo. Fractures of other types did not occur in the RCT of this dose of zoledronic acid, prohibiting estimates of the effect of this dose in relation to other types of fracture.

0.5 mg Every 3 Months. Among postmenopausal women, only one RCT testing a 0.5 mg dose every three months was available.[112] The trial recorded two fracture events, and had small numbers of participants. Risk of nonvertebral fracture was not statistically significantly different with zoledronic acid vs. placebo. Fractures of other types did not occur in the RCT of this dose of zoledronic acid, prohibiting estimates of effectiveness of this dose in relation to other types of fracture.

1 mg Every 3 Months. Among postmenopausal women, only one RCT testing a 1 mg dose every 3 months was available.[112] The trial recorded three fracture events and had small numbers of participants. Risk of nonvertebral fracture was not statistically significantly different with zoledronic acid vs. placebo. Fractures of other types did not occur in the RCT of this dose of zoledronic acid, prohibiting estimates of the effect of this dose in relation to other types of fracture.

Using the criteria of Gartlehner et al.[25], to assess the applicability of the two studies newly identified for this report, we determined that their applicability was moderate to high.

In summary, in comparison with placebo, zoledronic acid reduces the risk of clinical fractures, nonvertebral fractures, vertebral fractures, and hip fractures.

Table 13. Randomized controlled trials assessing risk of intravenous zoledronic acid relative to placebo, by dose and frequency among postmenopausal women

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Zoledronic Acid	Number of Fractures, Placebo	Odds Ratio (95% CI)
		5 Milligrams Once			
Original 2007 report					
Black, 2007[111]	36 months	Any clinical	308/3,667	456/3,563	0.63 (0.54, 0.72)
Black, 2007[111]	36 months	Nonvertebral	292/3,650	388/3,626	0.73 (0.62, 0.85)
Black, 2007[111]	36 months	Morphometric vertebral	92/2,788	310/2,844	0.32 (0.26, 0.39)
Black, 2007[111]	36 months	Clinical vertebral	19/3,800	84/3,231	0.23 (0.16, 0.34)
Black, 2007[111]	36 months	Hip	52/3,714	88/3,520	0.56 (0.40, 0.78)
Update report					
Lyles, 2007[113]	24 months	Hip fracture	23/1,065	33/1,062	0.69 (0.41, 1.17)
Lyles, 2007[113]	24 months	Any fracture	92/1,065	139/1,062	0.63 (0.48, 0.83)
Lyles, 2007[113]	24 months	Nonvertebral	79/1,065	107/1062	0.72 (0.53, 0 .93)
Lyles, 2007[113]	24 months	Vertebral	21/1,065	39/1,062	0.54 (0.32, 0.90)
		4 Milligrams Once			
Original 2007 report					
Reid, 2002[112]	12 months	Nonvertebral	1/60	1/59	0.98 (0.06, 15.91)
Reid, 2002[112]	12 months	Vertebral	0/60	0/59	NC
Update report: ***No new studies***					
		2 Milligrams, Every 6 Months			
Original 2007 report					
Reid, 2002[112]	12 months	Nonvertebral	1/61	1/59	0.97 (0.06, 15.65)
Reid, 2002[112]	12 months	Vertebral	0/61	0/59	NC
Update report					
Chapman, 2009[114]	24 months	Nonvertebral	0/10	0/12	NC
Chapman, 2009[114]	24 months	Vertebral	0/10	0/12	NC
		0.25 Milligrams, Every 3 Months			
Original 2007 report					
Reid, 2002[112]	12 months	Nonvertebral	0/60	1/59	0.13 (0.00, 6.71)
Reid, 2002[112]	12 months	Vertebral	0/60	0/59	NC
Update report: ***No new studies***					
		0.5 Milligrams, Every 3 Months			
Original 2007 report					
Reid, 2002[112]	12 months	Nonvertebral	1/58	1/59	1.02 (0.06, 16.46)
Reid, 2002[112]	12 months	Vertebral	0/58	0/59	NC
Update report: ***No new studies***					

Table 13. Randomized controlled trials assessing risk of intravenous zoledronic acid relative to placebo, by dose and frequency among postmenopausal women (continued)

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Zoledronic Acid	Number of Fractures, Placebo	Odds Ratio (95% CI)
1 Milligram, Every 3 Months					
Reid, 2002[112]	12 months	Nonvertebral	2/53	1/59	2.2 (0.22, 21.7)
Reid, 2002[112]	12 months	Vertebral	0/53	0/59	NC
Update report: ***No new studies***					

NC = not calculable

Biologics

Since the completion of the original report, a new class of agents has been approved for the treatment of osteoporosis in postmenopausal women. The one agent currently constituting this class is the human monoclonal antibody denosumab.

Denosumab

Prior Systematic Reviews

We found one systematic review of fracture risk associated with denosumab relative to placebo or no treatment.[115] (Tables 14 and 15) The systematic review included data from 3 RCTs encompassing 919 participants and assessed risk of clinical fractures, although participants in one of the studies comprised only cancer patients.[116] The risk of clinical fracture was reduced, but not statistically significantly so, with denosumab versus placebo (RR 0.74, 95% CI: 0.33, 1.64) (Table 15); however including only 3 trials, the meta-analysis may have been underpowered to detect a change in fracture risk.

Original Placebo-Controlled Studies

Two placebo-controlled trials of denosumab were identified for the current report, two years and 36 months in duration (Jadad scores of 2 and 1), respectively (Table 16).[117,118] The smaller RCT of shorter duration (two years)[117] and with fewer fracture events (nine nonvertebral and one vertebral) found no statistically significant difference in risk of vertebral or nonvertebral fracture with denosumab vs. placebo. The much larger RCT (more than 3,600 participants) reported a statistically significantly lower risk of fracture with denosumab vs. placebo.[118] In this study, denosumab was associated with a 41 percent lower risk of hip fracture (OR 0.59, 0.36, 0.94), a 20 percent lower risk of nonvertebral fracture (OR 0.8, 0.67, 0.95), a 60 percent lower risk of multiple new vertebral fracture (OR 0.4, 0.26, 0.61), a 66 percent lower risk of new clinical vertebral fracture (OR 0.34, 0.24, 0.48), and a 66 percent lower risk of vertebral fracture (OR 0.34 0.27, 0.42). Given the larger numbers of participants (several times as many patients as all prior RCTs put together) and longer trial duration, this latter study provides a better estimate of fracture risk reduction associated with denosumab. Using the criteria of Gartlehner et al., to assess the applicability of the two studies newly identified for this report, we determined that the applicability of the smaller study was moderate[117] and the applicability of the larger study was high.[118]

In summary, compared to placebo, denosumab reduces the risk of vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis.

Table 14. Randomized controlled trials included in meta-analysis of effect of Denosumab on fracture relative to placebo or no treatment by fracture type

	Meta-analysis (Author, Year)
	Anastasilakis, 2009[115]
	Fracture Type
RCTs (Author, Year)	A
Bone, 2008 [117]	X
Ellis, 2008 [116]	X
Lewiecki, 2007[119]	X

A = all; X = included in pooled analysis

Table 15. Pooled risk estimates of fracture for denosumab relative to placebo or no treatment

Author, Year	# Studies	Sample Size	RR	(95% CI)
Clinical Fractures				
Original 2007 report: ***No comparable studies from the original report***				
Update report				
Anastasilakis, 2009[115]	3	919	0.74	(0.33, 1.64)

Table 16. Denosumab versus placebo

Author, Year	Study Duration	Fracture Type	Number of Fractures, Denosumab	Number of Fractures, Placebo	Odds Ratio (95% CI)
Original report: ***No comparable studies from the original report***					
Update report					
Cummings, 2009[118]	36 months	Hip fracture	26/3,714	43/3,583	0.59 (0.36, 0.94)
Cummings, 2009[118]	36 months	Nonvertebral	238/3,662	293/3,663	0.8 (0.67, 0.95)
Cummings, 2009[118]	36 months	Multiple new vertebral	23/3,833	59/3,688	0.4 (0.26, 0.61)
Cummings, 2009[118]	36 months	New clinical vertebral	29/3,625	92/3,538	0.34 (0.24, 0.48)
Bone, 2008[117]	2 years	Nonvertebral	2/166	7/166	0.32 (0.09, 1.2)
Cummings, 2009[118]	36 months	Vertebral	86/3,739	264/3,667	0.34 (0.27, 0.42)
Bone, 2008[117]	2 years	Vertebral	0/166	1/166	0.14 (0, 6.82)

Selective Estrogen Receptor Modulators (SERMs)

In this section, we present results regarding the effects of the SERM raloxifene on fracture prevention. Although the original report included tamoxifen, it was excluded from this report, as it is not primarily used for osteoporosis prevention or treatment. A newer agent, lasofoxifene, has been tested for its efficacy in preventing fracture but is excluded in this report, as it has not been approved for use in the U.S.

Raloxifene

Prior Systematic Reviews

No new meta-analyses regarding antifracture effects of raloxifene were identified since the last report. The prior report found consistent evidence for a statistically significant reduction in vertebral fractures, ranging from 19-41 percent, with raloxifene vs. placebo (Table 17). In contrast, studies found that, compared to placebo, raloxifene does not decrease the risk of nonvertebral, hip, or wrist fractures.

Original Placebo-Controlled Studies

Since the original 2007 report, we have added eight new estimates of fracture risk with raloxifene relative to placebo from two studies (Jadad scores of 4 and 3) (Table 18). [120,121] All but one RCT was consistent with a statistically significant reduction in vertebral fracture risk, ranging from 34 percent -to 44 percent, with raloxifene vs. placebo. The exception was the original RCT with five fracture events (RR 1.72, 0.26, 11.05).[122] However, raloxifene was not associated with a statistically significantly decrease in the risk of nonvertebral (two RCTs), hip (one RCT), or wrist (one RCT) fractures.[120,121] We conclude that, compared to placebo, raloxifene decreases the risk of vertebral fractures, but not nonvertebral, hip, or wrist fractures.

Using the criteria of Gartlehner et al.[25] to assess the applicability of the newly identified studies, we determined their applicability to be moderately high although one study was a large clinical trial with many exclusion criteria.

Table 17. Risk estimates of fracture for raloxifene relative to placebo or no treatment among postmenopausal women as reported in prior meta-analyses.*

Author, Year	# Studies	Sample Size	RR	(95% CI)
Vertebral Fractures				
Schachter, 2005[123]				
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[32]				
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[124]				
60 mg	5	5,600	0.60	(0.49, 0.74)
120/150 mg	4	5,403	0.51	(0.41, 0.64)
Non-vertebral Fractures				
Stevenson, 2005[32]				
Women with severe osteoporosis or osteoporosis	1	6,828	0.92	(0.79, 1.07)
Hip Fractures				
Stevenson, 2005[32]				
Women with severe osteoporosis or osteoporosis	1	6,828	1.12	(0.65, 1.95)
Wrist Fractures				
Stevenson, 2005[32]				
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 18. Risk of vertebral fracture for raloxifene, relative to placebo

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Serm	Number of Fractures, Placebo	Odds Ratio (95% CI)
Vertebral Fracture					
Original 2007 Report					
Reid, 2004[122]	36 months	Vertebral	4/193*	1/90	1.72 (0.26, 11.05)
Update Report					
Ensrud, 2008[120]	5.6 years	Vertebral	64/5,044	97/5,057	0.66 (0.48, 0.90)
Silverman, 2008[121]	3 years	Vertebral	43/1,849	77/1,885	0.57 (0.39, 0.82)
Silverman, 2008[121]	3 years	Vertebral - with prevalent fracture	50/1,849	90/1,885	0.56 (0.40, 0.79)
Silverman, 2008[121]	3 years	Vertebral - without prevalent fracture	33/1,849	58/1,885	0.58 (0.38,.88)
Clinical Vertebral					
Original 2007 Report					
Barrett-Connor[125]	5.6 years	Clinical	64/5,044	97/5,057	0.66 (0.48. 0.90)
Update Report: ***No new studies***					
Nonvertebral					
Original Report: ***No comparable studies from the original report***					
Update Report					
Ensrud, 2008[120]	5.6 years	Nonvertebral	428/5,044	438/5,057	0.99 (0.86, 1.13)
Silverman, 2008[121]	3 years	Nonvertebral	60/1,849	99/1,885	0.61 (0.44, 0.84)
Hip/femur					
Original Report: ***No comparable studies from the original report***					
Update Report					
Ensrud, 2008[120]	5.6 years	Hip/femur fracture	89/5,044	103/5,057	0.86 (0.65, 1.15)
Wrist					
Original Report: ***No comparable studies from the original report***					
Update Report					
Ensrud, 2008[120]	5.6 years	Wrist	107/5,044	111/5,057	0.97 (0.74, 1.26)

*60 mg and 150 mg dose groups combined.

Peptide Hormones

In this section, we present the results of studies assessing the effects of parathyroid hormone (PTH, i.e., teriparatide, PTH [1-34]) on fracture risk. The original report included the peptide hormone calcitonin, but it has been excluded from this report at the subject matter experts' request, since most authorities no longer consider calcitonin to be appropriate treatment for osteoporosis.

Parathyroid Hormone

Parathyroid hormone (PTH) has been investigated for use in osteoporosis in several forms, including PTH 1-34 (teriparatide) and PTH 1-84. However, only teriparatide is approved for use in the US for treating osteoporosis.

Prior Systematic Reviews

The original report identified one systematic review on parathyroid hormone.[32] The meta-analysis conducted for this review included data from five RCTs of teriparatide and examined risk of vertebral, nonvertebral, and hip fractures. One additional systematic review was identified for the current report[126] (Table 19); it provided two new pooled estimates regarding fracture risk with use of teriparatide versus placebo or no treatment (Table 20). Teriparatide was associated with reduced relative risk of vertebral fractures, with RR's ranging from 0.31 to 0.36, and reduced relative risk of nonvertebral fractures, with RR's ranging from 0.60 to 0.65.

Original Placebo-Controlled Studies

No new studies of teriparatide were identified for this report. The original report included three studies of teriparatide (Table 21).[127-129]

All Fractures. Compared to placebo, teriparatide was associated with a statistically significant 84 percent reduction (one RCT).[128]

Vertebral Fractures. In the RCT with the fewest number of vertebral fracture events, vertebral fracture risk was no different with PTH than placebo;[128] however, the remainder of the RCTs demonstrated vertebral fracture risk to be statistically significantly lower with PTH than with placebo (RRs ranging from 0.34-0.44.[127,129,130]

Nonvertebral Fractures. For nonvertebral fractures, risk with teriparatide was not statistically different from that of placebo in three trials.[127,129,130]

This finding contrasts with a pooled analysis[126] that included two of the three trials along with three other trials, and found a statistically significant 38 percent relative risk reduction with teriparatide treatment.

In summary, compared to placebo, teriparatide, the form of PTH currently available in the U.S., is associated with reduced risk of vertebral fractures and nonvertebral fractures among postmenopausal women with osteoporosis.

Table 19. Randomized controlled trials included in meta-analysis of effect of parathyroid hormone on fracture relative to placebo by fracture type

	Systematic Review (Author, Year)							
	Stevenson, 2005[32]					Vestergaard, 2007[126]		
	Fracture Type							
RCTs (Author, Year)	V	NV	H	W	Hum	V	NV	H
Cosman, 2004 [131]						X	X	X
Cosman, 2001	X							
Greenspan, 2005[132]						X	X	
Kurland, 2000 [133]								X
Lane, 1998						X	X	X
Neer, 2001 [134]	X	X	X	X	X	X	X	
Orwoll, 2003 [135]						X	X	

V = vertebral; NV = nonvertebral; H = hip; X = included in pooled analysis

Table 20. Pooled risk estimates of fracture for parathyroid hormone relative to placebo or no treatment*

Author, Year	# Studies	Sample Size	RR	(95% CI)
Vertebral Fractures				
Original 2007 Report				
Stevenson, 2005[32]				
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)
Update Report				
Vestergaard, 2007 [126]	7	4,359	0.36	(0.28, 0.47)
Nonvertebral Fractures				
Original 2007 Report				
Stevenson, 2005[32]				
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)
Update Report				
Vestergaard, 2007[126]	5	2,377	0.62	(0.48, 0.82)
Hip Fractures				
Original 2007 Report				
Stevenson, 2005[32]				
Subjects with severe osteoporosis	1	NR	0.50	(0.09, 2.73)
Update Report: ***no new studies***				
Wrist Fractures				
Original 2007 Report				
Stevenson, 2005[32]				
Subjects with severe osteoporosis	1	NR	0.54	(0.22, 1.35)
Update Report: ***No new studies***				
Humerus Fractures				
Original 2007 Report				
Stevenson, 2005[32]				
Subjects with severe osteoporosis	1	NR	0.80	(0.22, 2.98)
Update Report: ***No new studies***				

*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 21. Risk of fracture for parathyroid hormone, relative to placebo, by fracture group

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Teriparatide	Number of Fractures, Placebo	Odds Ratio (95% CI)
All Fractures					
Original 2007 Report					
Kaufman, 2005[128]	30 months	Moderate or severe	2/176*	7/103	0.16 (0.04, 0.65)
Update Report: ***No new studies***					
Vertebral Fractures					
Original 2007 Report					
Gallagher, 2005[127]	21 months	Vertebral	22/403	62/398	0.34 (0.22, 0.54)
Kaufman, 2005[128]	30 months	Vertebral	10/176*	12/103	0.44 (0.18, 1.09)
Update Report: ***No new studies***					
Nonvertebral Fractures					
Original 2007 Report					
Gallagher, 2005[127]	21 months	Nonvertebral	30/467	46/464	0.63 (0.39, 1.00)
Orwoll, 2003[129]	11 months	Nonvertebral	3/290*	3/147	0.48 (0.09, 2.62)
Update Report: ***No new studies***					

*20 µg and 40 µg dose groups combined.

Steroid Hormones

This section presents the results of studies of menopausal estrogen therapy for women. The original report included both estrogen/progestin and testosterone; however, testosterone has been omitted from this report as it has not been and is not likely to be approved for prevention or treatment of osteoporosis.

Menopausal Estrogen Therapy or Combination Estrogen Plus Progestogen Therapy for Women

The original report relied strongly on data from the Women's Health Initiative (WHI), which enrolled postmenopausal women in a randomized comparison of menopausal hormone therapy and assessed a number of different outcomes (cardiovascular, neurologic, etc.) in addition to fracture outcomes. Of note, women were not selected for inclusion based on a diagnosis of osteopenia or osteoporosis, and thus the WHI would not, strictly speaking, be an eligible study for inclusion in this evidence report. Nevertheless, the WHI dwarfs all other studies of menopausal hormone therapy in size and scope and provides the best evidence about its benefits and harms. The WHI, in both its estrogen-only comparison and its estrogen and progesterone comparison, provided strong evidence that menopausal hormone therapy reduces the risk of vertebral fracture and hip fracture.

Original Placebo-Controlled Studies

We found one study that provided two new estimates of effects of menopausal estrogen therapy on fracture risk relative to placebo, one for vertebral, and one for nonvertebral fracture (Jadad score 5) (Table 22).[136] Overall, RCTs were 24 months, 36 months, or 48 months in duration. Among both the older and the new RCTs, only the RCT with the largest number of vertebral fracture events found a significant association between menopausal estrogen therapy and reduction in risk of overall fractures, vertebral fractures, or nonvertebral fractures compared to placebo.[137]

Head-to-head trials did not compare antifracture effects of menopausal estrogen therapy alone (ET) and menopausal estrogen + progestogen therapy (EPT). Too few studies and low numbers of fracture events (Table 22) did not permit us to make conclusions regarding relative effectiveness of ET and EPT.

The number of events in all trials was very low, sample sizes in these trials were less than 200 subjects (compared to several thousand in studies of bisphosphonates) and confidence intervals are very wide, meaning that clinically important effects cannot be excluded. Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study, we determined its applicability to be moderately low; the population was small and consisted entirely of women with primary biliary cirrhosis.

Table 22. Risk of fracture for menopausal estrogen therapy, relative to placebo, by fracture group

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Estrogen†	Number of Fractures, Placebo or Control	Odds Ratio (95% CI)
All Fractures					
Original 2007 report					
Bone, 2000[58]	24 months	Any clinical	10/143	4/50	0.86 (0.25, 2.97)
Greenspan, 2003[59]	36 months	Clinical	5/93	9/93	0.54 (0.18, 1.60)
Update Report: *No new studies*					
Vertebral Fractures					
Original 2007 Report					
Ishida, 2004[137]	24 months	Vertebral	7/66*	17/66†	0.36 (0.15, 0.88)
Reid, 2004[122]	36 months	Vertebral	1/102	1/90	0.88 (0.05, 14.27)
Wimalawansa, 1998[138]	48 months	Vertebral	2/15*	5/14†	0.31 (0.06, 1.64)
Update Report					
Boone, 2006[136]	24 months	Vertebral	0/16	2/15	0.12 (.01, 1.98)
Nonvertebral Fractures					
Original 2007 Report					
Wimalawansa, 1998[138]	48 months	Nonvertebral	1/15*	1/14†	0.93 (0.06, 15.69)
Update Report					
Boone, 2006[136]	24 months	Nonvertebral	0/16	0/15	NC

NC = not calculable

*Bone, 2000: conjugated equine estrogen; Greenspan, 2003: conjugated equine estrogen±medroxyprogesterone acetate; Reid, 2004: conjugated equine estrogen; Wimalawansa, 1998: conjugated equine estrogen+norgestrel; Boon, 2006: combination topical (patch) estradiol+norethindrone acetate.

†Control group.

Dietary Supplements

This section presents the results of studies examining the effects of calcium with or without vitamin D; and various forms of vitamin D, with or without calcium, on preventing and treating osteoporotic fractures.

Calcium and Vitamin D

Prior Systematic Reviews

For calcium alone, four systematic reviews conducted meta-analyses that included a total of 23 RCTs comparing fracture risk with calcium to that of placebo or no treatment (Table 23). Of these four meta-analyses, one meta-analysis examined vertebral fracture risk, two examined nonvertebral fracture risk, two examined hip fracture risk, and one examined overall fracture risk.

For vitamin D alone, 16 meta-analyses addressed a total of 43 RCTs comparing fracture risk with vitamin D compared to placebo or no treatment (Table 24). Of these 16 meta-analyses, nine meta-analyses examined vertebral fracture risk, 12 examined nonvertebral fracture risk, nine examined hip fracture risk, and three examined overall fracture risk.

Calcium alone did not reduce vertebral or nonvertebral fracture risk significantly relative to placebo or no treatment (Table 25). Although there was a statistically significantly (64 percent) increased risk of hip fracture associated with calcium supplementation in one pooled estimate,[139] the pooled estimate of another meta-analysis with an almost 10-fold higher number of included participants found a statistically significant 25 percent reduction in relative risk of hip fracture with calcium compared to placebo.[140] There was a statistically significantly higher reduction in overall fracture risk with calcium ≥ 1,200 mg/d compared to <1,200mg/d.[141] Thus, data on calcium supplementation alone and fracture risk are conflicting.

In general, in systematic reviews of vitamin D alone, results varied markedly across studies. Some discrepancies across estimates are certainly due to methodological differences, in that many pooled analyses varied in whether they compared vitamin D to placebo, to calcium, or to either calcium or placebo (Table 26). Although a large number of comparisons are displayed in the table, we focus here on the comparisons between vitamin D, administered with or without calcium, and placebo (head-to-head comparisons of calcium and vitamin D are reported later).

Vertebral Fractures. For vertebral fractures, compared to placebo, vitamin D was associated with statistically significant reductions in risk among people with primary osteoporosis: 15 (95% CI: 10, 20) for alfacalcidol or calcitriol, 1.6 (0.4, 2.6) for standardized vitamin D vs. placebo.[142] However, among populations not selected on the basis of osteoporotic fracture,[143,144] those with prior fractures,[145] women with severe osteoporosis[32] or those taking glucocorticoid treatment,[142] vitamin D (versus placebo) was not associated with statistically significant vertebral fracture risk reduction. In comparison with placebo, vitamin D + calcium was not associated with statistically significant reductions in vertebral fracture in populations selected or not selected for prior osteoporotic fractures.[32,143,145,146]

There were no statistically significant differences in vertebral risk in comparisons of alfacalcidol vs. vitamin D + calcium, or calcitriol vs. vitamin D.[145] In one pooled analysis, neither 10 μg[e] nor 20 μg doses of vitamin D altered vertebral fracture risk in comparison with placebo, even when given in conjunction with calcium.[146] In summary, pooled analyses suggest that vitamin D compared to placebo may reduce the risk of vertebral fractures, but results are not consistent across the pooled studies. In the pooled analyses, various forms of vitamin D do not appear to have differing effects on vertebral fracture risk.

Nonvertebral Fracture. Statistically significant decreases in nonvertebral fracture risk were found for vitamin D compared to placebo in several pooled analyses: standard vitamin D (vitamin D2, D3, or 25(OH)D) among elderly women not selected for prior osteoporotic fracture (RR 0.87), vitamin D analogues for primary osteoporosis, and standard vitamin D for primary osteoporosis.[142] In contrast, the following were not associated with statistically significant reductions in nonvertebral fracture risk: alfacalcidol, calcitriol, or vitamin D among people not selected on the basis of prior osteoporotic fracture, calcitriol among women with severe osteoporosis.[32,143,145]

In combination with calcium, vitamin D was associated with a statistically significant reduction in nonvertebral fracture risk among populations not selected on the basis of prior osteoporotic fractures.[143,147] Among institutionalized persons, vitamin D + calcium was associated with 15 percent decrease (statistically significant) in nonvertebral fracture risk.[145] In contrast, vitamin D + calcium was not associated with a statistically significantly decreased risk of nonvertebral fractures among those who were not selected on the basis of prior osteoporotic fractures, those who were selected on the basis of prior osteoporotic fractures, or among community-dwellers.[145] Standard vitamin D doses of ≥700 IU/d + calcium are associated with statistically significant reductions in nonvertebral fracture risk among institutionalized persons (RR 0.80).[148]

In summary, compared to placebo, vitamin D + calcium decreases the risk of nonvertebral fractures among the institutionalized by 15-20 percent. Vitamin D may be effective compared to placebo in reducing risk among populations with primary osteoporosis, although evidence was not consistent.

Hip Fracture. For hip fracture, compared to placebo, alfacalcidol reduced relative risk of fracture by 84 percent.[143] Standard vitamin D was not statistically significantly more effective than placebo in reducing hip fracture risk among those who were not selected, nor among those who were selected, on the basis of previous osteoporotic fractures.[140,143,146] Nor was calcitriol more effective than placebo in reducing hip fracture risk among those not selected on the basis of prior osteoporotic fractures.[145] One pooled estimate even showed a statistically significantly increased risk of hip fracture in associated with injection of vitamin D compared to placebo.[146]

[e] Some studies report vitamin D doses in international units(IU), whereas some report the doses in micrograms (μg). One IU vitamin D is equivalent to 0.025 μg cholecalciferol. We report doses in the units used in individual studies.

In contrast to the situation with vitamin D alone, vitamin D + calcium (vs. placebo) was associated with statistically significantly reduced risk of hip fracture, ranging about 20 to 30 percent, in those selected or not selected on the basis of prior osteoporotic fractures (in some studies), not selected on the basis of low BMD, and among the institutionalized.[32,140,143,145,147] Vitamin D + calcium did not decrease hip fracture risk more than placebo among community dwellers and general populations, even at high (≥700 IU/d) doses.[145,148] Vitamin D doses of 10 µg were not effective in decreasing hip fracture risk unless they were given with calcium; the RR of hip fracture with vitamin D 10 µg + calcium vs. placebo was 0.74 (0.60, 0.91).[146] Dosing of ≥700 IU of vitamin D was associated with a 28 percent lower risk of hip fractures among institutionalized persons (RR 0.72, 95% CI: 0.59, 0.88).[148]

A new systematic review found that vitamin D supplementation did not statistically significantly alter hip fracture risk, but the authors analyzed vitamin D plus calcium and vitamin D jointly, in comparison to a reference group of placebo or calcium, respectively.[149]

In summary, evidence was most consistent for beneficial effects of vitamin D administered with calcium on the risk for hip fracture, as opposed to alone, especially among institutionalized persons. There is increasing evidence in recent years that an adequately high dose of vitamin D is required for reduction of hip fractures, and that heterogeneity in vitamin D dosing across studies (in addition to heterogeneous baseline risk across studies) may have partly explained prior conflicting evidence regarding antifracture effects of vitamin D.

Nonvertebral Nonhip Fracture. The one available estimate suggested that vitamin D with calcium was associated with statistically significant reduction in nonvertebral nonhip fracture risk compared to calcium alone, but not to placebo.

Overall Fracture Risk. For overall risk of clinical fractures, although some pooled estimates showed no significant benefit of vitamin D, several pooled analyses showed efficacy of oral vitamin D alone (7 percent lower relative risk vs. placebo) and efficacy of vitamin D + calcium in reducing overall clinical fractures about 10 to 15 percent compared to placebo.[141,146] Vitamin D injection did not reduce overall clinical fracture risk compared with placebo. As was the case for hip fractures, there was evidence for the importance of adequately high doses of vitamin D in relation to clinical fractures. Compared to placebo, doses of <800 IU/d did not statistically significantly reduce overall fracture risk, whereas doses ≥800 IU/day were associated with 16 percent lower overall fracture risk.[141] Vitamin D 10 µg with calcium, but not without calcium, was associated with statistically significantly lower overall fracture risk compared to placebo.[146] A similar pattern was apparent for vitamin D 20 µg with and without calcium, whereby the relative risk of fracture was decreased with vitamin D 20 µg + calcium (although not statistically significantly so), and not with vitamin D 20 µg alone. In summary, the strongest evidence for benefits of vitamin D on reducing overall fracture risk are for oral vitamin D combined with calcium, and in doses of ≥800 IU daily.

Original Placebo-Controlled Trials

For this report, one new RCT of calcium+vitamin D+ an environmental modification, two studies of vitamin D + calcium, three new RCTs of vitamin D alone, and two studies of calcium alone were identified.

Calcium+Vitamin D+Environmental Modification. In one RCT, a combined calcium + vitamin D + environmental modification intervention reduced the overall risk of fracture among women, but not men (Table 27) (Jadad score 0).[150]

Among women, but not men, a combination calcium + vitamin D and environmental safety modification was efficacious in reducing overall fracture risk (RR 0.73, 0.56, 0.93) (Table 27).[150] Using the criteria of Gartlehner et al.[25]to assess the applicability of this study, we determined its applicability to be moderately high.

Calcium+Vitamin D. Three RCTs from the original report[151-153] and two new RCTs identified for this report[150] assessed the effects of calcium+vitamin D on fracture risk. One of the newer RCTs was a population-based study that reported lower risks of overall, distal forearm, and upper extremity fractures with vitamin D (800 IU) and calcium vs. placebo among a group of elderly women living at a Northern (Finnish) latitude (Jadad score 2) , but none of the decreases in risk reached statistical significance.[154] Thus, with the exception of one RCT showing a 25 percent lower overall risk of fracture,[150] the risks of fractures (overall), vertebral fractures, hip fractures, and wrist fractures were not statistically different with calcium plus vitamin D compared to placebo (Table 28). Using the criteria of Gartlehner et al.[25] to assess the applicability of the new studies, we determined their applicability to be moderately high to high.

Calcium Alone. Four RCTs from the original report[67,153,155,156] and two new RCTs identified for this report[157,158] assessed the effect of calcium alone on fracture risk (Jadad scores 1 and 2). With the exception of one RCT from the original report that showed a 37 percent lower overall risk of fracture,[156] the risks of fractures (overall), vertebral fractures, and wrist fractures were not statistically different with calcium compared to placebo (Table 29). Using the criteria of Gartlehner et al.[25] to assess the applicability of the new studies, we determined their applicability to be low. Both small studies, one study enrolled only hospital inpatients and the other enrolled only men with congestive heart failure.

Vitamin D Alone. Four RCTs from the original report[137,153,159,160] and four new RCTs identified for this report[161-164] assessed the effect of vitamin D alone on fracture risk (Jadad scores for new studies 4, 5, 3, and 5). One of the RCTs that examined hip fracture risk in relation to vitamin D[160] showed an 88 percent lower risk (0.01, 0.90);[160] but two RCTs showed an increased risk for hip fracture, 49 percent in one case (95% CI: 1.03, 2.18)[162] and 26 percent in the other (95% CI: 0.64, 2.49).[164] The risks of fractures (overall), vertebral fractures, nonvertebral fractures, and wrist fractures were not statistically different with vitamin D compared to placebo (Table 30). Using the criteria of Gartlehner et al.[25] to assess the applicability of the new studies, we determined their applicability to be moderately high to high.

Table 23. Randomized controlled trials included in systematic reviews of effect of calcium on fracture relative to placebo or no treatment

	Systematic Review (Author, Year)					
	Shea, 2002[165]		Bischoff-Ferrari, 2007[139]		Boonen, 2007[140]	Tang, 2007[141]
	Fracture Type					
RCTs (Author, Year)	**V**	**NV**	**NV**	**H**	**H**	**A**
Bischoff-Ferrari, 2006/2008[166]			X	X		
Chapuy, 1992[167]						X
Chapuy, 1994[168]					X	
Chapuy, 2002[169]					X	X
Chevally, 1994[170]	X	X	X			X
Dawson-Hughes, 1997[171]					X	X
Fujita, 2004[158]						X
Grant, 2005[153]			X	X	X	X
Hansson, 1987[172]	X					
Harwood, 2004[173]						X
Jackson, 2006[151]					X	X
Larsen, 2004[150]						X
Peacock, 2000[174]						X
Porthouse, 2005[152]					X	X
Prince, 1995[175]						X
Prince, 2006[156]			X	X		
Recker, 1996[176]	X					X
Reid, 1993[177]	X					X
Reid, 1995[178]			X	X		
Reid, 2006[67]			X	X		X
Riggs, 1998[179]	X	X	X			X

V = vertebral, NV = non-vertebral, H = hip, A = all; X = Included in pooled analysis

Table 24. Randomized controlled trials included in systematic reviews of effect of vitamin D on fracture relative to placebo or no treatment

	Systematic Review (Author, Year)																																	
	Ave, 2005[143]			Bis, 2005[180]		Pap, 2002[181]		Ste, 2005[32]		Ric, 2004[182]		Ric, 2005[142]		Abr, 2010[146]			Ave, 2009[145]					Ber, 2010[147]		Bis, 2009[183]		Boo, 2007[140]	Iza, 2007[148]		Jac, 2007[184]		O'Do, 2008[144]		Tan, 2007[141]	Lai, 2010[149]
	Fracture Type																																	
RCTs (Author, Year)	**V**	**NV**	**H**	**NV**	**H**	**V**	**NV**	**V**	**NV**	**V**	**NV**	**V**	**NV**	**A**	**V**	**H**	**A**	**V**	**NV**	**H**	**W**	**NV**	**H**	**NV**	**H**	**H**	**NV**	**H**	**V**	**NV**	**V**	**NV**	**A**	**H**
Adachi, 1996[185]												X																						
Aloia, 1988[186]								X		X																								
Avenell, 2004[187]	X		X														X	X	X	X													X	
Baeksgaard, 1998[188]						X																												
Bolton-Smith, 2007[189]																			X															
Cannigia, 1984[190]						X		X										X													X			
Chapuy, 1992[167]							X						X						X	X		X	X											
Chapuy, 1994[168]				X	X																			X	X	X	X	X						
Chapuy, 2002[169]				X	X														X	X		X	X	X	X	X	X	X						
Dawson-Hughes, 1997[171]				X	X		X					X							X	X				X		X	X							
Dukas, 2004[191]		X																	X															
Ebeling, 2001[192]										X		X																						
Flicker, 2005[193]																	X	X		X				X								X		
Gallagher, 1989[194]										X			X					X																
Gallagher, 1990[195]										X		X																						
Gallagher, 2001[196]			X			X			X	X	X	X	X					X	X	X											X	X		
Gorai,1999[197]		X																	X												X			
Grant, 2005[153]	X													X	X	X	X	X	X	X				X	X	X		X		X			X	X
Geusens, 1986[198]						X																												
Harwood, 2004[173]			X														X		X	X														
Hayashi, 1992[199]										X		X																						
Ishida, 2004[137]																		X	X	X											X	X		
Jackson, 2006[151]														X	X	X		X	X	X				X	X	X		X						
Jensen, 1985[200]																															X			
Komulainen, 1998[201]													X						X											X				
Larsen, 2004[150]														X	X	X																		

Table 24. Randomized controlled trials included in systematic reviews of effect of vitamin D on fracture relative to placebo or no treatment (continued)

	Systematic Review (Author, Year)																																	
	Ave, 2005[143]			Bis, 2005[180]		Pap, 2002[181]		Ste, 2005[32]		Ric, 2004[182]		Ric, 2005[142]		Abr, 2010[146]			Ave, 2009[145]					Ber, 2010[147]		Bis, 2009[183]		Boo, 2007[140]	Iza, 2007[148]		Jac, 2007[184]		O'Do, 2008[144]		Tan, 2007[141]	Lai, 2010[149]
	Fracture Type																																	
RCTs (Author, Year)	V	NV	H	NV	H	V	NV	V	NV	V	NV	V	NV	A	V	H	A	V	NV	H	W	NV	H	NV	H	H	NV	H	V	NV	V	NV	A	H
Law, 2006[163]																	X			X														X
Lips, 1996[202]			X	X	X		X						X				X			X				X	X	X	X	X		X				X
Lyons, 2007[203]														X	X	X	X			X				X	X									X
Menczel, 1994[204]											X		X																					
Meyer, 2002[205]			X	X	X								X	X		X	X			X				X		X	X	X						X
Orimo, 1987[206]						X						V																						
Orimo, 1994[207]												X																			X	X		
Ott, 1989[208]																															X	X		
Peacock, 2000[174]																	X			X									X	X				
Pfeifer, 2008[209]																								X										
Porthouse, 2005[152]														X	X	X			X	X			X			X		X						
Reid, 1993[177]																										X								
Sato, 1999[210 211]																				X														
Smith, 2007[162]							X							X	X	X	X			X														X
Tilyard, 1992[212]																															X	X		
Trivedi, 2003[213]												X					X			X				X	X	X	X	X	X	X				X
Ushiroyama, 2001[214]																			X												X			

V = vertebral; NV = nonvertebral; H = hip; A = all; W = wrist/forearm; X = included in pooled analysis

References for systematic reviews: Avenell, Cochrane Database Syst Rev, 2005[143]; Bischoff-Ferrari, JAMA, 2005[180]; Papadimitropoulos, Endocr Rev, 2002[181]; Stevenson, Health Technol Assess, 2005[32]; Richy, Osteoporos Int, 2004[182]; Richy, Calcif Tissue Int, 2005[142]; Abrahamsen, BMJ, 2010[146]; Avenell, Cochrane Database Syst Rev, 2009[145]; Bergman, Curr Med Res Opin, 2010[147]; Bischoff-Ferrari, Arch Intern Med, 2009[183]; Boonen, J Clin Endocrinol Metab, 2007[140]; Izaks, BMC Musculoskelet Disord, 2007[148]; Jackson, Qjm, 2007[184]; O'Donnell, J Bone Miner Metab, 2008[144]; Tang, Lancet, 2007[141]; Lai, BMC Public Health, 2010[149]

Table 25. Pooled risk estimates of fracture for calcium relative to placebo, or no treatment

Author, Year	# Studies	Sample Size	RR	(95% CI)
Vertebral Fractures				
Original Report				
Shea, 2002[165*,†]	5	576	0.77	(0.54, 1.09)
Nonvertebral Fractures				
Original Report				
Shea, 2002[165*,†]	2	222	0.86	(0.43, 1.72)
Update Report				
Bischoff-Ferrari, 2007[139]	5	6,740	0.92	(0.81, 1.05)
Hip				
Original Report: ***No comparable studies from the original report***				
Update Report				
Bischoff-Ferrari, 2007[139]				
Men and women	4	6,504	1.64	(1.02, 2.64)
Boonen, 2007[140]	10	54,592	0.75	(0.58, 0.96)
All Types of Fracture				
Original Report: ***No comparable studies from the original report***				
Update Report				
Tang, 2007[141‡]	9			
Any calcium		6,517	0.90	(0.80, 1.00)
Calcium <1,200 mg/d		47,359	0.94	(0.89, 0.99)
Calcium ≥1,200 mg/d		5,266	0.80	(0.72, 0.89)

*Postmenopausal women only.
†In one included study, participants received a baseline vitamin D injection.
‡Age 50 and over. P value for comparison of RR of fracture for studies of <1,200 mg vs. ≥1,200 mg/d was 0.006.

Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment

Author, Year	# Studies	Sample Size	RR	(95% CI)	Comparison
Vertebral Fractures					
Original 2007 Report					
Avenell, 2005[143]					
Not selected on basis of prior osteoporotic fracture	2	2,953	0.96	(0.42, 2.21)	Standard vitamin D [D2, D3, or 25(OH)D] vs. placebo
Selected on basis of prior osteoporotic fracture	1	2,745	3.97	(0.44, 35.45)	Standard vitamin D [D2, D3, or 25(OH)D] vs. placebo
Either selected or not selected on basis of prior osteoporotic fracture	3	5,698	1.13	(0.50, 2.55)	Standard vitamin D [D2, D3, or 25(OH)D] vs. placebo
	2	2,708	0.34	(0.01, 8.34)	Standard vitamin D [D2, D3, or 25(OH)D] + calcium vs. placebo/control
	3	327	0.75	(0.40, 1.41)	Calcitriol vs. placebo/control
Papadimitropoulos, 2000[181]					
Postmenopausal women	1	160	0.33	(0.01, 8.05)	Standard vitamin D [D2, D3, or 25(OH)D] vs. calcium or placebo
	7	970	0.64	(0.44, 0.92)	Calcitriol (1,25-OH vitamin D) vs. calcium or placebo
	8	1,130	0.63	(0.45, 0.88)	Either Standard vitamin D or Calcitriol vs. calcium or placebo
Richy, 2004[182]					
Primary osteoporosis	9	1,665	0.53	(0.47, 0.60)	Alfacalcidol or calcitriol vs. calcium or placebo
	6	896	0.52	(0.41, 0.67)	Calcitriol vs. calcium or placebo
	3	769	0.53	(0.46, 0.61)	Alphacalcidol vs. calcium or placebo
	2	106	0.33	(0.07, 1.51)	GC-induced (calcitriol only) vs. calcium or placebo
Richy, 2005[142]					
Primary osteoporosis (24 mos)	5	1,972	15%*	(10, 20%)	Alfacalcidol or calcitriol vs. placebo
	2	3,075	1.6%*	(0.4, 2.6%)	Standard vitamin D vs. placebo
GC treatment	3	300	9%	(-2, 22%)	Alfacalcidol or calcitriol vs. placebo
	1	62	6%	(-23, 10%)	Standard vitamin D vs. placebo
Stevenson, 2005[32]					
Women with severe osteoporosis	3	109	1.02	(0.44, 2.32)	Calcitriol vs. placebo
Elderly women not selected for BMD	1	NR	4.44	(0.50, 39.03)	Calcitriol vs. placebo
			2.95	(0.21, 71.21)	Calcium + vitamin D vs. placebo

Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)	Comparison
Update Report					
Avenell, 2009 [145]					
Persons sustaining new vertebral fracture or deformity Either selected or not selected on basis of prior osteoporotic fracture	5	9,138	0.90	(0.42, 1.92)	Vitamin D alone vs. placebo or no treatment
Persons sustaining new vertebral fracture Selected on the basis of previous osteoporotic fracture	2	2,681	0.14	(0.01, 2.77)	Vitamin D plus calcium vs. calcium
Persons sustaining new vertebral fracture or deformity Either selected or not selected on the basis of prior osteoporotic fracture	3	2,976	2.21	(1.08, 4.53)[†]	Vitamin D vs. calcium
Persons sustaining new vertebral fracture Either selected or not selected on basis of prior osteoporotic fracture	3	38,990	0.91	(0.75, 1.11)	Vitamin D plus calcium vs. placebo or no treatment
Persons sustaining new vertebral fracture Selected on the basis of a previous osteoporotic fracture	1	132	0.65	(0.33, 1.27)	Alfacalcidol vs. placebo or no treatment
Persons sustaining new vertebral deformity Selected on the basis of previous osteoporotic fracture	3	259	0.50	(0.20, 1.23)	Alfacalcidol plus calcium vs. Calcium
	1	23	0.95	(0.52, 1.74)	Alfacalcidol vs. calcium[‡]
Persons sustaining new vertebral fracture or deformity Selected on the basis of previous osteoporotic fracture	1	148	0.81	(0.29, 2.30)	Alfacalcidol vs. vitamin D and calcium[‡]
Persons sustaining new vertebral deformity Either selected or not selected on the basis of previous osteoporotic fracture	3	327	0.75	(0.40, 1.41)	Calcitriol vs. placebo or no treatment[‡]
Persons developing new vertebral deformity Selected on the basis of previous osteoporotic fracture	1	86	1.50	(0.58, 3.85)	Calcitriol plus calcium vs. calcium[c]
	2	84	0.79	(0.41, 1.52)	Calcitriol plus vitamin D and calcium vs. vitamin D and calcium[‡]
	2	556	1.69	(0.25, 11.28)	Calcitriol vs. calcium
	2	96	1.38	(0.55, 3.47)	Calcitriol vs. vitamin D
Jackson, 2007 [184]					
Women (and men) Not selected on the basis of previous osteoporotic fracture	2	902	1.22	(0.64, 2.31)	Cholecalciferol vs. calcium or placebo

Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)	Comparison
O'Donnell, 2008 [144]					
Postmenopausal women and older men	13	1,396	0.89	(0.57, 1.39)	Calcitriol or alfacalcidol vs. calcium or placebo
	5	410	0.50	(0.25, 0.98)	Alfacalcidol vs. calcium or placebo
	8	986	1.19	(0.70, 2.02)	Calcitriol vs. calcium or placebo
DiPART Group 2010[146]	n/a	n/a	0.85#	(0.66, 1.11)	Vitamin D plus Calcium vs. placebo or control
	n/a	n/a	1.12#	(0.70, 1.79)	Vitamin D vs. placebo or control
	n/a	n/a	0.86#	(0.65, 1.14)	10 µg vitamin D with calcium vs. placebo or control
	n/a	n/a	0.97#	(0.48, 1.98)	20 µg with calcium vs. placebo or control
	n/a	n/a	1.10#	(0.69, 1.76)	20 µg without calcium vs. placebo or control
			Nonvertebral Fractures		
Original 2007 Report					
Avenell, 2005[143]					
Not selected on basis of prior osteoporotic fracture	2	466	0.40	(0.05, 3.08)	Alphacalcidol vs. placebo/control
	1	246	0.46	(0.18, 1.18)	Calcitriol vs. placebo/control
	7	10,376	0.87	(0.78, 0.97)	Vitamin D (D2, D3, or 25 (OH) D) + calcium vs. placebo/control
Bischoff-Ferrari, 2005[180]	7	9,820	0.83	(0.70, 0.98)	All doses (D2, D3) +/- calcium vs. placebo or calcium
	5	6098	0.77	(0.68, 0.87)	700-800IU/d +/- calcium vs. placebo or calcium
	2	3,722	1.03	(0.86, 1.24)	400IU/d +/- calcium vs. placebo or calcium
Stevenson, 2005 [32]					
Women with severe osteoporosis or osteoporosis	1	86	2.50	(0.51, 12.19)	Calcitriol vs. placebo
Elderly women not selected for BMD	1	213	0.46	(0.17, 1.27)	Calcitriol vs. placebo
	1	3,270	0.79	(0.69, 0.92)	Vitamin D vs. placebo
Papadimitropoulos, 2002[181]					
Postmenopausal women	3	5399	0.78	(0.55, 1.09)	Standard vitamin D [D2, D3, or 25(OH)D] vs. calcium or placebo
	3	788	0.87	(0.29, 2.59)	Calcitriol (1,25-OH vitamin D) vs. calcium or placebo
	6	6,187	0.77	(0.57, 1.04)	Either Standard vitamin D or Calcitriol vs. calcium or placebo
Richy, 2004[182]					
Primary osteoporosis	11	1310	0.34	(0.16, 0.71)	Calcitriol or alphacalcidol vs. calcium or placebo
Richy, 2005[142]					
Primary osteoporosis	7	913	8%^	(2, 13%)	Vitamin D analogues vs. placebo
	6	7,058	2%^	(1, 3%)	Standard vitamin D vs. placebo

Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)	Comparison
Update Report					
Bergman, 2010[147]	4	3,510	0.77**	(0.63, 0.93)†	Cholecalciferol (D3) plus calcium vs. placebo
Avenell, 2009[145]					
Persons sustaining new nonvertebral fracture Not selected on the basis of prior osteoporotic fracture	1	3,440	0.96	(0.80, 1.15)	Vitamin D alone vs. placebo or no treatment
Persons sustaining new nonvertebral fracture Either selected or not selected on the basis of prior osteoporotic fracture	4	3,061	0.96	(0.79, 1.16)	Vitamin D plus calcium vs. calcium alone
	3	2,976	1.08	(0.90, 1.31)	Vitamin D vs. calcium
	9	46,781	0.95	(0.90, 1.00)	Vitamin D plus calcium vs. placebo or no treatment
Selected on the basis of prior osteoporotic fracture	4	6,134	0.93	(0.79, 1.10)	Vitamin D plus calcium vs. placebo or no treatment
Not selected on the basis of prior osteoporotic fracture	5	40,647	0.95	(0.90, 1.01)	Vitamin D plus calcium vs. placebo or no treatment
Selected on the basis of institutional residence	2	3,853	0.85	(0.74, 0.98)	Vitamin D plus calcium vs. placebo or no treatment
Selected on the basis of community residence	7	42,928	0.97	(0.91, 1.02)	Vitamin D plus calcium vs. placebo or no treatment
Either selected or not selected on the basis of prior osteoporotic fracture	5	744	0.39	(0.15, 1.00)	Alfacalcidol vs. placebo or no treatment
Not selected on the basis of prior osteoporotic fracture	1	246	0.46	(0.18, 1.18)	Calcitriol vs. placebo or no treatment
Selected on the basis of prior osteoporotic fracture	2	663	1.19	(0.09, 15.77)	Calcitriol vs. calcium
	1	86	1.16	(0.40. 3.37)	Calcitriol vs. vitamin D
Bischoff-Ferrari, 2009[183]					
Persons ≥65 years of age	12	42,279	0.86	(0.77, 0.96)	Vitamin D +/- calcium vs. calcium or placebo, all trials
Persons ≥65 years of age	9	33,265	0.80	(0.72, 0.89)	Vitamin D +/- calcium vs. calcium or placebo, (≥400IU/d
Institutionalized persons	4	6,951	0.85	(0.76, 0.94)	Vitamin D +/- calcium vs. calcium or placebo
O'Donnell, 2008 [144]	6	1,014	0.51	(0.30, 0.88)	Calcitriol or alfacalcidol +/- calcium vs. calcium or placebo
Jackson, 2007 [184]					
All participants	6	8,524	0.96	(0.84, 1.09)	Vitamin D3 +/- calcium vs. calcium or placebo
Postmenopausal women	3	622	0.81	(0.48, 1.34)	Vitamin D3 +/- calcium vs. calcium or placebo

Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)	Comparison
Izaks, 2007[148]					
Institutionalized persons	3	n/a	0.80	(0.70, 0.90)	Standard Vitamin D (D2, D3, or 25 (OH) Vit D2) ≥700IU/d + calcium vs. placebo[††]
General population	4	n/a	0.88	(0.75, 1.04)	Standard Vitamin D (D2, D3, or 25 (OH) Vitamin D2) ≥700IU/d + calcium vs. placebo
Hip Fractures					
Original 2007 Report					
Avenell, 2005[143]					
Not selected on basis of prior osteoporotic fracture	4	15,948	1.20	(0.98, 1.47)	Standard vitamin D [D2, D3, or 25(OH)D] vs. placebo or control
Selected on basis of prior osteoporotic fracture	3	2,820	1.08	(0.72, 1.62)	Standard vitamin D [D2, D3, or 25(OH)D] vs. placebo or control
Either selected or not selected on basis of prior osteoporotic fracture	7	18,668	1.17	(0.98, 1.41)	Standard vitamin D [D2, D3, or 25(OH)D] vs. placebo or control
	7	10,376	0.81	(0.68, 0.96)	Standard vitamin D [D2, D3, or 25(OH)D] + calcium vs. placebo or control
Not selected on basis of prior osteoporotic fracture	3	239	0.16	(0.04, 0.69)	Alphacalcidol vs. placebo or control
	1	246	0.33	(0.01, 8.10)	Calcitriol (1,25-OH vitamin D) vs. placebo or control
Bischoff-Ferrari, 2005[180]	5	9294	0.88	(0.69, 1.13)	All doses (D2, D3) +/- calcium vs. placebo or calcium
	3	5,572	0.74	(0.61, 0.88)	700-800IU/d +/- calcium vs. placebo or calcium
	2	3,722	1.15	(0.88, 1.50)	400IU/d +/- calcium vs. placebo or calcium
Stevenson 2005 [32]					
Elderly women not selected for low BMD	2	2,886	0.72	(0.59, 0.88)	Vitamin D3 + calcium vs. placebo
Update Report					
Bergman, 2010[147]	5	7,473	0.70[**]	(0.63, 0.90)[†]	Cholecalciferol (D3) + calcium vs. placebo
Avenell, 2009[145]					
Persons sustaining new hip fracture Selected or not selected on basis of prior osteoporotic fracture	9	24,749	1.15	(0.99, 1.33)	Vitamin D (D2, D3, or 25(OH)D) alone vs. placebo or no treatment
	4	6,988	0.83	(0.61, 1.12)	Vitamin D (D2, D3, or 25(OH)D)+ calcium vs. calcium alone
Selected on basis of prior osteoporotic fracture	2	2,718	0.90	(0.61, 1.32)	Vitamin D (D2, D3, or 25(OH)D) vs. calcium
	4	6,134	1.02	(0.71, 1.47)	Vitamin D (D2, D3, or 25(OH)D) + calcium vs. placebo or no treatment
Not selected on basis of prior osteoporotic fracture	4	40,524	0.81	(0.71, 0.93)[†]	Vitamin D (D2, D3, or 25(OH)D) + calcium vs. placebo or no treatment
Either selected or not selected on basis of prior osteoporotic fracture	8	46,658	0.84	(0.73, 0.96)[†]	Vitamin D (D2, D3, or 25(OH)D) + calcium vs. placebo or no treatment

Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)	Comparison
Selected on basis of institutional residence	2	3,853	0.75	(0.62, 0.92)†	Vitamin D (D2, D3, or 25(OH)D) + calcium vs. placebo or no treatment
Selected on basis of community residence	6	42,805	0.91	0.76, 1.08)	Vitamin D (D2, D3, or 25(OH)D) + calcium vs. placebo or no treatment
Either selected or not selected on basis of prior osteoporotic fracture	4	371	0.18	(0.05, 0.67)†	Alfacalcidol vs. placebo or no treatment
Selected on basis of prior osteoporotic fracture	1	113	0.20	(0.01, 4.00)	Alfacalcidol plus calcium vs. calcium‡
Not selected on basis of prior osteoporotic fracture	1	246	0.33	(0.01, 8.10)	Calcitriol vs. placebo or no treatment‡
Bischoff-Ferrari, 2009[183]	8	40,886	0.91	(0.78, 1.05)	Oral Vitamin D (all types and doses analyzed jointly) +/- calcium vs. calcium or placebo
	5	31,872	0.82	(0.69, 0.97)	Oral Vitamin D ≥400IU/d +/- calcium vs. calcium or placebo
Boonen, 2007[140]					
Postmenopausal women or older men (≥50 years)	10‡‡	54,592	0.75	(0.58, 0.96)†	Vitamin D + calcium vs. Vitamin D
	4		1.10	(0.89, 1.36)	Vitamin D vs. placebo/no treatment
	6		0.82	(0.71, 0.94)†	Vitamin D + calcium vs. placebo
DIPART Group, 2010[146]	7	68,517	0.74#	(0.60, 0.91)†	Vitamin D with or without calcium vs. placebo or control
	n/a	n/a	0.84#	(0.70, 1.01)†	Vitamin D plus Calcium vs. placebo or control
	n/a	n/a	1.09#	(0.92, 1.29)	Vitamin D vs. placebo or control
	n/a	n/a	0.93#	(0.81, 1.06)	Vitamin D oral vs. placebo or control
	n/a	n/a	1.46#	(1.99, 2.13)	Vitamin D injected vs. placebo or control
	n/a	n/a	0.74#	(0.60, 0.91)	10 ug vitamin D with calcium vs. placebo or control
			1.10#	(0.74, 1.64)	10 ug vitamin D without calcium vs. placebo or control##
	n/a	n/a	1.30#	(0.88, 1.92)	20ug with calcium vs. placebo or control
	n/a	n/a	1.08#	(0.89, 1.30)	20ug without calcium vs. placebo or control
Izaks, 2007[148]					
Institutionalized persons	2	n/a	0.72	(0.0.59, 0.88)	Standard Vitamin D (D2, D3, or 25 (OH) Vit D2) ≥700IU/d + calcium vs. placebo
General population	2	n/a	1.04	(0.72, 1.50)	Standard Vitamin D (D2, D3, or 25 (OH) Vitamin D2) ≥700IU/d + calcium vs. placebo

Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)	Comparison
Lai, 2010[149]	7	25,680	1.13	(0.98, 1.29)	Standard Vitamin D (D2 or D3) vs. placebo or control
<800IU/day	2	3,722	1.14	(0.86, 1.49)	Standard Vitamin D (D2 or D3) vs. placebo or control
≥800IU/day	5	21,958	1.12	(0.96, 1.32)	Standard Vitamin D (D2 or D3) vs. placebo or control
	3	16,597	1.21	(0.99, 1.48)	Vitamin D2
	4	9,083	1.06	(0.88, 1.28)	Vitamin D3
Nonvertebral, Non-hip Fractures					
Original Report: *No comparable studies from the original report*					
Bergman, 2010[147]	5	7,473			
			0.84**	(0.67, 1.04)†	Cholecalciferol (D_3) plus calcium vs. placebo
			0.64**	(0.38, 0.99)†	Cholecalciferol (D3) plus calcium vs. calcium
All Types of Fracture					
Original Report: *No comparable studies from the original report*					
Avenel, 2006[143]					
Persons sustaining any new fracture	8	18,935	1.02	(0.93, 1.11)	Vitamin D (D2, D3, or 25 (OH)D) vs. placebo or control
Richy, 2004[182]					
Primary osteoporosis	11	1,310	0.52	(0.46, 0.59)	Calcitriol or alphacalcidol vs. calcium or placebo
Update Report					
Tang, 2007[141‡,#]	17	52,625	0.88	(0.83, 0.95)	Calcium and calcium plus vitamin D vs. placebo
	8	55,751	0.87	(0.77, 0.97)	Vitamin D plus calcium vs. placebo
	8	9,437	0.84	(0.75, 0.94)	≥800 IU vs. placebo
	8	36,671	0.87	(0.71, 1.05)	<800 IU vs. placebo
DIPART Group, 2010[146]	n/a	n/a	0.92#	(0.86, 0.99)†	Vitamin D plus Calcium vs. placebo or control (p=0.025)
	n/a	n/a	1.01#	(0.92, 1.12)	Vitamin D vs. placebo or control
	n/a	n/a	0.93†,#	(0.87, 0.99	Vitamin D oral vs. placebo or control
	n/a	n/a	1.11#	(0.95, 1.31)	Vitamin D injected vs. placebo or control
	n/a	n/a	0.91†,#	(0.85, 0.99)	10 µg vitamin D with calcium vs. placebo or control
			0.93#	(0.67, 1.28)	10 µg vitamin D without calcium vs. placebo or control
	n/a	n/a	0.95#	(0.80, 1.14)	20 µg with calcium vs. placebo or control
	n/a	n/a	1.02#	(0.92, 1.14)	20 µg without calcium vs. placebo or control

Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment (continued)

Author, Year	# Studies	Sample Size	RR	(95% CI)	Comparison
Avenell, 2009[145]					
Persons sustaining any new fracture Selected or not selected on basis of prior osteoporotic fracture	10	25,016	1.01	(0.93, 1.09)†	Vitamin D (D2, D3, or 25 (OH)D) vs. placebo or control
Persons sustaining any new fracture Not selected on the basis of prior osteoporotic fracture	2	927	0.76	0.48, 1.21	Vitamin D (D2, D3, or 25 (OH)D) plus calcium vs. calcium

Table Notes: Calcitriol is 1,25 dihydroxyvitamin D3 (1,25 (OH)2 D3), which is equivalent to renal and liver activation; Alfacalcidol is 1-alpha-hydrovitamin D3, which is equivalent to renal activation; Ergocalciferol is Vitamin D2; Cholecalciferol is Vitamin D3; Calcidiol is 25-hydroxyvitamin D (25 (OH)D), which is equivalent to liver activation; for Avenell, 2009, Vitamin D refers to either D2, D3, or 25(OH)D.

*Fracture results were expressed as rate differences, so the results are presented not as a relative risk but rather as risk difference. Difference between treatments was significant and favored the analogs (P < 0.001, delta RD = 13.4% (95%CI, 7.7 to 19.8).

†Statistically significant.

‡New vertebral deformities.

#Individual patient data HR for trials using vit D + Ca cf. vitamin D alone.

^Results expressed as rate difference (RD, difference in fracture rate between treatment and placebo or no treatment).

**Odds ratio.

††This study could not examine lower dose (400 IUD/d) Vitamin D because there were too few studies to allow meta-analysis.

‡‡Ca + vitamin D vs. vitamin D alone indirect comparison: 6 trials of vitamin D + Ca vs. 4 trials of vitamin D alone.

##According to the author 10µg means 400 IU and 20ug means 800 IU.

Table 27. Calcium/vitamin D group and environmental and health group versus placebo

Author, Year	Study Duration	Fracture Type	Number of Fractures, Both Programs*	Number of Fractures, Placebo	Odds Ratio (95% CI)
Original Report: ***No comparable studies from the original report***					
Update Report					
Larsen, 2004[150]	42 months	All fractures – men	33/954	26/843	1.13 (0.67, 1.89)
Larsen, 2004[150]	42 months	All fractures – women	131/157	141/1,273	0.73 (0.56, 0.93)

*Calcium/Vitamin D group & Environmental & Health Group.

Table 28. Risk of vertebral fracture for calcium plus vitamin D, relative to placebo

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Calcium Plus Vit D	Number of fractures, Placebo or Control	Odds Ratio (95% CI)
All Fractures					
Original Report					
Grant, 2005[153]	62 months	New	104/1,306	196/1,332	0.95 (0.76, 1.18)
Jackson, 2006[151]	84 months	Total	2,101/18,176	2,158/18,106	0.97 (0.91, 1.03)
Porthouse, 2005[152]	24 months	All	24/607	22/602	1.09 (0.6, 1.96)
Update Report					
Larsen, 2005[150]	42 months	All fractures – men	60/1,974	26/843	0.99 (0.62, 1.57)
Larsen, 2005[150]	42 months	All fractures – women	285/2,983	141/1,273	0.75 (0.6, 0.94)
Salovaara, 2010[154]	36 months	Any	78/1,586	94/1,609	0.83 (0.61, 1.13)
Vertebral Fractures					
Original 2007 Report					
Grant, 2005[153]	62 months	Clinical vertebral	0/1,306	1/1,332	0.14 (0, 6.96)
Jackson, 2006[151]	84 months	Clinical vertebral	181/18,176	197/18,106	0.91 (0.75, 1.12)
Update Report					
Salovaara, 2010[154]	36 months	Vertebral	9/1586	13/1609	0.70 (030, 1.63)
Hip Fractures					
Original 2007 Report					
Grant, 2005[153]	62 months	Proximal femur	46/1,306	41/1,332	1.15 (0.75, 1.76)
Jackson, 2006[151]	84 months	Hip	175/18,176	199/18,106	0.87 (0.71, 1.07)
Porthouse, 2005[152]	24 months	Hip	5/607	2/602	2.35 (0.53, 10.36)
Update Report					
Salovaara, 2010[154]	36 months	Hip	4/1,586	2/1,609	1.98 (0.4, 9.81)
Wrist Fractures					
Original 2007 Report					
Grant, 2005[153]	62 months	Distal forearm	33/1,306	28/1,332	1.21 (0.73, 2.01)
Jackson, 2006[151]	84 months	Lower arm or wrist	565/18,176	557/18,106	1.01 (0.9, 1.14)
Update Report					
Salovaara, 2010[154]	36 months	Distal forearm	23/1,586	32/1,609	0.73 (0.43, 1.24)

Table 29. Risk of fracture for calcium, relative to placebo, by fracture group

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Calcium	Number of Fractures, Placebo or Control†	Odds Ratio (95% CI)
		All Fractures			
Original 2007 Report					
Campbell, 2004[155]	60 months	New symptomatic vertebral and non-vertebral	7/85	7/95*	1.13 (0.38, 3.35)
Prince, 2006[156†]	60 months	Any site	110/728	126/728	0.85 (0.64, 1.12)
Prince, 2006[156‡]	60 months	Any site	43/422	63/409	0.63 (0.42, 0.94)
Update Report: ***No new studies***					
		Vertebral Fractures			
Original 2007 Report					
Campbell, 2004[155]	60 months	New symptomatic or semi-quantitative vertebral	15/85	19/95*	0.86 (0.41, 1.81)
Grant, 2005[153]	62 months	Clinical vertebral	3/1311	1/1332	2.77 (0.39, 19.65)
Prince, 2006[156†]	60 months	Vertebral deformity	44/431	50/450	0.91 (0.59, 1.40)
Prince, 2006[156‡]	60 months	Vertebral deformity	22/306	32/305	0.66 (0.38, 1.16)
Reid, 2006[67]	60 months	Vertebral	27/739	38/732	0.70 (0.42, 1.14)
Update Report					
Frost, 2007[157]	12 months	Vertebral	1/17	1/16	0.94 (0.06, 15.72)
Fujita, 2007[158]	2 years	Vertebral	2/7	3/6	0.43 (0.05, 3.73)
Fujita, 2007[158]	2 years	Vertebral	0/6	3/6	0.09 (0.01, 1.06)
		Wrist Fractures			
Original 2007 Report					
Grant, 2005[153]	62 months	Distal forearm	33/1,311	28/1,332	1.20 (0.72, 2.00)
Prince, 2006[156†]	60 months	Wrist or hand	21/724	20/741	1.08 (0.58, 2.00)
Prince, 2006[156‡]	60 months	Wrist or hand	10/417	12/414	0.82 (0.35, 1.92)
Reid, 2006[67]	60 months	Distal forearm	28/739	44/732	0.62 (0.39, 1.00)
Update Report: ***No new studies***					

*Control group.
†Intention to treat analysis.
‡Compliant with medication.

Table 30. Risk of vertebral fracture for vitamin D, relative to placebo

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Vit D	Number of Fractures, Placebo	Odds Ratio (95% CI)
All Fractures					
Original 2007 Report					
Torres, 2004[159]	12 months	Symptomatic	0/41	0/45	NC
Update Report					
Sanders, 2010[164]	35.5 months	Any	155/1,131	125/1,125	1.27 (0.99, 1.63)
Vertebral Fractures					
Original 2007 Report: *No studies from the original report*					
Update Report					
Shiraki, 1996[161]	2 years	Vertebral	2/37	3/42	0.75 (0.12, 4.55)
Sanders, 2010[164]	35.5 months	Vertebral	35/1,131	28/1,125	1.25 (0.76, 2.06)
Nonvertebral Fractures					
Original 2007 Report: *No studies from the original report*					
Update Report					
Smith, 2007[162]	36 Months	Nonvertebral	306/4,727	279/4,713	1.1 (0.93, 1.3)
Shiraki, 1996[161]	2 Years	Nonvertebral	0/37	3/42	0.15 (0.01, 1.44)
Shiraki, 1996[161]	10 Months	Nonvertebral	64/1,762	51/1,955	1.41 (0.97, 2.04)
Hip Fractures					
Original 2007 report					
Sato, 2005[160]	24 months	Hip	0/24	4/24	0.12 (0.01, 0.90)
Update Report					
Smith, 2007[162]	36 months	Hip or femur	66/4,727	44/4,713	1.49 (1.03, 2.18)
Law, 2006[163]	10 months	Hip	24/1,762	20/1,955	1.34 (0.74, 2.42)
Sanders, 2010[164]	35.5 months	Hip	19/1,131	15/1,125	1.26 (0.64, 2.49)
Wrist Fractures					
Original 2007 Report					
Grant, 2006[153]	62 months	Distal forearm	33/1,343	28/1,332	1.17 (0.71, 1.95)
Ishida, 2004[137]	24 months	Vertebral	11/66	17/66	0.58 (0.25, 1.34)
Update Report					
Smith, 2007[162]	36 months	Wrist	64/4,727	52/4,713	1.23 (0.85, 1.77)

NC = not calculable

Lifestyle Interventions

This section presents the results of studies of lifestyle interventions such as physical activity programs on the risk for osteoporotic fracture. The original report assessed the results of interventions aimed at preventing falls, which may indirectly help decrease the risk for osteoporotic fractures; however, assessing this category of indirect interventions was determined to be beyond the scope of this report.

Physical Activity

Prior Systematic Reviews

One systematic review evaluated the effects of physical activity relative to placebo on fracture risk (Table 31). The systematic review, which encompassed data from seven RCTs, examined fractures overall, vertebral fractures, hip fractures, and wrist fractures. Information from RCTs regarding effects of physical activity on fracture risk is available only for vertebral fractures (Table 32). In the one pooled estimate (three studies), the RR of vertebral fractures was not significantly different with physical activity relative to placebo or no treatment. However, the specific physical activity interventions, and the comparators (e.g. upper body exercise, heat/massage, electrotherapy) differed across the trials.

A RCT of a one-month exercise intervention that enrolled 160 Finnish women with osteopenia reported fracture rates after an average of seven years of followup (Jadad 2, moderately high applicability). The rate of incident fractures during followup was 0.05 per thousand person years in the exercise group, compared with 0.08 in the control group (Poisson incidence RR 0.68 [95% CI: 0.34, 1.32]). No hip fractures occurred in the exercise group, compared with 5 hip fractures in the control group.[215] However, the study was not designed with sufficient statistical power to detect a difference in antifracture efficacy between groups.

Table 31. Randomized controlled trials included in systematic review of effect of physical activity on fracture relative to placebo or no treatment by fracture type

	Systematic Review (Author, Year)			
	Lock, 2006 [216]			
	Fracture Type			
RCTs (Author, Year)	**A**	**V**	**H**	**W**
Ebrahim, 1997 [217]		X		
Jensen, 2002 [218]			X	
Preisinger, 1996 [219]	X	X		X
Sato, 2003 [220]			X	
Sinaki, 1989 [221]		X		
Sinaki, 2002 [222]		X		
Vetter, 1992 [223]	X		X	

A = all; V = vertebral; H = hip; W = wrist/forearm; X = included in pooled analysis

Table 32. Pooled risk estimates of fracture for physical activity relative to placebo or no treatment

Author, Year	# Studies	Sample Size	RR	(95% CI)
Vertebral Fractures				
Original 2007 Report: No comparable studies from the original report				
Update Report				
Lock, 2006 [216]	3	322	0.52	(0.17, 1.60)

Head-to-Head Comparisons of Agents

This section presents the results of studies that directly compared the effect of one agent against that of another agent (within the same class or across classes) within the same study.

Menopausal Estrogen Therapy vs. Bisphosphonate therapy

No new studies were identified for this comparison. Studies that directly compared fracture risk in association with menopausal estrogen therapy to fracture risk with bisphosphonate therapy spanned 12 months to 48 months in duration and collectively addressed vertebral, nonvertebral, and overall clinical fractures (Table 33). The odds of fracture with menopausal estrogen therapy compared to alendronate, etidronate, risedronate, or pamidronate were not statistically significantly different. Numbers of studies and fracture events were too sparse for us to determine relative efficacy of any one type of ET or EPT regimen compared to bisphosphonate therapy.

Bisphosphonate Therapy Versus Calcium

No new studies were identified for this comparison. The two trials performing direct comparisons of bisphosphonates and calcium included very small numbers of fracture events: 12 symptomatic vertebral or nonvertebral fractures in one trial, and one atraumatic vertebral fracture in the other trial (Table 34). In these two studies, the odds of fracture with bisphosphonates relative to calcium were not statistically significantly different.

Bisphosphonate Therapy Versus Raloxifene

No new studies were identified for this comparison. The bisphosphonates that were directly compared to raloxifene in RCTs were alendronate and risedronate (Table 35). The odds for overall fracture, vertebral fracture, nonvertebral fracture, hip fracture, and wrist fracture with raloxifene vs. alendronate were not statistically significantly different. These comparisons are based on three RCTs. Because RCTs directly comparing risedronate with raloxifene had no fracture events, we could not provide comparisons of the odds of fracture with the two agents.

Alendronate vs. Risedronate in Women With Osteoporosis

No new studies were identified for this comparison. In four RCTs, the odds of overall fractures with alendronate versus risedronate were not statistically different (Table 36). Numbers of fractures were insufficient to permit comparisons for vertebral, hip, and wrist fractures.

Alendronate vs. PTH Among Postmenopausal Women

No new studies were identified for this comparison. In the one available direct comparison of alendronate vs. PTH with respect to fracture risk, the odds of nonvertebral fracture were not statistically significantly different with alendronate versus PTH (Table 37).

Alendronate 10 mg/day vs. Teriparatide 20 µg/day

In one 36-month RCT of people taking glucocorticoids, newly identified for this report (Jadad score 2),[224] the odds of vertebral fracture were higher, and the risk of nonvertebral fracture was similar, with alendronate 10 mg/day versus teriparatide 20 µg/day (Table 38). Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study, we determined its applicability to be moderately high.

Alendronate + Vitamin D vs. Alendronate + Alfacalcidol

In one 24-month RCT, newly identified for this report (Jadad score 0),[56] the odds of nonvertebral and vertebral fractures were similar with alendronate + vitamin D vs. alendronate + alfacalcidol (Table 39). Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study, we determined its applicability to be moderately high.

Alfacalcidol + Prednisolone + Alendronate vs. Alfacalcidol + Prednisolone

One RCT newly identified for this report reported a 90 percent lower odds of vertebral fracture with alfacalcidol + prednisolone + alendronate vs. alfacalcidol + prednisolone (Jadad score 1) (Table 40).[225] Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study, we determined its applicability to be low.

Alendronate vs. Alendronate + Calcium

A RCT newly identified for this report found a three-fold higher odds of any clinical fracture with alendronate vs. alendronate + calcium (Table 41).[226] Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study, we determined its applicability to be moderately high; however, the study assessed and reported fractures as adverse events.

Rocaltrol + Caltrate D vs. Caltrate D

A 12-month RCT newly identified for this report found that rocaltrol + Caltrate D did not statistically significantly decrease the odds of vertebral fracture compared to Caltrate D (Jadad score 3) (Table 42).[227] Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study, we determined its applicability to be moderately high.

Risedronate vs. Zoledronic Acid

No new studies were identified for this comparison. In one 12-month RCT identified for the original report, the odds of subclinical vertebral fracture with risedronate was similar to that with zoledronic acid (Table 43).[228]

Etidronate vs. Calcitonin

No new studies were identified for this comparison. Two RCTs identified for the original report found that the odds of vertebral fracture with etidronate and calcitonin were not statistically significantly different (Table 44).[137,229]

Raloxifene vs. Menopausal Estrogen Therapy

No new studies were identified for this comparison. One RCT identified for the original report found that the odds of vertebral fracture with raloxifene and menopausal estrogen therapy were not statistically significantly different (Table 45).[230]

Menopausal Estrogen Therapy vs. Vitamin D

One new RCT was identified for this report. In an RCT identified for the original report, the odds of vertebral fracture associated with estrogen (conjugated equine estrogen plus medroxyprogesterone acetate) were decreased compared to vitamin D, but not significantly so (Table 46).[137] Another RCT, newly identified for this report that examined vertebral and nonvertebral fractures in aggregate found that the odds of fracture were not statistically significantly different with menopausal estrogen + progestogen therapy vs. vitamin D. (Jadad score 3).[231] Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study,

we determined its applicability to be moderately low: the population comprised a small group of asthma patients who were using glucocorticoids.

Calcium vs. Vitamin D or Vitamin D vs. Calcium

Six systematic reviews encompassing seven RCTs reported pooled risk estimates for vitamin D vs. calcium. One systematic review assessed overall fractures, six assessed nonvertebral fractures, four assessed hip fractures, and one assessed wrist fractures (Table 48). Table 26 presents pooled estimates of the antifracture effects of vitamin D vs. calcium. Based on the pooled analyses of trials directly comparing vitamin D alone with calcium alone, the antifracture effects of calcium and vitamin D are not statistically significantly different from each other for hip, vertebral, or nonvertebral fractures.

No new original studies were identified for this comparison. In one RCT of 62 months duration identified for the original report, the odds of overall fracture, vertebral fracture, hip fracture, and wrist fracture were not statistically significantly different with calcium vs. vitamin D (Table 47).[153]

In summary, studies that performed head-to-head comparisons of FDA-approved pharmacotherapies for osteoporosis have not discerned statistically significantly different effects on fracture risk reduction.

Table 33. Fractures with bisphosphonate relative to menopausal estrogen therapy or menopausal estrogen plus progestogen therapy among postmenopausal women

Author, Year	Study Duration	Fracture Type	Number of Fractures, Bisphosphonate	Number of Fractures, Estrogen*	Odds Ratio (95% CI)
Alendronate					
Original 2007 Report					
Hosking, 1998[48]	24 months	Nonvertebral	44/897	6/204	1.58 (0. 56, 4.43)
Bone, 2000[58]	24 months	Clinical	5/92	10/143	0.77 (0. 26, 2.25)
Greenspan, 2003[59]	34 months	Clinical	7/93	5/93	1.43 (0. 44, 4.58)
Update report: ***No new studies***					
Etidronate					
Original 2007 Report					
Ishida, 2004[137]	24 months	Vertebral	8/66	7/66†	1.16 (0. 40, 3.39)
Wimalawansa, 1998[138]	48 months	Nonvertebral	1/14	1/15	1.07 (0. 06, 18.10)
Wimalawansa, 1998[138]	48 months	Vertebral	3/14	2/15	1.73 (0. 26, 11.50)
Update report: ***No new studies***					
Risedronate					
Original 2007 Report					
Tauchmanova, 2006[228]	12 months	Subclinical vertebral	2/15	1/15	2.05 (0.20, 21.36)
Update report: ***No new studies***					
Pamidronate					
Original 2007 Report					
Tauchmanova, 2006[228]	12 months	Subclinical vertebral	3/15	1/15	3.05 (0.38, 24.18)
Update report: ***No new studies***					

*Hosking: participants received estrogen plus progestin; Bone, 2005: conjugated equine estrogen; Greenspan, 2003: conjugated equine estrogen ±medroxyprogesterone acetate; Ishida, 2004: conjugated equine estrogen+medroxyprogesterone acetate; Wimalawansa, 1998: conjugated equine estrogen+norgestrel; Tauchmanova, 2006: estradiol+progesterone.

Table 34. Randomized controlled trials assessing fractures with bisphosphonates relative to calcium, by bisphosphonate

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Bisphosphonate	Number of Fractures, Calcium	Odds Ratio (95% CI)
Etidronate					
Original 2007 Report					
Campbell, 2004[155]	60 months	New symptomatic, vertebral or nonvertebral	5/81	7/85	0.74 (0. 23, 2.38)
Update Report: ***No new studies***					
Pamidronate					
Boutsen, 1997[232]	12 months	Atraumatic vertebral	1/14	0/13	6.88 (0.14, 347.65)
Update Report: ***No new studies***					

Table 35. Fractures with bisphosphonates relative to raloxifene

Author, Year	Study Duration	Fracture Type	Number of Fractures, Bisphosphonate	Number of Fractures, Raloxifene	Odds Ratio (95% CI)
Alendronate					
Total Fractures					
Original 2007 Report					
Luckey, 2004[233]	12 months	All clinical	5/221	8/230	0.65 (0.22, 1.95)
Uchida, 2005[234]	12 months	Vertebral or nonvertebral	22/713	20/699	1.08 (0.59, 2.0)
Update Report: ***No new studies***					
Vertebral Fractures					
Original 2007 Report					
Muscoso, 2004[235]	24 months	Vertebral	6/1,000	0/100	NC
Uchida, 2005[234]	12 months	Vertebral	8/713	5/699	1.56 (0.52, 4.65)
Update Report: ***No new studies***					
Nonvertebral Fractures					
Original 2007 Report					
Uchida, 2005[234]	12 months	Nonvertebral	14/713	15/699	0.94 (0.44, 1.91)
Update Report: ***No new studies***					
Hip Fractures					
Original 2007 Report					
Muscoso, 2004[235]	24 months	Femoral	3/1,000	0/100	NC
Uchida, 2005[234]	12 months	Hip	1/713	2/699	0.5 (0.05, 4.84)
Update Report: ***No new studies***					
Wrist Fractures					
Original 2007 Report					
Muscoso, 2004[235]	24 months	Radial	1/1,000	0/100	NC
Uchida, 2005[234]	12 months	Wrist	6/713	8/699	0.74 (0.26, 2.11)
Update Report: ***No new studies***					
Risedronate					
Vertebral Fractures					
Original 2007 Report					
Muscoso, 2004[235]	24 months	Vertebral	0/100	0/100	NC
Update Report: ***No new studies***					
Hip Fractures					
Original 2007 Report					
Muscoso, 2004[235]	24 months	Femoral	0/100	0/100	NC
Update Report: ***No new studies***					
Wrist Fractures					
Original 2007 Report					
Muscoso, 2004[235]	24 months	Radial	0/100	0/100	NC
Update Report: ***No new studies***					

NC = not calculable

Table 36. Fractures with alendronate relative to risedronate, by fracture type among postmenopausal women with osteoporosis

Author, Year	Study Duration	Type of Fracture	Number of Fractures, Alendronate	Number of Fractures, Risedronate	Odds Ratio (95% CI)
All Fractures					
Original 2007 Report					
Bonnick, 2006[236]	24 months	Clinical	34/410	34/415	1.01 (0.62, 1.66)
Hosking, 2003[60]	12 months	Clinical	6/172	6/178	1.04 (0.33, 3.27)
Rosen, 2005[237]	12 months	Any	26/520	20/533	1.35 (0.75, 2.43)
Muscoso, 2004[235]	12 months	Total	2/1,000	0/100	3.01 (0.02, 373.9)
Update Report: ***No new studies***					
Vertebral Fractures					
Original 2007 report					
Muscoso, 2004[235]	12 months	Vertebral	2/1,000	0/100	NC
Muscoso, 2004[235]	24 months	Vertebral	4/1,000	0/100	NC
Update Report: ***No new studies***					
Hip Fractures					
Muscoso, 2004[235]	12 months	Femoral	1/1,000	0/100	NC
Muscoso, 2004[235]	24 months	Femoral	2/1,000	0/100	NC
Update Report: ***No new studies***					
Wrist Fractures					
Original 2007 Report					
Muscoso, 2004[235]	12 months	Radial	1/1,000	0/100	NC
Muscoso, 2004[235]	24 months	Radial	0/1,000	0/100	NC
Update Report: ***No new studies***					

NC = not calculable

Table 37. Fractures with alendronate relative to PTH (Teriparatide) among postmenopausal women

Author, Year	Study Duration	Fracture Type	Number of Fractures, Alendronate	Number of Fractures, PTH	Odds Ratio (95% CI)
Nonvertebral					
Original 2007 Report					
Body, 2002[238]	14 months	Nonvertebral	10/73	3/73	3.24 (1.04, 10.07)
Update Report: ***No new studies***					

Table 38. Alendronate 10mg/day versus teriparatide 20 µg/day among individuals taking glucocorticoids

Author, Year	Study Duration	Fracture Type	Number of Fractures, Alendronate 10 mg/day	Number of Fractures, Teriparatide 20 µg/day	Odds Ratio (95% CI)
Original 2007 Report: ***No comparable studies from the original report***					
Update Report					
Saag, 2009[224]	36 MOS	Nonvertebral	15/214	16/214	0.93 (0.45, 1.95)
Saag, 2009[224]	36 MOS	Vertebral	13/169	3/173	3.79 (1.39, 10.32)

Table 39. Alendronate plus vitamin D versus alendronate plus alfacalcidol

Author, Year	Study Duration	Fracture Type	Number of Fractures, Alendronate + vit. d	Number of Fractures, Alendronate + Alfacalcidol	Odds Ratio (95% CI)
Original 2007 Report: ***No comparable studies from the original report***					
Update Report					
Ringe, 2007[56]	24 months	Nonvertebral	6/30	4/30	1.6 (0.42, 6.16)
Ringe, 2007[56]	24 months	Vertebral	4/30	1/30	3.62 (0.59, 22.26)

Table 40. Alfacalcidol plus prednisolone and alendronate versus alfacalcidol plus prednisolone

Author, Year	Study Duration	Fracture Type	Number of Fractures, Alfacalcidol + Prednisolone & Alendronate	Number of Fractures, Alfacalcidol	Odds Ratio (95% CI)
Original 2007 Report: ***No comparable studies from the original report***					
Update Report					
Okada, 2008[225]	18 months	Vertebral	0/17	4/16	0.1 (0.01, 0.81)

Table 41. Alendronate versus alendronate plus calcium

Author, Year	Study Duration	Fracture Type	Number of Fractures, Alendronate	Number of Fractures, Alendronate + Calcium	Odds Ratio (95% CI)
Any Clinical Fracture					
Original 2007 report: ***No comparable studies from the original report***					
Update Report					
Bonnick, 2007[226]	2 years	Any clinical fracture	28/281	9/282	3.01 (1.54, 5.85)

Table 42. Rocaltrol+Caltrate D versus Caltrate D

Author, Year	Study Duration	Fracture Type	Number of Fractures, Rocaltrol+Caltrate D	Number of Fractures, Caltrate D	Odds Ratio (95% CI)
Original 2007 Report: ***No comparable studies from the original report***					
Update Report					
Xia, 2009[227]	12 months	Vertebral	1/74	2/76	0.52 (0.05, 5.1)

Table 43. Risk of fracture for risedronate relative to zoledronic acid, by fracture type

Author, Year	Study Duration	Fracture Type	Number of Fractures, Risedronate	Number of Fractures, Zoledronic Acid	Odds Ratio (95% CI)
Subclinical Vertebral Fractures					
Original 2007 Report					
Tauchmanova, 2006[228]	12 months	Subclinical vertebral fractures	2/15	3/15	0.63 (0.10, 4.15)
Update Report: ***No new studies***					

Table 44. Fractures with etidronate relative to calcitonin, by fracture type

Author, Year	Study Duration	Fracture Type	Number of Fractures, Etidronate	Number of Fractures, Calcitonin	Odds Ratio (95% CI)
Vertebral					
Original 2007 Report					
Ishida, 2004[137]	24 months	Vertebral	8/66	8/66	1.00 (0. 35, 2.83)
Garcia-Delgado, 1997[229]	18 months	Vertebral	3/14	4/13	0.63 (0. 12, 3.39)
Update Report: ***No new studies***					

Table 45. Risk of fracture for raloxifene, relative to estrogen, among postmenopausal women

Author, Year	Study Duration	Fracture Type	Number of Fractures, Raloxifene	Number of Fractures, Estrogen	Odds Ratio (95% CI)
Vertebral Fractures					
Original 2007 Report					
Reid, 2004[122]	36 months	Vertebral	4/193*	1/102	1.9 (0.03, 12.22)
Update Report: ***No new studies***					

*60 and 150 mg dose groups combined.

Table 46. Risk of fracture for estrogen, relative to vitamin D, by anatomical fracture site

Author, Year	Study Duration	Fracture Type	Number of Fractures, Estrogen*	Number of Fractures, Vitamin D	Odds Ratio (95% CI)
Vertebral Fractures					
Original 2007 Report					
Ishida, 2004[137]	24 months	Vertebral	7/66*	11/66	0.6 (0.22, 1.62)
Update Report: ***No new studies***					
Vertebral & Nonvertebral Fractures					
Original Report: ***no comparable studies from the original report***					
Update Report					
Campbell, 2009[231]	5 years	Vertebral & non-vertebral-menopausal hormone therapy	0/23	3/24	0.13 (0.01, 1.31)

*For Ishida, 2004: CEE plus medroxyprogesterone; for Campbell, 2009: minimum estrogen dose of 2 mg estradiol or 0.625 mg CEE or 50 µg transdermal estradiol.

Table 47. Risk of fracture for calcium, relative to vitamin D, by fracture group

Author, Year	Study Duration	Fracture Type	Number of Fractures, Calcium	Number of Fractures, Vitamin D*	Odds Ratio (95% CI)
All Fractures					
Original 2007 Report					
Grant, 2005[153]	62 months	New	189/1,311	212/1,343	0.90 (0.73, 1.11)
Update Report: ***No new studies***					
Vertebral Fractures					
Original 2007 Report					
Grant, 2005[153]	62 months	Clinical vertebral	3/1,311	4/1,343	0.77 (0.17, 3.39)
Update Report: ***No new studies***					
Hip					
Original 2007 Report					
Grant, 2005[153]	62 months	Proximal femur	49/1,311	47/1,343	1.07 (0.71, 1.60)
Update Report: ***No new studies***					
Wrist					
Original 2007 Report					
Grant, 2005[153]	62 months	Distal forearm	33/1,311	33/1,343	1.02 (0.63, 1.67)
Update Report: ***No new studies***					

*Control group.

Table 48. Randomized controlled trials included in systematic review of effect of vitamin D on fracture relative to calcium by fracture type

	Systematic Review (Author, Year)														
	Avenell, 2009[145]					Bergman, 2010[147]		Bischoff-Ferrari, 2009[183]		Izaks, 2007[148]		Jackson, 2007[184]		O'Donnell, 2008[144]	
	Fracture Type														
RCTs (Author, Year)	**A**	**NV**	**H**	**V**	**W**	**NV**	**H**	**NV**	**H**	**NV**	**H**	**V**	**NV**	**V**	**NV**
Avenell, 2004 [187]	X	X	X	X											
Grant, 2005[153]			X	X											
Peacock, 2000[174]	X														
Pfeifer, 2000[239]						X	X	X		X			X		
Pfeifer, 2008[209]								X							
Shiraki, 1996 [161]														X	X
Trivedi, 2003[213]						X	X								

A = all; NV = nonvertebral; H = hip; V = vertebral; W = wrist/forearm; X = included in pooled analysis

Combinations or Sequential Use of Above

No RCTs tested combinations of osteoporosis therapies or sequential use of osteoporosis therapies in relation to fracture outcomes.

Key Question 2: How Does Fracture Risk Reduction Resulting From Treatments Vary Between Individuals With Different Risks for Fracture as Determined by Bone Mineral Density, FRAX or Other Risk Assessment Score, Prior Fractures, age, sex, Race/Ethnicity and Glucocorticoid use, and Other Factors (e.g., Community Dwelling vs. Institutionalized, Vitamin D Deficient vs. not)?

Key Findings for Key Question 2

- **Bone Mineral Density.** Moderate evidence (post hoc analysis of one large RCT) showed that low femoral neck BMD did not predict the effect of alendronate on clinical vertebral or nonvertebral fracture risk. Post hoc analysis of two-year followup data from a large RCT of postmenopausal women with osteopenia and no prevalent vertebral fractures showed that risedronate significantly reduced the risk of fragility fracture in this group, comparable to reductions seen in women with osteoporosis.
- **FRAX Risk Assessment.** Moderate evidence (post hoc analysis of data from one large RCT) showed no effect of fracture risk as assessed by WHO/FRAX on the effects of raloxifene in reducing risk for morphometric vertebral fracture among elderly women.
- **Prevalent Fractures.**
    - Evidence is insufficient regarding the association between prevalent fractures and the efficacy of alendronate in reducing the risk for fractures. Post hoc analysis of a large RCT) showed that prevalent vertebral fractures do not predict the efficacy of alendronate; however another post hoc analysis of data from the same trial found that alendronate reduced the risk of incident nonvertebral fractures to a greater extent among women without prevalent fractures (but with T-scores ≤-2.5) than among women *with* prevalent fractures or without prevalent fractures and with T-score -2 to -2.5.
    - Evidence is insufficient regarding prevalent fracture and the efficacy of raloxifene. A post hoc analysis of one large RCT showed that raloxifene decreased the risk of major nonvertebral fracture among women with prevalent vertebral fracture, but not among women without prevalent vertebral fracture. However, two other RCTs found no influence of prevalent fracture.
    - Evidence is moderate (a post hoc analysis of one RCT) that prevalent fractures increased the relative efficacy of teriparatide in preventing fractures in postmenopausal women.
- **Age.**
    - In general, a high level of evidence suggests that bisphosphonates are at least as effective for older persons as for younger.
    - One RCT found no effect of age on the efficacy of risedronate.
    - One RCT found no influence of age on the effect of zoledronic acid in lowering the risk for vertebral or nonvertebral fractures but found that only women under 75 experienced a benefit in reduced risk for hip fracture. Another RCT found that

age influences the effect of zoledronic acid on the risk for vertebral fracture risk but not the risk for nonvertebral or hip fracture. However these studies were not powered to detect differences across age groups.
    - The relative effect of teriparatide on reducing the incidence of new vertebral fractures and nonvertebral fragility fractures was statistically indistinguishable in younger and older patients.
- **Sex.**
    - Evidence is insufficient regarding the effectiveness of therapies to prevent or treat osteoporosis in men. Only one RCT was identified that actually assessed the effect of sex on response to treatment. This study found that calcium plus vitamin D_3 reduced the risk of fracture among elderly women but not elderly men.
- **Race/Ethnicity.**
    - A high level of evidence (one post hoc pooled analysis of two RCTs) showed that raloxifene decreases the risk of vertebral fracture but not non-vertebral or hip fracture among Asian women; this finding is similar to that of US and international studies of raloxifene.
- **Glucocorticoid Treatment.**
    - Evidence is insufficient regarding the effect of glucocorticoid treatment on response to therapies. One new RCT found that teriparatide treatment was more effective in reducing risk of vertebral fractures than alendronate but equally effective in reducing risk for nonvertebral fractures.
- **Renal Function.**
    - Evidence is insufficient from trials assessing the effect of renal function on the efficacy of alendronate, raloxifene, and teriparatide. Two trials report no effect of renal function on the effects of these agents. However, in a third trial, impaired renal function reduced the efficacy of zoledronic acid in preventing vertebral (but not nonvertebral or hip) fractures.

Overview of Results for Key Question 2

To respond to this question, we identified reports of original research and post hoc analyses of original research data that conducted stratified analyses of fracture risk reduction. Evidence Table C-2 in Appendix C includes a table that summarizes key aspects of post hoc and subgroup analyses pertinent to this question of whether fracture reduction during osteoporosis pharmacotherapy varies according to differing risk factors and other individual characteristics. The prespecified risk factors on which we focused are each addressed individually below.

Baseline Bone Mineral Density

In a post hoc analysis of FIT/FLEX, postmenopausal women with low femoral neck BMD who had initially completed 5 years of oral alendronate therapy were assigned to receive alendronate for 5 further years or placebo.[240] Both treatment arms received calcium and vitamin D. Cumulative incidence of nonvertebral and clinical vertebral fractures did not significantly differ among women who had lower BMD at baseline than among women with higher femoral neck BMD.

A post hoc analysis of risedronate efficacy was performed among women with femoral T-score between -1 and -2.5 without prevalent fracture (osteopenia).[241] Cumulative 2-year fragility fracture incidence was statistically significantly (73 percent) lower among women assigned to

risedronate compared with women assigned to placebo, and comparable to reductions seen in women with osteoporosis.

FRAX or Other Risk Assessment Score

In a post hoc analysis of the MORE raloxifene trial, the decrease in risk of overall clinical fracture and of incident morphometric vertebral fractures associated with raloxifene vs. placebo did not very statistically significantly according to FRAX score.[242] Moreover, at age 75 years, vertebral fracture risk reduction was 31 percent irrespective of FRAX score. At younger ages, effectiveness increased with decreasing fracture risk.

Prior Fractures (Prevention vs. Treatment)

In a post hoc analysis of FIT/FLEX, postmenopausal women with low femoral neck BMD who had initially completed 5 years of alendronate therapy were assigned to receive alendronate for 5 further years or placebo.[240] Both treatment groups received calcium and vitamin D. Cumulative incidence of nonvertebral and clinical vertebral fractures did not significantly differ among women who had prevalent vertebral fractures at baseline.

In another post hoc analysis of the FIT trial with the same 5-year extension as the previously described study, among women with prevalent vertebral fracture at baseline, continued alendronate reduced the risk of clinical (but not morphometric) vertebral fractures, but not morphometric or nonvertebral fractures.[243] In contrast, among women without vertebral fractures at baseline, alendronate continuation reduced nonvertebral fractures among women with baseline femoral neck T-score ≤-2.5, but not with T-score between -2 and -2.5.

An extension of the MORE trial of raloxifene examined the relative efficacy of raloxifene among women with, compared to without, prevalent vertebral fractures.[244] Although raloxifene did not statistically significantly influence nonvertebral fracture risk, raloxifene did decrease the risk of major nonvertebral fracture (clavicle, humerus, wrist, pelvis, hip, lower leg) among women with prevalent vertebral fracture, but not among women without prevalent vertebral fracture at baseline.

A post hoc analysis examined the effects of raloxifene on new vertebral fractures according to the presence or absence of prevalent fractures.[245] The efficacy of raloxifene compared to placebo on decreasing vertebral fractures did not differ statistically significantly between women with and without prevalent fractures, (-8.21%, -0.75% vs. -2.83%, -1.21%, respectively).

Among postmenopausal women with osteoporosis who were randomized to teriparatide therapy in the Fracture Prevention Trial, the absolute benefit of teriparatide was greater among women with the highest number and severity of prevalent vertebral fractures.[246]

Age

A post hoc analysis examined the relationship between age and the effect of risedronate treatment on fracture risk among postmenopausal women with osteoporosis.[247] Irrespective of age, compared to placebo, treatment decreased the risk of each type of fracture statistically significantly: RR any fracture 0.58 (0.48, 0.70), RR clinical fracture 0.54 (0.41, 0.69), RR nonvertebral fracture 0.59 (0.44, 0.79), and RR morphometric vertebral fracture 0.54 (0.43, 0.68). In another post hoc analysis of postmenopausal women with osteoporosis, zoledronic acid significantly reduced clinical fractures, clinical vertebral fractures, and non-vertebral fractures to a similar extent among women younger than 75 years and women ≥75 years, so that treatment efficacy did not vary statistically significant according to age.[248] However, only women aged less

than 75 years, but not 75 years or over, had a statistically significant reduction in hip fracture risk at 3 years.

In a post hoc analysis of the HORIZON trial, antifracture effects of zoledronic acid was evaluated in relation to subgroups defined by age, body mass index, and renal function.[249] The effects of zoledronic acid on reducing vertebral fracture risk were statistically significantly greater among women < 70 years old. However, no such treatment-age interaction was apparent for nonvertebral or hip fractures.

In a post hoc analysis of the MORE raloxifene trial, antifracture effects of raloxifene vs. placebo was higher at younger ages.[242]

In a post hoc analysis of the Fracture Prevention Trial of postmenopausal women with osteoporosis, the relative risk of new vertebral fracture associated with teriparatide vs. placebo was similar among age subgroups.[250] The relative risk of vertebral fracture was 0.35 among both women under 75 years and women 75 and over (statistically significant in both cases). For nonvertebral fractures, relative risk of fracture was 0.41 among women under 75 years (statistically significant), and 0.75 (not statistically significant) among women 75 years and over. However, treatment by age interactions were not statistically significant.

Compared to placebo, annual intramuscular injection of vitamin D_2 (ergocalciferol) 300,000 IU for 3 years among men and women aged 75 years and over did not reduce the risk of any first fracture, or wrist fracture, and it increased the risk of hip fracture (HR 1.49, 95% CI: 1.02, 2.18).[162] Associations of vitamin D_2 with fracture risk did not vary according to sex, age, previous fracture, or mobility.

Sex

The 2007 report found “few studies that assessed the effect of [these] agents to reduce fracture risk among men.” Since that time, there continue to be no published trials assessing the antifracture effects of any of these agents in men that are comparable to the large (thousands of subjects), international, placebo-controlled trials that exist for women. In this update review, we identified nine trials that enrolled either all male subjects or had greater than 50 percent male subjects enrolled. However, these trials were either about special populations (cystic fibrosis,[55,114] congestive heart failure,[157] Parkinson’s disease,[72] cardiac transplant patients,[106]), were not powered to detect fracture risk outcomes,[74] or were open-label.[73]

Two trials of Vitamin D were large, included sufficient numbers of men, and reported fracture outcomes. A factorial, cluster-randomized intervention study administered calcium carbonate and vitamin D_3 400 IU to community-dwelling residents aged 66+ years-old.[150] Overall osteoporotic fracture risk was statistically significantly reduced among women offered calcium and vitamin D (RR 0.81, 95% CI: 0.68, 0.95). In contrast, possibly because fractures were relatively rare in the elderly men, fracture risk was not statistically significantly reduced among the male participants. In another trial, among 9,440 men and women over the age of 75 living in Wales, those randomized to receive 300,000 IU of ergocalciferol by intramuscular injection had no statistically significant benefit in terms of overall fracture reduction or fracture at specific sites. In fact, women had an increased risk of wrist fracture in the Vitamin D treated group; there were no statistically significant differences seen in men.[162]

Race/Ethnicity

A post hoc analysis of the HORIZON trial in 323 Chinese women from Taiwan and Hong Kong found that once-yearly zoledronic acid was associated with a significant 52 percent reduction in morphometric vertebral fracture at 3 years (RR 0.48, 95% CI 0.24, 1.00).[251]

A pooled analysis of two studies of Asian postmenopausal women with osteoporosis (one Chinese, one Japanese) examined the effects of raloxifene (60 mg/d or 120 mg/d vs. placebo).[252] Raloxifene statistically significantly reduced the incidence of vertebral fractures and any new clinical fractures, but not nonvertebral fractures, compared to placebo.

Other Factors

Glucocorticoid Use

As described above, a small 18-month study that compared patients treated with glucocorticoid and given alendronate with those given alfacalcidol observed a small decrease in the risk for fracture among patients taking alendronate (0.68, 95% CI: 0.12, 3.99), but the study was not powered to assess fracture risk.[57] Also, as described above, in a 36-month RCT of people taking glucocorticoids, newly identified for this report (Jadad score 2),[224] the odds of vertebral fracture were higher, and the risk of nonvertebral fracture was similar, with alendronate 10 mg/day vs. teriparatide 20 µg/day (Table 38). Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study, we determined its applicability to be moderately high. Another RCT newly identified for this report that examined vertebral and nonvertebral fractures in aggregate found that the odds of fracture were not significantly different with menopausal estrogen + progestogen therapy vs. vitamin D. (Jadad score 3).[231] Using the criteria of Gartlehner et al.[25] to assess the applicability of the new study, we determined its applicability to be moderately low: the population comprised a small group of asthma patients who were using glucocorticoids.

Renal Function

In a subgroup analysis of the FIT alendronate trial of women with osteoporosis, alendronate reduced the risk of spine fractures and overall clinical fractures to a similar extent to those without reduced renal function.[253,254]

A post hoc analysis from the MORE raloxifene trial showed that irrespective of kidney function (creatinine clearance level at baseline), raloxifene treatment was associated with a reduction in vertebral fractures, and no effect on nonvertebral fractures, compared to placebo.[255]

In a post hoc analysis of the HORIZON trial, antifracture effects of zoledronic acid were evaluated in relation to subgroups defined by age, body mass index, and renal function.[249] The effects of zoledronic acid on reducing vertebral fracture risk were statistically significantly greater among women who were overweight or obese, and those who had creatinine clearance >60 ml/minute. However, no such treatment-factor interactions were apparent for nonvertebral or hip fractures. In contrast, in another post-hoc analysis, the lower incidence of vertebral and nonvertebral fractures in teriparatide-treated versus placebo-treated patients was statistically consistent among patients with normal and impaired renal function.[256]

Timing of Initiation of Treatment

A post hoc study focused on the timing of administration of zoledronic acid among men and women in the first 90 days after surgical hip fracture repair.[257] Clinical fracture reduction was

statistically significant, and was not significantly different, among participants who had initiated zoledronic acid within 6 weeks (33 percent) compared with after 6 weeks (37 percent).

Cystic Fibrosis

A systematic review that included five trials of persons with cystic fibrosis (CF) who had not undergone lung transplants assessed the efficacy of bisphosphonates for fracture prevention in this group.[258] Bisphosphonates increased BMD but had no significant effect on incident fracture in this population, a finding attributed, at least in part, to the small sample size and short duration of followup.

Studies Assessing Multiple Subgroups in a Single Manuscript

A post hoc analyses of the RUTH raloxifene trial performed several stratified analyses, with associated statistical interaction testing, to determine if certain factors predicted the efficacy of raloxifene in reducing vertebral fracture risk among women with, or at high risk for, coronary heart disease.[120] Age, smoking, prior fracture, family history of hip fracture, weight loss in the past year, and body mass index were each found not to be statistically significantly associated with the risk of clinical vertebral fractures with raloxifene vs. placebo.

In a RCT, oral vitamin D_2 (ergocalciferol) 100,000 IU or placebo was administered every four months for 3 years to institutionalized men and women in Wales.[203] Compared with placebo, vitamin D was not associated with statistically significant reduction in the incidence of first fracture. In subgroup analyses, the authors report no statistically significant difference in fracture incidence between intervention and control according to mobility level, cognitive function, visual acuity, and type of care home, but details of these subgroup analyses are not provided.

Key Question 3: Regarding Treatment Adherence and Persistence:

a) What are the Adherence and Persistence With Medications for the Treatment and Prevention of Osteoporosis?
b) What Factors Affect Adherence and Persistence?
c) What are the Effects of Adherence and Persistence on the Risk of Fractures?

For this question, we identified two new systematic reviews, 18 RCTs, and 59 observational studies.

Key Findings for Key Question 3

- Definitions of adherence and persistence vary widely across studies and over time.
- Adherence rates are higher in clinical trials than in real life and therefore in observational studies, which likely reflects the select populations and controlled environments in trials.
- The rates of adherence and persistence observed in the studies reviewed for this report reflect closely the rates seen and examined in prior systematic reviews on the topic, as well as the previous report. Adherence and persistence as measured in observational studies is poor. In the US studies, overall, about half of patients appeared to show persistence with osteoporosis treatment at 1 year, with adherence ranging widely across studies.

- Many potential barriers have been identified to adherence and persistence. Five of the most commonly assessed in published studies include age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of the osteoporosis medications. The frequency with which these potential barriers appear in the literature does not necessarily correspond to their importance as barriers/factors related to adherence.
- Age, history of fracture, and number of concurrent medications do not appear to have an important independent association with adherence/persistence.
- Dosing frequency appears to affect adherence/persistence to a point: adherence is improved with weekly compared to daily regimens, but current evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens.
- Adverse effects—and concerns about adverse effects—appear to be important predictors of adherence and persistence. Evidence from a systematic review and 15 out of 17 observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral or both).
- The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.

Key Question 3a: What are the Adherence and Persistence With Medications for the Treatment and Prevention of Osteoporosis?

Several methods of measuring adherence are used in the medical literature, including self-report (which suffers from recall bias and may overestimate adherence); electronic devices (which are accurate but expensive); pill counts (which are limited in that the use of pills is assumed if not counted in the bottle); and administrative databases from pharmacies or health plans (which have the advantage of being objective and providing information over a large time span, but are limited in that they include only what is in the database)

Using the databases to measure adherence can be done in several ways. Commonly used is the medication possession ratio (MPR), which is a ratio of the days of medication supplied divided by the days between the first fill and the last fill of the medication. Also measured are the proportion of days covered (PDC), for which pharmacy fills are used to determine what proportion of all days within a specified time period a patient had enough medication, and the percentage of doses taken as prescribed, which is the percentage of prescribed doses taken as directed by the patient during a specified time. Persistence, on the other hand, is typically measured either as a continuous variable and reported as the number of days on a medication until discontinuation or as a dichotomous variable, reporting the proportion of study subjects still on the medication after a period of time.

In the original report, we identified 10 studies that assessed adherence to osteoporosis medications, and 12 studies that assessed persistence.[14] Adherence was poor across the 10 observational studies that included alendronate, etidronate, risedronate, calcitonin, menopausal hormone therapy, raloxifene, and calcium/vitamin D, with often less than half of patients achieving a medication possession ratio (MPR) over 80 percent. The adherence rates varied widely across studies. The randomized trials reviewed generally showed higher levels of adherence, with some trials approaching 100 percent adherence. Persistence rates were just as variable across the 12 studies reviewed, with discontinuation rates at 1 year ranging from a low of 14 percent to a high of 84 percent.

Prior Systematic Reviews and Meta-analyses

Several recent systematic reviews and meta-analyses have been published on the topic of adherence to medications for osteoporosis.[141,259-263] However, each review varies in quality and completeness, and each also reports a wide range of adherence/persistence rates across studies. Cramer reviewed 14 observational studies through May 2006, limiting to those using pharmacy claims databases, and found that the 1-year persistence with bisphosphonates ranged from 17.9 percent to 78.0 percent, and the mean MPR ranged from 0.59 to 0.81.[259] A more recent systematic review and meta-analysis, by Imaz and colleagues, included all studies from the Cramer systematic review and extended the search through March 2009 to include 15 observational studies of adherence/persistence to bisphosphonates.[260] They limited their review to studies using administrative data and pool adherence/persistence rates for only a small minority of included studies (also excluding those studies that focus on dosing regimen effects). In their systematic review of persistence rates, they included five studies with 236,540 patients followed for one year, and found a pooled persistence mean of 184 days, with a range from 98 days to 243 days. In the meta-analysis of bisphosphonate adherence, the authors included only five studies that used the MPR, and found a pooled MPR mean of 66.9 percent with a range from 54 percent to 81 percent over one year. Finally, Siris et al published a systematic review of treatment adherence, focusing on 17 observational studies published through November 2007 that examined the relationship between adherence and fracture rates.[262] Adherence and persistence were both described as poor, with a wide range of rates reported in studies, as seen in the review by Imaz.

Most prior reviews of adherence/persistence to osteoporosis medications excluded randomized trials, as rates of adherence in trials are unlikely to reflect true real-world adherence.[261] However, a previous systematic review of interventions to improve adherence/persistence with osteoporosis medications was published in 2009 by Gleeson et al., reviewing the literature from January 1990 until July 2008.[263] Only seven relevant randomized trials (interventions to improve adherence) were found, of which five provided complete adherence/persistence rates for analysis. Few interventions were successful, with three out of the five adherence interventions showing statistically significant improvements in adherence (with modest effect sizes), and only one out of the five showing improvements in persistence. The interventions included telephone followups, counseling, and informational brochures. As in the present review, the authors described inconsistent definitions of adherence and persistence that preclude meta-analytic comparisons between groups. The adherence rates were measured using techniques that ranged from pill counts, to administrative data, to self-reported questionnaires, with rates of adherence (however defined) ranging from 41 percent to 76 percent in the control groups of these trials. The definition and rates of persistence similarly varied. The authors conclude that there are no clear trends in successful intervention techniques in the reviewed studies, although “periodic followup interaction between patients and health professionals appears to be beneficial.”[263]

Rates of Adherence in new Studies

Randomized Trials

Just as in the observational studies discussed above, the measurement of adherence and persistence in trials suffers from methodologic limitations. These limitations are coupled with limited ability to generalize findings of adherence/persistence in the trials to the population not enrolled in trials. Nonetheless, several of the trials included in this review report rates of adherence and/or persistence and are discussed below (Table 49).[55,264,265 74,85,86,120,136,266-271] Note that most trials report adherence rates for only those who complete the study, which leads to higher than typical adherence rates, as those who stop the drug due to side effects or adverse events drop out of the study.

Three trials of alendronate report adherence rates.[55,264,265] A randomized trial of a combination tablet of alendronate and vitamin D alone compared to the combination tablet plus additional vitamin D reported high levels of adherence over 24 weeks, with 96 percent of the patients on the combination pill and 94 percent in the comparator group reporting missing fewer than 6 tablets.[264] In a 12-month randomized trial comparing alendronate to placebo among patients with cystic fibrosis, 93 percent of patients in the alendronate arm were adherent to therapy, meaning they received at least 80 percent of the study drug (although the exact method to measure this adherence is unknown).[55] In a three-year randomized single blind trial in Taiwan of patients on alendronate plus menopausal hormone therapy compared to alone, the authors report a 100 percent adherence rate over the study; more than 85 percent of pills were consumed by participants at each study visit.[265]

Five trials of risedronate reported adherence rates.[74,85,86,266,267] In two randomized trials comparing daily versus monthly doses of risedronate (one using 75 mg dose on two consecutive days each month,[85] and the other using 150 mg monthly[86], adherence was high for all groups based on tablet counts; over 95 percent of study participants took at least 80 percent of their pills over the course of the 2-year studies. In a small randomized trial of 44 Greek women, comparing weekly risedronate to daily teriparatide, rates of adherence for both groups were high.87 percent of risedronate patients were adherent based on pill counts and 93 percent of teriparatide patients were adherent based on volume of medication remaining at each visit.[266] However, the thresholds for determining adherence were not provided. In an open-label randomized trial of an adherence intervention (included in the prior systematic review of adherence interventions,[263] patients on risedronate were randomized to receive feedback about bone turnover).[267] There was no difference in persistence with therapy (defined as discontinuation of therapy) between the intervention group (80 percent persistence at 1 year) and the control group (77 percent persistence at 1 year). Both groups had unexpectedly high levels of adherence. In a study of men with osteoporosis comparing 35 mg risedronate weekly with placebo, adherence based on pill count was high, with 98 percent of risedronate patients "compliant with drug" (exact definition of compliance is not described).[74]

Two studies report on adherence with monthly ibandronate using data from the CURRENT trial, a six-month trial of monthly ibandronate among postmenopausal women currently taking weekly alendronate or risedronate.[268,269] The trial was industry-funded and compared women at baseline to 6 months after starting ibandronate without a control group. Adherence was measured using drugs dispensed and returned and defined as taking at least five of the six specified doses. Overall, 94 percent of women were adherent to therapy,[269] and among those with baseline gastrointestinal symptoms, 90 percent were adherent.[268]

Two studies reported adherence with raloxifene.[120,270] In a secondary analysis of data from the RUTH trial, which compared raloxifene 60mg/day to placebo over five years, when adherence was defined based on pill count showing at least 70 percent of pills taken, approximately 70 percent of study subjects were defined as adherent.[120] In a small randomized trial of 137 postmenopausal Japanese women, comparing raloxifene to alfacalcidol and to the combination of the two, both adherence and persistence were measured.[270] Adherence was defined based on an MPR greater than 80 percent over the one-year study. Persistence was defined as continuing to take the therapy at one year, which was operationalized as reporting taking medication at least seven of the last 14 days immediately prior to the one-year visit. Persistence rates at one year were 61 percent, 65 percent, and 55 percent for alfacalcidol, raloxifene, and the combination, respectively. The percent of patients adherent at one year was 78 percent for alfacalcidol, 94 percent in the raloxifene group, and 78 percent in the combination group; these differences were not statistically significant.

One additional study included teriparatide.[271,272] In this uncontrolled open-label intervention, women who had failed previous antiresorptive treatment were administered teriparatide. Adherence was defined as administering more than 80 percent of daily injections; adherence was 89 percent at six months, and 82 percent at 18 months.

One RCT examined adherence to calcium and vitamin D supplementation in older women over a 3-year period.[273] Adherence was defined as taking at least 80 percent of study medication, although the exact measurement of adherence was not provided. Overall, 63.8 percent of women achieved an 80 percent level of adherence.

Finally, one small (31 participants) double-blind randomized trial compared transdermal estrogen/progestin with placebo for treatment of osteoporosis in postmenopausal women with primary biliary cirrhosis.[136] Adherence rates were not specifically reported except that participants overall used 82 percent of patches supplied to them, with no difference between groups.

Table 49. Clinical trials reporting adherence/persistence rates

Author, Year	Drug(s)	Trial Length (Months)	Adherence Definition	Adherence (Persistence) Rate
Binkley, 2009[264]	Alendronate +Vitamin D	6	Missed <6 doses	94%
Papaioannou, 2008[55]	Alendronate	12	Received at least 80% study drug	93%
Tseng, 2006[265]	Alendronate + HRT	36	Consuming >85% of Pills	100%
Delmas, 2008[85]	Risedronate (two doses/ month)	24	Consuming at least 80% of pills	96%
Delmas, 2008[86]	Risedronate (one dose/month)	24	Consuming at least 80% of pills	97%
Anastasilakis, 2008[266]	Risedronate (one dose/week) Teriparatide	12	Pill Count (threshold not reported) Volume of med remaining	87% 93%
Boonen, 2009[74]	Risedronate (one dose/week)	24	Pill count (threshold not reported)	98%
Delmas, 2007[267]	Risedronate (one dose/day)	12	% patients ‘persistent’ and compliant’	77%
Bonnick, 2009[269]	Ibandronate (one dose/month)	6	Taking at least 5 of 6 doses dispensed	94%
Binkley, 2009[268]	Ibandronate (one dose/month)	6	Taking at least 5 of 6 doses dispensed	90%

Table 49. Clinical trials reporting adherence/persistence rates (continued)

Author, Year	Drug(s)	Trial Length (Months)	Adherence Definition	Adherence (Persistence) Rate
Ensrud, 2008[120]	Raloxifene	60	Consuming at least 80% of pills	70%
Gorai, 2009[270]	Raloxifene	12	Adherence: MPR>80% Persistence: percent taking pills 7 of last 14 days prior to one year visit	65% 94%
Adachi, 2007[271]	Teriparatide	6 18	Administering >80% daily injections	89% 82%
Boone, 2006[136]	Transdermal HRT	24	Percent of patches used (overall)	82%
Orwoll 2010[274]	Alendronate (one dose/month)	24	Consuming >80% pills	81%
Brown 2009[275]	Denosumab vs. Alendronate	12		
Kendler 2010[276]	Denosumab vs. Alendronate	12	Denosumab: taking both injections Alendronate: MEMS >80%	90.5% (89.7%) 78.2% (79.8%)
Karkkainen 2010[273]	Calcium + Vitamin D	36	Received at least 80% study drug	63.8%

Observational Studies

Adherence and persistence rates in observational studies are substantially lower than those in clinical trials. Our review found rates of adherence and persistence similar to the prior meta-analyses on the topic,[260,262] although, as in prior studies, the rates and methods of measurement of adherence vary widely. In total, 59 observational studies contributed to our analysis of 'real-world' adherence and persistence rates (i.e. coming from data outside of the clinical trial setting).[277-317] Twenty studies focused on adherence alone,[278-284 277,285-287,318-326] 13 studies focused on persistence alone,[288-293 294-298,327,328] and 24 studies examined both adherence and persistence.[299-315,329-331] All but three of the studies used pharmacy claims database analysis.[324,327,332] In two of the studies, [316,317] the actual outcome measured could not be determined from the article; each of those were small non-US studies that describe rates of "adherence" in their results, but whether they truly measured adherence or persistence is not clear. Adherence and persistence rates for all of these studies can be found in the adherence evidence table in Appendix C.

Of the included studies, 25 examined adherence/persistence exclusively in the US; these studies are discussed further below. All of these studies are industry funded except for a small study of 198 men at a single VA[278] and a larger study of seniors in the Pennsylvania PACE prescription assistance program.[322] Thirteen of the articles describe adherence only,[278,281,282,286,287,318,319,321-324,333,334] six describe persistence only,[291-293,297,298,327] and six describe both adherence and persistence.[304,306-308,331,332] None of the articles describe primary nonadherence (nonfulfillment), which refers to prescriptions not filled at a pharmacy after they are written. All studies included bisphosphonate use, except one that described adherence to and persistence with teriparatide.[331]

Adherence

Ten of the thirteen adherence studies employed the MPR or PDC threshold of more than 80 percent for their calculations of adherence and used pharmacy claims data. These ten studies all found rates of adherence well under 50 percent.

Several of these studies used data from large US health plans. In a study of 101,000 health plan members, 44 percent of individuals had an MPR over 80 at 1 year, 39 percent at 2 years, and 35 percent at 3 years.[282] Similarly, in a study of 3,658 women in one health plan, 45 percent had an MPR over 80 percent for their bisphosphonate.[286] Two other studies of individuals in health plans revealed low rates of adherence (32 percent had an MPR over 80 percent at 12 months,[318] and 48.7 percent had a PDC greater than 80 percent at 12 months.[321] In the only large nonindustry-funded study examining adherence in a US health plan, researchers examined 32,697 seniors in the Pennsylvania PACE program, finding that 49.8 percent of those on bisphosphonates had a PDC greater than 80 percent, 52.6 percent of those on raloxifene, and only 10 percent of those on calcitonin.[322] Finally, an examination of 21,655 members of a large health plan found 42.7 percent adherent among commercially insured members, and 33.7 percent among those in Medicare Advantage plans.[333]

Several of the studies used the MarketScan claims database, which combines data from many large employers, health plans, and government organizations. In a study of 61,000 women in this database, 49 percent had an MPR over 80 percent on monthly ibandronate, 49 percent on weekly bisphosphonate, and 23 percent on daily bisphosphonate.[281] In another large study of 460,584 women from MarketScan using bisphosphonates for variable periods of time, 32.7 percent of women had an MPR >80% [319]. Finally, 5,500 new users of once-weekly bisphosphonates, again from the MarketScan database, had adherence rate of 37 percent at 12 months if they did not switch medications, 48 percent if they switched to another weekly bisphosphonate, and 42 percent if they switched to a once-monthly bisphosphonate.[323]

The studies that did not use pharmacy claims were substantially smaller in size. In a study of 176 women from a group practice that used the number of months a prescription was obtained during the study period as the measure of adherence, overall 70 percent of women were adherent to daily bisphosphonates, and 69 percent to estrogen.[287] Another study of 25 women receiving free alendronate/cholecalciferol for 6 months found an adherence rate by pill count of 52 percent.[324] In the final adherence-only study, and the only study to include only men, 198 men at a VA in Wisconsin had an average adherence of 54 percent for alendronate, as measured by the prescription refill ratio at 2 years.[278]

Two studies examining both adherence and persistence to bisphosphonates reported a mean MPR among over 200,000 respondents of 83 percent for weekly and 78 percent for monthly bisphosphonates at six months,[307] and 80 percent and 75 percent at 12 months.[308] The two other studies used the proportion of days covered as their adherence measurement: One found a rate of adherence (defined by proportion of days covered [PDC] over 60 percent) at one year of 55 percent and 45 percent at two years,[304] and the other found an overall rate of adherence of 61 percent at one year.[306] The final study that examined both adherence and persistence to bisphosphonates used a questionnaire to examine cross sectional self-reported adherence (based on missing at least 1 dose over the last month) and found a rate of 65 percent.[332]

Data on adherence to teriparatide come from two analyses from the MarketScan databases.[331] In the analysis of 2,218 commercially insured and Medicare beneficiaries, 58 percent had an MPR greater than 80 percent at 6 months, and in the analysis of 824 Medicaid beneficiaries, only 33.5 percent had an MPR over 80 percent at 6 months.

Persistence

The studies that report on persistence have as much variability in their results and methods as the adherence studies already discussed. Of the six studies above that discuss both adherence and persistence, one defined persistence using a refill gap of 30 days (i.e. discontinuation of drug is defined by a gap of 30 days or greater between refills),[306] one used a gap of 60 days,[331] while two others use a gap of more than 90 days,[307,308] and one used a questionnaire to determine if patients had stopped taking their medication for more than a month.[332] Persistence at 12 months was an average of 196 days in the study using a 30-day gap, and 250 days in the study using a gap greater than 90 days.[308] In each of the studies of bisphosphonate that used pharmacy claims data, fewer than half of the patients were still persistent at 12 months. In the one study of 729 patients that used a questionnaire, 65.8 percent of patients were persistent. In the study of teriparatide, in which persistence was measured based on a gap of 60 days, 56.9 percent of patients overall were persistent at 1 year.[331] The final study examining adherence and persistence appeared to combine the two measures,[304] such that they reported the percent of individuals still on the medication with a PDC over 60 percent (55 percent overall at one year).

In those studies that focused specifically on persistence, rates of persistence were similarly low. In a study of 211,319 health plan members that defined persistence as filling at least one day of medication each month, 56 percent of weekly bisphosphonate users, and 40 percent of daily users were persistent at one year.[291] In a study of 1,092 patients using one national pharmacy chain, persistence at seven months (based on continuing to take the bisphosphonate) was 55 percent overall.[298] The one study that was based on self report and defined discontinuation as, "no medication for at least 3 months," found a rate of persistence at one year of 66 percent.[327]

The remaining three persistence studies all used a gap of over 30 days to define nonpersistence. In a study of 4,769 health plan members on alendronate, overall persistence at two years was 43 percent, with persistence defined as being on alendronate without a gap for at least 182 days, or six months.[292] A larger study of 91,630 health plan members reported that approximately 30 percent of patients starting on bisphosphonates were no longer on the medication after 90 days, based on a gap of 30 days for weekly and 45 days for monthly bisphosphonates.[293] Finally, in a study of 166,000 patients from the Information Management System (IMS) database, mean one-year persistence was 116 days, 113 days, and 98 days for weekly alendronate, weekly risedronate, and monthly ibandronate, respectively.[297] Only approximately half of all individuals in the study persisted with the medication after their first prescription (based on a gap of less than 30 days).

In summary, the rates of adherence and persistence seen in the reviewed studies reflect closely the rates seen and examined in prior systematic reviews on the topic, as well as the previous report. Adherence and persistence are poor, variable, and measured in different ways and over different periods of time. In the US studies, overall about half of patients appeared to be persistent at one year, with adherence ranging widely across studies.

Key Question 3b: What Factors Affect Adherence and Persistence?

An evidence review of the factors affecting adherence and persistence with medications for osteoporosis is fraught with challenges, the most important of which is the tremendous heterogeneity in how adherence is defined and measured. Additionally, medication-taking is a "private behavior" and is not easily measurable and is subject to the 'Hawthorne Effect,' where subjects change their behavior because they know they are being studied.[335,336] To fully understand how patients take their medications, they cannot know they are being studied, which is rarely the case. Not only is adherence difficult to measure, but the factors affecting adherence are often measured in different ways across studies, further complicating a synthesis of the literature. No prior systematic review has been published on the factors affecting adherence and persistence to drugs for osteoporosis.

In the original report, we identified 25 studies that discussed factors that may affect adherence or persistence with medications for osteoporosis.[14] Side effects (five studies), absence of symptoms (four studies), comorbid conditions (two studies), age (four studies), ethnicity and socioeconomic status (4 studies), and dosing regimens (eight studies) were reviewed. Studies consistently reported higher adherence and persistence rates with weekly bisphosphonate dosing as compared to daily, and additional patient preference studies reported patients preferred less frequent dosing of medications. These findings are consistent with prior systematic reviews of regimen complexity that found that more complex regimens (increased dosing frequency) are associated with decreased adherence across a range of diseases.[337-340]

For the current report, we identified 41 studies that discussed factors potentially affecting adherence or persistence or associated with adherence or persistence. Evidence Table C-5 in Appendix C lists each of the potential barriers (or factors) identified in the review, ordered by the number of studies discussing each particular potential barrier. Many of the barriers listed are reviewed in only a few studies. We focus the discussion below on five of the top factors that are discussed, acknowledging that several other barriers/factors related to adherence are important, including some not listed here. Cost-sharing, the presence of comorbidities, knowledge about osteoporosis, and several other factors are important barriers to osteoporosis medication adherence but are not discussed in detail below.

Age

We identified 31 articles that included age as a factor in predicting medication adherence or persistence. None of the studies had their main focus on the effect of age, but rather they all had age as a covariate in analyses predicting adherence or persistence. Most of the articles focused on bisphosphonates. Several included bisphosphonates in analyses of all osteoporosis medications,[318,320,327,330,341] and three included raloxifene in addition to bisphosphonates.[283,299,313] One study focused exclusively on teriparatide,[331] and one focused on calcium and vitamin D.[314] Almost all used pharmacy records and automated measures of adherence/persistence in their analyses except five.[283,285,299,320,332] Two of these studies were small international studies: one from Croatia[285] that examined only unadjusted correlations between age and adherence, and the other from the Czech Republic.[283] The latter, interestingly, found no association between age and 'drug compliance,' but found an association between decreased 'compliance with dosing instructions' and increased age, which illustrates the very complicated nature of adherence measurement.

The results overall were mixed, with four studies finding increased age associated with better adherence,[280,300,309,332] four studies finding increased age associated with worse adherence[283,285,314,321] (although two of these studies[285,314] examined only unadjusted results), and fourteen studies finding no association between age and adherence or persistence[278,298,303,305,306,313,317 318,320,327-329,331,341] (note: some overlap is possible between studies that examined both persistence and adherence). In those studies that examined persistence, six found increased age associated with better persistence,[291,292,295,300,309,330] and six found increased age associated with worse persistence.[290,294,296,297,299,314] One study of 729 women from a large multispecialty clinic in the US that used only self-report to measure persistence and adherence found mixed results, with age associated with better adherence but no association of age with persistence.[332]

Eleven of the reviewed articles assessing the effect of age on adherence/persistence were based in the U.S.,[278,291,292,297,298,306 318,321,327,331,332] and these also revealed mixed results. All focused exclusively on bisphosphonates, except one that examined teriparatide,[331] in which age had no association with persistence. Three studies found no independent effect of age on adherence or persistence,[278,298,306,318] and two others examined only persistence and also found no association.[327,331] Those studies that found an association between age and adherence were evenly split between an association with age and better adherence [280,300,309] and an association with worse adherence.[283,285,314,321]

Only two studies found that age was associated with increased persistence.[291,292] The latter[292] was only an unadjusted comparison, using data from a large US health plan to examine the relationship between persistence and fracture risk for 4,769 patients on alendronate; 46 percent of patients who were older (over age 65) were persistent to their meds, compared to 43 percent of 55-64 year olds, and 41 percent of 45-54 year olds. The one study that found increased age associated with lower persistence[297] used IMS longitudinal prescription data for 166,000 women to examine difference in persistence between weekly and monthly bisphosphonates; in adjusted analyses, the rate of discontinuation of bisphosphonates and the odds of discontinuing were both higher for older patients compared to younger patients (50-54 year olds).

The reviewed literature, both US-based and non-US-based, would suggest that age by itself cannot be used as a predictor of adherence or persistence in the treatment of osteoporosis.

History of Fracture

Sixteen studies assessed prior history of fracture as a factor in adherence. Of the 16, four were US studies;[278,327,331,332] the remainder were conducted in Canada (two),[296,342] Croatia (one),[285] Czech Republic (one),[283] France (two),[305,320] Germany (one),[312] Japan,[328] Netherlands (one),[280] Sweden,[341] and UK (two).[300,315]

Three of the sixteen studies found that a history of prior (osteoporotic) fracture was significantly associated with increased rates of adherence and persistence to osteoporosis therapy,[280,312,341] 12 studies found no significant association between prior fracture and adherence or persistence to osteoporotic medications, and one study found an association between prior fracture and increased risk for discontinuing.[328]

The three studies that identified an association with prior fracture were observational studies based on large administrative databases. One study of 8,822 Dutch women, 45 and over, who had a diagnosis of postmenopausal osteoporosis and were new users of alendronate or risedronate, found that osteoporotic fracture or hospitalization for osteoporosis in the year before the start of therapy was associated with decreased odds of noncompliance (adjusted OR 0.65;

95% CI: 0.47, 0.88), as measured by MPR.[280] In a second study, among 4,451 German women 45 and older who were enrolled in a health plan for at least 90 days between 2000 and 2004 and were prescribed oral bisphosphonates for the treatment of osteoporosis, MPR-based adherence was higher in those with previous fractures than in those with no prior fractures (61.6 percent vs.55.6 percent at 180 days; 42.1 percent vs. 39.7 percent at 720 days).[312] A third study, which identified 56,586 participants in the Swedish Prescribed Drug Register through prescriptions for alendronate, risedronate, strontium, and raloxifene between 2005 and 2009, used survival analysis to measure persistence and MPR to measure compliance in persistent individuals. Any prevalent fracture was associated with a higher rate of persistence (HR 0.96, 95% CI: 0.93, 0.99, p<0.01). All three studies were industry-funded.

None of the US studies found a link between prior fracture and persistence or adherence. In one US study, among 198 male veterans treated with alendronate for osteoporosis, adherence during the first year of treatment (as determined by prescription refill ratio in pharmacy records) was not associated with prior fracture, although the response rate in this study was very low.[278] A 2010 prospective cohort study of 3,007 adults (the POSSIBLE US study) found no increased chance of discontinuing or switching medication among adults with a history of fracture after the age of 45 (HR 1.01, 95% CI: 0.87, 1.18).[327] A study of all adults 45 and over with at least one prescription claim in the MarketScan database for teriparatide from 2004 to 2006 (n=3,042) found no difference in time to discontinuation or gaps in use between individuals with prior vertebral, hip, or other fractures and those with no prior fractures; the population comprised those with commercial, Medicare, and Medicaid coverage.[331] Finally, a cross-sectional survey and medical record review of 729 adults in a multiple-specialty clinic who received a prescription for a bisphosphonate between 2006 and 2007 found no difference in persistence with the medications between those with documented prevalent vertebral fracture and those without.[332]

Therefore, the literature we identified does not point to an association between prior history of fracture and medication adherence or persistence.

Dosing Frequency

We identified 20 articles that examined the effect of dosing frequency on adherence. Five studies compared monthly to weekly dosing regimens.[297,305,307,308,323] Twelve studies compared weekly to daily regimens,[280,283,291,292,300,306,309,310,311,313,317,341] and three studies compared monthly, weekly, and daily regimens.[281,320,330] Out of the 20, 15 were industry-funded; the five studies not funded by industry report on results from Australia, Israel, Belgium, and the Czech Republic.[283,309,310,313,317]

Of the five studies that directly compare monthly to weekly dosing regimens,[281,297,305,307,308,323] all found a significant difference in adherence between the dosing regimens, with three favoring weekly and two favoring monthly. In a study of 240,000 patients from the IMS database in the US, mean adherence and persistence were significantly improved in weekly risedronate compared to monthly ibandronate, although the adherence results were no different when focusing on adherence in new users.[307] The mean MPR and mean days persistent on medication were 83.3 percent and 144 days, respectively, for risedronate, while the mean MPR and days' persistence for monthly ibandronate were 78.5 percent and 100 days, respectively. The study was industry-funded and authored. Very similar results were found in a 2009 study by the same authors and funders examining the same drugs;[308] some differences in results between the overall sample and new users led the authors to conclude that adherence and

persistence were similar for monthly ibandronate and weekly risedronate dosing, although in the overall sample, adherence and persistence were significantly better among weekly users. In yet another study using the IMS prescription database, this time of 166,000 women newly started on bisphosphonates, and industry-funded and, in part, industry-authored, mean persistence was worse with monthly ibandronate (98 days mean persistence) than with weekly alendronate and risedronate (116 days and 113 days, respectively).[297] However, after removing patients who failed to refill after their first prescription, persistence was the same across the three bisphosphonates.

In a study of almost 3,000 patients from France comparing monthly ibandronate to weekly bisphosphonate, partly industry-funded and authored, adherence and persistence were superior with monthly ibandronate compared to weekly bisphosphonates.[305] In an interrupted time-series analysis of new users of once-weekly bisphosphonates in the MarketScan databases, those who switched to one-monthly treatment had a decrease in the number of adherence failures, while no change in adherence was found for those who did not switch or those who switched to another weekly agent (although the proportion of those adherent was lower in the once-monthly switchers than one-weekly switchers).[323]

Three studies included rates of adherence or persistence with daily, weekly, and monthly osteoporosis medications.[281,320,330]In a study of 61,000 new users of bisphosphonates from the MarketScan database, there were no differences between monthly and weekly users in adherence over one year (49 percent with MPR over 80), although users of daily bisphosphonates had worsened rate of adherence (23 percent with MPR >80 percent).[281] In an analysis of the Dutch IMS database, only small (but statistically significant) differences in adherence (MPR greater than 80 percent) were observed between monthly ibandronate (89 percent) and the weekly or daily bisphosphonates (91 to 93 percent);[330] Persistence with monthly bisphosphonates was similar to weekly bisphosphonates and better than daily. Finally, in an analysis in France using the Morisky scale to measure adherence using self-report, monthly administration had higher adjusted odds (OR 2.23 95% CI: 1.37, 3.64) for adherence than daily (monthly vs. weekly was not studied).[320] In the same analysis, sponsored by the makers of ibandronate, users of monthly treatment were more satisfied with their treatment than those on weekly or daily regimens

The remaining 12 studies found that overall adherence to and persistence with bisphosphonates was improved in weekly compared to daily regimens. Three of the studies were based in the US[291,292,306] and all but three[310,311,317] found that weekly regimens resulted in improved adherence and/or persistence than daily regimens. The three studies finding no effect of dosing regimen on adherence were small predominately non-US studies whose main goal was something other than studying the relationship between dosing frequency and adherence: the studies examined 793 patients in Australia,[317] 1,376 patients in Belgium,[310] and 200 patients in the Czech Republic.[283]

In summary, the evidence points to improved adherence for bisphosphonates in weekly rather than daily dosing. This conclusion is supported by prior literature, including the prior evidence review,[14] prior systematic reviews[337-340]and prior meta-analyses.[306] The evidence reviewed here also suggests that monthly bisphosphonates do not result in better adherence/persistence than weekly treatment, although there are too few studies in this area to make any firm conclusions and the industry sponsorship of these individual studies may have introduced bias.

Number of Concurrent Medications

Polypharmacy is often cited as a potential barrier to medication adherence. In the current review, the use of concomitant medications was included in the analysis of medication adherence/persistence in 15 studies.[278,280,283-285,297-299,305,306,315,316,318,329,332] However, the definition of concomitant medication use differed substantially across studies; in some cases the number of medications present among study participants at baseline was analyzed, whereas in other cases the number of medications dispensed in the year prior to the start of bisphosphonates was studied, and in other cases the variable was dichotomized, to indicate whether or not patients took concomitant medications at all. In no case was concurrent medication use the primary independent predictor of interest in these studies, but instead was an included covariate. Note that causality is difficult to establish in studies linking the number of concurrent medications with adherence. Almost by definition, patients who are more adherent or persistent with medications are likely to be taking more medications; thus any relationship between adherence/persistence and number of concomitant medications may be seriously confounded.

Only three of the 15 studies[280,297,306] found a significant association between the number of concomitant medications and medication adherence. All other studies found no relationship. In a study of 2,741 postmenopausal women with osteoporosis from the US that focused on dosing regimens, the number of medications used 90 days prior to bisphosphonate use was an independent predictor of persistence (not adherence), although the direction of this association is not indicated.[306] In a large cohort study of new female users of bisphosphonates from the PHARMO data base in the Netherlands, the number of comedications in the year prior to starting the bisphosphonate was associated with adherence.[280] Women using more than 10 medications in the prior year had 1.87 times the odds of nonadherence compared to women using no medications, with smaller but significant odds ratios for women using fewer medications as compared to no medication. Finally, in a large U.S. study using the IMS database, number of unique medication classes dispensed in the 12 months prior to the start of bisphosphonate therapy was an independent predictor of persistence (adherence not measured).[297]

The remaining 12 studies found no independent association between number of medications and medication adherence or persistence. In each case, concomitant medication use was defined differently, and in each case was a covariate in the analysis rather than the main independent variable of interest. The four additional US-based studies[278,298,318,332] (out of a total of seven that assessed concurrent medications) included the only all-male sample included in this review (with 198 male veterans from one VA medical center),[278] and a telephone interview of 1,092 women with a low response rate of 33 percent.[298] In the latter study, respondents who were adherent took more medications at baseline than nonadherents, although the medication variable was not included in the final multivariate model (and is likely explained as a function of, rather than a cause of, the respondents' nonadherence). In the other two studies, one of which was a study of 142 women developing a prediction rule for very low adherence (MPR <20%) and the other a study of 729 women using self-reported adherence and persistence, the number of medications taken daily had no independent association with adherence, although certain beliefs about medications related to concomitant medication use were relevant.[318,332] For example, agreeing that one was taking too many different medications was one of the seven predictors included in the final prediction rule for low adherence, even though number of concomitant medications was not an independent predictor.[318]

In conclusion, the evidence does not support a firm role for the number of concomitant medications in determining adherence or persistence to bisphosphonates, although variability in

how concomitant medication use is measured is a substantial limitation to assessing the literature. In addition, the actual number of medications taken may be less important to determine adherence and persistence than beliefs about the value of those medications and any additional new medication.

Adverse Effects

Nine studies assessed the association of adverse effects from medications used to treat osteoporosis with treatment adherence and/or persistence.[278,290,316,317 280,283,298,318,327] All nine reported a significant effect of medication-associated adverse events on adherence or persistence. Among the studies, four were conducted in the US,[278,298,318,327] two were Japanese,[290,316] and the remainder were conducted in Australia,[317] Netherlands,[280] and the Czech Republic.[283]

In one US study of 198 male veterans treated with alendronate for osteoporosis, adherence was determined by prescription refill ratio in pharmacy records. During the two-year interval following onset of alendronate therapy, nonadherent men were significantly more likely than adherent men to describe side effects of alendronate (47 percent versus 29 percent, p=0.01).[278]

The second US study assessed persistence with bisphosphonate treatment among 1,092 women by analyzing pharmacy claims data (the outcome measured was discontinuation for seven months). Troublesome side effects were the most common reason for discontinuation of bisphosphonates (OR 6.78, 95% CI: 4.67, 9.86).[298] In a third study, 3,000 postmenopausal women on osteoporosis treatment were followed for one year and reported persistence with medications;[327] the probability of either discontinuing or switching their original medication was greater for those who attributed more severe side effects to their osteoporosis therapy. Finally, in an analysis of 142 women developing a prediction rule for very low adherence (MPR<20%), worry about side effects (as opposed to actually experiencing side effects, which was not measured) was an important independent predictor of low adherence.[318]

In summary, adverse effects—and concerns about adverse effects— do appear, based on the literature, to be an important factor affecting adherence and persistence with bisphosphonates and other osteoporosis medications as well.

Key Question 3c: What are the Effects of Adherence and Persistence on the Risk of Fractures?

In the original report, three observational studies examining the effect of adherence on risk of fracture were identified, and in all three studies, the fracture risk varied with the level of adherence. In one study, low adherence (MPR <80%) was associated with a 17 percent increased risk of fracture.[343] In a second study, adherence to medications was associated with a 25 percent relative risk reduction for all osteoporotic fractures, and persistence with therapy was associated with a 29 percent reduction in vertebral fractures and a 45 percent reduction in hip fractures. A third study[344] found that women who were adherent (MPR>80%) had a 16 percent lower fracture rate. All three of these studies were included in the systematic review described below.

For the present report, we identified one high-quality systematic review,[260] one comprehensive systematic review without meta-analysis,[262] two randomized trials,[120,345] and seventeen observational studies[277,279,282,286,292,300,302,304,311-313,319,322,333,334,341,346] that examined the association between adherence/persistence/compliance and fracture risk. All of the observational studies utilized registries or claims databases from pharmacy and/or medical records. Eight of the studies were based solely on US data.[282,286,292,304,319,322,333,334] The RCTs and 15 of the 17 observational studies found that decreased adherence was associated with an increased risk of

fracture (either vertebral, nonvertebral or both), although the risk varied depending on the drug examined and on whether use was for primary or secondary prevention of osteoporosis.

Below we describe the two reviews as well as the original studies identified in our search. Eight of the studies we identified were already included in the systematic reviews (four in the review by Imaz, five in the review by Siris, and one in both). Table 50 shows the studies included in each review as well those included in the original report and those identified for this report). These studies are described only briefly; the others are described in more detail.

Systematic Reviews and Meta-analyses

Imaz conducted a meta-analysis of articles published prior to March 22, 2009 on the association of adherence to bisphosphonate treatment with fracture risk,[260] adopting the following definition of persistence: “the duration of time from the initiation to discontinuation of therapy.” Compliance (adherence) was defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.” For persistence, the included studies had to define “discontinuation” as a gap in refills greater than 30 days within one year of beginning treatment for osteoporosis. Compliance studies were limited to those that used the MPR for at least one year. The assessment of the influence of low compliance on fracture risk included observational studies that compared participants determined to be of higher and lower compliance over 1 to 2.5 years. The authors conducted meta-analyses based on data at one year of follow up, to assess overall persistence (mean persistent days) and compliance (MPR), and the estimated association between level of compliance and fracture risk. Included studies reported only clinical fractures as their key outcomes. The meta-analysis to assess the association of level of bisphosphonate compliance with fracture risk combined data from eight studies. Six of the studies (171,063 patients) reported total fracture risk, for a pooled risk of 1.46 (95% CI: 1.34, 1.60). The risk for site-specific fractures was lower among more compliant bisphosphonate users than less compliant bisphosphonate users: 16 percent for nonvertebral fractures (pooled RR 1.16 95% CI: 1.07, 1.26) and 28 percent for hip fractures (pooled RR 1.28, 95% CI: 1.06, 1.53). In sensitivity analyses, the authors found that the effect of varying levels of compliance on fracture risk was further affected by sole use of bisphosphonates versus concurrent use of menopausal hormone therapy.

Siris conducted a systematic review of the literature prior to November 2007 (but not a meta-analysis).[262] Eligible for inclusion were observational or retrospective analyses of compliance, persistence, and adherence with treatment for osteoporosis and their relation to fracture rates. Excluded were RCTs, meta-analyses, case-control studies, and reviews of previously published data. Compliance and persistence were defined as above.

Of the 461 citations identified by the literature review, 17 were found to meet the inclusion criteria, including both published articles and abstracts (Table 50). The duration of followup varied from 2 to 7.5 years. The authors noted that direct comparisons of fracture rates were not possible because of the various methodologies used in the different studies and the additional variables that were included in the analyses. In U.S.-based studies, fracture risk was reduced 18.7 percent to 23 percent over 2 years.[304] In general, the studies supported the findings that individuals with the highest compliance with bisphosphonate treatment (>90% MPR) had a reduced risk for fracture compared to people with low levels of compliance (<30%) (OR, 0.70: 95% CI: 0.52, 0.93). However, in five studies that showed a decreased risk of fracture with increasing compliance, no dose-response relationship was observed between compliance and fracture risk.

Table 50. Adherence studies included in systematic reviews

	Review	
Original Studies	Imaz	Siris
Blouin, 2008*	X	
Briesacher, 2006		X (abstract)
Briesacher, 2007*		X
Caro, 2004†	X	X
Curtis, 2007(M444)		X (abstract)
Curtis, 2008*	X	X
Gallagher, 2008[300*]	X	
Goettsch, 2005		X (abstract)
Gold, 2007[292*]		X
Gothe, 2007		X (abstract)
Huybrechts, 2006†	X	X
Jaglal, 2007		X (abstract)
Mccombs, 2004		X
Penning-van Beest, 2008 *,†	X	X
Rabenda, 2008*		X
Sebaldt, 2004		X (abstract)
Sheehy, 2009	X	
Siris, 2006†	X	X
Van den Boogaard, 2006*		X
Weycker, 2007		X

*Identified in the search for the current report.
†Included in the original report.

The original studies included in these reviews that were also identified for the current report included several that assessed the association between compliance and fracture risk in unique populations or had particularly unique findings. For example, in the study by Blouin et al.,[277] of community-dwelling elderly (over 68) women, the association increased when the analyses were limited to women over 80 years of age (RR 1.48; 95% CI: 1.19, 1.85), and the effect of lower compliance increased with increasing duration of followup. A US study by Curtis et al[282] that was also included in the Siris review utilizing administrative claims data from a U.S. health care organization for approximately 17 million adults also found an increased risk for fracture with increasing age at the same level of adherence. The study by Gallagher,[300] which included a wider age range (adults 18 years of age and older), also found an inverse linear relationship between compliance with bisphosphonate therapy and risk for fracture ($p < 0.05$).

A retrospective cohort study by Penning-van Beest,[279] included in both reviews stratified over 8,000 new bisphosphonate users in the PHARMO Record Linkage System into quintiles of compliance (MPR), finding that the least compliant (<20 percent) were 80 percent more likely to be hospitalized for a fracture than the most compliant (≥90%). Using the same database, Van den Boogaard[311] (included in the Siris review) conducted a case control study of 541 women hospitalized for an osteoporotic fracture (compared to 5,283 matched controls, all new users of bisphosphonates) and found that persistence with treatment for at least one year reduced the fracture rate at one year (OR 0.74; 95% CI: 0.57, 0.95) and two years (OR 0.68; 95% CI: 0.47, 0.96).

Using a Cox proportional hazards model, a study by Gold[292] (included in the Siris review) that assessed the effect of persistence with alendronate among 4,769 women, 45 years of age and older, with commercial insurance coverage, found a 26 percent decrease in the risk for fracture among those who were persistent. Similarly, in a study by Rabenda[313] of 99,924 postmenopausal women, aged 45 years or older, identified from a national social security database, the risk of hip

fracture increased 0.4 percent (OR 0.996; 95% CI: 0.994, 0.998; p <.001) for each decrease in MPR and hip fracture risk differed significantly between persistent and nonpersistent women (HR: 0.404; 95% CI: 0.357, 0.457).

Original RCTs and Observational Studies not Included in Prior Reviews

Ensrud conducted an analysis of the effect of compliance using the global, multicenter, randomized, double-blind, placebo-controlled trial of raloxifene, RUTH (n = 10,101).[120] Women 55 years of age or older, who were one or more years postmenopausal and had established coronary heart disease (CHD) or were at high risk for CHD were included. Fractures (vertebral or nonvertebral), which were a secondary endpoint of the trial, were reported by participants and confirmed by x-ray or medical records. In these analyses, the authors assessed the effect of raloxifene on vertebral and nonvertebral fractures across fracture risk. When the analyses were limited to the women who were at least 70 percent adherent to treatment on the basis of pill count, fracture risk did not change.

The second randomized trial actually examined the relationship between placebo adherence and fracture using data from the Fracture Intervention Trial, a randomized trial of over 6,000 women testing the efficacy of alendronate. [345]. The analysis was performed because of concern about the “healthy adherer” effect, in which the relationship between adherence and fracture outcomes is confounded by other factors/behaviors that may lower the risk of fractures in adherent patients not related to medication use. Here, the authors find that women with high compliance with placebo had fewer hip fractures compared to those with lower compliance with placebo (rate of 3.6 per 1,000 person years vs. 5.0 per 1,000 person years), although the results were not statistically significant. There was no relationship between adherence to placebo and any other fractures.

Cadarette et al. also examine the possibility of a healthy adherer effect using an observational cohort of older women in Pennsylvania who were new users of bisphosphonates, calcitonin, and raloxifene. [322] In cox proportional hazards model, the authors found no difference in nonvertebral fracture risk between different levels of adherence to calcitonin, bisphosphonates for primary prevention, or raloxifene for secondary prevention; they do however find that patients with high adherence to bisphosphonates for secondary prevention had lower fracture rates (HR 0.53, 95% CI: 0.38, 0.74). The authors had hypothesized that, since only the bisphosphonates have good evidence to support their role in reducing nonvertebral fracture risk, if adherence to calcitonin and raloxifene had been associated with fracture prevention, that would have been evidence of a healthy adhere effect. Both this study and the RCT discussed above thus find no strong evidence for a healthy adherer effect in osteoporosis and fracture prevention.

Four additional observational studies using data from the US found an association between adherence to bisphosphonates and lower fracture risk. Abrahamsen conducted a matched cohort study with data from a national registry.[302] Individuals with a baseline fracture (except hip) (160,565) were included, and the study analyzed the association between first hip/femoral fractures and bisphosphonate compliance (MPR). A higher MPR was associated with a lower risk of fracture at both the hip (HR = 0.47; 95% CI: 0.34, 0.65; p<0.001) and atypical sites (HR 0.28; 95% CI: 0.12, 0.63; p < 0.01) Siris et al examine over 460,000 women from two large medical claims databases from 2001-2008 and find that women with the highest adherence (MPR>80%) had significantly lower hazard ratios for both vertebral (HR 0.78, 95% CI: 0.70, 0.87) and nonvertebral (HR 0.91, 95% CI: 0.87, 0.96) fractures. In another study from US claims

data, 16,295 commercially insured women and 5,360 Medicare Advantage women were studied to determine the association between low adherence (MPR <50%) and risk of any fracture. [333]. The analysis, which controlled for baseline fracture risk, did find that, compared to those with high adherence (MPR >80%), low adherence among commercial patients was associated with higher fracture risk (HR=1.37, 95% CI: 1.12, 1.68), but there was no relationship among Medicare Advantage patients (HR 1.07, 95% CI: 0.83, 1.38). Finally, a large study using both the Ingenix and MarketScan databases, examined new users of risedronate and raloxifene and compared risk of hip fracture among those with high adherence (MPR>80%) and low adherence.[334] Among those on risedronate therapy, the incidence of hip fracture decreased from baseline to 12 month follow up among those adherent (RR 0.70, 95% CI: 0.59, 0.84) while hip fracture incidence did not change among those not adherent to therapy. There was no effect for raloxifene on hip fracture in either the adherent or nonadherent population.

A German study assessed the effects of both persistence and adherence on fracture risk. Hoer[312]conducted a retrospective cohort study using claims data covering approximately 1.4 million lives through the German statutory sickness fund. Individuals were identified who were at least 45 years old with at least one prescription for an oral bisphosphonate for treatment of osteoporosis (3,289/4,451 were women). The main outcomes were incident fractures of the femur, hip, wrist and hand, lumbar vertebrae, forearm and shoulder/upper arm within 180, 360, and 720 days after initiation of treatment. Among individuals with a prior fracture, persistence was associated with a 29 percent reduction in fracture risk at 180 days and a 45 percent reduction at 360 days; however, at 720 days, decrease in fracture risk was nonsignificant (9 percent). For people with no prior fracture, fracture risk was not significantly affected by treatment persistence, possibly due to the low incident fracture rate. When the effect of *adherence* was assessed, it was associated with a significantly reduced fracture risk (HR 0.61; 95% CI: 0.47, 0.78) in the whole group, in those with a prior fracture (HR 10.32; 95% CI: 8.09, 13.16) and in those older than 65 years (HR 1.61; 95% CI: 1.24, 2.07). An additional German study of 4,000 women from the IMS database who were newly prescribed a bisphosphonate found that women with an MPR greater than 80 percent had fewer fractures (defined using ICD-10 codes) than did nonadherent women (88.1 percent vs. 85 percent fracture free, p=0.01);[346] in multivariate cox regression analysis, treatment compliance remained associated with risk of fracture, although many important confounders were not present in the model.

Two of the observational studies found no relationship between adherence and risk of fracture (in addition to the subpopulation of Medicare Advantage patients in the above study[333]). Feldstein[286] conducted a retrospective cohort study in a not-for-profit group-model HMO. The authors identified women 55 years of age and older eligible for treatment (1,829) and matched them with similar controls (1,829) for a total cohort of 3,658. Among treated women, fracture risk was not significantly different for MPR less than 80 percent or greater than 80 percent. A separate study of 56,586 Swedish users of alendronate, risedronate, strontium, and raloxifene found no significant relationship between adherence as measured by MPR and risk of fracture;[341] the study measured adherence only during the time the patient was persistent with therapy and measured hospitalized fractures. The study did find a relationship between treatment persistence and lower risk of fracture; compared to less than one month on treatment, those on treatment for one month to one year had a lower rate of fracture (HR 0.86, 95% CI: 0.72, 1.02), as did those on therapy one to two years (HR 0.67, 95% CI: 0.56, 0.82) and two to three years (HR 0.59, 95% CI: 0.48, 0.72). However, the study may not have adjusted for all relevant confounders (such as

BMD) and may have overestimated risk of fractures, since all fractures were included in the analysis regardless of cause

In summary, most of the studies analyzed, with the notable exception of a large placebo-controlled trial of raloxifene, found an association between adherence or persistence and fracture risk. No strong evidence of a “healthy adherer” effect was observed, although subsequent observational studies should account for the possibility of this effect when studying the relationship between hip fractures and bisphosphonate adherence.

Key Question 4: What are the Short- and Long-term Harms (Adverse Effects) of the Above Therapies (When Used Specifically To Treat or Prevent low Bone Density/Osteoporotic Fracture), and do These Vary by any Specific Subpopulations (e.g., the Subpopulations Identified in Key Question 2)?

For this question, we included 11 systematic reviews, 67 RCTs, 12 large observational studies, and six post-hoc analyses.

Key Findings for Key Question 4

- **Acute Coronary Syndrome, Including Myocardial Infarction (MI).** Evidence is low (a new meta-analysis of 15 placebo-controlled trials of calcium (administered for bone health in all cases but one) for a small but significant increase in the risk for myocardial infarction in pooled results of five trials that contributed patient-level data; however serious concerns have been raised about methodological issues that may have led to bias.
- **Atrial Fibrillation.** Evidence is insufficient regarding the risk for this event. The original report identified one study that showed a significant increase in the risk of atrial fibrillation for zoledronic acid relative to placebo but another that did not; the current report identified one additional trial that when pooled with the two earlier trials of zoledronic acid, showed a significant increase in the risk for atrial fibrillation. A large Bayesian meta-analysis among users of bisphosphonates that did not reach statistical significance and several additional meta-analyses showed mixed results. In March 2010, the FDA issued a followup to its 2007 safety review, noting the inconsistency in the data and requesting that providers and patients report such side effects. Thus, a relationship between zoledronic acid and atrial fibrillation is unproven but still an area of active surveillance.
- **Pulmonary Embolism (PE).** The original report identified two large studies that showed higher odds for PE among raloxifene participants than among placebo participants. The current report identified two additional studies that when pooled with the original two, showed even higher risk for PE. Evidence is high for an increased risk for this event.
- **Venous Thromboembolic Events.** The original report identified four studies that showed higher risk of thromboembolic events for raloxifene-treated participants than for placebo participants. For the current report, four additional studies were identified that narrowed the confidence interval. Evidence is high for an increased risk for this event.
- **Vasomotor Flushing (hot Flashes).** A pooled analysis of eight studies, three from the original report and five identified for the current report that compared raloxifene and placebo found a significant increase in vasomotor flushing among raloxifene users. Evidence is high for an increased risk for this event.

- **Esophageal Cancer.** Four large observational studies identified for this report examined the risk of esophageal cancer among users of bisphosphonates. A prospective cohort study using a UK database found no increase in the risk for esophageal cancer but two nested case control studies on the same dataset did identify an increased risk. A nested case control study of patients with Barrett's Esophagus who developed esophageal cancer also found no association with use of bisphosphonates. Evidence is insufficient regarding the risk for this event.
- **Mild Upper Gastrointestinal (GI) Events.** We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as "mild upper GI events." Pooled analysis of 50 studies of alendronate showed greater odds of all mild upper gastrointestinal (GI) events for alendronate than for placebo. In a head-to-head comparison of alendronate with denosumab, alendronate was also more strongly associated with mild upper GI events than was denosumab. Evidence is high regarding the risk for alendronate and mild upper GI events.
- **Osteonecrosis of the Jaw.** The original report identified case series and case reports describing 41 cases of osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates. One trial, two large observational studies, a post hoc analysis, and a systematic review that reported on the incidence of osteonecrosis of the jaw among individuals taking bisphosphonates to prevent or treat osteoporosis were identified for the current report. Cohort and case control studies range in their estimates of the incidence of osteonecrosis of the jaw associated with the use of bisphosphonates to prevent or treat osteoporosis from fewer than one case to 28 cases per 100,000 person-years of treatment. Thus evidence is high that the prevention and treatment of osteoporosis remains a relatively minor contributor to the development of osteonecrosis of the jaw.
- **Atypical Fractures of the Femur.** Seven observational studies, a pooled analysis of three trials, and a comprehensive review identified a small increase in the risk for atypical, low-trauma subtrochanteric fragility fractures of the femur with long-term use of bisphosphonates for prevention or treatment of osteoporosis. Based on this American Society of Bone and Mineral Research review, on 13 October 2010, the Food and Drug Administration, which has been conducting its own ongoing review of atypical subtrochanteric femur fracture, updated the risk of atypical fractures to the Warnings and Precautions level, acknowledging that the risk remains low compared with the numbers of osteoporotic fractures prevented by the drugs. Evidence is low for this conclusion.
- **Rashes, Injection Site Reactions, and Infection.** Pooled analysis of four trials of denosumab found an increased rate of rash but no increase in the rate of injection site reactions for the biological agent denosumab, compared with placebo. Based on evidence for an increased risk of infection, the FDA has issued a Risk Evaluation and Mitigation Strategy for the drug. A systematic review of four trials confirms the increased risk for infection. Evidence is high for these conclusions.

For these analyses, we pooled the results of the controlled trials found through our primary electronic searches for the present report with the results of the trials identified for the original report. We focus on the adverse events that were identified as most important by our Technical Expert Panel (TEP) and other subject matter experts: cardiovascular, malignancy, upper gastrointestinal, osteonecrosis, and low-stress subtrochanteric/femur fractures. To evaluate the prevalence of adverse events selected for special attention, we also performed broader literature searches focused on those adverse events. For particularly rare adverse events, where aggregated

data from large clinical trials might not provide a sufficient sample size to observe any cases, we searched for relevant reports with other study designs, including cohorts, case control studies, and even case series and case reports.

Below, we present the results by drug class and category of events. For each category, we also provide a summary of the findings of the original report. All results are expressed as odds ratios. Because many adverse events are quite rare, we also calculated the risk differences (the percentages that reported the adverse event) for each type of event; the text and tables report only the significant risk differences (RDs). Table C-5 (Appendix C) displays all the adverse events identified for the present report. This table includes information on cancer, cardiac, dermatologic, ear/nose/throat, gastrointestinal (serious, mild), genitourinary, gynecologic, hematologic, hypertension, immunologic, metabolic, musculoskeletal, neurologic, peripheral vascular disease, psychiatric, pulmonary, renal, special senses, sweats/fever/hot flashes, and death not otherwise specified.

Bisphosphonates

Table 52 shows the risks of adverse events for bisphosphonates compared with placebo. Forest plots were constructed for comparisons comprising ten or more studies.

Cardiovascular Events

We classified the following adverse event descriptions as serious cardiac events: acute coronary syndrome (including myocardial infarction), atrial fibrillation, cardiac death, ventricular arrhythmia, and death due to arrhythmia.

Acute Coronary Syndrome

Neither the original report nor the updated pooled analyses showed any differences between any of the bisphosphonates and placebo regarding the incidence of acute coronary syndrome. Pooled odds ratios (OR) were 3.59 (95% CI: 0.35, 180.00), 1.06 (95% CI: 0.41, 2.96), 0.4 (0.06, 2.39), and 0.82 (95% CI: 0.55, 1.21) for alendronate,[59,347,348] ibandronate,[104,349] risedronate,[74,350,351] and zoledronic acid[111,113] vs. placebo.

Atrial Fibrillation

The original report identified two large trials that showed a trend toward an increased incidence of atrial fibrillation (AF) with alendronate and a significantly increased incidence with once-yearly zoledronic acid relative to placebo, respectively.[111,352] The current report identified several new original studies and systematic reviews. A meta-analysis of all RCTs of at least 3 months duration on the use of alendronate to treat or prevent osteoporosis by the Merck Corporation (32 trials, more than 17,000 participants) found no effect of alendronate on the incidence of atrial fibrillation.[353] A pooled analysis of the results of the pivotal trials of ibandronate showed no effect on the incidence of AF.[354] One new study of zoledronic acid was pooled with the original study to show an increase in the incidence of AF with zoledronic acid (pooled OR 1.45, 95% CI: 1.14, 1.86).[113]

Five systematic reviews were identified that combined studies of different bisphosphonates. Two 2009 systematic reviews that conducted meta-analyses of the same four trials and two observational studies reported a significant association between bisphosphonate exposure and the risk for serious atrial fibrillation.[355,356] A 2009 Bayesian meta-analysis that included four original reports of RCTs (including the two large trials described above), two post hoc analyses of combined data from multiple RCTs, and three observational studies found a nonsignificantly

increased risk of AF among bisphosphonate users (pooled OR for overall risk of AF from RCTs 1.18, 95% CI: 0.84, 1.66; pooled OR for serious AF from RCTs 1.59, 95% CI: 0.61, 3.75; pooled OR for observational studies 1.25, 95% CI: 0.98, 1.73).[357] A 2010 systematic review of seven observational studies found no evidence for an association between bisphosphonate use and increased risk for atrial fibrillation; however, the I-squared statistic suggested moderate heterogeneity.[358] A 2010 systematic review of 16 RCTs, observational studies, and prior systematic reviews that included some of the same studies as the systematic reviews identified for the original report found some evidence of an association of bisphosphonate use with increased risk for AF.[359] Consistent with this evidence, in March 2010, the FDA issued a followup to its 2007 safety review, noting the inconsistency in the data and requesting that providers and patients report side effects.[360]

Cerebrovascular Accidents (CVA) and Death

We found no trials of alendronate that reported CVAs. In two older trials of ibandronate (OR 0.32, 95% CI: 0, 27.3),[104,108] and one older trial[111] and one new trial of zoledronic acid[113] (OR 1.13, 95% CI: 0.9, 1.42) that reported CVE, there were no significant differences between the drugs and placebo. Two studies of zoledronic acid vs. placebo that assessed the incidence of cerebrovascular death found a nonsignificant increase in the treated group (OR 1.5, 95% CI: 0.87, 2.64).[111,113]

Pulmonary Embolism (PE)

We found no trials of alendronate, ibandronate, or zoledronic acid that reported PE. In two trials of risedronate vs. placebo, one old[89] and one new,[74] differences between drug and placebo were not significant (OR 0.74, 95% CI: 0.08, 8.89).

Thromboembolic Events

We found no trials of ibandronate, risedronate, or zoledronic acid that reported thromboembolic events. In one trial of alendronate, there was no significant difference between drug and placebo (OR Inf+, 95% CI: 0.03, Inf+, where Inf+ signifies positive infinity. An upper limit of Inf+ results when 0 events occur in the second treatment group. A true OR cannot be estimated because the denominator is 0; thus, the estimate is infinity.).[59]

Cardiovascular Death

The original report found no differences between alendronate (in two trials),[347,348] ibandronate (in two trials),[104,349] or risedronate (in one trial),[351] and placebo in cardiac death; no studies were found for that report on zoledronic acid that reported cardiovascular deaths. For the present report, one new study on zoledronic acid,[113] and one new study on risedronate[74] found no differences (pooled OR for risedronate Inf+, 95% CI: 0.13, Inf+); and zoledronic acid (OR 0.61 95% CI: 0.26, 1.37).

Cancer

Breast Cancer

The original report identified one study of ibandronate that found no significant differences with placebo on the risk for breast cancer (OR Inf+, 95% CI: 0.01, Inf+);[104] breast cancer was not reported in trials of the other bisphosphonates. The current report identified one study on alendronate that found no significant differences (OR Inf+, 95% CI: 0.09, Inf+).[361]

Colon Cancer

No trials of the bisphosphonates reported on colon cancer in either report. A large case control study of bisphosphonate use and gastrointestinal cancers in the UK found no differences in the risk for colorectal cancer between users of bisphosphonates and matched controls (RR 0.87, (95% CI: 0.77, 1.00).[362]

Esophageal Cancer

No trials examined the incidence of esophageal cancer in the original report. Four large observational studies examined the incidence of esophageal cancer among bisphosphonate users. A cohort study (Newcastle-Ottawa [N-O] 8/9) that extracted data from the UK General Practice Research Database on 41,826 users and a matched set of controls (81 percent women, mean age 70, mean followup time 4.5 years) found no difference in the risk for esophageal cancer between cohorts (adjusted HR 1.07, 95% CI: 0.77, 1.49).[363] A case-control study (N-O 9/9) that used the same database and matched 2,954 cases with 14,721 controls (36 percent women, mean followup time 7.7 years) found that individuals with at least one prescription for oral bisphosphonates had a significantly increased risk for esophageal cancer (adjusted RR 1.30, 95% CI: 1.02, 1.66, p=0.02).[362] Pooling two additional large observational studies found a significantly increased risk for esophageal cancer in the bisphosphonate-treated group (pooled OR 1.23, 95% CI: 1.01, 1.49).[362,363] A third (case-control) study (N-O 5/9: reported in a letter) that used the same database to conduct a case-control analysis on individuals diagnosed with esophageal cancer found an increased likelihood of bisphosphonate use among cases (OR 1.24, 95% CI: 1.08, 1.44 for men and women together; OR 1.40, 95% CI: 1.18, 1.67 for women alone).[364] A fourth (case-control) study (N-O 9/9) examined the association between bisphosphonate use and development of esophageal cancer in a nested case control study of patients with Barrett's Esophagus. Among 116 cases (out of a cohort of over 11,000 patients) and 696 matched controls, no increased risk for esophageal cancer was observed among those who used bisphosphonates.[365]

Gastrointestinal Cancer

The original report identified one study each on ibandronate[366] and risedronate[367] that found no significant differences in the risk for [in the risk for gastrointestinal cancers (not otherwise specified).

Lung Cancer

No trials of the bisphosphonates reported on lung cancer in the original report. The current report identified one trial on risedronate that found no differences (OR 0.49, 95% CI: 0.01, 38.4).[74]

Gastrointestinal (Serious)

We classified the following adverse events as serious gastrointestinal adverse events: upper gastrointestinal perforations, ulcerations and bleeds (PUBs); deaths due to PUBs; upper gastrointestinal (other); esophageal (serious); and hepatobiliary (serious). No differences were seen for total serious GI adverse events among any of the bisphosphonates (Figures 3 and 4). Perforations, ulcerations, and bleeds (PUB) were reported (for both active treatment and placebo groups) in trials of all the bisphosphonates except zoledronic acid. The only significant difference was seen in two pooled trials of oral daily ibandronate in the original report, in which participants in the treatment group had lower odds of esophageal ulcerations than did placebo participants (OR 0.33, 95% CI: 0.14, 0.74); [107,366] 10 trials of alendronate [368,369] [361,370-376] (Figure

5) and seven trials of risedronate showed similar trends.[60,90-92,97,377,378] One head-to-head comparison of alendronate with risedronate reported one death due to PUB in the alendronate group (compared with none in the risedronate group (OR 0, 95% CI: 0, 40).[60]

No significant differences were seen among any of the comparisons of other serious upper gastrointestinal events (alendronate vs. placebo OR 1.06, 95% CI: 0.74, 1.51;[375,376,379-381] risedronate vs. placebo OR 1.03, 95% CI: 0.78, 1.36).[88,89,91,351]

Nonsignificant increases in the risk for serious esophageal adverse events were seen in five studies comparing alendronate with placebo (OR 1.39, 0.75, 2.65)[44,371,375,382,383] and one study comparing ibandronate with placebo (OR1.5, 95% CI: 0.12, 78.7),[107] but not in four studies of risedronate vs. placebo (OR 0.74, 95% CI: 0.38, 1.46).[90,92,94,97]

No hepatobiliary adverse events were reported for bisphosphonates.

To estimate the possible role of dosing frequency and route of administration in the development of serious GI events among bisphosphonate users, we conducted further pooled analyses. Because few such comparisons were conducted within studies, we compared the pooled OR for studies with daily oral administration to those with weekly oral administration; injections or infusions every three, six, or 12 months; and cyclic dosing schedules. Too few studies reported serious GI side effects to see any differences according to dosing schedule (Table 51).

Figure 3. Total serious gastrointestinal adverse events in trials of alendronate versus placebo

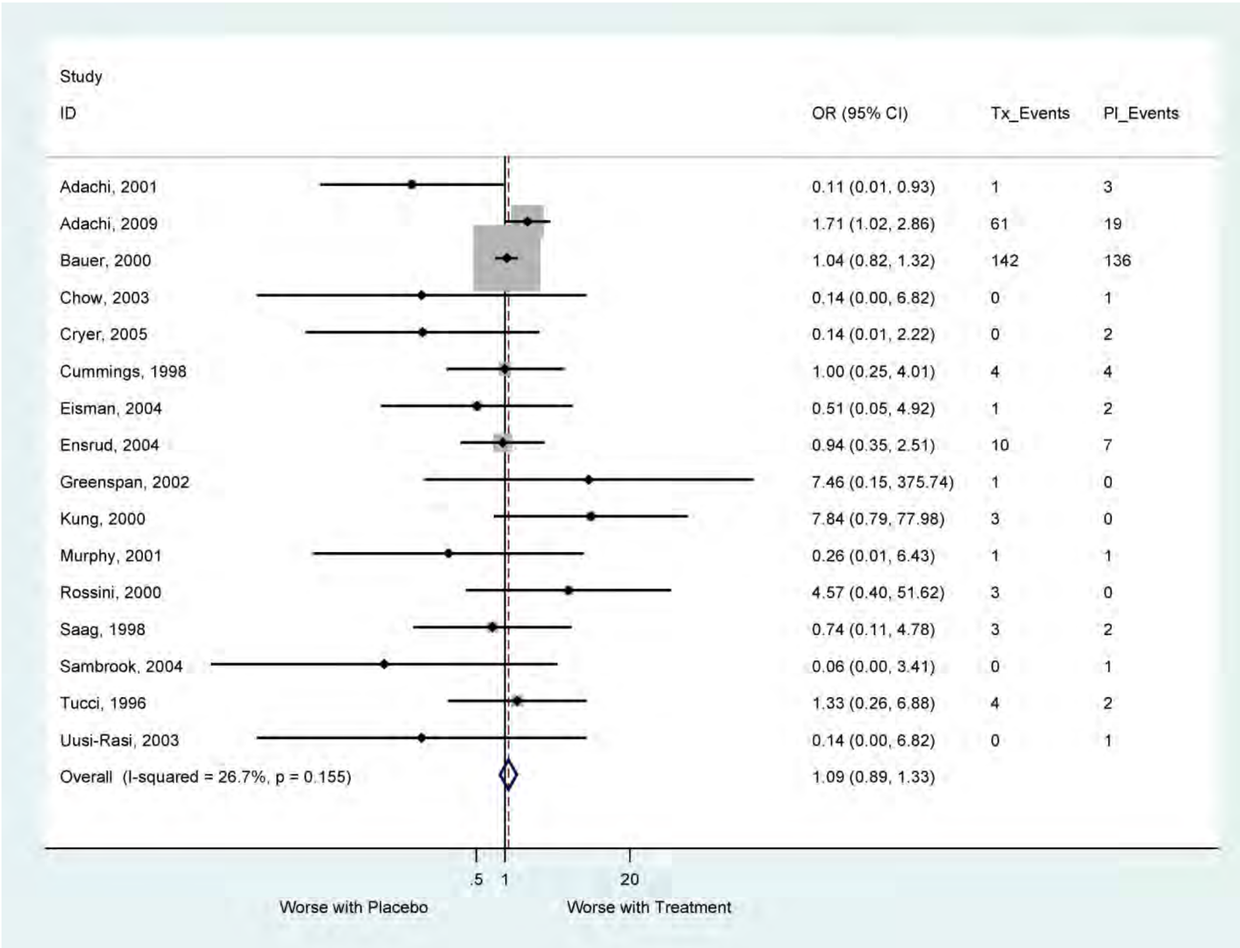


Figure 4. Total serious gastrointestinal adverse events in trials of risedronate versus placebo

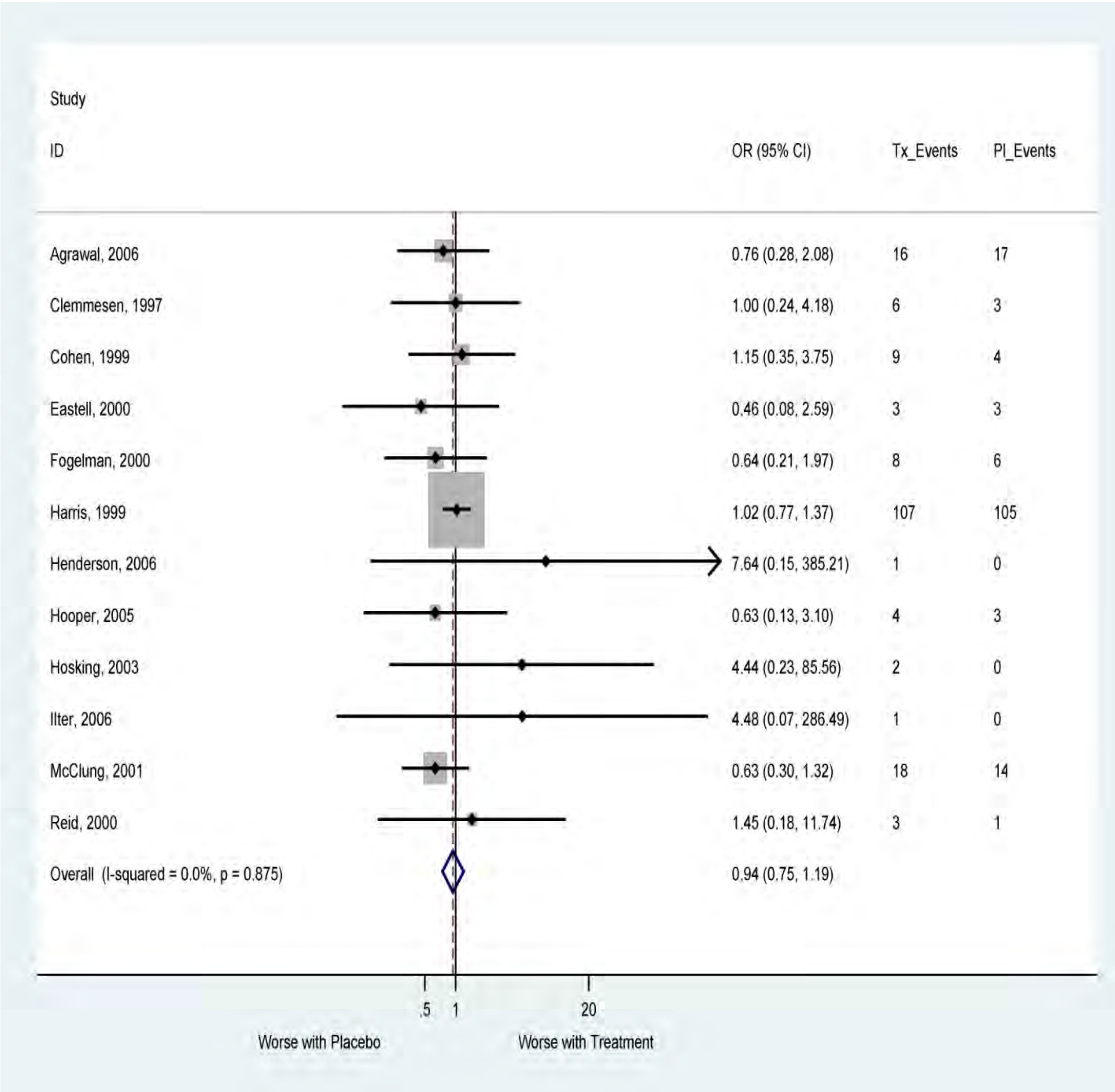


Figure 5. Upper gastrointestinal perforations, ulcers, or bleeds in trials of alendronate versus placebo

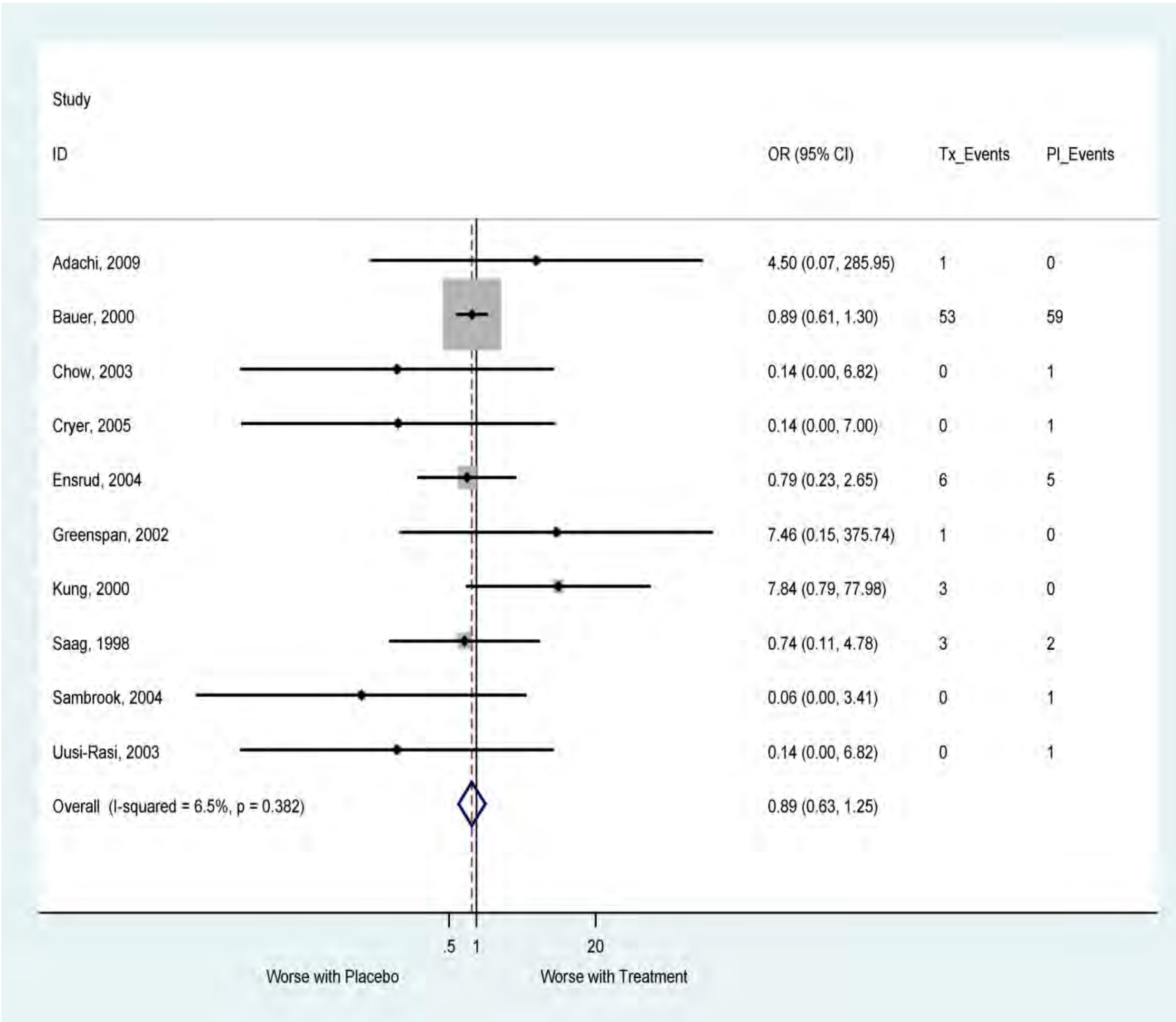


Table 51. Gastrointestinal adverse events by dosing schedule and route of administration

Drug and Dosing Comparison	Number of Included Studies	Drug 1 Number of events	Drug 1 Sample Size	Drug 2 Number of Events	Drug 2 Sample Size	Odds Ratio (95% Confidence Interval)[a]
Mild Adverse Events						
Alendronate daily oral vs. placebo	42	3,799	10,062	3,249	8,323	1.03 (0.96, 1.1)
Alendronate weekly oral vs. placebo	7	225	1,179	159	1,077	1.56 (1.24, 1.98)*
Alendronate weekly oral vs. denosumab every 3 or 6 months injection	1	26	46	97	314	2.9 (1.48, 5.77)*
Alendronate weekly oral vs. denosumab every 6 months injection	1	168	586	164	593	1.05 (0.81, 1.37)
Alendronate daily oral vs. raloxifene daily oral	3	77	832	40	822	1.99 (1.32, 3.04)*
Alendronate weekly oral vs. raloxifene daily oral	3	79	513	83	520	0.95 (0.67, 1.35)
Alendronate daily oral vs. estrogen	4	78	255	68	306	1.57 (1, 2.46)
Alendronate weekly oral vs. risedronate daily oral	1	5	219	4	222	1.27 (0.27, 6.5)
Alendronate weekly oral vs. risedronate weekly oral	2	159	1,040	154	1,066	1.07 (0.83, 1.37)
Alendronate weekly oral vs. zoledronic acid 1, 5mg injection	1	2	112	6	113	0.33 (0.03, 1.87)
Alendronate weekly oral vs. zoledronic acid, 1 dose injection	1	24	59	29	69	0.95 (0.44, 2.03)
Alendronate daily oral vs. calcium	1	157	281	82	138	0.86 (0.56, 1.33)
Alendronate daily oral vs. vitamin D	8	143	612	120	557	1.2 (0.88, 1.62)
Risedronate weekly vs. teriparatide 25 microgram daily injection	1	2	22	2	22	1 (0.07, 15.1)
Risedronate daily oral vs. placebo	16	2001	9,239	1231	5,349	1.04 (0.95, 1.13)
Risedronate daily or weekly oral vs. placebo	1	22	82	9	41	1.3 (0.5, 3.6)
Risedronate weekly oral vs. placebo	2	25	76	21	74	1.44 (0.44, 4.89)
Risedronate 35mg weekly oral vs. placebo	1	22	191	9	93	1.21 (0.51, 3.13)
Raloxifene daily oral vs. placebo	7	279	7,097	126	3,714	1.01 (0.81, 1.27)
Raloxifene 1 dose oral vs. placebo	1	1	102	6	102	0.16 (0, 1.35)
Raloxifene daily oral vs. estrogen	2	16	671	16	804	1.13 (0.52, 2.45)
Raloxifene daily oral vs. vitamin D	1	1	45	0	44	Inf+(0.03, Inf+)
Ibandronate daily oral vs. placebo	2	247	641	68	192	1.07 (0.75, 1.53)
Ibandronate daily or every two days oral vs. placebo	2	637	2,113	307	1,056	1.05 (0.89, 1.24)
Ibandronate weekly oral vs. placebo	1	23	472	5	158	1.57 (0.57, 5.37)
Ibandronate monthly oral vs. placebo	1	44	108	12	36	1.37 (0.59, 3.35)
Ibandronate every 3 months injection vs. placebo	3	844	2,404	412	1,104	0.96 (0.83, 1.12)
Ibandronate once-a-month 150 mg oral vs. placebo	1	9	87	2	48	2.64 (0.51, 26.1)

Table 51. Gastrointestinal adverse events by dosing schedule and route of administration (continued)

Drug and Dosing Comparison	Number of Included Studies	Drug 1 Number of Events	Drug 1 Sample Size	Drug 2 Number of Events	Drug 2 Sample Size	Odds Ratio (95% Confidence Interval)[a]
Ibandronate every 3 months injection vs.	2	31	110	35	109	0.83 (0.44, 1.54)
Zoledronic acid every 3 or 6 months injection vs. placebo	1	26	292	3	59	1.82 (0.53, 9.73)
Zoledronic acid every 3 months injection vs. placebo	1	9	55	8	51	1.05 (0.33, 3.44)
Zoledronic acid 1 dose or every 12 months injection vs. placebo	1	21	181	16	202	1.52 (0.73, 3.24)
Denosumab every 3 or 6 months injection vs. placebo	1	97	314	9	46	1.83 (0.83, 4.5)
Denosumab every 6 months injection vs. placebo	2	104	4,052	61	4,042	1.73 (1.24, 2.42)*
Teriparatide daily 20 or 40 microgram injection vs. placebo	1	99	1,093	44	544	1.13 (0.77, 1.68)
Teriparatide daily injection vs. placebo	1	34	290	5	147	3.76 (1.42, 12.6)*
Serious Adverse Events						
Alendronate daily vs. placebo	15	229	7,217	177	6,803	1.13 (0.92, 1.4)
Alendronate daily vs. weekly	0					
Alendronate weekly vs. placebo	4	2	892	4	788	0.5 (0.05, 3.52)
Alendronate weekly vs. cyclic daily (1 month on, 2 months off) vs. placebo	1	3	42	0	41	Inf+ (0.42, Inf+)[†]
Alendronate weekly vs. cyclic daily (1 month on, 2 months off) vs. vitamin D	1	1	35	0	34	Inf+ (0.02, Inf+)[†]
Risedronate daily vs. placebo	9	152	4,880	133	4,575	1.13 (0.87, 1.45)
Risedronate daily vs. weekly vs. placebo	1	1	41	0	41	Inf+ (0.03, Inf+)[†]
Risedronate weekly vs. placebo	1	16	31	17	29	0.76 (0.24, 2.35)
Risedronate daily vs. cyclic (2 weeks on, 10 weeks off) vs. placebo	2	9	128	6	84	1 (0.3, 3.61)
Ibandronate daily vs. placebo	2	15	1,141	18	1,137	0.83 (0.39, 1.75)
Ibandronate every 3 months injected vs. placebo	1	79	956	42	950	1.95 (1.31, 2.94)*
Alendronate weekly vs. risedronate daily	1	0	219	2	222	0 (0, 5.39)
Alendronate weekly vs. risedronate weekly	1	1	520	1	533	1.03 (0.01, 80.6)
Alendronate daily vs. raloxifene	1	104	716	77	707	1.39 (1, 1.93)
Alendronate weekly vs. denosumab every 6 months	1	0	586	4	593	0 (0, 1.53)

*Significant difference.

†Inf+ signifies positive infinity. An upper limit of Inf+ results when 0 events occur in the second treatment group. A true OR cannot be estimated because the denominator is 0; thus, the estimate is infinity.

Gastrointestinal (Mild)

We categorized gastrointestinal conditions such as reflux and esophageal irritation, nausea, vomiting, heartburn, diarrhea, and constipation as “Mild.” Pooled analyses of 50 studies of alendronate and ten studies of ibandronate showed no differences in overall mild gastrointestinal symptoms (Figures 6 and 7, respectively); pooled analysis of 21 studies of risedronate showed an increase in mild gastrointestinal adverse events compared with placebo (Figure 8).

Pooled analysis of 49 studies of alendronate showed greater odds of all mild upper gastrointestinal (GI) events (Figure 9) than did placebo (OR 1.08, 95% CI: 1.01, 1.15).[38,39,44,46,50,51,58-61,63,64,347,348,361,369-376,379,380,382,383,385-406] There were no differences between ibandronate, risedronate (Figure 10), or zoledronic acid and placebo regarding any mild upper GI events. Pooled analysis of 25 studies of alendronate showed no differences in reflux esophagitis between alendronate and placebo-treated groups (Figure 11); pooled analysis of 13 studies showed no differences in reflux esophagitis between risedronate and placebo (Figure 12). Pooled analysis of 24 studies showed a nonsignificant increase in other upper GI adverse events for alendronate over placebo (Figure 13), and pooled analysis of 13 studies showed no effect for risedronate (Figure 14).

Head-to-head comparisons of a bisphosphonate with another agent showed one significant difference in mild GI events. Pooled analysis of six studies showed an increased risk of mild GI events for alendronate compared with raloxifene (RD 0.025 95% CI: 0.002, 0.047).[233,385,406-409]

To estimate the possible role of dosing frequency and route of administration in the development of mild GI events among bisphosphonate users, we conducted further pooled analyses. Because few such comparisons were conducted within studies, we compared the pooled OR for studies with daily oral administration to those with weekly oral administration; and injections or infusions every three, six, or 12 months; and cyclic dosing schedules. In an indirect comparison, weekly alendronate was more strongly associated with mild GI adverse events than was daily alendronate, when compared with placebo (Table 51).

Figure 6. Total mild gastrointestinal adverse events in trials of alendronate versus placebo

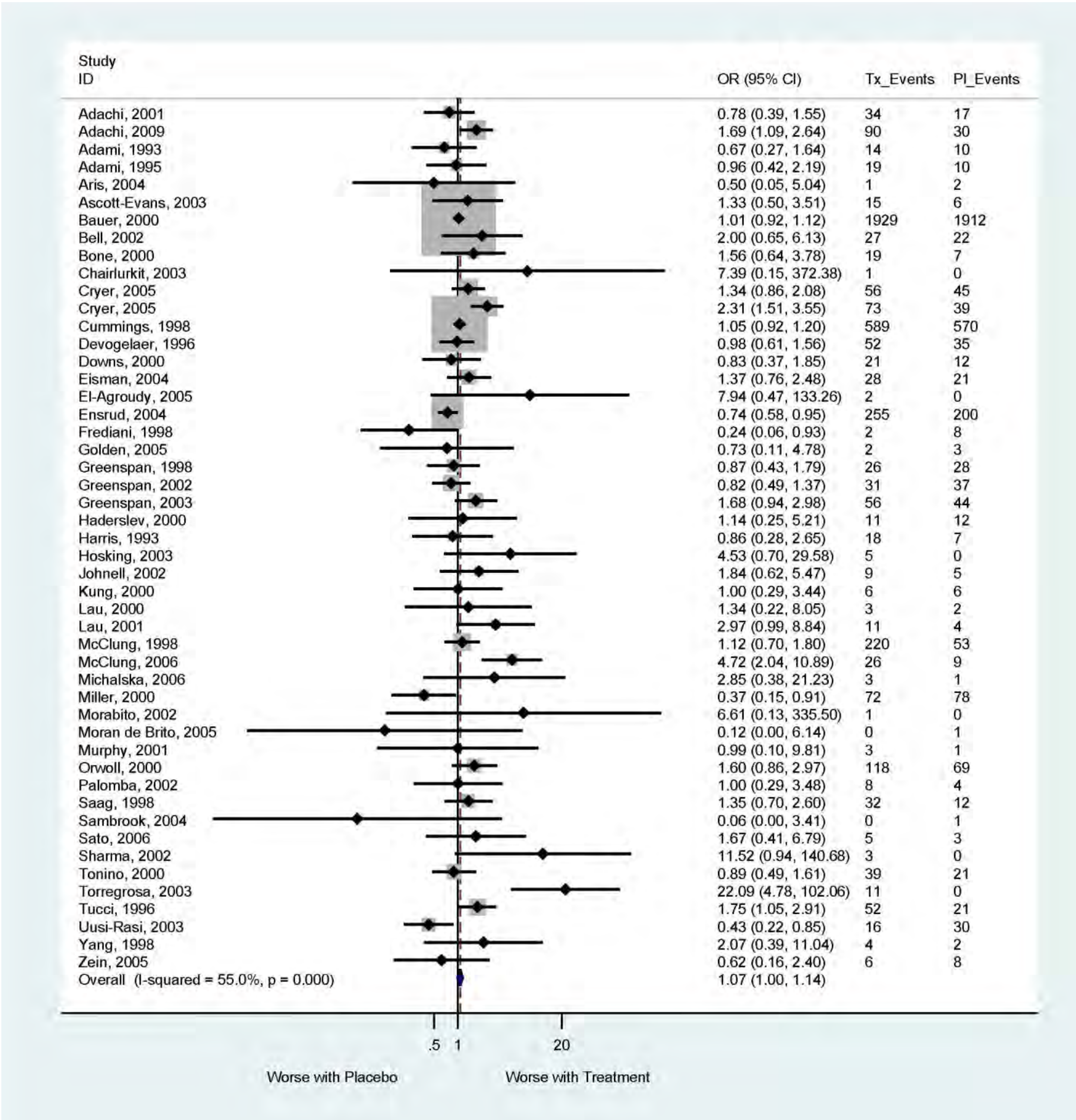


Figure 7. Total mild gastrointestinal adverse events in trials of ibandronate versus placebo

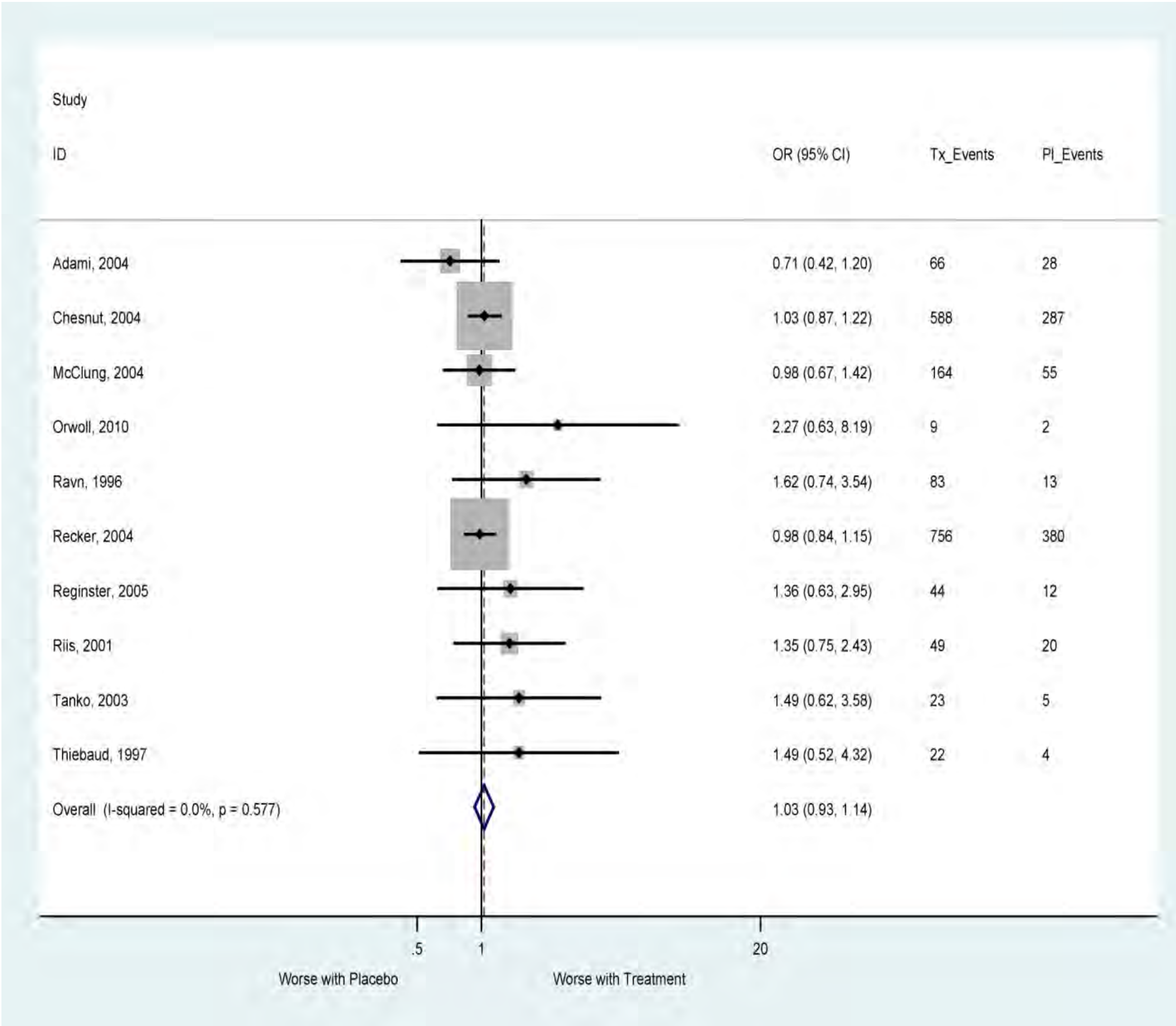


Figure 8. Total mild gastrointestinal adverse events in trials of risedronate versus placebo

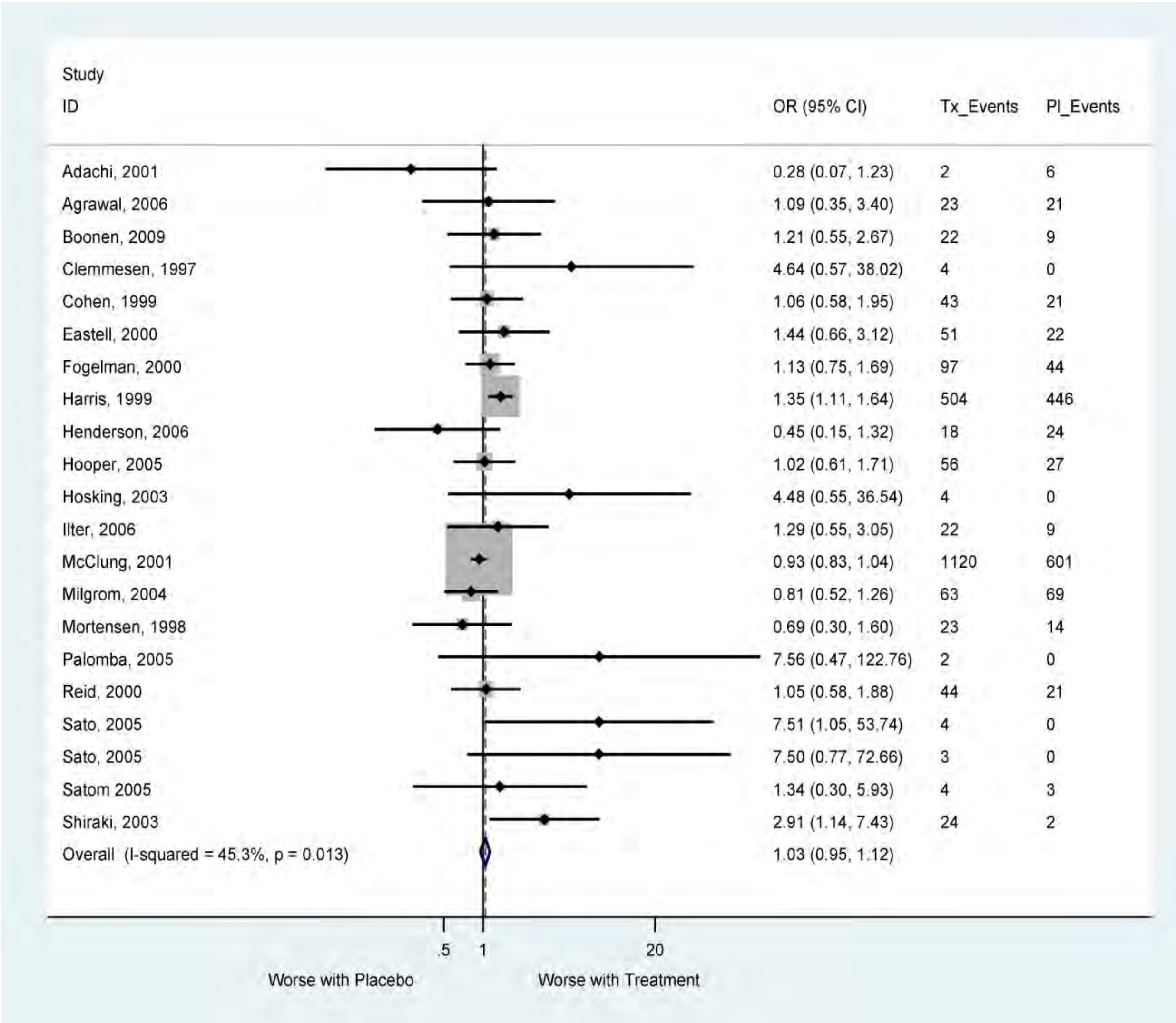


Figure 9. Mild upper gastrointestinal adverse events in trials of alendronate versus placebo

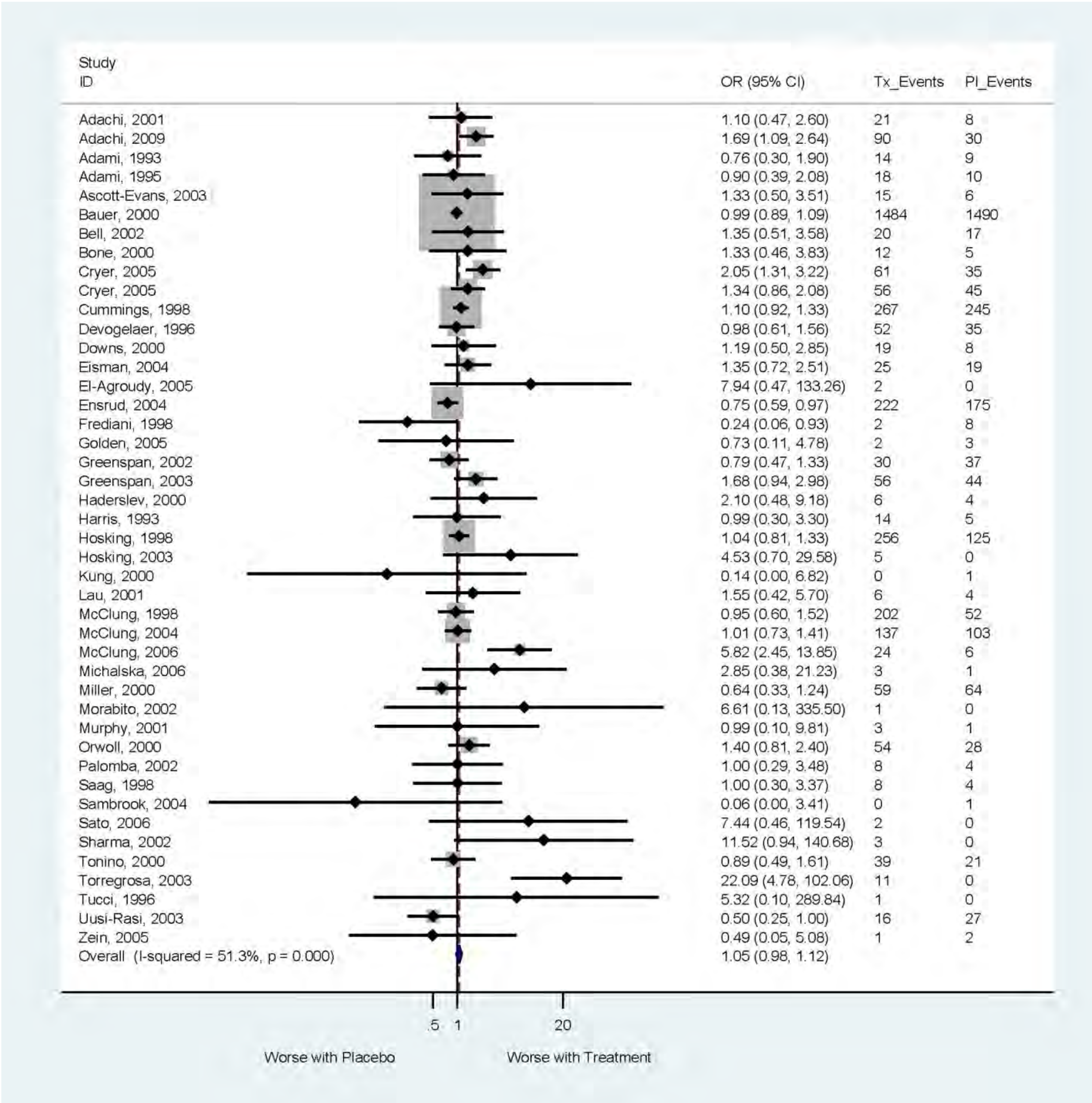


Figure 10. Mild upper gastrointestinal adverse events in trials of risedronate versus placebo

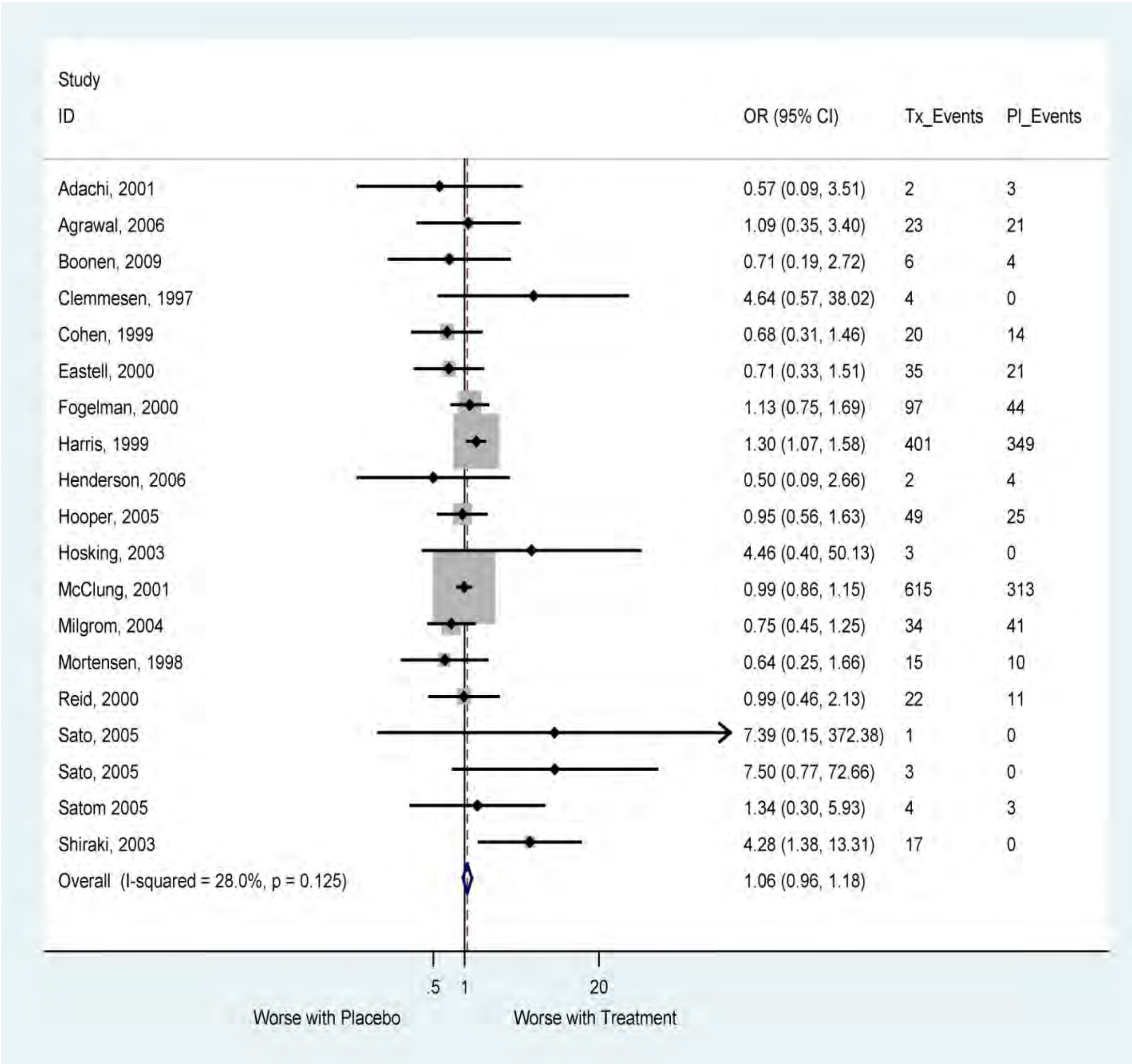


Figure 11. Reflux and esophageal adverse events in trials of alendronate versus placebo

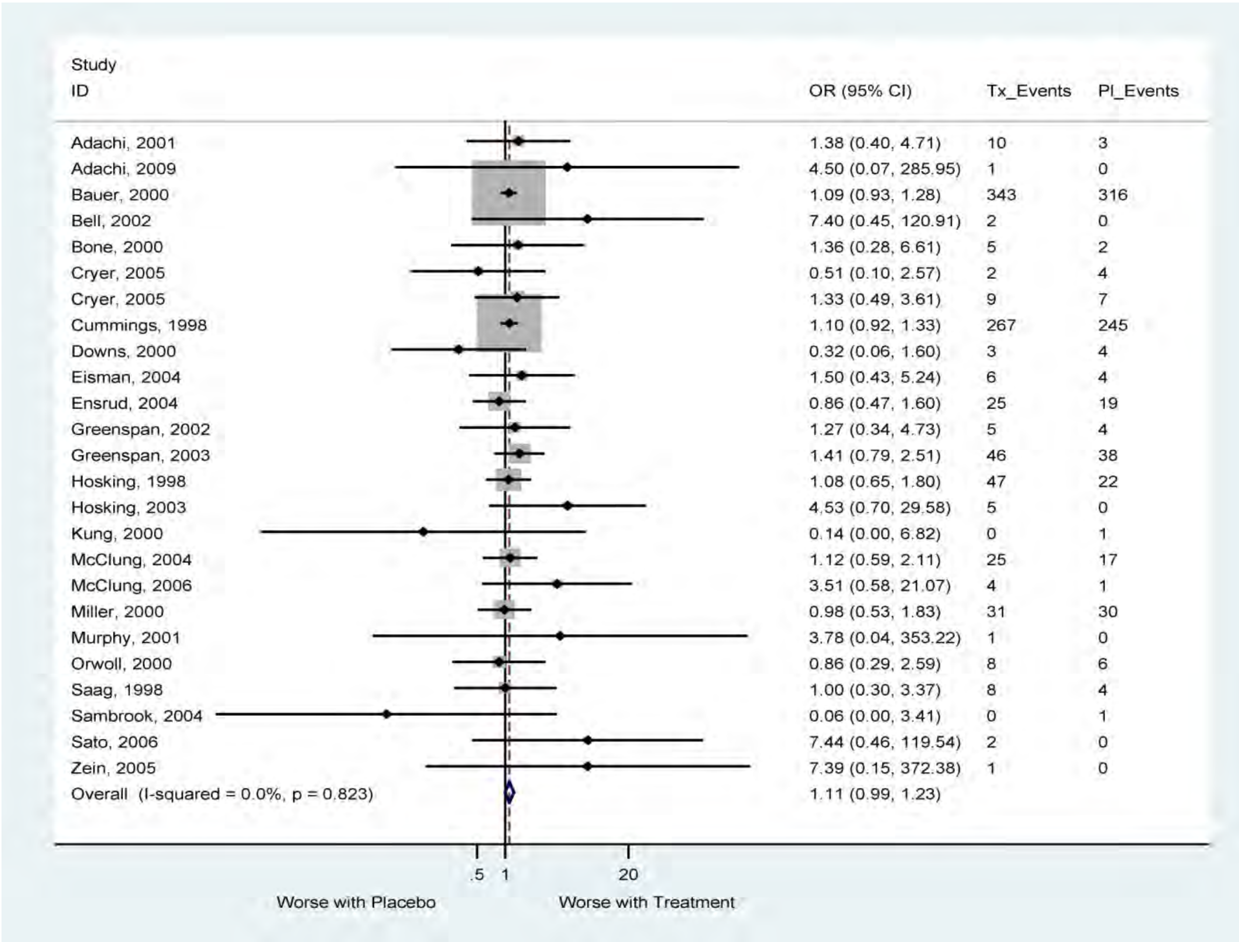


Figure 12. Reflux and esophageal adverse events in trials of risedronate versus placebo

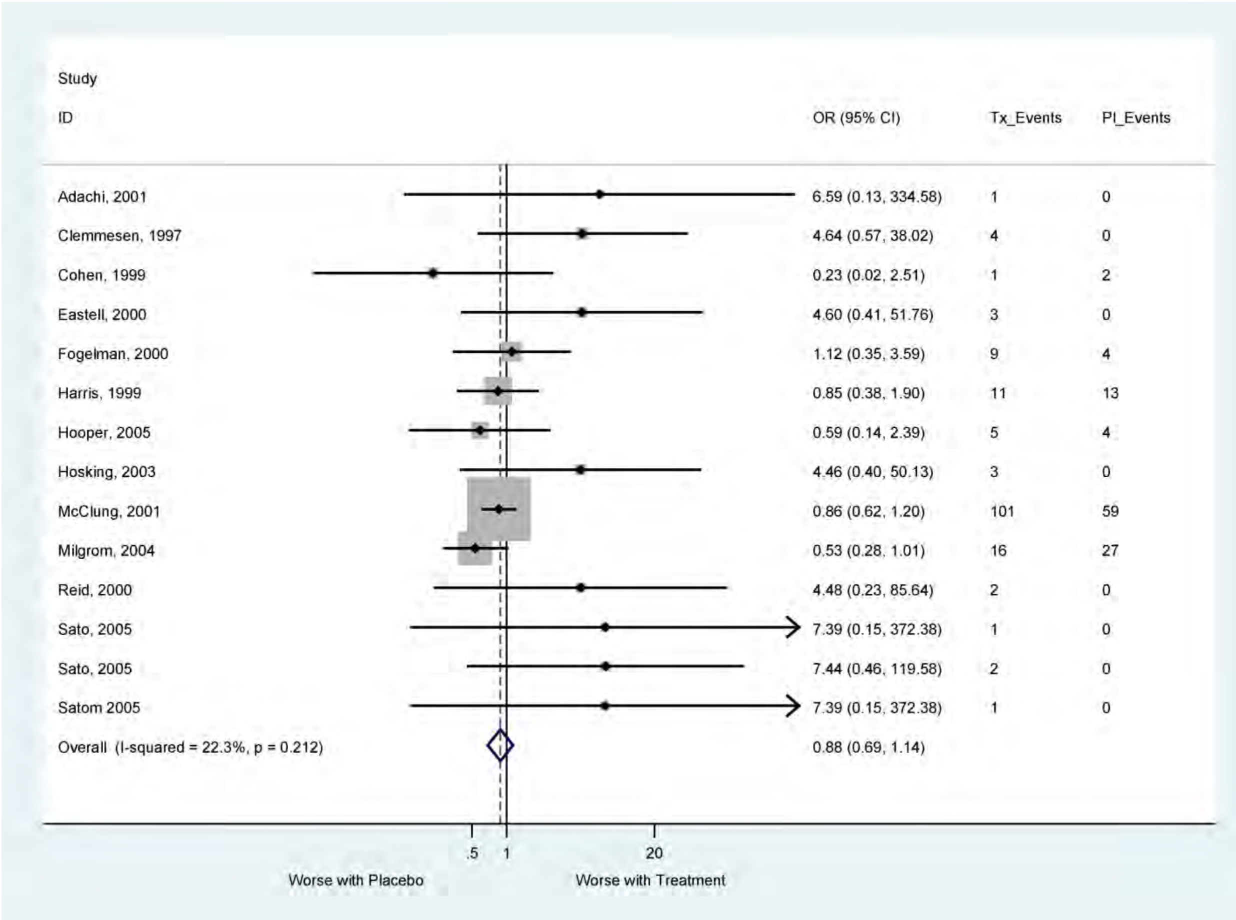


Figure 13. Mild upper gastrointestinal adverse events other than reflux and esophageal adverse events in trials of alendronate versus placebo

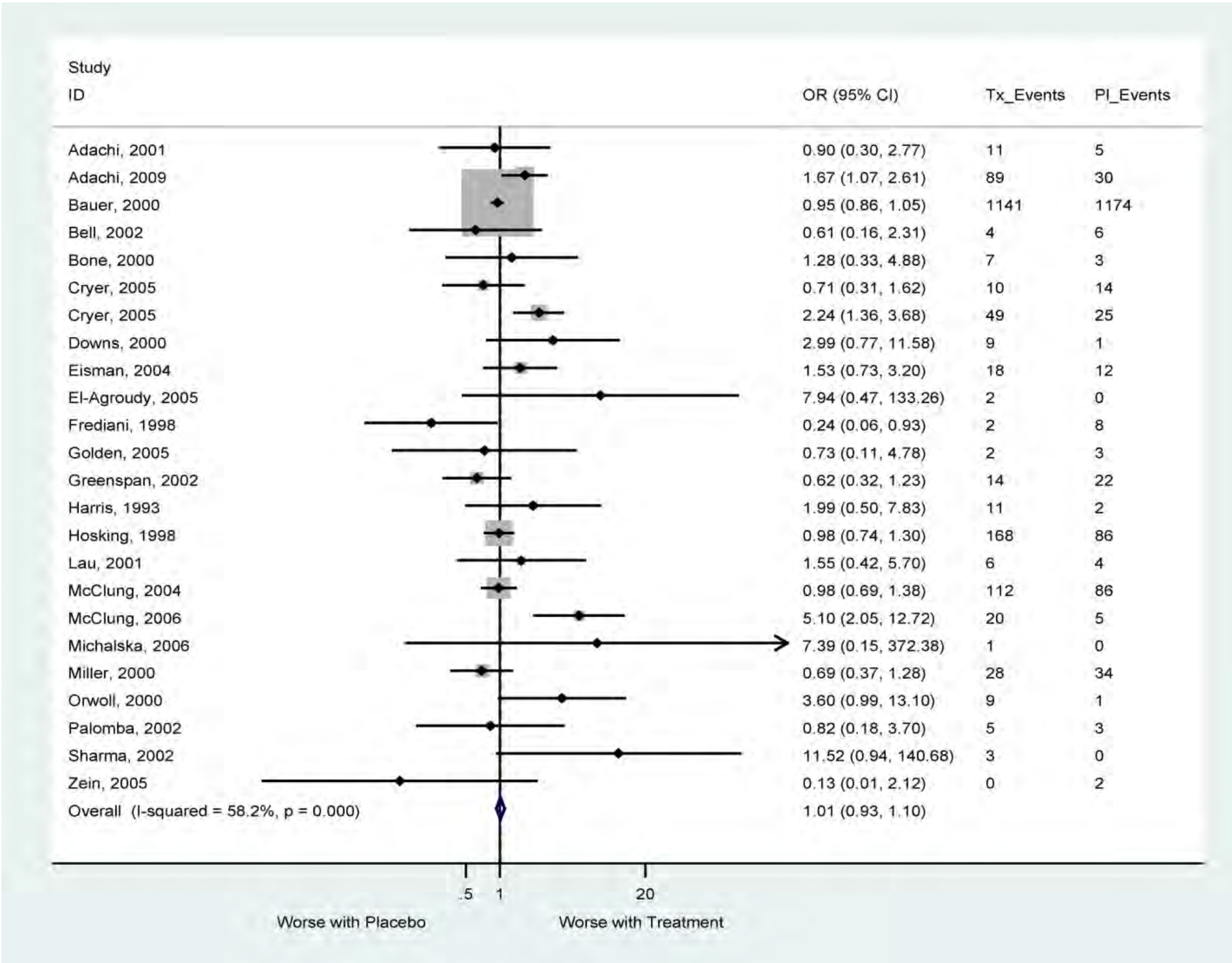
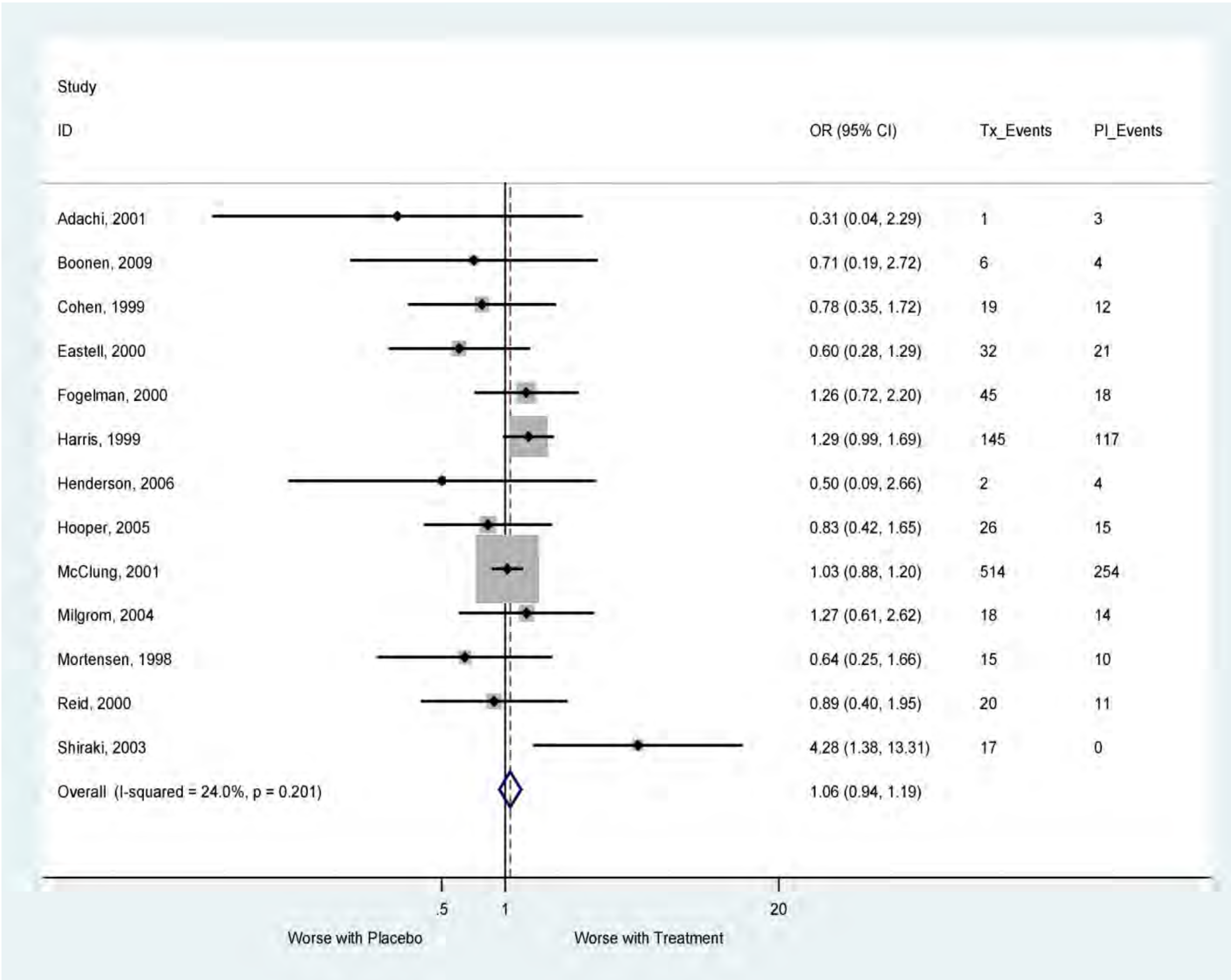


Figure 14. Mild upper gastrointestinal adverse events other than reflux and esophageal adverse events in trials of risedronate versus placebo



Musculoskeletal

This category includes arthritis and arthralgias; myalgias, cramps, and limb pain; atypical fractures; and osteonecrosis.

Pooled analysis of 17 trials showed no effect of alendronate on total musculoskeletal events (Figure 15). In three pooled trials identified for the original report,[111,112,417] zoledronic acid participants had higher odds of these events than did placebo participants (OR 4.52, 95% CI: 3.78, 5.43). Three trials were identified for the current report,[113,114,418] and the difference was smaller but still significant (OR3.36, 95% CI: 2.96, 3.82).

In two head-to-head trials identified for the original report,[238,419] alendronate participants had greater odds of these events than did participants taking teriparatide (OR 3.84, 95% CI: 2.22, 6.80).

Arthritis and Arthralgias

Pooled analysis of two trials comparing alendronate with placebo showed a decreased risk for arthritis and arthralgias in the treated group (OR 0.27, 95% CI: 0.09, 0.70; RD -0.111, 95%

CI: -0.223, 0.001)),[61,63] but an increased risk among individuals taking zoledronic acid in four pooled trials (OR 2.67, 95% CI: 2.14, 3.35; RD 0.039, 95% CI: 0.028, 0.044).[111-113,417] One trial of ibandronate vs. placebo[411] and five trials of risedronate vs. placebo[74,82,95,97,384] found no significant differences.

In two head-to-head trials, alendronate was significantly less likely to be associated with arthritis and arthralgias than denosumab (OR 0.65, 95% CI: 0.46, 0.92).[61,275]

Myalgias, Cramps, and Limb Pain

Studies were identified that compared alendronate, ibandronate, and zoledronic acid with placebo. Pooled analysis of two trials of ibandronate[108,420] and six trials of zoledronic acid[111-114,417,421] showed increased risk for this category of events for the active treatments over placebo (OR 2.25, 95% CI: 1.57, 3.29 and OR 4.15, 95% CI: 3.41, 5.08; RD 0.071, 95% CI: 0.063, 0.080, respectively)

Atypical Fractures

This category of adverse events was not included in the original report.

A post hoc (secondary) analysis was conducted with the combined results of three large RCTs of bisphosphonates (FIT, FLEX, and HORIZON/PFT) that included review of fracture records for all reported hip and femur fractures to identify fractures "below the lesser trochanter and above the distal metaphyseal flare," and to assess whether these fractures represented atypical fractures. This review of 284 records (among 14,195 women) identified 12 such fractures (relative HR 1.03, 95% CI: 0.06, 16.46 for alendronate in the FIT trial; 1.50, 95% CI: 0.25, 9.00 for zoledronic acid use in the HORIZON/PFT; 1.33, 95% CI: 0.12, 14.67 for longer-term alendronate use in the FLEX trial).[422] The authors concluded that although no significant increase in the atypical fractures was seen, the analysis was underpowered to draw definitive conclusions.

A case series that reviewed 152 femoral fractures among 152 elderly patients (mean age 78±5, 87 percent women) admitted to an Australian tertiary care center from 2003 through 2008 found that of 20 fractures classified (blind to treatment) as atypical, 17 of the patients were on oral bisphosphonate therapy at the time of the fracture. Fifteen were taking alendronate (mean duration 5.1 years) and two were taking risedronate (mean duration 3 years). Of those 132 whose fractures did not fulfill the criteria for being atypical, two patients were taking alendronate (mean duration 3.5 years), and one was taking risedronate (one year). Other factors associated with fracture risk were history of low-energy fracture, prolonged glucocorticoid use, active rheumatoid arthritis, and low serum vitamin D levels.[423]

On 14 September, 2010, a task force of the American Society of Bone and Mineral Research (ASBMR) on atypical subtrochanteric fracture published a comprehensive review of the published and unpublished literature on the association between atypical femur fractures and the use of bisphosphonates that included the two studies just described and that concluded that although the risk for this type of fracture is low, it appears to increase with increasing duration of use of bisphosphonates for the treatment of osteoporosis.[424] The task force determined that "Based on published and unpublished data and the widespread use of bisphosphonates the incidence of atypical femoral fractures associated with bisphosphonate therapy for osteoporosis appears to be very low, particularly compared to the number of vertebral, hip and other fractures that are prevented by bisphosphonates. Moreover, a causal association between bisphosphonates and atypical fractures has not been established." Based on this review, on 13 October 2010, the Food and Drug Administration, which has been conducting its own ongoing review of atypical

subtrochanteric femur fracture, updated the risk of atypical fractures to the Warnings and Precautions level, stating "…Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates."[425] This warning pertains to alendronate, risedronate, ibandronate, and zoledronic acid used in the prevention and treatment of osteoporosis.

A nested case control study that was not included in the ASBMR review assessed the possible association between use of bisphosphonates and other osteoporosis medications and a different type of atypical fracture, nonunion fractures of the humerus, among a large cohort of older adults (cases of nonunion were identified as those with an orthopedic procedure associated with nonunion 91 to 365 days after an initial humerus fracture). In fully-adjusted multi-variate analysis, use of a bisphosphonate in the post-fracture period was associated with an increased risk of nonunion (OR 2.37, 95% CI: 1.13, 4.96). This increase was also seen in the small subpopulation of individuals with no prior history of osteoporosis or fractures (OR 1.91, 95% CI: 0.75, 4.83).[426]

A systematic review of cases and case series that described atypical femoral fractures among users of bisphosphonates and appeared just prior to the ASBMR statement identified 141 women with such fractures, treated for an average of 71.5±40.0 months.[427] Risk factors associated with the fractures included use of glucocorticoids and proton pump inhibitors.

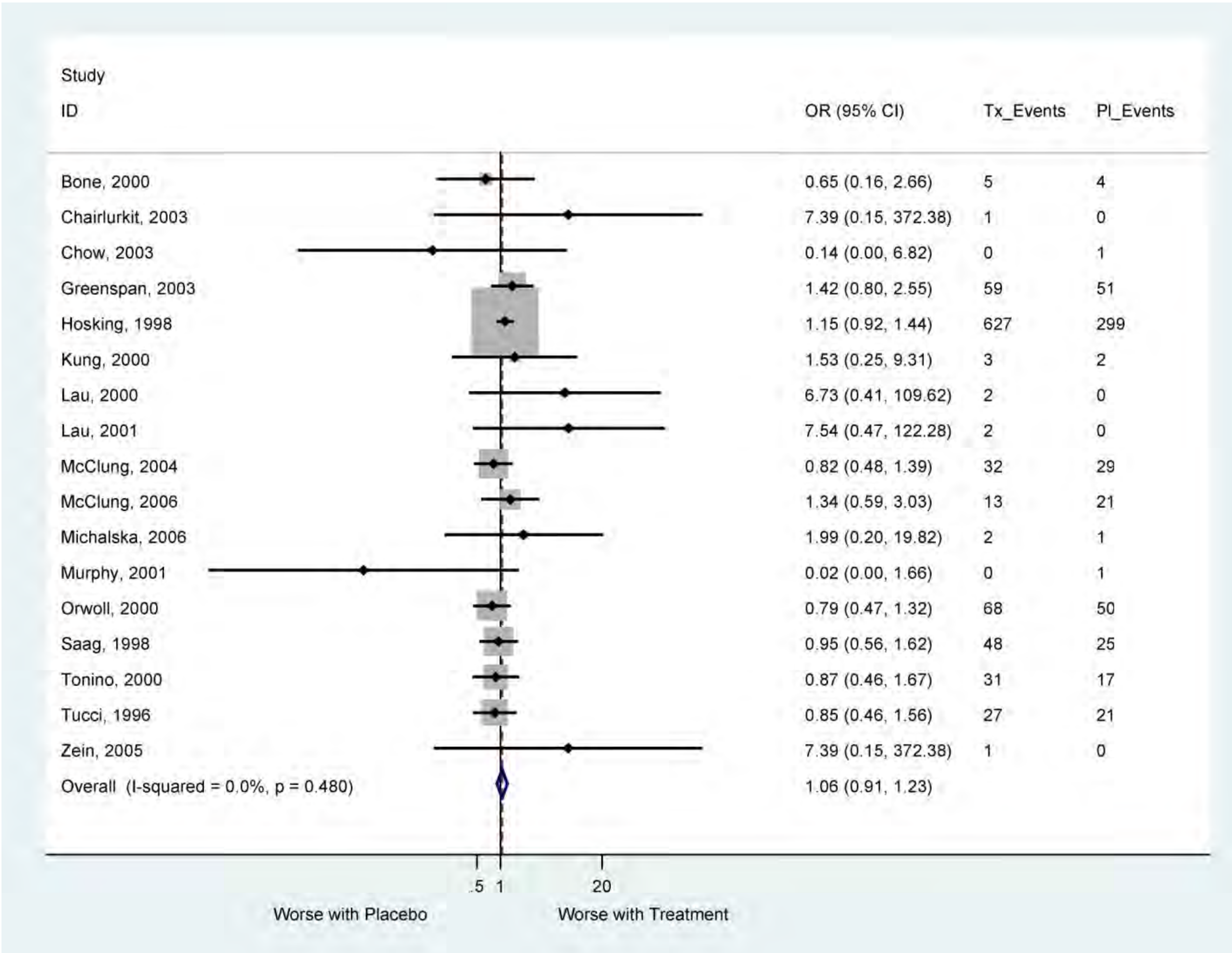
One nested case control and five cohort studies appeared concurrent with or subsequent to the ASBMR report. The nested case control study (N-O 9/9) found that use of bisphosphonates for five or more years was associated with an increased risk of subtrochanteric or femoral fracture (adjusted OR, 2.74; 95% CI: 1.25, 6.02); however, the overall incidence was low: 71 among 52,595 women over one year (0.13 percent).[428] A 2011 epidemiological study that examined age-adjusted trends in the incidence of subtrochanteric fragility fractures and osteoporotic femoral fractures in the National Inpatient Sample and compared it to trends in the use of bisphosphonates for osteoporosis from 1996 to 2007 found approximately one new fragility fracture for every 100 fewer hip fractures.[429] A cohort study that included more than 40,000 men and women in the Danish National Hospital Discharge Register (N-O 9/9) found an increase in the risk for atypical fractures among users of alendronate compared with nonusers (HR 2.6, 95% CI: 2.29, 2.95); however, higher cumulative doses were not associated with a greater risk than smaller cumulative doses, suggesting the possibility that osteoporosis itself could be responsible for the fractures.[430] A subsequent study of subtrochanteric fractures among users of alendronate and raloxifene in the same database by another group (N-O 8/9) found an increase in the rate of such fractures among alendronate users (HR 2.41, 95% CI: 1.78, 3.27) compared with users of raloxifene but also found that the increased risk was present prior to the start of therapy.[431] Finally, a large 2011 cohort study (N-O 9/9) that used propensity-score matching of individuals in health care utilization databases from two US states found no increased risk of subtrochanteric fracture among individuals with at least one prescription for a bisphosphonate for osteoporosis therapy compared with those with prescriptions for calcitonin or raloxifene (HR 1.03, 95% CI: 0.70. 1.52);[432] however, the proportion of the cohort treated with bisphosphonates longer than 5 years was sufficiently small that an association of long-term use with atypical fractures could not be ruled out.

Osteonecrosis of the Jaw

The original report identified case series and case reports describing 41 cases of osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates. Cases involved pamidronate, zoledronic acid, and alendronate. One trial, two large observational studies, a post

hoc analysis, and a systematic review that reported on the incidence of osteonecrosis of the jaw among individuals taking bisphosphonates to prevent or treat osteoporosis were identified for the current report. A RCT that assessed the effect of one intravenous dose of zoledronic acid for the prevention of osteoporosis reported no cases of osteonecrosis of the jaw over the following three years.[418] A large recent case series reviewed 2,408 cases of osteonecrosis of the jaw to assess the possible association between use of bisphosphonates and osteonecrosis.[433] Of these cases, 88 percent were associated with intravenous therapy, primarily with zoledronic acid. Whereas 89 percent of the total cases were associated with the treatment of a malignant condition, ten percent were associated with the prevention or treatment of osteoporosis (treatment of Paget's disease and other benign conditions accounted for the remaining one percent). A survey of more than 8,000 members of a northern California integrated health care system who had received chronic oral bisphosphonates identified 9 cases of osteonecrosis of the jaw, for an estimated frequency of 28 cases per 100,000 person-years of treatment and a prevalence of 0.10 percent (95% CI: 0.05, 0.20).[434] After the identification of one case of osteonecrosis of the jaw in the HORIZON PFT trial of once yearly zoledronic acid for the treatment of osteoporosis,[435] the incidence was assessed in the remaining four HORIZON trials: No further cases of osteonecrosis of the jaw were identified, among more than 5,900 patients, resulting in an incidence of less than 1 in 14,200 patient-treatment years.[436] One systematic review identified five reports that attempted to estimate the frequency of osteonecrosis of the jaw among individuals treated for osteoporosis: the composite estimate was less than one case per 100,000 person-years of exposure.[437]Thus the prevention and treatment of osteoporosis remains a relatively minor contributor to the development of osteonecrosis of the jaw.

Figure 15. Musculoskeletal adverse events in trials of alendronate versus placebo



Fracture Healing

The association between bisphosphonate use and subsequent fracture healing has been examined in one post hoc analysis and one nested case-control study. A post hoc analysis of patients in the HORIZON PFT trial assessed the relationship between timing of administration of zoledronic acid and fracture healing among patients who experienced a new hip fracture; the study found no association between the timing of infusion of zoledronic acid and delayed fracture healing.[438] A nested case control study that assessed bisphosphonate use among individuals with nonunion of humeral fractures (81 cases in more than 19,000 with humeral fractures) found increased odds of nonunion fractures among patients who took bisphosphonates in the post-fracture period (OR 2.37, 95% CI: 1.13, 4.96) regardless of prior history of osteoporosis or fracture.[426]

Metabolic Adverse Events

This category includes hyper- and hypocalcemia, and hypercalciuria. No studies compared the effects of bisphosphonates with placebo with respect to hypercalcemia or hypercalciuria. In two trials included in the original report, alendronate patients had increased odds of

hypocalcemia relative to placebo patients.[379,402] Two trials of zoledronic acid, one included in the original report[439] and one identified for the present report,[113] found an increased risk for hypocalcemia with zoledronic acid compared with placebo (OR 7.22, 95% CI: 1.81, 42.70).

Adverse Events in Subpopulations

A post hoc analysis of the Fracture Intervention Trial, which assessed the effect of alendronate on fracture prevention in postmenopausal women, assessed whether adverse events differed between women of normal and impaired renal function.[254]No differences were seen in adverse events.

A 24-month multicenter randomized double-dummy comparative effectiveness trial compared the incidence of adverse events between a once-yearly intravenous infusion of zoledronic acid (5 mg) and weekly oral alendronate (70-mg capsule) in 261 men with primary or hypogonadism-induced osteoporosis.[274] The overall incidence of adverse events and serious adverse events was similar in both groups (93.5 percent vs. 93.2 percent and 17.6 percent vs. 20.9 percent, respectively). Within 3 days after administration, the incidence of many adverse events (e.g., arthralgia, myalgias, chills, fatigue, headache, and pyrexia was higher in the group receiving zoledronic acid, but the differences disappeared after 3 days.

The safety of once yearly infusions of zoledronic acid was also assessed in a post-hoc analysis of the 3-year HORIZON-PFT randomized placebo-controlled trial, which enrolled 323 women with osteoporosis in Taiwan and Hong Kong.[251] The overall incidence of adverse events was lower in the treatment group than in the placebo group (20 percent vs. 33 percent, p=0.012). As with the previous study, the most frequently occurring symptoms in the first three days after infusion were pyrexia, arthralgia, myalgia, fatigue, and headache. Eight participants in the zoledronic acid group and three in the placebo group died during the study. No inflammatory ocular disorders, atrial fibrillation, osteonecrosis of the jaw, abnormalities in hematology or biochemistry values or in serum creatinine or calculated creatinine clearance were observed.

Table 52. Risks of Adverse Events for bisphosphonates versus placebo

Event Group	Alendronate		Ibandronate		Risedronate		Zoledronic acid	
	# of Trials	OR (95% CI)	# of Trials	OR (95% CI)	# of Trials	OR (95% CI)	# of Trials	OR (95% CI)
Cardiovascular								
Acute Coronary Syndrome	3	3.59 (0.35, 180)	2	1.06 (0.41, 2.96)	3	0.4 (0.06, 2.39)	2	0.82 (0.55, 1.21)
Cerebrovascular Death	2	Inf+(0.13, Inf+)*	2	1.06 (0.41, 2.96)	2	Inf+ (0.13, Inf+)*	2	0.61 (0.26, 1.37)
Atrial Fibrillation	1	1.26 (0.96, 1.66)	0	NR	1	Inf+ (0.02, Inf+)*	2	1.45 (1.14, 1.86)
Cerebrovascular Accidents (serious)	0	NR	2	0.32 (0, 27.3)	0	NR	2	1.13 (0.9, 1.42)
Pulmonary Embolism	0	NR	0	NR	2	0.74, (0.08, 8.89)	0	NR
Thromboembolic Events	1	Inf+ (0.03, Inf+)*	0	NR	0	NR	0	NR
Cancer								
Breast Cancer	1	Inf+ (0.09, Inf+)*	1	Inf+ (0.01, Inf+)*	0	NR	0	NR
Colon Cancer	0	NR	0	NR	0	NR	0	NR
Esophageal Cancer	No trials examined individual bisphosphonates. Pooled results for two observational studies: OR 1.23 (1.01, 1.49); see text for descriptions of findings of additional observational studies.							
Lung Cancer	0	NR	0	NR	1	0.49 (0.01, 38.4)	0	NR
Osteosarcoma	0	NR	0	NR	0	NR	0	NR
GI (mild)								
GI (mild) All	50	1.08 (1.01, 1.15)	10	1.03 (0.92, 1.14)	21	1.03 (0.95, 1.13)	3	1.44 (0.84, 2.5)
GI (Serious)								
Esophageal (serious)	5	1.39 (0.75, 2.65)	1	1.5 (0.12, 78.7)	4	0.74 (0.38, 1.46)	0	NR
Upper GI Perforations, Ulcers, or Bleeds (not esophageal)	10	0.88 (0.66, 1.18)	2	0.33 (0.14, 0.74)	7	0.64 (0.27, 1.53)	0	NR
Musculoskeletal								
Arthritis and Arthralgias	3	0.27 (0.09, 0.70)	1	0.53 (0.11, 2.43)	5	0.77 (0.45, 1.32)	5	2.31 (1.90, 2.82)
Myalgias, Cramps, Limb Pain	4	1.14 (0.18, 8.18)	2	2.25 (1.57, 3.29)	0	NR	6	4.15 (3.41, 5.08)
Atypical Fractures	See text for description of comprehensive review and subsequent observational studies of all bisphosphonates.							
Osteonecrosis of the Jaw	See text for description of reviews and observational studies.							

INF = infinite; OR = odds ratio; NR = not reported

*For comparisons with zero events in one arm the odds ratio and the upper bound of the confidence interval is infinity.

SERMS

Table 53 shows the risks of adverse events for the SERM raloxifene compared with placebo.

Cardiovascular

A pooled analysis of 16 trials showed a small but significant increase in serious cardiovascular adverse effects for raloxifene compared with placebo (Figure 16).

Acute Coronary Syndrome

The original report identified four trials of raloxifene[122,440-442] that found no significant effect of the drug compared with placebo. For the current report, we identified an additional three trials;[121,443,444] the pooled OR for the seven trials was 1.07 (95% CI: 0.95, 1.21).

Atrial Fibrillation

One study was identified for the current report that compared the risk of atrial fibrillation between raloxifene- and placebo-treated patients; this study found no effect (OR 0.97 95% CI: 0.82, 1.14).[443]

Cardiovascular Death

The original report identified two trials of raloxifene[440,442] that reported cardiac deaths and found no differences between drug and placebo. One additional study was identified for the current report;[443] the pooled OR for the three studies was 1.03 (95% CI: 0.89, 1.20), again showing no difference.

CVA

The original report identified three trials of raloxifene[441,442,445] that reported CVA; there were no significant differences between either drug and placebo. The current report identified three new studies of raloxifene[121,443,444] that reported on CVAs; pooled analysis of the six raloxifene studies found no significant effect on the risk for CVA (OR 1.12, 95% CI: 1.00, 1.25).

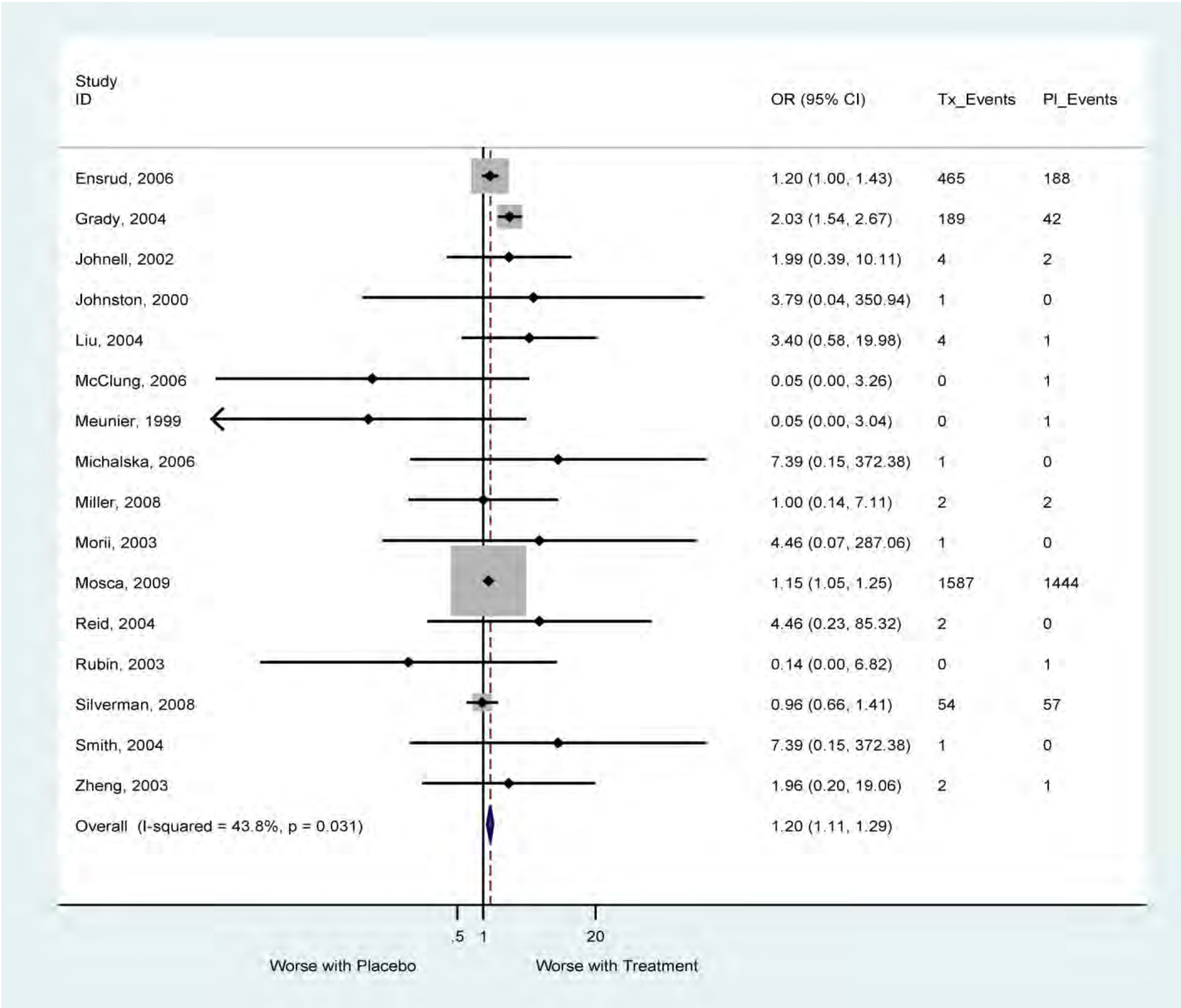
Pulmonary Embolism

The original report identified two large studies that showed higher odds for pulmonary embolism among raloxifene participants than among placebo participants (OR 6.26, 95% CI: 1.55, 54.80).[440,446] The current report identified two additional studies[121,443]; among the four studies, the pooled odds ratio for pulmonary embolism in the treated group was 5.27 (95% CI: 1.29, 46.4).

Venous Thromboembolic Events

The original report identified four studies that showed higher risk of thromboembolic events for raloxifene-treated participants than for placebo participants (OR 2.08, 95% CI: 1.47, 3.02).[406,440,447,448] For the current report, four additional studies were identified (OR 1.63, 95% CI: 1.36, 1.98) that narrowed the confidence interval (RD 0.011 95% CI: 0.007, 0.014).[121,443,444,449]

Figure 16. Serious cardiovascular adverse events in trials of raloxifene versus placebo



Cancer

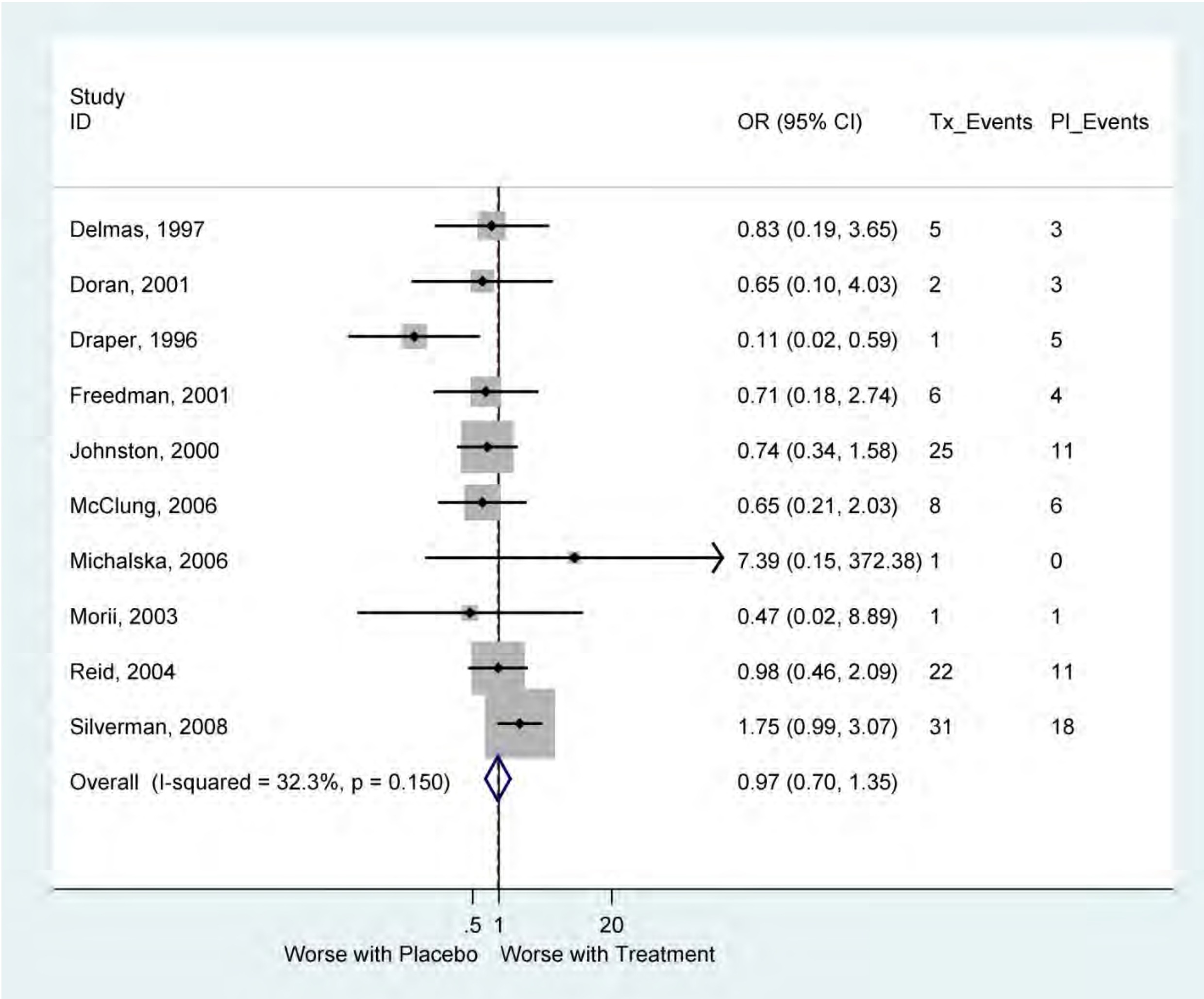
Breast Cancer

The original report identified two studies that, when pooled, showed no significant differences between raloxifene and placebo.[440,447] For the current report, two additional studies were identified.[121,444] Pooled analysis of the four studies also showed no significant difference (OR 0.79, 95% CI: 0.32, 1.97). A pooled analysis of ten studies found no increase in overall breast abnormalities with raloxifene compared with placebo (Figure 17).

Lung Cancer

The original report identified two placebo-controlled trials of raloxifene, [440,446] that reported lung cancer and found no significant differences. No new studies were found that reported on lung cancer risk.

Figure 17. Breast abnormalities (other than cancer) in trials of raloxifene versus placebo



Gastrointestinal (Serious)

PUBs

Two studies identified for the current report found no significant difference in the incidence of these events between raloxifene and placebo.[445,456]

Gastrointestinal (Mild)

The original report identified and pooled eight placebo-controlled trials of raloxifene and found no significant difference in the incidence of mild GI events (OR 0.98 95% CI: 0.78, 1.22).[122,385,406,440,445,447,450,457] One new study identified for this report did not change that finding (OR 0.97 95% CI: 0.78, 1.21).[456]

Musculoskeletal

This category includes arthritis and arthralgia; and myalgias, muscle cramps, and limb pain. A pooled analysis of 13 studies identified a significant increase in such events for raloxifene compared with placebo (Figure 18). A pooled analysis of 11 placebo-controlled trials, seven identified for the original report[122,406,441,445,447,457,458] and four identified for the current report,[121,444,449,456] found a significant increase in myalgias, cramps, and limb pain for raloxifene (OR 1.53, 95% CI: 1.29, 1.81; RD 0.031, 95% CI: 0.019, 0.043) (Figure 19). A single placebo-controlled study found no effect on reports of arthritis and arthralgias for raloxifene (OR Inf+ 95% CI 0.01, Inf+).[450]

Figure 18. Musculoskeletal adverse events in trials of raloxifene versus placebo

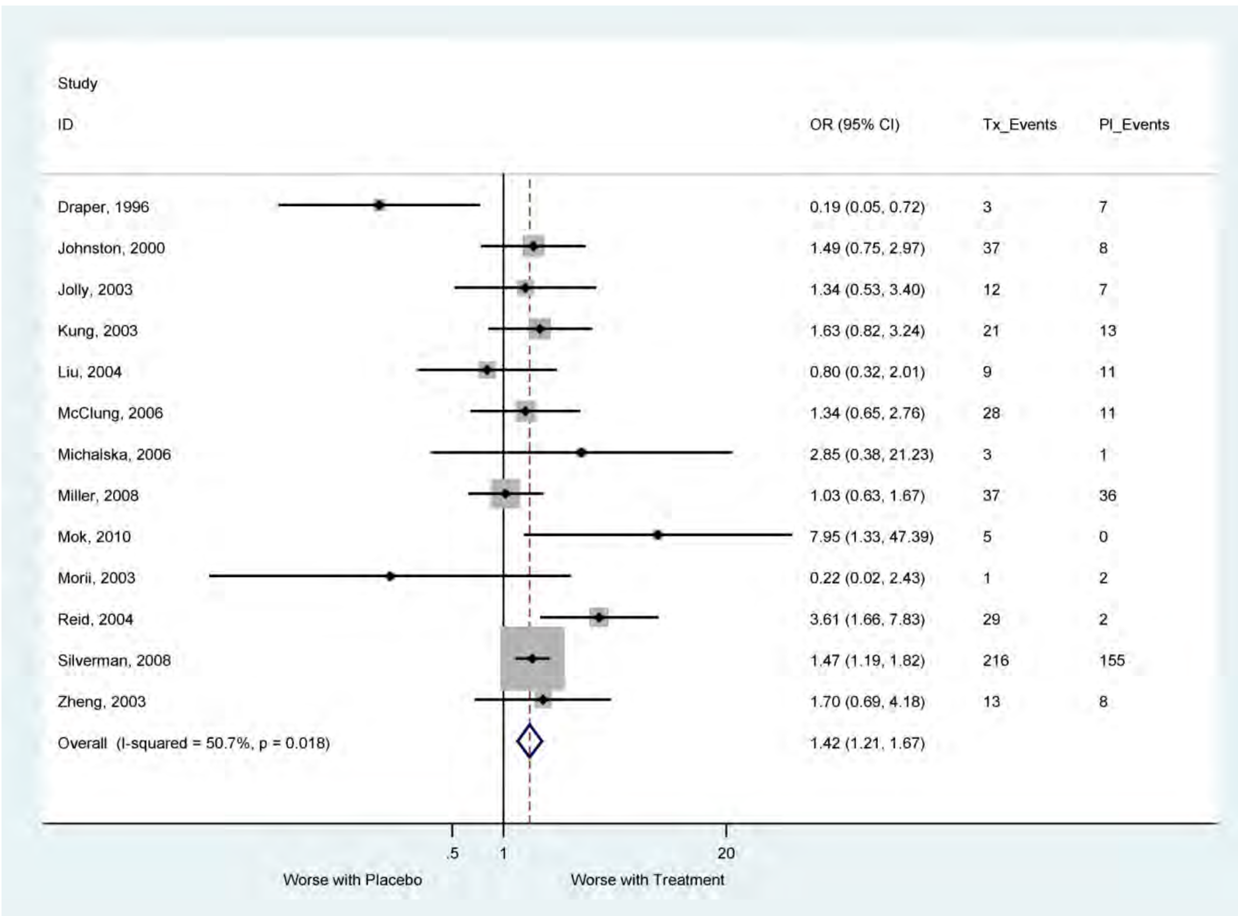
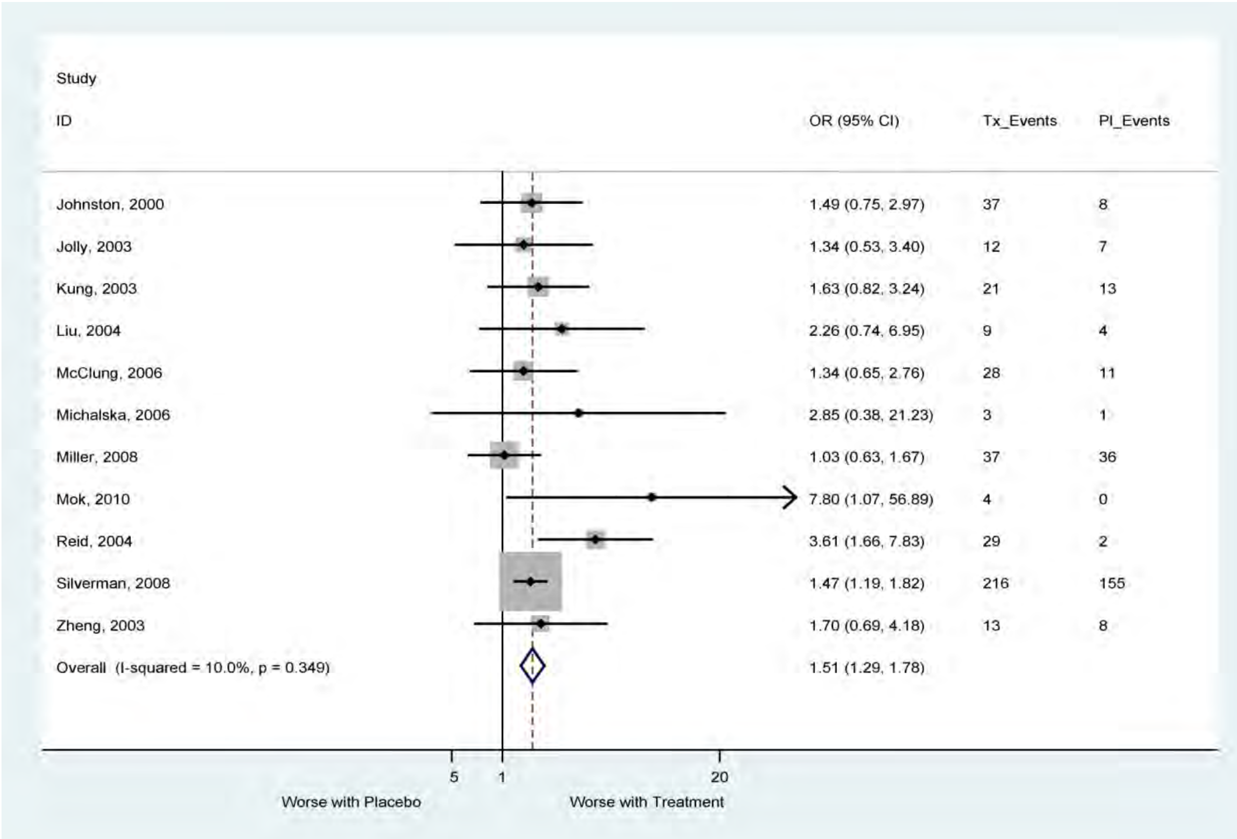


Figure 19. Myalgias, cramps, and limb pain in trials of raloxifene versus placebo



Sweats/Fever/Vasomotor Flushing/Hot Flashes

This category includes fever, hot flashes (vasomotor flushing), weight gain, pain, and flushing. A pooled analysis of eight placebo-controlled trials found that raloxifene significantly increased the incidence of hot flashes and flushing over that of placebo (OR 1.58 95% CI: 1.35, 1.84; RD 0.046 95% CI: 0.031, 0.060) (Figure 20).[121,122,385,447,452,457-459]

Figure 20. Sweats/fever/vasomotor flushing (hot flashes) in trials of raloxifene versus placebo

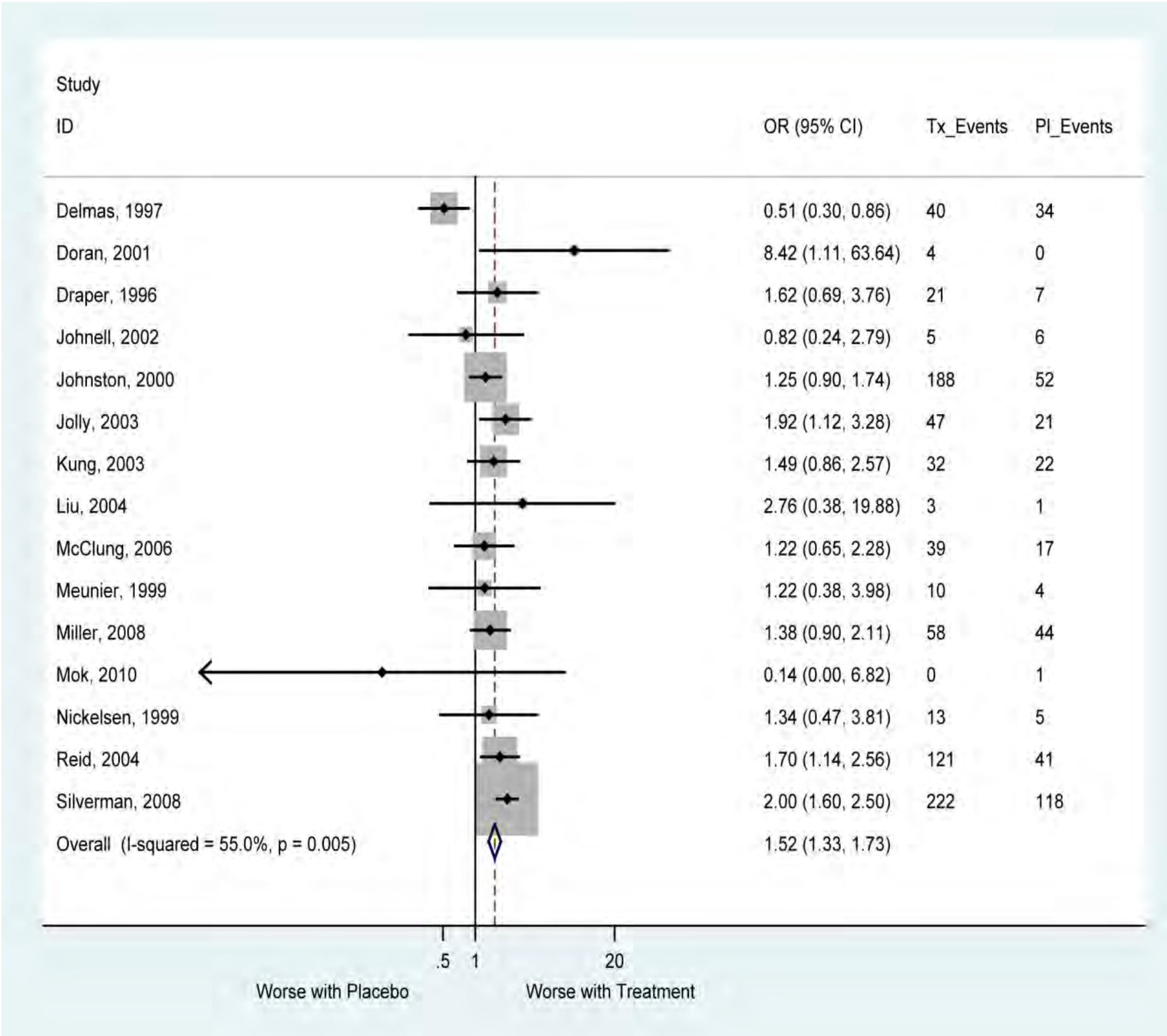


Table 53. Risks of adverse events for raloxifene versus placebo

Event Group	Raloxifene	
	Number of Trials	OR (95% CI)
Cardiovascular		
Acute Coronary Syndrome	7	1.07 (0.95, 1.21)
Cardiovascular Death	3	1.03 (0.89, 1.20)
Cerebrovascular Accidents	6	1.12 (1.00, 1.25)
Pulmonary Embolism	4	5.27 (1.29, 46.4)*
Thromboembolic Events	8	1.63 (1.36, 1.98)*
Cancer		
Breast Cancer	4	0.79 (0.32, 1.97)
Colon Cancer	0	NR
Lung Cancer	2	0.39 (0.01, 7.87)
Osteosarcoma	0	NR
GI		
GI (mild)	9	0.97 (0.78, 1.21)
Upper GI (excluding esophagus)	3	1.1 (0.68, 1.81)
Reflux and Esophageal	0	NR
GI (serious)	1	0.49 (0.01, 39.1)
Esophageal (serious)	0	NR
Upper GI Perforations, Ulcers, or Bleeds (not esophageal)	1	0.33 (0.01, 4.17)
Musculoskeletal		
Myalgias, Cramps, and Limb Pain	11	1.53 (1.29, 1.81)
Arthritis and Arthralgias	1	Inf+ (0.01, Inf+)
Sweats/Fevers/Hot Flashes		
Hot flashes	8	1.58 (1.35, 1.84)

*Statistically Significant.

Parathyroid Hormone

Table 54 shows the risks of adverse events for parathyroid hormone (teriparatide) compared with placebo.

Cardiovascular

Acute Coronary Syndrome, Including Myocardial Infarction

No studies were identified for the original or the current report that reported on these events with use of parathyroid hormone (PTH).

Cardiac Death

The original or current report identified no trials of PTH that reported cardiac death.

CVA

The original and current report found no trials of PTH that reported CVA.

Pulmonary Embolism

No trials were identified for the original or the current report that reported pulmonary embolism with use of PTH.

Venous Thromboembolic Events

No trials were identified for the original or the current report of that reported thromboembolic events with use of PTH.

Cancer

The original report identified two placebo controlled trials of teriparatide that reported on the incidence of various types of cancer.[129,134] Participants in the teriparatide groups had lower odds of cancer than did placebo participants (OR 0.49, 95% CI: 0.27, 0.90; RD -0.018, 95% CI: -0.034, -0.003)). Incidences for specific types of cancers such as breast cancer, colon cancer, lung cancer, or osteosarcoma were not reported in these trials. The current report identified no trials that reported on cases of cancer with use of PTH.

Gastrointestinal (Mild)

Upper Gastrointestinal

The original report identified two placebo-controlled trials of teriparatide[129,134] that reported on mild upper GI events and found no significant differences between treatment and placebo groups regarding mild upper GI adverse events. For the current report, there were no new studies of teriparatide.

Gastrointestinal (Serious)

Upper GI PUBs

No trials of PTH were identified that reported these events.

Neurologic (Mild)

This category consisted of headaches. A pooled analysis of two placebo-controlled trials of teriparatide showed a significant increase in reports of headache in the treated group (OR 1.44 95% CI: 1.24, 1.67).[129,130,134]

Metabolic

This category comprised hypercalcemia, hypercalciuria, hypocalcemia, and hyperuricemia.

Hypercalcemia

A pooled analysis of three placebo-controlled trials of teriparatide showed a significant increase in reports of hypercalcemia (OR 12.9 95% CI: 10.49, 16.00).[130,133,134,460]

Adverse Events in Subpopulations

A post-hoc analysis of the FPT assessed the association between impaired renal function and the risk for adverse effects from the use of teriparatide among postmenopausal women with mild or moderate renal impairment. Women with renal impairment tended to be older, had been postmenopausal longer, and lower baseline BMD. Teriparatide therapy was associated with mild hypercalcemia regardless of renal function status, and with a dose-dependent increase in the

incidence of hyperuricemia regardless of renal function but no increase in the risk for gout, arthralgia, or nephrolithiasis.[256]

Table 54. Risks of adverse events for parathyroid hormone versus placebo

Event Group	PTH	
	Number of Trials	OR (95% CI)
Cardiovascular		
Acute Coronary Syndrome	1	0.97 (0.01, 76.1)
Cardiac Death	1	0.97 (0.01, 76.1)
Cerebrovascular Events (serious)	1	0 (0.0, 37.8)
Pulmonary Embolism	0	NR
Thromboembolic Events	0	NR
Cancer		
Cancer, not specified	2	0.49 (0.27, 0.9)*
Breast Cancer	0	NR
Colon Cancer	0	NR
Lung Cancer	0	NR
Osteosarcoma	0	NR
GI		
GI (mild)	2	1.39 (0.98, 2.00)
Upper GI (excluding esophagus)	2	1.39 (0.98, 2.00)*
Reflux and Esophageal	0	NR
GI (serious)	0	NR
Esophageal (serious)	0	NR
Upper GI Perforations, Ulcers or Bleeds (not esophageal)	0	NR
Neurologic (mild)		
Headaches	3	1.44 (1.24, 1.67)*
Metabolic		
Hypercalcemia	4	12.9 (10.49, 16.00)*

*Statistically significant

Estrogen or Estrogen Plus Progestin

The original report described in detail the harms associated with menopausal hormone therapy that were identified in the WHI; these harms included venous thromboembolic events, stroke, and a variable effect on breast cancer. Routine use of hormone replacement therapy in postmenopausal women is now discouraged. Two followup analyses of data from the Women's Health Initiative were identified that assessed the association between estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women in the wake of the declining use of menopausal hormone therapy. One assessment reported that the elevated incidence of breast cancer associated with use of estrogen plus progestin declined significantly over the two years following discontinuation of the combined therapy and that this change was not associated with any change in the frequency of mammography.[461] A subsequent report presented an intention-to-treat analysis of cumulative breast cancer incidence after a mean followup of 11 years: combined therapy was associated with more invasive breast cancers than placebo (HR 1.25, 95% CI: 1.07, 1.46), tumors that were more likely to be node positive (HR 1.78, 95% CI: 1.23, 1.58), and more deaths attributed to breast cancer (HR 1.96, 95% CI: 1.00, 4.04).[462]

Denosumab

Denosumab was not examined in the original report. Table 55 shows the risks of adverse events for denosumab compared with placebo.

Gastrointestinal (Mild)

Upper Gastrointestinal

Pooled results from one placebo-controlled trial identified for the original report showed an increase in reflux and esophageal complaints as well as other mild upper GI adverse events with denosumab (OR 2.13 95% CI: 1.11, 4.4; RD 0.013, 95% CI: 0.006, 0.019).[61]

Dermatologic

This category includes reactions at the site of injection/application and rash. No significant increases were found in reports of injection site reactions in one placebo-controlled trial of denosumab (OR Inf+ 95% CI: 0.06, Inf+).[463] Pooled results of three placebo-controlled trials identified an increase in rash (OR 2.01 95% CI: 1.5, 2.73; RD 0.016, 95% CI: 0.009, 0.023).[61,117,118]

Other

Upon approval of denosumab for release, the FDA issued a Risk Evaluation and Mitigation Strategy for the drug that cited an increased risk for infection.[464] A recent meta-analysis[465] that updated a previous meta-analysis[115] with the addition of a large RCT[118] found a significantly increased risk of infection in the group given denosumab (OR 1.28, 95% CI: 1.02, 1.60; p=0.04, I^2=44%). When a study that enrolled only participants with cancer was excluded,[116] a small increased risk remained (RR=1.25, 95% CI: 1.00, 1.59; p=0.05, I^2=41%).

Table 55. Risks of adverse events for biologics (denosumab)

Event Group	Denosumab	
	Number of Trials	OR (95% CI)
Cardiovascular		
Cardiac (serious)	3	1.04 (0.87, 1.25)
Cardiac Death	0	NR
Atrial Fibrillation	1	1.00 (0.57, 1.73)
Cerebrovascular Events	1	1.03 (0.7, 1.54)
Thromboembolic Events	0	NR
Cancer		
Cancer	2	0.49 (0.27, 0.9)*
Breast Cancer	0	NR
Colon Cancer	0	NR
Lung Cancer	0	NR
Osteosarcoma	0	NR

Table 55. Risks of adverse events for biologics (denosumab) (continued)

Event Group	Denosumab	
	Number of Trials	OR (95% CI)
GI (mild)		
Reflux and Esophageal	2	2.13 (1.11, 4.4)*
GI (serious)	0	NR
Esophageal (serious)	0	NR
Upper GI Perforations, Ulcers or Bleeds (not esophageal)	0	NR
Dermatologic		
Injection Site Reactions	1	Inf+ (0.06, Inf+)
Rash	4	2.01 (1.5, 2.73)*
Infection		
Infection – Not otherwise specified and not pulmonary, GI, ear, eye	4	1.01 (0.92, 1.1)
Infection†	4	1.28 (1.02, 1.60)
Infection, excluding Ellis, 2008†	3	1.25 (1.00, 1.59)
Genitourinary		
Urinary Tract Infection	3	1.78 (0.96, 3.45) RD 0.030 (-0.017, 0.077)

*Statistcally significant.
†Previously published pooled analysis.[465]

Vitamin D and Calcium

Table 56 shows the risks of adverse events for vitamin D and calcium compared with placebo.

Cardiovascular

Acute Coronary Syndrome, Including MI

No studies identified for the original or the current report found any cases of acute coronary syndromes in trials of vitamin D or calcium. A new meta-analysis of 15 placebo-controlled trials of calcium (administered for bone health in all cases but one) identified a small but significant increase in the risk for myocardial infarction in pooled results of five trials that contributed patient-level data (HR 1.31, 95% CI: 1.02, 1.67, p=0.035).[466] The pooled results of trial-level data showed a similar effect (pooled RR 1.27, 95% CI: 1.01, 1.59, p=0.038). However, a number of letters written in response to the review pointed out multiple concerns with the analyses that could have resulted in biased results. The analysis excluded any studies that co-administered vitamin D with calcium (whereas guidelines recommend administering both); the study did not account for dietary calcium or vitamin D intake or status; and compliance with calcium supplementation was poor (as is usually the case). MI was not a pre-specified endpoint in any of the studies; the MI data for the study that more than half the reported events were unpublished, and in this same study, supplements were mailed and adverse events were assessed through mailed patient surveys (whose response rate was not revealed) and not verified by chart review; and compliance with Ca supplementation was not verified among patients who reported an MI.[467,468]

CVA

No reports of CVA were identified for the original report. One placebo-controlled trial of calcium identified for the current report found an increase in CVA among users (OR 1.56 95% CI: 1.05, 2.33).[469]

Cancer

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

Gastrointestinal (Serious)

No events were reported in trials of vitamin D or calcium.

Gastrointestinal (Mild)

In one trial of calcium[155] [original report says ref. 269 included also] and one trial of vitamin D,[396] identified for the original report, there were no significant differences between treatment and placebo groups regarding mild upper GI adverse events. One new trial that assessed the association of vitamin D to mild gastrointestinal events was identified for the current report; no difference was seen.[470]

Metabolic

A single placebo-controlled trial of Vitamin D identified for the current report showed an increased risk for hypercalciuria (OR 19.8, 95% CI: 3.19, 819).[470]

Table 56. Dietary supplements (Vitamin D and calcium)

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
Myocardial infarction	5	1.31 (1.02, 1.67)*†	0	NR
Cerebrovascular Events (serious)	1	1.56 (1.05, 2.33)*	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

Table 56. Dietary supplements (Vitamin D and calcium) (continued)

Event Group	Calcium		Vitamin D	
	Number of Trials	OR (95% CI)	Number of Trials	OR (95% CI)
GI				
GI (mild)	1	0.79 (0.33, 1.87)	1	0.27 (0.04, 1.11)
Upper GI (excluding esophagus)	1	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
Metabolic				
Hypercalciuria	0	NR	1	19.8 (3.19, 819)

*Significantly different.
†Hazard ratio.

Key Question 5: With Regard to Treatment for Preventing Osteoporotic Fracture:

a) How Often Should Patients be Monitored (via Measurement of Bone Mineral Density) During Therapy, how Does Bone Density Monitoring Predict Antifracture Benefits During Pharmacotherapy, and Does the Ability of Monitoring to Predict Antifracture Effects of a Particular Pharmacologic Agent Vary Among the Pharmacotherapies?
b) How Does the Antifracture Benefit Vary With Long-term Continued use of Pharmacotherapy, and What are the Comparative Antifracture Effects of Continued Long-term Therapy With the Various Pharmacotherapies?

For this question, we identified one systematic review and 4 RCTs.

Key Findings for Key Question 5

- No evidence exists from RCTs regarding how often patients' BMD should be monitored during osteoporosis therapy
- A high level of evidence exists from RCTs that lumbar spine and femoral neck BMD changes from serial monitoring predict only a small percentage of the change or do not predict the change in fracture risk from treatment with antiresorptives, including alendronate, risedronate, raloxifene, and teriparatide
- In RCTs, even people who lose BMD during antiresorptive therapy benefit from a substantial reduction in risk of vertebral fracture. Greater increases in BMD did not necessarily predict greater decreases in fracture risk. Thus, improvement in spine bone mineral density during treatment with currently available osteoporosis medications accounts for a predictable but small part of the observed reduction in the risk of vertebral fracture. Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment. Evidence is high for this conclusion.

- Evidence is moderate (one large RCT) that, compared to using alendronate for 5 years followed by discontinuation after 5 years, continuous use of alendronate for 10 years resulted in a lower risk of vertebral fracture.

Summary of Findings for Key Question 5

Key Question 5a1: How Often Should Patients be Monitored via Measurement of Bone Mineral Density During Therapy?

We did not identify any RCTs that have directly compared various schedules of serial BMD monitoring during osteoporosis pharmacotherapy in relation to optimal fracture prediction.

However, post hoc analyses from RCTs of pharmacotherapy have addressed the related important question of the extent to which changes in BMD during pharmacotherapy predict the magnitude of antifracture effects of pharmacotherapy. These analyses are discussed below.

Key Question 5a2: How Does Bone Density Monitoring Predict Antifracture Benefits During Pharmacotherapy?

Prior Systematic Reviews

Cummings and colleagues performed a meta-analysis to assess the evidence on the relation between improvement in spine BMD and reduction in risk of vertebral fracture in postmenopausal women receiving anti-resorptive treatment (etidronate, alendronate, tiludronate, risedronate, estradiol, raloxifene, and calcitonin).[471] The authors used logistic regression models to estimate the proportion of the reduction in risk of an outcome (e.g., vertebral fracture) explained by the effects of treatment on an intermediary variable (spine bone mineral density). The proportion of the reduction in the risk of fracture (p) that was explained by changes in a marker was estimated as follows: $p =(1-\beta^*/\beta)$ where β = log (unadjusted odds ratio [OR]) and β^* = log (OR adjusted for bone mineral density). Based on data from 12 trials, they concluded that the reduction in vertebral fracture risk was greater than predicted from improvement in BMD. That is, based on improvement in BMD, treatments would have been predicted to reduce fracture risk by 20 percent, whereas treatments actually reduced fracture risk by 45 percent. The study concluded that improvement in spine BMD during treatment with antiresorptive drugs accounts for a small part of the observed reduction in vertebral fracture risk.

A new meta-analysis reported that there was no association between BMD changes and reduction in risk of fracture among patients receiving calcium with or without vitamin D supplementation, so that the fracture reduction effects of calcium and/or vitamin D may be via a mechanism that is independent of BMD.[472]

Post hoc Analyses of Randomized Controlled Trial Data

Alendronate

Studies from the Fracture Intervention Trial (FIT) of alendronate vs. placebo (5 mg daily for the first two years, then 10 mg/day) among postmenopausal women showed that among participants taking at least 60 percent of assigned study medication, women who gained 0 percent to 4 percent of BMD after 1-2 years during treatment had a decrease in vertebral risk of 51 percent (OR = 0.49, 95% CI: 0.30, 0.78) after 3-4 years of followup. However, women who had lost 0 percent to 4 percent of lumbar spine BMD during alendronate therapy had a 60 percent

lower risk of vertebral fractures (OR = 0.40, 95% CI: 0.16, 0.99) compared to their counterparts assigned to placebo[473] Bell and colleagues analyzed 3-year followup data from FIT.[474] Nearly all (97.5 percent of) participants gained BMD during alendronate treatment. However, the between-person variation in the effects of alendronate was small in magnitude compared with the within-person variation. The study concluded that monitoring bone mineral density in postmenopausal women in the first three years after starting treatment with a potent bisphosphonate is unnecessary and may be misleading. In another analysis of the FIT data, improvement in spine BMD after one year of alendronate use explained only 16 percent (95% CI: 11, 27) of the reduction in the risk of vertebral fracture after three years of therapy.[471f]

Risedronate

Among postmenopausal osteoporotic women assigned to 2.5 mg or 5 mg daily of risedronate, the incidence of nonvertebral fractures during followup of up to three years was not different between women whose spine BMD decreased (cumulative fracture incidence of 7.8 percent) and those whose spine BMD increased (cumulative fracture incidence 6.4 percent) (hazard ratio 0.79, 95% CI: 0.50, 1.25).[475] Another study by the same authors estimated the proportion of fracture risk reduction attributable to change in BMD by calculating the ratio of the regression coefficients, where the numerator is the risk reduction explained by the surrogate, and the denominator is the overall risk reduction by treatment. Similarly, the incidence of nonvertebral fractures among women treated with risedronate was not different between women whose femoral neck BMD decreased (7.6 percent) and those femoral neck BMD increased (7.5 percent) (hazard ratio 0.93, 95% CI: 0.68, 1.28). This study reported that fracture risk was similar (about 10 percent), in risedronate-treated women whose increases in BMD were <5 percent, (the median change from baseline) and those whose increases were ≥5 percent.[476] Thus, greater increases in BMD did not necessarily predict greater decreases in vertebral fracture risk. Similarly, the incidence of nonvertebral fractures among women treated with risedronate was not different between women whose femoral neck BMD decreased (7.6 percent) and those whose femoral neck BMD increased (7.5 percent) (hazard ratio 0.93, 95% CI: 0.68, 1.28). Changes in lumbar spine and femoral neck explained 12% (95% CI: 2, 21) of the reduction in nonvertebral fracture risk associated with risedronate therapy. Changes in femoral neck BMD explained 7 percent (95% CI: 2, 13) of reduction in nonvertebral fracture risk associated with risedronate therapy.[475]

Ibandronate

In a post-hoc pooled analysis of two RCTs, increases in hip and lumbar spine BMD during oral or intravenous ibandronate administration were statistically significantly associated with vertebral fracture rate.[477] However, changes in total hip and lumbar spine BMD explained only 23 percent to37 percent of the antifracture effect at 2 and 3-year followup.

[f] The dose of alendronate in FIT was 5 mg daily for 1st two years, and then 10 mg/day.

Raloxifene

Sarkar and colleagues analyzed data from the Multiple Outcomes of Raloxifene Evaluation (MORE) Trial of raloxifene (60 mg or 120 mg) vs. placebo in postmenopausal women with osteoporosis.[478] The reduction in fracture risk with raloxifene was similar regardless of percentage change in lumbar spine or femoral neck BMD at three years. At any percentage change in femoral neck and lumbar spine BMD at one year, raloxifene treatment decreased the risks of new vertebral fractures at three years by 38 percent and 41 percent, respectively. The magnitude of change in BMD during raloxifene therapy accounted for 4 percent of the observed vertebral fracture reduction, i.e. 96 percent of reduction in vertebral fracture risk in women assigned to raloxifene therapy was unexplained.

Teriparatide

In the Fracture Prevention Trial (teriparatide 20 or 40 µg/day vs. placebo in postmenopausal women), women who lost greater than 4 percent at the femoral neck during the first 12 months of teriparatide treatment had significant reductions in vertebral fracture risk compared to placebo during a median of 19 month followup (RR 0.11, 95% CI: 0.03, 0.45).[479] Compared to women assigned to placebo, the decrease in vertebral fracture risk in women assigned to teriparatide was similar across categories of femoral neck BMD change from baseline to 12 months. Vertebral fracture risk was decreased among women who lost femoral neck BMD during teriparatide therapy. Among women assigned to teriparatide, increases in spine BMD accounted for 30 percent to 41 percent of the reduction in vertebral fracture risk.[480]

Summary of Results of KQ5a2: BMD Monitoring and Fracture Risk Reduction During Osteoporosis Pharmacotherapy

Among patients treated with bisphosphonates, raloxifene, or teriparatide, increases in lumbar spine and femoral neck BMD from serial BMD monitoring predict only a small proportion of antifracture effects. In RCTs, even people who lose BMD during anti-resorptive therapy benefit from a substantial reduction in risk of vertebral fracture. Greater increases in BMD did not necessarily predict greater decreases in fracture risk. Thus, improvement in spine bone mineral density during treatment with currently available osteoporosis medications accounts for a predictable but small part of the observed reduction in the risk of vertebral fracture. Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment.

The reason for the low association of changes in BMD and fracture risk reduction during pharmacotherapy appears to be that the majority of fracture risk reduction results from improvements in non-BMD determinants of bone strength.[480]

Key Question 5a3: Does the Ability of Monitoring To Predict Antifracture Efficacy of a Particular Pharmacologic Agent Vary Among the Pharmacotherapies?

We did not identify RCTs or systematic reviews that conducted head-to-head comparisons of the ability of monitoring to predict antifracture effects among various pharmacotherapies.

Key Question 5b: How Does the Antifracture Benefit Vary With Long-term Continued use of Pharmacotherapy, and What are the Comparative Antifracture Efficacies of Continued Long-term Therapy With the Various Pharmacotherapies?

Some studies, such as those of Ensrud and colleagues,[120] focused on the effects of extended duration of therapy (this is discussed in the section of key question 1 above), but did not focus on the comparison of longer with shorter duration of therapy. A goal of this report was to examine studies that directly compared longer (3 to 5 years or longer) vs. shorter durations of therapy.

The only studies that we found that met these criteria, i.e. that focused on the comparison of longer with shorter durations of therapy were open-label extensions of the FIT RCT. In the FLEX 5-year extension of the FIT RCT (original trial alendronate vs. placebo for 5 years among postmenopausal women), several analyses have addressed longer (10-year) vs. shorter (5-year) therapy with alendronate. At 10-year followup, the cumulative risk of nonvertebral fractures was not significantly different between those continuing (19 percent) and discontinuing (18.9 percent) alendronate.[240] Among women who continued alendronate, there was a significantly lower risk of clinically-recognized vertebral fractures (5.3 percent for placebo vs. 2.4 percent for alendronate; RR, 0.45; 95% CI: 0.24, 0.85) but no significant reduction in morphometric vertebral fractures. In a recent post hoc analysis of the FLEX data investigators assessed whether baseline BMD or pre-existing fracture could influence the effects of longer duration (10 year vs. 5 years) of therapy. Among women without vertebral fracture at FLEX baseline, alendronate continuation reduced nonvertebral fracture among women with FLEX baseline femoral neck T-scores of -2.5 or less [RR 0.50, 95% CI: 0.26, 0.96] but not among women with T-scores between -2.5 and -2 or less (RR 0.79, 95% CI: 0.37, 1.66) or with T-scores of greater than -2 (RR 1.41, 95% CI: 0.75, 2.66; p for interaction =.019). The investigators concluded that the continuation of alendronate for 10 years instead of stopping after 5 years reduces nonvertebral fracture risk in women without prevalent vertebral fracture whose femoral neck T-scores, achieved after 5 years of alendronate, are -2.5 or less but does not reduce risk of nonvertebral fracture risk among women without prevalent vertebral fractures whose T-scores are >-2.[243] Thus a limitation of this analysis is that it is post hoc with caveat these data support the thesis that certain features predict continued fracture reduction with a 10-year instead of 5 year duration of alendronate therapy: BMD T-score above -2 if women have baseline fractures, and BMD T-score <-2 if women do not have baseline fractures. The primary analysis of FLEX supports the thesis that for other women there is no evidence of a benefit on nonvertebral fracture reduction by continuing alendronate for ten as opposed to five years.

Data supporting the effectiveness of osteoporosis pharmacotherapy are much stronger for people who have established osteoporosis, as opposed to primary prevention. Regarding glucocorticoid-induced osteoporosis, the original review identified evidence from a systematic review and six additional RCTs. Results of these studies were mixed and overall the evidence was inconclusive, although suggestive of possible benefits for bisphosphonates. We did not identify any new studies to alter these conclusions.

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

Limitations of the Review

This review is an update of an earlier comparative effectiveness review. Because of the vast size of the existing literature, for both the earlier review and this review, we have relied in part on previously published systematic reviews and have not conducted new meta-analyses pooling the findings of all existing trials. Therefore, the findings may be less comprehensive than they might be. Further, because we did not conduct new meta-analyses, we cannot account quantitatively for the heterogeneity of the literature.

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 effects of these treatments. Because we did not conduct new meta-analyses to calculate pooled effect sizes for efficacy, we cannot estimate the actual publication bias in this literature.

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. The Jadad scores of the trials newly identified for this report ranged from 0 to 5 (mean, 2.9; median, 3). Thus the quality of included studies is a potential limitation for this report.

Other Potential Sources of Bias

In addition to the possible influence of study quality, we recognize several additional potential sources of bias: the applicability of the studies to the population that would be likely to benefit from the agents of interest and the potential bias inherent in interpreting adverse event data from studies.

We assessed the applicability of the trials included in the report using the method of Gartlehner et al.[25] In general, most trials were moderately to highly applicable to the population of persons at risk of osteoporosis (although the proportion of men enrolled in most of the trials is small). The exceptions tended to be smaller trials focused on groups of individuals with a

particular disease or condition that increased their risk for osteoporosis; thus the results of these trials would certainly be applicable to those populations.

Any assessment of a broad range of potential adverse effects may be subject to findings due to chance alone. Interpretation of statistically significant differences needs to consider the size of the effect, the consistency of the finding, the possibility of other reasons for the effect, and biological plausibility, among other things.

Conclusions

With the above limitations in mind, we reached the conclusions displayed in the table below (Table 57). Changes in conclusion in this report, compared to the 2007 report are presented in **bold.**

Table 57. Summary of evidence

Strength of Evidence		Conclusion
Key Question 1. What are the comparative benefits in fracture risk reduction among the following treatments for low bone density:		
a. Bisphosphonates	High	Vertebral fractures: alendronate, risedronate, ibandronate, and zoledronic acid reduce the risk of vertebral fractures among postmenopausal women with osteoporosis.
	High	Non-vertebral fractures: alendronate, risedronate, and zoledronic acid reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis.
	High	Hip fractures: alendronate, risedronate and zoledronic acid reduce the risk of hip fractures among postmenopausal women with osteoporosis. **The effect of ibandronate is unclear, since hip fracture risk reduction was not a separately reported outcome in trials reporting nonvertebral fractures.**
	Low	Wrist fractures: alendronate reduces the risk of wrist fractures among postmenopausal women with osteoporosis. **Risedronate in a pooled analysis of two trials was associated with a lower risk of wrist fractures, but this did not quite reach the conventional level of statistical significance.**
	Insufficient	Data are insufficient from head-to-head trials of bisphosphonates to prove or disprove superiority for the prevention of fractures for any agent.
	Insufficient	Data are insufficient from head-to-head trials of bisphosphonates compared to calcium, **teriparatide,** or raloxifene to prove or disprove superiority for the prevention of fractures.
	Moderate	Based on six RCTs, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison with menopausal hormone therapy.
b. 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.
c. Denosumab	**High**	**Denosumab reduces the risk of vertebral, nonvertebral and hip fractures in postmenopausal women with osteoporosis.**
d. Menopausal hormone therapy	**High**	Menopausal hormone therapy reduces the risk of vertebral and hip fractures in postmenopausal women.
	Moderate	**Menopausal hormone therapy does not reduce fracture risk significantly in postmenopausal women with established osteoporosis.**
e. PTH (teriparatide)	**High**	**Teriparatide reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.**
	Moderate	**Teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.**
f. SERMs (raloxifene)	High	Raloxifene **reduces the risk of** vertebral fractures among postmenopausal women with osteoporosis.
g. Vitamin D	**Low-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.
h. Exercise in comparison to above agents	**Insufficient**	There are no data from RCTs to inform this question. **One RCT that assessed the effect of a brief exercise program on fracture risk found a small decrease in risk of fractures among exercisers but the study was not powered to detect differences in fracture risk.**

Table 57. Summary of evidence (continued)

Strength of Evidence	Conclusion
Key Question 2. How does fracture risk reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), *risk assessment score,* ***prior fractures (prevention vs. treatment),[g] age, sex, race/ethnicity, and glucocorticoid use?***	
High	Alendronate, ibandronate, risedronate, teriparatide, raloxifene, **zoledronic acid,** and **denosumab** reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis.
Moderate	**Low femoral neck BMD does not predict the effects of alendronate on clinical vertebral or nonvertebral fracture risk.**
Insufficient	**Prevalent fracture predicted the effect of alendronate on fracture risk in one study but not another.**
Low-moderate	**Risedronate reduces the risk of fragility fracture among postmenopausal women with osteopenia who do not have prevalent vertebral fractures.**
Insufficient	**Prevalent fracture predicts the efficacy of raloxifene for fracture prevention in some studies but not others.**
Moderate	**Prevalent fractures increase the relative efficacy of teriparatide in preventing fractures.**
Moderate	Raloxifene prevents fractures in postmenopausal women at low risk for fracture **as assessed by FRAX.**
Insufficient	Teriparatide and risedronate **but not calcium and vitamin D** reduce risk of fracture among *men*.
High	**In general age does not predict the efficacy of bisphosphonates or teriparatide.**
High	**Raloxifene decreases the risk for vertebral fracture but not nonvertebral or hip fracture among postmenopausal Asian women, similar to other postmenopausal women.**
Moderate-High	Among *subjects treated with glucocorticoids*, fracture risk reduction was demonstrated for alendronate, risedronate, and **teriparatide.**
Insufficient	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*.
Insufficient	**Evidence is inconclusive on the effects of renal function on the efficacy of alendronate, raloxifene, and teriparatide in preventing fractures.**
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*.
Key Question 3. What are the adherence 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?	
Moderate	**Eighteen RCTs reported rates of adherence to therapy. Twelve trials with bisphosphonates and two trials with denosumab reported high levels of adherence (majority with over 90% adherence). Two trials with raloxifene had adherence rates 65-70%.**

[g] Prevention vs. treatment: If a person begins pharmacotherapy after having sustained fractures (i.e., the person has prevalent fractures), the therapy is considered treatment because the person, by definition, has osteoporosis and the medication is being administered to treat the condition. When these medications are administered to individuals with no prior fractures, these are individuals who have been identified as being at risk for osteoporosis (due to low bone density), but who don't actually (yet) have osteoporosis. They are being given the medication to prevent the onset of osteoporosis (i.e., further lowering of bone density and/or a first fracture).

Table 57. Summary of evidence (continued)

Strength of Evidence	Conclusion
High	**There is evidence from 58 observational studies, including 24 using U.S. data, that adherence and persistence with therapy with bisphosphonates, calcium, and vitamin D is poor in many patients with osteoporosis. One study described adherence with teriparatide. No studies describe primary nonadherence (i.e. nonfulfillment).**
Moderate	**Based on evidence from 41 observational studies, many factors affect adherence and persistence with medications including, but not limited to, dosing frequency, side effects of medications, co-morbid conditions, knowledge about osteoporosis, and cost. Age, prior history of fracture, and concomitant medication use do not appear to have an independent association with adherence or persistence.**
High	**Based on 20 observational studies, dosing frequency appears to affect adherence/persistence: adherence is improved with weekly compared to daily regimens, but current evidence is lacking to show that monthly regimens improve adherence over that of weekly regimens.**
Moderate	**Evidence from a systematic review and 15 out of 17 observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, nonvertebral or both).**
Low	**The evidence on adherence to raloxifene, teriparatide, and other drugs and its association with fracture risk is insufficient to make conclusions.**
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?	
High	Participants who took raloxifene showed higher odds for pulmonary embolism than did participants who took a placebo. Raloxifene participants also had greater odds of thromboembolic events.
High	Estrogen and estrogen-progestin combination participants had higher odds of cerebrovascular accident (CVA) and thromboembolic events than did placebo participants.
High	**A pooled analysis of ten trials found an increased risk with raloxifene for myalgias, cramps, and limb pain.**
High	We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as “mild upper GI events.” Our pooled analyses **showed alendronate had a slightly increased risk of** mild upper GI events. Alendronate participants also had higher odds of mild upper GI events in head-to-head trials vs. menopausal hormone therapy. **Pooled analysis also showed alendronate users to be at an increased risk for mild GI events compared to denosumab. Denosumab was also associated with an increase in mild GI events.**
Low	**A new systematic review of 15 placebo-controlled trials of calcium (administered for bone health in all trials but one) identified a statistically significant increase in the risk of myocardial infarction; however serious concerns have been expressed about possible bias.**
Moderate	**Teriparatide-treated participants showed a significant increase in hypercalcemia.**
Insufficient	The literature is equivocal on the potential association between bisphosphonates and the risk of atrial fibrillation.
High	**One trial, one post hoc analysis of three trials, two large observational studies, and a review of 2,408 cases of osteonecrosis of the jaw in patients taking bisphosphonates for osteoporosis prevention or treatment found that the incidence of osteonecrosis of the jaw in this group was small, ranging from less than one to 28 cases per 100,000 person-years of treatment.**
High	**Our pooled analysis of eight trials found an increased risk with raloxifene of hot flashes.**
Low	**Limited data from clinical trials and observational studies support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Data are not consistent, nevertheless these data were sufficient for FDA to issue a Warning**

Table 57. Summary of evidence (continued)

Strength of Evidence	Conclusion
	regarding this possible adverse event.
Moderate	A pooled analysis of three trials of teriparatide found an increased risk of headaches.
High	A pooled analysis of four trials of denosumab found an increased risk of rash but no increase in the risk for injection-site reactions.
Moderate	A small number of clinical trials have reported an increased risk of hypocalcemia in patients treated with alendronate and zoledronic acid.
Insufficient	Four observational studies that assessed whether the use of an oral bisphosphonate is associated with an increased risk of esophageal cancer had mixed findings.
High	A pooled analysis of four trials of denosumab found an increased risk for infection.
Key Question 5a. How often should patients be monitored (via measurement of bone mineral density) during therapy?	
Insufficient	The role of BMD monitoring during therapy has not been explicitly studied; therefore any conclusions must be based on indirect evidence.
High	Changes in BMD during therapy account for only a small proportion of the decrease in fracture risk; while some studies suggest that greater change in BMD in active therapy groups predicts greater antifracture efficacy, these changes have not been demonstrated to apply to individuals. Even patients who continue to lose BMD during therapy have had statistically significant benefits in fracture reduction. Clinical guidance is lacking on appropriate responses to declines in BMD under active therapy, such as increasing medication dose, or the influence of discontinuing therapy among individuals who experience declines in BMD under active therapy but may nonetheless derive fracture protection.
Key Question 5b. How does the antifracture benefit vary with long-term continued use of pharmacotherapy?	
Moderate	One large RCT showed that after 5 years of initial alendronate therapy, vertebral fracture risk and nonvertebral fracture risk were lower if alendronate was continued for an additional 5 years instead of discontinued.
Low	A post hoc analysis of this same trial reported that there were statistically significant nonvertebral fracture risk reductions for women who at baseline had no vertebral fracture but had a BMD score of –2.5 or less.

Discussion

This report provides a comprehensive summary of the systematic reviews and RCTs that evaluated the effect of various agents on fracture risk. Across these studies there is a high level of evidence that alendronate, risedronate, ibandronate, zoledronic acid, raloxifene, denosumab, and teriparatide each reduce the risk of vertebral fractures among postmenopausal women with osteoporosis. A high level of evidence shows that alendronate, risedronate, zoledronic acid, and denosumab each reduce the risk of nonvertebral fractures among postmenopausal women with osteoporosis. There is a high level of evidence that alendronate, risedronate, denosumab, and zoledronic acid each decrease the risk of hip fractures among postmenopausal women with osteoporosis. A high level of evidence supports the effectiveness of menopausal hormone therapy in decreasing vertebral fracture and hip fracture risk, and the effectiveness of teriparatide in reducing nonvertebral fracture risk. Accordingly, each of these agents is FDA-approved for therapy of osteoporosis. Studies directly comparing the antifracture effects among various bisphosphonates are few and do not provide conclusive evidence supporting the effectiveness of one bisphosphonate over another, despite some basic scientific evidence for why they might differ.[481] Neither is there evidence for statistically significant differences in the effects of bisphosphonates compared to raloxifene, teriparatide, or menopausal hormone therapy. Multiple RCTs do not demonstrate the effectiveness of calcium alone in reducing risk of vertebral, nonvertebral, or hip fractures. However it is critical to note that the currently approved prescription osteoporosis therapies are only proven efficacious in RCTs that administered concurrent calcium and vitamin D. A moderate level of evidence supports the effectiveness of vitamin D in combination with calcium in reducing hip fracture risk among institutionalized persons. No RCTs of exercise interventions have demonstrated a reduction in fracture risk.

This report reviewed evidence regarding whether the effectiveness of osteoporosis therapy may vary according to certain characteristics. Few data informed the question of whether antifracture effects varied by baseline FRAX score. In post hoc analyses of RCTs, the effectiveness of alendronate in decreasing vertebral fracture risk among postmenopausal women with T-score between -2 and -2.5 was confined to women with baseline vertebral fractures. Evidence was inconsistent regarding whether raloxifene's effectiveness against fracture risk was more pronounced among women with baseline vertebral fracture. Post hoc analyses suggest that age may modify the effect of risedronate or zoledronic acid on fracture, with a more pronounced effect among women less than 70 to 75 years-old. Few studies address relative effectiveness of osteoporosis pharmacotherapy according to race/ethnicity, age, or sex.

The data described in this report and the prior evidence review document variable and overall poor adherence and persistence with medications for osteoporosis. Any comprehensive evidence review of the factors affecting adherence and persistence with medications for osteoporosis is fraught with challenges, the most important of which is the tremendous heterogeneity in how adherence and persistence are defined and measured. This problem is not unique to the osteoporosis literature. Nonetheless, in the prior evidence review 25 studies were identified that discussed factors affecting adherence, and in the current review we identified 58 new studies describing the factors affecting adherence or persistence or associated with adherence or persistence. The factors discussed were numerous, and we describe in detail five of the most commonly studied (i.e., age, prior history of fracture, dosing frequency, polypharmacy, and adverse events). Of these five, the data support only dosing frequency and adverse events as independent factors related to adherence or persistence. Weekly dosing of bisphosphonates

appears to improve adherence and persistence compared to daily dosing, although the evidence for any additional improvement in adherence using monthly or less frequently dosed bisphosphonates is scant. The role of once yearly bisphosphonates in improving adherence is unclear, and any potential improvement in adherence based on dosing frequency must be balanced by potential barriers to improved adherence such as cost and necessity of IV infusion. For all of these factors that potentially affect adherence and persistence, there is only very limited understanding of how the factors interact, and their relative influence on adherence and persistence when they coexist.

Despite the many barriers to adherence discussed in the literature, very few interventions to improve osteoporosis medication adherence have been successful. Gleeson performed a comprehensive systematic review of the topic[263] identifying only 7 relevant randomized trials of adherence interventions, none of which were double blinded and only one of which included fracture outcomes. Of the three out of five successful adherence interventions, each included some version of enhanced communication between patient and healthcare provider, which may provide a clue for how to move forward on addressing the adherence problem. Gleeson comment on the necessity of standardizing the measurement of adherence in the literature, which is a conclusion we reach as well.

The data on the relationship between poor adherence and fracture risk are clear, and the inverse relationship between adherence and fracture risk persists, with worse adherence to bisphosphonates associated with increased risk of fracture. However, in the current review, these data all come from observational studies. The one randomized trial that assessed the role of adherence in fracture reduction studied raloxifene[120] and found no difference in antifracture effects between those who were at least 70 percent adherent and those who were not. Note that adherence in randomized trials of bisphosphonates is quite high (often >90%) (adherence being a frequent requirement for inclusion in the analyses), meaning that the power to detect small differences in fracture outcomes among those adherent versus not would be limited. Nevertheless, efforts could be made to report these subgroup differences in randomized trials if additional data on this topic were desired. The evidence for a "healthy adherer" effect in the two studies examined was not high, although subsequent observational studies should account for the possibility of this effect when studying the relationship between hip fractures and bisphosphonate adherence.

We reviewed evidence regarding adverse effects of osteoporosis pharmacotherapies. Zoledronic acid was associated with a statistically significantly increased risk of atrial fibrillation in a pooled analysis, but not in a meta-analysis. Thus, no association is yet proven, and further elucidation is required. Bisphosphonates are generally targeted to older individuals, so future studies will benefit from careful attention to the contribution of increasing age itself as a determinant of atrial fibrillation risk. Women taking raloxifene had higher odds of deep vein thrombosis, thromboembolic events, and vasomotor flushing. Compared to placebo, women taking estrogen or estrogen-progestin therapy had higher odds of stroke and thromboembolic events. Raloxifene increases the risk of myalgias, cramps, and limb pain. Several agents (alendronate, teriparatide, and denosumab) were associated with mild upper GI events (acid reflux, esophageal irritation, nausea, vomiting, and/or heartburn). We found low evidence that calcium therapy statistically significantly increased the risk of myocardial infarction, and that PTH increased risk of hypercalcemia. Compared to placebo, women taking menopausal estrogen therapy had lower odds, and women taking combined estrogen + progestin therapy had higher odds, of breast cancer. In a single study, estrogen + progestin therapy decreased the odds of

colon cancer. The vast majority (89 percent) of cases of osteonecrosis of the jaw among users of bisphosphonates are related to treatment of malignancy, and 88 percent of cases occurred in people taking intravenous therapy. Limited inconsistent data support a possible association between bisphosphonate use and atypical subtrochanteric femur fracture. Moderate evidence suggests that teriparatide increases risk of headaches, and that denosumab increases risk of rash.

For clinicians, this report contributes information that may inform prescribing decisions. Bisphosphonates and denosumab are the only agents for which there is a high level of evidence for reduction in hip fracture risk. For reduction in vertebral fracture risk, there is a high level of evidence supporting the use of bisphosphonates, raloxifene, denosumab, and teriparatide. Raloxifene is not effective in reducing the risk of hip or nonvertebral fractures. Evidence for antifracture effects of currently available osteoporosis therapies is greatest among those with established osteoporosis, meaning with existing fracture, or with T-score less than -2.5. Because at least half of osteoporotic fractures occur in individuals with T scores between -1 and -2.5, clinicians require the ability to identify which individuals with T-scores between -1 and -2.5 are likely to experience fracture. Older individuals are as likely to benefit from treatment as younger individuals, in terms of reduced fracture risk. With the advent of tools such as the WHO FRAX, selection of treatment candidates will likely be refined. Emerging research is judging the antifracture effects of medications according to level of baseline FRAX score.

Post hoc analyses of open-label extension data support the thesis that certain features predict continued fracture reduction with a 10-year instead of 5-year duration of alendronate therapy: BMD T-score above -2 if women have baseline fractures, and BMD T-score <-2 if women do not have baseline fractures. It is unknown if these same precepts will hold with other osteoporosis pharmacotherapies. We cannot provide information regarding comparative effectiveness of various agents when used long-term, because studies have not directly compared the antifracture effects of longer durations of therapy among various therapies.

Clinicians should be aware that, among people taking FDA-approved osteoporosis pharmacotherapy, changes in BMD are poor predictors of antifracture effects. Serial BMD monitoring may be useful for other purposes, and this area of research is under active investigation.

Future Research

Compared to the evidence available at the time of our prior report, additional evidence has emerged to clarify differences in anti-fracture efficacy between pharmacologic agents used to treat osteoporosis (e.g. hip fracture reduction only demonstrated for bisphosphonates and denosumab), and even among bisphosphonates (e.g. hip fracture reduction demonstrated for zoledronic acid, alendronate, and risedronate, but not ibandronate) among postmenopausal women with established osteoporosis. Nonetheless, data are thin regarding comparative effectiveness between different agents and several concerns remain:

1. Whom should we treat? What is the balance of benefits and harms for postmenopausal women without established osteoporosis? The existing evidence shows that the strength of evidence for a benefit of treatment (in terms of fracture risk reduction) is low to moderate for postmenopausal women with osteopenia and without prevalent fractures and for men compared with postmenopausal women with established osteoporosis for whom the evidence is high. Given the established adverse events associated with treatment, and newly identified risks such as atypical subtrochanteric femur fractures, the question of whom to treat outside of postmenopausal women with established osteoporosis is perhaps less clear now than it was before. One way forward is to move away from BMD-based measures of risk and conduct trials that use a risk assessment- based method of identifying patients, such as the FRAX. Such risk assessment methods can incorporate other variables known to be associated with risk of fracture that go beyond BMD. Re-analysis of existing trials should assess whether application of FRAX estimates post-hoc allows for identification of subgroups of subjects at higher or lower risk than the typical subjects.
2. How long should we treat? The evidence base here is especially thin – the existing evidence is really just one trial, and one post hoc analysis of that trial, which suggests that treatment beyond five years with alendronate does not have a benefit in nonvertebral fracture risk reduction, except possibly in women with low BMD at baseline. Should treatment be for three years, four years, five years, or more? And what patient-level factors are important (such as the aforementioned low BMD at baseline) in terms of determining length of treatment? "Drug holidays" have been advocated by some clinicians – what are the benefits and harms of such holidays? When should they be timed? For how long should the "holiday" last? Could the efficacy of drug holidays vary according to pharmacologic profiles (e.g. route or frequency of administration) of the various bisphosphonates? And should all therapies be subject to a holiday, a point raised by a recent basic science analysis of denosumab?[482]
3. For people who are good candidates for treatment, how can we improve adherence? There is a moderate to high level of evidence that adherence is commonly poor, and that poor adherence is associated with worse fracture outcomes. This work needs to consider not just the dosing barriers to adherence, but the other factors reported in the evidence (e.g., side effects, knowledge about osteoporosis, and cost.) The role of newer therapies administered once or twice yearly in improving adherence and persistence, and their cost-effectiveness, should be investigated.
4. For patients on treatment, should we monitor changes in BMD, and if so, how often? While no studies have examined explicitly the benefits and harms of BMD monitoring while on therapy, the practice remains popular, although the rationale for it is not clear. Post hoc analyses of trials of treatment show that changes in BMD while on

treatment only modestly predict fracture risk reduction, and even patients whose BMD declines while on treatment have statistically significant reductions in fracture risk.

5. What is the comparative effectiveness of sequential treatment (following treatment with one class of agent by treatment with another)? We identified no clinical trials on the use of sequential treatment, although anecdotal evidence suggests that it is done in clinical practice (either intentionally, in the belief that it is superior to continued treatment with a single agent, or because some individuals do not respond to or cannot tolerate a particular agent). Thus studies are needed to assess the effectiveness of sequential regimens.
6. We need to remain vigilant for possible rare side effects. The identification – since our prior 2007 report – of an association between bisphosphonate use and atypical subtrochanteric fractures of the femur demonstrates the importance of the continuing need for surveillance, as this identification was not widely reported until after well more than a decade of widespread use.

Note: Several studies in this report have been retracted and are highlighted below. More information is located on the journals' websites and the Retraction Watch database.

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Abbreviations

ACE	Annual Cumulative Exposure
ACP	American College of Physicians
AE	Adverse Events
AF	Atrial Fibrillation
AHRQ	Agency for Healthcare Research and Quality
BALP	Bone Alkaline Phosphatase
BMD	Bone Mineral Density
CABG	Coronary Artery Bypass Graft
CEE	Conjugated Equine Estrogen
CER	Comparative Effectiveness Review
CFOS	Cystic Fibrosis Osteoporosis Study
CHD	Coronary Heart Disease
CI	Confidence Interval
CTX	Carboxy-Terminal Collagen Crosslinks
CVA	Cerebrovascular Accidents
DVT	Deep Venous Thrombosis
DXA	Dual Energy X-ray Absorptiometry
E	Estradiol
EPC	Evidence-based Practice Center
EPT	Combined Estrogen-Progestogen Therapy
ET	Estrogen Therapy
FDA	Food and Drug Administration
FIT	Fracture Intervention Trial
FRAX	Fracture Risk Assessment Tool
GC	Glucocorticoid
GI	Gastrointestinal
H	Hip
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly
HR	Hazard Ratio
HT	Hormone Therapy (encompassing both ET and EPT)
IMS	Information Management System
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KQ	Key Question
Local Therapy	Vaginal ET administration that does not result in clinically significant systematic absorption
MeSH	Medical Subject Headings
MI	Myocardial Infarction
MORE	Multiple Outcomes of Raloxifene Evaluation
MPA	Medroxyprogesterone
MPR	Medication Possession Ratio
NC	Not Calculable
NE	Norgestimate

NE	Not Estimable
NR	Not Reported
NV	Non-Vertebral
NYHA	New York Heart Association
OR	Odds-ratios
PDC	Proportion of days covered
PE	Pulmonary Embolism
Progestogen	Encompassing both progesterone and progestin
PTH	Parathyroid Hormone
PUB	Perforations, Ulcerations, and Bleeds
RCT	Randomized Controlled Trial
RD	Rate Difference
RR	Relative Risks
SCHIP	State Children's Health Insurance Program
SERM	Selective Estrogen Receptor Modulator
SRC	Scientific Resource Center
Systematic therapy	HT administration that results in absorption in the blood high enough to provide clinically significant effects
TEP	Technical Expert Panel
Timing of HT initiation	Length of time after menopause when HT is initiated
TOP	Treatment of Osteoporosis with Parathyroid Hormone Study
UTI	Urinary Tract Infection
V	Vertebral
VA	Veterans Administration
VERT	Vertebral Efficacy with Risedronate Therapy
W	Wrist/Forearm
YRS	Years

Appendix A. Search Methodology

LOW BONE DENSITY
SEARCH METHODOLOGIES

INITIAL SEARCHES RAN SEPTEMBER 2009, COVERING 2005-DECEMBER2009 UPDATE SEARCHES PERFORMED IN OCTOBER/NOVEMBER 2010 COVERING JUNE 2009-OCT/NOV 2010. FINAL UPDATE SEARCH PERFORMED IN MARCH 2011 COVERING NOV 2010-END OF MARCH 2011. PUBMED ALERTS WERE SENT PERIODICALLY THROUGH THE PROJECT.

SEARCH #1A (Run 9/4/09):
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-8/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab
NOT
animal* NOT (human OR humans*)

NUMBER OF ITEMS RETRIEVED: 1953

==

SEARCH #1B (Run 9/4/09):
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-8/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
bisphosphonate*
NOT
animal* NOT (human OR humans*)

NUMBER OF ITEMS RETRIEVED: 1018

==

SEARCH #2A:
DATABASE SEARCHED & TIME PERIOD COVERED:
International Pharmaceutical Abstracts – 2005-6/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2n)mineral OR bone(2n)density
AND
alendronate? OR fosamax OR risedronate? OR actonel OR etidronate? OR didronel OR ibandronate? OR boniva OR pamidronate? OR aredia OR zoledronic()acid OR zometa OR droloxifene? OR denosumab

NUMBER OF ITEMS RETRIEVED: 522

==

SEARCH #2B:
DATABASE SEARCHED & TIME PERIOD COVERED:
International Pharmaceutical Abstracts – 2005-6/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2n)mineral OR bone(2n)density
AND
bisphosphonate?

NUMBER OF ITEMS RETRIEVED: 263

==

SEARCH #3A:
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 2005-9/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2n)mineral OR bone(2n)density
AND
alendronate? OR fosamax OR risedronate? OR actonel OR etidronate? OR didronel OR ibandronate? OR boniva OR pamidronate? OR aredia OR zoledronic()acid OR zometa OR droloxifene? OR denosumab

NUMBER OF ITEMS RETRIEVED: 2471

===

SEARCH #3B:
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 2005-6/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2n)mineral OR bone(2n)density
AND
bisphosphonate?
NOT
Results of Search 3A

NUMBER OF ITEMS RETRIEVED: 558

===

SEARCH #4A (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-9/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
raloxifene* OR evista OR tamoxifen* OR nolvadex OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene* OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms

NUMBER OF ITEMS RETRIEVED: 780

===

SEARCH #4B (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-9/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
strontium

NUMBER OF ITEMS RETRIEVED: 222

==

SEARCH #4C (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-9/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh]
OR bone density
AND
tibolone

NUMBER OF ITEMS RETRIEVED: 69

==

SEARCH #4D (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-9/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh]
OR bone density
AND
pth OR parathyroid hormone*
NOT
animal* NOT (human OR humans) OR rat OR rats OR mice
NOT
Results of previous searches

NUMBER OF ITEMS RETRIEVED: 1486

==

SEARCH #4E (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-9/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh]
OR bone density
AND

"Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol*
NOT
animal* NOT (human OR humans) OR rat OR rats OR mice OR monkey*
NOT
Results of previous searches

NUMBER OF ITEMS RETRIEVED: 927

==

SEARCH #4F (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-9/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
calcium
NOT
animal* NOT (human OR humans) OR rat OR rats OR mice
NOT
Results of previous searches

NUMBER OF ITEMS RETRIEVED: 2874

==

SEARCH #4G (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-9/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
vitamin d
NOT
animal* NOT (human OR humans) OR rat OR rats OR mice OR monkey*
NOT
Results of previous searches

NUMBER OF ITEMS RETRIEVED: 655

==

SEARCH #4H (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-9/2009

SEARCH STRATEGY:
teriparatide
NOT
pth OR parathyroid hormone*

NUMBER OF ITEMS RETRIEVED: 216
==

SEARCH #4I (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase– 2005-11/5/2009

LANGUAGE: English
OTHER LIMITERS: Human

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2w)mineral OR bone(2n)density/ in Title, Subject Heading fields
and
calcium or vitamin()d ORr estrogen OR oestrogen OR estradiol? OR lasofoxifene? OR pth OR parathyroid()hormone? OR teriparatide OR forteo OR preos OR raloxifene? OR evista OR selective()estrogen()receptor()modulator? OR serm OR serms OR exercise OR physical()activity/ in Title, Subject Heading fields
NOT
editorial OR letter

NUMBER OF ITEMS RETRIEVED: 8608
==

SEARCH #4J (Efficacy) :
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase– 2005-11/17/2009

LANGUAGE: English
OTHER LIMITERS: Human

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2w)mineral OR bone(2n)density in Title, Subject Heading fields
and
lasofoxifene? OR denosumab OR pth OR parathyroid()hormone? OR teriparatide? OR forteo OR preos
NOT
editorial OR letter

NUMBER OF ITEMS RETRIEVED: 2793
==

SEARCH #5A (Compliance) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-10/14/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher* OR persistence
NOT
animal* NOT (human OR humans)

NUMBER OF ITEMS RETRIEVED: 1258

==

SEARCH #5B(Compliance revision) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-10/14/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher* OR persistence
AND
alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR raloxifene* OR evista OR tamoxifen* OR nolvadex OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene* OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms OR calcium OR pth OR parathyroid hormone* OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR vitamin d OR testosterone OR exercise* OR exercising OR physical activity OR "Exercise Therapy"[Mesh] OR drug therapy OR drug[tiab] OR drugs[tiab] OR medication* OR therapy[tiab] OR therapies[tiab] OR treatment[tiab]

NUMBER OF ITEMS RETRIEVED: 953
NUMBER OF ITEMS RETRIEVED AFTER MANUALLY REMOVING DUPLICATES FROM SEARCH 4A AND REMOVING ANIMAL-ONLY STUDIES: **389**

==

SEARCH #6A(Frax) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-11/11/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
frax

NUMBER OF ITEMS RETRIEVED: 49
==

SEARCH #6B(Frax) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-11/11/2009

LANGUAGE: English

SEARCH STRATEGY:
frax

NUMBER OF ITEMS RETRIEVED: 100
==

SEARCH #6C(Frax) :
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 2005-11/12/2009

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture? OR bone(2w)mineral OR bone(2n)density
AND
frax

NUMBER OF ITEMS RETRIEVED: 31
==

SEARCH #7(Monitoring) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-11/11/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND

monitor*
NOT
animal* NOT (human OR humans)

NUMBER OF ITEMS RETRIEVED: 1369
==

SEARCH #8(Related Articles) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-11/11/2009

SEARCH STRATEGY:
"Related Articles" search on:
Bell, K.J.L., "Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data." BMJ Online First, 2009.

BMJ. 2009 Jun 23;338:b2266.

NUMBER OF ITEMS RETRIEVED: 100
==

SEARCH #9A(Adverse Effects) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-11/17/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture* OR bone mineral OR fractures[mh] OR bone density
AND
"adverse effects "[Subheading] OR ("Drug Toxicity"[Mesh] OR "toxicity "[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab]
AND
raloxifene* OR evista OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms OR calcium OR "vitamin d" OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR oestrogen OR pth OR parathyroid hormone* OR teriparatide OR forteo OR preos OR alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab
NOT
animal* NOT (human OR humans) OR rat[ti] OR rats[ti] OR mice[ti] OR murine[ti]
NOT
review[pt]

NUMBER OF ITEMS RETRIEVED: 1746
==

SEARCH #9B(Adverse Effects) :

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-11/17/2009

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis OR osteopenia OR osteopaenia OR fracture* OR bone mineral OR fractures[mh] OR bone density
AND
"adverse effects "[Subheading] OR ("Drug Toxicity"[Mesh] OR "toxicity "[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab]
AND
alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate OR bisphosphonates
NOT
animal* NOT (human OR humans) OR rat[ti] OR rats[ti] OR mice[ti] OR mouse[ti] OR murine[ti]
NOT
review[pt]

NUMBER OF ITEMS RETRIEVED: 877
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SEARCH #9C(Adverse Effects) :
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-12/3/2009

LANGUAGE: English
OTHER LIMITERS: Human

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate* OR raloxifene OR lasofoxifene OR serm OR serms OR selective estrogen receptor modulator* OR calcium OR "vitamin d" OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR oestrogen OR pth OR parathyroid hormone* OR teriparatide OR forteo OR preos
AND
"adverse effects "[Subheading] OR ("Drug Toxicity"[Mesh] OR "toxicity "[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab] OR risk OR risks OR risking

OR
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND

raloxifene OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR oestrogen OR (hormone* AND menopaus*)
AND
thrombosis OR thrombophlebitis OR phlebitis OR clot OR clots OR clotting

OR
alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate*
AND
esophageal OR esophagus OR fibrillat*

OR
raloxifene
AND
flash* OR flush*

NUMBER OF ITEMS RETRIEVED (AFTER REMOVAL OF DUPLICATES): 441

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PUBMED ALERT – ESTABLISHED 12/2009
meta-analysis as topic OR meta analy*[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab]
Limits: English

Note – Records pertinent to low bone density project are identified and sent to research staff

FINAL SEARCH RESULTS FILTERING:
Search results were aggregated into one master EndNote file, where duplicates were removed. Animal-only studies were identified by searching both "Animal NOT Human" in the Keyword field and terms for specific animals in the title, and were manually removed from the database.

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SEARCHES PERFORMED IN OCTOBER/NOVEMBER 2010 COVERING FROM JUNE 2009-OCT/NOV 2010:

SEARCH #1A PUBMED (BISPHOSPHONATES)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/2009-11/12/2010
LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND

alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate*
NOT
animal* NOT (human OR humans*)
NOT
mice OR mouse OR murine OR rat OR rats

NUMBER OF ITEMS RETRIEVED: 1030

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SEARCH #1B PUBMED (SERMS)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/2009-11/12/2010
LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
raloxifene* OR evista OR tamoxifen* OR nolvadex OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene* OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms
NOT
animal* NOT (human OR humans*)
NOT
mice OR mouse OR murine OR rat OR rats

NUMBER OF ITEMS RETRIEVED: 204

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SEARCH #1C PUBMED (TESTOSTERONE/ EXERCISE)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/2009-11/12/2010
LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
testosterone OR exercise* OR exercising OR physical activity OR "Exercise Therapy"[Mesh] NOT
animal* NOT (human OR humans*)
NOT
mice OR mouse OR murine OR rat OR rats

NUMBER OF ITEMS RETRIEVED: 846

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SEARCH #1D PUBMED (OTHER TREATMENTS)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/2009-11/12/2010
LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
strontium OR tibolone OR pth OR parathyroid hormone* OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR calcium OR vitamin d OR teriparatide OR forteo OR preos
NOT
animal* NOT (human OR humans*)
NOT
mice OR mouse OR murine OR rat OR rats

NUMBER OF ITEMS RETRIEVED: 2312

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SEARCH #1E PUBMED (COMPLIANCE)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/2009-11/12/2010
LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher* OR persistence
NOT
animal* NOT (human OR humans*)

NUMBER OF ITEMS RETRIEVED: 458

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SEARCH #1F PUBMED (FRAX)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/2009-11/12/2010

LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh]
OR bone density
AND
frax

NUMBER OF ITEMS RETRIEVED: 89

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SEARCH #1G PUBMED (MONITORING)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/2009-11/12/2010
LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh]
OR bone density
AND
monitor*

NUMBER OF ITEMS RETRIEVED: 516

==

SEARCH #1H PUBMED (ADVERSE EFFECTS)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 6/2009-11/15/2010
LANGUAGE: English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh]
OR bone density
AND
"adverse effects "[Subheading] OR ("Drug Toxicity"[Mesh] OR "toxicity "[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab] OR ((raloxifene OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR oestrogen OR (hormone* AND menopaus*) AND (thrombosis OR thrombophlebitis OR phlebitis OR clot OR clots OR clotting)) OR ((alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate*) AND (esophageal OR esophagus OR fibrillat*)) OR (raloxifene AND (flash* OR flush*))
NOT
animal* NOT (human OR humans)

NUMBER OF ITEMS RETRIEVED: 3069

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SEARCH #2A EMBASE (BISPHOSPHONATES)
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 6/2009-11/17/2010
LANGUAGE: English

SEARCH STRATEGY:
'osteoporosis'/exp OR osteoporosis OR 'osteopenia'/exp OR osteopenia OR osteopaenia OR fracture* OR (('bone'/exp OR bone) AND ('mineral'/exp OR mineral)) OR (('bone'/exp OR bone) AND ('density'/exp OR density))
AND
alendronate* OR 'fosamax'/exp OR fosamax OR risedronate* OR 'actonel'/exp OR actonel OR etidronate* OR 'didronel'/exp OR didronel OR ibandronate? OR 'boniva'/exp OR boniva OR pamidronate* OR 'aredia'/exp OR aredia OR zoledronic AND ('acid'/exp OR acid) OR 'zometa'/exp OR zometa OR droloxifene* OR 'denosumab'/exp OR denosumab OR bisphosphonate*

NUMBER OF ITEMS RETRIEVED: 991

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SEARCH #2B EMBASE (OTHER TREATMENTS)
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 6/2009-11/17/2010
LANGUAGE: English

SEARCH STRATEGY:
'osteoporosis'/exp OR osteoporosis OR 'osteopenia'/exp OR osteopenia OR osteopaenia OR fracture* OR (('bone'/exp OR bone) AND ('mineral'/exp OR mineral)) OR (('bone'/exp OR bone) AND ('density'/exp OR density))
AND
'calcium' OR 'calcium'/exp OR calcium OR 'vitamin d'/exp OR 'vitamin d' OR 'estrogen' OR 'estrogen'/exp OR estrogen OR 'oestrogen' OR 'oestrogen'/exp OR oestrogen OR estradiol* OR lasofoxifene* OR 'pth' OR 'pth'/exp OR pth OR 'parathyroid' OR 'parathyroid'/exp OR parathyroid AND hormone* OR 'teriparatide' OR 'teriparatide'/exp OR teriparatide OR 'forteo' OR 'forteo'/exp OR forteo OR 'preos' OR 'preos'/exp OR preos OR raloxifene* OR 'evista' OR 'evista'/exp OR evista OR (selective AND ('estrogen' OR 'estrogen'/exp OR estrogen) AND ('receptor' OR 'receptor'/exp OR receptor) AND modulator*) OR 'serm' OR 'serm'/exp OR serm OR serms OR 'exercise' OR 'exercise'/exp OR exercise OR (physical AND activity)
AND
humans

NUMBER OF ITEMS RETRIEVED: 2074

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SEARCH #2B EMBASE (FRAX)
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 6/2009-11/17/2010
LANGUAGE: English

SEARCH STRATEGY:
'osteoporosis'/exp OR osteoporosis OR 'osteopenia'/exp OR osteopenia OR osteopaenia OR fracture* OR (('bone'/exp OR bone) AND ('mineral'/exp OR mineral)) OR (('bone'/exp OR bone) AND ('density'/exp OR density))
AND
frax
AND
humans

NUMBER OF ITEMS RETRIEVED: 84

==

SEARCH #3 INTERNATIONAL PHARMACEUTICAL ABSTRACTS
DATABASE SEARCHED & TIME PERIOD COVERED:
International Pharmaceutical Abstracts – 2009-10/2010 (NOTE – THIS SEARCH COVERED ALL OF 2009)
LANGUAGE: English

SEARCH STRATEGY:
OSTEOPOROSIS OR OSTEOPENIA OR OSTEOPAENIA OR FRACTURE? OR BONE(2N)MINERAL OR BONE(2N)DENSITY
AND
ALENDRONATE? OR FOSAMAX OR RISEDRONATE? OR ACTONEL OR ETIDRONATE? OR DIDRONEL OR IBANDRONATE? OR BONIVA OR PAMIDRONATE? OR AREDIA OR ZOLEDRONIC()ACID OR ZOMETA OR DROLOXIFENE? OR DENOSUMAB OR BISPHOSPHONATE?

NUMBER OF ITEMS RETRIEVED: 110

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SEARCHES PERFORMED MARCH 2011:

SEARCH #1A PUBMED (BISPHOSPHONATES)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 11/2010-3/14/2011
LANGUAGE:

English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate*

NUMBER OF ITEMS RETRIEVED: 376

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SEARCH #1B PUBMED (SERMS)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 11/2010-3/14/2011
LANGUAGE:
English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
raloxifene* OR evista OR tamoxifen* OR nolvadex OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene* OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms

NUMBER OF ITEMS RETRIEVED: 72

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SEARCH #1C PUBMED (TESTOSTERONE/ EXERCISE)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 11/2010-3/14/2011
LANGUAGE:
English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
testosterone OR exercise* OR exercising OR physical activity OR "Exercise Therapy"[Mesh])

NUMBER OF ITEMS RETRIEVED: 230

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SEARCH #1D PUBMED (OTHER TREATMENTS)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 11/2010-3/14/2011
LANGUAGE:
English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
strontium OR tibolone OR pth OR parathyroid hormone* OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR calcium OR vitamin d OR teriparatide OR forteo OR preos

NUMBER OF ITEMS RETRIEVED: 839

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SEARCH #1E PUBMED (COMPLIANCE)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 11/2010-3/14/2011
LANGUAGE:
English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher* OR persistence

NUMBER OF ITEMS RETRIEVED: 130

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SEARCH #1F PUBMED (FRAX)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 11/2010-3/14/2011
LANGUAGE:
English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density

AND
frax

NUMBER OF ITEMS RETRIEVED: 39

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SEARCH #1G PUBMED (MONITORING)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 11/2010-3/14/2011
LANGUAGE:
English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
monitor*

NUMBER OF ITEMS RETRIEVED: 139

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SEARCH #1H PUBMED (ADVERSE EFFECTS)
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 11/2010-3/14/2011
LANGUAGE:
English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density
AND
adverse effects[Subheading] OR Drug Toxicity[Mesh] OR toxicity[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab]) OR thrombosis OR thrombophlebitis OR phlebitis OR clot OR clots OR clotting OR esophageal OR esophagus OR fibrillat* OR (raloxifene AND (flash* OR flush*))

NUMBER OF ITEMS RETRIEVED: 721

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SEARCH #2 EMBASE (ALL TOPICS)
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase –2010-3/14/2011 (NOTE – THIS SEARCH COVERED ALL OF 2010)
LANGUAGE:
English

SEARCH STRATEGY:
'osteoporosis' OR 'osteoporosis'/exp OR osteoporosis OR 'osteopenia' OR 'osteopenia'/exp OR osteopenia OR osteopaenia OR fracture* OR 'bone mineral'/exp OR 'bone mineral' OR 'bone minerals' OR (bone* AND dens*)
AND
alendronate* OR 'fosamax'/exp OR 'fosamax' OR risedronate* OR 'actonel'/exp OR 'actonel' OR etidronate* OR 'didronel'/exp OR 'didronel' OR ibandronate? OR 'boniva'/exp OR 'boniva' OR pamidronate* OR 'aredia'/exp OR 'aredia' OR zoledron* OR 'zometa'/exp OR 'zometa' OR droloxifene* OR 'denosumab'/exp OR 'denosumab' OR bisphosphonate* OR 'calcium' OR 'calcium'/exp OR calcium OR 'vitamin d'/exp OR 'vitamin d' OR 'estrogen' OR 'estrogen'/exp OR estrogen OR 'oestrogen' OR 'oestrogen'/exp OR oestrogen OR estradiol* OR lasofoxifene* OR 'pth' OR 'pth'/exp OR pth OR 'parathyroid' OR 'parathyroid'/exp OR parathyroid AND hormone* OR 'teriparatide' OR 'teriparatide'/exp OR teriparatide OR 'forteo' OR 'forteo'/exp OR forteo OR 'preos' OR 'preos'/exp OR preos OR raloxifene* OR 'evista' OR 'evista'/exp OR evista OR 'selective estrogen receptor' OR 'selective estrogen receptors' OR 'selective oestrogen receptor' OR 'selective oestrogen receptors' OR 'serm'/exp OR 'serm' OR serms OR 'exercise' OR 'exercise'/exp OR exercise OR (physical AND activity) OR frax OR monitor* OR noncomplian* OR 'non compliant' OR 'non compliance' OR nonadher* OR 'non adherent' OR 'non adherence' OR refuse OR refusal OR 'treatment refusal'/exp OR 'treatment refusal' OR complian* OR comply OR complies OR complying OR adher* OR persistence
AND
Humans

NUMBER OF ITEMS RETRIEVED: 2027

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SEARCH #3A INTERNATIONAL PHARMACEUTICAL ABSTRACTS
DATABASE SEARCHED & TIME PERIOD COVERED:
International Pharmaceutical Abstracts –2010-3/21/2011 (NOTE – THIS SEARCH COVERED ALL OF 2010)

SEARCH STRATEGY:
OSTEOPOROSIS OR OSTEOPENIA OR OSTEOPAENIA OR FRACTURE? OR BONE(2N)MINERAL OR BONE(2N)DENSITY
AND
ALENDRONATE? OR FOSAMAX OR RISEDRONATE? OR ACTONEL OR ETIDRONATE? OR DIDRONEL OR IBANDRONATE? OR BONIVA OR PAMIDRONATE? OR AREDIA OR ZOLEDRONIC()ACID OR ZOMETA OR DROLOXIFENE? OR DENOSUMAB OR BISPHOSPHONATE?

NUMBER OF ITEMS RETRIEVED: 61

==

SEARCH #3B INTERNATIONAL PHARMACEUTICAL ABSTRACTS
OSTEOPOROSIS OR OSTEOPENIA OR OSTEOPAENIA OR FRACTURE? OR BONE(2N)MINERAL OR BONE(2N)DENSITY
NOT
RESULTS OF SEARCH #1
NUMBER OF ITEMS RETRIEVED:144

Combined results from Searches 3A and 3B, after manually removing animal studies and duplicates from selected previous searches: 91

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COMBINED TOTAL OF ALL SEARCHES – DUPLICATES NOT REMOVED: 16,447
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PubMed ALERT (established 6/3/11)
osteoporosis OR osteopenia OR osteopaenia OR fracture* OR bone mineral OR fractures[mh] OR bone density
AND
alendronate* OR fosamax OR risedronate* OR actonel OR etidronate* OR didronel OR ibandronate* OR boniva OR pamidronate* OR aredia OR zoledronic acid OR zometa OR droloxifene* OR denosumab OR bisphosphonate* OR raloxifene* OR evista OR tamoxifen* OR nolvadex OR emblon OR fentamox OR soltamox OR tamofen OR bazedoxifene* OR lasofoxifene* OR selective estrogen receptor modulators OR serm OR serms OR strontium OR tibolone OR pth OR parathyroid hormone* OR "Estrogens"[Mesh] OR "Estrogens "[Pharmacological Action] OR estrogen*[tiab] OR estradiol* OR calcium OR vitamin d OR teriparatide OR forteo OR preos OR testosterone OR exercise* OR exercising OR physical activity OR "Exercise Therapy"[Mesh] OR noncomplian* OR non-complian* OR nonadher* OR non-adher* OR refuse OR refusal OR treatment refusal OR patient compliance OR complian* OR comply OR complies OR complying OR adher* OR persistence OR frax OR monitor* OR ("adverse effects "[Subheading] OR ("Drug Toxicity"[Mesh] OR "toxicity "[Subheading]) OR adverse OR harm OR harmful OR safe[tiab] OR safety[tiab] OR toxic*[tiab] OR thrombosis OR thrombophlebitis OR phlebitis OR clot OR clots OR clotting OR esophageal OR esophagus OR fibrillat* OR flash* OR flush*))

Limits: English

Alert results:
6/12/11 – 163 total.
Removed: 6 dups, 18 animal-only studies
139 results.

Appendix B. Data Abstraction Forms

Short Form Screener for all studies

RAND EPC LBD2 – Full-text Screener

Article ID:________________ Reviewer:________________

First Author: ________________________________ (Last Name Only)

Study Number: ___of___ Description:________________
(Enter '1of 1' if only one) (if more than one study)

1. Does this study include humans?
   - No .... 1 **STOP**
   - Yes 2

2. Study design: *Check all that apply*
   - Descriptive (historical, editorial, etc.) .... ☐ **STOP**
   - Background .... ☐ **GO TO 11**
   - Review/meta-analysis .... ☐
   - Randomized clinical trial .... ☐
   - Trial with open-label extension .... ☐
   - Controlled clinical trial .... ☐
   - Cohort/case control - 1000+ subjects .... ☐
   - Cohort/case control - under 1,000 subjects .... ☐
   - Case Report .... ☐
   - Other: ________________ ☐

3. Intervention(s) studied: *Check all that apply*
   - Alendronate (Fosamax) ☐
   - Bisphosphonates ☐
   - Calcium ☐
   - Vitamin D ☐
   - Denosumab ☐
   - Estrogen ☐
   - Etidronate (Didronel) ☐
   - Ibandronate (Boniva) ☐
   - Lasofoxifene ☐
   - Pamidronate (Aredia) (APD) ☐
   - PTH (Teriparatide) (Forteo) ☐
   - PTH (1-84) (Preos) ☐
   - Raloxifene (Evista) ☐
   - Risedronate (Actonel) ☐
   - Strontium ranelate ☐
   - Zoledronic acid (Zometa) ☐
   - Physical activity ☐
   - None of the above ☐

4. Which outcomes are used? *Check all that apply*
   - Bone density .... ☐
   - Bone formation or bone turnover .... ☐
   - Fractures .... ☐
   - Adverse events .... ☐
   - Adherence .... ☐
   - None of the above .... ☐ **STOP**

5. Does the article contain data on any of the following? *Check all that apply*
   - Efficacy .... ☐
   - Safety/adverse events .... ☐
   - Adherence .... ☐
   - Risk assessment .... ☐
   - DXA (Bone density monitoring) .... ☐
   - None of the above .... ☐ **STOP**

6. Participant enrollment criteria: *Check all that apply*
   - Healthy .... ☐
   - Osteopenia/low bone density .... ☐
   - Osteoporosis .... ☐
   - Fracture .... ☐
   - Other: ________________ ☐
   - None of the above .... ☐ **STOP**

7. Does the population comprise only persons currently being treated for cancer, Paget's disease, or multiple myeloma?
   - No 1
   - Yes .... 2 **STOP**

8. Study population: *Check all that apply*
   - Men .... ☐
   - Pre-menopausal women .... ☐
   - Post-menopausal women .... ☐
   - Women otherwise undefined .... ☐
   - Other: ________________ ☐
   - Unclear .... ☐

   Age
   - Adults 65 and over .... ☐
   - Adults under 65 .... ☐
   - Other: ________________ ☐
   - Unclear .... ☐

   Race
   - Exclusively Caucasian .... ☐
   - Non-Caucasian included .... ☐
   - Other: ________________ ☐
   - Unclear .... ☐

   Other
   - Steroid-induced osteoporosis .... ☐
   - Kidney disease .... ☐
   - Liver transplant .... ☐
   - Other: ________________ ☐
   - Other: ________________ ☐

9. Is the study part of a named trial?
   - No 1
   - Yes: ________________ 2

10. Do you think this article might be a duplicate or include the same data as another study?
    - No 1
    - Yes: ________________ 2

11. Is there a reference that needs to be checked in order to complete this screener?
    - No 1
    - Yes: ________________ 2

Notes

☐ Check here if this study was from the original LBD report.

Long Form for Trials

RAND EPC – LBD Update
Detailed Abstraction Form for Trials

Article ID:________________ Reviewer: ____________
First Author: ______________________________________
Study Number: ___of ____ Description:________
(Enter '1 of 1' if only one) (if more than one study)

1. Are all arms the same intervention? CIRCLE ONE
   No 0
   Yes .... 1 STOP

2. Is the study design trial with crossover? CIRCLE ONE
   No 0
   Yes .... 1 STOP

Notes:

IDs of studies that contributed data to this form:

IDs of other related studies:

3. What were the study's inclusion criteria? CHECK ALL THAT APPLY

Ambulatory .... ❑ 00
Men .... ❑ 01
Pre-menopausal women .... ❑ 02
Post-menopausal women NOS .... ❑ 03
  >6 months .... ❑ 04
  >1 year .... ❑ 05
  >2 years .... ❑ 06
  >5 years .... ❑ 07
Women otherwise undefined .... ❑ 08
Age under _____ years .... ❑ 09
Age over _____ years .... ❑ 10
Osteopenia NOS .... ❑ 11
Osteoporosis NOS .... ❑ 12

T-Score	Hip	Spine	NOS
≤ -1.0	❑ 13	❑ 14	❑ 15
≤ -2.0	❑ 16	❑ 17	❑ 18
≤ -2.5	❑ 19	❑ 20	❑ 21

Radiographic fractures, clinically silent .... ❑ 22
Clinical fractures, radiographically confirmed .... ❑ 23
Clinical fractures, no radiographic confirmation .... ❑ 24
Clinical fractures, radiographic conf. unclear .... ❑ 25
Osteoporosis score based on T-score and/or fractures and/or radiography .... ❑ 26
Osteoporosis score based on FRAX .... ❑ 27
Corticosteroid use .... ❑ 28
Menopausal hormone therapy .... ❑ 29

Not Reported .... ❑ 99

Additional inclusion criteria

Page 1 of 8

RAND EPC – LBD Update
Detailed Abstraction Form for Trials

4. What were the study's exclusion criteria?

CHECK ALL THAT APPLY

- Ambulatory ☐ 00
- Age under _____ years ☐ 01
- Age over _____ years ☐ 02
- Pregnancy ☐ 03
- Carcinoma or suspected carcinoma ☐ 04
- Cardiovascular disease ☐ 05
- Diabetes ☐ 06
- Endocrine disease (not diabetes) NOS ☐ 07
  - Hypothyroidism ☐ 08
  - Hyperthyroidism ☐ 09
  - Hyperparathyroidism ☐ 10
  - Hypoparathroidism ☐ 11
- Hypocalcemia ☐ 12
- Hypercalcemia ☐ 13
- Vitamin D deficiency ☐ 14
- Hepatic insufficiency ☐ 15
- Metabolic bone disorder other than osteoporosis (e.g. Paget's, renal osteodystrophy, osteomalacia, rheumatoid arthritis, SLE) ☐ 16
- LS spine abnormalities prohibiting DXA ☐ 17
- Organ transplantation ☐ 18
- Renal insufficiency ☐ 19
- Gastrointestinal disease ☐ 20
  - Sprue ☐ 21
  - Inflammatory bowel disease ☐ 22
  - Malabsorption syndrome ☐ 23
  - Upper GI ☐ 24
  - Nephrolithiasis ☐ 25
- Urolithiasis ☐ 26
- Venous thromboembolic disease ☐ 27
  - Active ☐ 28
  - Ever ☐ 29
- Anticonvulsants ☐ 30
- Aluminum ☐ 31
- Bisphosphonates ☐ 32
- Calcitonin ☐ 33
- Calcium includes antacids ☐ 34
- Coumarins ☐ 35
- Fluoride ☐ 36
- H2-blockers ☐ 37
- Hormone use NOS ☐ 40
  - Androgen ☐ 41
  - Menopausal hormonal therapy ☐ 42
  - Estrogen agonists including estrogen ☐ 43
  - Progestin ☐ 44
  - SERMS ☐ 45
  - Estrogen agonists ☐ 46
  - Anabolic steroids ☐ 47
  - Testosterone ☐ 48
  - Contraception ☐ 49
  - Previous PTH use ☐ 50
- Lipid lowering agents ☐ 51
- Proton pump inhibitors ☐ 52
- Vitamin D use ☐ 53
- Corticoids/Glucocorticoids ☐ 54
- Gallium nitrate ☐ 55
- Mithramycin ☐ 56
- Medications known to affect skeleton ☐ 57
- Not Reported ☐ 99

Additional exclusion criteria:

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5. Were patients class-naive? CIRCLE ONE
   - Yes 1
   - No 2
   - Not reported 9

6. Randomization: Was the study described as randomized and was the sequence generation for the randomization appropriate? CIRCLE ONE
   - Yes, method adequate 1
   - Yes, but method unclear or inadequate 2
   - No, not randomized 3

7. Did the method of randomization provide for concealment of allocation?* CIRCLE ONE
   - Yes 1
   - No 2
   - Concealment not described 8

*Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.

8. Is the study described as*: CIRCLE ONE
   - Double blind 1
   - Single blind, patient 2
   - Single blind, outcome assessment 3
   - Single blind, not described 4
   - Blind, NOS 5
   - Open 6
   - Blinding not described 8
   - Not applicable 9

*This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.

9. If reported, was the method of double blinding appropriate? CIRCLE ONE
   - Yes 1
   - No 2
   - Double blinding method not described 8
   - Not applicable 9

10. Were outcome assessors masked to the treatment allocation?* CIRCLE ONE
   - Yes 1
   - Yes, but not described 2
   - No 3
   - Not reported 9

*Outcome Assessor blinding adequacy should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: **for patient-reported outcomes** in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"

11. Was the care provider masked to the treatment allocation?* CIRCLE ONE
   - Yes 1
   - Yes, but not described 2
   - No 3
   - Not reported 9

*This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful

12. Was the patient masked to the treatment allocation? CIRCLE ONE
   - Yes 1
   - Yes, but not described 2
   - No 3
   - Not reported 9

13. Was the withdrawal/drop-out rate described and was the reason given?
    - Yes described for all 1
    - Yes described for some 2
    - Not described 3
    - Unclear 8
    - Not applicable 9

14. Was the withdrawal/drop-out rate acceptable (e.g., 20% short term, 30% long term)?
    - Yes 1
    - No..2
    - Don't know 9

15. Were cointerventions avoided or similar among index and control groups?*
    - Yes 1
    - No..2
    - Don't know 9

*This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.

16. Was an intention to treat (ITT) analysis described? Were all participants' data included in the analysis, according to the treatment group to which they were originally assigned, regardless of whether they completed the treatment/study?
    - Yes 1
    - Possibly 2
    - No, unlikely.....................................3
    - N/A (no controls/effectiveness analysis) ..9

17. Sample size: (Enter N or 999 for not reported)

Screened: ________ Eligible: ________

Enrolled: ________ Withdrawn: ________

Loss to follow-up: ________

18. Was there a run-in and/or wash-out period?
    - Run-in only 1
    - Wash-out only...................................2
    - Both run-in and wash-out 3
    - Neither 4
    - Unclear...8
    - Not applicable...................................9

19. What was the study's setting? CHECK ALL
    - Multi-center .... ❑
    - Single setting .... ❑
    - Ambulatory/community practice .... ❑
    - VA Health Care System .... ❑
    - Long term care facility................... ❑
    - Other: ________________________ ... ❑
    - Setting not reported .... ❑

20. Where was the study conducted? CHECK ALL
    - US .... ❑
    - Canada .... ❑
    - South/Central America .... ❑
    - UK.. ❑
    - Western Europe.............................. ❑
    - Eastern Europe............................... ❑
    - Australia/New Zealand .... ❑
    - Japan .... ❑
    - Asia (not Japan)............................. ❑
    - Other ________________________ ... ❑
    - Not reported .... ❑

21. What was the study's funding source? CHECK ALL
    - Government .... ❑
    - Hospital.. ❑
    - Industry .... ❑
    - Private (non-industry)..................... ❑
    - Other ________________________ ... ❑
    - Unclear .... ❑
    - Not reported SKIP TO Q23 .... ❑

22. Did the article include a statement on the role of the funder?
    - Yes 1
    - No 2
    - Not applicable..................................9

23. What was the percent of female participants? ENTER NUMBER OR 999.9

______ ______ ______ . ______%

24. What racial/ethnic groups were studied? CHECK ALL
    - Caucasian .... ❑
    - African Ancestry .... ❑
    - Hispanic.. ❑
    - Asian .... ❑
    - Native American .... ❑
    - Eskimo/Inuit.................................... ❑
    - Other ________________________ ...... ❑
    - Not reported .... ❑

25. What were the subjects' ages?
Enter 999 for not reported
Mean | Median .... ___________
Age Range .... _______ to _______

26. What were the comorbidities reported in the study? CHECK ALL THAT APPLY
- Asthma .... ❑
- Breast cancer .... ❑
- COPD .... ❑
- Diabetes .... ❑
- EtOH use .... ❑
- Glucocorticoid use .... ❑
- Hypertension .... ❑
- Rheumatoid arthritis .... ❑
- SLE .... ❑
- PUD .... ❑
- Pancreatitis .... ❑
- Bleeding .... ❑
- Renal calculi .... ❑
- Other: ______________________ .... ❑
- Not reported .... ❑

27. Were groups similar at baseline, in terms of age, BMI (or equivalent) and race/ethnicity (if US study)?
- Yes 1
- No 2
- Not reported 9

28. Did the placebo/control group receive standard care?
- Yes 1
- No 2
- Not reported 9

29. What was the method of adverse events assessment? CHECK ALL
- Monitored .... ❑
- Elicited by investigator .... ❑
- Reported spontaneously by patient .... ❑
- Other: ______________________ ...... ❑
- Not reported .... ❑

INTERVENTIONS

30. Interventions given to EVERYONE in the study:

Interventions given to everyone		Dose	Units	Frequency	Duration of treatment	Units
None 0	___	___	___	___	___	___
Calcium 1	___	___	___	___	___	___
Estrogen 2	___	___	___	___	___	___
Testosterone 3	___	___	___	___	___	___
Vitamin D 4	___	___	___	___	___	___
Corticosteroids 5	___	___	___	___	___	___
Other ________ .. 6	___	___	___	___	___	___
Other ________ .. 7	___	___	___	___	___	___
		Enter # or range 996 Unclear 997 Variable 998 Not applicable 999 Not reported	Enter a number 1 g 2 mg 3 µg 4 IU 97 Unclear 98 Not applicable 99 Not reported	Enter a number 1 Daily 2 Weekly 3 Monthly 4 Yearly 96 Unclear 97 Variable 98 Not applicable 99 Not reported	Enter a number 996 Unclear 997 Variable 998 Not applicable 999 Not reported	Enter a number 1 Day 2 Week 3 Month 4 Year 97 Unclear 98 Not applicable 99 Not reported

31. Total number of arms:

____

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32.

Arm/ Group	Sample size	Interventions ENTER CODE		Dose ENTER # OR RANGE	Units ENTER CODE	Frequency ENTER CODE	Tx Duration ENTER #	Units ENTER CODE
1	______ N ENTERING ______ N COMPLETING ______ N ANALYZED ______ # OF EXCLUSIONS	Usual care ....00 Placebo.............01 Control ....02 Alendronate ......03 Etidronate ....07 Ibandronate ......08 Pamidronate ......09 Risedronate ....12 Zoledronic acid .15 Calcitonin ....04 PTH (teriparatide) ..10 PTH (1-84)......301 Lasifoxifene ....302 Raloxifine ....11 Estrogen ....06 Estrogen patch 303 Est./progest. ....304 Progesterone ...100 Testosterone ......14 Denosumab ......05 Calcium.............16 Flouride.............73 Strontium ....305 Vitamin D ....17 Vitamin K ....71 Exercise............18	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____
2	______ N ENTERING ______ N COMPLETING ______ N ANALYZED ______ # OF EXCLUSIONS Enter # 9997 Unclear 9998 Not applicable 9999 Not reported		____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____ Enter # or range 997 Unclear 998 N/A 999 Not reported	____ ____ ____ ____ ____ ____ Enter a number 1. g 2. mg 3. µg 4. I U 97 Unclear 98 Not applicable 99 Not reported	____ ____ ____ ____ ____ ____ Enter a number 1. Daily 2. Weekly 3. Monthly 4. Yearly 97 Unclear 98 Not applicable 99 Not reported	____ ____ ____ ____ ____ ____ Enter a number 996 Unclear 997 Variable 998 Not applicable 999 Not reported	____ ____ ____ ____ ____ ____ Enter a number 1 Day 2 Week 3 Month 4 Year 97 Unclear 98 Not applicable 99 Not reported

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Arm/ Group	Sample size	Interventions ENTER CODE		Dose ENTER # OR RANGE	Units ENTER CODE	Frequency ENTER CODE	Tx Duration ENTER #	Units ENTER CODE
3	______ N ENTERING ______ N COMPLETING ______ N ANALYZED ______ # OF EXCLUSIONS	Usual care ....00 Placebo............01 Control ....02 Alendronate ......03 Etidronate ....07 Ibandronate ....08 Pamidronate ......09 Risedronate ....12 Zoledronic acid .15 Calcitonin ....04 PTH (teriparatide) ..10 PTH (1-84) ......301 Lasifoxifene ....302 Raloxifine ....11 Estrogen ....06 Estrogen patch 303 Est./progest. ....304 Progesterone ...100 Testosterone ......14 Denosumab ......05 Calcium............16 Flouride............73 Strontium ....305 Vitamin D ....17 Vitamin K ....71 Exercise............18	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______
4	______ N ENTERING ______ N COMPLETING ______ N ANALYZED ______ # OF EXCLUSIONS Enter # 9996: Unclear 9998: Not applicable 9999: Not reported		______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______ Enter # or range 997 Unclear 998 N/A 999 Not reported	______ ______ ______ ______ ______ ______ Enter a number 1 g 2 mg 3 µg 4 IU 97 Unclear 98 Not applicable 99 Not reported	______ ______ ______ ______ ______ ______ Enter a number 1 Daily 2 Weekly 3 Monthly 4 Yearly 97 Unclear 99 Not applicable 99 Not reported	______ ______ ______ ______ ______ ______ Enter a number 996 Unclear 997 Variable 998 Not applicable 999 Not reported	______ ______ ______ ______ ______ ______ Enter a number 1 Day 2 Week 3 Month 4 Year 97 Unclear 98 Not applicable 99 Not reported

OUTCOMES

33. Did the article report the following? CHECK ALL
- Adherence .... ☐
- Contamination .... ☐

Adherence: The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (for ex: surgery), this item is irrelevant.
Contamination: refers to whether some portion of the placebo group actually received/used the active intervention.

34. Are fractures specified as the primary outcome?
- Yes 1
- No 2

35. Which outcomes were measured? CHECK ALL
- Bone mineral density by DXA – Hip...... ☐ 01
- Bone mineral density by DXA - Spine ... ☐ 02
- Hip fracture .... ☐ 03
- Proximal humerus fracture..................... ☐ 04
- Radial fracture .... ☐ 05
- Vertebral fracture.................................. ☐ 06
- Non-vertebral fracture............................ ☐ 07
- Total fractures .... ☐ 08
- Radiographic vertebral fractures............ ☐ 09
- Symptomatic vertebral fractures .... ☐ 10
- Other ______________________ .... ☐ 11
- Other ______________________ .... ☐ 12
- Other ______________________ .... ☐ 13
- None of the above .... ☐ 99

36. When were fracture outcomes measured?

Baseline?	YES / NO	
Follow-up	**Time from baseline**	**Unit** 1: Day 2: Week 3: Month 4: Year 5: Unclear 8: Not reported 9: Variable
1st		
2nd		
3rd		
4th		
5th		
6th		
7th		
8th		
9th		
10th		
11th		
12th		
13th		
14th		
15th		
Additional		

Long Form for Observational Studies (Questions highlighted in yellow)

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Answer only the questions that are highlighted

Article ID: ______________ Reviewer: __________
First Author: ________________________________
Study Number: ___of___ Description:___ ____
(Enter '1 of 1' if only one) (if more than one study)

1. Are all arms the same intervention? CIRCLE ONE
   - No 0
   - Yes .... 1 STOP

2. Is the study design trial with crossover? CIRCLE ONE
   - No 0
   - Yes .... 1 STOP

Notes:

IDs of studies that contributed data to this form:

IDs of other related studies:

3. What were the study's inclusion criteria? CHECK ALL THAT APPLY
   - Ambulatory .... ❑ 00
   - Men .... ❑ 01
   - Pre-menopausal women .... ❑ 02
   - Post-menopausal women NOS .... ❑ 03
     - >6 months .... ❑ 04
     - >1 year .... ❑ 05
     - >2 years .... ❑ 06
     - >5 years .... ❑ 07
   - Women otherwise undefined .... ❑ 08
   - Age under _____ years .... ❑ 09
   - Age over _____ years .... ❑ 10
   - Osteopenia NOS .... ❑ 11
   - Osteoporosis NOS .... ❑ 12

T-Score	Hip	Spine	NOS
≤ -1.0	❑ 13	❑ 14	❑ 15
≤ -2.0	❑ 16	❑ 17	❑ 18
≤ -2.5	❑ 19	❑ 20	❑ 21

   - Radiographic fractures, clinically silent .... ❑ 22
   - Clinical fractures, radiographically confirmed .... ❑ 23
   - Clinical fractures, no radiographic confirmation .... ❑ 24
   - Clinical fractures, radiographic conf. unclear .... ❑ 25
   - Osteoporosis score based on T-score and/or fractures and/or radiography .... ❑ 26
   - Osteoporosis score based on FRAX .... ❑ 27
   - Corticosteroid use .... ❑ 28
   - Menopausal hormone therapy .... ❑ 29
   - Not Reported .... ❑ 99

Additional inclusion criteria:

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Answer only the questions that are highlighted

4. What were the study's exclusion criteria?

CHECK ALL THAT APPLY

- Ambulatory ☐ 00
- Age under _____ years ☐ 01
- Age over _____ years ☐ 02
- Pregnancy ☐ 03
- Carcinoma or suspected carcinoma ☐ 04
- Cardiovascular disease ☐ 05
- Diabetes ☐ 06
- Endocrine disease (not diabetes) NOS ☐ 07
  - Hypothyroidism ☐ 08
  - Hyperthyroidism ☐ 09
  - Hyperparathyroidism ☐ 10
  - Hypoparathroidism ☐ 11
- Hypocalcemia ☐ 12
- Hypercalcemia ☐ 13
- Vitamin D deficiency ☐ 14
- Hepatic insufficiency ☐ 15
- Metabolic bone disorder other than osteoporosis (e.g. Paget's, renal osteodystrophy, osteomalacia, rheumatoid arthritis, SLE) ☐ 16
- LS spine abnormalities prohibiting DXA ☐ 17
- Organ transplantation ☐ 18
- Renal insufficiency ☐ 19
- Gastrointestinal disease ☐ 20
  - Sprue ☐ 21
  - Inflammatory bowel disease ☐ 22
  - Malabsorption syndrome ☐ 23
  - Upper GI ☐ 24
  - Nephrolithiasis ☐ 25
- Urolithiasis ☐ 26
- Venous thromboembolic disease ☐ 27
  - Active ☐ 28
  - Ever ☐ 29
- Anticonvulsants ☐ 30
- Aluminum ☐ 31
- Bisphosphonates ☐ 32
- Calcitonin ☐ 33
- Calcium includes antacids ☐ 34
- Coumarins ☐ 35
- Fluoride ☐ 36
- H2-blockers ☐ 37
- Hormone use NOS ☐ 40
  - Androgen ☐ 41
  - Menopausal hormonal therapy ☐ 42
  - Estrogen agonists including estrogen ☐ 43
  - Progestin ☐ 44
  - SERMS ☐ 45
  - Estrogen agonists ☐ 46
  - Anabolic steroids ☐ 47
  - Testosterone ☐ 48
  - Contraception ☐ 49
  - Previous PTH use ☐ 50
- Lipid lowering agents ☐ 51
- Proton pump inhibitors ☐ 52
- Vitamin D use ☐ 53
- Corticoids/Glucocorticoids ☐ 54
- Gallium nitrate ☐ 55
- Mithramycin ☐ 56
- Medications known to affect skeleton ☐ 57
- Not Reported ☐ 99

Additional exclusion criteria:

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Answer only the questions that are highlighted

5. **Were patients class-naive?** CIRCLE ONE
   - Yes 1
   - No 2
   - Not reported 9

6. Randomization: Was the study described as randomized and was the sequence generation for the randomization appropriate? CIRCLE ONE
   - Yes, method adequate 1
   - Yes, but method unclear or inadequate 2
   - No, not randomized 3

7. Did the method of randomization provide for concealment of allocation?* CIRCLE ONE
   - Yes 1
   - No 2
   - Concealment not described 8

*Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.

8. Is the study described as*: CIRCLE ONE
   - Double blind 1
   - Single blind, patient 2
   - Single blind, outcome assessment 3
   - Single blind, not described 4
   - Blind, NOS 5
   - Open 6
   - Blinding not described 8
   - Not applicable 9

*This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.

9. If reported, was the method of double blinding appropriate? CIRCLE ONE
   - Yes 1
   - No 2
   - Double blinding method not described 8
   - Not applicable 9

10. **Were outcome assessors masked to the treatment allocation?*** CIRCLE ONE
   - Yes 1
   - Yes, but not described 2
   - No 3
   - Not reported 9

*Outcome Assessor blinding adequacy should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: **for patient-reported outcomes** in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"

11. Was the care provider masked to the treatment allocation?* CIRCLE ONE
   - Yes 1
   - Yes, but not described 2
   - No 3
   - Not reported 9

*This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful

12. Was the patient masked to the treatment allocation? CIRCLE ONE
   - Yes 1
   - Yes, but not described 2
   - No 3
   - Not reported 9

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13. Was the withdrawal/drop-out rate described and was the reason given?
- Yes described for all 1
- Yes described for some 2
- Not described 3
- Unclear 8
- Not applicable 9

14. Was the withdrawal/drop-out rate acceptable (e.g., 20% short term, 30% long term)?
- Yes 1
- No 2
- Don't know 9

15. Were cointerventions avoided, similar, or controlled for among index and control groups?*
- Yes 1
- No 2
- Don't know 9

*This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.

16. Was an intention to treat (ITT) analysis described? Were all participants' data included in the analysis, according to the treatment group to which they were originally assigned, regardless of whether they completed the treatment/study?
- Yes 1
- Possibly 2
- No, unlikely 3
- N/A (no controls/effectiveness analysis) ..9

17. Sample size: (Enter N or 999 for not reported)

Screened: ________ Eligible: ________

Enrolled: ________ Withdrawn: ________

Loss to follow-up: ________

18. Was there a run-in and/or wash-out period?
- Run-in only 1
- Wash-out only 2
- Both run-in and wash-out 3
- Neither 4
- Unclear 8
- Not applicable 9

19. What was the study's setting? CHECK ALL
- Multi-center ....☐
- Single setting ....☐
- Ambulatory/community practice ....☐
- VA Health Care System ....☐
- Long term care facility ....☐
- Other: ________________ ...☐
- Setting not reported ....☐

20. Where was the study conducted? CHECK ALL
- US ....☐
- Canada ....☐
- South/Central America ....☐
- UK ....☐
- Western Europe ....☐
- Eastern Europe ....☐
- Australia/New Zealand ....☐
- Japan ....☐
- Asia (not Japan) ....☐
- Other ________________ ...☐
- Not reported ....☐

21. What was the study's funding source? CHECK ALL
- Government ....☐
- Hospital ....☐
- Industry ....☐
- Private (non-industry) ....☐
- Other ________________ ...☐
- Unclear ....☐
- Not reported SKIP TO Q23 ....☐

22. Did the article include a statement on the role of the funder?
- Yes 1
- No 2
- Not applicable 9

23. What was the percent of female participants?
ENTER NUMBER OR 999.9

_____ _____ _____ . _____%

24. What racial/ethnic groups were studied? CHECK ALL
- Caucasian ....☐
- African Ancestry ....☐
- Hispanic ....☐
- Asian ....☐
- Native American ....☐
- Eskimo/Inuit ....☐
- Other ________________ .....☐
- Not reported ....☐

X1. From where were patients identified? CIRCLE ONE
- Single clinic or hospital 1
- Single long-term care facility 2
- Multiple clinic 3
- Single community 4
- Regional ________________ 5
- Nat'l/Int'l ________________ 6
- Other ________________ 7
- Unclear 9

X2. How were patients selected? CIRCLE ONE
- Population-based, systematic, or representative sample 1
- Combination 2
- Part of a trial 3
- Other ________________ 4
- Unclear 9

25. What were the subjects' ages?
Enter 999 for not reported

Mean | Median .... ____________

Age Range .... _______ to _______

26. What were the comorbidities reported in the study? CHECK ALL THAT APPLY

- Asthma .... ☐
- Breast cancer .... ☐
- COPD .... ☐
- Diabetes .... ☐
- EtOH use .... ☐
- Glucocorticoid use ...... ☐
- Hypertension .... ☐
- Rheumatoid arthritis .... ☐
- SLE .... ☐
- PUD .... ☐
- Pancreatitis .... ☐
- Bleeding .... ☐
- Renal calculi .... ☐
- Other: ______________________ .... ☐
- Not reported .... ☐

27. Were groups similar at baseline, in terms of age, BMI (or equivalent) and race/ethnicity (if US study)?

- Yes 1
- No 2
- Not reported 9

28. Did the placebo/control group receive standard care?

- Yes 1
- No 2
- Not reported 9

29. What was the method of adverse events assessment? CHECK ALL

- Monitored .... ☐
- Elicited by investigator .... ☐
- Reported spontaneously by patient .... ☐
- Other: ______________________ ...... ☐
- Not reported .... ☐

INTERVENTIONS

30. Interventions given to EVERYONE in the study:

Interventions given to everyone		Dose	Units	Frequency	Duration of treatment	Units
None 0						
Calcium 1	____	____	____	____	____	____
Estrogen 2	____	____	____	____	____	____
Testosterone 3	____	____	____	____	____	____
Vitamin D 4	____	____	____	____	____	____
Corticosteroids 5	____	____	____	____	____	____
Other _________ .. 6	____	____	____	____	____	____
Other _________ .. 7	____	____	____	____	____	____
		Enter # or range 996. Unclear 997. Variable 998. Not applicable 999. Not reported	Enter a number 1. g 2. mg 3. µg 4. I.U. 97. Unclear 98. Not applicable 99. Not reported	Enter a number 1. Daily 2. Weekly 3. Monthly 4. Yearly 96. Unclear 97. Variable 99. Not applicable 99. Not reported	Enter a number 996. Unclear 997. Variable 998. Not applicable 999. Not reported	Enter a number 1. Day 2. Week 3. Month 4. Year 97. Unclear 98. Not applicable 99. Not reported

31. Total number of arms:

____

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Answer only the questions that are highlighted

32.

Arm/ Group	Sample size	Interventions ENTER CODE		Dose ENTER # OR RANGE	Units ENTER CODE	Frequency ENTER CODE	Tx Duration ENTER #	Units ENTER CODE
1	______ N ENTERING ______ N COMPLETING ______ N ANALYZED ______ # OF EXCLUSIONS	Usual care.........00 Placebo.............01 Control ....02 Alendronate ......03 Etidronate ....07 Ibandronate ......08 Pamidronate......09 Risedronate ....12 Zoledronic acid.15 Calcitonin ....04 PTH (teriparatide)..10 PTH (1-84)......301 Lasifoxifene ....302 Raloxifine ....11 Estrogen ....06 Estrogen patch 303 Est./progest. ....304 Progesterone ...100 Testosterone......14 Denosumab ......05 Calcium.............16 Flouride............73 Strontium ....305 Vitamin D ....17 Vitamin K.........71 Exercise............18	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____
2	______ N ENTERING ______ N COMPLETING ______ N ANALYZED ______ # OF EXCLUSIONS Enter # 9997. Unclear 9998. Not applicable 9999. Not reported		____ ____ ____ ____ ____ ____	____ ____ ____ ____ ____ ____ Enter # or range 997. Unclear 998. N/A 999. Not reported	____ ____ ____ ____ ____ ____ Enter a number 1. g 2. mg 3. µg 4. IU 97. Unclear 98. Not applicable 99. Not reported	____ ____ ____ ____ ____ ____ Enter a number 1. Daily 2. Weekly 3. Monthly 4. Yearly 97. Unclear 98. Not applicable 99. Not reported	____ ____ ____ ____ ____ ____ Enter a number 996. Unclear 997. Variable 998. Not applicable 999. Not reported	____ ____ ____ ____ ____ ____ Enter a number 1. Day 2. Week 3. Month 4. Year 97. Unclear 98. Not applicable 99. Not reported

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RAND EPC – LBD Update
Detailed Abstraction Form for Observational studies
Answer only the questions that are highlighted

Arm/ Group	Sample size	Interventions ENTER CODE		Dose ENTER # OR RANGE	Units ENTER CODE	Frequency ENTER CODE	Tx Duration ENTER #	Units ENTER CODE
3	______ N ENTERING ______ N COMPLETING ______ N ANALYZED ______ # OF EXCLUSIONS	Usual care.........00 Placebo..............01 Control ....02 Alendronate ......03 Etidronate ....07 Ibandronate ....08 Pamidronate ......09 Risedronate ....12 Zoledronic acid.15 Calcitonin ....04 PTH (teriparatide) ...10 PTH (1-84).......301 Lasifoxifene ....302 Raloxifine ....11 Estrogen ....06 Estrogen patch 303 Est./progest.......304 Progesterone ...100 Testosterone......14 Denosumab ......05 Calcium..............16	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______

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4	______ N ENTERING ______ N COMPLETING ______ N ANALYZED ______ # OF EXCLUSIONS Enter # 9996. Unclear 9998. Not applicable 9999. Not reported		______ ______ ______ ______ ______ ______	______ ______ ______ ______ ______ ______ Enter # or range 997. Unclear 998. N/A 999. Not reported	______ ______ ______ ______ ______ ______ Enter a number 1. g 2. mg 3. µg 4. I.U 97. Unclear 98. Not applicable 99. Not reported	______ ______ ______ ______ ______ ______ Enter a number 1. Daily 2. Weekly 3. Monthly 4. Yearly 97. Unclear 99. Not applicable 99. Not reported	______ ______ ______ ______ ______ ______ Enter a number 996. Unclear 997. Variable 998. Not applicable 999. Not reported	______ ______ ______ ______ ______ ______ Enter a number 1.Day 2.Week 3.Month 4.Year 97. Unclear 98. Not applicable 99. Not reported

OUTCOMES

33. Did the article report the following? CHECK ALL

- Adherence .... ☐
- Contamination .... ☐

Adherence: The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (for ex: surgery), this item is irrelevant.

Contamination: refers to whether some portion of the placebo group actually received/used the active intervention.

34. Are fractures specified as the primary outcome?

- Yes 1
- No 2

35. Which outcomes were measured? CHECK ALL

- Bone mineral density by DXA – Hip...... ☐ 01
- Bone mineral density by DXA - Spine ... ☐ 02
- Hip fracture .... ☐ 03
- Proximal humerus fracture...................... ☐ 04
- Radial fracture .... ☐ 05
- Vertebral fracture.................................... ☐ 06
- Non-vertebral fracture............................. ☐ 07
- Total fractures .... ☐ 08
- Radiographic vertebral fractures............ ☐ 09
- Symptomatic vertebral fractures............ ☐ 10
- Other ____________________ .... ☐ 11
- Other ____________________ .... ☐ 12
- Other ____________________ .... ☐ 13
- None of the above .... ☐ 99

36. When were fracture outcomes measured?

Baseline?	YES / NO	
Follow-up	**Time from baseline**	**Unit** 1: Day 2: Week 3: Month 4: Year 5: Unclear 8: Not reported 9: Variable
1st		
2nd		
3rd		
4th		
5th		
6th		
7th		
8th		
9th		
10th		
11th		
12th		
13th		
14th		
15th		
Additional		

QUALITY OF COHORT STUDIES

37. Are primary outcomes assessed using valid and reliable measures?

CIRCLE ONE

- Yes 1
- No 2
- Unclear/Not reported 9

38. Are outcome measures implemented consistently across all study participants?

CIRCLE ONE

- Yes 1
- No 2
- Unclear/Not reported 9

39. Were the important confounding and modifying variables taken into account in the design and analysis?

CIRCLE ONE

- Yes 1
- No 2
- Unclear/Not reported 9

40. How was the non-exposed cohort selected?

CIRCLE ONE

- Drawn from the same community as the exposed cohort 1
- Drawn from a different source 2
- No description of the derivation of the non-exposed cohort 3

41. How was exposure to LBD drugs/exercise ascertained?

CIRCLE ONE

- Secure record (e.g. medical records) 1
- Structured interview 2
- Written self report 3
- Claims data 4
- No description 9

42. Was it demonstrated that the outcome of interest was not present at the start of the study?

CIRCLE ONE

- Yes 1
- No 2
- Unclear/Not reported 9

Long Form for Adherence Studies

LBD2 Medication Adherence Long Form

Article ID: ______________ Reviewer: ______________

First Author: ______________________________ (Last Name Only)

Study Number: ___ of ___ (Enter '1of 1' if only one) Description: ______________ (if more than one study)

1. Study design CIRCLE ONE

- Cross-sectional 1
- Observational cohort (two or more points) 2
- Case control 3
- RCT 4
- CCT 5
- Unclear 9

2. Was the study conducted exclusively in the US?

- Yes 1
- No 2
- Unclear 9

3. From where were the patients identified? CHECK ONE AND SPECIFY WHICH, BELOW

- National 1
- Multiple sites 2
- Multi-State 3
- State 4
- Health plan 5
- Single clinic/hosp/ pharmacy 6
- Multiple clinics 7
- Other 8
- Unclear 98
- Not specified 99

Specify: ______________________

4. Recruitment method CIRCLE ONE

- Random sample 1
- All patients with disease from study site 2
- Participants in clinical trial 3
- Claims data from payers 4
- Consecutive patients 5
- Convenience sample 6
- Volunteers, response to ads 7
- Other method: ______________ 8
- Unclear 98
- Not specified 99

5. Participant numbers ENTER NUMBER

- Invited to participate ..... ________
- Enrolled ..... ________
- Responding at baseline ..... ________
- Responding at final follow-up ..... ________

6. Participants PERCENT

- Male ..... ________
- Seniors (65 and older) ..... ________
- Black/African American ..... ________
- Hispanic ..... ________
- Non-hispanic White ..... ________
- American Indian/Alaska Native ..... ________
- Asian Pacific Islander ..... ________
- Other racial group (____________) ..... ________
- Other racial group (____________) ..... ________

7. Type of adherence CHECK ALL THAT APPLY

- Non-fulfillment ..... ☐
- Non-persistence... ..... ☐
- Non-adherence ..... ☐
- Overadherence ..... ☐
- Discontinuation ..... ☐
- Not Specified ..... ☐
- Other (________________) ..... ☐

8. How is adherence assessed? CHECK ALL THAT APPLY

- Self-report/diary ..... ☐
  - Questionnaire ..... ☐
  - Telephone interview ..... ☐
  - In-person interview ..... ☐
- Pill count (by someone other than patient) ..... ☐
- Electronic monitoring ..... ☐
- Pharmacy records/claims data ..... ☐
- Medical records ..... ☐
- Biological evidence ..... ☐
- Clinical response ..... ☐
- Other (________________) ..... ☐
- Unclear ..... ☐
- Not specified ..... ☐

LBD2 Medication Adherence Long Form

9. What is the length of time over which adherence is being measured (in months)?

____

10. Which key questions does this article answer? CHECK ALL THAT APPLY

- Adherence and persistence to medications for the treatment and prevention of osteoporosis ☐
- Factors that affect adherence and persistence ☐
- Effects of adherence and persistence on the risk of fractures ☐
- None of the above ☐

11. Which barriers and/or predictors? CHECK ALL THAT APPLY

	Discussed	Adjusted For	
Patient characteristics	☐	☐	01
Age	☐	☐	02
Gender	☐	☐	03
Race/ethnicity	☐	☐	04
Marital status	☐	☐	05
Employment status	☐	☐	06
Socioeconomics status	☐	☐	07
Education	☐	☐	08
Prescription insurance status	☐	☐	09
Depression	☐	☐	10
Costs/insurance	☐	☐	11
Other: ________	☐	☐	12
Other: ________	☐	☐	13
Other: ________	☐	☐	14
Other: ________	☐	☐	15
Other: ________	☐	☐	16
Other: ________	☐	☐	17

12. How is adherence measured? CHECK ALL THAT APPLY

- Never filled prescription ☐
- Delayed filling prescription ☐
  - # Days: ______ # Weeks: ______
  - Undefined ☐
- Discontinuation ☐
  - a) After ______ months
  - b) After ______ months
- Medication possession ratio ☐
  - # Days in reporting period: ______
  - ☐ Dichotomous ☐ Continuous
  - Cutoff Point: ______
- Proportion of Days Covered ☐
  - # Days in reporting period: ______
  - ☐ Dichotomous ☐ Continuous
  - Cutoff Point: ______
- Prescription refill ratio ☐
  - # Days in reporting period: ______
  - ☐ Dichotomous ☐ Continuous
  - Cutoff Point: ______
- Prescribed doses taken with specified period ☐
  - # Days in reporting period: ______
  - ☐ Dichotomous ☐ Continuous
  - Cutoff Point: ______
- Validated scale ☐
  - Specify: ______
  - ☐ Dichotomous ☐ Continuous
  - Cutoff Point: ______
- Other ________ ☐
- Other ________ ☐
- Unclear ☐
- Not specified ☐

LBD2 Medication Adherence Long Form

RESULTS

Group	Rate	
Overall:		☐ Adherence ☐ Persistence
Arm 1:		☐ Adherence ☐ Persistence
Arm 2:		☐ Adherence ☐ Persistence
Arm 3:		☐ Adherence ☐ Persistence
Arm 4:		☐ Adherence ☐ Persistence
Subgroups (specify):		
		☐ Adherence ☐ Persistence
		☐ Adherence ☐ Persistence
		☐ Adherence ☐ Persistence
		☐ Adherence ☐ Persistence
		☐ Adherence ☐ Persistence
		☐ Adherence ☐ Persistence
		☐ Adherence ☐ Persistence

NOTES

Appendix C. Evidence Tables

Contents

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Papaioannou et al., 2008[55] Alendronate (Fosamax) Location: Canada Trial: CFOS Setting: Multicenter Jadad: 5 Age Mean/Range: 29/NR 39% Female Race: Not reported Screened: NR Eligible: 90 Enrolled: 56 Withdrawn: 9 Lost to follow-up: NR Analyzed: 56 Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient	Inclusion criteria: Age over 17 years, T-Score ≤ -1.0 NOS, Confirmed cystic fibrosis Exclusion criteria: Metabolic bone disorder other than osteoporosis, Organ transplantation, Renal insufficiency, Gastrointestinal disease, Corticoids/Glucocorticoids, Medications known to affect skeleton Interventions: Placebo Weekly for 12 Month(s) vs. 70mg of Alendronate Weekly for 12 Month(s) All received: Vitamin D, Calcium No run-in or wash-out Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures	Vertebral at 12 MOS: Alendronate vs Placebo: 0.0% vs 8.3% OR = 0.14 (95% CI 0.01, 2.23)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Fahrleitner-Pammer et al., 2009[106] Ibandronate (Boniva) Location: Western Europe Setting: Single setting Jadad: 5 Age Mean/Range: 44/NR 100% Male Race: Caucasian Screened: 58 Eligible: 35 Enrolled: 35 Withdrawn: 3 Lost to follow-up: 0 Analyzed: 32 Method of AE Assessment: Monitored	Inclusion criteria: Men, Cardiac transplant just prior to study entry Exclusion criteria: Carcinoma or suspected carcinoma, Hyperthyroidism, Hyperparathyroidism, Hypocalcemia, Vitamin D deficiency, Renal insufficiency, Calcium includes antacids, Vitamin D use, Use of OP drugs; Liver enzymes more than 3x upper limit of normal; Prior transplant Interventions: Placebo every 3 Months for 1 Year(s) vs. 2mg of Ibandronate every 3 Months for 1 Year(s) All received: Calcium, Vitamin D, Triple immunosuppressive treatment No run-in or wash-out Fracture outcomes assessed at baseline, 12 months Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Radiographic vertebral fractures	Vertebral - incident morphometric at 12 MOS: Ibandronate vs Placebo: 13.0% vs 53.0% OR = 0.15 (95% CI 0.04, 0.60) NNT=2.3 (95% CI 1.4-6.2)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Boonen et al., 2009[74] Risedronate (Actonel) Location: US, Western Europe, Eastern Europe, Australia/New Zealand, Lebanon Setting: Multicenter Jadad: 3 Age Mean/Range: 61/36-84 100% Male Race: Caucasian, Hispanic, Asian, Indian ? Screened: 994 Eligible: NR Enrolled: 284 Withdrawn: NR Lost to follow-up: NR Analyzed: 284 Method of AE Assessment: Unclear	Inclusion criteria: Ambulatory, Men, Age over 29 years, T-score: Lumbar spine (LS) T-score < or equal to -2.5 and Femoral neck t-score < or equal to -1 or LS < or equal to -1 and < or equal to 2 Exclusion criteria: 20 OP (exc. Due to 10 hypogonodism with no Testosterone treatment); > 1 OP fracture at screening or 1 within 6 months before screening; increased fracture risk Interventions: Placebo Weekly for 24 Month(s) vs. 35mg of Risedronate Weekly for 24 Month(s) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline, 24 months Outcomes: Bone mineral density by DXA - Spine, Vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, BMD proximal femur	Vertebral at 2 YRS: Risedronate 35mg/wk vs Placebo: 0.0% vs 0.0% OR = 4.45 (95% CI 0.23, 85.68)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Delmas et al., 2008[85] Risedronate (Actonel) Location: US, Canada, South America, UK, Western Europe, Eastern Europe Setting: Multicenter Jadad: 1 Age Mean/Range: 65/NR 100% Female Race: Not reported Screened: 3,027 Eligible: NR Enrolled: 1,231 Withdrawn: 183 Lost to follow-up: 2 Analyzed: 1,046 Method of AE Assessment: Monitored, Elicited by investigator, Assessed and recorded	Inclusion criteria: Ambulatory, Post-menopausal women >5 years, Age over 49 years, T-Score ≤ -2.5 Spine & T-score < 2 (lumbar spine) + 1 prevalent fracture Exclusion criteria: Any bone-active drugs within 3 months of 1st dose of study drug; drug or alcohol abuse; BMI > 32 Interventions: 5mg of Risedronate Daily for 1 Year(s) vs. 75mg of Risedronate 2 consecutive days/mo for 1 Year(s) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at 12 months Outcomes: Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BMD proximal femur	Vertebral at 12 MOS: Risedronate 75mg 2CDM vs Risedronate 5mg/day: 1.1% vs 1.3% OR = 0.85 (95% CI 0.29, 2.54)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Delmas et al., 2008[86] Risedronate (Actonel) Location: US, Canada, South America, Western Europe, Eastern Europe, Australia/New Zealand, Lebanon Setting: Multicenter Jadad: 2 Age Mean/Range: 65/NR 100% Female Race: Caucasian, African Ancestry, Hispanic, Other Screened: 2,221 Eligible: NR Enrolled: 1,294 Withdrawn: 198 Lost to follow-up: NR Analyzed: 1,292 Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Ambulatory, Post-menopausal women >5 years, Age over 49 years, T-Score ≤ -2.5 Spine, Good general health; at least 3 evaluable lumbar vertebral bodies Exclusion criteria: Carcinoma or suspected carcinoma, Hyperthyroidism (uncorrected), Hyperparathyroidism, Hypocalcemia, Hypercalcemia, LS spine abnormalities prohibiting DXA, Renal insufficiency, Bisphosphonates, Calcitonin, Fluoride, Menopausal hormonal therapy, Estrogen agonists including estrogen, SERMS, Anabolic steroids, Previous PTH use, Corticoids/Glucocorticoids, Any condition that could prevent drug completion; Drug/alcohol abuse; Bilateral hip prostheses; BMI > 32 5; Strontium use; Allergy to BPs; Abnormal clinical labs; Osteomalacia; lumbar spine T-score < -5.0 Interventions: 5mg of Risedronate Daily for 1 Year(s) vs. 150mg of Risedronate Monthly for 1 Year(s) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD proximal femur, Bone Turnover	Vertebral at 12 MOS: Risedronate 150mg CMD vs Risedronate 5mg/day: 1.2% vs 1.2% OR = 0.99 (95% CI 0.37, 2.65)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Palomba et al., 2008[75] Risedronate (Actonel) Location: Western Europe Setting: Multicenter Jadad: 3 Age Mean/Range: 52/NR 100% Female Race: Not reported Screened: NR Eligible: NR Enrolled: 90 Withdrawn: NR Lost to follow-up: 9 Analyzed: 81 Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Post-menopausal women NOS, T-Score ≤ -2.5 Spine, Inflammatory bowel disease in remission for = 6 mos. Exclusion criteria: Carcinoma or suspected carcinoma, Endocrine disease (not diabetes) NOS, Hyperparathyroidism, Hypoparathyroidism, Hypocalcemia, Hypercalcemia, Vitamin D deficiency, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Gastrointestinal disease, Bisphosphonates, Calcitonin, Fluoride, H2-blockers, Androgen, Menopausal hormonal therapy, Estrogen agonists including estrogen, Progestin, SERMS, Anabolic steroids, Testosterone, Proton pump inhibitors, Corticoids/Glucocorticoids, Medications known to affect skeleton, Metabolic disorders; treatment with Thiazide diuretics; Hyper-or hypophosphatemia; BMI < 18 or > 30; Smoking > 10 cigarettes/d, drinking > 3 alcoholic beverages/d, major med cond., vitamin D def.; needs that caused gastric irritation Interventions: Placebo vs. 35mg of Risedronate Weekly for 3 Year(s) All received: Calcium, Vitamin D Wash-out only Fracture outcomes assessed at baseline, 2 years, 3 years Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures, All cause mortality, Bone Turnover	Non-vertebral at 2 YRS: Risedronate vs Placebo: 2.5% vs 9.8% OR = 0.20 (95% CI 0.05, 0.85) NNT=6.9 (95% CI 4.8-48.1) Vertebral at 2 YRS: Risedronate vs Placebo: 10.0% vs 17.1% OR = 0.55 (95% CI 0.16, 1.95) Non-vertebral at 3 YRS: Risedronate vs Placebo: 2.5% vs 17.1% OR = 0.29 (95% CI 0.05, 1.75) Vertebral at 3 YRS: Risedronate vs Placebo: 7.5% vs 22.0% OR = 0.32 (95% CI 0.10, 1.09)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Ringe et al., 2009[73] Risedronate (Actonel) Location: Western Europe Setting: Single setting Jadad: 1 Age Mean/Range: 57/NR 100% Male Race: Caucasian Screened: 580 Eligible: NR Enrolled: 316 Withdrawn: 16 Lost to follow-up: 0 Analyzed: 300 Method of AE Assessment: Unclear	Inclusion criteria: Men, T-Score ≤ -2.0 Hip, T-Score ≤ -2.5 Spine, Osteoporosis score based on T-score and/or fractures and/or radiography Exclusion criteria: Hypocalcemia, Bisphosphonates, Fluoride, Hypersensitivity to bisphosphonates Interventions: Placebo Daily for 2 Year(s) + 500 or 800mg of Calcium Daily for 2 Year(s) + 1µg of Alfacalcidol Daily for 2 Year(s) or 1000I.U. of Vitamin D Daily for 2 Year(s) vs. 5mg of Risedronate Daily for 2 Year(s) + 1000mg of Calcium Daily for 2 Year(s) + 800I.U. of Vitamin D Daily for 2 Year(s) vs. 5mg of Risedronate Daily for 2 Year(s) + 1000mg of Calcium Daily for 2 Year(s) + 800I.U. of Vitamin D Daily for 2 Year(s) No run-in or wash-out Fracture outcomes assessed at baseline, 2 years Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, BMD femoral neck, Back pain, Change in height	Non-vertebral - in ref 12 at 12 MOS: Risedronate vs Placebo: 6.3% vs 10.8% OR = 0.57 (95% CI 0.26, 1.25) Non-vertebral at 24 MOS: Risedronate vs Placebo: 11.8% vs 22.3% OR = 0.48 (95% CI 0.26, 0.87) NNT=9.6 (95% CI 5.3-49.8)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Chapman et al., 2009[114] Zoledronic acid (Zometa) Location: Australia/New Zealand Setting: Multicenter Jadad: 2 Age Mean/Range: NR 23% Female Race: Not reported Screened: NR Eligible: NR Enrolled: 22 Withdrawn: NR Lost to follow-up: NR Analyzed: 22 Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient	Inclusion criteria: Men, Women otherwise undefined, Age over 17 years, T-Score ≤ -2.0 Hip, T-Score ≤ -2.0 Spine, Cystic fibrosis Exclusion criteria: Pregnancy, Hyperthyroidism, Hyperparathyroidism, Hypocalcemia, Hepatic insufficiency, Renal insufficiency, Bisphosphonates, Pre-existing fragility factors, on waiting list for lung transplant, hypogonadism, considered not being able to complete study Interventions: Placebo every 3 months for 21 Month(s) vs. 4-2mg of Zoledronic acid every 3 months for 21 Month(s) All received: Calcium, Vitamin D Run-in/wash-out unclear Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Radiographic vertebral fractures, All cause mortality, DXA distal forearm	Non-vertebral at 24 MOS: Zoledronic acid (IV) vs Placebo: 0.0% vs 0.0% OR = NC Vertebral at 24 MOS: Zoledronic acid (IV) vs Placebo: 0.0% vs 0.0% OR = NC

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Lyles et al., 2007[113] Zoledronic acid (Zometa) Location: US, Canada, South America, Western Europe, Eastern Europe Setting: Multicenter Jadad: 5 Age Mean/Range: 75/NR 76% Female Race: Caucasian, African Ancestry, Hispanic, Other Screened: 2,664 Eligible: 2,127 Enrolled: 2,127 Withdrawn: 302 Lost to follow-up: 63 Analyzed: 2,127 Method of AE Assessment: Unclear	Inclusion criteria: Ambulatory, Age over 50 years, Hip fracture repair within previous 90 days; Inability or unwillingness to take an Oral BP Exclusion criteria: Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis, Bisphosphonates without washout, Fluoride, Previous PTH use without washout, Strontium use; Sensitivity to BP; Potential to become pregnant; Creatinine clearance < 30 ml/min; Serum Ca > 11mg/dL or < 8mg/dL; Life expectancy < 6 months; Dementia without surrogate consent Interventions: Placebo Yearly for 1.9 Years (median) vs. 5mg of Zoledronic acid Yearly for 1.9 Years (median) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Hip fracture, Non-vertebral fracture, Total fractures, Radiographic vertebral fractures	Any fracture at 24 MOS: Zoledronic acid 5 mg vs Placebo: 8.6% vs 13.9% OR = 0.63 (95% CI 0.48, 0.83) NNT=22.5 (95% CI 14.1-55.2) Hip fracture at 24 MOS: Zoledronic acid 5 mg vs Placebo: 2.0% vs 3.5% OR = 0.69 (95% CI 0.41, 1.17) Non-vertebral at 24 MOS: Zoledronic acid 5 mg vs Placebo: 7.6% vs 10.7% OR = 0.72 (95% CI 0.53, 0.97) NNT=37.6 (95% CI 19.8-386.6) Vertebral at 24 MOS: Zoledronic acid 5 mg vs Placebo: 1.7% vs 3.8% OR = 0.54 (95% CI 0.32, 0.90) NNT=58.8 (95% CI 32.2-339.6)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Saag et al., 2009[224] Alendronate (Fosamax), PTH (Teriparatide) (Forteo) Location: Not reported Setting: Multicenter Jadad: 2 Age Mean/Range: 57/NR 81% Female Race: Caucasian Screened: 417 Eligible: 429 Enrolled: 428 Withdrawn: 170 Lost to follow-up: 17 Analyzed: 428 Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Ambulatory, Men, Women otherwise undefined, Age over 20 years, T-Score ≤ -2.0 Hip, T-Score ≤ -2.0 Spine, Corticosteroid use Exclusion criteria: Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Gastrointestinal disease, Bisphosphonates, Fewer than 3 lumbar vertebrae that could be evaluated, abnormal laboratory values Interventions: 10mg of Alendronate Daily for 36 Month(s) + Placebo vs. 20µg of PTH (teriparatide) Daily for 36 Month(s) + Placebo All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline, 36 months Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, CTX, PINP	Non-vertebral at 36 MOS: Alendronate 10mg/day vs Teriparatide 20mug/day: 7.0% vs 7.5% OR = 0.93 (95% CI 0.45, 1.94) Vertebral at 36 MOS: Alendronate 10mg/day vs Teriparatide 20mug/day: 7.7% vs 1.7% OR = 3.79 (95% CI 1.39, 10.32)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Okada et al., 2008[225] Alendronate (Fosamax), Vitamin D Location: Japan Setting: Single setting Jadad: 1 Age Mean/Range: 34/17-47 100% Female Race: Asian Screened: NR Eligible: 47 Enrolled: 47 Withdrawn: 14 Lost to follow-up: NR Analyzed: 33 Method of AE Assessment: Monitored	Inclusion criteria: Pre-menopausal women, Age under 48 years, Age over 16 years, Autoimmune disease Exclusion criteria: Metabolic bone disorder other than osteoporosis, Renal insufficiency, Corticoids/Glucocorticoids, Medications known to affect skeleton, Pregnancy, Lactation Interventions: 1µg of Vitamin D Daily for 18 Month(s) vs. 1µg of Vitamin D Daily for 18 Month(s) + 5mg of Alendronate Daily for 18 Month(s) All received: Prednisolone, Calcium No run-in or wash-out Fracture outcomes assessed at baseline, 12 months, 18 months Outcomes: Bone mineral density by DXA - Spine, Vertebral fracture, Radiographic vertebral fractures	Vertebral at 18 MOS: Alfacalcidol + prednisolone + alendronate vs Alfacalcidol + prednisolone: 0.0% vs 25.0% OR = 0.10 (95% CI 0.01, 0.81) NNT=4.0 (95% CI 2.2-26.4)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Ringe et al., 2007[56] Alendronate (Fosamax), Vitamin D Location: Not reported Trial: AAC TRIAE Setting: Single setting Jadad: 0 Age Mean/Range: 66/NR 63% Female Race: Not reported Screened: NR Eligible: NR Enrolled: 90 Withdrawn: NR Lost to follow-up: NR Analyzed: 90 Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Men, Post-menopausal women NOS, Osteoporosis NOS, T-Score ≤ -2.5 Hip, Clinical fractures, radiographic conf. unclear, T-score spine < -3.0 Exclusion criteria: Bisphosphonates, Fluoride, Previous PTH use, Secondary osteoporosis Interventions: 1µg of Alfacalcidol Daily for 24 Month(s) + 500mg of Calcium Daily for 24 Month(s) vs. 70mg of Alendronate Weekly for 24 Month(s) + 1000mg of Calcium Weekly for 24 Month(s) + 1000I.U. of Alfacalcidol Daily for 24 Month(s) vs. 1µg of Alfacalcidol Daily for 24 Month(s) + 70mg of Alendronate Weekly for 24 Month(s) + 500mg of Calcium Weekly for 24 Month(s) No run-in or wash-out Fracture outcomes assessed at baseline, 24 months Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Total fractures, Radiographic vertebral fractures, All cause mortality, Falls	Non-vertebral at 24 MOS: Alendronate + calcium + vitamin d vs Alfacalcidol + calcium: 20.0% vs 13.3% OR = 1.60 (95% CI 0.42, 6.16) Vertebral at 24 MOS: Alendronate + calcium + vitamin d vs Alfacalcidol + calcium: 13.3% vs 16.7% OR = 0.77 (95% CI 0.19, 3.15)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
de Nijs et al., 2006[57] Alendronate (Fosamax), Vitamin D Location: Western Europe Trial: STOP Setting: Multicenter Jadad: 5 Age Mean/Range: 61/NR 62% Female Race: Caucasian, African Ancestry, Other Screened: 210 Eligible: 201 Enrolled: 201 Withdrawn: 38 Lost to follow-up: NR Analyzed: 163 Method of AE Assessment: Monitored	Inclusion criteria: Men, Women otherwise undefined, Age under 91 years, Age over 17 years, Corticosteroid use, Rheumatic disease Exclusion criteria: Hypothyroidism, Hyperthyroidism, Hyperparathyroidism, Hypocalcemia, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Nephrolithiasis, Bisphosphonates, Calcitonin, Fluoride, Hormone use NOS, Androgen, Testosterone, Vitamin D use, Corticoids/Glucocorticoids, Glucocoricoids > 12 weeks; pregnant; breast feeding; hypercalciuria Interventions: 10mg of Alendronate Daily for 18 Month(s) + Placebo Daily for 18 Month(s) vs. 1µg of Alfacalcidol Daily for 18 Month(s) + Placebo Daily for 18 Month(s) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures	Non-vertebral at 18 MOS: Alendronate vs Alfacalcidol: 2.0% vs 3.0% OR = 0.68 (95% CI 0.12, 3.99)

Evidence Table C-1. Randomized Controlled Trials
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Campbell et al., 2009[231] Estrogen, Etidronate (Didronel) Location: UK Setting: Multicenter Jadad: 3 Age Mean/Range: NR/NR 100% Female Race: Not reported Screened: NR Eligible: 47 Enrolled: 50 Withdrawn: 3 Lost to follow-up: NR Analyzed: NR Method of AE Assessment: NR	Inclusion criteria: Ambulatory, Post-menopausal women NOS, Age under 60 years, Osteoporosis NOS, Corticosteroid use, Asthmatics Exclusion criteria: Not Reported Interventions: Control vs. 2mg of Estrogen Daily for 5 Year(s) + 0.625mg of Estrogen Daily for 5 Year(s) + 50µg of Estrogen patch for 5 Year(s) vs. 400mg of Etidronate Daily for 5 years for 2 weeks every 3 months Year(s) vs. 400mg of Etidronate Daily for 5 years for 2 weeks every 3 months Year(s) + 50µg of Estrogen patch for 5 Year(s) + 2mg of Estrogen Daily for 5 Year(s) + 0.625mg of Estrogen Daily for 5 Year(s) Run-in/wash-out unclear Fracture outcomes assessed at baseline, 2 years, 3 years, 4 years, 5 years Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures	Vertebral & nonvertebral at 5 YRS: Etidronate vs No etidronate: 4.0% vs 8.0% OR = 0.48 (95% CI 0.05, 4.82) Vertebral & nonvertebral- MHT at 5 YRS: Menopausal hormone therapy vs No menopausal hormone therapy: 0.0% vs 13.0% OR = 0.13 (95% CI 0.01, 1.31)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Sato et al., 2007[72] Vitamin D, Risedronate (Actonel) Location: Japan Setting: Single setting Jadad: 5 Age Mean/Range: 71/NR 100% Male Race: Japanese Screened: NR Eligible: 279 Enrolled: 242 Withdrawn: 19 Lost to follow-up: NR Analyzed: 223 Method of AE Assessment: Monitored, Elicited by investigator	Inclusion criteria: Men, Age over 64 years, Parkinson disease Exclusion criteria: Cardiovascular disease, Hypothyroidism, Hyperthyroidism, Hyperparathyroidism, Hepatic insufficiency, Renal insufficiency, Bisphosphonates, Calcitonin, Calcium includes antacids, Estrogen agonists including estrogen, Vitamin D use, Corticoids/Glucocorticoids, Parkinson disease at stage 5 of Hoehn and Yahr stage; Vitamin K intake; History of non-vertebral fracture, secondary osteoporosis. Interventions: Placebo Daily for 2 Year(s) vs. 2.5mg of Risedronate Daily for 2 Year(s) All received: Vitamin D Run-in/wash-out unclear Fracture outcomes assessed at baseline Outcomes: Hip fracture, All cause mortality, BMD of metacarpal	Hip at 2 YRS: Risedronate vs Placebo: 2.5% vs 7.4% OR = 0.35 (95% CI 0.11, 1.12)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Ensrud et al., 2008[120] Raloxifene (Evista) Location: US, Canada, South America, UK, Western Europe, Eastern Europe, Asia, South Africa and Israel Setting: Multicenter Jadad: 4 Age Mean/Range: 68/NR 100% Female Race: Caucasian, African Ancestry, Hispanic, Asian Screened: 11,767 Eligible: 10,356 Enrolled: 10,101 Withdrawn: 2,062 Lost to follow-up: NR Analyzed: 10,101 Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient	Inclusion criteria: Ambulatory, Post-menopausal women >1 year, Age over 54 years, Coronary Heart Disease (CHD) or increase risk for CHD (based on list of criteria and score) Exclusion criteria: Carcinoma or suspected carcinoma, Hepatic insufficiency, Renal insufficiency, Androgen, Menopausal hormonal therapy, Estrogen agonists including estrogen, Progestin, SERMS, Estrogen agonists, Anabolic steroids, Testosterone, MI within past 3 mos; NYHA class III or IV heart failure; Severe postmenopausal symptoms (reg. # RT); Current/recent participation in a clinical trial; CABG or perc. Graft within 3 mos.; Life expectancy < 5 years; Unexplained uterine bleeding within past 6 mos.; History of DVT, pulmonary embolism; Jaundice; Poor med/psych risk for treatment with investigational drug Interventions: Placebo for 5.6 Year(s) vs. 60mg of Raloxifene Daily for 5.6 Year(s) No run-in or wash-out Fracture outcomes assessment time variable Outcomes: Hip fracture, Vertebral fracture, Non-vertebral fracture, Symptomatic vertebral fractures, All cause mortality, Wrist fracture	Hip/femur fracture at 5.6 YRS: Raloxifene 60mg/day vs Placebo: 1.8% vs 2.0% OR = 0.86 (95% CI 0.65, 1.15) Non-vertebral at 5.6 YRS: Raloxifene 60mg/day vs Placebo: 8.5% vs 8.7% OR = 0.99 (95% CI 0.86, 1.13) Vertebral at 5.6 YRS: Raloxifene 60mg/day vs Placebo: 1.3% vs 1.9% OR = 0.66 (95% CI 0.48, 0.90) NNT=154.0 (95% CI 87.9-620.7) Wrist at 5.6 YRS: Raloxifene 60mg/day vs Placebo: 2.1% vs 2.2% OR = 0.97 (95% CI 0.74, 1.26)

Evidence Table C-1. Randomized Controlled Trials
SERMs

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Ishani et al., 2008[255] Raloxifene (Evista) Location: US, Canada, South America, UK, Western Europe, Eastern Europe, Asia, Israel Setting: Multicenter Jadad: 2 Age Mean/Range: 67/31-80 100% Female Race: Caucasian Screened: 22,379 Eligible: NR Enrolled: 7,705 Withdrawn: 877 Lost to follow-up: 389 Analyzed: 7,705 Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient, Reported in original report	Inclusion criteria: Ambulatory, Post-menopausal women >2 years, Osteoporosis score based on T-score and/or fractures and/or radiography, Femoral neck or lumbar spine BMD T-score = -2.5 or low BMD and = 1 moderate or severe vertebral fracture or = 2 mild fracture or = 2 moderate fracture Exclusion criteria: Carcinoma or suspected carcinoma, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Malabsorption syndrome, Women were excluded if they had experienced bone disease other than osteoporosis, substantial postmenopausal symptoms or abnormal uterine bleeding, taken an androgen calcitonin, or bisphosphonate within the previous 2 months; been receiving fluoride therapy for more than 3 months during the previous 2 years; undergone systemic glucocorticoid therapy for more than 1 month within the past year; taken antiseizure drugs or pharmacologic doses of cholecalciferol; had a history of thromboembolic disorders within the last 10 years (except in association with an injury); experienced endocrine disorders requiring therapy (except in association with an injury); experienced endocrine disorders requiring therapy (except for type 2 diabetes or hypothyroidism); had serum creatine levels above 225nmol/L (2.5 mg/dL); had active renal lithiasis, abnormalepatic function, or untreated malabsorption; or consumed more than 4 alcoholic drinks per day. In addition, we excluded women with pathologic fractures, those from whom satisfactory thoracic and lumbar radiographs could not be obtained, and those with fewer than 2 lumbar and 4 thoracic vertebrae that were evaluable. Interventions: Placebo Daily for 3 Year(s) vs. 60mg of Raloxifene Daily for 3 Year(s) vs. 120mg of Raloxifene Daily for 3 Year(s) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline, 24 months, 36 . Outcomes: Bone mineral density by DXA - Spine, Hip fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral neck, Bone Turnover	Number of people with fracture not reported for every arm

Evidence Table C-1. Randomized Controlled Trials
SERMs

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Silverman et al., 2008[121] Raloxifene (Evista), Bazedoxifene Location: US, Canada, South America, Western Europe, Eastern Europe, Australia/New Zealand, Asia, South Africa Setting: Multicenter Jadad: 3 Age Mean/Range: 66/NR 100% Female Race: Caucasian, Other Screened: 26,749 Eligible: NR Enrolled: 7,492 Withdrawn: 2,501 Lost to follow-up: NR Analyzed: 7,492 Method of AE Assessment: Monitored, Elicited by investigator, Reported spontaneously by patient	Inclusion criteria: Ambulatory, Post-menopausal women >2 years, Age under 86 years, Age over 54 years, Osteoporosis score based on T-score and/or fractures and/or radiography, Healthy (Tscore -2.5 - -4); Low BMD or radiographically confirmed vertebral fracture and BMD = -4.0 Exclusion criteria: Carcinoma or suspected carcinoma, Metabolic bone disorder other than osteoporosis, Bisphosphonates, Calcitonin, Androgen, Estrogen agonists including estrogen, Progestin, SERMS, Previous PTH use, Vitamin D use, Conditions interfering w/DXA, pathological vertebral fracture; Vasomotor symptoms req. treatment; serious conditions e.g. endometrial hyperplasia; cancer within 10 years of study; endocrine disorders requiring treatment; untreated malabsorption disorders; DVT (active or History); pulmonary embolism; retinal vein thrombosis; elevated fasting cholesterol or triglycerides ' Interventions: Placebo for 3 Year(s) vs. 60mg of Raloxifene Daily for 3 Year(s) vs. 20mg of Bazedoxifene Daily for 3 Year(s) vs. 40mg of Bazedoxifene Daily for 3 Year(s) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline, 12 months, 24 months, 36 months Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, BMD femoral neck, CTX, Osteocalcin	Non-vertebral at 3 YRS: Bazedoxifene 20mg vs Placebo: 5.7% vs 6.3% OR = 0.89 (95% CI 0.67, 1.20) Bazedoxifene 40mg vs Placebo: 5.6% vs 6.3% OR = 0.86 (95% CI 0.64, 1.15) Raloxifene 60mg/day vs Placebo: 5.9% vs 6.3% OR = 0.61 (95% CI 0.44, 0.84) NNT=49.8 (95% CI 30.3-139.6) Vertebral at 3 YRS: Bazedoxifene 20mg vs Placebo: 2.3% vs 4.1% OR = 0.56 (95% CI 0.39, 0.80) NNT=55.4 (95% CI 34.2-145.8) Bazedoxifene 40mg vs Placebo: 2.5% vs 4.1% OR = 0.61 (95% CI 0.43, 0.87) NNT=63.5 (95% CI 36.8-230.6) Raloxifene 60mg/day vs Placebo: 2.3% vs 4.1% OR = 0.57 (95% CI 0.39, 0.82) NNT=56.8 (95% CI 34.6-158.2) Vertebral - w/ prevalent fracture at 3 YRS: Bazedoxifene 20mg - w/ prevalent fracture vs Placebo - w/ prevalent fracture: 2.6% vs 4.8% OR = 0.54 (95% CI 0.39, 0.76) NNT=45.9 (95% CI 29.6-102.5) Bazedoxifene 40mg - w/ prevalent fracture vs Placebo - w/ prevalent fracture: 2.8% vs 4.8% OR = 0.58 (95% CI 0.41, 0.81) NNT=50.1 (95% CI 31.1-128.2) Raloxifene 60mg/day - w/ prevalent fracture vs Placebo - w/ prevalent fracture: 2.7% vs 4.8% OR = 0.56 (95% CI 0.40, 0.79) NNT=48.3 (95% CI 30.4-116.7) Vertebral - w/out prevalent fracture at 3 YRS: Bazedoxifene 20mg - w/out prevalent fracture vs Placebo - w/out prevalent fracture: 2.0% vs 3.1% OR = 0.65 (95% CI 0.43, 0.98) NNT=94.2 (95% CI 48.4-1750) Bazedoxifene 40mg - w/out prevalent fracture vs Placebo - w/out prevalent fracture: 2.1% vs 3.1% OR = 0.67 (95% CI 0.45, 1.01) Raloxifene 60mg/day - w/out prevalent fracture vs Placebo - w/out prevalent fracture: 1.8% vs 3.1% OR = 0.58 (95% CI 0.38, 0.88) NNT=77.4 (95% CI 43.9-326.5)

Evidence Table C-1. Randomized Controlled Trials
Denosumab

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Cummings et al., 2009[118] Denosumab Location: US, Canada, South America, UK, Western Europe, Eastern Europe, Australia/New Zealand Trial: FREEDOM Setting: Multicenter Jadad: 0 Age Mean/Range: 72/60-90 100% Female Race: Not reported Screened: NR Eligible: NR Enrolled: 7,868 Withdrawn: 60 Lost to follow-up: NR Analyzed: 7,393 Method of AE Assessment: Monitored	Inclusion criteria: Ambulatory, Post-menopausal women NOS, Age under 90 years, Age over 60 years, T-Score ≤ -2.5 Hip, T-Score ≤ -2.5 Spine Exclusion criteria: Vitamin D deficiency, Metabolic bone disorder other than osteoporosis, Bisphosphonates, Calcitonin, Fluoride, Menopausal hormonal therapy, SERMS, Previous PTH use, Vitamin D use, Corticoids/Glucocorticoids, T-score < -4.0 @ hip or lumbar spine; Severe prevalent vertebral fracture Interventions: Placebo 2X per Year for 36 Month(s) vs. 60mg of Denosumab 2X per Year for 36 Month(s) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline, 2 years, 3 years Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Hip fracture, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, All cause mortality, BALP, BMD femoral trochanter, New vertebral fracture, Time to first hip fracture, Time to first non-vertebral fracture	Hip fracture at 36 MOS: Denosumab vs Placebo: 0.7% vs 1.2% OR = 0.59 (95% CI 0.36, 0.94) NNT=200.0 (95% CI 105.7-1854) Multiple new vertebral at 36 MOS: Denosumab vs Placebo: 0.6% vs 1.6% OR = 0.40 (95% CI 0.26, 0.61) NNT=100.0 (95% CI 67.9-189.9) New clinical vertebral at 36 MOS: Denosumab vs Placebo: 0.8% vs 2.6% OR = 0.34 (95% CI 0.24, 0.48) NNT=55.5 (95% CI 41.7-83.3) Non-vertebral at 36 MOS: Denosumab vs Placebo: 6.5% vs 8.0% OR = 0.80 (95% CI 0.67, 0.95) NNT=66.7 (95% CI 37.2-319.9) Vertebral at 36 MOS: Denosumab vs Placebo: 2.3% vs 7.2% OR = 0.34 (95% CI 0.27, 0.42) NNT=20.4 (95% CI 17.1-25.4)

Evidence Table C-1. Randomized Controlled Trials
Estrogen

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Boone et al., 2006[136] Estrogen Location: Canada Setting: Multicenter Jadad: 5 Age Mean/Range: 55/NR 100% Female Race: Not reported Screened: 355 Eligible: 91 Enrolled: 31 Withdrawn: 9 Lost to follow-up: NR Analyzed: 31 Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Ambulatory, Post-menopausal women NOS, Age under 66 years, Primary biliary cirrhosis; normal PAP, pelvic exam, breast exam; Hemoglobin > 80mg/L Exclusion criteria: Vitamin D deficiency, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Organ transplantation, Estrogen agonists including estrogen, Progestin, Medications known to affect skeleton, Liver transplant; Serum bilirubin >120 mmol/l; Contraindications to estrogen use; nonambulatory or immobile > 3 mos in prev year; known sensitivity to patch Interventions: Placebo for 24 Month(s) vs. 0.05mg of Estrogen patch Daily for 24 Month(s) + 0.25mg of Est./progestin for 24 Month(s) All received: Calcium, Vitamin D No run-in or wash-out Fracture outcomes assessed at baseline, 24 months Outcomes: Bone mineral density by DXA - Spine, Radiographic vertebral fractures, All cause mortality, BALP, NTX	Non-vertebral at 24 MOS: Estrogen/progestin vs Placebo: 0.0% vs 0.0% OR = NC Vertebral at 24 MOS: Estrogen/progestin vs Placebo: 0.0% vs 13.3% OR = 0.12 (95% CI 0.01, 1.98)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Frost et al., 2007[157] Calcium Location: Western Europe Setting: Single setting Jadad: 1 Age Mean/Range: 52/NR 100% Male Race: German Screened: 40 Eligible: 40 Enrolled: 40 Withdrawn: 7 Lost to follow-up: NR Analyzed: 33 Method of AE Assessment: NR	Inclusion criteria: Men, CHF Class 1, II or III Stable CHF for 3 months Exclusion criteria: Hyperthyroidism, Hyperparathyroidism, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Inflammatory bowel disease, Medications known to affect skeleton Interventions: Placebo for 1 Year(s) vs. 1000mg of Calcium Daily for 1 Year(s) No run-in or wash-out Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture	Vertebral at 12 MOS: Calcium 1000mg/day vs Placebo: 5.9% vs 6.3% OR = 0.94 (95% CI 0.06, 15.72)

Evidence Table C-1. Randomized Controlled Trials
Calcium/Vitamin D

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Fujita et al., 2004[158] Calcium Location: Japan Trial: KATSURAGI CALCIUM STUDY Setting: Single setting Jadad: 2 Age Mean/Range: 80/NR 100% Female Race: Asian Screened: NR Eligible: NR Enrolled: 58 Withdrawn: NR Lost to follow-up: NR Analyzed: 19 Method of AE Assessment: NR	Inclusion criteria: Women otherwise undefined, Hospitalized Exclusion criteria: Not Reported Interventions: Placebo Daily for 2 Year(s) vs. 900mg of AAA- absorbable algal calcium Daily for 2 Year(s) vs. 900mg of Calcium carbonate Daily for 2 Year(s) No run-in or wash-out Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Radiographic vertebral fractures, All cause mortality, DXA Whole body	Vertebral at 2 YRS: Active absorbable algal calcium vs Placebo: 0.0% vs 50.0% OR = 0.09 (95% CI 0.01, 1.06) Calcium carbonate vs Placebo: 28.6% vs 50.0% OR = 0.43 (95% CI 0.05, 3.73)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Law et al., 2006[163] Vitamin D Location: UK Setting: Multicenter Jadad: 3 Age Mean/Range: 85/NR 76% Female Race: Not reported Screened: NR Eligible: 3,717 Enrolled: 3,717 Withdrawn: NR Lost to follow-up: 669 Analyzed: 3,717 Method of AE Assessment: Monitored	Inclusion criteria: Age over 59 years Exclusion criteria: Carcinoma or suspected carcinoma, Bisphosphonates, Calcium includes antacids, Previous PTH use, Vitamin D use, Temporary residents-respite care Interventions: Control every 3 Months vs. 2.5mg of Vitamin D every 3 Months No run-in or wash-out Fracture outcomes assessment time unclear Outcomes: Non-vertebral fracture, All cause mortality, Falls	Hip at 10 MOS: Vitamin d vs Placebo: 1.3% vs 1.0% OR = 1.34 (95% CI 0.74, 2.42) Non-vertebral at 10 MOS: Vitamin d vs Placebo: 3.6% vs 2.6% OR = 1.41 (95% CI 0.97, 2.04)

Evidence Table C-1. Randomized Controlled Trials
Calcium/Vitamin D

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Lyons et al., 2007[203] Vitamin D Location: UK Setting: Multicenter, Longterm care, Shelters and other residential Jadad: 5 Age Mean/Range: 84/NR 76% Female Race: Not reported Screened: 5,745 Eligible: 4,443 Enrolled: 3,440 Withdrawn: 699 Lost to follow-up: 1,606 Analyzed: 3,440 Method of AE Assessment: Monitored	Inclusion criteria: Men, Women otherwise undefined, Residence in nursing homes or sheltered housing Exclusion criteria: Vitamin D use, Contra-indication to vitamin D supplementation Interventions: Placebo vs. 2.5 or 100,000mg of Vitamin D(ergocalciferol) 3 X per year for 3 Year(s) No run-in or wash-out Fracture outcomes assessment time variable Outcomes: Hip fracture, Radial fracture, Vertebral fracture, Non-vertebral fracture, Symptomatic vertebral fractures, All cause mortality, BALP, Time to 1st fracture	All sites - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 14.1% vs 15.6% OR = 0.89 (95% CI 0.73, 1.07) All sites - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 11.9% vs 12.7% OR = 0.93 (95% CI 0.76, 1.14) Hip - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 7.4% vs 7.3% OR = 1.00 (95% CI 0.78, 1.29) Hip - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 6.5% vs 6.1% OR = 1.08 (95% CI 0.82, 1.42) Hip/wrist/forearm - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 9.3% vs 8.8% OR = 1.06 (95% CI 0.84, 1.34) Hip/wrist/forearm - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 8.1% vs 7.3% OR = 1.11 (95% CI 0.87, 1.43) Hip/wrist/forearm/vertebrae - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 9.5% vs 9.5% OR = 1.00 (95% CI 0.80, 1.26) Hip/wrist/forearm/vertebrae - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 8.3% vs 7.9% OR = 1.06 (95% CI 0.83, 1.35) Other Fracture - All Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 4.6% vs 6.1% OR = 0.74 (95% CI 0.55, 0.99) NNT=64.8 (95% CI 32.8-2550) Other Fracture - First Fracture at 3 YRS: Vitamin D (ergocalciferol) vs Placebo: 3.6% vs 4.8% OR = 0.73 (95% CI 0.53, 1.02)

Evidence Table C-1. Randomized Controlled Trials
Calcium/Vitamin D

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Sanders et al., 2010[164] Vitamin D Location: Australia/New Zealand Trial: VIT. D Setting: Single setting, Community Jadad: 5 Age Mean/Range: NR/NR 100% Female Race: Not reported Screened: 4,718 Eligible: 3,139 Enrolled: 2,258 Withdrawn: 226 Lost to follow-up: NR Analyzed: 2,258 Method of AE Assessment: Monitored	Inclusion criteria: Women otherwise undefined, Age over 69 years, Community-dwelling; Residing in Southern Victoria Australia; High risk for fracture (e.g. maternal fx hx, past fx hx, fall hx) Exclusion criteria: Hypercalcemia (greater than 2.65 mm/l, coreted x albumin), Renal insufficiency (Creatinine greater than 150 mmd/l), Vitamin D use (greater than or equal to 400Iu), Inability to provide consent or HX; Institutional residence; Calcitriol use; Antifracture therapy Interventions: 500,000I.U. of Vitamin D Yearly for 3-5 Year(s) vs. Placebo Yearly for 3-5 Year(s) No run-in or wash-out Fracture outcomes assessment time unclear Outcomes: Non-vertebral fracture, All cause mortality, BALP	Ankle at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 0.7% vs 1.1% OR = 0.66 (95% CI 0.28, 1.60) Any fracture at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 13.7% vs 11.1% OR = 1.27 (95% CI 0.99, 1.63) Clavicle/scapula at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 0.4% vs 0.1% OR = 3.31 (95% CI 0.57, 19.13) Colles at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 2.3% vs 2.0% OR = 1.13 (95% CI 0.64, 1.99) Foot/toes at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 1.5% vs 1.1% OR = 1.41 (95% CI 0.68, 2.93) Hand/fingers at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 0.5% vs 0.3% OR = 1.94 (95% CI 0.52, 7.19) Hip at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 1.7% vs 1.3% OR = 1.26 (95% CI 0.64, 2.49) Humerus at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 1.3% vs 1.2% OR = 1.07 (95% CI 0.51, 2.22) Lower leg at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 0.5% vs 0.4% OR = 1.19 (95% CI 0.37, 3.90) Other forearm at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 1.2% vs 0.6% OR = 1.95 (95% CI 0.83, 4.60) Pelvis at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 0.7% vs 0.4% OR = 1.94 (95% CI 0.63, 6.04)

Evidence Table C-1. Randomized Controlled Trials
Calcium/Vitamin D

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Sanders et al., 2010[164] Continued		Ribs/sternum at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 0.5% vs 0.6% OR = 0.85 (95% CI 0.29, 2.53) Skull/facial bones at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 0.7% vs 0.4% OR = 1.94 (95% CI 0.63, 6.04) Upper leg/patella at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 0.7% vs 0.5% OR = 1.33 (95% CI 0.46, 3.79) Vertebral at 2.96 YRS: Vitamin D (cholealciferol) vs Placebo: 3.1% vs 2.5% OR = 1.25 (95% CI 0.76, 2.06)
Shiraki et al., 1996[161] Vitamin D Location: Japan Setting: Multicenter Jadad: 4 Age Mean/Range: 72/NR 100% Female Race: Asian Screened: NR Eligible: NR Enrolled: 113 Withdrawn: 34 Lost to follow-up: NR Analyzed: 113 Method of AE Assessment: NR	Inclusion criteria: Ambulatory, Women otherwise undefined, Age over 59 years, Osteoporosis NOS Exclusion criteria: Hypothyroidism, Hyperthyroidism, Hyperparathyroidism, Hypoparathyroidism, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Renal insufficiency, No osteoporosis treatment within 6 months Interventions: Placebo Daily for 2 Year(s) vs. 0.75µg of Vitamin D Daily for 2 Year(s) All received: Calcium No run-in or wash-out Fracture outcomes assessed at baseline, 12 months, 18 months, 24 months Outcomes: Bone mineral density by DXA - Spine, Radiographic vertebral fractures, All cause mortality, BMD-DXA Whole body	Non-vertebral at 2 YRS: 1a-hydroxy vitamin d vs Placebo: 0.0% vs 7.1% OR = 0.15 (95% CI 0.01, 1.44) Vertebral at 2 YRS: 1a-hydroxy vitamin d vs Placebo: 5.4% vs 7.1% OR = 0.75 (95% CI 0.12, 4.55)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Smith et al., 2007[162] Vitamin D Location: UK Setting: Multicenter, Community Jadad: 5 Age Mean/Range: 79/NR 54% Female Race: Not reported Screened: 13,487 Eligible: 11,302 Enrolled: 9,440 Withdrawn: 4,570 Lost to follow-up: NR Analyzed: 9,440 Method of AE Assessment: Monitored, Elicited by investigator	Inclusion criteria: Men, Women otherwise undefined, Age over 74 years Exclusion criteria: Carcinoma or suspected carcinoma, Hypocalcemia, Renal insufficiency, Nephrolithiasis, Vitamin D use, Treated osteoporosis, bilateral total hip replacement, sarcoidosis Interventions: Placebo Yearly for 3 Year(s) vs. 300,000I.U. of Vitamin D Yearly for 3 Year(s) No run-in or wash-out Fracture outcomes assessed at baseline, 12 months, 18 months, 24 months, 36 months Outcomes: Bone mineral density by DXA - Hip, Hip fracture, Radial fracture, Non-vertebral fracture, All cause mortality, Falls	Hip or femur at 36 MOS: Vitamin d vs Placebo: 1.4% vs 0.9% OR = 1.49 (95% CI 1.03, 2.18) Non-vertebral at 36 MOS: Vitamin d vs Placebo: 6.5% vs 5.9% OR = 1.10 (95% CI 0.93, 1.30) Wrist at 36 MOS: Vitamin d vs Placebo: 1.4% vs 1.1% OR = 1.23 (95% CI 0.85, 1.77)

Evidence Table C-1. Randomized Controlled Trials
Calcium/Vitamin D

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Larsen et al., 2004[150] Calcium, Vitamin D Location: Western Europe Setting: Community practices Jadad: 0 Age Mean/Range: 75/NR 60% Female Race: Not reported Screened: NR Eligible: 9,605 Enrolled: NR Withdrawn: NR Lost to follow-up: NR Analyzed: 9,605 Method of AE Assessment: NR	Inclusion criteria: Ambulatory, Men, Women otherwise undefined, Age over 65 years Exclusion criteria: People living in nursing homes. Severely impaired persons living in sheltered homes for the elderly. Mental retardation and cannot give consent. Interventions: Control vs. 1000mg of Calcium Daily + 400I.U. of Vitamin D Daily vs. Usual care vs. 1000mg of Calcium Daily + 400I.U. of Vitamin D Daily No run-in or wash-out Fracture outcomes assessed at baseline Outcomes: Proximal humerus fracture, Radial fracture, Vertebral fracture, Non-vertebral fracture, All cause mortality, BALP, BMD femoral trochanter, Pelvic fractures, Hospital admission, For fracture	All fractures - men at 42 MOS: Both programs vs Placebo: 3.5% vs 3.1% OR = 1.13 (95% CI 0.67, 1.89) Calcium & vitamin d vs Placebo: 3.0% vs 3.1% OR = 0.99 (95% CI 0.62, 1.57) Environment & health program vs Placebo: 3.0% vs 3.1% OR = 0.99 (95% CI 0.62, 1.58) All fractures - women at 42 MOS: Both programs vs Placebo: 8.3% vs 11.1% OR = 0.73 (95% CI 0.56, 0.93) NNT=36.1 (95% CI 20.1-174.8) Calcium & vitamin d vs Placebo: 8.6% vs 11.1% OR = 0.75 (95% CI 0.60, 0.94) NNT=41.2 (95% CI 22.6-232.7) Environment & health program vs Placebo: 8.9% vs 11.1% OR = 0.78 (95% CI 0.62, 0.97) NNT=45.8 (95% CI 23.9-533.2)

Evidence Table C-1. Randomized Controlled Trials
Calcium/Vitamin D

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Salovaara et al., 2010[154] Calcium, Vitamin D Location: Western Europe, Finland Trial: OSPRE Setting: Community, regional Jadad: 2 Age Mean/Range: 67/65-71 100% Female Race: Caucasian Screened: 5,407 Eligible: 5,407 Enrolled: 3,432 Withdrawn: 513 Lost to follow-up: 56 Analyzed: 3,195 Method of AE Assessment: Reported spontaneously by patient	Inclusion criteria: Women otherwise undefined, Age over 64 years, Living in Saronia, Finlad; No previous trial participation Exclusion criteria: None Interventions: Control vs. 1000mg of Calcium Daily for 3 Year(s) + 800I.U. of Vitamin D Daily for 3 Year(s) No run-in or wash-out Fracture outcomes assessment time variable Outcomes: Bone mineral density by DXA - Spine, Hip fracture, Proximal humerus fracture, Vertebral fracture, Non-vertebral fracture, All cause mortality, BALP, BMD femoral trochanter	Ankle at 3 YRS: Vitamin D & calcium vs Placebo: 0.7% vs 0.7% OR = 0.93 (95% CI 0.41, 2.11) Antebrachium at 3 YRS: Vitamin D & calcium vs Placebo: 0.0% vs 0.1% OR = 0.14 (95% CI 0.00, 6.92) Any fracture at 3 YRS: Vitamin D & calcium vs Placebo: 4.9% vs 5.8% OR = 0.83 (95% CI 0.61, 1.13) Cervical spine at 3 YRS: Vitamin D & calcium vs Placebo: 0.0% vs 0.1% OR = 0.14 (95% CI 0.00, 6.92) Clavicula at 3 YRS: Vitamin D & calcium vs Placebo: 0.1% vs 0.1% OR = 1.01 (95% CI 0.06, 16.23) Crus at 3 YRS: Vitamin D & calcium vs Placebo: 0.0% vs 0.1% OR = 0.14 (95% CI 0.00, 6.92) Diaphyseal humerus at 3 YRS: Vitamin D & calcium vs Placebo: 0.0% vs 0.2% OR = 0.14 (95% CI 0.01, 1.32) Distal forarem at 3 YRS: Vitamin D & calcium vs Placebo: 1.5% vs 2.0% OR = 0.73 (95% CI 0.43, 1.24) Elbow at 3 YRS: Vitamin D & calcium vs Placebo: 0.0% vs 0.2% OR = 0.14 (95% CI 0.01, 1.32) Face and scull at 3 YRS: Vitamin D & calcium vs Placebo: 0.3% vs 0.1% OR = 1.98 (95% CI 0.40, 9.81) Foot at 3 YRS: Vitamin D & calcium vs Placebo: 0.4% vs 0.3% OR = 1.42 (95% CI 0.46, 4.40)

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Salovaara et al., 2010[154] Continued		Hand at 3 YRS: Vitamin D & calcium vs Placebo: 0.5% vs 0.2% OR = 1.98 (95% CI 0.64, 6.15) Hip at 3 YRS: Vitamin D & calcium vs Placebo: 0.3% vs 0.1% OR = 1.98 (95% CI 0.40, 9.81) Lumbal spine at 3 YRS: Vitamin D & calcium vs Placebo: 0.4% vs 0.7% OR = 0.56 (95% CI 0.22, 1.46) Non-vertebral fracture at 3 YRS: Vitamin D & calcium vs Placebo: 4.5% vs 5.1% OR = 0.87 (95% CI 0.63, 1.21) Osteoporotic fracture at 3 YRS: Vitamin D & calcium vs Placebo: 2.6% vs 3.2% OR = 0.82 (95% CI 0.54, 1.23) Pelvis at 3 YRS: Vitamin D & calcium vs Placebo: 0.1% vs 0.1% OR = 0.52 (95% CI 0.05, 5.01) Proximal humerus at 3 YRS: Vitamin D & calcium vs Placebo: 0.4% vs 0.4% OR = 1.01 (95% CI 0.33, 3.15) Scapula at 3 YRS: Vitamin D & calcium vs Placebo: 0.2% vs 0.0% OR = 7.51 (95% CI 0.78, 72.22) Thoracal spine at 3 YRS: Vitamin D & calcium vs Placebo: 0.2% vs 0.1% OR = 1.51 (95% CI 0.26, 8.75) Thorax at 3 YRS: Vitamin D & calcium vs Placebo: 0.3% vs 0.4% OR = 0.73 (95% CI 0.23, 2.26) Vertebral at 3 YRS: Vitamin D & calcium vs Placebo: 0.6% vs 0.8% OR = 0.70 (95% CI 0.30, 1.63)

Evidence Table C-1. Randomized Controlled Trials
Calcium/Vitamin D

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Xia et al., 2009[227] Calcium, Vitamin D Location: Asia Setting: Multicenter Jadad: 3 Age Mean/Range: 70/67-74 100% Female Race: Asian Screened: NR Eligible: NR Enrolled: 150 Withdrawn: 8 Lost to follow-up: NR Analyzed: 142 Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Post-menopausal women NOS, Age over 65 years, T-Score ≤ -1.0 Spine, BMI: 18-30 Exclusion criteria: Hypothyroidism, Hyperthyroidism, Hyperparathyroidism, Hypoparathyroidism, Hypocalcemia, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Bisphosphonates, Calcitonin, Fluoride, Estrogen agonists including estrogen, SERMS, Anabolic steroids, Testosterone, Previous PTH use, Corticoids/Glucocorticoids, Tibolone use; calcitriol use within 3 months; Interventions: 600mg of Calcium Daily for 12 Month(s) + 125I.U. of Vitamin D Daily for 12 Month(s) vs. 0.25µg of Rocaltrol Daily for 12 Month(s) + 600mg of Calcium Daily for 12 Month(s) + 125I.U. of Vitamin D Daily for 12 Month(s) Run-in/wash-out unclear Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture	Vertebral at 12 MOS: Rocaltrol+Caltrate D vs Caltrate D: 1.4% vs 2.6% OR = 0.52 (95% CI 0.05, 5.10)

Evidence Table C-1. Randomized Controlled Trials
Physical Activity

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Korpelainen et al., 2010[215] Physical activity Location: Oulu, Finland Setting: Single setting Jadad: 2 Age Mean/Range: 73/71-74 100% Female Race: Caucasian Screened: 1,689 Eligible: 623 Enrolled: 160 Withdrawn: 60 Lost to follow-up: NR Analyzed: 160 Method of AE Assessment: NR	Inclusion criteria: Ambulatory, Women otherwise undefined, Born 1924-1927 (71-74 years); T-score > -2.0 (hip, distal radius) Exclusion criteria: Menopausal hormonal therapy, Corticoids/Glucocorticoids, Hip, distal radius T-score < -2.0; use of osteoporosis medications; acute or unstable chronic illness; use of walking aid devices other than cane; severe cognitive impairement; bilateral hip replacement; malignant neoplasm Interventions: Control vs. Exercise Weekly + 20mg of Exercise Daily No run-in or wash-out Fracture outcomes assessment time variable Outcomes: Bone mineral density by DXA - Hip, All cause mortality, BALP, BMD femoral trochanter	Proximal fracture at 7.1 YRS: Exercise vs Placebo: 17.6% vs 52.2% OR = 0.22 (95% CI 0.11, 0.41) NNT=2.9 (95% CI 2.1-4.8)

AE=Adverse Event, NR=Not Reported

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
Schwartz 2010 [243] (FLEX) Alendronate	1,099 postmenopausal women aged 55 to 81 years with low femoral neck BMD (0.68 g/cm2) originally randomized to oral alendronate for 5 years (5 mg/d for 2 years, 10 mg thereafter). Women in active tx were then randomized to 5 mg/d (n=329) or 10mg/d (n=333) or placebo (n=437) for 5 additional years. All women also offered daily supplement containing 500 mg of calcium and 250 U of vitamin D.	Post hoc analysis of FLEX to assess whether anti-fracture efficacy of continued alendronate differed by FN T-score and vertebral fracture status at FLEX baseline and by BMD changes during alendronate use during the FIT.	Women without vertebral fracture at baseline (n=720): continuation of alendronate decreased non-vertebral fracture in women with FLEX baseline FN T-score ≤-2.5 (RR 0.50, 95% CI 0.26, 0.96) but not in women with T-score>-2.5 and ≤-2 (RR 0.79, 95% CI 0.37, 1.66) or with T-score >-2 (RR 1.41, 95% CI 0.75, 2.66) (p for interaction 0.019).	Continuing alendronate for 10 years instead of stopping after 5 years reduces risk of non-vertebral fracture in women without prevalent vertebral fracture and with FN T-score was ≤-2.5 but in women whose FN T-score was <-2.5
Black 2006 [240] (FIT/FLEX) Alendronate	1,099 postmenopausal women aged 55 to 81 years with low femoral neck BMD (0.68 g/cm2) originally randomized to oral alendronate for 5 years (5 mg/d for 2 years, 10 mg thereafter). Women in active tx were then randomized to 5 mg/d (n=329) or 10mg/d (n=333) or placebo (n=437) for 5 additional years. All women also offered daily supplement containing 500 mg of calcium and 250 U of vitamin D. Assessed effect of continuing vs. stopping treatment after 5 years	1°: Hip BMD 2°: BMD at other sites Fracture incidence was exploratory outcome measure Lateral spine radiographs were obtained at FLEX baseline and at 36 and 60 months for morphometric vertebral fracture ascertainment. Adverse events	(see [240] for results of the original FIT and FLEX trials) After 5 years, the cumulative risk of nonvertebral fractures (RR, 1.00; 95% CI, 0.76-1.32) was not significantly different between those continuing (19%) and discontinuing (18.9%) alendronate. Among those who continued, there was a significantly lower risk of clinically recognized vertebral fractures (5.3% for placebo and 2.4% for alendronate; RR, 0.45; 95% CI, 0.24-0.85) but no significant reduction in morphometric vertebral	Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers but *no higher fracture risk* other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			fractures (11.3% for placebo and 9.8% for alendronate; RR, 0.86; 95% CI, 0.60-1.22). Likewise, there was no difference in clinically recognized "any," nonvertebral, hip, or forearm fractures. The post hoc subgroup fracture analysis did not show significant trends with lower BMD or prevalent vertebral fractures at FLEX baseline for either nonvertebral or clinical vertebral fractures. However, the incidence of both types of fractures in the placebo group increased with lower baseline BMD or prevalent fracture. To compare nonvertebral fracture incidence in FIT and FLEX, they ran proportional hazards models among alendronate-treated participants with study and age as predictors and found that after adjustment for age, fracture incidence was similar in the 2 studies.	benefit by continuing beyond 5 years
Jamal 2007[254] (FIT)	Postmenopausal women enrolled in fit (6,458); renal function estimated by	Post hoc analysis of risk of spinal and clinical fractures	Alendronate increased BMD regardless of eGFR, but women	Alendronate is equally safe and effective in women with

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
Alendronate	creatinine clearance (eGFR) 581 women with severely reduced eGFR (9.9%)	with alendronate treatment in women with reduced vs. normal eGFR	with reduced eGFR had a 5.6% (95% CI: 4.8–6.5) increase in total hip BMD compared with 4.8% (95% CI: 4.6–5.0) among women with normal to moderate renal dysfunction (interaction: *p* _ 0.04). Compared with placebo, alendronate increased spine BMD by 6.6 ± 5.8%, but there was no significant interaction for the increase in spine BMD (interaction: *p* _ 0.75). Treatment with alendronate reduced the risk of clinical fractures to a similar degree in those with (OR: 0.78; 95% CI: 0.51–1.21) and without reduced renal function (OR: 0.80; 95% 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 (OR: 0.72; 95% CI: 0.31–1.7) and without reduced renal function (OR: 0.50; 95% CI: 0.32–0.76; *p* for interaction_0.44). There were no differences in adverse events	and without abnormal renal function

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			by renal function	
Miller 2010 [477] Ibandronate (BONE Trial and another trial)	Postmenopausal women with osteoporosis from two trials: 2.5 mg daily or 20 mg every other day for 12 doses every 3 months oral (n=1,419) vs. placebo (n=706); 0.5 mg and 1 mg every 3 months iv (n=1,911) vs. placebo (n=949) Inclusion criteria: 55-80 years of age, ≥5 years since menopause with a BMD T score of -2.0 to -5.0 in at least one lumbar vertebra, and in the BONE study, 1-4 prevalent vertebral fractures (T4-L4) but two or fewer prevalent LS fractures. All patients received 500 mg elemental calcium and 400 IU vitamin D.	Post-hoc analysis to assess association between increases in hip and spine BMD and vertebral fracture risk	Moving averages plots showed that BMD increases associated with ibandronate were consistently associated with decreased fracture rates. With oral ibandronate, year-2 and 3 increases in total-hip BMD and year-3 increase in spine BMD were associated with 3-year vertebral fracture rate (RRR for 1% change in BMD: hip 7.9% (95% CI 2.1, 13.5, p=0.0084), LS 4.7% (95% CI -0.1, 9.3. p=0.0565) With iv ibandronate, increase in total-hip BMD at yrs. 1, 2, and 3 and LS increases at yrs. 2 and 3 were associated with vertebral fracture rate (RRR at yr. 3 for 1% change from baseline: hip 11.6% (95% CI 7.0. 16.0, p<0.0001), LS 6.9% (95% CI 2.9, 10.6, p=0.0008). Pooled analysis showed changes in total-hip and LS BMD were associated with 3-yr vertebral fracture risk reduction.	Changes in BMD explained a substantial proportion of the anti-fracture effect of oral and iv ibandronate; increased BMD in postmenopausal women with osteoporosis is associated vertebral fracture risk reduction.
Watts 2005[475] Risedronate	Postmenopausal osteoporotic women from three trials on 2.5 or 5 mg	Post-hoc analysis to assess association between change in	3,979 patients had baseline and follow-up DXA measurements,	In postmenopausal osteoporotic women taking

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
	risedronate (n=2,561) or placebo (1,418)	BMD and fracture risk	either LS or FN Incident nonvertebral fractures: 138 (10.9% placebo) 169 (77% treated) Reduction in fracture risk 32% (HR 0.68(0.54, 0.85, p<0.001)) Among 123 patients with incident fractures for whom paired FN or LS DXA measures were available, LS BMD increased from baseline in 100 (6.4%) and decreased from baseline in 23 (7.8%), so there was no difference in fracture response across changes in BMD(numbers represent cumulative change over 3 years). Similar results were found for FN BMD: of 162 patients with fractures, 100 (7.5%) had increased BMD and 62 (7.6%) had decreased FN BMD.	risedronate, change in LS or FN BMD was not related to nonvertebral fracture incidence over 3 years
Siris 2008[241] (VERT NA BMD NA and MN) Risedronate	Post-hoc analysis of 620 postmenopausal women with osteopenia (femoral neck T-score between −1 and −2.5 SD and no prevalent fracture) from 4 trials who received 5 mg risedronate (n=311) or placebo (n=309) daily 1.5-3 yrs	Effect of risedronate on fragility fracture risk in subgroup of women with osteopenia, where outcome was defined as a composite of a patient's incident morphometric vertebral and	Cumulative 3-yr fragility fracture incidence 6.9% vs. 2.0% in placebo vs. active treatment (73% decrease p=0.023) Sensitivity analysis excluded women with LS BMD≤-2.5	Risedronate significantly reduced fracture risk in osteopenic women. Magnitude of effect same in sensitivity analysis subset

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
		osteoporosis-related nonvertebral fractures (i.e., six fracture types including clavicle, humerus, wrist, pelvis, hip or leg fractures), chosen to include all radiographically confirmed fractures		
Boonen 2010 [247] (VERT NA and MN, BMD NA and MN) Risedronate	Post-hoc analysis of relationship between age and effect of treatment on fracture risk Postmenopausal women with osteoporosis as defined by prevalent vertebral fractures, low BMD, or both treated with 5mg risedronate/d or placebo for 1-3yrs (1-2 yrs BMD; 3 yrs VERT) (n=3,229; 1,618 placebo and 1,611 risedronate) Average age 68, mean lumbar T-score -2.6, 72% had at least one prevalent vertebral fracture All women received 1000 mg Ca/d and if baseline vitamin D levels were low, received vitamin D supplementation	ITT analysis of incidence of OP-related fractures (any new morphometric vertebral or radiographically confirmed clinical fracture of the hip, pelvis, wrist, humerus, clavicle, or leg, or symptomatic vertebral fractures), clinical fractures, nonvertebral fractures, and morphometric fractures Age difference between placebo and treated group with same fracture risk and 3-year fracture risk	Irrespective of treatment, fracture risks were greater in older patients($p<0.001$): RR (CI) Any: 1.04 (1.02, 1.05) Clinical: 1.04 (1.03, 1.06) Nonvertebral: 1.05 (1.03, 1.07) Morph vertebral: 1.03 (1.02, 1.05) Irrespective of age, treatment reduced the risk of each type of fracture ($p<0.001$): Any: 0.58 (0.48, 0.70) Clinical: 0.54 (0.41, 0.69) Nonvertebral: 0.59 (0.44, 0.79) Morph vertebral: 0.54 (0.43, 0.68) 3-year fracture risks were markedly greater in the placebo group for each age group and	Patients treated with risedronate have a significantly lower fracture risk, similar to that of untreated patients 10-20 years younger

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			each fracture type Comparing ages of pts who were at the same risk, patients in the placebo group were 10-20 years younger than treated patients with the same risk, depending on fracture type (any: 15.1 years; clinical: 14.4 yrs; nonvertebral: 10.3 yrs; morphometric vertebral: 19.8 yrs)	
Watts 2009 (2CDM trial)[483] Risedronate	Post-hoc (re-)analysis of Delmas et al., 2008[85] study that originally compared 2 consecutive days/month dosing strategy with daily treatment, head-to-head using a historical placebo control Inclusion criteria: Ambulatory, Post-menopausal women >5 years, Age over 49 years, LS T-Score≤-2.5 , or < 2 with 1 prevalent fracture Interventions: 5mg of Risedronate Daily vs.	BMD, semi-quantitative assessment of vertebral fractures	1-year fracture incidences: Placebo: 5.1% Historical risedronate 5mg/d: 1.0% Current risedronate 5mg/d: 1.5% Current 2CDM 75mg: 1.1% Vertebral fracture RR: Current risedronate 5mg/d: 0.28(0/08, 1.11)(p=0.016) Current 2CDM 75mg: 0.21(0.05, 0.88)(p=0.036) (79% risk reduction)	Use of historical control data may be viable alternative for comparing anti-fracture efficacy in trials that lacked a placebo control. Use of risedronate on 2 consecutive days a month reduced vertebral fracture risk at 1 year compared with placebo

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
	75mg of Risedronate for 1 year vs. VERT placebo participants as historical control All received calcium, Vitamin D (n=1,229, 616 2CDM, 613 5mg/d)			
Grbic 2010[436] Zoledronic acid (HORIZON PFT, HORIZON RFT, GIO, Male OP, Prevention of OP)	Post-hoc analysis of 5 trials of zoledronic acid (5mg once yearly) vs. placebo in 11,500 patients Inclusion criteria: varied (postmenopausal women with osteoporosis, men and women with recent low-trauma hip fracture, individuals with glucocorticoid-induced osteoporosis (vs. risedronate), men with osteoporosis (vs. alendronate), postmenopausal women with osteopenia) Exclusion criteria: varied	Osteonecrosis of the jaw (blindly adjudicated from all maxillofacial adverse events) Serum β c-telopeptide	1 case osteonecrosis of the jaw in a treated patient, 1 case in a placebo treated patient	Incidence of osteonecrosis of the jaw as less than 1 per 14,200 patient treatment years. Serum β c-telopeptide was not linked with risk for osteonecrosis of the jaw
Hwang 2010[251] Zoledronic acid (HORIZON PFT)	Subgroup analysis to assess the efficacy of once-a-year zoledronic acid (5 mg infusion, 3 consecutive years) vs. placebo among Chinese women with osteoporosis, from Taiwan and Hong Kong Inclusion criteria: free of severe or chronic disabling conditions other than osteoporosis, FN T-score ≤-2.5 or <1.5 with radiographic documentation of at least 2 mild or 1	1° New vertebral fractures 2° Any clinical fracture, any clinical vertebral fracture, any nonvertebral fracture, and changes in BMD at hip, FN, and trochanter AEs	AT 36 months, zoledronic acid treatment was associated with significant decreases in risk for morphometric vertebral fracture and clinical vertebral fracture ($p<0.05$); significant increases in hip, FN, and trochanteric BMD (4.9, 4.3, and 7.0%, respectively, $p<0.001$). AEs were comparable in all groups.	Once-a-year zoledronic acid treatment reduced vertebral fracture risk in Chinese women with postmenopausal osteoporosis.

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
	moderate vertebral fracture; Exclusion criteria: secondary osteoporosis; other diseases affecting bone metabolism; use of PTH, NaF, strontium, anabolic steroids, growth hormone within 6 months or systemic corticosteroids within 12 months; significant renal or hepatic disease; malignant neoplasm; serum calcium >11mg/d; untreated hypocalcemia. Patients previously treated with a BP underwent washout with length depending on length of BP use. All patients received 1,000-1,500 mg elemental calcium and 400-1,200IU vitamin D. Patients were divided into 2 strata: those who did not take any other osteoporosis medication, and those allowed to continue on menopausal hormones, raloxifene, calcitonin, tibolone, tamoxifen, dehydroepiandrosterone, ipriflavone, or medroxyprogesterone			
Eastell 2009 [249] (HORIZON-PFT)	Original study details and results in Black et al., 2007) Postmenopausal women ages 65-89, w/ FN T-score≤-2.5 with or without	1°: New vertebral and hip fractures 2°: nonvertebral fractures, any clinical vertebral fracture, any	Zoledronic decreased vertebral fracture risk in all subgroups except those previously treated with BPs.	ZOL appears more effective in preventing vertebral fracture in younger women, overweight women, and

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
Zoledronic Acid	evidence of prevalent vertebral fracture OR T-score≤-1.5 with radiological evidence of at least 2 mild or 1 moderate vertebral fracture. Prior oral BP use was allowed with washout duration dependent on previous use. Stratification by baseline BP medication use. 3-year study of IV zoledronic acid, once yearly Subgroup analysis Effect of age, BMI, and renal function	clinical fracture, change in FN BMD	Significant treatment-factor interactions were found for vertebral fracture and age (greater effects for younger women, <70), BMI (greater effects for women who were overweight or obese), and Creatinine clearance (greater effect for >60ml/min) No significant effects were found for hip fractures or nonvertebral fractures or across BMD changes	women with normal renal function but was not affected by fracture risk factors or FN BMD.
Eriksen 2009 [257] (HORIZON-**Recurrent** Fracture Trial [RFT]) Zoledronic Acid (ZOL)	Men and women (n=2,127, 1,065 on active treatment and 1,062 on placebo), mean age 75, 76% women were administered ZOL within 90 days of surgical hip repair. Median follow-up time 1.9 yrs Post-hoc analysis Timing of first dose of zoledronic acid after hip fracture	1°: Time to first new clinical fracture of the axial or appendicular skeleton 2°: change in BMD of non-fractured hip, time to clinical vertebral, nonvertebral, hip fractures	Overall study showed 35% reduction in clinical fracture risk and 28% reduction in mortality with ZOL Timing of 1st dose within (46% pts) or later than 6 weeks postop showed dosing later than 6 weeks was associated with greater increase in BMD at 12 mos, but BMD was similar at 24 mos. Clinical fracture reduction in pts dosed within 6 weeks was 33% ($p<0.05$) compared with 37% ($p<0.05$) in patients dosed later than 6 weeks. (so no difference	Administration of zoledronic acid to patients suffering low-trauma hip fracture 2 weeks or later after surgical repair increases hip BMD and indices significant reductions in risk of subsequent clinical vertebral, nonvertebral, and hip fractures and reduces mortality

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			with timing) Additional analysis looked at dosing at 2-week intervals from 0-12 weeks. Most patients received a first dose at 4-6 weeks, which was associated with significantly decreased anti-fracture efficacy; because of the small sample sizes in the other 2-week intervals, all CIs crossed 1. With the exception of the ≤2-week period, all intervals shoed a consistent reduction in clinical fractures regardless of the timing of infusion. Mortality: All time periods except the ≤2-week period were associated with decreased all-cause mortality. Excluding the ≤2-week period, all other intervals showed larger RR reduction in time to next fracture and mortality. Clinical fractures reduced by 41% (p=0.0002), Nonvertebral fractures reduced by 44% (p=0.0077), Clinical vertebral fractures reduced by 53% (p=0.0084) Hip fractures reduced by 48%	

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			(p=0.0305) Mortality reduced by 30% (p=0.0095)	
Boonen 2010 [248] (HORIZON PFT and RFT) Zoledronic Acid	All (postmenopausal) female patients 75 years and over enrolled in one of the two trials (n=3,887) (compared with women <75, n=5,467) Post-hoc analysis of post-menopausal women ≥75 with osteoporosis	Incidence of any clinical fracture, clinical vertebral, or nonvertebral fracture in women 75 and over with osteoporosis	Incidence of any clinical fracture (p<0.001), clinical vertebral fracture (p<0.001), or nonvertebral fracture (p<0.002) in postmenopausal women ≥75 was significantly lower in the ZOL group compared with placebo over 3 years Benefit in relative risk reduction of clinical fractures, clinical vertebral fractures, and nonvertebral fractures was comparable in patients younger than 75 and those ≥75 1 and 3 years after treatment; treatment by age group interactions were not significant. However patients <75 showed a benefit in hip fracture reduction at 3 yrs that was not seen in those ≥75 (p=0.04 for treatment-by-age group interaction)	Post hoc analysis showed that once yearly ZOL is safe and effective in elderly postmenopausal women (≥75) with osteoporosis
Siris 2005 [244] (MORE)	CORE breast cancer trial open-label follow-up to MORE trial (8-year follow-up) n=4,011women (2,725	2° outcome new nonvertebral fractures	Risk of at least one new nonvertebral fracture: Treated: 22.8%	After 8 years of treatment, raloxifene had no significant effect on nonvertebral

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
(CORE) Raloxifene	received 60 mg/d raloxifene, 1286 placebo) Inclusion: ≤80 years, postmenopausal >2 years with hip or spinal T-score≤-2.5 or radiographically confirmed clinical fractures Exclusion: SERMS, hormone therapy, estrogen-dependent cancer, history of venous thromboembolism, treatment with cholestyramine, presence of severe postmenopausal symptoms requiring hormones, unblinding to MORE study assignment		Placebo 22.9% HR 1.00, (0.82, 1.21) Risk of at least one new fracture at 6 major nonvertebral sites (clavicle, humerus, wrist, pelvis, hip, lower leg): 17.5% in both groups Posthoc Poisson analysis showed no overall effect on nonvertebral fracture risk, but a decreased risk at the 6 sites in women with prevalent vertebral fracture: HR 0.78 (0.63, 0.96) Lumbar spine and femoral neck BMD were significantly increased from baseline and significantly greater than untreated (lumbar spine: 4.3% from baseline and 2.2% from placebo; femoral neck: 1.9% from baseline, 3.0% from placebo)	fracture risk, except among women with prevalent vertebral fracture at baseline. However the study may not be powered to assess fractures
Nakamura 2006 [252] Raloxifene	Pooled analysis of two studies of Asian women (one Chinese, one Japanese) with postmenopausal osteoporosis being treated with raloxifene 60 mg/d or 120 mg/d vs. placebo Inclusion: ≥2 years postmenopausal ≤80 years	2° outcome: clinical vertebral and nonvertebral fractures, radiographically confirmed	In 1st year of treatment, incidence of new clinical vertebral fractures were significantly decreased in both the 60 mg and pooled groups vs. placebo data not shown but p=0.01 for 60 mg and p=0.002 for pooled 60 and 120 mg	Among Asian women, raloxifene (60, 120 mg) is effective in decreasing incident clinical vertebral fracture but not new nonvertebral fracture

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
	1° OP=L2-L4 T-score≤-2.5 Exclusion: 2 ° OP, pathologic fractures, severe postmenopausal symptoms requiring hormones, history of or suspected breast carcinoma, history of any other cancer within previous 5 years except excised superficial lesions, abnormal uterine bleeding, history of DVT or TE disorders, endocrine disorders requiring pharmacotherapy, acute or chronic hepatic disorder, impaired renal function; use of any bone active agents within 6 months prior to study Japanese women: N=97 placebo, 92 raloxifene 60 mg/d, 95 raloxifene 120 mg/d Chinese women: N=102 placebo, 102 raloxifene 60 mg/d Women did not differ in mean age, BMI, years post menopause; Japanese women may have had more prevalent vertebral fractures and lower T-scores		Incidence of new nonvertebral fractures was not significantly decreased from placebo: 60 mg: RR 0.41 (0.08, 2.09) Pooled 60, 120: RR 0.28 (0.05, 1.41) Incidence of any new clinical fractures decreased significantly in both groups from placebo: 60 mg: RR 0.17 (0.04, 0.75) (p=0.01) Pooled: RR 0.11 (0.03, 0.51)	
Sontag 2010 [245] (MORE) Raloxifene	Randomized double-blind placebo-controlled international trial enrolled two subgroups, one with BMD≤-2.5 and one with low BMD and prevalent	Post-hoc analysis to compare effect on new fractures by prevalent fracture status and to compare effect on risk for	Effect of raloxifene on absolute risk difference for fractures and for invasive breast cancer did not differ between those with	In women with and without prevalent fractures, the benefit of raloxifene for decreasing risk of fractures

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
	vertebral fractures: treatment consisted of 60 or 120 mg/d raloxifene or placebo and Ca/vitamin D. Trial duration was 3 years plus one additional open year (n=7705)	fractures and breast cancer vs. adverse events (venous thromboembolism [VTE])	and without prevalent fracture (-8.21%, -0.75% vs. -2.83%, -1.21%, respectively). IN those with, and without, prevalent fracture, risk for VTE was +0.91% and 0.28% respectively (trial not powered to test difference in these two numbers)	and invasive breast cancer outweigh the potential increases in VTE
Kanis 2010 [242] (MORE) Raloxifene	See Sontag[242]	Post-hoc analysis to assess the association between FRAX score and efficacy for clinical and vertebral fracture prevention	Raloxifene treatment was associated with an 18% decrease in the risk for all clinical fractures (HR 0.82, 95% CI 0.71, 0.95, p=0.0063) and 42% decrease in incident morphometric vertebral fractures (HR 0.58, 95% CI 0.48, 0.69, p<0.001) No significant interaction was seen between fracture risk as assessed by FRAX and treatment efficacy. Efficacy was greater at lower ages. At the 90th percentile for age (75 years), risk reduction was 31% irrespective of FRAX. At younger ages, efficacy was higher and increased further with decreasing fracture probability.	Overall, the efficacy of raloxifene in reducing fracture risk was not associated with FRAX-determined fracture probability but at younger ages, efficacy was higher and increased with decreasing FRAX-determined probability

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
Miller 2006 [256] (FPT) Teriparatide	Postmenopausal women randomized to daily self-administered subcutaneous injections of teriparatide (20, 40 mcg/day) with calcium and vitamin D or placebo (n=1,637) Inclusion criteria: serum creatinine ≤2 mg/dl and other normal lab values Exclusion criteria: diagnosis of current or recent disease affecting bone metabolism	Post-hoc analysis to assess efficacy and safety of teriparatide in women with mild or moderate renal impairment, as defined by glomerular filtration rate (GFR) (mildly impaired: GFR 50-79 ml/min; moderately impaired: GFR 30-49 ml/min)	Teriparatide reduced vertebral and non-vertebral fracture risk similarly in patients with normal and impaired renal function. (treatment-by-subgroup interactions p>0.05). Adverse events: Across renal function categories, teriparatide increased 4-6-hour post does serum calcium compared with placebo; however, this increase was not significant for 20 mcg/day teriparatide. Teriparatide was associated with increased incidence of elevated uric acid, with highest incidence in patients with moderately impaired renal function and in those receiving 40 mcg/d. however, risk for gout, arthralgia, and nephrolithiasis was not increased in any group	Teriparatide efficacy was not affected by renal function. Moderately impaired renal function was associated with a greater risk for elevated uric acid but not with any other adverse effects
Chen 2006 [480] (FPT) Teriparatide	Postmenopausal women randomized to 20 or 40 ug/d teriparatide or placebo (n=1637)	Post-hoc analysis of association between change in BMD and fracture risk	In the teriparatide group, change in fracture risk was positively associated with change in spine BMD; in the placebo group, change in fracture risk was inversely	Increases in BMD accounted for approximately 1/3 of the vertebral fracture risk reduction; the majority of risk reduction resulted from non-BMD determinants of bone

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			related to change in spine BMD. In treated group, those with lowest BMD at baseline had largest % increases in BMD, confounding the relationship with fracture risk. In the placebo group, both baseline BMD and change in BMD affected change in fracture risk. In the treated group, neither baseline BMD nor change in BMD predicted change in fracture risk (although both contributed).Mean spine BMD increase in treated patients 0.09 g/cm^2 across tertiles of baseline spine BMD. Large changes and small changes resulted in similar fracture risk if endpoint BMD were similar. Teriparatide decreased fracture risk regardless of endpoint BMD. Depending on baseline BMD, teriparatide accounted for 30% to 41% of reduction in fracture risk.	strength
Boonen 2006 [250] FPT Teriparatide	Postmenopausal women randomized to 20 ug/d teriparatide or placebo (n=1085)+CA/vitamin D	Post-hoc analysis: of efficacy of teriparatide in women older ≥75(n=244) vs. <75(n=841)	Teriparatide reduced the risk of new vertebral fractures similarly in the older and younger women:	Age did not affect the treatment efficacy (or safety) of teriparatide in postmenopausal women with

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
			<75: RR 0.35, Adjusted RR 9.2% (NNT=11, p<0.01) ≥75: RR 0.35, adjusted RR9.9%, (NNT=11, p<0.05) Nonvertebral fragility fractures: <75: RR 0.41, Adjusted RR 3.5% (NNT=29, p<0.05) ≥75: RR 0.75, adjusted RR 1.1%, (NNT=11, p=0.661) Treatment by age interactions were not significant	osteoporosis.
Prevrhal 2009 [246] FPT Teriparatide	Postmenopausal women randomized to 20 or 40 ug/d teriparatide or placebo (see [484] (n=1637)	Reassessment of FPT data using combination of quantitative and qualitative radiology of spine	Using blinded quantitative radiographic (re-)assessment, vertebral fracture risk was reduced in the teriparatide (vs. placebo) groups by 84% (RR 0.16, p<0.001); risk of ≥2 fractures was reduced by 94% (RR 0.06, p<0.001). Fractures in teriparatide group were of lesser severity. Absolute benefit of teriparatide was greatest in those with highest number and severity of prevalent vertebral fractures	Quantitative morphometry confirmed effects of teriparatide on vertebral fracture risk
Watts 2009 [479]	Postmenopausal women randomized to 20 or 40 ug/d teriparatide or	Post-hoc analysis by FN i.e., association between FN BMD	Treated women had a significantly reduced risk of	At 12 months after baseline, loss of FN BMD in

Author, Year, ID# (Trial(s)) Drug	Subgroup (n) or Condition	Outcome(s)	Findings	Conclusions
FPT Teriparatide	placebo (see [484] (n=1637) Analysis on a subset of participants who had FN BMD and spinal radiographs performed at baseline and 12 months	and fracture efficacy	new vertebral fractures (compared with placebo) regardless of change in FN BMD at 1 year. Women who lost FN BMD still had significant reductions in vertebral fracture risk relative to placebo (RR 0.11, 95% CI 0.03, 0.45). Risk reduction in treated group was similar across categories of FN BMD change (loss >4% to gain>4%). Treatment resulted in significant increases in lumbar spine BMD over placebo regardless of FN BMD changes.	postmenopausal women treated with teriparatide is nevertheless consistent with good treatment response in terms of reduction in risk of vertebral fracture

Notes: BMD bone mineral density; CI confidence interval; FN femoral neck; HR hazard ratio; ITT intention to treat; LS lumbar spine; NNT number needed to treat; RR risk ratio; VTE venous thromboembolism

Evidence Table C-3. Large Randomized Controlled Trials from Original Report
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Cummings et al., 1998[44] Alendronate (Fosamax) Location: US Trial: FIT Setting: Multicenter Jadad: 5 Age Mean/Range: NR 100% Female Race: Not reported Screened: 26,137 Eligible: 10,668 Enrolled: 4,432 Withdrawn: 298 Lost to follow-up: NR Analyzed: 4,432 Method of AE Assessment: Monitored, Elicited by investigator	Inclusion criteria: Post-menopausal women >2 years, Age under 80 years, Age over 54 years, Osteopenia NOS, Femoral neck BMD lesser than 0.68 g/cm2. No vertebral fracture Exclusion criteria: Cardiovascular disease, Hepatic insufficiency, Renal insufficiency, Malabsorption syndrome, Upper GI, Bisphosphonates, Calcitonin, Fluoride, Estrogen agonists including estrogen, Dysepsia requiring daily treatment; Hypertension; Medical problem for 3 years that prevent from participating in study Interventions: Placebo Daily for 2 Year(s) vs. 5mg of Alendronate Daily for 1 Year(s) followed by 10mg of Alendronate Daily for 1 Year(s) All received: Calcium, Vitamin D Run-in/wash-out unclear Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures	Any clinical fracture at 48 MOS: Alendronate vs Placebo: 12.3% vs 14.1% OR = 0.85 (95% CI 0.72, 1.02) Any nonvertebral fracture at 48 MOS: Alendronate vs Placebo: 11.8% vs 13.3% OR = 0.87 (95% CI 0.73, 1.04) Hip fracture at 48 MOS: Alendronate vs Placebo: 0.9% vs 1.1% OR = 0.82 (95% CI 0.45, 1.49) Other clinical fracture at 48 MOS: Alendronate vs Placebo: 8.2% vs 10.2% OR = 0.79 (95% CI 0.64, 0.96) NNT=49.9 (95% CI 27.0-327.0) Vertebral fracture, ≥1 at 48 MOS: Alendronate vs Placebo: 2.1% vs 3.8% OR = 0.55 (95% CI 0.38, 0.79) NNT=58.8 (95% CI 36.6-150.3) Vertebral fracture, ≥2 at 48 MOS: Alendronate vs Placebo: 0.2% vs 0.5% OR = 0.42 (95% CI 0.15, 1.21) Wrist at 48 MOS: Alendronate vs Placebo: 3.7% vs 3.2% OR = 1.16 (95% CI 0.84, 1.60)

Evidence Table C-3. Large Randomized Controlled Trials from Original Report
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Fogelman et al., 2000[90] Risedronate (Actonel) Location: UK, Western Europe Setting: Multicenter Jadad: 1 Age Mean/Range: NR 100% Female Race: Not reported Screened: NR Eligible: NR Enrolled: 543 Withdrawn: 178 Lost to follow-up: NR Analyzed: 541 Method of AE Assessment: Elicited by investigator, Reported spontaneously by patient	Inclusion criteria: Post-menopausal women >1 year, Age under 80 years, T-Score ≤ -2.0 Spine Exclusion criteria: Carcinoma or suspected carcinoma, Hyperthyroidism, Hyperparathyroidism, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Vitamin D use, Medications known to affect skeleton Interventions: Placebo Daily for 24 Month(s) vs. 2.5mg of Risedronate Daily for 24 Month(s) vs. 5mg of Risedronate Daily for 24 Month(s) All received: Calcium No run-in or wash-out Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Radiographic vertebral fractures	Fracture counts reported at baseline only

Evidence Table C-3. Large Randomized Controlled Trials from Original Report
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Harris et al., 1999[91] Risedronate (Actonel) Location: US Trial: VERT Setting: Multicenter Jadad: 5 Age Mean/Range: NR 100% Female Race: Not reported Screened: 9,400 Eligible: 2,458 Enrolled: 2,458 Withdrawn: 1,674 Lost to follow-up: 35 Analyzed: 2,246 Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Ambulatory, Post-menopausal women >5 years, Age under 85 years, T-Score ≤ -2.0 Spine, Radiographic fractures, clinically silent, Clinical fractures, radiographically confirmed Exclusion criteria: Bisphosphonates, Calcitonin, Fluoride, Estrogen agonists including estrogen, Progestin, Estrogen agonists, Anabolic steroids, Conditions that might interfere with the evalation of bone loss; Use of calcitriol and cholecalciferol Interventions: Placebo Daily for 3 Year(s) vs. 2.5mg of Risedronate Daily for 1 Year(s) vs. 5mg of Risedronate Daily for 3 Year(s) All received: Calcium Run-in/wash-out unclear Fracture outcomes assessed at baseline, 2 years, 3 years Outcomes: Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures	New vertebral fracture at 36 MOS: Risedronate 5mg vs Placebo: 8.8% vs 13.7% OR = 0.61 (95% CI 0.44, 0.85) NNT=20.2 (95% CI 12.1-61.8) Non-vertebral fracture at 36 MOS: Risedronate 5mg vs Placebo: 4.1% vs 6.4% OR = 0.63 (95% CI 0.40, 0.97) NNT=43.2 (95% CI 22.3-634.4)

Evidence Table C-3. Large Randomized Controlled Trials from Original Report
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Reginster et al., 2000[485] Risedronate (Actonel) Location: Western Europe, Australia/New Zealand Trial: VERT Setting: Multicenter Jadad: 2 Age Mean/Range: NR 100% Female Race: Not reported Screened: 4,400 Eligible: NR Enrolled: 1,226 Withdrawn: 684 Lost to follow-up: NR Analyzed: 1,222 Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Ambulatory, Post-menopausal women >5 years, Age under 86 years, Radiographic fractures, clinically silent, Clinical fractures, radiographically confirmed Exclusion criteria: LS spine abnormalities prohibiting DXA, Bisphosphonates, Calcitonin, Fluoride, Estrogen agonists including estrogen, Progestin, Estrogen agonists, Anabolic steroids, Vitamin D use Interventions: Placebo Daily for 3 Year(s) vs. 2.5mg of Risedronate Daily for 3 Year(s) vs. 5.0mg of Risedronate Daily for 3 Year(s) All received: Calcium, Vitamin D Run-in/wash-out unclear Fracture outcomes assessed at baseline, 2 years, 3 years Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures	New vertebral fracture at 36 MOS: Risedronate 5mg vs Placebo: 15.4% vs 25.7% OR = 0.53 (95% CI 0.37, 0.77) NNT=9.7 (95% CI 6.1-23.1) Osteoporosis-related nonvertebral fracture at 36 MOS: Risedronate 5mg vs Placebo: 8.9% vs 12.6% OR = 0.68 (95% CI 0.44, 1.06)

Evidence Table C-3. Large Randomized Controlled Trials from Original Report
Bisphosphonates

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Black et al., 2007[111] Zoledronic acid (Zometa) Location: US, Canada, South America, Western Europe, Eastern Europe, Asia Trial: Horizon Setting: Multicenter Jadad: 3 Age Mean/Range: NR 100% Female Race: Not reported Screened: 18,421 Eligible: NR Enrolled: 7,765 Withdrawn: NR Lost to follow-up: NR Analyzed: 7,736 Method of AE Assessment: Monitored, Elicited by investigator	Inclusion criteria: Age under 90 years, Age over 64 years, T-Score ≤ -2.5 Hip, Tscore -1.5 or less with radiologic evidence of at least 2 mild vertebral fractures or one moderate vertebral fracture Exclusion criteria: Hypocalcemia, Hypercalcemia, Renal insufficiency, Fluoride, Anabolic steroids, Previous PTH use, Corticoids/Glucocorticoids, Previous use of strontium Interventions: Placebo Yearly for 2 Year(s) vs. 5mg of Zoledronic acid Yearly for 2 Year(s) - 3 doses total All received: Calcium, Vitamin D Run-in/wash-out unclear Fracture outcomes assessed at baseline, 24 months, 36 months Outcomes: Bone mineral density by DXA - Hip, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures	Any clinical fracture at 36 MOS: Zoledronic acid 5mg vs Placebo: 10.9% vs 16.0% OR = 0.65 (95% CI 0.56, 0.75) NNT=19.7 (95% CI 14.6-30.3) Clinical vertebral fracture at 36 MOS: Zoledronic acid 5mg vs Placebo: 0.7% vs 2.9% OR = 0.28 (95% CI 0.19, 0.41) NNT=44.0 (95% CI 33.8-63.2) Hip fracture at 36 MOS: Zoledronic acid 5mg vs Placebo: 1.8% vs 3.1% OR = 0.60 (95% CI 0.43, 0.83) NNT=80.5 (95% CI 48.8-229.2) Morphometric vertebral fracutre at 36 MOS: Zoledronic acid 5mg vs Placebo: 3.3% vs 10.9% OR = 0.31 (95% CI 0.26, 0.39) NNT=13.1 (95% CI 11.2-15.9) Multiple morphometric vertebral fractures at 36 MOS: Zoledronic acid 5mg vs Placebo: 0.2% vs 2.3% OR = 0.20 (95% CI 0.12, 0.31) NNT=48.4 (95% CI 37.8-67.4) Non-vertebral at 36 MOS: Zoledronic acid 5mg vs Placebo: 10.3% vs 13.6% OR = 0.73 (95% CI 0.63, 0.86) NNT=30.7 (95% CI 20.2-63.9)

Evidence Table C-3. Large Randomized Controlled Trials from Original Report
SERMs

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Ettinger et al., 1999[486] Raloxifene (Evista) Location: US, Canada, Other countries not specified Trial: MORE Setting: Multicenter Jadad: 1 Age Mean/Range: 31-80 100% Female Race: Not reported Screened: 22,379 Eligible: NR Enrolled: 7,705 Withdrawn: 1,804 Lost to follow-up: NR Analyzed: 7,755 Method of AE Assessment: Monitored, Elicited by investigator	Inclusion criteria: Post-menopausal women >2 years, T-Score ≤ -2.5 Hip, T-Score ≤ -2.5 Spine, Radiographic fractures, clinically silent, Clinical fractures, radiographically confirmed Exclusion criteria: Carcinoma or suspected carcinoma, Endocrine disease (not diabetes) NOS, Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, LS spine abnormalities prohibiting DXA, Renal insufficiency, Malabsorption syndrome, Nephrolithiasis, Urolithiasis, Ever venous thromboembolic disease, Bisphosphonates, Calcitonin, Fluoride, Androgen, Estrogen agonists including estrogen, Corticoids/Glucocorticoids, Substantial postmenopausal symptoms; Abnormal uterine bleeding; Anti-seizure medications; Pharmacologic doses of cholecalciferol; Consumed greater than 4 alcoholic drinks a day; Pathologic fractures Interventions: Placebo Daily for 3 Year(s) vs. 60 or 120mg of Raloxifene Daily for 3 Year(s) All received: Calcium Run-in/wash-out unclear Fracture outcomes assessed at baseline, 36 months Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Vertebral fracture, Non-vertebral fracture, Radiographic vertebral fractures, Symptomatic vertebral fractures	Ankle at 36 MOS: Raloxifene (30&60mg) vs Placebo: 0.7% vs 1.1% OR = 0.59 (95% CI 0.35, 1.00) NNT=235.8 (95% CI 113.4-2957) Hip fracture at 36 MOS: Raloxifene (30&60mg) vs Placebo: 0.8% vs 0.7% OR = 1.11 (95% CI 0.64, 1.93) Non-vertebral fracutre at 36 MOS: Raloxifene (30&60mg) vs Placebo: 8.5% vs 9.3% OR = 0.91 (95% CI 0.77, 1.07) Vertebral fracutre at 36 MOS: Raloxifene (30&60mg) vs Placebo: 6.0% vs 10.1% OR = 0.55 (95% CI 0.45, 0.67) NNT=24.5 (95% CI 18.2-37.5) Wrist at 36 MOS: Raloxifene (30&60mg) vs Placebo: 2.9% vs 3.3% OR = 0.88 (95% CI 0.67, 1.15)

Evidence Table C-3. Large Randomized Controlled Trials from Original Report
Parathyroid hormone

Citation & Study info	Eligibility, Interventions, Outcomes	Results - Number of people with fracture
Neer et al., 2001[134] PTH (Teriparatide) (Forteo) Location: 17 countries not listed Setting: Multicenter Jadad: 0 Age Mean/Range: NR 100% Female Race: Caucasian, Other Screened: 9,347 Eligible: NR Enrolled: 1,637 Withdrawn: NR Lost to follow-up: NR Analyzed: NR Method of AE Assessment: Monitored, Reported spontaneously by patient	Inclusion criteria: Ambulatory, Post-menopausal women >5 years, T-Score ≤ -1.0 Hip, T-Score ≤ -1.0 Spine, Radiographic fractures, clinically silent Exclusion criteria: Hepatic insufficiency, Metabolic bone disorder other than osteoporosis, Renal insufficiency, Urolithiasis, Medications known to affect skeleton, Alcohol and drug abuse; Taking drugs that affect metabolism Interventions: Placebo Daily for 24 Month(s) vs. 20µg of PTH (teriparatide) Daily for 24 Month(s) vs. 40µg of PTH (teriparatide) Daily for 24 Month(s) All received: Calcium, Vitamin D Run-in/wash-out unclear Fracture outcomes assessed at baseline Outcomes: Bone mineral density by DXA - Hip, Bone mineral density by DXA - Spine, Non-vertebral fracture, Radiographic vertebral fractures	Non-vertebral fracture, ≥1 at 21 MOS: PTH, 20 mug vs Placebo: 6.3% vs 9.7% OR = 0.63 (95% CI 0.40, 0.97) NNT=28.9 (95% CI 15.0-426.6) PTH, 40 mug vs Placebo: 5.8% vs 9.7% OR = 0.58 (95% CI 0.37, 0.90) NNT=25.3 (95% CI 14.1-127.9) Vertebral fracture, ≥1 at 21 MOS: PTH, 20 mug vs Placebo: 5.0% vs 14.3% OR = 0.34 (95% CI 0.22, 0.54) NNT=10.7 (95% CI 7.6-18.1) PTH, 40 mug vs Placebo: 4.4% vs 14.3% OR = 0.31 (95% CI 0.20, 0.49) NNT=10.1 (95% CI 7.3-16.3)

AE=Adverse Event, NR=Not Reported

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Abrahamsen et al., 2009[302] Alendronate (Fosamax)	No	National: Registries-Denmark	10,613	99	Fulfillment, Persistence, Adherence	Pharmacy records/claims data	Prescription refill ratio	3C	Unclear	Overall, (Adherence rates not reported)
Berecki-Gisolf et al., 2008[317] Bisphosphonates	No	National: Australia	793	0	Unclear	Pharmacy records/claims data	Time until first Gap in refill	3A, 3B	No	Overall, 170.0 days Adherence
Berry et al., 2010[324] Alendronate (Fosamax), Vitamin D	Yes	Single clinic/ hosp/pharmacy: Hebrew Rehab	25	16	Adherence	Pill count	Prescribed doses taken with specified period, 180 days in reporting period, Dichotomous, Cutoff Point: 75.0	3A	Yes	Alendronate/Cholecalciferol, 52.0% Adherence Ca + Vit. D, 58.0% Adherence
Blouin et al., 2007[303] Alendronate (Fosamax), Etidronate (Didronel)	No	State: Quebec, Canada	4,130	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months Medication possession ratio, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0	3A, 3B	No	Overall, 60.8% Adherence, 47.8% Persistence Once weekly alendronate, 54.7% Persistence Once weekly risedronate, 45.2% Persistence Once daily alendronate, 48.2% Persistence Once daily risedronate, 47.1% Persistence Raloxifene, 48.0% Persistence Nasal Calcitonin, 25.2% Persistence
Blouin et al., 2008[277] Alendronate (Fosamax), Risedronate (Actonel)	No	National: Claims Database	30,259	0	Adherence	Pharmacy records/claims data	Cutoff Point: 0.8 Prescription refill ratio, Dichotomous, Cutoff Point: < 80%	3C	No	Cases (Fracture), 54.3% Adherence Controls (No Fracture), 59.3% Adherence

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Briesacher et al., 2007[304] Alendronate (Fosamax), Risedronate (Actonel)	Yes	National: Medstat Databases	17,988	6	Persistence, Adherence	Pharmacy records/claims data	Proportion of Days Covered	3A, 3C	Yes	Overall-1st year, 55.0% Adherence and Persistence Overall-2nd year, 45.0% Adherence and Persistence Overall-3rd year, 41.0% Adherence and Persistence
Briesacher et al., 2010[281] Bisphosphonates	Yes	Market scan database	61,125	10	Adherence	Pharmacy records/claims data	Medication possession ratio, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0	3A, 3B	Yes	Monthly ibandronate, 49.0% Adherence, (MPR>80) Weekly bisphosphonate, 49.0% Adherence, (MPR>80) Daily bisphosphonate, 23.0% Adherence, (MPR>80)
Briesacher et al., 2010[323] Bisphosphonates	Yes	National: Marketscan database	5,505	6	Adherence	Pharmacy records/claims data	Medication possession ratio, Dichotomous, Cutoff Point: 80.0	3A, 3B	Yes	Once-monthly switchers, 42.0% Adherence, (Adherence at 12 months) Once-weekly switchers, 48.0% Adherence, (Adherence at 12 months) Nonswitchers, 37.0% Adherence, (Adherence at 12 months)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Cadarette et al., 2010[322] Bisphosphonates, Raloxifene (Evista)	Yes	Health plan: PACE program	32,697	0	Adherence	Pharmacy records/claims data	Proportion of Days Covered, Dichotomous, Cutoff Point: 80.0	3A, 3C	No	Bisphosphonate Users, 49.8% Adherence, (Adherence at 6 months) Calcitonin, 10.3% Adherence, (Adherence at 6 months) Raloxifene, 52.6% Adherence, (Adherence at 6 months)
Castelo-Branco et al., 2009[314] Calcium, Vitamin D	No	Multiple clinics: Spain	7,624	6	Persistence, Adherence	Questionnaire	Validated scale, Morisky	3A, 3B	Unclear	Overall, 72.3% Persistence, 31.2% Adherence, (Morisky among persistent patients only)
Copher et al., 2010[321] None of the interventions	Yes	Health plan	1,587	0	Adherence	Pharmacy records/claims data	Proportion of Days Covered, Dichotomous, Cutoff Point: 80.0	3A, 3B	Yes	Overall, 48.7% Adherence
Cotte et al., 2009[305] Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	No	National: France	2,990	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation Medication possession ratio, Dichotomous, Continuous	3A, 3B	Yes	Monthly ibandronate, 47.5% Persistence Weekly bisphosphonate, 30.4% Persistence Monthly ibandronate, 74.1% Adherence, (MPR>80) Weekly bisphosphonate, 65.8% Adherence, (MPR>80)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Cramer et al., 2006[306] Study 1 of 3 Alendronate (Fosamax), Bisphosphonates, Risedronate (Actonel)	Yes	Integrated Healthcare Information Services	2,741		Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months Proportion of Days Covered, 365 days in reporting period, Continuous Time until discontinuation	3A, 3B	Yes	Overall, 61.0% Adherence, 196.0 days Persistence Weekly bisphosphonate, 69.0% Adherence, 227.0 days Persistence, 44.0% Persistence, (Persistence at 12 months) Daily bisphosphonate, 58.0% Adherence, 185.0 days Persistence, 32.0% Persistence, (Persistence at 12 months)
Curtis et al., 2008[282] Bisphosphonates	Yes	Health plan	101,038	5	Adherence	Pharmacy records/claims data	Medication possession ratio, Dichotomous, Continuous	3A, 3C	Yes	Overall, 39.0% Two years Adherence, (MPR>80 %), 35.0% Three years Adherence, (MPR>80 %) Overall-Daily, 38.0% One year Adherence, (MPR>80 %) Overall-Weekly, 45.0% One year Adherence, (MPR>80 %)
Dugard et al., 2009[315] Bisphosphonates	No	Multiple sites: England	254	0	Persistence, Adherence	Written prescriptions	Discontinuation, 12 months, 60 months Observed # of RX's written divided by expected, annually	3A, 3B	No	Overall, 44.0% Adherence, (Adherence at 12 months), 74.0% Persistence, (Persistence at 12 months), 23.0% Adherence, (Adherence at 60 months), 50.0% Persistence, (Persistence at 60 months)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Ettinger et al., 2006[291] Bisphosphonates	Yes	Multi-State: NDC Health Database	211,319	0	Persistence	Pharmacy records/claims data	Discontinuation, 12 months Proportion with at least 1 day of medication each month	3A, 3B	Yes	Weekly bisphosphonate, 56.7% Persistence, (Persistence at 12 months) Daily bisphosphonate, 40.0% Persistence, (Persistence at 12 months)
Feldstein et al., 2009[286] Bisphosphonates	Yes	Health plan: HMO-Oregon and Washington	3,658	0	Adherence	Pharmacy records/claims data	Proportion of Days Covered	3A, 3C	Yes	Overall-MPR>80 %, 45.0% patients Adherence
Ferrari et al., 2011[334] Raloxifene (Evista), Risedronate (Actonel)	Yes	Health plan: Ingenix and Marketscan	124,461	0	Adherence	Pharmacy records/claims data	Medication possession ratio, Dichotomous, Cutoff Point: 80.0	3A, 3C	Yes	Raloxifene, 48.0% Adherence Adherence, 42.0% Adherence
Foster et al., 2010[331] Study 1 of 2 PTH (Teriparatide) (Forteo)	Yes	National: Market Scan Databases (commercial and medicare)	2,218	10	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months Medication possession ratio, Dichotomous, Cutoff Point: 80.0 Time until Gap > 60 days	3A, 3B	Yes	Overall, 58.0% 6 months Adherence, (MPR > 80 %), 0.74 Mean MPR Adherence, (Adherence at 6 months), 0.66 Mean MPR Adherence, (Adherence at 12 months) 70.0% 12 months Persistence, (Discontinuation), 56.9% 12 months Persistence, (Gap > 60 days)
Foster et al., 2010[331] Study 2 of 2 PTH (Teriparatide) (Forteo)	Yes	National: Marketscan-medicaid	824	9	Persistence, Adherence	Medical records	Discontinuation, 12 months Medication possession ratio, Dichotomous, Cutoff Point: 80.0 Time until Gap > 60 days	3A, 3B	Yes	Overall, 33.5% 6 months Adherence, (MPR > 80 %), 0.62 Mean MPR Adherence, (At 6 months), 0.55 Mean MPR Adherence, (At 12 months), 60.0% 12 months Persistence, (Discontinuation)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Gallagher et al., 2008[300] Alendronate (Fosamax), Risedronate (Actonel)	No	National: General Practice Research Database UK	44,531	19	Persistence, Adherence	Medical records, Prescriptions dispensed	Discontinuation Medication possession ratio	3A, 3B, 3C	Yes	Overall, 58.0% At 12 months Persistence
Gold et al., 2006[307] Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	Yes	IMS longitudinal Database	240,001	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 6 months Medication possession ratio, 180 days in reporting period, Continuous, Time until Gap > 90 days	3A, 3B	Yes	Weekly risedronate, 83.3% mean MPR, 144.3 days Mean Persistence, 56.0% Persistence, (Persistence at 6 months) Monthly ibandronate, 78.5% mean MPR, 100.1 days Mean Persistence, 29.0% Persistence, (Persistence at 6 months) New users-Monthly ibandronate, 78.0% Adherence, 92.1 days Mean Persistence New users-Weekly risedronate, 79.6% Adherence, 103.5 days Mean Persistence
Gold et al., 2007[292] Alendronate (Fosamax)	Yes	Health plan	4,769	0	Persistence	Pharmacy records/claims data	Delayed filling prescription 30 days	3B, 3C	Yes	Overall, 42.6% Persistence
Gold et al., 2009[308] Ibandronate (Boniva), Risedronate (Actonel)	Yes	IMS Health	263,383	7	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months Medication possession ratio, Continuous Gap > 90 days, Cumulative Drug Availability	3A, 3B	Yes	Weekly risedronate, 80.0% mean MPR, 64.5% mean CDA, 250.0 days Mean Persistence, 40.0% Persistence, (Persistence at 12 months) Monthly ibandronate, 74.7% mean MPR, 43.4% mean CDA, 151.0 days Persistence, 18.0% Persistence, (Persistence at 12 months)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Grazio et al., 2008[285] Alendronate (Fosamax)	No	Multiple clinics: Croatia	102	6	Adherence	Unclear	Proportion of Days Covered, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0 Prescribed doses taken with specified period, 365 days in reporting period, Dichotomous, Cutoff Point: 100.0	3A, 3B	Unclear	Overall, 65.7% Adherence, (Percent with Perfect Adherence)
Hadji et al., 2011[346] Bisphosphonates	No	National: Germany	4,147	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 24 months Prescribed doses taken with specified period, Dichotomous, Cutoff Point: 80.0 Gap > 30 days	3A, 3C	Yes	Overall, 51.0% Adherence, 13.1% Persistence
Halpern et al., 2011[333] Alendronate (Fosamax), Ibandronate (Boniva), Raloxifene (Evista), Risedronate (Actonel)	Yes	Health plan: i3 Innouus	21,655	0	Adherence	Pharmacy records/claims data	Medication possession ratio, 540 days in reporting period, Dichotomous, Cutoff Point: 80.0	3A, 3C	Yes	Commerical Insurance, 42.7% Adherence Medicare Advantage, 33.7% Adherence
Hansen et al., 2008[278] Alendronate (Fosamax)	Yes	Single clinic/ hosp/pharmacy: Wisconsin VA medical center	198	100	Adherence	Pharmacy records/claims data	Prescription refill ratio, 730 days in reporting period, Dichotomous	3A, 3B	Unclear	Overall, 54.0% Adherence, (At 2 years)
Harris et al., 2009[293] Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	Yes	Health plan: i3 Research Database	91,630	0	Persistence	Pharmacy records/claims data	Delayed filling prescription 30 days for weekly meds and 45 days for monthly meds	3A	Yes	Overall, 70.1% 90 days Persistence Monthly oral Ibandronate, 73.3% Adherence Weekly Bisphosphonate, 69.7% Adherence

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Hoer et al., 2009[312] Bisphosphonates	No	Health plan: German Statutory Sickness Fund	4,451	26	Persistence, Adherence	Pharmacy records/claims data	Discontinuation Medication possession ratio, 180/360/720 days in reporting period, Dichotomous, Cutoff Point: 0.8	3B, 3C	Yes	Overall, 43.7% 12 months Adherence Patients with previous fractures, 47.3% 12 months Persistence
Huas et al., 2010[320] None of the interventions	No	National	1,217	0	Adherence	Questionnaire	Validated scale, Morisky, Dichotomous, Cutoff Point: 4.0	3A, 3B	Yes	Overall, 65.5% Adherence
Ideguchi et al., 2007[294] Alendronate (Fosamax), Bisphosphonates, Etidronate (Didronel), Risedronate (Actonel)	No	Single clinic/ hosp/pharmacy: Japan	1,307	15	Persistence	Pharmacy records/claims data	Discontinuation	3A, 3B	Unclear	Overall, 74.8% Persistence, (Persistence at 12 months), 60.6% Persistence, (Persistence at 36 months), 51.7% Persistence, (Persistence at 60 months)
Ideguchi et al., 2008[290] Bisphosphonates	No	Single clinic/ hosp/pharmacy: Yokohanna, Japan	1,307	15	Persistence	Pharmacy records/claims data	Discontinuation	3A, 3B	Unclear	(Data not Interpretable)
Iwamoto et al., 2009[328] Alendronate (Fosamax)	No	Single clinic/ hosp/pharmacy: Japan	72	0	Persistence	Unclear	Discontinuation	3A, 3B	Unclear	Overall, 80.6% Persistence, (Persistence at 3 years)
Jones et al., 2008[295] Alendronate (Fosamax), Risedronate (Actonel)	No	State: Ontario	62,897	0	Persistence	Pharmacy records/claims data	Discontinuation, 12 months	3A, 3B	Unclear	Weekly risedronate, 54.4% Persistence, (Persistence at 12 months) Weekly alendronate, 56.3% Persistence, (Persistence at 12 months)
Kamatari et al., 2007[316] Alendronate (Fosamax), Risedronate (Actonel)	No	Multiple clinics: Japan	208	3	Unclear	Pharmacy records/claims data	No refill 28 days after due	3B	Unclear	Overall, 78.0% Adherent

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Kertes et al., 2008[309] Bisphosphonates	No	Health plan: Maccabi, Israel	4,448	0	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months Medication possession ratio, 365 days in reporting period, Dichotomous, Continuous, Cutoff Point: 0.8 # of days until gap > 30 days	3A, 3B	Unclear	Overall, 66.0% mean MPR Adherence, 52.5% Adherence, (MPR>80), 216.0 days Mean Persistence, 46.0% Persistence, (Persistence at 12 months)
Landfeldt et al., 2011[341] Alendronate (Fosamax), Raloxifene (Evista), Risedronate (Actonel), Strontium ranelate	No	National: Sweden	56,586	14	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months Medication possession ratio, Dichotomous, Cutoff Point: 80.0	3A, 3B, 3C	Yes	Overall, 95.0% Adherence Alendronate, 51.7% Persistence Risedronate, 50.6% Persistence Raloxifene, 42.4% Persistence Strontium, 18.4% Persistence PTH, 70.3% Persistence
McHorney et al., 2007[298] Bisphosphonates	Yes	National Retail Pharmacy Chain	1,092	0	Persistence	Telephone interview, Pharmacy records/claims data	Discontinuation, 7 months	3A, 3B	Yes	Overall, 55.0% Persistence, (Persistence at 7 months)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Netelenbos et al., 2010[330]	No	National: Netherlands IMS Data			Persistence, Adherence	Pharmacy records/claims data	Medication possession ratio, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0 Gap > 6 months (persistence)	3A, 3B	Yes	Overall, 91.0% Adherence, (Adherence at 12 months), 43.0% Persistence, (Persistence at 12 months) Weekly risedronate, 91.5% Adherence, 45.4% Persistence Daily risedronate, 91.6% Adherence, 40.2% Persistence Weekly alendronate, 91.2% Adherence, 43.4% Persistence Daily alendronate, 92.2% Adherence, 23.0% Persistence Monthly ibandronate, 89.0% Adherence, 46.3% Persistence Raloxifene, 91.5% Adherence, 33.3% Persistence Strontium, 79.1% Adherence, 22.0% Persistence
Palacios et al., 2009[284] Bisphosphonates, Calcium, Vitamin D, Estrogen, PTH (Teriparatide) (Forteo), Raloxifene (Evista), Strontium ranelate	No	Multiple clinics: Spain	1,179	0	Adherence	Questionnaire	Haynes and Sackett and Morisky combination	3A, 3B	Unclear	Overall, 39.2% Adherence

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Penning-van Beest et al., 2008[279] Alendronate (Fosamax), Bisphosphonates, Risedronate (Actonel)	No	Pharmo	8,822	0	Adherence	Pharmacy records/claims data	Medication possession ratio, 90 days in reporting period, Dichotomous, Cutoff Point: 0.8	3A, 3C	Yes	Overall, 58.0% At 1 year Adherence, 66.0% At 6 months Adherence
Penning-van Beest et al., 2008[280] Bisphosphonates	No	Pharmo Database	8,822	0	Adherence	Pharmacy records/claims data	Medication possession ratio, 365 days in reporting period, Dichotomous	3A, 3B	Yes	Overall, 58.0% Adherence, (MPR>80) Weekly bisphosphonate, 64.3% Adherence, (MPR>80) Daily bisphosphonate (after July 2000), 52.0% Adherence, (MPR>80) Daily bisphosphonate (before July 2000), 47.5% Adherence, (MPR>80)
Rabenda et al., 2008[313] Alendronate (Fosamax), Raloxifene (Evista)	No	National	99,924	0	Persistence, Adherence	Pharmacy records/claims data, Medical records	Medication possession ratio, 365 days in reporting period, Dichotomous Proportion of Days Covered	3A, 3B, 3C	Unclear	Overall, 64.7% mean MPR, 40.4% at 12 months Persistence, 35.7% weeks Median Persistence Daily alendronate, 58.6% Adherence, (48.1 % had a 12 month MPR = 80 %; 40.4 % in daily therapy; 57 % in weeky therapy; y = 80 %) Weekly alendronate, 70.5% Adherence

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Rabenda et al., 2008[310] Alendronate (Fosamax)	No	National: Belgium	1,376	0	Persistence, Adherence	Pharmacy records/claims data	Medication possession ratio, 365 days in reporting period, Dichotomous, Cutoff Point: 80.0 Gap > 35 days	3A, 3B	Unclear	Overall, 48.7% Adherence, (MPR>80), 67.0% mean MPR Adherence, 41.0% Persistence, (Persistence at 12 months) Daily alendronate, 65.9% Adherence, (MPR>80) Weekly alendronate, 67.7% Adherence, (MPR>80)
Ringe et al., 2007[299] Alendronate (Fosamax), Raloxifene (Evista), Risedronate (Actonel)	No	Multiple sites: Europe, Lebanon, South Africa	5,198	0	Persistence, Adherence	In-person interview	Discontinuation, 12 months Prescribed doses taken with specified period, 365 days in reporting period, Dichotomous	3A, 3B	Yes	Overall, 80.8% Persistence, (Persistence at 12 months) Raloxifene, 80.0% Adherence, 82.0% Persistence, (Persistence at 12 months) Daily alendronate, 79.0% Adherence, 83.0% Persistence, (Persistence at 12 months) Weekly alendronate, 65.0% Adherence, 74.0% Persistence, (Persistence at 12 months) Daily risedronate, 76.0% Adherence, 79.0% Persistence, (Persistence at 12 months)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Ringe et al., 2009[288] Alendronate (Fosamax), Risedronate (Actonel)	No	Single clinic/ hosp/pharmacy: Germany	204	0	Persistence	In-person interview	Discontinuation, 12 months	3A	No	Generic alendronate, 68.0% Persistence, (Persistence at 12 months) Brand fosamax, 84.0% Persistence, (Persistence at 12 months) Brand actonel, 94.0% Persistence, (Persistence at 12 months)
Roughead et al., 2009[301] Bisphosphonates	No	National: Australian Veterans	42,885	37	Persistence, Adherence	Pharmacy records/claims data	Discontinuation, 12 months Medication possession ratio, Dichotomous, Continuous, Cutoff Point: 0.8 Gap > 105 days	3A	No	Overall, 81.0% Adherence, (MPR>80), 66.0% mean MPR Adherence, 53.0% Persistence, (Persistence at 12 months)
Schousboe et al., 2010[332] None of the interventions	Yes	Single clinic/ hosp/pharmacy: Park Nicollet Health Services	729	7	Persistence, Adherence	Questionnaire	Missing = 1 dose by self report over last month, Stopping med for > 1 month	3A, 3B	Yes	Overall, 65.4% Adherence, 65.8% Persistence
Sewerynek et al., 2009[289] Alendronate (Fosamax)		Single clinic/ hosp/pharmacy: Poland	118	0	Persistence	Not specified	Unclear	3A	Unclear	(Data not Interpretable)
Sheehy et al., 2009[296] Alendronate (Fosamax), Risedronate (Actonel)	No	Quebec	32,804	10	Persistence	Pharmacy records/claims data	Refill gap > 1.5 x length of Rx	3A, 3B	Unclear	(Data on adherence rates not available)
Siris et al., 2010[319] Bisphosphonates	Yes	Health plan: Market scan and Ingenix Data	460,584	0	Adherence	Pharmacy records/claims data	Medication possession ratio, Dichotomous, Cutoff Point: 80.0	3A, 3C	Unclear	Overall, 32.7% Adherence, (MPR > 80 %)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Solomon et al., 2010[318] Bisphosphonates, Estrogen, PTH (Teriparatide) (Forteo), Raloxifene (Evista)	Yes	Single clinic/ hosp/pharmacy	142	0	Fulfillment, Adherence	Pharmacy records/claims data	Medication possession ratio, 365 days in reporting period, Dichotomous, Cutoff Point: 20.0	3A, 3B	Yes	Overall, 65.0% Adherence, (MPR > 20 %), 32.0% Adherence, (MPR > 80 %)
Tosteson et al., 2010[327] Bisphosphonates, Estrogen, Lasofoxifene, PTH (Teriparatide) (Forteo)	Yes	Multiple clinics	3,006	0	Persistence, Discontinuation	Questionnaire	Discontinuation	3A, 3B	Yes	Overall, 66.0% Persistence, (At 12 months)
Van den Boogaard et al., 2006[311] Alendronate (Fosamax), Bisphosphonates, Etidronate (Didronel), Risedronate (Actonel)	No	National: Pharmo	14,760	0	Persistence, Adherence	Pharmacy records/claims data	Continuous use (refill gap less than 7 days)	3A, 3B, 3C	Yes	Overall, 43.6% At one year Adherence, (Percentage of persistent patients by 15 % decreased number of osteoparotic fractures by 4 %), 27.4% At two years Adherence Daily alendronate, 33.2% At one year Adherence Weekly alendronate, 47.9% At one year Adherence Daily risedronate, 33.4% At one year Adherence Weekly risedronate, 47.4% At One year Adherence

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Vytrisalova et al., 2008[283] Alendronate (Fosamax), Vitamin D, Raloxifene (Evista), Risedronate (Actonel)	No	Multiple clinics: Czech Republic	200	0	Adherence	Questionnaire	Prescribed doses taken with specified period, 30 days in reporting period, Dichotomous, Cutoff Point: 0.8 Following dosing instructions	3A, 3B	Unclear	Overall, 89.0% Adherence, (MPR>80), 58.0% Adherence, (Following dosing instructions) Bisphosphonates, 89.0% Adherence, (MPR>80) Raloxifene, 94.0% Adherence, (MPR>80) Calcitonin, 88.0% Adherence, (MPR>80)
Weiss et al., 2007[297] Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	Yes	IMS longitudinal database	165,955	0	Persistence	Pharmacy records/claims data	Discontinuation, 1 months # of days until Gap > 30 days	3A, 3B	Yes	Weekly alendronate, 116.0 days Mean Persistence, 54.2% Persistence, (Failing to refill after 1st rx) Weekly risedronate, 113.0 days Mean Persistence, 52.3% Persistence, (Failing to refill after 1st rx) Monthly ibandronate, 98.0 days Mean Persistence, 45.5% Persistence, (Failing to refill after 1st rx)

Evidence Table C-4. Adherence

Author, Year, Drug, Design	Exclu-sively in the US?	From where were the patients identified?	Number enrolled:	% Male	Type of adherence	How is adherence assessed?	How is adherence measured?	Key question(s) discussed in article	Industry funded?	Adherence Persistence Rates
Yood et al., 2003[287] Bisphosphonates, Estrogen, Raloxifene (Evista)	Yes	Group Practice	176	0	Fulfillment, Adherence	Pharmacy records/claims data	# of prescriptions filled	3A	Yes	Overall-Participants, 70.1% Compliance Overall-Refusers, 66.5% Compliance Alendronate and Etidronate-All, 70.7% Compliance Alendronate and Etidronate-Bisphon participants, 74.5% Compliance Estrogen- All, 69.3% Compliance Estrogen- Participants, 69.7% Compliance
Ziller et al., 2010[329] Raloxifene (Evista)	No	Single clinic/ hosp/pharmacy	300	0	Persistence, Adherence	Questionnaire, Medical records, physician recall	Discontinuation, 12 months, 24 months Unknown questionnaire assessing number of tablets ingested combined with MPR > 80	3A, 3B	Yes	Overall, 31.7% One year Adherence, 48.0% Persistence, (At 48 months)

Key Questions: 3A = Adherence and persistence to medications for the treatment and prevention of osteoporosis; 3B = Factors that affect adherence and persistence; 3C = Effects of adherence and persistence on the risk of fractures

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Abrahamsen et al., 2010[430] Alendronate (Fosamax)	Alendronate vs Untreated: Subtrochanteric or diaphyseal fractures: 1.0%(412/39,567) vs 0.4%(637/158,268)
Adachi et al., 2009[361] Alendronate (Fosamax)	Alendronate monohydrate 10 mg/day vs Placebo: Any adverse event: 57.0%(166/291) vs 51.7%(76/147) Breast cancer: 0.7%(2/291) vs 0.0%(0/147) Death: 0.0%(0/291) vs 0.0%(0/147) Diverticulitis: 0.3%(1/291) vs 0.0%(0/147) Dyspepsia: 7.9%(23/291) vs 0.0%(0/147) Esophageal spasm: 0.3%(1/291) vs 0.0%(0/147) Non-serious upper GI bleed: 0.3%(1/291) vs 0.0%(0/147) Serious adverse event: 1.4%(4/291) vs 0.7%(1/147) Serious upper GI event: 20.3%(59/291) vs 12.9%(19/147) Upper GI event: 22.7%(66/291) vs 20.4%(30/147) Withdrawals: 18.6%(54/291) vs 11.6%(17/147)
Hagino et al., 2009[487] Alendronate (Fosamax)	Alendronate 5 mg vs Minodronate 1 mg: Any adverse event: 84.4%(114/135) vs 88.8%(119/134) Abnormal lab data: 21.5%(29/135) vs 29.1%(39/134) Drug related GI AE: 9.6%(13/135) vs 14.2%(19/134) Gastrointestinal adverse event: 37.0%(50/135) vs 39.6%(53/134) Serious adverse event: 2.2%(3/135) vs 4.5%(6/134) Withdrawals: 10.4%(14/135) vs 8.2%(11/134)
Heckbert et al., 2008[488] Alendronate (Fosamax)	Alendronate (current user) vs No alendronate: Atrial fibrillation: all: 47.4%(27/57) vs 42.1%(672/1,598)

Author, Year, Drug, Trial name	Adverse events reported
Lems et al., 2006[489] Alendronate (Fosamax)	Alendronate 5 mg/day + Calcium 1000 mg/day + Vitamin D 400 mg/day vs Placebo + Calcium 1000 mg/day + Vitamin D 400 mg/day: Any adverse event: 68.1%(64/94) vs 72.5%(50/69) Any serious adverse event: 12.8%(12/94) vs 17.4%(12/69) Cardiovascular disease: 4.3%(4/94) vs 8.7%(6/69) Dyspepsia: 18.1%(17/94) vs 14.5%(10/69) Gastroenteritis: 1.1%(1/94) vs 2.9%(2/69) Infection: 2.1%(2/94) vs 0.0%(0/69) Malignancy: 0.0%(0/94) vs 1.4%(1/69) New incident vertebral deformities: 9.6%(9/94) vs 2.9%(2/69) Other: 11.7%(11/94) vs 17.4%(12/69) Patients with upper GI effects: 17.0%(16/94) vs 17.4%(12/69) Stomatitis: 1.1%(1/94) vs 1.4%(1/69) Ulcer: 3.2%(3/94) vs 2.9%(2/69) Upper GI symptoms: 2.1%(2/94) vs 1.4%(1/69) Withdrawals: 16.0%(15/94) vs 24.6%(17/69) Withdrawals due to adverse events: 16.0%(15/94) vs 21.7%(15/69)
Papaioannou et al., 2008[55] Alendronate (Fosamax) Trial: CFOS	Alendronate 70 mg/week + Calcium 1000 mg + Vitamin D 800 IU vs Placebo 70 mg/week + Calcium 1000 mg + Vitamin D 800 IU: Any adverse event: 55.6%(15/27) vs 65.5%(19/29) Any serious adverse event: 25.9%(7/27) vs 10.3%(3/29) Bronchial superinfection: 3.7%(1/27) vs 0.0%(0/29) Constipation: 3.7%(1/27) vs 3.4%(1/29) Difficulty swallowing: 3.7%(1/27) vs 0.0%(0/29) Esophagitis: 3.7%(1/27) vs 0.0%(0/29) Exacerbation of cystic fibrosis: 11.1%(3/27) vs 10.3%(3/29) GI upset: 3.7%(1/27) vs 0.0%(0/29) Hypoglycemic seizure: 3.7%(1/27) vs 0.0%(0/29) Intestinal obstruction: 3.7%(1/27) vs 3.4%(1/29) Nausea and/or vomiting: 11.1%(3/27) vs 13.8%(4/29) Reflux: 3.7%(1/27) vs 0.0%(0/29) Stomach pain/burn: 3.7%(1/27) vs 3.4%(1/29) Withdrawals: 14.8%(4/27) vs 17.2%(5/29)
Yan et al., 2009[490] Alendronate (Fosamax)	Alendronate 70 mg/week + Calcium 500 mg/day + Vitamin D 200 IU/day vs Placebo week + Calcium 500 mg/day + Vitamin D 200 IU/day: Any adverse event: 43.2%(121/280) vs 36.8%(103/280) Abdominal distention: 2.5%(7/280) vs 0.7%(2/280) Abdominal pain: 6.8%(19/280) vs 4.6%(13/280) Acid regurgitation: 1.8%(5/280) vs 3.6%(10/280) Dyspepsia: 1.1%(3/280) vs 2.9%(8/280) Nausea: 4.3%(12/280) vs 2.9%(8/280) Upper GI event: 16.8%(47/280) vs 15.4%(43/280) Vomiting: 0.4%(1/280) vs 0.7%(2/280)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Bunch et al., 2009[491] Bisphosphonates	Bisphosphonate (angiographic database) vs Bisphosphonate (health plan database) vs No bisphosphonate (angiographic database) vs No bisphosphonate (health plan database): Atrial Fibrillation: 10.2%(10/98) vs 2.9%(220/7,489) vs 10.1%(964/9,525) vs 2.6%(792/29,996) Death: 32.7%(32/98) vs 1.8%(134/7,489) vs 18.8%(1,791/9,525) vs 2.0%(606/29,996) Myocardial infarction: 10.2%(10/98) vs 0.9%(68/7,489) vs 7.8%(739/9,525) vs 1.1%(343/29,996)
Cardwell et al., 2010[363] Bisphosphonates	Bisphosphonates vs Control: Esophageal cancer: 0.2%(79/41,826) vs 0.2%(72/41,826) Gastric cancer: 0.1%(37/41,826) vs 0.1%(43/41,826)
Cartsos et al., 2008[492] Bisphosphonates	Intravenous bisphosphonate: Cancer Group vs Intravenous bisphosphonate: Osteoporosis group vs No bisphosphonate: Cancer Group vs No bisphosphonate: Osteoporosis group vs Oral bisphosphonate: Cancer Group vs Oral bisphosphonate: Osteoporosis group: Inflammatory necrosis of jaw: 0.5%(39/8,207) vs 0.5%(9/1,751) vs 0.1%(251/235,553) vs 0.1%(339/263,352) vs 0.1%(31/24,579) vs 0.1%(150/176,889) Surgery: Cancer Process: 0.1%(6/8,533) vs 0.0%(0/1,853) vs 0.1%(161/235,553) vs 0.0%(105/263,352) vs 0.0%(11/25,025) vs 0.0%(58/179,827) Surgery: Necrotic Process: 0.2%(20/8,533) vs 0.2%(4/1,853) vs 0.0%(81/235,553) vs 0.0%(73/263,352) vs 0.0%(7/25,025) vs 0.0%(43/179,827)
Green et al., 2010[362] Bisphosphonates	Bisphosphonates vs Control: Colorectal cancer: 15.1%(276/1,831) vs 16.8%(10365/61,832) Esophageal cancer: 20.7%(90/435) vs 16.6%(2,864/17,240) Stomach cancer: 15.4%(49/319) vs 16.8%(1,969/11,706)
McHorney et al., 2007[298] Bisphosphonates	Bisphosphonates: Non-adherence: 44.6%(453/1,015) Non-adherence due to adverse events: 6.6%(67/1,015)
Payer et al., 2009[493] Bisphosphonates, None of the interventions	Bisphosphonates: GI and muscular AE: 33.0%(672/2,035) Gastrointestinal symptoms: 28.0%(570/2,035) Muscular side effects: 32.0%(651/2,035) Symptoms of Reflux: 37.0%(753/2,035) Withdrawals due to adverse events: 0.0%(0/2,035)

Author, Year, Drug, Trial name	Adverse events reported
Eisman et al., 2008[494] Ibandronate (Boniva) Trial: DIVA	Intravenous ibandronate 2 mg every 2mo plus oral placebo + Calcium 500 mg + Vitamin D 400 IU vs Intravenous ibandronate 3 mg every 3mo plus oral placebo + Calcium 500 mg + Vitamin D 400 IU vs Intravenous placebo plus 2.5 mg daily oral ibandronate + Calcium 500 mg + Vitamin D 400 IU: Any adverse event: 88.6%(397/448) vs 85.3%(400/469) vs 87.7%(408/465) Anemia: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Any serious adverse event: 16.3%(73/448) vs 13.2%(62/469) vs 14.4%(67/465) Death due to acute pancreatitis: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Death due to gallbladder cancer: 0.0%(0/448) vs 0.0%(0/469) vs 0.2%(1/465) Death due to myocardial infarction: 0.2%(1/448) vs 0.4%(2/469) vs 0.0%(0/465) Death due to pulmonary edema: 0.0%(0/448) vs 0.0%(0/469) vs 0.2%(1/465) Death due to pulmonary embolism: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Death due to ventricular arrhythmia and aortic dissection: 0.0%(0/448) vs 0.0%(0/469) vs 0.2%(1/465) Drug hypersensitivity: 0.0%(0/448) vs 0.2%(1/469) vs 0.0%(0/465) Esophageal ulcer: 0.0%(0/448) vs 0.2%(1/469) vs 0.0%(0/465) Gastric ulcer: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Gastritis: 0.0%(0/448) vs 0.4%(2/469) vs 0.0%(0/465) Gastrointestinal ulcer: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) General flu-like symptoms: 1.6%(7/448) vs 4.5%(21/469) vs 18.9%(88/465) Increased hepatic enzyme: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Influenza-like illness / acute-phase reaction: 5.6%(25/448) vs 4.9%(23/469) vs 1.5%(7/465) Melena: 0.0%(0/448) vs 0.2%(1/469) vs 0.0%(0/465) Myocardial infarction: 0.0%(0/448) vs 0.4%(2/469) vs 0.0%(0/465) Osteonecrosis of jaw: 0.0%(0/448) vs 0.0%(0/469) vs 0.0%(0/465) Polymyalgia rheumatica: 0.2%(1/448) vs 0.0%(0/469) vs 0.0%(0/465) Renal adverse event: 4.5%(20/448) vs 3.2%(15/469) vs 3.9%(18/465) Temporal arteritis: 0.0%(0/448) vs 0.2%(1/469) vs 0.0%(0/465) Withdrawals: 19.4%(87/448) vs 20.7%(97/469) vs 17.4%(81/465)
Lewiecki et al., 2010[354] Ibandronate (Boniva) Trial: BONE, MOBILE, DIVA	Ibandronate vs Placebo: Non-serious atrial fibrillation: 0.4%(29/6,830) vs 0.5%(10/1,924) Serious atrial fibrillation: 0.4%(28/6,830) vs 0.4%(8/1,924)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
McClung et al., 2009[495] Ibandronate (Boniva)	Ibandronate 150 mg monthly + Calcium 500 mg/day + Vitamin D 400 IU/day vs Placebo + 150 mg monthly + Calcium 500 mg/day + Vitamin D 400 IU/day: Any adverse event: 77.9%(60/77) vs 77.1%(64/83) Any serious adverse event: 3.9%(3/77) vs 1.2%(1/83) Arthralgia: 15.6%(12/77) vs 9.6%(8/83) Bacterial infection: 1.3%(1/77) vs 1.2%(1/83) Chest pain: 1.3%(1/77) vs 0.0%(0/83) Death: 0.0%(0/77) vs 0.0%(0/83) Dyspepsia: 5.2%(4/77) vs 4.8%(4/83) GI disorder: 31.2%(24/77) vs 24.1%(20/83) Gastroesophageal reflux disease: 5.2%(4/77) vs 3.6%(3/83) Influenza-like illness: 5.2%(4/77) vs 0.0%(0/83) Life-threatening adverse event: 0.0%(0/77) vs 0.0%(0/83) Myalgia: 6.5%(5/77) vs 2.4%(2/83) Nausea: 6.5%(5/77) vs 3.6%(3/83)
Orwoll et al., 2010[411] Ibandronate (Boniva) Trial: STRONG	Ibandronate vs Placebo: Any AE: 52.9%(46/87) vs 41.7%(20/48) Acute phase reaction: 3.4%(3/87) vs 4.2%(2/48) Any serious AE not leading to death: 6.9%(6/87) vs 8.3%(4/48) Arthralgia: 5.7%(5/87) vs 10.4%(5/48) Back pain: 4.6%(4/87) vs 6.3%(3/48) Constipation: 2.3%(2/87) vs 4.2%(2/48) Deaths: 1.1%(1/87) vs 4.2%(2/48) Drug-related AE: abdominal pain: 3.4%(3/87) vs 0.0%(0/48) Nasopharyngitis: 8.0%(7/87) vs 0.0%(0/48) Nausea: 4.6%(4/87) vs 0.0%(0/48) New morphometric vertebral fractures: 1.1%(1/87) vs 4.2%(2/48) Pain in extremity: 2.3%(2/87) vs 4.2%(2/48) Upper respiratory tract infection: 3.4%(3/87) vs 2.1%(1/48) Withdrawals: due to AE: 4.6%(4/87) vs 6.3%(3/48)
Stakkestad et al., 2008[496] Ibandronate (Boniva) Trial: MOBILE	Oral ibandronate 100 mg/month + Calcium 500-1500 mg/day + Vitamin D 400 IU vs Oral ibandronate 150 mg/month + Calcium 500-1500 mg/day + Vitamin D 400 IU: Any adverse event: 56.0%(201/359) vs 53.1%(191/360) Chest pain: 0.0%(0/359) vs 0.3%(1/360) Death from Pancreatic cancer: 0.0%(0/359) vs 0.3%(1/360) Serious AE: 7.8%(28/359) vs 7.5%(27/360) Serious upper GI event: 0.0%(0/359) vs 0.0%(0/360) Upper GI event: 4.5%(16/359) vs 6.9%(25/360)

Author, Year, Drug, Trial name	Adverse events reported
Adami et al., 2005[497] Risedronate (Actonel)	Risedronate 15 mg/day vs Risedronate 5 mg/day vs Placebo: Abdominal pain: 8.0%(49/609) vs 9.1%(57/628) vs 7.2%(45/622) Duodenal ulcer: 0.7%(4/609) vs 0.0%(0/628) vs 0.3%(2/622) Duodenitis: 0.5%(3/609) vs 0.6%(4/628) vs 0.2%(1/622) Dyspepsia: 5.1%(31/609) vs 6.2%(39/628) vs 5.8%(36/622) Dysphagia: 0.5%(3/609) vs 0.6%(4/628) vs 0.6%(4/622) Esophageal ulcer: 0.0%(0/609) vs 0.2%(1/628) vs 0.0%(0/622) Esophagitis: 0.8%(5/609) vs 0.5%(3/628) vs 0.6%(4/622) GI disorder: 2.8%(17/609) vs 3.8%(24/628) vs 3.5%(22/622) GI hemorrhage: 0.2%(1/609) vs 0.0%(0/628) vs 1.0%(6/622) Gastritis: 1.5%(9/609) vs 2.1%(13/628) vs 2.1%(13/622) Hematemesis: 0.0%(0/609) vs 0.6%(4/628) vs 0.0%(0/622) Melena: 0.2%(1/609) vs 0.0%(0/628) vs 0.2%(1/622) Peptic ulcer: 0.0%(0/609) vs 0.2%(1/628) vs 0.0%(0/622) Stomach ulcer: 0.7%(4/609) vs 0.3%(2/628) vs 0.3%(2/622) Substernal chest pain: 0.2%(1/609) vs 0.3%(2/628) vs 0.3%(2/622)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Barrera et al., 2005[498] Risedronate (Actonel) Trial: PEM	Risedronate 5mg/d or 30 mg/d: AEs: all: 3.1%(405/13,180) Allergy: 0.0%(2/13,180) Anemia: 0.0%(1/13,180) Conjunctivitis: 0.0%(3/13,180) Constipation: 1.2%(153/13,180) Deaths: cerebral vascular accident: 0.2%(28/13,180) Deaths: chronic obstructive pulmonary disease: 0.2%(30/13,180) Deaths: myocardial infarction: 0.3%(34/13,180) Diarrhea: 2.3%(305/13,180) Diplopia: 0.0%(1/13,180) Dry eye: 0.0%(6/13,180) Dry skin: 0.0%(1/13,180) Duodenitis: 0.0%(1/13,180) Dyspepsia: 6.5%(858/13,180) Edema: 1.4%(183/13,180) Episcleritis: 0.0%(1/13,180) Esophageal reflux: 0.0%(1/13,180) Facial edema: 0.0%(6/13,180) Fluid retention: 0.0%(1/13,180) GI unspecified: 1.6%(210/13,180) Hair loss: 0.0%(1/13,180) Headache/migraine: 1.6%(208/13,180) Hematemesis: 0.0%(3/13,180) Intolerance: 2.4%(315/13,180) Irritation of the eye: 0.0%(1/13,180) Jaundice: 0.0%(1/13,180) Malaise/lassitude: 1.6%(214/13,180) Melena: 0.0%(1/13,180) Menorrhagia: 0.0%(1/13,180) Mouth ulcer: 0.0%(4/13,180) Myalgia: 1.1%(140/13,180) Nausea/vomiting: reported in 2-6 month of treatment: 3.9%(515/13,180) Pain abdomen: 2.2%(295/13,180) Pain joint: 1.7%(223/13,180) Painful eye: 0.0%(1/13,180)

Author, Year, Drug, Trial name	Adverse events reported
Barrera et al., 2005[498] Continued	Risedronate 5mg/d or 30 mg/d: Palpitation: 0.0%(1/13,180) Paresthesia: 0.0%(1/13,180) Photosensitivity: 0.0%(2/13,180) Pruritus: 0.0%(4/13,180) Rash: 1.3%(166/13,180) Rectal hemorrhage: 0.0%(1/13,180) Respiratory tract infection higher: 1.8%(243/13,180) Respiratory tract infection lower: 3.1%(407/13,180) Skin irritation: 0.0%(1/13,180) Sore eye: 0.0%(5/13,180) Sore mouth: 0.0%(2/13,180) Stevens-Johnson syndrome: 0.0%(1/13,180) Swollen tongue: 0.0%(1/13,180) Ulceration of ileostomy site: 0.0%(1/13,180) Unspecified AE: 1.2%(155/13,180) Urticaria: 0.0%(3/13,180) Visual disturbance: 0.0%(1/13,180) Discontinued drug: all: 26.0%(3,423/13,180)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Boonen et al., 2009[74] Risedronate (Actonel)	Risedronate 35 mg/wk vs Placebo: AEs: any: 70.2%(134/191) vs 73.1%(68/93) AEs: serious: 15.2%(29/191) vs 16.1%(15/93) Arthralgia: 5.8%(11/191) vs 8.6%(8/93) Atrial fibrillation: 1.0%(2/191) vs 3.2%(3/93) Back pain: 6.8%(13/191) vs 2.2%(2/93) Benign prostatic hyperplasia: 4.7%(9/191) vs 3.2%(3/93) Chest pain: 0.0%(0/191) vs 2.2%(2/93) Constipation: 8.4%(16/191) vs 5.4%(5/93) Death due to lung neoplasm: 0.0%(0/191) vs 1.1%(1/93) Death due to pulmonary embolism: 0.0%(0/191) vs 1.1%(1/93) Death due to shock: 0.0%(0/191) vs 1.1%(1/93) Death due to small lung cancer: 0.5%(1/191) vs 0.0%(0/93) Death due to sudden cardiac event: 0.5%(1/191) vs 0.0%(0/93) Headache: mild: 4.7%(9/191) vs 0.0%(0/93) Headache: moderate: 0.5%(1/191) vs 0.0%(0/93) Influenza: 5.8%(11/191) vs 5.4%(5/93) Myocardial infarction: 1.0%(2/191) vs 3.2%(3/93) Nasopharyngitis: 5.8%(11/191) vs 5.4%(5/93) Pain in extremity: 4.7%(9/191) vs 3.2%(3/93) Pulmonary embolism: 1.0%(2/191) vs 1.1%(1/93) Sudden cardiac death: 0.5%(1/191) vs 0.0%(0/93) Upper GI AEs: dyspepsia: 3.1%(6/191) vs 4.3%(4/93) Withdrawals: due to AE: 3.7%(7/191) vs 9.7%(9/93) Withdrawals: total: 8.4%(16/191) vs 19.4%(18/93)
Delmas et al., 2007[267] Risedronate (Actonel) Trial: IMPACT	Risedronate No reinforcement vs Risedronate Reinforcement: Death: 0.3%(3/1,154) vs 0.1%(1/1,228) Withdrawals: Total: 13.2%(152/1,154) vs 12.1%(149/1,228) Withdrawals: due to AE: 8.9%(103/1,154) vs 7.4%(91/1,228)
Delmas et al., 2008[85] Risedronate (Actonel)	Risedronate 5mg vs Risedronate 75mg: Arthralgia: 9.5%(58/613) vs 10.4%(64/616) Back pain: 10.8%(66/613) vs 8.8%(54/616) Fever or influenza-like illness: 0.0%(0/613) vs 0.6%(4/616) Moderate to severe upper GI Treatment-emergent AE: 6.2%(38/613) vs 7.5%(46/616) Treatment-emergent AE: all: 81.2%(498/613) vs 84.7%(522/616) Treatment-emergent AE: possibly or probably related serious: 0.5%(3/613) vs 0.6%(4/616) Treatment-emergent AE: resulting in death: 0.5%(3/613) vs 0.3%(2/616) Treatment-emergent AE: serious: 4.7%(29/613) vs 7.5%(46/616) Upper GI Treatment-emergent AE: 21.2%(130/613) vs 22.2%(137/616) Withdrawals: total: 14.8%(91/613) vs 14.6%(90/616)

Author, Year, Drug, Trial name	Adverse events reported
Delmas et al., 2008[86] Risedronate (Actonel)	Risedronate 150mg a month vs Risedronate 5mg/d: AEs: all: 79.2%(515/650) vs 78.5%(504/642) AE potentially associated with acute phase reaction: 1.4%(9/650) vs 0.2%(1/642) AEs: serious AE: 6.2%(40/650) vs 4.2%(27/642) Arthralgia: 5.5%(36/650) vs 7.3%(47/642) Atrial fibrillation: 0.6%(4/650) vs 0.5%(3/642) Constipation: 5.8%(38/650) vs 7.3%(47/642) Deaths: 0.0%(0/650) vs 0.5%(3/642) Diarrhea: 8.2%(53/650) vs 4.7%(30/642) Influenza: 8.9%(58/650) vs 4.2%(27/642) Osteonecrosis of the jaw: 0.0%(0/650) vs 0.0%(0/642) Selected musculoskeletal AE: 15.5%(101/650) vs 17.1%(110/642) Upper GI tract AE: 19.8%(129/650) vs 17.1%(110/642) Upper abdominal pain: 8.2%(53/650) vs 6.1%(39/642) Withdrawals: due to AE: 8.6%(56/650) vs 9.5%(61/642)
Li et al., 2005[499] Risedronate (Actonel)	Placebo + CaltrateD 600 mg vs Risedronate Sodium 5 mg + Caltrate D 600 mg: Withdrawals: 13.3%(4/30) vs 6.7%(2/30) Withdrawals due to adverse events: 3.3%(1/30) vs 6.7%(2/30)
Mok et al., 2008[500] Risedronate (Actonel)	Placebo + Elemental calcium 1000 mg/day vs Risedronate 5 mg/day + Elemental calcium 1000 mg/day: Allergic skin rash: 0.0%(0/60) vs 1.7%(1/60) Confirmed esophagitis: 0.0%(0/60) vs 0.0%(0/60) Death: 5.0%(3/60) vs 3.3%(2/60) Diarrhea: 0.0%(0/60) vs 5.0%(3/60) Dizziness: 1.7%(1/60) vs 0.0%(0/60) Dyspepsia/epigastric pain: 5.0%(3/60) vs 16.7%(10/60) Endoscopic gastritis: 5.0%(3/60) vs 5.0%(3/60) Heartburn: 0.0%(0/60) vs 1.7%(1/60) Nausea: 1.7%(1/60) vs 0.0%(0/60) Skin itching: 1.7%(1/60) vs 1.7%(1/60) Transient urticaria: 1.7%(1/60) vs 0.0%(0/60) Withdrawals: 13.3%(8/60) vs 15.0%(9/60) Withdrawals due to adverse events: 0.0%(0/60) vs 3.3%(2/60)

Evidence Table C-5. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Palomba et al., 2008[75] Risedronate (Actonel)	Placebo + 1,500 mg/d 1,25 dihydroxyvitamin 800 UI/d vs Risedronate 35 mg/week + 1,500 mg/d 1,25 dihydroxyvitamin 800 UI/d: Abdominal pain: 8.9%(4/45) vs 6.7%(3/45) Constipation: 2.2%(1/45) vs 2.2%(1/45) Death from MI: 2.2%(1/45) vs 0.0%(0/45) Dyspepsia: 4.4%(2/45) vs 4.4%(2/45) Dysphagia: 0.0%(0/45) vs 2.2%(1/45) Flatulence: 6.7%(3/45) vs 4.4%(2/45) Headache: 0.0%(0/45) vs 2.2%(1/45) Heartburn: 2.2%(1/45) vs 6.7%(3/45) Leg cramps: 2.2%(1/45) vs 0.0%(0/45) Withdrawals: 8.9%(4/45) vs 11.1%(5/45)
Ringe et al., 2009[73] Risedronate (Actonel)	Placebo + Calcium + Vitamin D 800 IU/day vs Risedronate 5 mg/day + Calcium + Vitamin D 800 IU/day: Withdrawals: 6.3%(10/158) vs 3.8%(6/158) Withdrawals due to adverse events: 0.0%(0/158) vs 0.0%(0/158)

Author, Year, Drug, Trial name	Adverse events reported
Ste-Marie et al., 2009[501] Risedronate (Actonel)	Risedronate 100 mg/mo + Elemental Calcium 1000 mg/day + Vitamin D 400 IU/day vs Risedronate 150 mg/mo + Elemental Calcium 1000 mg/day + Vitamin D 400 IU/day vs Risedronate 200 mg/mo + Elemental Calcium 1000 mg/day + Vitamin D 400 IU/day vs Risedronate 5 mg/day + Elemental Calcium 1000 mg/day + Vitamin D 400 IU/day: Any adverse event: 52.7%(48/91) vs 61.4%(54/88) vs 56.8%(50/88) vs 51.5%(53/103) Abdominal pain: 2.2%(2/91) vs 6.8%(6/88) vs 9.1%(8/88) vs 3.9%(4/103) Abdominal pain upper: 4.4%(4/91) vs 11.4%(10/88) vs 8.0%(7/88) vs 6.8%(7/103) Any serious adverse event: 1.1%(1/91) vs 5.7%(5/88) vs 3.4%(3/88) vs 2.9%(3/103) Arthralgia: 4.4%(4/91) vs 9.1%(8/88) vs 5.7%(5/88) vs 5.8%(6/103) Back pain: 3.3%(3/91) vs 6.8%(6/88) vs 3.4%(3/88) vs 1.9%(2/103) Cervical spine stenosis: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Chest pain: 0.0%(0/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 1.0%(1/103) Chronic bronchitis: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Coronary artery atherosclerosis: 0.0%(0/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 1.0%(1/103) Coronary artery disease: 0.0%(0/91) vs 0.0%(0/88) vs 1.1%(1/88) vs 0.0%(0/103) Death: 0.0%(0/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 0.0%(0/103) Diarrhea: 7.7%(7/91) vs 4.5%(4/88) vs 10.2%(9/88) vs 2.9%(3/103) Dyspepsia: 7.7%(7/91) vs 5.7%(5/88) vs 5.7%(5/88) vs 2.9%(3/103) Erosive esophagitis: 0.0%(0/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 1.0%(1/103) Headache: 2.2%(2/91) vs 6.8%(6/88) vs 5.7%(5/88) vs 4.9%(5/103) Hypertension: 0.0%(0/91) vs 0.0%(0/88) vs 1.1%(1/88) vs 0.0%(0/103) Malignant lung neoplasm: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Moderate or severe upper GI event: 2.2%(2/91) vs 9.1%(8/88) vs 6.8%(6/88) vs 3.9%(4/103) Myalgia: 4.4%(4/91) vs 3.4%(3/88) vs 4.5%(4/88) vs 0.0%(0/103) Nasopharyngitis: 2.2%(2/91) vs 5.7%(5/88) vs 5.7%(5/88) vs 3.9%(4/103) Nausea: 3.3%(3/91) vs 3.4%(3/88) vs 8.0%(7/88) vs 1.9%(2/103) Ovarian cyst: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Paraparesis: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Pheochromocytoma: 1.1%(1/91) vs 0.0%(0/88) vs 0.0%(0/88) vs 0.0%(0/103) Pneumonia: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Supraventricular tachycardia: 0.0%(0/91) vs 0.0%(0/88) vs 1.1%(1/88) vs 0.0%(0/103) Tendon rupture: 0.0%(0/91) vs 1.1%(1/88) vs 0.0%(0/88) vs 0.0%(0/103) Upper GI event: 13.2%(12/91) vs 22.7%(20/88) vs 19.3%(17/88) vs 18.4%(19/103) Upper respiratory tract infection: 5.5%(5/91) vs 9.1%(8/88) vs 9.1%(8/88) vs 3.9%(4/103) Urinary tract infection: 3.3%(3/91) vs 1.1%(1/88) vs 2.3%(2/88) vs 5.8%(6/103)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Boonen et al., 2008[502] Zoledronic acid (Zometa)	Placebo + Calcium + Vitamin D vs Zoledronic Acid 5 mg + Calcium + Vitamin D: AEs: all: 93.9%(3,618/3,852) vs 95.5%(3,687/3,862) AEs: deaths: 2.9%(112/3,852) vs 3.4%(131/3,862) AEs: serious AE: 30.1%(1,160/3,852) vs 29.2%(1,127/3,862) Apical granuloma: 0.0%(1/3,852) vs 0.0%(0/3,862) Bone fistula: 0.0%(1/3,852) vs 0.0%(0/3,862) Bone infarction: 0.0%(0/3,852) vs 0.0%(1/3,862) Bone lesion: 0.0%(0/3,852) vs 0.0%(1/3,862) Bone lesion excision: 0.0%(1/3,852) vs 0.0%(0/3,862) Dental Caries: 0.6%(23/3,852) vs 0.5%(18/3,862) Dental alveolar anomaly: 0.0%(1/3,852) vs 0.0%(0/3,862) Dental necrosis: 0.1%(3/3,852) vs 0.0%(0/3,862) Dry socket: 0.1%(3/3,852) vs 0.0%(0/3,862) Estimated creatinine clearance < 30 ml/min: overall: 4.2%(152/3,658) vs 4.4%(160/3,621) Estimated creatinine clearance decreased by ≥ 30%: ml/min: overall: 4.8%(177/3,658) vs 5.0%(182/3,621) Exostosis: 0.5%(19/3,852) vs 0.4%(17/3,862) Increase in serum creatinine > 0.5 mg/100ml: overall: 2.0%(77/3,767) vs 2.8%(104/3,752) Mouth ulceration: 0.3%(10/3,852) vs 0.3%(11/3,862) Osteitis: 0.2%(7/3,852) vs 0.2%(7/3,862) Osteitis deformans: 0.0%(1/3,852) vs 0.0%(1/3,862) Osteolysis: 0.0%(0/3,852) vs 0.0%(1/3,862) Osteomyelitis: 0.0%(0/3,852) vs 0.1%(2/3,862) Osteomyelitis chronic: 0.0%(0/3,852) vs 0.0%(1/3,862) Osteonecrosis of jaw: 0.0%(1/3,852) vs 0.0%(1/3,862) Osteonecrosis of the hip: 0.1%(2/3,852) vs 0.1%(5/3,862) Periodontitis: 0.3%(12/3,852) vs 0.2%(7/3,862) Periostitis: 0.1%(2/3,852) vs 0.0%(0/3,862) Sinusitis: 2.7%(103/3,852) vs 2.2%(86/3,862) Sinusitis bacterial: 0.0%(1/3,852) vs 0.0%(1/3,862) Sinusitis fungal: 0.0%(0/3,852) vs 0.0%(1/3,862) Soft tissue inflammation: 0.0%(0/3,852) vs 0.0%(1/3,862) Soft tissue injury: 0.3%(12/3,852) vs 0.3%(11/3,862) Soft-tissue disorder: 0.0%(1/3,852) vs 0.0%(0/3,862) Soft-tissue infection: 0.0%(1/3,852) vs 0.0%(0/3,862) Tooth abscess: 0.5%(18/3,852) vs 0.6%(23/3,862) Urinary protein level > 2+: overall: 0.5%(19/3,758) vs 0.5%(19/3,749) Discontinuation: due to AE: 1.8%(69/3,852) vs 2.1%(81/3,862) Discontinuation: total: 15.3%(590/3,852) vs 16.2%(625/3,862)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Chapman et al., 2009[114] Zoledronic acid (Zometa)	Zoledronic acid IV 2mg vs Placebo: Fever, rigor, bone pain in legs and chest: 10.0%(1/10) vs 0.0%(0/12) Flu-like illness: 80.0%(8/10) vs 8.3%(1/12) Musculoskeletal pain: 40.0%(4/10) vs 16.7%(2/12) Severe pain restricting movement requiring hospitalization: 10.0%(1/10) vs 0.0%(0/12)
Grey et al., 2010[418] Zoledronic acid (Zometa)	Zoledronic acid vs Placebo: Atrial fibrillation: 0.0%(0/25) vs 0.0%(0/25) Ocular inflammation: 0.0%(0/25) vs 0.0%(0/25) Osteonecrosis of the jaw: 0.0%(0/25) vs 0.0%(0/25) Other fracture: 16.0%(4/25) vs 8.0%(2/25) Symptomatic hypocalcemia: 0.0%(0/25) vs 0.0%(0/25)
Lyles et al., 2007[113] Zoledronic acid (Zometa)	Zoledronic acid vs Placebo: Any AE: 82.3%(867/1,054) vs 80.6%(852/1,057) Adjudicated hypocalcemia: 0.3%(3/1,054) vs 0.0%(0/1,057) Any serious AE: 38.3%(404/1,054) vs 41.2%(436/1,057) Arrhythmia: 2.3%(24/1,054) vs 3.7%(39/1,057) Arthralgia: 3.1%(33/1,054) vs 2.2%(23/1,057) Atrial fibrillation: any event: 2.8%(29/1,054) vs 2.6%(27/1,057) Bone pain: 3.2%(34/1,054) vs 1.0%(11/1,057) Death: 9.6%(101/1,054) vs 13.3%(141/1,057) Death from cardiovascular causes: 3.4%(36/1,054) vs 4.9%(52/1,057) Death from cardiovascular disease: 1.0%(11/1,054) vs 1.7%(18/1,057) Death from cerebrovascular disease: 0.7%(7/1,054) vs 0.7%(7/1,057) Falls: 9.7%(102/1,054) vs 11.4%(120/1,057) Headache: 1.5%(16/1,054) vs 0.9%(9/1,057) Influenza-like symptoms: 0.6%(6/1,054) vs 0.3%(3/1,057) Musculoskeletal pain: 3.1%(33/1,054) vs 1.2%(13/1,057) Myalgia: 4.9%(52/1,054) vs 2.7%(29/1,057) Myocardial infarction: 1.2%(13/1,054) vs 1.6%(17/1,057) Ocular events possibly related to a study drug: 0.4%(4/1,054) vs 0.1%(1/1,057) Pyrexia: 8.7%(92/1,054) vs 3.1%(33/1,057) Renal event: increase in serum creatinine>0.5 mg/dl: 6.2%(55/886) vs 5.6%(50/900) Stroke: fatal event: 0.9%(9/1,054) vs 0.6%(6/1,057) Stroke: serious adverse event: 4.4%(46/1,054) vs 3.6%(38/1,057) Withdrawals: due to AE: 2.0%(21/1,054) vs 1.7%(18/1,057) Withdrawals: total: 18.3%(193/1,054) vs 29.9%(316/1,057)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
McClung et al., 2007[503] Zoledronic acid (Zometa)	Alendronate 70 mg/wk vs Zoledronic acid 5mg/wk: AEs: any: 95.5%(107/112) vs 114.2%(129/113) AEs: serious AE: 9.8%(11/112) vs 10.6%(12/113) Arthralgia: 10.7%(12/112) vs 17.7%(20/113) Back pain: 11.6%(13/112) vs 7.1%(8/113) Bronchitis: 1.8%(2/112) vs 5.3%(6/113) Cough: 5.4%(6/112) vs 2.7%(3/113) Death: 0.0%(0/112) vs 0.0%(0/113) Diarrhea: 1.8%(2/112) vs 5.3%(6/113) Fatigue: 1.8%(2/112) vs 9.7%(11/113) Headache: 13.4%(15/112) vs 16.8%(19/113) Hypocalcemia: 0.0%(0/112) vs 0.0%(0/113) Lab renal abnormality: 0.0%(0/112) vs 1.8%(2/113) Pain: 2.7%(3/112) vs 6.2%(7/113) Pain in extremity: 5.4%(6/112) vs 7.1%(8/113) Sinusitis: 4.5%(5/112) vs 6.2%(7/113) Upper respiratory tract infection: 12.5%(14/112) vs 8.0%(9/113) Urinary tract infection: 6.3%(7/112) vs 8.0%(9/113) Withdrawals: due to AE: 0.9%(1/112) vs 3.5%(4/113)

Author, Year, Drug, Trial name	Adverse events reported
McClung et al., 2009[421] Zoledronic acid (Zometa)	Placebo at randomization and at month 24 vs Zoledronic acid 5 mg at randomization and at month 24 vs Zoledronic acid 5 mg at randomization and placebo at month 24: Arthralgia: 19.3%(39/202) vs 27.3%(54/198) vs 18.8%(34/181) Atrial fibrillation: 0.0%(0/202) vs 0.0%(0/198) vs 0.0%(0/181) Back pain: 11.9%(24/202) vs 18.2%(36/198) vs 16.6%(30/181) Chills: 3.0%(6/202) vs 18.2%(36/198) vs 18.2%(33/181) Chills 3 or < days after an infusion: 1.5%(3/202) vs 16.7%(33/198) vs 18.2%(33/181) Chills >3 days after an infusion: 1.5%(3/202) vs 1.5%(3/198) vs 1.1%(2/181) Death due to sepsis: 0.0%(0/202) vs 0.5%(1/198) vs 0.0%(0/181) Fatigue: 4.0%(8/202) vs 14.6%(29/198) vs 9.9%(18/181) Headache: 11.4%(23/202) vs 14.6%(29/198) vs 20.4%(37/181) Long-term effects on renal function: 0.0%(0/202) vs 0.0%(0/198) vs 0.0%(0/181) Myalgia: 6.9%(14/202) vs 19.2%(38/198) vs 22.7%(41/181) Myalgia 3 or < days after an infusion: 2.0%(4/202) vs 15.7%(31/198) vs 20.4%(37/181) Myalgia >3 days after an infusion: 5.4%(11/202) vs 4.5%(9/198) vs 4.4%(8/181) Nasopharyngitis: 11.4%(23/202) vs 13.6%(27/198) vs 9.4%(17/181) Nausea: 7.9%(16/202) vs 17.7%(35/198) vs 11.6%(21/181) Nausea 3 or < days after an infusion: 2.0%(4/202) vs 12.1%(24/198) vs 8.8%(16/181) Nausea >3 days after an infusion: 5.9%(12/202) vs 6.6%(13/198) vs 3.9%(7/181) Osteonecrosis of the jaw: 0.0%(0/202) vs 0.0%(0/198) vs 0.0%(0/181) Pain: 3.5%(7/202) vs 24.2%(48/198) vs 14.9%(27/181) Pain 3 or < days after an infusion: 2.0%(4/202) vs 19.7%(39/198) vs 13.8%(25/181) Pain >3 days after an infusion: 1.5%(3/202) vs 6.1%(12/198) vs 1.1%(2/181) Pain in extremity: 9.9%(20/202) vs 11.1%(22/198) vs 16.0%(29/181) Pyrexia: 4.5%(9/202) vs 21.7%(43/198) vs 21.0%(38/181) Pyrexia 3 or < days after an infusion: 1.5%(3/202) vs 17.2%(34/198) vs 19.3%(35/181) Pyrexia >3 days after an infusion: 3.0%(6/202) vs 5.1%(10/198) vs 4.4%(8/181) Serious adverse event: 11.4%(23/202) vs 8.6%(17/198) vs 11.6%(21/181) Total number of participants with an AE: 92.1%(186/202) vs 93.9%(186/198) vs 95.6%(173/181) Total number of participants with an AE 3 or < days after an infusion: 24.8%(50/202) vs 61.6%(122/198) vs 63.0%(114/181) Total number of participants with an AE >3 days after an infusion: 91.6%(185/202) vs 90.9%(180/198) vs 89.5%(162/181) Upper respiratory tract infection: 11.4%(23/202) vs 13.6%(27/198) vs 10.5%(19/181) Urinary tract infection: 12.4%(25/202) vs 11.1%(22/198) vs 8.8%(16/181)
Etminan et al., 2008[504] Alendronate (Fosamax), Etidronate (Didronel)	Oral Bisphosphonate: Aseptic osteonecrosis: 28.3%(58/205)

Author, Year, Drug, Trial name	Adverse events reported
Emkey et al., 2009[505] Alendronate (Fosamax), Ibandronate (Boniva) Trial: MOTION	Alendronate 70 mg weekly + Calcium 500 mg + Vitamin D 400 IU vs Ibandronate 150 mg monthly + Calcium 500 mg + Vitamin D 400 IU: Any adverse event: 73.6%(632/859) vs 75.4%(659/874) All GI adverse events: 28.9%(248/859) vs 30.3%(265/874) Arthralgia: 5.7%(49/859) vs 5.4%(47/874) Back pain: 5.2%(45/859) vs 6.9%(60/874) Death: 0.5%(4/859) vs 0.2%(2/874) Duodenal ulcer: 0.1%(1/859) vs 0.0%(0/874) Dyspepsia: 5.6%(48/859) vs 6.9%(60/874) Erosive duodenitis: 0.1%(1/859) vs 0.0%(0/874) Esophagitis ulcerative: 0.1%(1/859) vs 0.0%(0/874) GI hemorrhagic: 0.1%(1/859) vs 0.0%(0/874) Gastric ulcer: 0.2%(2/859) vs 0.1%(1/874) Gastritis erosive: 0.2%(2/859) vs 0.1%(1/874) Gastritis hemorrhagic: 0.1%(1/859) vs 0.0%(0/874) Hypertension: 5.9%(51/859) vs 7.8%(68/874) Influenza: 4.2%(36/859) vs 5.6%(49/874) Intestinal hemorrhagic: 0.1%(1/859) vs 0.0%(0/874) Musculoskeletal and general disorders: 3.0%(26/859) vs 6.8%(59/874) Nasopharyngitis: 4.8%(41/859) vs 5.8%(51/874) Perforations, ulcers and bleeding: 0.9%(8/859) vs 0.5%(4/874) Rectal hemorrhage: 0.1%(1/859) vs 0.2%(2/874) Serious adverse event: 6.4%(55/859) vs 4.5%(39/874) Upper-GI adverse event: 17.2%(148/859) vs 17.5%(153/874) Upper-GI hemorrhage: 0.1%(1/859) vs 0.0%(0/874)
Hadji et al., 2008[506] Alendronate (Fosamax), Ibandronate (Boniva) Trial: BALTTO II	Alendronate 70 mg weekly + Calcium + Vitamin D vs Ibandronate 150 mg monthly + Calcium + Vitamin D: Any adverse event: 34.6%(117/338) vs 37.5%(126/336) Constipation: 1.2%(4/338) vs 3.0%(10/336) Death: 0.0%(0/338) vs 0.0%(0/336) Diarrhea: 3.3%(11/338) vs 1.5%(5/336) Dyspepsia: 1.8%(6/338) vs 0.9%(3/336) GI disorder: 8.6%(29/338) vs 8.3%(28/336) Gastro-esophageal reflux disease: 0.6%(2/338) vs 1.2%(4/336) General disorders: 2.1%(7/338) vs 1.5%(5/336) Infections and infestations: 1.2%(4/338) vs 2.1%(7/336) Musculoskeletal and connective tissue disorder: 4.7%(16/338) vs 3.3%(11/336) Nervous system disorders: 1.2%(4/338) vs 2.1%(7/336) Serious AE: 1.8%(6/338) vs 2.4%(8/336) Severe GI events: 2.7%(9/338) vs 0.3%(1/336) Upper GI event: 7.1%(24/338) vs 5.7%(19/336) Withdrawals due to AE: 0.9%(3/338) vs 0.3%(1/336)

Author, Year, Drug, Trial name	Adverse events reported
Li et al., 2009[507] Alendronate (Fosamax), Ibandronate (Boniva)	Alendronate 70 mg/week + Calcium 500 mg/day + Vitamin D 200 IU/day vs Intravenous ibandronate 2 mg every 3mo + Calcium 500 mg/day + Vitamin D 200 IU/day: Acute renal failure: 0.0%(0/79) vs 0.0%(0/79) Bone pain after 1 month: 3.8%(3/79) vs 2.5%(2/79) Bone pain after 2-12 months: 0.0%(0/79) vs 0.0%(0/79) Fever after 1 month: 1.3%(1/79) vs 3.8%(3/79) Fever after 2-12 months: 0.0%(0/79) vs 0.0%(0/79) Influenza-like symptoms after 1 month: 7.6%(6/79) vs 12.7%(10/79) Influenza-like symptoms after 2-12 months: 3.8%(3/79) vs 0.0%(0/79) Muscle pain after 1 month: 5.1%(4/79) vs 29.1%(23/79) Muscle pain after 2-12 months: 3.8%(3/79) vs 0.0%(0/79) Osteonecrosis of jaw after 1 month: 0.0%(0/79) vs 0.0%(0/79) Osteonecrosis of jaw after 2-12 months: 0.0%(0/79) vs 0.0%(0/79) Other after 1 month: 0.0%(0/79) vs 3.8%(3/79) Other after 2-12 months: 0.0%(0/79) vs 0.0%(0/79) Peptic side effects after 1 month: 3.8%(3/79) vs 1.3%(1/79) Peptic side effects after 2-12 months: 2.5%(2/79) vs 0.0%(0/79) Withdrawals: 3.8%(3/79) vs 5.1%(4/79) Withdrawals due to adverse events: 1.3%(1/79) vs 2.5%(2/79)
Cadarette et al., 2009[508] Alendronate (Fosamax), Risedronate (Actonel)	Alendronate vs Risedronate: Any upper GI diagnosis or procedure: 18.2%(1,058/5,818) vs 18.8%(867/4,602) Gastroprotective treatment: 31.7%(1,843/5,818) vs 34.5%(1,588/4,602) Hospitalization for upper GI bleed: 0.3%(16/5,818) vs 0.3%(15/4,602) Switched between therapies: 1.9%(111/5,818) vs 1.3%(60/4,602) Upper GI disease: 10.5%(612/5,818) vs 11.0%(508/4,602) Upper GI endoscopy: 2.3%(134/5,818) vs 2.0%(90/4,602) Upper GI symptom: 11.4%(662/5,818) vs 11.2%(516/4,602)
Reid et al., 2006[509] Alendronate (Fosamax), Risedronate (Actonel) Trial: FACTS-INT'L	Alendronic acid 10 mg/day + Elemental calcium 1000 mg + Vitamin D 400 IU vs Risedronic acid 5mg/day + Elemental calcium 1000 mg + Vitamin D 400 IU: Any adverse event: 65.4%(306/468) vs 67.1%(314/468) Any serious adverse event: 5.1%(24/468) vs 10.0%(47/468) Death: 0.4%(2/468) vs 0.9%(4/468) Serious upper GI event: 0.4%(2/468) vs 0.9%(4/468) Upper GI event: 20.3%(95/468) vs 20.1%(94/468) Withdrawals: 8.1%(38/468) vs 9.4%(44/468)
Breart et al., 2009[510] Alendronate (Fosamax), Strontium ranelate	Alendronate sodium vs Control: Venous thromboembolism: 0.7%(140/20,084) vs 0.5%(61/11,546)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Saag et al., 2007[511] Alendronate (Fosamax), Zoledronic acid (Zometa)	Alendronate vs Zoledronic acid: Any AE: 78.0%(46/59) vs 79.7%(55/69) Abdominal distension: 6.8%(4/59) vs 2.9%(2/69) Abdominal pain: 5.1%(3/59) vs 1.4%(1/69) Arthralgia: 10.2%(6/59) vs 5.8%(4/69) Back pain: 0.0%(0/59) vs 5.8%(4/69) Chest pain: 1.7%(1/59) vs 1.4%(1/69) Chills: 1.7%(1/59) vs 1.4%(1/69) Clinical remarkable changes in vital signs: 0.0%(0/59) vs 0.0%(0/69) Constipation: 5.1%(3/59) vs 1.4%(1/69) Death: 0.0%(0/59) vs 0.0%(0/69) Diarrhea: 0.0%(0/59) vs 2.9%(2/69) Dizziness: 5.1%(3/59) vs 0.0%(0/69) Dyspepsia: 5.1%(3/59) vs 10.1%(7/69) Elevation in alanine aminotransferase (ALT): 3.4%(2/59) vs 18.8%(13/69) Eructation: 5.1%(3/59) vs 1.4%(1/69) Fatigue: 5.1%(3/59) vs 2.9%(2/69) Flatulence: 3.4%(2/59) vs 1.4%(1/69) Headache: 15.3%(9/59) vs 8.7%(6/69) Hypocalcemia: 0.0%(0/59) vs 0.0%(0/69) Influenza-like illness: 1.7%(1/59) vs 1.4%(1/69) Low calcium levels: 0.0%(0/59) vs 0.0%(0/69) Muscle spasms: 6.8%(4/59) vs 4.3%(3/69) Myalgia: 3.4%(2/59) vs 7.2%(5/69) Nasopharyngitis: 3.4%(2/59) vs 10.1%(7/69) Nausea: 6.8%(4/59) vs 1.4%(1/69) Osteoarthritis: 5.1%(3/59) vs 5.8%(4/69) Pain: 0.0%(0/59) vs 0.0%(0/69) Pain in extremity: 6.8%(4/59) vs 2.9%(2/69) Pyrexia: 1.7%(1/59) vs 0.0%(0/69) Rash: 1.7%(1/59) vs 1.4%(1/69) Serious AE: 5.1%(3/59) vs 2.9%(2/69) Shoulder pain: 5.1%(3/59) vs 0.0%(0/69) Sinusitis: 5.1%(3/59) vs 4.3%(3/69) Upper respiratory tract infection: 11.9%(7/59) vs 7.2%(5/69) Withdrawals: 8.5%(5/59) vs 8.7%(6/69)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Reid et al., 2009[512] Risedronate (Actonel), Zoledronic acid (Zometa)	Intravenous Zoledronic acid 5 mg + 1 g Calcium + Vitamin D 400-1200 IU/day + oral placebo vs Oral risedronate 5 mg/day + 1 g Calcium + Vitamin D 400-1200 IU/day + Intravenous placebo: Any adverse event: 77.4%(322/416) vs 66.9%(279/417) Abdominal pain: 2.4%(10/416) vs 1.9%(8/417) Acute renal failure: 0.2%(1/416) vs 0.5%(2/417) Allergic dermatitis: 0.5%(2/416) vs 1.9%(8/417) Anemia: 2.4%(10/416) vs 2.9%(12/417) Anxiety: 1.0%(4/416) vs 1.2%(5/417) Any serious adverse event: 18.3%(76/416) vs 18.5%(77/417) Arthralgia: 9.9%(41/416) vs 7.4%(31/417) Asthenia: 3.8%(16/416) vs 3.6%(15/417) Asymptomatic hypocalcemia: 0.2%(1/416) vs 0.0%(0/417) Atrial fibrillation: 0.7%(3/416) vs 0.0%(0/417) Back pain: 4.3%(18/416) vs 6.2%(26/417) Baseline creatinine clearance </= 30% after given drug: 0.2%(1/416) vs 0.5%(2/417) Baseline creatinine clearance ≤ 60ml/min and ≥ 30% after given drug: 0.2%(1/416) vs 0.5%(2/417) Blepharitis: 0.2%(1/416) vs 0.0%(0/417) Blurred vision: 0.0%(0/416) vs 0.5%(2/417) Bone pain: 3.1%(13/416) vs 2.2%(9/417) Bronchitis: 1.2%(5/416) vs 1.4%(6/417) Cataract: 1.7%(7/416) vs 1.7%(7/417) Chest pain: 0.5%(2/416) vs 0.7%(3/417) Chills: 3.4%(14/416) vs 0.7%(3/417) Conjunctivitis: 1.2%(5/416) vs 0.2%(1/417) Constipation: 2.2%(9/416) vs 2.4%(10/417) Contusion: 1.9%(8/416) vs 0.5%(2/417) Creatinine clearance < 30 mL/min after given drug: 1.0%(4/416) vs 1.0%(4/417) Death: 1.0%(4/416) vs 0.7%(3/417) Depression: 1.7%(7/416) vs 1.7%(7/417) Diarrhea: 3.6%(15/416) vs 2.4%(10/417) Diplopia: 0.0%(0/416) vs 0.2%(1/417) Dizziness: 2.4%(10/416) vs 1.0%(4/417) Dyspepsia: 5.5%(23/416) vs 4.3%(18/417) Episcleritis: 0.0%(0/416) vs 0.2%(1/417) Fall: 1.7%(7/416) vs 1.0%(4/417) Fatigue: 3.1%(13/416) vs 1.4%(6/417) Gastritis: 1.2%(5/416) vs 1.4%(6/417

Author, Year, Drug, Trial name	Adverse events reported
Reid et al., 2009[512] Continued	Intravenous Zoledronic acid 5 mg + 1 g Calcium + Vitamin D 400-1200 IU/day + oral placebo vs Oral risedronate 5 mg/day + 1 g Calcium + Vitamin D 400-1200 IU/day + Intravenous placebo: Gastro-esophageal reflux: 1.2%(5/416) vs 1.4%(6/417) Headache: 5.3%(22/416) vs 2.4%(10/417) Hypertension: 4.3%(18/416) vs 4.1%(17/417) Increase of lacrimation: 0.0%(0/416) vs 0.2%(1/417) Influenza: 3.4%(14/416) vs 1.9%(8/417) Influenza-like illness: 6.0%(25/416) vs 1.0%(4/417) Insomnia: 1.9%(8/416) vs 1.4%(6/417) Joint swelling: 1.0%(4/416) vs 0.5%(2/417) Keratoconjunctivitis sicca: 0.7%(3/416) vs 0.0%(0/417) Musculoskeletal chest pain: 1.9%(8/416) vs 0.0%(0/417) Musculoskeletal pain: 1.4%(6/416) vs 1.7%(7/417) Musculoskeletal stiffness: 1.2%(5/416) vs 0.2%(1/417) Myalgia: 9.1%(38/416) vs 3.4%(14/417) Nasopharyngitis: 2.9%(12/416) vs 2.6%(11/417) Nausea: 9.6%(40/416) vs 8.4%(35/417) Edema peripheral: 2.9%(12/416) vs 2.2%(9/417) Osteonecrosis of long bones: 0.2%(1/416) vs 0.0%(0/417) Osteonecrosis of the jaw: 0.0%(0/416) vs 0.0%(0/417) Pain in limbs: 3.1%(13/416) vs 1.2%(5/417) Palpitations: 1.0%(4/416) vs 0.7%(3/417) Paresthesia: 1.4%(6/416) vs 0.5%(2/417) Pneumonia: 1.4%(6/416) vs 1.9%(8/417) Proteinuria: 1.0%(4/416) vs 0.7%(3/417) Pyrexia: 12.7%(53/416) vs 3.6%(15/417) Rash: 0.7%(3/416) vs 1.9%(8/417) Rectal Haemorrhage: 1.0%(4/416) vs 0.0%(0/417) Sciatica: 2.4%(10/416) vs 0.2%(1/417) Serum creatinine increase by >44 umol/L: 1.9%(8/416) vs 1.4%(6/417) Sinusitis: 1.2%(5/416) vs 2.2%(9/417) Supraventricular tachycardia: 0.2%(1/416) vs 0.0%(0/417) Upper abdominal pain: 5.0%(21/416) vs 3.1%(13/417) Upper respiratory tract infection: 2.4%(10/416) vs 1.9%(8/417) Urinary tract infection: 5.0%(21/416) vs 4.1%(17/417) Vertigo: 1.9%(8/416) vs 1.2%(5/417) Vomiting: 4.8%(20/416) vs 2.4%(10/41
Grosso et al., 2009[513] Alendronate (Fosamax), Bisphosphonates, Risedronate (Actonel)	Bisphosphonates (either Alendronate 10mg daily or 70mg weekly OR Risedronate 5mg daily or 35mg weekly): Atrial fibrillation or atrial flutter: 8.3%(3,335/40,253)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Hong et al., 2009[514] Alendronate (Fosamax), Bisphosphonates, Risedronate (Actonel)	Bisphosphonates: Osteonecrosis of the jaw (BRONJ): 0.1%(7/9,882)
Blumentals et al., 2009[515] Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel)	Alendronate/Risedronate weekly vs Ibandronate 150 mg/mo: Severe GI events: during the follow-up period: 0.8%(70/8,608) vs 0.5%(45/8,608) Use of healthcare services: GI drugs: 24.6%(2,115/8,608) vs 25.7%(2,209/8,608) Use of healthcare services: GI endoscopy: 1.6%(139/8,608) vs 1.8%(158/8,608) Use of healthcare services: GI specialist visits: 5.7%(487/8,608) vs 6.2%(535/8,608) Use of healthcare services: X-ray use: 0.4%(34/8,608) vs 0.3%(23/8,608) Use of healthcare services: emergency care: 7.1%(611/8,608) vs 6.5%(562/8,608) Use of healthcare services: hospitalization: 4.2%(365/8,608) vs 3.8%(325/8,608) Use of healthcare services: outpatient visits: 69.2%(5,959/8,608) vs 71.5%(6,155/8,608) Use of healthcare services: outpatient visits related to GI diagnoses: 2.3%(201/8,608) vs 2.7%(233/8,608) Use of healthcare services: outpatient visits related to musculoskeletal diagnoses: 25.9%(2,230/8,608) vs 26.1%(2,246/8,608)
Ideguchi et al., 2007[294] Alendronate (Fosamax), Bisphosphonates, Etidronate (Didronel), Risedronate (Actonel)	Bisphosphonates: Any adverse event: 9.5%(124/1,307) Diarrhea and/or constipation: 0.9%(12/1,307) Elevated liver function: 0.2%(3/1,307) Gastric pain: 4.6%(60/1,307) Heartburn: 0.5%(6/1,307) Increase of creatine kinase: 0.1%(1/1,307) Increase of creatinine: 0.3%(4/1,307) Laboratory abnormalities: 0.6%(8/1,307) Stomatitis: 0.6%(8/1,307)
Bonnick et al., 2007[226] Alendronate (Fosamax), Calcium	Alendronate 10 mg/d vs Alendronate 10mg/d +Ca 1000 mg/d vs Calcium 100 mg/d: Clinical AEs: any: 93.2%(262/281) vs 87.9%(248/282) vs 91.3%(126/138) Clinical AEs: deaths: 0.4%(1/281) vs 0.7%(2/282) vs 0.0%(0/138) Clinical AEs: drug-related: 39.1%(110/281) vs 34.8%(98/282) vs 35.5%(49/138) Clinical AEs: serious: 10.7%(30/281) vs 14.2%(40/282) vs 19.6%(27/138) Upper GI AEs: any: 34.9%(98/281) vs 34.8%(98/282) vs 38.4%(53/138) Upper GI AEs: drug-related: 21.0%(59/281) vs 20.6%(58/282) vs 21.0%(29/138) Upper GI AEs: serious: 0.7%(2/281) vs 0.0%(0/282) vs 1.4%(2/138) Withdrawals: total: 29.5%(83/281) vs 32.6%(92/282) vs 30.4%(42/138)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Brown et al., 2009[275] Alendronate (Fosamax), Denosumab Trial: DECIDE	Alendronate 70 mg/wk vs Denosumab 60 mg/6 mos: AEs: all AEs: 82.3%(482/586) vs 80.9%(480/593) AEs: serious AE: 6.3%(37/586) vs 5.7%(34/593) Arthralgia: 9.6%(56/586) vs 12.6%(75/593) Asymptomatic grade 2 decrease in albumin-adjusted serum calcium concentrations: 0.0%(0/586) vs 0.2%(1/593) Benign neoplasms of the breast: 0.0%(0/586) vs 0.3%(2/593) Benign neoplasms of the kidney: 0.0%(0/586) vs 0.3%(2/593) Benign neoplasms of the thyroid gland: 0.3%(2/586) vs 0.2%(1/593) Deaths: 0.2%(1/586) vs 0.2%(1/593) GI disorders: 28.7%(168/586) vs 27.7%(164/593) Infections - bronchitis: 3.6%(21/586) vs 3.2%(19/593) Infections - influenza: 7.2%(42/586) vs 6.9%(41/593) Infections - nasopharyngitis: 7.3%(43/586) vs 7.6%(45/593) Infections - serious: 1.0%(6/586) vs 1.5%(9/593) Infections - serious abscessed limb: 0.2%(1/586) vs 0.0%(0/593) Infections - serious diverticulitis: 0.0%(0/586) vs 0.5%(3/593) Infections - serious ear infection: 0.0%(0/586) vs 0.2%(1/593) Infections - serious infected cyst: 0.2%(1/586) vs 0.0%(0/593) Infections - serious localized infection (finger): 0.0%(0/586) vs 0.2%(1/593) Infections - serious pneumonia: 0.5%(3/586) vs 0.2%(1/593) Infections - serious pseudomembranous colitis: 0.0%(0/586) vs 0.2%(1/593) Infections - serious pyelonephritis: 0.0%(0/586) vs 0.2%(1/593) Infections - serious sepsis: 0.0%(0/586) vs 0.2%(1/593) Infections - serious upper respiratory tract infection: 0.2%(1/586) vs 0.0%(0/593) Infections - serious urosepsis: 0.0%(0/586) vs 0.2%(1/593) Infections - upper respiratory tract infection: 4.4%(26/586) vs 6.1%(36/593) Infections - urinary tract infection: 2.9%(17/586) vs 3.0%(18/593) Malignant neoplasm - serious breast cancer: 0.2%(1/586) vs 0.3%(2/593) Malignant neoplasm - serious gastric cancer: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious metastases to liver: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious metastatic neoplasm: 0.2%(1/586) vs 0.0%(0/593) Malignant neoplasm - serious mycosis fungoides: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious ovarian cancer recurrent: 0.2%(1/586) vs 0.0%(0/593) Malignant neoplasm - serious renal cell carcinoma stage unspecified: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious small cell lung cancer metastatic: 0.2%(1/586) vs 0.0%(0/593) Malignant neoplasm - serious squamous cell carcinoma: 0.0%(0/586) vs 0.2%(1/593) Malignant neoplasm - serious vaginal cancer: 0.2%(1/586) vs 0.0%(0/593) Neoplasms (benign or malignant): 2.6%(15/586) vs 3.5%(21/593) Withdrawals: due to all AE: 1.7%(10/586) vs 1.3%(8/593) Withdrawals: total: 9.2%(54/586) vs 6.1%(36/593)

Evidence Table C-5. Adverse Events

Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Kendler et al., 2009[516] Alendronate (Fosamax), Denosumab Trial: STAND	Alendronate 70 mg weekly + Calcium 1000 mg + Vitamin D 400 IU vs Subcutaneous denosumab 60 mg/6 months + Calcium 1000 mg + Vitamin D 400 IU: Any adverse event: 78.7%(196/249) vs 77.9%(197/253) Arthralgia: 10.4%(26/249) vs 5.9%(15/253) Back pain: 11.6%(29/249) vs 10.7%(27/253) Bronchitis: 5.6%(14/249) vs 6.3%(16/253) Clinical fractures: 1.6%(4/249) vs 3.2%(8/253) Constipation: 4.8%(12/249) vs 5.1%(13/253) Death: 0.0%(0/249) vs 0.4%(1/253) GI disorder: 24.1%(60/249) vs 22.9%(58/253) Infections: 37.3%(93/249) vs 43.9%(111/253) Nasopharyngitis: 10.8%(27/249) vs 13.4%(34/253) Neoplasms (benign or malignant): 3.6%(9/249) vs 3.6%(9/253) Pain in an extremity: 8.4%(21/249) vs 4.7%(12/253) Serious adverse event: 6.4%(16/249) vs 5.9%(15/253) Serious infection: 1.2%(3/249) vs 0.4%(1/253) Serious neoplasms (benign or malignant): 1.2%(3/249) vs 1.2%(3/253) Withdrawals: total: 4.4%(11/249) vs 4.0%(10/253)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Miller et al., 2008[517] Alendronate (Fosamax), Denosumab	Alendronate + Calcium 1000mg/day + Vitamin D 400 IU/day vs Denosumab + Calcium 1000mg/day + Vitamin D 400 IU/day vs Placebo + Calcium 1000mg/day + Vitamin D 400 IU/day: Any adverse event: 95.7%(44/46) vs 93.3%(293/314) vs 93.5%(43/46) Adverse event requiring hospitalization: 0.0%(0/46) vs 3.2%(10/314) vs 0.0%(0/46) Anemia: 13.0%(6/46) vs 1.6%(5/314) vs 2.2%(1/46) Arthralgia: 17.4%(8/46) vs 23.6%(74/314) vs 30.4%(14/46) Back pain: 15.2%(7/46) vs 20.1%(63/314) vs 13.0%(6/46) Bronchitis: 8.7%(4/46) vs 8.3%(26/314) vs 10.9%(5/46) Constipation: 13.0%(6/46) vs 6.4%(20/314) vs 2.2%(1/46) Death due to Adenocarcinoma: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46) Death due to Brain neoplasm: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46) Death due to Cerebral vascular accident: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46) Death due to gastric cancer: 0.0%(0/46) vs 0.3%(1/314) vs 0.0%(0/46) Development of neutralizing antibodies to denosumab: 0.0%(0/46) vs 0.0%(0/314) vs 0.0%(0/46) Diarrhea: 8.7%(4/46) vs 8.9%(28/314) vs 13.0%(6/46) Dyspepsia: 26.1%(12/46) vs 12.4%(39/314) vs 6.5%(3/46) Gastroesophageal reflux disease: 15.2%(7/46) vs 12.7%(40/314) vs 4.3%(2/46) Headache: 10.9%(5/46) vs 12.1%(38/314) vs 17.4%(8/46) Hypertension: 10.9%(5/46) vs 15.3%(48/314) vs 4.3%(2/46) Infections: 69.6%(32/46) vs 66.2%(208/314) vs 67.4%(31/46) Influenza-like illness: 15.2%(7/46) vs 13.1%(41/314) vs 10.9%(5/46) Muscle spasms: 10.9%(5/46) vs 10.2%(32/314) vs 15.2%(7/46) Nasopharyngitis: 13.0%(6/46) vs 19.1%(60/314) vs 15.2%(7/46) Nausea: 21.7%(10/46) vs 12.1%(38/314) vs 4.3%(2/46) Osteoarthritis: 13.0%(6/46) vs 4.1%(13/314) vs 8.7%(4/46) Pain in extremity: 15.2%(7/46) vs 17.5%(55/314) vs 17.4%(8/46) Peripheral edema: 6.5%(3/46) vs 4.8%(15/314) vs 10.9%(5/46) Serious Infections: 0.0%(0/46) vs 3.2%(10/314) vs 0.0%(0/46) Serious adverse events: 17.4%(8/46) vs 17.8%(56/314) vs 10.9%(5/46) Shoulder pain: 8.7%(4/46) vs 9.6%(30/314) vs 15.2%(7/46) Sinusitis: 13.0%(6/46) vs 11.8%(37/314) vs 19.6%(9/46) Symptomatic hypocalcemia: 0.0%(0/46) vs 0.0%(0/314) vs 0.0%(0/46) Upper respiratory tract infection: 30.4%(14/46) vs 28.0%(88/314) vs 23.9%(11/46) Urinary tract infection: 13.0%(6/46) vs 13.1%(41/314) vs 4.3%(2/46) Withdrawals: 37.0%(17/46) vs 36.9%(116/314) vs 37.0%(17/46)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Tseng et al., 2006[265] Alendronate (Fosamax), Estrogen	Alendronate 10 mg + Equine estrogen .625 mg + Medroxyprogesterone 5 mg + Calcium carbonate 500 mg/d vs Placebo + Equine estrogen .625 mg + Medroxyprogesterone 5 mg + Calcium carbonate 500 mg/d: Back pain: 1.3%(1/79) vs 1.4%(1/72) Epigastralgia: 1.3%(1/79) vs 0.0%(0/72) Epigastric discomfort: 0.0%(0/79) vs 2.8%(2/72) Esophageal irritation: 2.5%(2/79) vs 0.0%(0/72) General discomfort: 0.0%(0/79) vs 1.4%(1/72) Hemoptysis: 0.0%(0/79) vs 1.4%(1/72) Intolerance to menopausal hormone therapy: 2.5%(2/79) vs 1.4%(1/72) Light stroke: 0.0%(0/79) vs 1.4%(1/72) Withdrawals: 36.7%(29/79) vs 38.9%(28/72) Withdrawals due to adverse events: 7.6%(6/79) vs 9.7%(7/72)
Saag et al., 2009[224] Alendronate (Fosamax), PTH (Teriparatide) (Forteo)	Alendronate 10 mg/day + Calcium + Vitamin D vs Teriparatide 20 ug/day + Calcium + Vitamin D: Any adverse event: 86.0%(184/214) vs 90.7%(194/214) Anemia: 7.9%(17/214) vs 5.1%(11/214) Any serious adverse event: 29.9%(64/214) vs 32.7%(70/214) Death: 7.0%(15/214) vs 4.2%(9/214) Dyspepsia: 7.0%(15/214) vs 4.2%(9/214) Dyspnea: 2.8%(6/214) vs 7.5%(16/214) Fatigue: 1.9%(4/214) vs 4.2%(9/214) Gastritis: 3.7%(8/214) vs 7.9%(17/214) Headache: 6.5%(14/214) vs 8.9%(19/214) Influenza: 11.2%(24/214) vs 8.4%(18/214) Insomnia: 1.4%(3/214) vs 5.6%(12/214) Joint injury: 2.8%(6/214) vs 0.5%(1/214) Nasopharyngitis: 6.1%(13/214) vs 3.3%(7/214) Nausea: 8.4%(18/214) vs 16.8%(36/214) Rash: 4.7%(10/214) vs 1.9%(4/214) Urinary tract infection: 13.6%(29/214) vs 10.3%(22/214) Viral infection: 0.0%(0/214) vs 2.3%(5/214) Weight loss: 4.2%(9/214) vs 0.0%(0/214) Withdrawals: 44.9%(96/214) vs 42.5%(91/214)
Antoniucci et al., 2007[518] Alendronate (Fosamax), PTH184 (Preos) Trial: PATH	PTH 100 ug/d alone vs PTH 100 ug/d +alendronate 10 mg/d: AE other than hypercalciuria: 1.7%(2/119) vs 3.4%(2/59) Concurrent serum and urinary calcium elevations: 1.7%(2/119) vs 0.0%(0/59) Hypercalcemia: 13.4%(16/119) vs 15.3%(9/59) Hypercalciuria: 8.4%(10/119) vs 11.9%(7/59)

Author, Year, Drug, Trial name	Adverse events reported
Huang et al., 2009[519] Alendronate (Fosamax), Raloxifene (Evista)	Alendronate 10 mg/day OR 70 mg/weekly vs Raloxifene 60 mg: Acute myocardial infarction: 5.8%(1,216/21,037) vs 4.7%(294/6,220) Atrial fibrillation: 3.2%(663/21,037) vs 2.5%(158/6,220)
Sanad et al., 2011[409] Alendronate (Fosamax), Raloxifene (Evista)	Alendronate vs Raloxifene: Chest pain: 6.8%(3/44) vs 2.2%(1/46) Constipation: 2.3%(1/44) vs 0.0%(0/46) Deep vein thrombosis: 0.0%(0/44) vs 2.2%(1/46) Diarrhea: 2.3%(1/44) vs 2.2%(1/46) Epigastric pain: 6.8%(3/44) vs 4.3%(2/46) Heartburn: 6.8%(3/44) vs 2.2%(1/46) Hot flashes: 6.8%(3/44) vs 8.7%(4/46) Sweating: 4.5%(2/44) vs 4.3%(2/46) Urticaria: 0.0%(0/44) vs 2.2%(1/46)
Binkley et al., 2009[264] Alendronate (Fosamax), Vitamin D	Alendronate 70 mg +Vitamin D 2800 IU vs Alendronate 70 mg +Vitamin D 5600 IU: Clinical AE: with ≥1 AE: 51.5%(168/326) vs 47.2%(154/326) Clinical AE: with drug related AE: 4.0%(13/326) vs 5.2%(17/326) Clinical AE: with serious AE: 4.0%(13/326) vs 4.9%(16/326) Clinical AE: with serious drug related AE: 0.3%(1/326) vs 0.0%(0/326) Death (due to cerebellar hemorrhage): 0.3%(1/326) vs 0.0%(0/326) Lab AE: with ≥1 AE: 8.3%(27/326) vs 7.7%(25/326) Lab AE: with drug related AE: 0.3%(1/326) vs 2.8%(9/326) Lab AE: with serious AE: 0.0%(0/326) vs 0.0%(0/326) Lab AE: with serious drug related AE: 0.0%(0/326) vs 0.0%(0/326) Withdrawals: 2.8%(9/326) vs 4.6%(15/326)
Ringe et al., 2007[56] Alendronate (Fosamax), Vitamin D Trial: AAC TRIAE	Alendronate 70 mg/week + Calcium 1000 mg/day + Vitamin D 1,000 IU/day vs Alfacalcidol 1 ug/day + Alendronate 70 mg/week + Calcium 500 mg/day vs Alfacalcidol 1 ug/day + Vitamin D 1,000 IU/day: Arthralgia: 3.3%(1/30) vs 0.0%(0/30) vs 0.0%(0/30) Back pain: 70.0%(21/30) vs 20.0%(6/30) vs 56.7%(17/30) Bone pain: 0.0%(0/30) vs 0.0%(0/30) vs 3.3%(1/30) Epigastric pain: 6.7%(2/30) vs 3.3%(1/30) vs 0.0%(0/30) Headache: 0.0%(0/30) vs 0.0%(0/30) vs 6.7%(2/30) Heartburn: 3.3%(1/30) vs 0.0%(0/30) vs 0.0%(0/30) Hypercalcemia: 0.0%(0/30) vs 0.0%(0/30) vs 0.0%(0/30) Hypercalciuria: 0.0%(0/30) vs 3.3%(1/30) vs 13.3%(4/30) Meteoric: 0.0%(0/30) vs 0.0%(0/30) vs 3.3%(1/30) Nausea: 0.0%(0/30) vs 3.3%(1/30) vs 0.0%(0/30) Obstipation: 6.7%(2/30) vs 6.7%(2/30) vs 6.7%(2/30) Soft bowels: 3.3%(1/30) vs 0.0%(0/30) vs 0.0%(0/30) Withdrawals due to adverse events: 0.0%(0/30) vs 0.0%(0/30) vs 0.0%(0/30)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
de Nijs et al., 2006[57] Alendronate (Fosamax), Vitamin D Trial: STOP	Alendronate 10 mg + Elemental Calcium 500 mg + Vitamin D 400 IU vs Placebo (alfacalcidol) + Elemental Calcium 500 mg + Vitamin D 400 IU: Abdominal pain: 5.0%(5/100) vs 4.0%(4/101) Adverse events: 68.0%(68/100) vs 66.3%(67/101) Adverse events related to the study: 21.0%(21/100) vs 13.9%(14/101) Death: 2.0%(2/100) vs 1.0%(1/101) Death: Perforated sigmoid colon due to diverticulitis: 1.0%(1/100) vs 0.0%(0/101) Death: cerebrovascular accident: 0.0%(0/100) vs 1.0%(1/101) Death: non-Hodgkin's lymphoma: 1.0%(1/100) vs 0.0%(0/101) Death: stroke: 0.0%(0/100) vs 1.0%(1/101) Diarrhea: 3.0%(3/100) vs 6.9%(7/101) Dyspepsia: 7.0%(7/100) vs 7.9%(8/101) Gastrointestinal adverse event: 35.0%(35/100) vs 51.5%(52/101) Headache: 7.0%(7/100) vs 7.9%(8/101) Hypercalcemia (calcium > 10.8 mg/dl): 3.0%(3/100) vs 6.9%(7/101) Hypocalcemia (calcium <8.8 mg/dl): 36.0%(36/100) vs 20.8%(21/101) Increase in creatinine (>.2 mg/dl): 8.0%(8/100) vs 15.8%(16/101) Laboratory Adverse events: 47.0%(47/100) vs 43.6%(44/101) Nausea: 2.0%(2/100) vs 7.9%(8/101) Other adverse events: 18.0%(18/100) vs 16.8%(17/101) Other symptoms: 18.0%(18/100) vs 24.8%(25/101) Skin disorder: 11.0%(11/100) vs 8.9%(9/101) Withdrawals: 21.0%(21/100) vs 16.8%(17/101) Withdrawals due to adverse events: 6.0%(6/100) vs 6.9%(7/101)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
Obermayer-Pietsch et al., 2008[520] Bisphosphonates, PTH (Teriparatide) (Forteo) Trial: EUROFORS	Teriparatide 20 ug/day + Calcium 500 mg/day + Vitamin D 400-800 IU/day: Any adverse event: 78.2%(394/504) Abdominal pain upper: 3.8%(19/504) Any serious adverse event: 17.5%(88/504) Arthralgia: 11.7%(59/504) Back pain: 5.2%(26/504) Bronchitis: 4.6%(23/504) Constipation: 4.2%(21/504) Contusion: 3.0%(15/504) Depression: 3.0%(15/504) Diarrhea: 6.2%(31/504) Dizziness: 5.0%(25/504) Dyspepsia: 3.0%(15/504) Edema peripheral: 3.0%(15/504) Headache: 6.9%(35/504) Hypercalcemia: 5.0%(25/504) Hypertension: 8.9%(45/504) Influenza: 4.0%(20/504) Muscle cramp: 6.2%(31/504) Nasopharyngitis: 6.3%(32/504) Nausea: 12.5%(63/504) Pain in extremity: 7.3%(37/504) Urinary tract infection: 3.4%(17/504) Withdrawals: 5.6%(28/504) Withdrawals due to adverse events: 1.2%(6/504)
Kim et al., 2010[432] Bisphosphonates, Raloxifene (Evista)	Bisphosphonates vs Raloxifene: Diaphyseal femur fracture: 0.1%(24/17,028) vs 0.1%(13/16,787) Subtrochanteric femur fracture: 0.2%(36/17,028) vs 0.2%(34/16,787)
Sato et al., 2007[72] Vitamin D, Risedronate (Actonel)	Placebo + Vitamin D2 vs Risedronate 2.5mg + Vitamin D2: Abdominal pain: 2.5%(3/121) vs 3.3%(4/121) Death or intercurrent illness: 3.3%(4/121) vs 3.3%(4/121) Esophagitis: 0.0%(0/121) vs 2.5%(3/121) Withdrawals: 7.4%(9/121) vs 8.3%(10/121)

Evidence Table C-5. Adverse Events
Bisphosphonates

Author, Year, Drug, Trial name	Adverse events reported
McComsey et al., 2007[521] Alendronate (Fosamax), Calcium, Vitamin D	Alendronate 70 mg weekly + Calcium carbonate 500 mg/2x day + Vitamin D 200 IU/2x day vs Placebo + Calcium carbonate 500 mg/2x day + Vitamin D 200 IU/2x day: Any adverse event: 69.0%(29/42) vs 57.5%(23/40) Abdominal pain: 0.0%(0/42) vs 2.5%(1/40) Cardiovascular system event: 2.4%(1/42) vs 10.0%(4/40) Chemistry abnormalities: 14.3%(6/42) vs 17.5%(7/40) Dyspepsia: 2.4%(1/42) vs 0.0%(0/40) Dysphagia: 2.4%(1/42) vs 0.0%(0/40) Endocrinology system event: 7.1%(3/42) vs 5.0%(2/40) GI event: 4.8%(2/42) vs 10.0%(4/40) General body event: 14.3%(6/42) vs 17.5%(7/40) Grade 3+ lab toxicities: 16.7%(7/42) vs 15.0%(6/40) Grade 3+ signs/symptoms: 0.0%(0/42) vs 15.0%(6/40) Hematological system event: 2.4%(1/42) vs 2.5%(1/40) Hepatic system event: 35.7%(15/42) vs 30.0%(12/40) Metabolic event: 11.9%(5/42) vs 10.0%(4/40) Neurological system event: 4.8%(2/42) vs 10.0%(4/40) Pain and burning in mouth: 2.4%(1/42) vs 0.0%(0/40) Pancreatic event: 7.1%(3/42) vs 7.5%(3/40) Renal event: 2.4%(1/42) vs 2.5%(1/40) Respiratory system event: 4.8%(2/42) vs 7.5%(3/40) Retrosternal pain: 0.0%(0/42) vs 2.5%(1/40) Serious adverse event: 19.0%(8/42) vs 35.0%(14/40) Skin event: 2.4%(1/42) vs 5.0%(2/40) Stomatitis: 2.4%(1/42) vs 0.0%(0/40) Swelling and pain in tongue: 2.4%(1/42) vs 0.0%(0/40) Urogenital system event: 0.0%(0/42) vs 5.0%(2/40) Withdrawals: 7.1%(3/42) vs 7.5%(3/40)

Author, Year, Drug, Trial name	Adverse events reported
Vestergaard et al., 2010[522] Alendronate (Fosamax), Etidronate (Didronel), Ibandronate (Boniva), Pamidronate (Aredia) (APD), PTH (Teriparatide) (Forteo), Raloxifene (Evista), Risedronate (Actonel)	Alendronate vs Clodronate vs Ibandronate vs Raloxifene vs Risedronate vs Teriparatide vs Zoledronic acid: Atrial fibrillation: 1.3%(729/55,090) vs 2.1%(12/566) vs 0.0%(0/612) vs 1.1%(55/4,831) vs 0.0%(0/1,452) vs 0.0%(0/303) vs 0.0%(0/22)
Vestergaard et al., 2009[523] Alendronate (Fosamax), Etidronate (Didronel), Ibandronate (Boniva), Pamidronate (Aredia) (APD), PTH184 (Preos), Raloxifene (Evista), Risedronate (Actonel), Strontium	Alendronate vs Clodronate vs Ibandronate vs Raloxifene vs Risedronate vs Zoledronic acid vs Control: Deep venous thromboembolism or pulmonary embolism: 0.4%(200/55,090) vs 1.6%(9/566) vs 0.0%(0/612) vs 0.5%(24/4,831) vs 0.0%(0/1,452) vs 0.0%(0/22) vs 0.5%(1,528/310,683)

Author, Year, Drug, Trial name	Adverse events reported
Gorai et al., 2009[270] Raloxifene (Evista)	Alfacalcidol 1 ug/d vs Alfacalcidol 1 ug/d +Raloxifene 60 mg/d vs Raloxifene 60 mg/d: Alopecia areata: 0.0%(0/44) vs 0.0%(0/48) vs 2.2%(1/45) Angina attack: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Calcaneodynia: 2.3%(1/44) vs 0.0%(0/48) vs 0.0%(0/45) Cramp of limb: 0.0%(0/44) vs 0.0%(0/48) vs 4.4%(2/45) Diaphoresis: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Digestive symptom (nausea, gastralgia): 0.0%(0/44) vs 6.3%(3/48) vs 2.2%(1/45) Diverticula of the colon (abdominal pain lower): 2.3%(1/44) vs 0.0%(0/48) vs 0.0%(0/45) Dizziness: 2.3%(1/44) vs 0.0%(0/48) vs 2.2%(1/45) Gallstones: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Headache: 2.3%(1/44) vs 0.0%(0/48) vs 2.2%(1/45) Hepatic function disorder: 0.0%(0/44) vs 2.1%(1/48) vs 2.2%(1/45) Hot flash: 2.3%(1/44) vs 0.0%(0/48) vs 2.2%(1/45) Hypercalciuria: 9.1%(4/44) vs 0.0%(0/48) vs 0.0%(0/45) Itching Paresthesia: 0.0%(0/44) vs 0.0%(0/48) vs 6.7%(3/45) Knee pain: 2.3%(1/44) vs 0.0%(0/48) vs 0.0%(0/45) Leg cramp: 0.0%(0/44) vs 4.2%(2/48) vs 4.4%(2/45) Leg edema: 0.0%(0/44) vs 0.0%(0/48) vs 2.2%(1/45) Myalgia: 2.3%(1/44) vs 0.0%(0/48) vs 2.2%(1/45) Numbness of lower extremities: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Sweaty: 0.0%(0/44) vs 0.0%(0/48) vs 2.2%(1/45) Symptoms of menopause: 0.0%(0/44) vs 4.2%(2/48) vs 0.0%(0/45) Thoracic pain: 0.0%(0/44) vs 2.1%(1/48) vs 0.0%(0/45) Weigh increased: 0.0%(0/44) vs 0.0%(0/48) vs 2.2%(1/45) Withdrawals: due to AE: 11.4%(5/44) vs 12.5%(6/48) vs 15.6%(7/45)

Author, Year, Drug, Trial name	Adverse events reported
Miller et al., 2008[444] Raloxifene (Evista)	Bazedoxifene 10mg vs Bazedoxifene 20mg vs Bazedoxifene 40mg vs Raloxifene 60 mg/d vs Placebo: AEs: any: 95.3%(306/321) vs 96.0%(309/322) vs 94.4%(301/319) vs 92.3%(287/311) vs 95.8%(297/310) AEs: any serious AE: 9.0%(29/321) vs 11.5%(37/322) vs 10.3%(33/319) vs 9.3%(29/311) vs 9.0%(28/310) AEs: any treatment emergent AE: 93.1%(299/321) vs 94.4%(304/322) vs 91.5%(292/319) vs 89.7%(279/311) vs 93.2%(289/310) Breast cancer: 0.3%(1/321) vs 0.6%(2/322) vs 0.0%(0/319) vs 0.3%(1/311) vs 0.6%(2/310) Cerebral hemorrhage: 0.3%(1/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.0%(0/311) vs 0.0%(0/310) Cerebral ischemia: 0.0%(0/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.3%(1/311) vs 0.0%(0/310) Cerebrovascular accident: 0.0%(0/321) vs 0.0%(0/322) vs 0.3%(1/319) vs 0.0%(0/311) vs 0.0%(0/310) Deaths: 0.6%(2/321) vs 0.0%(0/322) vs 0.9%(3/319) vs 0.0%(0/311) vs 0.3%(1/310) Deep venous thrombosis: 0.0%(0/321) vs 0.6%(2/322) vs 0.0%(0/319) vs 0.0%(0/311) vs 0.3%(1/310) Endometrial cancer: 0.0%(0/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.0%(0/311) vs 0.3%(1/310) Endometrial hyperplasia: 0.0%(0/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.0%(0/311) vs 0.0%(0/310) Hot flushes: 19.6%(63/321) vs 20.8%(67/322) vs 24.1%(77/319) vs 18.6%(58/311) vs 14.2%(44/310) Leg cramps: 9.3%(30/321) vs 12.1%(39/322) vs 11.9%(38/319) vs 11.9%(37/311) vs 11.6%(36/310) Myocardial infarction: 0.0%(0/321) vs 0.6%(2/322) vs 0.3%(1/319) vs 0.0%(0/311) vs 0.3%(1/310) Phlebitis (superficial): 0.3%(1/321) vs 0.3%(1/322) vs 0.9%(3/319) vs 0.0%(0/311) vs 0.3%(1/310) Pulmonary embolus: 0.0%(0/321) vs 0.0%(0/322) vs 0.3%(1/319) vs 0.0%(0/311) vs 0.0%(0/310) Retinal vein thrombosis: 0.0%(0/321) vs 0.0%(0/322) vs 0.0%(0/319) vs 0.3%(1/311) vs 0.0%(0/310) Withdrawals: due to AE: 16.2%(52/321) vs 17.1%(55/322) vs 17.9%(57/319) vs 13.8%(43/311) vs 15.2%(47/310) Withdrawals: total: 32.1%(103/321) vs 30.4%(98/322) vs 30.4%(97/319) vs 28.0%(87/311) vs 27.4%(85/310)
Mok et al., 2010[456] Raloxifene (Evista)	Raloxifene vs Placebo: Aching: 1.8%(1/57) vs 0.0%(0/57) Atypical chest pain: 0.0%(0/57) vs 7.0%(4/57) Depression: 0.0%(0/57) vs 3.5%(2/57) Dizziness/vertigo: 5.3%(3/57) vs 1.8%(1/57) Duodenal ulcer: 0.0%(0/57) vs 1.8%(1/57) Dyspepsia/heartburn: 5.3%(3/57) vs 8.8%(5/57) Flushing: 0.0%(0/57) vs 1.8%(1/57) Headache: 1.8%(1/57) vs 1.8%(1/57) Leg cramps: 7.0%(4/57) vs 0.0%(0/57) Skin rash: 1.8%(1/57) vs 1.8%(1/57) Tinnitus: 1.8%(1/57) vs 0.0%(0/57)

Author, Year, Drug, Trial name	Adverse events reported
Mosca et al., 2009[443] Raloxifene (Evista)	Raloxifene 60 mg/d vs Placebo: Atrial fibrillation: 6.4%(323/5,044) vs 6.6%(334/5,057) Deaths: VTE: 0.2%(10/5,044) vs 0.1%(5/5,057) Deaths: all cardiovascular deaths: 7.2%(362/5,044) vs 7.0%(355/5,057) Deaths: cerebrovascular (stroke): 1.2%(59/5,044) vs 0.8%(39/5,057) Deaths: hemorrhagic: 0.2%(10/5,044) vs 0.2%(12/5,057) Deaths: ischemic: 0.6%(29/5,044) vs 0.3%(16/5,057) Deaths: noncoronary deaths: 2.1%(107/5,044) vs 1.6%(81/5,057) Deaths: stroke undetermined: 0.4%(19/5,044) vs 0.2%(11/5,057) Stroke: Hemorrhagic: 0.4%(18/5,044) vs 0.6%(30/5,057) Stroke: Ischemic: 3.9%(198/5,044) vs 3.4%(171/5,057) Stroke: Undetermined: 0.8%(39/5,044) vs 0.6%(30/5,057) Stroke: all: 4.9%(249/5,044) vs 4.4%(224/5,057) Transient ischemic attacks: 1.7%(86/5,044) vs 1.8%(91/5,057) VTE event: all: 2.0%(103/5,044) vs 1.4%(71/5,057) VTE event: deep vein thrombosis: 1.3%(65/5,044) vs 0.9%(47/5,057) VTE event: intracranial (retinal vein) thrombosis: 0.2%(8/5,044) vs 0.1%(6/5,057) VTE event: other: 0.0%(2/5,044) vs 0.0%(1/5,057) VTE event: pulmonary embolism: 0.7%(36/5,044) vs 0.5%(24/5,057)
Silverman et al., 2008[121] Raloxifene (Evista), Bazedoxifene	Bazedoxifene 20mg vs Bazedoxifene 40mg vs Raloxifene 60mg vs Placebo: AEs: any AE: 95.8%(1,806/1,886) vs 95.7%(1,792/1,872) vs 96.0%(1,775/1,849) vs 96.2%(1,813/1,885) AEs: any serious AE: 20.3%(382/1,886) vs 19.7%(368/1,872) vs 18.6%(344/1,849) vs 18.7%(353/1,885) Breast carcinoma: 0.3%(5/1,886) vs 0.2%(4/1,872) vs 0.4%(7/1,849) vs 0.4%(8/1,885) Breast cyst/fibrocystic breast disease: 0.7%(13/1,886) vs 0.6%(12/1,872) vs 1.7%(31/1,849) vs 1.0%(18/1,885) Deaths: 0.9%(17/1,886) vs 0.7%(13/1,872) vs 1.0%(19/1,849) vs 0.6%(11/1,885) Deep vein thrombosis: 0.4%(8/1,886) vs 0.5%(10/1,872) vs 0.4%(8/1,849) vs 0.1%(1/1,885) Endometrial carcinoma: 0.0%(0/1,886) vs 0.1%(2/1,872) vs 0.1%(2/1,849) vs 0.2%(3/1,885) Endometrial hyperplasia: 0.1%(1/1,886) vs 0.1%(1/1,872) vs 0.1%(1/1,849) vs 0.1%(1/1,885) Hemorrhagic stroke: 0.1%(1/1,886) vs 0.1%(1/1,872) vs 0.1%(2/1,849) vs 0.3%(5/1,885) Indeterminate: 0.4%(7/1,886) vs 0.2%(3/1,872) vs 0.2%(4/1,849) vs 0.2%(4/1,885) Ischemic stroke: 0.6%(11/1,886) vs 0.8%(15/1,872) vs 0.5%(9/1,849) vs 0.6%(11/1,885) Leg cramps: 10.9%(205/1,886) vs 10.9%(204/1,872) vs 11.7%(216/1,849) vs 8.2%(155/1,885) Myocardial infarction: 0.4%(8/1,886) vs 0.4%(8/1,872) vs 0.3%(6/1,849) vs 0.4%(8/1,885) Pulmonary embolus: 0.3%(5/1,886) vs 0.2%(3/1,872) vs 0.2%(4/1,849) vs 0.2%(4/1,885) Retinal vein thrombosis: 0.1%(2/1,886) vs 0.1%(1/1,872) vs 0.0%(0/1,849) vs 0.2%(3/1,885) Strokes: total: 1.0%(19/1,886) vs 1.0%(19/1,872) vs 0.8%(15/1,849) vs 1.1%(20/1,885) Vasodilatation: 12.6%(238/1,886) vs 13.0%(243/1,872) vs 12.0%(222/1,849) vs 6.3%(118/1,885) Venous thromboembolic events: 0.7%(13/1,886) vs 0.6%(12/1,872) vs 0.5%(10/1,849) vs 0.3%(5/1,885) Withdrawals: due to AE: 14.3%(269/1,886) vs 14.4%(270/1,872) vs 14.2%(262/1,849) vs 12.7%(240/1,885) Withdrawals: total: 33.5%(632/1,886) vs 34.3%(643/1,872) vs 32.3%(597/1,849) vs 33.4%(629/1,885)

Evidence Table C-5. Adverse Events
SERMs

Author, Year, Drug, Trial name	Adverse events reported
Pelayo et al., 2008[524] Calcium, Raloxifene (Evista)	Raloxifene (60 mg/d) +CC (600 mg/d) vs Raloxifene (60 mg/d) +OHC (712 mg/d): Constipation: 0.0%(0/42) vs 4.2%(2/48) Hot flashes: 7.1%(3/42) vs 8.3%(4/48) Mild leg swelling: 2.4%(1/42) vs 4.2%(2/48) Nephrolithiasis: 0.0%(0/42) vs 2.1%(1/48) Nonspecific GI problems: 7.1%(3/42) vs 6.3%(3/48) Withdrawals due to adverse events: 9.5%(4/42) vs 14.6%(7/48) Withdrawals: total: 11.9%(5/42) vs 16.7%(8/48)
Anastasilakis et al., 2008[266] PTH (Teriparatide) (Forteo), Raloxifene (Evista)	Risedronate 35 mg/wk vs Teriparatide 20 ug/d: Total number of any AE: 31.8%(7/22) vs 50.0%(11/22) Bone pain: 4.5%(1/22) vs 13.6%(3/22) Dizziness: 0.0%(0/22) vs 9.1%(2/22) Epigastric pain: 9.1%(2/22) vs 0.0%(0/22) Flushes: 0.0%(0/22) vs 4.5%(1/22) Hypercalcaemia: 4.5%(1/22) vs 9.1%(2/22) Nausea: 0.0%(0/22) vs 9.1%(2/22) Renal colic: 0.0%(0/22) vs 4.5%(1/22) Substernal burn: 13.6%(3/22) vs 0.0%(0/22)

Evidence Table C-5. Adverse Events
Parathyroid hormone

Author, Year, Drug, Trial name	Adverse events reported
Miller et al., 2007[460] PTH (Teriparatide) (Forteo) Trial: TPTD Study A	Teriparatide 20ug/d vs Teriparatide 40ug/d vs Placebo: Hematuria: 0.8%(4/527) vs 0.7%(4/541) vs 1.1%(6/536) Hypercalcemia at 4-h after a dose: 2.1%(11/527) vs 5.2%(28/541) vs 0.4%(2/536) Hypercalciuria: 12.0%(63/527) vs 7.0%(38/541) vs 10.1%(54/536) Kidney calculus: 0.4%(2/527) vs 0.0%(0/541) vs 0.4%(2/536) Kidney pain: 0.6%(3/527) vs 0.2%(1/541) vs 0.0%(0/536) Normal urinary calcium excretion and hypercalcemia: 0.9%(5/527) Predose (>16 h after injection) hypercalcemia: 0.2%(1/527) vs 0.0%(0/541) vs 0.2%(1/536) Urinary tract calcifications: 0.2%(1/527) vs 0.2%(1/541) vs 0.0%(0/536) Urolithiasis: 1.1%(6/527) vs 0.4%(2/541) vs 0.4%(2/536)
Miller et al., 2007[460] PTH (Teriparatide) (Forteo) Trial: TPTD Study B	Teriparatide 20ug/d vs Teriparatide 40ug/d vs Placebo: Hypercalciuria at 1 month: 18.6%(27/145) vs 19.7%(26/132) vs 15.6%(22/141) Kidney calculus: 1.4%(2/145) vs 0.8%(1/132) vs 0.7%(1/141) Kidney pain: 0.0%(0/145) vs 0.8%(1/132) vs 0.0%(0/141) Urolithiasis: 3.4%(5/145) vs 3.8%(5/132) vs 3.5%(5/141)
Recker et al., 2009[525] PTH (Teriparatide) (Forteo), Strontium ranelate	Teriparatide: ≥1 predose serum calcium level>2.75mM: 7.7%(3/39) AEs: ≥1 AE: 41.0%(16/39) AEs: serious AE: 2.6%(1/39) Above ULN in total alkaline phosphatase: 28.2%(11/39) Above ULN in uric acid: 30.8%(12/39) Cerebrovascular accident: 0.0%(0/39) Lymphoma: 0.0%(0/39) Parathyroid adenoma: 0.0%(0/39) Withdrawals: due to AE: 5.1%(2/39) Withdrawals: total: 15.4%(6/39)

Evidence Table C-5. Adverse Events

Denosumab

Author, Year, Drug, Trial name	Adverse events reported
Bone et al., 2008[117] Denosumab	Denosumab 60 mg/6 mos vs Placebo: Any AE: 94.0%(156/166) vs 94.6%(157/166) AE in >10% subjects: arthralgia: 24.7%(41/166) vs 25.3%(42/166) AE in >10% subjects: back pain: 19.9%(33/166) vs 19.9%(33/166) AE in >10% subjects: constipation: 10.8%(18/166) vs 4.8%(8/166) AE in >10% subjects: headache: 15.7%(26/166) vs 11.4%(19/166) AE in >10% subjects: influenza: 9.0%(15/166) vs 10.8%(18/166) AE in >10% subjects: nasopharyngitis: 21.7%(36/166) vs 18.7%(31/166) AE in >10% subjects: pain in extremity: 14.5%(24/166) vs 12.0%(20/166) AE in >10% subjects: pharyngolaryngeal pain (sore throat): 9.0%(15/166) vs 3.0%(5/166) AE in >10% subjects: rash: 8.4%(14/166) vs 3.0%(5/166) AE in >10% subjects: shoulder pain: 10.2%(17/166) vs 6.0%(10/166) AE in >10% subjects: sinusitis: 6.0%(10/166) vs 10.2%(17/166) AE in >10% subjects: upper respiratory tract infection: 11.4%(19/166) vs 13.3%(22/166) AE in >10% subjects: urinary tract infection: 10.8%(18/166) vs 10.2%(17/166) Deaths: 0.0%(0/166) vs 0.0%(0/166) Serious AE: gastrointestinal disorder: 1.2%(2/166) vs 0.0%(0/166) Serious AE: hepatobiliary disorder: 0.0%(0/166) vs 0.6%(1/166) Serious AE: infection: 4.8%(8/166) vs 0.6%(1/166) Serious AE: injury, poisoning, or procedural complication: 1.2%(2/166) vs 0.6%(1/166) Serious AE: musculoskeletal or connective tissue disorder: 1.8%(3/166) vs 1.2%(2/166) Serious AE: neoplasm - B cell lymphoma: 0.0%(0/166) vs 0.6%(1/166) Serious AE: neoplasm - breast cancer in situ: 0.6%(1/166) vs 0.0%(0/166) Serious AE: neoplasm - mycosis fungoides: 0.6%(1/166) vs 0.0%(0/166) Serious AE: neoplasm - ovarian cancer: 0.6%(1/166) vs 0.0%(0/166) Serious AE: neoplasm - uterine cancer: 0.6%(1/166) vs 0.0%(0/166) Serious AE: nervous system disorder: 0.0%(0/166) vs 0.6%(1/166) Serious AE: psychiatric disorder: 0.0%(0/166) vs 0.6%(1/166) Serious AE: reproductive system or breast disorder: 0.6%(1/166) vs 0.6%(1/166) Withdrawals: 6.0%(10/166) vs 9.0%(15/166) Withdrawals due to AE: 0.6%(1/166) vs 1.2%(2/166)

Evidence Table C-5. Adverse Events
Denosumab

Author, Year, Drug, Trial name	Adverse events reported
Cohen et al., 2008[526] Denosumab Trial: DENOSUMAB RA STUDY CORP	Denosumab 180 mg injections + Elemental Calcium 500-1000 mg + Vitamin D 400-800 IU vs Denosumab 60 mg injections + Elemental Calcium 500-1000 mg + Vitamin D 400-800 IU vs Subcutaneous placebo + Elemental Calcium 500-1000 mg + Vitamin D 400-800 IU: Any adverse event: 77.8%(56/72) vs 84.5%(60/71) vs 89.3%(67/75) Arthralgia: 5.6%(4/72) vs 8.5%(6/71) vs 2.7%(2/75) Bronchitis: 5.6%(4/72) vs 4.2%(3/71) vs 4.0%(3/75) Cough: 1.4%(1/72) vs 8.5%(6/71) vs 6.7%(5/75) Death: 0.0%(0/72) vs 0.0%(0/71) vs 0.0%(0/75) Infection requiring hospitalization: 2.8%(2/72) vs 1.4%(1/71) vs 1.3%(1/75) Influenza: 9.7%(7/72) vs 2.8%(2/71) vs 0.0%(0/75) Nasopharyngitis: 6.9%(5/72) vs 7.0%(5/71) vs 12.0%(9/75) Neoplasm: 1.4%(1/72) vs 1.4%(1/71) vs 2.7%(2/75) Rhematoid arthritis flare: 29.2%(21/72) vs 29.6%(21/71) vs 33.3%(25/75) Serious adverse event: 8.3%(6/72) vs 4.2%(3/71) vs 9.3%(7/75) Sinusitis: 11.1%(8/72) vs 5.6%(4/71) vs 10.7%(8/75) Upper respiratory tract infection: 12.5%(9/72) vs 15.5%(11/71) vs 8.0%(6/75) Urinary tract infection: 4.2%(3/72) vs 5.6%(4/71) vs 1.3%(1/75) Withdrawals due to adverse events: 1.4%(1/72) vs 0.0%(0/71) vs 1.3%(1/75)

Evidence Table C-5. Adverse Events
Denosumab

Author, Year, Drug, Trial name	Adverse events reported
Cummings et al., 2009[118] Denosumab Trial: FREEDOM	Denosumab 60 mg/6 mos vs Placebo: AEs: all: 92.8%(3,605/3,886) vs 93.1%(3,607/3,876) AEs: serious: 25.8%(1,004/3,886) vs 25.1%(972/3,876) Atrial fibrillation: 0.7%(29/3,886) vs 0.7%(29/3,876) Cancer: overall: 4.8%(187/3,886) vs 4.3%(166/3,876) Cancer: serious: 3.7%(144/3,886) vs 3.2%(125/3,876) Cardiovascular event: 4.8%(186/3,886) vs 4.6%(178/3,876) Cellulitis (including erysipelas): overall: 1.2%(47/3,886) vs 0.9%(36/3,876) Cellulitis (including erysipelas): serious: 0.3%(12/3,886) vs 0.0%(1/3,876) Concussion: 0.0%(1/3,886) vs 0.3%(11/3,876) Coronary heart disease: 1.2%(47/3,886) vs 1.0%(39/3,876) Deaths: 1.8%(70/3,886) vs 2.3%(90/3,876) Decrease in serum calcium to levels below 8mg: 0.1%(4/3,886) vs 0.1%(5/3,876) Delayed fracture healing: 0.1%(2/3,886) vs 0.1%(4/3,876) Development of neutralizing antibodies to denosumab: 0.0%(0/3,886) vs 0.0%(0/3,876) Eczema: 3.0%(118/3,886) vs 1.7%(65/3,876) Falling: 4.5%(175/3,886) vs 5.7%(219/3,876) Flatulence: 2.2%(84/3,886) vs 1.4%(53/3,876) Hypocalcemia: 0.0%(0/3,886) vs 0.1%(3/3,876) Infection: overall: 52.9%(2,055/3,886) vs 54.4%(2,108/3,876) Infection: serious: 4.1%(159/3,886) vs 3.4%(133/3,876) Local reactions: 0.8%(33/3,886) vs 0.7%(26/3,876) Opportunistic infections: 0.1%(4/3,886) vs 0.1%(3/3,876) Osteonecrosis of the jaw: 0.0%(0/3,886) vs 0.0%(0/3,876) Peripheral vascular disease: 0.8%(31/3,886) vs 0.8%(30/3,876) Stroke: 1.4%(56/3,886) vs 1.4%(54/3,876) Withdrawals: due to AE: 2.4%(93/3,886) vs 2.1%(81/3,876)

Author, Year, Drug, Trial name	Adverse events reported
Boone et al., 2006[136] Estrogen	17ß-estradiol (0.05 mg/d) then norethisterone acetate (0.24 mg/d) + 17ß-estradiol (0.05 mg/d)® vs Placebo: Withdrawals: total: 50.0%(8/16) vs 6.7%(1/15)

Evidence Table C-5. Adverse Events
Calcium/Vitamin D

Author, Year, Drug, Trial name	Adverse events reported
Bolland et al., 2008[469] Calcium	Calcium vs Placebo: Angina: 6.8%(50/732) vs 9.6%(71/739) Death: 4.6%(34/732) vs 3.9%(29/739) Myocardial infarction: 4.2%(31/732) vs 1.9%(14/739) Other chest pain: 2.2%(16/732) vs 2.0%(15/739) Stroke: 5.5%(40/732) vs 3.8%(28/739) Sudden death: 0.5%(4/732) vs 0.1%(1/739) Transient ischaemic attack: 4.5%(33/732) vs 2.8%(21/739)
Lewis et al., 2011[527] Calcium Trial: CAIFOS	Calcium vs Placebo: At least one vascular event: 13.2%(96/730) vs 14.0%(102/730) Deaths: Arrhythmia: 1.4%(10/730) vs 2.2%(16/730) Deaths: Cerebrovascular disease (excl. hemorrhage): 2.7%(20/730) vs 3.0%(22/730) Deaths: Heart failure: 1.9%(14/730) vs 3.7%(27/730) Deaths: Ischemic heart disease: 4.7%(34/730) vs 4.9%(36/730) Deaths: Peripheral arterial disease (excl. hemorrhage): 0.1%(1/730) vs 0.5%(4/730) Hospitalization: Arrhythmia: 5.3%(39/730) vs 5.5%(40/730) Hospitalization: Cerebrovascular disease (excl. hemorrhage): 6.2%(45/730) vs 7.8%(57/730) Hospitalization: Heart failure: 3.0%(22/730) vs 3.8%(28/730) Hospitalization: Ischemic heart disease: 11.6%(85/730) vs 11.6%(85/730) Hospitalization: Peripheral arterial disease (excl. hemorrhage): 2.6%(19/730) vs 2.5%(18/730) Total vascular deaths: 8.1%(59/730) vs 9.9%(72/730) Total vascular hospitalization: 21.9%(160/730) vs 23.2%(169/730)
Matsumoto et al., 2005[470] Vitamin D	ED-71 0.5ug/d vs ED-71 0.75ug/d vs ED-71 1.0ug/d vs Placebo: ≥1 episode of hypercalcemia over 2.6mmol/liter: 7.3%(4/55) vs 5.5%(3/55) vs 23.2%(13/56) vs 0.0%(0/53) ≥1 episode of hypercalciuria over 0.1mmol/liter GF: 7.3%(4/55) vs 9.1%(5/55) vs 25.0%(14/56) vs 0.0%(0/53) AEs: any serious AE: 10.9%(6/55) vs 12.7%(7/55) vs 5.4%(3/56) vs 7.5%(4/53) Blood calcium increased: 7.3%(4/55) vs 5.5%(3/55) vs 23.2%(13/56) vs 0.0%(0/53) Conjunctivitis: 3.6%(2/55) vs 5.5%(3/55) vs 0.0%(0/56) vs 0.0%(0/53) Cystitis NOS: 7.3%(4/55) vs 10.9%(6/55) vs 1.8%(1/56) vs 1.9%(1/53) Headache: 1.8%(1/55) vs 5.5%(3/55) vs 5.4%(3/56) vs 0.0%(0/53) Stomachache NOS: 7.3%(4/55) vs 0.0%(0/55) vs 1.8%(1/56) vs 0.0%(0/53) Urine calcium increased: 7.3%(4/55) vs 9.1%(5/55) vs 25.0%(14/56) vs 1.9%(1/53)
Sanders et al., 2010[164] Vitamin D Trial: VIT. D	Vitamin D vs Placebo: Cancer: 0.6%(7/1,131) vs 0.9%(10/1,125) Cardiovascular events: 15.1%(171/1,131) vs 1.2%(13/1,125) Death nos: 3.5%(40/1,131) vs 4.2%(47/1,125) Injury including fracture: 15.2%(172/1,131) vs 12.1%(136/1,125)

Evidence Table C-5. Adverse Events
Calcium/Vitamin D

Author, Year, Drug, Trial name	Adverse events reported
Salovaara et al., 2010[154] Calcium, Vitamin D Trial: OSPRE	Vitamin D + calcium vs Placebo: Death NOS: 0.9%(15/1,586) vs 0.8%(13/1,609)
Xia et al., 2009[227] Calcium, Vitamin D	Caltrate D (600 mg calcium and 125 iu vitamin D) vs Rocaltrol (0.25 ug/d) +Caltrate D (600 mg calcium and 125 iu vitamin D): Calcification: 0.0%(0/76) vs 0.0%(0/74) Renal lithiasis: 0.0%(0/76) vs 0.0%(0/74) Withdrawals: total: 5.3%(4/76) vs 5.4%(4/74)

Evidence Table C-5. Adverse Events
Physical Activity

Author, Year, Drug, Trial name	Adverse events reported
Korpelainen et al., 2010[215] Physical activity	Exercise vs Placebo: Death due to cancer: 1.2%(1/84) vs 2.6%(2/76) Death due to cardiovascular disease: 0.0%(0/84) vs 6.6%(5/76) Death due to external cause: 0.0%(0/84) vs 1.3%(1/76)

Drugs: CEE=Conjugated Equine Estrogen, PTH=Parathyroid Hormone
AEs: MI=Myocardial Infarction, UTI=Urinary Tract Infection, GI=Gastrointestinal

Evidence Table C-6. Applicability Assessments

Citations	Drugs	Primary Care	Inclusion/exclusion minimal*	Outcome= fx	Duration>6mos/Adherence	Adverse events	Sample size**	ITT	Total
Bone, 2008[117]	Denosumab	y	y	y	y/n	y	332	n	5.5 out of 7
Bonnick, 2007[226]	alendronate vs. alendronate+calcium	y	y (many exclusion criteria)	n (fx reported as AEs)	y/y	y	484	y (modified)	6 out of 7
Boone, 2006[136]	estrogen	n	n (PM women with primary biliary cirrhosis)	y	y/y	y	31	n	3 out of 7
Boonen, 2009[74]	risedronate	y	y (male)	y	y/n	y	284	y	6.5 out of 7 but men
Campbell, 2009[231]	estrogen (and etidronate)	y	n (GC users w/asthma)	y	y/n	n	47	n	2.5 out of 7
Chapman, 2009[114]	zoledronic acid	n	n(CF)	y	y/y	y	22	y	4 out of 7
Cummings, 2009[118]	Denosumab	y	y (many exclusion criteria)	y	y/y	y	7,868	y	7 out of 7
de Nijs, 2006[57]	alendronate and vitamin D	n	n (GC-users w/autoimmune diseases)	y	y/n	y	163	n	3.5 out of 7
Delmas, 2008[85]	risedronate	y	p (excl users of other osteoporosis meds and obese women)	y	y/y	y	1,231	n	5 out of 7
Delmas, 2008[86]	risedronate	y	p (excl users of other osteoporosis meds and many comorbidities)	y	y/y	y	1,294	n	5 out of 7
Ensrud, 2008[120]	raloxifene	y	n (women w/CHD; many exclusion criteria)	y	y/y	y	10,101	y	6 out of 7
Fahrleitner-Pammer, 2009[106]	ibandronate	n	n (male heart transplant)	y	y/n	y	35	n	2.5 out of 7
Frost, 2007[157]	calcium	n	n (men with CHF)	y	y/n	y	33	n	2.5 out of 7
Fujita, 2004[158]	calcium	n	n(hosp women)	y	y/n	n	19	n	1.5 out of 7
Ishani, 2008[255]	raloxifene	y	y (stratification by renal failure status)	y	y/n	y	7,492	y	6.5 out of 7
Korpelainen, 2010[215]	Physical activity	y	y (population based)	y	n/n	y	160	y	6 out of 7

Evidence Table C-6. Applicability Assessments

Citations	Drugs	Primary Care	Inclusion/exclusion minimal*	Outcome= fx	Duration>6mos/Adherence	Adverse events	Sample size**	ITT	Total
Larsen, 2004[150]	Calcium and Vitamin D	y	y	y	y/n	n	9,605	y	5.5 out of 7
Law, 2006[163]	Vitamin D	y	y	y	y/n	n	3,717	y	5.5 out of 7
Lyles, 2007[113]	zoledronic acid	y	y (prior hip fx)	y	y/nr (not relevant, once-yearly)	y	2,127	y	7 out of 7
Lyons. 2007[203]	Vitamin D	y	y	y	y/y	y(mort only)	3,440	y	7 out of 7
Okada, 2008[225]	alendronate and vitamin D	y	n (GC-users w/autoimmune diseases)	y	y/n	y	47	n	4.5 out of 7
Palomba, 2008[75]	risedronate	n	n (IBD pts)	y	y/y	y	90	y	4 out of 7
Papaioannou, 2008[55]	alendronate	n	n (CF)	y	y/y	y	56	y	4 out of 7
Ringe, 2007[56]	alendronate and vitamin D	y	y	y	y/n	y	90	y	5.5 out of 7
Ringe, 2009[73]	risedronate	y	n (male, small German clinic)	y	y/n	y	316	y	5.5 out of 7 but men
Saag, 2009[224]	alendronate and PTH	y	n (GC-users)	y	y/n	y	428	y	5.5 out of 7
Salovaara, 2010 [154]	Calcium and vitamin D	y	y (population-based)	y	y/y	y	3,195	y	7 out of 7
Sanders, 2010 [164]	Vitamin D	y	y	y	y/y	y	2,256	y	7 out of 7
Sato, 2007[72]	Risedronate and vitamin D	n	n (males with Parkinsons)	y	y/n	y	223	n	3.5 out of 7
Shiraki, 1996[161]	Vitamin D	y	y	y	y/n	n	113	y	5.5 out of 7
Silverman, 2008[121]	raloxifene	y	n (many exclusion criteria, incl vitamin D use)	y	y/n	y	7,492	y	5.5 out of 7
Smith, 2007[162]	Vitamin D	y	y	y	y/y	y	9,440	y	7 out of 7
Xia, 2009[227]	Calcium and Vitamin D	y	y (Chinese women)	y	y/n	y	150	y	6.5 out of 7

*p=probably
**n<100 considered "no"

Appendix D. List of Excluded Studies

Excluded at Short Form Review

Reject: Irrelevant Design (N=213)

1. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. Br Dent J. 2010 Nov 13;209(9):451.

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18. Badamgarav E, Fitzpatrick LA. A new look at osteoporosis outcomes: the influence of treatment, compliance, persistence, and adherence. Mayo Clin Proc. 2006 Aug;81(8):1009-12.

19. Bagan JV, Jimenez Y, Murillo J, Hernandez S, Poveda R, Sanchis JM, et al. Jaw osteonecrosis associated with bisphosphonates: multiple exposed areas and its relationship to teeth extractions. Study of 20 cases. Oral Oncol. 2006 Mar;42(3):327-9.

20. Baio G, Barbagallo M, D'Avola G, Di Luccio A, Di Tanna GL, Falaschi P, et al. Improving adherence in osteoporosis: a new management algorithm for the patient with osteoporosis. Expert Opin Pharmacother. 2011 Feb;12(2):257-68.

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Reject: Population Not Relevant (N=40)

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Excluded at Long Form

Adherence, Inappropriate for Analysis (N=8)

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