Draft Comparative Effectiveness Review

Number XX

Comparative Effectiveness of Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis – An Update to the 2007 Report

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

This information is distributed solely for the purposes of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the Agency for Healthcare Research and Quality. It does not represent and should not be construed to represent an Agency for Healthcare Research and Quality or Department of Health and Human Services determination or policy.

Contract No.

Prepared by:

Investigators:

This report is based on research conducted by the *XXX* EPC under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. *XXX*). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials noted, for which further reproduction is prohibited without the specific permission of copyright holders.

Suggested Citation: {USE ONLY IN FINAL REPORT. DO NOT INCLUDE IN DRAFT} [Authors]. Comparative Effectiveness of [Topic]. Comparative Effectiveness Review No. [#]. (Prepared by [EPC] under Contract No. [#].) Rockville, MD: Agency for Healthcare Research and Quality. [Month Year]. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Preface

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

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (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 e-mail 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

Acknowledgments

Technical Expert Panel

Disclosure: Service as a TEP member or peer reviewer should not be construed as agreeing with or endorsing the content of the 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 2006 through December 2009.

Review Methods: After review by two investigators against pre-determined 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, ibandronate, zoledronic acid, denosumab, and teriparatide reduce the risk of vertebral and non-vertebral fractures among postmenopausal women with osteoporosis. Raloxifene reduces the risk of vertebral but not non-vertebral fractures. Teriparatide and risedronate decrease the risk of fracture among men. Among those treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate. Few studies have compared treatments head-to-head.

Adherence to therapy with bisphosphonates is poor in patients with osteoporosis. Many factors affect adherence to medications, including 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. 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 an increased risk of fracture.

Assessment of adverse effects finds that raloxifene is associated with an increased risk for pulmonary embolism and mild cardiac events; calcium is associated with a significantly increase risk of myocardial infarction; 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: The existing evidence shows that fracture risk reduction is greatest in women with established osteoporosis and/or prevalent fractures. Data are less robust for postmenopausal women with osteopenia and without prevalent fractures. Further evidence is needed on the benefits of treatment for other populations, including men; on the benefits and risks of long-term treatment; on the need (if any) for monitoring bone density, and on methods to improve adherence.

Contents

Executive Summary ES-1

Chapter 1. Introduction 1
Background 1
Diagnosis and Risk Factors 1
Therapy 2
The FDA Approval Process 3
The 2007 Comparative Effectiveness Review 5
This Report 5
Scope and Key Questions 6
Chapter 2. Methods 13
Topic Development 13
Search Strategy 13
Study Eligibility Criteria 14
Study Selection 15
Data Extraction 16
Data Synthesis 16
Efficacy and Effectiveness 17
Adherence 17
Adverse Events 19
Quality Assessment 20
Applicability 21
Rating the Body of Evidence 22
Peer Review and Public Commentary 24
Chapter 3. Results 26
Literature Search 26
Key Question 1: What are the comparative benefits in fracture 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 28
Key Points 28
Overview of results 29
Agents Compared with Placebo 29
Head-to-Head Comparisons of Agents. 93
Combinations or sequential use of above 107
Key Question 2: How does fracture 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) ... 108
Key Points 108
Overview of Results 109
Key Question 3: Regarding treatment adherence and persistence, ... 114

a) What are the adherence and persistence to medications for the treatment and prevention of osteoporosis,..... 114
b) what factors affect adherence and persistence, and..... 114
c) what are the effects of adherence and persistence on the risk of fractures? 114
Key Points..... 114
Key Question 3A: What are the adherence and persistence to medications for the treatment and prevention of osteoporosis 115
Key Question 3B: What factors affect adherence and persistence 122
Key Question 3C: Effects of adherence and persistence on the risk of fractures..... 126
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)? 130
Key Points..... 130
Bisphosphonates 132
SERMS 139
Parathyroid Hormone..... 141
Estrogen or Estrogen Plus Progestin..... 143
Denosumab 143
Vitamin D and Calcium 145
Key Question 5: With regard to treatment for preventing osteoporotic fracture:..... 147
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? 147
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?..... 147
Key Points..... 147
Summary of Findings..... 148
Chapter 4. Summary and Discussion..... 153
Limitations 153
Publication Bias 153
Study Quality 153
Other Potential Sources of Bias 153
Conclusions..... 154
Discussion..... 160
Future Research 162
References..... 164
Abbreviations..... 191

Tables

Table A. Summary of Evidence..... ES-19
Table 1. Prescription Drugs Indicated for Prevention and Treatment of Low Bone Density/Osteoporosis 9

Table 2. Grading the strength of a body of evidence: Required domains and their definitions ... 22
Table 3. Randomized controlled trials included in meta-analyses of effect of alendronate on fracture relative to placebo or no treatment, by fracture type. ... 31
Table 4. Pooled risk estimates of fracture risk associated with alendronate, relative to placebo or no treatment, among postmenopausal women.* ... 34
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) .. 37
Table 6. Randomized controlled trials included in meta-analyses of effect of risedronate on fracture relative to placebo or no treatment ... 41
Table 7. Pooled risk estimates of fracture for risedronate, relative to placebo or no treatment.[a] . 42
Table 8. Risk of fracture for risedronate, relative to placebo, by dose and fracture group ... 44
Table 9. Randomized controlled trials assessing risk of fracture for risedronate, relative to different doses of risedronate, by fracture group (not included in prior meta-analyses) ... 46
Table 10. Randomized controlled trials included in meta-analysis of effect of ibandronate on fracture relative to placebo or no treatment by fracture type ... 49
Table 11. Pooled risk estimates of fracture for ibandronate, relative to lower dose, placebo, or no treatment, among postmenopausal women ... 50
Table 12. Randomized controlled trials assessing risk of fracture for ibandronate, any dose, relative to placebo, by anatomical fracture site (not included in prior meta-analyses) ... 52
Table 13. Randomized controlled trials assessing risk of intravenous zoledronic acid relative to placebo, by dose and frequency among postmenopausal women ... 55
Table 14. Randomized controlled trials included in meta-analysis of effect of Denosumab on fracture relative to placebo or no treatment by fracture type ... 58
Table 15. Pooled risk estimates of fracture for denosumab relative to placebo or no treatment .. 58
Table 16. Denosumab vs. placebo ... 59
Table 17. Risk estimates of fracture for raloxifene relative to placebo or no treatment among postmenopausal women as reported in prior meta-analyses.* ... 61
Table 18. Risk of vertebral fracture for raloxifene, relative to placebo ... 62
Table 19. Randomized controlled trials included in meta-analysis of effect of parathyroid hormone on fracture relative to placebo by fracture type ... 64
Table 20. Pooled risk estimates of fracture for parathyroid hormone relative to placebo or no treatment.* ... 65
Table 21. Risk of fracture for parathyroid hormone, relative to placebo, by fracture group ... 66
Table 22. Risk of fracture for menopausal estrogen therapy, relative to placebo, by fracture group ... 68
Table 23. Randomized controlled trials included in meta-analysis of effect of calcium on fracture relative to placebo or no treatment ... 73
Table 24. Randomized controlled trials included in meta-analyses of effect of vitamin D on fracture relative to placebo or no treatment ... 74
Table 25. Pooled risk estimates of fracture for calcium relative to placebo, or no treatment ... 76
Table 26. Pooled risk estimates of fracture for Vitamin D relative to placebo, vitamin D plus calcium, or no treatment ... 77
Table 27. Calcium/Vitamin D group and Environmental and Health group vs. placebo ... 87
Table 28. Risk of vertebral fracture for calcium plus vitamin D, relative to placebo ... 88
Table 29. Risk of fracture for calcium, relative to placebo, by fracture group ... 89
Table 30. Risk of vertebral fracture for vitamin D, relative to placebo ... 90

Table 31. Randomized controlled trials included in meta-analysis of effect of physical activity on fracture relative to placebo or no treatment by fracture type 92
Table 32. Pooled risk estimates of fracture for physical activity relative to placebo or no treatment 92
Table 33. Fractures with bisphosphonate relative to menopausal estrogen therapy or menopausal estrogen plus progestogen therapy among postmenopausal women 96
Table 34. Randomized controlled trials assessing fractures with bisphosphonates relative to calcium, by bisphosphonate 97
Table 35. Fractures with bisphosphonates relative to raloxifene 98
Table 36. Fractures with alendronate relative to risedronate, by fracture type among postmenopausal women with osteoporosis 100
Table 37. Fractures with alendronate relative to PTH (Teriparatide) among postmenopausal women 101
Table 38. Alendronate 10mg/day vs. teriparatide 20mug/day among individuals taking glucocorticoids 101
Table 39. Alendronate plus vitamin d vs. alendronate plus alfacalcidol 102
Table 40. Alfacalcidol plus prednisolone and alendronate vs. alfacalcidol plus prednisolone . 102
Table 41. Alendronate vs. alendronate plus calcium 102
Table 42. Rocaltrol+Caltrate D vs Caltrate D 103
Table 43. Risk of fracture for risedronate relative to zoledronic acid, by fracture type 103
Table 44. Fractures with etidronate relative to calcitonin, by fracture type 103
Table 45. Risk of fracture for raloxifene, relative to estrogen, among postmenopausal women 104
Table 46. Risk of fracture for estrogen, relative to vitamin D, by anatomical fracture site 104
Table 47. Risk of fracture for calcium, relative to vitamin D, by fracture group 105
Table 48. Randomized controlled trials included in meta-analysis of effect of vitamin D on fracture relative to calcium by fracture type 106
Table 49. Clinical Trials Reporting Adherence/Persistence Rates 119
Table 50. Adherence studies included in Systematic Reviews 127
Table 51. Risks of Adverse Events for bisphosphonates vs. placebo 137
Table 52. Risks of Adverse Events for Raloxifene vs. Placebo 141
Table 53. Risks of Adverse Events for Parathyroid Hormone vs. placebo 143
Table 54. Risks of Adverse Events for Biologics (Denosumab) 144
Table 55. Dietary Supplements (Vitamin D and Calcium) 146
Table 56. Summary of Evidence 155

Figures

Figure S1. Analytic Framework 8
Figure 1. Analytic Framework 12
Figure 2. Literature Flow 27

Appendixes

Appendix A: Search Methodology
Appendix B Data Abstraction Forms
Appendix C: Evidence Tables

Appendix D: List of Excluded Studies
Appendix E: Peer Reviewers and Technical Expert Panel Members (to be added for final report)

Appendices and evidence tables are provided electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/XXX/XXX.pdf.

Comparative Effectiveness of Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis – An Update to the 2007 Report

Executive Summary

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

The full report and this summary are available at
www.effectivehealthcare.ahrq.gov/reports/final.cfm

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. In addition to fractures, the clinical complications of osteoporosis include disability and chronic pain. Approximately 44 million people in the United States are affected by osteoporosis or low bone density. It is especially common in postmenopausal women, but one in five men will experience an osteoporosis-related fracture at some point in his lifetime.

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. 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). 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.

Diagnosis and Risk Factors

The clinical diagnosis of osteoporosis is based on results of bone mineral density (BMD) measurement 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, 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. However, in premenopausal women and men under 50 years, bone density is 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. Because the majority of fractures occur in patients with low bone mass rather than osteoporosis, 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, 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.

Several algorithms have been devised and validated for the prediction of osteoporotic risk. Current National Osteoporosis Foundation guidelines as well as others endorse the use of the FRAX to select candidates for treatment. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. 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) and the 10-year risk of hip fracture. 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.

Therapy

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.

Denosumab, approved by the Food and Drug Administation (FDA) in May 2010, a biological agent, is a monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption.

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. 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.

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 and the quality-of-life issues that arise from the dosing instructions for some of the agents, 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. 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 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.

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 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 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* 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 of treatment. The 1994 Guidance Document also provided requirements for approval of agents for prevention of osteoporosis (in individuals at high risk but without history of osteoporotic fracture). Only agents that have already been approved for treatment of osteoporosis can be approved for prevention. For prevention, BMD may serve as an appropriate–and sufficient–outcome measure for efficacy in double-blind 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, estrogen was exempted from the fourth requirement (demonstration of effectiveness for fracture prevention) and was approved for 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

---

* 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.

risk. These implications of the current guidance have heightened interest in evaluating the effectiveness data for drugs approved to treat and prevent osteoporosis.

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.

The review found good 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 good 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 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 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 bisphosphonates and calcium. 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 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. 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 and lasifoxifene, 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. 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; once-a-year 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-a-month). 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 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 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 sub-question 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 S1 shows the analytic framework that guided the report).

Key Question 1. What are the comparative benefits in *fracture 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 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,[†]

[†] 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)

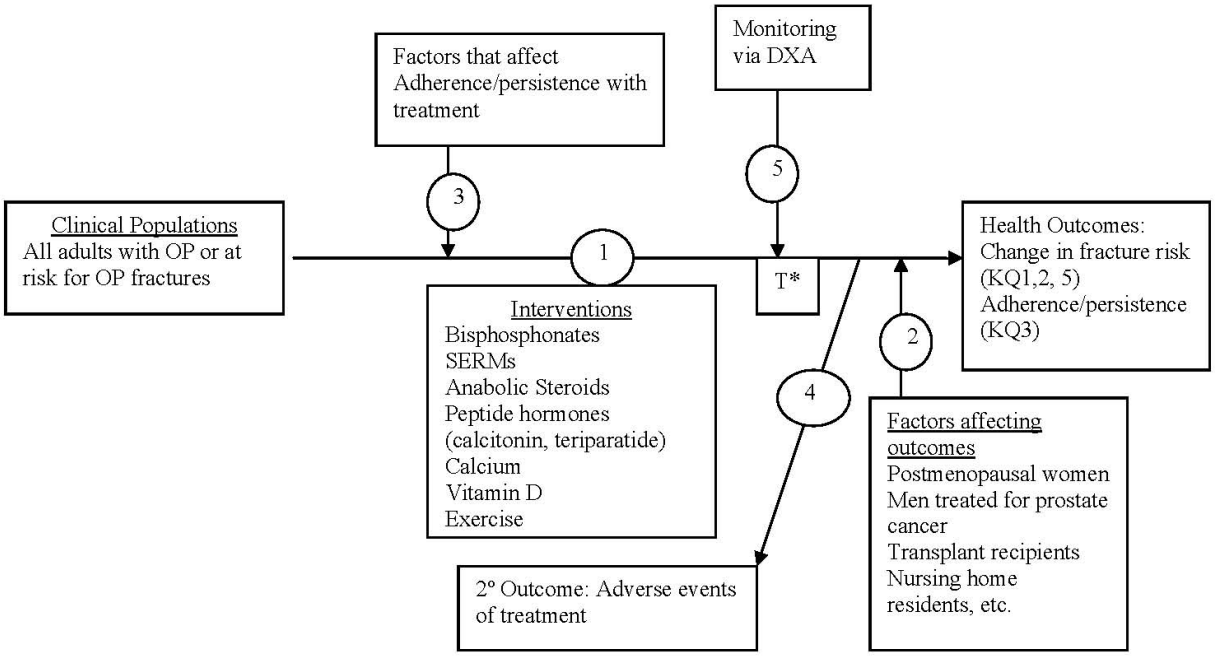
a) What are the adherence and persistence to medications for the treatment and prevention of osteoporosis,
b) what factors affect adherence and persistence, and
c) what are the effects of adherence and persistence on the risk of fractures?

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?

Figure S1. 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

Search Strategy

Our basic search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) key word 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 2006 to December 2009. 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 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 and meta-analyses not captured in our primary search strategy, we also searched MEDLINE®, the Cochrane Database of Systematic Reviews, the websites of the National Institute for Clinical Excellence, and the NHA Health Technology Assessment Programme. We also manually searched 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.

Limited update searches were conducted automatically throughout the study and a complete update search will be conducted during the review period. Any new articles identified by these searches or identified by the TEP or reviewers will be subjected to the same screening process as the articles from the original searches.

Study Eligibility Criteria

To identify studies for this report, we used the following inclusion 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 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 follow-up time of 6 months were included
- Design: Only RCTs were included in the assessment of effectiveness; however, for the assessment of effects in subgroups for which no RCTs were available and for the assessment of the effect of adherence on effectiveness, large (more than 1000 participants) observational studies 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 (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>1000) 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 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 1000 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 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 (over 1000 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 KQ 5 (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 follow-ups 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, non-vertebral, hip, wrist, and humerus. For each of the drug comparisons, we first summarized fracture data from published systematic reviews and meta-analyses in tables. Data abstracted from individual controlled clinical trials were grouped by fracture type within each drug comparison of interest. Based on 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 non-vertebral 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 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 meta-analyses 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 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 (including those in the original report), we performed a meta-analysis to estimate the pooled OR and its associated 95% 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, 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). 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 studies was assessed using the following questions:

- 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?

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.

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. This method is based on one developed by the Grade Working Group, 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.

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: 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 meta-analyses (from both the original and current report) that assessed the effects of interventions compared to placebo: nine meta-analyses and 10 RCTs for alendronate, 10 meta-analyses and 13 RCTs for risedronate, three meta-analyses and three RCTs for ibandronate, four RCTs for zoledronic acid, one meta-analysis and two RCTs for denosumab, three meta-analyses and three RCTs for raloxifene, two meta-analyses and three RCTs for teriparatide, six RCTs for menopausal estrogen therapy, four meta-analyses and six RCTs for calcium alone, 15 meta-analyses and seven RCTs for vitamin D alone, four RCTs for vitamin D plus calcium, and one meta-analysis for physical activity.

- There is good evidence from RCTs that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, PTH, and raloxifene prevent vertebral fractures in postmenopausal women with osteoporosis
- There is good evidence from RCTs that alendronate, risedronate, ibandronate, zoledronic acid, and denosumab prevent non-vertebral fractures in postmenopausal women with osteoporosis

- There is good evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab prevent hip fractures in postmenopausal women with osteoporosis
- The original report found good evidence that estrogen is associated with a reduced incidence of vertebral, non-vertebral 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 meta-analysis and several RCTs, that there is no difference between calcium alone and placebo in preventing vertebral and nonvertebral fractures; however, calcium significantly reduced hip fracture risk in one pooled analysis, and overall fracture risk in another pooled analysis
- According to a large body of literature, vitamin D had varying results depending on dose, analogs and population. Vitamin D, 700 to 800 I.U. daily, particularly when given with calcium, reduces the risk of hip and non-vertebral fractures among institutionalized populations (one meta-analysis), and the risk of overall fractures (a second meta-analysis)
- There is evidence from six previously published meta-analyses that there is no difference in vertebral, non-vertebral, or hip fracture risk with administration of vitamin D alone compared to administration of calcium alone
- RCTs on the effect of physical activity compared to placebo showed no effect on fracture prevention. No studies compared the effect of physical activity to that of other interventions
- Based on limited data from four head-to-head trials, within the bisphosphonate class, superiority for the prevention of fractures has not been demonstrated for any agent
- Based on limited head-to-head trial data, superiority for the prevention of fractures has not been reported for bisphosphonates in comparison with calcium (two trials), PTH (teriparatide, two trials), or raloxifene (three trials)
- Based on six head-to-head RCTs, there was no difference in fracture incidence between bisphosphonates and menopausal hormone therapy
- Based on one head-to-head trial, the combination of alendronate and calcium significantly decreased the risk for any type of clinical fracture compared with alendronate alone
- Based on limited head-to-head trial data (two trials), there was no difference in fracture incidence between menopausal hormone therapy and raloxifene or vitamin D.
- No RCTs tested combinations of osteoporosis therapies or sequential use of osteoporosis therapies in relation to fracture outcomes

Key Question 2: How does fracture 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.

- Bone Mineral Density. Post hoc analysis of one large RCT found no evidence that low femoral neck BMD predicts the effect of alendronate on clinical vertebral or non-vertebral fracture risk. Post hoc analysis of two-year follow-up 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. 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 fracture among elderly women
- Prevalent Fractures. Post hoc analysis of a large RCT found no evidence that prevalent vertebral fractures predicts the efficacy of alendronate; however another post hoc analysis of data from the same trial found that the risk of incident non-vertebral fractures among women without prevalent fractures (but with T-scores ≤-2.5) was decreased (by alendronate) compared with that of women *with* prevalent fractures or without prevalent fractures and with T-score -2 to -2.5
- A post hoc analysis of one large RCT showed that raloxifene decreased the risk of major non-vertebral 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
- A post hoc analysis of one RCT showed that prevalent fractures increased the relative efficacy of teriparatide in preventing fractures in postmenopausal women
- Age. In general, bisphosphonates were at least as effective for older persons as for younger, at least in terms of a decrease in relative risk, although one RCT found an effect of age on the effectiveness of risedronate in preventing any type of fracture
- One RCT found no influence of age on the effect of zoledronic acid in lowering the risk for vertebral or non-vertebral fractures but found that only women under 75 experienced a benefit in reduced risk for hip fracture. However another RCT found that age influences the effect of zoledronic acid on vertebral fracture risk but not the risk for non-vertebral or hip fracture
- One RCT found no effect of age on the influence of teriparatide on vertebral fracture but found an effect on the risk of non-vertebral fracture
- Sex. 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. 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
- Renal Function. Evidence from two trials supports a lack of effect of renal function on the efficacy of alendronate and raloxifene; however impaired renal function reduced the efficacy of zoledronic acid in preventing vertebral (but not non-vertebral or hip) fractures

Key Question 3: Treatment Adherence and Persistence Rates, Barriers, and Effects on Fracture Risk

For this question, we identified two new systematic reviews, 15 RCTs, and 41 observational studies.

- 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 meta-analyses 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 barriers have been identified to adherence and persistence. Five of the most commonly discussed include age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of the osteoporosis medications
- 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 appear to be an important predictor of adherence and persistence.
- Evidence from a meta-analysis and ten out of eleven observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, non-vertebral 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: Short and Long-Term Harms of the Included Therapies and Variance by Subpopulations

For this question, we included one meta-analysis, 61 RCTs and two large observational studies.

- *Acute Coronary Syndrome, Including Myocardial Infarction(MI).* 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
- *Atrial Fibrillation.* 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 also showed an increase but it did not reach statistical significance
- *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.
- *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.
- *Mild Cardiovascular Events*: A pooled analysis of four studies, three from the original report and one identified for the current report that compared raloxifene and placebo found a significant increase in these events among raloxifene users.
- *Esophageal Cancer.* Two 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 a nested case control study on the same dataset did identify an increased risk
- *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
- *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. No trials were identified for the current report that reported on the incidence of osteonecrosis of the jaw among individuals taking bisphosphonates to prevent or treat osteoporosis. However, a large recent case series that reviewed 2408 cases of osteonecrosis of the jaw to assess the possible association between use of bisphosphonates and osteonecrosis found that 88 percent were associated with intravenous therapy, primarily with zoledronic acid,

and ten percent of those were associated with the prevention or treatment of osteoporosis. Thus the prevention and treatment of osteoporosis remains a relatively minor contributor to the development of osteonecrosis of the jaw

- *Atypical Fractures of the Femur.* A large case series, a pooled analysis of three trials, and a comprehensive review identified an 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 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
- *Rashes and Injection Site Reactions*: 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

Key Question 5: Frequency of Bone Mineral Density Monitoring during Treatment and Effect of Long-term Treatment on Antifracture Efficacy or Effectiveness

For this question, we identified one meta-analysis and 4 RCTs.

- No evidence exists from RCTs regarding how often patients' BMD should be monitored during osteoporosis therapy
- Strong 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 from one large RCT showed no higher fracture risk other than for clinical vertebral fractures with use of alendronate for more than five years

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

Key Question	Strength of Evidence	Conclusion
1. What are the comparative benefits in fracture 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, **ibandronate** and zoledronic acid reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis.
	High	Hip: alendronate, risedronate and zoledronic acid reduce the risk of hip fractures among postmenopausal women with osteoporosis. **The effect of ibandronate is unclear, since hip fracture risk reduction was not a separately reported outcome in trials reporting non-vertebral fractures.**
	Low	Wrist: 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.**
	Low	Based on limited data from head-to-head trials, within the bisphosphonate class, superiority for the prevention of fractures has not been demonstrated for any agent.
	Low	Based on limited data from head-to-head trials, superiority for the prevention of vertebral fractures has not been demonstrated for bisphosphonates in comparison with calcium, raloxifene or **teriparatide**.
	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 sub analysis in one of the RCTs demonstrated a reduction in fracture risk with calcium relative to placebo among compliant subjects.

Key Question	Strength of Evidence	Conclusion
c. Denosumab	**High**	**Denosumab reduces the risk of vertebral, no-vertebral and hip fractures in postmenopausal women with osteoporosis.**
d. Menopausal hormone therapy	**Strong**	Menopausal hormone therapy reduces the risk of vertebral and hip fractures.
e. PTH (teriparatide)	**High** **Moderate**	**Teriparatide reduces the risk of vertebral fractures in postmenopausal women with osteoporosis**. **Teriparatide reduces the risk of non-vertebral fractures in postmenopausal women with osteoporosis.**
f. SERMs (raloxifene)	High	Raloxifene **reduces the risk of** vertebral fractures.
g. Vitamin D	Moderate	The effect of vitamin D on fracture risk is uncertain. Among a number of meta-analyses, some reported a reduced risk for vitamin D relative to placebo, some did not. There was no reduction in fracture risk for vitamin D relative to placebo in a large, high quality RCT published after the meta-analyses.
h. Exercise in comparison to above agents.	None	There are no data from RCTs to inform this question.
2. How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), prior fractures (prevention vs. treatment)?	High High Low High Moderate Low	Alendronate, etidronate, ibandronate, risedronate, teriparatide, and raloxifene reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis. Raloxifene prevents fractures in postmenopausal women at low risk for fracture. Teriparatide, risedronate, and calcitonin reduce risk of fracture among men. Among subjects treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate. Reduction in fracture risk for subjects treated with alendronate, risedronate, or vitamin D has been demonstrated in populations at increased risk for fracture due to conditions that increase the risk of falling including stroke with hemiplegia, Alzheimer's disease, and Parkinson's. There are limited and inconclusive data on the effect of agents for the prevention and treatment of osteoporosis on transplant recipients and patients treated with chronic corticosteroids.

Key Question	Strength of Evidence	Conclusion
3. What are the adherence and persistence to medications for the treatment and prevention of osteoporosis, the factors that affect adherence and persistence, and the effects of adherence and persistence on the risk of fractures?	**Moderate**	**15 RCTs reported rates of adherence to therapy. 10 trials with bisphosphonates reported high levels of adherence (majority with over 90% adherence). Two trials with raloxifene had adherence rates 65-70%.**
	High	**There is evidence from 37 observational studies, including 14 using US data, that adherence and persistence to therapy with bisphosphonates, and calcium and vitamin D is poor in many patients with osteoporosis. No studies describe primary nonadherence (i.e. nonfulfillment).**
	Moderate	**Based on evidence from 30 observational studies, many factors affect adherence and persistence to 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 16 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 meta-analysis and ten out of eleven observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, non-vertebral 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	Strength of Evidence	Conclusion
4. What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?	High	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.**
	Moderate	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. **Compared to placebo, teriparatide users also had an increased risk of mild upper GI events. 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.**
	Moderate	**A new meta-analysis 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.**
	Moderate	**PTH and teriparatide treated participants showed a significant increase in hypercalcemia.**
	Moderate	Zoledronic acid is associated with an increased risk of atrial fibrillation relative to placebo.
	Moderate	**A review of 2,408 cases of osteonecrosis of the jaw in patients taking bisphosphantes found that 89 percent of the cases were associated with treatment of malignancy and 88 percent of cases involved intravenous therapy, previously zoledronic acid.**
	Moderate	**Our pooled analysis of four trials found an increased risk with raloxifene in mild cardiac events (those other than death, myocardial infarction, atrial fibrillation, and ventricular arrhythmia.**
	Moderate	**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,**

Key Question	Strength of Evidence	Conclusion
	Moderate	A pooled analysis of four trials of denosumab found an increased risk of rash.
	Low	A small number of clinical trials have reported an increased risk of hypocalcaemia in patients treated with alendronate and zoledronic acid.
	Low	There is a signal from observational studies that use of an oral bisphosphonate is associated with an increased risk of esophageal cancer.
5a. How often should patients be monitored (via measurement of bone mineral density) during therapy?	Low	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 are associated with a minority of antifracture efficacy; even patients who continue to lose BMD during therapy have had statistically significant benefits in fracture reduction.
5b. How does the antifracture benefit vary with long-term continued use of pharmacotherapy?	Moderate	One large RCT showed no higher fracture risk other than for clinical vertebral fractures with use of alendronate for five additional years compared to placebo, after having been already treated with alendronate for 5 years.
	Low	A post hoc analysis of this same trial reported that there were statistically significant non vertebral 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 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
- 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 strong level of evidence for reduction in hip fracture risk
- For reduction in vertebral fracture risk, there is strong evidence supporting the use of bisphosphonates, raloxifene, and teriparatide
- Raloxifene has shown to be not effective in reducing the risk of hip or non-vertebral fractures.
- There are no controlled trial data regarding anti-fracture efficacy of pharmacotherapy for idiopathic osteoporosis in men, so the comparative efficacy of available treatments has not been assessed among men with idiopathic osteoporosis
- 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. It is unknown if these same precepts will hold 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 to the evidence available at the time of the prior report, the issue now seems settled that treatment with any of the FDA-approved agents discussed in this report will, in general, decrease the risk for most kinds of osteoporotic fractures for postmenopausal women with established osteoporosis. While data are thin regarding the comparative effectiveness or efficacy between different agents, the evidence that does exist supports the thesis that any

comparative differences, if they exist at all, will be small. More important than comparative effectiveness between agents are the following concerns:

1) Who should we treat? What is the balance of benefits and harms for postmenopausal women without established osteoporosis? **The existing evidence shows that the benefits of treatment (in terms of fracture risk reduction) are less robust for postmenopausal women with osteopenia and without prevalent fractures than they are for women with established osteoporosis.** 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.

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 5 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 3 years, 4 years, 5 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?

3) For people who are good candidates for treatment, how can we improve adherence? There is moderate to strong evidence that adherence is commonly poor, and that poor adherence is associated with worse fracture outcomes. Addressing this issue requires considering not just the dosing barriers to adherence, but the other factors identified in the studies (side effects, knowledge about osteoporosis, cost, and comorbid conditions/concomitant medication use.)

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) We need to remain vigilant for possible rare side effects. The identification – since the prior 2007 report – of an association between bisphosphonate use and atypical subtrochanteric fractures of the femur demonstrates the importance of the need for continuing surveillance, as this identification did not occur until after more than a decade of widespread use.

Chapter 1. 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 44 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 is 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,[‡] 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. However, in premenopausal women and men under 50, bone density is 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

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

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 (i.e. previous osteoporotic fracture), rheumatoid arthritis, current smoking, alcohol intake (3 or more drinks/day), low BMD, vitamin D deficiency, low calcium intake, 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 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) and the 10-year risk of hip fracture. 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.[11, 12]

Therapy

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

---

[§] 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.

compounds that bind reversibly to mineralized bone surfaces and disrupt resorption by the osteoclasts.

A biological agent, denosumab, approved by the FDA in May 2010 is a monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption.

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 and the quality-of-life issues that arise from the dosing instructions for some of the agents, 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.[13] 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.

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[**] 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 of treatment. The 1994 Guidance Document also provided requirements for approval of agents for prevention of osteoporosis (in individuals at high risk but without history of osteoporotic fracture).[14] 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, estrogen was exempted from the fourth requirement (demonstration of effectiveness for fracture prevention) and was approved for 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.

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

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

[**] 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.

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.[15]

The review found good 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 good 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 bisphosphonates and calcium. 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 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.[16] 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; once-a-year 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-a-month). 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 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 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,[††]

a) What are the adherence and persistence to medications for the treatment and prevention of osteoporosis,
b) what factors affect adherence and persistence, and
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.

[††] 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

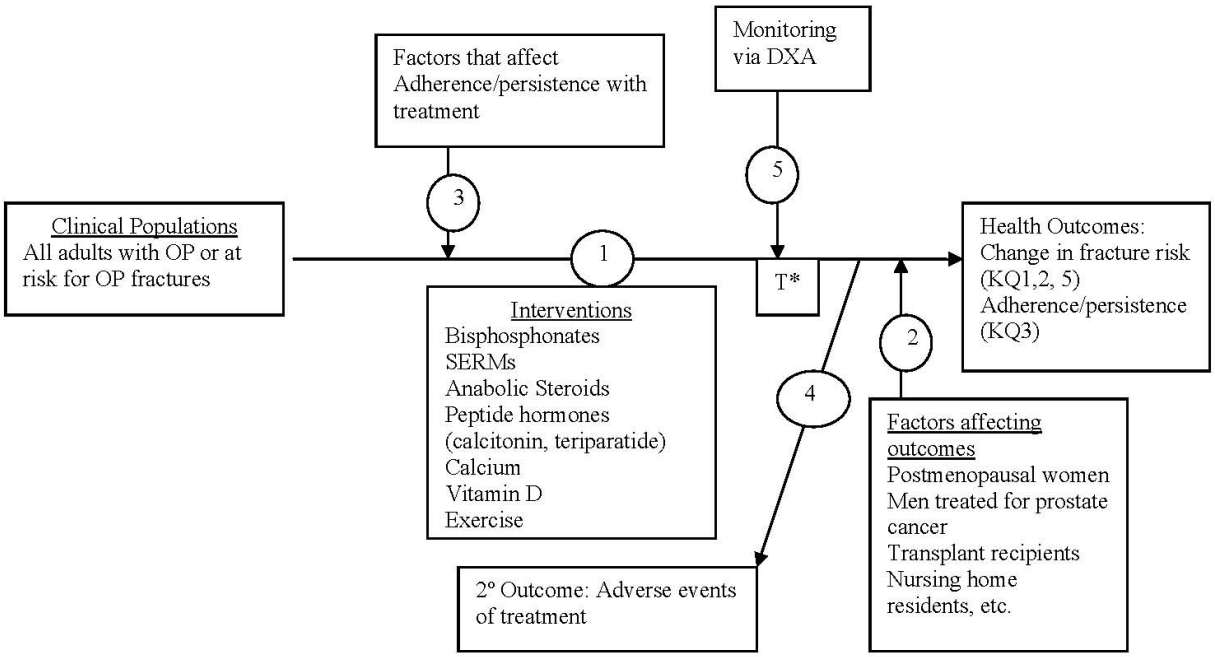
Drug	Trade name(s)	Labeled indications	Dosing	Dose adjustments for special populations
Bisphosphonates				
Alendronate Source: Merck & Co., Inc., March 2010)	Fosamax®	Indicated for treatment and prevention of osteoporosis in postmenopausal women; increasing bone mass in men with osteoporosis; treatment 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	Treatment of postmenopausal women with osteoporosis
			70 mg (as tablet or oral solution) once weekly, or one 10 mg tablet daily	Treatment of men with osteoporosis
			One 35 mg tablet weekly or one 5 mg tablet daily	Prevention of osteoporosis in postmenopausal women
			One 5mg tablet daily	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	No dose adjustment necessary
Risedronate	Actonel® Actonel w/ calcium®	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	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

			once weekly 35mg with 1250 mg calcium carbonate tablets to be taken 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
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)/Medroxyprogesterone (MPA)	Prempro®	Indicated for prevention of postmenopausal	0.3 mg CEE/1.5 mg MPA daily;0.45 CEE/1.5 mg MPA;	n/a

		osteoporosis	0.625 mg CE/2.5 mg MPA; 0.625 CEE/5 mg MPA	
Estradiol(E)/norgestimate(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
Biologicals				
denosumab	ProliaTM®	Indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture	60 mg injected subcutaneously twice yearly	n/a

This figure 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.

Chapter 2. 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[15] 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 2006 to December 2009. 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.

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 and meta-analyses not captured in our primary search strategy, we also searched MEDLINE®, the Cochrane Database of Systematic Reviews, the websites of the National Institute for Clinical Excellence, and the NHA Health Technology

Assessment Programme. We also manually searched 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. We identified all original studies included in the new meta-analyses, added this information to the tables of prior meta-analyses created for the original report, and added the pooled findings of the new meta-analyses to the tables of pooled results created for the original report (any original studies included in these meta-analyses were excluded from subsequent pooled analyses for this report).

Limited update searches were conducted automatically throughout the study and a complete update search will be conducted during the review period. Any new articles identified by these searches or identified by the TEP or reviewers will be subjected to the same screening process as the articles from the original searches.

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 follow-up time of 6 months were included.

Design: Only RCTs were included in the assessment of effectiveness; however, for the assessment of effects in subgroups for which no RCTs were available and for the assessment of the effect of adherence on effectiveness, large (more than 1000 participants) observational studies 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>1000) 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 interpreatation 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 1000 participants), we assessed whether any subgroup analyses were reported and extracted those data separately. To ensure no subgroup analyses were missed, we re-screened 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 > 1000) that reported fracture or BMD or markers of bone turnover for one or more of the drugs of interest and that reported one or more AE, 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 KQ 5 (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 follow-ups 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 follow-up; 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 follow-up; 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, non-vertebral, hip, wrist, and humerus. For each of the drug comparisons, we first summarized fracture data from published systematic reviews and meta-analyses in tables. Data abstracted from individual controlled clinical trials were grouped by fracture type within each drug comparison of interest. Based on 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 non-vertebral fractures). The primary outcome for our analysis of effectiveness is the number of people who reported at least one fracture. Because the occurrence of a fracture was fairly rare, and zero events were often observed in at least one of the treatment groups, odds-ratios (OR) were calculated using the Peto method.[18] When analyzing outcomes with rare events, the Peto method has been shown to give the least biased estimate.[19] An OR with a value less than one indicates that the odds of having a fracture is less in the intervention group than in the comparison group. Trials that reported zeros in both groups have an undefined OR and were excluded from any meta-analysis. Because fractures are rare events, the OR approximates the relative risk (RR) of fracture. In some instances, we combined data from multiple study arms in an individual study to calculate a single OR for comparisons of interest. In these instances, the same outcome had been reported for each of the arms, and the individuals in each arm were unique. For example, to develop on OR for the risk of vertebral fractures regardless of dose, subjects in the various dose groups were combined and compared with subjects in the placebo group.

Wherever possible, data were presented separately for subgroups of interest. We provide narrative descriptions of the outcomes of each study 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).[20] 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."[20]

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 non-adherent 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.

Meta-analyses 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 meta-analyses.

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.[21] 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 meta-analyses 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 a meta-analysis to estimate the pooled OR and its associated 95% confidence interval. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed; generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analyses using the statistical software package StatXact Procs for SAS Users.[22] For events that were reported in only one trial, an OR is calculated and reported.

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

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).[23] Across a broad array of meta-analyses, an evaluation found that studies scoring 0-2 report exaggerated results compared with studies scoring 3-5.[24] 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 studies was assessed using relevant portions of the Newcastle-Ottawa Scale for cohort studies.[25] Items assessed 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 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?

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.[26]

Based on the method of Gartlehner et al.,[27] 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.[28] This method is based on one developed by the Grade Working Group,[29] 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.

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

Domain	Definition and Elements	Score and Application
		evidence bases (even mega-trials) cannot be judged with respect to consistency. In that instance, use "Consistency unknown (single study)."
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 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

Chapter 3. Results

Literature Search

The initial searches found a total of 16,466 citations. A further search was done on related articles that produced 213 total citations. Reference mining brought in a further 217 citations. All 16, 896 citations were imported into EndNote. In total, reviewers selected 2,174 relevant titles for abstract review out of 16,896 titles identified in the searches (see Figure 2). Of these 2,174, 1,897 titles were identified from the electronic literature searches, 232 were identified from reference mining, and 45 came from a preliminary search.(Figure 2) Abstract review resulted in rejection of 1,523 articles. Reasons for abstract exclusion included: articles were not on osteoporosis (527), design (705), fracture not reported (only in effectiveness abstracts) (219), population (72). Seven articles were not found and 127 were already in the original report. Thus, 517 full-text articles were available for the next stage of screening (short form).

Screening of retrieved articles resulted in further exclusion of 312. Reasons for exclusion include: design not relevant for analyses (201 articles), outcomes not relevant to project (42 articles), no enrollment criteria (three articles), population not relevant to project (33 articles), interventions not relevant to project (33 articles). Nine 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 196 articles accepted based on short form review, 63 articles-reported on adherence, of which 7 were rejected for not answering a key question. Of 55 trials with fracture outcomes, only 32 were accepted for analysis. The remaining 23 were follow-up studies and post hoc analyses which are described in KQ 1 and KQ 2. Of ten observational articles with fracture outcomes, only 9 were included. The remaining article was a post hoc analysis. Of 126 articles that reported adverse events, 89 of those were trials, of which 26 were rejected for being duplicate studies, having no adverse event data reported, or being crossover studies. The remaining 37 were large cohorts analyzed for adverse events; however all but two were excluded because sufficient data were obtained from RCTs. Thus 63 articles were analyzed for adverse events.

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.[15]

Figure 2 below displays the flow as described above.

Figure 2. Literature Flow

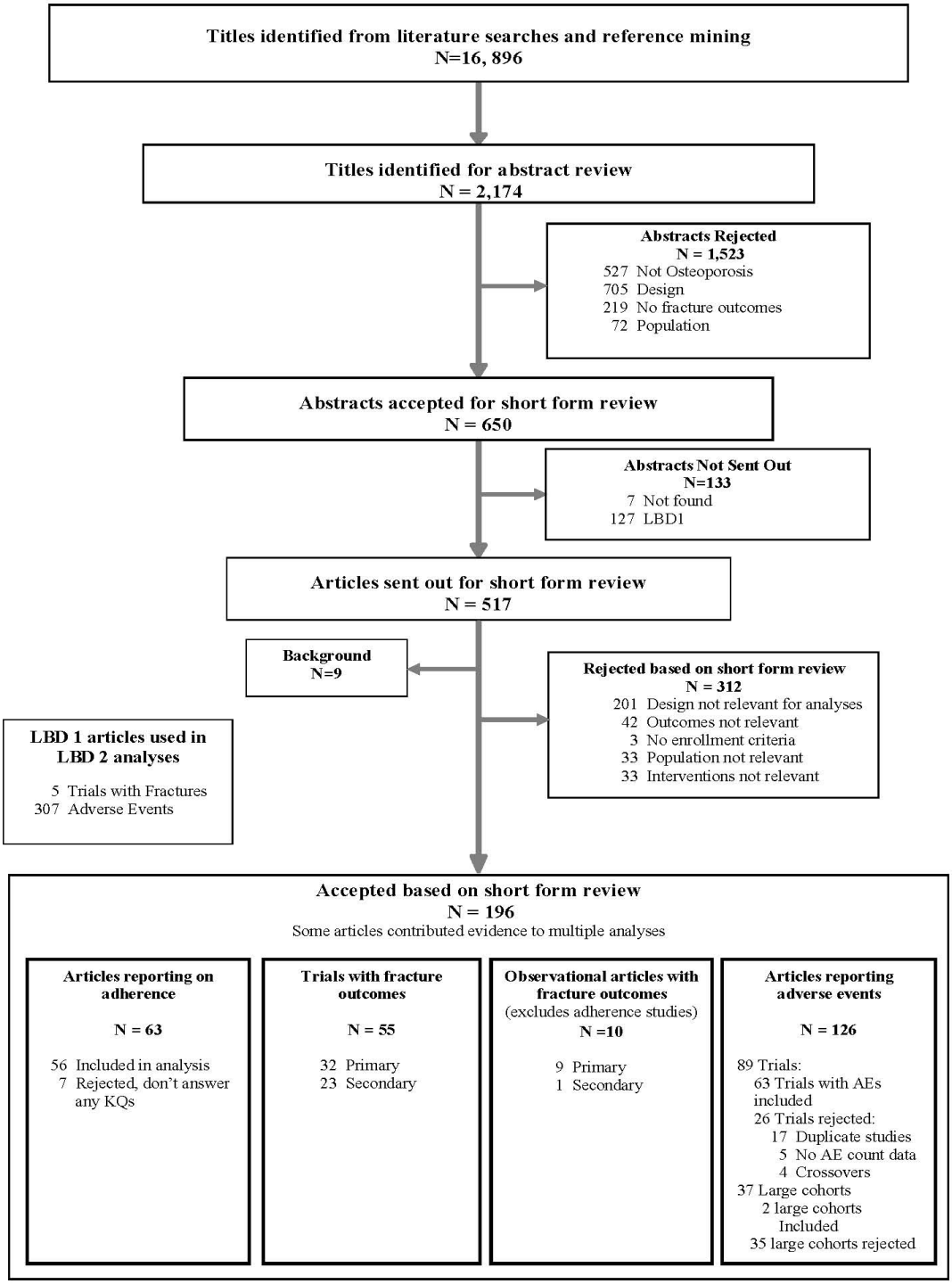


Figure Notes: KQ-Key Question; AE-Adverse Event

Key Question 1: What are the comparative benefits in fracture 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

Key Points

- There is good evidence from RCTs that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, PTH, and raloxifene prevent vertebral fractures in postmenopausal women with osteoporosis.
- There is good evidence from RCTs that alendronate, risedronate, ibandronate, zoledronic acid, and denosumab prevent non-vertebral fractures in postmenopausal women with osteoporosis.
- There is good evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab prevent hip fractures in postmenopausal women with osteoporosis.
- The original report found good evidence that estrogen is associated with a reduced incidence of vertebral, non-vertebral and hip fractures; however studies identified for this report, which were focused on postmenopausal women with established osteoporosis, did not show significant reductions in fracture risk.
- The evidence is moderate, based on a published meta-analysis and several RCTs that there is no difference between calcium alone and placebo in preventing vertebral and nonvertebral fractures; however, calcium significantly reduced hip fracture risk in one pooled analysis, and overall fracture risk in another pooled analysis.
- According to a large body of literature, vitamin D had varying results depending on dose, analogs and population. Vitamin D, 700 to 800 I.U. daily, particularly when given with calcium, reduces the risk of hip and non-vertebral fractures among institutionalized populations (one meta-analysis), and the risk of overall fractures (a second meta-analysis)
- There is evidence from meta-analyses that there is no difference in vertebral, non-vertebral, or hip fracture risk with administration of vitamin D alone compared to administration of calcium alone.
- There is limited evidence from a published meta-analysis of three relatively heterogeneous RCTs on the effect of exercise compared to placebo that showed no effect on fracture prevention. No studies compared the effect of physical activity to that of other interventions.
- Based on limited data from head-to-head trials, within the bisphosphonate class, superiority for the prevention of fractures has not been demonstrated for any agent.

- Based on limited head-to-head trial data, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison with calcium, PTH (teriparatide), or raloxifene.
- Based on head-to-head RCTs, there was no difference in fracture incidence between bisphosphonates and menopausal hormone therapy.
- Based on one head-to-head trial, the combination of alendronate and calcium significantly decreased the risk for any type of clinical fracture compared with alendronate alone.
- Based on limited head-to-head trial data, there was no difference in fracture incidence between menopausal hormone therapy and raloxifene or vitamin D.
- No RCTs tested combinations of osteoporosis therapies or sequential use of osteoporosis therapies in relation to fracture outcomes.

Overview of results

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 meta-analyses and systematic reviews presented in the original report as well as meta-analyses 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.[30] Subsequently, for each medication, we present results of original studies published subsequent to the meta-analyses. 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 meta-analyses and original studies not included in a prior meta-analysis 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 meta-analyses and the original studies they included; then we show the actual findings of those 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 meta-analyses and original studies not included in a prior meta-analysis 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 US.

Alendronate

PRIOR META-ANALYSES. We identified nine meta-analyses evaluating the antifracture efficacy of alendronate compared to placebo or no treatment[31-39] (Table 3). In aggregate, the meta-analyses included data from 17 RCTs, the characteristics of which are summarized in Table 3. Of the nine meta-analyses, five assessed vertebral fracture risk, six assessed non-vertebral fracture risk, six assessed hip fracture risk, and four assessed wrist fracture risk.

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

	Meta-analysis (Author, Year)																				
	Cra, 2002[31]				Kar, 1997[32]			Pap, 2004[33]	Ste, 2005[34]				Boo, 2005[36]	Ngu, 2006[35]	Saw, 2005[37]		Jan, 2009[38]	Wel, 2008[39]			
	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[40]	X	X			X	X	X														
Ascott Evans, 2003[41]																		X	X	X	
Black, 1996[42]	X	X	X	X				X	X	X	X	X	X	X			X	X	X	X	X
Bone, 1997[43]	X	X																X	X		
Bonnick, 1998[44]		X						X						X							
Chesnut, 1995[45]	X	X			X	X	X											X	X		
Cummings, 1998[46]	X	X						X	X		X	X	X	X			X	X	X	X	X
Dursun, 2001[47]									X									X			
Greenspan, 1998[48]								X											X	X	X
Greenspan, 2002[49]														X						X	
Hosking, 1998[50]	X	X																X	X		
Liberman, 1995[51]	X	X			X	X	X	X	X	X	X	X	X	X			X		X	X	X
McClung, 1998[52]	X	X																			
Orwoll, 2000[53]																				X	X
Pols, 1999[54]		X								X				X				X	X	X	X
Ringe, 2004[55]															X	X					
Weinstein, 1994[56]					X	X	X														

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

References for meta-analyses: Cranney, Endocr Rev, 2002[31]; Karpf, JAMA, 1997[32]; Papapoulous, Osteoporos Int, 2004[33]; Stevenson, Health Technol Assess, 2005[34]; Boonen, Osteoporos Int, 2005[36]; Nguyen, J Bone Miner Res, 2006[35]; Sawka, BMC Musculoskelet Disord, 2005[37]; Jansen, Curr Med Res Opin, 2009[38]; Wells, Cochrane Database Syst Rev, 2008[39]

Table 4 lists the meta-analyses 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 non-vertebral 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, non-vertebral 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).

NEW ORIGINAL PLACEBO-CONTROLLED STUDIES. Characteristics of RCTs that examined fracture risk with alendronate (and were not included in a prior meta-analysis) vs. placebo are displayed in Table 5. Seven studies were included in the original report and three studies were newly identified for this report.[57-59] 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 non-vertebral 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[27] 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 robust evidence that treatment of osteoporosis with alendronate 10 mg daily compared to placebo significantly reduces the risk of vertebral fracture, non-vertebral fracture, and hip fracture in patients with osteoporosis. Data are less compelling about non vertebral and hip fractures in patients with osteoporosis.

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

Type of fracture	# trials	Sample size	RR	(95% CI)
		Vertebral		
Original 2007 Report				
Cranney, 2002[31]				
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[37]	2	375	0.36	(0.17, 0.77)
Stevenson, 2005[34]				
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[38] 5-20mg/d	3	7,453	0.47	(0.35, 0.57)
Wells, 2008[39]				
All trials 5 mg	3	1314/1493	0.40	(0.29, 0.55)
10mg	4	3486/3670	0.55	(0.45, 0. 67)
Primary Prevention 5 mg	0	n/a	n/a	n/a
10 mg	1	2214/2218	0.55	(0.38, 0.80)
Secondary Prevention 5 mg	3	1314/1493	0.40	(0.29, 0.55)
10 mg	3	1272/1452	0.55	(0.43, 0.69)
		Non-vertebral		
Original 2007 Report				
Boonen, 2005[36]	3	7,453	0.86	(0.76, 0.97)
Cranney, 2002[31]				
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[32]	5	1,602	0.71	(0.50, 1.00)
Sawka, 2005[37]	2	375	0.73	(0.32, 1.67)
Stevenson, 2005[34]				
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[39]				

All trials 5 mg	2	591/592	0.95	(0.34, 2.67)
10mg	5	4843/4638	0.84	(0.74, 0.94)
Primary Prevention 5 mg	1	498/501	1.50	(0.82, 3.05)
10mg	1	2214/2218	0.89	(0.76, 1.04)
Secondary Prevention 5 mg	1	93/91	0.55	(0.26, 1.18)
10 mg	4	2629/2420	0.77	(0.64, 0.92)
Hip				
Original 2007 Report				
Cranney, 2002[31]				
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[32]	5	1,602	0.46	(0.15, 1.36)
Nguyen, 2006[35]	6	10389	0.55	(0.27, 1.12)
Papapoulos, 2005[33]				
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[34]				
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[39]				
All trials 5 mg	0	n/a	n/a	n/a
10mg	6	5005/4802	0.61	(0.40, 0.92)
Primary Prevention 5 mg	0	n/a	n/a	n/a
10mg	1	2214/2218	0.79	(0.44, 1.44)
Secondary Prevention 5 mg	0	n/a	n/a	n/a
10 mg	5	2792/2584	0.47	(0.26, 0.85)
Forearm/Wrist				
Original 2007 Report				
Cranney, 2002[31]				
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[32]	5	1,602	0.39	(0.19, 0.78)
Stevenson, 2005[34]				
Subjects with osteoporosis or	2	5,426	0.67	(0.19, 2.32)

Osteopenia				
Subjects with osteoporosis or established osteoporosis	2	3,071	0.48	(0.31, 0.75)
Update Report				
Wells, 2008[39]				
All trials 5 mg	0	n/a	n/a	n/a
10mg	5	4843/4638	0.68	(0.34, 1.37)
Primary Prevention 5 mg	0	n/a	n/a	n/a
10mg	1	2214/2218	1.19	(0.87, 1.62)
Secondary Prevention 5 mg	0	n/a	n/a	n/a
10 mg	4	2629/2420	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[60]	24 months	Any clinical fracture	5/92	4/50	0.65 (0.16, 2.66)
Greenspan, 2003[61]	36 months	Clinical fracture	7/93	9/93	0.76 (0.27, 2.12)
Hosking, 2003[62]	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[63]	12 months	Clinical vertebral fracture	1/46	1/46	1.00 (0.06, 16.23)
Quandt, 2005[64]	54 months	Clinical vertebral fracture	12/1878	29/1859	0.43 (0.23, 0.79)
Zein, 2005[65]	12 months	New compression/vertebral fracture	1/14	0/13	6.88 (0.14, 347.7)
Update Report					
Papaioannou,2008[57]	12 months	Vertebral	0/23	2/24	0.14 (.01, 2.23)
Ringe, 2007[58a]	24 months	Vertebral	4/30	5/30	0.77 (0.19, 3.15)
		Non-Vertebral Fractures			
Original 2007 Report					
Zein, 2005[65]	12 months	Peripheral fracture	0/14	1/13	0.13 (0.00, 6.33)
Update Report					
de Nijs, 2006[59]	18 months	Non-vertebral	2/99	3/101	0.68(0.12,3.99)
Ringe, 2007[58a]	24 months	Non-vertebral	6/30	4/30	1.6 (0.42,6.16)
		Hip			
Original 2007 Report					
Sato, 2006[66]	48 months	Hip fracture	4/131	14/129	0.30 (0.12, 0.78)
Update Report: *No new studies*					

Author, year	Study duration	Type of fracture	Number of fractures, Alendronate	Number of fractures, placebo	Odds ratio (95% CI)
		Wrist			
Original 2007 Report					
McClung, 2006[63]	12 months	Radius, ulna, or both	0/46	0/46	NC
Update Report: *No new studies*					
		Humerus (Original 2007 report, no new studies for current report)			
McClung, 2006[63]	12 months	Humerus	0/46	0/46	NC
Update Report: *No new studies*					

NC=not calculable

[a] 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 META-ANALYSES: We found 10 meta-analyses that reported the relative risk of fracture with risedronate vs. placebo or no treatment[34-36, 67-73] (Table 6). Together, these meta-analyses encompassed 14 RCTs. Of the 10 meta-analyses, 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 non-vertebral 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 non-vertebral fracture risk. In the primary prevention setting, and with dosing of 2.5 mg daily, risedronate was not associated with reduction in non-vertebral fractures.

Four of the five available pooled estimates reported statistically significant reductions (ranging from 36%-40%) 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 meta-analysis 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.[74-77] 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.[78] Compared to placebo, risedronate 2.5 mg daily was associated with 71 percent reduced risk of non-vertebral fracture.[79] 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.[74, 79-81]

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.[82] The reduction of non-vertebral

fracture risk associated with risedronate 5 mg daily vs. placebo was not statistically significant in two comparisons.[82, 83] including one 12-month study of men with primary or secondary osteoporosis[83] but was significant in the same study at 24-months.[75]

Risedronate 30-35 mg weekly dose: Overall fracture risk was not statistically different with risedronate 30-35 mg weekly compared to placebo.[84, 85] In three of four comparisons, risedronate 35 mg weekly vs. placebo was not associated with a statistically significant reduction in risk of vertebral fractures.[76, 77, 86] In two of three comparisons involving the same population of postmenopausal women at 12, 24, and 36 months, the relative risk of non-vertebral fracture with risedronate 35 mg weekly vs. placebo was significantly decreased (0.13-0.20).[77, 86]

Using the criteria of Gartlehner et al.[27], 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 cormorbid 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.[87 88] 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 non-vertebral 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 non-vertebral 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.,[27] 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, non-vertebral, and hip fractures.

Table 6. Randomized controlled trials included in meta-analyses of effect of risedronate on fracture relative to placebo or no treatment

	Meta-analysis (Author, year)																	
	Cra, 2002[67]		Ste, 2005[34]				Boo, 2005[36]	Mil, 2005[68]	Ngu, 2006[35]	Wat, 2003[89]	Wal, 2000[70]	Bia, 2008[71]	Wel, 2008[72]				Zho, 2009[73]	
	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[90]	X	X											X	X				
Cohen, 1999[91]											X							
Fogelman, 2000[92]	X	X						X					X	X				
Harris, 1999[93]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		
Hooper, 2005[94]								X										
McClung, 1998[95]**		X						X					X	X				
McClung, 2001[96]**		X			X		X	X	X					X	X			
Mortensen, 1998[97]	X	X																
Reginster, 2000[98]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		
Reid, 2000[99]											X	X	X	X	X			
Reid, 2001[100]																	X	
Ringe, 2006[83]																	X	X
Sato, 2005[80]																		X
Sato, 2007[74]																		X

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

** same study reported in two different abstracts.

References for meta-analyses: Cranney, Endocr Rev, 2002[31]; Stevenson, Health Technol Assess, 2005[34]; Boonen, Osteoporos Int, 2005[36]; Miller, J Bone Miner Res, 2005[68]; Nguyen, J Bone Miner Res, 2006[35]; Watts, J Clin Endocrinol Metab, 2003[89]; Wallach, Calcif Tissue Int, 2000[70]; Bianchi, Curr Med Res Opin, 2008[71]; Wells, Cochrane Database Syst Rev, 2008[72]; Zhong, Clin Drug Investig, 2009[73]

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

Type of fracture	# studies	Sample size	RR	(95% CI)
		Vertebral		
Original 2007 Report				
Cranney, 2002[67]	5	2,604	0.64	(0.54, 0.77)
Miller, 2005[68]				
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	3088	0.32	(0.14, 0.46)
Stevenson, 2005[34]	2	2,064	0.62	(0.50, 0.77)
Update Report				
Zhong, 2009[73b]	4	1,022	0.31	(0.16, 0.60)
Wells, 2008[72]				
Overall 2.5mg	4	1460/1532	0.62	(0.46, 0.83)
5 mg	4	1534/1532	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	1333/1407	0.57	(0.42, 0.78)
5 mg	3	1405/1407	0.61	(0.50, 0.76)
		Non-vertebral		
Original 2007 Report				
Boonen, 2005[36]	3	11,770	0.81	(0.71, 0.92)
Cranney, 200244[67]	7	12,958	0.73	(0.61, 0.87)
Stevenson, 2005[34]	2	2,439	0.67	(0.50, 0.90)
Update Report				
Zhong, 2009[73b]	4	1,022	0.40	(0.23, 0.70)
Wells, 2008[72]				
Overall 2.5mg	2	235/305	0.50	(0.21, 1.19)
5 mg	5	7731/4666	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	7602/4541	0.80	(0.72, 0.90)
		Hip		
Original 2007 Report				

Type of fracture	# studies	Sample size	RR	(95% CI)
Nguyen, 2006[35]	3	7,196	0.66	(0.11, 3.68)
Stevenson, 2005[34]				
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[72]				
Overall 5 mg	3	7425/4361	0.74	(0.59,0.94)
Primary 5 mg	1	37/36	NE[c]	
Secondary 5 mg	3	7425/4361	0.74	(0.59,0.94)
		Wrist		
Original 2007 Report				
Stevenson, 2005[34]				
Subjects with severe osteoporosis	2	2,439	0.68	(0.43, 1.08)
Update Report				
Wells, 2008[72]				
Overall 5mg	2	1265/1263	0.67	(0.42, 1.07)
Primary 5 mg	1	37/36	NE	
Secondary 5 mg	2	1228/1227	0.67	(0.42, 1.07)

[a]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.

[b] Men

[c] NE: not estimable

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[85]	12 months	Fracture	2/43	0/44	7.75 (0.48, 125.9)
Hosking, 2003[62]	12 months	Clinically diagnosed vertebral or non-vertebral	6/178	2/89	1.47 (0.33, 6.52)
Milgrom, 2004[84]	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[78]	12 months	Vertebral	0/12	0/11	NC
Update Report: *No new studies*					
2.5 Mg Daily, Non-Vertebral					
Original 2007 Report					
Sato, 2005[79]	18 months	Non-vertebral	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[79]	18 months	Hip	5/231	19/230	0.29 (0.13, 0.66)
Sato, 2005[80]	18 months	Hip	2/134	10/133	0.25 (0.08, 0.78)
Sato, 2005[81]	12 months	Hip	1/172	7/173	0.22 (0.05, 0.88)
Update Report					
Sato, 2007[74]	24 months	Hip	3/121	9/121	0.35 (0.11, 1.12)
5.0 Mg Daily, Vertebral					
Original 2007 Report					
Sorensen, 2003[82]	24 months	Vertebral	15/109	29/103	0.42 (0.22, 0.81)
Update Report: *No new studies*					
5.0 Mg Daily, Non-Vertebral					
Original 2007 Report					
Sorensen, 2003[82]	24 months	Non-vertebral	7/135	11/129	0.59 (0.23, 1.54)
Update Report					
Ringe, 2009[75]	24 months	Nonvertebral	18/152	33/148	0.48 (0.26, 0.87)
Ringe, 2006[83]	12 months	Nonvertebral	10/158	17/158	0.57 (0.26, 1.25)

Author, year	Study duration	Type of fracture	Number of fractures, Risedronate	Number of fractures, placebo	Odds ratio (95% CI)
5.0 Mg Daily, Humerus					
Original 2007 Report					
Sorensen, 2003[82]	24 months	Humerus	3/136	6/130	0.48 (0.13, 1.81)
Update Report: *No new studies*					
30-35 Mg Weekly, All Fractures					
Greenspan, 2006[85]	12 months	Fracture	2/43	0/44	7.75 (0.48, 125.9)
Milgrom, 2004[84]	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[86]	12 months	Vertebral	5/40	14/41	0.30 (0.11, 0.84)
Update Report					
Boonen, 2009[76]	2 years	Vertebral	2/191	0/93	4.45 (0.23, 85.68)
Palomba, 2008[77]	2 years	Vertebral	4/40	7/41	0.55 (0.16, 1.95)
Palomba, 2008[77]	3 years	Vertebral	3/40	9/41	0.32 (0.1, 1.09)
35 Mg Weekly, Non-Vertebral					
Original 2007 Report					
Palomba, 2005[86]	12 months	Nonvertebral	0/40	4/41	0.13 (0.02, 0.95)
Update Report					
Palomba, 2008[77]	2 years	Nonvertebral	1/40	7/41	0.2 (0.05, 0.85)
Palomba, 2008[77]	3 years	Nonvertebral	1/40	4/41	0.29 (0.05, 1.75)

NC=not calculable.

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

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 17.5mg/Week					
Vertebral					
Original 2007 report					
Kishimoto, 2006[101]	48 weeks	Vertebral	6/222	5/227	1.23 (0.37, 4.00)
Update report: *No new studies*					
Risedronate 5 Mg/D vs. risedronate 35mg/Week					
Vertebral					
Original 2007 report					
Brown, 2002[102]	24 months	New morphometric vertebral	6/480	5/485	1.21 (0.37, 3.98)
Harris, 2004[103]	24 months	Morphometric vertebral	12/415	7/422	1.92 (0.75, 4.88)
Update report: *No new studies*					
Non-Vertebral					
Original 2007 report					
Brown, 2002[102]	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 50mg/Week					
Vertebral					
Original 2007 report					
Brown, 2002[102]	24 months	New morphometric vertebral	6/480	2/491	2.8 (0.7, 11.26)
Harris, 2004[103]	24 months	Morphometric vertebral	12/415	7/422	1.74 (0.70, 4.32)
Update report: *No new studies*					
Non-Vertebral					
Original 2007 report					
Brown, 2002[102]	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 50mg/Week					
Vertebral					
Original 2007 report					
Brown, 2002[102]	24 months	New morphometric vertebral	5/485	2/491	1.19 (0.68, 2.08)
Harris, 2004[103]	24 months	Morphometric	12/415	7/422	0.9 (0.30, 2.68)

Author, year	Study duration	Type of fracture	Number of fractures, risedronate, weekly*	Number of fractures, risedronate, daily	Odds ratio (95% CI)[#]
		vertebral			
Update report: No new studies					
Non-Vertebral					
Original 2007 report					
Brown, 2002[102]	24 months	Any non-vertebral	28/485	24/491	1.19 (0.68, 2.08)
Update report: *No new studies*					
Risedronate 150 mg daily for 2 consecutive days per month vs. risedronate 5mg/D					
Vertebral					
Original 2007 report: *No comparable studies from the original report*					
Update report					
Delmas, 2008[87]	12 months	Vertebral	6/616	7/613	0.85 (0.29, 2.54)
Delmas, 2008[88]	12 months	Vertebral	8/650	8/642	0.99 (0.37, 2.65)

*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

NC=not calculable.

Ibandronate

PRIOR META-ANALYSES. The antifracture effects of ibandronate vs. placebo or no treatment was examined in three meta-analyses (two specific to ibandronate[104, 105] and the third covering multiple bisphosphates)[38](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.[105] We include RCT evidence for the effect of ibandronate vs. placebo in reducing vertebral fracture risk (51% statistically significant). In postmenopausal women, the RR of non-vertebral 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 non-vertebral fracture and of clinical fracture, of approximately 30%, 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 meta-analyses (two included in the first report [106, 107] and one identified for this report[108]). 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).[106] 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 meta-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.[27] 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.[108]

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

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

	Meta-analysis (Author, year)			
	Cranney, 2009 [104]**	Harris, 2008 [105]		Jansen, 2009 [38]
	Fracture type*			
RCTs (Author, year)	**NV**	**A**	**NV**	**V**
Chestnut, 2004 [109]	X	X	X	X
Recker, 2004[110]	X	X	X	
Miller, 2005[111]	X			
Delmas, 2006[112]	X			

*V =vertebral, A =all, NV =non-vertebral; 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

Type of fracture	# studies	Sample size	RR	(95% CI)
		Vertebral		
Original Report: ***No comparable studies from the original report***				
Update Report:				
Jansen, 2009 [38]				
2.5 mg/d or 20 mg every other day	1	2.946	0.49	(0.26, 0.66)
		Non-vertebral		
Original Report: ***No comparable studies from the original report***				
Update Report				
Cranney, 2009 [104]				
Lower ACE (5.5 mg) vs. placebo[a]	3	3,212	1.073[b]	(0.79, 1.46)
Harris, 2008 [105]				
Key non-vertebral sites:				
Higher ACE (≥10.8 mg) all-years[c]	4	8,710	0.66[e, f]	(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 non-vertebral:				
Higher ACE (≥10.8 mg) all-years	4	8,710	0.70[f]	(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)

Type of fracture	# studies	Sample size	RR	(95% CI)
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)
Clinical vertebral and non-vertebral fractures [d]				
Original Report: ***No comparable studies from the original report***				
Update Report				
Harris, 2008[105]				
Higher ACE (≥10.8 mg) all-years	4	8,710	0.73 [f]	(0.56, 0.95)
Higher ACE (≥10.8 mg) two-years	4	8,710	0.71[f]	(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 [f]	(0.60, 0.97)

[a] 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

[b] Unadjusted hazard ratio

[c] 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.

[d] clinical trials include non-vertebral and symptomatic vertebral, all ascertained by x-ray.

[e] Adjusted hazard ratio

[f] Significantly different

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

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[106]	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[107]	12 months	Vertebral	1/40	1/40	1.00 (0.006, 16.27)
Update Report					
Fahrleitner-Pammer, 2009[108]	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 META-ANALYSES. We identified no prior meta-analyses 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.[113, 114] Since that report, two additional publications were identified for inclusion in this update (Jadad scores of 5 and 2).[115, 116] 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),[113] non-vertebral fracture among postmenopausal women and men and women post-hip fracture (RR 0.72-0.73, two RCTs),[113, 115] morphometric vertebral fracture (RR 0.32, one RCT), clinical vertebral fracture (0.23, one RCT),[113], and vertebral fracture among men and women post-hip fracture (RR 0.54, one RCT)[115] 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),[113] 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).[115]

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.[114] The trial recorded 2 fracture events, and had small numbers of participants. Risk of non-vertebral 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[114] and one for the current report[116]; only the older study reported any fractures. The trial recorded two fracture events, and had small numbers of participants. Risk of non-vertebral 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.[114] The trial recorded one fracture event and had small numbers of participants. Risk of non-vertebral 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.[114] The trial recorded two fracture events, and had small numbers of participants. Risk of non-vertebral 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.[114] The trial recorded three fracture events and had small numbers of participants. Risk of non-vertebral 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.[27], 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, non-vertebral fractures, vertebral fractures, and probably 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[113]	36 months	Any clinical	308/3667	456/3563	0.63 (0.54, 0.72)
Black, 2007[113]	36 months	Non-vertebral	292/3650	388/3626	0.73 (0.62, 0.85)
Black, 2007[113]	36 months	Morphometric vertebral	92/2788	310/2844	0.32 (0.26, 0.39)
Black, 2007[113]	36 months	Clinical vertebral	19/3800	84/3231	0.23 (0.16, 0.34)
Black, 2007[113]	36 months	Hip	52/3714	88/3520	0.56 (0.40, 0.78)
Update Report					
Lyles, 2007[115]	24 months	Hip fracture	23/1065	33/1062	0.69 (0.41, 1.17)
Lyles, 2007[115]	24 months	Any fracture	92/1065	139/1062	0.63 (0.48, 0.83)
Lyles, 2007[115]	24 months	Non-vertebral	79/1065	107/1062	0.72 (0.53, 0 .93)
Lyles, 2007[115]	24 months	Vertebral	21/1065	39/1062	0.54 (0.32, 0.90)
4 Milligrams Once					
Original 2007 report					
Reid, 2002[114]	12 months	Non-vertebral	1/60	1/59	0.98 (0.06, 15.91)
Reid, 2002[114]	12 months	Vertebral	0/60	0/59	NC
Update report: *No new studies*					
2 Milligrams, Every 6 Months					
Original 2007 report					
Reid, 2002[114]	12 months	Non-vertebral	1/61	1/59	0.97 (0.06, 15.65)
Reid, 2002[114]	12 months	Vertebral	0/61	0/59	NC
Update report					
Chapman, 2009[116]	24 months	Non-vertebral	0/10	0/12	NC
Chapman, 2009[116]	24 months	Vertebral	0/10	0/12	NC
0.25 Milligrams, Every 3 Months					
Original 2007 report					
Reid, 2002[114]	12 months	Non-vertebral	0/60	1/59	0.13 (0.00, 6.71)
Reid, 2002[114]	12 months	Vertebral	0/60	0/59	NC
Update report: *No new studies*					
0.5 Milligrams, Every 3 Months					
Original 2007 report					
Reid, 2002[114]	12 months	Non-vertebral	1/58	1/59	1.02 (0.06, 16.46)
Reid, 2002[114]	12 months	Vertebral	0/58	0/59	NC
Update report: *No new studies*					

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[114]	12 months	Non-vertebral	2/53	1/59	2.2 (0.22, 21.7)
Reid, 2002[114]	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 META-ANALYSES. We found one meta-analysis of fracture risk associated with denosumab relative to placebo or no treatment.[117] (Table 14) The meta-analysis included data from 3 RCTs encompassing 919 participants and assessed risk of clinical fractures. 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).

ORIGINAL PLACEBO-CONTROLLED STUDIES. Two placebo-controlled trials of denosumab vs. placebo were identified for the current report, two years and 36 months in duration (Jadad scores of 2 and 0, respectively)(Table 16).[118, 119] The smaller RCT of shorter duration (two years)[118] and with fewer fracture events (nine non-vertebral and one vertebral) found no statistically significant difference in risk of vertebral or non-vertebral fracture with denosumab vs. placebo. The much larger RCT (more than 3600 participants) reported statistically significantly lower risk of fracture with denosumab vs. placebo.[119] In this study, denosumab was associated with a 41 percent lower risk of hip fracture (RR 0.59, 0.36-0.94), a 20 percent lower risk of non-vertebral fracture (RR 0.8, 0.67, 0.95), a 60 percent lower risk of multiple new vertebral fracture (RR 0.4, 0.26, 0.61), a 66 percent lower risk of new clinical vertebral fracture (0.34, 0.24, 0.48), and a 66 percent lower risk of vertebral fracture 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[118] and the applicability of the larger study was high.[119]

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[117]
	Fracture type*
RCTs (Author, year)	**A**
Bone, 2008 [118]	X
Ellis, 2008 [120]	X
Lewiecki, 2007[121]	X

*A=all; X= Included in pooled analysis.

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

Type of fracture	**# studies**	**Sample size**	**RR**	**(95% CI)**
Clinical fractures				
Original 2007 Report: ***No comparable studies from the original report***				
Update Report				
Anastasilakis, 2009 [117]	3	919	0.74	(0.33, 1.64)

Table 16. Denosumab vs. 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[119]	36 months	Hip fracture	26/3714	43/3583	0.59 (0.36, 0.94)
Cummings, 2009[119]	36 months	Non-vertebral	238/3662	293/3663	0.8 (0.67, 0.95)
Cummings, 2009[119]	36 months	Multiple new vertebral	23/3833	59/3688	0.4 (0.26, 0.61)
Cummings, 2009[119]	36 months	New clinical vertebral	29/3625	92/3538	0.34 (0.24, 0.48)
Bone, 2008[118]	2 years	Non-vertebral	2/166	7/166	0.32 (0.09, 1.2)
Cummings, 2009[119]	36 months	Vertebral	86/3739	264/3667	0.34 (0.27, 0.42)
Bone, 2008[118]	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 in 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 US.

Raloxifene

PRIOR META-ANALYSES. 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%, with raloxifene vs. placebo (Table 17). In contrast, studies found that, compared to placebo, raloxifene does not decrease the risk of non-vertebral, 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). [122, 123] All but one RCT was consistent with a statistically significant reduction in vertebral fracture risk, ranging from 34 percent - 44 percent, with raloxifene vs. placebo. The exception was the original RCT with five fracture events (RR 1.72, 0.26, 11.05).[124] However, raloxifene was not associated with a statistically significantly decrease in the risk of non-vertebral (two RCTs), hip (one RCT), or wrist (one RCT) fractures.[122, 123] We conclude that, compared to placebo, raloxifene decreases the risk of vertebral fractures, but not non-vertebral, hip, or wrist fractures.

Using the criteria of Gartlehner et al.[27] 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.*

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Schachter, 2005[125]				
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[34]				
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[126]				
60 mg	5	5,600	0.60	(0.49, 0.74)
120/150mg	4	5,403	0.51	(0.41, 0.64)
Non-vertebral				
Stevenson, 2005[34]				
Women with severe osteoporosis or osteoporosis	1	6,828	0.92	(0.79, 1.07)
Hip				
Stevenson, 2005[34]				
Women with severe osteoporosis or osteoporosis	1	6,828	1.12	(0.65, 1.95)
Wrist				
Stevenson, 2005[34]				
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[124]	36 months	Vertebral	4/193†	1/90	1.72 (0.26, 11.05)
Update Report					
Ensrud, 2008[122]	5.6 years	Vertebral	64/5044	97/5057	0.66 (0.48, 0.90)
Silverman, 2008[123]	3 years	Vertebral	43/1849	77/1885	0.57 (0.39, 0.82)
Silverman, 2008[123]	3 years	Vertebral - with prevalent fracture	50/1849	90/1885	0.56 (0.40, 0.79)
Silverman, 2008[123]	3 years	Vertebral - without prevalent fracture	33/1849	58/1885	0.58 (0.38,.88)
		Clinical Vertebral			
Original 2007 Report					
Barrett-Connor[127]	5.6 years	Clinical	64/5,044	97/5,057	0.66 (0.48. 0.90)
Update Report: *No new studies*					
		Non-Vertebral			
Original Report: *No comparable studies from the original report*					
Update Report					
Ensrud, 2008[122]	5.6 years	Non-vertebral	428/5044	438/5057	0.99 (0.86, 1.13)
Silverman, 2008[123]	3 years	Non-vertebral	60/1849	99/1885	0.61 (0.44, 0.84)
		Hip/femur			
Original Report: *No comparable studies from the original report*					
Update Report					
Ensrud, 2008[122]	5.6 years	Hip/femur fracture	89/5044	103/5057	0.86 (0.65, 1.15)
		Wrist			
Original Report: *No comparable studies from the original report*					
Update Report					
Ensrud, 2008[122]	5.6 years	Wrist	107/5044	111/5057	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 META-ANALYSES. The original report identified one meta-analysis on parathyroid hormone.[34] The meta-analysis included data from five RCTs of teriparatide and examined risk of vertebral, non-vertebral, and hip fractures. One additional meta-analysis was identified for the current report[128] (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 non-vertebral fractures, with RR's ranging from 0.60 to 0.65. The meta-analysis includes an indirect comparison of vertebral fracture effects (from two individual RCTs, (RR 0.31).[129, 130] Based on one RCT that did not report sample sizes, the risk of hip, wrist, and humerus fractures was not statistically different with teriparatide versus placebo.

ORIGINAL PLACEBO-CONTROLLED STUDIES. No new studies of teriparatide were identified for this report. The original report included three studies of teriparatide(Table 21).[131-133]

All fractures: Compared to placebo, teriparatide was associated with a statistically significant 84 percent reduction (one RCT).[132]

Vertebral Fractures: In the RCT with the fewest number of vertebral fracture events, vertebral fracture risk was no different with PTH than placebo;[132, 134] 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.[131, 133, 135]

Non-vertebral Fractures: For non-vertebral fractures, risk with teriparatide was not statistically different from that of placebo in two trials.[131, 133-135]

This finding contrasts with the pooled analysis,[128] which included these two trials along with three other trials, and found a statistically significant 38 percent relative risk reduction with teriparatide treatment. Results on nonvertebral fractures are therefore somewhat inconsistent.

In summary, compared to placebo, PTH is associated with reduced risk of vertebral fractures, and probably with reduced risk of non-vertebral fractures.

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

	Meta-analysis (Author, year)		
	Vestergaard, 2007[128]		
	Fracture type*		
RCTs (Author, year)	V	NV	H
Cosman, 2004 [136]	X	X	X
Greenspan, 2005[129]	X		
Kurland, 2000 [137]			X
Neer, 2001 [130]	X	X	
Orwoll, 2003 [138]	X	X	

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

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

Type of fracture	# studies	Sample size	RR	(95% CI)
		Vertebral fractures		
Original 2007 Report				
Stevenson, 2005[34]				
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 [128]	7	4,359	0.36	(0.28, 0.47)
		Non-vertebral		
Original 2007 Report				
Stevenson, 2005[34]				
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 [128]	5	2,377	0.62	(0.48, 0.82)
		Hip		
Original 2007 Report				
Stevenson, 2005[34]				
Subjects with severe osteoporosis	1	NR	0.50	(0.09, 2.73)
Update report: *no new studies*				
		Wrist		
Original 2007 Report				
Stevenson, 2005[34]				
Subjects with severe osteoporosis	1	NR	0.54	(0.22, 1.35)
Update Report: *No new studies*				
		Humerus		
Original 2007 Report				
Stevenson, 2005[34]				

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[132]	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[131]	21 months	Vertebral	22/403	62/398	0.34 (0.22, 0.54)
Kaufman, 2005[132]	30 months	Vertebral	10/176†	12/103	0.44 (0.18, 1.09)
Update Report: *No new studies*					
		Non-Vertebral Fractures			
Original 2007 Report					
Gallagher, 2005[131]	21 months	Non-vertebral	30/467	46/464	0.63 (0.39, 1.00)
Orwoll, 2003[133]	11 months	Non-vertebral	3/290†	3/147	0.48 (0.09, 2.62)
Update Report: *No new studies*					

†20ug and 40ug 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. However, the WHI also reported harms associated with menopausal hormone therapy, including venous thromboembolic events, stroke, and a variable effect on breast cancer, such that routine use of hormone replacement therapy in postmenopausal women is now discouraged.

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 non-vertebral fracture (Jadad score 5) (Table 22).[139] 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 non-vertebral fractures compared to placebo.[140]

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.[27] 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[60]	24 months	Any clinical	10/143	4/50	0.86 (0.25, 2.97)
Greenspan, 2003[61]	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[140]	24 months	Vertebral	7/66†	17/66‡	0.36 (0.15, 0.88)
Reid, 2004[124]	36 months	Vertebral	1/102	1/90	0.88 (0.05, 14.27)
Wimalawansa, 1998[141]	48 months	Vertebral	2/15†	5/14‡	0.31 (0.06, 1.64)
Update Report					
Boone, 2006[139]	24 months	Vertebral	0/16	2/15	0.12 (.01, 1.98)
			Non-Vertebral Fractures		
Original 2007 Report					
Wimalawansa, 1998[141]	48 months	Non-vertebral	1/15†	1/14‡	0.93 (0.06, 15.69)
Update Report					
Boone, 2006[139]	24 months	Non-vertebral	0/16	0/15	NC

NC=not calculable; †Bone, 2000: conjugated equine estrogen; Greenspan, 2003: comjugated 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 META-ANALYSES. For calcium alone, four meta-analyses assessed 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 non-vertebral fracture risk, two examined hip fracture risk, and one examined overall fracture risk.

For vitamin D alone, 15 meta-analyses addressed a total of 43 RCTs comparing fracture risk with vitamin D compared to placebo or no treatment (Table 24). Of these 15 meta-analyses, nine meta-analyses examined vertebral fracture risk, 12 examined non-vertebral fracture risk, eight examined hip fracture risk, and three examined overall fracture risk.

Calcium alone did not reduce vertebral or non-vertebral 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,[142] 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.[143] There was a statistically significantly higher reduction in overall fracture risk with calcium ≥ 1200 mg/d compared to <1200mg/d.[144] Thus, data on calcium supplementation alone and fracture risk are conflicting.

In general, in meta-analyses 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.[145] However, among populations not selected on the basis of osteoporotic fracture,[146, 147] those with prior fractures,[148] women with severe osteoporosis[34] or those taking glucocorticoid treatment,[145] 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.[34, 146 148, 149]

There were no statistically significant differences in vertebral risk in comparisons of alfacalcidol vs. vitamin D + calcium, or calcitriol vs. vitamin D.[148] In one pooled analysis, neither 10 µg[‡‡] nor 20 µg doses of vitamin D altered vertebral fracture risk in comparison with placebo, even when given in conjunction with calcium.[149] 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.

Non-vertebral fracture: Statistically significant decreases in non-vertebral 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.[145] In contrast, the following were not associated with statistically significant reductions in non-vertebral fracture risk: alfacalcidol, calcitriol, or vitamin D among people not selected on the basis of prior osteoporotic fracture, calcitriol among women with severe osteoporosis.[34, 146, 148]

In combination with calcium, vitamin D was associated with a statistically significant reduction in non-vertebral fracture risk among populations not selected on the basis of prior osteoporotic fractures.[146, 150] Among institutionalized persons, vitamin D + calcium was associated with 15% decrease (statistically significant) in non-vertebral fracture risk.[148] In contrast, vitamin D + calcium was not associated with a statistically significantly decreased risk of non-vertebral 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.[148] Standard vitamin D doses of ≥700 IU/d + calcium are associated with statistically significant reductions in non-vertebral fracture risk among institutionalized persons (RR 0.80).[151]

In summary, compared to placebo, vitamin D + calcium decreases the risk of non-vertebral fractures among the institutionalized by 15%-20%. 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.[146] 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.[143, 146, 149] Nor was calcitriol more effective than placebo in reducing hip fracture risk among those not selected on the basis of prior osteoporotic fractures.[148] One pooled estimate even showed a statistically significantly increased risk of hip fracture in associated with injection of vitamin D compared to placebo.[149]

[‡‡] Some studies report vitamin D doses in international units(IU), whereas some report the doses in micrograms (ug). One IU vitamin D is equivalent to 0.025 ug 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%, 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.[34, 143, 146, 148, 150] 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.[148, 151] 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).[149] Dosing of ≥700 IU of vitamin D was associated with a 28% lower risk of hip fractures among institutionalized persons (RR 0.72, 95% CI 0.59-0.88).[151]

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.

Non-vertebral non-hip fracture. The one available estimate suggested that vitamin D with calcium was associated with statistically significant reduction in non-vertebral non-hip 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% lower relative risk vs. placebo) and efficacy of vitamin D + calcium in reducing overall clinical fractures about 10% to 15% compared to placebo.[144, 149] Vitamin D injection did not reduce overall clinical fracture risk compared to 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% lower overall fracture risk.[144] Vitamin D 10 ug with calcium, but not without calcium, was associated with statistically significantly lower overall fracture risk compared to placebo.[149] A similar pattern was apparent for vitamin D 20 ug with and without calcium, whereby the relative risk of fracture was decreased with vitamin D 20 ug + calcium (although not statistically significantly so), and not with vitamin D 20 ug 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).[152]

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).[152] Using the criteria of Gartlehner et al.[27] to assess the applicability of this study, we determined its applicability to be moderately high.

Calcium+ vitamin D. Three RCTs from the original report[153-155] and one new RCT identified for this report[152] assessed the effects of calcium+vitamin D on fracture risk. With the exception of one RCT showing a 25 percent lower overall risk of fracture,[152] 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.[27] to assess the applicability of the new study, we determined its applicability to be moderately high.

Calcium alone: Four RCTs from the original report[69, 155-157] and two new RCTs identified for this report[158, 159] 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,[157] 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.[27] 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[140, 155, 160, 161] and three new RCTs identified for this report[162-164] assessed the effect of vitamin D alone on fracture risk (Jadad scores for new studies 4, 5, and 3). Of the three RCTs examining hip fracture risk in relation to vitamin D,[161 164])[163] one RCT showed an 88 percent lower risk of hip fracture (0.01, 0.90),[161] and another RCT showed a 49 percent *higher* risk of hip fracture (1.03, 2.18).[163] The risks of fractures (overall), vertebral fractures, non-vertebral fractures, hip fractures, and wrist fractures were not statistically different with vitamin D compared to placebo (Table 30). Using the criteria of Gartlehner et al.[27] 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 meta-analysis of effect of calcium on fracture relative to placebo or no treatment

	Meta-analysis (Author, year)					
	Shea, 2002[165]		Bischoff-Ferrari, 2007[142]		Boonen, 2007[143]	Tang, 2007[144]
	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[159]						X
Grant, 2005[155]			X	X	X	X
Hansson, 1987[172]	X					
Harwood, 2004[173]						X
Jackson, 2006[153]					X	X
Larsen, 2004[152]						X
Peacock, 2000[174]						X
Porthouse, 2005[154]					X	X
Prince, 1995[175]						X
Prince, 2006[157]			X	X		
Recker, 1996[176]	X					X
Reid, 1993[177]	X					X
Reid, 1995[178]			X	X		
Reid, 2006[69]			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 meta-analyses of effect of vitamin D on fracture relative to placebo or no treatment

	Meta-analysis (Author, year)																																
	Ave, 2005[146]		Bis, 2005[180]		Pap, 2002[181]		Ste, 2005[34]		Ric, 2004[182]		Ric, 2005[145]		Abr, 2010[149]			Ave, 2009[148]					Ber, 2010[150]		Bis, 2009[183]		Boo, 2007[143]	Iza, 2007[151]		Jac, 2007[184]		O'Do, 2008[147]		Tan, 2007[144]
	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**
Adachi, 1996[185]												X																					
Aloia, 1988[186]								X		X																							
Avenell, 2004[187]	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										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					X
Dawson-Hughes, 1997[171]				X	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[155]	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													X
Hayashi, 1992[199]										X		X																					
Ishida, 2004[140]																		X	X	X											X	X	
Jackson, 2006[153]														X	X	X		X	X	X				X	X	X		X					X
Jensen, 1985[200]																															X		
Komulainen, 1998[201]													X						X											X			

	Meta-analysis (Author, year)																																
	Ave, 2005[146]			Bis, 2005[180]		Pap, 2002[181]		Ste, 2005[34]		Ric, 2004[182]		Ric, 2005[145]		Abr, 2010[149]			Ave, 2009[148]					Ber, 2010[150]		Bis, 2009[183]		Boo, 2007[143]	Iza, 2007[151]		Jac, 2007[184]		O'Do, 2008[147]		Tan, 2007[144]
	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**
Larsen, 2004[152]														X	X	X																	X
Law, 2006[164]																	X			X													
Lips, 1996[202]			X	X	X		X						X				X			X				X	X	X	X	X		X			
Lyons, 2007[203]														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					
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[154]														X	X	X			X	X			X			X		X					X
Reid, 1993[177]																										X							X
Sato, 1999[210 211]																				X													
Smith, 2007[163]							X							X	X	X	X			X													
Tilyard, 1992[212]																															X	X	
Trivedi, 2003[213]												X					X			X				X	X	X	X	X	X	X			
Ushiroyama, 2001[214]																			X												X		

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

References for meta-analysis: Avenell, Cochrane Database Syst Rev, 2005[146]; Bischoff-Ferrari, JAMA, 2005[180]; Papadimitropoulos, Endocr Rev, 2002[181]; Stevenson, Health Technol Assess, 2005[34]; Richy, Osteoporos Int, 2004[182]; Richy, Calcif Tissue Int, 2005[145]; Abrahamsen, BMJ, 2010[149]; Avenell, Cochrane Database Syst Rev, 2009[148]; Bergman, Curr Med Res Opin, 2010[150]; Bischoff-Ferrari, Arch Intern Med, 2009[183]; Boonen, J Clin Endocrinol Metab, 2007[143]; Izaks, BMC Musculoskelet Disord, 2007[151]; Jackson, Qjm, 2007[184]; O'Donnell, J Bone Miner Metab, 2008[147]; Tang, Lancet, 2007[144]

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

Type of fracture	# studies	Sample size	RR	(95% CI)
		Vertebral fractures		
Original Report				
Shea, 2002[a, b165]	5	576	0.77	(0.54, 1.09)
		Non-vertebral		
Original Report				
Shea, 2002 [a, b165]	2	222	0.86	(0.43, 1.72)
Update Report				
Bischoff-Ferrari, 2007[142]	5	6,740	0.92	(0.81, 1.05)
		Hip		
Original Report: ***No comparable studies from the original report***				
Update Report				
Bischoff-Ferrari, 2007[142]				
Men and women	4	6,504	1.64	(1.02, 2.64)
Boonen, 2007[143]	10[f]	54,592	0.75	(0.58, 0.96)
		All types		
Original Report: ***No comparable studies from the original report***				
Update Report				
Tang, 2007 [c144]	9			
Any calcium		6,517	0.90	(0.80, 1.00)
Calcium <1200mg/d		47,359	0.94	(0.89, 0.99)
Calcium ≥1200mg/d		5,266	0.80	(0.72, 0.89)

[a] Postmenopausal women only

[b] In one included study, participants received a baseline vitamin D injection

[c] Age 50 and over. P value for comparison of RR of fracture for studies of <1200 mg vs. ≥1200 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

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
			Vertebral Fractures		
Original 2007 Report					
Avenell, 2005[146]					
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	2745	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	5698	1.13	(0.50, 2.55)	Standard vitamin-D [D2, D3, or 25(OH)D] vs. placebo
				(0.01-8.34)	
Either selected or not selected on basis of prior osteoporotic fracture	2	2708	0.34	(0.40-1.41)	Standard vitamin-D [D2, D3, or 25(OH)D] + calcium vs. placebo/control
Either selected or not selected on basis of prior osteoporotic fracture	3	327	0.75		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
Postmenopausal women	7	970	0.64	(0.44, 0.92)	Calcitriol (1,25-OH vitamin D) vs. calcium or placebo
Postmenopausal women	8	1130	0.63	(0.45, 0.88)	Either Standard vitamin-D or Calcitriol vs. calcium or placebo
Richy, 2004[182]					
Primary osteoporosis	9	1665	0.53	(0.47, 0.60)	Alfacalcidol or calcitriol vs. calcium or placebo
Primary osteoporosis	6	896	0.52	(0.41, 0.67)	Calcitriol vs. calcium or placebo
Primary osteoporosis	3	769	0.53	(0.46, 0.61)	Alphacalcidol vs. calcium or placebo
Primary osteoporosis	2	106	0.33	(0.07, 1.51)	GC-induced (calcitriol only) vs. calcium or placebo
Richy, 2005[145]					
Primary osteoporosis (24 mos)	5	1972	15%[g]	(10, 20%)	Alfacalcidol or calcitriol vs. placebo
Primary osteoporosis (24 mos)	2	3075	1.6%[g]	(0.4, 2.6%)	Standard vitamin D vs. placebo
GC treatment	3	300	9%	(-2, 22%)	Alfacalcidol or calcitriol vs. placebo
GC treatment	1	62	6%	(-23, 10%)	Standard vitamin D vs. placebo

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
Stevenson, 2005[34]					
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
Elderly women not selected for BMD			2.95	(0.21-71.21)	Calcium + vitamin D vs. placebo
Update Report					
Avenell, 2009 [148]					
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)[d]	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
Persons sustaining new vertebral deformity Selected on the basis of previous	1	23	0.95	(0.52, 1.74)	Alfacalcidol vs. calcium[c]

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
osteoporotic fracture					
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[c]
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[c]
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]
Persons developing new vertebral deformity Selected on the basis of previous osteoporotic fracture	2	84	0.79	(0.41, 1.52)	Calcitriol plus vitamin D and calcium vs. vitamin D and calcium[c]
Persons developing new vertebral deformity Selected on the basis of previous osteoporotic fracture	2	556	1.69	(0.25, 11.28)	Calcitriol vs. calcium
Persons developing new vertebral deformity Selected on the basis of previous osteoporotic fracture	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
O'Donnell, 2008 [147]					
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[149]					
	n/a	n/a	0.85[b]	(0.66, 1.11)	Vitamin D plus Calcium vs. placebo or control
	n/a	n/a	1.12[b]	(0.70, 1.79)	Vitamin D vs. placebo or control

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
	n/a	n/a	0.86 [b]	(0.65, 1.14)	10 ug vitamin D with calcium vs. placebo or control
	n/a	n/a	0.97 [b]	(0.48, 1.98)	20ug with calcium vs. placebo or control
	n/a	n/a	1.10 [b]	(0.69, 1.76)	20ug without calcium vs. placebo or control
			Non-vertebral		
Original 2007 Report					
Avenell, 2005[146]					
Not selected on basis of prior osteoporotic fracture	2	466	0.40	(0.05, 3.08) (0.18-1.18)	Alphacalcidol vs. placebo/control
Not selected on basis of prior osteoporotic fracture	1	246	0.46	(0.78-0.97)	Calcitriol vs. placebo/control
Not selected on basis of prior osteoporotic fracture	7	10376	0.87		Vitamin D (D2, D3, or 25 (OH) D) + calcium vs. placebo/control
Bischoff-Ferrari, 2005[180]					
	7	9820	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	3722	1.03	(0.86, 1.24)	400IU/d +/- calcium vs. placebo or calcium
Stevenson, 2005 [34]					
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
Elderly women not selected for BMD	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
Postmenopausal women	3	788	0.87	(0.29, 2.59)	Calcitriol (1,25-OH vitamin D) vs. calcium or placebo
Postmenopausal women	6	6187	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[145]					
Primary osteoporosis					

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
	7	913	8%[†]	(2, 13%)	Vitamin D analogues vs, placebo
	6	7058	2%[†]	(1, 3%)	Standard vitamin D vs. placebo
Update Report					
Bergman, 2010[150]					
	4	3,510	0.77[e]	(0.63, 0.93)[d]	Cholecalciferol (D3) plus calcium vs. placebo
Avenell, 2009[148]					
Persons sustaining new non-vertebral fracture	1	3,440	0.96	(0.80, 1.15)	Vitamin D alone vs. placebo or no treatment
Not selected on the basis of prior osteoporotic fracture					
Persons sustaining new non-vertebral fracture	4	3,061	0.96	(0.79, 1.16)	Vitamin D plus calcium vs. calcium alone
Either selected or not selected on the basis of prior osteoporotic fracture					
Persons sustaining new non-vertebral fracture	3	2,976	1.08	(0.90, 1.31)	Vitamin D vs. calcium
Either selected or not selected on the basis of prior osteoporotic fracture					
Persons sustaining new non-vertebral fracture	9	46,781	0.95	(0.90, 1.00)	Vitamin D plus calcium vs. placebo or no treatment
Either selected or not selected on the basis of prior osteoporotic fracture					
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	2	663	1.19	(0.09, 15.77)	Calcitriol vs. calcium

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
osteoporotic fracture					
Selected on the basis of prior osteoporotic fracture	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 [147]	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
Izaks, 2007[151]					
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[h]
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		
Original 2007 Report					
Avenell, 2005[146]					
Not selected on basis of prior osteoporotic fracture	4	15948	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	2820	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	18668	1.17	(0.98, 1.41)	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	10376	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
Not selected on basis of prior osteoporotic fracture	1	246	0.33	(0.01, 8.10)	Calcitriol (1,25-OH vitamin D) vs. placebo or control

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
Bischoff-Ferrari, 2005[180]					
	5	9294	0.88	(0.69, 1.13)	All doses (D2, D3) +/- calcium vs. placebo or calcium
	3	5572	0.74	(0.61, 0.88)	700-800IU/d +/- calcium vs. placebo or calcium
	2	3722	1.15	(0.88, 1.50)	400IU/d +/- calcium vs. placebo or calcium
Stevenson 2005 [34]					
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[150]	5	7,473	0.70[e]	(0.63, 0.90)[d]	Cholecalciferol (D3) + calcium vs. placebo
Avenell, 2009 [148]					
Persons sustaining new hip fracture	9	24,749	1.15	(0.99, 1.33)	Vitamin D (D2, D3, or 25(OH)D) alone vs. placebo or no treatment
Selected or not selected on basis of prior osteoporotic fracture					
Selected or not selected on basis of prior osteoporotic fracture	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
Selected on basis of prior osteoporotic fracture	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)[d]	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)[d]	Vitamin D (D2, D3, or 25(OH)D) + calcium vs. placebo or no treatment
Selected on basis of institutional residence	2	3,853	0.75	(0.62, 0.92)[d]	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)[d]	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[c]
Not selected on basis of prior osteoporotic fracture	1	246	0.33	(0.01, 8.10)	Calcitriol vs. placebo or no treatment[c]
Bischoff-Ferrari, 2009[183]					

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
	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[143]					
Postmenopausal women or older men (≥50 years)	10[a]	54,592	0.75	(0.58, 0.96)[d]	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)[d]	Vitamin D + calcium vs. placebo
DIPART Group, 2010[149]	7	68,517	0.74[b]	(0.60, 0.91)[d]	Vitamin D with or without calcium vs. placebo or control
	n/a	n/a	0.84[b]	(0.70, 1.01)[d]	Vitamin D plus Calcium vs. placebo or control
	n/a	n/a	1.09[b]	(0.92, 1.29)	Vitamin D vs. placebo or control
	n/a	n/a	0.93[b]	(0.81, 1.06)	Vitamin D oral vs. placebo or control
	n/a	n/a	1.46[b]	(1.99, 2.13)	Vitamin D injected vs. placebo or control
	n/a	n/a	0.74[b]	(0.60, 0.91)	10 ug vitamin D with calcium vs. placebo or control
			1.10[b]	(0.74, 1.64)	10 ug vitamin D without calcium vs. placebo or control[i]
	n/a	n/a	1.30[b]	(0.88, 1.92)	20ug with calcium vs. placebo or control
	n/a	n/a	1.08[b]	(0.89, 1.30)	20ug without calcium vs. placebo or control
Izaks, 2007[151]					
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
Non-vertebral, non-hip					
Original Report: ***No comparable studies from the original report***					
Bergman, 2010[150]	5	7,473			
			0.84[e]	(0.67, 1.04)[d]	Cholecalciferol (D_3) plus calcium vs. placebo
			0.64[e]	(0.38, 0.99)[d]	Cholecalciferol (D3) plus calcium vs. calcium
All Types					
Original Report: ***No comparable studies from the original report***					
Avenel, 2006[146]	8	18,935	1.02	(0.93-1.11)	Vitamin D (D2, D3, or 25 (OH)D) vs. placebo

Type of fracture	# studies	Sample size	RR	(95% CI)	Comparison
Persons sustaining any new fracture					or control
Richy, 2004[182]					
Primary osteoporosis	11	1310	0.52	(0.46, 0.59)	Calcitriol or alphacalcidol vs. calcium or placebo
Update Report					
Tang, 2007[b, c144]					
	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[149]					
	n/a	n/a	0.92[b]	(0.86, 0.99)[d]	Vitamin D plus Calcium vs. placebo or control (p=0.025)
	n/a	n/a	1.01[b]	(0.92, 1.12)	Vitamin D vs. placebo or control
	n/a	n/a	0.93[b,d]	(0.87, 0.99	Vitamin D oral vs. placebo or control
	n/a	n/a	1.11[b]	(0.95, 1.31)	Vitamin D injected vs. placebo or control
	n/a	n/a	0.91[b,d]	(0.85, 0.99)	10 ug vitamin D with calcium vs. placebo or control
			0.93[b]	(0.67, 1.28)	10 ug vitamin D without calcium vs. placebo or control
	n/a	n/a	0.95[b]	(0.80, 1.14)	20ug with calcium vs. placebo or control
	n/a	n/a	1.02[b]	(0.92, 1.14)	20ug without calcium vs. placebo or control
Avenell, 2009[148]					
Persons sustaining any new fracture Selected or not selected on basis of prior osteoporotic fracture	10	25,016	1.01	(0.93, 1.09)[d]	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

[a]Ca + vitamin D vs. vitamin D alone indirect comparison: 6 trials of vitamin D + Ca vs. 4 trials of vitamin D alone

[b]Individual patient data HR for trials using vit D + Ca cf. vitamin D alone

[c]New vertebral deformities

[d]Statistically Significant

[e]Odds ratio

[f]Results expressed as rate difference (RD, difference in fracture rate between treatment and placebo or no treatment)."

[g] 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)

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

[i]According to the author 10µg means 400IU and 20ug means 800 IU

Table 27. Calcium/Vitamin D group and Environmental and Health group vs. 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[152]	42 months	All fractures – men	33/954	26/843	1.13 (0.67, 1.89)
Larsen, 2004[152]	42 months	All fractures – women	131/157	141/1273	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[155]	62 months	New	104/1306	196/1332	0.95 (0.76, 1.18)
Jackson, 2006[153]	84 months	Total	2101/18176	2158/18106	0.97 (0.91, 1.03)
Porthouse, 2005[154]	24 months	All	24/607	22/602	1.09 (0.6, 1.96)
Update Report					
Larsen, 2005[152]	42 months	All fractures – men	60/1974	26/843	0.99 (0.62, 1.57)
Larsen, 2005[152]	42 months	All fractures – women	285/2983	141/1273	0.75 (0.6, 0.94)
		Vertebral Fractures			
Original 2007 Report					
Grant, 2005[155]	62 months	Clinical vertebral	0/1306	1/1332	0.14 (0, 6.96)
Jackson, 2006[153]	84 months	Clinical vertebral	181/18176	197/18106	0.91 (0.75, 1.12)
Update Report: *No new studies*					
		Hip			
Original 2007 Report					
Grant, 2005[155]	62 months	Proximal femur	46/1306	41/1332	1.15 (0.75, 1.76)
Jackson, 2006[153]	84 months	Hip	175/18176	199/18106	0.87 (0.71, 1.07)
Porthouse, 2005[154]	24 months	Hip	5/607	2/602	2.35 (0.53, 10.36)
Update Report: *No new studies*					
		Wrist			
Original 2007 Report					
Grant, 2005[155]	62 months	Distal forearm	33/1306	28/1332	1.21 (0.73, 2.01)
Jackson, 2006[153]	84 months	Lower arm or wrist	565/18176	557/18106	1.01 (0.9, 1.14)
Update Report: *No new studies*					

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[156]	60 months	New symptomatic vertebral and non-vertebral	7/85	7/95†	1.13 (0.38, 3.35)
Prince, 2006[157]**	60 months	Any site	110/728	126/728	0.85 (0.64, 1.12)
Prince, 2006[157]***	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[156]	60 months	New symptomatic or semi-quantitative vertebral	15/85	19/95†	0.86 (0.41, 1.81)
Grant, 2005[155]	62 months	Clinical vertebral	3/1311	1/1332	2.77 (0.39, 19.65)
Prince, 2006[157]**	60 months	Vertebral deformity	44/431	50/450	0.91 (0.59, 1.40)
Prince, 2006[157]***	60 months	Vertebral deformity	22/306	32/305	0.66 (0.38, 1.16)
Reid, 2006[69]	60 months	Vertebral	27/739	38/732	0.70 (0.42, 1.14)
Update Report					
Frost, 2007[158]	12 months	Vertebral	1/17	1/16	0.94 (0.06, 15.72)
Fujita, 2007[159]	2 years	Vertebral	2/7	3/6	0.43 (0.05, 3.73)
Fujita, 2007[159]	2 years	Vertebral	0/6	3/6	0.09 (0.01, 1.06)
		Wrist			
Original 2007 Report					
Grant, 2005[155]	62 months	Distal forearm	33/1311	28/1332	1.20 (0.72, 2.00)
Prince, 2006[157]**	60 months	Wrist or hand	21/724	20/741	1.08 (0.58, 2.00)
Prince, 2006[157]***	60 months	Wrist or hand	10/417	12/414	0.82 (0.35, 1.92)
Reid, 2006[69]	60 months	Distal forearm	28/739	44/732	0.62 (0.39, 1.00)
Update Report: *No new studies*					

**: Intention to treat analysis;

***: Compliant with medication

†Control group.

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[160]	12 months	Symptomatic	0/41	0/45	NC
Update Report: *No new studies*					
		Vertebral Fractures			
Original 2007 Report: *No studies from the original report*					
Update Report					
Shiraki, 1996[162]	2 years	Vertebral	2/37	3/42	0.75 (0.12, 4.55)
		Non-Vertebral Fractures			
Original 2007 Report: *No studies from the original report*					
Update Report					
Smith, 2007[163]	36 Months	Non-vertebral	306/4727	279/4713	1.1 (0.93, 1.3)
Shiraki, 1996[162]	2 Years	Non-vertebral	0/37	3/42	0.15 (0.01, 1.44)
Shiraki, 1996[162]	10 Months	Non-vertebral	64/1762	51/1955	1.41 (0.97, 2.04)
		Hip			
Original 2007 report					
Sato, 2005[161]	24 months	Hip	0/24	4/24	0.12 (0.01, 0.90)
Update Report					
Smith, 2007[163]	36 months	Hip or femur	66/4727	44/4713	1.49 (1.03, 2.18)
Law, 2006[164]	10 months	Hip	24/1762	20/1955	1.34 (0.74, 2.42)
		Wrist			
Original 2007 Report					
Grant, 2006[155]	62 months	Distal forearm	33/1343	28/1332	1.17 (0.71, 1.95)
Ishida, 2004[140]	24 months	Vertebral	11/66	17/66	0.58 (0.25, 1.34)
Update Report					
Smith, 2007[163]	36 months	Wrist	64/4727	52/4713	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 META-ANALYSES. One meta-analysis evaluated the effects of physical activity relative to placebo on fracture risk (Table 31). The meta-analysis, 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.

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

	Meta-analysis (Author, year)			
	Lock, 2006 [215]			
	Fracture type*			
RCTs (Author, year)	**A**	**V**	**H**	**W**
Ebrahim, 1997 [216]		X		
Jensen, 2002 [217]			X	
Preisinger, 1996 [218]	X	X		X
Sato, 2003 [219]			X	
Sinaki, 1989 [220]		X		
Sinaki, 2002 [221]		X		
Vetter, 1992 [222]	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

Type of fracture	# studies	Sample size	RR	(95% CI)
		Vertebral fractures		
Original 2007 Report: No comparable studies from the original report				
Update Report				
Lock, 2006 [215]	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, non-vertebral, 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 non-vertebral 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, non-vertebral 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 non-vertebral 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),[223] the odds of non-vertebral and vertebral fracture were similar with alendronate 10 mg/day vs. teriparatide 20 µg/day (Table 38). Using the criteria of Gartlehner et al.[27] 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),[58] the odds of non-vertebral and vertebral fractures were similar with alendronate + vitamin D vs. alendronate + alfacalcidol (Table 39). Using the criteria of Gartlehner et al.[27] 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% lower odds of vertebral fracture with alfacalcidol + prednisolone + alendronate vs. alfacalcidol + prednisolone (Jadad score 1) (Table 40).[224] Using the criteria of Gartlehner et al.[27] 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).[225] Using the criteria of Gartlehner et al.[27] 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).[226] Using the criteria of Gartlehner et al.[27] 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).[227]

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).[140, 228]

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).[229]

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 to (Table 46).[140] Another RCT, newly identified for this report that examined vertebral and non-vertebral 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).[230] Using the criteria of Gartlehner et al.[27] 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 meta-analyses encompassing seven RCTs reported pooled risk estimates for vitamin D vs. calcium. One meta-analysis assessed overall fractures, six assessed non-vertebral 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 non-vertebral 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).[155]

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[50]	24 months	Non-vertebral	44/897	6/204	1.58 (0. 56, 4.43)
Bone, 2000[60]	24 months	Clinical	5/92	10/143	0.77 (0. 26, 2.25)
Greenspan, 2003[61]	34 months	Clinical	7/93	5/93	1.43 (0. 44, 4.58)
Update report: *No new studies*					
			Etidronate		
Original 2007 Report					
Ishida, 2004[140]	24 months	Vertebral	8/66	7/66†	1.16 (0. 40, 3.39)
Wimalawansa, 1998[141]	48 months	Non-vertebral	1/14	1/15	1.07 (0. 06, 18.10)
Wimalawansa, 1998[141]	48 months	Vertebral	3/14	2/15	1.73 (0. 26, 11.50)
Update report: *No new studies*					
			Risendronate		
Original 2007 Report					
Tauchmanova, 2006[227]	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[227]	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[156]	60 months	New symptomatic, vertebral or non-vertebral	5/81	7/85	0.74 (0. 23, 2.38)
Update Report: *No new studies*					
		Pamidronate			
Boutsen, 1997[231]	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[232]	12 months	All clinical	5/221	8/230	0.65 (0.22, 1.95)
Uchida, 2005[233]	12 months	Vertebral or non-vertebral	22/713	20/699	1.08 (0.59, 2.0)
Update Report: *No new studies*					
Vertebral Fractures					
Original 2007 Report					
Muscoso, 2004[234]	24 months	Vertebral	6/1000	0/100	NC
Uchida, 2005[233]	12 months	Vertebral	8/713	5/699	1.56 (0.52, 4.65)
Update Report: *No new studies*					
Non-Vertebral Fractures					
Original 2007 Report					
Uchida, 2005[233]	12 months	Non-vertebral	14/713	15/699	0.94 (0.44, 1.91)
Update Report: *No new studies*					
Hip					
Original 2007 Report					
Muscoso, 2004[234]	24 months	Femoral	3/1000	0/100	NC
Uchida, 2005[233]	12 months	Hip	1/713	2/699	0.5 (0.05, 4.84)
Update Report: *No new studies*					
Wrist					
Original 2007 Report					
Muscoso, 2004[234]	24 months	Radial	1/1000	0/100	NC
Uchida, 2005[233]	12 months	Wrist	6/713	8/699	0.74 (0.26, 2.11)
Update Report: *No new studies*					
		Risedronate			
Vertebral Fractures					
Original 2007 Report					
Mucoso, 2004[234]	24 months	Vertebral	0/100	0/100	NC
Update Report: *No new studies*					
Hip					
Original 2007 Report					
Mucoso, 2004[234]	24 months	Femoral	0/100	0/100	NC

Author, year	Study duration	Fracture type	Number of fractures, bisphosphonate	Number of fractures, raloxifene	Odds ratio (95% CI)
Update Report: *No new studies*					
Wrist					
Original 2007 Report					
Mucoso, 2004[234]	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[235]	24 months	Clinical	34/410	34/415	1.01 (0.62, 1.66)
Hosking, 2003[62]	12 months	Clinical	6/172	6/178	1.04 (0.33, 3.27)
Rosen, 2005[236]	12 months	Any	26/520	20/533	1.35 (0.75, 2.43)
Muscoso, 2004[234]	12 months	Total	2/1000	0/100	3.01 (0.02, 373.9)
Update Report: *No new studies*					
			Vertebral Fractures		
Original 2007 report					
Muscoso, 2004[234]	12 months	Vertebral	2/1000	0/100	NC
Muscoso, 2004[234]	24 months	Vertebral	4/1000	0/100	NC
Update Report: *No new studies*					
			Hip		
Muscoso, 2004[234]	12 months	Femoral	1/1000	0/100	NC
Muscoso, 2004[234]	24 months	Femoral	2/1000	0/100	NC
Update Report: *No new studies*					
			Wrist		
Original 2007 Report					
Muscoso, 2004[234]	12 months	Radial	1/1000	0/100	NC
Muscoso, 2004[234]	24 months	Radial	0/1000	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)
			Non-Vertebral		
Original 2007 Report					
Body, 2002[237]	14 months	Non-vertebral	10/73	3/73	3.24 (1.04, 10.07)
Update Report: *No new studies*					

Table 38. Alendronate 10mg/day vs. teriparatide 20mug/day among individuals taking glucocorticoids

Author, year	Study duration	Fracture type	Number of fractures, alendronate 10mg/day	Number of fractures, teriparatide 20mug/day	Odds ratio (95% CI)
Original 2007 Report: *No comparable studies from the original report*					
Update Report					
Saag, 2009[223]	36 MOS	Non-vertebral	15/214	16/214	0.93 (0.45, 1.95)
Saag, 2009[223]	36 MOS	Vertebral	13/169	3/173	3.79 (1.39, 10.32)

Table 39. Alendronate plus vitamin d vs. 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[58]	24 months	Non-vertebral	6/30	4/30	1.6 (0.42, 6.16)
Ringe, 2007[58]	24 months	Vertebral	4/30	1/30	3.62 (0.59, 22.26)

Table 40. Alfacalcidol plus prednisolone and alendronate vs. 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[224]	18 months	Vertebral	0/17	4/16	0.1 (0.01, 0.81)

Table 41. Alendronate vs. 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[225]	2 years	Any clinical fracture	28/281	9/282	3.01 (1.54, 5.85)

Table 42. Rocaltrol+Caltrate D vs 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[226]	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	Type of fracture	Number of fractures, risedronate	Number of fractures, zoledronic acid	Odds ratio(95% CI)
		Subclinical Vertebral Fractures			
Original 2007 Report					
Tauchmanova, 2006[227]	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	Type of fracture	Number of fractures, etidronate	Number of fractures, calcitonin	Odds ratio (95% CI)
		Vertebral			
Original 2007 Report					
Ishida, 2004[140]	24 months	Vertebral	8/66	8/66	1.00 (0. 35, 2.83)
Garcia-Delgado, 1997[228]	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[124]	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	Type of fracture	Number of fractures, estrogen†	Number of fractures, vitamin D	Odds ratio(95% CI)
		Vertebral Fractures			
Original 2007 Report					
Ishida, 2004[140]	24 months	Vertebral	7/66†	11/66	0.6 (0.22, 1.62)
Update Report: *No new studies*					
		Vertebral & Non-Vertebral Fractures			
Original Report: *no comparable studies from the original report*					
Update Report					
Campbell, 2009[230]	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 2mg estradiol or 0.625mg CEE or 50 ug 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[155]	62 months	New	189/1311	212/1343	0.90 (0.73, 1.11)
Update Report: *No new studies*					
		Vertebral Fractures			
Original 2007 Report					
Grant, 2005[155]	62 months	Clinical vertebral	3/1311	4/1343	0.77 (0.17, 3.39)
Update Report: *No new studies*					
		Hip			
Original 2007 Report					
Grant, 2005[155]	62 months	Proximal femur	49/1311	47/1343	1.07 (0.71, 1.60)
Update Report: *No new studies*					
		Wrist			
Original 2007 Report					
Grant, 2005[155]	62 months	Distal forearm	33/1311	33/1343	1.02 (0.63, 1.67)
Update Report: *No new studies*					

†Control group

Table 48. Randomized controlled trials included in meta-analysis of effect of vitamin D on fracture relative to calcium by fracture type

	Meta-analysis(Author, year)														
	Avenell, 2009[148]					Bergman, 2010[150]		Bischoff-Ferrari, 2009[183]		Izaks, 2007[151]		Jackson, 2007[184]		O'Donnell, 2008[147]	
	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[155]			X	X											
Peacock, 2000[174]	X														
Pfeifer, 2000[238]						X	X	X		X			X		
Pfeifer, 2008[209]								X							
Shiraki, 1996[162]														X	X
Trivedi, 2003[213]						X	X								

*A=all, NV=non-vertebral, 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 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 Points

- Bone Mineral Density. Post hoc analysis of one large RCT found no evidence that low femoral neck BMD predicts 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. Post hoc analysis of data from one large RCT showed no effect of fracture risk as assessed by WHO/FRAX on the effectiveness of raloxifene in reducing risk for morphometric fracture among elderly women.
- Prevalent Fractures. Post hoc analysis of a large RCT found no evidence that prevalent vertebral fractures predicts the efficacy of alendronate; however another post hoc analysis of data from the same trial found that the risk of incident non-vertebral fractures among women without prevalent fractures (but with T-scores ≤-2.5) was decreased (by alendronate) compared with that of women *with* prevalent fractures or without prevalent fractures and with T-score -2 to -2.5.
- Post hoc analyses of two RCTs found no influence of prevalent fracture on the effects of raloxifene. However, post hoc analysis of one large RCT showed that raloxifene decreased the risk of major non-vertebral fracture among women with prevalent vertebral fracture, but not among women without prevalent vertebral fracture.
- A post hoc analysis of one RCT showed that prevalent fractures increased the relative efficacy of teriparatide in preventing fractures in postmenopausal women
- Age. One RCT found an effect of age on the effectiveness of risedronate in preventing any type of fracture.
- One RCT found no influence of age on the effectiveness of zoledronic acid in lowering the risk for vertebral or non-vertebral fractures but found that only women under 75 experienced a benefit in reduced risk for hip fracture. However

another RCT found that age influences the effect of zoledronic acid on vertebral fracture risk but not the risk for non-vertebral or hip fracture.
- One RCT found no effect of age on the influence of teriparatide on vertebral fracture but found an effect on the risk of non-vertebral fracture.
- Sex. 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. 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.
- Renal Function. Evidence from two trials supports a lack of effect of renal function on the efficacy of alendronate and raloxifene; however impaired renal function reduced the efficacy of zoledronic acid in preventing vertebral (but not non-vertebral or hip) fractures.

Overview of Results

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.

Bone mineral density

In a posthoc 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.[239] 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.

A posthoc analysis of risedronate efficacy was performed among women with femoral T-score between -1 and -2.5 without fracture.[240] Cumulative 2-year fragility fracture incidence was statistically significantly (73%) lower among women assigned to risedronate compared with women assigned to placebo.

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.[241] Moreover, at age 75 years,

vertebral fracture risk reduction was 31% irrespective of FRAX score. At younger ages, effectiveness increased with decreasing fracture risk.

Prior fractures (prevention vs. treatment)

In a posthoc 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.[239] 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 non-vertebral fractures.[242] In contrast, among women without vertebral fractures at baseline, alendronate continuation reduced non-vertebral 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.[243] Although raloxifene did not statistically significantly influence non-vertebral fracture risk, raloxifene did decrease the risk of major non-vertebral 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.[244] 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.[245]

Age

A post hoc analysis examined the relationship between age and the effect of risedronate treatment on fracture risk among postmenopausal women with osteoporosis.[246] 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 statistically 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.[247] However, only women aged less than 75 years, but not ≥75 years, 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.[248] 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 non-vertebral or hip fractures.

In a post hoc analysis of the MORE raloxifene trial, antifracture effects of raloxifene vs. placebo was higher at younger ages.[241]

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.[249] The relative risk of vertebral fracture was 0.35 among both women aged under 75 years and women aged ≥75 years (statistically significant in both cases). For non-vertebral 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 old, 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).[163] 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% male subjects enrolled. However, these trials were either about special populations (cystic fibrosis,[57, 116] congestive heart failure,[158] Parkinson's disease,[74] cardiac transplant patients,[108]) or were not powered to detect fracture risk outcomes,[76] or were not open-label.[75]

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.[152] 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 9440 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.[163]

Race/ethnicity

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).[250] Raloxifene statistically significantly reduced the incidence of vertebral fractures and any new clinical fractures, but not non-vertebral fractures, compared to placebo.

Other factors

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.[251]

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 non-vertebral fractures, compared to placebo.[252]

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.[248] 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 non-vertebral or hip fractures.

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.[253] Clinical fracture reduction was statistically significant, and was not significantly different, among participants who had initiated zoledronic acid within 6 weeks (33%) compared with after 6 weeks (37%).

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.[122] 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, four-monthly 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 to medications for the treatment and prevention of osteoporosis,

b) what factors affect adherence and persistence, and

c) what are the effects of adherence and persistence on the risk of fractures?

Key Points

- 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 meta-analyses 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 be persistent at 1 year, with adherence ranging widely across studies.
- Many barriers have been identified to adherence and persistence. Five of the most commonly discussed include age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of the osteoporosis medications.
- 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 appear to be an important predictor of adherence and persistence.

- Evidence from a meta-analysis and ten out of eleven observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, non-vertebral 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 to 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.[15] 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.

Meta-Analyses and Prior Reviews

Several recent systematic reviews and meta-analyses have been published on the topic of adherence to medications for osteoporosis.[144, 254-258] 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% to 78.0%, and the mean MPR ranged from 0.59 to 0.81.[254] 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.[255] 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 meta-analysis 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% 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.[257] 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.[256] 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.[258] 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 follow-ups, 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 follow-up interaction between patients and health professionals appears to be beneficial."[258]

Rates of Adherence in New Studies

i) 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).[57, 76, 87, 88, 122, 259-264134, 139, 265, 266] 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.[57, 259, 260] 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.[259] 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).[57] 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.[260]

Five trials of risedronate reported adherence rates.[76, 87, 88, 261, 262] In two randomized trials comparing daily versus monthly doses of risedronate (one using 75 mg dose on two consecutive days each month,[87] and the other using 150 mg monthly[88], 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.[261] 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,[258] patients on risedronate were randomized to receive feedback about bone turnover.[262] 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).[76]

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.[263, 264] The trial was funded by the makers of ibandronate, 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,[264] and among those with baseline gastrointestinal symptoms, 90 percent were adherent.[263]

Two studies reported adherence with raloxifene.[122, 265] 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.[122] 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.[265] 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 study included teriparatide.[134, 266] 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.

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.[139] 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 (mths)	Adherence Definition	Adherence (Persistence) Rate
Binkley, 2009[259]	Alendronate +Vitamin D	6	Missed <6 doses	94%
Papaioannou, 2008[57]	Alendronate	12	Received at least 80% study drug	93%
Tseng, 2006[260]	Alendronate + HRT	36	Consuming >85% of Pills	100%
Delmas, 2008[87]	Risedronate (two doses/ month)	24	Consuming at least 80% of pills	96%
Delmas, 2008[88]	Risedronate (one dose/month)	24	Consuming at least 80% of pills	97%
Anastasilakis, 2008[261]	Risedronate (one dose/week) Teriparatide	12	Pill Count (threshold not reported) Volume of med remaining	87% 93%
Boonen, 2009[76]	Risedronate (one dose/week)	24	Pill count (threshold not reported)	98%
Delmas, 2007[262]	Risedronate (one dose/day)	12	% patients 'persistent' and compliant'	77%
Bonnick, 2009[264]	Ibandronate (one dose/month)	6	Taking at least 5 of 6 doses dispensed	94%
Binkley, 2009[263]	Ibandronate (one dose/month)	6	Taking at least 5 of 6 doses dispensed	90%
Ensrud, 2008[122]	Raloxifene	60	Consuming at least 80% of pills	70%
Gorai, 2009[265]	Raloxifene	12	Adherence: MPR>80% Persistence: percent taking pills 7 of last 14 days prior to one year visit	65% 94%
Adachi, 2007[266]	Teriparatide	6 18	Administering >80% daily injections	89% 82%
Boone, 2006[139]	Transdermal HRT	24	Percent of patches used (overall)	82%

ii) 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,[255, 257] although, as in prior studies, the rates and methods of measurement of adherence vary widely. In total, 41 observational studies contributed to our analysis of 'real-world' adherence and persistence rates (i.e. coming from data outside of the clinical trial setting).[267-307] Eleven studies focused on adherence alone[267-277], 11 studies focused on persistence alone,[278-283 284-288] and 17 studies examined both adherence and persistence.[289-305] In two of the studies [306, 307], 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.

Fourteen of the included studies 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.[268] Five of the articles describe adherence only,[268, 271, 272, 276, 277] five describe persistence only,[281-283, 287, 288] and four describe both adherence and persistence.[294, 296-298] None of the articles describe primary nonadherence (non-fulfillment), which refers to prescriptions not filled at a pharmacy after they are written. All examined bisphosphonate use, except one that also described adherence to estrogen.[277]

Three of the five adherence studies examining the rates of bisphosphonate use employed the MPR threshold of more than 80 for their calculations. 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.[272] Similarly, in a study of 3658 women in a health plan, overall 45 percent had an MPR over 80 for their bisphosphonate.[276] In another large study of 61,000 women in the MarketScan database, 49 percent had an MPR over 80 on monthly ibandronate, 49 percent on weekly bisphosphonate, and 23 percent on daily bisphosphonate.[271] In a much smaller 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.[277] In the final adherence only study, and the only study to include 100 percent 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.[268]

Two studies examining both adherence and persistence reported a mean MPR among over 200,000 respondents on bisphosphonates of 83 percent for weekly and 78 percent for monthly bisphosphonates at six months,[297] and 80 percent and 75 percent at 12 months.[298] 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,[294] and the other found an overall rate of adherence of 61 percent at one year.[296]

The studies that report on persistence have as much variability in their results and methods as the adherence studies already discussed. Of the four 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),[296] while two others use a gap of more than 90 days.[297, 298] 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.[298] In each of these studies, fewer than half of the patients were still persistent at 12 months. The final study examining

adherence and persistence appeared to combine the two measures,[294] 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.[281] 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.[288]

The remaining three persistence studies all used a gap of over 30 days to define non-persistence. 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.[282] 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.[283] 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.[287] 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 meta-analyses 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.[308, 309] 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.[15] 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.[310-313]

For the current report, we identified 30 studies that discussed factors affecting adherence or persistence. Evidence Table C-5 in Appendix C lists each of the barriers identified in the review, ordered by the number of studies discussing each particular 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 but not discussed in detail below.

i) Age

We identified 21 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. All of the articles focused on bisphosphonates except for four: three that included raloxifene in addition to bisphosphonates,[273, 289, 303] and one that focused exclusively on calcium and Vitamin D.[304] Almost all used pharmacy records and automated measures of adherence/persistence in their analyses except three.[273, 275, 289] Two of these studies were small international studies: one from Croatia[275] that examined only unadjusted correlations between age and adherence, and the other from the Czech Republic.[273] 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 three studies finding increased age associated with better adherence,[270, 290, 299] three studies finding increased age associated with worse

adherence[273, 275, 304] (although two of these studies[275, 304] examined only unadjusted results), and seven studies finding no association between age and adherence or persistence[268, 288, 293, 295, 296, 303, 307] (note: some overlap is possible between studies that examined both persistence and adherence). In those studies that examined persistence, five found increased age associated with better persistence,[281, 282, 285, 290, 299] and six found increased age associated with worsened persistence.[280, 284, 286, 287, 289, 304]

Only six of the reviewed articles assessing the effect of age on adherence/persistence were based in the US.[268, 281, 282, 287, 288, 296] Half of those articles found no independent effect of age on adherence or persistence.[268, 288, 296] Two studies found that age was associated with increased persistence.[281, 282] The latter[282] 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[287] 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 would suggest that age by itself cannot be used as a predictor of adherence or persistence in the treatment of osteoporosis.

ii) History of Fracture

Ten studies assessed prior history of fracture as a factor in adherence. Of the ten, only one was a US study;[268] the remainder were conducted in Canada (two),[286, 314] Croatia (one),[275] Czech Republic (one),[273] France (one),[295] Germany (one), [302]Netherlands (one),[270] and UK (two).[290, 305]

Two of the ten studies found that prior (osteoporotic) fracture was significantly associated with increased rates of adherence and persistence to bisphosphonate use[270];[302] the remaining eight studies found no significant association between prior fracture and adherence or persistence to osteoporotic medications.

Both 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 increased odds of compliance (adjusted OR 0.65; 95% CI 0.47–0.88), as measured by MPR.[270] In the 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).[302] Both studies were industry-funded.

In the 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.[268]

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

iii) Dosing Frequency

We identified 16 articles that examined the effect of dosing frequency on adherence. Four studies compared monthly to weekly dosing regimens.[287, 295, 297, 298] 11 studies compared weekly to daily regimens,[270, 281, 282, 290, 296, 299, 300, 303, 307 273, 301] and one study compared monthly, weekly, and daily regimens.[271] Out of the 16, 11 were funded by the makers of bisphosphonates; The five studies not funded by industry report on results from Australia, Israel, Belgium, and the Czech Republic.[273, 299, 300, 303, 307]Of the five studies that compare monthly to weekly dosing regimens,[271, 287, 295, 297, 298] four[287, 295, 297, 298] found a significant difference in adherence between the dosing regimens, with three favoring weekly and one 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.[297] 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 funded and the report written by the makers of risedronate. Very similar results were found in a 2009 study by the same authors and funders examining the same drugs;[298] 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, funded and authored in part by Merck, mean persistence was worse with monthly ibandronate (98 days mean persistence) than with weekly alendronate and risedronate (116 days and 113 days, respectively).[287] 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, funded and authored in part by the makers of ibandronate, adherence and persistence were superior with monthly ibandronate compared to weekly bisphosphonates.[295] Finally, in a study of 61,000 new users of bisphosphonates from the market scan 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).[271]

The remaining 11 studies overall find that adherence to bisphosphonates is improved in weekly compared to daily regimens. Three of the studies were based in the US[281, 282, 296] and all but three[300, 301, 307] 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,[307] 1376 patients in Belgium,[300] and 200 patients in the Czech Republic.[273]

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,[15] prior systematic reviews[310-313]and prior meta-analyses.[296] 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.

iv) 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 12 studies.[268, 270, 273-275, 287-289, 295, 296, 305, 306] 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 12 studies[270, 287, 296] 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.[296] In a large cohort study of new female users of bisphosphonates from the PHARMO data base in the Netherlands, the number of co-medications in the year prior to starting the bisphosphonate was associated with adherence.[270] Women using more than 10 medications in the prior year had 1.87 times the odds of non-adherence 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 US 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).[287]

The remaining nine studies found no independent association between number of medications and medication adherence or persistence. In each case, concomitant medication use was defined differently, but in each case was a covariate in the analysis rather than the main independent variable of interest. The two additional US-based studies[268, 288] (out of a total of four discussing concurrent medications) comprised the only 100 percent male sample included in this review (with 198 male veterans from one VA medical center)[268] and a telephone interview of 1,092 women with an unfortunately low response rate of 33 percent.[288] 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 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.

v) Adverse Effects

Seven studies assessed the association of adverse effects from medications used to treat osteoporosis with treatment adherence and/or persistence.[268, 280, 306, 307 270, 273, 288] All seven reported a significant effect of medication-associated adverse events on adherence or persistence. Among the studies, two were conducted in the US,[268, 288] two were Japanese,[280, 306] and the remainder were conducted in Australia,[307] Netherlands,[270] and the Czech Republic.[273]

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, non-adherent men were significantly more likely than adherent men to describe side effects of alendronate (47 percent versus 29 percent, p=0.01).[268]

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).[288]

In summary, adverse effects do appear, based on the literature, to be an important factor affecting adherence and persistence with bisphosphonates.

Key Question 3C: 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% increased risk of fracture.[315] In a second study, adherence to medications was associated with a 25% relative risk reduction for all osteoporotic fractures, and persistence with therapy was associated with a 29% reduction in vertebral fractures and a 45% reduction in hip fractures. A third study[316]found that women who were adherent (MPR <80%) had a 16% 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 meta-analysis,[255] one comprehensive systematic review without meta-analysis,[257] one randomized trial,[122] and eleven observational studies[267, 269, 272, 276, 282, 290, 292, 294, 301-303] 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. Four of the studies were based solely on US data.[272, 276, 282, 294] The RCT and ten of the eleven observational studies found that decreased adherence was associated with an increased risk of fracture (either vertebral, non-vertebral or both).

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.

Imaz conducted a meta-analysis of articles published prior to March 22, 2009 on the association of adherence to bisphosphonate treatment with fracture risk,[255] 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% for non-vertebral fractures (pooled RR 1.16 95% CI 1.07, 1.26) and 28% 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).[257] 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 follow up 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 US-based studies, fracture risk was reduced 18.7% to 23% over 2 years.[294] 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, the relationship between compliance and fracture risk was non-linear.

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[290#]	X	
Goettsch, 2005		X (abstract)
Gold, 2007[282#]		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

*Included in the original report; #Identified in the search for the current 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.,[267] 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 follow-up. A US study by Curtis et al[272] 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,[290] 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,[269] included in both reviews stratified over 8000 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[301](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[282] (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[303] 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% (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 non-persistent 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).[122] 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 non-vertebral), 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 non-vertebral fractures across fracture risk. When the analyses were limited to the women who were at least 70% adherent to treatment on the basis of pill count, fracture risk did not differ from that of the total study population.

Abrahamsen conducted a matched cohort study with data from a national registry.[292] 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<.001) and atypical sites (HR = 0.28; 95% CI = 0.12 – 0.63; p < 0.01),.

In contrast, Feldstein[276] 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 <80% or □80%.

A German study assessed the effects of both persistence and adherence on fracture risk. Hoer[302]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 (3289/4451 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% reduction in fracture risk at 180 days and a 45% reduction at 360 days; however, at 720 days, decrease in fracture risk was non-significant (9%). 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).

In summary, most of the studies analyzed, with the notable exception of a large placebo-controlled trial, found an association between adherence or persistence and fracture risk.

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 Points

- *Acute Coronary Syndrome, Including Myocardial Infarction(MI).* 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.
- *Atrial Fibrillation.* 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 also showed an increase that did not reach statistical significance.
- *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.
- *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.
- *Mild Cardiovascular Events*: A pooled analysis of four studies, three from the original report and one identified for the current report that compared raloxifene and placebo found a significant increase in these events among raloxifene users
- *Esophageal Cancer.* Two 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 a nested case control study on the same dataset did identify an increased risk.
- *Mild Upper 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.

- *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. No trials were identified for the current report that reported on the incidence of osteonecrosis of the jaw among individuals taking bisphosphonates to prevent or treat osteoporosis. However, a large recent case series that reviewed 2408 cases of osteonecrosis of the jaw to assess the possible association between use of bisphosphonates and osteonecrosis found that 88 percent were associated with intravenous therapy, primarily with zoledronic acid, and ten percent of those were associated with the prevention or treatment of osteoporosis. Thus the prevention and treatment of osteoporosis remains a relatively minor contributor to the development of osteonecrosis of the jaw.
- *Atypical Fractures of the Femur.* A large case series, a pooled analysis of three trials, and a comprehensive review identified an 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 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.
- *Rashes and Injection Site Reactions*: 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.

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 selected adverse events, we also performed broader literature searches for the adverse events selected for special attention. 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. A table that displays all the adverse events identified for the present report is included as Appendix C. That 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 51 shows the risks of adverse events for bisphosphonates compared with placebo.

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. Mild cardiac events were all other cardiac adverse event descriptions not classified as serious.

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,[61, 317, 318] ibandronate,[106, 319] risedronate,[76, 320, 321] and zoledronic acid[113, 115] 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.[113, 322] The current report identified one new study that when pooled with the original study showed an increase in the incidence of AF with zoledronic acid (pooled OR 1.45, 95% CI 1.14, 1.86).[115] A 2009 Bayesian meta-analysis that included four original reports of RCTs (including the two large trials just described), two post hoc analyses of combined data from multiple RCTs, and three observational studies found a non-significantly 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).[323]

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),[106, 110] and one older trial[113] and one new trial of zoledronic acid[115] (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 non-significant increase in the treated group (OR 1.5, 95% CI 0.87, 2.64).[113, 115]

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[91] and one new,[76] 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+).[61]

Cardiovascular death. The original report found no differences between alendronate (in two trials),[317, 318] ibandronate (in two trials),[106, 319] or risedronate (in one trial),[321] 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,[115] and one new study on risedronate[76] found no differences (pooled OR for risedronate Inf+, 95% CI 0.13, Inf+); and zoledronic acid (OR 0.61 95% CI0.26, 1.37).

Mild Cardiac Events: No findings for mild cardiac events were identified for the original report. For the current report, no differences were observed between any of the bisphosphonates and placebo regarding mild cardiac events.

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+);[106] 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+).[324]

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).[325]

Esophageal Cancer. No trials examined the incidence of esophageal cancer in the original report. Two large observational studies examined the incidence of esophageal cancer among bisphosphonate users. A study 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 follow-up 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).[326] A case-control study that used the same database and matched 2,954 cases with 14,721 controls (36 percent women, mean follow-up 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).[325] 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).[325, 326]

Gastrointestinal Cancer. The original report identified one study each on ibandronate[327] and risedronate[328] 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).[76]

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).

Perforations, ulcerations, and bleeds (PUB) were reported 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); [109, 327] 10 trials of alendronate [329, 330 324, 331-337] and seven trials of risedronate showed similar trends.[62, 92-94, 99, 338, 339] 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).[62]

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;[336, 337, 340-342] risedronate vs. placebo OR 1.03, 95% CI 0.78, 1.36).[90, 91, 93, 321]

Non-significant 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) [46, 332, 336, 343, 344] and one study comparing ibandronate with placebo (OR1.5, 95% CI 0.12, 78.7),[109] but not in four studies of risedronate vs. placebo (OR 0.74, 95% CI, 0.38, 1.46).[92, 94, 96, 99]

No hepatobiliary adverse events were reported for bisphosphonates.

Gastrointestinal - Mild

We categorized gastrointestinal conditions such as reflux and esophageal irritation, nausea, vomiting, heartburn, diarrhea, and constipation as "Mild." Pooled analysis of 50 studies of alendronate showed greater odds of all mild upper gastrointestinal (GI) events than did placebo (OR 1.08, 95% CI 1.01, 1.15). [40, 41, 46, 48, 52, 53, 60-63, 65, 66, 317, 318, 324, 330-337, 340, 341, 343-366] There were no differences between ibandronate, risedronate, or zoledronic acid and placebo regarding any mild upper GI events and no significant differences for alendronate regarding any specific type of event in this category.

Head-to-head comparisons of a bisphosphonate vs. another agent showed one significant difference in mild GI events. Pooled analysis of three new studies showed a significantly increased risk for alendronate vs. denosumab (OR 1.35, 95% CI 1.08, 1.70).[63, 367]

Musculoskeletal

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

In three pooled trials identified for the original report,[113, 114, 368] zoledronic acid participants had higher odds of these events than did placebo participants (OR 4.52, 95% CI 3.78, 5.43). Two studies were identified for the current report,[115, 116] and the difference was smaller but still significant (OR2.94 95% CI 2.58, 3.36).

In two head-to-head trials identified for the original report,[237, 369] 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 three 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),[63, 65] but an increased risk among individuals taking zoledronic acid in four pooled trials (OR 2.67, 95% CI 2.14, 3.35).[113-115, 368] One trial of ibandronate vs. placebo[370] and five trials of risedronate vs. placebo[76, 84, 97, 99, 371] found no significant differences.

In three 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).[63, 367]

Myalgias, cramps, and limb pain. Studies were identified that compared alendronate, ibandronate, and zoledronic acid with placebo. Pooled analysis of two trials of ibandronate[110, 372] and five trials of zoledronic acid[113-116, 368] 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 4.64, 95% CI 3.72, 5.85 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).[373] 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.[374]

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.[375] 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.[376] 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, non-union fractures of the humerus, among a large cohort of older adults (cases of non-union were identified as those with an orthopedic procedure associated with non-union 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 non-union (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).[377]

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. No trials were identified for the current report that reported on the incidence of osteonecrosis of the jaw among individuals taking bisphosphonates to prevent or treat osteoporosis. However, a large recent case series reviewed 2408 cases of osteonecrosis of the jaw to assess the possible association between

use of bisphosphonates and osteonecrosis.[378] 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). Thus the prevention and treatment of osteoporosis remains a relatively minor contributor to the development of osteonecrosis of the jaw.

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.[340, 362] Two trials of zoledronic acid, one included in the original report[379] and one identified for the present report,[115] found an increased risk for hypocalcemia with zoledronic acid compared with placebo (OR 7.22, 95% CI 1.81, 42.70).

Table 51. Risks of Adverse Events for bisphosphonates vs. placebo

	Alendronate		Ibandronate		Risedronate		Zoledronic acid	
Event Group	# 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)
CerebrovascularDeath	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 studies 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)	2	1.34 (0.6, 3.21)
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)	4	2.67 (2.14, 3.35)
Myalgias, Cramps, Limb Pain	4	1.14 (0.18, 8.18)	2	2.25 (1.57, 3.29)	0	NR	5	4.64 (3.72, 5.85)
Atypical Fractures	See text for description of comprehensive review and subsequent observational study of all bisphosphonates							
Osteonecrosis of the Jaw	See text for description of recent case series							

Table Notes: 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 52. shows the risks of adverse events for SERMS compared with placebo.

Cardiovascular

Acute coronary syndrome. The original report identified four trials of raloxifene[124, 380-382] that found no significant effect of the drug compared with placebo. For the current report, we identified an additional three trials;[123, 383, 384] 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).[383]

Cardiovascular death. The original report identified two trials of raloxifene[380, 382] that reported cardiac deaths and found no differences between drug and placebo. One additional study was identified for the current report;[383] 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[381, 382, 385] that reported CVA; there were no significant differences between either drug and placebo. The current report identified three new studies of raloxifene[123, 383, 384] 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).[380, 386] The current report identified two additional studies[123, 383]; 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.[366, 380, 387, 388] (OR 2.08, 95% CI 1.47, 3.02). For the current report, four additional studies were identified (OR 1.63, 95% CI 1.36, 1.98) that narrowed the confidence interval.[123, 383, 384, 389]

Mild Cardiosvascular Events. A pooled analysis of four studies, three from the original report[345, 387, 390] and one identified for the current report[123] that compared raloxifene and placebo found a significant increase in these events among raloxifene users (pooled OR 1.92, 95% CI 1.55, 2.38).

Cancer

Breast Cancer. The original report identified two studies that, when pooled, showed no significant differences between raloxifene and placebo.[380, 387] For the current report, two

additional studies were identified.[123, 384] Pooled analysis of the four studies also showed no significant difference (OR 0.79, 95% CI0.32, 1.97).

Lung Cancer. The original report identified two placebo-controlled trials of raloxifene, [380, 386] that reported lung cancer and found no significant differences. No new studies were found that reported on lung cancer risk.

Gastrointestinal (serious)

PUBs. One study identified for the current report found no significant difference in the incidence of these events between raloxifene and placebo.[385]

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).[124, 345, 366, 380, 385, 387, 390, 391]

Musculoskeletal

This category includes arthritis and arthralgia; and myalgias, muscle cramps, and limb pain. A pooled analysis of 10 placebo-controlled trials, seven identified for the original report[124, 366, 381, 385, 387, 390, 392] and three identified for the current report,[123, 384, 389] found a significant increase in myalgias, cramps, and limb pain for raloxifene (OR 1.51, 95% CI 1.27, 1.79). Single placebo-controlled studies found no effect on reports of arthritis and arthralgias for raloxifene (OR Inf+ 95% CI 0.01, Inf+).[391]

Sweats/Fever/Hot Flashes

This category includes fever, hot flashes, weight gain, pain, and flushing. A pooled analysis of five placebo-controlled trials found that raloxifene significantly increased the incidence of hot flashes over that of placebo (OR 1.27 95% CI 1.02, 1.58).[124, 387, 392-394] A second pooled analysis of this same five trials identified a significant increase in flushing among raloxifene recipients (OR 1.42 95% CI 1.0., 2.02).

Table 52. Risks of Adverse Events for Raloxifene vs. 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)*
Mild Cardiovascular Events	4	1.92 (1.55, 2.38)*
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)	8	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	10	1.51 (1.27, 1.79)
Arthritis and Arthralgias	1	Inf+ (0.01, Inf+)

Parathyroid Hormone

Table 53 shows the risks of adverse events for parathyroid hormone 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.[130, 133] Participants in the teriparatide groups had lower odds of cancer than did placebo participants (OR 0.49, 95% CI, 0.27, 0.90). Incidences for specific types of cancers such as breast cancer, colon cancer, lung cancer, or osteosarcoma were not reported in these trials. The current report identified no trials that reported on cases of cancer with use of PTH.

Gastro-intestinal (mild)

Upper gastro-intestinal. The original report identified two placebo-controlled trials of teriparatide[130, 133] 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.

Gastro-intestinal (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).[130, 133, 135]

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% CI10.49, 16.00).[130, 135, 137, 395]

Table 53. Risks of Adverse Events for Parathyroid Hormone vs. placebo

Event Group	PTH Number of Trials	PTH 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)*

Table Notes: *=statistically significant

Estrogen or Estrogen Plus Progestin

No new trials of estrogen or estrogen plus progestin were identified for the current report that reported adverse events.

Denosumab

Denosumab was not examined in the original report. Table 54 shows the risks of adverse events for denosumab compared with placebo.

Gastro-intestinal (mild)

Upper gastro-intestinal. Pooled results from two placebo-controlled trials identified for this 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).[63]

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+).[396] Pooled results of four placebo-controlled trials identified an increase in rash (OR 2.01 95% CI 1.5, 2.73).[63, 118, 119]

Table 54. Risks of Adverse Events for Biologics (Denosumab)

	Denosumab	
Event Group	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
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 – Not otherwise specified and not pulmonary, GI, ear, eye	4	1.01 (0.92, 1.1)
Genitourinary		
Urinary Tract Infection	3	1.78 (0.96, 3.45)

Vitamin D and Calcium

Table 55 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. However, 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% confidence interval 1.02 to 1.67, P=0.035).[397] The pooled results of trial-level data showed a similar effect (pooled RR 1.27, 95% confidence interval 1.01 to 1.59, P=0.038).

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).[398]

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[156] [original report says ref. 269 included also] and one trial of vitamin D,[356] 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.[399]

Metabolic

A single placebo-controlled trial of Vitamin D identified for the current report showed an increased risk for hypercalciuria (OR 19.8, 95% CI3.19, 819).[399]

Table 55. 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
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	o	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?

Key Points

- No evidence exists from RCTs regarding how often patients' BMD should be monitored during osteoporosis therapy.
- Strong 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 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.
- Evidence from one large RCT showed no higher fracture risk other than for clinical vertebral fractures with use of alendronate for more than five years.

Summary of Findings

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.

5a2. How does bone density monitoring predict antifracture benefits during pharmacotherapy?

PRIOR META-ANALYSES

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).[400] Based on data from 12 trials, Cummings and colleagues 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%, whereas treatments actually reduced fracture risk by 45%. 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.

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% 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 follow-up. 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[401] Bell and colleagues analyzed 3-year follow-up data from FIT.[402] 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%

confidence interval 11%-27%) of the reduction in the risk of vertebral fracture after three years of therapy.[400§§]

Risedronate: Among postmenopausal osteoporotic women assigned to 2.5 mg or 5 mg daily of risedronate, the incidence of nonvertebral fractures during follow-up of up to three years was not different between women whose spine BMD decreased (7.8 percent) and those whose spine BMD increased (6.4 percent) (hazard ratio 0.79, 95% CI 0.50-1.25).[403] Another study by the same authors 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.[404] 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 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.

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.[405] For any percentage change, either an increase or a decrease in femoral neck of lumbar spine BMD at one year or three years, women assigned to raloxifene had a statistically significantly lower vertebral fracture risk compared with placebo-treated women. The reduction in fracture risk with raloxifene was similar regardless of percentage change in 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 follow-up (RR 0.11, 95% CI 0.03-0.45).[406] 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. Among women assigned to teriparatide, increases in spine BMD accounted for 30 percent to 41 percent of the reduction in vertebral fracture risk.[407]

---

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

Summary: 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[407]

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 meta-analyses that performed head-to-head comparisons of the ability of monitoring to predict antifracture effects among various pharmacotherapies.

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,[122] 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 follow-up, the cumulative risk of nonvertebral fractures was not significantly different between those continuing (19%) and discontinuing (18.9%) alendronate.[239] Among women who continued alendronate, there was a significantly lower risk of clinically-recognized vertebral fractures (5.3% for placebo vs. 2.4% 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 non-vertebral 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 non-vertebral 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 non-vertebral fracture risk among women without prevalent vertebral fractures whose T-scores are >-2.[242] 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 in the primary prevention setting. Regarding glucocorticoid-induced osteoporosis, the original review identified evidence from a meta-analysis 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.

Chapter 4. Summary and Discussion

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

Limitations

Publication Bias

Our literature search procedures were extensive and included canvassing experts from academia and industry for studies. However, it is possible that other unpublished trial results exist for the treatments included in our report. Publication bias may occur, resulting in an overestimation of the effects of these treatments. Nevertheless, Begg's and Egger's tests revealed no evidence of publication bias.

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 one additional potential sources of bias, two unique to this report, namely the applicability of the studies to the population that would be likely to benefit from the agents of interest. We assessed the applicability of the trials included in the report using the method of Gartlehner et al.[27] 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.

Conclusions

With the above limitations in mind, we reached the conclusions displayed in the table below (Table 56). Changes in conclusion in this report, compared to the 2007 report are presented in **bold.**

Table 56. Summary of Evidence

Key Question	Strength of Evidence	Conclusion
1. What are the comparative benefits in fracture 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, **ibandronate** and zoledronic acid reduce the risk of non-vertebral fractures among postmenopausal women with osteoporosis.
	High	Hip: alendronate, risedronate and zoledronic acid reduce the risk of hip fractures among postmenopausal women with osteoporosis. **The effect of ibandronate is unclear, since hip fracture risk reduction was not a separately reported outcome in trials reporting non-vertebral fractures.**
	Low	Wrist: 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.**
	Low	Based on limited data from head-to-head trials, within the bisphosphonate class, superiority for the prevention of fractures has not been demonstrated for any agent.
	Low	Based on limited data from head-to-head trials, superiority for the prevention of vertebral fractures has not been demonstrated for bisphosphonates in comparison with calcium, raloxifene or **teriparatide**.
	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, no-vertebral and hip fractures in postmenopausal women with osteoporosis.**

Key Question	Strength of Evidence	Conclusion
d. Menopausal hormone therapy	**Strong**	Menopausal hormone therapy reduces the risk of vertebral and hip fractures.
e. PTH (teriparatide)	**High** **Moderate**	**Teriparatide reduces the risk of vertebral fractures in postmenopausal women with osteoporosis**. **Teriparatide reduces the risk of non-vertebral fractures in postmenopausal women with osteoporosis.**
f. SERMs (raloxifene)	High	Raloxifene **reduces the risk of** vertebral fractures.
g. Vitamin D	Moderate	The effect of vitamin D on fracture risk is uncertain. Among a number of meta-analyses, some reported a reduced risk for vitamin D relative to placebo, some did not. There was no reduction in fracture risk for vitamin D relative to placebo in a large, high quality RCT published after the meta-analyses.
h. Exercise in comparison to above agents.	None	There are no data from RCTs to inform this question.
2. How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), prior fractures (prevention vs. treatment)?	High High Low High Moderate Low	Alendronate, etidronate, ibandronate, risedronate, teriparatide, and raloxifene reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis. Raloxifene prevents fractures in postmenopausal women at low risk for fracture. Teriparatide, risedronate, and calcitonin reduce risk of fracture among men. Among subjects treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate. Reduction in fracture risk for subjects treated with alendronate, risedronate, or vitamin D has been demonstrated in populations at increased risk for fracture due to conditions that increase the risk of falling including stroke with hemiplegia, Alzheimer's disease, and Parkinson's. There are limited and inconclusive data on the effect of agents for the prevention and treatment of osteoporosis on transplant recipients and patients treated with chronic corticosteroids.

Key Question	Strength of Evidence	Conclusion
3. What are the adherence and persistence to medications for the treatment and prevention of osteoporosis, the factors that affect adherence and persistence, and the effects of adherence and persistence on the risk of fractures?	**Moderate**	**15 RCTs reported rates of adherence to therapy. 10 trials with bisphophonates reported high levels of adherence (majority with over 90% adherence). Two trials with raloxifene had adherence rates 65-70%.**
	High	**There is evidence from 37 observational studies, including 14 using US data, that adherence and persistence to therapy with bisphosphonates, and calcium and vitamin D is poor in many patients with osteoporosis. No studies describe primary nonadherence (i.e. nonfulfillment).**
	Moderate	**Based on evidence from 30 observational studies, many factors affect adherence and persistence to 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 16 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 meta-analysis and ten out of eleven observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, non-vertebral 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	Strength of Evidence	Conclusion
4. What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?	High	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.**
	Moderate	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. **Compared to placebo, teriparatide users also had an increased risk of mild upper GI events. Pooled analysis also showed alendronate users to be at a increased risk for mild GI events compared to denosumab. Denosumab was also associated with an increase in mild GI events.**
	Moderate	**A new meta-analysis 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.**
	Moderate	**PTH and teriparatide treated participants showed a significant increase in hypercalcemia.**
	Moderate	Zoledronic acid is associated with an increased risk of atrial fibrillation relative to placebo.
	Moderate	**A review of 2,408 cases of osteonecrosis of the jaw in patients taking bisphosphantes found that 89 percent of the cases were associated with treatment of malignancy and 88 percent of cases involved intravenous therapy, previously zoledronic acid.**
	Moderate	**Our pooled analysis of four trials found an increased risk with raloxifene in mild cardiac events (those other than death, myocardial infarction, atrial fibrillation, and ventricular arrhythmia.**
	Moderate	**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,**

Key Question	Strength of Evidence	Conclusion
	Moderate	A pooled analysis of four trials of denosumab found an increased risk of rash.
	Low	A small number of clinical trials have reported an increased risk of hypocalcaemia in patients treated with alendronate and zoledronic acid.
	Low	There is a signal from observational studies that use of an oral bisphosphonate is associated with an increased risk of esophageal cancer.
5a. How often should patients be monitored (via measurement of bone mineral density) during therapy?	Low	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 are associated with a minority of antifracture effects; even patients who continue to lose BMD during therapy have had statistically significant benefits in fracture reduction.
5b. How does the antifracture benefit vary with long-term continued use of pharmacotherapy?	Moderate	One large RCT showed no higher fracture risk other than for clinical vertebral fractures with use of alendronate for five additional years compared to placebo, after having been already treated with alendronate for 5 years.
	Low	A post hoc analysis of this same trial reported that there were statistically significant non vertebral 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 meta-analyses 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, ibandronate, zoledronic acid, and denosumab each reduce the risk of non-vertebral 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. Strong evidence supports the effectiveness of menopausal hormone therapy in decreasing vertebral fracture and hip fracture risk, and the effectiveness of teriparatide in reducing non-vertebral fracture risk. Accordingly, each of these agents is FDA-approved for therapy of osteoporosis. Studies directly comparing the antifracture effects among various bisphosphonates do not support the effectiveness of one bisphosphonate over another. 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, non-vertebral, 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 30 new studies describing the factors affecting 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.

Despite the many barriers to adherence discussed in the literature, very few interventions to improve osteoporosis medication adherence have been successful. Gleeson et al performed a comprehensive systematic review of the topic[258] 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 et al 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[122] and found no difference in antifracture effects between those who were at least 70% 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.

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, 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 and thromboembolic events. 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 moderate 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. Raloxifene may increase risk of mild cardiac events (other than death, myocardial infarction, atrial fibrillation, and/or ventricular arrhythmias). 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 strong level of evidence for reduction in hip fracture risk. For reduction in vertebral fracture risk, there is strong evidence supporting the use of bisphosphonates, raloxifene, and teriparatide. Raloxifene is not effective in reducing the risk of hip or non-vertebral 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, the issue now seems settled that treatment with any of the FDA-approved agents discussed in this report will decrease the risk for all or most kinds of osteoporotic fractures for postmenopausal women with established osteoporosis. While data are thin regarding comparative effectiveness between different agents, the evidence that does exist supports the thesis that any comparative differences, if they exist at all, will be small, at least between the bisphosphonates. More important than comparative effectiveness between agents are the following concerns:

1) Who should we treat? What is the balance of benefits and harms for postmenopausal women without established osteoporosis? The existing evidence shows that the benefits of treatment (in terms of fracture risk reduction) are less robust for postmenopausal women with osteopenia and without prevalent fractures than they are for women with established osteoporosis and even less robust for men with or at risk for osteoporosis. 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.

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 5 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 3 years, 4 years, 5 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?

3) For people who are good candidates for treatment, how can we improve adherence? There is moderate to strong 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 (side effects, knowledge about osteoporosis, cost, and comorbid conditions/concomitant medication use.)

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 did not occur until after well more than a decade of widespread use.

References

1. NIH Consensus Development Panel on Osteoporosis Prevention D, Theapy. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285(6):785-95.

2. Sasser ACR, M. D. Birnbaum, H. G. Oster, E. F. Lufkin, E. Mallet, D. Economic burden of osteoporosis, breast cancer, and cardiovascular disease among postmenopausal women in an employed population. Womens Health Issues. 2005 May-Jun;15(3):97-108.

3. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC. 2010.

4. Burge RD-H, B. Solomon, D. H. Wong, J. B. King, A. Tosteson, A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007 Mar;22(3):465-75.

5. Nelson HD, Haney EM, Dana T, Bougatsos C, Chou R. Screening for Osteoporosis: An update for the U.S. Preventive Services Task Force. Annals of Internal Medicine. 2010;153(2):1-11.

6. Kanis JAM, L. J., 3rd Christiansen, C. Johnston, C. C. Khaltaev, N. The diagnosis of osteoporosis. J Bone Miner Res. 1994 Aug;9(8):1137-41.

7. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. WHO Fracture Risk Assessment Tool. [cited]; Available from: http://www.shef.ac.uk/FRAX/.

8. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008 Apr;19(4):385-97.

9. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int. 2007;18(8):1033-46.

10. Lewiecki EM, Binkley N. Evidence-based medicine, clinical practice guidelines, and common sense in the management of osteoporosis. Endocr Pract. 2009 Sep-Oct;15(6):573-9.

11. Kanis JA, Johansson H, Oden A, McCloskey EV. Assessment of fracture risk. Eur J Radiol. 2009 Sep;71(3):392-7.

12. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC. 2008.

13. Colman EG. The Food and Drug Administration's Osteoporosis Guidance Document: past, present, and future. J Bone Miner Res. 2003;18(6):1125-8.

14. Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis. Rockville, MD: Food and Drug Administration, Division of Metabolic and Endocrine Drug Products; 1994 Contract No.: Document Number|.

15. MacLean CA, A. Cartor, J. Chen, S. Desai, S.B. Grossman, J. Maglione, M. McMahon, M. McNamara, M. Mojica, W. Newberry, S. Ranganath, V. Suttorp, M. Timmer, M. Tringale, C. Valentine, D. Zhou, A. . Comparitive Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis. (Prepared by Southern California/RAND Evidence-based Practice Center under Contract No. 290-02-000.) Rockville, MD. Agency for Healthcare Research and Quality. December 2007. Available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

16. Shekelle PG, Newberry SJ, Maglione M, Shanman R, Johnsen B, Carter J, et al. Evaluation of the need to update comparative effectiveness reviews. Rockville, MD: Agency for Healthcare Research and Quality: October 2009. Available at: www.effectivehealthcare.ahrq.gov/ehc/products/125/331/2009_0923UpdatingReports.pdf. 2009.

17. SAS. SAS System for Windows Version 9.2 ed. Cary, NC: SAS Institute Inc.; 2008.

18. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis. 1985;27(5):335-71.

19. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2006.

20. Cramer JAR, A. Burrell, A. Fairchild, C. J. Fuldeore, M. J. Ollendorf, D. A. Wong, P. K. Medication compliance and persistence: terminology and definitions. Value Health. 2008 Jan-Feb;11(1):44-7.

21. World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. Geneva, Switzerland: World Health Organization; 2003 [updated 2003; cited]; Available from: http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.

22. StatXact. StatXact 9 for Windows. . Version 9.0.1 ed. ed. Cambridge, MA: Cytel Software Corporation; 2009.

23. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

24. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998;352(9128):609-13.

25. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. Newcastle- Ottawa Quality Assessment Scale, Cohort Studies. Quality Assessment Scales for Observational Studies. 2004.

26. Fullerton DS, Atherly DS. Formularies, therapeutics, and outcomes: new opportunities. Med Care. 2004;42(4 Suppl):III39-44.

27. Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. A simple and valid tool distinguished efficacy from effectiveness studies. J Clin Epidemiol. 2006 Oct;59(10):1040-8.

28. Owens DKL, K.N. Atkins, D. Et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol 2010;63(5):513-23.

29. Atkins DB, D. Briss, P. A. Eccles, M. Falck-Ytter, Y. Flottorp, S. Guyatt, G. H. Harbour, R. T. Haugh, M. C. Henry, D. Hill, S. Jaeschke, R. Leng, G. Liberati, A. Magrini, N. Mason, J. Middleton, P. Mrukowicz, J. O'Connell, D. Oxman, A. D. Phillips, B. Schunemann, H. J. Edejer, T. T. Varonen, H. Vist, G. E. Williams, J. W., Jr. Zaza, S. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.

30. Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA. Using existing systematic reviews in complex systematic reviews. Ann Intern Med. 2008 May 20;148(10):776-82.

31. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev. 2002;23(4):508-16.

32. Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston CC, Jr., Adami S, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. JAMA. 1997;277(14):1159-64.

33. Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. Osteoporos Int. 2005;16(5):468-74.

34. Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess. 2005;9(22):1-160.

35. Nguyen ND, Eisman JA, Nguyen TV. Anti-hip fracture efficacy of biophosphonates: a Bayesian analysis of clinical trials. J Bone Miner Res. 2006;21(2):340-9.

36. Boonen S, Laan RF, Barton IP, Watts NB. Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies. Osteoporos Int. 2005;16(10):1291-8.

37. Sawka AM, Papaioannou A, Adachi JD, Gafni A, Hanley DA, Thabane L. Does alendronate reduce the risk of fracture in men? A meta-analysis

incorporating prior knowledge of anti-fracture efficacy in women. BMC Musculoskelet Disord. 2005;6:39.

38. Jansen JP, Bergman GJ, Huels J, Olson M. Prevention of vertebral fractures in osteoporosis: mixed treatment comparison of bisphosphonate therapies. Curr Med Res Opin. 2009 Aug;25(8):1861-8.

39. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008(1):CD001155.

40. Adami S, Passeri M, Ortolani S, Broggini M, Carratelli L, Caruso I, et al. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. Bone. 1995;17(4):383-90.

41. Ascott-Evans BH, Guanabens N, Kivinen S, Stuckey BG, Magaril CH, Vandormael K, et al. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. Arch Intern Med. 2003;163(7):789-94.

42. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348(9041):1535-41.

43. Bone HG, Downs RW, Jr., Tucci JR, Harris ST, Weinstein RS, Licata AA, et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. J Clin Endocrinol Metab. 1997;82(1):265-74.

44. Bonnick S, Rosen C, Mako B, et al. Alendronate vs calcium for treatment of osteoporosis in postmenopausal women. Bone. 1998;23(Suppl 5):S476.

45. Chesnut CH, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. The American journal of medicine. 1995;99(2):144-52.

46. Cummings SRB, D. M. Thompson, D. E. Applegate, W. B. Barrett-Connor, E. Musliner, T. A. Palermo, L. Prineas, R. Rubin, S. M. Scott, J. C. Vogt, T. Wallace, R. Yates, A. J. LaCroix, A. Z. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280(24):2077-82.

47. Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. Int J Clin Pract. 2001;55(8):505-9.

48. Greenspan SL, Parker RA, Ferguson L, Rosen HN, Maitland-Ramsey L, Karpf DB. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. J Bone Miner Res. 1998;13(9):1431-8.

49. Greenspan SL, Schneider DL, McClung MR, Miller PD, Schnitzer TJ, Bonin R, et al. Alendronate improves bone mineral density in elderly women with osteoporosis residing in long-term care facilities. A randomized, double-blind, placebo-controlled trial.[summary for patients in Ann Intern Med. 2002 May 21;136(10):I54; PMID: 12020160]. Annals of Internal Medicine. 2002;136(10):742-6.

50. Hosking D, Chilvers CE, Christiansen C, Ravn P, Wasnich R, Ross P, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. N Engl J Med. 1998;338(8):485-92.

51. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med. 1995;333(22):1437-43.

52. McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J, Weinstein RS, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. Annals of internal medicine. 1998;128(4):253-61.

53. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the

treatment of osteoporosis in men. N Engl J Med. 2000;343(9):604-10.

54. Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Wilkin TJ, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Foxamax International Trial Study Group. Osteoporos Int. 1999;9(5):461-8.

55. Ringe JD, Dorst A, Faber H, Ibach K. Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. Rheumatol Int. 2004;24(2):110-3.

56. Weinstein RS, Bone H, Tucci J, et al. Alendronate treatment of osteoporosis in elderly women. J Bone Miner Res. 1994;9(Suppl 1):S144.

57. Papaioannou A, Kennedy CC, Freitag A, Ioannidis G, O'Neill J, Webber C, et al. Alendronate once weekly for the prevention and treatment of bone loss in Canadian adult cystic fibrosis patients (CFOS trial). Chest. 2008 Oct;134(4):794-800.

58. Ringe JD, Farahmand P, Schacht E, Rozehnal A. Superiority of a combined treatment of Alendronate and Alfacalcidol compared to the combination of Alendronate and plain vitamin D or Alfacalcidol alone in established postmenopausal or male osteoporosis (AAC-Trial). Rheumatol Int. 2007 Mar;27(5):425-34.

59. de Nijs RN, Jacobs JW, Lems WF, Laan RF, Algra A, Huisman AM, et al. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. N Engl J Med. 2006 Aug 17;355(7):675-84.

60. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab. 2000;85(2):720-6.

61. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA. 2003;289(19):2525-33.

62. Hosking D, Adami S, Felsenberg D, Andia JC, Valimaki M, Benhamou L, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. Current medical research and opinion. 2003;19(5):383-94.

63. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med. 2006;354(8):821-31.

64. Quandt SA, Thompson DE, Schneider DL, Nevitt MC, Black DM. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of-1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. Mayo Clin Proc. 2005;80(3):343-9.

65. Zein CO, Jorgensen RA, Clarke B, Wenger DE, Keach JC, Angulo P, et al. Alendronate improves bone mineral density in primary biliary cirrhosis: a randomized placebo-controlled trial. Hepatology. 2005;42(4):762-71.

66. Sato Y, Iwamoto J, Kanoko T, Satoh K. Alendronate and vitamin D2 for prevention of hip fracture in Parkinson's disease: A randomized controlled trial. Mov Disord. 2006.

67. Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev. 2002;23(4):517-23.

68. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. J Bone Miner Res. 2005;20(12):2105-15.

69. Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, et al. Randomized controlled trial of calcium in healthy older women. Am J Med. 2006;119(9):777-85.

70. Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int. 2000;67(4):277-85.

71. Bianchi G, Sambrook P. Oral nitrogen-containing bisphosphonates: a systematic review of randomized clinical trials and vertebral fractures. Curr Med Res Opin. 2008 Sep;24(9):2669-77.

72. Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008(1):CD004523.

73. Zhong ZM, Chen JT. Anti-fracture efficacy of risedronic acid in men: A meta-analysis of randomized controlled trials. Clin Drug Investig. 2009;29(5):349-57.

74. Sato Y, Honda Y, Iwamoto J. Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease. Neurology. 2007 Mar 20;68(12):911-5.

75. Ringe JD, Farahmand P, Faber H, Dorst A. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. Rheumatol Int. 2009 Jan;29(3):311-5.

76. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. J Bone Miner Res. 2009 Apr;24(4):719-25.

77. Palomba S, Manguso F, Orio F, Jr. , Russo T, Oppedisano R, Sacchinelli A, et al. Effectiveness of risedronate in osteoporotic postmenopausal women with inflammatory bowel disease: a prospective, parallel, open-label, two-year extension study. Menopause. 2008 Jul-Aug;15(4 Pt 1):730-6.

78. Kanaji A, Higashi M, Namisato M, Nishio M, Ando K, Yamada H. Effects of risedronate on lumbar bone mineral density, bone resorption, and incidence of vertebral fracture in elderly male patients with leprosy. Lepr Rev. 2006;77(2):147-53.

79. Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Arch Intern Med. 2005;165(15):1737-42.

80. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. Arch Intern Med. 2005;165(15):1743-8.

81. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate therapy for prevention of hip fracture after stroke in elderly women. Neurology. 2005;64(5):811-6.

82. Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003;32(2):120-6.

83. Ringe JD, Faber H, Farahmand P, Dorst A. Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. Rheumatol Int. 2006;26(5):427-31.

84. Milgrom C, Finestone A, Novack V, Pereg D, Goldich Y, Kreiss Y, et al. The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits. Bone. 2004;35(2):418-24.

85. Greenspan SL, Bhattacharya RK, Sereika SM, Brufsky A, Vogel VG. Prevention of Bone Loss in Survivors of Breast Cancer: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Clin Endocrinol Metab. 2006.

86. Palomba S, Orio F, Jr., Manguso F, Falbo A, Russo T, Tolino A, et al. Efficacy of risedronate administration in osteoporotic postmenopausal women affected by inflammatory bowel disease. Osteoporos Int. 2005;16(9):1141-9.

87. Delmas PD, Benhamou CL, Man Z, Tlustochowicz W, Matzkin E, Eusebio R, et al. Monthly dosing of 75 mg risedronate on 2 consecutive days a month: efficacy and safety results. Osteoporos Int. 2008 Jul;19(7):1039-45.

88. Delmas PD, McClung MR, Zanchetta JR, Racewicz A, Roux C, Benhamou CL, et al. Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. Bone. 2008 Jan;42(1):36-42.

89. Watts NB, Josse RG, Hamdy RC, Hughes RA, Manhart MD, Barton I, et al. Risedronate prevents new vertebral fractures in postmenopausal women at high risk. J Clin Endocrinol Metab. 2003;88(2):542-9.

90. Clemmesen B, Ravn P, Zegels B, Taquet AN, Christiansen C, Reginster JY. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. Osteoporos Int. 1997;7(5):488-95.

91. Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 1999;42(11):2309-18.

92. Fogelman IR, C. Smith, R. Ethgen, D. Sod, E. Reginster, J. Y. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. J Clin Endocrinol Metab. 2000;85(5):1895-900.

93. Harris STW, N. B. Genant, H. K. McKeever, C. D. Hangartner, T. Keller, M. Chesnut, C. H., 3rd Brown, J. Eriksen, E. F. Hoseyni, M. S. Axelrod, D. W. Miller, P. D. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999;282(14):1344-52.

94. Hooper MJ, Ebeling PR, Roberts AP, Graham JJ, Nicholson GC, D'Emden M, et al. Risedronate prevents bone loss in early postmenopausal women: a prospective randomized, placebo-controlled trial. Climacteric. 2005;8(3):251-62.

95. McClung M, Bensen W, Bolognese M, Bonnick S, Ettinger M, Harris S, et al. Risedronate increases bone mineral density at the hip, spine and radius in postmenopausal women with low bone mass. Osteoporosis International. 1998;8(Suppl 3):111.

96. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344(5):333-40.

97. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC, Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. J Clin Endocrinol Metab. 1998;83(2):396-402.

98. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11(1):83-91.

99. Reid DM, Hughes RA, Laan RF, Sacco-Gibson NA, Wenderoth DH, Adami S, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res. 2000;15(6):1006-13.

100. Reid DM, Adami S, Devogelaer JP, Chines AA. Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy. Calcif Tissue Int. 2001;69(4):242-7.

101. Kishimoto H, Fukunaga M, Kushida K, Shiraki M, Itabashi A, Nawata H, et al. Efficacy and tolerability of once-weekly administration of 17.5 mg risedronate in Japanese patients with involutional osteoporosis: a comparison with 2.5-mg once-daily dosage regimen. J Bone Miner Metab. 2006;24(5):405-13.

102. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int. 2002;71(2):103-11.

103. Harris ST, Watts NB, Li Z, Chines AA, Hanley DA, Brown JP. Two-year efficacy and tolerability of risedronate once a week for the treatment of women with postmenopausal osteoporosis. Curr Med Res Opin. 2004;20(5):757-64.

104. Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, et al. Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. Osteoporos Int. 2009 Feb;20(2):291-7.

105. Harris ST, Blumentals WA, Miller PD. Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Curr Med Res Opin. 2008 Jan;24(1):237-45.

106. Ravn P, Clemmesen B, Riis BJ, Christiansen C. The effect on bone mass and bone markers of different doses of ibandronate: a new bisphosphonate for prevention and treatment of postmenopausal osteoporosis: a 1-year, randomized, double-blind,

placebo-controlled dose-finding study. Bone. 1996;19(5):527-33.

107. Grotz W, Nagel C, Poeschel D, Cybulla M, Petersen KG, Uhl M, et al. Effect of ibandronate on bone loss and renal function after kidney transplantation. Journal of the American Society of Nephrology : JASN. 2001;12(7):1530-7.

108. Fahrleitner-Pammer A, Piswanger-Soelkner JC, Pieber TR, Obermayer-Pietsch BM, Pilz S, Dimai HP, et al. Ibandronate prevents bone loss and reduces vertebral fracture risk in male cardiac transplant patients: a randomized double-blind, placebo-controlled trial. J Bone Miner Res. 2009 Jul;24(7):1335-44.

109. Chesnut Iii CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2004;19(8):1241-9.

110. Recker R, Stakkestad JA, Chesnut CH, 3rd, Christiansen C, Skag A, Hoiseth A, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone. 2004;34(5):890-9.

111. Miller PD, McClung MR, Macovei L, Stakkestad JA, Luckey M, Bonvoisin B, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res. 2005 Aug;20(8):1315-22.

112. Delmas PD, Adami S, Strugala C, Stakkestad JA, Reid DMea. Intravenous Ibandronate Injections in Postmenopausal Women With osteoporosis: one-year results from the dosing intravenous administration study. Arthritis and Rheumatism. 2006;54(6):1838-46.

113. Black DMD, P. D. Eastell, R. Reid, I. R. Boonen, S. Cauley, J. A. Cosman, F. Lakatos, P. Leung, P. C. Man, Z. Mautalen, C. Mesenbrink, P. Hu, H. Caminis, J. Tong, K. Rosario-Jansen, T. Krasnow, J. Hue, T. F. Sellmeyer, D. Eriksen, E. F. Cummings, S. R. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-22.

114. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med. 2002;346(9):653-61.

115. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007 Nov 1;357(18):1799-809.

116. Chapman I, Greville H, Ebeling PR, King SJ, Kotsimbos T, Nugent P, et al. Intravenous zoledronate improves bone density in adults with cystic fibrosis (CF). Clin Endocrinol (Oxf). 2009 Jun;70(6):838-46.

117. Anastasilakis AD, Toulis KA, Goulis DG, Polyzos SA, Delaroudis S, Giomisi A, et al. Efficacy and Safety of Denosumab in Postmenopausal Women with Osteopenia or Osteoporosis: A Systematic Review and a Meta-analysis. Horm Metab Res. 2009 Jun 17.

118. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab. 2008 Jun;93(6):2149-57.

119. Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis. N Engl J Med. 2009 Aug 11.

120. Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol. 2008 Oct 20;26(30):4875-82.

121. Lewiecki EM, Miller PD, McClung MR, Cohen SB, Bolognese MA, Liu Y, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. J Bone Miner Res. 2007 Dec;22(12):1832-41.

122. Ensrud KE, Stock JL, Barrett-Connor E, Grady D, Mosca L, Khaw KT, et al. Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. J Bone Miner Res. 2008 Jan;23(1):112-20.

123. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, et al. Efficacy of bazedoxifene in reducing new vertebral

fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res. 2008 Dec;23(12):1923-34.

124. Reid IR, Eastell R, Fogelman I, Adachi JD, Rosen A, Netelenbos C, et al. A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. Arch Intern Med. 2004;164(8):871-9.

125. Schachter HM, Clifford TJ, Cranney A, Barrowman NJ, Moher D. Raloxifene for primary and secondary prevention of osteoporotic fractures in postmenopausal women: a systematic review of efficacy and safety evidence. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment; 2005. Report No.: Report No. 50 Contract No.: Document Number|.

126. Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int. 2006;17(2):313-6.

127. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355(2):125-37.

128. Vestergaard P, Jorgensen NR, Mosekilde L, Schwarz P. Effects of parathyroid hormone alone or in combination with antiresorptive therapy on bone mineral density and fracture risk--a meta-analysis. Osteoporos Int. 2007 Jan;18(1):45-57.

129. Greenspan SL, Bone HG, Marriott TBEa. Preventing the first vertebral fracture in postmenopausal women with low bone mass using PTH(1-84): results from the TOP study (Abstract). J Bone Miner Res. 2005;20(S56).

130. Neer RMA, C. D. Zanchetta, J. R. Prince, R. Gaich, G. A. Reginster, J. Y. Hodsman, A. B. Eriksen, E. F. Ish-Shalom, S. Genant, H. K. Wang, O. Mitlak, B. H. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344(19):1434-41.

131. Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH. Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. The Journal of clinical endocrinology and metabolism. 2005;90(3):1583-7.

132. Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int. 2005;16(5):510-6.

133. Orwoll ES, Scheele WH, Paul S. The effects of teriparatide[human parathyroid hormone(1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003;18:9-17.

134. Fogelman I, Fordham JN, Fraser WD, Spector TD, Christiansen C, Morris SA, et al. Parathyroid hormone(1-84) treatment of postmenopausal women with low bone mass receiving hormone replacement therapy. Calcif Tissue Int. 2008 Aug;83(2):85-92.

135. Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med. 2007 Mar 6;146(5):326-39.

136. Cosman F, Lindsay R. Therapeutic potential of parathyroid hormone. Curr Osteoporos Rep. 2004;2(1):5-11.

137. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab. 2000;85(9):3069-76.

138. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al. The effect of teriparatide. J Bone Miner Res. 2003;18(1):9-17.

139. Boone RH, Cheung AM, Girlan LM, Heathcote EJ. Osteoporosis in primary biliary cirrhosis: a randomized trial of the efficacy and feasibility of estrogen/progestin. Dig Dis Sci. 2006 Jun;51(6):1103-12.

140. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi

Osteoporosis Prevention Study. The American Journal of Medicine. 2004;117(8):549-55.

141. Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med. 1998;104(3):219-26.

142. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr. 2007 Dec;86(6):1780-90.

143. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab. 2007 Apr;92(4):1415-23.

144. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007 Aug 25;370(9588):657-66.

145. Richy F, Schacht E, Bruyere O, Ethgen O, Gourlay M, Reginster JY. Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. Calcif Tissue Int. 2005;76(3):176-86.

146. Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2005(3):CD000227.

147. O'Donnell S, Moher D, Thomas K, Hanley DA, Cranney A. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. J Bone Miner Metab. 2008;26(6):531-42.

148. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2009(2):CD000227.

149. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010;340:b5463.

150. Bergman GJ, Fan T, McFetridge JT, Sen SS. Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis. Curr Med Res Opin. 2010 May;26(5):1193-201.

151. Izaks GJ. Fracture prevention with vitamin D supplementation: considering the inconsistent results. BMC Musculoskelet Disord. 2007;8:26.

152. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res. 2004 Mar;19(3):370-8.

153. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354(7):669-83.

154. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ. 2005;330(7498):1003.

155. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet. 2005;365(9471):1621-8.

156. Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. Thorax. 2004;59(9):761-8.

157. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med. 2006;166(8):869-75.

158. Frost RJ, Sonne C, Wehr U, Stempfle HU. Effects of calcium supplementation on bone loss and

fractures in congestive heart failure. Eur J Endocrinol. 2007 Mar;156(3):309-14.

159. Fujita T, Ohue M, Fujii Y, Miyauchi A, Takagi Y. Reappraisal of Katsuragi calcium study, a prospective, double-blind, placebo-controlled study of the effect of active absorbable algal calcium (AAACa) on vertebral deformity and fracture. J Bone Miner Metab. 2004;22(1):32-8.

160. Torres A, Garcia S, Gomez A, Gonzalez A, Barrios Y, Concepcion MT, et al. Treatment with intermittent calcitriol and calcium reduces bone loss after renal transplantation. Kidney Int. 2004;65(2):705-12.

161. Sato Y IJKTSK. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovasc Dis. 2005;20(3):187-92.

162. Shiraki M, Kushida K, Yamazaki K, Nagai T, Inoue T, Orimo H. Effects of 2 years' treatment of osteoporosis with 1alphahydroxy vitamin D3 on bone mineral density and incidence of fracture: a placebo-controlled, double-blind prospective study. Endocr J. 1996;43(2):211-20.

163. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford). 2007 Dec;46(12):1852-7.

164. Law M, Withers H, Morris J, Anderson F. Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. Age Ageing. 2006 Sep;35(5):482-6.

165. Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev. 2002;23(4):552-9.

166. Meunier PJ, Roux C, Ortolani S, Diaz-Curiel M, Compston J, Marquis P, et al. Effects of long-term strontium ranelate treatment on vertebral fracture risk in postmenopausal women with osteoporosis. Osteoporos Int. 2009 Oct;20(10):1663-73.

167. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992;327(23):1637-42.

168. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ. 1994;308(6936):1081-2.

169. Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int. 2002;13(3):257-64.

170. Chevalley T, Rizzoli R, Nydegger V, Slosman D, Rapin CH, Michel JP, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int. 1994;4(5):245-52.

171. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337(10):670-6.

172. Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. Calcif Tissue Int. 1987;40(6):315-7.

173. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. Age Ageing. 2004;33(1):45-51.

174. Peacock M, Liu G, Carey M, McClintock R, Ambrosius W, Hui S, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. J Clin Endocrinol Metab. 2000;85(9):3011-9.

175. Prince R, Devine A, Dick I, Criddle A, Kerr D, Kent N, et al. The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1995;10(7):1068-75.

176. Recker RR, Hinders S, Davies KM, Heaney RP, Stegman MR, Lappe JM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. J Bone Miner Res. 1996;11(12):1961-6.

177. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Effect of calcium supplementation on bone loss in postmenopausal women. N Engl J Med. 1993;328(7):460-4.

178. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. Am J Med. 1995 Apr;98(4):331-5.

179. Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ, 3rd. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. J Bone Miner Res. 1998;13(2):168-74.

180. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293(18):2257-64.

181. Papadimitropoulos E, Wells G, Shea B, Gillespie W, Weaver B, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev. 2002;23(4):560-9.

182. Richy F, Ethgen O, Bruyere O, Reginster JY. Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int. 2004;15(4):301-10.

183. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009 Mar 23;169(6):551-61.

184. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. Qjm. 2007 Apr;100(4):185-92.

185. Adachi JD, Bensen WG, Bianchi F, Cividino A, Pillersdorf S, Sebaldt RJ, et al. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year followup. J Rheumatol. 1996;23(6):995-1000.

186. Aloia JF, Vaswani A, Ellis K, Yuen K, Cohn SH. A model for involutional bone loss. J Lab Clin Med. 1985;106(6):630-7.

187. Avenell A, Grant AM, McGee M, McPherson G, Campbell MK, McGee MA. The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. Clin Trials. 2004;1(6):490-8.

188. Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. Osteoporos Int. 1998;8(3):255-60.

189. Bolton-Smith C, McMurdo ME, Paterson CR, Mole PA, Harvey JM, Fenton ST, et al. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. J Bone Miner Res. 2007 Apr;22(4):509-19.

190. Caniggia A, Delling G, Nuti R, Lore F, Vattimo A. Clinical, biochemical and histological results of a double-blind trial with 1,25-dihydroxyvitamin D3, estradiol and placebo in post-menopausal osteoporosis. Acta Vitaminol Enzymol. 1984;6(2):117-28.

191. Dukas L, Bischoff HA, Lindpaintner LS, Schacht E, Birkner-Binder D, Damm TN, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc. 2004;52(2):230-6.

192. Ebeling PR, Russell RG. Teriparatide (rhPTH 1-34) for the treatment of osteoporosis. Int J Clin Pract. 2003;57(8):710-8.

193. Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. J Am Geriatr Soc. 2005 Nov;53(11):1881-8.

194. Gallagher JC, Riggs BL, Recker RR, Goldgar D. The effect of calcitriol on patients with

postmenopausal osteoporosis with special reference to fracture frequency. Proc Soc Exp Biol Med. 1989;191(3):287-92.

195. Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol. A randomized controlled study. Ann Intern Med. 1990;113(9):649-55.

196. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab. 2001;86(8):3618-28.

197. Gorai I, Chaki O, Taguchi Y, Nakayama M, Osada H, Suzuki N, et al. Early postmenopausal bone loss is prevented by estrogen and partially by 1alpha-OH-vitamin D3: therapeutic effects of estrogen and/or 1alpha-OH-vitamin D3. Calcif Tissue Int. 1999;65(1):16-22.

198. Geusens P, Dequeker J. Long-term effect of nandrolone decanoate, 1 alpha-hydroxyvitamin D3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: a double-blind controlled study. Bone Miner. 1986;1(4):347-57.

199. Hayashi Y, Fujita T, Inoue T. Decrease of vertebral fracture in osteoporotics by administration of 1a-hydroxy-vitamin D3. Journal of Bone and Mineral Metabolism. 1992;10(2):50-4.

200. Jensen GF, Meinecke B, Boesen J, Transbol I. Does 1,25(OH)2D3 accelerate spinal bone loss? A controlled therapeutic trial in 70-year-old women. Clin Orthop Relat Res. 1985 Jan-Feb(192):215-21.

201. Komulainen MH, Kroger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, et al. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. Maturitas. 1998;31(1):45-54.

202. Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med. 1996;124(4):400-6.

203. Lyons RA, Johansen A, Brophy S, Newcombe RG, Phillips CJ, Lervy B, et al. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int. 2007 Jun;18(6):811-8.

204. Menczel J, Foldes J, Steinberg R, Leichter I, Shalita B, Bdolah-Abram T, et al. Alfacalcidol (alpha D3) and calcium in osteoporosis. Clin Orthop Relat Res. 1994(300):241-7.

205. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res. 2002;17(4):709-15.

206. Orimo H, Shiraki M, Hayashi T, Nakamura T. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D3. Bone Miner. 1987;3(1):47-52.

207. Orimo H, Shiraki M, Hayashi Y, Hoshino T, Onaya T, Miyazaki S, et al. Effects of 1 alpha-hydroxyvitamin D3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. Calcif Tissue Int. 1994;54(5):370-6.

208. Ott SM, Chesnut CH, 3rd. Calcitriol treatment is not effective in postmenopausal osteoporosis. Ann Intern Med. 1989;110(4):267-74.

209. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009 Feb;20(2):315-22.

210. Sato Y, Kuno H, Kaji M, Saruwatari N, Oizumi K. Effect of ipriflavone on bone in elderly hemiplegic stroke patients with hypovitaminosis D. Am J Phys Med Rehabil. 1999;78(5):457-63.

211. Sato Y, Manabe S, Kuno H, Oizumi K. Amelioration of osteopenia and hypovitaminosis D by 1alpha-hydroxyvitamin D3 in elderly patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;66(1):64-8.

212. Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med. 1992;326(6):357-62.

213. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men

and women living in the community: randomised double blind controlled trial. BMJ. 2003;326(7387):469.

214. Ushiroyama T, Ikeda A, Sakai M, Higashiyama T, Ueki M. Effects of the combined use of calcitonin and 1 alpha-hydroxycholecalciferol on vertebral bone loss and bone turnover in women with postmenopausal osteopenia and osteoporosis: a prospective study of long-term and continuous administration with low dose calcitonin. Maturitas. 2001;40(3):229-38.

215. Lock CA, Lecouturier J, Mason JM, Dickinson HO. Lifestyle interventions to prevent osteoporotic fractures: a systematic review. Osteoporos Int. 2006 Jan;17(1):20-8.

216. Ebrahim S, Thompson PW, Baskaran V, Evans K. Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. Age Ageing. 1997 Jul;26(4):253-60.

217. Jensen J, Lundin-Olsson L, Nyberg L, Gustafson Y. Fall and injury prevention in older people living in residential care facilities. A cluster randomized trial. Ann Intern Med. 2002 May 21;136(10):733-41.

218. Preisinger E, Alacamlioglu Y, Pils K, Bosina E, Metka M, Schneider B, et al. Exercise therapy for osteoporosis: results of a randomised controlled trial. Br J Sports Med. 1996 Sep;30(3):209-12.

219. Sato Y, Metoki N, Iwamoto J, Satoh K. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients. Neurology. 2003 Aug 12;61(3):338-42.

220. Sinaki M, Wahner HW, Offord KP, Hodgson SF. Efficacy of nonloading exercises in prevention of vertebral bone loss in postmenopausal women: a controlled trial. Mayo Clin Proc. 1989 Jul;64(7):762-9.

221. Sinaki M, Itoi E, Wahner HW, Wollan P, Gelzcer R, Mullan BP, et al. Stronger back muscles reduce the incidence of vertebral fractures: a prospective 10 year follow-up of postmenopausal women. Bone. 2002;30(6):836-41.

222. Vetter NJ, Lewis PA, Ford D. Can health visitors prevent fractures in elderly people? BMJ. 1992 Apr 4;304(6831):888-90.

223. Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: Thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009 Nov;60(11):3346-55.

224. Okada Y, Nawata M, Nakayamada S, Saito K, Tanaka Y. Alendronate protects premenopausal women from bone loss and fracture associated with high-dose glucocorticoid therapy. J Rheumatol. 2008 Nov;35(11):2249-54.

225. Bonnick S, Broy S, Kaiser F, Teutsch C, Rosenberg E, DeLucca P, et al. Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. Curr Med Res Opin. 2007 Jun;23(6):1341-9.

226. Xia WB, Zhang ZL, Wang HF, Meng XW, Zhang Y, Zhu GY, et al. The efficacy and safety of calcitriol and/or Caltrate D in elderly Chinese women with low bone mass. Acta Pharmacol Sin. 2009 Mar;30(3):372-8.

227. Tauchmanova L, De Simone G, Musella T, Orio F, Ricci P, Nappi C, et al. Effects of various antireabsorptive treatments on bone mineral density in hypogonadal young women after allogeneic stem cell transplantation. Bone Marrow Transplant. 2006;37(1):81-8.

228. Garcia-Delgado I PSG-FLRERJJHF. Calcitonin, etidronate, and calcidiol treatment in bone loss after cardiac transplantation. Calcified tissue international. 1997;60(2):155-9.

229. Lindsay R, Ste-Marie LG, Scheele WH. Bone mineral density changes during an 18 month observational period following discontinuation of recombinant human parathyroid humone (1-34) treatment of postmenopausal women receiving hormone replacement therapy. JAMA. 2004.

230. Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM. Hormone replacement therapy (HRT) or etidronate for osteoporosis in postmenopausal asthmatics on glucocorticoids: a randomised factorial trial. Scott Med J. 2009 Feb;54(1):21-5.

231. Boutsen Y, Jamart J, Esselinckx W, Stoffel M, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intermittent

intravenous pamidronate: a randomized trial. Calcif Tissue Int. 1997;61(4):266-71.

232. Luckey M, Kagan R, Greenspan S, Bone H, Kiel RD, Simon J, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause. 2004;11(4):405-15.

233. Uchida S, Taniguchi T, Shimizu T, Kakikawa T, Okuyama K, Okaniwa M, et al. Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: a double-blind, randomized study. J Bone Miner Metab. 2005;23(5):382-8.

234. Muscoso E, Puglisi N, Mamazza C, Lo Giudice F, Testai M, Abbate S, et al. Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study. Eur Rev Med Pharmacol Sci. 2004;8(2):97-102.

235. Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SA, et al. Comparison of Weekly Treatment of Postmenopausal Osteoporosis with Alendronate versus Risedronate Over Two Years. J Clin Endocrinol Metab. 2006.

236. Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res. 2005;20(1):141-51.

237. Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, et al. A randomized double-blind trial to compare the efficacy of teriparatide. J Clin Endocrinol Metab. 2002;87(10):4528-35.

238. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res. 2000;15(6):1113-8.

239. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006 Dec 27;296(24):2927-38.

240. Siris ES, Simon JA, Barton IP, McClung MR, Grauer A. Effects of risedronate on fracture risk in postmenopausal women with osteopenia. Osteoporos Int. 2008 May;19(5):681-6.

241. Kanis JA, Johansson H, Oden A, McCloskey EV. A meta-analysis of the efficacy of raloxifene on all clinical and vertebral fractures and its dependency on FRAX(R). Bone. 2010 Jun 18;47(729-735).

242. Schwartz AV, Bauer DC, Cummings SR, Cauley JA, Ensrud KE, Palermo L, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: The FLEX trial. J Bone Miner Res. 2010 Jan 8;25(5):976-82.

243. Siris ES, Harris ST, Eastell R, Zanchetta JR, Goemaere S, Diez-Perez A, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res. 2005 Sep;20(9):1514-24.

244. Sontag A, Wan X, Krege JH. Benefits and risks of raloxifene by vertebral fracture status. Curr Med Res Opin. 2009 Nov 12;26(1):71-6.

245. Prevrhal S, Krege JH, Chen P, Genant H, Black DM. Teriparatide vertebral fracture risk reduction determined by quantitative and qualitative radiographic assessment. Current Medical Research and Opinion. 2009 Apr;25(4):921-8.

246. Boonen S, Klemes AB, Zhou X, Lindsay R. Assessment of the relationship between age and the effect of risedronate treatment in women with postmenopausal osteoporosis: a pooled analysis of four studies. J Am Geriatr Soc. 2010 Apr;58(4):658-63.

247. Boonen S, Black DM, Colon-Emeric CS, Eastell R, Magaziner JS, Eriksen EF, et al. Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. J Am Geriatr Soc. 2010 Feb;58(2):292-9.

248. Eastell R, Black DM, Boonen S, Adami S, Felsenberg D, Lippuner K, et al. Effect of once-yearly zoledronic acid 5 mg on fracture risk and change in femoral neck bone mineral density. J Clin Endocrinol Metab. 2009 Jun 30;94(9):3215-25.

249. Boonen S, Marin F, Mellstrom D, Xie L, Desaiah D, Krege JH, et al. Safety and efficacy of teriparatide in elderly women with established osteoporosis: bone anabolic therapy from a geriatric

perspective. J Am Geriatr Soc. 2006 May;54(5):782-9.

250. Nakamura T, Liu JL, Morii H, Huang QR, Zhu HM, Qu Y, et al. Effect of raloxifene on clinical fractures in Asian women with postmenopausal osteoporosis. J Bone Miner Metab. 2006;24(5):414-8.

251. Warriner AH, Outman RC, Saag KG, Berry SD, Colon-Emeric C, Flood KL, et al. Management of osteoporosis among home health and long-term care patients with a prior fracture. South Med J. 2009 Apr;102(4):397-404.

252. Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE. The effect of raloxifene treatment in postmenopausal women with CKD. J Am Soc Nephrol. 2008 Jul;19(7):1430-8.

253. Eriksen EF, Lyles KW, Colon-Emeric CS, Pieper CF, Magaziner JS, Adachi JD, et al. Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture. J Bone Miner Res. 2009 Jul;24(7):1308-13.

254. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int. 2007 Aug;18(8):1023-31.

255. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int. 2010 Dec 5;21(11):1943-51.

256. Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc. 2007 Dec;82(12):1493-501.

257. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. Am J Med. 2009 Feb;122(2 Suppl):S3-13.

258. Gleeson T, Iversen MD, Avorn J, Brookhart AM, Katz JN, Losina E, et al. Interventions to improve adherence and persistence with osteoporosis medications: a systematic literature review. Osteoporos Int. 2009 Jun 5.

259. Binkley N, Ringe JD, Reed JI, Ljunggren O, Holick MF, Minne HW, et al. Alendronate/vitamin D3 70 mg/2800 IU with and without additional 2800 IU vitamin D3 for osteoporosis: results from the 24-week extension of a 15-week randomized, controlled trial. Bone. 2009 Apr;44(4):639-47.

260. Tseng LN, Sheu WH, Ho ES, Lan HH, Hu CC, Kao CH. Effects of alendronate combined with hormone replacement therapy on osteoporotic postmenopausal Chinese women. Metabolism. 2006 Jun;55(6):741-7.

261. Anastasilakis AD, Goulis DG, Polyzos SA, Gerou S, Koukoulis GN, Efstathiadou Z, et al. Head-to-head comparison of risedronate vs. teriparatide on bone turnover markers in women with postmenopausal osteoporosis: a randomised trial. Int J Clin Pract. 2008 Jun;62(6):919-24.

262. Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2007 Apr;92(4):1296-304.

263. Binkley N, Martens MG, Silverman SL, Derman RJ, Greenwald M, Kohles JD, et al. Improved GI tolerability with monthly ibandronate in women previously using weekly bisphosphonates. South Med J. 2009 May;102(5):486-92.

264. Bonnick SL, Silverman S, Tanner SB, Martens M, Bachmann G, Kohles JD, et al. Patient Satisfaction in Postmenopausal Women Treated with a Weekly Bisphosphonate Transitioned to Once-Monthly Ibandronate. J Womens Health (Larchmt). 2009 Jun 29.

265. Gorai I, Tanaka Y, Hattori S, Iwaoki Y. Assessment of adherence to treatment of postmenopausal osteoporosis with raloxifene and/or alfacalcidol in postmenopausal Japanese women. J Bone Miner Metab. 2009 Aug 6;28(2):176-84.

266. Adachi JD, Hanley DA, Lorraine JK, Yu M. Assessing compliance, acceptance, and tolerability of teriparatide in patients with osteoporosis who fractured while on antiresorptive treatment or were intolerant to previous antiresorptive treatment: an 18-month, multicenter, open-label, prospective study. Clin Ther. 2007 Sep;29(9):2055-67.

267. Blouin J, Dragomir A, Moride Y, Ste-Marie LG, Fernandes JC, Perreault S. Impact of noncompliance with alendronate and risedronate on

the incidence of nonvertebral osteoporotic fractures in elderly women. Br J Clin Pharmacol. 2008 Jul;66(1):117-27.

268. Hansen KE, Swenson ED, Baltz B, Schuna AA, Jones AN, Elliott ME. Adherence to alendronate in male veterans. Osteoporos Int. 2008 Mar;19(3):349-56.

269. Penning-van Beest FJ, Erkens JA, Olson M, Herings RM. Loss of treatment benefit due to low compliance with bisphosphonate therapy. Osteoporos Int. 2008 Apr;19(4):511-7.

270. Penning-van Beest FJ, Erkens JA, Olson M, Herings RM. Determinants of non-compliance with bisphosphonates in women with postmenopausal osteoporosis. Curr Med Res Opin. 2008 May;24(5):1337-44.

271. Briesacher BA, Andrade SE, Harrold LR, Fouayzi H, Yood RA. Adoption of once-monthly oral bisphosphonates and the impact on adherence. Am J Med. 2010 Mar;123(3):275-80.

272. Curtis JR, Westfall AO, Cheng H, Lyles K, Saag KG, Delzell E. Benefit of adherence with bisphosphonates depends on age and fracture type: results from an analysis of 101,038 new bisphosphonate users. J Bone Miner Res. 2008 Sep;23(9):1435-41.

273. Vytrisalova M, Blazkova S, Palicka V, Vlcek J, Cejkova M, Hala T, et al. Self-reported compliance with osteoporosis medication-qualitative aspects and correlates. Maturitas. 2008 Jul-Aug;60(3-4):223-9.

274. Palacios S, Sanchez-Borrego R, Neyro JL, Quereda F, Vazquez F, Perez M. Knowledge and compliance from patients with postmenopausal osteoporosis treatment. Menopause Int. 2009 Sep;15(3):113-9.

275. Grazio S, Babic-Naglic D, Kehler T, Curkovic B. Persistence of weekly alendronate: a real-world study in Croatia. Clin Rheumatol. 2008 May;27(5):651-3.

276. Feldstein AC, Weycker D, Nichols GA, Oster G, Rosales G, Boardman DL, et al. Effectiveness of bisphosphonate therapy in a community setting. Bone. 2009 Jan;44(1):153-9.

277. Yood RA, Emani S, Reed JI, Lewis BE, Charpentier M, Lydick E. Compliance with pharmacologic therapy for osteoporosis. Osteoporos Int. 2003 Dec;14(12):965-8.

278. Ringe JD, Moller G. Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis. Rheumatol Int. 2009 May 9;29(3):311-5.

279. Sewerynek E, Dabrowska K, Skowronska-Jozwiak E, Zygmunt A, Lewinski A. Compliance with alendronate 10 treatment in elderly women with postmenopausal osteoporosis. Endokrynol Pol. 2009 Mar-Apr;60(2):76-81.

280. Ideguchi H, Ohno S, Takase K, Ueda A, Ishigatsubo Y. Outcomes after switching from one bisphosphonate to another in 146 patients at a single university hospital. Osteoporosis International. 2008 Dec;19(12):1777-83.

281. Ettinger MP, Gallagher R, MacCosbe PE. Medication persistence with weekly versus daily doses of orally administered bisphosphonates. Endocr Pract. 2006 Sep-Oct;12(5):522-8.

282. Gold DT, Martin BC, Frytak JR, Amonkar MM, Cosman F. A claims database analysis of persistence with alendronate therapy and fracture risk in post-menopausal women with osteoporosis. Curr Med Res Opin. 2007 Mar;23(3):585-94.

283. Harris ST, Reginster JY, Harley C, Blumentals WA, Poston SA, Barr CE, et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the eValuation of IBandronate Efficacy (VIBE) database fracture study. Bone. 2009 May;44(5):758-65.

284. Ideguchi H, Ohno S, Hattori H, Ishigatsubo Y. Persistence with bisphosphonate therapy including treatment courses with multiple sequential bisphosphonates in the real world. Osteoporos Int. 2007 Oct;18(10):1421-7.

285. Jones TJ, Petrella RJ, Crilly R. Determinants of persistence with weekly bisphosphonates in patients with osteoporosis. J Rheumatol. 2008 Sep;35(9):1865-73.

286. Sheehy O, Kindundu CM, Barbeau M, LeLorier J. Differences in persistence among different weekly oral bisphosphonate medications. Osteoporos Int. 2009 Aug;20(8):1369-76.

287. Weiss TW, Henderson SC, McHorney CA, Cramer JA. Persistence across weekly and monthly bisphosphonates: analysis of US retail pharmacy prescription refills. Curr Med Res Opin. 2007 Sep;23(9):2193-203.

288. McHorney CA, Schousboe JT, Cline RR, Weiss TW. The impact of osteoporosis medication beliefs and side-effect experiences on non-adherence to oral bisphosphonates. Curr Med Res Opin. 2007 Dec;23(12):3137-52.

289. Ringe JD, Christodoulakos GE, Mellstrom D, Petto H, Nickelsen T, Marin F, et al. Patient compliance with alendronate, risedronate and raloxifene for the treatment of osteoporosis in postmenopausal women. Curr Med Res Opin. 2007 Nov;23(11):2677-87.

290. Gallagher AM, Rietbrock S, Olson M, van Staa TP. Fracture outcomes related to persistence and compliance with oral bisphosphonates. J Bone Miner Res. 2008 Oct;23(10):1569-75.

291. Roughead EE, Ramsay E, Priess K, Barratt J, Ryan P, Gilbert AL. Medication adherence, first episode duration, overall duration and time without therapy: The example of bisphosphonates. Pharmacoepidemiol Drug Saf. 2009 March 12;18(1):69-75.

292. Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res. 2009 Jun;24(6):1095-102.

293. Blouin J, Dragomir A, Ste-Marie LG, Fernandes JC, Perreault S. Discontinuation of antiresorptive therapies: a comparison between 1998-2001 and 2002-2004 among osteoporotic women. J Clin Endocrinol Metab. 2007 Mar;92(3):887-94.

294. Briesacher BA, Andrade SE, Yood RA, Kahler KH. Consequences of poor compliance with bisphosphonates. Bone. 2007 Nov;41(5):882-7.

295. Cotte FE, Fardellone P, Mercier F, Gaudin AF, Roux C. Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. Osteoporos Int. 2009 May 21.

296. Cramer JA, Lynch NO, Gaudin AF, Walker M, Cowell W. The effect of dosing frequency on compliance and persistence with bisphosphonate therapy in postmenopausal women: a comparison of studies in the United States, the United Kingdom, and France. Clin Ther. 2006 Oct;28(10):1686-94.

297. Gold DT, Safi W, Trinh H. Patient preference and adherence: comparative US studies between two bisphosphonates, weekly risedronate and monthly ibandronate. Curr Med Res Opin. 2006 Dec;22(12):2383-91.

298. Gold DT, Trinh H, Safi W. Weekly versus monthly drug regimens: 1-year compliance and persistence with bisphosphonate therapy. Curr Med Res Opin. 2009 Aug;25(8):1831-9.

299. Kertes J, Dushenat M, Vesterman JL, Lemberger J, Bregman J, Friedman N. Factors contributing to compliance with osteoporosis medication. Isr Med Assoc J. 2008 Mar;10(3):207-13.

300. Rabenda V, Vanoverloop J, Fabri V, Mertens R, Sumkay F, Vannecke C, et al. Low incidence of anti-osteoporosis treatment after hip fracture. J Bone Joint Surg Am. 2008 Oct;90(10):2142-8.

301. van den Boogaard CH, Breekveldt-Postma NS, Borggreve SE, Goettsch WG, Herings RM. Persistent bisphosphonate use and the risk of osteoporotic fractures in clinical practice: a database analysis study. Curr Med Res Opin. 2006 Sep;22(9):1757-64.

302. Hoer A, Seidlitz C, Gothe H, Schiffhorst G, Olson M, Hadji P, et al. Influence on persistence and adherence with oral bisphosphonates on fracture rates in osteoporosis. Patient Prefer Adherence. 2009;3:25-30.

303. Rabenda V, Mertens R, Fabri V, Vanoverloop J, Sumkay F, Vannecke C, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. Osteoporos Int. 2008 Jun;19(6):811-8.

304. Castelo-Branco C, Cortes X, Ferrer M. Treatment persistence and compliance with a combination of calcium and vitamin D. Climacteric. 2009 Dec 1.

305. Dugard MN, Jones TJ, Davie MW. Uptake of treatment for osteoporosis and compliance after bone density measurement in the community. J Epidemiol Community Health. 2009 Aug 13.

306. Kamatari M, Koto S, Ozawa N, Urao C, Suzuki Y, Akasaka E, et al. Factors affecting long-term compliance of osteoporotic patients with bisphosphonate treatment and QOL assessment in actual practice: alendronate and risedronate. J Bone Miner Metab. 2007;25(5):302-9.

307. Berecki-Gisolf J, Hockey R, Dobson A. Adherence to bisphosphonate treatment by elderly women. Menopause. 2008 Sep-Oct;15(5):984-90.

308. Park DJ, TR. Medication Adherence and Aging. In: Fisk AR, WA, editor. Handbook of Human Factors and the Older Adult. San Diego: Academic Press; 1997. p. 257-88.

309. McCarney RW, J. Iliffe, S. van Haselen, R. Griffin, M. Fisher, P. The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol. 2007;7:30.

310. Claxton AJC, J. Pierce, C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001 Aug;23(8):1296-310.

311. Ingersoll KSC, J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med. 2008 Jun;31(3):213-24.

312. Iskedjian ME, T. R. MacKeigan, L. D. Shear, N. Addis, A. Mittmann, N. Ilersich, A. L. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Ther. 2002 Feb;24(2):302-16.

313. Saini SDS, P. Kaulback, K. Dubinsky, M. C. Effect of medication dosing frequency on adherence in chronic diseases. Am J Manag Care. 2009 Jun;15(6):e22-33.

314. Binkley N, Krueger D. Combination therapy for osteoporosis: considerations and controversy. Curr Osteoporos Rep. 2005 Dec;3(4):150-4.

315. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone. 2006;38(6):922-8.

316. Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporos Int. 2004;15(12):1003-8.

317. Chailurkit LO, Jongjaroenprasert W, Rungbunnapun S, Ongphiphadhanakul B, Sae-tung S, Rajatanavin R. Effect of alendronate on bone mineral density and bone turnover in Thai postmenopausal osteoporosis. Journal of bone and mineral metabolism. 2003;21(6):421-7.

318. Palomba S, Orio F, Jr., Colao A, di Carlo C, Sena T, Lombardi G, et al. Effect of estrogen replacement plus low-dose alendronate treatment on bone density in surgically postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87(4):1502-8.

319. Riis BJ, Ise J, von Stein T, Bagger Y, Christiansen C. Ibandronate: a comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. J Bone Miner Res. 2001;16(10):1871-8.

320. Zegels B, Eastell R, Russell RG, Ethgen D, Roumagnac I, Collette J, et al. Effect of high doses of oral risedronate (20 mg/day) on serum parathyroid hormone levels and urinary collagen cross-link excretion in postmenopausal women with spinal osteoporosis. Bone. 2001;28(1):108-12.

321. Agrawal S, Krueger DC, Engelke JA, Nest LJ, Krause PF, Drinka PJ, et al. Between-meal risedronate does not alter bone turnover in nursing home residents. J Am Geriatr Soc. 2006;54(5):790-5.

322. Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. N Engl J Med. 2007;356(18):1895-6.

323. Mak A, Cheung MW, Ho RC, Cheak AA, Lau CS. Bisphosphonates and atrial fibrillation: Bayesian meta-analyses of randomized controlled trials and observational studies. BMC Musculoskelet Disord. 2009;10:113.

324. Adachi JD, Faraawi RY, O'Mahony MF, Nayar A, Massaad R, Evans JK, et al. Upper gastrointestinal tolerability of alendronate sodium monohydrate 10 mg once daily in postmenopausal women: a 12-week, randomized, double-blind, placebo-controlled, exploratory study. Clin Ther. 2009 Aug;31(8):1747-53.

325. Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ. 2010;341:c4444.

326. Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA. 2010 Aug 11;304(6):657-63.

327. McClung MR, Wasnich RD, Recker R, Cauley JA, Chesnut CH, 3rd, Ensrud KE, et al. Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. J Bone Miner Res. 2004;19(1):11-8.

328. Adachi JD, Adami S, Miller PD, Olszynski WP, Kendler DL, Silverman SL, et al. Tolerability of risedronate in postmenopausal women intolerant of alendronate. Aging (Milano). 2001;13(5):347-54.

329. Chow CC, Chan WB, Li JK, Chan NN, Chan MH, Ko GT, et al. Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab. 2003;88(2):581-7.

330. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med. 1998;339(5):292-9.

331. Sambrook PN, Rodriguez JP, Wasnich RD, Luckey MM, Kaur A, Meng L, et al. Alendronate in the prevention of osteoporosis: 7-year follow-up. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2004;15(6):483-8.

332. Ensrud KE, Barrett-Connor EL, Schwartz A, Santora AC, Bauer DC, Suryawanshi S, et al. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. J Bone Miner Res. 2004;19(8):1259-69.

333. Uusi-Rasi K, Kannus P, Cheng S, Sievanen H, Pasanen M, Heinonen A, et al. Effect of alendronate and exercise on bone and physical performance of postmenopausal women: a randomized controlled trial. Bone. 2003;33(1):132-43.

334. Greenspan S, Field-Munves E, Tonino R, Smith M, Petruschke R, Wang L, et al. Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. Mayo Clin Proc. 2002;77(10):1044-52.

335. Kung AW, Yeung SS, Chu LW. The efficacy and tolerability of alendronate in postmenopausal osteoporotic Chinese women: a randomized placebo-controlled study. Calcif Tissue Int. 2000;67(4):286-90.

336. Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, et al. Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. Arch Intern Med. 2000;160(4):517-25.

337. Cryer B, Binkley N, Simonelli C, Lewiecki EM, Lanza F, Chen E, et al. A randomized, placebo-controlled, 6-month study of once-weekly alendronate oral solution for postmenopausal osteoporosis. Am J Geriatr Pharmacother. 2005;3(3):127-36.

338. Eastell R, Devogelaer JP, Peel NF, Chines AA, Bax DE, Sacco-Gibson N, et al. Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. Osteoporos Int. 2000;11(4):331-7.

339. Ilter E, Karalok H, Tufekci EC, Batur O. Efficacy and acceptability of risedronate 5 mg daily compared with 35 mg once weekly for the treatment of postmenopausal osteoporosis. Climacteric. 2006;9(2):129-34.

340. Tucci JR, Tonino RP, Emky RD, Peverly CA, Kher U, Santora AC. Effect of three years of oral alendronate treatment in postmenopausal women with osteoproris. Am J Med. 1996;101(5):488-501.

341. Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum. 2001;44(1):202-11.

342. Rossini M, Gatti D, Girardello S, Braga V, James G, Adami S. Effects of two intermittent alendronate regimens in the prevention or treatment of postmenopausal osteoporosis. Bone. 2000;27(1):119-22.

343. Eisman JA, Rizzoli R, Roman-Ivorra J, Lipschitz S, Verbruggen N, Gaines KA, et al. Upper

gastrointestinal and overall tolerability of alendronate once weekly in patients with osteoporosis: results of a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2004;20(5):699-705.

344. Murphy MG, Weiss S, McClung M, Schnitzer T, Cerchio K, Connor J, et al. Effect of alendronate and MK-677 (a growth hormone secretagogue), individually and in combination, on markers of bone turnover and bone mineral density in postmenopausal osteoporotic women. The Journal of clinical endocrinology and metabolism. 2001;86(3):1116-25.

345. Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87(3):985-92.

346. Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, et al. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. J Clin Endocrinol Metab. 2000;85(9):3109-15.

347. Torregrosa JV, Moreno A, Gutierrez A, Vidal S, Oppenheimer F. Alendronate for treatment of renal transplant patients with osteoporosis. Transplantation proceedings. 2003;35(4):1393-5.

348. Bell NH, Bilezikian JP, Bone HG, Kaur A, Maragoto A, Santora AC, et al. Alendronate increases bone mass and reduces bone markers in postmenopausal African-American women. The Journal of clinical endocrinology and metabolism. 2002;87(6):2792-7.

349. Sharma RK, Kaushal R, Gupta A, Gupta S, Gultai S, Sharma AP. Role of oral alendronate in prevention of bone loss in adult nephrotics on steroid treatment. Indian Journal of Nephrology. 2002;12(4):186.

350. Lau EM, Woo J, Chan YH, Li M. Alendronate for the prevention of bone loss in patients on inhaled steroid therapy. Bone. 2001;29(6):506-10.

351. Haderslev KV, Tjellesen L, Sorensen HA, Staun M. Alendronate increases lumbar spine bone mineral density in patients with Crohn's disease. Gastroenterology. 2000;119(3):639-46.

352. Lau EM, Woo J, Chan YH, Griffith J. Alendronate prevents bone loss in Chinese women with osteoporosis. Bone. 2000;27(5):677-80.

353. Downs RW, Jr., Bell NH, Ettinger MP, Walsh BW, Favus MJ, Mako B, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. J Clin Endocrinol Metab. 2000;85(5):1783-8.

354. Miller PD, Woodson G, Licata AA, Ettinger MP, Mako B, Smith ME, et al. Rechallenge of patients who had discontinued alendronate therapy because of upper gastrointestinal symptoms. Clinical therapeutics. 2000;22(12):1433-42.

355. Yang TS, Tsan SH, Chen CR, Chang SP, Yuan CC. Effects of alendronate on bone turnover markers in early postmenopausal women. Zhonghua Yi Xue Za Zhi (Taipei). 1998;61(10):568-76.

356. Frediani B, Allegri A, Bisogno S, Marcolongo R. Effects of combined treatment with calcitriol plus alendronate on bone mass and bone turnover in postmenopausal osteoporosis: Two years of continuous treatment. Clinical Drug Investigation. 1998;15(3):235-44.

357. Devogelaer JP, Broll H, Correa-Rotter R, Cumming DC, De Deuxchaisnes CN, Geusens P, et al. Oral alendronate induces progressive increases in bone mass of the spine, hip, and total body over 3 years in postmenopausal women with osteoporosis. Bone. 1996;18(2):141-50.

358. Harris ST, Gertz BJ, Genant HK, Eyre DR, Survill TT, Ventura JN, et al. The effect of short term treatment with alendronate on vertebral density and biochemical markers of bone remodeling in early postmenopausal women. J Clin Endocrinol Metab. 1993;76(6):1399-406.

359. Adami S, Baroni MC, Broggini M, Carratelli L, Caruso I, Gnessi L, et al. Treatment of postmenopausal osteoporosis with continuous daily oral alendronate in comparison with either placebo or intranasal salmon calcitonin. Osteoporos Int. 1993;3 Suppl 3:S21-7.

360. Cryer B, Miller P, Petruschke RA, Chen E, Geba GP, Papp AE. Upper gastrointestinal tolerability of once weekly alendronate 70 mg with concomitant non-steroidal anti-inflammatory drug use. Aliment Pharmacol Ther. 2005;21(5):599-607.

361. Morabito N, Lasco A, Gaudio A, Crisafulli A, Di Pietro C, Meo A, et al. Bisphosphonates in the treatment of thalassemia-induced osteoporosis. Osteoporos Int. 2002;13(8):644-9.

362. El-Agroudy AE, El-Husseini AA, El-Sayed M, Mohsen T, Ghoneim MA. A prospective randomized study for prevention of postrenal transplantation bone loss. Kidney Int. 2005;67(5):2039-45.

363. Golden NH, Iglesias EA, Jacobson MS, Carey D, Meyer W, Schebendach J, et al. Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2005;90(6):3179-85.

364. Moran de Brito CM, Battistella LR, Saito ET, Sakamoto H. Effect of alendronate on bone mineral density in spinal cord injury patients: a pilot study. Spinal Cord. 2005;43(6):341-8.

365. Aris RM, Lester GE, Caminiti M, Blackwood AD, Hensler M, Lark RK, et al. Efficacy of alendronate in adults with cystic fibrosis with low bone density. Am J Respir Crit Care Med. 2004;169(1):77-82.

366. Michalska D, Stepan JJ, Basson BR, Pavo I. The effect of raloxifene after discontinuation of long-term alendronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2006;91(3):870-7.

367. Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res. 2009 Jan;24(1):153-61.

368. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. The Journal of urology. 2003;169(6):2008-12.

369. McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med. 2005;165(15):1762-8.

370. Orwoll ES, Binkley NC, Lewiecki EM, Gruntmanis U, Fries MA, Dasic G. Efficacy and safety of monthly ibandronate in men with low bone density. Bone. 2010 Apr;46(4):970-6.

371. Henderson S, Hoffman N, Prince R. A double-blind placebo-controlled study of the effects of the bisphosphonate risedronate on bone mass in patients with inflammatory bowel disease. Am J Gastroenterol. 2006;101(1):119-23.

372. Stakkestad JA, Benevolenskaya LI, Stepan JJ, Skag A, Nordby A, Oefjord E, et al. Intravenous ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. Ann Rheum Dis. 2003;62(10):969-75.

373. Black DM, Kelly MP, Genant HK, Palermo L, Eastell R, Bucci-Rechtweg C, et al. Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur. N Engl J Med. 2010 Mar 24;362(19):1761-71.

374. Girgis CM, Sher D, Seibel MJ. Atypical femoral fractures and bisphosphonate use. N Engl J Med. 2010 May 13;362(19):1848-9.

375. Shane EB, D. Ebeling, P. R. Abrahamsen, B. Adler, R. A. Brown, T. D. Cheung, A. M. Cosman, F. Curtis, J. R. Dell, R. Dempster, D. Einhorn, T. A. Genant, H. K. Geusens, P. Klaushofer, K. Koval, K. Lane, J. M. McKiernan, F. McKinney, R. Ng, A. Nieves, J. O'Keefe, R. Papapoulos, S. Sen, H. T. van der Meulen, M. C. Weinstein, R. S. Whyte, M. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010 Sep 14.

376. US Food and Drug Administration (FDA). FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures 2010.

377. Solomon DH, Hochberg MC, Mogun H, Schneeweiss S. The relation between bisphosphonate use and non-union of fractures of the humerus in older adults. Osteoporos Int. 2009 Jun;20(6):895-901.

378. Abrahamsen B. Bisphosphonate adverse effects, lessons from large databases. Curr Opin Rheumatol. 2010 Jul;22(4):404-9.

379. Crawford BA, Kam C, Pavlovic J, Byth K, Handelsman DJ, Angus PW, et al. Zoledronic acid

prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2006;144(4):239-48.

380. Grady D, Ettinger B, Moscarelli E, Plouffe L, Jr., Sarkar S, Ciaccia A, et al. Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. Obstet Gynecol. 2004;104(4):837-44.

381. Zheng S, Wu Y, Zhang Z, Yang X, Hui Y, Zhang Y, et al. Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in postmenopausal women: a randomized clinical trial in Beijing. Chin Med J (Engl). 2003;116(8):1127-33.

382. Ensrud K, Genazzani AR, Geiger MJ, McNabb M, Dowsett SA, Cox DA, et al. Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. Am J Cardiol. 2006;97(4):520-7.

383. Mosca L, Grady D, Barrett-Connor E, Collins P, Wenger N, Abramson BL, et al. Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. Stroke. 2009 Jan;40(1):147-55.

384. Miller PD, Chines AA, Christiansen C, Hoeck HC, Kendler DL, Lewiecki EM, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res. 2008 Apr;23(4):525-35.

385. Liu JL, Zhu HM, Huang QR, Zhang ZL, Li HL, Qin YJ, et al. Effects of raloxifene hydrochloride on bone mineral density, bone metabolism and serum lipids in Chinese postmenopausal women with osteoporosis: a multi-center, randomized, placebo-controlled clinical trial. Chin Med J (Engl). 2004;117(7):1029-35.

386. Smith MR, Fallon MA, Lee H, Finkelstein JS. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. The Journal of clinical endocrinology and metabolism. 2004;89(8):3841-6.

387. Johnston CC, Jr., Bjarnason NH, Cohen FJ, Shah A, Lindsay R, Mitlak BH, et al. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women: three-year data from 2 double-blind, randomized, placebo-controlled trials. Arch Intern Med. 2000;160(22):3444-50.

388. Meunier PJ, Vignot E, Garnero P, Confavreux E, Paris E, Liu-Leage S, et al. Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene Study Group. Osteoporos Int. 1999;10(4):330-6.

389. McClung MR, Siris E, Cummings S, Bolognese M, Ettinger M, Moffett A, et al. Prevention of bone loss in postmenopausal women treated with lasofoxifene compared with raloxifene. Menopause. 2006 May-Jun;13(3):377-86.

390. Kung AW, Chao HT, Huang KE, Need AG, Taechakraichana N, Loh FH, et al. Efficacy and safety of raloxifene 60 milligrams/day in postmenopausal Asian women. J Clin Endocrinol Metab. 2003;88(7):3130-6.

391. Morii H, Ohashi Y, Taketani Y, Fukunaga M, Nakamura T, Itabashi A, et al. Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. Osteoporos Int. 2003;14(10):793-800.

392. Jolly EE, Bjarnason NH, Neven P, Plouffe L, Jr., Johnston CC, Jr., Watts SD, et al. Prevention of osteoporosis and uterine effects in postmenopausal women taking raloxifene for 5 years. Menopause. 2003;10(4):337-44.

393. Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med. 1997;337(23):1641-7.

394. Nickelsen T, Lufkin EG, Riggs BL, Cox DA, Crook TH. Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in postmenopausal women. Psychoneuroendocrinology. 1999;24(1):115-28.

395. Miller PD, Bilezikian JP, Diaz-Curiel M, Chen P, Marin F, Krege JH, et al. Occurrence of hypercalciuria in patients with osteoporosis treated with teriparatide. J Clin Endocrinol Metab. 2007 Sep;92(9):3535-41.

396. Bekker PJ, Holloway DL, Rasmussen AS, Murphy R, Martin SW, Leese PT, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2004;19(7):1059-66.

397. Bolland MJ, Grey AB, Gamble GD, Reid IR. Effect of Osteoporosis Treatment on Mortality: A Meta-Analysis. J Clin Endocrinol Metab. 2010 Jan 15.

398. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. Bmj. 2008 Feb 2;336(7638):262-6.

399. Matsumoto T, Miki T, Hagino H, Sugimoto T, Okamoto S, Hirota T, et al. A new active vitamin D, ED-71, increases bone mass in osteoporotic patients under vitamin D supplementation: a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2005 Sep;90(9):5031-6.

400. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med. 2002 Mar;112(4):281-9.

401. Chapurlat RD, Palermo L, Ramsay P, Cummings SR. Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. Osteoporos Int. 2005;16(7):842-8.

402. Bell KJ, Hayen A, Macaskill P, Irwig L, Craig JC, Ensrud K, et al. Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. BMJ. 2009;338:b2266.

403. Watts NB, Geusens P, Barton IP, Felsenberg D. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. J Bone Miner Res. 2005 Dec;20(12):2097-104.

404. Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. J Clin Densitom. 2004;7(3):255-61.

405. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res. 2002;17(1):1-10.

406. Watts NB, Miller PD, Kohlmeier LA, Sebba A, Chen P, Wong M, et al. Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment. J Bone Miner Res. 2009 Jun;24(6):1125-31.

407. Chen P, Miller PD, Delmas PD, Misurski DA, Krege JH. Change in lumbar spine BMD and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. J Bone Miner Res. 2006 Nov;21(11):1785-90.

408. Cummings SR, Ensrud K, Delmas PD, Lacroix AZ, Vukicevic S, Reid DM, et al. Lasofoxifene in Postmenopausal Women with Osteoporosis. N Engl J Med. 2010 Feb 25;362(8):686-96.

409. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998 Dec 23-30;280(24):2077-82.

410. Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. J Bone Miner Res. 2007 Apr;22(4):503-8.

411. Reginster JM, H. W. Sorensen, O. H. Hooper, M. Roux, C. Brandi, M. L. Lund, B. Ethgen, D. Pack, S. Roumagnac, I. Eastell, R. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11(1):83-91.

412. Watts NB, Chines A, Olszynski WP, McKeever CD, McClung MR, Zhou X, et al. Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int. 2008 Mar;19(3):365-72.

413. Watts NB, Brown JP, Cline G. Risedronate on 2 Consecutive Days a Month Reduced Vertebral Fracture Risk at 1Year Compared With Historical Placebo. J Clin Densitom. 2010 Nov 24;13(1):56-62.

414. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007 May 3;356(18):1809-22.

415. Ettinger BB, D. M. Mitlak, B. H. Knickerbocker, R. K. Nickelsen, T. Genant, H. K. Christiansen, C. Delmas, P. D. Zanchetta, J. R. Stakkestad, J. Gluer, C. C. Krueger, K. Cohen, F. J. Eckert, S. Ensrud, K. E. Avioli, L. V. Lips, P. Cummings, S. R. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;282(7):637-45.

416. Prince R, Sipos A, Hossain A, Syversen U, Ish-Shalom S, Marcinowska E, et al. Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. J Bone Miner Res. 2005 Sep;20(9):1507-13.

417. Reginster JM, H. Sorensen, O. H. Randomized trial of the effects of risedronate on vetebral fractures in women with established postmenopausal osteoporosis. Osteoposos Int. 2000;11:83-91.

418. Mamdani M, Kopp A, Hawker G. Hip fractures in users of first- vs. second-generation bisphosphonates. Osteoporos Int. 2007 Dec;18(12):1595-600.

419. Curtis JR, Westfall AO, Cheng H, Saag KG, Delzell E. RisedronatE and ALendronate Intervention over Three Years (REALITY): minimal differences in fracture risk reduction. Osteoporos Int. 2009 Jun;20(6):973-8.

420. Abelson A, Ringe JD, Gold DT, Lange JL, Thomas T. Longitudinal change in clinical fracture incidence after initiation of bisphosphonates. Osteoporos Int. 2009 Sep 1.

421. Langsetmo LA, Morin S, Richards JB, Davison KS, Olszynski WP, Prior JC, et al. Effectiveness of antiresorptives for the prevention of nonvertebral low-trauma fractures in a population-based cohort of women. Osteoporos Int. 2009 Feb;20(2):283-90.

422. Adami S, Giannini S, Bianchi G, Sinigaglia L, Di Munno O, Fiore CE, et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporos Int. 2009 Feb;20(2):239-44.

423. Langdahl BL, Rajzbaum G, Jakob F, Karras D, Ljunggren O, Lems WF, et al. Reduction in Fracture Rate and Back Pain and Increased Quality of Life in Postmenopausal Women Treated with Teriparatide: 18-Month Data from the European Forsteo Observational Study (EFOS). Calcif Tissue Int. 2009 Oct 13;85(6):484-93.

424. Vestergaard P, Rejnmark L, Mosekilde L. Fracture reducing potential of hormone replacement therapy on a population level. Maturitas. 2006 Jun 20;54(3):285-93.

425. Nieves JW, Barrett-Connor E, Siris ES, Zion M, Barlas S, Chen YT. Calcium and vitamin D intake influence bone mass, but not short-term fracture risk, in Caucasian postmenopausal women from the National Osteoporosis Risk Assessment (NORA) study. Osteoporos Int. 2008 May;19(5):673-9.

426. Feskanich D, Willett W, Colditz G. Walking and leisure-time activity and risk of hip fracture in postmenopausal women. JAMA. 2002 Nov 13;288(18):2300-6.

427. Hagino H, Nishizawa Y, Sone T, Morii H, Taketani Y, Nakamura T, et al. A double-blinded head-to-head trial of minodronate and alendronate in women with postmenopausal osteoporosis. Bone. 2009 Jun;44(6):1078-84.

428. Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident atrial fibrillation in women. Arch Intern Med. 2008 Apr 28;168(8):826-31.

429. Lems WF, Lodder MC, Lips P, Bijlsma JW, Geusens P, Schrameijer N, et al. Positive effect of alendronate on bone mineral density and markers of bone turnover in patients with rheumatoid arthritis on chronic treatment with low-dose prednisone: a randomized, double-blind, placebo-controlled trial. Osteoporos Int. 2006;17(5):716-23.

430. Yan Y, Wang W, Zhu H, Li M, Liu J, Luo B, et al. The efficacy and tolerability of once-weekly alendronate 70 mg on bone mineral density and bone turnover markers in postmenopausal Chinese women with osteoporosis. J Bone Miner Metab. 2009;27(4):471-8.

431. Bunch TJ, Anderson JL, May HT, Muhlestein JB, Horne BD, Crandall BG, et al. Relation of bisphosphonate therapies and risk of developing atrial fibrillation. Am J Cardiol. 2009 Mar 15;103(6):824-8.

432. Cartsos VM, Zhu S, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. J Am Dent Assoc. 2008 Jan;139(1):23-30.

433. Payer J, Cierny D, Killinger Z, Sulkova I, Behuliak M, Celec P. Preferences of patients with post-menopausal osteoporosis treated with bisphosphonates--the VIVA II study. J Int Med Res. 2009 Jul-Aug;37(4):1225-9.

434. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol. 2008 Mar;35(3):488-97.

435. Lewiecki EM, Cooper C, Thompson E, Hartl F, Mehta D, Papapoulos SE. Ibandronate does not increase risk of atrial fibrillation in analysis of pivotal clinical trials. Int J Clin Pract. 2010 May;64(6):821-6.

436. McClung MR, Bolognese MA, Sedarati F, Recker RR, Miller PD. Efficacy and safety of monthly oral ibandronate in the prevention of postmenopausal bone loss. Bone. 2009 Mar;44(3):418-22.

437. Stakkestad JA, Lakatos P, Lorenc R, Sedarati F, Neate C, Reginster JY. Monthly oral ibandronate is effective and well tolerated after 3 years: the MOBILE long-term extension. Clin Rheumatol. 2008 Aug;27(8):955-60.

438. Adami S, Pavelka K, Cline GA, Hosterman MA, Barton IP, Cohen SB, et al. Upper gastrointestinal tract safety of daily oral risedronate in patients taking NSAIDs: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2005 Oct;80(10):1278-85.

439. Barrera BA, Wilton L, Harris S, Shakir SA. Prescription-event monitoring study on 13,164 patients prescribed risedronate in primary care in England. Osteoporos Int. 2005 Dec;16(12):1989-98.

440. Li Y, Zhang Z, Deng X, Chen L. Efficacy and safety of risedronate sodium in treatment of postmenopausal osteoporosis. J Huazhong Univ Sci Technolog Med Sci. 2005;25(5):527-9.

441. Mok CC, Tong KH, To CH, Siu YP, Ma KM. Risedronate for prevention of bone mineral density loss in patients receiving high-dose glucocorticoids: a randomized double-blind placebo-controlled trial. Osteoporos Int. 2008 Mar;19(3):357-64.

442. Ste-Marie LG, Brown JP, Beary JF, Matzkin E, Darbie LM, Burgio DE, et al. Comparison of the effects of once-monthly versus once-daily risedronate in postmenopausal osteoporosis: a phase II, 6-month, multicenter, randomized, double-blind, active-controlled, dose-ranging study. Clin Ther. 2009 Feb;31(2):272-85.

443. Boonen S, Sellmeyer DE, Lippuner K, Orlov-Morozov A, Abrams K, Mesenbrink P, et al. Renal safety of annual zoledronic acid infusions in osteoporotic postmenopausal women. Kidney Int. 2008 Sep;74(5):641-8.

444. McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone. 2007 Jul;41(1):122-8.

445. Etminan M, Aminzadeh K, Matthew IR, Brophy JM. Use of oral bisphosphonates and the risk of aseptic osteonecrosis: a nested case-control study. J Rheumatol. 2008 Apr;35(4):691-5.

446. Emkey R, Delmas PD, Bolognese M, Borges JL, Cosman F, Ragi-Eis S, et al. Efficacy and tolerability of once-monthly oral ibandronate (150 mg) and once-weekly oral alendronate (70 mg): additional results from the Monthly Oral Therapy With Ibandronate For Osteoporosis Intervention (MOTION) study. Clin Ther. 2009 Apr;31(4):751-61.

447. Hadji P, Minne H, Pfeifer M, Bourgeois P, Fardellone P, Licata A, et al. Treatment preference for monthly oral ibandronate and weekly oral alendronate in women with postmenopausal osteoporosis: A randomized, crossover study (BALTO II). Joint Bone Spine. 2008 May;75(3):303-10.

448. Li M, Xing XP, Zhang ZL, Liu JL, Liu DG, Xia WB, et al. Infusion of ibandronate once every 3 months effectively decreases bone resorption markers

and increases bone mineral density in Chinese postmenopausal osteoporotic women: a 1-year study. J Bone Miner Metab. 2009 Oct 24.

449. Cadarette SM, Katz JN, Brookhart MA, Sturmer T, Stedman MR, Levin R, et al. Comparative gastrointestinal safety of weekly oral bisphosphonates. Osteoporos Int. 2009 Oct;20(10):1735-47.

450. Reid DM, Hosking D, Kendler D, Brandi ML, Wark JD, Weryha G, et al. Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis : results of FACTS -international. Clin Drug Investig. 2006;26(2):63-74.

451. Breart G, Cooper C, Meyer O, Speirs C, Deltour N, Reginster JY. Osteoporosis and venous thromboembolism: a retrospective cohort study in the UK General Practice Research Database. Osteoporos Int. 2009 Oct 6.

452. Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W. A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone. 2007 May;40(5):1238-43.

453. Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2009 Apr 11;373(9671):1253-63.

454. Grosso A, Douglas I, Hingorani A, MacAllister R, Smeeth L. Oral bisphosphonates and risk of atrial fibrillation and flutter in women: a self-controlled case-series safety analysis. PLoS One. 2009;4(3):e4720.

455. Hong JW, Nam W, Cha IH, Chung SW, Choi HS, Kim KM, et al. Oral bisphosphonate-related osteonecrosis of the jaw: the first report in Asia. Osteoporos Int. 2009 Jul 25.

456. Blumentals WA, Harris ST, Cole RE, Huang L, Silverman SL. Risk of severe gastrointestinal events in women treated with monthly ibandronate or weekly alendronate and risedronate. Ann Pharmacother. 2009 Apr;43(4):577-85.

457. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, et al. Effects of Denosumab on Bone Mineral Density and Bone Turnover in Postmenopausal Women Transitioning from Alendronate Therapy. J Bone Miner Res. 2009 Jul 13.

458. Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone. 2008 Aug;43(2):222-9.

459. Antoniucci DM, Sellmeyer DE, Bilezikian JP, Palermo L, Ensrud KE, Greenspan SL, et al. Elevations in serum and urinary calcium with parathyroid hormone (1-84) with and without alendronate for osteoporosis. J Clin Endocrinol Metab. 2007 Mar;92(3):942-7.

460. Huang WF, Tsai YW, Wen YW, Hsiao FY, Kuo KN, Tsai CR. Osteoporosis treatment and atrial fibrillation: alendronate versus raloxifene. Menopause. 2009 Aug 12;17(1):57-63.

461. Obermayer-Pietsch BM, Marin F, McCloskey EV, Hadji P, Farrerons J, Boonen S, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res. 2008 Oct;23(10):1591-600.

462. McComsey GA, Kendall MA, Tebas P, Swindells S, Hogg E, Alston-Smith B, et al. Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV. Aids. 2007 Nov 30;21(18):2473-82.

463. Vestergaard P, Schwartz K, Pinholt EM, Rejnmark L, Mosekilde L. Risk of atrial fibrillation associated with use of bisphosphonates and other drugs against osteoporosis: a cohort study. Calcif Tissue Int. 2010 May;86(5):335-42.

464. Vestergaard P, Schwartz K, Pinholt EM, Rejnmark L, Mosekilde L. Use of bisphosphonates and raloxifene and risk of deep venous thromboembolism and pulmonary embolism. Osteoporos Int. 2009 Oct 27;21(9):1591-7.

465. Pelayo I, Haya J, De la Cruz JJ, Seco C, Bugella JI, Diaz JL, et al. Raloxifene plus ossein-

hydroxyapatite compound versus raloxifene plus calcium carbonate to control bone loss in postmenopausal women: a randomized trial. Menopause. 2008 Nov-Dec;15(6):1132-8.

466. Recker RR, Marin F, Ish-Shalom S, Moricke R, Hawkins F, Kapetanos G, et al. Comparative effects of teriparatide and strontium ranelate on bone biopsies and biochemical markers of bone turnover in postmenopausal women with osteoporosis. J Bone Miner Res. 2009 Aug;24(8):1358-68.

467. Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT, et al. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. Arthritis Rheum. 2008 May;58(5):1299-309.

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 tbat 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 Calcuable
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