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Screening for Osteoporosis: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation

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Structured Abstract

Background: Osteoporosis and related fractures are common in older individuals and lead to premature mortality, loss of function and independence, reduced quality of life, and high costs. Despite its importance, osteoporosis is under detected in the United States. This review updates evidence since the 2002 U.S. Preventive Services Task Force recommendation on osteoporosis screening.

Purpose: To determine the effectiveness and harms of osteoporosis screening in reducing fractures for men and postmenopausal women without known previous fractures; the performance of risk-assessment instruments and bone measurement tests in identifying persons with osteoporosis; optimal screening intervals; and efficacy and harms of medications to reduce primary fractures.

Data Sources: Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the 4th Quarter of 2009), MEDLINE (January 2001 to December 2009), reference lists, and Web of Science searches.

Study Selection: Randomized, controlled trials of screening or medications with fracture outcomes published in English; performance studies of validated risk-assessment instruments; and systematic reviews and population-based studies of bone measurement tests or medication harms.

Data Extraction: Data on patient populations, study design, analysis, follow-up, and results were abstracted; study quality was rated by using criteria developed by the USPSTF.

Data Synthesis: Risk-assessment instruments are modest predictors of low bone density (area under the curve, 0.13 to 0.87; 14 instruments) and fractures (area under the curve, 0.48 to 0.89; 11 instruments); simple and complex instruments perform similarly. Dual-energy x-ray absorptiometry predicts fractures similarly for men and women; calcaneal quantitative ultrasonography also predicts fractures, but correlation with dual-energy x-ray absorptiometry is low. Repeating a bone density measurement up to 8 years after an initial measurement does not significantly improve predictive performance for fracture outcomes. For postmenopausal women, bisphosphonates, parathyroid hormone, raloxifene, and estrogen reduce primary vertebral fractures; bisphosphonates reduce primary nonvertebral fractures in sensitivity analysis. Medications are effective for bone density T-scores of -2.5 or less for women without previous known fractures. Primary prevention trials are lacking for men. Bisphosphonates are not consistently associated with serious adverse events; raloxifene and estrogen increase thromboembolic events; estrogen increases stroke; and estrogen with progestin increases coronary heart disease and breast cancer.

Limitations: Trials of screening with fracture outcomes, screening intervals, and medications to reduce primary fractures, particularly enrolling men, are lacking.

Conclusions: Although methods to identify risk for osteoporotic fractures are available and mediations to reduce fractures are effective, no trials directly evaluate screening effectiveness, harms, and intervals.

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CHAPTER 1. INTRODUCTION

Purpose of Review and Prior USPSTF Recommendation

This systematic evidence review is an update for the U.S. Preventive Services Task Force (USPSTF) recommendation on screening for osteoporosis. In 2002, based on results of a previous review,[1, 2] the USPSTF recommended bone density screening for women age ≥65 years and women age 60–64 years at increased risk for osteoporotic fractures (B Recommendation).[3, 4] They made no recommendations for or against screening postmenopausal women age <60 years or women age 60–64 years without increased risk (C Recommendation). Men were not considered in the prior recommendation. (See **Appendix A1** for a list of all abbreviations included in this report.)

The USPSTF made additional conclusions about the state of the evidence in 2002 including:

- The risk for osteoporosis and fractures increases with age and other factors.
- Although there are many risk factors for low bone density and fractures, female sex, older age, and lower body weight (<70 kg) are the strongest predictors of low bone density. There is less evidence to support the use of other individual risk factors as a basis for identifying high-risk women (for example, smoking, weight loss, family history, decreased physical activity, alcohol or caffeine use, or low calcium and vitamin D intake).
- At any given age, black women on average have higher bone mineral density than white women and are thus less likely to benefit from screening.
- Bone density measurements accurately predict the risk for fractures in the short term.
- Among different bone measurement tests performed at various anatomical sites, bone density measured at the femoral neck by dual-energy x-ray absorptiometry (DXA) is the best predictor of hip fracture and is comparable to forearm measurements for predicting fractures at other sites.
- The likelihood of being diagnosed with osteoporosis varies greatly depending on the site and type of bone measurement test; the number of sites tested; the brand of densitometer used; and the relevance of the reference range.
- Treating asymptomatic women with osteoporosis reduces their risk for fractures.

Several evidence gaps were identified including:

- No trials have evaluated the effectiveness of screening on reducing fractures or fracture-related morbidity or mortality; therefore, there is no direct evidence that screening improves outcomes.
- No studies have evaluated the optimal intervals for repeated screening.
- There are no data to determine the appropriate age to stop screening, and few data on osteoporosis treatment in women age ≥85 years.
- Few published studies address screening and treatment for younger postmenopausal women.
- No bone density studies or treatment trials include large numbers of non-white women.

- Although there are several methods to estimate risk for osteoporosis and fractures using risk factors, the accuracy and clinical applicability of these methods in identifying high risk individuals in practice have not been demonstrated.
- Peripheral bone density tests have not been extensively studied for screening. Further research is needed to define the appropriate use of these technologies.
- It is unknown whether women who have a similar overall risk for fracture, but different bone densities, will benefit similarly from treatment.
- There is little empirical data on potential harms of screening.
- Data for men are lacking.

This update focuses on new studies and evidence gaps that were unresolved at the time of the 2002 recommendation. These include the effectiveness and harms of osteoporosis screening in reducing fractures and fracture-related health outcomes for men as well as postmenopausal women without known previous fractures; the performance of risk-assessment instruments and bone measurement tests in identifying individuals with osteoporosis; optimal screening intervals; and efficacy and harms of medications to reduce primary fractures in a screening-detected population.

The USPSTF considers the value of clinical interventions to prevent the onset of a condition or to treat asymptomatic individuals who have developed important risk factors or preclinical disease.[5] For osteoporosis, the focus is on the identification of individuals with low bone mass and risk factors in order to prevent fractures. The target populations for this review include postmenopausal women and men age >50 years without known previous osteoporosis related fragility fractures or secondary causes of osteoporosis (e.g., corticosteroid users, transplant recipients, cancer patients). Individuals with these conditions undergo a different course of evaluation and management and are not considered screening candidates. This distinction becomes somewhat blurred for the large number of individuals with undiagnosed vertebral fractures who are included in the screening pool because their fractures have been undetected. Also, many individuals with previous fractures have never been appropriately evaluated for osteoporosis and may be diagnosed during the course of routine screening.

The USPSTF has a U.S. perspective and focuses on technologies, therapies, and practices that are feasible in primary care clinical settings across the United States. Recommendations are based on the strength of evidence of benefits and harms. Costs are not considered in the recommendation, but may be used contextually by the USPSTF.

Condition Definition

Osteoporosis is a systemic skeletal condition characterized by low bone mass and microarchitectural deterioration of bone tissue that increases bone fragility and risk for fractures.[6] Osteoporosis may occur without a known cause, or secondary to another condition. These include corticosteroid therapy, excessive alcohol use, primary or secondary hypogonadism, low calcium intake, vitamin D deficiency, smoking, antiepileptic drug use, thyrotoxicosis, primary hyperparathyroidism, chronic liver or kidney disease, rheumatoid

arthritis, diabetes, human immunodeficiency virus, organ transplantation, multiple myeloma, and others.

Osteoporosis is diagnosed in individuals on the basis of presence of a fragility fracture or by bone mass measurement criteria. A fragility fracture results from forces that would not normally cause a fracture, such as a hip or wrist fracture from falling from standing height or a vertebral compression fracture. Although specific fracture sites have been considered more characteristic of osteoporosis, fractures occurring at nearly every anatomical site have been associated with osteoporosis.

Bone mineral density (BMD) criteria were developed by the World Health Organization (WHO) from epidemiologic data that describe the normal distribution of BMD in a young healthy reference population.[7] Osteoporosis is diagnosed when the BMD at the spine, hip, or wrist is 2.5 or more standard deviations (SD) below the reference mean. Low bone density or mass (sometimes referred to as osteopenia) is diagnosed when BMD is between 1.0–2.5 SD below the reference mean. BMD criteria for osteoporosis identify only one aspect of the condition. Other important components, such as rate of bone loss and quality of bone, are not well characterized clinically.

The number of standard deviation units above or below the young healthy mean is called the T-score. A Z-score is the number of standard deviation units above or below the mean for one's own age group. Although intended for epidemiologic purposes, T-scores have been used as selection criteria for trials of therapies. They are now used to identify individuals with low BMD and to make treatment decisions.

Prevalence and Burden of Disease

Estimates indicate that as many as 50 percent of Americans age >50 years will be at risk for osteoporotic fractures during their lifetimes.[6] This translates to 12 million individuals with osteoporosis by 2012.[6] Specific prevalence rates depend on how bone density is measured and characteristics of the population. Rates for women are higher than for men; rates vary by race, with the highest rates in whites; and rates for all demographic groups increase with age.[8–10] Despite differences between demographic groups, osteoporosis is common in all of them.

Fracture rates are particularly sensitive to increasing age because fractures are multi-factorial outcomes. For example, 5 percent of 50-year-old women and 25 percent of 80-year-old women have had at least one vertebral fracture.[11] Older individuals have much higher fracture rates than younger individuals with the same bone density because of increasing risks from other factors such as bone quality and tendency to fall.[12]

All types of fractures are associated with higher mortality rates.[13–16] Men are more likely than women to die in the year after a hip fracture, with mortality rates for men estimated up to 37.5 percent.[17] Although less often causing death, fractures at other sites can adversely impact function and quality of life, resulting in chronic pain, disability, and high costs. These include

direct care expenditures estimated to be 12.2 to 17.9 billion per year in 2002 dollars[6] in addition to lost productivity of patients and their caregivers.

Risk Factors

Several risk factors for osteoporosis and fractures have been identified from an extensive research base. Large prospective population-based studies, such as the Study of Osteoporotic Fractures (SOF) for women in the United States, provide well-developed multivariable models of risk factors for osteoporosis and fractures.[18] These factors have been incorporated into risk assessment instruments to identify candidates for BMD testing or drug therapy. This report includes a review of these instruments (Key Question 2).

Rationale for Screening/Screening Strategies

Bone measurement tests are used to predict fractures, to diagnose osteoporosis, and to select patients for treatment. Among bone measurement tests at various sites, DXA of the hip is the strongest predictor of hip fracture.[19–21] Most DXA testing includes measurements at the hip and lumbar spine (central DXA). Diagnostic criteria are based on these DXA measurements, most randomized controlled trials of drug therapies have used them as inclusion criterion, and they have become the gold standard. It is, therefore, difficult for clinicians to make decisions for patients identified as having osteoporosis by other tests, even if they are also equally predictive of BMD and fractures.

Several other types of bone measurement tests are available, and many studies have been done to determine their advantages and disadvantages compared to central DXA. The most clinically applicable procedures measure bone mass at peripheral anatomic sites. Currently, the most commonly used non-DXA test in the United States is quantitative ultrasound (QUS) of the calcaneus (heel). QUS avoids ionizing radiation, and is inexpensive, portable, and feasible for primary care settings. DXA uses radiation, is hospital-based, more costly, and requires interpretation of results. QUS measures ultrasound waves across the bone using different parameters (broadband ultrasound attenuation [22], speed of sound [SOS], velocity of sound [VOS], quantitative ultrasound index [QUI], and stiffness). These parameter values are lower in osteoporotic bone than in healthy bone. This report includes a review of QUS (Key Question 3).

Interventions/Treatment

Current Drug Therapies

The U.S. Food and Drug Administration (FDA) has approved a number of medications for prevention and/or treatment of osteoporosis including drugs in the bisphosphonate class, parathyroid hormone, calcitonin, raloxifene, and estrogen. Testosterone is used for treatment

and/or prevention of osteoporosis in men. Although the mechanisms of these drugs vary, all of them decrease fracture risk by increasing bone mineral density. Drugs vary in their adverse events, modes of administration, and dosing frequency. This report includes a review of trials of these medications for primary fracture prevention (Key Questions 5 and 6).

Emerging Drug Therapies

New therapeutic strategies are being developed to target aspects of the bone remodeling pathway that are not addressed by current drugs. Denosumab is an investigational human monoclonal antibody to RANK-ligand that inhibits osteoclast differentiation and activation. It is given by subcutaneous injection every 6 months. In recent trials, denosumab has been shown to decrease bone resorption,[23] increase BMD at the hip and spine,[23–25] and decrease hip and spine fractures in postmenopausal women (3-year follow-up).[26]

Other pathways also show promise as therapeutic targets for osteoporosis. The WNT signaling pathway directs mesenchymal stem cells to become chondrocytes or osteoblasts.[27] Drugs targeting the WNT pathway can shift differentiation toward osteoblasts.[28] Antibodies toward various aspects of the WNT pathway may shift bone remodeling toward bone formation. Sclerostin, DKK-1, and osteoprotegerin (OPG) are agents of the WNT pathway that are currently being targeted in development of new osteoporosis therapies.

Cathepsin K (Cat K) is a cysteine protease expressed by osteoclasts and involved in resorption of bone matrix. Balicatib and odanocatib inhibit human Cat K and uncouple bone remodeling processes in favor of bone formation. A trial of odanacatib versus placebo in postmenopausal women with osteoporosis by BMD T-score showed improvement in BMD at the spine and total hip.[29]

Current Clinical Practice

Despite increased awareness of the magnitude and consequences of osteoporosis and recommendations for screening and treatment from multiple groups, osteoporosis is under detected and inadequately treated in the United States.[30, 31] Reasons for this are unclear, although the differing recommendations for identifying candidates for testing and treatment, confusion in interpreting results of testing, and fragmentation of health care may contribute.[32] Usually the fracture itself is treated by an acute care team in hospital emergency departments and orthopedic services, while screening, prevention, and treatment are addressed in another context.

Recommendations of Other Groups

Recommendations of other groups are summarized in **Table 1**.

CHAPTER 2. METHODS

Key Questions and Analytic Framework

Based on evidence gaps identified from the previous review and using the methods of the USPSTF,[33–35] the USPSTF and Agency for Healthcare Research and Quality (AHRQ) developed Key Questions for this review. Investigators created an analytic framework incorporating the Key Questions and outlining the patient populations, interventions, outcomes, and harms of the screening process (**Figure 1**). The target populations include postmenopausal women and men age >50 years without known previous osteoporosis-related fragility fractures or secondary causes of osteoporosis.

Key Questions include:

1. Does screening for osteoporosis and low bone density reduce osteoporosis-related fractures and/or fracture-related morbidity and mortality in the target populations? These include postmenopausal women (age <60 years, 60–64 years at increased risk for osteoporotic fractures, 60–64 years not at increased risk for osteoporotic fractures, and ≥65 years) and men >50 years.
2. What valid and reliable risk-assessment instruments stratify women and men into risk categories for osteoporosis or fractures?
3. A. How well does DXA predict fractures in men?
   B. How well do peripheral bone measurement tests predict fractures?
   C. What is the evidence to determine screening intervals for osteoporosis and low bone density?
4. What are the harms associated with osteoporosis screening?
5. Do medications for osteoporosis and low bone density reduce osteoporosis-related fracture rates and/or fracture-related morbidity and mortality in the target populations?
6. What are the harms associated with medications for osteoporosis and low bone density?

Harms of screening include consequences of false-positive and false-negative tests, patient anxiety and other psychosocial responses, unnecessary treatment, as well as adverse outcomes from medications.

Two additional Contextual Questions are also included. Contextual Questions are addressed as a narrative, not systematic, review of relevant studies. Their purpose is to provide background information for determining recommendations:

1. What is the validity and reliability of T-score test results as they relate to ethnic minorities? (No studies addressed this question.)
2. What are emerging therapies for treatment of osteoporosis and low bone density that reduce fracture risk? (This information is included in the Introduction.)

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the 4th Quarter 2009), and MEDLINE (January 2001 to December 2009) for relevant studies and systematic reviews. Search strategies and additional details are described in **Appendix B1**. We also conducted secondary referencing by manually reviewing reference lists of key papers and searching citations using Web of Science.[36]

Study Selection

We selected studies on the basis of inclusion and exclusion criteria developed for each key question (**Appendix B2**). **Appendix B3** shows the results of our literature search and selection process. Studies excluded after review of the full-text articles, and reasons for their exclusion, are listed in **Appendix B4**.

We included randomized controlled trials (RCTs) with fracture or fracture-related morbidity and mortality outcomes to determine the effectiveness of osteoporosis screening and studies of any design to determine harms from screening.

To determine the accuracy and clinical applicability of risk-assessment instruments, we included studies of externally validated instruments that reported performance characteristics. Instruments were included if they were derived from an initial population and then tested in a separate population; derived from computer modeling, consensus, or another study, and then tested in a novel population; or derived from any source and tested against T-scores or actual fracture rates in a population. We did not include internally validated measures (imputation methods or cross-validation) in the final tables. To determine the performance of bone measurement tests in predicting fractures, we limited studies to existing systematic reviews and technology assessments of procedures currently used in U.S. practice and large population-based studies relevant to primary care settings. We included any studies providing data about screening intervals.

To evaluate the efficacy and harms of medications to reduce fractures in a screening-detected population, we included RCTs and meta-analyses of RCTs that reported fracture and fracture-related outcomes and adverse effects for medications used in the United States. Outcomes included specific types of fractures; fracture-related morbidity, including loss of function, pain, quality of life, and other reported health outcomes; and fracture-related mortality. We excluded non-drug therapies because they are addressed in other reviews for the USPSTF (calcium, vitamin D, exercise, fall prevention) and combination therapies. We focused on trials that enrolled patients without known prior osteoporosis-related fragility fractures, such as vertebral compression or hip fractures, and without known secondary causes for osteoporosis, because this population is most relevant to screening. We defined primary prevention trials as studies that met one of the following criteria:

1) Trial excluded individuals with previous vertebral or other presumably osteoporotic fractures.
2) Trial permitted individuals with previous osteoporotic fractures, but the overall proportion of participants with fractures was <20 percent, or the trial reported results separately for participants with and without previous fractures. We considered trials meeting this criterion to be applicable to primary prevention based on epidemiologic data.[37]
3) Trial did not report the proportion of participants with previous osteoporotic fractures, but inclusion criteria did not select individuals on the basis of presence of a previous fracture, and mean BMD T-scores were ≥-3.0. This threshold was selected because placebo-controlled trials that enrolled >20 percent of women with previous fractures reported mean baseline BMD T-scores <-3.0.[38–41]

We determined harms from good- and fair-quality systematic reviews that pooled primary and secondary prevention trials after verifying data abstraction and statistical analyses, and large controlled observational studies. For osteonecrosis of the jaw, we included systematic reviews summarizing evidence from case reports and series.

Data Abstraction and Quality Rating

We abstracted details about the patient population, study design, analysis, follow-up, and results. By using predefined criteria developed by the USPSTF,[33] two investigators rated the quality of studies (good, fair, poor) and resolved discrepancies by consensus. We assessed the overall strength of the body of evidence for each key question (good, fair, poor) by using methods developed by the USPSTF on the basis of the number, quality, and size of studies; consistency of results between studies; and directness of evidence (described in **Appendices B5**, **B6**, and **B7**).[33]

Data Synthesis and Analysis

We pooled results of primary prevention trials of bisphosphonates for various fracture outcomes (vertebral, nonvertebral, hip, wrist, and ankle) using the random effects Mantel-Haenszel method in Review Manager (RevMan) Version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We chose the random-effects model because of differences in study participant characteristics such as baseline BMD, proportion of participants with previous fractures, and risk factors for osteoporosis. We also stratified results by type of bisphosphonate if sufficient data for pooling were available. For trials that evaluated several doses, we focused on outcomes for doses similar to those currently recommended in the package inserts approved by the FDA.

Sensitivity Analysis

Several trials included in the meta-analyses reported few, rare, or zero fracture events. The primary analyses excluded trials with zero events in both groups, resulting in loss of data, and applied a constant continuity correction of 0.5 for trials with zero events in one group, potentially biasing inferences.[42, 43] In addition, the random-effects Mantel-Haenszel method we used may be unsuitable when events are rare.[42] We therefore conducted sensitivity analyses to determine the effects of alternate pooling methods on estimates using the Peto odds ratio (OR), fixed-effects Mantel-Haenszel method with an alternative continuity correction (inverse of the sample size of the opposite treatment group), and the pooled arcsine difference with and without zero event trials.[43, 44]

We assessed statistical heterogeneity with the I^2 statistic, and when present, we assessed effects of dose and duration of trials on results. We also assessed the effects of methodologic quality on the basis of our ratings using predefined criteria as described above.

To determine if baseline BMD affected results, we conducted an analysis that stratified trials according to the mean baseline BMD (T-score <-2.0 versus >-2.0). For trials that did not report mean baseline T-scores, we calculated them from mean baseline BMD at the femoral neck by using the FRAX Patch program (FRAX Patch version 1.4, Oregon Osteoporosis Center, Portland, Oregon). We verified that in trials that reported mean baseline T-scores and BMD, reported T-scores were similar to results by using FRAX Patch. If femoral neck BMD was not reported, we used baseline total hip BMD. The FRAX Patch program includes adjustments according to densitometer manufacturer. If the manufacturer was not reported, we calculated T-scores for all three manufacturers included in the FRAX Patch and averaged the scores.

To determine if our criteria for selecting primary prevention trials affected results, we conducted sensitivity analyses on fracture estimates that included trials that enrolled up to 40 percent of participants with previous vertebral fractures, or did not report baseline vertebral fracture rates and reported a baseline BMD T-score <-3.0.[38, 40, 45–48]

Outcomes Table and Screening Strategies

To estimate the effect of screening 10,000 postmenopausal women with DXA for primary fracture prevention, we created an outcomes table on the basis on assumptions from the reviewed studies. Although these calculations have important limitations and underestimate the uncertainty in the evidence, they provide an illustration of the clinical application of the evidence and may be useful to clinicians and the USPSTF. Data include age-specific prevalence rates expressed in 5-year intervals,[49] and treatment effects based on results of the Fracture Intervention Trial (FIT) for women without previous vertebral fractures with T-scores ≤-2.5.[50]

To determine the influence of risk factors in selecting women for densitometry screening, we estimated10-year risks for major osteoporotic and hip fractures for U.S. white women by using the online FRAX calculator (http://www.shef.ac.uk/FRAX/).[51] By using risk estimates for 65-

year-old women aged ≥65 years with no additional risk factors as the reference case, we identified age- and risk factor-specific categories of women with similar or higher risk estimates.

Review of Draft

The draft report was reviewed by content experts listed in **Appendix B8**, USPSTF members, AHRQ Project Officers, and collaborative partners.

CHAPTER 3. RESULTS

Key Questions 1 and 4. Does screening for osteoporosis and low bone density reduce osteoporosis-related fractures and/or fracture-related morbidity and mortality in postmenopausal women and men age >50 years? What are the harms associated with osteoporosis screening?

Summary

We identified no trials of the effectiveness of screening and no studies evaluating potential harms from screening. Adverse outcomes from medications are addressed in Key Question 6 below.

Key Question 2. What valid and reliable risk-assessment instruments stratify women and men into risk categories for osteoporosis or fractures?

Summary

Several risk-assessment instruments have been developed to identify individuals at risk for low bone density or fractures. Thirty-three studies evaluated 21 externally validated clinical risk-assessment instruments and reported performance estimates of the area under the curve (AUC)

for the receiver-operating characteristic (ROC) curve predicting either bone density or fractures. Twenty-three studies of 14 instruments to predict low BMD (T-scores ≤-2.5) reported AUC estimates ranging from 0.13 to 0.87, with most between 0.60 and 0.80. Eleven studies of 11 instruments to predict fractures reported AUC estimates from 0.48 to 0.89. Additional studies combined a risk-assessment instrument with bone densitometry, quantitative ultrasound, or radiograph finding, usually resulting in higher AUC estimates than the individual components. Although some instruments had high AUC estimates in selected studies, none demonstrated high estimates in several studies. Instruments with fewer risk factors often did as well or better than those with more and none performed consistently better than the others. Few instruments have been validated in men. No studies are available that demonstrate improved fracture outcomes when using risk-assessment instruments in clinical practice to identify individuals for screening and treatment.

Detailed Findings

Sixty-four publications evaluated risk-assessment instruments to predict either BMD[52–86] or fractures.[74, 87–115] Ten studies assessed the performance of risk-assessment instruments in combination with peripheral bone mass measurements to predict DXA-measured BMD[61, 67, 69, 73, 76, 93] or fractures,[91, 95, 97, 101] and two studies evaluated prediction of DXA-measured BMD by dental radiographs.[63, 68] Three additional studies evaluated the use of risk-assessment instruments in clinical settings by measuring referrals for DXA,[116] initiation of treatment and rates of hip and total fractures,[117] or comparing various screening strategies in predicting fracture risk.[93]

Several risk-assessment instruments have been externally validated (**Table 2**; **Appendix Table D2**). Others were developed for a single study and are either internally validated or non validated (**Appendix Table D1** includes all validated and non validated risk-assessment instruments).

Risk-Assessment Instruments Predicting Bone Density

We identified 36 studies that reported the performance of various instruments to predict BMD T-score ≤-2.5, including 23 studies of 14 externally validated instruments that report AUC values for the ROC curve[52–54, 56, 57, 60–62, 65–67, 69–74, 76–82, 85] and 13 studies evaluating instruments that were not externally validated or that did not report AUC values.[55, 58, 59, 63, 64, 68, 75, 76, 78, 83, 84, 86] The AUC for the ROC curve for the externally validated instruments ranged from 0.13 to 0.87.

Instruments with fewer risk factors often had similar or higher AUC estimates as than those with more risk factors. For example, the Osteoporosis Self-assessment Screening Tool (OST) includes only age and weight, has similar AUC estimates as other more complicated instruments, and has been validated in both men[52, 69] and women.[61, 64, 66, 67, 70, 74, 76, 77, 85] A recent meta-analysis of OST in postmenopausal women evaluated its performance in ruling out osteoporosis (T-score ≤-2.5).[118] In the combined analyses, the summary negative likelihood ratio for ruling out a T-score <-2.5 in white women was 0.19 at the femoral neck (seven studies) and 0.43 (five studies) at the lumbar spine. However, the meta-analysis was limited by including studies that were published only as abstracts,[119, 120] using retrospective data collection, using non-representative study

populations, reporting the number of participant withdrawals inadequately, and reporting uninterpretable test results.[118]

Evaluations of several instruments, including simple calculated osteoporosis risk estimation (SCORE), osteoporosis risk assessment instrument (ORAI), body weight criterion, and osteoporosis index of risk (OSIRIS), have been based on cross-sectional analyses of cohort data. For instruments that were evaluated prospectively, studies were limited by including small numbers of participants or participants recruited from specialty clinics. Five studies include men.[52, 69, 81, 82, 116]

Risk-Assessment Instruments Predicting Fracture

We identified 30 studies reporting the performance of risk-assessment instruments to predict fractures, including 11 studies of 11 externally validated instruments that report AUC for the ROC curve[74, 88, 90, 96, 98, 100, 103, 104, 112, 113, 115] and 19 studies that either did not report the AUC value or evaluated instruments that were not externally validated.[87, 89, 91–95, 97, 99, 101, 102, 105–111, 114] The AUC estimates for the studies of externally validated instruments ranged from 0.48 to 0.89.

Methodologic limitations of these studies are similar to those of the BMD risk-assessment instrument studies. Two studies were cross-sectional, evaluating prevalent fractures at the same time as risk factors.[114, 115] One instrument was designed to assess subclinical vertebral fractures[114] identifying risk for current rather than future fractures. Other studies used prospective cohort or randomized controlled trial study designs with prospective collection of fracture data reducing potential bias. For these studies, instruments were developed from risk factors assessed at baseline.

Six studies included men and women;[90, 103, 104, 109, 111, 113] all others included women only. Three large studies evaluated the FRAX instrument,[104] an instrument developed and validated within the Women's Health Initiative (WHI) cohort,[112] and another from the National Osteoporosis Risk Assessment (NORA) study population.[108]

The World Health Organization and National Osteoporosis Foundation recently developed the FRAX instrument to predict individual fracture risks.[104, 121] FRAX estimates adjust for nationality and include femoral neck BMD if available and age, sex, height, body mass index (BMI), previous fracture, family history of fracture, glucocorticoid use, current smoking status, daily alcohol use of 3 units or more, rheumatoid arthritis, and other secondary causes (insulin dependent diabetes mellitus, osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypogonadism or premature menopause [<45 years], chronic malnutrition or malabsorption, and chronic liver disease). FRAX was derived from combined data from 46,340 individuals from nine different cohorts in Europe, Canada, United States (Rochester, MN), and Japan; seven of the development cohorts included men.[104] Linear regression modeling identified risk factors that were subsequently tested in 230,486 individuals from 11 validation cohorts; one cohort (Miyama) included men.[104] While the risk calculator is available on a website (http://www.shef.ac.uk/FRAX/), the source code is not accessible.

The AUC estimates for FRAX ranged between 0.54 and 0.78 for osteoporotic fractures,[98, 104, 113] and 0.65 and 0.81 for hip fractures.[104] We did not identify studies that prospectively tested FRAX in clinic populations or determined its effectiveness in selecting patients for therapy.

Three studies compared FRAX with simple models, such as age and BMD or age and fracture history, and found the simple models performed as well as FRAX in predicting hip and other clinical fractures[98, 110] and vertebral fractures.[96] Among women enrolled in SOF with risk factor assessment at baseline and 10 years of follow-up, the AUC for hip fracture was 0.75 for FRAX with femoral neck BMD included, 0.71 for FRAX without femoral neck BMD, and 0.76 for age and femoral neck BMD alone.[98] The same SOF data were used to evaluate FRAX across levels of BMD to predict hip fracture. The resulting AUCs were 0.79, 0.69, 0.59 for normal, low bone density, and osteoporosis (T-score <-2.5), respectively. For predicting nonvertebral fractures, the AUCs were 0.59, 0.58, and 0.63, respectively.[122]

The FRAX model was also evaluated using data from the placebo group of the Fracture Intervention Trial (FIT).[96] This study compared AUCs for several combinations of risk factors including FRAX with and without femoral neck BMD. Results indicated that models using baseline vertebral fractures, age, and femoral neck BMD yielded the highest AUC (0.76). In comparison, FRAX yielded an AUC of 0.71 with femoral neck BMD included, and an AUC of 0.68 without femoral neck BMD.[96]

Use of Risk-Assessment Instruments in Clinical Practice

Three studies evaluated the use of risk-assessment instruments in clinical practice.[93, 116, 117] Women randomly sampled from member lists of a health maintenance organization were randomized to one of three screening strategies involving use of BMD testing or evaluation by risk instruments followed by BMD testing if results indicated increased risk.[117] The groups included: 1) universal screening (everyone offered DXA testing), 2) SCORE (invited for DXA testing only if the SCORE result was >7), and 3) SOF criteria (invited for DXA testing only if they had five or more hip fracture risk factors). DXA testing was performed in 100 percent of the universal group, 73.8 percent of the SCORE group, and 6.9 percent of the SOF group. Osteoporosis treatment rates did not differ between groups.[117]

In another study, a pre-post evaluation of a screening strategy to improve referral for DXA enrolled men attending a rheumatology clinic.[116] They were evaluated with a SOF-based 10-item checklist. Prior to the checklist intervention, 14 percent of men over age 65 had a prior DXA (5 percent of black and 29 percent of white men), whereas after the checklist intervention 32 percent of the men had a DXA request (23 percent of black and 46 percent of white men).[116]

A third study used the EPIDOS prospective cohort to compare several screening strategies in order to predict fracture risk. Participants underwent either: 1) DXA; 2) QUS; 3) QUS followed by DXA if suggested by QUS results; 4) weight and DXA measurement for those <59 kg followed by clinical risk assessment for those in the low-medium BMD category; and 5) a combined strategy with weight and QUS measurement, then hip DXA, followed by a clinical evaluation. Sensitivity was highest for the combined strategy (53 percent versus 15–36 percent

for the others), although specificity was similar (80 percent versus 86–95 percent for the others).[93]

Risk Factors in Combination with Bone Mass Measures

Several studies assessed QUS, central DXA, or peripheral DXA in combination with risk factors to predict either BMD or fracture. Generally, these studies found that QUS in combination with clinical risk factors, with or without DXA, improved identification of individuals with osteoporosis or fractures. The Osteoporosis Risk Assessment by Composite Linear Estimate (ORACLE) risk instrument (which includes QUS) was developed, validated, and compared to QUS alone, and to OST.[76] Both QUS and ORACLE had higher AUC estimates (0.81 [SE, 0.030]) than ultrasonometric bone profile index (ultrasonometric bone profile index [UBPI], 0.71 [SE, 0.034]), or the ultrasound derived T-score (0.69 [SE, 0.035]).[76] The use of the stiffness index by QUS in combination with risk factors yielded a higher AUC estimate than either QUS or the risk factors alone.[101] Models including QUS plus other risk factors reported AUC estimates ranging from 0.672 to 0.689.[95]

Combing the OST risk-assessment instrument with QUS measurements improved the AUC estimate.[69] In another study, risk factors in combination with BUA performed better than risk factors alone.[73]

In a study comparing two ultrasound systems, the CUBA Clinical BUA had an AUC estimate of 0.766 for predicting a T-score of ≤-2.5.[61] This estimate was higher than the AUC for the Sunlight Omnisense system (separately or in combination; range, 0.582 to 0.698), for all clinical risk prediction instruments tested in this cohort (OSIRIS, Study of Osteoporosis Fractures–Study Utilizing Risk Factors [SOFSURF], ORAI, OST, SCORE, body weight [pBW]) (which ranged 0.664 to 0.747), and higher than the velocity of sound by QUS at the calcaneous (0.723).[61]

In a study comparing several different risk instruments with both QUS (CubaClinical and Achilles) and peripheral DXA (Peripheral Instantaneous X-ray Imager [PIXI]), PIXI had the highest independent AUC at 0.80.[67] When combined with the risk instruments, PIXI + OSIRIS had an AUC of 0.82.[67]

Measures of hip geometry by DXA (hip strength analysis [HAS], hip axis length [HAL], and compressive stress [c-stress]) were also included in predictive models.[91] Models including compressive stress plus age and BMI had higher AUC estimates than these variables alone (0.875) or for age plus femoral neck BMD (0.856). However, HAS has been less reliable and its reproducibility is lower than conventional DXA.[91]

Two studies evaluated the use of dental radiographs for predicting osteoporosis compared to DXA.[63, 68] Among women ages 45–70 years, the AUC estimate for femoral neck BMD was 0.835 using manually initialized fit of mandibular radiographs, compared to 0.861 using ORAI and 0.732 using the National Osteoporosis Foundation (NOF) index.[63] For prediction of osteoporosis at any of the three sites (total hip, femoral neck, and lumbar spine), the AUC estimate for manual reading of the dental radiographs was better than automated reading, and

also better than either ORAI or the NOF index. The manual reading had 94 percent sensitivity but 29.5 percent specificity.[63] A separate study reported wide variation in intraobserver assessments for both the lower and upper jaw periapical radiographs. Across all observers, the diagnostic odds ratios ranged from 2.76 to 7.71 for the upper jaw and 2.20 to 15.35 for the lower jaw.[68]

Key Question 3a. How well does DXA predict fractures in men?

Summary

Although DXA is the current gold standard for diagnosing osteoporosis and making treatment decisions, it is an imperfect predictor of fractures. Its role in predicting fractures in men has only recently been evaluated in large studies. The Rotterdam Study is a large population-based prospective study that includes men and women and reports incident vertebral and nonvertebral fractures several years after obtaining baseline DXA. In this study, for each standard deviation reduction in femoral neck BMD, the hazard ratio for various fracture outcomes was increased to similar levels for men and women. Additional studies of DXA in men are generally consistent with these findings, although DXA of the femoral neck was associated with a higher risk for hip fracture in men enrolled in Osteoporotic Fractures in Men Study (MrOS) compared with women in SOF.

Detailed Findings

Evaluations of DXA in predicting fractures in men, and comparing men with women, were reported from two large, good-quality prospective cohort studies.[123–125] The Rotterdam Study compared women and men age 55 years or older from the same community at the same time.[123, 124] This study utilized a prospective, population-based cohort to investigate the incidence of and risk factors for chronic diseases including osteoporosis. A total of 4,731 women and 3,075 men obtained baseline DXA measurements of the femoral neck, and 2,022 women and 1,527 men obtained baseline lateral radiographs of the thoracolumbar spine. Nonvertebral fracture outcomes were determined an average of 6.8 years later from fracture reports provided by physicians in the community using a computerized reporting system and from reviewing hospital records. Fractures were verified by research physicians using a standardized protocol. Incident vertebral fractures were evaluated 6.3 years after the baseline examination using follow-up radiographs. Vertebral fractures were diagnosed using morphometric criteria.

Age-adjusted hazard ratios for vertebral and nonvertebral incident fractures were similar for men and women. For each gender-specific standard deviation (SD) decrease in BMD, the hazard ratio

for all nonvertebral fractures was 1.4 (95 percent confidence interval [95% CI], 1.2–1.6) for men and 1.5 (95% CI, 1.4–1.6) for women, and were similar for several site-specific fractures (**Table 3**).[123, 124] The hazard ratio for vertebral fractures was 1.8 (95% CI, 1.3–2.4) for men and 1.9 (95% CI, 1.6–2.4) for women.

The Rotterdam Study also reported that the incidence rate for nonvertebral fractures was higher for women than men in all age groups, incidence rates increased with age for both men and women at all levels of BMD, and the relative risks for nonvertebral fractures were higher in lower BMD categories. However, despite the ability of BMD to predict fractures, subjects with normal BMD also incurred fractures at fairly high incidence rates (6.6 nonvertebral fractures/1,000 person years for men; 13.4 nonvertebral fractures/1,000 person years for women).[123] These findings were similar for vertebral fractures, although the incidence of vertebral fractures was also higher in individuals with previous vertebral fractures.[124]

A study of BMD and risk for hip and nonvertebral fractures that compared men enrolled in MrOS with women in SOF reported similar results as the Rotterdam Study.[125] However, in this study, DXA of the total hip or femoral neck was associated with a higher risk for hip fracture in men (femoral neck RH, 3.68 [95% CI, 2.68 to 5.05]) than women (femoral neck RH, 2.48 [95% CI, 2.09 to 2.95]). Subjects in MrOS and SOF were older than those in the Rotterdam Study, men and women were recruited from different geographic regions in the United States, and they were followed for approximately 4 years but at different times. Additional studies of the performance of DXA in predicting fractures in men are consistent with the findings of the Rotterdam Study and MrOS.[126–128] Variations in estimates are likely due to the different patient populations enrolled in the studies, study designs, and other factors.

Key Question 3b. How well do peripheral bone measurement tests predict fractures?

Summary

Several peripheral bone measurement tests have been developed, although clinical practice and recent research focus on QUS of the calcaneous (heel). Large studies of postmenopausal women and men indicate that QUS obtained at the calcaneus using various types of devices can predict fractures as well as DXA of the femoral neck, hip, or spine, although variation exists across studies. However, QUS is not a good predictor of DXA as determined by a recent meta-analysis that indicated AUC estimates of 0.74–0.77 depending on the QUS parameter used. Also, it is unclear how results of QUS can be used to select individuals for drug therapies that were proven efficacious based on DXA criteria.

Detailed Findings

Postmenopausal Women

Several large studies evaluated the performance of various bone measurement tests in predicting fractures in women.[129–135] Although results vary, overall, DXA and QUS have similar AUC estimates and odds ratios for fracture outcomes (**Table 4**). For all fractures combined, AUC estimates range from 0.59–0.66 and ORs from 1.81–2.16 for DXA of the femoral neck. For QUS, AUC estimates are approximately 0.60, and ORs range from 1.26–2.25. In one study that included DXA of the distal radius, the AUC estimate was 0.64 (95% CI, 0.59–0.68) and OR for all fractures 1.47 (95% CI, 1.28–1.68).[132]

Men

Studies evaluating the performance of bone measurement tests in predicting fractures in men examined the same technologies used for women (**Table 4**).[126–128, 131, 136] Results are similar for DXA and QUS. For hip fractures specifically, DXA of the femoral neck is associated with higher risk ratios than QUS for men and women in most studies.

QUS Compared to DXA

QUS predicts most fractures as well as DXA and offers distinct advantages, such as lower cost, portability, ease of use, and avoidance of ionizing radiation. However, it is not clear how to apply the results of QUS testing to patient management. Currently, standardized diagnostic criteria for osteoporosis uses DXA not QUS cutpoints, and clinical trials of drug therapies used DXA testing in its selection criteria. To be clinically useful, QUS results would need to be similar to DXA.

To address this issue, a systematic review and meta-analysis of the accuracy QUS compared to DXA in identifying patients with osteoporosis evaluated 25 studies published prior to October 2005.[137] Included studies evaluated several parameters including BUA, SOS, QUI, and stiffness. Studies varied by subject characteristics, such as location (Europe, United States, Asia), sample size (110–722), prevalence of osteoporosis using DXA criteria (7–38 percent), age (46–64 years), and sex. No studies described the race or ethnicity of subjects. Studies also varied in their use of ultrasound devices, DXA references sites (lumbar spine, femoral neck, total hip), and reference populations to determine T-scores (manufacturers, national, local). All of these factors are important sources of heterogeneity. Potential sources of bias identified in the systematic review include insufficient information to determine participant selection methods, time between QUS and DXA, and whether QUS and DXA results were interpreted independently of each other.

Eleven studies in the systematic review contributed to a summary ROC curve for the QUS index parameter.[137] Results for all studies indicated AUC 0.76 (95% CI, 0.72–0.79), and results

specifically for postmenopausal women were AUC 0.75 (95% CI, 0.66–0.82). These results were similar for the other QUS parameters (broadband attenuation AUC, 0.77 [95% CI, 0.73–0.81]; SOS and VOS AUC, 0.74 [95% CI, 0.71–0.77]; and stiffness AUC, 0.79 [95% CI, 0.71–0.86]).

Summary estimates of the sensitivity and specificity for the QUS Index parameter indicated wide ranges of sensitivity and specificity at various T-score thresholds.[137] For example, for the QUS index parameter T-score cutoff threshold of -1 that is commonly used in screening, sensitivity was 79 percent (95% CI, 69–86) and specificity was 58 percent (95% CI, 44–70) for identifying individuals with DXA T-scores ≤-2.5 at the hip or spine. These values changed at different cutoffs, but at no cutoff were the sensitivity and specificity both high.

Key Question 3c. What is the evidence to determine screening intervals for osteoporosis and low bone density?

Summary

In a large good-quality prospective cohort study of 4,124 women age ≥65 years from SOF, repeating a BMD measurement up to 8 years after an initial measurement did not significantly change AUC and risk ratio estimates for nonvertebral, hip, or vertebral fractures.[138] No studies of screening intervals have been conducted in men or other groups of women.

Key Question 5. Do medications for osteoporosis and low bone density reduce osteoporosis-related fracture rates and/or fracture-related morbidity and mortality in the target populations?

Summary

For postmenopausal women without previous fractures, trials indicate that bisphosphonates, parathyroid hormone, raloxifene, and estrogen reduce primary vertebral fractures. Bisphosphonates reduce primary nonvertebral fractures in sensitivity analysis. No trials report effects on fracture-related morbidity and mortality. The only trial that stratified results according to baseline BMD reported reduced fractures only for women with baseline T-scores ≤-2.5.[50]

More trials have been published that focus on secondary prevention in postmenopausal women, and several systematic reviews and meta-analyses include both primary and secondary prevention trials. For secondary prevention in postmenopausal women, the bisphosphonates alendronate, etidronate, and risedronate are similarly effective at decreasing vertebral fractures compared to placebo. Alendronate and risedronate, but not etidronate, also reduce nonvertebral fractures including hip fractures. Evidence for the newer bisphosphonates zoledronic acid and ibandronate is consistent with evidence for the other bisphosphonates. Of the other medications, parathyroid hormone, calcitonin, and raloxifene reduce vertebral fractures, and parathyroid hormone reduces nonvertebral fractures.

For men, there are no primary prevention trials of bisphosphonates. Based on two secondary prevention trials, alendronate reduces the risk of vertebral fractures compared to placebo, but not nonvertebral fractures. A single trial of parathyroid hormone reported a trend towards decreased vertebral and nonvertebral fractures, but the number of fractures was small and results did not reach statistical significance. There were no trials of other agents with fracture outcomes in men. No trials report other fracture-related morbidity or mortality outcomes.

Detailed Findings

See **Appendix D** for detailed evidence, quality, and supplemental tables.

Primary Prevention Trials

Postmenopausal women

Bisphosphonates. Fifteen placebo-controlled RCTs of bisphosphonates met inclusion criteria (**Table 5**, **Appendix Tables D3** and **D4**), including seven trials of alendronate,[47, 50, 139–143] three etidronate,[144–146] four risedronate,[41, 147–149] and one zoledronic acid.[150] Excluded trials are listed in **Appendix Table D5**. FIT met criteria for good-quality.[50] Of 13 trials rated fair-quality, eight lacked information on randomization, allocation concealment, or outcomes blinding[41, 142–144, 146, 148–150]; and five trials did not report intention-to-treat analysis or blinding of providers.[47, 139, 140, 145, 147] One poor-quality trial did not report blinding, intention-to-treat analysis, or attrition.[141]

In 11 trials, mean baseline femoral neck BMD (or total hip BMD if femoral neck BMD was not available) T-scores were -1.0 to -2.5[47, 50, 139–141, 143–145, 148–150]; one trial enrolled women with T-scores <-2.5[41]; and three trials enrolled women with T-scores >-1.0.[142, 146, 147] Five trials excluded or did not enroll women with previous vertebral fractures[50, 139, 140, 144, 150]; two trials enrolled >20 percent of participants with previous vertebral fractures but reported results in the subgroup of women without prior fractures[41, 47]; and the remainder did not report the proportion of women with previous fractures. The mean age of participants was <65 years in all of the trials except FIT (mean age 68 years).[50] FIT enrolled over 4,000 patients, followed them for four years, and was the only trial designed to evaluate fracture rates as a primary outcome.[50] All but three other

trials[41, 47, 142] randomized fewer than 200 participants, followed them for 1–2 years, and evaluated change in BMD as the primary outcome.

Rates of new vertebral fractures ranged from 0 to 24 percent for bisphosphonates and from 0 to 28 percent for placebo in 12 trials reporting this outcome (**Table 5**).[47, 50, 139–142, 144–150] Rates of fractures may have varied because of differences in baseline BMD, other risk factors for osteoporotic fractures, duration of follow-up, and methods used to identify new fractures (e.g., actively soliciting symptoms and/or routine x-rays versus symptomatic or passive reporting only). Six trials reported no vertebral fractures in either bisphosphonate- or placebo-treated patients[139, 140, 142, 144, 149, 150]; and three of these trials identified new vertebral fractures clinically (i.e., did not perform routine spine radiography to identify fractures), potentially missing asymptomatic fractures.[139, 149, 150]

Bisphosphonates reduced vertebral fractures compared with placebo (relative risk [RR], 0.66 [95% CI, 0.50–0.89]; I^2, 0 percent; seven trials) (**Table 6**, **Appendix Figure C1**).[47, 50, 141, 145–148] Five trials recorded zero vertebral fractures and did not contribute to the pooled estimate in the primary analysis.[139, 140, 142, 144, 149, 150] Excluding one trial that identified only one new clinical vertebral fracture and did not perform routine spine radiography to identify additional fractures did not change results.[146] Results based on alternative methods for pooling were nearly identical (**Table 7**). FIT, the large (n=4,432) 4-year trial of alendronate, contributed two-thirds of the total number of patients (n=6,782) and vertebral fractures (169) in the analysis (RR, 0.55 [95% CI, 0.38–0.80]).[50] Subgroup analyses of the other individual bisphosphonates evaluated in these trials (etidronate, risedronate, or zoledronic acid) were limited by small numbers of fractures (range, 0 to 20 events) for drugs other than alendronate. Removing the poor-quality trial did not significantly change estimates.[141] Including all trials, the absolute risk for vertebral fracture was 1.9 percent for bisphosphonates compared to 3.1 percent for placebo. Based on FIT alone, the number needed to treat (NNT) was 60 to prevent one or more vertebral fractures (3.8 versus 2.1 percent).

Total nonvertebral fractures were reported in 10 trials.[50, 139, 142, 143, 145–150] Rates of any fracture (vertebral or nonvertebral) could be estimated from nine trials, though in most cases we had to assume that fractures at different sites occurred in different patients.[50, 139, 142, 145–150] One trial reported no fractures with either alendronate or placebo.[139] In the other trials, nonvertebral fracture rates ranged from 0 to 12 percent for subjects randomized to bisphosphonates and 2 to 13 percent for those randomized to placebo. Similar ranges were observed for rates of any fracture.

For total nonvertebral fractures, a pooled analysis of trials indicated no statistically significant effects for bisphosphonates compared with placebo (RR, 0.83 [95% CI, 0.64–1.08]; I^2, 15 percent; nine trials), although trends favored the bisphosphonates (**Table 6**, **Appendix Figure C2**).[50, 142, 143, 145–150] Differences were also not significant for alendronate specifically (RR, 1.08 [95% CI, 0.62–1.88]; I^2, 67 percent; two trials).[50, 142] Subgroup analyses of other bisphosphonates were limited by small numbers of fractures (range, 5 to 18 events). One trial recorded zero nonvertebral fractures and did not contribute to the primary analysis.[139] Results were statistically significant when estimated using alternative pooling methods (Peto OR, 0.84 [95% CI, 0.72–0.98]; fixed effects Mantel Haenszel with inverse sample size continuity

correction RR, 0.86 [95% CI, 0.74–0.99]) (**Table 7**). For any type of fracture (vertebral and nonvertebral), results were similar (RR, 0.89 [95% CI, 0.77–1.03]; I^2, 0 percent; eight trials) (**Appendix Figure C3**).[50, 142, 145–150] As in the analysis of vertebral fractures, FIT heavily influenced results (RR for nonvertebral fractures, 0.89 [95% CI, 0.76–1.04]; RR for any type of fracture, 1.08 [95% CI, 0.62–1.88]).[50] Results for hip, wrist, or ankle fractures showed no statistically significant differences between bisphosphonates and placebo, but were limited by small numbers of fractures (**Table 6**, **Appendix Figures C4**, **C5**, and **C6**).

For the sensitivity analysis based on a broader definition for primary prevention, we added five trials that enrolled up to 40 percent of patients with baseline vertebral compression fractures[38, 40, 45, 47, 48] and one trial that enrolled patients with a mean baseline BMD T-score of -4.3 (baseline fractures not reported).[46] Estimates for vertebral fracture were similar to the primary analysis, and the estimate for hip fracture remained statistically non-significant (**Appendix Table D6** and **Appendix Figures C7** and **C8**). Although the result for hip fractures neared statistical significance (RR 0.65 [95% CI, 0.42–1.01]), only five additional hip fractures were included in the sensitivity analysis.[40, 47] The point estimate for total nonvertebral fractures also remained similar, but reached statistical significance with the inclusion of the additional trials (RR, 0.82 [95% CI, 0.69–0.96]; I^2, 5 percent; 14 trials) (**Appendix Figure C9**).[38, 40, 45–48, 50, 142, 145–150] This was primarily due to the addition to the analysis of a large trial (83 of the 136 additional events in the sensitivity analysis were reported by this trial) with a vertebral fracture prevalence just over our threshold for inclusion as a primary prevention trial (21 percent).[47] A sensitivity analysis that only added this trial would have resulted in borderline statistical significance (RR, 0.84 [95% CI, 0.70–1.00]). We could not adequately assess whether estimates of bisphosphonates for fracture efficacy varied between trials according to the mean baseline BMD of participants. For vertebral fracture, bisphosphonates were only superior to placebo in the subgroup of trials that enrolled patients with a mean femoral BMD T-score of -2.0 or worse (RR, 0.55 [95% CI, 0.38–0.80]), but this estimate is based solely on FIT[50] (**Appendix Figure C10**). There was no difference between bisphosphonates and placebo in seven trials that enrolled patients with mean femoral BMD T-score of -1.0 to -2.0 (RR, 0.93 [95% CI, 0.49–1.76]), but only 28 vertebral fractures were reported in three trials.[141, 145, 148, 149] For all nonvertebral fractures, there was no difference between bisphosphonates and placebo for any subgroup of trials stratified according to mean femoral BMD T-score (**Appendix Figure C11**). Hip fractures were only reported in three trials that each enrolled patients with mean femoral BMD T-score of -2.0 or worse.[41, 50, 143]

FIT was the only individual trial to report results stratified according to baseline BMD.[50] It found that alendronate was associated with decreased risk of any clinical fracture (RR, 0.64 [95% CI, 0.50–0.82]) and vertebral fracture (RR, 0.50 [95% CI, 0.31–0.82]) in women with baseline femoral neck T-scores <-2.5, with a NNT of about 15 and 34, respectively. In women with T-scores between -1.6 and -2.0 or -2.0 and -2.5, there was a non-statistically significant trend towards decreased risk of vertebral fracture (RR, 0.82 [95% CI, 0.33–2.07] and RR, 0.54 [95% CI, 0.28–1.04], respectively), but no effect on any clinical fracture (RR, 1.14 [95% CI, 0.82–1.60] and RR, 1.03 [95% CI, 0.77–1.39], respectively).

Parathyroid hormone. One large, fair-quality (n=2,532) RCT evaluated effects of parathyroid hormone on risk of fractures after 18 months in postmenopausal women with BMD T-score

<-3.0 and no prevalent vertebral fractures (81 percent of participants), or a T-score <-2.5 and one to four prevalent fractures (19 percent) (**Table 5**).[151] For women without a baseline fracture, parathyroid hormone decreased the risk of new vertebral fractures from 2.1 to 0.7 percent (RR, 0.32 [95% CI, 0.14–0.75]) with a NNT of 71 (42 to 248). Among all participants, there was no difference in risk of new nonvertebral fracture (RR, 0.97 [95% CI, 0.71–1.33]).

Testosterone and calcitonin. We identified no trials that evaluated efficacy of testosterone or calcitonin for primary prevention of fractures.

Raloxifene. The Multiple Outcomes of Raloxifene (MORE) trial included women with BMD T-scores <-2.5 with or without previous vertebral fractures (37 percent with prior fractures).[152] Raloxifene reduced vertebral fractures (RR, 0.60 [95% CI, 0.53–0.69]), but not nonvertebral or hip fractures compared to placebo (**Table 5**).[152] Results were similar for women with and without prior vertebral fractures and for women using two different doses of raloxifene (60 or 120 mg/day).[152, 153]

The Raloxifene Use for the Heart (RUTH) trial was designed primarily to determine the effects of raloxifene on coronary events and invasive breast cancer, and fractures were secondary outcomes (**Table 5**).[154] Participants were selected for these trials based on cardiac risk factors rather than BMD or fracture status. RUTH reported reduced clinical vertebral fractures (RR, 0.65 [95% CI, 0.47–0.89]), but not nonvertebral fractures (RR, 0.96 [95% CI, 0.84–1.09]) among raloxifene users compared to placebo, consistent with results of MORE.[154] A meta-analysis of both trials provided estimates for vertebral (RR, 0.61 [95% CI, 0.54–0.69)] and nonvertebral fractures (RR, 0.97 [95% CI, 0.87–1.09]) (**Table 6**).[155, 156]

Estrogen with and without progestin. The WHI trial is the largest prevention trial of estrogen (conjugated equine estrogen [CEE]) with and without progestin (medroxyprogesterone acetate [MPA]) reporting fracture outcomes in postmenopausal women. The estrogen with progestin trial reported reduced risks for clinical vertebral (RR, 0.65 [95% CI, 0.46–0.92]), hip (RR, 0.67 [95% CI, 0.47–0.96]), wrist (RR, 0.71 [95% CI, 0.59–0.85]), and all fractures combined (RR, 0.76 [95% CI, 0.69–0.83]) for estrogen with progestin users compared to placebo (**Table 6**).[157] These results are statistically significant when using the nominal confidence intervals (nCI), but are not significant when using adjusted confidence intervals (aCI) (hip fracture RR, 0.67 [95% aCI, 0.41–1.10]).

All women in the estrogen only WHI trial had prior hysterectomies and differed from women in the estrogen with progestin trial by a number of other characteristics.[158] These subject differences compromise direct comparisons between trials, although fracture outcomes are similar. Women using estrogen had reduced risks compared to placebo for clinical vertebral (RR, 0.62 [95% nCI, 0.42–0.93; 95% aCI, 0.34–1.13]), hip (RR, 0.61 [95% nCI, 0.41–0.91; 95% aCI, 0.33–1.11]), and all fractures combined (RR, 0.70 [95% nCI, 0.63–0.79; 95% aCI, 0.59–0.83]) (**Table 6**).[158] Significance levels vary, however, depending on whether nominal or adjusted approaches are used.

Men

The only primary prevention trial for men evaluated parathyroid hormone; we identified no trials of bisphosphonates, calcitonin, testosterone, or other agents.

Parathyroid hormone. A good-quality randomized, placebo-controlled trial evaluated effects of parathyroid hormone on risk of fractures after 11 months in men with osteoporosis (baseline BMD lumbar spine T-scores, -2.0 to -2.4) (**Table 6**).[159] Results indicated a trend towards reduced risk of vertebral (RR, 0.49 [95% CI, 0.22–1.09]) and nonvertebral (RR, 0.51 [95% CI, 0.10–2.48]) fractures with parathyroid hormone, but the number of fractures was small and results did not reach statistical significance.[159, 160]

Systematic Reviews of Primary and Secondary Prevention Trials

Several existing systematic reviews of osteoporosis treatments include analyses that pooled results of primary and secondary prevention trials as well as results for men and women. Such evidence may not be fully applicable to screening for primary prevention of osteoporotic fractures in individuals without prior fractures, but may help inform estimates of treatment efficacy.

Bisphosphonates. We identified three good-quality[161–163] and one fair-quality[164] systematic reviews on effects of bisphosphonates on fractures (**Table 8**). All of the systematic reviews included trials enrolling patients with previous vertebral or nonvertebral fractures. Three of the systematic reviews classified trials that enrolled patients with a BMD T-score <-2.0 to be "secondary prevention" trials even if patients had no prior fracture (i.e., they used a more restrictive definition for primary prevention than we did).[161–163] Most of the trials were not designed with sufficient statistical power to assess fracture rates as a primary outcome.

Three systematic reviews of alendronate,[162] etidronate,[163] and risedronate[161] in postmenopausal women each found the bisphosphonate associated with a statistically significant decreased risk of vertebral fracture compared to placebo (**Table 8**, **Appendix Tables D7** and **D8**). Relative risk point estimates ranged from 0.55 to 0.63. Statistically significant but smaller effects on nonvertebral and hip fracture were observed with alendronate (RR, 0.84 [95% CI, 0.74–0.94] and RR, 0.61 [95% CI, 0.40–0.92], respectively) and risedronate (RR, 0.80 [95% CI, 0.72–0.90] and RR, 0.74 [95% CI, 0.59–0.94], respectively), but not etidronate.

A fourth systematic review focused on effects of alendronate in men with osteoporosis (about half with vertebral fractures at baseline).[164] In two trials (n=375),[165, 166] alendronate was associated with a decreased risk of vertebral fractures (OR, 0.35 [95% CI, 0.17–0.77]) and a non-statistically significant trend towards decreased risk of nonvertebral fractures (OR, 0.73 [95% CI, 0.32–1.67]). We found similar results based on relative risk estimates (rather than odds ratios) using a random effects model (RR, 0.41 [95% CI, 0.21–0.80] for vertebral fracture and RR, 0.75 [95% CI, 0.35–1.60] for nonvertebral fracture) (**Appendix Figures C12** and **C13**). These estimates are consistent with those observed in the systematic review of alendronate for postmenopausal women.[162]

Two large, placebo-controlled trials evaluated effects of ibandronate on fractures in

postmenopausal women.[167, 168] One trial (n=2,862; 54 percent with prior vertebral fracture) found that relatively low-dose intravenous ibandronate had no statistically significant effect on fracture risk.[168] After three years, rates of vertebral fractures were 9.2 percent for intravenous ibandronate 1 mg every 3 months, 8.7 percent for 0.5 mg every 3 months, and 10.7 percent for placebo. Rates of any clinical fracture were 10.8 percent, 10.2 percent, and 12.6 percent, respectively. The second trial (n=2,946; all with prior vertebral fractures) found relatively higher oral doses of ibandronate associated with a statistically significant, approximately 50 percent reduction in risk of vertebral fractures, but had no statistically significant effect on the rate of any clinical osteoporotic fracture or clinical nonvertebral fracture.[167] Rates of all new vertebral fractures were 4.7 percent for oral ibandronate 2.5 mg daily, 4.9 percent for 20 mg every other day for 12 doses each month, and 9.6 percent for placebo, and rates of acute clinical vertebral fractures were 5.1 percent, 5.8 percent, and 10.4 percent, respectively. We excluded a meta-analysis of individual patient data from four large (n=8,710) Phase III trials,[167–172] including the two placebo-controlled trials,[167, 168] because it pooled data across placebo- and active-controlled trials, did not report search methods, and failed to assess quality of included trials.[173]

Zoledronic acid. Two large, placebo-controlled trials evaluated effects of zoledronic acid on risk of new fractures in postmenopausal women (n=3,889; two-thirds with baseline vertebral fracture)[174] and in women (75 percent) or men (25 percent) following a hip fracture (n=1,065).[175] Both found that zoledronic acid reduced the risk of vertebral fracture (RR, 0.30 [95% CI, 0.24–0.38] and hazard ratio [HR], 0.54 [95% CI, 0.32–0.92], respectively), nonvertebral fracture (HR, 0.75 [95% CI, 0.64–0.87] and HR, 0.73 [95% CI, 0.55–0.98], respectively), and hip fracture (HR, 0.59 [95% CI, 0.42–0.83] and HR, 0.70 [95% CI, 0.41–1.19]) compared to placebo.

Calcitonin. A fair-quality systematic review found calcitonin for postmenopausal osteoporosis significantly reduced the risk of vertebral fracture risk compared to placebo (RR, 0.46 [95% CI, 0.25–0.87]).[176] Although the pooled estimate was based on data from four trials,[177–180] one trial (the Prevent Recurrence of Osteoporotic Fractures [PROOF] trial) contributed 1,108 of the 1,404 patients included in the analysis.[177] Estimates of treatment benefit were less pronounced in the PROOF trial (RR, 0.79 [95% CI, 0.62–1.00]) compared to the pooled estimate. Effects of calcitonin on nonvertebral fractures were not statistically significant (RR, 0.52 [95% CI, 0.22–1.23]; three trials[177, 179, 181]). The trials included in the pooled analyses had methodological shortcomings, including high loss to follow-up, which ranged from 18.7 to 59.3 percent (in PROOF).

Parathyroid hormone. A good-quality systematic review found parathyroid hormone to be associated with a significant reduction in both vertebral (RR, 0.37 [95% CI, 0.28–0.47]; four trials[160, 182–184]) and nonvertebral (RR, 0.62 [95% CI, 0.46–0.82]; two trials[159, 184]) fractures compared to placebo in men or women.[185] Only one of the four trials scored 4 or higher on the 5-point Jadad scale.[159]

In the two trials that evaluated women, we calculated estimates for vertebral (RR, 0.35 [95% CI, 0.25–0.47]; I^2=0; two trials[182, 184]) and nonvertebral fractures (RR, 0.60 [95% CI, 0.43–0.85]; one trial[184]) that were very similar to estimates based on all trials (**Appendix Figures C14** and **C15**). One of the two trials that evaluated men was very small (n=18) and did not contribute significantly to results.[183] The other trial (n=437) is described in the section on primary

prevention studies.

Testosterone. A good-quality systematic review identified no trials of testosterone therapy that reported fracture outcomes.[186] We found no relevant trials of testosterone therapy not included in the systematic review.

Relative effectiveness of osteoporosis drugs. A fair-quality systematic review found no differences in fracture outcomes in trials comparing bisphosphonates versus estrogen (six trials), bisphosphonates versus parathyroid hormone (one trial), or bisphosphonates versus SERMs (three trials).[187] Estimates from all of the head-to-head trials were imprecise, because none of the head-to-head trials were large enough to evaluate fracture rates as a primary outcome. A large (n=43,135), good-quality cohort study based on administrative claims data found no differences in nonvertebral fractures between risedronate, raloxifene, and alendronate users.[188] Patients who received calcitonin experienced more nonvertebral fractures than those who received alendronate (HR, 1.40 [95% CI, 1.20–1.63]). In the subgroup of patients with a fracture history, raloxifene recipients experienced more nonvertebral fractures than alendronate recipients (HR, 1.78 [95% CI, 1.20–2.63]).

Key Question 6. What are the harms associated with medications for osteoporosis and low bone density?

Summary

A summary of evidence for major adverse outcomes of medications based on published, randomized placebo-controlled trials and systematic reviews is described in **Table 9**.

Evidence from good-quality systematic reviews of alendronate,[162] etidronate,[163] and risedronate,[161] and large trials of ibandronate and zoledronic acid found no differences between any bisphosphonate and placebo in rates of withdrawal or withdrawals due to adverse events. There are case reports of serious upper gastrointestinal adverse events such as perforations, ulcers, bleeds, esophagitis, or esophageal ulceration with all bisphosphonates, but there is no clear increased risk when compared to placebo, given that they are taken in accordance with current recommendations to prevent esophagitis. Evidence on risk of atrial fibrillation with bisphosphonates is mixed, with some studies showing increased risk[174, 189] and other showing no increased risk.[175, 190, 191] A review by the FDA on atrial fibrillation risk is ongoing, but found no evidence of an increased risk from placebo-controlled trials.[192] There are case reports of osteonecrosis of the jaw in patients taking bisphosphonates for osteoporosis, primarily in individuals with cancer receiving intravenous doses higher than that used for osteoporosis treatment or prevention.[193] Although the incidence appears to be very low, there is no reliable evidence for estimating the incidence of osteonecrosis. There are also case reports of severe

musculoskeletal symptoms with all of the bisphosphonates; atypical, low-energy fractures of the femoral diaphysis in long-term users of alendronate; and esophageal adenocarcinoma.

Evidence on harms associated with calcitonin, parathyroid hormone, and testosterone for treatment of osteoporosis is extremely limited due to sparse data from relatively small numbers of trials and inconsistent reporting of adverse events.

Raloxifene users have more thromboembolic events compared to placebo. Estrogen with progestin increases thromboembolic events, stroke, coronary heart disease among older users, and breast cancer. Estrogen alone increases thromboembolic events and stroke.

Detailed Findings

Interpreting evidence on harms is challenging because of differences in how assiduously adverse events were sought, differences in how adverse events were defined, and because many trials did not report specific adverse events of interest. We included evidence on adverse events from studies of both primary and secondary prevention.

Bisphosphonates

Overall withdrawals and withdrawals due to adverse events

Three good-quality systematic reviews found no differences between alendronate,[162] etidronate,[163] and risedronate[161] versus placebo in rates of overall withdrawals or withdrawals due to adverse events. There was also no difference between zoledronic acid and placebo in overall withdrawals or withdrawal due to adverse events in two large pivotal trials,[174, 175] or between ibandronate and placebo in three large trials.[168, 194, 195]

Gastrointestinal adverse events

A systematic review found etidronate and pamidronate associated with an increased risk of mild upper gastrointestinal (GI) events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn) compared to placebo (OR, 1.33 [95% CI, 1.21–1.46]; 18 studies, and OR, 3.14 [95% CI, 1.93–5.21]; seven studies, respectively).[187] A number of the etidronate and pamidronate studies that showed increased risk of GI events were older studies, when clinical awareness of methods for administering bisphosphonates to reduce GI adverse effects may have been limited. The systematic review found no differences between alendronate, ibandronate, risedronate, or zoledronic acid compared to placebo in risk of mild upper GI events.

Esophageal ulcerations and other serious upper gastrointestinal complications have been reported with all bisphosphonates. For example, a postmarketing surveillance study published in 1996, before preventive dosing measures were widely instituted for bisphosphonates, reported serious or severe esophageal adverse events in 51 of 470,000 patients who received alendronate.[196] The systematic review[187] found etidronate associated with higher odds of perforations, ulcerations,

and bleeds compared to placebo or non-use of etidronate in three studies (OR, 1.32 [95% CI, 1.04–1.67]), and a higher risk of esophageal ulceration in one study (OR, 0.33 [95% CI, 0.14–0.74]). However, almost all of the data (371 of 373 total cases of esophagitis/esophageal ulcers or peptic ulcers) on serious GI events associated with etidronate came from one large (n=24,000) postmarketing cohort study.[197] In this study, etidronate was associated with an increased risk of serious GI adverse events only when the control group included individuals both with and without osteoporosis. When the control group was restricted to individuals with osteoporosis not taking a bisphosphonate, cyclical etidronate was not associated with a higher risk of esophagitis/esophageal ulcers (1.2 versus 1.2 percent) or peptic ulcers (0.7 versus 0.7 percent).[197]

No other bisphosphonate was associated with a higher rate of esophageal ulcerations or other serious upper GI complications compared to placebo.[187, 198] The systematic review found daily ibandronate to be associated with a lower rate of perforations, ulcers, and bleeds compared to placebo in two trials.[187] However, the estimate was primarily based on a single trial that reported nearly all of the events, and the overall number of events was low (10 cases of duodenal ulcer in nearly 2,000 patients randomized to ibandronate 2.5 mg daily or placebo).[194]

The FDA recently issued a report summarizing 54 cases of esophageal adenocarcinoma associated with bisphosphonate (primarily alendronate) use, and called for studies investigating a possible association.[199]

Cardiovascular adverse events

The large (n=7,714) Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly [HORIZON] Pivotal Fracture Trial of once-yearly zoledronic acid for postmenopausal osteoporosis reported an increased risk of serious atrial fibrillation compared to placebo, with an absolute increased risk of 0.8 percent (1.3 percent or 40/4,862 versus 0.5 percent or 20/3,852; $p<0.001$), but not an increased risk of any (serious or non-serious) atrial fibrillation (2.4 percent versus 1.9 percent; $p=0.12$).[174] The smaller HORIZON Recurrent Fracture Trial did not find zoledronic acid associated with increased risk of either serious (1.1 percent or 12/1,054 versus 1.3 percent or 14/1,057; $p=0.84$) or any (2.8 percent or 29/1,054 versus 2.6 percent or 27/1,057) atrial fibrillation.[175] Following publication of the HORIZON trials, the authors of the FIT trial (n=6,459) pointed out in a letter to the editor that data submitted to the FDA (but not reported in the journal publication of FIT) showed alendronate to be associated with a non-statistically significant trend towards increased risk for serious atrial fibrillation (1.5 percent versus 1.0 percent; HR, 1.51 [95% CI, 0.97–2.40]), although, as in the HORIZON Pivotal Fracture Trial, there was no difference in risk of any atrial fibrillation (HR, 1.14 [95% CI, 0.83–1.57]).[200] The HORIZON and FIT trials used blinded adjudication to verify potential cases of atrial fibrillation. A pooled analysis of five trials found risedronate 2.5 mg or 5 mg associated with a similar risk of non-adjudicated serious or any atrial fibrillation compared to placebo (0.5 percent or 24/4,998 versus 0.6 percent or 29/5,020 versus 0.5 percent or 24/5,048; $p=0.49$ for serious atrial fibrillation; and 1.3 percent or 66/4,998 versus 1.4 percent or 70/5,020 versus 1.4 percent or 70/5,048; $p=1.0$).[190] The quality of this analysis is difficult to assess because the data are presented as a letter to the editor, with no description of the methods used.

Two population-based case-control studies reached conflicting conclusions regarding the association between bisphosphonate use in women and atrial fibrillation.[189, 191] The larger of the two studies (13,586 cases and 68,054 controls in Denmark) found no association between current or former bisphosphonate use (primarily etidronate and alendronate) versus no use (adjusted RR, 0.95 [95% CI, 0.84–1.07] and 1.04 [95% CI, 0.90–1.21], respectively).[191] A smaller Washington state study (719 cases and 966 controls) found any use (past or current) of alendronate associated with an increased risk of atrial fibrillation compared to no use (OR, 1.86 [95% CI, 1.09–3.15]).[189] This study identified and verified atrial fibrillation and other variables by review of clinical records, supplemented by patient interviews. The Danish study relied on information available from administrative databases (e.g., discharge diagnoses of atrial fibrillation and other medical conditions). The studies also differed in terms of which variables were adjusted for in the analysis. The Washington state study adjusted for age, treated hypertension, calendar year, and the diagnostic of osteoporosis and any cardiovascular disease, and the Danish study adjusted for age, presence of various hospital diagnoses, use of various drugs, and diagnosis of alcoholism or acute alcohol intoxication.

The FDA issued an interim report of an ongoing review on risk of atrial fibrillation associated with bisphosphonates in November 2008.[192] Based on data from nearly 20,000 patients treated with bisphosphonates in placebo-controlled trials, it found no clear association between bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation. The absolute difference in event rates between each of the bisphosphonates and placebo arms varied from 0 to 3 per 1,000.

Musculoskeletal adverse events

A systematic review found zoledronic acid associated with a higher odds of musculoskeletal events (muscular and joint pain, arthritis, and muscle cramps) compared to placebo (OR, 4.52 [95% CI, 3.48–5.43]; three trials).[187] Risedronate was associated with a lower odds of musculoskeletal events compared to placebo (OR, 0.40 [95% CI, 0.29–0.54]; nine trials). Most of the nine trials included in this analysis enrolled patients with secondary osteoporosis or with a previous fracture. However, three trials included at least some patients with primary osteoporosis.[148, 166, 201] One of these trials found a significant improvement in severity of back pain among risedronate patients relative to placebo,[166] but there were no differences in incidence of musculoskeletal pain between risedronate and placebo in the other two trials.[148, 201] Case reports of atypical, low-energy fractures of the femoral diaphysis in long-term users of alendronate have also been reported, though the incidence is unknown.[202–204] There are case reports of severe musculoskeletal pain with all bisphosphonates, including risedronate, that may be reversible after discontinuing the medication.

Osteonecrosis

A FDA report summarized data from 151 case reports of osteonecrosis of the jaw through 2003.[193] The vast majority (139 cases) occurred in cancer patients who received high-dose intravenous pamidronate or zoledronic acid. Only 12 cases were reported in patients who received alendronate for osteoporosis. No evidence exists to reliably estimate the incidence of osteonecrosis in patients taking standard doses of bisphosphonates for osteoporosis. The

HORIZON Pivotal Fracture Trial (n=7,714) identified one case of possible osteonecrosis of the jaw in patients receiving intravenous zoledronic acid and in one patient receiving placebo, based on pre-defined criteria (exposed bone in the maxillofacial area with delayed healing for more than six weeks despite appropriate care) applied by an independent, blinded adjudication committee.[205] Osteonecrosis was not evaluated or reported in other trials of bisphosphonates.

Adherence

A systematic review identified five large studies of administrative databases that found that adherence rates were about 10 percent higher with weekly compared to daily bisphosphonates.[187] Even with weekly bisphosphonates, adherence rates range from 45 to 69 percent. Three other studies included in the systematic review found that rates of fracture prevention consistently correlated with levels of adherence to therapy.

Calcitonin, Parathyroid Hormone, and Testosterone

Evidence on harms associated with calcitonin, parathyroid hormone, and testosterone for treatment of osteoporosis is limited by relatively small numbers of trials and inconsistent reporting of adverse events. A systematic review found that calcitonin did not increase risk of acute coronary syndrome compared to placebo (OR, 0.98 [95% CI, 0.07–13.7]; three trials).[187] It also found that calcitonin, testosterone, and parathyroid hormone were not associated with increased risk of cancer, although estimates were very imprecise. Neither calcitonin nor parathyroid hormone was associated with increased risk of mild gastrointestinal events. No evidence exists to estimate risk of serious gastrointestinal events.

Raloxifene

A meta-analysis of trials of raloxifene reports statistically significant elevated risks for thromboembolic events (RR, 1.60 [95% CI, 1.15–2.23]; two trials)[155, 156] (**Table 9**). Risks for coronary heart disease, stroke, endometrial cancer, and all cause death are similar for raloxifene and placebo.[155, 156] Raloxifene significantly reduces risk for invasive breast cancer in women without preexisting breast cancer (RR, 0.53 [95% CI, 0.34–0.84]; two trials).[155, 156] Several additional symptoms are associated with raloxifene use including, most commonly, influenza syndrome, leg cramps, peripheral edema, and hot flashes.[152–154]

Estrogen

The WHI primary prevention trial provides the most complete data about adverse outcomes of estrogen with and without concurrent use of progestin compared to placebo. Results have been reported in numerous publications since the main trial results were released in 2002.[206] Coronary heart disease and breast cancer were the main outcome measures of the WHI, and the estrogen with progestin trial was discontinued early when safety parameters for breast cancer were exceeded in the treatment group (HR, 1.24 [95% CI, 1.01–1.54])[207] (**Table 9**). Coronary heart

disease events were also increased in the estrogen with progestin trial (HR, 1.24 [95% CI, 1.00–1.54]).[208] However, secondary analysis of WHI data suggested that women starting hormone therapy within 10 years from the onset of menopause had a reduced risk of coronary heart disease compared with those who started later.[209] Neither breast cancer[210] nor coronary heart disease[211] were increased among estrogen users in the estrogen alone trial.

Thromboembolic events were significantly elevated among estrogen users compared to placebo in both trials,[212, 213] similar to results from raloxifene trials (**Table 9**). Risks for strokes were also higher in estrogen users for both trials,[158, 214] although the level of significance varied if using nominal versus adjusted confidence intervals. Estrogen with progestin did not increase risk for endometrial cancer[215] and reduced risk for colon cancer[212] compared to placebo. Women using estrogen alone had similar all cause death and colon cancer outcomes as women using placebo.[158]

CHAPTER 4. DISCUSSION

Summary of Review Findings

Table 10 summarizes the evidence reviewed for this update, and an outcomes table providing an illustration of the clinical application of the evidence is described in **Table 11** and **Figure 2** and **Figure 3**. No RCTs evaluated the overarching questions of the effectiveness and harms of screening for osteoporosis in reducing fractures and fracture-related outcomes for postmenopausal women and men. Therefore, no direct evidence that screening improves outcomes is available. Support for population screening would be based on evidence that individual risk for fracture can be estimated and fractures can be significantly reduced for those at risk.

Although many different risk-assessment instruments have been developed and tested, most include similar variables, such as age and weight. Studies that report AUC estimates for validated instruments demonstrate that they are modest predictors of low bone density or fracture, and simpler models perform as well as more complex ones, such as FRAX. No studies determined the effectiveness of these instruments in improving fracture outcomes.

Data from large population-based cohorts indicate that the predictive performance of DXA is similar for men and women. Calcaneal QUS using various types of devices can predict fractures of the femoral neck, hip, or spine in men and women, although variation exists across studies. Quantitative ultrasound has low correlation with DXA, and it is not clear how QUS can be used to select individuals for medications that were proven efficacious on the basis of DXA criteria.

Data are lacking to determine how frequently to obtain bone measurements, although one study indicated no advantage to repeated measures that were 8 years apart.[138]

No trials of medications report effects on fracture-related morbidity and mortality. For postmenopausal women, bisphosphonates, parathyroid hormone, raloxifene, and estrogen reduce primary vertebral fractures. Bisphosphonates significantly reduce nonvertebral fractures in sensitivity analyses that used alternative pooling methods or broadened our definition of primary prevention—consistent with meta-analyses of secondary prevention trials of alendronate and risedronate.[161, 162] Estrogen also reduces nonvertebral fractures in trials when using unadjusted estimates, but results are not statistically significant when estimates are adjusted. In the only primary prevention trial that stratified results according to baseline BMD, benefits were only observed in patients with T-scores $\leq$-2.5.[50] For men, no primary prevention trials of bisphosphonates exist, and results from a single trial of parathyroid hormone did not reach statistical significance.

Trials and safety reviews have not supported consistent associations with serious upper gastrointestinal adverse events, atrial fibrillation, or osteonecrosis of the jaw in otherwise healthy patients taking bisphosphonates for fracture prevention. The FDA has recently highlighted case reports of esophageal cancer and severe musculoskeletal pain. An analysis of data from three trials published after our searches found no association between bisphosphonate use and atypical fractures of the subtrochanteric of diaphyseal femur, with an event rate of 2.3 per 10,000 patient-years.[216] Evidence on harms associated with calcitonin and parathyroid hormone for treatment of osteoporosis is limited. Raloxifene and estrogen with and without progestin increase thromboembolic events; estrogen with and without progestin increases stroke; and estrogen with progestin increases coronary heart disease among older users and breast cancer.

Limitations

Osteoporotic fractures result from several factors, and this review is limited by its focus on only some of them. Consideration of vision, physical function, risk for falls, and secondary causes of osteoporosis, for example, is also important in reducing fractures. However, these conditions are beyond the scope of this review.

Studies of risk-assessment instruments are limited by their lack of inclusion of men, and for many, by their study designs (cross-sectional analysis, consecutive rather than population-based recruitment). Several instruments include history of previous fracture, which is more relevant to case-finding than screening. Comparing AUC estimates of instruments is an imprecise method, and may not lend itself as the best method for assessing which instrument has better discriminate ability.

Studies of DXA and peripheral bone measurement tests are limited by their study designs and use of various measures. In general, however, the large population-based prospective studies provide a good method for evaluating the predictive performance of these tests. Studies that report both men and women and adjust for important confounders are the most robust. The consistency of findings across studies also attests to the reliability of the results. The biggest

limitation relates to the applicability of estimates derived from populations to an individual in a clinical setting.

Trials of drug therapies vary in size, duration, quality, and applicability. The most important limitations to this evidence include the lack of primary prevention trials and trials that enroll men or enroll patients with mild bone loss (i.e., baseline BMD T-scores between -10 and -2.5). Applying the results of clinical trials to patient care is especially difficult when selection criteria are rigid and study subjects do not represent the community population. This is particularly true in older populations where co-morbidities and use of multiple medications are common would disqualify them for most RCTs.

Future Research

Future research needs to focus on critical evidence gaps. Trials of the efficacy and harms of screening in reducing fractures and fracture-related outcomes are needed. Initial studies of screening effects support a benefit, but require collaborative evidence from large RCTs.[217–221] In addition, studies about acceptability and barriers to screening and treatment, harms, optimal intervals, and starting and stopping ages would inform screening approaches. Screening will most likely detect many individuals with secondary causes of osteoporosis or prior fragility fractures who were not appropriately identified previously. Although they are not part of the true screening pool, identifying them and initiating appropriate management is important also. Studies capturing this aspect of detection would also be useful. Research that includes all types of interventions would provide a more comprehensive approach to fracture prevention. These include not only drug therapies, but also functional assessment, safety evaluations, vision examinations, nutrition, and others. Fracture registries that track individuals over time would be useful in determining effective prevention approaches, and evaluate if screening-detected individuals benefit over the long-term compared to those not screened.

Conclusions

Osteoporosis and osteoporosis-related fractures are common in aging men and women in the United States. Fractures cause premature mortality, loss of independence and function, reduced quality of life, and substantial financial costs. Although methods to identify individuals with increased risk for osteoporotic fractures are available, and medications to reduce fractures are effective, no trials directly evaluate screening effectiveness, harms, and intervals.

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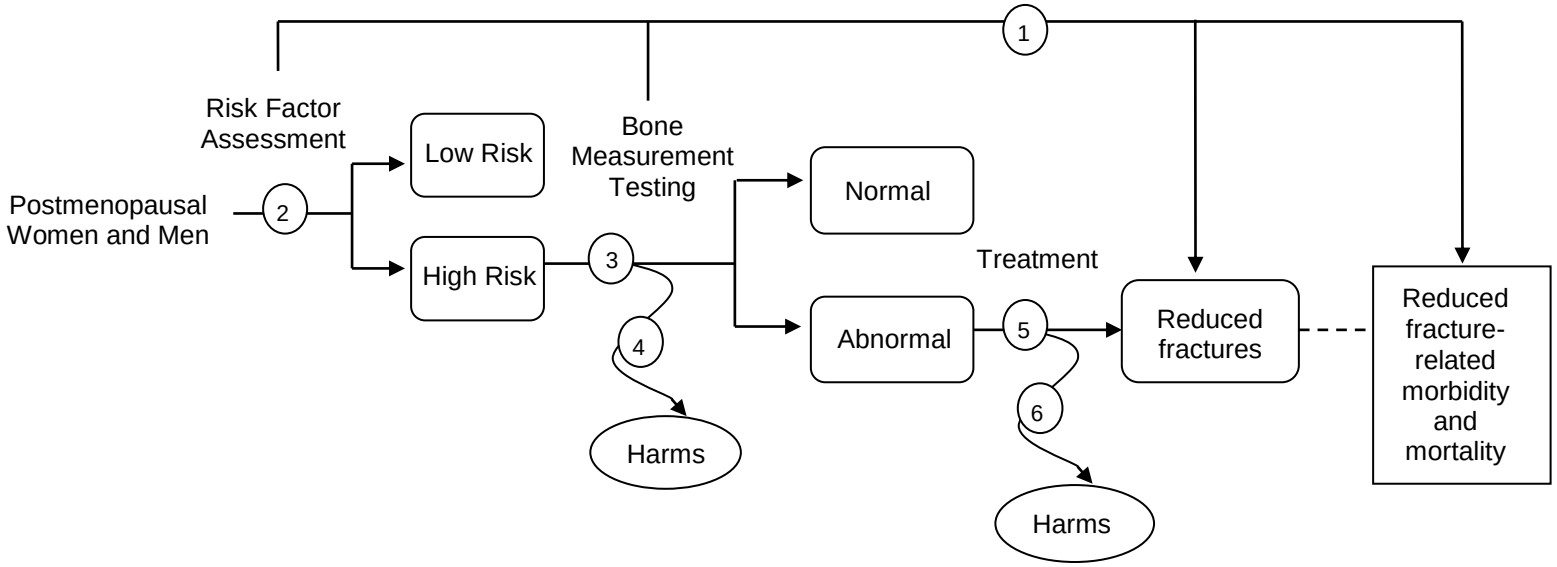
Figure 1. Analytic Framework and Key Questions



KEY QUESTIONS

1. Does screening for osteoporosis and low bone density reduce osteoporosis-related fractures and/or fracture-related morbidity and mortality in:
   a. Women
   - Postmenopausal women younger than age 60 years.
   - Age 60–64 years at increased risk for osteoporotic fractures.
   - Age 60–64 years not at increased risk for osteoporotic fractures.
   - Over age 65 years.

   b. Men over age 50 years
2. What valid and reliable risk assessment instruments stratify women and men into risk categories for osteoporosis or fractures?
3. a. How well does dual-energy x-ray absorptiometry (DXA) predict fractures in men?
   b. How well do peripheral bone measurement tests predict fractures?
   c. What is the evidence to determine screening intervals for osteoporosis and low bone density?
4. What are the harms associated with osteoporosis screening?
5. Do medications for osteoporosis and low bone density reduce osteoporosis-related fracture rates and/or fracture-related morbidity and mortality in the target populations?
6. What are the harms associated with medications for osteoporosis and low bone density?

Figure 2. Number of Women Needed to Screen to Prevent One Fracture in 5 Years

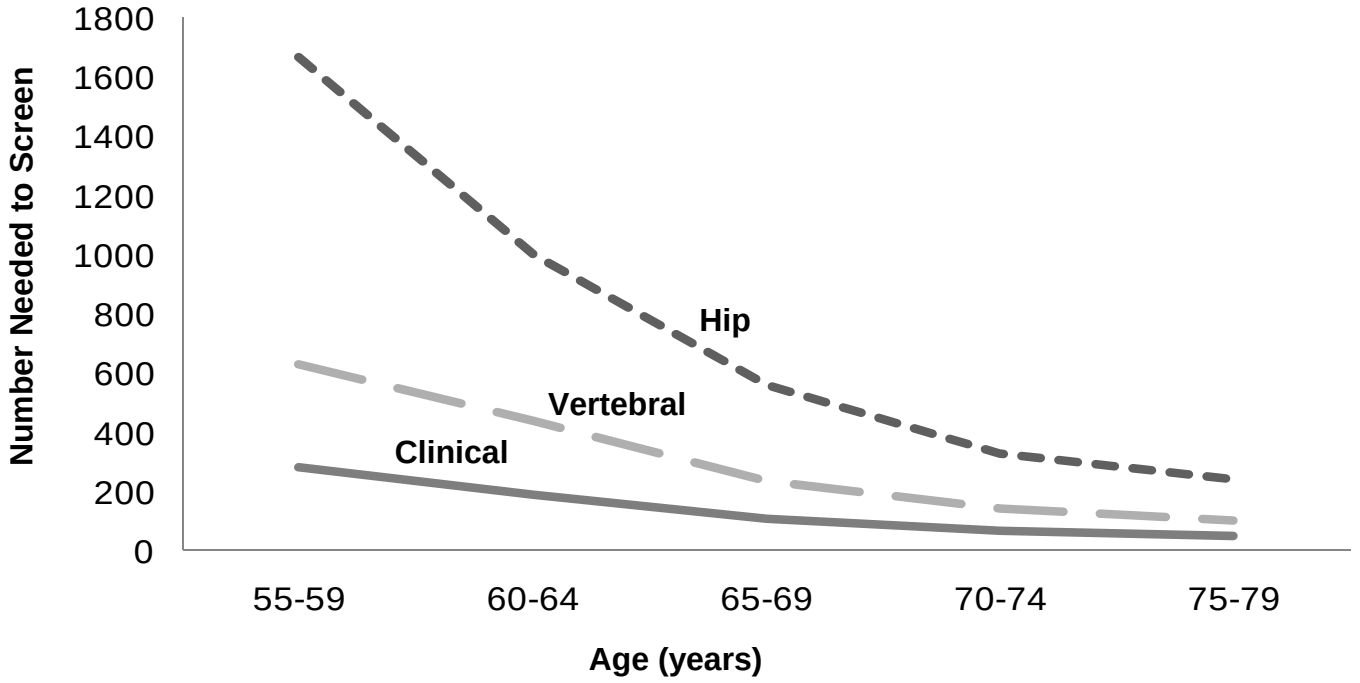


Figure 3. 10-year Risks for Major Osteoporotic and Hip Fractures for Women from the FRAX Calculator

	Age (years)								
Risk Factor	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**
Risk for Osteoporotic Fracture - none or one risk factor									
None	3.7	5.7	7.6	9.3	12.0	15.0	20.0	23.0	20.0
Low BMI*	3.8	5.9	7.9	9.8	12.0	16.0	22.0	24.0	21.0
Parent had hip fracture	7.3	11.0	15.0	18.0	18.0	25.0	34.0	39.0	35.0
Current smoker	3.9	6.0	8.1	10.0	13.0	16.0	22.0	25.0	21.0
Daily alcohol use†	4.4	6.9	9.1	11.0	14.0	19.0	25.0	28.0	25.0
Risk for Hip Fracture - none or one risk factor									
None	0.2	0.4	0.7	1.2	2.4	4.6	7.6	9.4	8.7
Low BMI	0.3	0.6	1.0	1.9	3.6	6.8	11.0	13.0	12.0
Parent had hip fracture	0.3	0.5	0.9	1.6	5.0	15.0	24.0	29.0	26.0
Current smoker	0.3	0.5	1.0	1.8	3.5	6.5	11.0	13.0	11.0
Daily alcohol use	0.3	0.5	1.0	1.9	3.6	6.9	11.0	14.0	13.0
Risk for Osteoporotic or Hip Fracture - >one risk factor									
Low BMI + parent hip fracture	7.4/0.4	11.0/0.7	15.0/1.4						
Low BMI + smoker	4.0/0.5	6.2/0.8	8.5/1.5						
Low BMI + daily alcohol	4.5/0.5	7.1/0.8	9.6/1.6						
Parent hip fracture + smoker	7.6/0.4	12.0/0.7	15.0/1.3						
Parent hip fracture + daily alcohol	8.7/0.4	13.0/0.7	17.0/1.3						
Current smoker + daily alcohol	4.6/0.4	7.2/0.8	9.8/1.5						
Low BMI + parent hip fracture + smoker	7.8/0.6	12.0/1.1	16.0/2.0						
Low BMI + parent hip fracture + alcohol	8.8/0.6	14.0/1.1	18.0/2.1						
Low BMI + smoker + alcohol	4.9/0.7	7.6/1.3	10.0/2.3						
Parent hip fracture + smoker + alcohol	9.1/0.6	14.0/1.1	18.0/2.0						
All 4 risk factors	9.3/0.9	14.0/1.7	19.0/3.1						

Abbreviations: BMI = body mass index; FRAX = online risk calculator (http://www.shef.ac.uk/FRAX/).

*Normal BMI=25.0 kg/m^2 based on average height 163 cm (64 in.), weight 66.5 kg (147 lbs). Low BMI=22.1 kg/m^2 based on average height (163 cm (64 in.), weight 56.7 kg (125 lbs).

†Daily alcohol use of 3 or more units/day (approximately 3 oz.).

Table 1. Recommendations of Other Groups

Organization, year	Population	Recommendations	Basis for recommendation
Association of Clinical Endocrinologists (AACE), 2003[222]	Post-menopausal women	**Indications for BMD Testing:** 1. All women age ≥65 years. 2. All adult women with a history of one or more fractures not caused by severe trauma, such as a motor vehicle accident. 3. Younger postmenopausal women who have clinical risk factors for fractures (low body weight <57.6 kg [127 lb], or a family history of spine or hip fracture)	Combination of evidence-based and expert opinion
American Association of Family Physicians (AAFP), 2002[223]	Post-menopausal women	1. Routinely screen women age ≥65. 2. Routinely screen women age ≥60 at increased risk for osteoporotic fractures.	Evidence-based
American College of Physicians (ACP), 2008[224]	Asymptomatic men	1. Periodically perform individualized assessment of risk factors for osteoporosis in older men (Grade: strong recommendation; moderate-quality evidence). 2. Obtain DXA testing for men who are at increased risk for osteoporosis and are candidates for drug therapy (Grade: strong recommendation; moderate-quality evidence).	Evidence-based
International Society of Clinical Densitometry (ISCD), 2007[225]	Men and post-menopausal women	**Indications for BMD Testing:** 1. Women age ≥65. 2. Postmenopausal women age <65 with risk factors for fracture. 3. Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication use. 4. Men age ≥70. 5. Men age <70 with clinical risk factors for fracture. 6. Adults with a fragility fracture. 7. Adults with a disease or condition associated with low bone mass or bone loss. 8. Adults taking medications associated with low bone mass or bone loss. 9. Anyone being considered for pharmacologic therapy for osteoporosis. 10. Anyone being treated for osteoporosis, to monitor treatment effect. 11. Anyone not receiving therapy in whom evidence of bone loss would lead to treatment. 12. Women discontinuing estrogen should be considered for bone density testing according to the indications listed above.	Evidence-based

Table 1. Recommendations of Other Groups

Organization, year	Population	Recommendations	Basis for recommendation
National Institutes of Health (NIH), 2000[226]	Men and post-menopausal women	BMD should be considered in patients receiving glucocorticoid therapy for 2 months or more and patients with other conditions that place them at high risk for osteoporotic fracture. However, the value of universal screening, especially in perimenopausal women, has not been established.	Combination of evidence-based and expert opinion
National Osteoporosis Foundation (NOF), 2008[227]	Men age >50 and post-menopausal women	1. Women age ≥65 and men age ≥70, recommend BMD testing. 2. Postmenopausal women and men age 50-70, recommend BMD testing when you have concern based on their risk factor profile. 3. Recommend BMD testing to those who have suffered a fracture, to determine degree of disease severity.	Combination of evidence-based and expert opinion
Royal College of Physicians (RCP), 2000[228]	Men and post-menopausal women	BMD testing by DXA (at the hip and/or spine) for those at high risk, with previous fragility fracture, or frail/increased fall risk.	Evidence-based
United Kingdom National Screening Committee (UKNSC), 2006[229]	Post-menopausal women	Does not recommend screening.	Evidence-based
WHO, 2008 World Health Organization (WHO), 2008[230]	Men and women ages 40-90 years	DXA and an assessment tool for case-finding high risk individuals (FRAX™) should be used to evaluate fracture risks of men and women.	Evidence-based

Abbreviations: BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry.

Table 2. Performance of Externally Validated Risk-Assessment Instruments That Report AUC*

Instrument or Study, Year (References)	Studies, *n*	Participants, *n*	Components	Range of AUC (95% CI)†
Instruments that predict low bone density‡				
ABONE[56]	1	2,365	Age, weight, estrogen use	0.72 ± 0.02
Body weight[56, 57, 61, 62, 69, 70]	6	9,065	Weight <70 kg	0.13–0.79
DOEScore[74]	1	1,256§	Age, weight, previous fracture	0.75
Gnudi et al, 2005[65]	1	1,187§	Weight, age at menarche, years since menopause, uses arms to rise from seated position, previous fracture, mother had fracture	0.74
Masoni et al, 2005[71]	1	195§	BMI, >10 years since menopause, calcium intake <1200 mg/day, previous fracture, kyphosis	0.83 (0.76–0.91)
MORES[81]	1	2,995§	Age, weight, history of COPD	0.84 (0.81–0.87)
NOF Guideline[56, 62, 72]	3	3,092	Age, weight, previous fracture, age >40 years, current smoker, parent had hip, wrist, or spine fracture, age ≥50 years	0.60–0.70
OPERA[79]	1	1,522	Age, weight, previous fracture, early menopause, systemic glucocorticoid use	Femoral neck, 0.81 (0.79–0.83); lumbar spine, 0.87 (0.85–0.88)
ORAI[56, 57, 60-62, 66, 67, 70, 72, 77]	10	11,093	Age, weight, current estrogen use	0.32–0.84
OSIRIS[61, 67, 70, 73, 80]	5	2,657	Age, weight, current estrogen use, previous fracture	0.63–0.80
OST[52, 61, 62, 66, 67, 69, 70, 76, 77, 82]	10	13,825§	Age, weight	0.33–0.89

Table 2. Performance of Externally Validated Risk-Assessment Instruments That Report AUC*

Instrument or Study, Year (References)	Studies, *n*	Participants, *n*	Components	Range of AUC (95% CI)†
SCORE[53, 54, 56, 60, 61, 66, 67, 72, 77]	9	13,710	Age, weight, race, rheumatoid arthritis, estrogen use, fracture age >46 years	0.66–0.87
SOF[54]	1	416	Age, current weight less than weight at age 25 years, and 13 additional variables‖	0.54 (0.48–0.60)
SOFSURF[61]	1	208	Age, weight, smoking status, previous postmenopausal fracture	0.72 (0.77–0.67)
Instruments that predict fracture				
ABONE[115]	1	469	Age, weight, estrogen use	Any fracture, 0.63 (0.54-0.71)
Body weight <70 kgs (154 lbs)[115]	1	469	Weight	Any fracture, 0.60 (0.52–0.68)
DOEScore[74]	1	1,256§	Age, weight, previous fracture	0.48
EPESE[90]	1	7,654§	Age >75 years, BMI, female, white, previous stroke, cognitive, ADL or vision impairments, antiepileptic drug use	Any fracture, 0.64–0.69; hip fracture, 0.76–0.79
Fracture index (SOF)[88]	1	14,461§	Age, weight, fracture age >50 years, mother had hip fracture age >50 years, weight ≤57 kgs (125 lbs, current smoker, uses arms to rise from seated position, total hip BMD T-score	Hip fracture, 0.71 with BMD; 0.77 without BMD
FRAX[96, 98, 104, 113]	4	286,499§	Age, BMI, previous fracture, family history of fracture, glucocorticoid use, current smoker, alcohol use 3 units/day or more, rheumatoid arthritis, hip BMD T-score if available	Osteoporotic fracture, 0.54–0.78; hip fracture, 0.65–0.81
Garvan nomogram[113]	1	200	Age, sex, femoral neck BMD, body weight, history of fractures age >50 years, history of falls within the previous 12 month	0.76–0.84

Table 2. Performance of Externally Validated Risk-Assessment Instruments That Report AUC*

Instrument or Study, Year (References)	Studies, *n*	Participants, *n*	Components	Range of AUC (95% CI)†
Minimum data set[100]	1	1,427§	Age, weight, height, locomotion, recent fall, ADL score, cognition score, urinary incontinence	Any fracture, 0.63 (0.55–0.71)
ORAI[115]	1	469	Age, weight, current estrogen use	Any fracture, 0.65 (0.57–0.73)
QFracture[103]	1	3,633,812§	Age, BMI, estrogen use, smoking status, daily alcohol use, parental history of osteoporosis¶, rheumatoid arthritis, cardiovascular disease, type 2 diabetes, asthma, tricyclic antidepressants, corticosteroids, history of falls, menopausal symptoms¶ , chronic liver disease, gastrointestinal malabsorption¶	Any fracture, 0.86–0.89
WHI[112]	1	161,808§	Age, weight, self-reported health, height, fracture age ≥55 years, race, physical activity, smoking status, parent had hip fracture, corticosteroid or hypoglycemic agent use	Hip fracture, 0.80 (0.75–0.85) with BMD; 0.71 (0.66–0.76) without BMD

Abbreviations: ABONE = age, body size, no estrogen; ADL = activities of daily living; AUC = area under the curve; BMD = bone mineral density; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DOEScore = Dubbo Osteoporosis Epidemiology Study; EPESE = Established Populations for the Epidemiologic Study of the Elderly; MORES = male osteoporosis risk estimation score; NOF = National Osteoporosis Foundation; OPERA = osteoporosis prescreening risk assessment; ORAI = osteoporosis risk assessment instrument; OSIRIS = osteoporosis index of risk; OST = osteoporosis self-assessment tool; RR = risk ratio; SCORE = simple calculated osteoporosis risk estimation; SOF = Study of Osteoporotic Fractures; SOFSURF = Study of Osteoporosis Fractures—Study Utilizing Risk Factors; WHI = Women's Health Initiative.

* Includes studies of externally validated instruments reporting performance measures with AUC estimates.
† Where provided or calculated for individual study results.
‡ Bone mineral density T-score of −2.5 or less.
§ Includes both derivation and validation cohorts.
|| Additional variables include first-degree relative who had a hip fracture; previous fracture age >50 y; no walking for exercise; uses arms to rise from seated position; current use of benzodiazepine, anticonvulsants, or corticosteroids; resting pulse >80 beats/min; on feet <4 h/d; diagnosed with dementia; not using menopausal hormone therapy; height ≥5'7" at age 25 y; race other than black.
¶ Variables used for calculating QFracture score for women but not for men.

Table 3. Results of the Rotterdam Study of DXA and Fractures in Men and Women

Type of Fracture	Men Age-adjusted Hazard Ratios* (95% CI)	Women Age-adjusted Hazard Ratios* (95% CI)
All nonvertebral†	1.4 (1.2 to 1.6)	1.5 (1.4 to 1.6)
Wrist	1.6 (1.0 to 2.6)	1.5 (1.3 to 1.8)
Hip	2.3 (1.6 to 3.3)	2.1 (1.7 to 2.5)
Vertebral‡	1.8 (1.3 to 2.4)	1.9 (1.6 to 2.4)

Abbreviations: CI= confidence interval; DXA = dual energy x-ray absorptiometry.

*Per gender-specific standard deviation reduction in femoral neck BMD.
†Nonvertebral fracture results from Schuit et al, 2004.[123]
‡Vertebral fracture results from Van der Klift et al, 2002.[124]

Table 4. Recent Studies Comparing Performance of Bone Measurement Tests in Predicting Fractures

Study (reference)	Participants, *n*	Type of fracture	Bone measurement test	AUC (95% CI or SE)	RR for fracture (95% CI)*	
Women†						
Hans et al, 1996[129]	5662	Hip	DXA femoral neck QUS BUA QUS SOS	Not reported	1.9 (1.6-2.4)‡ 2.0 (1.6-2.4) 1.7 (1.4-2.1)	
Bauer et al, 1997[130]	6189	Nonvertebral; hip	DXA femoral neck SXA calcaneus QUS BUA	Not reported	1.3 (1.1-1.5)§ 1.4 (1.2-1.6) 1.3 (1.2-1.5)	2.6 (1.9-3.8)§ 2.2 (1.9-3.0) 2.0 (1.5-2.7)
Khaw et al, 2004[131]	8328	All	QUS BUA QUS SOS	Not reported	1.90 (1.36-2.66) 1.62 (1.26-2.08)	
Alexander et al, 2005[132]	1034	All	DXA spine DXA femoral neck DXA distal radius QUS SOS QUS UBPI	0.60 (0.56-0.65) 0.66 (0.62-0.71) 0.64 (0.59-0.68) 0.60 (0.56-0.65) 0.60 (0.55-0.64)	1.35 (1.19-1.54) 1.81 (1.51-2.16) 1.47 (1.28-1.68) 1.26 (1.12-1.42) 1.55 (1.26-1.90)	
Gluer et al, 2005[231]	87	Vertebral	DXA spine QUS SOS QUS BUA QUS stiffness	Not reported	2.13 (1.08-4.16) 2.58 (1.17-5.68) 2.13 (1.04-4.34) 2.83 (1.26-6.34)	
Stewart et al, 2006[134]	775	All	DXA lumbar spine DXA femoral neck QUS BUA	0.63 (0.60-0.67) 0.59 (0.56-0.63) 0.62 (0.59-0.66)	1.80 (1.17-2.77) 2.16 (1.35-3.47) 2.25 (1.51-3.34)	
Frediani et al, 2006[135]	1534	Vertebral	DXA spine DXA femoral neck QUS stiffness QUS stiffness + DXA spine QUS stiffness + DXA fem neck	0.95 (0.3) 0.89 (0.3) 0.93 (0.4) 0.97 (0.2) 0.95 (0.3)	4.18 (3.05-6.82)‖ 3.13 (2.76-6.90) 4.18 (3.35-7.13)	

Table 4. Recent Studies Comparing Performance of Bone Measurement Tests in Predicting Fractures

Study (reference)	Participants, *n*	Type of fracture	Bone measurement test	AUC (95% CI or SE)	RR for fracture (95% CI)*	
Men						
Mulleman et al, 2002[126]	102	All	DXA lumbar spine	0.80 (0.71-0.88)	2.8 (1.6-5.0)¶	
			DXA femoral neck	0.73 (0.64-0.82)	1.9 (1.1-3.2)	
			DXA hip	0.81 (0.71-0.88)	3.4 (1.6-7.0)	
			QUS BUA	0.69 (0.60-0.78)	1.6 (1.0-2.4)	
			QUS SOS	0.75 (0.66-0.83)	2.3 (1.4-3.6)	
			QUS stiffness	0.74 (0.65-0.83)	2.1 (1.3-3.3)	
Khaw et al, 2004[131]	6471	All	QUS BUA	Not reported	1.87 (1.23-2.86)#	
			QUS SOS		1.65 (1.17-2.33)	
Gonnelli et al, 2005[127]	407	All	DXA hip	Not reported	3.4 (2.5-4.8)	
			QUS stiffness		3.2 (2.3-4.5)	
			Combined		6.1 (2.6-14.3)	
Varenna et al, 2005[136]	4832	Nonvertebral; hip	QUS BUA	Not reported	1.38 (1.22-1.59)**	2.24 (1.61-3.08)**
			QUS SOS		1.27 (1.17-1.38)	2.19 (1.56-3.11)
			QUS stiffness		1.14 (0.96-1.40)	1.71 (1.18-3.24)
Bauer et al, 2007[128]	5608	Nonvertebral; hip	DXA femoral neck	Not reported	1.6 (1.4-1.9)§	3.5 (2.5-4.9)§
			DXA hip		1.6 (1.4-1.9)	2.9 (2.2-4.0)
			QUS BUA		1.6 (1.4-1.8)	2.0 (1.5-2.8)
			QUS SOS		1.6 (1.4-1.9)	2.2 (1.6-3.1)
			QUS QUI		1.6 (1.4-1.9)	2.2 (1.6-3.1)

Abbreviations: AUC = area under receiver operating characteristic curve; BMD = bone mineral density; BUA = broadband ultrasound attenuation; CI = confidence interval; DXA = dual energy x-ray absorptiometry; QUI = quantitative ultrasound index (combines BUA and SOS); QUS = quantitative ultrasound measured at the calcaneus in all studies; RR = risk ratio; SOS = speed of sound; SXA = single x-ray absorptiometry; UBPI = ultrasound bone profile index.

*For studies reporting more than one type of fracture, results for the first type are provided first, then results for the second type.
†Adapted from Canadian Agency for Drugs and Technologies in Health Technology Report, Issue 94, December 2007. Data from EPIDOS (Hans et al, 1996[129]) and SOF (Bauer et al, 1997[130]) included for completeness.
‡Per standard deviation reduction in BMD or QUS measure, adjusted for age, weight, and clinic center.
§Per standard deviation reduction in BMD or QUS measure, adjusted for age and clinic.
‖Adjusted for years of menopause, weight, height, and BMI.
¶ Per standard deviation reduction in BMD or QUS measure.
# Per standard deviation reduction in QUS measure, adjusted for age, prior fracture, smoking status, weight, and height.
**Per standard deviation reduction in QUS measure, adjusted for age, weight, calcium intake, current smoking, regular walking outside, bedridden periods >2 months.

Table 5. Placebo-controlled Primary Prevention Trials of Medications

Study (references)	Participant characteristics	Intervention; duration	Fracture rates (drug; placebo); RR (95% CI)			Quality rating
			Vertebral	Nonvertebral	Hip	
Bisphosphonates*						
Alendronate						
Ascott-Evans et al, 2003[139]†	Postmenopausal women age <80 years with 85% of enrollees <65 years; mean T-score -2.3; no prior fractures	Alendronate 10 mg/day; 1 year	0/95; 0/47 RR not estimable	0/95; 0/47 RR not estimable	NR	Fair
Chesnut et al, 1995[140]‡	Women at least 5 years postmenopausal; age 43-75 with mean age 63 years; mean hip T-score -1.1; no prior fractures	Alendronate 10 mg/day; 2 years	0/30; 0/31 RR not estimable	Unclear	NR	Fair
Fracture Intervention Trial (FIT), 1998[50, 232]‡	Women at least 2 years postmenopausal; mean age 67.7 years; mean T-score -2.2; no prior fractures	Alendronate 5 mg/day; 2 years, then 10 mg; 2 years	43/2214; 78/2218 0.55 (0.38-0.80)	261/2214; 294/2218 0.89 (0.76-1.04)	19/2214; 24/2218 0.79 (0.44-1.44)	Good
Dursun et al, 2001[141]‡	Postmenopausal women mean age 61.2 years; mean T-score -1.5; prior fracture unknown	Alendronate 10 mg/day; 1 year	12/51; 14/50 0.84 (0.43-1.63)	NR	NR	Poor
Hosking et al, 1998[142]	Women ≥6 months postmenopausal; mean age 53.3 years; mean T-score -0.1; prior fracture unknown	Alendronate 5 mg/day; 2 years	0/498; 0/502§ RR not estimable	22/498;14/502§ 1.58 (0.82-3.06)	NR	Fair
Liberman et al, 1995[47]‡	≥5 years postmenopausal; mean age 64 years; mean T-score -2.2; 21% with prior vertebral fracture	Alendronate 10 mg/day; 3 years	4/384; 5/253§ 0.53 (0.14-1.94)	NR	NR	Fair
Pols et al, 1999[143]	Women ≥3 years postmenopausal; mean age 63.0 years; mean T-score -2.0; unknown prior fracture	Alendronate 10 mg/day; 1 year	Not assessed	19/950; 37/958 0.52 (0.30-0.89)	2/950; 3/958 0.67 (0.11-4.01)	Fair

Table 5. Placebo-controlled Primary Prevention Trials of Medications

Study (references)	Participant characteristics	Intervention; duration	Fracture rates (drug; placebo); RR (95% CI)			Quality rating
			Vertebral	Nonvertebral	Hip	
Etidronate						
Herd et al, 1997[144]‡	Women 1-10 years postmenopausal; mean age 54.8 years; mean T-score -1.3; no prior fracture	Cyclical etidronate 400 mg/day; 2 years	0/75; 0/77 RR not estimable	NR	NR	Fair
Meunier et al, 1997[145]‡	Women 6-60 months postmenopausal; mean age 52.7 years; mean T-score -1.1; unknown prior fracture	Cyclical etidronate 400 mg/day; 2 years	1/27; 0/27 3.00 (0.13-70.53)	2/27; 3/27 0.67 (0.12-3.68)	NR	Fair
Pouilles et al, 1997[146]†	Women 6-60 months postmenopausal; mean age 53.8 years; mean T-score -0.8; unknown prior fracture	Cyclical etidronate 400 mg/day; 2 years	1/54; 0/55 3.05 (0.13-73.37)	1/54; 6/55 0.51 (0.13-1.93)	NR	Fair
Risedronate						
Hooper et al, 2005[147]‡	Women 6-36 months postmenopausal; mean age 53 years; mean T-score -0.7; unknown prior fracture	Risedronate 5 mg/day; 2 years	10/129; 10/125 0.97 (0.42-2.25)	5/129; 6/125 0.81 (0.25-2.58)	NR	Fair
McClung et al, 2001[41]	Mean age 74 years; mean T-score -3.7; some women with prior fracture, results reported for women with no baseline fracture (43% of enrollees)	Risedronate 2.5 or 5 mg/day; 3 years	NR	NR	14/1773; 12/875 0.58 (0.27 to 1.24)	Fair
Mortensen et al, 1998[148]‡	Women 6-60 months postmenopausal; mean age 51.5 years; mean T-score -1.1; unknown prior fracture	Risedronate 5 mg/day; 2 years treatment (follow-up 3 years)	1/37; 0/36 0.97 (CI 0.90-1.05)	0/37; 3/36 0.14 (0.01-2.60)	0/37; 0/36 RR not estimable	Fair

Table 5. Placebo-controlled Primary Prevention Trials of Medications

Study (references)	Participant characteristics	Intervention; duration	Fracture rates (drug; placebo); RR (95% CI)			Quality rating
			Vertebral	Nonvertebral	Hip	
Valimaki et al, 2007[149]†	Women ≥5 years postmenopausal; osteoporosis risk factors or low hip BMD; mean age 65.9 years; mean T-score -1.2; unknown prior fracture	Risedronate 5 mg/day; 2 years	0/114; 0/56 RR not estimable	2/114; 2/56 0.49 (0.07-3.40)	0/114; 0/56 RR not estimable	Fair
Zoledronic acid						
Reid et al, 2002[150]†‡	Women ≥5 years postmenopausal; mean age 64.2 years; mean T-score -1.2; no prior vertebral fracture	Zoledronic acid 4 mg over 1 year in 1 to 4 infusions for 3 years	0/174; 0/56 RR not estimable	4/174; 1/59 1.36 (0.15-11.89)	NR	Fair
Parathyroid hormone						
Greenspan et al, 2007[151]‡	Postmenopausal with mean age 64.4 years; T-score ≤ -3.0 and no prevalent vertebral fractures or T-score -2.5 with 1 to 4 vertebral fractures; mean T-score -2.2; 19% with prior vertebral fracture	Parathyroid hormone 100 µg daily injection; 18 months	7/1050; 21/1011 0.32 (0.14-0.75) For those without baseline fracture	72/1286; 72/1246 0.97 (0.71-1.33) For all participants	NR	Fair
Orwoll et al, 2003[159]‡	Men with mean age 59 years; mean T-score -2.7; unknown prior fracture	Teriparatide 20 or 40 µg daily injection; 11 months	NR	2/151 (20 ug); 1/139 (40 ug); 3/147 (placebo)	NR	Good

Table 5. Placebo-controlled Primary Prevention Trials of Medications

Study (references)	Participant characteristics	Intervention; duration	Fracture rates (drug; placebo); RR (95% CI)			Quality rating
			Vertebral	Nonvertebral	Hip	
Selective Estrogen Receptor Modulators						
Multiple Outcomes of Raloxifene Evaluation (MORE), 1999, 2002, 2005[152, 153, 233]‡	Postmenopausal women; median age 66.9 years; mean femoral neck or lumbar spine T-score -2.57; 37% with prior vertebral fractures	Raloxifene 60 or 120 mg/day; 4 years	169/2259 (60 mg); 159/2277 (120 mg); 287/2292 (placebo)‖ 0.64 (0.63-0.76) (60 mg) 0.57 (0.48-0.69) (120 mg)	548/4536 (both doses combined); 296/2292 0.93 (0.81-1.06)	56/4536 (both doses combined); 29/2292 0.97 (0.62-1.52)	Good
Raloxifene Use for the Heart (RUTH), 2006, 2008[154, 234]†‡	Postmenopausal women with heart disease or risk factors; median age 67.5 years; unknown prior fracture	Raloxifene 60 mg/day; 5.6 years	6/5044; 97/5057 0.65 (0.47-0.89)	428/5044; 438/5057 0.96 (0.84-1.09)	NR	Good
Estrogen						
Women's Health Initiative (WHI), 2003[157]†‡	Postmenopausal women; mean age 63.3 years; mean lumbar spine T-score -1.28 in subset; 14% with prior fractures after age 55	CEE 0.625 mg/day + MPA 2.5 mg/day; 5.6 years	41/8506; 60/8102 0.65 (nCI 0.46-0.92)	Wrist fracture: 189/8506; 245/8102 0.71 (nCI 0.59-0.85)	52/8506; 73/8102 0.67 (nCI 0.47-0.96); (aCI 0.41-1.10)	Fair
Women's Health Initiative (WHI), 2004[158]†‡	Postmenopausal women; mean age 63.6 years; unknown BMD; 12% with prior fracture	CEE 0.625 mg/day; 6.8 years	39/5310; 64/5429 0.62 (nCI 0.63-0.79); (aCI 0.34-1.13)	NR	38/5310; 64/5429 0.61 (nCI 0.41-0.91); (aCI 0.33-1.11)	Fair

Abbreviations: aCI = adjusted confidence interval; BMD = bone mineral density; CEE = conjugated equine estrogen; CI = confidence interval; MPA = medroxyprogesterone acetate; nCI = nominal confidence interval; NR = not reported; RR = relative risk.

*BMD T-scores for bisphosphonate trials are based on femoral neck measurements and calculated using the FRAX patch instrument, unless stated otherwise.
†Clinical vertebral fractures only.
‡Radiologically-confirmed fracture incidence.
§Subgroup of women with no prior vertebral compression fractures.
‖Figures interpolated from in-text graph.

Table 6. Fracture Outcomes of Placebo-controlled Primary Prevention Trials*

	Type of Fracture									
	Vertebral		Nonvertebral		Hip		Wrist		Ankle	
Medication	Risk ratio (95% CI)	No. trials	Risk ratio (95% CI)	No. trials	Risk ratio (95% CI)	No. trials	Risk ratio (95% CI)	No. trials	Risk ratio (95% CI)	No. trials
Bisphosphonates										
Alendronate	0.60 (0.44-0.83)[47, 50, 141]	3	0.88 (0.55-1.40)[50, 142, 143]	3	0.78 (0.44-1.38)[50, 143]	2	0.76 (0.27-2.16)[50, 143]	2	0.40 (0.08-2.07)[143]	1
Combined bisphos-phonates	0.66 (0.50-0.89)[47, 50, 141, 145-148]	7	0.83 (0.64-1.08)[50, 142, 143, 145-150]	9	0.70 (0.44-1.11)[41, 50, 143]	3	0.67 (0.25-1.82)[50, 143, 149]	3	0.33 (0.08-1.44)[143, 149]	2
Parathyroid hormone										
	Women: 0.32 (0.14-0.75)[151] Men: 0.49 (0.22-1.09)[159]	Women: 1 Men: 1	Women: 0.97 (0.71-1.33)[151] Men: 0.51 (0.10-2.48)[159]	Women: 1 Men: 1	No evidence		No evidence		No evidence	
Raloxifene										
	0.61 (0.54-0.69)[152, 154]	2	0.97 (0.87-1.09)[154, 233]	2	0.97 (0.62-1.52)[152]	1	0.83 (0.66-1.05)[152]	1	0.94 (0.60-1.47)[152]	1
Estrogen										
Estrogen with progestin†	0.66 (0.46-0.92)[157]‡	1	No evidence		0.67 (0.47-0.96)[157]	1	0.71 (0.69-0.85)[157]	1	0.71 (0.69-0.85)[157]	1
Estrogen alone§	0.62 (0.42-0.93)[158]‡	1	No evidence		0.61 (0.41-0.91)[158]	1	No evidence		No evidence	

Abbreviation: CI = confidence interval.

*Results for postmenopausal women unless otherwise indicated.
† Data presented with nominal CIs; adjusted CI for hip (0.41-1.10) and not provided for other sites.
‡ Clinical vertebral fractures.
§ Data presented with nominal CIs; adjusted CIs include: vertebral (0.34-1.13), hip (0.33-1.11).

Table 7. Sensitivity Analysis for Trials With Few, Rare, or Zero Fracture Events

	Fracture outcome				
Alternative method	**Vertebral**	**Non-vertebral**	**Hip**	**Wrist**	**Ankle**
Arcsin difference, zero event trials included	-0.03 (-0.05, 0.00)	-0.03 (-0.05, 0.00)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)	-0.03 (-0.09, 0.02)
Arcsin difference, zero event trials excluded	-0.03 (-0.06, -0.01)	-0.03 (-0.05, 0.00)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)	-0.03 (-0.09, 0.02)
Zero event trials excluded					
Mantel-Haenszel relative risk, random-effects model, constant continuity correction (added 0.5 to each arm)	0.66 (0.49-0.89)	0.83 (0.64-1.08)	0.78 (0.44-1.38)	0.67 (0.25-1.82)	0.33 (0.08-1.44)
Peto odds ratio	0.63 (0.47-0.84)	0.84 (0.72-0.98)	0.78 (0.44-1.38)	1.05 (0.78-1.41)	0.33 (0.08-1.35)
Mantel-Haenszel relative risk, fixed effects model, variable continuity correction (added inverse of the sample size in the opposite treatment arm)	0.65 (0.49-0.85)	0.86 (0.74-0.99)	0.78 (0.44-1.38)	1.03 (0.77-1.38)	0.32 (0.07-1.49)

Table 8. Summary of Fracture Risks From Published Meta-analyses of Primary and Secondary Prevention Trials of Bisphosphonates

Review	Population	Vertebral fracture	Non-vertebral fracture	Hip fracture
Alendronate Wells et al, 2008[162]	Postmenopausal women	RR 0.55 (0.45 to 0.67) I^2=0%, 4 trials	RR 0.84 (0.74 to 0.94) I^2=20%, 5 trials	RR 0.61 (0.40 to 0.92) I^2=0%, 6 trials
Alendronate Sawka et al, 2005[164]	Men	OR 0.36 (0.17 to 0.77) I^2=0, 2 trials	OR 0.73 (0.32 to 1.67) I^2=0, 2 trials	Not reported
Etidronate Wells et al, 2008[163]	Postmenopausal women	RR 0.59 (0.36 to 0.96) I^2=0%, 7 trials	RR 0.98 (0.68 to 1.42) I^2=0%, 6 trials	RR 1.20 (0.37 to 3.88) I^2=0%, 3 trials
Risedronate Wells et al, 2008[161]	Postmenopausal women	RR 0.63 (0.51 to 0.77) I^2=0%, 4 trials	RR 0.80 (0.72 to 0.90) I^2=0%, 5 trials	RR 0.74 (0.59 to 0.94) I^2=0%, 3 trials

Abbreviations: OR = odds ratio; RR = relative risk.

Table 9. Adverse Health Outcomes From Medication Studies

Adverse Outcome	Evidence (Risk Ratio; 95% CI; trials, *n**)
Bisphosphonates	
Withdrawals	No differences with placebo for alendronate[162], etidronate[163], risedronate,[161] zoledronic acid,[174, 175] and ibandronate[168, 194, 195]
Gastrointestinal events	• Mild upper gastrointestinal events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn) were associated with etidronate and pamidronate in meta-analyses of trials;[187] however, several trials were conducted before current preventive dosing measures were widely practiced and may not be relevant. No associations with alendronate, ibandronate, risedronate, or zoledronic acid • Serious events including esophageal ulcerations have been reported for all bisphosphonates, although some trials predate preventive measures[196] and another uses a noncomparable control group[197] • Esophageal adenocarcinoma was reported by the FDA in 54 cases of bisphosphonate users[199]
Atrial fibrillation	• Data from the HORIZON trial of zoledronic acid,[174] the FIT trial of alendronate,[200] and a meta-analysis of risedronate trials[190] suggest associations with severe atrial fibrillation • Observational studies of alendronate and etidronate reported conflicting results[189, 191] • A report from the FDA based on data from nearly 20,000 patients treated with bisphosphonates in placebo-controlled trials found no associations with atrial fibrillation[192]
Musculoskeletal symptoms	• Zoledronic acid was associated with increased muscular and joint pain, arthritis, and muscle cramps (4.52; 3.48-5.43; 3 trials)[187] • Severe reversible musculoskeletal pain has been reported for all bisphosphonates
Osteonecrosis of the jaw	A report from the FDA described 151 case reports of osteonecrosis of the jaw through 2003.[193] Of these, 139 occurred in cancer patients using high-dose intravenous pamidronate or zoledronic acid and 12 in patients using alendronate
Parathyroid Hormone	
Cancer	No association (0.49; 0.27-0.90; 3 trials)[187]
Mild gastrointestinal events	No association (1.39; 0.98-2.00; 2 trials)[187]
Calcitonin	
Acute coronary syndrome	No association (0.98; 0.07-13.7; 3 trials)[187]
Cancer	No association[187]
Mild gastrointestinal events	No association (0.96; 0.63-1.48; 15 trials)[187]

Table 9. Adverse Health Outcomes From Medication Studies

Adverse Outcome	Evidence (Risk Ratio; 95% CI; trials, *n**)
Raloxifene	
Thromboembolic events	Increased (1.60; 1.15-2.23; 2 trials)[156]
Coronary heart disease	No association (0.95; 0.84-1.06; 2 trials)[156]
Stroke	No association (0.96; 0.67-1.38; 2 trials)[156]
Breast cancer	Reduced risk for invasive breast cancer in older women without preexisting cancer 0.44 (0.27-0.71; 2 trials)[156]
Endometrial cancer	No association (1.14; 0.65-1.98; 2 trials)[156]
Others	Increased vasomotor symptoms and leg cramps[156]
Estrogen	
Thromboembolic events	Increased with E+P (2.06; 1.57-2.70)[212]; results for E-alone were not statistically significant when all events were combined (1.32; 0.99-1.75),[213] but were increased for DVT (1.47; 1.06-2.06) and PE (1.37; 1.12-4.40) when evaluated separately in the WHI[213]
Coronary heart disease	Increased with E+P (1.24; 1.00-1.54)[208]† but not with E-alone (0.95;0.79-1.16)[211] in the WHI. Women starting E+P within 10 years from the onset of menopause had reduced risk compared with those starting later[209]
Stroke	Increased with E+P (1.31; 1.02-1.68)[214] and E-alone (1.39; 1.10-1.77)[158]‡ in the WHI
Breast cancer	Increased with E+P (1.24; 1.01-1.54)[207] but not with E-alone (0.80; 0.62-1.04)[210] in the WHI
Endometrial cancer	No association with E+P (0.81; 0.48-1.36)[215] in the WHI
Others	Decreased colon cancer with E+P (0.54; 0.36-00.82),[235] but not E-alone (1.08; 0.75-1.55)[158] in the WHI. Increased vaginal bleeding

Abbreviations: CI = confidence interval; DVT= deep vein thrombosis; E-alone = estrogen without concomitant use of progestin; E+P = estrogen and concomitant use of progestin; FDA = U. S. Food and Drug Administration; FIT = Fracture Intervention Trial; HORIZON = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly trial; WHI = Women's Health Initiative.

*If meta-analysis.
†Adjusted CI = 0.97-1.60.
‡Adjusted CI = 0.97-1.99.

Table 10. Summary of the Evidence

Number of studies	Design	Limitations	Consistency	Applicability	Overall quality	Findings
Effectiveness and Harms of Osteoporosis Screening in Reducing Fractures, Morbidity, and Mortality (Key Questions 1 and 4)						
No trials						
Performance of Risk Assessment Instruments to Stratify Individuals into Risk Categories (Key Question 2)						
21 risk assessment instruments (in 33 articles) with BMD or fracture outcomes that reported AUC for the ROC curve and were externally validated; Subset of 64 total articles of risk assessment instruments	Cohort, cross-sectional	Most studies are cross-sectional and instruments have not been applied to a prospective clinical population	Not consistent	Difficult to apply population-determined results to individuals in a clinical setting	Fair	Although several risk instruments have been developed and validated, their performance in predicting low bone density or fracture is modest; simple models perform as well as complex ones, and none demonstrates superiority over the others.
Performance of Dual-energy X-ray Absorptiometry in Predicting Fractures in Men (Key Question 3a)						
5 studies	Prospective cohort	Few large studies include men	Consistent	Population estimates may not apply to individuals	Fair to good	DXA is not a perfect predictor, but for each standard deviation reduction in femoral neck BMD, the hazard ratio for various fracture outcomes was increased to similar levels for men and women.

Table 10. Summary of the Evidence

Number of studies	Design	Limitations	Consistency	Applicability	Overall quality	Findings
Performance of Peripheral Bone Measurement Tests in Predicting Fractures (Key Question 3b)						
5 studies in men; 7 studies in postmenopausal women; and 1 systematic review	Prospective cohort, retrospective cohort, cross-sectional	Variability in how measures were used; focus on QUS	Consistent	Population estimates may not apply to individuals	Fair to good	Calcaneal QUS can predict fractures of the femoral neck, hip, or spine, although variation exists across studies. Correlation between DXA and QUS is low.
Screening Intervals (Key Question 3c)						
1 study	Prospective cohort	Only one relevant study in postmenopausal women	Not applicable	Population estimates may not apply to individuals, particularly those different from the study cohort	Fair	Repeating a BMD measurement up to 8 years after an initial measurement did not significantly improve predictive performance for nonvertebral, hip, or vertebral fractures.
Efficacy of Medications for Reducing Osteoporosis-related Fractures (Key Question 5)						
For women: 15 trials of bisphosphonates; 1 trial of PTH; 2 trials and 1 meta-analysis of raloxifene; 2 trials of estrogen For men: 1 trial of PTH	RCTs	Strength of evidence varies by medication	Consistent	Primary prevention trials are most applicable to a screen-detected population	Poor to good	For women, bisphosphonates, PTH, raloxifene, and estrogen with or without progestin reduce vertebral fractures. Bisphosphonates reduce nonvertebral fractures in sensitivity analysis. Medications are effective for BMD T-scores ≤ -2.5. For men, one trial of PTH showed trends for reduced fractures that were not statistically significant.

Table 10. Summary of the Evidence

Number of studies	Design	Limitations	Consistency	Applicability	Overall quality	Findings
Harms Associated with Medications for Osteoporosis and Low Bone Density (Key Question 6)						
21 studies of bisphosphonates; 1 systematic review of calcitonin and PTH; 5 studies of raloxifene; 8 studies of estrogen	RCTs, observational studies, case reports and series	Strength of evidence varies by medication	Consistent	Applicable	Poor to good	Serious GI events have been reported for all bisphosphonates, but they are not associated with a higher rate of serious GI events compared to placebo in controlled studies; results are mixed for atrial fibrillation and an FDA review found no increased risk. There are case reports of osteonecrosis, severe musculoskeletal pain, and esophageal cancer, but the incidence and degree of risk are difficult to estimate. Raloxifene and estrogen increase thromboembolic events; estrogen increases stroke; estrogen with progestin increases coronary heart disease and breast cancer.

Abbreviations: AUC = area under the curve; BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; PTH = parathyroid hormone; QUS = quantitative ultrasound; RCTs = randomized controlled trials; ROC = receiver operating characteristic.

Table 11. Screening Outcomes for Women Without Prior Vertebral Fractures

Assumptions based on population estimates and results of the Fracture Intervention Trial (FIT) for women with T-score ≤ -2.5.

	Age (years)				
Variable	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**
Assumptions					
Number undergoing screening	10,000	10,000	10,000	10,000	10,000
Prevalence of osteoporosis (T-score -2.5 or less)*	0.0445	0.0650	0.1200	0.2025	0.2850
RR for clinical fracture with alendronate (95% CI 0.50-0.82)†	0.64	0.64	0.64	0.64	0.64
RR for vertebral fracture with alendronate (95% CI 0.31-0.82)†	0.50	0.50	0.50	0.50	0.50
RR for hip fracture with alendronate (95% CI 0.18-0.97)†	0.44	0.44	0.44	0.44	0.44
Outcomes, *n*					
Cases of osteoporosis identified (10,000 x prevalence)	445	650	1200	2025	2850
Clinical fractures expected with no therapy (24.50%)†	109	159	294	496	698
Clinical fractures expected with therapy (16.38%)†	73	106	197	332	467
Clinical fractures prevented	36	53	97	164	231
Vertebral fractures expected with no therapy (7.25%)†	32	47	87	147	207
Vertebral fractures expected with therapy (3.63%)†	16	24	44	74	103
Vertebral fractures prevented	16	23	43	73	104
Hip fractures expected with no therapy (2.75%)†	12	18	33	56	78
Hip fractures expected with therapy (1.25%)†	6	8	15	25	36
Hip fractures prevented	6	10	18	31	42
Number needed to screen (NNS) to prevent fractures for 5 years					
NNS to prevent one clinical fracture	278	187	103	61	43
NNS to prevent one vertebral fracture	625	435	233	137	96
NNS to prevent one hip fracture	1,667	1,000	556	323	238

Abbreviations: CI = confidence interval; FIT = Fracture Intervention Trial; RR = risk ratio.

*From Melton et al, 1992.[49]

†From results of FIT for women with BMD T-score of femoral neck -2.5 or less (Cummings et al, 1998[50]). Event rates have been recalculated for 5-years.

Appendix A. Abbreviations

Abbreviation	Definition
ABONE	age, body size, no estrogen
aCI	adjusted confidence interval
ADL	activities of daily living
AE	adverse events
AHRQ	Agency for Healthcare Research and Quality
AUC	area under the curve
AUROC	area under the receiver operating characteristic
BMD	bone mineral density
BMI	body mass index
BUA	broadband ultrasound attenuation
BW	body weight
CaMOS	Canadian Multicentre Osteoporosis Study
Cat K	Cathepsin K
CEE	conjugated equine estrogen
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
C-stress	compressive stress
DOES	Dubbo Osteoporosis Epidemiology Study
DXA	dual-energy x-ray absorptiometry
EPESE	Established Population for Epidemiology Studies of the Elderly Study
FDA	U.S. Food and Drug Administration
FIT	Fracture Intervention Trial
FN	femoral neck
GI	gastrointestinal
HAL	hip axis length
HAS	hip strength analysis
HMO	health maintenance organization
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Trial
HR	hazard ratio
HR	heart rate
HRT	hormone replacement therapy
IBIS	International Breast Cancer Intervention Study
LASA	Longitudinal Aging Study Amsterdam
LIFT	Long-Term Intervention on Fractures with Tibolone Study
LS	lumbar spine
MORES	Multiple Outcomes of Raloxifene Study
MPA	medroxyprogesterone acetate
MrOS	Osteoporotic Fractures in Men Study
nCI	nominal confidence interval
NHANES	National Health and Nutrition Examination Survey
NNS	number needed to screen
NNT	number needed to treat
NOF	National Osteoporosis Foundation
NORA	National Osteoporosis Risk Assessment Tool
NPV	negative predictive value
NR	not reported
NSABP	National Surgical Adjuvant Breast Cancer Prevention Study
OPERA	Osteoporosis Prescreening Risk Assessment
OPG	osteoprotegerin
OPRA	Osteoporosis Prospective Risk Assessment
OR	odds ratio
ORACLE	Osteoporosis Risk Assessment by Composite Linear Estimate Study
ORAI	Osteoporosis Risk Assessment Instrument
OSIRIS	Osteoporosis Index of Risk

Appendix A. Abbreviations

Abbreviation	Definition
OST	Osteoporosis Self-assessment Screening Tool
PCT	placebo-controlled trial
PIXI	Peripheral Instantaneous X-ray Imager
PPV	positive predictive value
PROOF	Prevent Recurrence of Osteoporotic Fractures Study
PTH	parathyroid hormone
QUI	quantitative ultrasound index
QUS	quantitative ultrasound
RA	rheumatoid arthritis
RCT	randomized, controlled trial
RH	relative hazard
ROC	receiver operating characteristic
RR	relative risk
RR	risk ratio
RUTH	Raloxifene Use for the Heart Trial
SCORE	Simple Calculated Osteoporosis Risk Estimation Study
SD	standard deviation
SE	standard error
SEMOF	Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk
SOF	Study of Osteoporotic Fractures Study
SOFSURF	Study of Osteoporosis Fractures—Study Utilizing Risk Factors
SOS	speed of sound
TH	total hip
UBPI	ultrasound bone profile index
VA	U.S. Department of Veterans Affairs
VOS	velocity of sound
WHI	Women's Health Initiative
WHO	World Health Organization

Appendix B1. Search Strategies

Screening

Database: *Ovid MEDLINE; Cochrane Central Register of Controlled Trials*

1 exp Osteoporosis/di, ra, ri, us
2 exp Osteoporosis/
3 exp Mass Screening/
4 screen$.mp.
5 2 and 3
6 1 and 5
7 5 or 6
8 Bone Density/
9 8 and (3 or 4)
10 7 or 9
11 exp Fractures, Bone/
12 fractur$.mp.
13 exp "Bone and Bones"/
14 12 and 13
15 11 or 14
16 10 and 15
17 limit 16 to English language
18 limit 16 to abstracts
19 17 or 18

Database: *Cochrane Database of Systematic Reviews*

1 osteoporo$.mp. or bone densit$.ti,ab.
2 screen$.ti,ab.
3 1 and 2

Screening Interval

Database: *Ovid MEDLINE; Cochrane Central Register of Controlled Trials*

1 exp Osteoporosis, Postmenopausal/ or exp Osteoporosis/ or osteoporosis.mp.
2 bone density.mp. or exp Bone Density/
3 densit$.mp.
4 (low adj2 bone).mp.
5 3 and 4
6 osteopeni$.mp.
7 1 or 2 or 5 or 6
8 screen$.mp. or exp Mass Screening/
9 test$.mp.
10 8 or 9
11 7 and 10
12 interval.mp.
13 11 and 12
14 limit 13 to ("middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

Risk

Database: *Ovid MEDLINE; Cochrane Central Register of Controlled Trials*

1 exp Osteoporosis/
2 exp Bone Density/
3 1 or 2
4 exp risk/
5 3 and 4
6 exp Cohort Studies/
7 exp Meta-Analysis/
8 exp case-control studies/
9 exp "Sensitivity and Specificity"/

10 Evidence-Based Medicine/
11 6 or 7 or 8 or 9 or 10
12 5 and 11
13 limit 12 to humans
14 limit 13 to English language
15 limit 13 to abstracts
16 14 or 15

Database: ***Cochrane Database of Systematic Reviews***
1 osteoporo$.mp.
2 bone densit$.mp.
3 osteopeni$.mp.
4 1 or 2 or 3
5 risk$.mp.
6 4 and 5
7 (woman or women$ or female).mp.
8 (man or men$ or male).mp.
9 7 or 8
10 6 and 9
11 (child$ or adolescen$).
12 10 not 11

Testing

Database: ***Ovid MEDLINE; Cochrane Central Register of Controlled Trials***
1 exp Osteoporosis/
2 exp Calcaneus/us
3 exp Bone Density/
4 1 or 2 or 3
5 exp Ultrasonography/
6 dxa.mp.
7 dexa.mp.
8 sxa.mp.
9 bua.mp.
10 qct.mp.
11 exp Tomography, X-Ray Computed/
12 quantitat$.mp.
13 11 and 12
14 densitometry/ or absorptiometry, photon/
15 qus.mp.
16 mxa.mp.
17 mrx.mp.
18 ra.mp.
19 dip.mp.
20 sos.mp.
21 ubps.mp.
22 spa.mp.
23 dpa.mp.
24 or/5-10
25 or/13-23
26 24 or 25
27 4 and 26
28 limit 27 to humans
29 limit 28 to english language
30 limit 28 to abstracts
31 29 or 30

32 meta-analysis.mp. or exp Meta-Analysis/
33 (cochrane or medline).tw.
34 search$.tw.
35 32 or 33 or 34
36 "Review Literature as Topic"/ or systematic review.mp.
37 35 or 36
38 31 and 37
39 randomized controlled trial.mp. or exp Randomized Controlled Trial/
40 randomized controlled trial.pt.
41 controlled clinical trial.mp. or exp Controlled Clinical Trial/
42 controlled clinical trial.pt.
43 clinical trial.mp. or exp Clinical Trial/
44 clinical trial.pt.
45 or/39-44
46 limit 45 to humans
47 31 and 46
48 38 or 47

Database: ***Cochrane Database of Systematic Reviews***

1 dxa.mp.
2 dexa.mp.
3 sxa.mp.
4 bua.mp.
5 qct.mp.
6 qus.mp.
7 mxa.mp.
8 mrx.mp.
9 ra.mp.
10 dip.mp.
11 sos.mp.
12 ubps.mp.
13 spa.mp.
14 dpa.mp.
15 osteoporo$.mp.
16 bone densit$.mp.
17 calcaneus.mp.
18 ultrasonograph$.mp.
19 ultrasound.mp.
20 tomograph$.mp.
21 quantitativ$.mp.
22 20 and 21
23 or/1-14
24 or/17-19
25 or/22-24
26 15 or 16
27 25 and 26

Testing in Men

Database: ***Ovid MEDLINE; Cochrane Central Register of Controlled Trials***

1 exp Osteoporosis/
2 exp Calcaneus/us
3 exp Bone Density/
4 1 or 2 or 3
5 exp Ultrasonography/
6 dxa.mp.

7 dexa.mp.
8 sxa.mp.
9 bua.mp.
10 qct.mp.
11 exp Tomography, X-Ray Computed/
12 quantitat$.mp.
13 11 and 12
14 densitometry/ or absorptiometry, photon/
15 qus.mp.
16 mxa.mp.
17 mrx.mp.
18 ra.mp.
19 dip.mp.
20 sos.mp.
21 ubps.mp.
22 spa.mp.
23 dpa.mp.
24 or/5-10
25 or/13-23
26 24 or 25
27 4 and 26
28 limit 27 to humans
29 limit 28 to English language
30 limit 28 to abstracts
31 29 or 30
32 (men or male).ti.
33 31 and 32
34 (female or woman or women).mp.
35 33 not 34
36 from 35 keep 1-305

Treatment

Bisphosphonates

Database: *Ovid MEDLINE* (Systematic Reviews)
1 meta-analysis.mp. or exp Meta-Analysis/
2 (cochrane or medline).tw.
3 search$.tw.
4 1 or 2 or 3
5 "Review Literature as Topic"/ or systematic review.mp.
6 4 or 5
7 exp Diphosphonates/
8 (alendronate or risedronate or etidronate or ibandronate or pamidronate or zoledronic acid).mp.
9 7 or 8
10 exp Osteoporosis/
11 exp Bone Density/
12 10 or 11
13 9 and 12
14 limit 13 to humans
15 limit 14 to English language
16 limit 14 to abstracts
17 15 or 16
18 6 and 17

Database: *Ovid MEDLINE* (Trials); ***Cochrane Central Register of Controlled Trials***
1 exp Diphosphonates/

2 (alendronate or risedronate or etidronate or ibandronate or pamidronate or zoledronic acid).mp.
3 1 or 2
4 exp Osteoporosis/
5 exp Bone Density/
6 4 or 5
7 3 and 6
8 limit 7 to humans
9 limit 8 to english language
10 limit 8 to abstracts
11 9 or 10
12 randomized controlled trial.mp. or exp Randomized Controlled Trial/
13 randomized controlled trial.pt.
14 controlled clinical trial.mp. or exp Controlled Clinical Trial/
15 controlled clinical trial.pt.
16 clinical trial.mp. or exp Clinical Trial/
17 clinical trial.pt.
18 or/12-17
19 limit 18 to humans
20 11 and 19

Database: ***Cochrane Database of Systematic Reviews***
1 bisphosphonates.mp.
2 diphosphonates.mp.
3 (alendronate or risedronate or etidronate or pamidronate or zoledronic acid).mp.
4 1 or 2 or 3
5 osteoporo$.mp.
6 osteopen$.mp.
7 bone densit$.mp.
8 5 or 6 or 7
9 4 and 8

Bisphosphonates – Adverse Effects

Database: ***Ovid MEDLINE***
1 osteoporosis.mp.
2 bone densit$.mp.
3 1 or 2
4 (alendronate or risendronate or etidronate or ibandronate or pamidronate or zoledronic acid).mp.
5 diphosphonate$.mp.
6 bisphosphonate$.mp.
7 or/4-6
8 (harm$ or safety or adverse).mp.
9 7 and 8
10 3 and 9

Calcitonin

Database: ***Ovid MEDLINE*** (systematic reviews)
1 meta-analysis.mp. or exp Meta-Analysis/
2 (cochrane or medline).tw.
3 search$.tw.
4 1 or 2 or 3
5 "Review Literature as Topic"/ or systematic review.mp.
6 4 or 5
7 exp Calcitonin/ad, ae, ct, tu, to
8 exp Osteoporosis/
9 exp Bone Density/

10 7 and (8 or 9)
11 limit 10 to humans
12 limit 11 to English language
13 limit 11 to abstracts
14 6 and 13
15 meta-analysis.mp. or exp Meta-Analysis/
16 (cochrane or medline).tw.
17 search$.tw.
18 15 or 16 or 17

Database: ***Ovid MEDLINE*** (Trials); ***Cochrane Central Register of Controlled Trials***
1 exp Calcitonin/ad, ae, ct, tu, to
2 exp Osteoporosis/
3 exp Bone Density/
4 1 and (2 or 3)
5 limit 4 to humans
6 limit 5 to english language
7 limit 5 to abstracts
8 randomized controlled trial.mp. or exp Randomized Controlled Trial/
9 randomized controlled trial.pt.
10 controlled clinical trial.mp. or exp Controlled Clinical Trial/
11 controlled clinical trial.pt.
12 clinical trial.mp. or exp Clinical Trial/
13 clinical trial.pt.
14 or/8-13
15 limit 14 to humans
16 7 and 15

Database: ***EBM Reviews - Cochrane Database of Systematic Reviews***
1 calcitonin.mp.
2 osteoporo$.mp.
3 osteopen$.mp.
4 bone densit$.mp.
5 2 or 3 or 4
6 1 and 5

Estrogen

Database: ***Ovid MEDLINE*** (systematic reviews)
1 meta-analysis.mp. or exp Meta-Analysis/
2 (cochrane or medline).tw.
3 search$.tw.
4 1 or 2 or 3
5 "Review Literature as Topic"/ or systematic review.mp.
6 4 or 5
7 exp Hormone Replacement Therapy/
8 exp Estrogens/ad, ae, ct, tu, to
9 exp Estradiol Congeners/ad, ae, ct, tu, to
10 (replac$ adj5 (estrogen$ or hormon$)).mp.
11 7 or 8 or 9 or 10
12 exp Osteoporosis/
13 exp Bone Density/
14 exp Fractures, Bone/
15 fractur$.mp.
16 12 or 13 or 14 or 15
17 11 and 16

18 limit 17 to humans
19 limit 18 to English language
20 limit 18 to abstracts
21 19 or 20
22 6 and 21

Database: ***Ovid MEDLINE*** (Trials); ***Cochrane Central Register of Controlled Trials***
1 exp Hormone Replacement Therapy/
2 exp Estrogens/ad, ae, ct, tu, to
3 exp Estradiol Congeners/ad, ae, ct, tu, to
4 (replac$ adj5 (estrogen$ or hormon$)).mp.
5 1 or 2 or 3 or 4
6 exp Osteoporosis/
7 exp Bone Density/
8 exp Fractures, Bone/
9 fractur$.mp.
10 6 or 7 or 8 or 9
11 5 and 10
12 limit 11 to humans
13 limit 12 to english language
14 limit 12 to abstracts
15 13 or 14
16 randomized controlled trial.mp. or exp Randomized Controlled Trial/
17 randomized controlled trial.pt.
18 controlled clinical trial.mp. or exp Controlled Clinical Trial/
19 controlled clinical trial.pt.
20 clinical trial.mp. or exp Clinical Trial/
21 clinical trial.pt.
22 or/16-21
23 limit 22 to humans
24 15 and 23

Database: ***EBM Reviews - Cochrane Database of Systematic Reviews***
1 hormone replacement therapy.mp.
2 estradiol.mp.
3 estrogen$.mp.
4 (replac$ adj5 (estrogen$ or hormon$)).mp.
5 1 or 2 or 3 or 4
6 osteoporo$.mp.
7 osteopen$.mp.
8 bone densit$.mp.
9 6 or 7 or 8
10 5 and 9

Parathyroid Hormone

Database: ***Ovid MEDLINE*** (systematic reviews)
1 meta-analysis.mp. or exp Meta-Analysis/
2 (cochrane or medline).tw.
3 search$.tw.
4 1 or 2 or 3
5 "Review Literature as Topic"/ or systematic review.mp.
6 4 or 5
7 exp Parathyroid Hormone/ad, ae, tu, to
8 exp Osteoporosis/
9 exp Bone Density/

10 7 and (8 or 9)
11 limit 10 to humans
12 limit 11 to English language
13 limit 11 to abstracts
14 12 or 13
15 6 and 14

Database: ***Ovid MEDLINE*** (Trials); ***Cochrane Central Register of Controlled Trials***
1 exp Parathyroid Hormone/ad, ae, tu, to
2 exp Osteoporosis/
3 exp Bone Density/
4 1 and (2 or 3)
5 limit 4 to humans
6 limit 5 to english language
7 limit 5 to abstracts
8 6 or 7
9 randomized controlled trial.mp. or exp Randomized Controlled Trial/
10 randomized controlled trial.pt.
11 controlled clinical trial.mp. or exp Controlled Clinical Trial/
12 controlled clinical trial.pt.
13 clinical trial.mp. or exp Clinical Trial/
14 clinical trial.pt.
15 or/9-14
16 limit 15 to humans
17 8 and 16

Database: Cochrane Database of Systematic Reviews
1 parathyroid$.mp.
2 hormon$.mp.
3 pth.mp.
4 (1 and 2) or 3
5 osteoporo$.mp.
6 osteopen$.mp.
7 bone densit$.mp.
8 5 or 6 or 7
9 4 and 8
10 from 9 keep 1-14
11 limit 10 to recently updated reviews
12 limit 10 to new reviews
13 11 or 12

SERMs
Database: ***Ovid MEDLINE***
1 tamoxifen.mp. or exp Tamoxifen/
2 raloxifene.mp. or exp Raloxifene/
3 1 or 2
4 bone density.mp. or exp Bone Density/
5 exp Osteoporosis/ or osteoporosis.mp.
6 fractur$.mp.
7 exp Fractures, Bone/
8 exp Hormone Replacement Therapy/
9 (replac$ adj5 (hormon$ or estrogen$)).mp.
10 4 or 5 or 6 or 7 or 8 or 9
11 3 and 10
12 exp breast neoplasms/

13 11 not 12
14 limit 13 to humans
15 limit 14 to English language
16 limit 14 to abstracts
17 15 or 16

Testosterone

Database: *Ovid MEDLINE* (systematic reviews)

1 meta-analysis.mp. or exp Meta-Analysis/
2 (cochrane or medline).tw.
3 search$.tw.
4 1 or 2 or 3
5 "Review Literature as Topic"/ or systematic review.mp.
6 4 or 5
7 exp Osteoporosis/
8 exp Bone Density/
9 7 or 8
10 exp Testosterone/ad, ae, ct, tu, to
11 9 and 10
12 exp Testosterone Congeners/ad, ae, tu, ct, to
13 9 and 12
14 11 or 13
15 limit 14 to humans
16 limit 15 to English language
17 limit 15 to abstracts
18 16 or 17
19 6 and 18
20 from 19 keep 1-5

Database: *Ovid MEDLINE* (Trials); ***Cochrane Central Register of Controlled Trials***

1 exp Osteoporosis/
2 exp Bone Density/
3 1 or 2
4 exp Testosterone/ad, ae, ct, tu, to
5 3 and 4
6 exp Testosterone Congeners/ad, ae, tu, ct, to
7 3 and 6
8 5 or 7
9 limit 8 to humans
10 limit 9 to english language
11 limit 9 to abstracts
12 10 or 11
13 randomized controlled trial.mp. or exp Randomized Controlled Trial/
14 randomized controlled trial.pt.
15 controlled clinical trial.mp. or exp Controlled Clinical Trial/
16 controlled clinical trial.pt.
17 clinical trial.mp. or exp Clinical Trial/
18 clinical trial.pt.
19 or/13-18
20 limit 19 to humans
21 12 and 20

Database: *Cochrane Database of Systematic Reviews*

1 testosterone.mp.
2 osteoporo$.mp.

Appendix B1. Search Strategies

3 osteopen$.mp.
4 bone densit$.mp.
5 2 or 3 or 4
6 1 and 5

Appendix B2. Inclusion and Exclusion Criteria for Each Key Question

Key Question 1. Screening

Include

Paper addresses Key Question 1 and

- includes osteoporosis and low bone density
- limited to fracture outcomes

Exclude

Reason:	Details:
Paper may be relevant to background and context, but does not meet inclusion criteria	
Wrong population	Premenopausal women, men <50, not applicable to U.S. population, have secondary causes of osteoporosis, already on treatment medications
Wrong intervention	Screening with technology not used in the U.S., screening with risk factors not applicable to the U.S.
Wrong outcomes	Not validated fractures, fracture-related morbidity, or fracture-related mortality
Wrong study design	Not randomized controlled trial or nonrandomized comparison
Wrong publication type	Review article, letter, editorial, results reported elsewhere, no original data
Non-English language	
Not human population	
Methodological issues not included in other exclusion criteria	
Systematic review before the year 2002	

Key Question 2. Risk

Include

Paper addresses Key Question 2 and

- limited to risk assessment instruments

Exclude

Reason:	Details:
Paper may be relevant to background and context, but does not meet inclusion criteria	
Wrong population	Not comparable or applicable to U.S. adult population
Wrong intervention	Not an evaluation of a risk assessment tool
Wrong outcomes	Evaluation of single risk factor
Wrong study design	For example, assessment of risk factors by regression analysis of a population

Wrong publication type	Review article, letter, editorial, results reported elsewhere, no original data
Non-English language	
Not human population	
Methodological issue not included in other exclusion criteria	
Systematic review before the year 2002	

Key Question 3. Testing

Include

Paper addresses Key Question 3 and

- must be applicable to U.S. technologies (e.g., DXA or peripheral bone measurement tests)

Exclude

Reason:	**Details:**
Paper may be relevant to background and context, but does not meet inclusion criteria	
Wrong population	KQ3a: women or men <50, not applicable to U.S. population, have secondary causes of osteoporosis, already on treatment medications KQ3b and KQ3c: premenopausal women, men <50, not applicable to U.S. population, have secondary causes of osteoporosis, already on treatment medications
Wrong intervention	Screening with technology not used in the U.S.
Wrong outcomes	KQ3a and KQ3b: not validated fractures
Wrong study design	Not diagnostic test study
Wrong publication type	Review article, letter, editorial, results reported elsewhere, no original data
Non-English language	
Not human population	
Methodological issue not included in other exclusion criteria	
Systematic review before the year 2002	

Key Question 4. Harms of Screening

Include

Paper addresses Key Question 4 and

- any study design

Appendix B2. Inclusion and Exclusion Criteria for Each Key Question

Exclude

Reason:	Details:
Paper may be relevant to background and context, but does not meet inclusion criteria	
Wrong population	
Wrong intervention	
Wrong outcomes	
Wrong study design	
Wrong publication type	Review article, letter, editorial, results reported elsewhere, no original data
Non-English language but otherwise relevant	
Not human population	
Methodological issue not included in other exclusion criteria	
Systematic review before the year 2002	

Key Question 5. Treatment

Include

Paper addresses Key Question 5 and

- limited to systematic evidence reviews of RCTs
- limited to RCTs of drug therapies

Exclude

Reason:	Details:
Paper may be relevant to background and context, but does not meet inclusion criteria	
Wrong population	
Wrong intervention	Drug not currently in use in the U.S.
Wrong outcomes	Not fracture or fracture-related morbidity or mortality
Wrong study design	Not randomized controlled trial or systematic review of randomized controlled trials
Wrong publication type	Review article, letter, editorial, results reported elsewhere, no original data
Non-English language but otherwise relevant	
Not human population	
Methodological issue not included in other exclusion criteria	
Systematic review before the year 2002	

Appendix B2. Inclusion and Exclusion Criteria for Each Key Question

Key Question 6. Harms of Treatment

Include

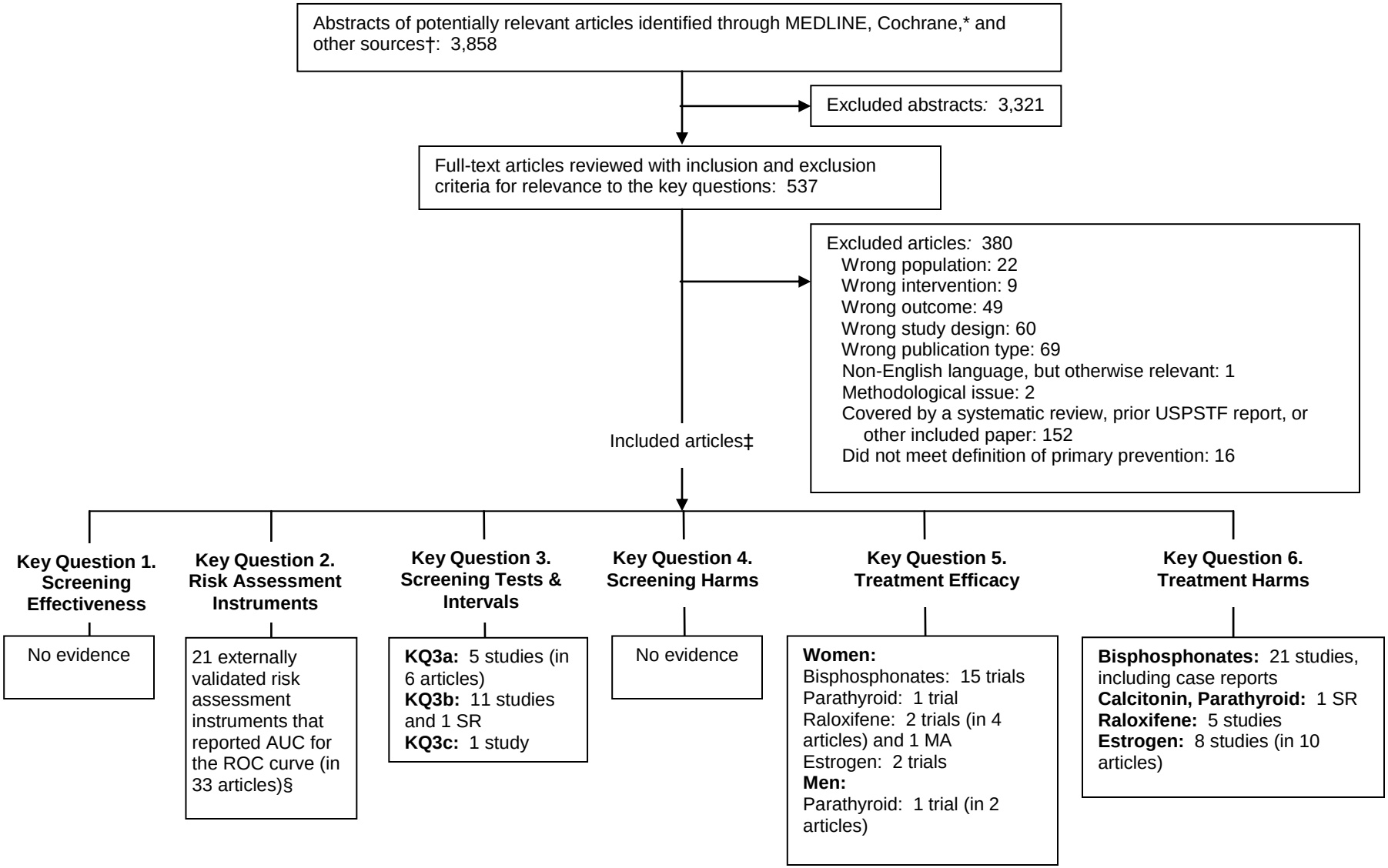
Paper addresses Key Question 6 and

- any study design
- limited to drug therapies

Exclude

Reason:	Details:
Paper may be relevant to background and context, but does not meet inclusion criteria	
Wrong population	
Wrong intervention	
Wrong outcomes	
Wrong study design	
Wrong publication type	Review article, letter, editorial, results reported elsewhere, no original data
Non-English language but otherwise relevant	
Not human population	
Methodological issue not included in other exclusion criteria	
Systematic review before the year 2002	

Appendix B3. Article Flow by Key Question



Abbreviations: AUC = area under the curve; MA = meta-analysis; ROC = receiver operating characteristic; SR = systematic review.

*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Identified from reference lists, suggested by experts, etc.
‡ Some articles were included for more than one key question.
§Subset of 64 total articles describing risk assessment instruments.

Appendix B4. Excluded Studies

Wrong population

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Appendix B4. Excluded Studies

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Appendix B4. Excluded Studies

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Methodological issue

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Did not meet definition of primary prevention

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Appendix B5. U.S. Preventive Services Task Force Quality Rating Criteria for RCTs and Observational Studies

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test
- Random or consecutive selection of patients
- Screening cutoff pre-determined
- All patients undergo the reference standard

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria; screening cutoffs pre-stated.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients (i.e. applicable to most screening settings).

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Appendix B5. U.S. Preventive Services Task Force Quality Rating Criteria for RCTs and Observational Studies

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Reference: Harris et al, 2001[33]

Appendix B6. Quality Assessment for Osteoporosis Risk Assessment Papers

1. Is the risk assessment tool appropriate for a primary care screening tool?
2. Does the study evaluate diagnostic test performance in a population other than the one used to derive the instrument?
3. Does the study evaluate a consecutive clinical series of patients or a random subset?
4. Does the study adequately describe the population in which the risk instrument was tested (BMD reported)?
5. Does the study adequately describe the instrument evaluated?
6. Does the study include appropriate criteria in the instrument (must include age and some measure of body weight or size)?
7. Does the study adequately describe the method used to calculate the risk index?
8. Does the study use appropriate criteria to assess the risk factors (uses either a validated questionnaire or other corroborated method)?
9. Does the study evaluate outcomes or the reference standard in all patients enrolled (up to 10% loss considered acceptable)?
10. Was the reference standard (BMD or fracture assessment) performed consistently without regard for the results of the risk assessment?
11. Does the study evaluate outcomes blinded to results of the screening instrument?

Reference: Adapted from Harris et al, 2001[33]

Appendix B7. Quality Rating Criteria for Systematic Reviews

Overall quality rating for each systematic review is based on the below questions. Ratings are summarized as: *Good, Fair,* or *Poor*:

Criteria:

- Search dates reported?
- Search methods reported?
- Comprehensive search?
- Inclusion criteria reported?
- Selection bias avoided?
- Validity criteria reported?
- Validity assessed appropriately?
- Methods used to combine studies reported?
- Findings combined appropriately?
- Conclusions supported by data?

Definitions of ratings based on above criteria:

Good: Meets all criteria: reports comprehensive and reproducible search methods and results; reports pre-defined criteria to select studies and reports reasons for excluding potentially relevant studies; adequately evaluates quality of included studies and incorporates assessments of quality when synthesizing data; reports methods for synthesizing data and uses appropriate methods to combine data qualitatively or quantitatively; conclusions supported by the evidence reviewed.

Fair: Studies will be graded fair if they fail to meet one or more of the above criteria, but the limitations are not judged as being major.

Poor: Studies will be graded poor if they have a major limitation in one or more of the above criteria.

Created from the following publications: Harris et al, 2001[33]; National Institute for Health and Clinical Excellence, 2006[236]; and Oxman and Guyatt, 1991[237]

Appendix B8. Expert Reviewers

Robert A. Adler, MD
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Director, Coordinating Center
University of California at San Francisco

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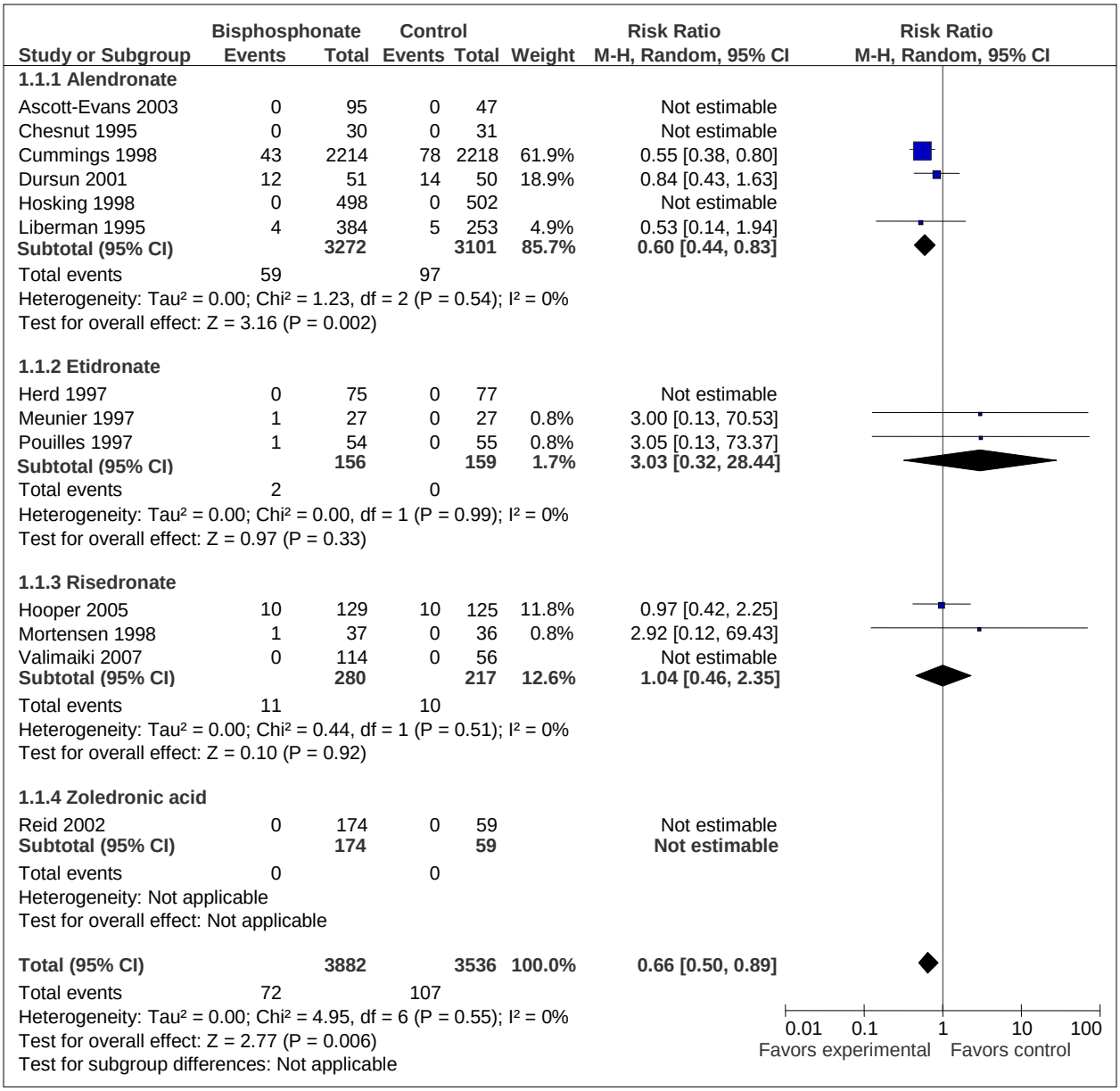
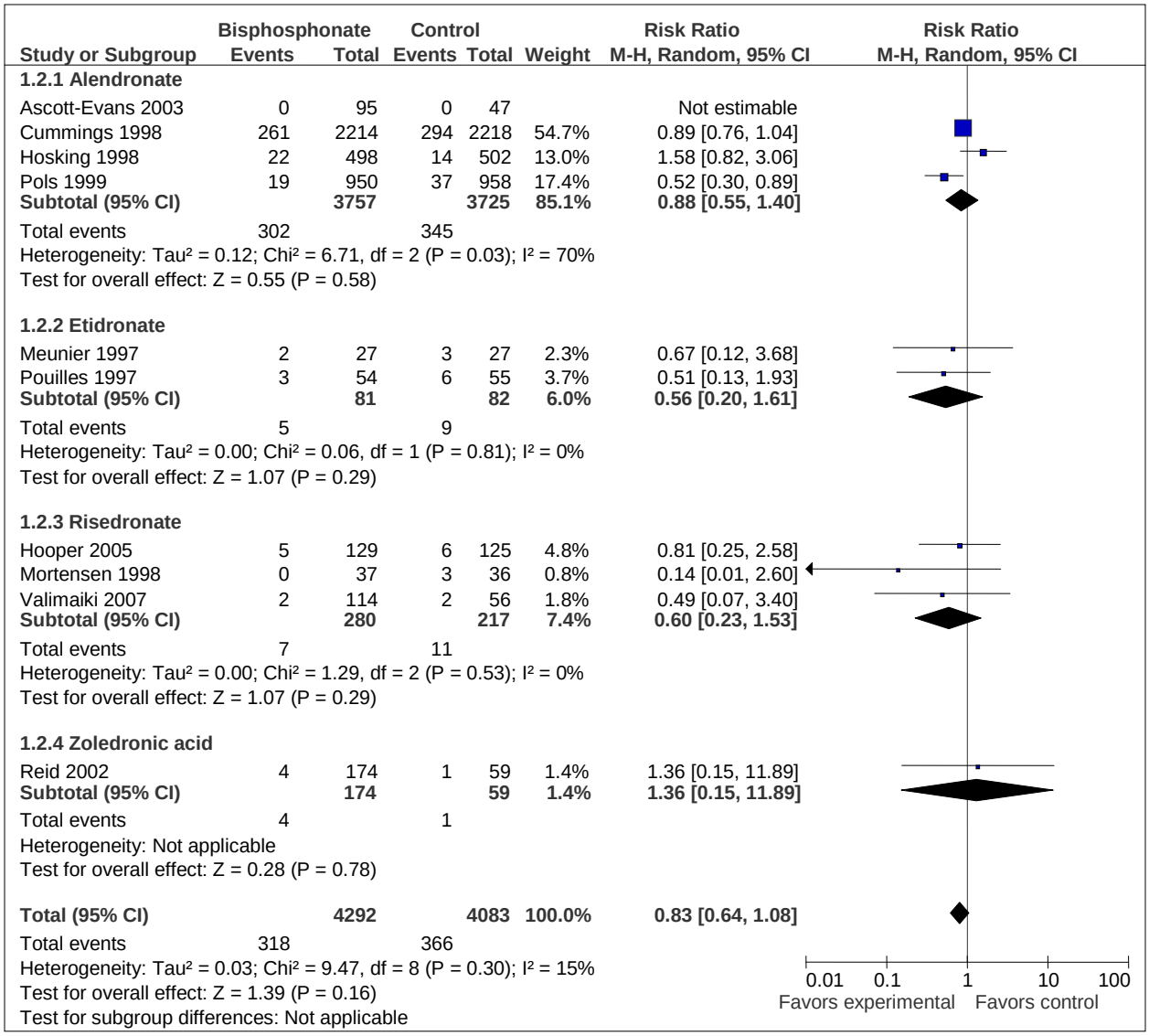
Eric Orwoll, MD
Associate Dean, Department of Medicine: Endocrinology, Diabetes, and Clinical Nutrition
Oregon Health and Science University

Anna Tosteson, ScD
Professor of Medicine and Community and Family Medicine
The Dartmouth Institute for Health Policy and Clinical Practice
Dartmouth Medical School

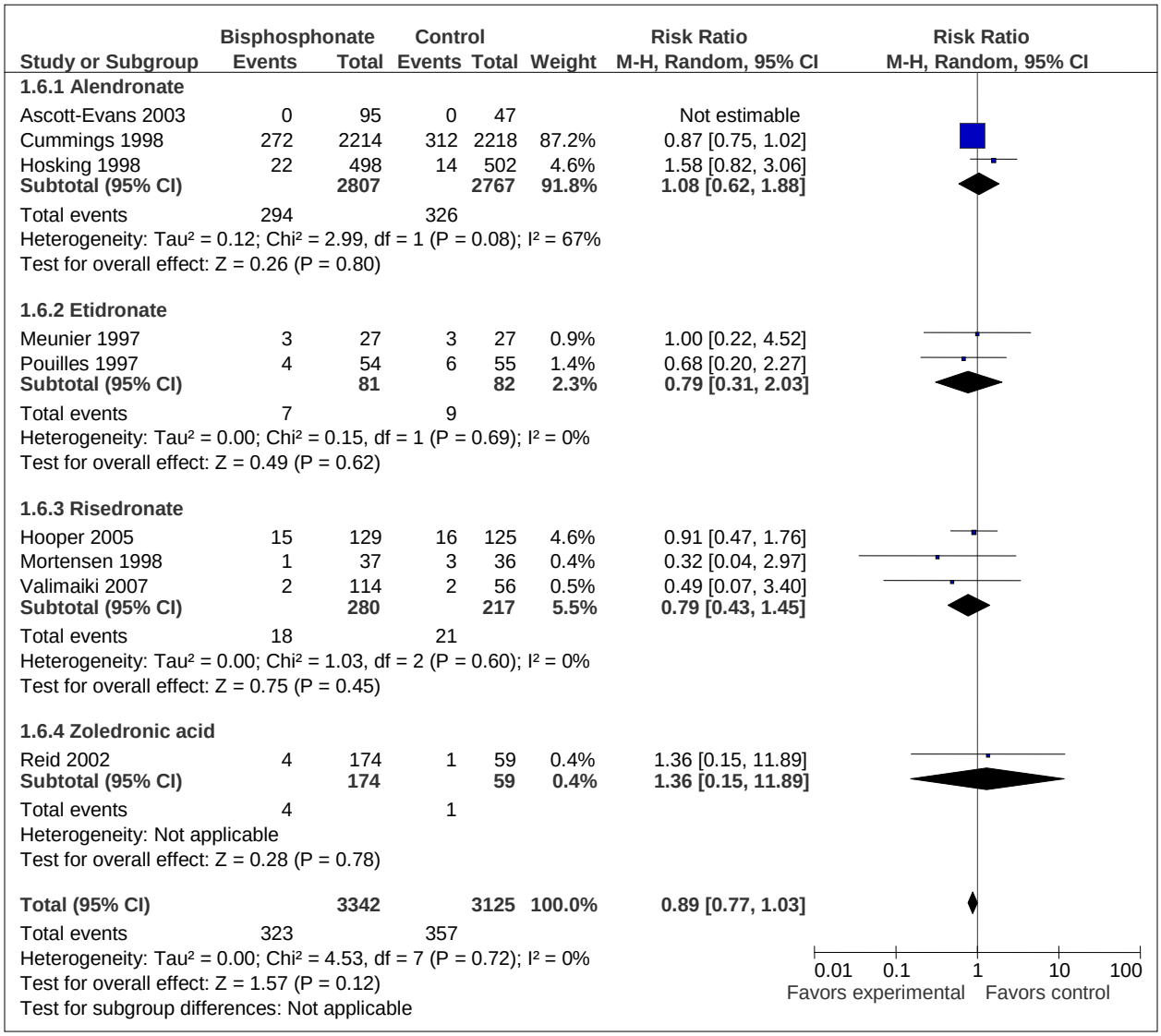
Appendix Figure C1. Vertebral Fractures: Primary Prevention Trials of Bisphosphonate vs. Placebo



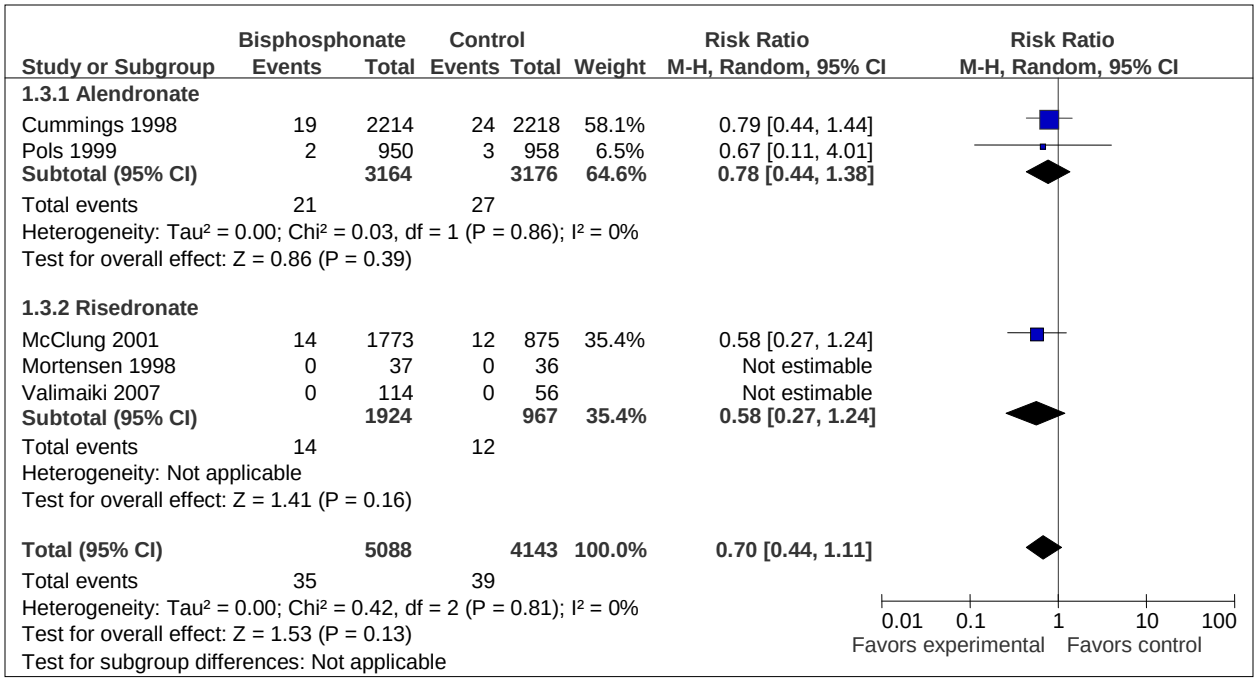
Appendix Figure C2. Total Nonvertebral Fractures: Primary Prevention Trials of Bisphosphonate vs. Placebo



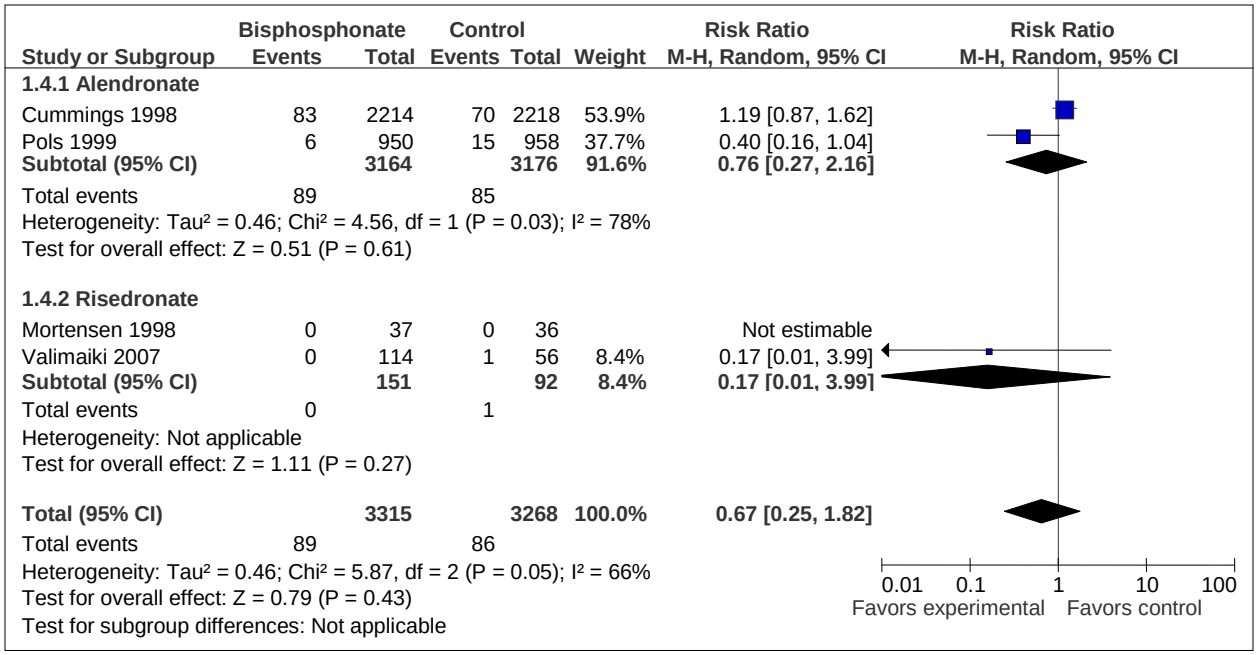
Appendix Figure C3. Total Fracture: Primary Prevention Trials of Bisphosphonate vs. Placebo



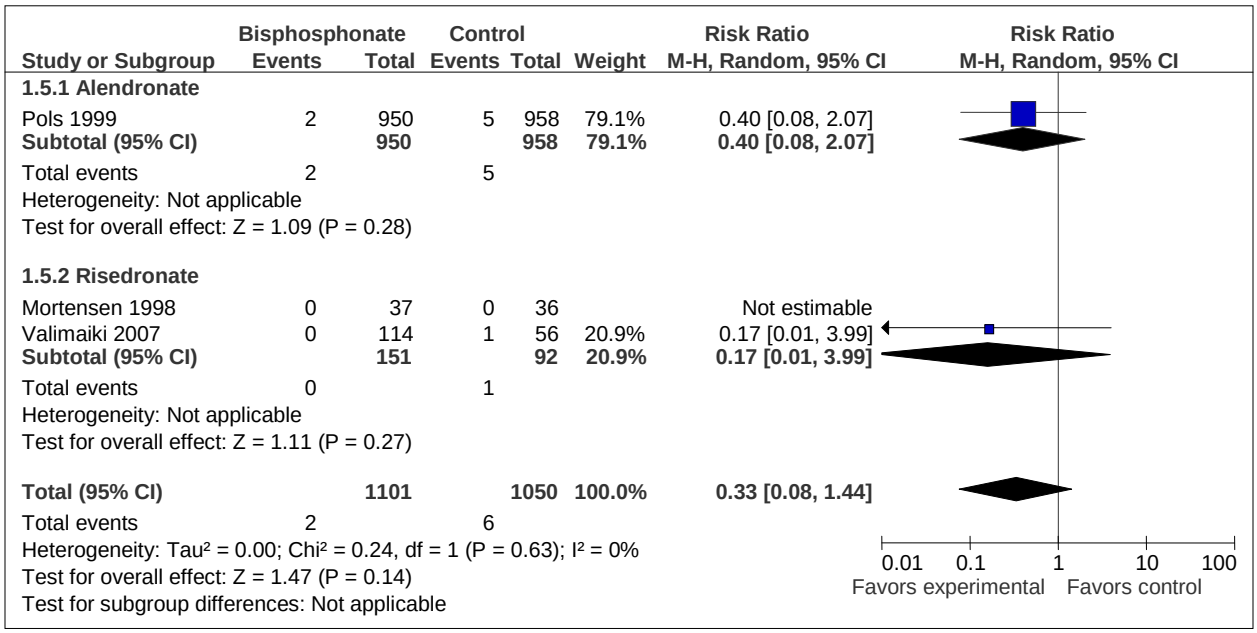
Appendix Figure C4. Hip Fractures: Primary Prevention Trials



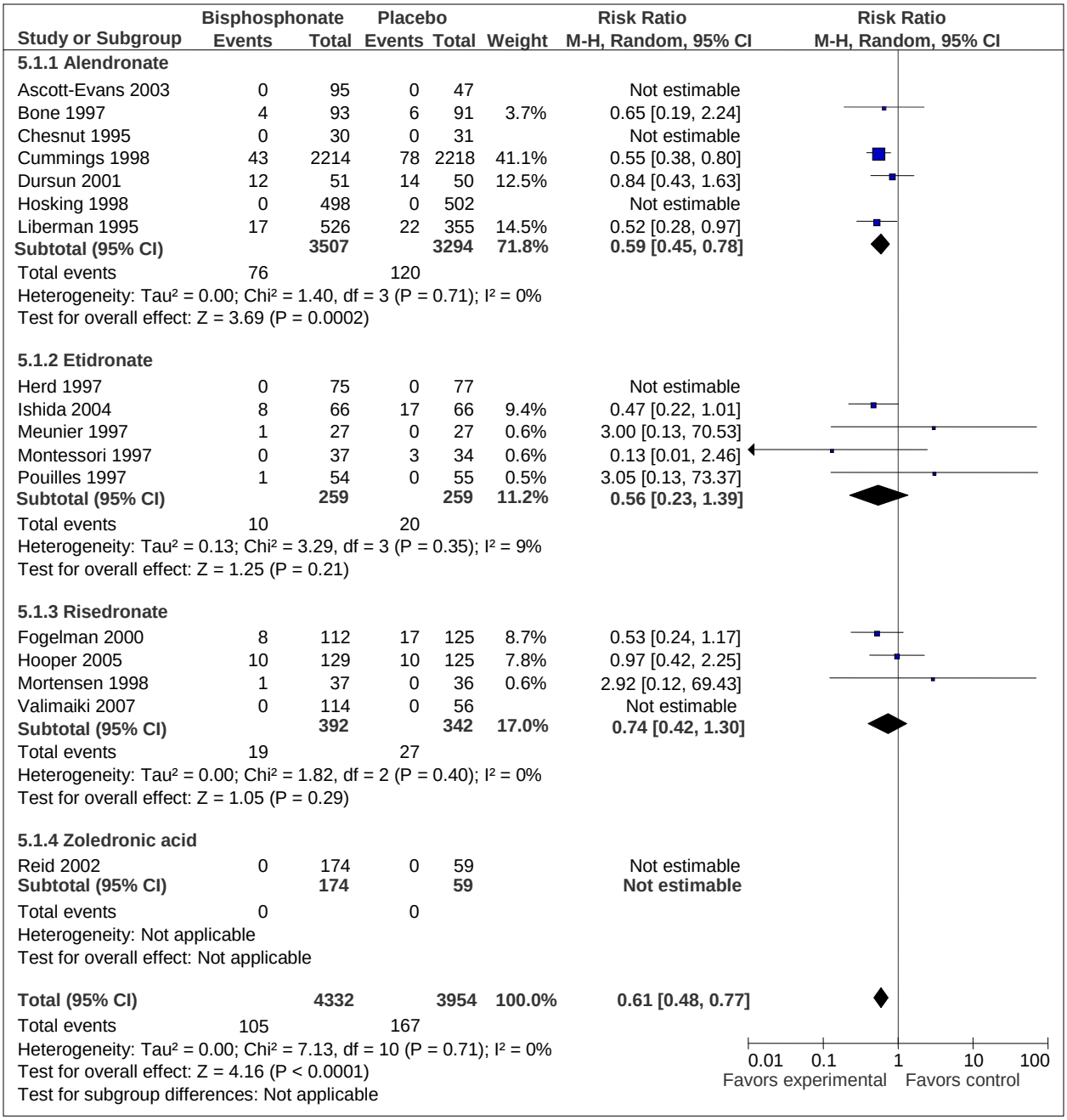
Appendix Figure C5. Wrist Fractures: Primary Prevention Trials of Bisphosphonate vs. Placebo



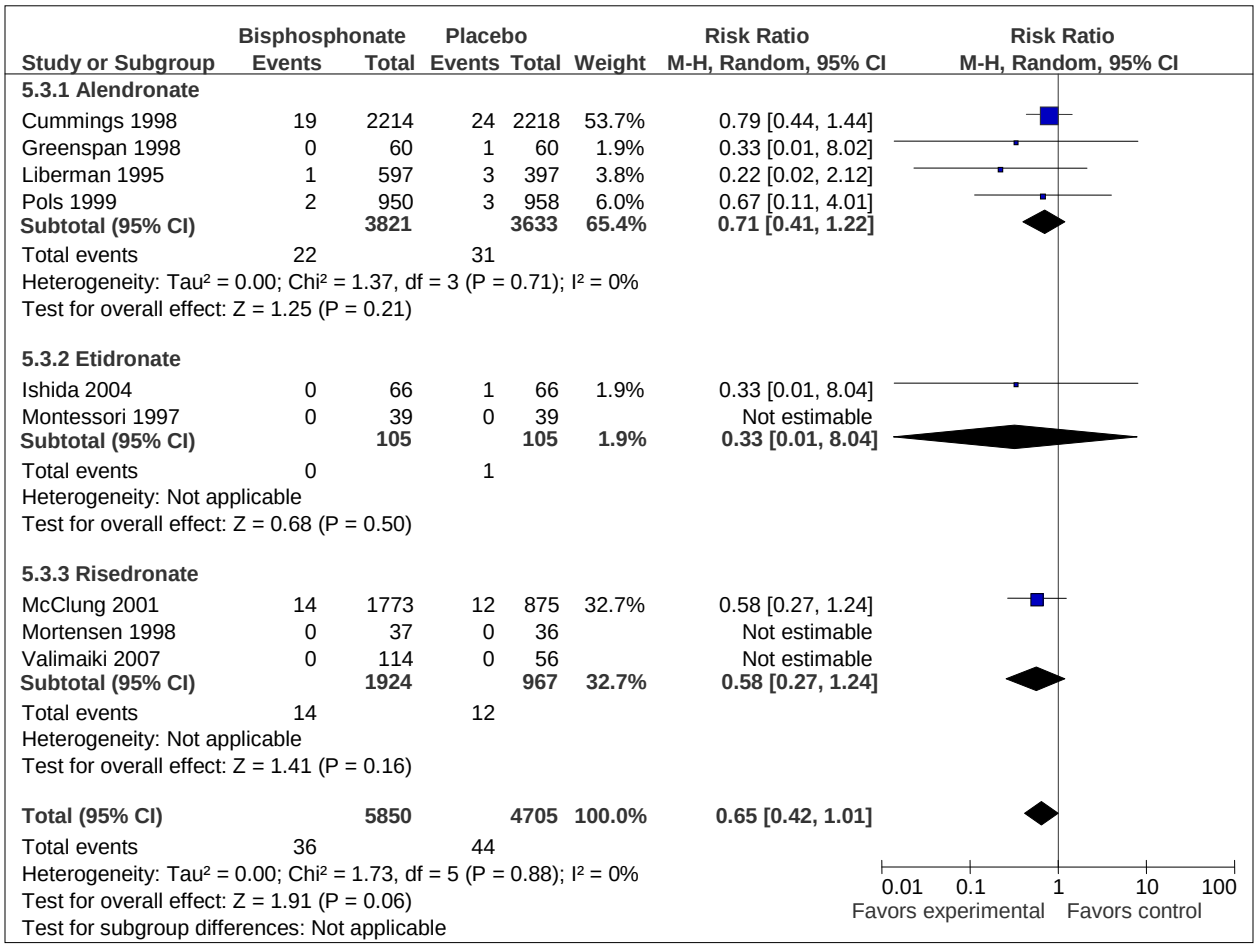
Appendix Figure C6. Ankle Fractures: Primary Prevention Trials of Bisphosphonate vs. Placebo



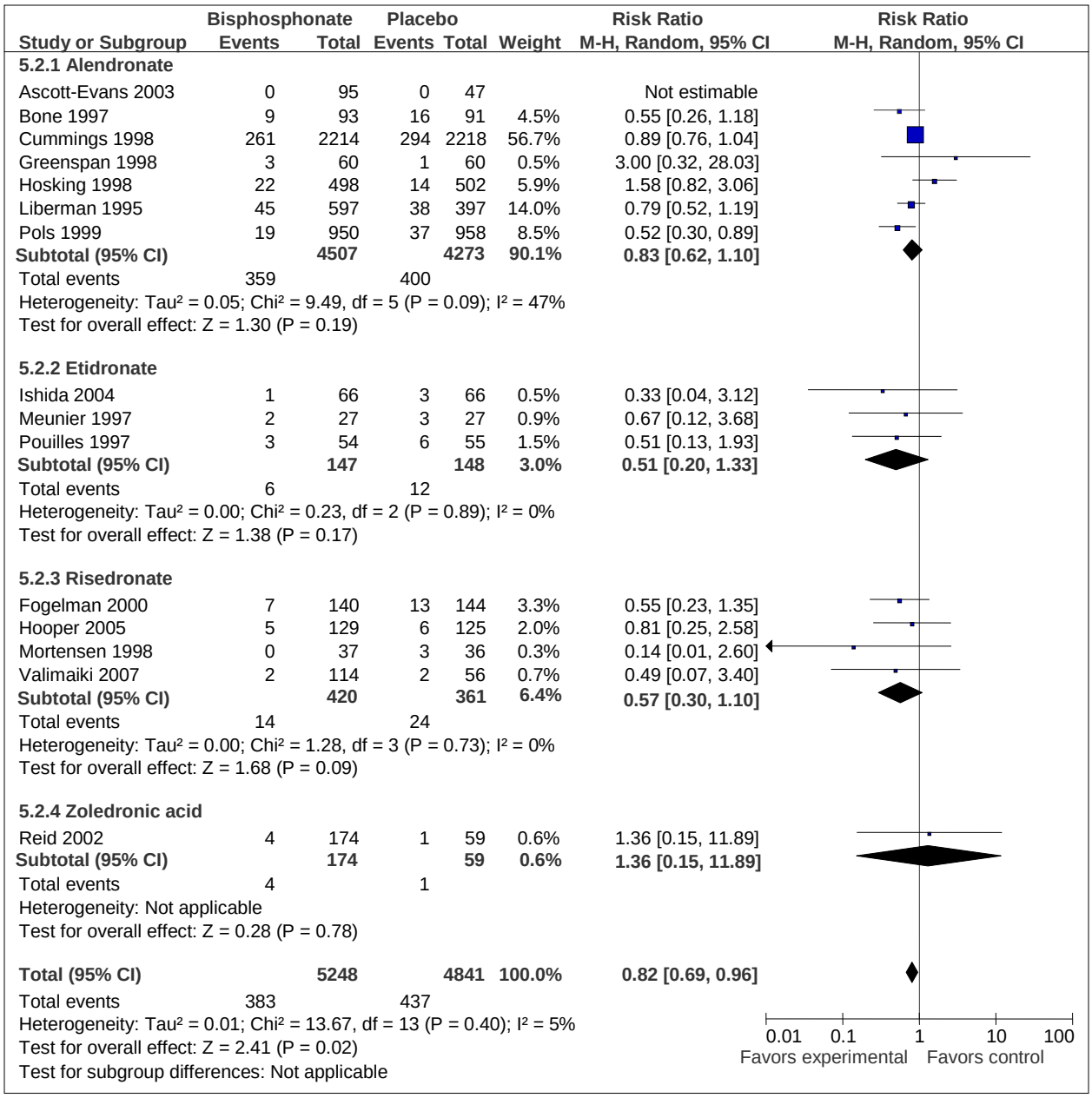
Appendix Figure C7. Vertebral Fractures: Sensitivity Analysis Including Additional Primary Prevention Trials of Bisphosphonate vs. Placebo



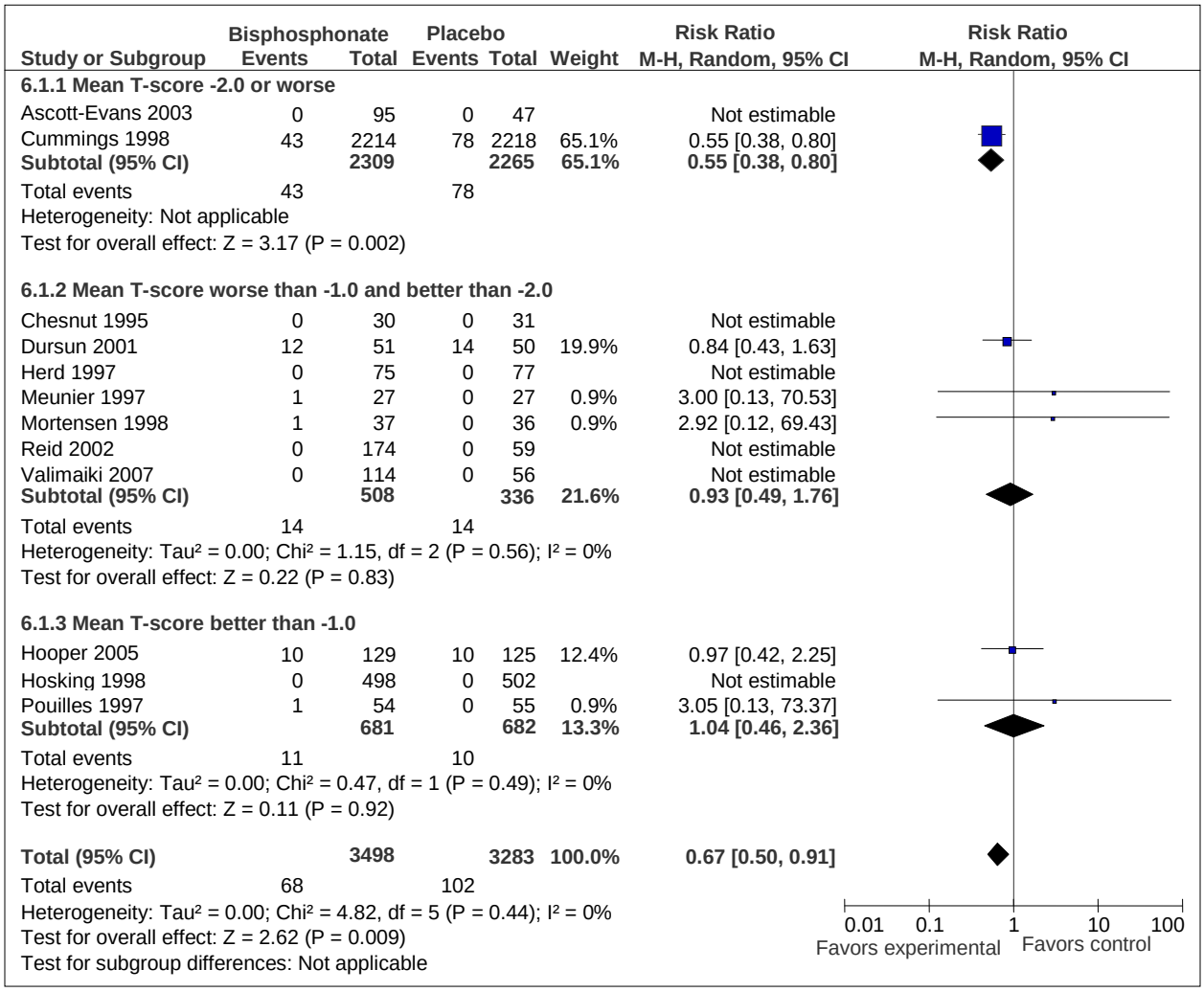
Appendix Figure C8. Hip Fracture: Sensitivity Analysis Including Additional Primary Prevention Trials of Bisphosphonate vs. Placebo



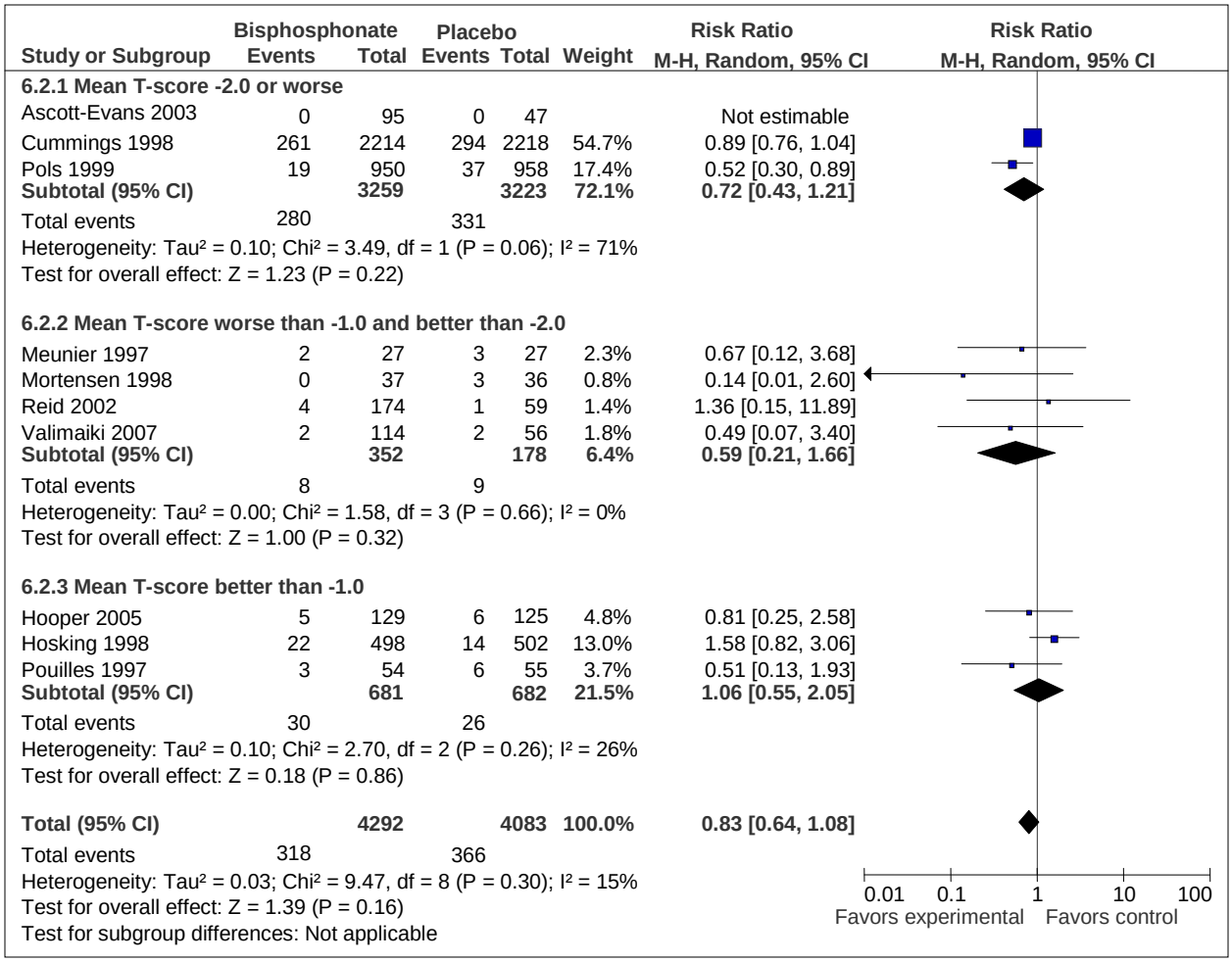
Appendix Figure C9. Total Nonvertebral Fractures: Sensitivity Analysis Including Additional Primary Prevention Trials of Bisphosphonate vs. Placebo



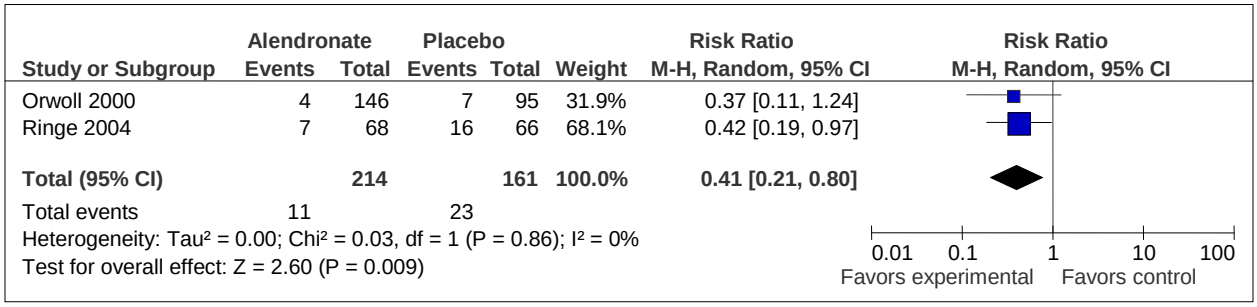
Appendix Figure C10. Vertebral Fracture: Bisphosphonate vs. Placebo, Stratified by Baseline BMD



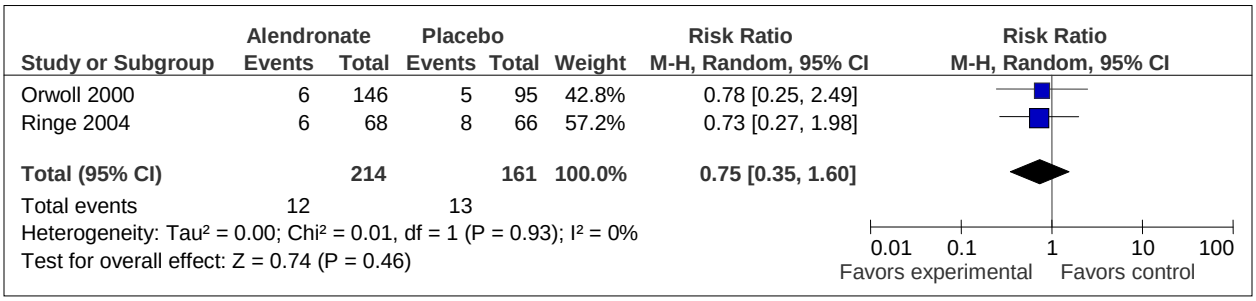
Appendix Figure C11. Nonvertebral Fracture: Bisphosphonate vs. Placebo, Stratified by Baseline BMD



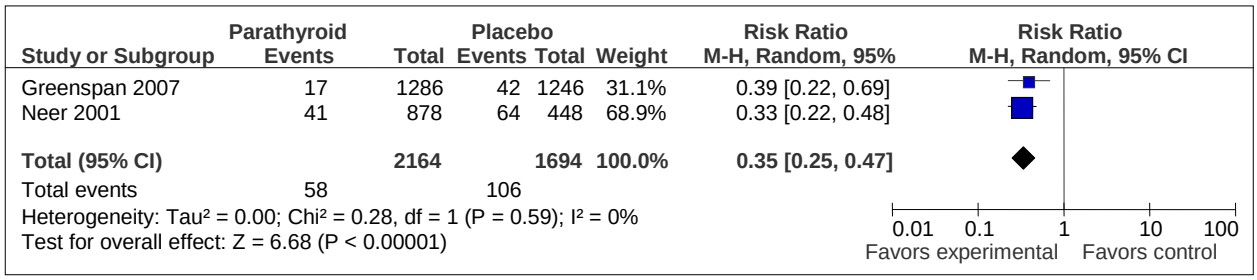
Appendix Figure C12. Vertebral Fractures: Primary and Secondary Trials of Alendronate vs. Placebo in Men



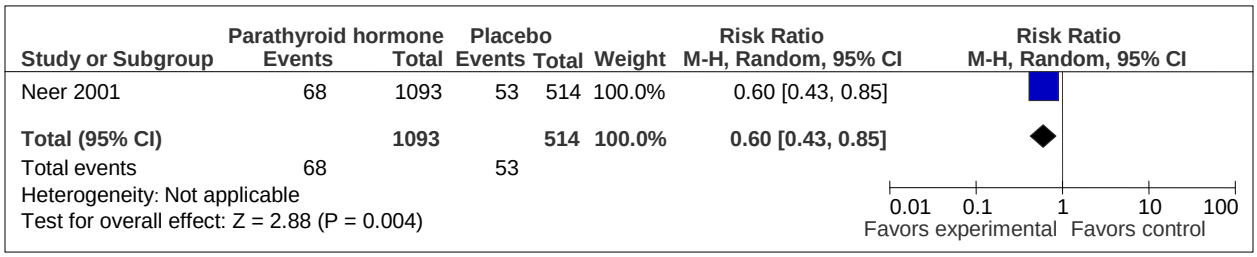
Appendix Figure C13. Total Nonvertebral Fractures: Primary and Secondary Prevention Trials of Alendronate vs. Placebo in Men



Appendix Figure C14. Vertebral Fractures: Primary and Secondary Prevention Trials of Parathyroid Hormone vs. Placebo in Women



Appendix Figure C15. Total Nonvertebral Fractures: Primary and Secondary Prevention Trials of Parathyroid Hormone vs. Placebo in Women



Appendix Table D1. Studies of Risk Assessment

Study	Population Setting, n	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Adler et al, 2003[52]	181 men recruited from pulmonary and rheumatology clinics at a VA	Mean BMD: Spine 1.094 (SD 0.2) FN 0.802 (SD 0.18) TH 0.973 (SD 0.18)	Only patients with no prior DXA were eligible	Cross-sectional analysis
Ahmed et al, 2006[87]	Tromso study - all residents of Tromso born 1969 or earlier (n=27,159 overall, 5795 women age 55-74), final n=1410	Mean BMD in those without hip fractures: Forearm 0.37 (SD 0.06) Mean BMD in those with hip fractures: Forearm 0.33 (SD 0.06)	Women ages 65 and older, no prior hip fracture,	Analysis of prospective cohort data
Ben Sedrine et al, 2001[53]	White women from Belgium, n=4035	Prevalence of osteoporosis (T≤-2.5): TH 9.5% FN 18.5% LS (L2–4) 24.3%	All pts presenting for BMD measurement (spontaneous or referred) with data available	Regression to identify factors predicting low bone mass, additive scoring

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Adler et al, 2003[52]	BMD T score of -2.5 or below	OST	OST cutoff of 3 provided a sens of 93%, spec of 66%. AUC at LS = 0.85 (0.731-0.960) AUC at FN=0.814 (0.717-0.910) AUC at TH=0.866 (0.768-0.963) AUC at any site=0.836 (0.747-0.924)	Yes
Ahmed et al, 2006[87]	Fracture	Risk factors to complement Cummings' risk score: weight loss or BMD <20kg/m2, height ≥168 cm, maternal history of hip fracture, any non-hip fracture since age 50, self-reported good or poor health, physically inactivity (none), benzodiazepine use, anticonvulsant drug use, pulse >80 beats/min, caffeine ≥ 2 cups of coffee/day, unable to rise from chair without help, self-reported hyperthyroidism, age >80 at time of BMD measurement, forearm BMD	Risk score screening had PPV = 11% (CI 3.7-18.2%); selective BMD testing among those with 5 or more risk factors identifies 7 or 8 women with hip fractures as osteoporotic, the eight being osteopenic. 49 hip fracture among 1410 women >65 years. 5 women had 5 risk factors and normal BMD; 14 women had 5 risk factors and low bone mass, 54 women had 5 risk factors and BMD <-2.5.	This is a validation study of Cummings SOF-derived risk instrument
Ben Sedrine et al, 2001[53]	BMD	SCORE: age, weight race, rheumatoid arthritis, history of nontraumatic fracture after age 45 years , and estrogen use.	For T score ≤ -2.5 with a SCORE cut-off of 6: FN AUC=0.75 (SE=0.010) TH AUC=0.78 (SE 0.012) LS AUC=0.66 (SE 0.10) Any site AUC=0.71 (SE 0.009) Results also reported for Sens, Spec, PPV and NPV presented for T scores ≤ -2.0, T score ≤ -1.0 and T score ≤ -2.5, for SCORE cutoff points of 6 and 8	Yes - This is a validation study of SCORE

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Black et al, 2001[88]	Developed in SOF, n=7782 postmenopausal women; Validated in EPIDOS n=6679	Overall mean TH BMD: 0.76 Mean hip BMD in those without fracture: 0.76 Mean hip BMD in those with fracture: 0.65	Women age 65 and older, recruited from population-based listings, 6 U.S. sites	Analysis of SOF prospective cohort data (logistic regression)
Brenneman et al, 2003[54]	416 women selected from managed care (group health) enrollment and invited for BMD testing	BMD T scores taken at proximal femur, TH, and spine on each subject: -2.5 or less: n=126 (30.3%) -2.0 or less: n=205 (49.3%) -1.0 or less: n=335 (80.5%)	Included if age 60 and older without prior diagnosis of osteoporosis	OPRA RCT comparison of SCORE and SOF
Cadarette et al, 2000[55]	CaMOS; 1,376 (926 for derivation, 450 for validation) cognitively normal women ≥45 years from 3 Ontario sites	Development cohort: Mean FN BMD: 0.74 (0.13 SD) Mean LS BMD: 0.97 (0.17 SD) Validation cohort: Mean FN BMD: 0.74 (0.13 SD) Mean L BMD: 0.97 (0.18 SD)	Excluded women with diagnosis of osteoporosis or taking bone active meds other than ovarian hormones	Cross-sectional analysis of cohort data (logistic regression) baseline DXA and covariates

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Black et al, 2001[88]	Fracture	FRACTURE index (derived from SOF): age, fracture after age 50 years , maternal hip fracture, weight ≤ 125 lbs, smoking status and use of arms to stand from chair, with and without BMD T score	AUROC for FRACTURE index with and without BMD measurements. Also present 5 year risk of vertebral and non-vertebral fracture by quintile of FRACTURE score AUROC for Hip Fracture, without BMD in the model: 0.714 (no CI given); with BMD in the model 0.766	Validated using EPIDOS fracture study (n=6679 women).
Brenneman et al, 2003[54]	BMD at NOF and WHO criteria (T scores ≤ -2.5, -2.0, -1.5; also assessed agreement between SCORE, SOF and the treatment/ testing thresholds recommended by NOF, WHO (T≤ -2.5) and SOF*	SCORE ≥ 7, SOF ≥ 5	Sens, spec and AUROC presented for SCORE and SOF, for NOF treatment guideline, WHO criteria and SOF-based intervention. Respectively, SCORE identified 89%, 93% and 96% of women below the thresholds for intervention; SOF identified 30%, 32% and 85%. SCORE AUROC for identifying women recommended for treatment by NOF = 0.73 (SE 0.03); for identifying women with T score < -2.5 =0.73 (SE0.03); for identifying those recommended by SOF* = 0.68 (SE 0.03). SOF-based tool AUCROC for identifying women recommended for treatment by NOF = 0.56 (SE 0.03); for identifying women with T ≤ -2.5=0.54 (0.03); recommended for treatment by SOF decision rule*	Yes - this is a validation study of other measures
Cadarette et al, 2000[55]	BMD at 3 levels: 1) T score < -1.0 2) T score ≤ -2.0 3) T score ≤ -2.5 (compared to normal BMD for young Canadian women)	"Osteoporosis Risk Assessment": age (45-54=0 pts; 55-64=5 pts; 65-74=9 pts; ≥75=15 pts), weight (60kg; 60-69kg:or ≥70kg) current estrogen use (yes/no). Women with score ≥ 9 would be selected for DXA screening	Derivation cohort: 1) Sens = 77.1% Spec = 45.1% PPV 32.5% 2) Sens = 90% Spec = 45.1% PPV =32.5% Area under ROC = 0.789 (SE 0.017) 3) Sens = 97.0%; spec = 41.3% PPV 0 16.9%. ROC presented is for derivation cohort only, not the validation cohort	Yes, validated in 450 women. 1) Sens =77.2% Spec = 56.8% PPV = 71.3% 2) Sens = 93.3% Spec = 46.4% PPV = 16.9% 3) Sens = 94.4% Spec = 41.4% PPV 18%

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Cadarette et al, 2001[56]	2365 menopausal women from the CaMOS	Baseline: 755 (31.7%) had normal BMD, 1390 (58.3%) had BMD T score between -1.0 and -2.5, 239 (10.0%) had T score <-2.5	Excluded women with physician-diagnosed bone disease, use of bone sparing medication other than ovarian hormones, missing data for any of the risk factors required by decision rules or NOF guidelines	Cross-sectional analysis of cohort data
Cadarette et al, 2004[57]	Women aged ≥45 presenting for BMD testing and women attending two family practice clinics affiliated with the University of Toronto. 140 women from prospective recruitment and 504 from retrospective recruitment	238 (38.5%) had normal BMD; 290 (45%) had BMD T score between -1.0 and -2.5, 106 (16.5%) had BMD ≤ -2.5	Excluded women using bone sparing drug other than hormone replacement, prior fragility fracture, secondary cause for osteoporosis or missing DXA	Combination of prospective and retrospective chart review methods

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Cadarette et al, 2001[56]	BMD at 3 levels: 1) T score < -1.0 2) T score ≤ -2.0 3) T score ≤ -2.5	NOF, SCORE, ORAI, ABONE, weight criterion (women <70 kg)	AUC for T score ≤-2.5: NOF = 0.70 (0.02) SCORE = 0.80 (0.01) ORAI = 0.79 (0.01) ABONE = 0.72 (0.02) Weight criterion = 0.79 (0.02)	Yes - this is a validation study of other measures
Cadarette et al, 2004[57]	BMD T score ≤ -2.5	Body weight criterion, ORAI, OST equation (previously described) and OST chart tool developed for this study	ORAI sens = 92.5%,spec 38.7% OST equation sens = 95.3%, spec = 39.6% OST chart sens = 91.5%, spec = 45.7% Body weight sens = 93.4%, spec = 34.6% AUC results: ORAI: 0.802 (SE 0.02) OST chart: 0.818 (SE 0.02) OST equation: 0.822 (SE 0.02) Body weight: 0.733 (SE 0.02)	Yes - this is primarily a validation study of other measures; OST chart tool is new and not validated

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Carranza-Lira et al, 2002[58]	400 post-menopausal women, Mexico City	Mean FN BMD = 0.858 (SD 0.128). Mean L-L4 = 1.028 (SD 0.147).	Enrolled consecutive attendees at menopause clinic	Cross-sectional analysis of cohort data (logistic regression)
Carranza-Lira et al, 2002[59]	1,088 post-menopausal women, Mexico City	Mean L1-L4 BMD: 0.987 (0.157 SD) Mean BMD in FN: 0.834 (0.130 SD) Mean BMD in Ward's triangle: 0.705 (0.147 SD)	Enrolled consecutive attendees at menopause clinic	Cross-sectional analysis of cohort data (logistic regression), and comparison with T test.
Carroll et al, 1997[89]	117 women ages 40-80	Mean LS BMD = 0.86±0.16gm/cm2 (SD)	Postmenopausal women (normal and osteoporotic) who were screened for or qualified to participate in osteoporosis trials. Targeted recruitment of normal and those with atraumatic vertebral fractures	Cross-sectional analysis of cohort data

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Carranza-Lira et al, 2002[58]	BMD (unclear what the cut-off was)	Age, BMI, time since menopause (each assigned a score	Present odds ratios for the risk factors (time since menopause, BMI, age). No ROC presented	Yes. Appears that the validation study (this one) includes the women in the derivation cohort (above), but also validated against T score
Carranza-Lira et al, 2002[59]	BMD (unclear what the cut-off was)	Age, BMI, time since menopause (each assigned a score	Sens/spec appears to be correlation between clinical index and BMD at LS and FN. No ROC presented	Yes. Appears that the validation study (this one) includes the women in the derivation cohort (above), but also validated against T score
Carroll et al, 1997[89]	Vertebral Fracture	BMD, age, years since menopause and weight	Figure of ROC presented for T score ranging 0 to -4.0, but no actual numbers given	No

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Cass et al, 2006[60]	N=226 postmenopausal women age $\geq$ 45 years	Normal BMD in 49-68% (reported by race/ethnic group	Recruited from university based family medicine clinic	Cross-sectional analysis of prospectively collected data
Colon-Emeric et al, 2002[90]	Duke and Iowa EPESE study Community dwelling older men and women age 65 and older. N=4,149 from Duke and 3,505 from Iowa	BMD not reported	Probability sample of community-dwelling adults	Analysis of prospective cohort data

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Cass et al, 2006[60]	BMD	Female, age ≥45 years; excluded women taking bone active medication or those with other bone diseases (Paget's, hip replacement) and women who exceeded the weight limit of the DXA scanner	ROC overall for ORAI 0.74 (0.63-0.84); for SCORE 0.67 (0.54-0.79)	Yes - this study is a validation of SCORE and ORAI instruments
Colon-Emeric et al, 2002[90]	Fracture (hip and all fractures)	Gender (female), age > 75 years , white race, BMI <22.8 kg/m2, history of stroke, cognitive impairments (Short Portable Mental Status Questionnaire ≥3 errors), 1 or more ADL impairments, one of more Rosow-Breslau impairments, anti-epileptic drug use	ROC presented for 3 models predicting fracture in each cohort. Significant risk factors for all subsequent fractures and/or hip fracture in the developmental cohort included: female sex (relative hazard 1.9–2.3), lowest quartile of BMI (1.3), Caucasian race (2.1–2.8), 1+ Rosow–Breslau physical function impairments (1.8–2.1), age 75+ years (2.1), history of stroke (1.9), cognitive impairment (2.2), 1+ impairments in the activities of daily living (1.5) and anti-seizure medication use (2.0). Three predictive models were highly significantly correlated with subsequent fractures with c-statistics in the developmental cohort at 3 and 6 years of 0.640–0.789. A simple count of risk factors had similar discriminative ability to the full model with a linear 35–65% increase in hazard of all fractures and hip fracture for each additional risk factor	Yes – this is a validation of Duke results using Iowa cohort. Sex, BMI and Rosow–Breslau impairment achieved significance in the validation cohort

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Cook et al, 2005[61]	208 postmenopausal women (69% osteopenic or osteoporotic)	Osteoporotic at LS or hip: 21.6% (n=45) Osteopenic: 47.6% (n=99) Normal BMD: 30.8% (n=64)	Recruited through DXA clinics at Great Western Hospital, Swindon, UK. All were referred due to presence of 1+ clinical risk factor for osteoporosis. No exclusion criteria	Cross sectional
Crabtree et al, 2002[91]	Women > age 60 who suffered hip fracture, approached after surgery for evaluation with DXA on contralateral hip	NR	Subjects were a randomized subsample from two of the 10 participating sites for EVOS (European Vertebral Osteoporosis Study). 68 cases were from 2 sites, 800 controls from 11 centers	Case control study of Lunar DXA to predict fracture. Mainly a study of DXA - BMD, BMC, comparative stress, fall index, hip axis length (HAL)

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Cook et al, 2005[61]	BMD as measured by DXA at the LS and TH. Compares use of ultrasound techniques to use of questionnaires	8 tools assessed: OST (age and body weight) ORAI (age, weight and estrogen use) OSIRIS (age, weight, HRT use and history of low trauma fracture) SOFSURF (derived from SOF, includes age, weight, smoking, and history of postmenopausal fracture) pBW (body weight with >70 kg = low risk, between 57-70kg = moderate risk, and <57 kg = high risk) SCORE (race, rheumatoid arthritis, history of non-traumatic fracture, HRT use, age and weight) Sunlight Omnisense ultrasound CUBA Clinical ultrasound	Compared AUC for the ROC curves for each risk system and for the two ultrasound systems. AUC for T score of -2.5 was best for OSIRIS (0.747). Reported for each risk tool and for U/S measures for T score of -2.5, -2.0 and -1.0. Overall correlation between the questionnaires was moderate to excellent (r2=0.46-0.95). Compared sens/spec for various cut-off points for the risk instruments also. OSIRIS AUROC=0.747 (0.805-0.702) SOFSURF AUROC=0.717 (0.77-0.670) ORAI AUROC = 0.664 (0.739-0.595) OST AUROC= 0.716 (0.775-0.669) SCORE AUROC= 0.720 (0.779-0.674) Distal radius AUROC=0.676 (0.731-0.628) Proximal phalanx AUROC=0.678 (0.737-0.629) Mid-shaft tibia AUROC=0.582 (0.645-0.521) Sunlight combined AURCO=0.698 (0.751-0.654) BUS calcaneus AUROC=0.766 (0.805-0.743) VOS calcaneus AUROC=0.723 (0.781-0.676) pBW AUROC=0.655 (0.708-0.684)	Yes - this is a validation study of previously derived instruments.
Crabtree et al, 2002[91]	Fracture	Age, BMI, FN BMD, c-stress in various combinations	FN-BMD AUROC curve was highest: 0.827 (no CI given). Age AUROC 0.788 (no CI given) Lower FN-BMD AUROC = 0.795 Upper FN-BMD AURCO = 0.825 BMI AUROC= 0.741 Compressive stress AUROC = 0.746 FN-BMD and age, AUROC = 0.856 Compressive stress and age, AUROC = 0.847 FN-BMD, age, and BMI = 0.863 Compressive stress, age and BMI AUROC = 0.875	No

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
D'Amelio et al, 2005[62]	Postmenopausal women presenting for BMD testing, n=525 Caucasian women	32.2% were osteopenic, 20.4% were normal, 47.4% were osteoporotic	NR	Cross-sectional analysis of prospectively collected data
Dargent-Molina et al, 2002[92]	Data from 7,575 French women age $\geq$ 75 years from the EPIDOS study. Subset of these for derivation and testing	Mean BMD FN: 0.71 (SD 0.11)	Women with hip fracture or bilateral hip replacement were excluded. From the complete cohort, this analysis excluded women with prolonged corticotherapy or immobilization	Analysis of prospective cohort data. Derivation of risk score used 1,588 women with weight below median and T score between -3.5 and -2.5 to determine risk factors (multivariate analysis); used entire analytic sample (n=6933) to evaluate sens/spec. Goal was to use risk assessment for those women with FN T-score between -2.5 and -3.5, those with weight below average and compare this to those identified as high risk on the basis of FN BMD <-3.5 alone

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
D'Amelio et al, 2005[62]	BMD	NOF, OST, Body weight, ORAI and AMMEB decision rule (age, years after menopause, age at menarche and BMI)	AUC for osteoporosis: NOF = 0.60; OST = 0.33, ORAI = 0.2, body weight = 0.13, AMMEB decision rule = 0.71-0.73. No SE or CI reported.	Yes, this is a validation of other measures (NOF, OST, body weight and ORAI). AMMEB is not validated
Dargent-Molina et al, 2002[92]	Fracture	Weight is used to select those in whom to measure BMD (yes for those with weight <59kg). Evaluated risk factors were age, history of falling, tandem walk, gait speed and visual acuity. Tried to simplify the score by excluding visual acuity, gait speed and tandem walk. Final score = age, history of falling, tandem walk, gait speed	Proposed strategy has a sens of 37.3% and spec of 15.5% for hip fracture. Reports incidence per 1,000 woman-years for fracture, according to risk score. The use of clinical risk score for women with T score between -3.5 and -2.5 and weight below average improves sens over BMD alone. Selective BMD screening followed by clinical risk assessment has approximately the same discriminant value for hip fracture as systematic BMD screening	No. The risk score (threshold) was derived from the overall cohort (n=7575) and was evaluated using a subset of that cohort (n=5910)

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Dargent-Molina et al, 2003[93]	5,910 women, mean age 80.5 years. EPIDOS	Mean BMD FN: 0.72 (SD 0.11)	From EPIDOS French cohort study	Comparison of screening strategies: 1) BMD alone, 2) QUS alone; 3) QUS triage followed by BMD, and 4) selective BMD screening followed by clinical evaluation.
De Laet et al, 2005[94]	Theoretical modeling paper that used risk factors from women in the Rotterdam Study, but arbitrary weights to calculate risk scores	NR	Rotterdam cohort	Created a theoretical continuous risk score for women age 55 years and older using arbitrary weights, based on age, BMD and previous fracture. Tested this risk indicator for normality. Assumed normal distribution for the risk indicators.
Devlin et al, 2007[63]	671 women age 45-70 years.	TH, FN, LS	Excluded pregnant women	Compared diagnostic ability of dental radiographs to NOF and ORAI

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Dargent-Molina et al, 2003[93]	Fracture	Weight is used to select women for DXA. Clinical risk factors evaluated after DXA included age, fall history, balance performance and gait speed	Reports sens and spec for the screening strategies. Determined that all 4 strategies were equivalent in distinguishing high risk (>20 per 1,000 person years) from a person at low risk (below the average population). Two strategies with best discriminatory value compared to systematic BMD screening are 1) QUS triage and 2) selective BMD screening + clinical evaluation. QUS triage: sens 32%, spec 89% selective BMD screen + clinical evaluation: sens 36%, spec 86%. No ROC given	No
De Laet et al, 2005[94]	Fracture	Age, BMD, previous fracture	Gradient (Score/SD) ranges from 2-5. The proportion (%) of individuals detected according to a certain score/SD depends on the population risk. For example, a score/SD of 4, and a risk threshold (risk vs. population risk) of 2 (double the population risk), 24% percent of the individuals are identified	No
Devlin et al, 2007[63]	BMD	NOF (age >65, weight <57.6kg, maternal/parental history of fracture, current smoking, personal history of fracture) vs. ORAI (age, weight, estrogen)	Manual and digital radiographs of inferior mandibular cortex correlated with hip BMD (correlation coefficient = 0.328-0.460, p<0.001). ROC curves for the 3 risk tools are shown. Both manual and digital performed as well as ORAI which was superior to NOF	No

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Diez-Perez et al, 2007[95]	5,201 Caucasian women age ≥65 years in Spain	Mean BMD of right calcaneus (heel bone) Fracture group: n=311 0.403 (SD −1.58) Non-fracture group: n=4835 0.439 (SD −1.26)	Excluded Paget's disease, mult myeloma, known bone metastases, creatinine <265 umol/dL, serum ca >11.0 mg/dL, immobilization for >3 months, anomalies of the R foot interfering with U/S, therapeutic doses of fluoride (>20mg-day) for >3 months of past 2 years, or participation in any investigational study of pharmaceuticals	Cohort study with average of 3.1 years of follow-up
Donaldson et al, 2009[96]	3221 Caucasian women from placebo group of FIT, age 55-81	FN BMD T score > -2.5: n=1276	Women who were postmenopausal for 2 years or more, with low FN BMD	Analysis of risk factors and BMD from placebo group of FIT (cohort)
Durosier et al, 2008[97]	12,958 women from EPISEM which includes: 7062 women from SEMOF and 5896 from EPIDOS. Ages 70-100 years old	BMD reported for EPIDOS cohort only. Mean FN BMD T score = -2.6	NR	Longitudinal evaluation of 3 year fracture outcomes for women in 3 cohorts with risk factors and BMD ultrasound measurements

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Diez-Perez et al, 2007[95]	Fracture (incident non-spine fragility fracture)	Best model included age, history of falls, family history of fracture, personal history of fracture, Ca intake (dairy products) <250mg/day and either QUI or e-BMD T score	AUCs: All non-spine fracture = 0.672 (SE=0.016) Main non-spine fractures (hip, wrist/forearm, humerus, pelvis, clavicle, leg) = 0.680 (SE=0.017) Hip fractures 0.686 (SE=0.41) Wrist/forearm fractures = 0.676 (SE 0.026) Humerus fractures=0.689 (SE 0.038)	No
Donaldson et al, 2009[96]	Fracture	FRAX with and without age and FN BMD	Age alone: 0.65 (CI 0.62-0.69) FN BMD: 0.66 (0.63-0.70) FN BMD + age: 0.71 (0.67-0.74) FRAX without FN BMD: 0.68 (0.65-0.71) FRAX with FN BMD: 0.71 (0.68-0.74) history of fracture + age: 0.68 (0.65-0.71) history of fracture + FN BMD + age: 0.72 (0.69-0.75) baseline vertebral fracture + FN BMD + age: 0.76 (0.72-0.79) baseline vertebral fracture + FRAX with FN BMD: 0.75 (0.72-0.78)	Yes – this is validation of FRAX
Durosier et al, 2008[97]	Fracture (3 year follow-up)	5 clinical risk factors, age, BMI and QUS-derived heel SI expressed as a Z-score (validation of Hans)	No ROC reported. kappa statistic is 0.16 for all three groups. 79% of the hip fracture group was correctly classified as high risk. Among osteoporotic women, 66.4% classified in high risk group, 29% in moderate risk group and 4.6% in low-risk group	Yes – this is validation of CRF plus ultrasound (Hans, 2008)

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Ensrud et al, 2009[98]	SOF: 6252 women age 65 and older.	Mean FN BMD 0.65 (SD 0.11)	All those from SOF cohort who had data available to calculate FRAX score	Longitudinal study of cohort data
Ettinger et al, 2005[99]	Derivation: KPMC Northern California enrollment, ≥ age 45 (70% non-Hispanic white, 7.5% AA, 8% Latino, 13.5% Asian) females. Validation: Canadian Multicentre Osteoporosis Study and SOF cohorts	NR	Entire membership data used	Model derived from Geelong Australia study
Geusens et al, 2002[64]	1102 postmenopausal women from U.S. clinics, 3374 women from Rotterdam Study, 23,833 women screened for study of alendronate, 4204 women from general practice in the Netherlands	BMD at hip. Mean FN T score = -1.36	Excluded if any medical problems that precluded 3 years of participation, severe malabsorption, BP > 210mm Hg systolic or 105 mmHg diasolic, myocardial infarction within 6 months, unstable angine, hypothyroidism, hyperthyroidism, hyperparathyroidism, significant renal or hepatic dysfunction, history of major GI mucosal erosive disease, recurrent or recent ulcer disease, esophageal/gastric varicies, or dyspepsia requiring daily medication	Cross-sectional analysis of data from several different sources

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Ensrud et al, 2009[98]	Fracture (10 years of follow-up)	FRAX with BMD vs. age + BMD, and FRAX without BMD vs. age + fracture history alone	ROC for hip fracture: FRAX without BMD: 0.71 (95% CI 0.68-0.73) age + prior fracture: 0.71 (0.68-0.73) (p for comparison = 0.91) ROC for major osteoporotic fracture: FRAX without BMD: 0.64 (95% CI 0.62-66) age + prior fracture: 0.64 (0.62-0.66) (p for comparison = 0.89) FRAX without BMD: 0.61 (95% CI 0.59-0.62) age + prior fracture: 0.61 (0.59-0.63) (p for comparison: 0.70)	Yes – this is validation of FRAX and simple models
Ettinger et al, 2005[99]	Fracture	Model included modified age-based expected fracture risk with 1) low body weight, current smoking, hip fracture in mother or sister, personal fracture history and 2) deviation of BMD from age-expected value (Z score)	The model predicted non-spine fracture rates 2-fold higher than SOF and 3-fold higher than CaMOS. Model predicted spine fractures that were about 3-fold higher than CaMOS and similar to the rate in SOF. No ROC presented	Yes - Validated by comparison to actual fracture rates in CaMOS Study and SOF (instrument overestimates the fracture rates observed in SOF and CaMOS)
Geusens et al, 2002[64]	BMD	OST, ORAI, SCORE, SOFSURF and NOF definition (T score $\leq$-2.5)	AUC NR OST < -3 had LR of 8.71 ORAI >17 had LR of 5.60 SCORE > 15 had LR of 7.62 SOFSURF > 4 had LR of 0.82	This is a validation study of other measures

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Girman et al, 2002[100]	1427 white female nursing home residents age >65 years (average age 85), from 47 randomly selected nursing homes in Maryland	Mean BMD taken from distal radius of the dominant arm: 0.302 (SD -3.5)	Age >65, absence of terminal cancer and bone mets, not comatose, at least one wrist/forearm free of prosthetic implants and open lesions, not admitted for rehab only, able to have BMD measured	Prospective study with 18 months follow-up. Test of a scoring algorithm derived from minimum data set variables
Gnudi et al, 2005[65]	1187 consecutive white postmenopausal women from Bologna Italy, recruited from 1366 who were screened (709 development, 478 validation)	Mean BMD Development group n=709 Spine (L2–L4) 0.864 ± 0.158 FN 0.684 ± 0.106 (SD –2.0 ± 0.9) Validation group n=478 Spine (L2–L4) 0.879 ± 0.171[a] FN 0.691 ± 0.112[a] (SD –1.9 ± 0.9[a]) [a] T-Test: not significant compared to the development group	Women with diabetes, hyperthyroidism, liver, kidney and lung failure, malignancies, rheumatoid arthritis and long-term immobilization and those treated with glucocorticoids or other drugs known to affect bone mass	Cross-sectional analysis, logistic regression
Gourlay et al, 2005[66]	4,035 postmenopausal women age 45-96 years in Belgium; this paper focused on women ages 45-65	Mean BMD FN 45–64 years: n=2539 0.730 (0.118) 65-96 years: n=1496 0.657 (0.107)	Recruited from outpatient osteoporosis center. Excluded premenopausal pts, those with Paget's or advance OA	Secondary data analysis (previously recruited sample)

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Girman et al, 2002[100]	Fracture	Age, weight, height, locomotion on the unit (independent, supervised or limited assistance needed), fall in past 180 days, ADL score (>4, ≤4), MDS cognition scale score (≤3, >3), incontinence (usually continent or usually not, vs. occasionally incontinent)	OR for predicting fracture vs. not was 1.3 (95% CI = 1.2-1.5) in the derivation cohort. Sens for predicting fracture in validation cohort was 70.2% with spec of 38.6%, OR 2.1 (95% CI = 1.4-3.0). C-statistic for fracture = 0.63+0.043	Yes - Algorithm derived from a subset of the data, with the remainder serving as validation cohort
Gnudi et al, 2005[65]	BMD at spine and FN by DXA	For T score cutoff of -2.5: years since menopause, age at menarche, weight, previous fracture, maternal fracture, arm help to get up from standing. For T score cutoff of -2.0: years since menopause, weight, maternal fracture, arm help to get up from sitting and age	709 women from the first 8 months of enrollment in the development group. Sens reports for 99%, 98% and 97% at various cutoffs for each T score threshold. Sens ranges from 13.8-32.1% AUC: 0.744, SE 0.023	Yes – validated in 478 subjects from the last 6 months of enrollment
Gourlay et al, 2005[66]	BMD by DXA	OST, ORAI, and SCORE base on data obtained from chart review (age, weight, race, history of rheumatoid arthritis, history of non-traumatic fracture of wrist, rib or hip after age 45, and estrogen use)	Compared area under ROC of the three risk assessment tools, and compared the area under ROC for age groups: 45-64 and age > 65years. Presented LR's for the 3 risk tools (scores of low, medium, high). OST (Transformed to -OST) for age 45-64: OST AUC = 0.768 (0.730- 0.806) ORAI AUC 0.750 (0.714-0.787) SCORE AUC 0.757 (0.715-0.799) for age ≥65: OST AUC = 0.762 (0.730-0.794) ORAI AUC = 0.747 ().714-0.779) SCORE AUC = 0.745 (0.712-0.777)	Yes - this was a validation of previously derived scoring tools

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Hans et al, 2008[101]	EPISEM: 12,958 women between age 70-100 yr, from two prospective multicenter population-based cohorts (EPIDOS and SEMOF) in French and Swiss women	NR	NR	Combined prospective cohort studies
Harrison et al, 2006[67]	70 osteoporotic and 137 non-osteoporotic white women ages 55-70 referred for BMD	Mean MBD: hip FN TH LS (L1 L4) Non-Osteoporotic patients: 0.463 (SD -0.46) Osteoporotic patients: 0.369 (SD -1.64)	Reasons for referral included suggested osteopenia on radiograph, low trauma fracture, estrogen deficiency, secondary causes of osteoporosis, glucocorticoid excess or therapy, monitoring of therapy, or other reason (family history)	Cross-sectional; logistic regression used to build risk model using 1) presence or absence of osteoporosis at TH, FN or LS, 2) one risk index OSIRIS, and 3) peripheral T score measurement. Peripheral scanners and OSIRIS regression coefficients were multiplied by 10 and rounded-off to integers. Combined algorithm = integer multiplied by peripheral T score measure or risk index and these summed to produce combination algorithms

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Hans et al, 2008[101]	Hip fracture at 3.2±0.9 year	Stiffness index derived by combining BUA and SOS from calcaneal ultrasound. Clinical risk factors included: BMI, history of fracture after age 50, chair test, history of fall in past 12 months, current smoking, diabetes mellitus	Combined ages: AUC=0.66 for gradient of risk for stiffness index alone. AUC=0.62 for risk factors alone. AUC = 0.70 for combined stiffness index plus risk factors	No
Harrison et al, 2006[67]	Hip BMD measured by DXA, and calcaneal BMD measured by QUS (McCue Cuba Clinical and GE Lunar Achilles methods) and peripheral DXA (GE Lunar PIXI)	ORAI, OSIRIS, SCORE, OST, and combinations of scan + risk index: PIXA + OSIRIS, CubaClinical+OSIRIS and Achilles+OSIRIS. OSIRIS was chosen because it had the highest ROC	AUC for ROC for BMD: Achilles 0.77, CubaClinical 0.75, PIXI 0.80, SCORE 0.67, ORAI 0.67, OSIRIS 0.70, OST 0.69, CubaClinical+OSIRIS 0.78, PIXI+OSIRIS 0.82, Achilles+OSIRIS 0.81	Yes - this is a validation of previously published instruments alone and in conjunction with BMD by QUS

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Henry et al, 2008[102]	Women > 50 years who had sustained a fracture of hip, spine, humerus, and wrist after low-trauma event (n=291, mean age 72); and a control population who had not sustained a fracture (n=823); mean age 70 years	BMD at FN ranges from 0.710-0.844 g/cm^2	Pathologic fractures excluded	Case control
Hippisley-Cox et al, 2009[103]	535 practices in England and Wales. Men and women. Derivation cohort: 2,357,895 Validation cohort: 1,275,917	NR	Excluded if prior fracture	Analysis of administrative data – development of the risk assessment tool by proportional hazards regression, and subsequent validation
Kanis et al, 2007[104]	9 population based cohorts for development and 11 population based cohorts for validation	NR, but available from published reports of each cohort	Varied for each cohort	Meta-analysis of individual person-level data, with regression to derive risk factors

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Henry et al, 2008[102]	Fracture	Fracture Risk Score (T score, age and interaction term derived from discriminant analysis)	No AUC reported	No, this was derivation
Hippisley-Cox et al, 2009[103]	Fracture	QFracture: 17 risk factors identified from derivation cohort	ROC for hip fracture: 0.89 for women and 0.86 for men. ROC for overall fracture: 0.79 for women 0.69 for men	Yes, separate validation cohort
Kanis et al, 2007[104]	Fracture	Risk factors chosen based on prior work. Age, BMI, family history of fracture, glucocorticoids, prior fracture, even smoking, alcohol use, rheumatoid arthritis, and FN BMD	Risk factors were chosen based on prior work. AUC for hip fracture age 50: BMD along	Yes, separate validation cohorts

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
LaCroix et al, 2005[117]	Women aged 60-80 randomly sampled from HMONTHS and followed for 33 months (recruited 9,268 women	Mean BMD TH posterior–anterior spine	Excluded women on hormone therapy or osteoporosis medication for the previous 12 months	RCT of three screening strategies: 1) Universal screening group - all offered BMD testing 2) SCORE group, invited for BMD only if $\geq$7 on the SCORE questionnaire 3) SOF group, invited for BMD only if $\geq$ 5 hip fracture risk factors
Leslie et al, 2003[105]	213 consecutive Caucasian postmenopausal women presenting to bone density program in Sr. Boniface General Hospital, age 50-88	Mean BMD: TH 0.872 (SD 0.143) Hip t-score (-1.1±1.2) Hip z-score (0.0±1.1)	Excluded women with age <50, non-white, and those for whom the risk factor profile was incomplete	Comparison of two strategies for predicting absolute fracture risk using BMD alone or with clinical risk factors
Leslie et al, 2009[106]	16,205 white women $\geq$50 years of age living in Manitoba, CA who had a bone density between 1998-2002	Baseline BMD T scores: TH: -1.1$\pm$1.2 FN: -1.3$\pm$1.2 LS: -1.3$\pm$1.2	For patients with more than one DXA measurement, only the first was used	Retrospective cohort study

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
LaCroix et al, 2005[117]	1) Initiation of osteoporosis treatment; 2) Fracture rate (hip and total) over 33 months of follow-up. 3) Knowledge of osteoporosis 4) change in fracture risk factors 5) satisfaction with the program	Universal - none SCORE: age, race/ethnicity, RA, prior fracture, ever taken estrogen, current weight. SOF: health status, AA race, smoking, 1st degree relative with hip fracture, weight loss since age 25, dementia, use of corticosteroids, anti-epileptic medications, long-acting benzodiazepines, walk for exercise, get up and go unassisted, prior fracture at age 50 or older, current age >80 years, postmenopausal not on hormone therapy, ambulation <4 hrs/day, HR>80 bpm at rest, height of 5'7"or taller at age 25	Osteoporosis treatment rates did not differ among all women contacted, but were slightly higher among universal and SCORE groups (NS). BMD testing was performed in 100% of the universal group, 73.8% of the SCORE group, and 6.9% of the SOF group	Yes - this is a validation study of SCORE, SOF
Leslie et al, 2003[105]	Absolute fracture risk, but not known fracture risk	Comparison of two models: 1) full model which includes age, clinical risk factors, bone density -this described in Leslie 2003 Journal of Clinical Densitometry and 2) BMD alone. Full model starts with risk estimates for average women of equal age then sequentially incorporates the clinical risk factors and TH BMD (fracture after age 50, reduced health status, unable to rise from chair without arms, height at age 25 >168cm, past hyperthyroidism,height loss > 3cm, fall in past 12 mo, on feet < 4 hrs per day, current smoker, family history, current weight < 57.8kg	Average results for the two models were similar, but there was considerable scatter in the Bland-Altman plots indicating a large amount of disagreement between the risk estimates	Yes, this is a validation study of Osteoporosis Canada risk instrument
Leslie et al, 2009[106]	Fracture	Simplified (semiquantitative) system uses age, sex, measured BMD; estimation of 100-yearabsolute fracture risk is summarized on a pocket-sized laminated card available from the author	No ROC presented	Yes

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Lindh et al, 2008[68]	600 women aged 45-70 from 4 centers (Greece, Sweden, UK and Belgium). Recruited at routine/emergent dental visits, from hospital/university/local staff and advertisements/ word of mouth, and women undergoing DXA with noted T score <-2.5	473 people had normal BMD, 127 had T score <-2.5	Targeted a high risk population that included those with known osteoporosis, prior fragility fracture, early menopause, low body weight (thinness), family history of osteoporosis or loss of height. Excluded women with prior treatment for low BMD, secondary osteoporosis, primary hyperparathyroidism, thyrotoxicosis, malabsorption, liver disease, alcoholism	Cross sectional analysis, inter-rater reliability was evaluated between 5 observers
Lynn et al, 2008[69]	4,658 U.S. Caucasian men and 1914 Hong Kong Chinese men	Reported elsewhere	MrOS: community-dwelling older men (age $\geq$65 years) in the U.S. Similar for Hong Kong. Excluded if bilateral hip replacements or unable to walk without assistance	Cross-sectional analysis of cohort data

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Lindh et al, 2008[68]	BMD T score ≤ -2.5	Periapical radiography of the premolar region of the upper and lower jaw	AUC NR. Diagnostic LR for various patterns at the upper and lower jaws ranged from 2.20 to 15.35	No.
Lynn et al, 2008[69]	BMD T score ≤-2.5	MOST = body weight and QUI. OST, body weight and QUI also evaluated separately	AUC for T score < -2.5 at any site (LS, TH or FN): OST = 0.714 (SE 0.012). MOST=0.799 (includes QUI). QUI = 0.738 (SE 0.014). Weight = 0.702 (SE 0.014)	Yes - this is a validation of OST, MOST, QUI and weight

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Martinez-Aguila et al, 2007[70]	665 Spanish postmenopausal women (mean age 54) referred by gynecologist for BMD testing. Frequency of osteoporosis at either LS or FN = 17.6% (16.7% at LS, 3.8% at FN)	Mean BMD: LS 0.906 ± 0.146 t-score: -1.19 ±1.38 z-score: -0.14 ± 1.14 FN 0.742 ± 0.108 t-score: -0.90 ± 0.99 z-score: -0.02 ± 1.10	Excluded women with age < 40 or > 69 and missing data	Cross-sectional
Masoni et al, 2005[71]	195 (131 + 64) postmenopausal women attending menopause clinic (original cohort and separate validation cohort)	Mean BMD Lumbar (L2-L4) (grouped post-test) Normal: n= 33 1.0037 ± 0.017 Osteopenic n= 52 0.816 ± 0.005 Osteoporotic n= 46 0.660 ± 0.008	Excluded primary hyperparathyroidism, Paget´s, estrogen treatment	Cross-sectional
Mauck et al, 2005[72]	202 women age > 45 years enrolled in the Rochester Epidemiology Project	Mean BMD FN: Greater than −2.0 95 (47) −2.0 or less 107 (53) −2.5 or less 69 (34) Age 45-64 years 11 (5) Age 65 years 58 (29) LS: −2.5 or less 15 (7) Age 45-64 years 3 (1) Age 65 years 12 (6)	Secondary data analysis, cross-sectional	Excluded dementia, pregnancy, radiation workers, those participating in a trial of osteoporosis medications

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Martinez-Aguila et al, 2007[70]	BMD	Comparison of 4 decision rules: ORAI, OST, OSIRIS and body weight criterion	AUROC, sens, spec, PPV, NPV or 4 tools in total population. AUC for OST = 0.640 (0.586-0.694) ORAI = 0.615 (0.560-0.671) OSIRIS = 0.630 (0.573-0.687) BWC = 0.586 (0.532-0.639) In a subset of 507 women without low impact fracture: OST = 0.661 (0.599-0.724) ORAI 0.634 (0.570-0.699) OSIRIS = 0.635 (0.566-0.704) Body weight criterion = 0.585 (0.522-0.648)	Yes - This was a validation testing of 4 instruments
Masoni et al, 2005[71]	BMD	Final model included BMD, calcium intake, menopause > 10 years, kyphosis, personal fax, kyphosis and personal fracture	ROC = 0.833 (0.757-0.909). Also report probability of osteoporosis for various risk factors combinations.	Yes - Validated in 64 people
Mauck et al, 2005[72]	BMD	Comparison of 3 risk prediction rules: SCORE, ORAI, and NOF (age >65, weight<57.6kg, history of fracture after age 40, family history of fracture after age 50, current smoker)	ORAI LR=1.5 (ROC 0.84) SCORE LR=1.3 (ROC 0.87) NOF LR=1.1 (ROC 0.70)	Yes - this is a validation study of ORAI, SCORE, NOF

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
McGrother et al, 2002[107]	1289 women age ≥70 years followed for 5.5 years or until death. Population-based sample from England.	Mean BMD: BUA of the calcaneus (heel bone) 65.2 (SD 21.4)	Invited by letter from Chiropody clinic in Leicestershire, England, included women in residential care	Multivariate analysis of 3 and 5 year follow-up data
Miller et al, 2004[108]	57,421 postmenopausal white women with baseline T score -2.5 to -1.0	Mean BMD: Forearm / Heel (pooled results) With fracture (n = 1130) −1.72 (SD 0.41) With no fracture (n = 56 291) −1.61 (SD 0.40)	Age < 50, osteoporosis, BMD measured within past 12 months, use of bisphosphonate, calcitonin or raloxifene, participation in any other trial for osteoporosis	Multivariate analysis using classification trees

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
McGrother et al, 2002[107]	Fracture	3 year model: weight, trunk maneuver, epilepsy, kyphosis, poor circulation, short term steroid use. 5 year model: weight, reported poor health, epilepsy, age	OR for 3 year and 5 years models, also AUROC for both. ROC for 3 year = 0.82 ROC for 5 year = 0.73	Not – Internal validation only (cross-validation in SAS using a one-step approximation method)
Miller et al, 2004[108]	Fracture	NORA 32 risk factors entered into regression tree to build algorithm. Tree-based prediction rule included: previous fracture, T score by central DXA, health status (fair or poor), poor mobility (2 or more positive responses to 4 questions)	Algorithm correctly classified 74.1% of women who experienced a fracture within 1 year. Identified 55% of women as being at risk for fracture	No – Internal validation only (10-fold cross validation by splitting the data into approximately 10 parts)

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Minnock et al, 2008[73]	274 postmenopausal women, Caucasian referred to DXA scanning clinic at Great Western Hospital, Swindon, UK	23.8% had BMD T score of ≤-2.5 at any site	Excluded if disease known to cause secondary osteoporosis	Cross sectional analysis of prospectively collected data
Nguyen et al, 2004[74]	1256 women from the DOES	Mean BMD: Development cohort (n=846) FN 0.77±0.13 LS 1.03 ± 0.19 Validation cohort (n=410) FN 0.77 ± 0.13 LS 1.03 ± 0.19	Women age ≥60 years living in Dubbo	Analysis of longitudinal cohort data. Development and validation performed by randomly dividing the sample into two groups: 846 for development and 410 for validation) of the DOEScore
Nguyen et al, 2007[109]	1208 women and 740 men (98% Caucasian) from the DOES with 13 years of follow-up	Mean BMD: FN −0.12 (HR 2.62) LS −0.20 (HR 2.37)	Population-based recruitment, age ≥60 years living in Dubbo, Australia.	Development of a nomogram-based risk assessment tool using Bayesian model average analysis leading to most parsimonious model

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Minnock et al, 2008[73]	BMD by DXA	QUS measurement using CUBA Clinical system and Sunlight Omnisense; combined QUS measurement with risk factors. Also tested OSIRIS	OSIRIS ROC = 0.80 (those between ages 60 and 80). ROC for risk factors alone = 0.85 (TH) and 0.79 (lumbar spine). Questionnaire and broadband ultrasound attenuation: 0.82 for LS and 0.91 for TH	Yes for OSIRIS. The new measure described here is not validated
Nguyen et al, 2004[74]	BMD and Fracture	DOEScore: Age, body weight and history of fracture. Compared to FOSTA, SOFSURF, ORAI	ROC curves for DOEScore only; also compared sens and spec for DOEScore with FOSTA, SOFSURF and ORAI . AUC for T score <-2.5 =0.75 AUC for T score <-2.0 = 0.72 (LR+=1.49). AUC for incident fracture = 0.48. DOEScore for T <-2.5 in valid cohort LR+=1.71). DOEScore for T<-2.0 in validation cohort LR+=1.49. LR+ for FOSTA = 0.54 LR+ for SOFSURF = 1.23. LR+ for ORAI = 1.88	Yes Sens = 0.82 and Spec = 0.52 for selecting women with T score < -2.5 in the validation cohort
Nguyen et al, 2007[109]	Fracture	Age, BMD (FN BMD T-score), prior fracture, fall in the last 12 months	ROC curves: women AUC=0.85 (no CI) men AUC=0.85 (no CI) Compared this to BMD alone: men 0.78 (no CI) women 0.80 (no CI)	No

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Pluijm et al, 2009[110]	4157 women age ≥ 60 years from the Rotterdam Study (mean follow-up 8.9 year), 762 women age ≥65 year from the LASA study (mean follow-up 6.0 years)	NR	Rotterdam is a prospective, ongoing cohort study of men and women age 55, in Rotterdam. LASA is an ongoing cohort study of older men and women (55-85) in the Netherlands (west, northeast and south regions). Exclusions include missing data for both hips and fragility fractures	Linear regression to identify risk factors and develop a risk score. Validation by imputation
Reginster et al, 2004[75]	889 postmenopausal women from rheumatology clinics in France	NR. 16.6% and 24.2% of the development and validation cohorts had BMD T score < -2.5	Postmenopausal women seen in rheumatology clinics	Cohort recruitment was not standardized or sequential. Two participants recruited by each rheumatologist. Cross-sectional evaluation
Richards et al, 2007[111]	6646 men and women from CaMOS, 71.2% women and 95.6% white	Mean BMD: TH, FN, Trochanter LS (L1–L4)	Only those who underwent baseline BMD testing were included in analysis. Original cohort was population based, enrolling women living within 50km of 1 of 9 regional centers, non-institutionalized	Comparison of 3 risk prediction tools
Richards et al, 2008[116]	Men > age 50 attending a rheumatology clinic	Low BMD: 29 (57%)	Male patients over the age of 50 who completed a checklist were eligible. Patients with a prior diagnosis of osteoporosis were on treatment for osteoporosis, or previously had a DXA were excluded	Men presenting for clinic were given a checklist of risk factors. Retrospective comparison evaluating DXA requests before and after the intervention

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Pluijm et al, 2009[110]	Hip fracture and fragility fracture (hip, pelvis, proximal humerus and wrist)	Age, prior fracture, body weight <60kg, use of a walking aid and current smoking	AUC = 0.77 for hip fracture, 0.71 for fragility fracture. Compared this to FRAX which had AUC of 0.76	No – internal validation only (validation by imputation: models were constructed in each of five data sets that were completed by imputation; then internally validated using bootstrapping techniques)
Reginster et al, 2004[75]	BMD	Age, body weight, current HRT use and history of previous low impact fracture	No ROC presented. In validation cohort, prevalence of osteoporosis in those with OSIRIS score <-3 was 62%. Prevalence of osteoporosis in those with OSIRIS score > +1 was 16.8%	Yes, this is the validation of OSIRIS as previously published
Richards et al, 2007[111]	Fracture	1) Age, sex and 2 clinical risk factors; 2) comprehensive - age, sex, BMD and seven clinical risk factors; and 3) WHO 1994 BMD based system	Prevalence of high risk for osteoporotic fracture by age group for men and for women. Comparison of T score $\leq$ -2.5, simplified risk factor system and comprehensive risk factor system. No ROC reported	Yes - This is a validation study of other risk assessment instruments
Richards et al, 2008[116]	Clinician referral of pt for DXA	Adapted the SOF ten-item checklist to be used for men, leaving off question about hypogonadism because of concern about acceptance. Final risk factors: weight <130 lbs, fracture after age 50, medications (seizure, thyroid, steroid), alcohol >3/day, rheumatoid arthritis, avoid dairy, elderly relatives with fracture, hormonal therapy for prostate cancer, shorter now than at age 25, ever smoked >10 cigarettes/day for >10 years	Before the checklist intervention: 14% of men over age 65 had DXA, 5% of AA and 29% of whites. After the checklist intervention: 32% of men had DXA request, 23% of AA and 46% of whites.	No

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Richy et al, 2004[76]	Two cohorts of postmenopausal women aged 45 years and older recruited from public screening: 407 in development cohort and 202 in validation cohort	Mean BMD: FN Development cohort: 0.72 (0.13) Validation cohort: 0.73 (0.15)	Osteoporosis, Paget disease, RA, use of bone active drugs other than HRT	Comparison of QUS at the phalanx alone, in ORACLE to OST
Robbins et al, 2007[112]	93,676 women from the observation al component of WHI (development) and 68,132 women from the clinical trial (for validation) Tested the addition of BMD in 10,750 women who had BMD measured by DXA	BMD performed only on 10,750 women. Pts not recruited on the basis of osteoporosis	Postmenopausal women aged 50-79. Women were ineligible if they did not want to discontinue hormone therapy upon entry, or had a history of breast cancer; they were ineligible for the diet portion if they already followed a low-fat diet or too frequently ate away from home; they were ineligible for the calcium/vitamin D component if they had a history of kidney stones or were unwilling to limit vitamin D intake. Those who were screened for the clinical trial but were ineligible or unwilling to participate in randomization were asked to enroll in the observational study	Prospective cohort study derived from both observational cohort and RCT cohort. 5 years of follow-up

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Richy et al, 2004[76]	Femoral neck BMD	ORACLE index constructed from validation cohort by use of logistic regression. QUS UBPI, age, BMI, current HRT use, and history of fracture at age > 45 years	In the derivation cohort, AUC for ORACLE were 0.81 for osteoporosis (T<-2.5) and 0.76 for low bone mass or osteoporosis (T<-1.0). Cutoff of 0.27 for ORACLE sens was 90% and spec was 50% for osteoporosis. AUC for OST = 0.76 (SE0.033, CI 0.70-0.83) AUC for ORACLE = 0.81 (SE 0.03, CI 0.75-0.87)	Yes - In the validation cohort, AUC for identifying osteoporosis and low bone mass were 81% and 76% for ORACLE, 69% and 64% for QUS T score, 71% and 68% for QUS UBPI, and 76% and 75% for OST, respectfully
Robbins et al, 2007[112]	Hip Fracture at 5 years	General health, height, weight, fracture after age 55yr, race/ethnicity, physical activity, current smoking, parental hip fracture, corticosteroid use, diabetes, age	In development cohort: AUROC for all 11 risk factor model: 0.80 AUROC for age alone: 0.76 AUROC for all predictors except age: 0.67 All other risk factor had AUC <0.60 individually. (no CI given). In the validation cohort: 0.80 (0.77-0.83) In the 10,750 women who had BMD measured: AUC for BMD alone = 0.79 (0.73-0.85) WHI algorithm AUC = 0.71 (0.66-0.76) DXA plus WHI algorithm =0.80 (0.75-0.85)	Yes, used RCT cohort for the validation; performed secondary analyses excluding and including each different treatment arm with no change in AUC (all 0.78-0,81)

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Rud et al, 2005[77]	2016 white women recruited for the Danish Osteoporosis Prevention Study	Mean BMD: LS (L2–L4): 1.027 (0.139) FN: 0.797 (0.114) TH:0.917 (0.118)	Excluded: metabolic bone disease including osteoporosis (non-traumatic vertebral fractures on x-ray), 2) current estrogen or past 3 months, 3) current glucocorticoid use, 4) current or past malignancy, 5) thromboembolic disease, 6) newly diagnosed or uncontrolled chronic disease or 7) alcohol or drug dependency.	Test of SCORE; ORAI and OST as to whether they yield 90% sens; compare performance of case finding based on presence of a major risk factor vs. the three decision rules for younger women with low BMD for densitometry
Russell et al, 2001[78]	989 postmenopausal women > age 45, referred for DXA BMD testing (95% Caucasian)	Mean BMD: Spine Hip	Outpatients from Northern Alberta, referred for DXA, otherwise unselected.	Assessment of SCORE to predict BMD
Salaffi et al, 2005[79]	1,522 postmenopausal women > age 50, who underwent DXA (outpatient osteoporosis center) in Italy	Mean BMD: FN: 0.701 ± 0.125 LS (L1–L4): 0.889 ± 0.146	Exclude those taking bone active medications (ovarian hormones, calcitonin, bisphosphonates, fluoride)	Development and validation of OPERA tool

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Rud et al, 2005[77]	BMD by DXA at L2-L4, FN and TH	SCORE, ORAI, and OST vs. case finding based on presence of a major risk factor (CFMRF). CFMRF defined as one or more of the following: age at natural menopause < 45 years, secondary amenorrhea > 1 year, hip fracture in mother, BMD <19kb-m2, fragility fracture >45 years (wrist, hip, spine, rib, humerus, pelvis), rheumatoid arthritis, COPD, immobilization > 1 month after age 45 years	ROC analysis for various cut-offs for all 4 risk assessment tools (sens, spec, PPV, NPV, number needed to refer to identify one women with lowest T score $\leq$ -2.5)	Yes for SCORE, ORAI and OST. No for CFMRF
Russell et al, 2001[78]	BMD (T score < -2.5)	Age, atraumatic fracture history over age 45, rheumatoid arthritis, race, estrogen treatment, weight	False positives, true positives, true negatives, and false positives for L spine and FN, by age group	Yes - This is a validation study of SCORE, approach of using cut-point of <10 validated in prospective study of 54 pts over age 65
Salaffi et al, 2005[79]	BMD	Estrogen (never), diseases affecting the skeleton, late puberty (after age 15), family history of osteoporosis and > 6 months use of medications affecting the skeleton	ROC, discriminatory performance for T = -2.5 at the LS and FN, by number of variables in the algorithm (1-5)	Yes - This was the validation of the OPERA tool, derived from systematic review of the literature about risk factors, and expert input for content validity

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Sandhu et al, 2010[113]	Medical records of patients attending Fracture and Bone and Calcium clinics in Sydney Australia; n=200. 56 men and 144 women Caucasian age 60-90	Mean T score for groups (men/women, fracture/no fracture): -1.7 to -2.2	Included if data available; excluded if any prior major osteoporotic fracture, any treatment with bone-specific agent for > 30 months, or presence of metabolic bone disorder (Paget's, skeletal mets)	Chart review
Sedrine et al, 2002[80]	1303 postmenopausal women from outpatient clinic	Mean BMD Spine: 1.210 (± 0.15) TH: 0.890 (± 0.10) FN: 0.850 (± 0.10)	Inclusion based on menopausal status, age 60-80, absence of prior or current pharmacologic treatment for osteoporosis other than HRT, calcium or vitamin D	Retrospective database analysis
Shepherd et al, 2007[81]	Men age $\geq$ 50 years. 1497 in development cohort and 1498 in validation cohort (randomly assigned)	Details of the sampling and data collection have been described elsewhere: National Center for Health Statistics. National Health and Nutrition Examination Survey. http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm. Accessed June 21, 2006	Men age $\geq$ 50 years included in NHANES III dataset who had a valid DXA	Development and validation of MORES tool via regression analysis. Excluded any variable with >10% missing

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group?
Sandhu et al, 2010[113]	Fracture	FRAX and Garvan nomogram	Mean ROC (SD) for women: Garvan: 0.84 (0.03) FRAX-US 0.77 (0.04) FRAX-UK 0.78 (0.04) Men: Garvan: -.76 (0.07) FRAX-US 0.54 (0.07) FRAX-UK 0.57 (0.08)	This is a validation of FRAX and Garvan nomogram
Sedrine et al, 2002[80]	BMD	OSIRIS: age, weight, current HRT and prior low impact fracture	Sens, spec, PPV and NPV for various OSIRIS index scores. Values ranged from -8 to +12. The AUC or the ROC curves for OSIRIS was 0.71	Yes - This is a validation study of OSIRIS
Shepherd et al, 2007[81]	BMD	MORES: age, weight and history of COPD	Sens, spec, ROC curves for MORES score of $\geq$6: sens = 0.91, spec = 0.58, AUROC=0.822	Yes. In validation cohort, sens=0.95, spec =0.61, and AUROC=0.832

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Sinnott et al, 2006[82]	N=128, African American men recruited from general medicine clinics at the Jesse Brown VA Medical Center	FN BMD 1.02 (0.18) g/cm^2	Excluded if history or evidence of metabolic bone disease, atraumatic fractures, history of any medical conditions predisposing to low bone mass, history of cancer in preceding 10 years or use of medications that cause or treat low bone mass (except Calcium and vitamin D)	Cross-sectional analysis, logistic regression.
Smeltzer et al, 2005[83]	307 women with disabilities who underwent peripheral BMD screening, age 20-84. Mean T score was -1.1±1.8	Mean BMD: Os calcis (heel) -1.10 ± 1.8	Convenience sample of women with disabilities recruited from health fairs or educational workshops	Cross-sectional
Timmer et al, 2009[84]	206 patients over 50 presenting to ER with low-energy fall	41% had osteoporosis; 44% had osteopenia; 16% had normal BMD	Excluded if dementia, on treatment for osteoporosis, short life expectancy, living in a nursing home or refusing to participate	Prospective

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Sinnott et al, 2006[82]	BMD by DXA	OST, weight alone, BMI alone and heel T-score by ultrasound	For BMD T score by DXA < -2.5 Heel T score : 0.93 (95% CI 0.87-0.99) Weight (<85kg): 0.75 (0.57-0.92) BMI: 0.67 (0.47-0.87) OST: 0.89 (0.75-1.03)	Yes - This was validation of OST and body weight
Smeltzer et al, 2005[83]	BMD	SCORE: age, weight race, rheumatoid arthritis, history of hip/rib/wrist fracture and estrogen use	Sens, spec, accuracy for SCORE $\geq$6 for predicting T $\leq$ -2.5 and $\leq$ -2.0. For T $\leq$ -2.5, sens = 65.7%, spec = 61%	Yes - This was a validation study of SCORE for women with disabilities
Timmer et al, 2009[84]	BMD	Their own prediction rule for the risk of osteoporosis (BMD) in patients presenting to the ER with low-energy fracture	AUC=0.79 after optimism correction	No - internal validation only. ("internally validated with a standard bootstrap procedure")

Appendix Table D1. Studies of Risk Assessment

Study	Population Setting N	BMD Details (baseline mean, site) g/cm^2	Inclusion/ Exclusion criteria	Study Design
Vogt et al, 2000 et al.[114]	25,816 women age ≥ 55 years. From FIT intervention trial	Mean BMD FN: Vertebral fracture: n=2680 0.563 (0.068) No vertebral fracture: n=10,371 0.591 (0.059)	Used data from the recruitment phase of FIT intervention trial to assess ability of questionnaire to identify women with existing vertebral fractures	Cross-sectional. Includes development of tool the vertebral fracture index (PVFI) from data obtained at screening visit for FIT trial, to predict prevalent vertebral fracture
Wallace et al, 2004[85]	174 postmenopausal Africa-American women recruited from churches in east Texas	Mean BMD FN: Normal (± -1.0SD) 122 (70.1%) Osteopenia (-1.0SD> t-score >-2.5SD) 26 (14.9%) Osteoporosis (± -2.5SD) 26 (14.9%)	Screened by personal physician for participation. Inclusion criteria: apparently healthy, ≥5 year post-menopause; U.S. native age 35-80. Exclusions: renal disease, GI disorder affective digestion and absorption, long-term use of meds known to affect bone	Cross-sectional
Wei et al, 2004[115]	469 women military primary care clinic age ≥ 40 year (mean age 69)	NR, only 39% reported having had prior BMD testing; not done as part of the study	At least 40 years old, presenting for routine medical care. Excluded if not menopausal	Cross-sectional survey
Wildner et al, 2003[86]	959 postmenopausal non-Hispanic women age ≥51 from NHANES	Mean BMD: Whole proximal femur FN	NHANES phase 3 participants, with acceptable hip bone scan	Development of predictive model based on regression; determined use of weight and age gave optimal sens/spec

Appendix Table D1. Studies of Risk Assessment

Study	Outcome (BMD/ Fracture)	Risk Factors Included in Calculation	Results	Validation in a second group? Results
Vogt et al, 2000 et al.[114]	Prevalent Vertebral Fracture	PVFI: history of vertebral fracture, history of nonvertebral fracture, age, height loss and diagnosis of osteoporosis	PVFI score of ≥ 4 sens = 65.5%, spec = 68.6%. Excluding 881 women who reported a prior vertebral fracture, PVFI score ≥4 sens was 53.6% and spec was 70.7%	No
Wallace et al, 2004[85]	Low BMD defined as T score ≤ -2.0	Comparison of ABONE, ORAI, OST, SCORE and body weight. ABONE = age, body size, no estrogen	Sens, spec, NPV, PPV, AUC for ROC. ABONE ≥ 2: sens 73.0%, spec 59.6%. ORAI ≥9: sens 65.6%, spec 78.9%. OST <2: sens 75.4%, spec 75.0%. SCORE ≥6: sens 83.6%, spec 53.9%. Weight <70kg: sens 68.9%,spec 69.2%. Discriminatory performance of OST: cut-off of ≤ -1 for OST has sens of 91.0% and spec of 48.1%	Yes - This is a validation study of other instruments
Wei et al, 2004[115]	Fracture History (self-reported)	Comparison of ORAI, ABONE, body weight < 70 kg	ORAI ≥9: sens 83%, spec 31%, RR of fracture 2.0. ABONE ≥2: sens 74%, 46% specific, RR 2.2. weight: 64% sens, 56% specific, RR 2.0. ORAI >9: AUC= 0.65 (0.57-0.73) ABONE >2: AUC =0.63 (0.54-0.71) weight: AUC= 0.60 (0.52-0.68)	Yes - This is a validation study of other instruments
Wildner et al, 2003[86]	TH BMD: T score ≤ -2.5, and also at T scores of -2.3, -2.0, -1.7, -1.5	Comparison of several models with different numbers of risk factors. Preferred model included age and measured weight	AUC, c-value; sens, spec, PPV, and NPV for various T score cut-offs. Using age and weight to predict T score of ≤ -2.5 at the total proximal femur: sens = 31.75%, spec = 97.40%, PPV=75.00, NPV 85.32	No

Abbreviations: ADL = activities of daily living; AUC = area under the curve; AUROC = area under the receiver operating characteristic; BMD = bone mineral density; BUA = broadband ultrasound attenuation; c-stress = compressive stress; CaMOS = Canadian Multicentre Osteoporosis Study; CI = confidence interval; DOES = Dubbo Osteoporosis Epidemiology Study; DXA = dual-energy x-ray absorptiometry; EPESE = Established Population for Epidemiology Studies of the Elderly; FIT = Fracture Intervention Trial; FN = femoral neck; HRT = hormone replacement therapy; LASA = Longitudinal Aging Study Amsterdam; LS = lumbar spine; MORES = Multiple Outcomes of Raloxifene Study; MrOS = Osteoporotic Fractures in Men Study; NHANES = National Health and Nutrition Examination Survey; NOF = National Osteoporosis Foundation; NORA = National Osteoporosis Risk Assessment tool; NPV = negative predictive value; NR = not reported; ORACLE = Osteoporosis Risk Assessment by Composite Linear Estimate Study; OPERA = Osteoporosis Prescreening Risk Assessment; OPRA = Osteoporosis

Appendix Table D1. Studies of Risk Assessment

Prospective Risk Assessment; OR = odds ratio; ORAI = Osteoporosis Risk Assessment Instrument; OSIRIS = Osteoporosis Index of Risk; OST = Osteoporosis Self-assessment Screening Tool; PIXI = Peripheral Instantaneous X-ray Imager; PPV = positive predictive value; QUI = quantitative ultrasound index; QUS = quantitative ultrasound; RA = rheumatoid arthritis; RCT = randomized controlled trial; ROC = receiver operating characteristic; SCORE = Simple Calculated Osteoporosis Risk Estimation study; SD = standard deviation; SE = standard error; SEMOF = Swiss Evaluation of the Methods of measurement of Osteoporotic Fracture risk; sens = sensitivity; SOF = Study of Osteoporotic Fractures; SOFSURF = Study of Osteoporosis Fractures—Study Utilizing Risk Factors; spec = specificity; TH = total hip; UBPI = ultrasound bone profile index; VA = Veteran's Administration; WHI = Women's Health Initiative; WHO = World Health Organization.

*SOF-based decision rule: Intervene if fracture after age 50; measure BMD if SOF score is >5, and intervene among those who meet intervention criteria (age<65 with T score <-2.5; age >65 with >5 risk factors and Z score -0.43; or previous fracture after age 50).

Appendix Table D2. Descriptions of Variables Included in Validated Risk Instruments

Name of Instrument	References	Age	Weight	Other	Scoring Method and Interpretation
ABONE	Cadarette et al, 2001[56] Wallace et al, 2004[85] Wei et al, 2004[115]	X	X	Estrogen	Age: 1 point if >65 years Weight: 1 point if <63.5 kg Estrogen therapy: 2 points if currently taking; 0 points if not taking. Score ≥ 2 as high risk
Body weight criterion (pBW)	Cadarette et al, 2001[56] Cadarette et al, 2004[57] Cook et al, 2005[61] D'Amelio et al, 2005[62] Lynn et al, 2008[69] Martinez-Aguila et al, 2007[70] Wallace et al, 2004[85] Wei et al, 2004[115]		X		Weight in kg as only risk consideration Weight >70kg = low risk Weight 50-70 kg = moderate risk Weight <57kg = high risk
Carranza-Lira et al, 2002	Carranza-Lira et al, 2002[58, 59]	X	X (BMI)	Time since menopause	1 point for each: age >48, BMI <32 for spine and <30 for FN, time since menopause >5 years.
DOEScore	Nguyen et al, 2004[74]	X	X	Prior fracture	Sum of points: Age <65=1, 65-69=1, 70-74 and 75-79=2, 80-84=3, 85+=4, 80-84 =8, 85-89=11, 90+=16; Weight: <55kg =1, 55-59 and 60-64kg=2; 65-69kg=3; 70-74kg=4; 75-70kg=6 Prior Fracture: No=1; Yes=2 <10 vs. >10 for T score <-2.5
Gnudi et al, 2005	Gnudi et al, 2005[65]		X	Age at menarche, years since menopause, arm help to rise from seated position, pervious fracture, maternal history of fracture	Clinical risk factors for the validation group were entered into the regression model for the development group to arrive at a T score

Appendix Table D2. Descriptions of Variables Included in Validated Risk Instruments

Name of Instrument	References	Age	Weight	Other	Scoring Method and Interpretation
EPESE	Colon-Emeric et al, 2002[90]	X (>75 years)	X (BMI)	Female sex, white race, BMI, history of stroke, cognitive impairment (SPMSQ≥3 errors), 1+ ADL impairments, 1+ Rosow-Breslau impairments, antiepileptic drug use	Full score is weighting with parameter estimates obtained from logistic regression Risk score is weighted count of risk factors with B rounded to nearest 0.5. Risk count is unweighted sum of risk factors
Ettinger et al, 2005	Ettinger et al, 2005[99]	X	X	Height, current smoking, mother or sister with hip fracture, prior non-spine fracture, Z score at hip and spine	Computer model for risk calculation given in the appendix
Fracture Index	Black et al, 2001[88]	X	X	Fracture after age 50, maternal hip fracture after age 50, weight ≤125 lbs, current smoking, uses arms to stand from chair, total hip T score	Sum of points: 1 point for each 5 years over age 65 (up to 5 points for those >age 85), 1 point each for personal fracture, family history of fracture, weight <125, current smoking, 2 points for no/don't know on chair stand; T score >-1 (0 point), T between -1 and -2 (2 points), T score between - 2 and -2.5 (3 point), T score <-2.5 (4 points)
FRAX	Donaldson et al, 2009[96] Ensrud et al, 2009[98] Kanis et al, 2007[104] Sandhu et al, 2010[113]	X	X (BMI)	Age, sex, BMI, family history of fracture, glucocorticoid use, prior fracture, current smoking, alcohol, rheumatoid arthritis, hip T score	Risk calculator is available at www.shef.ac.uk, but the algorithm itself (equation for obtaining the risk score) is not published.

Appendix Table D2. Descriptions of Variables Included in Validated Risk Instruments

Name of Instrument	References	Age	Weight	Other	Scoring Method and Interpretation
Minimum Data Set (Girman et al, 2002)	Girman et al, 2002[100]	X	X	Height, locomotion on unit, Fall in past 180 days, ADL score, MDS cognition scale score, urinary incontinence	Age 75-84=1 point, age 85-94=2 points, age ≥95=3 points; weight<170lbs=1 point; height≤58 inches=2 points, height >58 inches and ≤63 inches = 1 point; fall = 1 point, ADL ≤4 = 1 point; MDS cognition scale score ≤3 = 1 point; occasionally incontinent (vs. usually continent or usually incontinent) = 1 point. Sum of scores. If sum≤4 the observed 18 months fracture rate = 8.05%; if score >4 the observed fracture rate = 15.25.
Masoni et al, 2005	Masoni et al, 2005[71]		X (BMI)	>10 years since menopause, calcium intake<1200 mg/day, personal history of fracture, kyphosis, personal history of fracture + kyphosis	Risk calculated from regression equation
MORES	Shepherd et al, 2007[81]	X	X	History of COPD	Sum of points: Age 56-74 years = 3 points; ≥75 years = 4 points. Weight ≤70 kg = 6 point; weight >70kg but ≤80kg = 4 points. >80 kg = 0 points; COPD = 3 points
NOF guideline 1994	Cadarette et al, 2001[56] D'Amelio et al, 2005[62] Devlin et al, 2007[63] Geusens et al, 2002[64] Mauck et al, 2005[72]	X	X	Personal history of any fracture >age 40, current smoking, maternal and/or parental history of hip, wrist or spine fracture ≥ age 50	1 point for each: age >65, weight < 57.6 kg, personal history of any fracture >age 40, current smoking, maternal and/or parental history of hip, wrist or spine fracture >age 50
Osteoporosis Canada simplified score	Leslie et al, 2009[106] Richards et al, 2007[111]	X		BMD, systemic corticosteroid use, prior fragility fracture, gender	Within age and gender categories, corticosteroid use and prior fracture tallied (1 point for each). Absolute fracture rates obtained from Malmo population data

Appendix Table D2. Descriptions of Variables Included in Validated Risk Instruments

Name of Instrument	References	Age	Weight	Other	Scoring Method and Interpretation
OPERA	Salaffi et al, 2005[79]	X	X	History of minimal trauma fracture, early menopause, systemic glucocorticoids	One point for each risk factor
ORAI	Cook et al, 2005[61] Cass et al, 2006[60] Cadarette et al, 2000[55] Cadarette et al, 2001[56] Cadarette et al, 2004[57] Devlin et al, 2007[63] Geusens et al, 2002[64] Gourlay et al, 2005[66] Harrison et al, 2006[67] Martinez-Aguila et al, 2007[70] Mauck et al, 2005[72] Nguyen et al, 2004[74] Rud et al, 2005[77] Wallace et al, 2004[85] Wei et al, 2004 [115]	X	X	Current use of estrogen	Sum: +2 points for non-current estrogen use, +9 points for weight <60kg or +3 points for weight between 60-70kg, 0 points for weight >70 kg. +15 points for age ≥75 years; +9 points for ages between 65-74; +5 points for ages between 55-64, 0 points for ages 45-54. Score 9 = low risk >9 and <17 = moderate risk >17 = high risk 23:23
OSIRIS	Cook et al, 2005[61] Harrison et al, 2006[67] Martinez-Aguila et al, 2007[70] Minnock et al, 2008[73] Reginster et al, 2004[75] Sedrine et al, 2002[80]	X	X	Estrogen and history of fracture	Current age (-2) and truncated to integer, weight in kg times 2 and truncated to integer, +2 points if current HRT, and -2 points if history of prior low impact fracture. >+1 = low risk; < +1; >-3 = intermediate risk; <-3 high risk

Appendix Table D2. Descriptions of Variables Included in Validated Risk Instruments

Name of Instrument	References	Age	Weight	Other	Scoring Method and Interpretation
OST	Adler et al, 2003[52] Cadarette et al, 2001[56] Cadarette et al, 2004[57] Cass et al, 2006[60] Cook et al, 2005[61] D'Amelio et al, 2005[62] Geusen et al, 2002[64] Gourlay et al, 2005[66] Harrison et al, 2006[67] Martinez-Aguila et al, 2007[70] Mauck et al, 2005[72] Richy et al, 2004[76] Rud et al, 2005[77] Wallace et al, 2004[85]	X	X		(Weight in Kg minus age in years) (0.2), truncated to the integer. OR (Weight in kg) (0.2) minus (0.2) (age in years); drop last digit from each to give integer and add the resulting values together. For Caucasians: >+2 = low risk; +2 to -3 moderate risk; <-3; high risk for low BMD
SCORE	Brenneman et al, 2003[54] Cadarette et al, 2001[56] Cass et al, 2006[60] Cook et al, 2005[61] Geusens et al, 2002[64] Gourlay et al, 2005[66] Harrison et al, 2006[67] La Croix et al, 2005[117] Mauck et al, 2005[72] Rud et al, 2005[77] Russell et al, 2001[78] Sedrine et al, 2001[53] Smeltzer et al, 2005[83] Wallace et al, 2004[85]	X	X	Race/ethnicity, rheumatoid arthritis, estrogen use and history of fracture after age 45	Sum: + 5 points for race other than Black, +4 points for RA, +4 points for each non-traumatic fracture after age 45; +1 if never estrogen, 3 times the first digit of pt's age and -1 times the patients weight in lbs, divided by ten and truncated to an integer. < +7 = low risk; > +7 to < +15 = moderate risk; > +15 = high risk Some use SCORE >6 for BMD testing

Appendix Table D2. Descriptions of Variables Included in Validated Risk Instruments

Name of Instrument	References	Age	Weight	Other	Scoring Method and Interpretation
SOF/ Cummings	Ahmed et al, 2006[87] Brennamen et al, 2003[54] LaCroix et al, 2005[117] Richards et al, 2008[116]*	X	X	Weight < that at age 25,height at age 25 ≤168cm, maternal hip fracture, personal fracture after age 50, self-rated health - fair, poor or very poor; no walking for exercise, current use of benzodiazepines or anticonvulsants; resting pulse>80 bpm, caffeine >2 cups of coffee/day, inability to rise from chair without using arms, previous hyperthyroidism, age ≥80, on feet ≤4 hours/day, lowest quartile of depth perception, lowest quartile of contrast sensitivity, calcaneal BMD	Sum of weights for each factor; Age: 75=0, 76-79=1, 80-84=2, 85 and older =3. History of falling: No=0, Yes=1. Tandem walk: Able with or without trials=0, Unable=2. Gait speed >1.4mg/s=0, 1.0-1.4mg/s=1, 0.6 1.0m/s =2, <0.6m/s=3. Ahmed et al, 2006 allocated women into groups by number of risk factors. Score >5 is increased risk.
SOFSURF	Cook et al, 2005[61] Geusens et al, 2002[64] Nguyen et al, 2004[74]	X	X	Smoking, history of postmenopausal fracture	Index calculated as +0.2 points for every year over age 65, -0.2 points for every year under age 65; +3 points for weight below 130 lbs and +1 point for wet between 130-150 lbs, +1 point for current smoker, +1 point for history of post-menopausal fracture <0=low risk; 0 and <+4=intermediate risk; > +4 high risk

Appendix Table D2. Descriptions of Variables Included in Validated Risk Instruments

Name of Instrument	References	Age	Weight	Other	Scoring Method and Interpretation
WHI	Robbins et al, 2007[112]	X	X	Self-reported health, height (in), weight (lb), fracture at age ≥55 years, race/ethnicity (white/non-white), physical activity, smoking status, parental history of hip fracture, corticosteroid use, use of hypoglycemic agent	Age: (1/2 point per year) >50 Self reported health: fair/poor =3 points; good =1 point, very good =0 (all vs. excellent) Height: 1/2 point per inch >64 Weight: 1 point per 25 lb <200 Fracture at ≥55 years: yes =2 points (vs. no) Race/ethnicity: white =3 points (vs. non-white) Physical activity METS: inactive =1 point. Smoking status, current =3 points. Parental history of hip fracture: yes =1 point. Corticosteroid use: yes =3 points. Hypoglycemic agent use: yes =2 points. Total point score of 9 yields a probability of fracture of 0.1%; point total of 18 yields a probability of fracture of 1%; a point total of 24 yields a probability of fracture of 5%

Abbreviations: ABONE = Age, body size, no estrogen; ADL = activities of daily living; BMD = bone mineral density; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DOEScore = Dubbo Osteoporosis Epidemiology Study score; EPESE = Established Populations for the Epidemiologic Study of the Elderly; FN = femoral neck; HRT = hormone replacement therapy; MDS = minimum data set; METS = metabolic equivalents; MORES = Male Osteoporosis Risk Estimation Score; NOF = National Osteoporosis Foundation; OPERA = Osteoporosis Prescreening Risk Assessment; ORAI = Osteoporosis Risk Assessment Instrument; OSIRIS = Osteoporosis Index of Risk; OST = Osteoporosis Self-assessment Tool; SCORE = Simple Calculated Osteoporosis Risk Estimation; SOF = Study of Osteoporotic Fractures; SOFSURF = Study of Osteoporosis Fractures—Study Utilizing Risk Factors; WHI = Women's Health Initiative.

*Includes 10 items adapted from the SOF risk assessment instrument.

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Study design/ duration	Inclusion criteria	Population
Ascott-Evans et al, 2003[139]	Double-blind, randomized PCT 1 year	Postmenopausal aged <80 years; previous use of HRT for at least 1 year; baseline T-score -3.5 to -1.5	n=144 aged <65 years: 85% mean T-score: -2.3 previous fractures: excluded
Chesnut et al,1995[140]	Double-blind, randomized PCT 2 years	At least 5 years postmenopausal aged 43-75 years; lumbar spine BMD ≤0.88 g/cm^2 (~ -2.0 SD below normal)	n=188 mean age: 63 years mean hip T-score: -1.1 previous fractures: excluded
Cummings et al, 1998[50] Fracture Intervention Trial (FIT)	Double- blind, randomized PCT 4 years	At least 2 years postmenopausal age 55-80 years; femoral neck BMD ≤0.68 g/cm^2 (~ -1.6 SD below normal)	n=4,432 mean age: 67.7 years mean T-score: -2.2 previous fractures: excluded
Dursun et al, 2001[141]	Randomized PCT 1 year	Postmenopausal with BMD ≤-2.0 SD below mean at lumbar spine or femoral neck	n=151 mean age: 61.2 years mean T-score: -1.5 previous fractures: unknown
Greenspan et al, 2007[151]	Double-blind, randomized PCT 18 months	Postmenopausal age 45-54 years with T-score ≤ 3.0 below mean for young women with no prevalent vertebral fracture or T-score -2.5 with 1-4 vertebral fractures	n=2532 (n=2061 without baseline fracture) mean age: 64.4 years mean T-score: -2.2 previous fractures: 19%
Herd et al, 1997[144]	Double-blind, randomized PCT 2 years	1-10 years postmenopausal	n=152 mean age 54.8 years mean T-score: -1.3 prior fractures: excluded

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Interventions	Routine lumbar radiography to identify new fractures	Fractures
Ascott-Evans et al, 2003[139]	Alendronate 10 mg qd vs. placebo	No	Alendronate vs. placebo Any fracture: 0/95 (0%) vs. 0/47 (0%)
Chesnut et al,1995[140]	Alendronate 10 mg qd vs. placebo	Yes	Alendronate vs. placebo Vertebral fracture: 0/30 (0%) vs. 0/31 (0%) Non-vertebral fracture: 13 total, results not stratified by treatment group
Cummings et al, 1998[50] Fracture Intervention Trial (FIT)	Alendronate 5 mg qd for 2 years, then 10 mg qd for 1 year vs. placebo	Yes	Alendronate vs. placebo Vertebral fracture - first fracture: 43/2214 (1.9%) vs. 78/2218 (3.5%); RR 0.56 (CI 0.39-0.80; p=0.002) Nonvertebral fracture: 261/2214 (11.8%) vs. 294/2218 (13.3%) placebo; RR 0.88 (CI 0.74 to 1.04; p=0.13) Hip fracture: 19/2214 (0.9%) vs. 24/2218 (1.1%) Wrist fracture: 83/2214 (3.7%) vs. 70/2218 (3.2%)
Dursun et al, 2001[141]	Alendronate 10 mg + calcium 1000 mg qd vs. calcium 1000 mg qd	Yes	Alendronate vs. placebo Vertebral fracture: 12/51 (24%) vs. 14/50 (28%) Nonvertebral fracture: not reported
Greenspan et al, 2007[151]	PTH 100µg qd vs. placebo	Yes	PTH vs. placebo. Vertebral fracture (results for participants without baseline fracture): PTH 7/1050 (0.7%) vs. placebo 21/1011 (2.1%) Nonvertebral fracture (results not stratified by baseline fracture status): 72/1286 (5.6%) vs. 72/1246 (5.8%)
Herd et al, 1997[144]	Cyclical etidronate 400 mg qd vs. placebo	Yes	Etidronate vs. placebo Any fracture: 0/75 (0%) vs. placebo 0/77 (0%)

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Adverse events and withdrawals	Comments
Ascott-Evans et al, 2003[139]	Alendronate vs. placebo Withdrawals: 25/144 (17.3%); 12/95 (13%) vs. 13/49 (26%) Withdrawals due to AEs: 10/95 (10%) vs. 10/49 (20%)	Fracture incidence was not an efficacy outcome
Chesnut et al,1995[140]	Withdrawals: 34/188 (18%) overall (not stratified by treatment group) Other adverse events not stratified by treatment group	
Cummings et al, 1998[50] Fracture Intervention Trial (FIT)	Alendronate vs. placebo Withdrawals due to AEs: 221/2214 (9.9%) vs. 227/2218 (10.2%) All-cause mortality: 37/2214 (1.7%) vs. 40/2218 (1.8%) Any upper GI event: 1052/2214 (48%) vs. 1047/2218 (47%) Abdominal pain: 322/2214 (14%) vs. 325/2218 (15%) Esophagitis: 19/2214 (0.9%) vs. 10/2218 (0.5%) Esophageal ulcer: 4/2214 (0.2%) vs. 4/2218 (0.2%) Other esophageal: 44/2214 (2.0%) vs. 41/2218 (1.8%) Acid regurgitation/reflux: 204/2214 (9.2%) vs. 194/2218 (8.7%)	
Dursun et al, 2001[141]	Withdrawals due to AEs: none in either treatment group	
Greenspan et al, 2007[151]	Parathyroid hormone vs. placeboWithdrawals: 831/2532 (32.8%) Withdrawals dues to AEs: 154/1286 (12%) vs. 76/1246 (6.1%) All-cause mortality: 1/1286 (0.08%) vs. 2/1246 (0.16%) Arthralgia: 282/1286 (22%) vs. 276/1246 (22%) Myalgia: 64/1286 (5.0%) vs. 62/1246 (5.0%)	
Herd et al, 1997[144]	Etidronate vs. placebo Withdrawals: 11/75 (14.7%) vs. 6/77 (7.8%) Withdrawals due to AEs: 5/75 (6.7%) vs. 0/77 (0%) Back pain: 12/74 (16%) vs. 14/76 (18%)	Fracture incidence not an efficacy outcome

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Study design/ duration	Inclusion criteria	Population
Hooper et al, 2005[147]	Double-blind, randomized PCT 2 years	6-36 months postmenopausal	n=383 mean age: 53 years mean T-score: -0.7 previous fractures: unknown
Hosking et al,1998[142]	Double-blind, randomized PCT 2 years	≥6 months postmenopausal with no clinical or laboratory evidence of systemic disease	n= 1609 mean age 53.3 years mean T-score: -0.1 previous fractures: unknown
Liberman et al, 1995[47]	Double-blind, randomized PCT 3 years	Age 45-80 years, ≥5 years postmenopausal with BMD T-score worse than -2.5	n=637 (no prior fracture) mean age: 64 years (with or without prior fracture) mean T-score: -2.2 previous fracture: 21%
McClung et al, 2001[41]	Double-blind, randomized PCT 3 years	Women 70-79 years with BMD T-score worse than -4 or worse than -3 with non-skeletal risk factors for fall	n=2648 (no prior fracture) mean age: 74 years (with or without prior fracture) mean T-score: -3.7 (with or without prior fracture) previous fractures: results of subgroup with no previous fractures reported
Meunier et al,1997[145]	Double-blind, randomized PCT 2 years	6-60 months postmenopausal women within 15% of normal BMI, normal BMD (+/- 2SD expected value)	n=54 mean age: 52.7 years mean T-score: -1.1 previous fractures: not reported
Mortensen et al, 1998[148]	Double-blind, randomized PCT 2 years treatment, outcomes assessed through 3 years	6-60 months postmenopause, weight 45-90kg, within 25% of normal weight and height	n=111 mean age: 51.5 years mean T-score: -1.1 previous fractures: not reported

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Interventions	Routine lumbar radiography to identify new fractures	Fractures
Hooper et al, 2005[147]	Risedronate 2.5 to 5.0mg qd vs. placebo	Yes	Risedronate 2.5 mg vs. 5 mg vs. placebo Vertebral fractures: 11/127 (8.7%) vs. 10/129 (7.8%) vs. 10/125 (8.0%) Nonvertebral fractures: 3/127 (2.4%) vs. 5/129 (3.9%) vs. 6/125 (4.8%)
Hosking et al,1998[142]	Alendronate 5 mg qd vs. placebo	No	Alendronate vs. placebo Vertebral fracture: 0/498 (0%) vs. 0/502 (0%) Nonvertebral fracture: alendronate 2.5mg 22/499 (4.4%) vs. alendronate 5mg 22/498 (4.4%) vs. placebo 14/502 (2.8%)
Liberman et al, 1995[47]	Alendronate 5 or 10 mg qd for 3 years or 20 mg qd for 2 years followed by 5 mg qd for 1 year vs. placebo	Yes	Alendronate (all doses) vs. placebo Vertebral fracture (in women without prior vertebral fracture) 4/384 (1.0%) vs. 5/253 (2.0%)
McClung et al, 2001[41]	Risedronate 2.5 or 5 mg qd vs. placebo	No	Risedronate 2.5 or 5 mg vs. placebo Hip fracture (in women without prior vertebral fracture): 14/1773 (1.0%) vs. 12/875 (1.6%)
Meunier et al,1997[145]	Cyclical etidronate 400 mg qd vs. placebo	Yes	Etidronate vs. placebo Vertebral fracture: 1/27 (3.7%) vs. 0/27 (0%) Non-vertebral fracture: 2/27 (7.4%) vs. 3/27 (11%)
Mortensen et al, 1998[148]	Risedronate 5 mg (daily or 2-week cyclical dosing) vs. placebo	Yes	Risedronate daily vs. risedronate cyclic vs. placebo Vertebral fractures: 1/37 (2.7%) vs. 1/38 (2.6%) vs. 0/36 (0%) Nonvertebral fractures: 0/37 (0%) vs. 3/38 (7.9%) vs. 3/36 (8.3%)

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Adverse events and withdrawals	Comments
Hooper et al, 2005[147]	Risedronate vs. placebo Withdrawals: 52/256 (20%) vs. 32/125 (26%) Withdrawals due to AEs: 19/256 (7.4%) vs. 8/125 (6.4%) Abdominal pain: 18/256 (7.0%) vs. 6/125 (4.8%)	
Hosking et al,1998[142]	Withdrawals: 139/1609 (8.6%); 89/997 (8.9%) alendronate vs. 46/503 (9.2%) placebo vs. 4/110 (3.4%) estrogen-progestin Withdrawals due to AEs: 67/997 (6.7%) alendronate vs. 27/503 (5.4%) placebo vs. 15/110 (13.6%) estrogen-progestin Upper GI AEs, any type: 300/997 (30%) alendronate vs. 148/502 (29%) placebo vs. 31/110 (28%) estrogen-progestin CV AEs: 99/997 (10%) alendronate vs. 47/502 (9.4%) placebo vs. 15/110 (14%)	Baseline data and efficacy outcomes assessment included only women with baseline LS BMD and at least one on-treatment measurement; safety data included all randomized patients
Liberman et al, 1995[47]	Alendronate 10 mg vs. placebo (with or without vertebral fracture at baseline) Withdrawals: 26/196 (13.3%) vs. 65/397 (16.4%) Withdrawals due to AEs: 35/597 (5.8%; all doses of alendronate) vs. 24/397 (6.0%) Withdrawals due to upper GI AEs: 2/196 (1.0%) vs. 8/397 (2.0%) Abdominal pain: 13/196 (6.6%) vs. 19/397 (4.8%) Musculoskeletal pain: 8/196 (4.1%) vs. 10/397 (2.5%) Nausea: 7/196 (3.6%) vs. 16/397 (4.0%) Dyspepsia: 7/196 (3.6%) vs. 14/397 (3.5%) Constipation: 6/196 (3.1%) vs. 7/397 (1.8%) Diarrhea: 6/196 (3.1%) vs. 7/397 (1.8%)	Non-vertebral fractures not reported in subgroup of women without baseline fracture
McClung et al, 2001[41]	Risedronate 5 mg vs. placebo (with or without vertebral fracture at baseline) Withdrawal due to AEs: 550/3104 (18%) vs. 564/3134 (18%) Serious AEs: 943/3104 (30%) vs. 973/3134 (31%) Any AEs: 2786/3104 (89.8%) vs. 2805/3134 (89.5%) Any upper GI AEs: 657/3104 (21%) vs. 684/3134 (22%) Moderate to severe upper GI AEs: 279/3104 (9.0%) vs. 258/3134 (8.3%) Abdominal pain: 250/3104 (8.1%) vs. 288/3134 (9.2%) Dyspepsia: 255/3104 (8.2%) vs. 254/3134 (8.1%) Esophagitis: 54/3104 (1.7%) vs. 59/3134 (1.9%) Esophageal ulcer: 9/3104 (0.3%) vs. 14/3134 (0.4%)	Hip fractures reported in subgroup of women without baseline fracture
Meunier et al,1997[145]	Etidronate vs. placebo Withdrawals: 2/27 (7.4%) vs. 3/27 (11%) Withdrawals due to AEs: 0/27 (0%) vs. 2/27 (7.4%) Pain: 5/27 (18%) vs. 5/27 (18%) Abdominal pain: 4.27 (15%) vs. 1/27 (3.7%)	All reported fractures described as traumatic
Mortensen et al, 1998[148]	Risedronate vs. placebo Withdrawals: 15/111 (13.5%) overall Withdrawals due to AEs: 5/75 (6.7%) vs. 3/36 (8.3%) Abdominal pain: 8/75 (11%) vs. 4/36 (11%)	Nonvertebral fractures were all described as traumatic Withdrawals reported through year 1 - continuation in study beyond that point was at patient's discretion

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Study design/ duration	Inclusion criteria	Population
Orwoll et al, 2003[159]	Double blind, randomized PCT planned for 2 years, study stopped after median 11 months	Men age 30-85 years, ambulatory, free of chronic, disabling conditions other than osteoporosis, lumbar spine of proximal femur BMD ≥ -2 SD below mean for healthy young men	n=437 mean age: 59 years mean T-score -2.7 previous fractures: unknown
Pols et al, 1999[143]	Double-blind, randomized PCT 1 year	≤ 3 years postmenopause, ≥ 85 years, BMD of Lumbar spine (L2-4) ≥ -2 SD below the average for mature, menopausal women. Between > 20% and < 50% ideal body weight.	n = 1908 mean age: 63.0 years mean T-score: -2.0 previous fractures: unknown
Pouilles et al, 1997[146]	Double-blind, randomized PCT 2 years	6-60 months postmenopause women aged 45-60 years, within 20% of normal BMI	n=109 mean age: 53.8 years mean T-score: -0.8 previous fractures: unknown
Reid et al, 2002[150]	Double-blind, randomized PCT 1 year	Age 45-80 years, ≥5 years postmenopause, lumbar spine BMD ≤2.0 SD below the mean value for young adults; no more than one vertebral fracture at baseline	n=351 mean age: 64.2 years mean T-score: -1.2 previous fractures: excluded
Valimaki et al, 2007[149]	Double-blind, randomized PCT 2 years	≥5 years postmenopause , ≥osteoporosis risk factor or the presence of hip osteopenia	n=171 mean age: 65.9 years mean T-score: -1.2 previous fractures: unknown

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Interventions	Routine lumbar radiography to identify new fractures	Fractures
Orwoll et al, 2003[159]	Teriparatide 20 or 40 µg subcutaneous injection qd vs. placebo	Yes	Teriparatide 20 ug vs. 40 ug vs. placebo Vertebral fractures: not reported Nonvertebral fracture: 2/151 (1.3%) vs. 1/139 (0.7%) vs. 3/147 (2.0%)
Pols et al, 1999[143]	Alendronate 10 mg qd vs. placebo	No	Alendronate vs. placebo Vertebral fractures: not evaluated Nonvertebral fractures: 19/950 (2.0%) vs. 37/958 (3.9%) placebo Hip fracture: 2/950 (0.2%) vs. 3/958 (0.3%) Wrist fracture: 6/950 (0.6%) vs. 15/958 (1.6%) Ankle/lower leg fracture: 2/950 (0.2%) vs. 5/958 (0.5%)
Pouilles et al, 1997[146]	Cyclical etidronate 400mg qd vs. placebo	No	Etidronate vs. placebo Vertebral fracture: 1/54 (1.9%) vs. 0/55 (0%) Nonvertebral fracture: 3/54 (5.6%) vs. 6/55 (11%)
Reid et al, 2002[150]	Zoledronic acid 4 mg intravenous annually in 1 to 4 doses vs. placebo	Yes	Zoledronic acid 4 mg/year vs. placebo Vertebral fractures: 0/174 (0%) vs. 0/59 (0%) Nonvertebral fractures: 4/174 (2.3%) vs. 1/59 (1.7%)
Valimaki et al, 2007[149]	Risedronate 5mg qd vs. placebo	No	Risedronate vs. placebo Vertebral fracture: 0/114 (0%) vs. 0/56 (0%) Nonvertebral fracture: 2/114 (1.8%) vs. 2/53 (3.8%) Hip fracture: 0/114 (0%) vs. 0/56 (0%) Wrist fracture: 0/114 (0%) vs. 1/56 (1.8%) Ankle fracture: 0/114 (0%) vs. 1/56 (1.8%) All-cause mortality: 0/114 (0%) vs. 0/56 (0%)

Appendix Table D3. Primary Prevention Randomized Controlled Trials

Author year	Adverse events and withdrawals	Comments
Orwoll et al, 2003[159]	Teriparatide vs. placebo Withdrawals due to AEs: 32/290 (11.0%) vs. 7/147 (4.8%) Nausea: 34/290 (11.7%) vs. 5/147 (3.4%)	
Pols et al, 1999[143]	Alendronate vs. placebo Withdrawals due to AEs: 61/950 (6.4%) vs. 54/958 (5.6%)	
Pouilles et al, 1997[146]	Etidronate vs. placebo Withdrawals: 9/54 (17%) vs. 9/55 (16%) Withdrawals due to AEs: 1/54 (1.9%) vs. 0/55 (0%) Abdominal pain: 7/54 (13%) vs. 6/55 (11%)	9/10 fractures described as traumatic (1 non-traumatic, non-vertebral fracture)
Reid et al, 2002[150]	Zoledronic acid (any dose) vs. placebo Withdrawals: 35/351 (9.8%) overall Withdrawals due to AEs: 13/292 (4.6%) vs. 1/59 (1.7%) Myalgia: 41/292 (14%) vs. 1/59 (1.7%) Arthralgia: 46/292 (16%) vs. 9/59 (15%)	No patients had baseline vertebral fractures
Valimaki et al, 2007[149]	Risedronate vs. placebo Withdrawals: Not reported Withdrawals due to AEs: 10/115 (8.7%) vs. 9/55 (16%) placebo	

Abbreviations: AE = adverse events; BMD = bone mineral density; BMI = body mass index; CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; HRT = hormone replacement therapy; LS = lumbar spine; PCT = placebo controlled trial; PTH = parathyroid hormone; RR = relative risk; SD = standard deviation.

*BMD T-scores are based on femoral neck measurements and calculated using the FRAX Patch instrument, unless otherwise stated.

Appendix Table D4. Quality Ratings of Primary Prevention Randomized Controlled Trials

Author year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Blinding: patients	Blinding: providers	Blinding: outcome assessors or data analysts
Ascott-Evans et al, 2003[139]	Yes	Don't know	Yes	Yes	Yes	Yes	Yes
Chesnut et al,1995[140]	Don't know	Don't know	Yes	Yes	Yes	Yes	Yes
Cummings et al, 1998[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dursun et al, 2001[141]	Don't know	Don't know	No	Yes	Don't know	Don't know	Don’t know
Greenspan et al, 2007[238]	Yes	Yes	Yes	Yes	Yes	Yes	Don't know
Herd et al, 1997[144]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know
Hooper et al, 2005[147]	Yes	Don't know	Yes	Yes	Yes	Don't know	Don't know
Hosking et al, 1998[142]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know

Appendix Table D4. Quality Ratings of Primary Prevention Randomized Controlled Trials

Author year	Intention-to-treat analysis	Reporting of attrition, contamination, etc	Differential loss to follow-up or overall high loss to follow-up	Funding source	External validity	Quality score
Ascott-Evans et al, 2003[139]	Don't know	Yes	No	Merck	Aged <65 years: 84.7% Mean T-score: -2.3	Fair
Chesnut et al,1995[140]	No	Yes	Yes	Merck	Mean age 63 years Mean hip T-score: -1.1	Fair
Cummings et al, 1998[50]	Yes	Yes	Yes	Merck	Mean age 67.7 years Mean T-score: -2.2	Good
Dursun et al, 2001[141]	No	No	Don't know	Not reported	Mean age 61.2 years Mean T-score: -1.5	Poor
Greenspan et al, 2007[238]	Yes	Yes	No	NPS Pharmaceuticals	Mean age 64.4 years Mean T-score: -2.2	Fair
Herd et al, 1997[144]	Yes	Yes	Yes	Not reported	Mean age 54.8 years Mean T-score: -1.3	Fair
Hooper et al, 2005[147]	Yes	Yes	No	Proctor & Gamble	Mean age 53 years Mean T-score: -1.3	Fair
Hosking et al, 1998[142]	Yes	Yes	Yes	Merck	Mean age 53.3 years Mean T-score: -0.1	Fair

Appendix Table D4. Quality Ratings of Primary Prevention Randomized Controlled Trials

Author year	Random assignment	Allocation concealed	Groups similar at baseline	Eligibility criteria specified	Blinding: patients	Blinding: providers	Blinding: outcome assessors or data analysts
Liberman et al, 1995[47]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know
McClung et al, 2001[41]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know
Meunier et al, 1997[145]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know
Mortensen et al, 1998[148]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know
Orwoll et al, 2003[159]	Yes	Yes	Yes	Yes	Yes	Yes	Don't know
Pols et al, 1999[143]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know
Pouilles et al,1997[146]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know
Reid et al, 2002[150]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know
Valimaki et al, 2007[149]	Don't know	Don't know	Yes	Yes	Yes	Yes	Don't know

Appendix Table D4. Quality Ratings of Primary Prevention Randomized Controlled Trials

Author year	Intention-to-treat analysis	Reporting of attrition, contamination, etc	Differential loss to follow-up or overall high loss to follow-up	Funding source	External validity	Quality score
Liberman et al, 1995[47]	No	Yes	Yes	Merck	Mean age 64 years Mean T-score: -2.2	Fair
McClung et al, 2001[41]	Yes	Yes	Yes	Proctor & Gamble and Aventis Pharma	Mean age 74 years Mean T-score: -3.7	Fair
Meunier et al, 1997[145]	Don't know	Yes	Yes	Proctor & Gamble	Mean age 52.7 years Mean T-score: -1.1	Fair
Mortensen et al, 1998[148]	Yes	Yes	Yes	Proctor & Gamble	Mean age 51.5 years Mean T-score: -1.1	Fair
Orwoll et al, 2003[159]	Yes	Yes	No	Eli Lilly	Mean age 59 years Mean T-score: -2.7	Good
Pols et al, 1999[143]	Yes	Yes	Yes	Merck	Mean age 63.0 years Mean T-score: -2.0	Fair
Pouilles et al,1997[146]	Yes	Yes	Yes	Novartis	Mean age 53.8 years Mean T-score: -0.8	Fair
Reid et al, 2002[150]	Yes	Yes	Yes	Novartis	Mean age 64.2 years Mean T-score: -1.2	Fair
Valimaki et al, 2007[149]	Yes	Yes	Yes	Proctor & Gamble Sanofi-Aventis	Mean age 65.9 years Mean lT-score: -1.2	Fair

Appendix Table D5. Placebo-controlled Trials of Bisphosphonates Reporting Fracture Outcomes Classified as Secondary Prevention

Trial	Reason for exclusion
Alendronate	
Black et al, 1996[239]	100% of enrolled patients had prior vertebral fracture
Bone et al, 1997[38]	37% of enrolled patients had prior vertebral fracture
Greenspan et al, 1998[46]	Baseline vertebral fracture not reported; 55% of enrolled patients had osteoporosis at baseline according to WHO femoral neck criteria
Greenspan et al, 2002[39]	55% of enrolled patients had prior fracture (site not specified)
Orwoll et al, 2000[165]	50% of enrolled patients had prior vertebral fracture
Ringe et al, 2004[166]	54% of enrolled patients had prior vertebral fracture
Etidronate	
Ishida et al, 2004[40]	31% of enrolled patients had prior vertebral fracture
Lyritis et al, 1997[240]	100% of enrolled patients had prior vertebral fracture
Montessori et al, 1997[48]	36% of enrolled patients with radiologic studies (78/80 patients) had prior vertebral fracture
Pacifici et al, 1988[241]	100% of enrolled patients had prior vertebral fracture
Shiota et al, 2001[242]	60% of enrolled patients had prior vertebral fracture
Storm et al, 1990[243]	100% of enrolled patients had prior vertebral fracture
Watts et al, 1990[244]	100% of enrolled patients had prior vertebral fracture
Wimalawansa et al, 1998[245]	100% of enrolled patients had prior vertebral fracture
Risedronate	
Clemmesen et al, 1997[246]	100% of enrolled patients had prior vertebral fracture
Fogelman et al, 2000[45]	29% of enrolled patients had prior vertebral fracture
Harris et al, 1999[247]	80% of enrolled patients had prior vertebral fracture
McClung et al, 2001[41]	41% of enrolled patients had prior vertebral fracture among patients with baseline fracture data (2799/6876; 2455/9331 baseline fracture status unknown)
Reginster et al, 2000[248]	100% of enrolled patients had prior vertebral fracture

Appendix Table D5. Placebo-controlled Trials of Bisphosphonates Reporting Fracture Outcomes Classified as Secondary Prevention

Trial	Reason for exclusion
Ibandronate	
Chesnut et al, 2005[167]	100% of enrolled patients had prior vertebral fracture
Recker et al, 2004[168]	54% of enrolled patients had prior vertebral fracture
Zoledronic acid	
Black et al, 2007[174]	63% of enrolled patients had prior vertebral fracture
Lyles et al, 2007[175]	100% of enrolled patients had prior hip fracture

Appendix Table D6. Fracture Rates in Bisphosphonate Trials Only Included In Sensitivity Analyses

Trial	Intervention Duration Baseline BMD Baseline fracture	Radio-logically confirmed fracture incidence?	Vertebral fracture Active treatment vs. placebo Relative risk (95% CI)	Nonvertebral fracture Active treatment vs. placebo Relative risk (95% CI)	Hip fracture Active treatment vs. placebo Relative risk (95% CI)
Bisphosphonates					
Alendronate					
Bone et al, 1997[38]	Alendronate 5 mg 2 years T-score: -3.1 Previous vertebral fracture: 37%	Yes	4/93 (4%) vs. 6/91 (7%) RR 0.65 (0.19 to 2.24)	9/93 (10%) vs. 16/91 (18%) RR 0.55 (0.26 to 1.18)	NR
Greenspan et al, 1998[46]	Alendronate 5-10 mg 2.5 years T-score: -4.3 Unknown prior fracture	No	Not assessed	3/60 (5%) vs. 1/60 (2%) RR 3.00 (0.32 to 28)	0/60 (0%) vs. 1/60 (2%) RR 0.33 (0.01 to 8.02)
Liberman et al, 1995[47]	Alendronate 5 or 10 mg for 3 years, or 20 mg for two years and 5 mg for 1 year T-score: -3.1 Previous vertebral fracture: 21%	Yes	17/526 (3%) vs. 22/355 (6%) RR 0.52 (0.28 to 0.97)	45/597 (8%) vs. 38/397 (10%) RR 0.79 (0.52 to 1.19)	1/597 (0.2%) vs. 3/397 (1%) RR 0.22 (0.02 to 2.12)
Etidronate					
Ishida et al, 2004[40]	Cyclical etidronate 200 mg/day 2 years T-score: -1.9 Previous vertebral fracture: 31%	Yes	8/66 (12%) vs. 17/66 (26%) RR 0.47 (0.22 to 1.01)	1/66 (2%) vs. 3/66 (5%) RR 0.33 (0.04 to 3.12)	0/66 (0%) vs. 1/66 (2%) RR 0.33 (0.01 to 8.04)
Montessori et al, 1997[48]	Cyclical etidronate 400 mg/day 3 years T-score: -3.4 Previous vertebral fracture: 36%	Yes	0/37 (0%) vs. 3/34 (9%) RR 0.13 (0.01 to 2.46)	NR	0/39 (0%) vs. 0/39 (0%) RR not estimable

Appendix Table D6. Fracture Rates in Bisphosphonate Trials Only Included In Sensitivity Analyses

Trial	Intervention Duration Baseline BMD Baseline fracture	Radio-logically confirmed fracture incidence?	Vertebral fracture Active treatment vs. placebo Relative risk (95% CI)	Nonvertebral fracture Active treatment vs. placebo Relative risk (95% CI)	Hip fracture Active treatment vs. placebo Relative risk (95% CI)
Risedronate					
Fogelman et al, 2000[45]	Risedronate 5 mg/day 2 years T-score: -2.9 Previous vertebral fracture: 30%	Yes	8/112 (7.1%) vs. 17/125 (14%)* RR 0.53 (0.24 to 1.17)	7/140 (5%) vs. 13/144 (9%)* RR 0.55 (0.23 to 1.35)	Not reported

Abbreviations: BMD = bone mineral density; CI = confidence interval; NR = not reported; RR = relative risk.

*Intention-to-treat results not reported (sample sizes 180 for risedronate and 177 for placebo).

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Patients/trials
Cranney et al, 2002[176]	To review the effect of calcitonin on bone density and fractures in postmenopausal women	MEDLINE, EMBASE 1966-2000; conference abstracts, FDA proceedings	RCTs ≥1 year duration enrolling post-menopausal women, comparing calcitonin to placebo or calcium/vitamin D with fracture or BMD outcomes	30 trials; total n=3,993 Chesnut 2000 (n=1,255); Flicker 1997 (n=62); Grigoriou 1997 (n=45); Gurlek 1997 (n=20); Kapetanos 1997 (n=46); Ellerington 1996 (n=117); Hizmetli 1996 (n=107); Melis 1996 (n=102); Perez-Jaraiz 1996 (n=52); Thamsborg 1996 (n=72); Perez 1995 (n=73); Reginster 1995 (n=251); Reginster 1995 (n=150); Rico 1995 (n=72); Campodarve 1994 (n=236); Kollerup 1994 (n=54); Overgaard 1994 (n=134); Reginster 1994 (n=287); Meschia 1993 (n=46); Fioretti 1992 (n=60); Gennari 1992 (n=21); Overgaard 1992 (n=84); Perrone 1992 (n=85); Stevenson 1992 (n=86); Thamsborg 1991 (n=40); Meunier 1990 (n=109); Tremollieres 1990 (n=1990); Overgaard 1989 (n=52); Overgaard 1989 (n=40); Gennari 1985 (n=82)
Harris et al, 2008[173]	To assess the ability of ibandronate to reduce fracture risk relative to placebo	Not applicable	Not applicable	4 trials: total n=8,710 Chesnut 2005 - BONE trial (n=2,928); Recker 2004 - IV Fracture Prevention trial (n=2,860); Reginster 2006 and Miller 2005 - MOBILE trial (n=1,566); Eisman 2006 and Delmas 2006 - DIVA trial (n=1,356)
MacLean et al, 2008[187]	To compare the benefits in fracture reduction and the harms from adverse events of various therapies for osteoporosis	CCRCT, MEDLINE, ACP Journal Club 1966-2006	Efficacy: systematic reviews, meta-analyses, RCTs of low bone density treatments vs. placebo reporting fracture outcomes Safety: systematic reviews, RCTs and case-control or cohort studies with >1000 patients	Efficacy: 24 meta-analyses, 76 RCTs Safety: 417 RCTs, 25 controlled clinical trials, 42 observational studies, 9 case reports/case series on osteonecrosis; total number of patients not calculated

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main efficacy outcome
Cranney et al, 2002[176]	RCTs; 16 treatment trials, 13 prevention trials, 1 combination treatment/prevention; 15 blinded; 16 concealed treatment allocation	Mean age 50-70 years 27 trials, <50 years in 3 trials Mean baseline T-score -0.6 to -2.9 in 15 trials; not reported in 15 trials	Calcitonin 50-400 IU qd placebo calcium/vitamin D	Fracture incidence (also change in BMD)
Harris et al, 2008[173]	Double-blind RCTs reporting fracture outcomes	Age 66-69 years Baseline lumbar spine T-score -2.81 to -3.28	Ibandronate, varying doses, dosing schemes and methods of administration (IV and oral) placebo	Nonvertebral fracture incidence (also clinical fracture incidence)
MacLean et al, 2008[187]	Efficacy: 24 meta-analyses, 76 RCTs Safety: 417 RCTs, 25 controlled clinical trials, 42 observational studies, 9 case reports/case series on osteonecrosis	Men or women with primary or secondary osteoporosis or low bone density	Alendronate, etidronate, ibandronate, pamidronate risedronate, zoledronic acid calcitonin, estrogen, teriparatide, raloxifene, tamoxifen, testosterone, vitamin D, calcium	Fracture reduction

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Main efficacy results	Harms results	Conclusion	Quality Score	Comments
Cranney et al, 2002[176]	Vertebral fracture (4 trials): RR 0.46 (CI 0.25-0.87; p=0.02) Non-vertebral fracture (3 trials): RR 0.52 (CI 0.22 to 1.23; p-0.14)	Described as poorly reported across the trials; loss to follow-up was similar in calcitonin and control groups	Calcitonin reduces the incidence of vertebral fracture, but the magnitude of effect is unclear due to small sample sizes in the trials used to calculate relative risks and the use of random-effects modeling which may place undue weight on smaller studies	Fair	
Harris et al, 2008[173]	Non-vertebral fractures High-dose ibandronate: adjusted HR 0.70 (CI 0.50 to 0.99; p=0.41) Mid-dose ibandronate: adjusted HR 1.04 (CI 0.83 to 1.30; p=0.72) Any clinical fracture: High-dose ibandronate: adjusted HR 0.73 (CI 0.56 to 0.95; p=0.19) Mid-dose ibandronate: adjusted HR 0.92 (CI 0.77 to 1.09; p=0.33)	NR	High-dose ibandronate was associated with demonstrable reductions in risk of nonvertebral and clinical fracture	Not quality assessed	Results were stratified according to accumulated exposure; High-dose includes FDA-approved 150mg/month oral and 3 mg/3 months IV; Mid-dose includes FDA-approved 2.5mg qd
MacLean et al, 2008[187]	--	--	Data are insufficient to determine relative efficacy or safety of included therapeutic agents	Fair	

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Patients/trials
Vestergaard et al, 2007[185]	To examine the effects of parathyroid hormone (PTH) either alone or in combination with antiresorptive therapy on bone mineral density and fracture risk	CCRCT (1990-2005); MEDLINE (1951-2005); EMBASE (1974-2005); Science Citation Index (1945-2005); conference abstracts; reference lists	RCTs of PTH ≥6 months duration with fracture occurrence and/or BMD outcomes	13 trials; total n=5,455 Greenspan 2005 (n=2,531); Lane 1998 (n=51); Body 2002 (n=146); Cosman 2001 (n=126); Neer 2001 (n=1,326); Orwoll 2003 (n=437); Finkelstein 1998 (n=43); Finkelstein 2003 (n=73); Kurland 2000 (n=23); McClung 2005 (n=203); Black 2003 (n=238); Hodsman 2003 (n=206)
Wells et al, 2008[162] Alendronate	To assess the efficacy of alendronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women	CCRCT, MEDLINE, EMBASE 1966-2007	RCTs at least 1 year in duration enrolling postmenopausal women comparing alendronate to placebo or calcium/vitamin D	11 trials; total n=12,068 Ascott Evans 2003 (n=144); Cummings 1998 (n=4,432); Hosking 1998 (n=120) Black 1996 (n=2027); Bone 1997 (n=359); Chesnut 1995 (n=188); Durson 2001 (n=101); Greenspan 1998 (n=120); Greenspan 2002 (n=327); Liberman 1995 (n=994); Pols 1999 (n=1908)
Wells et al, 2008[163] Etidronate	To assess the efficacy of etidronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women	CCRCT, MEDLINE, EMBASE 1966-2007	RCTs at least 1 year in duration enrolling postmenopausal women comparing oral etidronate to placebo or calcium/vitamin D	11 RCTs; total n=1,248 Primary prevention: Herd 1997 (n=152); Meunier 1997 (n=54); Pouilles 1997 (n=109) Secondary prevention: Ishida 2004 (n=132); Lyritis 1997 (n=100); Montessori 1997 (n=80); Pacifici 1988 (n=57); Shiota 2001 (n=40); Storm 1990 (n=66); Watts 1990 (n=423); Wimalawansa 1998 (n=35)

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main efficacy outcome
Vestergaard et al, 2007[185]	RCTs; no further details on design provided Quality of included trials ranged from 2-4 pts (Jadad)	Men or women age ≥18 years with primary or secondary (i.e. corticosteroid-induced) osteoporosis	Parathyroid hormone I-34 or I-84 20-100ug qd, alone or in combination with hormone replacement therapy (2 studies), bisphosphonates (5 studies) or nafarelin (1 study)	Fracture incidence (also change in BMD)
Wells et al, 2008[162] Alendronate	10/11 double-blind RCTs; 1/11 RCT, blinding unclear	Post-menopausal women; age 53-78 years; baseline T-score -1.0 to -4.3	Alendronate 5-20mg qd calcium ≤500mg qd vitamin D 125-400 IU qd placebo	Fracture incidence
Wells et al, 2008[163] Etidronate	5/11 double blind	Postmenopausal women age 53-72 years; baseline T-score -0.8 to -4.3	Etidronate 200-400mg qd calcium (dose not consistently reported across included trials) placebo	Fracture incidence

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Main efficacy results	Harms results	Conclusion	Quality Score	Comments
Vestergaard et al, 2007[185]	PTH alone results (results for PTH in combination with other treatments were similar with overlapping CIs) Vertebral fracture (4 studies): RR 0.37 (CI 0.28 to 0.48; p<0.01) Non-vertebral fracture (2 studies): RR 0.62 (CI 0.46-0.82; p<0.01)	Back pain (5 studies): OR 0.68 (CI 0.53 to 0.87; p=0.09)	PTH - alone and in combination - reduced incidence of vertebral fracture and, to a lesser extent, non-vertebral fracture	Good	Results not pooled due to study heterogeneity
Wells et al, 2008[162] Alendronate	Primary prevention Vertebral fracture: RR 0.55 (CI 0.38 to 0.80; p=0.002) Non-vertebral fracture: RR 0.89 (CI 0.76 to 1.04; p=0.14) Hip fracture: RR 0.79 (CI 0.44 to 1.44; p=0.4) 5-year fracture risk (based on FRACTURE Index scores) Score 1-2: ARR 0.5%; NNT 200Score 3-4: ARR 1.1%; NNT 91Score 5: ARR 2.4%; NNT 42 Score 6-7: ARR 3.2%; NNT 31Score 8-13: ARR 5/0%; NNT 20 Secondary prevention Vertebral fracture: RR 0.55 (CI 0.43 to 0.69; p<0.001) Non-vertebral fracture: RR 0.77 (CI 0.64 to 0.92; p=0.005) Hip fracture: RR 0.47 (CI 0.26 to 0.85; p=0.01)	No difference in tolerability or withdrawals due to AEs between alendronate and placebo/control groups with the exception of increased incidence of GI events (RR 1.03; CI 0.98 to 1.08) and esophageal ulcer (RR 1.16; CI 0.39 to 3.45) in the alendronate group; no reports of osteonecrosis	For primary prevention, clinically important reduction in vertebral fractures but not other types of fractures; secondary prevention clinically and statistically significant reduction in vertebral, non-vertebral, hip and wrist fracture	Good	
Wells et al, 2008[163] Etidronate	Primary prevention Vertebral fracture: RR 3.03 (CI 0.32 to 28.44; p=0.3) Non-vertebral fracture: RR 0.56 (CI 0.20 to 1.61; p=0.3) Hip fracture: no evidence available Secondary prevention Vertebral fracture: RR 0.53 (CI 0.32 to 0.87; p=0.01) Non-vertebral fracture: RR 1.07 (CI 0.72 to 1.60; p=0.7) Hip fracture: RR 1.20 (CI 0.37 to 3.88; p=0.8)	Withdrawals: RR 0.91 (CI 0.71 to 1.26) Withdrawals due to AEs: RR 0.61 (CI 0.25 to 1.49) No statistically significant difference in AEs	No clinically or statistically significant reduction in fracture incidence was found with etidronate use with the exception of reducing vertebral fracture in a secondary prevention population	Good	

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Patients/trials
Wells et al, 2008[161] Risedronate	To assess the efficacy of risedronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women	CCRCT, MEDLINE, EMBASE 1966-2007	RCTs at least 1 year in duration enrolling postmenopausal women comparing risedronate to placebo or calcium / vitamin D	7 RCTs; total n=14,049 Hooper 2005 (n=381); Mortensen 1998 (n=111); Clemmesen 1997 (n=132; trial excluded from analysis due to study design); Fogelman 2000 (n=541); Harris 1999 (n=2,458); McClung 2001 (n=9,331); Reginster 2000 (n=1,222)
Men				
Sawka et al, 2005[164]	To systematically review the anti-fracture efficacy of alendronate in men with low bone mass or with a history of prevalent fracture and incorporate prior knowledge of alendronate efficacy in women in the analysis	CCRCT (through 2004), MEDLINE (1966-2004), EMBASE (1996-2004)	RCTs of alendronate with men comprising at least half of the study population with ≥1 year follow-up reporting fracture outcomes	2 trials; total n=375 Orwoll 2000 (n=241); Ringe 2004 (n=134)
Tracz et al, 2006[186]	To estimate the effect of testosterone use on bone health outcomes	CCRCT (through 2005), MEDLINE (1966-2005), EMBASE (1988-2005), reference lists, content expert files	RCTs of testosterone versus placebo reporting fractures as or BMD as an outcome	8 trials; total n=388 Amory 2004 (n=48); Crawford 2003 (n=34); Fairfield 2001 (n=50); Hall 1996 (n=30); Kenny 2001 (n=67); Reid 1996 (n=16); Snyder 1999 (n=108)

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main efficacy outcome
Wells et al, 2008[161] Risedronate	All double-blind studies	Postmenopausal women, age 51-78 years; baseline T-score -0.4 to 3.7	Risedronate 2.5; 5 mg qd cyclical risedronate 2.5; 5 mg qd calcium 1000 mg qd vitamin D 500 IU qd placebo	Fracture incidence
Men				
Sawka et al, 2005[164]	RCTs; one double-blind (Orwoll), one open-label (Ringe)	Mean age 63 years Baseline T-score -1.0 to -2.0	Alendronate 10mg qd calcium/vitamin D alfacalcidiol	Fracture incidence
Tracz et al, 2006[186]	RCTs; 7/8 studies blinded (know or presumed); 1 crossover study	Mean age 60-75 years in 6 trials; <60 years in 2 trials	Testosterone 200-250mg qd or 2.5mg patch placebo	Fracture incidence (and change in BMD)

Appendix Table D7. Treatment Systematic Reviews

Study, Year	Main efficacy results	Harms results	Conclusion	Quality Score	Comments
Wells et al, 2008[161] Risedronate	Primary prevention Vertebral fracture: RR 0.97 (CI 0.42 to 2.25; p=0.94) Non-vertebral fracture: RR 0.81 (CI 0.25 to 2.58; p=0.72) Hip fracture: inadequate evidence Secondary prevention Vertebral fracture: RR 0.61 (CI 0.5 to 0.76; p<0.001) Non-vertebral fracture: RR 0.80 (CI 0.72 to 0.90; p=0.0002) Hip fracture: RR 0.75 (CI 0.59 to 0.94; p=0.01)	Withdrawals (5 trials): RR 0.96 (CI 0.91 to 1.00) Withdrawals due to AEs (5 trials): RR 0.96 (CI 0.88 to 1.05) Adverse events - any upper GI event: RR 1.01 (CI 0.94 to 1.09) Other specific AEs not pooled, reported as generally no difference between risedronate and placebo	Primary prevention Vertebral fracture: RR 0.97 (CI 0.42 to 2.25; p=0.94) Non-vertebral fracture: RR 0.81 (CI 0.25 to 2.58; p=0.72) Hip fracture: inadequate evidence Secondary prevention Vertebral fracture: RR 0.61 (CI 0.5 to 0.76; p<0.001) Non-vertebral fracture: RR 0.80 (CI 0.72 to 0.90; p=0.0002) Hip fracture: RR 0.75 (CI 0.59 to 0.94; p=0.01)	Withdrawals (5 trials): RR 0.96 (CI 0.91 to 1.00) Withdrawals due to AEs (5 trials): RR 0.96 (CI 0.88 to 1.05) Adverse events - any upper GI event: RR 1.01 (CI 0.94 to 1.09) Other specific AEs not pooled, reported as generally no difference between risedronate and placebo	Primary prevention Vertebral fracture: RR 0.97 (CI 0.42 to 2.25; p=0.94) Non-vertebral fracture: RR 0.81 (CI 0.25 to 2.58; p=0.72) Hip fracture: inadequate evidence Secondary prevention Vertebral fracture: RR 0.61 (CI 0.5 to 0.76; p<0.001) Non-vertebral fracture: RR 0.80 (CI 0.72 to 0.90; p=0.0002) Hip fracture: RR 0.75 (CI 0.59 to 0.94; p=0.01)
Men					
Sawka et al, 2005[164]	Vertebral fracture: OR 0.36 (CI 0.17 to 0.77) Non-vertebral fracture: OR 0.73 (CI 0.32 to 1.67) Bayesian random effects model (incorporating data from women) Vertebral fracture: OR 0.44 (CRI 0.23 to 0.83) Nonvertebral fracture: OR 0.60 (CRI 0.29 to 1.44)	NR	Vertebral fracture: OR 0.36 (CI 0.17 to 0.77) Non-vertebral fracture: OR 0.73 (CI 0.32 to 1.67) Bayesian random effects model (incorporating data from women) Vertebral fracture: OR 0.44 (CRI 0.23 to 0.83) Nonvertebral fracture: OR 0.60 (CRI 0.29 to 1.44)	NR	Vertebral fracture: OR 0.36 (CI 0.17 to 0.77) Non-vertebral fracture: OR 0.73 (CI 0.32 to 1.67) Bayesian random effects model (incorporating data from women) Vertebral fracture: OR 0.44 (CRI 0.23 to 0.83) Nonvertebral fracture: OR 0.60 (CRI 0.29 to 1.44)
Tracz et al, 2006[186]	No studies reported on fracture outcomes	NR	No studies reported on fracture outcomes	NR	No studies reported on fracture outcomes

Abbreviations: AE = adverse effects; ARR = absolute risk reduction; BMD = bone mineral density; CI = confidence interval; CRI = corresponding credibility interval; GI = gastro-intestinal; HR = heart rate; NNT = number needed to treat; NR = not reported; OR = odds ratio; PTH = parathyroid hormone; RR = relative risk; RCT = randomized controlled trial.

Appendix Table D8. Quality Ratings of Systematic Reviews

Study, Year	Search dates	Search methods reported	Comprehensive search	Inclusion criteria reported	Selection bias avoided	Validity criteria reported	Validity assessed appropriately
Cranney et al, 2002[176]	MEDLINE, EMBASE 1966-2000; conference abstracts, FDA proceedings	Yes	Yes	Yes	Yes	Yes	Yes
MacLean et al, 2008[187]	CCRCT, MEDLINE, ACP Journal Club 1966-2006	Yes	Yes	Yes	Yes	Yes	Yes
Vestergaard et al, 2007[185]	CCRCT (1990-2005); MEDLINE (1951-2005); EMBASE (1974-2005); Science Citation Index (1945-2005); conference abstracts; reference lists	Yes	Yes	Yes	Yes	Yes	Yes
Wells et al, 2008[162] Alendronate	CCRCT, MEDLINE, EMBASE 1966-2007	Yes	Yes	Yes	Yes	Yes	Yes
Wells et al, 2008[163] Etidronate	CCRCT, MEDLINE, EMBASE 1966-2007	Yes	Yes	Yes	Yes	Yes	Yes
Wells et al, 2007[161] Risedronate	CCRCT, MEDLINE, EMBASE 1966-2007	Yes	Yes	Yes	Yes	Yes	Yes
Men							
Sawka et al, 2005[164]	CCRCT (through 2004), MEDLINE (1966-2004), EMBASE (1996-2004)	Yes	Yes	Yes	Yes	No	Can't tell
Tracz et al, 2006[186]	CCRCT (through 2005), MEDLINE (1966-2005), EMBASE (1988-2005), reference lists, content expert files	Yes	Yes	Yes	Yes	Yes	Yes

Appendix Table D8. Quality Ratings of Systematic Reviews

Study, Year	Methods used to combine studies reported	Findings combined appropriately	Conclusions supported by data	Quality score
Cranney et al, 2002[176]	Yes	Yes	Yes	Good
MacLean et al, 2008[187]	Yes	Partial	Partial	Fair
Vestergaard et al, 2007[185]	Yes	Yes	Yes	Good
Wells et al, 2008[162]	Yes	Yes	Yes	Good
Alendronate				
Wells et al, 2008[163]	Yes	Yes	Yes	Good
Etidronate				
Wells et al, 2007[161]	Yes	Yes	Yes	Good
Risedronate				
Men				
Sawka et al, 2005[164]	Yes	Yes	Yes	Fair
Tracz et al, 2006[186]	Yes	Yes	Yes	Good

Note: Harris et al, 2008 is a meta-analysis of individual patient data, and therefore is not assessed for quality.